PHILIPPINE COVID-19 LIVING CLINICAL PRACTICE GUIDELINES

As of January 2022

TREATMENT for COVID-19

EVIDENCE and RECOMMENDATIONS

Implementing Agency:

Institute of Clinical Epidemiology, National Institutes of Health
University of the Philippines, Manila

Cooperating Agency:

Philippine Society of Microbiology and Infectious Diseases

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Disease Prevention and Control Bureau

Disclaimer

As a living guideline, the recommendations will be updated, and new recommendations will be added as the evidence evolves. The living recommendations are based on the best evidence available in scientific literature at the time of its formulation. However, this living CPG is not a comprehensive guide to all practice questions and management options on COVID-19. This is not meant to restrict the practitioner in using sound clinical judgement and sharing the decision with the patient, and from considering other management options according to the patient's particular needs and preferences. This CPG can serve to inform policy, but it is not meant to serve as a basis for approving or denying financial coverage or insurance claims merely because of nonconformance with recommendations. Neither are the recommendations supposed to be considered as legal rules for dictating certain modes of action to the exclusion of others.

Contact Us

Send us an email at covidcpg.ph@gmail.com for any questions or clarifications on the outputs and process of this Living CPG. You may also suggest a clinical question for the consideration of the Living Clinical Practice Guidelines COVID-19 Taskforce.

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Quick Guide on How to Interpret the Evidence

Evidence on Therapy

Table 1. Ways of expressing effectiveness

Outcome	Summary of result within each group	Comparison of results between two groups
Dichotomous (e.g. lived or died, BP controlled or not)	Proportion (e.g. deaths per 100 patients)	Relative risk reduction, absolute risk reduction, relative risk (see Table 2)
	Rate = e.g. deaths per 100 patients	Hazard ratio = rate in treatment/rate in control group
Continuous (e.g. blood pressure in mmHg, quality of life on a scale of 0 to 1)	Mean (e.g. mean blood pressure)	Mean difference = mean in control – mean in treatment group

When researchers express the effect of treatment using the relative risk reduction, absolute risk reduction, or relative risk, they often give us a range of possibilities rather than a single estimate. This range of possibilities is called a '95% Confidence Interval (95% CI)' to mean 'we are 95% sure that the true effect of a drug lies in this range'. Go through Table 2, to discover how helpful 95% CIs are.

Table 2. Interpreting 95% Confidence Intervals (CIs)

Measure of effectiveness and interpretation of estimates	Interpretation of 95% Confidence Intervals (CIs)			
	Superior (treatment surely better than control)	Inferior (treatment surely worse than control)	Inconclusive (we need more studies)	Equivalent (the treatments are equal)[a]
Relative Risk (RR) = R_t/ R_c	Both ends of 95% CI <1.0	Both ends of 95% CI > 1.0	95% CI wide; straddles 1.0	95% CI narrow; straddles 1.0
<1.0 Treatment beneficial =1.0 Treatment no effect >1.0 Treatment harmful	Example: RR = 0.7 [95% CI: 0.6, 0.8]	Example: RR = 2.4 [95% CI: 1.8, 3.2]	Example: RR = 1 [95% CI: 0.2, 5.3]	Example: RR = 1 [95% CI: 0.9, 1.1]
Absolute Risk Reduction (ARR) = R_c - R_t (usually in percent)	Both ends of 95% CI >0%	Both ends of 95% CI <0%	95% CI straddles 0%; either end is far from 0%	95% CI straddles 0%; either end is close to 0%
>0% Treatment beneficial =0% Treatment no effect <0% Treatment harmful	Example: ARR = 2% [95% CI: 1%, 3%]	Example: ARR = -3% [95% CI: -7%, -1%]	Example: ARR = 1% [95% CI: -20%, 32%]	Example: ARR =0.2% [95% CI: -0.1%, 0.5%]

[a] In both inconclusive and equivalent results, the 95% CI interval straddles the point of no effect (ARR = 0% or RR = 1.0). One end reflects the worst possible harm, while the other end reflects the best possible benefit. The only difference is that, in equivalence, either end is close to "no effect" (i.e. any benefit is ignorable and any harm is ignorable too). Consider the ends of the 95% CI to make sure you agree that the benefits and harms are ignorable.

R_c is the rate of the outcomes in the Control group
R_t is the rate of the outcome in the Treatment group

Note: The interpretations in this table only hold if the dichotomous events are expressed as adverse rather than desirable events, e.g. death rather than survival, treatment failure rather that cure, or disease rather than disease-free. When dichotomous outcomes are expressed as desirable events, the interpretation of benefit and harm is reversed.

The balloons below (Figure 1) label the most important parts of the forest plot. Go through these labels and familiarize yourself with the anatomy of the graph. Once you feel sufficiently familiar with the anatomy, go through the notes below on what the forest plot can signify.

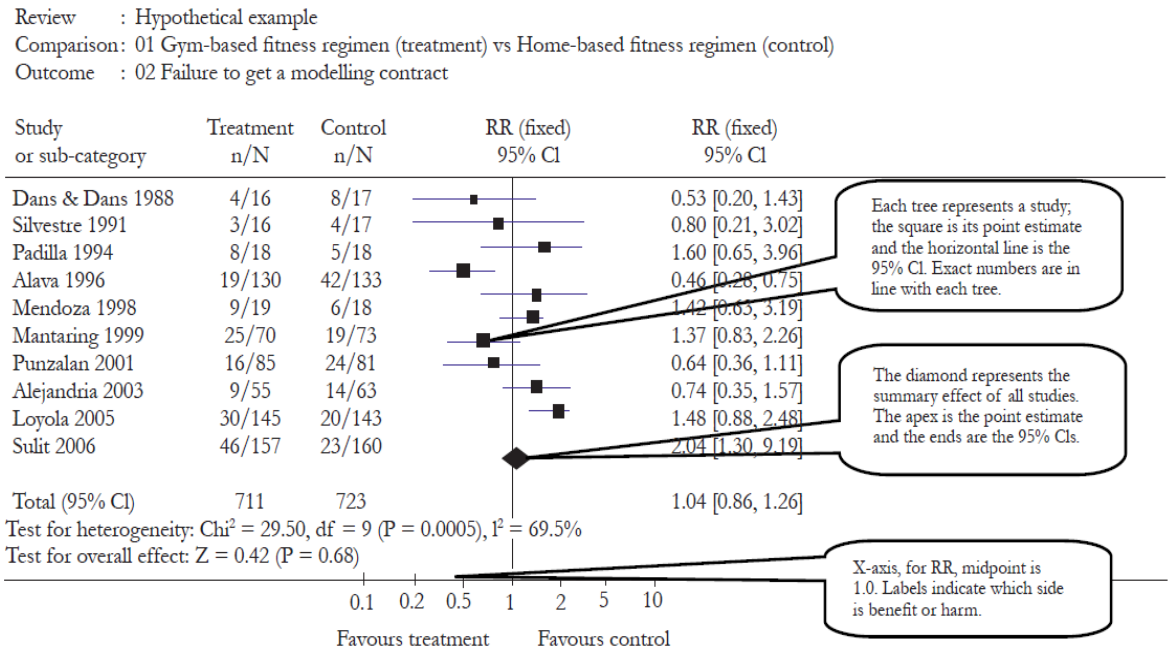

Figure 1. How to interpret forest plots

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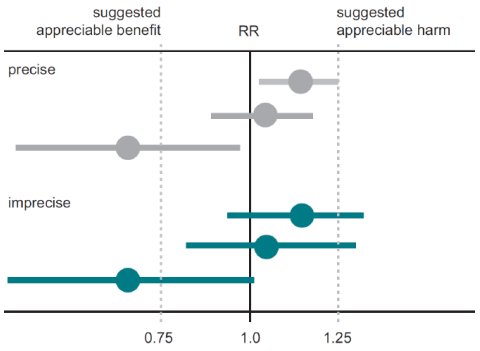
Dans, AL, et al. (2017). Painless Evidence-Based Medicine, 2nd Ed. UK: John Wiley & Sons Ltd.

GRADE Approach in Assessing the Quality of Evidence

(GRADE: Grading of Recommendations Assessment, Development and Evaluation)

These quality ratings apply to the body of evidence assessed for the research question, not to individual studies. Evidence based on randomized controlled trials is initially given a high-quality rating and evidence from observational studies is given a low-quality rating. The level is then adjusted according to the following criteria.

Table 3. Standard criteria for grading of evidence

Domain	Grade	Characteristic
Study Design	0	All randomized controlled trials
	-1	All observational studies
Study Design Limitations	0	Most of the pooled effect provided by studies, with low risk of bias ("A")
	-1	Most of the pooled effect provided by studies with moderate ("B") or high ("C") risk of bias. Studies with high risk of bias weighs <40%
	-2	Most of the pooled effect provided by studies with moderate ("B") or high ("C") risk of bias. Studies with high risk of bias weighs ≥40%
	Note: *Low risk of bias (no limitations or minor limitations) – "A"* *Moderate risk of bias (serious limitations or potentially very serious limitations including unclear concealment of allocation or serious limitations, excluding limitations on randomization or concealment of allocation) – "B"* *High risk of bias (limitations for randomization, concealment of allocation, including small blocked randomization (<10) or other very serious, crucial methodological limitations) – "C"*	
Imprecision	0	The confidence interval is precise according to the figure below. The total cumulative study population is not very small (i.e. sample size is more than 300 participants) and the total number of events is more than 30. 
	-1	One of the above-mentioned conditions is not fulfilled.
	-2	The two above-mentioned are not fulfilled.
	Note: *If the total number of events is less than 30 and the total cumulative sample size is appropriately large (e.g. above 3000 patients, consider not downgrading the evidence).* *If there are no events in both intervention and control groups, the quality of evidence in the specific outcome should be regarded as very low.*	
Inconsistency	0	No severe heterogeneity (I^2< 60% or X^2<0.05)
	-1	Severe, non-explained, heterogeneity (I^2 ≥60% or X^2<0.05)

Domain	Grade	Characteristic
		If heterogeneity could be caused by publication bias or imprecision due to small studies, downgrade only for publication bias or imprecision (i.e. the same weakness should not be downgraded twice)
Indirectness	0	No indirectness
	-1	Presence of indirect comparison, population, intervention, comparator, or outcome
Publication Bias	0	No evident asymmetry in the funnel plot or less than five studies to be plotted.
	-1	Evident asymmetry in funnel plot with at least five studies

Table 4. Quality of evidence in GRADE

Quality Level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

REFERENCE

Schünemann H, Brozek J, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group. Available at: https://gdt.gradepro.org/app/handbook/handbook.html.

Evidence Base

List of Questions

This section presents the evidence base for the recommendations on the treatment for COVID-19. The following key questions were addressed:

Q1. Should hydroxycholoroquine/chloroquine, with or without azithromycin be used in the treatment of patients with COVID-19 infection?

Q2. Should azithromycin be used in the treatment of patients with COVID-19 infection?

Q3. Among patients with COVID-19, favipiravir be used for treatment?

Q4. Should remdesivir be used in the treatment of patients with COVID-19 infection?

Q5. Among patients with COVID-19, should molnupiravir be used for treatment?

Q6. Should baloxavir be used in the treatment of patients with COVID-19 infection?

Q7. Should oseltamivir be used in the treatment of patients with COVID-19 infection?

Q8. Should lopinavir/ritonavir be used in the treatment of patients with COVID-19 infection?

Q9. Among patients with COVID-19, should tocilizumab be used for treatment?

Q10. Among patients with COVID-19, should baricitinib be used for treatment?

Q11. Among patients with COVID-19, should imatinib be used for treatment?

Q12. Among patients with COVID-19, should tofacitinib be used for treatment?

Q13. Among patients with COVID-19, should leronlimab be used for treatment?

Q14. Among patients with COVID-19, should infliximab be used for treatment?

Q15. Among patients with COVID-19, should bevacizumab be used for treatment?

Q16. Among patients with COVID-19, should ivermectin be used for treatment?

Q17. Among patients with COVID-19, should artesunate (artemisinin) be used for treatment?

Q18. Among patients with COVID-19, should colchicine be used for treatment?
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Q29. Should virgin coconut oil (VCO) be used in the treatment of patients with COVID-19 infection?
Q30. Among patients with COVID-19, should Lianhua be used for treatment?
Q31. Should famotidine be used in the treatment of patients with COVID-19 infection?
Q32. Should ibuprofen be used in the treatment of patients with COVID-19 infection?

Q1. Should hydroxycholoroquine/ chloroquine, with or without azithromycin be used in the treatment of patients with COVID-19 infection?

As of 19 February 2021

RECOMMENDATION

We recommend against the use of hydroxychloroquine/chloroquine, with or without azithromycin among patients with COVID-19 infection. *(Moderate certainty of evidence, Strong recommendation)*

Consensus Issues
None raised during panel meetings..

KEY FINDINGS

Twenty-two trials showed that hydroxychloroquine (HCQ)- containing treatment did not significantly improve the outcomes of patients with COVID-19 disease compared with placebo or standard of care. Eleven (11) trials provided evidence of low certainty that the use of HCQ for the treatment of COVID-19 infection was significantly associated with a higher risk of adverse events (i.e., diarrhea, headache, rashes, and fatigue). There was very limited evidence with low to very low certainty which showed that treatment with HCQ combined with azithromycin does not show any significant difference from placebo in any of the efficacy outcomes. Adverse events were more frequent with the hydroxychloroquine with azithromycin group compared to placebo.

INTRODUCTION

Anti-malarial and anti-inflammatory drugs from the 4-quinolone family, particularly hydroxychloroquine (HCQ) and chloroquine (CQ), have been proposed as possible effective treatments or even prophylaxis for SARS-CoV-2 infections. HCQ and CQ are immune modulators which block the production of inflammatory cytokines and suppresses cytokine storms which are critical in the pathogenesis of COVID-19 infections [1]. Some studies have also shown that CQ and HCQ cause glycolysation of ACE 2 receptors, making cells refractory to SARS-CoV-2 infection.[2] HCQ and CQ have previously been used in the treatment of other viral illness such as HIV, Dengue and Zika virus, with the former having lesser toxic effects of retinopathy, myopathy, neuropathy and cardiomyopathy.

REVIEW METHODS

A search for systematic reviews and meta-analysis was done on Pubmed on the treatment of COVID-19 infection, whether on hydroxychloroquine specifically or for all types of medications. The search terms used were “systematic reviews” and “COVID-19.” Identified reviews were assessed based on the Painless EBM systematic review appraisal form. Additional search for trials was done on March 17, 2021 using the Living OVerview of Evidence (L·OVE) platform, using hydroxychloroquine as the intervention and “RCT” and “with reported data” as additional filters to identify new trials that may not have been included in the living reviews.

RESULTS

Four (4) living systematic reviews were identified after a comprehensive search on PubMed: The Living Project [3] reviewed all treatments for COVID, with 33 RCTs incorporated its September 2020 publication, including 12 with HCQ in one arm. No active website could be found for an updated status of this review. One review was limited to studies on severe COVID cases [4], with regular updates as ePublications. Two other living systematic reviews, one by the Cochrane Collaboration [5,6,7], and the other by the McMaster University [8,9], have active websites that are updated regularly, covering all treatments for COVID-19. A search of the COVID living evidence registry, iloveevidence.com for relevant systematic reviews did not yield any additional living review. Based on a comparative appraisal of these living systematic reviews, the trials included in this rapid review were mainly from the trials identified by the Covid-nma project [7] with its last update on March 8, 2021. For this review, the COVID-nma project was accessed on March 16, 2021.

Additional search of a living evidence registry, iloveevidence.com, on March 9, 2021 yielded 4 additional studies that were not included in the COVID-NMA evidence base as of March 16, 2021 [10,11,12,13].

Twenty two (22) RCTs [10,11,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32] compared hydroxychloroquine-containing therapy with either placebo or standard of care alone. Three (3) trials compared hydroxychloroquine combined with azithromycin with placebo. [11,17,27] A total of 4682 patients were randomized to receive HCQ, and 435 were randomized to HCQ with azithromycin. Seven (7) RCTs (one of which had two different active control groups) compared HCQ-containing treatment with another treatment (azithromycin[33], ivermectin[13,34], ivermectin with doxycycline[35], febuxostat[36], favipiravir with interferon-beta[37], lopiravir/ritonavir [15], lopiravir/ritonavir with interferon-beta[15]). One trial compared chloroquine with favipiravir[38].

Characteristics of these included studies are detailed in Appendix 1.

Most of the trials in the review were assessed to be with high risk of bias because of being open labeled trials, although this was not deemed to impact their conclusions as outcomes were objective. One was quasi-randomized. Several trials were pre-terminated due to restrictions by regulators on the conduct of HCQ trials after publication of several studies showing lack of benefit and concerns regarding the unfavorable risk/benefit ratio.

The GRADE profile and summary of findings table is presented in Appendix 2.

Comparison 1: Hydroxychloroquine versus placebo or standard of care

Fifteen (15) trials provided high certainty evidence that hydroxychloroquine treatment did not reduce mortality rates when compared to placebo or standard of care (RR 0.99, 95% CI 0.45-2.18) (see Appendix 2). Moreover, several trials also showed no significant difference between HCQ and placebo or standard of care in terms of other treatment outcomes such as viral negative conversion, clinical improvement, and clinical recovery.

Ten (10) trials provided evidence of low certainty that the use of HCQ for the treatment of COVID-19 infection was significantly associated with a higher risk of adverse events (RR 1.83, 95%CI 1.12-2.97). The common side effects associated with HCQ reported in the trials include diarrhea, headache, rashes, and fatigue.

Comparison 2: Hydroxychloroquine + azithromycin versus placebo or standard of care

Three trials [11,17,27] provided very limited evidence with low to very low certainty that treatment with HCQ combined with azithromycin did not show any significant difference from placebo in any of the efficacy outcomes. Adverse events were more frequent with the hydroxychloroquine with azithromycin group compared to placebo (RR 1.42 95%CI 1.08, 1.87). One trial (17) provided data for most of the outcomes evaluated.

Comparison 3: Hydroxychloroquine/Chloroquine-containing treatment versus other active treatments

Results from six trials [15,33,35,38,36,37] also showed that treatment with HCQ did not show any significant difference from the other active treatments (azithromycin, ivermectin + doxycycline, febuxostat, favipiravir + interferon-beta, liponavir + ritonativir, liponative/ritonavir + interferon-beta) in the different outcomes measured (see Appendix 4a-h). One study showed significantly higher risk for mortality at 28 days with HCQ treatment, compared with ivermectin among patients with severe COVID-19 infection.[34]

RECOMMENDATIONS FROM OTHER GROUPS

The US-NIH recommends against the use of HCQ/CQ with or without azithromycin in the treatment of COVID-19 in hospitalized and non-hospitalized patients. [39] The Infectious Disease Society of America likewise recommends against HCQ/ HCQ with azithromycin for COVID-19 treatment.[40]

EARLY TERMINATION OF CLINICAL TRIALS

The major clinical trials investigating the effects of HCQ for COVID-19 infection, upon recommendation of their respective independent review committees, terminated participant recruitment after unblinded review of the results. On June 2020, the US NIH stopped the Outcomes Related to COVID-19 treated with hydrochloroquine among In-patients with symptomatic Disease study, or the ORCHID Study.[41] The chief investigators of the Recovery trial stopped enrolling participants to the HCQ arm of the trial after the review of the data by the Independent Data Monitoring Committee on the same month.[42] WHO, upon recommendation from the Solidarity Trial's International Steering Committee, discontinued the trial's HCQ arm in July 2020. [43]

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Appendix 1. Characteristics of Included Studies

HCQ / HCQ+Azithro vs placebo / standard of care

Study ID	Patients	Intervention (HCQ)	Comparator	Outcomes
Abd-Elsalam(14)	Suspected and confirmed COVID, all severities	HCQ 400mg BID on D1 then 200 mg BID x 15 days (n=97)	Standard care : paracetamol, antibiotic, oseltamivir x 5 days (n=97)	Recovery within 28 days, need for mechanical ventilation, death, mean duration to negative PCR, mean time to clinical improvement, mean time to discharge, outcome at D28
Ader (Discovery) (15)	>= 18 yo, hospitalized with PCR proven SARS-COV-2 infection and pulmonary rales, sPaO2 <=94%, or requiring supplemental O2	SOC plus HCQ 200mg to 400mg twice on D1 then 400mg OD x 9 days (n= 145)	Standard of Care (SOC) (n=148) SOC + lopinavir 400mg /ritonavir 100mg Q 12h x 14 days (n=145) SOC + lopinavir 400mg / ritonavir 100mg Q12 x 14 days + IFN-Beta 44ug SQ on D1, 3,6 (n=145) SOC + remdesivir 200mg IV on D1 then 100 mg OD x 10 days (n=145)	Clinical status at D15 (WHO Master protocol), at D29, time to an improvement of 2 categories or hospital discharge until D29, time to NEWS2 <= or hospital discharge until D29, 29-day mortality, viral load, grade 3 or 4 AE, SAE, premature suspension of patients or discontinuation of treatment
Amaravadi (16)	COVID positive at home (Cohort 1)	HCQ 400mg BID x 14days (C1)	Placebo (C1)	Time to release from quarantine; rate of hospitalization; treatment-related AE
	COVID positive hospitalized (Cohort 2)	High dose HCQ 600 mg BID x 14day	Low dose HCW 600 mg OD x 7 days	Time to discharge, rate of discharge at 14 days,
Bernal-Gonzales (13)	RT-PCR positive with pneumonia diagnosed by xray or CT with a pattern suggesting involvement from coronavirus with recently established hypoxemic respiratory failure or acute clinical deterioration of preexisting lung or heart disease; excluded those requiring high oxygen volumes	HCQ 400mg q 12H on D1 then 200mg q12H x 4 days (n=33) (later in trial, coadministered with dexamethasone 6mg IV q 24H x 10 days)	Placebo – calcium citrate 2 tabs q 12H on D1 then 1 tab q 12H x 4 days (n=37) Ivermectin 12 mg for those weighing <80 kg and 18 mg for those above 80kg (n= 36) (later in trial, coadministered with dexamethasone 6mg IV q 24H x 10 days)	Duration of hospitalization, respiratory deterioration, death, SOFA, CORADS
Cavalcanti (17)	18 years or older, hospitalized with suspected or confirmed COVID (not all with (+) PCR ; mild or moderate	HCQ 400mg BID x 7 days (n=221) HCQ 400mg BID plus azithromycin 500 mg OD x 7 days (n=217)	Standard case (immunomodulators, antibiotics, antivirals) (n=227)	Clinical status at D15 (score 1-7), clinical status at D7, indication for intubation at D15, supplemental oxygen within 15 days, LOS, inhospital death, AKI, respirator days
Chen C (18)	20-79 years, confirmed COVID, mild to moderate	HCQ 400mg D1 and 200mg BID x 6 days (n= 21)	Standard care (with antibiotics, oseltamivir) (n=12)	Proportion of negative PCR at D14; median time to negative PCR; time to clinical revocery, proportion of discharges at D14, mortality; safety
Chen J (19)	>=18 years, confirmed COVID	HCQ 400mg x 5 days (n=15)	Standard of care (n=15)	Viral clearance on Day 7; Mortality; radiological progression on CT,

Chen L (20)	18-75 years, positive PCR or with lung changes od COVID; moderate disease	Chloroquine 1000QD on Day 1 then 500mg QD x 9 days (n = 25->18); HCQ 200mg BID x 10 days, (n=28->18)	n=14 ->12	Clinical recovery time; Adverse events; Time to RNA negativity; LOS, changes on chest CT, duration of supplemental oxygenation, clinical status, mortality
Chen Z (21)	>=18 years; confirmed COVID mild disease	HCQ 400mg x 5 days (n=31)	Standard of care (n=31)	Severe AE, time to clinical recovery, changes in chest CT (pulmo recovery)
Dubee (22)	18 years and older, PCR positive or with CT findings, with risk factor; mild and moderate	HCQ 200mg BID x 9 days(n=123)	Placebo (n=124)	Composit of death and need for mechanical ventilation at da14;SAE at D28; clinical improvement ad D14 and D28, mortality at D14 and D28; PCR positive at D5 and D10
Hernandez-Cardenas (10)	Over 18 yo, <14 days from symptom onset of confirmed diagnosis of COVID-19 by RT PCR requiring hospitalization, requiring respiratory support	HCQ 200mg Q 12 H x 10 days (n= 106)	Sucrose-placebo x 10 days (n=108)	Mortality, proportion requiring ventilatory support after admission, duration of hospitalization, severe adverse events leading to treatment discontinuation, intervention or death
Horby (Recovery) (23)	At least 18yo, hospitalized, clinically suspected or confirmed COVID	HCQ 400mg x 10 days (n=1561)	Standard care (n- 3155)	Mortality at 28D; time to discharge, % discharge at D28; composite of mech vent, ECMO and death,
Kamran (24)	18-80 years, mild COVID, hospitalized	HCQ 400mg BID on D1 then 200 mg BID x 5 days (n=349)	Standard of care (n= 151) = vit C 2gms, vit D, paracetamol, Zinc	Disease progression ; PCR negative at d7 and d14
Johnston (11)	18-80 years old, lab confirmed SARS-CoV-2 infection, subgrouped to high and low risk cohorts	HCQ 400 mg BID on D1 then 200mg BID x 9 days + Folic acid (n=63) HCQ as above + Azitho 500mg on D1 then 250mg OD x 4 days (n= 74)	Ascorbic acid + Folic acid (n=80)	Development of LRTI (SpO2<93%) D14, COVID-related hospitalization, death, time to COVID symptom resolution, adverse vents, SAEs,
Lyngbakken (25)	18 years and above, PCR positive cases, moderate to severe	HCQ 400mg x 7 days (n=26)	Standard of care (n-27)	Rate of decline of viral load; in hospital death; clinical status at D14, LOS,
Mitja (26)	18 years or more, mild COVID, PCR-confirmed	HCQ 800mg on D1 then 400mg x 6 days (n-184), 157 PP	Standard care (n=169), 136 PP	Reduction of vidal load at day 3 and day 7; AE and SAE, clinical progression, time to resolution of symptoms
Omrani (27)	18 years and older, PCR positive, non-hospitalized, mild	HCQ 600mg x 7 days (n= 152) HCQ 600mg x 7 days plus Azithro 500mg then 250mg day 2-5 (n=152)	Placebo (n=152)	PCR negative at day6
Pan (28)	18 years and older, hospitalized with COVID 19; mild and moderate	HCQ 400mg x 10 days (n=909)	Standard care (n=954)	In hospital mortality; initiation of mech vent, LOS,
Self (29)	18 years and older; hospitalized, PCR positive, mild to severe	HCQ 400mg BID x 1 day then 200 mg BIDx 4 days (n=242)	Placebo x 5 days (n = 237)	Clnical status (covid who scale) at d14; covid score at D2.7.28, mortality ad D14 and D28, time to recovery, composite of death or ECMO, safety,
Skipper (30)	Non hospitalized; symptomtic covid case within 4 days of diagnosis, OR symptomatic high risk exposure	HCQ 800mg once then 600mg 6 to 8 hours later on D1 then 600mg OD x 4 days (n=244)	Placebo (folic acid 400mcg / lactose) (n=247)	Adverse events; hospitalization / ICU or detah at D14; symptom severity score

		PP = 212	PP = 211	
Tang (31)	>18 years, PCR positive mixed population, all severities	HCQ 1200mg x 3 days then 800mg x 14 days (n=75)	Standard of care (n=75)	PCR conversion at D28, 4, 7, 10,14,21, adverse events, alleviation of clinical symptoms
Ultrich (32)	PCR positive, hospitalized	HCQ 200mg x 5 days (n=61)	Placebo : calcium citrate 200mg x 5 days (n=67)	Progression to severe at 14 days, serious AEs, grade 3 or 4 AEs, change in COVID score, LOS,

HCQ vs other treatments

Study ID	Patients	Intervention	Comparator	Outcomes
Ader (Discovery) (15)	>= 18 yo, hospitalized with PCR proven SARS-COV-2 infection and pulmonary rales, sPaO2 <=94%, or requiring supplemental O2	HCQ 200mg to 400mg twice on D1 then 400mg OD x 9 days plus SOC (n= 145)	Standard of Care (SOC) (n=148) SOC + lopinavir 400mg /ritonavir 100mg Q 12h x 14 days (n=145) SOC + lopinavir 400mg / ritonavir 100mg Q12 x 14 days + IFN-Beta 44ug SQ on D1, 3,6 (n=145) SOC + remdesivir 200mg IV on D1 then 100 mg OD x 10 days (n=145)	Clinical status at D15 (WHO Master protocol), at D29, time to an improvement of 2 categories or hospital discharge until D29, time to NEWS2 <= or hospital discharge until D29, 29-day mortality, viral load, grade 3 or 4 AE, SAE, premature suspension of patients or discontinuation of treatment
Bernal-Gonzales (13)	RT-PCR positive with pneumonia diagnosed by xray or CT with a pattern suggesting involvement from coronavirus with recently established hypoxemic respiratory failure or acute clinical deterioration of preexisting lung or heart disease; excluded those requiring high oxygen volumes	HCQ 400mg q 12H on D1 then 200mg q12H x 4 days (n=33) (later in trial, coadministered with dexamethasone 6mg IV q 24H x 10 days)	Ivermectin 12 mg for those weighing <80 kg and 18 mg for those above 80kg (n= 36) Placebo (n=37) (later in trial, coadministered with dexamethasone 6mg IV q 24H x 10 days)	Duration of hospitalization, respiratory deterioration, death, SOFA, CORADS
Brown (33)	>18 years, hospitalized, lab-confirmed COVID, all severities	HCQ 400mg BID on D1 then 200mg x 4 days (n=43)	Azithro 500mg on D1 then 250mg x 4 days (n=42)	COVID ordinal scale on D14, adverse event, mortality at D28
Chowdhury (35)	PCR positive, O2sat >95%, normal chest xray	HCQ 400mg D1 then 200 mg BID x 9 days with azithro 500 mg OD x 5 days (n= 56)	Ivermectin 200ug/kg single dose + doxycycline 100mg BID x 10 days (n=60)	Negative PCR, time to negative PCR, adverse events
Dabbous (38)	18-80 years Mild or moderate COVID, PCR confirmed,	HCQ 400mg 12 hourly D1 then 200 mg 12 hourly x 9 days + Osaltamivir 75mg 12 hourly x 10 days + (n=	Favipiravir 3200 mg (1600mg 12 hourly) D1 then 1200mg (600mg 12 hourly) x 9 days	Time to viral negative conversion, radiological imporvement ad D14, discharge rate out of hspital
Davoodi (36)	With CT findings compatible with COVID 19, symptoms of respiratory tract infection	HCQ 200mg BID (n= 30)	Febuxostat 80 mg OD (n = 30)	Rate of hospitalization, rate of ICU admission, mortality rate, clinical improvement and improvement of CT findings at D14

Elgazzar (34)	18-80 yo, with mild, moderate or severe COVID, PCR confirmed	Mild-Mod : HCQ 400mg Q 12H on D1 then 200mg Q 12H x 5 days (n=100) Severe : HCQ 400mg Q 12H on D1 then 200mg Q 12H x 9 days (n=100) Plus SOC (Azithro, Paracetamol, Lactoferrin, Acetylcysteine)	Ivermectin 0.4mg/kg , max of 4 tabs (6mg/tab) OD x 4 days (n=200)	Clinical and lab improvement and /or 2 consecutive negative PCR taken at least 48 hrs apart, adverse events, mortality, hospital stay, recovery time
Khamis (37)	18-75 years, confirmed COVID, moderate to severe	HCQ 400mg BID on D1 then 200 mg BID x 7 days (n-44)	Favipiravir 1600mg D1 then 600mg BID x 10 days+ interferon beta-1b (600mg/8million IU (0.25g) x 5 days (n= 45)	Time to clinical recovery, ICU admission, mortality at D14

Appendix 2. Methodological Quality Assessment of Included Studies

Study ID	R1	R2	R3	R4	R5	Overall	Comments
HCQ/CQ vs Placebo							
Abd-Elsalam	L	U	H	L	L	H*	Unblinded
Ader	L	L	H	L	L	H*	Unblinded
Amravadi	U	U	H	H	L	H	Unpublished, data reported only in trial registry, pre-terminated; Cohort 2 is open label
Bernal Gonzales	U	U	L	H	L	H	Randomization and allocation concealment not described, pre-terminated
Cavalcanti	L	L	H	L	L	H*	Unblinded
Chen CP	L	U	H	L	L	H*	Unblinded
Chen L	U	U	H	H	L	H	Unblinded; >5%of randomized without data,
Chen J	H	H	H	L	L	H	Randomization based on the parity of the patient's medical record; unblinded
Chen Z	L	U	U	L	L	L	Patient blinded but outcome assessor unclear if blinded
Dubee	L	L	L	L	L	L	Trial prematurely stopped after 250 pxs due to slowdown of pandemic
Horby	L	L	H	L	L	H*	unblinded
Johnston	L	L	L	L	L	L	
Kamran	L	U	H	H	U	H	Unblinded; many missing data
Lyngbakken	L	H	H	L	L	H	Unblinded, no allocation concealment
Mitja	U	U	H	L	L	H	Open label; high lost to follow up but equally distributed
Omrani	L	L	L	L	L	L	
Pan	L	L	H	L	L	H*	Unblinded
Self	L	L	L	L	L	L	
Skipper	L	L	L	H	L	H	68 patients with missing data / lost to ffup
Tang	L	U	H	L	L	H*	Unblinded
Ultrich	U	U	H	H	L	H	Patient and investigator blinded but unblinding allowed, only 48% of patients with viral conversion data, 25% for mortality data
HCQ+Azi vs Placebo							
Cavalcanti	L	L	H	L	L	H*	Unblinded
Omrani	L	L	L	L	L	L	
HCQ/CQ vs Other treatments							
Ader	L	L	H	L	L	H*	Unblinded
Brown	U	L	H	L	L	H*	Method of randomization not specified unblinded
Chowdhury	H	H	H	L	L	H	Quasi-RCT (odd-even), unblinded
Dabbous	L	U	U	L	U	U	
Davoodi	L	L	L	L	L	L	
Elgazzar	U	U	U	L	L	U	
Khamis	L	U	H	L	U	H*	Unblinded

*H – assessed as high because of lack of blinding; but may be low risk for objective outcomes (eg. mortality)

R1- sequence generation
R2 – allocation concealment
R3 – blinding
R4 – incomplete outcome data
R5 – selective outcome reporting

L – low risk of bias
H – high risk of bias
U – uncertain / no information

Appendix 3: GRADE Evidence Profile

COMPARISON : Hydroxychloroquine versus Placebo / Standard of Care

NOTE : All included studies are Randomized Controlled Trials

CERTAINTY ASSESSMENT						NO. OF PATIENTS		EFFECT		CERTAINTY
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCQ	Placebo/ SOC	Relative (95% CI)	Risk difference	
Incidence of Viral negative conversion D7										
7	Not serious	Not serious	Not serious	Serious (wide confidence interval)	Not assessed	125/377 (33.2%)	120/352 (34.1%)	0.94 (0.83, 1.07)	20 fewer per 1000	+++ Moderate
Clinical improvement D28										
6	Serious (unblinded)	Not serious	Not serious	Not serious	Not assessed	1469/2243 (65.5%)	2524.3833 (65.8%)	0.97 (0.93, 1.01)	20 fewer per 1000 (from 46 fewer to 7 more)	+++ Moderate
WHO progression score (level 7 or above) D28										
10	Not serious	Not serious	Not serious	Serious (wide confidence interval)	None	91/1113 (8.2%)	95/1116 (8.5%)	0.96 (0.73, 1.25)	3 fewer per 1000 (from 23 fewer to 21 more)	+++ Moderate
Mortality D28										
16	Not serious	Not serious	Not serious	Not serious	None	589/4149 (14.2%)	941/5690 (16.5%)	1.08 (0.98, 1.18)	13 fewer per 1000 (from 3 fewer to 30 more)	++++ High
Adverse events										
11	Serious (unblinded)	Serious (significant heterogeneity)	Not serious	Not serious	none	547/1153 (47.4%)	344/1156 (29.8%)	1.71 (1.10, 2.67)	211 more per 1000 (from 30 more to 497 more)	++ Low
Serious adverse events										
12	Serious (unblinded, randomization)	Not serious	Not serious	Serious (wide confidence interval)	none	102/1254 (8.1%)	89/1242 (7.2%)	1.14 (0.90, 1.44)	10 more per 1000 (from 7 fewer to 32 more)	++ Low

COMPARISON : Hydroxychloroquine+Azithromycin versus Placebo / Standard of Care

NOTE : All included studies are Randomized Controlled Trials

CERTAINTY ASSESSMENT						NO. OF PATIENTS		EFFECT		CERTAINTY
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCQ + Azithro mycin	Placebo/ SOC	Relative (95% CI)	Risk difference	
Incidence of Viral negative conversion D7										
1	Not serious	Not assessed	Not serious	Serious (single study, wide confidence interval)	Not assessed	16/152 (10.5%)	18/147 (12.2%)	0.86 (0.46, 1.62)	17 fewer per 1000 (from 66 fewer to 76 more)	+ Very Low
Clinical improvement D7										
1	Some concern (allocation concealment)	Not serious	Not serious	Serious (wide confidence interval)	Not assessed	120/217 (55.3%)	117/229 (51.1%	1.08 (0.91, 1.29)	41 more per 1000 (from 46 fewer to 148 more)	++ Low
Clinical improvement D14 – D28										
1	Serious (allocation concealment)	Not serious	Not serious	Serious (wide confidence interval)	Not assessed	184/217 (84.8%)	195/229 (85.2%)	1.0 (0.92, 1.08)	0 fewer per 1000 (from 68 fewer to 68 more)	++ Low
WHO progression score (level 6 or above) D7										
1	Serious (unblinded)	Not assessed	Not serious	Serious (wide CI)	Not assessed	19/217 (8.8%)	17/229 (7.4%)	1.8 (0.63, 2.21)	13 fewer per 1000 (from 27 fewer to 90 more)	+ Very Low
WHO progression score (level 6 or above) D14-28										
1	Serious (unblinded)	Not assessed	Not serious	Serious (wide CI)	Not assessed	13/217 (6.0%)	15/229 (6.6%)	0.91 (0.45, 1.88)	6 fewer per 1000 (from 36 fewer to 58 more)	+ Very Low
WHO progression score (Level 7 or above) D7										
1	Not serious	Not assessed	Not serious	Serious (single study))wide CI)	Not assessed	16/217 (7.4%)	13/229 (5.7%)	1.30 (0.64, 2.64)	17 more per 1000 (from 20 fewer to 93 more)	+ Very Low
WHO progression score (level 7 or above) D14-28										
1	Not serious	Not assessed	Not serious	Serious (wide CI) (single study)	Not assessed	13/217 (6.0%)	13/229 (5.7%)	1.06 (0.50, 2.23)	3 fewer per 1000 (from 28 fewer to 70 more)	++ Very Low
Mortality D7										

CERTAINTY ASSESSMENT						NO. OF PATIENTS		EFFECT		CERTAINTY
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCQ + Azithromycin	Placebo/ SOC	Relative (95% CI)	Risk difference	
2	Not serious	Not assessed	Not serious	Serious (wide CI)	Not assessed	1/366 (0.3%)	3/375 (0.8%)	0.35 (0.04, 3.36)	5 fewer per 1000 (from 8 fewer to 19 more)	++ Low
Mortality D14-28										
2	Not serious	Not assessed	Not serious	Serious (wide CI)	Not assessed	3.366 (0.8%)	6/375 (1.6%)	0.53 (0.13, 2.08)	8 fewer per 1000 (from 14 fewer to 17 more)	++ Low
Adverse events D14-28										
1	Serious (unblinded)	Not assessed	Not serious	Serious (single study, wide confidence interval)	Not assessed	82/217 (37.8%)	61/229 (26.6%)	1.42 (1.08, 1.87)	112 more per 1000	+ Very Low
Serious adverse events D14-28										
2	Some concerns (allocation concealment, unblinded)	Not serious	Not serious	Serious (wide confidence interval)	Not assessed	3/217 (1.4%)	3/229 (1.3%)	1.06 (0.22, 5.17)	1 more per 1000 (from 10 fewer to 55 more)	+ Very Low

Appendix 4. Summary of Findings Tables for Hydroxychloroquine versus Other Treatment

Appendix 4a: HCQ vs Azithromycin (33)

	HCQ	Azithromycin	RR (95% CI)
Mortality D14 to D28	6/42 (14.3%)	1/43 (2.3%)	6.14 (0.77, 48.87)
Adverse events	39/42 (92.9%)	42/43 (97.7%)	0.95 (0.86, 1.05)
Serious adverse events	39/42 (92.9%)	42/43 (97.7%)	0.95 (0.86, 1.05)

Appendix 4b: HCQ vs Ivermectin (13)(34)

	HCQ	Ivermectin	RR (95%CI)
Mortality D28 (Mild/Moderate)	6/133 (4.5%)	5/136 (3.7%)	1.23 (0.38, 3.92)
Mortality D28 (Severe)	20/100 (20%)	2/100 (2%)	10.0 (2.4, 41.66)

Appendix 4c: HCQ +Azithromycin vs Ivermectin-Doxycycline (35)

	HCQ +Azithromycin	Ivermectin + Doxycycline	RR (95% CI)
Viral negative conversion D7	60/63 (95.2%)	54/62 (87.1%)	1.09 (0.98, 1.22)
Adverse events	26/62 (41.9%)	19/63 (30.1%)	1.39 (0.86, 2.24)
Time to negative PCR	9.33 (5-15 days)	8.93 (8-13 days)	Na
Mean duration of symptomatic recovery / Time to recovery	6.99 (4-12 days	5.93 (5-10 days)	na
Clinical recovery D7	71.4%	83.6%	na

Appendix 4d: HCQ vs Febuxostat (36)

	HCQ	Febuxostat	RR (95% CI)
Mortality, D7 and D14to D28	0/30	0/30	Not evaluable
improvement in Chest CT Scan/ X-ray,	47.4% improvement	58.5% improvement	NA

Appendix 4e: HCQ vs Favipiravir + Interferon Beta (37)

	HCQ	Favipiravir + interferon Beta	RR (95%CI)
Clinical improvement D14-28	31/45	29/44	1.05 (0.78, 1.4)
Mortality D14-28	6/45	5/44	1.17 (0.39, 3.57)

Appendix 4f: HCQ vs Lopinavir/Ritonavir (15)

	HCQ	Lopinavir/Ritonavir	RR (95%CI)
WHO score 7 at D28	27/151 (17.9%)	31/150 (20.7%)	0.87 (0.54, 1.38)
Viral negative conversion D7	50/81 (61.7%)	53/80 (66.3%)	0.93 (0.74, 1.18)
Mortality at D28	11/151 (7.3%)	14/150 (9.3%)	0.78 (0.37, 1.66)
Adverse events	109/151 (72,2%)	119/150 (79.3%)	0.91 (0.80, 1.03)
Serious adverse events	63/151 (41.7%)	76/150 (50.7%)	0.82 (0.64, 1.05)

Appendix 4g: HCQ vs Lopinavir/Ritonavir + Interferon-beta (15)

	HCQ	Lopi/Rito + IFBeta	RR (95% CI)
WHO score 7 at D28	27/151 (17.9%)	37/150 (24.7%)	0.72 (0.47, 1.13)
Viral negative conversion D7	50/81 (61.7%)	60/81 (74.1%)	0.83 (0.67, 1.03)
Mortality at D28	11/151 (7.3%)	18/150 (12.0%)	0.61 (0.30, 1.24)
Adverse events	109/151 (72.2%)	117/150 (78.0%)	0.93 (0.81, 1.05)
Serious adverse events	63/151 (41.7%)	78/150 (52.0%)	0.80 (0.63, 1.02)

Appendix 4h: CQ vs Favipiravir (38)

	Chloroquine (+ osaltamivir)	Favipiravir	RR (95%CI)
Mortality D28	2/48 (4.7%)	1/48 (2.1%)	2.0 (0.19, 21.33)
Time to viral negative conversion	8.1 days	8.3 days	na
Viral negative conversion D7	55%	48%	na
CT improvement/recovery D7	21/50 (52%)	21/50 (52%)	1.0 (0.63, 1.59)
Duration of hospitalization	15.89 +/- 4.75	13.29 +/- 5.86	na

Q2. Should azithromycin be used in the treatment of patients with COVID-19 infection?

As of 1 December 2021

RECOMMENDATION

We recommend against the use of azithromycin among hospitalized patients with moderate-to-severe COVID-19 infection. *(Moderate certainty of evidence, Strong recommendation)*

Consensus Issues
No issues were raised during the consensus panel meeting.

KEY FINDINGS

Based on 11 RCTs and one additional RCT for asymptomatic to mild COVID -19 patients, there was no significant difference in clinical outcomes with the use of azithromycin compared to placebo among patients with COVID-19 across all disease severity. Likewise, there was no significant difference in serious adverse events and cardiac arrythmias among all patients but there was a noted significantly higher risk among those given azithromycin for non-serious adverse events for the asymptomatic to mild group with diarrhea being the most common adverse event. This was not noted among the moderate to severe group.

INTRODUCTION

Due to the urgency of the problem of the COVID-19 pandemic, many scientists and healthcare workers have looked at existing safe drugs that can be used for treating COVID-19.[1] Among these, macrolides have been one of the medications thought to have the potential to fight this infection due to its immunomodulatory and anti-inflammatory effects on top of its antimicrobial action.[2] This may also be the reason why azithromycin, a macrolide, is the most frequently used antibacterial during the pandemic.[3] This review focuses on the efficacy and safety of azithromycin in management of COVID-19 patients.

REVIEW METHODS

Comprehensive literature search was done using PubMed, MedRxiv, Google scholar and Cochrane Library on October 30,2021 with the following Mesh terms: (1) COVID-19 or SARS-CoV-2, (2) macrolides or azithromycin. Since many observational and RCTs have been published regarding this topic, we opted to add filters to include only systematic reviews and meta-analyses. Further search for additional RCTs was planned and subsequently done depending on the last search of the most recent and highest quality SR or meta-analysis available. Post-exposure or prophylactic administration of antibiotics and observational studies were excluded.

RESULTS

We found three systematic reviews and one meta-analysis which investigated azithromycin as a treatment regimen for COVID-19. The most recent meta-analysis was published on June 2021, which already included the studies in the other three systematic reviews.[4] This meta-analysis aimed to assess the safety and efficacy of antibiotics which have antiviral and anti-inflammatory effects (i.e., azithromycin, clarithromycin, doxycycline) for treatment of COVID-19 (see Appendix 2). The study

included both peer and non-peer-reviewed articles. The review included patients who were treated as outpatients (asymptomatic to mild cases) and inpatients, including those admitted at the ICU (moderate to severe cases). The review included 11 studies covering 11281 adult participants. The studies were done in high to low healthcare-cost countries including Brazil, UK, USA, Qatar, Egypt, Iran, and Turkey. Azithromycin was the intervention across all studies, and it was compared to either placebo or standard of care. Dose of the intervention during the first day was consistent at 500mg given orally or through nasogastric tube or intravenously for severe cases. Further doses and duration of treatment however varied among studies after the first day. Four studies used the usual dose for azithromycin in bacterial infection which is 250mg per day while seven studies continued the 500mg dosage. Duration of treatment ranged from 3 days to 14 days. Standard of care (SoC) varied among the studies depending on the practice in their region with six studies using hydroxychloroquine, a drug known to have immunomodulatory and antiviral effects, as part of the SoC. Sensitivity analysis was performed whenever possible by comparing results when studies with some risk for bias, preprint articles, or mixed population (of suspected and RT-PCR confirmed cases) were removed. Risk of bias (RoB) of each included study was assessed using the Cochrane RoB 2.0 tool with half of the studies having low risk for bias and the remaining having some concerns. The overall quality of the systematic review was assessed using the AMSTAR-2 rating tool and it was noted to have a high rating for the overall confidence in the results of the review.

A follow-up search for additional randomized clinical trials using the same keywords was done to look for studies available after the last search done by the included review. One additional RCT (Oldenburg 2021) was found which used single dose oral azithromycin among outpatients with COVID-19 confirmed RT-PCR test within 7 days of the randomization period.[5] This study's initial primary outcome was hospital admission; however, due to low event rate, it was modified to resolution of symptoms at day 14. The study had some concerns for risk of bias for outcome measurement since it was based on self-reported symptoms of the participants. There was no physical contact between investigators and participants, and all communication was done electronically or via telephone. Investigational drugs and placebo were sent via courier.

Because azithromycin was used not just for its antimicrobial property, majority of the studies included participants that were given other antibiotics as part of the standard of care (SoC). We therefore added a sensitivity analysis excluding these studies. Only one study [2] which investigated the intervention in the moderate and severe group fulfilled this criterion, together with three studies who conducted their investigations among the asymptomatic and mild group.[4,5] The Recovery Trial [2] also provided separate data for patients requiring oxygen support (considered to have severe to critical disease based on the NIH severity classification). We opted to report this because those with severe disease may benefit more from the intervention.

Azithromycin vs Standard of Care/Placebo in Asymptomatic and Mild COVID-19 in the Outpatient Setting

There was inconclusive effect on all-cause mortality (RR 1.0, 95% CI 0.06-15.69) and admission to hospital or death at day 28 (RR 0.94, 95% CI 0.57-1.56) based on three studies. The trial that excluded those that received no other antibiotics showed no estimable result for all-cause mortality because of zero events in the intervention and

control group, while it showed inconclusive result for admission to hospital or death within 2 days, which is similar to the overall result (RR 0.82, 95% CI 0.39-1.71). Two studies, including the additional RCT found, showed no significant difference in symptom resolution at day 14 (RR 1.03, 95% CI 0.95-1.11) while two other studies showed similar results at day 28 (RR 0.96, 95% CI 0.79-1.15).

These results were also similar when only considering studies that did not include other antibiotics in their SoC (RR 1.01, 95% CI 0.75-1.35, one study for resolution at 14 days (RR 0.90, 95% CI 0.76-1.08, one study for resolution at day 28).
In terms of safety, two studies showed no serious adverse events for both and intervention and control groups (RR not estimable). No studies in the meta-analysis of Popp et al. presented data for cardiac arrhythmia. The RCT of Oldenburg showed that outpatients receiving azithromycin experienced more adverse events such as diarrhea, abdominal pain, nausea and vomiting than those receiving placebo after 3 days of azithromycin intake (RR 2.14, 95% CI 1.42-3.23). Diarrhea was noted to be the most common symptom with 41% of those given azithromycin experiencing it versus 17% in the placebo group.

The overall certainty of evidence was moderate for all-cause mortality and initial symptom resolution at day 14 and day 28 due to imprecision, while admission to hospital or death had low certainty due to risk of bias and imprecision. There was low certainty for serious adverse events due to risk of bias and because zero events were reported in both of the included studies, while a moderate certainty of evidence was determined for any adverse event due to some risk of bias for outcome assessment.

Azithromycin vs Standard of Care/Placebo in Hospitalized Patients with Moderate to Severe COVID-19
For efficacy, five studies were used in pooling results for this population. The primary outcome of all-cause mortality at day 28 pooled results from four studies and showed no significant effect for azithromycin (RR 0.98, 95% CI 0.90-1.06, high certainty). One study showed no effect for clinical worsening or death at day 28 (RR 0.95, 95% CI 0.87-1.03) while three studies noted no effect on clinical improvement at day 28 (RR 0.96, 95% CI 0.84-1.11).

In terms of safety, there were no noted serious adverse events (RR 1.11, 95% CI 0.89-1.40, 4 studies) or increased risk for cardiac arrhythmias when azithromycin was used (RR 0.92, 95% CI 0.73-1.15, 4 studies) for patients with moderate to severe disease. Likewise, there was no significant increase in the incidence of any adverse events although there was a small increase in risk when azithromycin was used (RR 1.20, 95% CI 0.92-1.57, 3 studies). Certainty of evidence for worsening and improvement of clinical status as well as for serious adverse events and cardiac arrhythmias were deemed moderate for issues of indirectness and risk of bias (see Appendix 4).

Azithromycin vs Standard of Care Without Other Antibiotics Among Patients With Severe COVID-19
From the total of 7763 patients included in the Recovery Trial, those who presented with severe disease (i.e., those that needed oxygen supplementation or needed mechanical ventilation) totaled 6355. For efficacy, the 28-day mortality was noted to be not significantly different between the two groups (RR 0.97, 95% CI 0.88-1.06), as with hospital discharge after 28 days of initiation of intervention (RR 1.02, 95% CI 0.98-

1.06). Among those requiring oxygen supplementation during admission, there was no noted difference in those who eventually needed mechanical ventilation (RR 0.95, 95% CI 0.87-1.03). For those who were on invasive mechanical ventilation at the start of the trial, there was also no difference in cessation of mechanical ventilation (RR 1.11, 95% CI 0.85-1.45).

In terms of safety, they investigated the occurrence of any major cardiac arrhythmias, a known adverse effect of azithromycin use. Although there was no result available for the severe population, data for the entire group (including moderate disease) was available and showed no significant difference between the control and the intervention groups (RR 0.90, 95% CI 0.72-1.14).

Azithromycin versus Other Antibiotics in the Outpatient and Inpatient Settings
One study comparing azithromycin to lincomycin in patients with moderate COVID-19 showed reduced viral clearance at day 6 (RR 0.40, 95% CI 0.17-0.93). One other study comparing azithromycin to clarithromycin showed no difference in time (MD days) to resolution of symptoms between the two regimens: for fever (MD -0.3, 95% CI -0.83-0.24; p=0.27), cough (MD -0.3, 95% CI -0.95-0.35; p=0.37), dyspnea (MD 0.1, 95% CI -0.76- 0.96; p=0.81), and GIT symptoms (MD 0.6, 95% CI 0.03-1.2; p=0.04).

OTHER FACTORS IN EVIDENCE TO DECISION

The wide interest in the use of azithromycin for COVID-19 management is mainly due to its antiviral and immunomodulatory effects that have been shown to result in improvement in patient status in those affected by other viral infections and pneumonia.[6] However, evidence from multiple studies have already shown its ineffectiveness in the absence of any bacterial co-infection. Even if it is readily available, the threat of antibiotic resistance, which contributes to increased financial burden and longer hospital stay, should be considered. The CDC is already concerned about outbreaks of bacterial resistance among COVID-19 units. It also warns that testing for antimicrobial resistance has been delayed in many areas due to the pandemic and the full effect may only be felt many years after.[7]

RECOMMENDATIONS FROM OTHER GROUPS

Azithromycin is not recommended in all populations whether for its antimicrobial or immunomodulatory effects according to the Australian living CPG and the NICE guidelines.[8,9] The US NIH's recommendation is also against the use of azithromycin whether in combination with hydroxychloroquine or chloroquine or as an antimicrobial agent in the outpatient setting.[10]

RESEARCH GAPS

There are currently 18 listed active ongoing studies investigating antibiotics in the treatment of COVID-19 across different disease severity.

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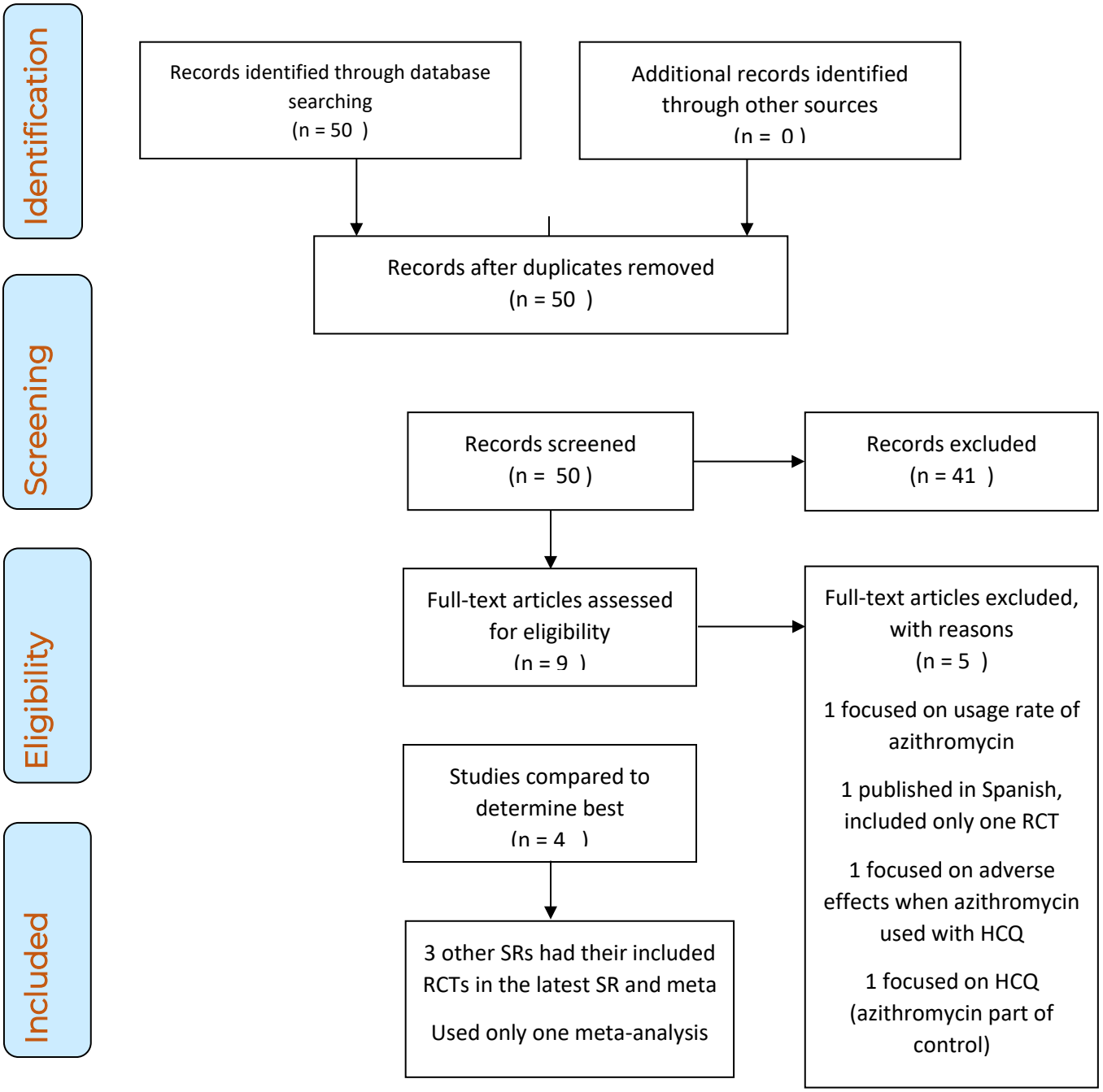
Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=7)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					• There has been an increasing use of antimicrobials in treatment of COVID-19 despite the reported low bacterial co-infection rate. Azithromycin, a macrolide, is the most frequently used given its additional anti-inflammatory and immunomodulatory effect.
Benefits	Large	Moderate (1)	Small (3)	Uncertain (3)			• Azithromycin compared to placebo or SoC alone did not result in any significant benefit both in the inpatient (moderate to severe) and outpatient setting (asymptomatic to mild)
Harm	Large	Small (4)	Uncertain (3)				• No significant difference in serious adverse effects and cardiac arrythmias in the inpatient setting while unsure evidence in the outpatient setting (no events in treatment and control group). However no report on antimicrobial resistance rate.
Certainty of Evidence	High	Moderate (3)	Low (3)	Very low (1)			
Balance of effects	Favors drug	Does not favor drug (7)	Uncertain				• Azithromycin is readily available however the possible effect of microbial resistance can lead to longer hospital stay
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (1)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability (2)			
Resources Required	Uncertain (1)	Large cost (2)	Moderate Cost (3)	Negligible cost (1)	Moderate savings	Large savings	
Certainty of evidence of required resources	No included studies (6)	Very low	Low	Moderate (1)	High		
Cost effectiveness	No included studies (5)	Favors the comparison (2)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (6)	Reduced	Probably no impact (1)	Increased			
Acceptability	Uncertain (1)	No (3)	Yes (3)				
Feasibility	Uncertain (3)	No (2)	Yes (2)				

Appendix 2. Search Yield and Results



Appendix 3. Characteristics of Included Reviews

Review Year Journal	Review aim	Search strategy	PICO	Data Analysis	Key Findings
Popp *et al* 2021 *Cochrane database of Systematic Reviews* [4]	To assess the efficacy and safety of antibiotics compared to each other, no treatment, standard of care alone or placebo or any other active intervention with proven efficacy for treatment of COVID-19 outpatients and inpatients	**Databases:** Medline, EMBASE, clinicaltrials.gov, WHO ICTRP, medRxiv, CENTRAL, Web of Science and WHO COVID-19 global literature on coronavirus disease **Language restrictions:** none **Strategy:** Complete search strategy available in appendix of published paper **Last date of search:** June 14, 2021 **Exclusion criteria:** Non-standard RCT designs (i.e. cluster-randomisation, cross-over trials), non-randomised interventional and observational studies. Antibiotic treatment for other coronavirus disease such as MERS or SARS	**Population:** Adults with RT-PCR confirmed diagnosis of COVID-19, both inpatient and outpatient **Intervention:** Any antibiotic given with antiviral and anti-inflammatory intent was eligible. All doses ang regimens were eligible **Control:** Standard of care, placebo, or co-interventions which is comparable to intervention arm, or other antibiotics **Outcome:** Analysed into two population groups: inpatients with moderate to severe COVID-19, and outpatients with asymptomatic or mild COVID-19 All-cause mortality at day 28, 60, time to event and at hospital discharge Clinical status at day 28, day 60, and up to the longest follow-up Quality of life Serious adverse evens Adverse events Cardiac arrhythmias Additional for outpatients: Admission to hospital or death at 28 days Symptom resolution **Study design:** RCTs **Preprints:** included	**Risk of bias:** Cochrane RoB 2.0 tool to assess bias arising from randomsation process, due to deviations from the intended interventions, due to missing outcome data, in measurement of the outcome, in selection of reported result **Publication bias:** Contour-enhanced funnel plots **Subgroup analysis** Inpatients with moderate to severe COVID-19 and outpatients with asymptomatic or mild COVID-19 Severity of condition at baseline based on the WHO clinical progression scale If sufficient studies, subgroup based on dose of antibiotic, route of administration and age (not enough for current review) **Sensitivity analysis** Including only low risk of bias or some concerns Comparison of preprint articles versus peer-reviewed artciles RT PCR confirmed COVID-19 versus mixed population **Statistical analysis** Heterogeneity using chi^2 test and I^2 statistic and 95% prediction interval If sufficiently homogenous, pooled data into meta-analysis using the random-effects model (RevMan web 2020). For dichotomous outcomes, using Mantel-Haenszel method while for continuous outcomes, used the inverse-variance method	11 studies included (11,281 adult participants) in qualitative synthesis, 10 studies included in quantitative synthesis (meta-analysis) 7 studies investigated treatment in inpatient settings 3 studies treatment in outpatient settings **Azithromycin vs SoC/placebo in inpatients** All-cause mortality at day 28: RR 0.98 (95% CI, 0.90-1.06), 4 studies, 8600 participants Clinical worsening or death at day 28: RR 0.95 (95% CI, 0.87-1.03), 1 study, 7311 participants Clinical improvement at day 28 RR 0.96 (95% CI, 0.84-1.11), 3 studies, 8172 Serious adverse evenets during study period RR 1.11 (95% CI, 0.89-1.40), 4 studies, 794 Arrythmia RR 0.92 (95% CI 0.73-1.15), 4 studies, 7865 participants Adverse events (any) RR 1.20 (95% CI, 0.92-1.57), 3 studies, 355 participants **Azithromycin vs SoC/placebo in outpatients** All-cause mortality at day 28 RR 1.0 (95% CI, 0.06-15.69), 3 studies, 876 participants

					Admission to hospital or death at 28 days RR 0.94 (95% CI, 0.57-1.56), 3 studies, 876 participants Symptom resolution at day 14 RR 1.03 (95% CI, 0.95-1.12), 1 study, 138 participants Symptom resolution at day 28 RR 0.95 (95% CI, 0.79-1.15), 2 studies, 549 participants Serious adverse events 0/454, 2 studies **Azithromycin vs other antibiotics in inpatients and outpatients**

Study ID	Study Design	Setting	Total population	Population	Intervention	Comparator	Outcomes
Oldenburg et al (ACTION)	Randomized controlled trial	Outpatients throughout the US	263 participants	2:1 individuals who tested positive for SARS-CoV-2 within 7 days before enrolment (symptomatic or asymptomatic) Exclusion: younger than 18yrs old, had self-reported macrolide allergy, concurrently taking HCQ if older than 55, concurrently taking nelfinavir or warfarin, pregnant, unable to receive study drug in the mail or to complete online questionnaires	Single oral dose 1.2g azithromycin suspension (sent via overnight mail) n=171	Placebo with similar packaging n=92	Self-reported absence of COVID-19 symptoms at day 14 Adverse events at day 3 Hospitalizsation and/or death by day 21, patient reported COVID-19 symptoms at day 21

Appendix 4. AMSTAR-2 rating for systematic reviews and meta-analysis

AMSTAR Items	Popp (2021)
Date of last search	June 14, 2021
Rating of overall confidence in the results of the review[§]	**HIGH**
1. Research questions, inclusion criteria include PICO components	YES
2.* Protocol registered before commencement of the review	YES
3. Selection of study designs to be included were explained	YES
4.* Adequacy of literature search	YES
5. Study selection done by at least 2 reviewers	YES
6. Data extraction done by at least 2 reviewers	YES
7.* Justification for excluding individual studies	YES
8. Described included studies in adequate detail	YES
9.* ROB from individual studies being included in the review	YES
10. Reported sources of funding for studies included	YES
11.* Appropriateness of meta-analytical methods	YES
12. Potential impact of ROB in individual studies	YES
13.* Consideration of ROB when interpreting review results	YES
14. Sufficient explanation of heterogeneity	YES
15.* Assessment of presence and likely impact of publication bias	YES
16. Reported potential COI sources, funding they received	YES

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Popp M, Stegemann M, Riemer M, Metzendorf M-I, Romero CS, Mikolajewska A, Kranke P, Meybohm P, Skoetz N, Weibel S. Antibiotics for the treatment of COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 10. Art. No.: CD015025.doi: 10.1002/14651858.CD015025.

NOTES:
[§] AMSTAR-2 rating for overall confidence.
*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.

- **High** - No or 1 non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- **Moderate** - More than 1 non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- **Low** - 1 critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- **Critically low** - More than 1 critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

Appendix 5. Cochrane Risk of Bias Assessment

Study	Randomization	Deviation from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Oldenburg	No concern	No concern	No concern	Some concern (self -reported, all communication done via telephone or email)	No concern	Some concern due to self-reporting of outcome

Appendix 6. Summary of Findings and Forest plots [4]

Summary of findings 1. Azithromycin compared to placebo or standard of care alone for inpatients with confirmed moderate to severe COVID-19

Patient or population: people with moderate to severe disease (WHO scale 4 to 9)

Setting: inpatient

Intervention: azithromycin

Comparison: placebo or standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty in the evidence (GRADE)	Comment
	Risk with placebo or standard of care	Risk with azithromycin				
All-cause mortality at day 28	223 per 1000	**219 per 1000** (201 to 236)	**RR 0.98** (0.90 to 1.06)	8600 (4 RCTs)	⊕⊕⊕⊕ High[a]	Azithromycin has little or no effect on all-cause mortality at day 28
Worsening of clinical status: participants with clinical deterioration (new need for invasive mechanical ventilation) or death at day 28	261 per 1000	**248 per 1000** (227 to 269)	**RR 0.95** (0.87 to 1.03)	7311 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	Azithromycin probably has little or no effect on worsening of clinical status or death at day 28
Improvement of clinical status: participants discharged alive at day 28	672 per 1000	**645 per 1000** (564 to 746)	**RR 0.96** (0.84 to 1.11)	8172 (3 RCTs)	⊕⊕⊕⊖ Moderate[c]	Azithromycin probably has little or no effect on improvement of clinical status at day 28
Quality of life at longest follow-up available	NA	NA	NA	(0 RCTs)	NA	No study was found that looked at quality of life.
Serious adverse events during the study period	214 per 1000	**238 per 1000** (190 to 300)	**RR 1.11** (0.89 to 1.40)	794 (4 RCTs)	⊕⊕⊕⊖ Moderate[d]	Azithromycin probably has little or no effect on serious adverse events during the study period

Any adverse events during the study period	333 per 1000	**400 per 1000** (306 to 523)	**RR 1.20** (0.92 to 1.57)	355 (3 RCTs)	⊕⊖⊖⊖ Low[e]	Azithromycin may increase any adverse events slightly during the study period
Cardiac arrhythmias during the study period	45 per 1000	**41 per 1000** (33 to 52)	**RR 0.92** (0.73 to 1.15)	7865 (4 RCTs)	⊕⊕⊕⊖ Moderate[f]	Azithromycin probably has little or no effect on cardiac arrhythmias during the study period

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk on the comparison group and the **relative effect** of the intervention (and its 95% confidence interval).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]No change of result in sensitivity analysis (RR 1.04; 95% CI 0.82 to 1.31; 837 participants; 3 studies) excluding studies with mixed populations (negative or unknown RT-PCR). Therefore, no downgrading of evidence for indirectness.
[b]Downgrade by one level for serious indirectness due to the effect estimate based on only one study with a mixed population (8.5% participants with negative or unknown RT-PCR).
[c]Downgrade by one level for serious heterogeneity (I^2 = 49%). No change of result in sensitivity analysis (RR 0.89; 95% CI 0.65 to 1.21; 402 participants; 2 studies) excluding studies with mixed populations (negative or unknown RT-PCR). Therefore, no downgrading of evidence for indirectness.
[d]Downgrade by one level for serious risk of bias due to an as-treated analysis in the study with the highest weight (97.0%). The certainty of evidence was not downgraded due to indirectness, even if the imprecision of the effect estimate had increased in the sensitivity analysis excluding the study with a mixed population (RR 0.98; 95% CI 0.26 to 3.60; 355 participants; 3 studies), as the same study was already the reason for downgrading due to risk of bias.
[e]Downgrade by one level for serious risk of bias due to non-blinded outcome assessment in the study with the highest weight (87.7%), and one level for serious imprecision due to few small studies.
[f]Downgrade by one level for serious indirectness due to the effect estimate based mainly (weight 99.1%) on two studies with mixed populations (8.5% and 11% participants with negative or unknown RT-PCR).

Summary of findings 2. Azithromycin compared to placebo or standard of care alone for outpatients with confirmed asymptomatic or mild COVID-19

Patient or population: people with mild disease (WHO scale 1 to 3)

Setting: outpatient

Intervention: azithromycin

Comparison: placebo or standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty in the evidence (GRADE)	Comment
	Risk with placebo or standard of care	Risk with azithromycin				
All-cause mortality at day 28	2 per 1000	**2 per 1000** (0 to 31)	**RR 1.00** (0.06 to 15.69)	876 (3 RCTs)	⨁⨁◯◯ Low[a]	Azithromycin may have little or no effect on all-cause mortality at day 28
Admission to hospital or death within 28 days	67 per 1000	**63 per 1000** (38 to 105)	**RR 0.94** (0.57 to 1.56)	876 (3 RCTs)	⨁⨁◯◯ Low[b]	Azithromycin may have little or no effect on admission to hospital or death within 28 days
Serious adverse events during the study period	Two studies assessed serious adverse events during the study period, but none of the participants in either group were affected		Not estimable	454 (2 RCTs)	⨁◯◯◯ Very low[d]	We are uncertain whether azithromycin increases or reduces serious adverse events.
Cardiac arrhythmias during the study period	NA	NA	NA	(0 RCTs)	NA	No study was found that looked at cardiac arrhythmias during the study period

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk on the comparison group and the **relative effect** of the intervention (and its 95% confidence interval).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

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GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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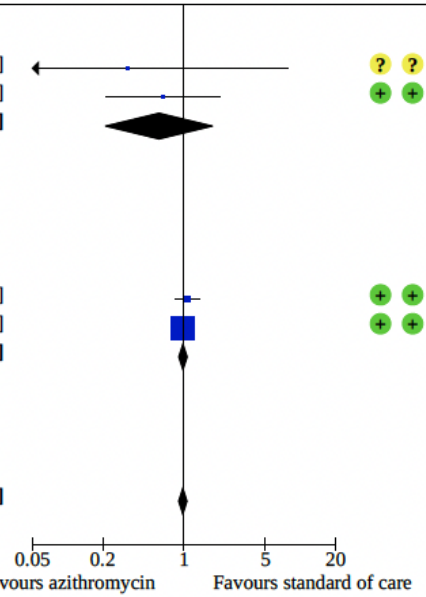
[a]Downgrade by one level for serious risk of bias due to possible trial context related deviations from the intended interventions in that study contributing events to the analysis; and by one level for serious imprecision due to a wide confidence interval and few events.
[b]Downgrade by one level for serious risk of bias due to possible trial context related deviations from the intended interventions in one study and lack of registering the outcome in another study; and by one level for serious imprecision due to a wide confidence interval.
[c]Downgrade by two levels for very serious imprecision due to the effect estimate based on one small study.
[d]Downgrade by one level for serious risk of bias due to possible trial context related deviations from the intended interventions in one study and lack of registering the outcome in the other study; and by two levels for very serious imprecision due to zero events in both studies.

Analysis 1.1. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 1: All-cause mortality at day 28

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care Events	Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Moderate disease (WHO 4 to 5)						
Sekhavati 2020 (1)	0	56	1	55	0.1%	0.33 [0.01 , 7.87]
Cavalcanti 2020 (2)	5	172	7	159	0.5%	0.66 [0.21 , 2.04]
Subtotal (95% CI)		**228**		**214**	**0.6%**	**0.61 [0.21 , 1.77]**
Total events:	5		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
1.1.2 Moderate to severe disease (WHO 4 to 9)						
Furtado 2020 (3)	90	212	73	183	12.3%	1.06 [0.84 , 1.35]
RECOVERY 2021 (4)	561	2582	1162	5181	87.1%	0.97 [0.89 , 1.06]
Subtotal (95% CI)		**2794**		**5364**	**99.4%**	**0.98 [0.90 , 1.07]**
Total events:	651		1235			
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**3022**		**5578**	**100.0%**	**0.98 [0.90 , 1.06]**
Total events:	656		1243			
Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 3 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Chi² = 0.76, df = 1 (P = 0.38), I² = 0%						



Footnotes

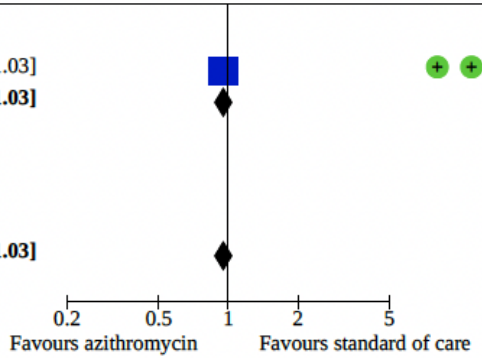
(1) Time point of outcome assessment (30 days); participants (WHO 4; only RT-PCR positive); comparator (standard of care)
(2) Time point of outcome assessment (28 days); participants (WHO 4-5; only RT-PCR positive); comparator (standard of care)
(3) Time point of outcome assessment (29 days); participants (WHO 5-7; only RT-PCR positive); comparator (standard of care)
(4) Time point of outcome assessment (28 days); participants (WHO 4-7; 91.5% RT-PCR positive); comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 2: Worsening of clinical status: participants with clinical deterioration (new need for invasive mechanical ventilation) or death at day 28

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care Events	Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.2.1 Moderate to severe disease (WHO 4-9)							
RECOVERY 2021 (1)	603	2430	1273	4881	100.0%	0.95 [0.87 , 1.03]	+ + + + + +
Subtotal (95% CI)		**2430**		**4881**	**100.0%**	**0.95 [0.87 , 1.03]**	
Total events:	603		1273				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.16 (P = 0.24)							
Total (95% CI)		**2430**		**4881**	**100.0%**	**0.95 [0.87 , 1.03]**	
Total events:	603		1273				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.16 (P = 0.24)							
Test for subgroup differences: Not applicable							



Footnotes

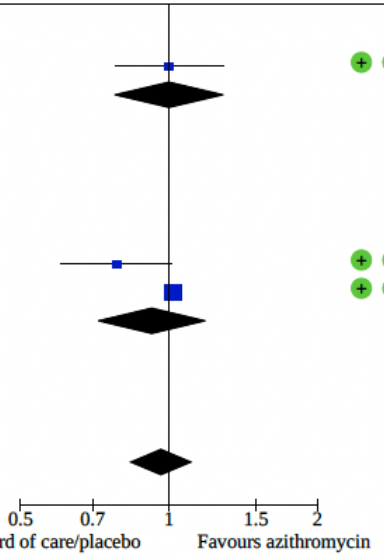
(1) Time point of outcome assessment (28 days); participants (WHO 4-6; 91.5% RT-PCR positive); comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 3: Improvement of clinical status: participants discharged alive at day 28

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.3.1 Moderate disease (WHO 4-5)							
CJWT629A12301 (1)	7	7	7	7	20.5%	1.00 [0.78 , 1.29]	+ + + + + +
Subtotal (95% CI)		**7**		**7**	**20.5%**	**1.00 [0.78 , 1.29]**	
Total events:	7		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
1.3.2 Moderate to severe disease (WHO 4-9)							
Furtado 2020 (2)	69	212	76	183	19.9%	0.78 [0.60 , 1.02]	+ + + + + +
RECOVERY 2021 (3)	1788	2582	3525	5181	59.6%	1.02 [0.99 , 1.05]	+ + + + + +
Subtotal (95% CI)		**2794**		**5364**	**79.5%**	**0.92 [0.72 , 1.18]**	
Total events:	1857		3601				
Heterogeneity: Tau² = 0.03; Chi² = 3.91, df = 1 (P = 0.05); I² = 74%							
Test for overall effect: Z = 0.63 (P = 0.53)							
Total (95% CI)		**2801**		**5371**	**100.0%**	**0.96 [0.84 , 1.11]**	
Total events:	1864		3608				
Heterogeneity: Tau² = 0.01; Chi² = 3.92, df = 2 (P = 0.14); I² = 49%							
Test for overall effect: Z = 0.53 (P = 0.60)							
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%							



Footnotes

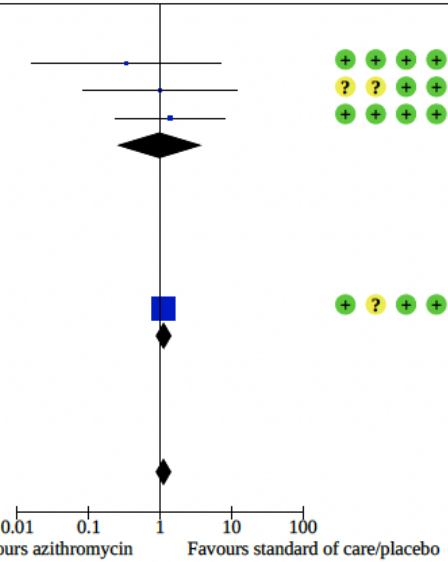
(1) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (placebo)
(2) Time point of outcome assessment (29 days); participants (WHO 5-7; only RT-PCR positive); comparator (standard of care)
(3) Time point of outcome assessment (28 days); participants (WHO 4-7; 91.5% RT-PCR positive); comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 4: Serious adverse events during the study period, defined as number of participants with any event

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Moderate disease (WHO 4-5)						
CJWT629A12301 (1)	0	7	1	7	0.6%	0.33 [0.02 , 7.02]
NCT04335552 (2)	1	5	1	5	0.8%	1.00 [0.08 , 11.93]
Cavalcanti 2020 (3)	3	172	2	159	1.6%	1.39 [0.23 , 8.19]
Subtotal (95% CI)		**184**		**171**	**3.0%**	**0.98 [0.26 , 3.60]**
Total events:	4		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.97)						
1.4.2 Moderate to severe disease (WHO 4-9)						
Furtado 2020 (4)	102	241	75	198	97.0%	1.12 [0.89 , 1.41]
Subtotal (95% CI)		**241**		**198**	**97.0%**	**1.12 [0.89 , 1.41]**
Total events:	102		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						
Total (95% CI)		**425**		**369**	**100.0%**	**1.11 [0.89 , 1.40]**
Total events:	106		79			
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						



Footnotes

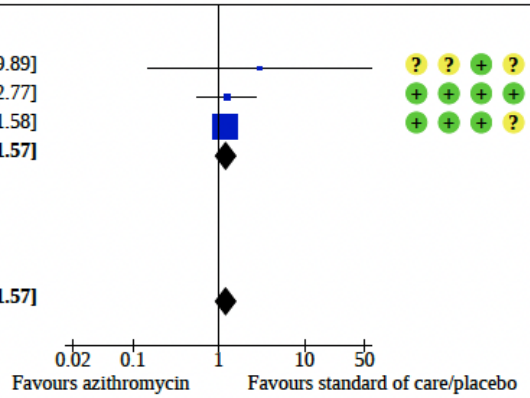
(1) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (placebo)
(2) Time point of outcome assessment (60 days); participants (WHO min. 4; only RT-PCR positive); comparator (standard of care)
(3) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (standard of care)
(4) Time point of outcome assessment (29 days); participants (WHO 5-7; 89% RT-PCR positive); comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 5: Adverse events (any grade) during the study period, defined as number of participants with any event

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.5.1 Moderate disease (WHO 4-5)							
NCT04335552 (1)	1	5	0	5	0.8%	3.00 [0.15 , 59.89]	? ? + ? ? ?
CJWT629A12301 (2)	5	7	4	7	11.5%	1.25 [0.56 , 2.77]	+ + + + + +
Cavalcanti 2020 (3)	68	172	53	159	87.7%	1.19 [0.89 , 1.58]	+ + + ? + ?
Subtotal (95% CI)		**184**		**171**	**100.0%**	**1.20 [0.92 , 1.57]**	
Total events:	74		57				
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 2 (P = 0.83); I² = 0%							
Test for overall effect: Z = 1.34 (P = 0.18)							
Total (95% CI)		**184**		**171**	**100.0%**	**1.20 [0.92 , 1.57]**	
Total events:	74		57				
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 2 (P = 0.83); I² = 0%							
Test for overall effect: Z = 1.34 (P = 0.18)							
Test for subgroup differences: Not applicable							



Footnotes

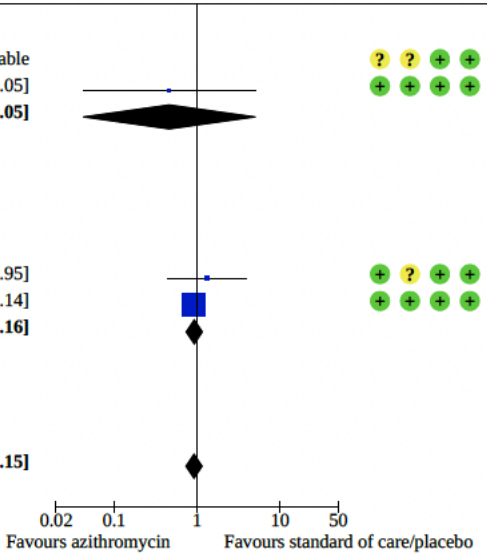
(1) Time point of outcome assessment (60 days); participants (WHO min. 4; only RT-PCR positive); comparator (standard of care)
(2) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (placebo)
(3) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 6: Cardiac arrhythmias during the study period

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Moderate disease (WHO 4-5)						
Sekhavati 2020 (1)	0	56	0	55		Not estimable
Cavalcanti 2020 (2)	1	172	2	159	0.9%	0.46 [0.04 , 5.05]
Subtotal (95% CI)		**228**		**214**	**0.9%**	**0.46 [0.04 , 5.05]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.6.2 Moderate to severe disease (WHO 4-9)						
Furtado 2020 (3)	8	241	5	198	4.1%	1.31 [0.44 , 3.95]
RECOVERY 2021 (4)	101	2314	224	4670	95.0%	0.91 [0.72 , 1.14]
Subtotal (95% CI)		**2555**		**4868**	**99.1%**	**0.92 [0.74 , 1.16]**
Total events:	109		229			
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**2783**		**5082**	**100.0%**	**0.92 [0.73 , 1.15]**
Total events:	110		231			
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.75 (P = 0.46)						
Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%						



Footnotes

(1) Time point of outcome assessment (30 days); participants (WHO 4; only RT-PCR positive); comparator (standard of care)
(2) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (standard of care)
(3) Time point of outcome assessment (29 days); participants (WHO 5-7; 89% RT-PCR positive); comparator (standard of care)
(4) Time point of outcome assessment (28 days); participants (WHO 4-7; 91.5% RT-PCR positive); comparator (standard of care)

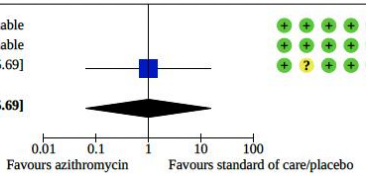
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.1. Comparison 2: Azithromycin compared to placebo or standard of care for outpatients with confirmed asymptomatic or mild COVID-19, Outcome 1: All-cause mortality at day 28

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Omrani 2020 (1)	0	152	0	152		Not estimable	+ + + + + +
PRINCIPLE 2021 (2)	0	186	0	236		Not estimable	+ + + + + +
Hinks 2020 (2)	1	75	1	75	100.0%	1.00 [0.06 , 15.69]	+ ? + + + ?
Total (95% CI)		**413**		**463**	**100.0%**	**1.00 [0.06 , 15.69]**	
Total events:	1		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Footnotes

(1) Time point of outcome assessment (21 days); participants (WHO 1-3; only RT-PCR positive); comparator (placebo)
(2) Time point of outcome assessment (28 days); participants (WHO 2-3; only RT-PCR positive); comparator (standard of care)

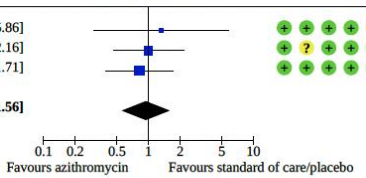
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Azithromycin compared to placebo or standard of care for outpatients with confirmed asymptomatic or mild COVID-19, Outcome 2: Admission to hospital or death within 28 days

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Omrani 2020 (1)	4	152	3	152	11.4%	1.33 [0.30 , 5.86]	+ + + + ? ?
Hinks 2020 (2)	11	75	11	75	42.0%	1.00 [0.46 , 2.16]	+ ? + + + ?
PRINCIPLE 2021 (2)	11	186	17	236	46.5%	0.82 [0.39 , 1.71]	+ + + + + +
Total (95% CI)		**413**		**463**	**100.0%**	**0.94 [0.57 , 1.56]**	
Total events:	26		31				

Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



Footnotes

(1) Time point of outcome assessment (21 days); participants (WHO 1-3; only RT-PCR positive); comparator (placebo)
(2) Time point of outcome assessment (28 days); participants (WHO 2-3; only RT-PCR positive); comparator (standard of care)

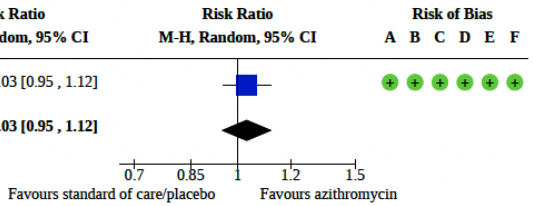
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: Azithromycin compared to placebo or standard of care for outpatients with confirmed asymptomatic or mild COVID-19, Outcome 3: All initial symptoms resolved (asymptomatic) at day 14

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Omrani 2020 (1)	66	69	64	69	100.0%	1.03 [0.95 , 1.12]	+ + + + + +
Total (95% CI)		**69**		**69**	**100.0%**	**1.03 [0.95 , 1.12]**	
Total events:	66		64				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable



Footnotes

(1) Time point of outcome assessment (14 days); participants (WHO 1-3; only RT-PCR positive); comparator (placebo)

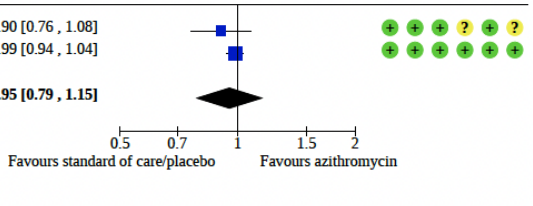
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: Azithromycin compared to placebo or standard of care for outpatients with confirmed asymptomatic or mild COVID-19, Outcome 4: All initial symptoms resolved (asymptomatic) at day 28

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
PRINCIPLE 2021 (1)	98	186	131	225	40.6%	0.90 [0.76 , 1.08]	+ + + ? + ?
Omrani 2020 (2)	67	69	68	69	59.4%	0.99 [0.94 , 1.04]	+ + + + + +
Total (95% CI)		**255**		**294**	**100.0%**	**0.95 [0.79 , 1.15]**	
Total events:	165		199				

Heterogeneity: Tau² = 0.02; Chi² = 4.51, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 0.51 (P = 0.61)
Test for subgroup differences: Not applicable



Footnotes

(1) Time point of outcome assessment (28 days); participants (WHO 2-3; only RT-PCR positive); comparator (standard of care)
(2) Time point of outcome assessment (21 days); participants (WHO 1-3; only RT-PCR positive); comparator (placebo)

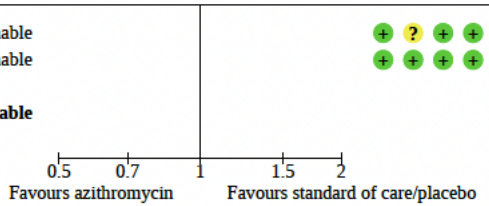
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.5. Comparison 2: Azithromycin compared to placebo or standard of care for outpatients with confirmed asymptomatic or mild COVID-19, Outcome 5: Serious adverse events during the study period, defined as number of participants with any event

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Hinks 2020 (1)	0	75	0	75		Not estimable	+	?	+	+	+	?
Omrani 2020 (2)	0	152	0	152		Not estimable	+	+	+	+	?	?
Total (95% CI)		**227**		**227**		**Not estimable**						
Total events:	0		0									

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Footnotes

(1) Time point of outcome assessment (28 days); participants (WHO 2-3; only RT-PCR positive); comparator (standard of care)
(2) Time point of outcome assessment (21 days); participants (WHO 1-3; only RT-PCR positive); comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Q3. Among patients with COVID-19, should favipiravir be used for treatment?

As of 8 November 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of favipiravir among patients diagnosed with COVID-19. *(Low certainty of evidence)*

Consensus Issues

Results from the study are mostly inconclusive and there are still no recommendations on the use of favipiravir outside clinical trials. There are ongoing clinical trials, including one local study currently recruiting participants. Results from these ongoing studies will help further evaluate the use of favipiravir in the treatment of COVID-19.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of favipiravir among patients diagnosed with COVID-19, unless in the context of a clinical trial. *(Very low certainty of evidence)*

Previous Consensus Issues

Given that there are on-going clinical trials on favipiravir, the recommendation explicitly stated that there was no recommendation on the use of favipiravir unless it will be used for clinical trials. In addition, there may be some implications with regard to possible reimbursements and will encourage patients to join the clinical trial.

WHAT'S NEW IN THIS VERSION?

This version includes data from one (1) multi-center randomized trial, which included SARS-CoV-2 RNA recurrent positive patients.

KEY FINDINGS

Seven (7) randomized controlled trials (RCTs) were found on the use of favipiravir among patients with COVID-19. Pooled results showed a modest benefit in clinical improvement on day 7 favoring favipiravir compared to standard of care; however, clinical improvement on day 28 showed no significant benefit. There was also significant benefit in time to clinical improvement and time to negative conversion. Incidence of viral negative conversion was not significantly different between favipiravir and standard of care. There was no significant difference on the incidence of adverse events and serious adverse events. Report on adverse events, although an important outcome, was not rated as a critical outcome to be included in the decision making. The overall certainty of evidence was rated low due to serious risk of bias, inconsistency, and very serious imprecision in several critical outcomes.

INTRODUCTION

Favipiravir is an oral RNA-dependent RNA polymerase inhibitor used as treatment for influenza and other RNA viruses.[2] It has also been shown to induce lethal mutations of viral RNA, resulting in viral load reduction. It is a potentially effective treatment for SARS-CoV-2.[1] Because of these, as well as recent clinical experience on its use for patients with COVID-19, several studies have been done to assess its clinical efficacy against coronavirus infections.

REVIEW METHODS

An updated systematic search was done from the date of last search March 31, 2021 until September 11, 2021 through MEDLINE, Cochrane Central, and Google Scholar using a combined MeSH and free text search coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and favipiravir. The term randomized controlled trial was added as method filter. The COVID-NMA Initiative was also reviewed and was the primary source for most of the RCTs included in this evidence summary as well as the pooled analysis. We searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. Only RCTs comparing favipiravir alone or with standard of care versus placebo or standard of care were included. We excluded studies that specifically compared favipiravir with other active treatments or as part of a combination treatment.

RESULTS

We found seven (7) RCTs that included 763 adults with RT-PCR confirmed COVID-19 infection ranging from mild to severe.[1-7] Six (6) studies included hospitalized and outpatient adults with newly confirmed COVID-19 infection, while 1 RCT included symptomatic hospitalized and outpatient adults who tested positive for COVID-19 after hospital discharge with two consecutive negative SARS-CoV-2 RNA tests from the initial infection. Favipiravir was used in different dosing strategies either alone or in combination with standard or supportive care, then compared to standard care. The characteristics of the included studies are summarized in Appendix 3.

Report on adverse events, although an important outcome, was not rated as a critical outcome to be included in the decision making. The overall certainty of evidence was rated low due to serious risk of bias, inconsistency, and very serious imprecision in the critical outcomes. All 7 studies had issues with performance bias. The risk of bias summary is in Appendix 4. The GRADE Evidence Summary is in Appendix 5.

Pooled results of three (3) studies [1,4,5] monitoring clinical improvement on day 7 (Figure 1) showed a modest effect favoring favipiravir compared to standard care with a relative risk (RR) of 1.58 (95% CI 1.15-2.16; $I^2 = 0\%$). However, clinical improvement on day 28 based on five (5) studies [1,2,4-6] (Figure 2) showed no clinical significance at an RR of 1.02 (95% CI 0.95-1.09; $I^2 = 0\%$).[9] Time to clinical improvement favored favipiravir in the pooled results of 3 studies [4-6] with an HR of 1.74 (95% CI 1.33-2.27; $I^2 = 43.6\%$) [8] (Figure 3). There was no significant difference in WHO progression score level 7 or above at day 28 between favipiravir and standard of care (RR 0.33, 95% CI 0.01-8.05; $I^2 = 0\%$) (Figure 4).
All-cause mortality by day 28 was monitored by five (5) studies, with only 2 studies reporting a death in the standard care group. Pooled effect also showed no significant difference between favipiravir and standard of care (RR 0.33 95% CI 0.04-3.16; $I^2 = 0\%$) (Figure 5).[1,3,4,6,7]

Incidence of viral negative conversion (Figures 6 and 7) was not significantly different between favipiravir and standard of care on day 3 (RR 1.22, 95% CI 0.99-1.50; $I^2 = 0\%$) based on pooled results from 3 studies [1,5,6] and on day 30 (RR 1.53, 95% CI 0.97–2.41; $I^2 = 0\%$; 1 RCT). However, for viral negative conversion on day 7 (based on 6 RCTs), although there is no significant difference between favipiravir and the standard of care, there is borderline heterogeneity (RR 1.10, 95% CI 0.96-1.27; $I^2 =$

44%; p = 0.07). The time to negative conversion favored favipiravir compared to standard care with a pooled HR of 1.40 (95% CI 1.11-1.76; I^2 = 0%) based on 3 studies (Figure 8).[5-7]

Pooled results on the incidence of adverse events showed no significant difference between favipiravir and standard care, however there was moderate heterogeneity (RR 1.37, 95% CI 0.90-2.06; I^2 = 64%; p = 0.03) (Figure 7). Adverse events from the studies ranged from hyperuricemia, hematologic effects, hepatobiliary disorders, gastrointestinal effects including diarrhea and nausea, skin disorders like rashes, to cardiac effects like bradycardia and chest pain.[1-7]

Serious adverse events such as acute respiratory distress syndrome, death from heart failure, bone fracture, and increasing oxygen desaturation were also reported in the studies. Pooled results also showed no significant difference between favipiravir and standard of care (RR of 1.45, 95% CI 0.59-3.55; I^2 = 0%) (Figure 10).[8]

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
NIH COVID-19 Treatment Guidelines (as of September 3, 2021)	No recommendations on the use of favipiravir for the treatment of COVID-19.[8-10]
Surviving Sepsis Campaign Guidelines (as of January 29, 2021)	
Infectious Diseases Society of America (as of September 3, 2021)	
Australian Guidelines for Clinical Care of People with COVID-19 (as of August 27, 2021)	Recommends against the use of favipiravir for the treatment of COVID-19 unless in the context of a randomized trial with appropriate ethical approval.[11]

RESEARCH GAPS

There are 24 ongoing trials on favipiravir compared to placebo or standard care listed in various clinical trial registries. An open label randomized controlled multi center trial in the Philippine setting has recently been registered at the NIH – U.S. National Library of Medicine's *clinicaltrials.gov* and is currently recruiting adult patients with non-severe disease. Updates will be added to this review as soon as results from these trials are available.

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11. Infectious Disease Society of America Guidelines on the Treatment and Management of Patients with COVID-19, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
12. Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v42.1 2021 August 27, https://app.magicapp.org/#/guideline/L4Q5An
13. NIH – U.S. National Library of Medicine, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/results?cond=Covid19+OR+coronavirus&term=favipiravir&cntry=&state=&city=&dist=
14. Chinese Clinical Trials Registry, ChiCTR, http://www.chictr.org.cn/searchprojen.aspx?title=&officialname=&subjectid=&secondaryid=&applier=&studyleader=&ethicalcommitteesanction=&sponsor=&studyailment=&studyailmentcode=&studytype=0&studystage=0&studydesign=0&minstudyexecutetime=&maxstudyexecutetime=&recruitmentstatus=0&gender=0&agreetosign=&secsponsor=&regno=&regstatus=0&country=&province=&city=&institution=&institutionlevel=&measure=favipiravir&intercode=&sourceofspends=&createyear=0&isuploadrf=&whetherpublic=&btngo=btn&verifycode=&page=1

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 6)

FACTORS	JUDGEMENT (N = 6)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					
Benefits	Large	Moderate (2)	Small (3)	Uncertain (1)			• Time to clinical improvement (HR 1.74, 95% CI 1.33-2.27), and time to negative conversion (HR 1.4, 95% CI 1.11-1.76) favored favipiravir
Harm	Large	Small (4)	Uncertain (2)				• There was no significant difference in the incidence of AE (RR 1.37, 95% CI 0.90-2.06) and SAE (RR 1.45, 95% CI 0.59-3.55)
Certainty of Evidence	High	Moderate (1)	Low (2)	Very low (3)			• Low due to serious risk of bias, inconsistency, and very serious imprecision in several critical outcomes.
Balance of effects	Favors drug (2)	Does not favor drug	Uncertain (4)				• The benefits and harms were both small with no significant difference in most of the main outcomes of interest
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate cost (5)	Negligible cost	Moderate savings (1)	Large savings	• Favipiravir (Avigan®) has a cost of USD 3 per 200mg tablet (Php 150.456) • Full treatment course requiring a total of 45 tablets per patient will amount to a total treatment cost of Php 9,000 or USD 135 per patient.
Certainty of evidence of required resources	No included studies (1)	Very low (1)	Low	Moderate (3)	High (1)		
Cost effectiveness	No included studies (3)	Favors the comparison (2)	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (3)	Reduced (1)	Probably no impact (1)	Increased (1)			
Acceptability	Uncertain (3)	No	Yes (3)				
Feasibility	Uncertain (1)	No	Yes (5)				

Appendix 2. Search Yield and Results

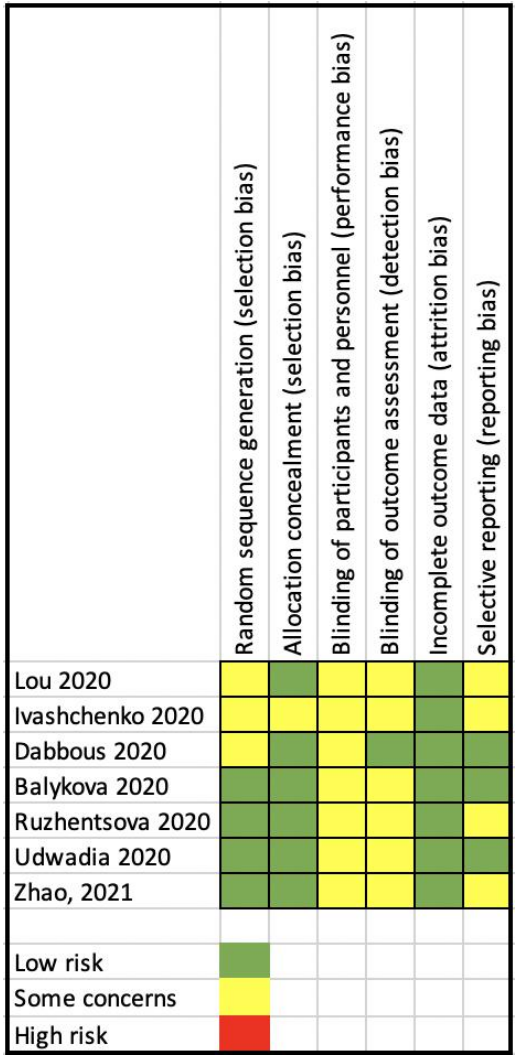
DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND favipiravir Filters: March 31, 2021 to September 11, 2021 and Randomized Controlled Trial	September 11, 2021 2:00PM	7	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 AND favipiravir AND “Randomized Controlled Trial” Filters: March 31, 2021 to September 11, 2021	September 11, 2021 2:15PM	17	1
COVID-NMA Initiative	Favipiravir	September 11, 2021 3:00PM	14	7
Google Scholar	Favipiravir AND COVID AND randomized controlled trial	September 11, 2021 3:10PM	55	7
ClinicalTrials.gov	Favipiravir Filters: Interventional (Clinical Trial), not yet recruiting, recruiting, enrolling by invitation, active not recruiting, completed, unknown status	September 11, 2021 3:15PM	33	19
Chinese Clinical Trial Registry	Favipiravir	September 11, 2021 3:18PM	8	1
EU Clinical Trials Register	COVID-19 AND Favipiravir	September 11, 2021 3:20PM	11	9
Republic of Korea - Clinical Research Information Service	Favipiravir	September 11, 2021 3:25PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Favipiravir	September 11, 2021 3:28PM	0	0
CenterWatch	Favipiravir	September 11, 2021 3:29PM	8	4
chinaxiv.org	Favipiravir	September 11, 2021 3:31PM	0	0
Medrxiv.org	Favipiravir Filters: March 31, 2021 to September 11, 2021	September 11, 2021 3:41PM	33	0
Biorxiv.org	Favipiravir Filters: March 31, 2021 to September 11, 2021	September 11, 2021 4:11PM	42	0

Appendix 3: Characteristics of Included Studies

Study & Setting	Treatment Intervention	Comparator	Design & Risk of Bias	Participants & Sample Size	Outcomes
Lou 2020[1] (China)	Favipiravir (1600 or 2200mg initial, then 600mg tid) up to 14 days + existing antiviral treatment	Baloxavir marboxil group: baloxavir marboxil (80 mg od) on day 1 and day 4; for patients who are still positive in virological test, they can be given again on day 7 + existing antiviral treatment Existing antiviral treatment or standard care: Lopinavir/ritonavir (400mg/100 mg bid or darunavir/cobicistat 800 mg/150 mg, qd and arbidol 200 mg tid)	RCT Some concerns in the risk of bias	30 hospitalized adults (ages 18-85) with COVID-19 infection of unclear severity	Primary Viral negative on day 14; Time from randomization to clinical improvement by 2 points on NEWS2 or live discharge (whichever came first) Secondary Viral negative on day 7; Incidence of mechanical ventilation on day 14; ICU Admission on Day 14; All-cause mortality on day 14.
Ivashchenko 2020[2] (Russia)	Favipiravir 1800/800mg (1800mg day 1; 800mg days 2-14) Favipiravir 1600/600mg (1600mg day 1; 600mg days 2-14)	Standard care according to Russian guidelines that included hydroxychloroquine or chloroquine; or lopinavir/ritonavir	RCT Some concerns in the risk of bias	60 hospitalized adults (ages 18 and above) with moderate PCR-confirmed COVID-19 on screening	Primary Elimination of SARS-CoV-2 at day 10 (by 2 negative PCR tests) Secondary Rate of viral clearance by day 5; Time to normalization of clinical symptoms; changes on CT scan by day 15; incidence and severity of adverse events
Dabbous 2020[3] (Egypt)	Favipiravir (600mg up to 10 days)	Standard care defined as Oseltamivir (75 mg 12 hourly for 10 days) and hydroxychloroquine (400 mg 12 hourly on day-one followed by 200 mg 12 hourly daily on day 2 to 10 days) conforming to the national standard of care therapy.	RCT Some concerns in the risk of bias	100 hospitalized adults (ages 18-80) with PCR-confirmed COVID-19 and mild to moderate symptoms according to the national protocol classification	Primary Viral clearance on days 3, 7 and 14 (2 successive negative PCRs 48hrs apart); Normalization of body temperature for 48 hrs; Improvement of radiological abnormalities at day 14 and discharge rate. Secondary Normalization of C-reactive protein and serum ferritin levels
Balykova 2020[4] (Russia)	Favipiravir (1200mg day 1 then 600mg for 14 days)	Standard care in accordance to the Temporary Guidelines of the Ministry of Health of Russia that included hydroxychloroquine + azithromycin; hydroxychloroquine, lopinavir + ritonavir	RCT Some concerns in the risk of bias	200 hospitalized adults (ages 18-80) with PCR-confirmed COVID-19 of moderate severity	Clinical improvement according to the WHO Categorical Scale of Clinical Improvement; Clinical and laboratory data; Improvement of CT scan of the chest organs and the clearance of the SARS-CoV-2 virus; The frequency and nature of the occurrence of adverse events; The need for invasive and non-invasive oxygen support; Mortality
Ruzhentsova 2020[5] (Russia) *Pre-print*	Favipiravir (1800mg bid on day 1, followed by a maintenance dose 800mg bid on days 2-10)	Standard care that included either umifenovir (200 mg 4 qid) + intranasal interferon alpha-2b (10000 IU/ml – 3 drops in each nasal channel 5 times a day), or hydroxychloroquine (400mg bid on day 1 followed by	RCT Some concerns in the risk of bias	168 hospitalized and outpatient adults (ages 18-60) with mild to moderate PCR-confirmed COVID-19 w/out respiratory failure	Primary Time to clinical improvement (based on a reduction of patient clinical status on at least 1 score according to WHO 8-Category Ordinal Scale for Clinical Improvement compared to

		200mg bid or 200mg bid on day 1 followed by 100mg bid) during the period up to 10 days, depending on the severity of the condition of the patient			screening; Time to viral clearance at day 28 (in 2 negative PCR results) Secondary Rate of clinical improvement at day 7; Viral clearance at day 5; Rate of clinical improvement at day 14; Rate of viral clearance at separate days; Time to body temperature normalization; Rate of resolution of resolution of lung changes on CT at day 14; Time to resolution of main disease symptoms; The rate of artificial lung ventilation; rate of transfer to ICU; Death rate during the 28 days
Udwadia 2020[6] (India)	Favipiravir (1800mg bid on day 1, 800mg bid) + standard supportive care for up to 14 days	Standard care that included antipyretics, cough suppressants, antibiotics, and vitamins (drugs with potential antiviral activity against SARS-CoV-2 and HCQ were prohibited)	RCT Some concerns on the risk of bias	150 hospitalized adults (ages 18-75) with PCR-confirmed COVID-19 and mild to moderate symptoms	Primary Viral clearance on negative RT-PCR result for 2 consecutive times (28 days maximum) and at hospital discharge Secondary Time to clinical cure based on clinician assessment; Time to first use of high flow supplemental oxygen/ ventilation/ECMO; Time to hospital discharge (RT-PCR negativity on 2 consecutive tests); Adverse events
Zhao, 2021[7] (China)	Favipiravir (1600mg bid on day 1 then 600mg bid from day 2 to 7) + standard treatment up to 14 days	Standard care	RCT Some concerns in the risk of bias	55 hospitalized and outpatient adults (ages 28-79) who tested re-positive for SARS-CoV-2 RNA by nasopharynggeal swab RT-PCR after discharge with mild to severe symptoms	Primary Time to achieve a consecutive twice (at intervals of >24 h) negative RT-PCR result for SARS-CoV-2 RNA in nasopharyngeal swab and sputum sample Secondary Adverse events

Appendix 4. Study Appraisal



Appendix 5. GRADE Evidence Profile

Author(s): Carla Marie L. Asis, MD
Question: Favipiravir compared to Standard care for COVID-19
Setting: Worldwide
Bibliography:

Lou Y, Liu L, Yao H, et al. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial. Eur J Pharm Sci. 2021;157:105631. doi:10.1016/j.ejps.2020.1056312.
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Ruzhentsova TA, Chukhliaev PV, Khavkina DA, Garbuzov AA, Oseshnyuk RA, Soluyanova TN, et. al. Phase 3 Trial of Coronavir (Favipiravir) in patients with mild to moderate COVID-19, https://ssrn.com/abstract=36969076. Udwadia ZR, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et, al. International Journal of Infections Diseases. 2021; 103:62-71 https://doi.org/10.1016/j.ijid.2020.11.1427.
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CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Favipiravir	Standard of care	Relative (95% CI)	Absolute (95% CI)		
Clinical improvement (follow-up: 7 days)												
3	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	88/216 (40.7%)	36/163 (22.1%)	**RR 1.58** (1.15 to 2.16)	**128 more per 1,000** (from 33 more to 256 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Clinical improvement (follow-up: 28 days)												
5	Randomised trials	Serious [b]	Not serious	Not serious	Not serious	None	209/327 (63.9%)	139/252 (55.2%)	**RR 1.02** (0.95 to 1.09)	**11 more per 1,000** (from 28 fewer to 50 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Time to clinical improvement (follow-up: 28 days)												
3	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	287	231	-	HR **1.74 higher** (1.33 higher to 2.27 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Favipiravir	Standard of care	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: mean 26.4 days)												
5	Randomised trials	Serious [c]	Not serious	Not serious	Serious[d]	None	0/274 (0.0%)	2/251 (0.8%)	**RR 0.33** (0.04 to 3.16)	**5 fewer per 1,000** (from 8 fewer to 17 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events (follow-up: mean 28.8 days)												
5	Randomised trials	Serious [c]	Serious[e]	Not serious	Serious[d]	None	161/363 (44.4%)	79/270 (29.3%)	**RR 1.37** (0.90 to 2.06)	**108 more per 1,000** (from 29 fewer to 310 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse events (follow-up: mean 26 days)												
5	Randomised trials	Serious [c]	Not serious	Not serious	Serious[d]	None	9/333 (2.7%)	5/260 (1.9%)	**RR 1.45** (0.59 to 3.55)	**9 more per 1,000** (from 8 fewer to 49 more)	⊕⊕◯◯ LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

[a] Issues in performance and detection bias in included studies
[b].Issues on selection, performance, detection, and reporting bias
[c] Issues on selection, performance, and detection bias
[d] Wide confidence interval
[e] Significant heterogeneity (I2=64%)

Appendix 6. Forest Plots

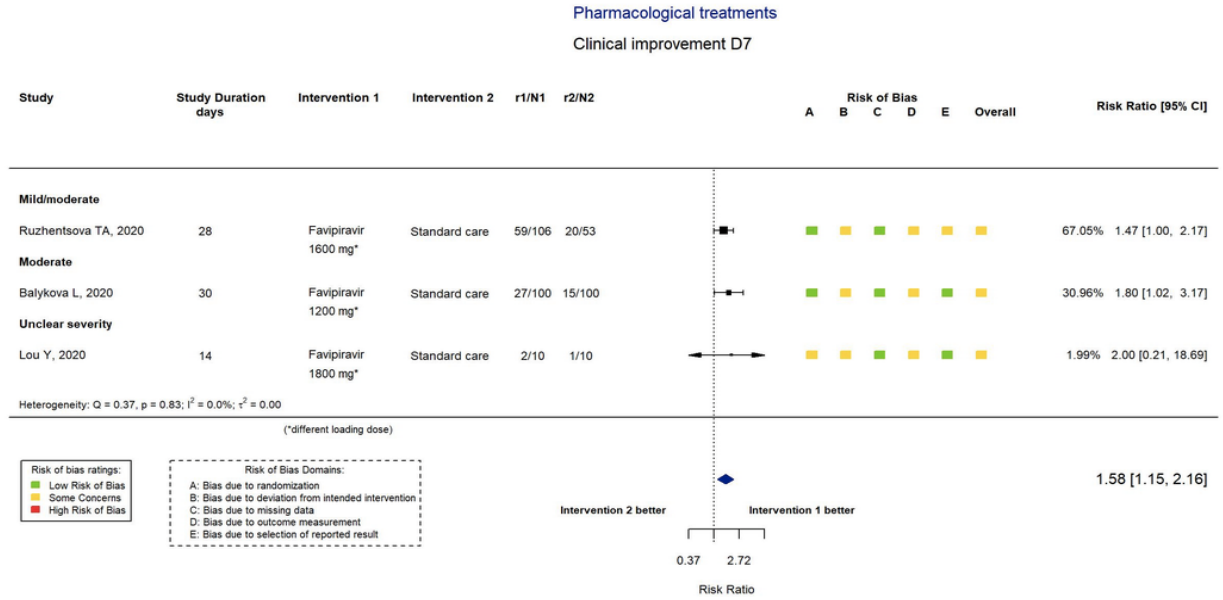

Figure 1. Clinical Improvement Day 7
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

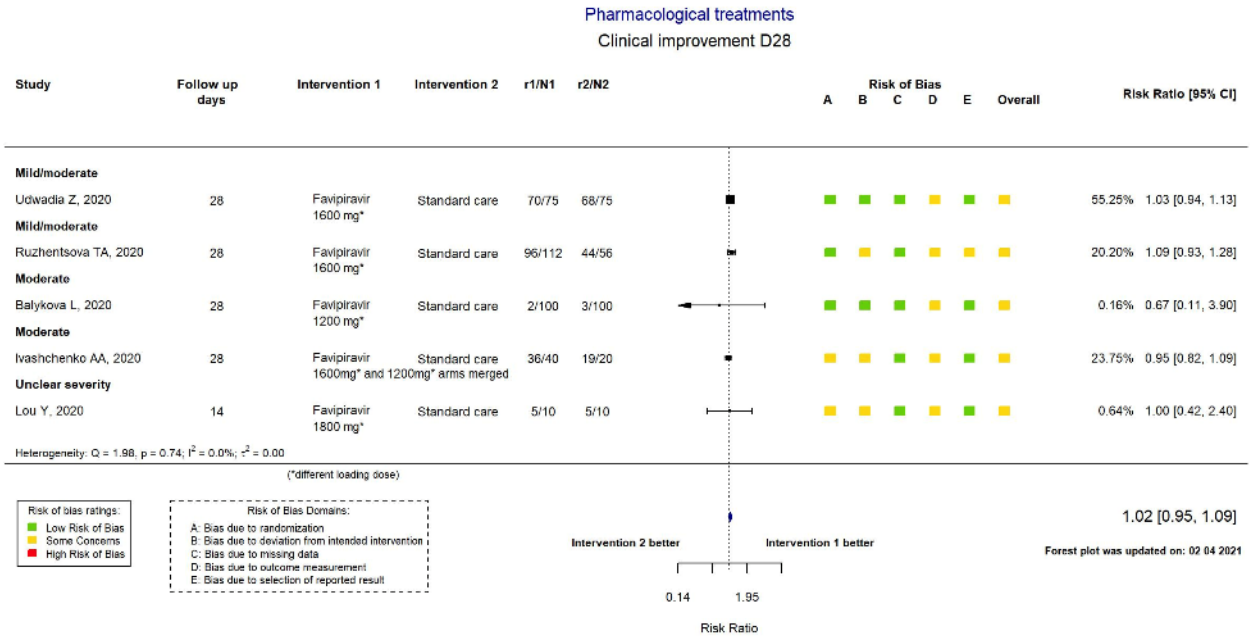

Figure 2. Clinical Improvement Day 28
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

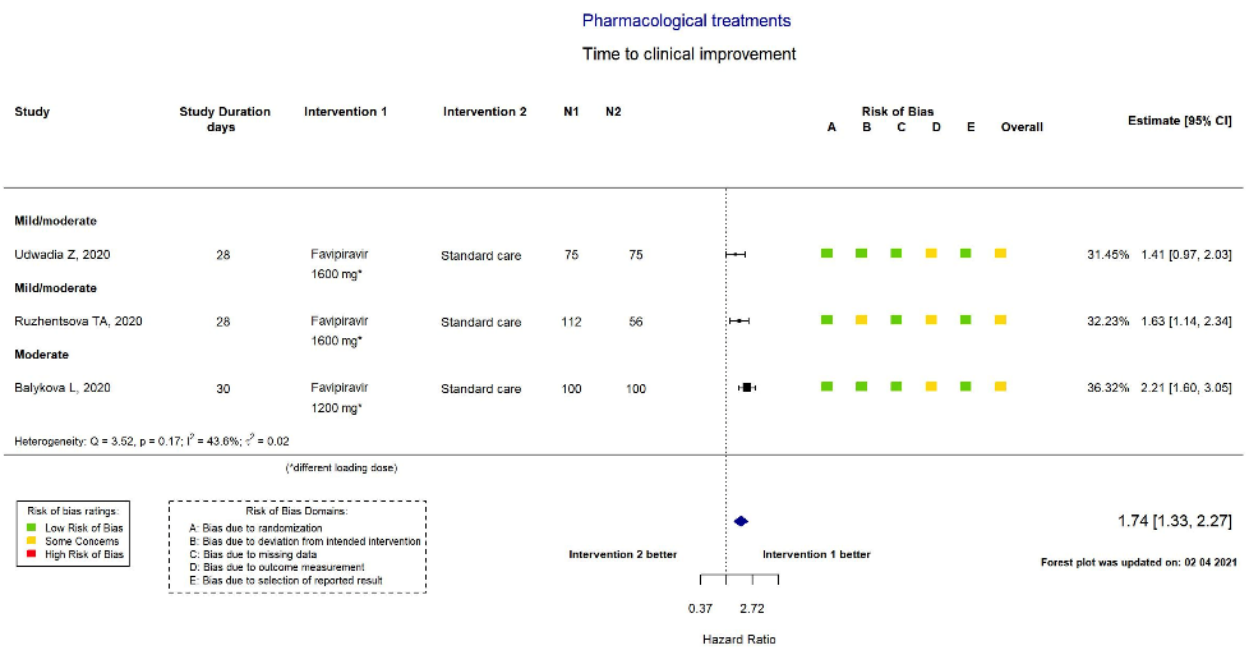

Figure 3. Time to Clinical Improvement
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

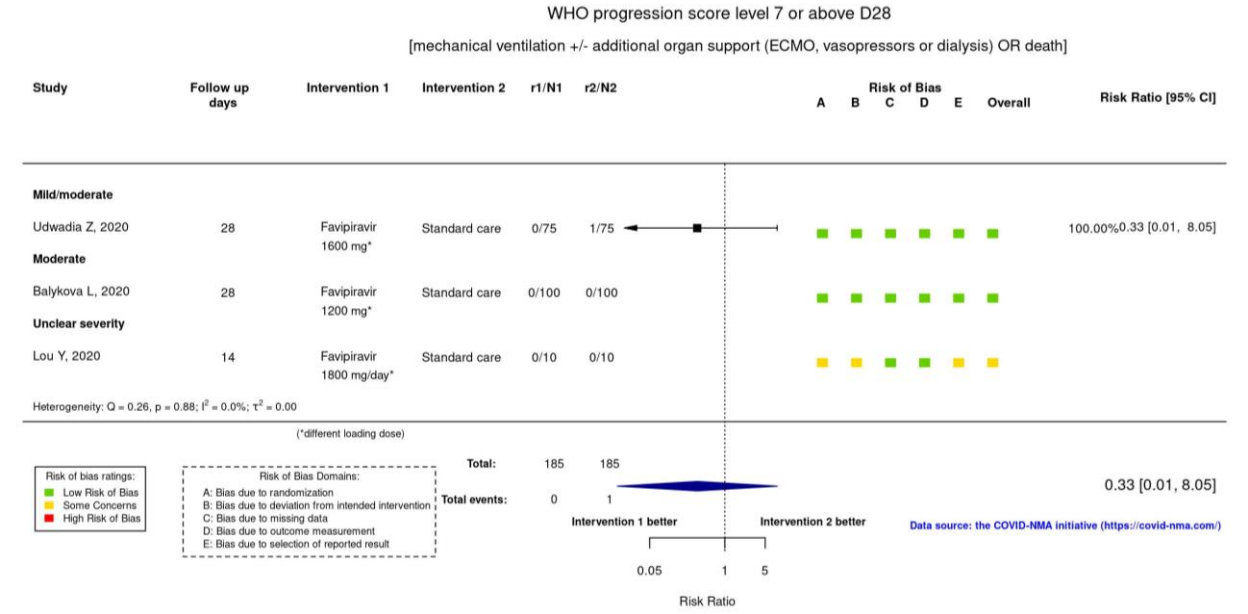

Figure 4. WHO progression score
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

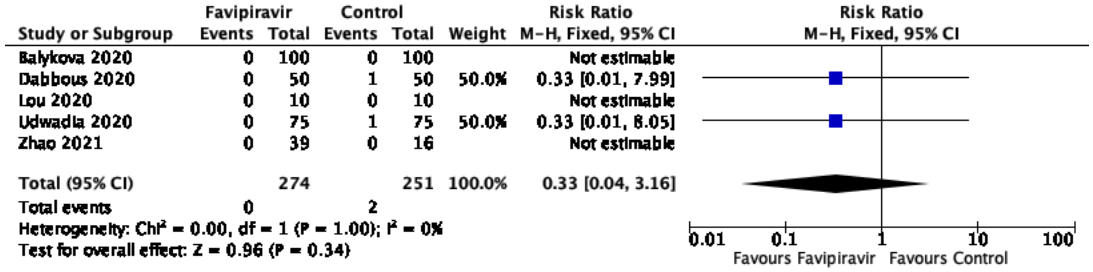

Figure 5. All-cause mortality

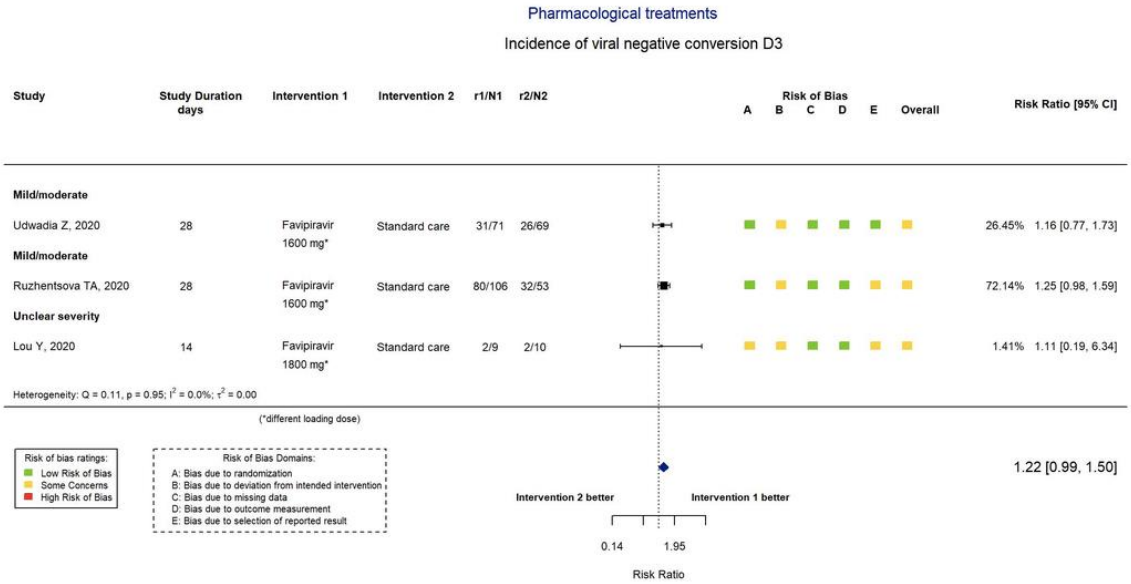

Figure 6. Incidence of Viral Negative Conversion Day 3
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

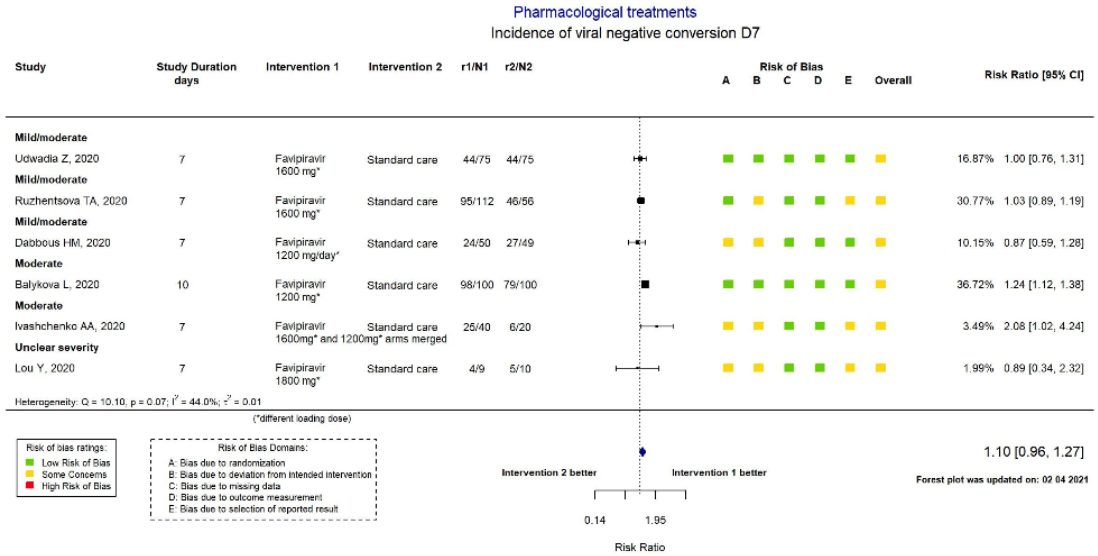

Figure 7. Incidence of Viral Negative Conversion Day 7
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

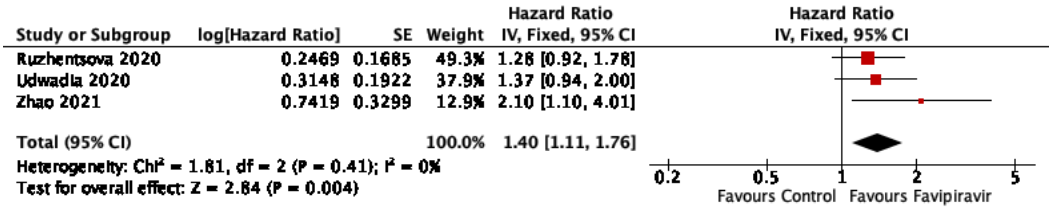

Figure 8. Time to Negative Conversion

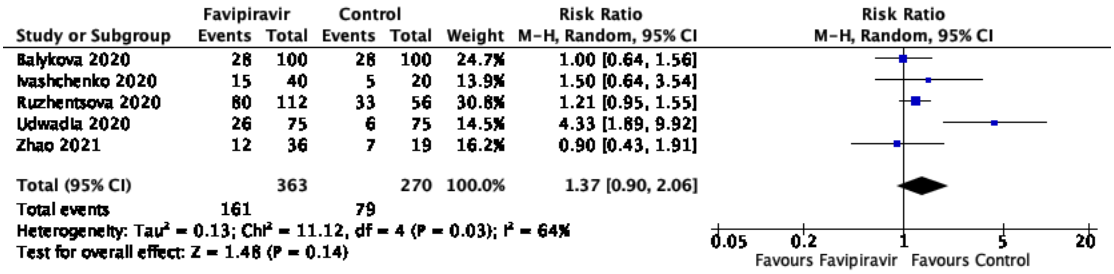

Figure 9. Adverse Events

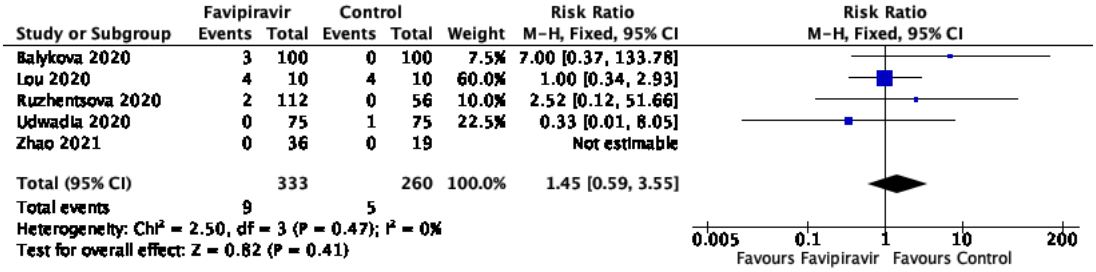

Figure 10. Serious Adverse Events

Appendix 7. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Efficacy of Favipiravir in Treatment of Mild & Moderate COVID-19 Infection in Nepal *Phase 3*	18 to 80 years confirmed COVID-19 by RT-PCR, mild to moderate	**MILD DISEASE** Experimental: Favipiravir (1800mg BID on day 1, 800mg BID from day 2 up to 5 days) Control: Placebo **MODERATE DISEASE** Experimental: Favipiravir (1800mg BID on day 1, 800mg BID from day 2 up to 10 days) Control: Remdesivir (200mg IV on day 1 then 100mg IV daily up to 10 days)	Primary outcome: Time to clinical improvement	Randomized, parallel assignment, open label
2. Clinical Trial of Favipiravir Treatment of Patients With COVID-19 *Phase 3*	18 to 74 years SARS-CoV-2 positive patients as measured by RT-PCR by nasopharyngeal sampling, hospitalized, moderate	Experimental: Favipiravir (1800mg BID on day 1, 800mg BID on day 2-14) Control: Supportive care (symptomatic therapy)	Primary outcome: Time to improvement in body temperature; Time to improvement in SpO2; Time to improvement in chest imaging findings; Time to improvement in negative SARS-CoV-2	Randomized, parallel assignment, open label
3. The Prevent Severe COVID-19 (PRESECO) Study *Phase 3*	18 years or older, tested positive for SARS-CoV-2 by RT-PCR assay using a respiratory tract sample, mild to moderate, non-hospitalized	Experimental: Favipiravir Control: Placebo	Primary outcome: Time to sustained clinical recovery	Randomized, parallel assignment, triple-blind, placebo-controlled
4. Clinical Trial Evaluating the Efficacy and Safety of Favipiravir in Moderate to Severe COVID-19 Patients *Phase 3*	21 to 80 years confirmed COVID-19 by RT-PCR, hospitalized, moderate or severe	Experimental: Favipiravir (1800mg BID on day 1, 800mg BID for next 9 days maximum) + supportive care Control: Placebo + standard of care	Primary: Time to resolution of hypoxia (Stage I)	Randomized, parallel assignment, double-blind, placebo-controlled
5. Clinical Study To Evaluate The Performance And Safety Of Favipiravir in COVID-19 *Phase 3*	18 to 75 years confirmed COVID-19 by RT-PCR, moderate	Experimental: Favipiravir (1800mg BID on day 1, 600mg TID on day 2 up to 14 days) Control: Placebo	Primary: Time from randomization to clinical recovery	Randomized; parallel assignment, double-blind, placebo-controlled
6. A Trial of Favipiravir Therapy in Adults With Mild Coronavirus Disease COVID-19 *Phase 2/3*	At least 18 years confirmed COVID-19 by PCR, mild	Experimental: Favipiravir (1800mg BID on day 1, then 800mg BID up to 7 days) Control: Placebo	Primary: Time from randomization to negativity in RT-PCR nucleic acid test for COVID-19 within 15 days of randomization	Randomized; parallel assignment, double-blind, placebo-controlled
7. An Adaptive Study of Favipiravir Compared to Standard of Care in	18 years and older confirmed COVID-19 by RT-PCR, hospitalized with moderate severity	Experimental: Favipiravir, lower dose (pilot stage; 1600mg BID on the 1st day followed by 600mg BID for 13 days)	Primary: Rate of viral elimination by Day 10 [pilot stage, dose selection]; Time to viral elimination [pivotal stage];	Randomized; sequential assignment, open label

Hospitalized Patients With COVID-19 *Phase 2/3*		Favipiravir, higher dose (pilot stage; 1800mg BID on the 1st day followed by 800mg BID for 13 days) *Dose for pivotal stage will be selected based on pilot study results.* Control: Standard of care (pilot stage & pivotal stages; might include hydroxychloroquine, chloroquine, lopinavir/ritonavir or other recommended schemes)	Time to clinical improvement [pivotal stage]	
8. A Multi-center, Randomized, Double-blind, Placebo-controlled, Phase 3 Study Evaluating Favipiravir in Treatment of COVID19 *Phase 3*	18 to 75 years confirmed COVID-19 by RT-PCR, moderate	Experimental: Favipiravir (1800mg BID on day 1, 600mg TID on day 2 up to 14 days) + supportive care Control: Placebo	Primary: Time from randomization to clinical recovery	Randomized; parallel assignment, double-blind, placebo-controlled
9. Safety and Efficacy of Maraviroc and/or Favipiravir With Standard Therapy in Severe COVID-19 Adults *Phase 2*	18 to 70 years confirmed COVID-19 by RT-PCR within 12 days post appearance of symptoms, hospitalized, severe, non-critical	Experimental: Maraviroc + currently used therapy for non-critical COVID patients (CT) Favipiravir + CT Maraviroc + Favipiravir + CT Control: CT (Enoxaparin, dexamethasone, and antibiotics if associated bacteremia is present)	Primary: Percentage of patients free of mechanical ventilation or death	Randomized; parallel assignment, open label
10. Study on Safety and Efficacy of Favipiravir (Favipira) for COVID-19 Patient in Selected Hospitals of Bangladesh *Phase 2/3*	18 to 65 years, respiratory samples tested positive for the novel coronavirus, non-severe	Experimental: Favipiravir 1600mg BID on day 1, 600mg BID on days 2-10 Control: Standard treatment (oxygen inhalation, oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, antibiotics and antiemetic drugs & the medication any patient is on due to any concomitant diseases)	Primary: Number of participants negative by RT-PCR for the virus at 4-10 days after initiation of therapy; Number of participants with lung condition change assessed with X-ray	Randomized, parallel assignment, double-blind, placebo-controlled
11. Favipiravir in High-risk COVID-19 Patients *Phase 3*	50 years and older, confirmed COVID-19 by RT-PCR, mild to moderate	Experimental: Favipiravir (1800mg BID on day 1, 800mg BID on days 2-5) Control: Standard of care only	Primary: Need for oxygen supplement	Randomized, parallel assignment, open label
12. Philippine Trial to Determine Efficacy and Safety of Favipiravir for COVID-19 *Phase 3*	18-74 years SARS-CoV-2-positive nasopharyngeal swab by RT-PCR test, non-severe presentation	Experimental: Favipiravir (1800mg bid on day 1, then 800mg bid from day 2 up to 14 days) + best supportive care or standard treatment Control: Best supportive care or standard treatment (oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, antibiotics and antiemetic drugs & the medication any patient is on due to any concomitant diseases)	Primary: Time from initiation of treatment to clinical improvement	Randomized, parallel assignment, open label
13. Corona Virus Disease 2019 Patients Whose	18 TO 80 years diagnosed with COVID-19, and the nucleic acid test of	Experimental: Favirapir (1600mg BID on day 1; 600mg BID from day 2-7 up to 14 days)	Primary outcome: Viral nucleic acid test negative conversion rate	Randomized, parallel assignment, open label

Nucleic Acids Changed From Negative to Positive	respiratory specimens such as sputum or nasopharyngeal swabs has been negative for two consecutive times after treatment (sampling time interval of at least 24 hours); The nucleic acid test of specimens such as sputum, throat swabs, blood, feces and other specimens was positive for COVID-19 during screening visits.	Control: Regular treatment group (treatments other than lopinavir and ritonavir, chloroquine phosphate, hydroxychloroquine sulfate, arbidol, and colomycin can be given)		
14. An Adaptive Clinical Trial of Antivirals for COVID-19 Infection *Phase 2*	18 years and older confirmed SARS-CoV-2 by nucleic acid testing	Experimental: Favipiravir (1800mg BID on day 1, 800mg BID for the next 13 days) Control: Placebo	Primary outcome: Time to virological cure	Randomized, parallel assignment, quadruple blind, placebo-controlled
15. Early Intervention in COVID-19: Favipiravir Verses Standard Care *Phase 3*	18 years and older suspected or confirmed COVID-19 infection	Experimental: Favipiravir (1800mg BID on day 1, 800mg BID from days 2-10) Control: Standard of care	Primary outcome: Time from randomization to a sustained clinical improvement (maintained for 24 hours) by two points on a seven-category ordinal scale or to discharge, whichever occurs first	Randomized, parallel assignment, open label
16. Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia *Phase 2/3*	18 to 75 years previously diagnosed with novel coronavirus pneumonia: the course of illness is no more than 14 days; if the course of the disease was more than 14 days, patient meets one of the following conditions can also be included in the group: (1) No apparent absorption or progression of chest radiograph was observed within 7 days; (2) respiratory symptoms (chest tightness, or cough, or breathing difficulties); (3) Test for viral nucleic acid positive within 3 days	Experimental: Favipiravir (1600mg BID on day 1, 600mg BID from days 2-10) + chloroquine phosphate (500mg BID on day 1, 500mg OD from days 2-3, 250mg OD from days 4-10) Favipiravir (1600mg BID on day 1, 600mg BID from days 2-10) Control: Placebo	Primary outcome: Time of Improvement or recovery of respiratory symptoms; Number of days from positive to negative for test of swab or sputum virus nucleic acid; Frequency of improvement or recovery of respiratory symptoms	Randomized, parallel assignment, double-blind
17. Study to Assess the Efficacy and Safety of Favipiravir-HU *Phase 2*	18 to 65 years PCR confirmed SARS-CoV-2 infection, asymptomatic or mild	Experimental: Favipiravir HU + standard of care Control: Placebo HU	Primary outcome: Percentage of virus copy number at Day 6 compared to baseline	Randomized, parallel assignment, double-blind, placebo-controlled
18. Study of Efficacy and Safety of TL-FVP-t vs. SOC in Patients With Mild to Moderate COVID-19 *Phase 3*	18 to 60 years, PCR verified SARS-CoV-2 infection, mild or moderate without respiratory failure	Experimental: Favipiravir (1800mg BID on day 1800mg BID from days 2-10) + standard of care Control: Standard of care including etiotropic therapy according to MoH of Russian Federation Recommendations for COVID-19 (umifenovir + intranasal recombinant interferon alpha, or hydroxychloroquine, or chloroquine, or mefloquine in recommended regimen) up to10 days	Primary outcome: Time to clinical improvement defined as reduction on at least 1 score of patient clinical status according to WHO 8-category Ordinal Scale for Clinical Improvement; Time to viral clearance as measured by PCR in oropharyngeal sampling	Randomized, parallel assignment, open label

19. Finding Treatments for COVID-19: A Trial of Antiviral Pharmacodynamics in Early Symptomatic COVID-19 (PLATCOV) *Phase 2*	18 to 50 years previously healthy with early symptomatic COVID-19 SARS-CoV-2 positive by lateral flow antigen test	Experimental: Favipiravir (1800mg BID D0 and 800mg BID for a further 6/7) Ivermectin (600 micrograms/kg/day for 7/7) Remdesivir (200mg D0 and 100mg for a further 4/7) Active comparator: Monoclonal antibodies (1,200mg casirivimab/ 1200mg imdevimab given once on D0) Control: No treatment (except antipyretics – paracetamol)	Primary outcome: Rate of viral clearance for repurposed drugs; Rate of viral clearance of positive control; Rate of viral clearance for small novel molecule drugs	Randomized, parallel assignment, open label
20. Safety and Efficacy of Favipiravir in COVID-19 Patients with Pneumonia −A randomized, double blind, placebo- controlled study *Phase 2*	18 to 85 years, positive for SARS-COV2 on RT-PCR test from respiratory specimen(s), categories 3 to 5 on the WHO ordinal scale	Experimental: Favipiravir Control: Placebo	Primary outcome: Time to clinical improvement measured as improvement for ≥ two categories on a 7-point ordinal scale	Randomized, double-blind, placebo-controlled
21. An Investigation of the Efficacy and Safety of Favipiravir in COVID-19 Patients with Mild Pneumonia *Phase 3*	18 to 74 years SARS-CoV-2-positive airway specimens by RT-PCR, with mild pneumonia	Experimental: Favipiravir Control: Supportive care (symptomatic therapy) up to 14 days	Primary outcome: Time from initiation of the study drug to the time of “improvement” in body temperature, SpO2, and chest imaging and negative SARS-CoV-2	Randomized, open label
22. A Randomised Controlled Trial of Early Intervention in Patients HospItalised with COVID-19: Favipiravir verses HydroxycholorquiNe & Azithromycin & Zinc vErsEs Standard CaRe *Phase 3*	18 years and older, suspected or confirmed COVID-19 infection	Experimental: Favipiravir Hydroxychloroquine Azithromycin Control: UK standard of care for COVID-19 infection	Primary outcome: Time to clinical improvement (post randomisation) by two points on a seven-category ordinal scale or live discharge from the hospital, whichever comes first	Randomized, parallel assignment, open label
23. An Investigation of the Efficacy and Safety of Favipiravir in COVID-19 Patients without Pneumonia *Phase 3*	18 to 74 years SARS-CoV-2-positive airway specimens by RT-PCR, without pneumonia	Experimental: Favipiravir Control: Supportive care (symptomatic therapy) up to 14 days	Primary outcome: Time from initiation of the study drug to the time of “improvement” in body temperature, SpO2, and chest imaging and negative SARS-CoV-2	Randomized, open label
24. Home treatment of elderly patients with symptomatic SARS-CoV-2 infection (COVID-19) : a multiarm, multi-stage (MAMS) randomized trial to	60 years or older with positive test for SARS-CoV-2 on a nasopharyngeal swab	Experimental: Imatinib (400mg qd from day 0-9) Favipiravir (2400mg bid on day 0, 1200mg bid from day 1-9) Telmisartan (20mg qd from day 0-9)	Primary outcome: Proportion of participants with an occurrence of hospitalization and/or death between D0 and D14 in each arm	Randomized, parallel assignment, open label

assess the efficacy and safety of several experimental treatments to reduce the risk of hospitalization or death (COVERAGE trial) *Phase 3*		Control: Complex of vitamins and trace elements (AZINC Forme et Vitalité®) 1 cap bid for 10 days		

Q4. Should remdesivir be used in the treatment of patients with COVID-19 infection?

As of 19 February 2021

RECOMMENDATIONS

We suggest against the use of remdesivir among COVID-19 patients who do not require oxygen supplementation and with O_2 saturation ≥94%. *(Low certainty of evidence, Weak recommendation)*

We suggest adding remdesivir to dexamethasone among patients with COVID-19 infection who have O_2 saturation <94% and/or requiring oxygen supplementation but are not on high flow oxygen or mechanical ventilation. (*Low certainty of evidence, Weak recommendation)*

We suggest against the use of remdesivir among patients with COVID-19 infection who are already on high flow oxygen, mechanical ventilation or ECMO. *(Low certainty of evidence, Weak recommendation)*

Consensus Issues
Early introduction of remdesivir in the treatment of COVID-19 is preferred because of its action on the polymerase resulting to less viral replication. Remdesivir is a relatively safe drug, however, its cost should be considered. Hence, routine use of the drug is not recommended. There are 26 ongoing trials pertaining to the efficacy and safety of remdesivir for the treatment of COVID-19.

KEY FINDINGS

Four randomized controlled trials on the use of remdesivir as treatment for COVI-19 were found. Low quality evidence shows that remdesivir has limited effect on all cause-mortality, clinical improvement, and initiation of mechanical ventilation among confirmed COVID-19 patients. However, remdesivir appears to be beneficial in the time to clinical improvement especially among cases needing supplemental oxygen but not high flow oxygen/ mechanical ventilation. Remdesivir did not show increased risk for serious adverse events. Availability and cost of intervention should be considered before making recommendation regarding its use locally.

INTRODUCTION

Remdesivir is an intravenously administered antiviral drug originally developed for the Ebola virus that is currently being evaluated as a potential treatment for COVID-19. It is a nucleotide analogue that inhibits RNA-dependent RNA polymerases.[1] Several in-vitro studies in cells, primates, and mice demonstrated its antiviral activities against an array of RNA viruses (e.g., MERS-COV, Ebola Virus, SARS-COV) [2-4]. An in-vitro study has shown that remdesivir can inhibit the growth of COVID-19 virus in infected Vero cells and inhibit infection in human cell line [5].

REVIEW METHODS

Trials found in the COVID-NMA living data (as of December 4, 2020) were included. Screening after their last search was done in Medline, Cochrane Library, MedRivx to check for newer trials. Randomized controlled trials on remdesivir compared to

placebo or standard of care on COVID-19 patients, regardless of severity were included.

RESULTS

There were 4 published randomized controlled clinical trials (RCTs) evaluating the effect of remdesivir compared to placebo and/or standard of care among confirmed COVID-19 patients (n=7,345). [6-10] All of these trials were included in the COVID-NMA Living Data which was last updated on December 4, 2020.[11] As of December 26, 2021, no new trials on remdesivir were found on MEDLINE. Meta-analysis from the COVID-NMA was adopted. Additional meta-analysis was done for the following outcomes: mechanical ventilation, duration of hospitalization, and duration of mechanical ventilation. Appendix 1 summarizes the characteristics of these included RCTs.

Three RCTs [6,7,10] were multi-national studies conducted in the United States, Europe, and parts of Asia, while one RCT [8] was conducted in China. Among the three multinational trials is the WHO Solidarity Trial that also looked at the effectiveness of hydroxychloroquine, lopinavir, and interferon beta-1a. Only one study [7] was conducted among moderate COVID-19 cases, which was diagnosed when patients demonstrated any radiographic evidence of pulmonary infiltrates and an oxygen saturation (SpO2) >94% on room air. Two studies [8,10] were conducted only among severe cases, which were characterized by radiographic infiltrates by imaging, an SpO2 ≤ 94% on room air requiring mechanical ventilation and/or supplemental oxygen, and other clinical signs. The WHO Solidarity trial included all hospitalized COVID-19 cases regardless of severity.

Overall, trends for remdesivir pointed towards potential benefit on all patient-important outcomes but did not reach statistical significance for mortality, initiation of mechanical ventilation, time to recovery/clinical improvement, duration of hospitalization, and duration on mechanical ventilation. Pooled results from 4 RCTs (n=7,345) showed that remdesivir did not decrease all-cause mortality (RR 0.90, 95% CI 0.73-1.11). Based on 2 RCTs (n = 839), clinical improvement among patients on remdesivir was not significantly different (RR 1.06, 95%CI 0.99 to 1.13) from those treated with standard care. There was a trend towards benefit in preventing initiation of mechanical ventilation based on 4 RCTs (n= 6,549), but this did not reach statistical significance (RR 0.65, 95%CI 0.39 to 1.08). Effects of remdesivir on viral conversion, duration of hospitalization, and duration on mechanical ventilation were uncertain due to wide interval estimates.

Remdesivir demonstrated limited beneficial effect in the incidence of recovery and recovery rate. From 2 RCTs (n = 1,658), the rate of recovery was faster in the remdesivir group compared to the placebo/standard care group (Rate Ratio 1.23, 95%CI 1.11-1.37). The rate of clinical improvement was also faster in the remdesivir group (RR 1.22, 95%CI 1.11 to 1.35) based on 3 RCTs (n = 1,895).

The incidence of adverse events was similar among the remdesivir group compared to those on standard of care alone (RR 0.93, 95%CI 0.85-1.01). Common adverse events were decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, increased blood creatinine level, hypoalbuminemia, rash, increased neutrophil and

increased blood glucose level. There were fewer serious adverse events in the remdesivir group (RR 0.60, 95% CI 0.38-0.96). Serious adverse events that were observed in both groups were respiratory failure and cardiopulmonary failure. Figures 1-8 (Appendix 3) illustrate the effect of remdesivir on various outcomes.
Subgroup analysis on mortality, incidence of clinical improvement/recovery, clinical improvement/ recovery rate and time to clinical improvement/recovery according to severity was done. Patients who had severe COVID-19 were more likely to benefit from remdesivir.

The use of remdesivir was associated with a trend towards benefit among severe patients (i.e., requiring oxygen) for mortality (RR 0.77, 95%CI 0.59 to 1.02). However, its effect remains uncertain for non-severe (RR 1.12, 95%CI 0.65 to 1.92) and critical COVID-19 cases (RR 0.94 0.50 to 1.75).

Incidence of recovery was significantly higher among severe COVID-19 on remdesivir (RR 1.09, 95%CI 1.01 to 1.18). Recovery rate was significantly better for the severe cases requiring oxygen (Rate Ratio 1.45, 95% CI 1.18 to 1.79) but still not on high-flow oxygen (Rate Ratio 1.09, 95%CI 0.76 to 1.57) and mechanical ventilation (Rate Ratio 0.98, 95% CI 0.70 to 1.37). This was noted from a significantly shorter time to recovery for severe/critical cases of 5 days (95%CI -4.93 days to -2.31 days) based on 2 RCTs (n=1,295).

RECOMMENDATIONS FROM OTHER GROUPS

There are varying recommendations regarding the use of remdesivir. The Infectious Disease Society of America (IDSA) and the US NIH recommend giving it to those with severe COVID-19 while WHO recommends against its use regardless of the severity.

As of December 17, 2020, WHO suggested against the use of remdesivir in addition to standard of care regardless of severity (conditional recommendation, low quality evidence) due to the lack of evidence on its effectiveness on patient important outcomes such as mortality, need of mechanical ventilation and time to clinical improvement. The WHO panel raised concerns about *"opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe COVID-19."* [12]

As of February 10, 2021, IDSA suggested against remdesivir for routine treatment of patients with oxygen saturation >94% and no supplemental oxygen and strongly urges for continued study. (Conditional recommendation, very low certainty of evidence) They also suggests the use of remdesivir for treatment of severe COVID-19 in hospitalized patients with $SpO_2 \leq 94\%$ on room air, including patients on supplemental oxygen, on mechanical ventilation and ECMO. (Conditional recommendation, moderate certainty of evidence)

As of February 11, 2021, the US NIH COVID-19 treatment guidelines panel (last updated: December 3, 2020) recommends the use of remdesivir with (BIII recommendation) or without dexamethasone (BIIa recommendation) for the treatment of COVID-19 in hospitalized patients who require supplemental oxygen but not on invasive ventilation, or ECMO. The recommendation is based on the results of the 3 RCTs included in this review with the exception of the SOLIDARITY trial. There is no recommendation for its use in hospitalized patients who do not require oxygen due to

lack of data. Remdesivir is also not recommended in patients with eGFR <30 mL/minute. Liver function tests and prothrombin time should be obtained in all patients before remdesivir is administered and during treatment as clinically indicated. The panel suggest discontinuing remdesivir if alanine transaminase (ALT) levels increase to >10 times the upper limit of normal and recommend discontinuing if an increase in ALT level and signs or symptoms of liver inflammation are observed.[13]

RESEARCH GAPS

As of January 7, 2021, 26 ongoing clinical trials on remdesivir were registered in ClinicalTrial.gov (Appendix 4).

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Appendix 1. Characteristics of Included Studies

Title/ Author	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
Spinner, 2020	USA Europe UK Asia	596	Hospitalized patients with moderate COVID-19	5- day course 10-day course	Standard care	Clinical status day 11 (primary) Adverse events Time to recovery
Beigel, 2020	USA Denmark UK Greece, Germany Korea Mexico Spain Japan Singapore	1059	Severe COVID-19 patients	10-day course	Placebo	Time to recovery Mortality Adverse events
Wang, 2020	China	237	Severe COVID-19 patients	10-day course	Placebo	Time to clinical improvement Mortality Viral load Adverse events
WHO Solidarity Consortium, 2020	Europe Canada Latin America Asia Africa	11,330 (Total) 5451 (Remdesivir and its control)	All hospitalized patients diagnosed with COVID 19	Group 1: remdesivir, Group 2: hydroxychloroquine, Group 3: lopinavir, Group 4:interferon beta-1a	Standard care	Mortality (primary) Mechanical ventilation Hospital duration

Appendix 2. GRADE Evidence Profile

Author(s): Ian Theodore G. Cabaluna
Question: Remdesivir compared to standard of care in Covid-19
Bibliography: https://covid-nma.com/

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	SOC	Relative (95% CI)	Absolute (95% CI)	CERTAINTY	IMPORTANCE
All cause mortality at Day 14-28 (follow up: mean 28 days)												
4	Randomised trials	Not serious	Not serious	Not serious	Serious	None	387/3838 (10.1%)	394/3507 (11.2%)	**RR 0.90** (0.73 to 1.11)	**11 fewer per 1,000** (from 30 fewer to 12 more)	⊕⊕⊕◯ MODERATE	
Incidence of recovery (follow up: 28 days)												
2	Randomised trials	Not serious	Not serious	Not serious	Not serious[a]	None	752/937 (80.3%)	522/721 (72.4%)	**RR 1.08** (1.02 to 1.14)	**58 more per 1,000** (from 14 more to 101 more)	⊕⊕⊕⊕ HIGH	
Mechanical Ventilation												
4	Randomised trials	Not serious	Serious[b]	Not serious	Serious[a]	None	363/3433 (10.6%)	384/3116 (12.3%)	**RR 0.90** (0.78 to 1.03)	**12 fewer per 1,000** (from 27 fewer to 4 more)	⊕⊕◯◯ LOW	
Duration of hospitalization (assessed with: days)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious[a]	None	699	599	-	MD **1.64 days lower** (4.02 lower to 0.75 higher)	⊕⊕⊕◯ MODERATE	
Duration on mechanical ventilation (assessed with: days)												
2	Randomised trials	Not serious	Serious	Not serious	Serious[a]	None	699	599	-	MD **2.75 days lower** (7.05 lower to 1.55 higher)	⊕⊕◯◯ LOW	
Viral negative conversion (follow up: 7 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[a]	None	66/131 (50.4%)	32/65 (49.2%)	**RR 1.02** (0.76 to 1.38)	**10 more per 1,000** (from 118 fewer to 187 more)	⊕⊕◯◯ LOW	

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	SOC	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	618/1095 (56.4%)	466/799 (58.3%)	**RR 0.93** (0.85 to 1.01)	**41 fewer per 1,000** (from 87 fewer to 6 more)	⊕⊕⊕⊕ HIGH	
Serious adverse events												
3	Randomised trials	Not serious	Not serious	Not serious	Serious [a]	None	33/1095 (3.0%)	32/799 (4.0%)	**RR 0.60** (0.38 to 0.96)	**16 fewer per 1,000** (from 25 fewer to 2 fewer)	⊕⊕⊕◯ MODERATE	
Recovery rate												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	721 participants -	937 participants 92.1%	**Rate ratio 1.22** (1.06 to 1.41) [Recovery / Clinical Improvement]	**-- per 1000 patient(s) per years** (from -- to --)	⊕⊕⊕⊕ HIGH	
Time to recovery (follow up: 28 days)												
3	Randomised trials	Not serious	Serious [e]	Not serious	Serious [a]	None	889	799	-	MD **1.89 days lower** (7.77 lower to 3.99 higher)	⊕⊕◯◯ LOW	
Incidence of clinical improvement (follow up: 28 days)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious [a]	None	166/278 (59.7%)	448/554 (80.9%)	**RR 1.06** (0.99 to 1.13)	**49 more per 1,000** (from 8 fewer to 105 more)	⊕⊕⊕◯ MODERATE	
Clinical improvement rate (follow up: 28 days)												
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	554 participants -	278 participants 92.1%	**RR 1.22** (1.11 to 1.35) [clinical improvement]	**203 more per 1,000** (from 101 more to 322 more) **203 more per 1,000** (from 101 more to 322 more)	⊕⊕⊕⊕ HIGH	

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	SOC	Relative (95% CI)	Absolute (95% CI)		
Time to clinical improvement												
2	Randomised trials	Not serious	Serious [f]	Not serious	Serious [a]	None	896	800	-	MD **1.87 days lower** (4.24 lower to 0.5 higher)	⨁⨁◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

[a] Downgraded by 1 level due to imprecision: wide confidence interval with possible benefit or harm
[b] Downgraded by 1 due to inconstinency: I2=82%
[c] Downgraded by 1 level due to inconsistency: result was heterogenous (I2=95)
[d] Risk of bias downgraded by 1: some concern with missing data
[e] Downgraded by 1 due to inconsistency: I2 - 93%
[f] Downgraded by 1 due to inconsistency: I2=64%

Appendix 3. Forest Plots

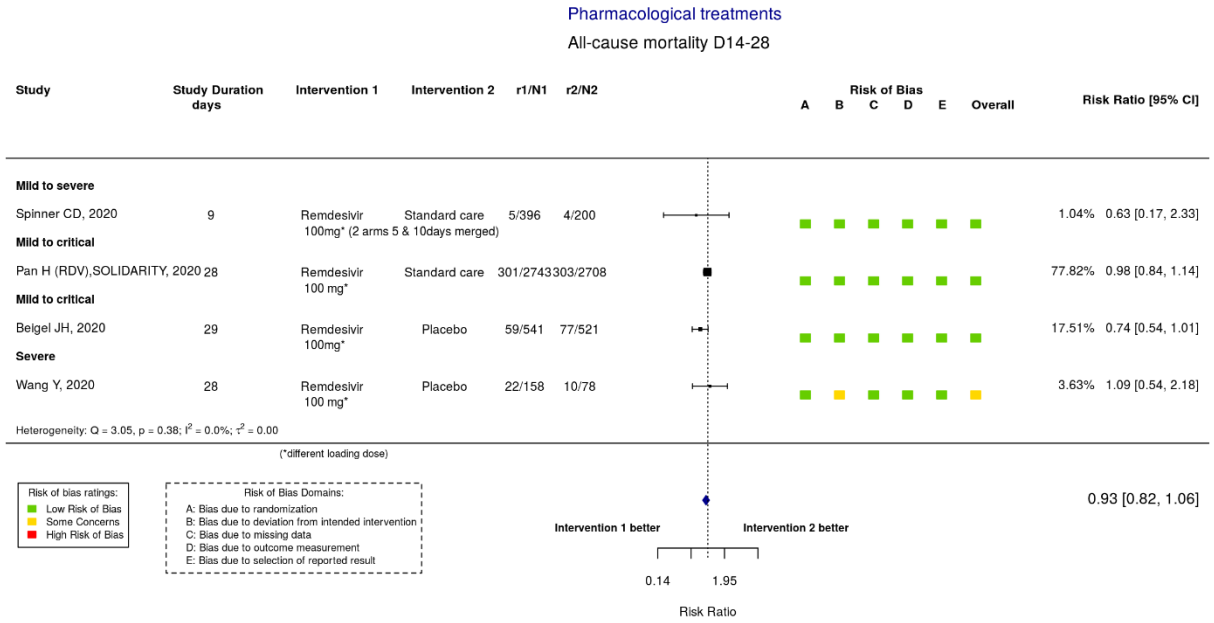

Figure 1. Pooled effect of remdesivir on all-cause mortality. Source: covid-nma.com

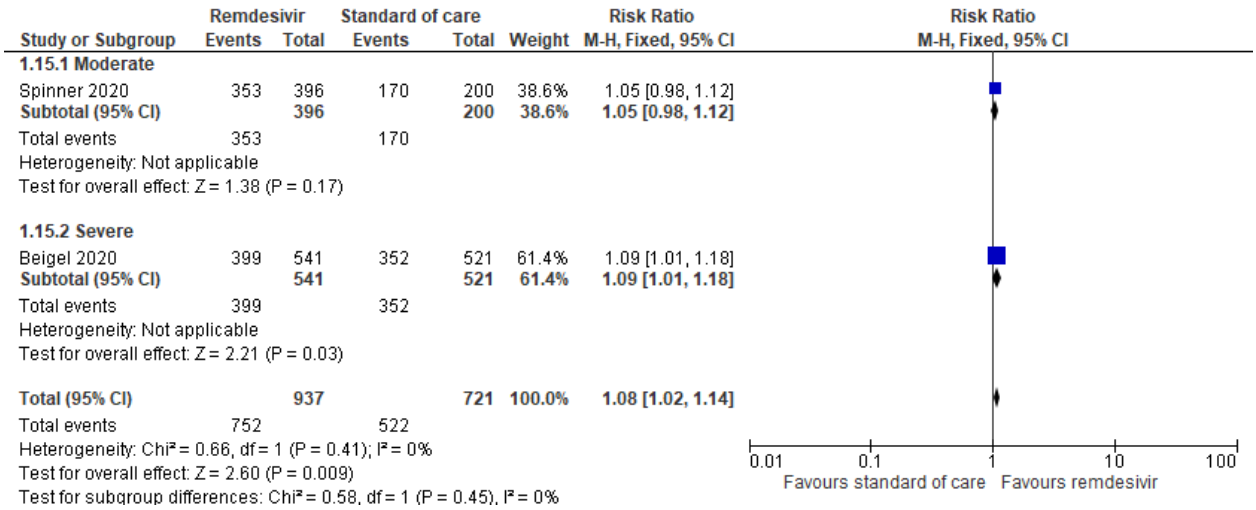

Figure 2. Pooled effect of remdesivir on incidence of recovery

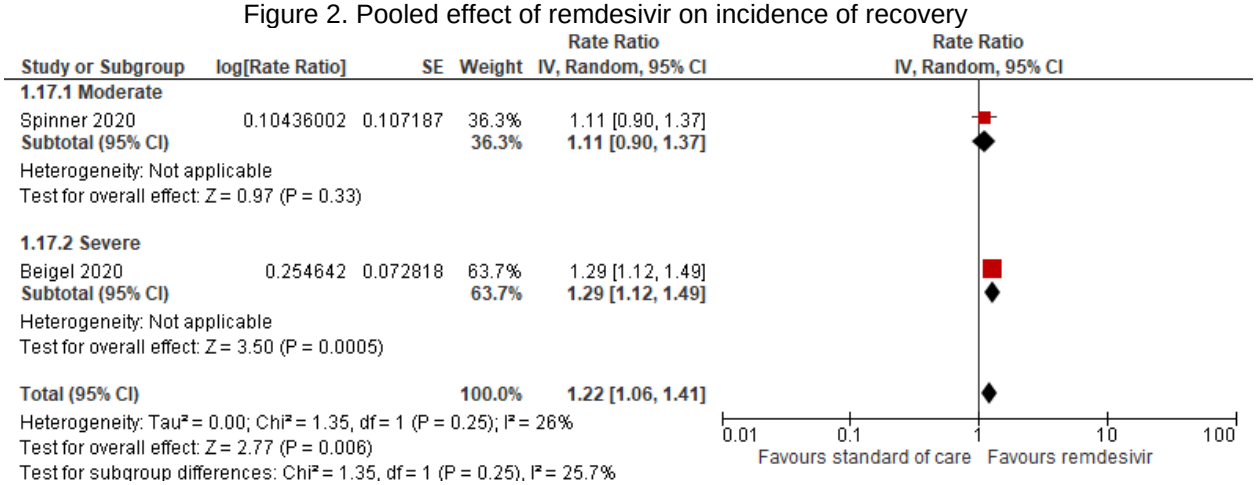

Figure 3. Pooled effect of remdesivir on recovery rate

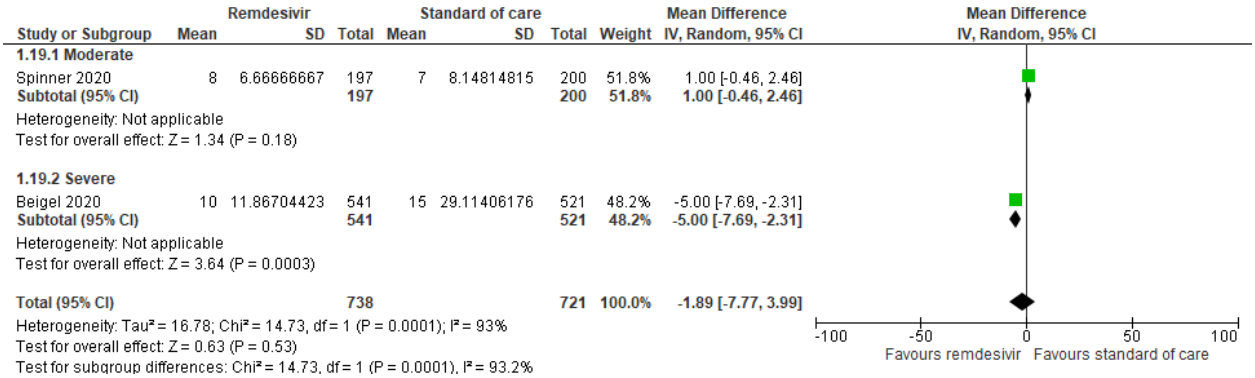

Figure 4. Pooled effect of remdesivir on time to recovery (days)

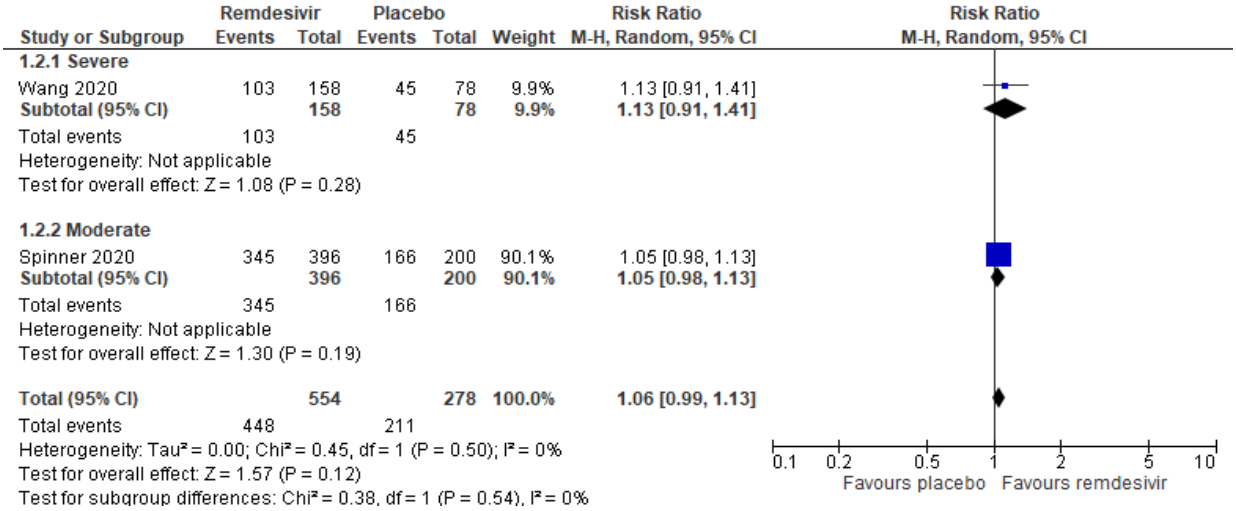

Figure 5. Pooled effect of remdesivir on the incidence of clinical improvement

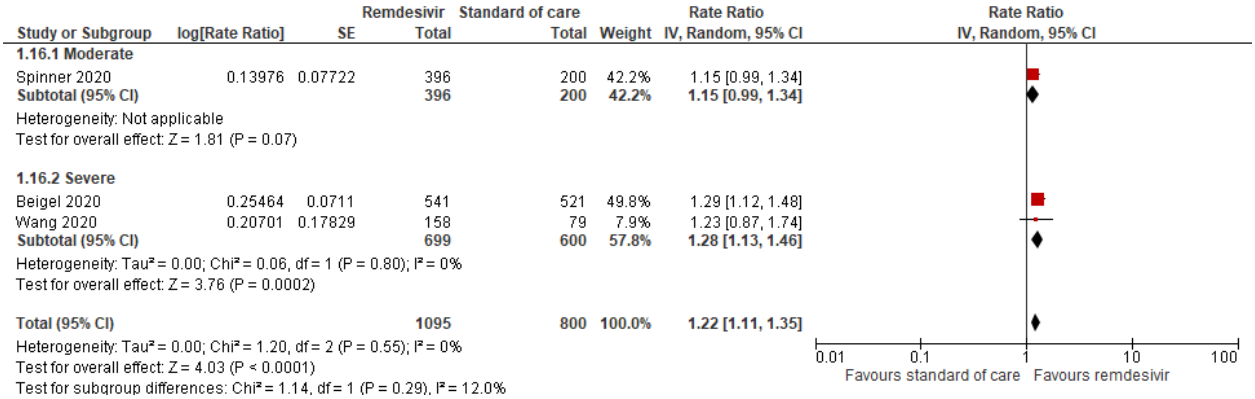

Figure 6. Pooled effect of remdesivir on clinical improvement rate

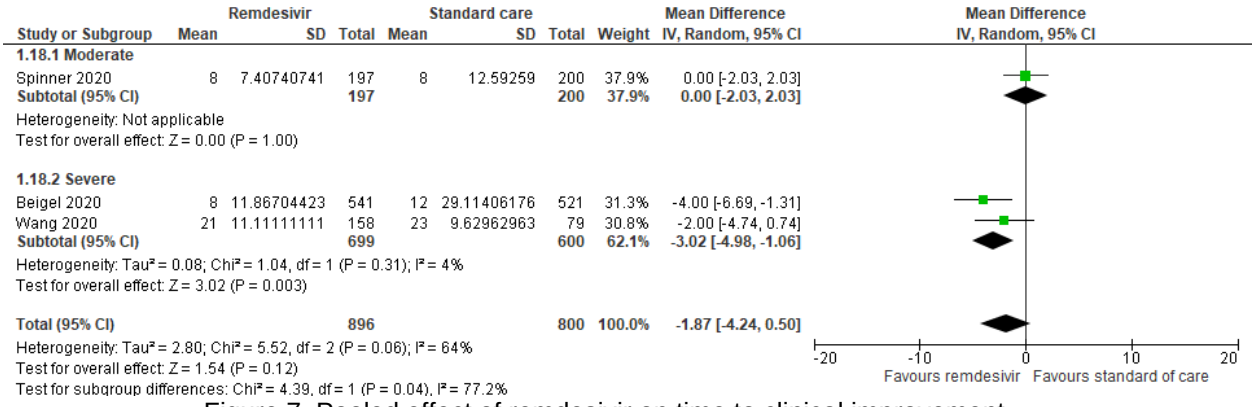

Figure 7. Pooled effect of remdesivir on time to clinical improvement

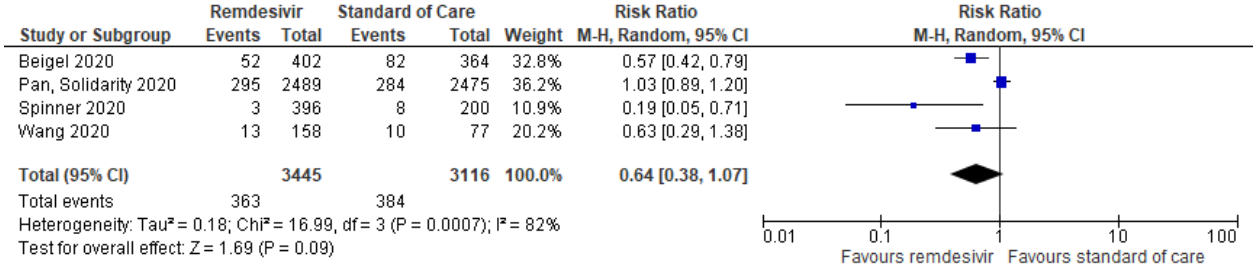

Figure 8. Pooled effect of remdesivir on initiation of mechanical ventilation

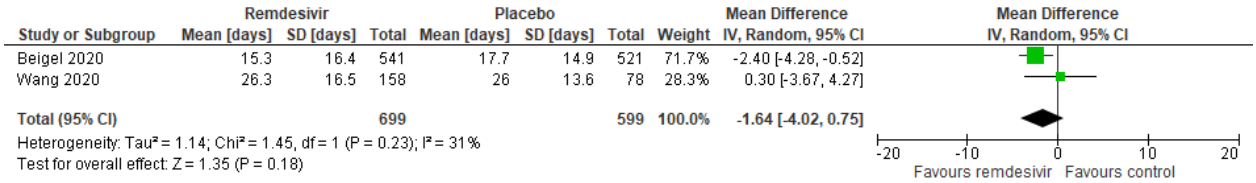

Figure 9. Pooled effect of remdesivir on duration of hospital stay (days)

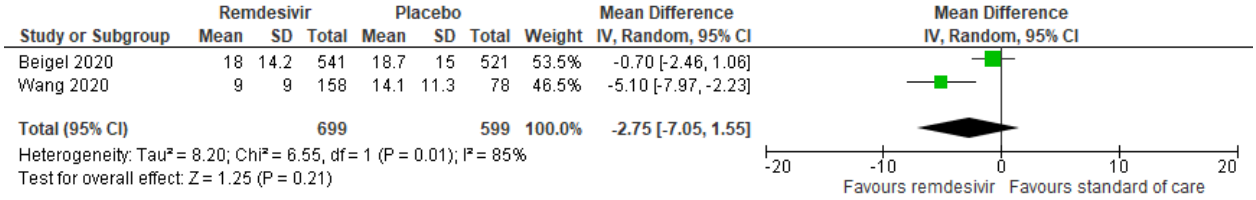

Figure 10.Pooled effect of remdesivir on duration on mechanical ventilation (days)

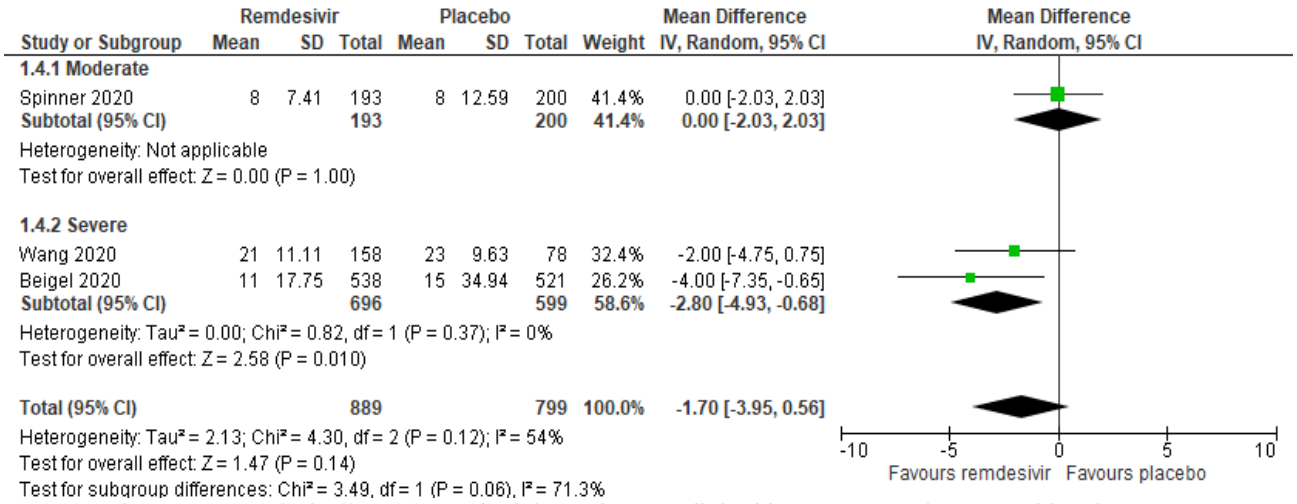

Figure 11. Pooled effect of remdesivir on time to clinical improvement/recovery(days)

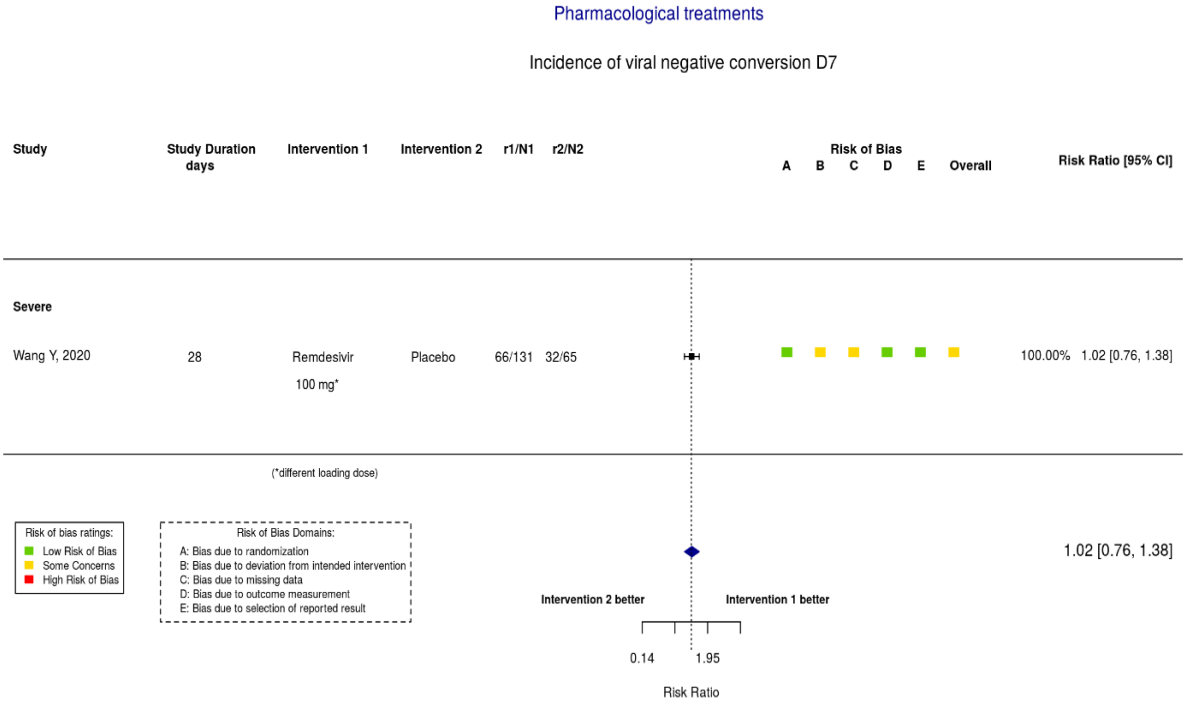

Figure 12. Effect of remdesivir on negative viral conversion. Source: COVID-nma.com

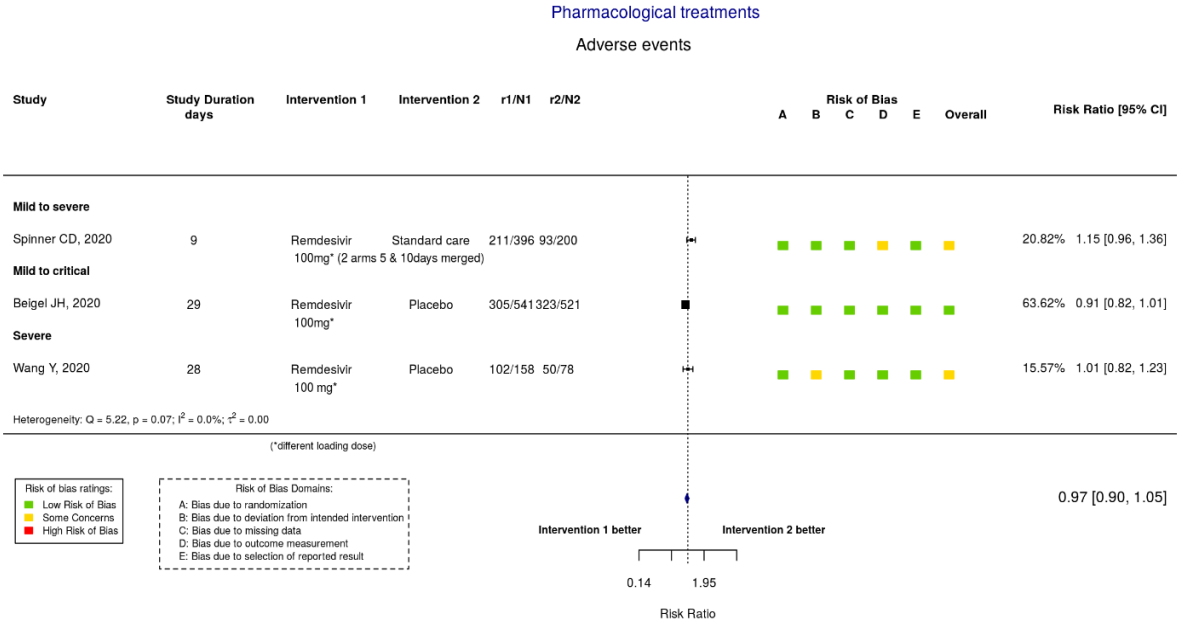

Figure 13. Pooled effect of remdesivir on the incidence adverse event. Source: covid-nma.com

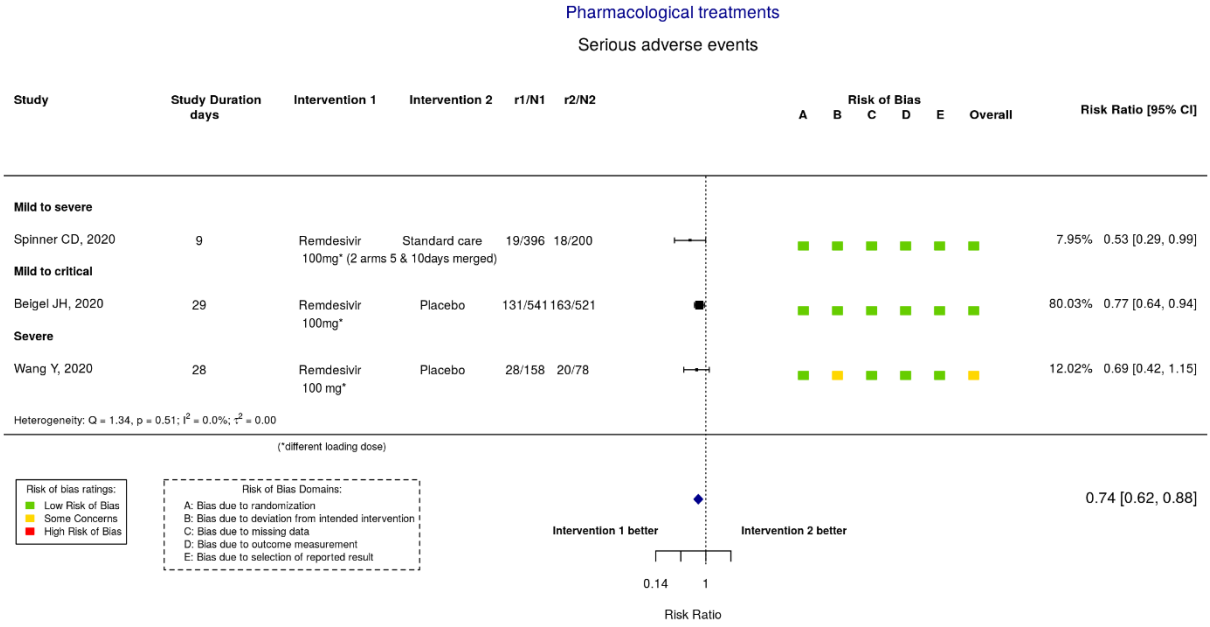

Figure 14. Pooled effect of remdesivir on the incidence of serious adverse events. Source: covid-nma.com

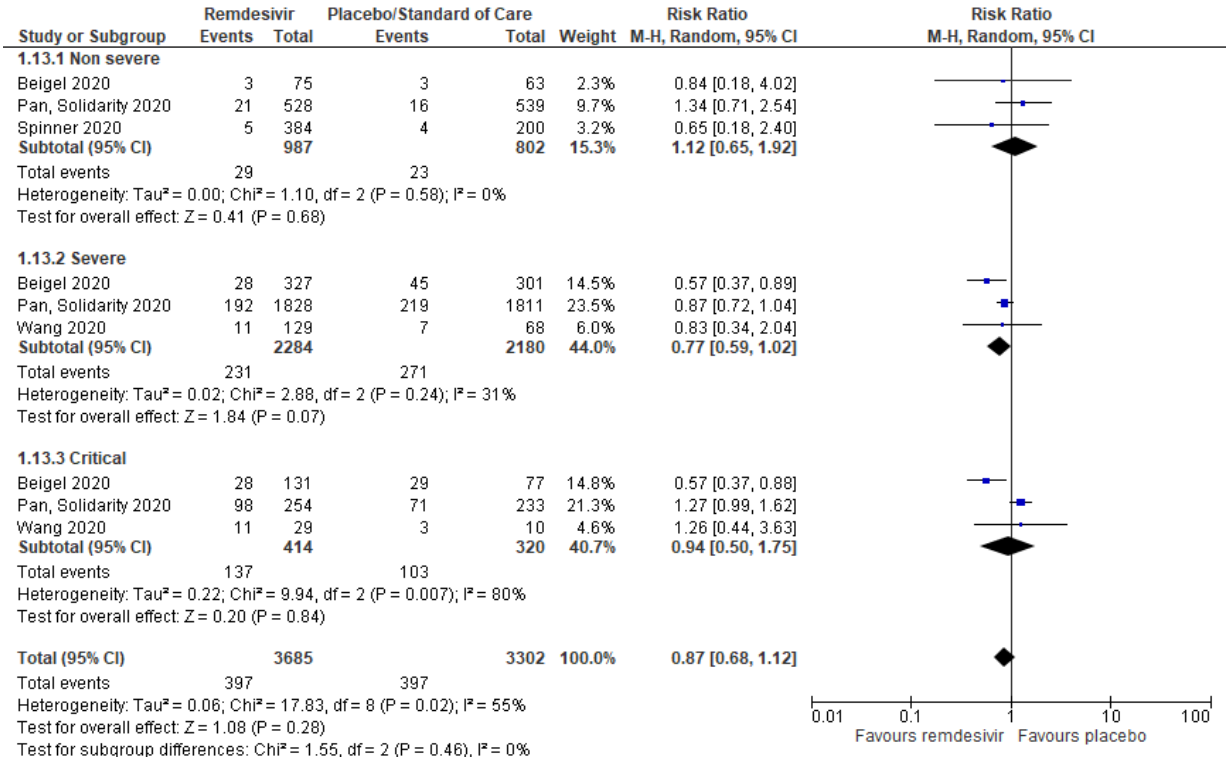

Figure 15. Sub-analysis of the results on mortality according to severity of disease

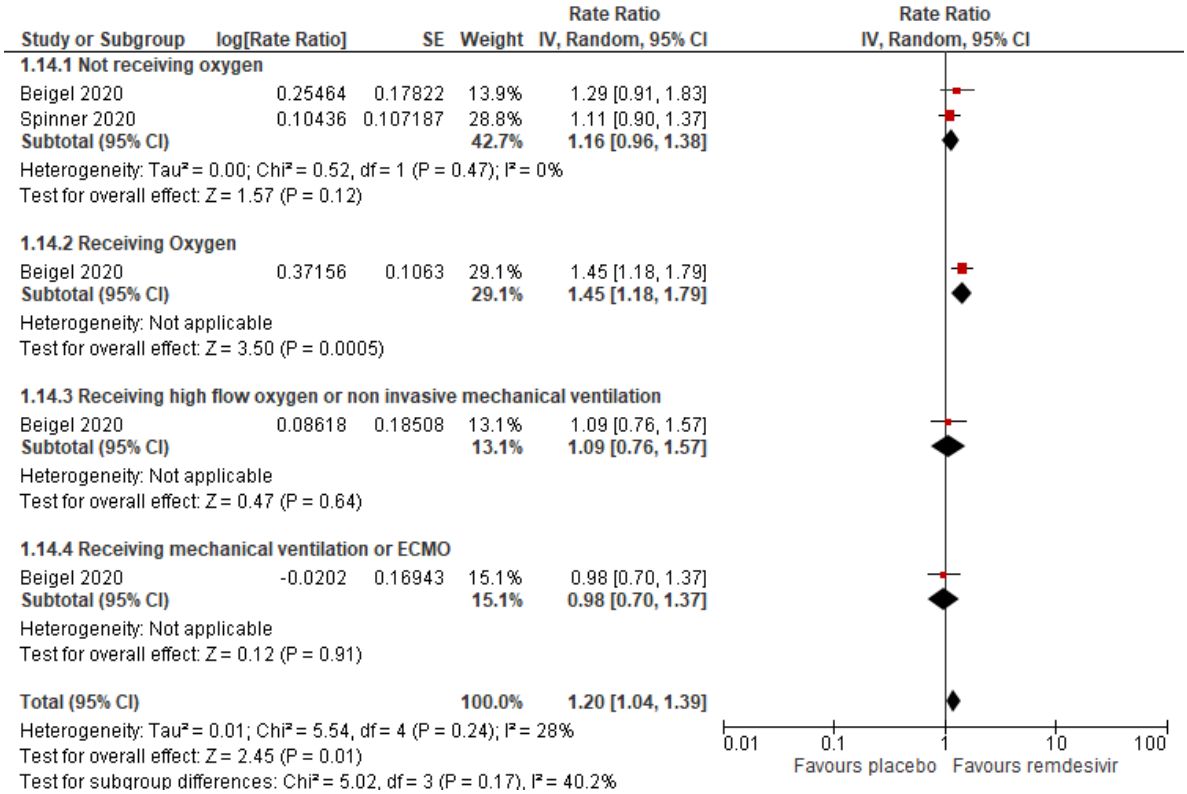

Figure 16. Sub-analysis of the results on recovery rate according to severity of disease

Appendix 4. Characteristics of Ongoing Studies

Title	Interventions	Sample Size
Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734â„¢) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19)	Drug: Remdesivir	52
Study in Participants With Early Stage Coronavirus Disease 2019 (COVID-19) to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation	Drug: Remdesivir (RDV)|Drug: Placebo	282
IFN-beta 1b and Remdesivir for COVID19	Drug: Interferon beta-1b|Drug: Remdesivir	100
Efficacy and Safety of Remdesivir and Tociluzumab for the Management of Severe COVID-19: A Randomized Controlled Trial	Drug: Remdesivir|Drug: Tocilizumab	150
Study to Evaluate the Efficacy and Safety of Remdesivir (GS-5734â„¢) Treatment of Coronavirus Disease 2019 (COVID-19) in an Outpatient Setting	Drug: RDV|Drug: Placebo to Match RDV	1264
A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared With Remdesivir Plus Placebo in Hospitalized Participants With Severe COVID-19 Pneumonia	Drug: Remdesivir|Drug: Tocilizumab|Drug: Placebo	500
Antiviral Activity and Safety of Remdesivir in Bangladeshi Patients With Severe Coronavirus Disease (COVID-19)	Drug: Remdesivir|Other: Standard of Care	60
Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial	Drug: Interferon beta-1a|Drug: Remdesivir	2900
REMdesivir-HU Clinical Study and Severe Covid-19 Patients	Drug: Remdesivir-HU	2000
Adaptive COVID-19 Treatment Trial 3 (ACTT-3)	Drug: Interferon beta-1a|Other: Placebo|Drug: Remdesivir	969
ACTIV-5 / Big Effect Trial (BET-B) for the Treatment of COVID-19	Biological: Lenzilumab|Other: Placebo|Drug: Remdesivir	200
ACTIV-5 / Big Effect Trial (BET-A) for the Treatment of COVID-19	Other: Placebo|Drug: Remdesivir|Biological: Risankizumab	200
Adaptive COVID-19 Treatment Trial 4 (ACTT-4)	Drug: Baricitinib|Drug: Dexamethasone|Other: Placebo|Drug: Remdesivir	1500
Efficacy of Ramdicivir and Baricitinib for the Treatment of Severe COVID 19 Patients	Drug: Remdesivir|Drug: Baricitinib|Drug: Tocilizumab	150
Efficacy of Favipiravir in Treatment of Mild & Moderate COVID-19 Infection in Nepal	Drug: Favipiravir|Drug: Placebo|Drug: Remdesivir	676
An International Randomized Trial of Additional Treatments for COVID-19 in Hospitalized Patients Who Are All Receiving the Local Standard of Care - WHO-SOLIDARITY-GERMANY	Other: Standard of Care (SoC)|Drug: Remdesivir	400
Remdesivir in COVID-19 Lahore General Hospital	Drug: Remdesivir	30
Remdesivir vs Chloroquine in Coronavirus Disease	Drug: Chloroquine or hydroxychloroquine|Drug: Remdesivir	120
Immune Modulators for Treating COVID-19	Drug: Infliximab|Drug: Abatacept|Drug: Remdesivir|Drug: cenicriviroc	2160
I-SPY COVID-19 TRIAL: An Adaptive Platform Trial for Critically Ill Patients	Drug: Remdesivir|Drug: Cenicriviroc|Drug: Icatibant|Drug: Razuprotafib|Drug: Apremilast	1500
The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients	Drug: Hydroxychloroquine|Drug: Remdesivir|Other: (Standard of Care) SoC	700
World Health Organization (WHO) COVID-19 Solidarity Trial for COVID-19 Treatments	Drug: Remdesivir|Drug: Acalabrutinib|Drug: Interferon beta-1a|Other: Standard of Care	100
Trial of Treatments for COVID-19 in Hospitalized Adults	Drug: Remdesivir|Drug: Lopinavir/ritonavir|Drug: Interferon Beta-1A|Drug: Hydroxychloroquine|Other: Standard of care	3100
Inpatient Treatment With Anti-Coronavirus Immunoglobulin (ITAC)	Drug: Hyperimmune immunoglobulin to SARS-CoV-2 (hIVIG)|Other: Placebo|Drug: Remdesivir	500
ACTIV-3: Therapeutics for Inpatients With COVID-19	Biological: LY3819253|Drug: Placebo|Biological: Remdesivir|Biological: VIR-7831|Biological: BRII-196/BRII-198	10000
Safety, Tolerability and Pharmacokinetics of Inhaled Nanoparticle Formulation of Remdesivir (GS-5734) and NA-831	Drug: Drug: NA-831 - 0.10 mg/kg|Drug: Placebo- 0.10 mg/kg|Drug: Drug: NA-831 - 0.20 mg/kg|Drug: Placebo- 0.20 mg/kg|Drug: Drug: GS-5734 - 1.00 mg/kg|Drug: Placebo- 1.00 mg/kg|Drug: Drug: GS-5734 - 2.00 mg/kg|Drug: Placebo- 2.00 mg/kg|Combination Product: Drugs: NA-831 (0.10 mg/kg) plus GS-5734 (1.00 mg/kg)|Combination Product: Placebo 0.10 mg + 1.00 mg/kg|Combination Product: Drugs: NA-831 (0.20 mg/kg) plus GS-5734 (2.00 mg/kg)|Combination Product: Placebo 0.20 mg + 2.00 mg/kg	45

Appendix 5. Subgroup analysis of outcomes on mortality, clinical improvement/ recovery rate, time to clinical improvement/recovery stratified according to severity

Outcomes	Pooled Relative Risk	95% CI
Mortality		
Non-severe (3 RCTs, n = 1,789)	1.12	0.65 to 1.92
Severe (3 RCTs, n = 4,464)	0.77	0.59 to 1.02
Critical (3 RCTs, n = 734)	0.94	0.50 to 1.75
Incidence of recovery		
Moderate (1 RCT, n = 596)	1.05	0.98 to 1.12
Severe (1 RCTs, n = 1062)	1.09	1.01 to 1.18
Recovery rate		
Non-severe (Not receiving O2) (2 RCTs, n= 734)	1.16	0.96 to 1.38
Severe		
Receiving O2 (1 RCT, n=435)	1.45	1.18 to 1.79
Receiving high flow O2 or non-invasive mechanical ventilation (1 RCT, n= 193)	1.09	0.76 to 1.57
Critical (Receiving mechanical ventilation) (1 RCT, n =285)	0.98	0.70 to 1.37
Time to recovery (days)		
Moderate (1 RCT, n = 596)	Mean Difference: 1	-0.46 to 2.46
Severe to Critical (2 RCTs, n =1295)	Mean Difference: -5	-7.69 to -2.31
Incidence of clinical improvement		
Moderate (1 RCT, n = 596)	1.05	0.98 to 1.13
Severe (1 RCT, n = 236)	1.13	0.91 to 1.41
Clinical Improvement Rate		
Moderate (1 RCT, n = 596)	1.15	0.99 to 1.34
Severe (2 RCTs, n = 1299)	1.28	1.13 to 1.46
Time to clinical improvement		
Moderate (1 RCT, n = 397)	Mean difference: 0	-2.03 to 2.03
Severe (2 RCTs, n = 1,299)	Mean difference: 3.02	-4.98 to -1.06

Q5. Among patients with COVID-19, should molnupiravir be used for treatment?

As of 19 February 2021

RECOMMENDATION

We suggest the use of molnupiravir within 5 days of symptom onset among non-hospitalized adult patients (18 years old and older) with mild to moderate COVID-19 infection with at least one risk factor* for progression. *(Low certainty of evidence, Weak recommendation)*

*Risk factors for progression include:
age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, serious heart conditions or diabetes mellitus

PREVIOUS RECOMMENDATION

We suggest the use of molnupiravir within 5 days of symptom onset among non-hospitalized patients with mild to moderate COVID-19 infection with at least one risk factor* for progression. *(Low certainty of evidence, Weak recommendation)*

***Risk factors for progression include:**
age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, serious heart conditions or diabetes mellitus

Previous Consensus Issues
Molnupiravir showed general net benefit, specifically for mortality. The drug should be given specifically within the given time period (within 5 days of symptom onset). There are still issues to consider about the availability and use since it is still limited (currently available under compassionate special permit issued by FDA).

WHAT'S NEW IN THIS VERSION?

Three (3) new published RCTs (Bernal 2021, Arribas 2021 and Fischer 2021) are included in this update. One (1) study is a published version of the previously included preprint (Fischer 2021).

KEY FINDINGS

Five (5) randomized controlled trials (RCTs) studied the effect of molnupiravir on the treatment of COVID-19 compared to standard of care and/or placebo. Molnupiravir significantly decreased the need for hospitalization at day 29. Subgroup analysis based on the severity showed significant reduction in mortality in non-hospitalized mild to moderate patients but did not show significant benefit among hospitalized mild to severe patients. For other critical outcomes, molnupiravir had no apparent effect on clinical improvement based on patient reported outcome measures (FLU-PRO), WHO COVID-19 ordinal scale, National Early Warning Score (NEWS2) and sustained recovery. Adverse events and serious adverse events were similar between molnupiravir and standard of care and/or placebo.

The phase 2a study had randomization issues and reporting bias. The serious risk of bias and imprecision led to the downgrading of evidence to low certainty.

INTRODUCTION

Molnupiravir is a small-molecule ribonucleoside prodrug of N-hydroxycytidine (NHC), which has activity against SARS-CoV-2 and other RNA viruses (coronaviruses, influenza virus, and encephalitic alphaviruses) in preclinical and in-vitro studies.[1,2]

After oral administration of molnupiravir, NHC circulates systemically and is phosphorylated intracellularly to NHC triphosphate. NHC triphosphate is incorporated into viral RNA by viral RNA polymerase and subsequently misdirects the viral polymerase to incorporate either guanosine or adenosine during viral replication. This leads to an accumulation of deleterious errors throughout the viral genome rendering the virus noninfectious and unable to replicate.
Consequently, molnupiravir was considered as a potential prophylactic and treatment agent against COVID-19 [1] and is considered safe and well-tolerated [3]

REVIEW METHODS

Pubmed, Cochrane Library, and Google Scholar were systematically searched using free text and MeSH terms for coronavirus infections, novel coronavirus, COVID-19, SARS-CoV-2, and molnupiravir. Preprints were sought in the following databases: medrxiv, biorxiv, and chinarxiv. Ongoing studies were also searched in *clinicaltrials.gov*, EU Clinical Trials Register, Cochrane COVID-19 study register, and other trial registries. The COVID-NMA Initiative was also searched. Any relevant cited references were manually searched

All RCTs that compared molnupiravir to standard of care or placebo in treating patients with confirmed COVID-19 infection were included. Eligible studies had at least one of the following outcomes: mortality, clinical deterioration, development of ARDS, need for mechanical ventilation (or ECMO), need for hospitalization, need for ICU admission, ICU/hospital length of stay, time to clinical improvement/recovery, radiographic improvement, virologic clearance by RT-PCR test, and adverse effects. For this review, no limits were placed on disease severity and age. Subgroup analysis by dose, disease severity, oxygen requirement, and age was planned. In order to compute for confidence intervals, we imputed 1 if a study had no event in the treatment arm.

RESULTS

Characteristics of included studies Five (5) published randomized controlled clinical trials (RCTs) (N = 1,835) investigated the effectiveness of molnupiravir among confirmed COVID-19 patients compared to placebo and/or standard of care.

Appendix 2 summarizes the characteristics of the included studies. One study is a phase 1 open-label RCT done in the UK [4], one study is a phase 2a RCT done in the US [5], three of the studies are multinational, one is a Phase2/3 trial done in 14 countries [6], one is a Phase 2/3 trial done in 15 countries [7] and one study is a Phase 3 trial done in 20 countries (Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Italy, Japan, Mexico, Philippines, Russian Federation, South Africa, Spain, Taiwan, UK, Ukraine and USA).[7] Study participants in four trials were non-hospitalized mild to moderate COVID-19 patients. [4,5,6,8]. While one study included mild to severe hospitalized patients [7]. Two of the trials included at least one risk factor for development of severe disease (age >60 years, active cancer, chronic

kidney disease, chronic obstructive pulmonary disease, obesity, serious heart conditions, diabetes mellitus or sickle cell disease).[6,8] Two studies included symptom onset within 5 days of randomization [4,8], while two studies included symptom onset within 7 days [5,6] and one study included symptom onset within 10 days [7]. One study compared molnupiravir given twice daily at 300mg, 600mg, and 800mg for 5 days to standard of care [4]. Three studies compared molnupiravir given twice daily at 200mg, 400mg, and 800mg for 5 days to placebo.[5-7] One study compared molnupiravir given 800mg twice daily for 5 days to placebo.[8] Only the results of molnupiravir given 800mg twice daily for 5 days in the phase 1 [4], phase 2a [5], phase 2/3 [6,7] studies compared to standard of care and/or placebo were pooled with the results of the Phase 3 study.[6] All of the studies administered molnupiravir orally or via nasogastric tube.

Overall Certainty of Evidence

The overall certainty of evidence was rated low due to serious risk of bias and serious imprecision on two of the critical outcomes (all-cause mortality and serious adverse events). The serious risk of bias was due to issues with randomization (imbalance in baseline characteristics of the treatment groups) in the Phase 2a study.[5] The molnupiravir group had a higher baseline prevalence of SARS-CoV-2 antibodies (30-35.3% vs. 18.2% in placebo).[5] Subgroup analysis on seronegative patients was done on the outcomes of isolation of infectious virus and time to viral RNA clearance.[5] However, it was unclear if the subgroup analysis was pre-planned. The risk of bias table is in Appendix 4. The GRADE Evidence profile is detailed in Appendix 5.

Critical outcomes

Molnupiravir showed no significant benefit in the all-cause mortality at day 29 (RR 0.51 95% CI 0.21, 1.25; I^2=48%; 4 RCTs, 1,822 participants) compared to standard of care and placebo. However, subgroup analysis on mortality based on severity showed significant benefit of molnupiravir on out-patient, mild to moderate diseases at day 29 (RR 0.23 95% CI 0.07, 0.81; I^2=0%; 3 RCTs, 1,675 participants) and no significant benefit on hospitalized, mild to severe diseases at day 29 (RR 4.35 95% CI 0.47, 39.92; 1 RCT, 147 participants).

Moreover, molnupiravir show significant reduction in the need for hospitalization at day 29 (RR 0.70 95% CI 0.50, 0.99; I^2=0%; 3 RCTs, 1,675 participants) compared to standard of care and placebo. Molnupiravir did not show significant benefit in clinical improvement by WHO COVID-19 ordinal scale (RR 0.98 95% CI 0.87, 1.10) in 1 study with 1,408 participants [8],by oxygen saturation levels (molnupiravir 800mg median 99%, range 96-100; vs. placebo median 97.5%, range 97-98), WHO COVID-19 ordinal scale (molnupiravir 800mg median 1, range 1-2; vs. placebo median 1, range 1-2), FLU-PRO (molnupiravir 800mg median 0.1, range 0-0.3; vs. placebo median 0.2, range 0-0.4), and NEWS2 (molnupiravir 800mg median 0.5, range 0-1 vs. placebo median 0, range 0-1) in 1 study with 10 participants.[4] and by sustained recovery (molnupiravir 800mg RR 1.01 95% CI 0.69-1.47, 147 participants [7].

Other non-critical outcomes

The use of molnupiravir 800mg twice daily showed no significant decrease in infectious viral isolation by day 3 (RR 0.11, 95% CI 0.01, 1.02) and by day 5 (RR 0.11, 95% CI 0.01, 1.02) compared to placebo in 1 study with 107 participants.

Molnupiravir 800mg significantly reduced the time to viral RNA clearance compared to placebo (median 14 days, 95% CI 13-14 for molnupiravir 800mg; median 15 days, 95% 15-27 for placebo; p = 0.013). Subgroup analysis for seronegative patients showed significant reduction in time to viral RNA clearance among those given molnupiravir 800mg compared to placebo (median 14 days vs. 27 days in placebo, p = 0.001).[5]

Adverse events

Pooled estimate on the risk for adverse events showed no significant difference between molnupiravir and placebo (RR 0.92, 95% CI 0.82, 1.05; I^2 = 0%). There was also no significant difference on the risk for serious adverse events (RR 1.03, 95% CI 0.76, 1.40; I^2 = 0%). The most common adverse events reported were nausea, diarrhea, cough, loss of smell/taste, headache, insomnia, increased ALT levels, thrombocytopenia, and pneumonia.[4-5,7] Serious adverse events reported were decreased oxygen saturation, acute respiratory failure, and cerebrovascular accident.[5,7]

EVIDENCE TO DECISION

A full treatment course of molnupiravir is estimated to cost Php 4,000 – 5,200.[9] The FDA granted emergency use authorization for molnupiravir as treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults 18 years old and above with a positive SARS-COV-2 diagnostic test and who are at risk for developing severe illness. [10]

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Australian Guideline on COVID-19 as of December 22, 2021 [11]	The study from the MOVe-OUT Study Group is under review by the Taskforce and a recommendation will be published in early 2022.
Infectious Diseases Society of America (IDSA) as of December 28, 2021 [12]	In ambulatory patients (>/= 18 years) with mild to moderate COVID-19 at high risk for progression to severe disease who have no other treatment options, the IDSA guideline panel suggests molnupiravir initiated within 5 days of symptom onset rather than no molnupiravir. (Conditional recommendation, Low certainty of evidence)
US-NIH Guidelines as of December 30, 2021 [13]	For nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression, the panel recommends using Molnupiravir 800 mg orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years ONLY when none of the following options: nirmatrelvir with ritonavir, sotrovimab, remdesivir can be used (CIIa)
Surviving Sepsis Campaign Guidelines on the management of COVID-19 in the ICU as of January 29, 2021 [14]	No statement on the use of molnupiravir for the treatment of COVID-19.
WHO Living Guidelines as of December 7, 2021 [15]	

RESEARCH GAPS

There are thirteen (13) ongoing RCTs on molnupiravir registered in different trial registries (Appendix 7). Five (5) studies are for treatment of mild to severe COVID-19, while one (1) study is for prophylaxis. An update of this review will be done once results of these trials are available.

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Appendix 1. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND ("Molnupiravir" [Mesh] OR molnupiravir) Filter; Publication December 2021 to January 2022	January 5, 2022 4:57PM	16	2
CENTRAL	{MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR MeSH descriptor: [COVID-19] OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND MeSH descriptor: [Molnupiravir] explode all trees OR molnupiravir	January 5, 2022 5:16 PM	24	15
COVID-NMA Initiative	Molnupiravir	January 5, 2022 5:13PM	2	2
Google Scholar	Molnupiravir AND COVID AND randomized trial Since 2021	January 5, 2022 5:25 PM	9	5
ClinicalTrials.gov	Molnupiravir,COVID-19 , COVID-19 pneumonia, investigational studies	January 5, 2022 5:35PM	2	1
Chinese Clinical Trial Registry	Molnupiravir AND COVID	January 5, 2022 5:37PM	0	0
EU Clinical Trials Register	Molnupiravir AND COVID	January 5, 2022 5:39PM	0	0
Republic of Korea - Clinical Research Information Service	Molnupiravir	January 5, 2022 5:40PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Molnupiravir	January 5, 2022 5:41 PM	4	4
CenterWatch	Molnupiravir	January 5, 2022 5:43PM	2	2
Cochrane COVID-19 study register	Molnupiravir (last month)	January 5, 2022 5:48PM	2	1
chinaxiv.org	Molnupiravir	January 5, 2022 5:50	0	0
Medrxiv.org	Molnupiravir AND COVID Filter: December 1, 2021 to January 5, 2022	January 5, 2022 5:54 PM	10	0
Biorxiv.org	Molnupiravir AND COVID Filter: December 1, 2021 to January 5, 2022	January 5, 2022 5:59PM	21	0

Appendix 2. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a phase I, open-label, dose-escalating, randomized controlled trial Khoo et al, 2021 (UK) [4]	N = 18 Outpatients aged ≥ 18 years with RT-PCR confirmed COVID-19 within 5 days of symptom onset, mild or moderate disease (no uncontrolled chronic conditions) Follow-up: 29 days	Molnupiravir 1. 300mg BID x 5 d 2. 600mg BID x 5 d 3. 800mg BID x 5 d Standard of care	Primary outcome: Dose-limiting toxicity over 7 days Secondary outcomes: • Adverse events • Serious adverse events • Oxygen saturation • Mortality (up to day 29) • Patient reported outcome measure (FLU-PRO) • WHO COVID-19 ordinal scale • National Early Warning Score (NEWS2)	Randomized, open label
Molnupiravir for Oral Treatment of COVID-19 in non-hospitalized Patients Bernal et al, 2021 MOVe-OUT study group (20 Countries)	N = 1,411 Non-hospitalized adults with laboratory confirmed COVID-19 with 5 days of symptom onset Mild to moderate disease At least one risk factor for development of severe disease: • Age >60 years; • Active cancer; • Chronic kidney disease; • Chronic obstructive pulmonary disease; • Obesity, • Diabetes mellitus Follow-up: Day 29	Molnupiravir 800mg twice daily for 5 days Placebo	Primary outcomes: • Hospitalization • Mortality • Adverse events Secondary outcome: • WHO-11 point clinical progression	Double- blind placebo-controlled trial
Newly included studies				
Phase 2/3 Trial of Molnupiravir for Treatment of Covid-19 in Nonhospitalized Adults Caraco et al. 2021 MOVe-OUT study group (14 countries)	N=150 Laboratory confirmed Covid-19 with onset of Covid-19 signs and/or symptoms up to 7 days before randomization Mild to moderate disease All mild disease with at least one risk factor for development of severe disease: • age > 60 years • active cancer • chronic kidney disease • chronic obstructive pulmonary disease • immunocompromised status/solid organ transplant recipient	Molnupiravir 1. 200mg BID x 5 d 2. 400mg BID x 5 d 3. 800mg BID x 5 d Placebo	Primary outcomes: • Hospitalization • Mortality • Adverse events Secondary outcome: WHO-11 point clinical progression	Double- blind placebo-controlled trial

	• obesity • serious heart conditions • diabetes mellitus • sickle cell disease Follow-up: Day 29			
A Phase 2a clinical trial of Molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus Fischer et al, 2021 (USA)	N = 202 Outpatients aged > 18 years with RT-PCR confirmed COVID-19 within 7 days of symptom onset Mild or moderate disease <u>Follow-up</u>: 28 days	Molnupiravir 1. 200mg BID x 5 d 2. 400mg BID x 5 d 3. 800mg BID x 5 d Placebo	<u>Primary outcomes:</u> • Time to viral RNA clearance • Adverse events <u>Secondary outcomes:</u> • Time to infectious virus elimination • Median viral RNA change from baseline • Severity/duration of self-reported symptoms SARS-CoV-2 antibody detection	Double- blind placebo-controlled trial
Randomized Trial of Molnupiravir or Placebo in Patients Hospitalized with Covid-19 Arribas J, et al (2021) MOVe-IN study group (15 countries)	N= 154 Adult patients requiring in-hospital treatment laboratory confirmed COVID-19 within ≤10 days symptom onset Mild to severe Follow-up: 29 days	Molnupiravir 1. 200mg BID x 5 d 2. 400mg BID x 5 d 3. 800mg BID x 5 d Placebo	<u>Primary outcomes</u> • Adverse events • Serious adverse events <u>Secondary outcomes:</u> • Sustained Recovery • <u>All-cause mortality</u>	Double- blind placebo-controlled trial

Appendix 3. Study Appraisal

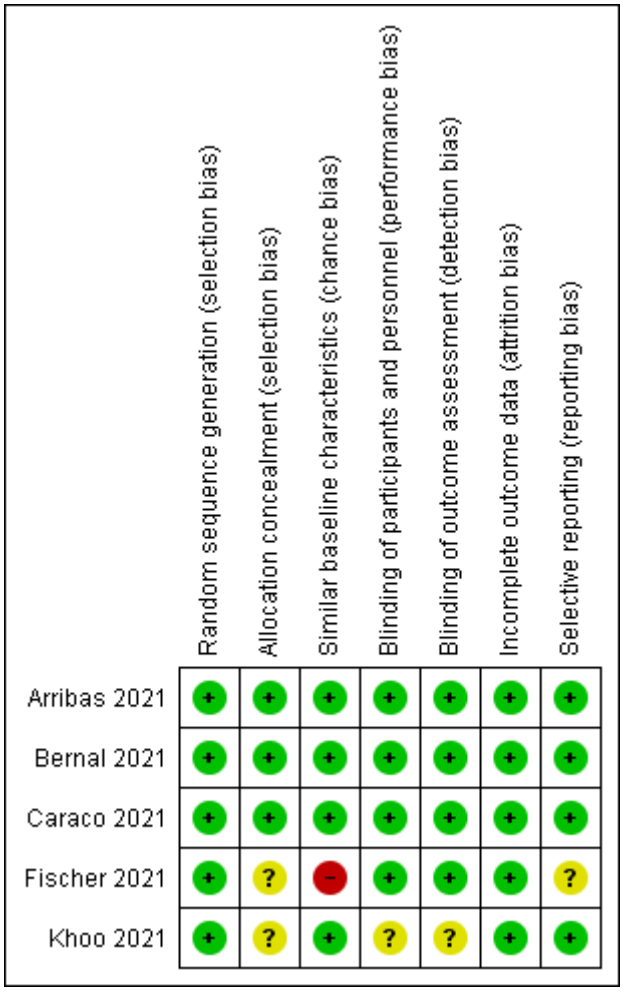

Figure 1. Risk of bias summary table

Appendix 4. GRADE Evidence Profile

Author(s): Katherine Ruth O. Relato, MD; Natasha Ann Esteban-Ipac, MD

Bibliography:

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comprison	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality, day 29												
4	Randomised trials	Serious [a]	Not serious	Not serious	Serious[b]	None	7/912 (0.8%)	14/910 (1.5%)	**RR 0.51** (0.21 to 1.25)	**8 fewer per 1,000** (from 12 fewer to 4 more)	⊕⊕◯◯ Low	CRITICAL
All-cause mortality (mild-moderate, out-patient)												
3	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	3/840 (0.4%)	13/835 (1.6%)	**RR 0.23** (0.07 to 0.81)	**12 fewer per 1,000** (from 14 fewer to 3 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
All-cause mortality (mild-severe, hospitalized)												
1	randomised trials	Not serious	Not serious	Not serious	Serious[b]	None	4/72 (5.6%)	1/75 (1.3%)	**RR 4.35** (0.47 to 39.92)	**45 more per 1,000** (from 7 fewer to 519 more)	⊕⊕⊕◯ Moderate	CRITICAL
Hospitalization												
3	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	52/840 (6.2%)	73/835 (8.7%)	**RR 0.70** (0.50 to 0.99)	**26 fewer per 1,000** (from 44 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Adverse Events												
5	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	302/917 (32.9%)	328/918 (35.7%)	**RR 0.92** (0.82 to 1.05)	**29 fewer per 1,000** (from 64 fewer to 18 more)	⊕⊕⊕◯ Moderate	CRITICAL
Serious Adverse Events												
5	Randomised trials	Serious [a]	Not serious	Not serious	Serious[b]	None	76/917 (8.3%)	74/918 (8.1%)	**RR 1.03** (0.76 to 1.40)	**2 more per 1,000** (from 19 fewer to 32 more)	⊕⊕◯◯ Low	CRITICAL

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comprison	Relative (95% CI)	Absolute (95% CI)		
Clinical Improvement												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	312/709 (44.0%)	314/699 (44.9%)	**RR 0.98** (0.87 to 1.10)	**9 fewer per 1,000** (from 58 fewer to 45 more)	⊕⊕⊕⊕ High	CRITICAL
Isolation of infectious virus by day 3												
1	Randomised trials	Very serious[a,c,d]	Not serious	Not serious	Serious[b,e]	None	1/53 (1.9%)	3/18 (16.7%)	**RR 0.11** (0.01 to 1.02)	**148 fewer per 1,000** (from 165 fewer to 3 more)	⊕◯◯◯ Very low	IMPORTANT
Isolation of infectious virus by day 5												
1	Randomised trials	Very serious[a,c,d]	Not serious	Not serious	Serious[b,e]	None	1/53 (1.9%)	3/18 (16.7%)	**RR 0.11** (0.01 to 1.02)	**148 fewer per 1,000** (from 165 fewer to 3 more)	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

[a] Dissimilar baseline characteristics of the treatment groups despite randomization. The molnupiravir group had a higher baseline prevalence of SARS-CoV-2 antibody (30-35.3% vs. 18.2% in placebo)

[b] Wide confidence interval

[c] Reporting bias

[d] Attrition bias (missing outcome data)

[e] Low sample size, does not reach optimal information size

Appendix 5. Forest Plots

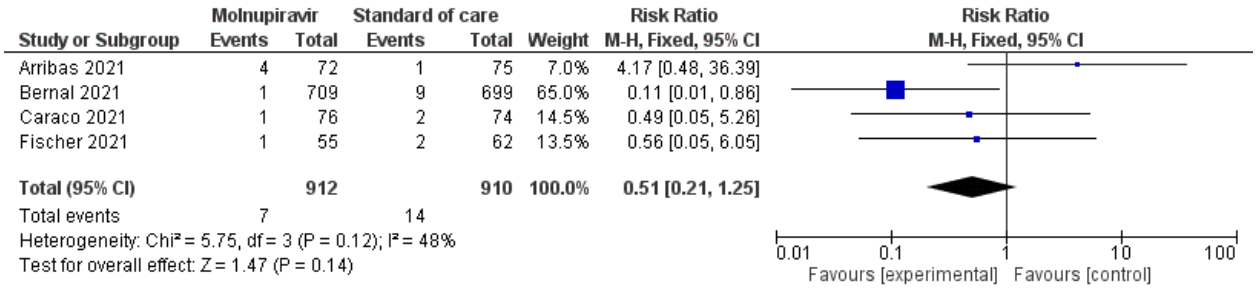

Figure 1. All-cause mortality Day 29

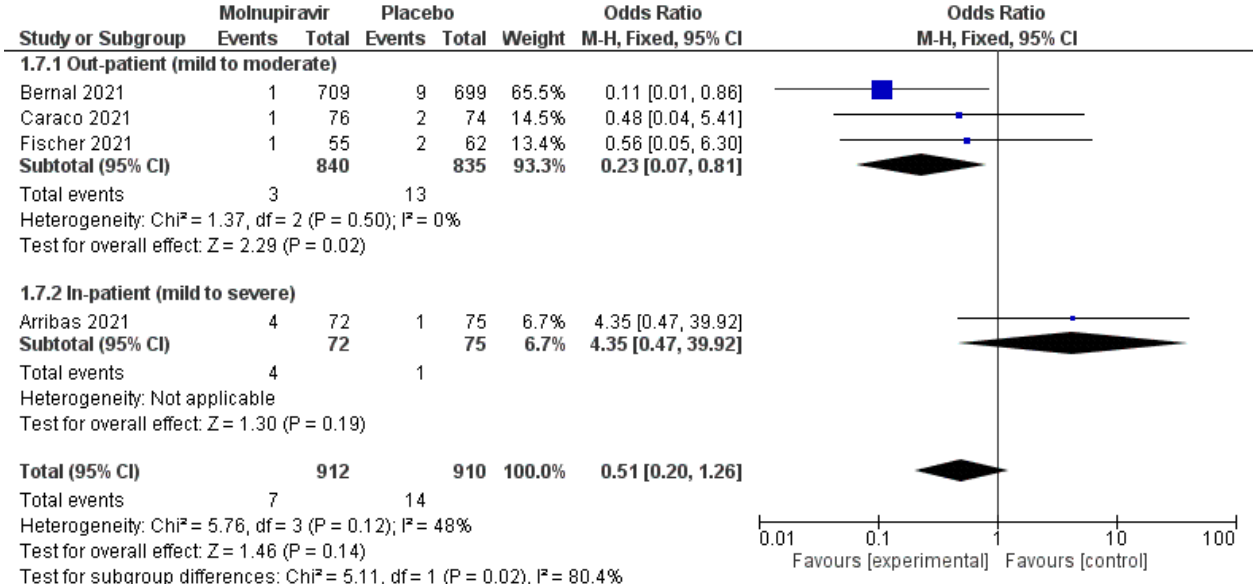

Figure 2. Subgroup analysis on mortality based on severity

Figure 3. Hospitalization

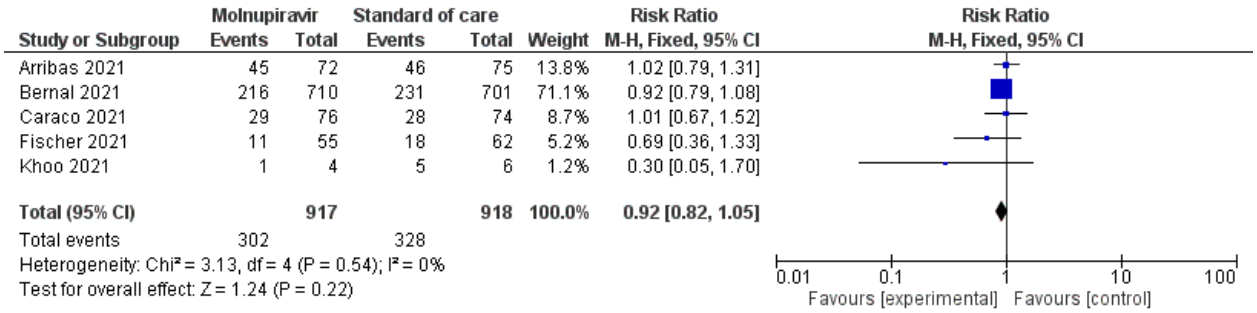

Figure 4. Adverse Events

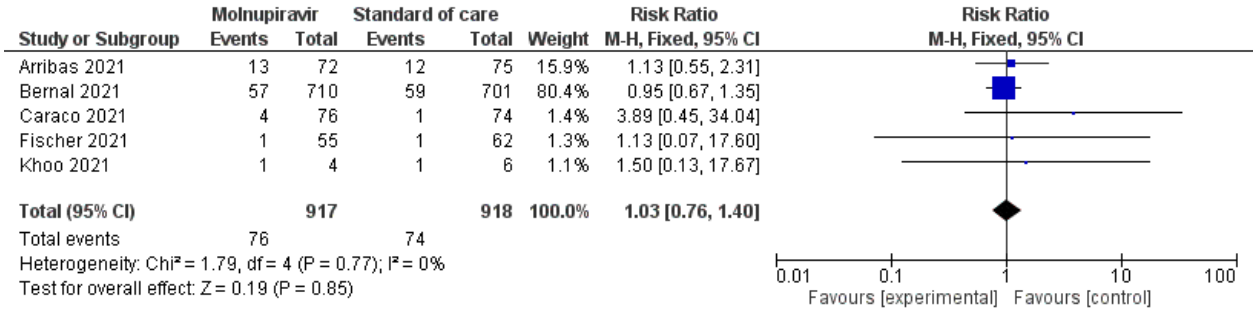

Figure 5. Serious Adverse Events

Appendix 6. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Study of MK-4482 for Prevention of Coronavirus Disease 2019 (COVID-19) in Adults (MOVe-AHEAD)	N = 1,332 Age ≥ 18 Does not have confirmed or suspected COVID-19 Lives in a household with an index case where the index case is a person with documented COVID-19 Must have: 1. A first positive SARS-CoV-2 test result from a sample collected within ≤5 days prior to randomization of the participant, and 2. At least 1 symptom attributable to COVID-19	Molnupiravir 800mg PO BID x 5 days Placebo (matching)	Primary outcomes: • Percentage of participants who develop COVID-19 (up to day 14) • Adverse events • Discontinuation rate due to adverse events Secondary outcomes: • Percentage of participants who develop COVID-19 (up to day 29) • RT-PCR positivity rate (up to day 14)	Randomized controlled trial
2. A prospective, randomized, parallel, multicentric, phase-III clinical trial of Molnupiravir 800 mg capsules and standard of care (SOC) compared to standard of care only in confirmed RT-PCR positive patients with mild COVID-19 (NOCOV)	N = 1,218 Age: 18 to 60 years old Confirmed COVID-19 infection (mild)	Molnupiravir 200mg PO BID x 5 days Standard of care (includes Ivermectin)	Primary outcome: • Hospitalization rate (up to day 14) Secondary outcomes: • Hospitalization rate (up to day 28) • Time to clinical improvement • Mortality (day 14) • RT-PCR negativity (day 10, day 15) • Adverse events	Randomized controlled trial
3. MK-4482 Ph 2/3 Study in Hospitalized Adults with COVID-19	N = 1,300 Age ≥ 18 Confirmed COVID-19 infection (mild, moderate, or severe) Initial onset of symptoms ≤ 10 days prior to randomization. At least 1 sign/symptom attributable to COVID-19	Molnupiravir x 5 days Placebo (matching)	Primary outcomes: • Time-to-sustained recovery (up to day 29) • Adverse events • Discontinuation rate due to adverse events Secondary outcomes: • Mortality (up to day 29) • Pulmonary score • WHO clinical progression scale	Randomized controlled trial
4. Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adults Participants with COVID-19	N = 1,850 Age ≥ 18 Confirmed COVID-19 infection (mild, moderate or severe) Onset of signs/symptoms attributable to COVID-19 for ≤5 days prior At least 1 characteristic or underlying medical condition associated with an increased risk of severe illness from COVID-19	Molnupiravir 200mg PO BID x 5 days 400mg PO BID x 5 days 800mg PO BID x 5 days Placebo (matching)	Primary outcomes: • Hospitalization rate (up to day 29) • 29-day mortality • Adverse events • Discontinuation rate due to adverse events Secondary outcomes: • Time to sustained resolution or improvement of symptoms • Time to progression of symptoms WHO clinical progression scale	Randomized controlled trial
5. A phase II/III clinical trial to understand the efficacy and safety of Molnupiravir 800 mg in the treatment of patients diagnosed with moderate COVID-19	Age 18 to 60 years old Confirmed COVID-19 infection (moderate)	Molnupiravir 800 mg BID Standard of care	Primary outcome: Clinical improvement at day 14	Randomized controlled trial

6. The safety of Molnupiravir and its effect on viral shedding of SARS-CoV-2 (END-COVID)	N = 96 Age ≥ 18 Confirmed COVID-19 infection Admitted in the hospital, anticipated to remain for ≥ 24 hours	Molnupiravir BID x 5 days Placebo	Virologic clearance (day 28) Adverse events Serious adverse events	Randomized controlled trial
7. Study to evaluate the efficacy and safety of Molnupiravir capsules Compare with the with Standard of Care Medications Care alone in patients who are suffering with Moderate COVID-19 disease	Age 18 to 60 years old Confirmed COVID-19 infection with presence of clinical features of dyspnea and or hypoxia, fever, cough with a risk factor for progressing to severe COVID-19	Molnupiravir 1600mg BID Standard of care	Clinical improvement at Day 14 Clinical improvement at Day 28	Open label randomized controlled trial
8. A Clinical Study to Test the Use of Capsule Molnupiravir in COVID-19 Patients with Mild Symptoms and without Lung Involvement	Age 18-60 years old Confirmed COVID-19 patient with mild COVID-19 disease without any evidence of breathlessness.	Molnupiravir 800mg q12 for 5 days Standard of care	Adverse Events Mortality Clinical Improvement Viral negative conversion	Open label randomized controlled trial
9. Clinical Trial to Evaluate the Efficacy and Safety of Molnupiravir Capsule in Treatment of Subjects with Moderate Coronavirus Disease (COVID-19)	Age 18-60 years old Confirmed COVID-19 patient Moderate COVID 19	Molnupiravir 800mg q12 for 5 days Standard of care	Clinical Improvement Day 14	Open label randomized controlled trial
10. A Prospective, Randomized, Multicenter, Open Label, Parallel Group Study To Evaluate Safety And Efficacy Of Oral Molnupiravir As Add On To Standard Of Care For Treatment Of Mild Patients With Covid-19 Disease	N = 1,218 Age 18-60 years old Confirmed COVID-19 patient Mild COVID 19	Molnupiravir 800mg q12 for 5 days Standard of care	Rate of hospitalization Day 14	Open label randomized controlled trial
11. A Clinical Study with Molnupiravir Capsules 800mg in COVID-19 Patients with Mild symptoms.	N = 1,220 Age 18-60 years old Confirmed COVID-19 patient Mild COVID 19	Molnupiravir 800mg q12 for 5 days Standard of care	Rate of hospitalization Day 14	Open label randomized controlled trial
12. MK4482-013 Phase 3 Study for Prevention of COVID-19 in Adults Spain	N = 1,340 Age 18 years and above Confirmed COVID-19 patient	Molnupiravir Placebo	Progression to severe disease day 14 Adverse event	Randomized double blind placebo controlled trial
13. Single and Multiple Dose Study of MK-4482 in Healthy Japanese Adults	N = 72 Age 20-60 years old previously healthy Confirmed COVID-19 patients	Molnupiravir 100-1600 mg BID for 11 doses Placebo	Adverse events	Randomized double blind placebo controlled trial

Q6. Should baloxavir be used in the treatment of patients with COVID-19 infection?

As of 20 May 2021

RECOMMENDATION

We suggest against the use of baloxavir as treatment for COVID-19 infection. *(Very low certainty of evidence, Weak recommendation)*

Consensus Issues

Only one small study was included in the review, which showed consistent result of no significant benefit across all the outcomes measured (i.e., need for mechanical ventilator/ ECMO, admission to ICU, hospitalization, clinical improvement at 14 days, adverse events and time to clinical improvement). It was noted that baloxavir is a repurposed drug for COVID-19 and is originally indicated for influenza. It costs Php 450 per tablet and is usually given within 48 hours from the onset of symptoms for the treatment of influenza. In terms of health equity, it was raised that since its benefit is yet to be established, resources should be allocated to more known and established drugs where the benefits are certain.

KEY FINDINGS

There was only one randomized controlled trial included in this review. Treatment with baloxavir did not lead to significant reduction in the need for invasive mechanical ventilation, admission to intensive care unit, hospitalization and clinical improvement (very low quality of evidence). There was no report of mortality in any of treatment arms. Currently, there are two ongoing clinical trials on the efficacy of baloxavir as treatment for COVID-19.

INTRODUCTION

Baloxavir is an oral antiviral agent that inhibits the initiation of viral mRNA which is an early step in virus replication [1-3]. Baloxavir marboxil is the prodrug and baloxavir acid is the active metabolite that inhibits cap-dependent endonuclease [4]. SARS-CoV-2 being an RNA virus, baloxavir is considered to be potentially effective against SARS-CoV-2 by blocking its RNA synthesis. Moreover, studies show that baloxavir has antiviral activity against SARS-CoV-2 in vitro [5]

REVIEW METHODS

We performed a comprehensive systematic search of related literature from Medline, CENTRAL, Love Platform App and COVID-19 NMA database. We also searched for ongoing clinical trials using ClinicalTrial.gov, Clinicaltrialsregister.eu and Chinese Clinical Trial Register. Freehand search using Google was also done to check for other sources of information. Search was conducted using the following search terms: “COVID-19,” “SARS-CoV-2” and “Baloxavir.” There was no limit as to the date, language and country of publication.

Eligible articles were evaluated using the following criteria:

Population	COVID-19 patients any age, co-morbidities and severity
Intervention/ Exposure	Baloxavir or Baloxavir Marboxil
Comparison	Usual standard of care, placebo, any active control
Outcomes	Mortality, clinical improvement, need for mechanical ventilations and adverse effects
Methodological filter	randomized controlled trials (RCT), observational clinical studies, systematic review and meta-analysis available

RESULTS

Thirty-one articles were initially screened but only one article matched our criteria. We found two ongoing clinical trials in the searched trial registers. Only one study was included in this review. The study of Lou et al. [5] is an exploratory randomized controlled open label trial. It enrolled 30 patients who were randomized equally into one of three arms. There was no limit in terms of severity in the inclusion criteria, however patients in all of the treatment arms had a National Early Warning Score (NEWS) 2 score of (4 [IQR 4,5]) or low to medium risk. The control group (n=10) was given the institution's existing antiviral treatment of lopinavir/ritonavir (400mg/100 mg, bid, per orem) or darunavir/cobicistat (800 mg/150 mg, qd, per orem) and arbidol (200 mg, tid, per orem.). All of them were used in combination with interferon-α inhalation (100,000 iu, tid or qid). The baloxavir group (n=10) was given this control treatment plus baloxavir marboxil at a dose of 80 mg once a day per orem on Day 1 and Day 4; the patients still positive virologically could be given again on Day 7. The favipiravir group (n=10) was given the control treatment plus favipiravir, the latter administered as a first dose of 1600 mg or 2200mg orally, followed by 600 mg thrice daily, with duration of administration not exceeding 14 days. In this study, the allocation concealment was unclear. It was unblinded, and the primary outcome of clinical improvement (with the use of the WHO score), as well as report of adverse events, involved clinical judgement that could be influenced by the knowledge of the intervention assignment. There was adequate follow up and there was no report of participant cross-over. There were imbalances among the treatment arms in terms of baseline characteristics: mean age (46.6 [SD 14.1] in control, 53.5 [12.5]) in baloxavir, 58 [8.1] in favipiravir), days from symptoms onset to randomization (13.6 [4.6] in control, 12.7 [SD 3.5] in baloxavir, 8.5 [3.7] in favipiravir) CRP (2.1 [0.32, 79.9] in control, 14.1 [IQR 0.65, 50.9] in baloxavir, 27.3 [0.32, 79.9] in favipiravir and viral load (Ct value) (29.6 [IQR 19.8, 37.1] in control, 28.2 [22.1, 36.8] in baloxavir and 25.4 [19.8, 36] in favipiravir). Time-Dependent Cox proportional hazards model was used to investigate the effects of these covariates and the results showed no association between these covariates and time to viral negativity. There was no report of mortality in any of the treatment arms. Each of the intervention groups was compared against the control group. The baloxavir group was not compared against the favipiravir group in this study. Baloxavir did not lead to significant reduction in the need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (RR 3.0; [95%CI 0.14, 65.9]), admission to ICU (RR 3; [95% CI 0.14, 65.9]), hospitalization (RR 0.67; [95% CI 0.27,1.66]) and clinical improvement at 14 days (RR 1.20; [95% CI 0.54, 2.67]).

RECOMMENDATIONS FROM OTHER GROUPS

There was no mention on the use of baloxavir marboxil as treatment for covid-19 in the Infectious Diseases Society of America (IDSA) treatment guidelines (April 14,

2021), World Health Organization (WHO) living guideline (March 31, 2021) and US-NIH treatment guideline (Feb 16, 2021). The Australian Living Clinical Practice Guidelines recommends not to use Baloxavir Marboxil as treatment for COVID-19 outside randomized trials with appropriate ethical approval (May 20, 2021).

RESEARCH GAPS

Currently there are two ongoing studies on the efficacy of baloxavir as treatment for COVID-19 (Appendix 3). More randomized controlled trials are needed to examine the use of baloxavir as treatment for COVID-19.

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Appendix 1. Characteristics of Included Studies

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
Lou et al, 2020 [5]	Confirmed COVID-19 patients who are still positive for SARS-CoV-2, they did not restrict inclusion as to severity but patients included had a mean NEWS2 score of 4 or low to medium risk.	The baloxavir group: control treatment plus baloxavir marboxil 80 mg once a day per orem on Day 1 and Day 4; if patients are still positive, they could be given again on Day 7 The favipiravir group: control treatment plus favipiravir administered as a first dose of 1600 mg or 2200mg orally, followed by 600 mg thrice day, with duration of administration not exceeding 14 days.	lopinavir/ritonavir (400mg/100 mg, bid, per orem) or darunavir/cobicistat (800 mg/150 mg, qd, per orem) and arbidol (200 mg, tid, per orem.)	Primary:1) percentage of patients with viral negative results at 14 days 2) time from randomization to clinical improvement of two points or live discharge Secondary: 1) percentage of patients with viral negative results at 7 days, 2) incidence of mechanical ventilation by day 14, ICU admission by day 14 and all cause mortality by day 14 Adverse events.	RCT

Appendix 2. GRADE Summary of Findings Table

Author(s): Faltado, Antonio Jr, Anna Angelica Macalalad-Josue
Question: Baloxavir compared to Standard of Care for COVID-19
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baloxavir	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	serious [a,b]	not serious	not serious	very serious [c]	none	No mortality reported in the treatment arms				⨁◯◯◯ VERY LOW	CRITICAL
Need for Mechanical Ventilator/ ECMO												
1	randomised trials	serious [a,b]	not serious	not serious	very serious [c,d]	none	1/10 (10.0%)	0/10 (0.0%)	**RR 3.00** (0.14 to 65.90)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Admission to ICU												
1	randomised trials	serious [a,b]	not serious	not serious	very serious [c,d]	none	1/10 (10.0%)	0/10 (0.0%)	**RR 3.00** (0.14 to 65.90)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Hospitalization												
1	randomised trials	serious [a,b]	not serious	not serious	very serious [c,d]	none	4/10 (40.0%)	6/10 (60.0%)	**RR 0.67** (0.27 to 1.66)	**198 fewer per 1,000** (from 438 fewer to 396 more)	⨁◯◯◯ VERY LOW	CRITICAL
Clinical Improvement at 14 days												
1	randomised trials	serious [a,b]	not serious	not serious	very serious [c,d]	none	6/10 (60.0%)	5/10 (50.0%)	**RR 1.20** (0.54 to 2.67)	**100 more per 1,000** (from 230 fewer to 835 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse Events (Respiratory Failure or ARDS)												
1	randomised trials	serious [a,b]	not serious	not serious	very serious [c,d]	none	6/10 (60.0%)	4/10 (40.0%)	**RR 1.50** (0.60 to 3.74)	**200 more per 1,000** (from 160 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Time to Clinical Improvement (2 points decrease from baseline score or hospital discharge)												
1	randomised trials	serious [a,b]	not serious	not serious	very serious [c,d]	none	10	10	-	SMD **0.56 SD higher** (0.34 lower to 1.45 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

Explanations

a. unclear allocation concealment
b. Unblinded
c. small sample size
d. wide confidence interval

Appendix 3. Characteristics of Ongoing Clinical Trials

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
ChiCTR2000029548 Randomized, open-label, controlled trial for evaluating the efficacy and safety of Baloxavir marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia patients	Randomized Controlled Trial, parallel assignment	China	COVID-19	BaloxavirMarboxil vs Favipiravir vs Lopinavir-Ritonavir	Primary Outcome: All-cause mortality, Time to viral negativity, Time to clinical improvement, incidence of mechanical ventilation, incidence of ICU admission.	unknown
ChiCTR2000029544 A randomized controlled trial for the efficacy and safety of Baloxavir Marboxil, Favipiravir tablets in novel coronavirus pneumonia (COVID-19) patients who are still positive on virus detection under the current antiviral therapy	Randomized Controlled Trial, parallel assignment	China	COVID-19	BaloxavirMarboxil vs Favipiravir vs Control group	Primary Outcome: Clinical Improvement Secondary Outcome: Patient status upgraded to ICU level, Oxygen supplementation, days with fever, days to discharge, SAEs	unknown

Q7. Should oseltamivir be used in the treatment of patients with COVID-19 infection?

As of 22 May 2021

RECOMMENDATION

We recommend against the use of oseltamivir as treatment for patients with COVID-19 infection. *(Very low certainty of evidence, Strong recommendation)*

Consensus Issues
The panel made a strong recommendation against the use of oseltamivir noting that the mortality rate among patients given the drug is higher compared to those given standard of care (i.e., 27% vs 6%). Likewise, results showed that the progression to severe disease is five times more likely among patients taking oseltamivir.

KEY FINDINGS

Based on the five retrospective cohort studies included in this review, oseltamivir was associated with increased risk of mortality ((Odds Ratio (OR), 4.20; [95%CI 4.03, 4.38], very low quality of evidence). Moreover, it was associated with risk of disease progression (OR 5.22; [95% CI, 2.00, 13.02], low quality of evidence) as well as longer time to viral clearance (standard mean difference (SMD) of 1.65 days longer (95% CI 1.27, to 2.03, low quality of evidence). Currently, there are five ongoing clinical trials on the efficacy of oseltamivir as treatment for COVID-19.

INTRODUCTION

Oseltamivir, a neuraminidase inhibitor, has been effective in treating influenza A and influenza B [1]. It has been hypothesized to inhibit SARS-CoV-2 proteases involved in the degradation of polyproteins that control viral replication [2]. However, an in-vitro study failed to show effectivity of oseltamivir against SARS-CoV-2 [3] while several other observational studies have conflicting results in terms of mortality benefits of oseltamivir in COVID-19 [4-6].

REVIEW METHODS

We performed a comprehensive systematic search of related literature from Medline, CENTRAL, Love Platform App and the COVID-19 NMA database. We also searched for preprint articles on medXriv, and searched for ongoing clinical trials using ClinicalTrial.gov, Clinicaltrialsregister.eu and Chinese Clinical Trial Register. Freehand search using Google was also done to check for other sources of information. Search was conducted using the following search terms: “COVID-19,” “SARS-CoV-2” and “Oseltamivir.” There was no limit with regard to the date, language and country of publication.

Eligible articles were evaluated using the following criteria:

Population	COVID-19 patients any age, co-morbidities and severity
Intervention/ Exposure	Oseltamivir
Comparison	Usual standard of care, placebo, any active control
Outcomes	Mortality, clinical improvement, progression free survival, need for mechanical ventilation and adverse effects
Methodological filter	randomized controlled trials (RCT), observational clinical studies, systematic review and meta-analysis available

RESULTS

We found no randomized controlled trials in our search. We obtained a total of five retrospective cohort studies: two from the search on Medline, CENTRAL, Love Platform App and COVID-19 NMA database, and three preprint articles on medXriv. We also found five ongoing clinical trials from our search of trial registries.

A total of five retrospective cohort studies with a total of 130,867 patients were included in this review, the pertinent details of which are shown in Appendix 1. The studies of Mancilla-Galindo et al., Chen et al. and Liu et al. were pre-prints and have not been peer reviewed. All of the studies enrolled confirmed COVID-19 patients by RT-PCR. The dose and duration of oseltamivir were not reported in all of the studies. The studies used electronic medical records and nationwide COVID-19 databases to collect data. There was no limit in terms of severity, although majority of patients included in the study of Chen et al. had mild to moderate COVID-19. All of the studies used statistical adjustments to reduce potential confounding and selection bias. The study of Mancilla-Galindo et al. used propensity score matching. All of the studies had adequate follow up. In this review, we found that oseltamivir use was associated with increased risk of mortality (Odds Ratio (OR), 4.20; [95% Confidence interval (CI) 4.03, 4.38], very low quality of evidence). Moreover, its use was associated with disease progression (OR, 5.22; [95% CI, 2.00, 13.02], low quality of evidence). In terms of time to viral clearance, Chen et al. showed that oseltamivir use had a standard mean difference (SMD) of 1.65 days longer (95% CI 1.27, 2.03) than the control group (low quality of evidence). However, Hu et al. reported that patients on oseltamivir had a lower risk of prolonged viral shedding (≥20 days) (Hazards Ratio (HR), 0.416; 95% CI, 0.279 to 0.620) compared to the control group (low quality of evidence).

RECOMMENDATIONS FROM OTHER GROUPS

There was no mention on the use of oseltamivir as treatment for COVID-19 in the Infectious Diseases Society of America (IDSA) treatment guidelines (April 14, 2021), World Health Organization (WHO) living guideline (March 31, 2021), US-NIH treatment guideline (Feb. 16, 2021) and Australian Living Clinical Practice Guidelines (May 20, 2021).

RESEARCH GAPS

Currently, there are five ongoing clinical trials on the use of oseltamivir as treatment for COVID-19.

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Appendix 1. Characteristics of Included Studies

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
Mancilla-Galido et al 2021	COVID-19 confirmed patients by RT-PCR Any severity (n=122,557)	Oseltamivir or Amantadine or lopinavir/ritonavir or rimantadine or zanamivir or antibiotic only or antiviral+ antibiotic Doses/duration unknown	No Antiviral/Antibiotic/standard of care	All-Cause Mortality	Real World multicenter, Retrospective cohort study
Lee et al 2020	COVID-19 confirmed patients by RT-PCR Any severity (n=7339)	Lopinavir/Ritonavir or HCQ or antibiotics ribavirin, oseltamivir or interferon Doses/duration unknown	Standard of Care	Mortality, Severe COVID-19	Retrospective Cohort study
Liu et al 2021	COVID-19 confirmed patients by RT-PCR Any severity (n=504)	Lopinavir/ritonavir or Arbidol or Oseltamivir	Standard of Care	Primary: In hospital death Secondary: Change in lesion size on CT scan	Retrospective Cohort
Chen et al 2020	COVID-19 confirmed patients by RT-PCR inpatient, any severity, even asymptomatic (n=284)	Oseltamivir or Arbidol or Lopinavir/Ritonavir/ Chloroquine or immunoglobulin or Corticosteroids or antibiotics plus standard of care	Standard of Care	Time to Viral RNA Clearance	Retrospective Cohort
Hu et al	COVID-19 confirmed patients by RT-PCR inpatient, any severity (n=183)	Arbidol or Oseltamivir or Lopinavir/Ritonavir or α interferon or Ribavirin plus standard of care	Standard of Care	Viral Shedding	Retrospective Cohort

Appendix 2. GRADE Summary of Findings Table

Author(s): Antonio L. Faltado Jr., Anna Angelica Macalalad-Josue
Question: Oseltamivir compared to Standard of Care for COVID-19
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oseltamivir	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	observational studies	not serious	serious [a]	not serious	not serious	none	2323/8499 (27.3%)	7648/121901 (6.3%)	**OR 4.20** (4.03 to 4.38)	**157 more per 1,000** (from 150 more to 164 more)	⨁◯◯◯ VERY LOW	CRITICAL
Progression to Severe Disease												
1	observational studies	not serious	not serious	not serious	not serious	none	8/19 (42.1%)	919/7520 (12.2%)	**OR 5.22** (2.00 to 13.02)	**299 more per 1,000** (from 96 more to 522 more)	⨁⨁◯◯ LOW	CRITICAL
Time to Viral Clearance (in days)												
1	observational studies	not serious	not serious	not serious	not serious	none	35	245	-	SMD **1.65 SD higher** (1.27 higher to 2.03 higher)	⨁⨁◯◯ LOW	IMPORTANT
Prolonged Viral Shedding >/=20 days												
1	observational studies	not serious	not serious	not serious	not serious	none	76/117 (65.0%)	21/66 (31.8%)	**HR 0.416** (0.279 to 0.620)	**171 fewer per 1,000** (from 217 fewer to 107 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **SMD:** Standardised mean difference; **HR:** Hazard Ratio

Explanations

a. inconsistent results across studies I2=92%

Appendix 3. Characteristics of Ongoing Clinical Trials

Trial ID	Title	Status	Population	Intervention	Comparator	Outcome
EUCTR2020-001610-38-DK	Irbesartan and Oseltamivir treatment of COVID-19 infection. - Covid-19 protection trial	Authorised	COVID 19	Irbesartan, Oseltamivir	Placebo	Preventing patients with Covid-19 infection treated at home in hospitalizing for this disease.
NCT04255017	An Open, Prospective/Retrospective, Randomized Controlled Cohort Study to Compare the Efficacy of Three Antiviral Drugs(Abidol Hydrochloride, Oseltamivir and Lopinavir/Ritonavir) in the Treatment of 2019-nCoV Pneumonia.	Recruiting	COVID 19	Abidol hydrochloride, Oseltamivir, Lopinavir/ritonavir	supportive care	Time for lung recovery;Rate of disease remission
NCT04558463	The Effectivity and Safety of Favipiravir Compared to Oseltamivir as Adjuvant Therapy for COVID-19: An Open Label Trial	Recruiting	Covid19	Favipravir	Oseltamivir	Clinical radiologic changes;Percentage of RT-PCR test convertion
IRCT20201202049566N1	Evaluation of treatment strategy Included : hydroxychloroquine ,naproxen and oseltamivir for outpatient patients with Covid 19	Not Recruiting	COVID 19	naproxen 500 mg twice daily, hydroxychloroquine 200 mg twice daily, and oseltamivir 75 mg twice daily for 5 days .	naproxen 500 mg twice daily, hydroxychloroquine 200 mg twice daily for 5 days	symptoms indicative of cough, shortness of breath, fever
NCT04303299	A 6 Week Prospective, Open Label, Randomized, in Multicenter Study of, Oseltamivir Plus Hydroxychloroquine Versus Lopipinavir/ Ritonavir Plus Oseltamivir Versus Darunavir/ Ritonavir Plus Oseltamivir Plus Hydroxychloroquine in Mild COVID-19 AND Lopipinavir/ Ritonavir Plus Oseltamivir Versus Favipiravir Plus Lopipinavir / Ritonavir Versus Darunavir/ Ritonavir Plus Oseltamivir Plus Hydroxychloroquine Versus Favipiravir Plus Darunavir and Ritonavir Plus Hydroxychloroquine in Moderate to Critically Ill COVID-19	Recruiting	COVID 19	Oseltamivir and other antiviral drugs	conventional quarantine	SARS-CoV-2 eradication time

Q8. Should lopinavir/ritonavir be used in the treatment of patients with COVID-19 infection?

As of 07 April 2021

RECOMMENDATION

We recommend against the use of lopinavir/ritonavir as treatment for COVID-19 infection. *(Moderate certainty of evidence, Strong recommendation)*

Consensus Issues
No issues were raised during the panel meeting.

KEY FINDINGS

Based on 5 RCTs enrolling both suspected and confirmed COVID-19 patients, lopinavir/ritonavir combination did not significantly affect clinical improvement, all-cause mortality, viral negative conversion, need for mechanical ventilation, or WHO progression score level 7 or higher, when compared to standard of care. No difference in adverse events were also seen between lopinavir/ritonavir and control groups. The overall quality of evidence ranged from low to high across different outcomes.

INTRODUCTION

Lopinavir is a known HIV-1 aspartate protease inhibitor with inhibitory activity against SARS-CoV-1. Ritonavir is combined with lopinavir to increase its plasma half-life through the inhibition of cytochrome p450 [1]. In vitro studies have shown that lopinavir reduced viral replication of MERS-CoV in Vero cells. When combined with ribavirin, LPV/r was also associated with fewer adverse events among patients with SARS-CoV-1 [2]. These in vitro tests and clinical trials were the basis for considering LPV/r for the treatment of COVID-19.

REVIEW METHODS

We searched for existing randomized controlled trials and living systematic reviews, including COVID-19 databases and CPGs (NICE, CENTRAL), publications (MEDLINE, Google Scholars, Ovid, Herdin), including pre-print (Medrxiv, Biorxiv, Chinaxiv) and trial registries (WHO, ICTRN, ChiCTR, EU). We used the following keywords: “lopinavir”, “ritonavir”, “Aspartate protease inhibitor”,” protease inhibitor”, “HIV protease inhibitors”, “cytochrome P-450 CYP3A inhibitors”, and “therapy”, RCT, systematic reviews and COVID-19 related terms in the search strategy, without language restrictions [last search April 02, 2021]. Reference lists of selected articles were reviewed for inclusion. Two reviewers independently performed title and abstract screening, identification of eligible full-text articles, and critical appraisal.

RESULTS

Outcomes

Five RCTs studied the efficacy of lopinavir/ritonavir with or without standard of care (SOC) versus SOC alone, in 8,354 hospitalized mild to severe COVID-19 adult patients: 1 study included mild-to-moderate cases [7]; 3 involved mild-to-critical and 1 studied severe cases only [4,5,8,16]. Standard of care in the 5 studies consisted of either oxygen supplementation, invasive or noninvasive ventilation, antibiotic therapy, vasopressor support, renal-replacement therapy, and/or extracorporeal membrane oxygenation (ECMO) when deemed necessary. The 3 multinational trials also studied

other repurposed drugs including remdesivir, hydroxychloroquine, and interferon. The existing standard of care in the country was adapted in these trials [5,8] (Appendix 1).

The regimen for oral lopinavir-ritonavir (400 mg and 100 mg) for all studies except one [7] was twice daily for at least 10 days or until hospital discharge, initiation of mechanical ventilation, or death. One study did not mention the dosage, frequency and duration of both intervention and control [7].

The studies reported the following outcomes: all-cause mortality (or at day 28), clinical improvement, viral negative titers at day 7, WHO progression score (level 7 or above), need for mechanical ventilation, adverse events and serious adverse events. The subgroups were based on severity (mild to moderate, mild to critical and severe) and ventilation (non-ventilated and ventilated).

Methodological Quality

The overall quality of evidence ranged from low to high across different outcomes (Appendix 2). downgrading occurred due to concerns related to risk of bias or study design, inconsistency, and/or imprecision issues. Risk of bias issues included unblinding of caregivers or recruiting staff [5,7,8]. There were also biases that arose from deviations in intervention [4,7]. Some patients in the LPV/r group did not complete their 14-day course due to gastrointestinal adverse events while another study had an imbalance in the corticosteroid administration. Outcome measures were observer-reported which may tend toward benefit or tend toward harm [4,5,8]. There was a large effect due to the three big multinational, multicenter studies which made the synthesis more precise.

Outcomes

No significant benefit was seen with lopinavir/ritonavir in all the seven primary outcomes examined (Appendix 2).

In terms of all-cause mortality, all five RCTs consistently showed no significant advantage of lopinavir/ritonavir over control (RR 1.02, 95%CI 0.93 – 1.12, I2=0%, 5 RCTs). Subgroup analysis based on severity showed mortality benefit in studies enrolling mild to critical cases (RR 1.03 [95% CI 0.93, 1.13], 3 studies, I2=0%) [5,8,16] and severe cases (RR 0.77 [95% CI 0.45, 1.30], 1 study) [4]. Refer to Appendix 1 Figures 2 and 3 for the relevant forest plots.

Lopinavir/ritonavir showed no significant effect on virologic clearance at day 5-8 [4,5,7] and need for mechanical ventilation at day 28 [8], a finding which was consistent across studies [Appendix 1. Figures 6,7]. The remaining outcomes, including clinical improvement, WHO progression score, adverse effects and serious adverse effects, likewise showed no evidence effect for lopinavir/ritonavir but with substantial heterogeneity (I2 = 55%, 73%, 57% and 77%, respectively). Subgroup analysis did not improve the degree of heterogeneity among the outcomes [Appendix 1. Figures 4,5,8,9]. Only one study measured the improvement of lung CT scan findings by day 14 with no significant difference between lopinavir/ritonavir and local standard of care (RR 0.81 [95%CI 0.62,1.05]. The study had a low quality of evidence with small sample size, unblinded treatment and deviations in interventions [7].

The results of the RECOVERY trial on 28-day mortality had a risk ratio of 1.05 (95%CI, 0.92 -1.19, p= 0.49). This prompted the Solidarity Data Safety Monitoring Board

(DSMB) to review their data. On June 23, 2020, Solidarity Trial's International Steering Committee advised to stop the lopinavir/ritonavir arm due to futility [8].

Based on three RCTs with low to moderate quality, the lopinavir/ritonavir and control groups did not differ in terms of both adverse events (RR 1.10 [95%CI 0.82, 1.48] I2 =0.0%) and serious adverse events (SAE) (RR 0.96 [95% CI 0.46, 2.02] I2 =0.77%) [4,5,7]. However, in one moderate-quality RCT (DISCOVERY Trial), a significantly higher number of patients in the LPV/r group experienced at least one SAE compared to the control group (76/144 or 52.8% vs 57/148 or 38.5%, p= 0.02), which prompted termination of the trial on June 2020 [5].

Common adverse events observed with LPV/r were nausea, vomiting, diarrhea, QTc prolongation and hepatotoxicity [12]. For SAEs, acute respiratory failure, acute kidney injury, acute respiratory distress syndrome, arrhythmia, pulmonary embolism and sepsis were reported [5].

RECOMMENDATIONS FROM OTHER GROUPS

The World Health Organization, US National Institute of Health (NIH) COVID-19 Treatment Guidelines Panel for Health, and the Australian National COVID-19 Clinical Evidence Taskforce (ANCCETF) all recommend against the use of lopinavir/ritonavir and other HIV protease inhibitors for the treatment of hospitalized and non-hospitalized COVID-19 patients, regardless of disease severity [9,12,14]. The Australian NCCETF further qualifies that its use may still be considered in the context of randomized clinical trials that are subject to ethical approval and as part of combined therapies that include lopinavir/ritonavir.

The Philippine Society of Microbiology and Infectious Diseases (July 2020) does not recommend lopinavir/ritonavir as a monotherapy, or in combination with HCQ or other immunomodulators, for treating hospitalized patients with probable or confirmed COVID-19 infection (strong recommendation, moderate quality of evidence) [15].

RESEARCH GAPS

There are 28 ongoing trials that included lopinavir/ritonavir, tested singly and/or in combination with other therapeutic agents (Appendix 3). About a third of them included hydroxychloroquine. The other drugs include remdesivir, oseltamivir, interferon, nitaxozamide, favipiravir, telmisartan, Xiyanping, ASCO9, arbidol, Chinese traditional medicines, and low dose radiotherapy. One study is exploring its use among COVID-19 patients with cancer.

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Appendix 1: Characteristics of Included Studies

Author, Year	Design	N	Population	Intervention	Comparator	Outcomes
Cao, 2020 May	RCT, open label	199 (I=99, C = 100)	hospitalized confirmed COVID19 with O2sat < 94%; median age 58 yrs (IIQR 49 TO 68)	Lopinavir 400 mg /Ritonavir 100 mg BID x 14 da;ys with Standard of Care (SOC	SOC alone	Primary : time to clinical improvement (improve at least 2 points from seven-category scale) or discharge from hospitallization; Mortality , duration of mech vent, duration of hospitalization, time to death; viral RNA detection over time, adverse events, serious adverse events
Yueping Li, 2020	RCT exploratory	86 (I = 34, C = 17) arbidol = 35	hospitalized confirmed mild to moderate COVID19 ages 19 to 79	Lopinavir/Ritonavir; Arbidol (dose, duration not mentioned)	SOC alone	Mean time and rate to negative conversion of SARS-CoV2 nucleic acid, Conversion rate from moderate to critical, rate of improvement of cough, chest CT, adverse events, severe adverse events
Pan, H, 2020 Oct (WHO Solidarity)	RCT, open laelled	11,266 (I = 1399, C = 1372) from 1411 and 1380 (excluded no consent but did ITT)	hospitalized confirmed COVID-19 patietns ages 18 and above, not known to receive any drug,	Lopinavir 400 mg /ritonavir 100 mg BID x 14 days	SOC	Mortality, initiation of ventilation,, hospitalization duration,
Ader, F2021 (DisCoVeRy trial)	RCT open-label, adaptive	583 (I = 144; C = 148)	18 y/o and older; hospitalized COVID-19 requiring oxygen and/or ventilatory support	lopinavir 400 mg/ ritonavir 100 mg BID x 14 days + SOC, SOC+ L/R + IFN beta; SOC + HCQ; SOC + remdesivir	SOC	Primary : clinical status at day 15 using WHO ordinal scale; Secondary : clinical status by day 29, time to hospital discharge, 29-day mortality, ventilator-free days until day 29, viral titers; safety analysis; adverse effects
Horby, 2020 (RECOVERY)	RCT, open-lae, platform trial	7825 (I = 1616, C = 3424) 2785 to other treatment	ages 18 yrs and older; clinically suspected or lab confirmed COVID19;	Lopinavir 400 mg /ritonavir 100 mg BID x 10 days or until discharge	SOC	Primary: 28day all-cause mortality; Secondary : time to discharge, initiation of mech vent, duration and receipt of ventilation, serious adverse reactions,

Appendix 2: GRADE Evidence Profile

Author(s): Eubanas, Bautista
Question: Lopinavir/ritonavir compared to Standard of Care for Covid-19
Setting: Hospitalized Confirmed COVID19 cases with mild to severe to critical

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lopinavir/ritonavir	SOC	Relative (95% CI)	Absolute (95% CI)		
All-Cause Mortality at day 28												
5	Randomised trials	Not serious	Not serious	Not serious	Not serious	Strong association	555/3293 (16.9%)	950/5061 (18.8%)	RR 1.02 (0.93 to 1.12)	4 more per 1,000 (from 13 fewer to 23 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical Recovery												
2	Randomised trials	Serious [a]	Serious [b]	Not serious	Not serious	None	1191/1715 (69.4%)	2452/3524 (69.6%)	RR 1.03 (0.92 to 1.15)	21 more per 1,000 (from 56 fewer to 104 more)	⊕⊕◯◯ LOW	CRITICAL
WHO progression score level 7 or above at Day 28 (mech vent +/- organ support (ECMO, vasopressors) or Death (follow up: range 7 days to 29 days)												
3	Randomised trials	Not serious	Not serious	Not serious	Very serious [c]	None	41/283 (14.5%)	48/269 (17.8%)	RR 0.79 (0.28 to 2.24)	37 fewer per 1,000 (from 128 fewer to 221 more)	⊕⊕◯◯ LOW	CRITICAL
Virologic clearance (viral negative conversion Day 7) by RT-PCR (follow up: range 5 days to 8 days)												
3	Randomised trials	Serious [d]	Not serious	Not serious	Serious [e]	None	85/173 (49.1%)	84/167 (50.3%)	RR 0.97 (0.80 to 1.18)	15 fewer per 1,000 (from 101 fewer to 91 more)	⊕⊕◯◯ LOW	CRITICAL
Mechanical Ventilation												
4	Randomised trials	Serious	Not serious	Not serious	Not serious	None	307/2807 (10.9%)	430/4387 (9.8%)	RR 1.10 (0.95 to 1.26)	10 more per 1,000 (from 5 fewer to 25 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse Effects (follow up: range 14 days to 28 days)												
3	Randomised trials	Serious [a]	Not serious	Not serious	Serious [f]	None	177/277 (63.9%)	154/265 (58.1%)	RR 1.10 (0.82 to 1.48)	58 more per 1,000 (from 105 fewer to 279 more)	⊕⊕◯◯ LOW	CRITICAL

Serious Adverse Events (follow up: range 21 days to 29 days)												
3	Randomised trials	Serious [a]	Serious [g]	Not serious	Very serious [h]	None	96/277 (34.7%)	89/265 (33.6%)	RR 0.96 (0.46 to 2.02)	13 fewer per 1,000 (from 181 fewer to 343 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

[a]. Risk of bias downgraded by 1 level due to some concerns regarding deviations from intended interventions and outcome measurement

[b]. Inconsistency downgraded by 1 due to heterogeneity I2 = 55%

[c]. Imprecision downgraded 2 levels because of very wide confidence intervals with possibility for benefit and the low number of participants

[d]. Risk of bias downgraded by 1 level because of some concerns with deviation from intended intervention and missing data

[e]. Imprecision downgraded one level due to small number of participants

[f]. Imprecision downgraded one level : due to wide confidence interval consistent with possibility for no effect and the possibility for harm and low number of participants

[g]. Inconsistency downgraded by 1 level : high heterogeneity I2 = 77%

[h]. Imprecision downgraded by 2 levels : due to very wide confidence interval consistent with possibility for benefit and the possibility of harm and low number of participants

Appendix 3. Forest Plots

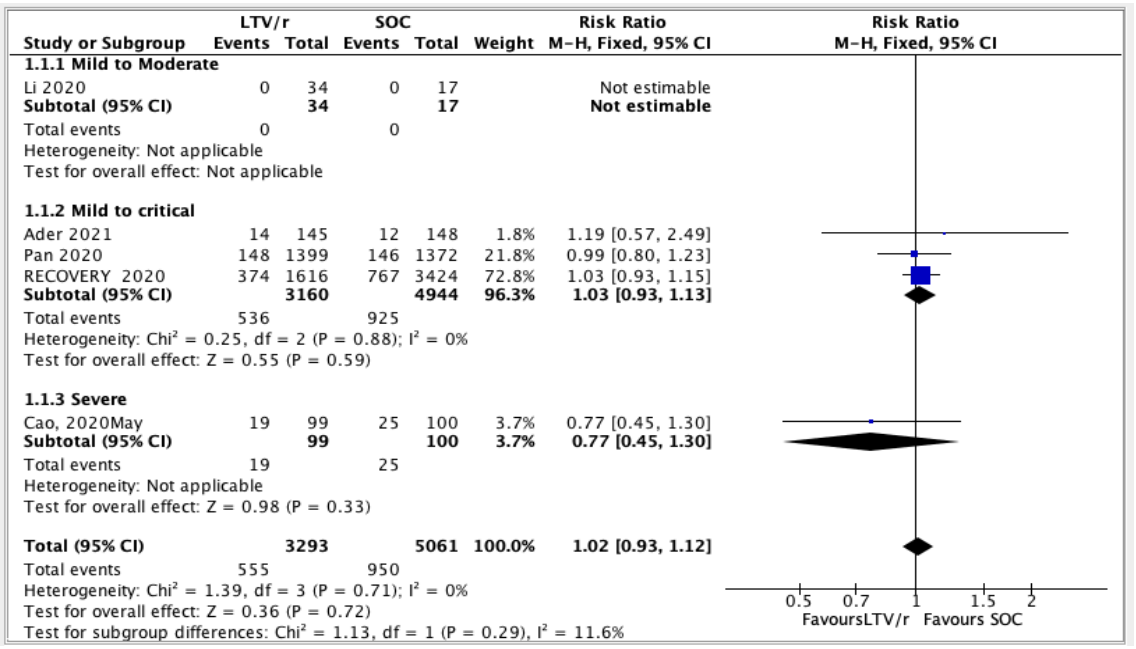

Figure 1. All-cause mortality at day 28, stratified according to disease severity

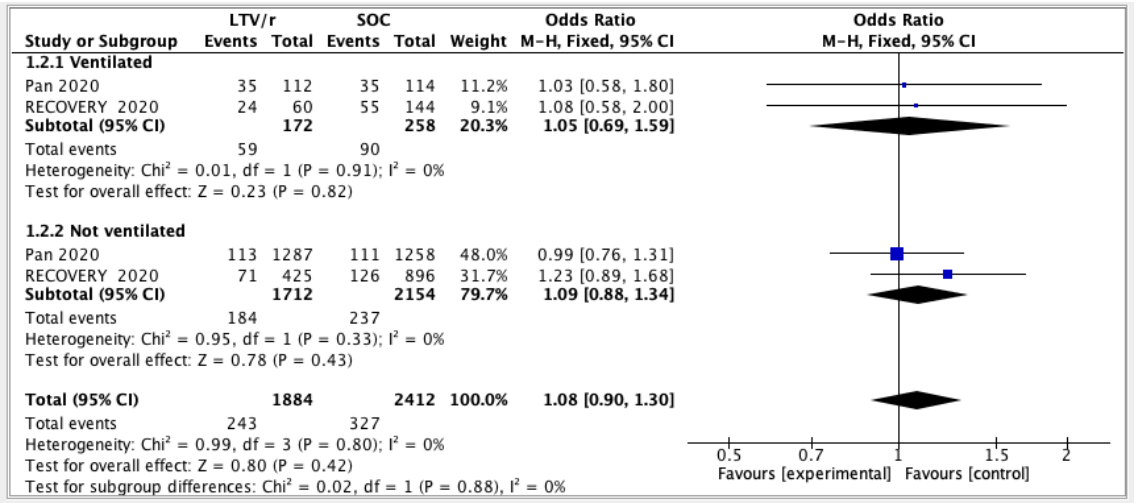

Figure 2. All-cause mortality (subgroup: respiratory support at entry)

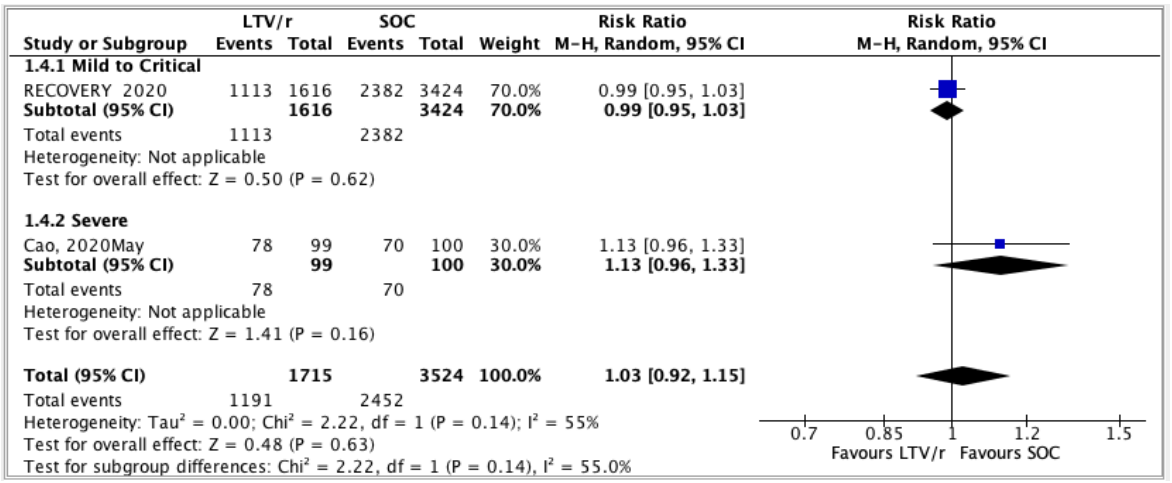

Figure 3. Clinical Improvement (subgroup: Severity)

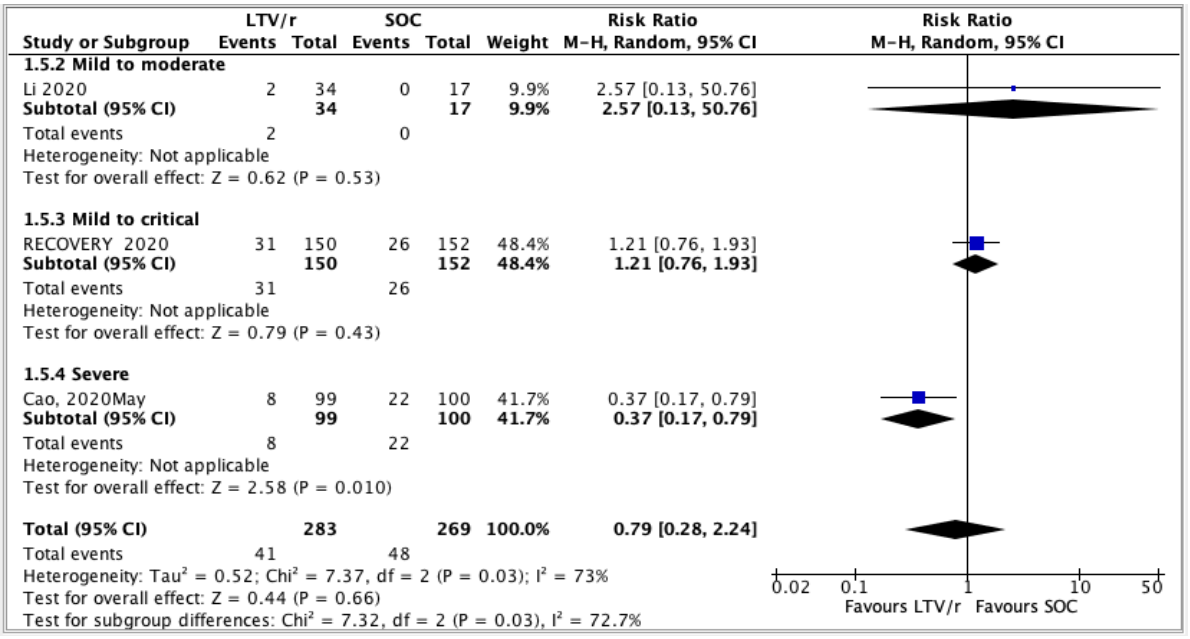

Figure 4. WHO progression score level 7 or above at day 28 (mechanical ventilation +/- organ support (ECMO, vasopressors or dialysis) OR death)

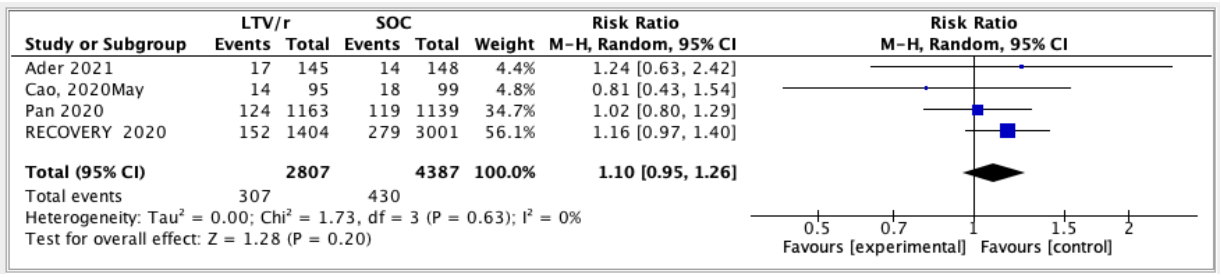

Figure 5. Need for mechanical ventilation

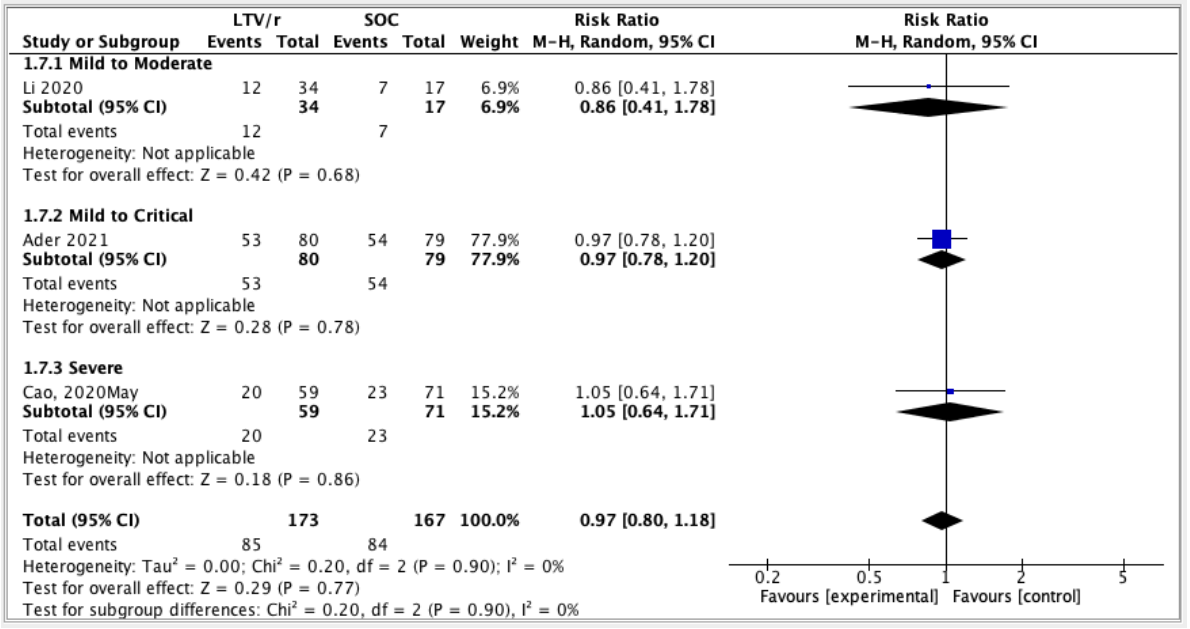

Figure 6. Virologic clearance by RT-PCR (viral negative conversion by day 7)

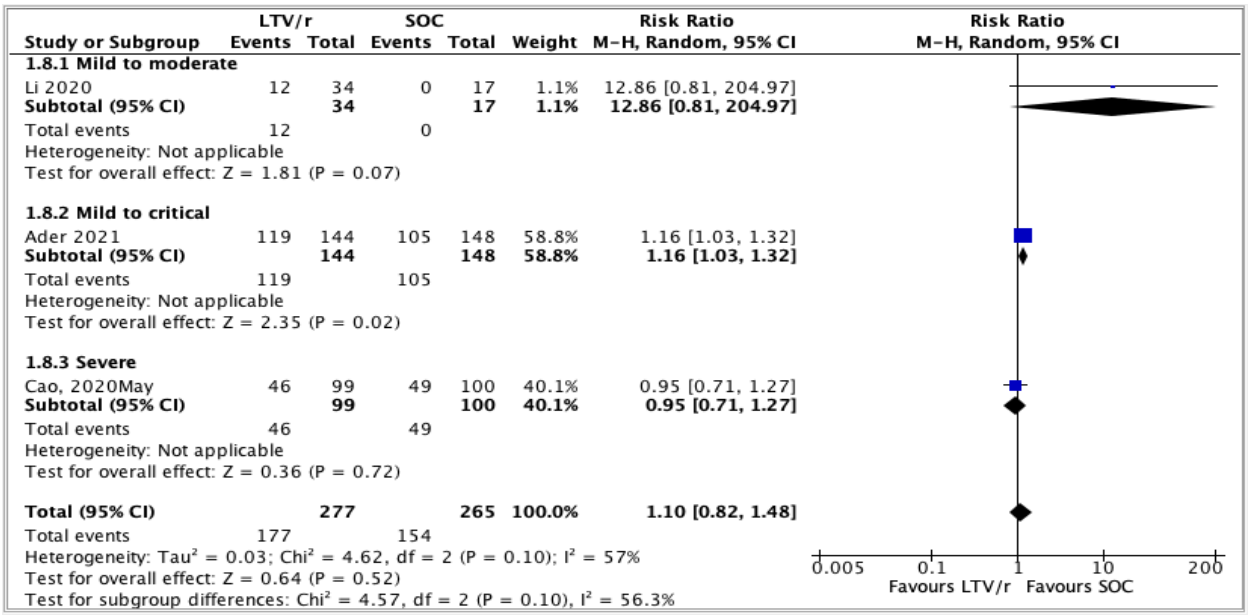

Figure 7. Adverse events

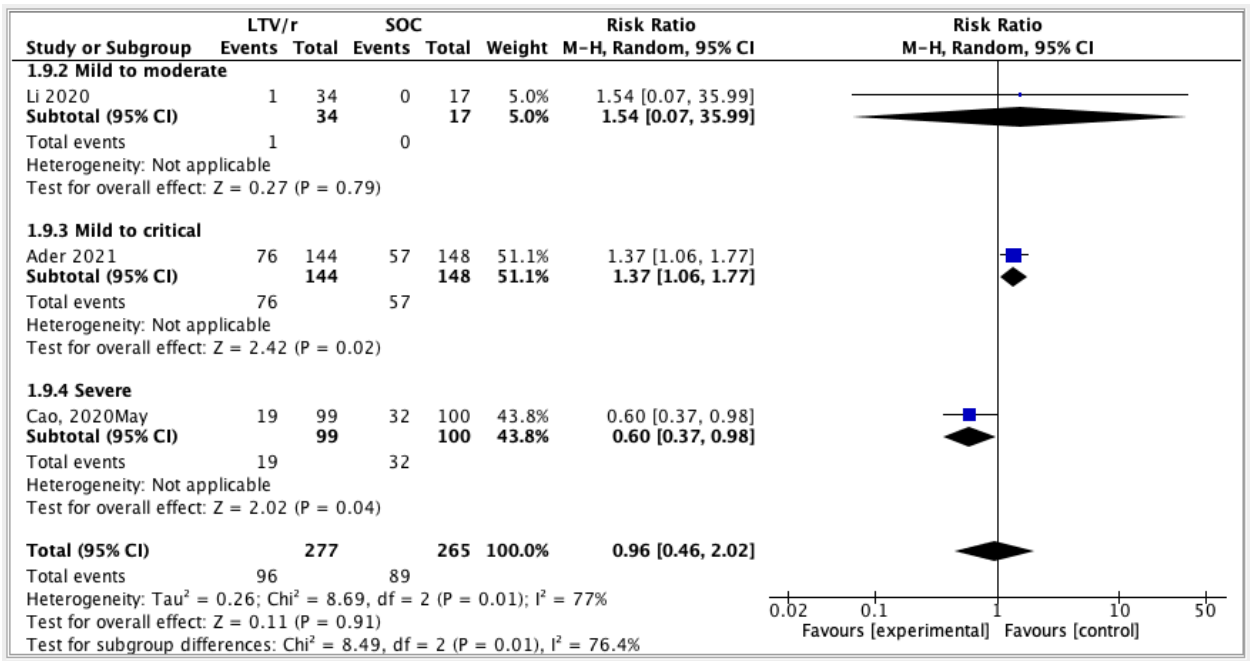

Figure 8. Severe adverse events

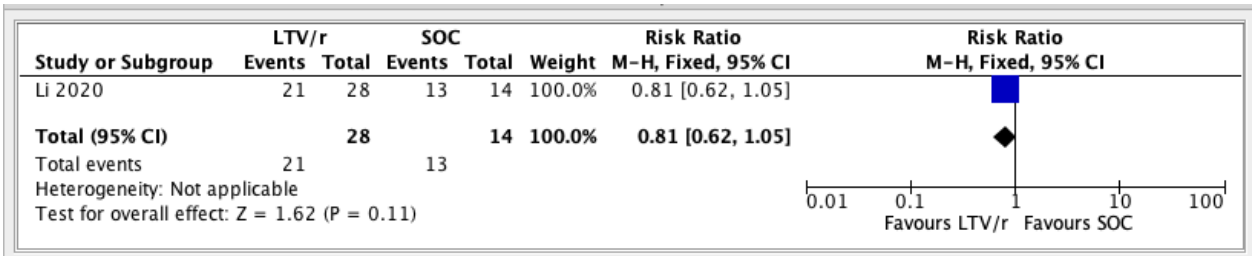

Figure 9. Improvement of CT scan at D14

Appendix 4. Table of Ongoing Studies

Registry Number	Institution, Country	N	COVID-19 severity	Intervention and Comparator
NCT04315948	Institut National de la Sant© Et de la Recherche M©dicale, France	3100	Moderate/severe/ critical	(1) Hydroxychloroquine *vs* (2) Remdesivir *vs* (3) L opinavir + ritonavir *vs* (4) Lopinavir + ritonavir + interferon beta1 *vs* (5) Standard of care
EUCTR2020-001549-38-DE	Gesundheit Nord gGmbH	800	Severe	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Lopinavir + ritonavir + interferon beta1 vs (4) Remdesivir vs (5) Standard of care
PER-010-20	OMS	1000	Moderate/severe/ critical	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) L opinavir + ritonavir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care
LBCTR2020043495	WHO	1000	Moderate/severe/ critical	(1) Chloroquine vs (2) Remdesivir vs (3) Lopinavi r + ritonavir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care
EUCTR2020-001366-11-IE	World Health Organisation	1000	No restriction on type of patients	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) L opinavir + ritonavir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care
NCT04409483	Epicentre	928	Mild	(1) Lopinavir + ritonavir vs (2) Standard of care
ChiCTR2000029539	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology	328	Mild	(1) Lopinavir + ritonavir vs (2) Standard of care
ChiCTR2000029308	Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital)	160	Severe	(1) Lopinavir + ritonavir vs (2) Standard of care
EUCTR2020-001528-32-IT	ISTITUTO NAZIONALE PER LE MALATTIE INFETTIVE "LAZZARO SPALLANZANI"	435	Mild	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Darunavir + cobicistat vs (4) Favipiravir vs (5) Standard of care
EUCTR-2020-001113-21-GB	University of Oxford	2500	Moderate/severe/ critical	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Interferon beta 1a vs (4) Dexamethasone vs (5) Placebo
EUCTR2020-001549-38-DE	Gesundheit Nord gGmbH	800	Severe	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Lopinavir + ritonavir + interferon beta1 vs (4) Remdesivir vs (5) Standard of care
NCT04455958	OHSU Knight Cancer Institute	75	No restriction on type of patients	(1) Lopinavir + ritonavir vs (2) Placebo
PACTR202006537901307	Drug for Neglected Diseases initiative	3000	Mild/moderate	(1) Hydroxychloroquine vs (2) Paracetamol vs (3) Lopinavir + ritonavir vs (4) Standard of care
CTRI/2020/06/026196	University Of Birmingham	6400	High risk patients	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + lopinavir + ritonavir vs (3) Lopinavir + ritonavir vs (4) Standard of care
EUCTR2020-002106-68-GB	University College London Comprehensive Clinical Trial Unit	240	Mild/moderate	(1) Lopinavir + ritonavir vs (2) Favipiravir vs (3) Lopinavir + ritonavir + favipiravir vs (4) Placebo
NCT04252885	Guangzhou 8th People's Hospital	125	No restriction on type of patients	(1) Lopinavir + ritonavir vs (2) Umifenovir vs (3) Standard of care
NCT04499677	University College, London	240	No restriction on type of patients	(1) Favipiravir + lopinavir/ritonavir vs (2) Lopinavir + ritonavir vs (3) Favipiravir vs (4) Placebo
NCT04328285	Centre Hospitalier Universitaire de Saint Etienne	1200	Health workers	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Placebo vs (4) Placebo
NCT04321174	St. Michael's Hospital, Toronto	1220	Close contacts to covid patients	(1) Lopinavir + ritonavir vs (2) Standard of care
NCT04255017	Tongji Hospital	400	Moderate/severe	(1) Umifenovir vs (2) Oseltamivir vs (3) Lopinavir + ritonavir vs (4) Standard of care
ISRCTN83971151	Multiple funders including the World Health Organization (Switzerland)	11266	Moderate/severe/ critical	(1) Chloroquine vs (2) Remdesivir vs (3) Lopinavi r + ritonavir vs (4) Lopinavir + ritonavir + interferon beta vs (5) Standard of care
NCT04330690	Sunnybrook Health Sciences Centre	440	No restriction on type of patients	(1) Lopinavir + ritonavir vs (2) Standard of care
EUCTR2020-001366-11-ES	FIB-HCSC	2500	No restriction on type of patients	(1) Chloroquine vs (2) Remdesivir vs (3) Lopinavi r + ritonavir vs (4) Lopinavir + ritonavir + interferon beta1a vs (5) Standard of care

EUCTR2020-001188-96-FR	CHU de Saint Etienne	1200	Health workers	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Placebo vs (4) Placebo
IRCT20200405046953N1	Iranian Ministry of Health and Medical Education, Deputy of Research and Technology	3000	Moderate/severe	1) Hydroxychloroquine vs (2) Remdesivir vs (3) Lopinavir + ritonavir vs (4) Lopinavir + ritonavir + interferon vs (5) Standard of care
NCT04351724	Medical University of Vienna	500	High risk patients	(1) Renin-Angiotensin-System-Blockade vs (2) Non-RAS blocking antihypertensive agent vs (3) Rivaroxaban vs (4) Hydroxychloroquine vs (5) Lopinavir + ritonavir vs (6) Clazakizumab vs (7) Placebo vs (8) Standard of care vs (9) Standard of care
NCT04307693	Asan Medical Center	150	Mild	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Standard of care
PER-010-20	OMS	1000	Moderate/severe/critical	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) Lopinavir + ritonavir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care
ChiCTR2000030187	Jingzhou First People's Hospital	60	No restriction on type of patients	(1) Lopinavir + ritonavir vs (2) Standard of care
NCT04364022	Calmy Alexandra	420	Close contacts to covid patients	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Standard of care
NCT04365582	Groupe Hospitalier Paris Saint Joseph	640	Mild	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Azithromycin vs (4) Standard of care
NCT04372628	Vanderbilt University Medical Center	900	Mild	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Placebo
PACTR202004893013257	National Institute of Health Research	6400	High risk patients	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + lopinavir + ritonavir vs (3) Lopinavir + ritonavir vs (4) Standard of care
LBCTR2020043495	WHO	1000	Moderate/severe/critical	(1) Chloroquine vs (2) Remdesivir vs (3) Lopinavir + ritonavir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care
NCT04381936	University of Oxford	15000	Moderate/severe/critical	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Convalescent plasma treatment vs (4) Tocilizumab vs (5) Other corticosteroids vs (6) Azithromycin vs (7) Immuno globulin vs (8) Standard of care
EUCTR2020-001366-11-IE	World Health Organisation	1000	No restriction on type of patients	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) Lopinavir + ritonavir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care
NCT04403100	Cardresearch	1968	Mild/moderate	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + lopinavir + ritonavir vs (3) Lopinavir + ritonavir vs (4) Placebo

Q9. Among patients with COVID-19, should tocilizumab be used for treatment?

As of 28 October 2021

RECOMMENDATIONS

We recommend the addition of tocilizumab to systemic steroids in patients showing rapid respiratory deterioration and/or requiring high doses of oxygen (high-flow nasal cannula, noninvasive or invasive mechanical ventilation) and with elevated biomarkers of inflammation (CRP). *(Moderate certainty of evidence, Strong recommendation)*

We recommend against the use of tocilizumab among patients with COVID-19 infection who do not require oxygen. *(Very low certainty of evidence, Strong recommendation)*

Consensus issues

Report on adverse events, although an important outcome, was not rated as a critical outcome to be included in the decision making. The over-all assessment of the certainty of evidence is based only on critical outcomes identified by the consensus panel, hence, the quality of evidence was retained as moderate.

There is no new evidence on the use of tocilizumab among patients with COVID-19 infection who do not require oxygen. Given the lack of evidence, potential adverse effects and risks, this recommendation also considers indiscriminate use to avoid misuse or overuse of tocilizumab among patients who do not require oxygen.

PREVIOUS RECOMMENDATIONS

We recommend the addition of tocilizumab to systemic steroids in patients showing rapid respiratory deterioration and/or requiring high doses of oxygen (high-flow nasal cannula, noninvasive or invasive mechanical ventilation) and with elevated biomarkers of inflammation (CRP). *(Moderate certainty of evidence; Strong recommendation)*

We recommend against the use of tocilizumab among patients with COVID-19 infection who do not require oxygen. *(Very low certainty of evidence; Strong recommendation)*

Previous Consensus Issues

The high cost and limited availability of tocilizumab should be considered in our local setting. The indiscriminate use, potential adverse effects (i.e., leukemia, TB reactivation), risks, and lack of evidence of tocilizumab on COVID-19 patients who do not require oxygenation should be taken into consideration as well. Tocilizumab may also be administered in the earlier part of the therapy in order to prevent the occurrence of cytokine storm.

WHAT'S NEW IN THIS VERSION?

This version includes three (3) RCTs (Derde 2021, Hamed 2021, and Hermine 2021) as well as an update on previous trials (Hermine 2020).

KEY FINDINGS

Fifteen (15) randomized controlled clinical trials (RCTs) (N = 8,937) that investigated the effectiveness of tocilizumab among confirmed hospitalized COVID-19 patients compared to placebo and/or standard of care was found. Tocilizumab significantly

reduced all-cause mortality, time to clinical improvement, and the need for mechanical ventilation, with no significant increase in adverse events among hospitalized patients.

INTRODUCTION

Tocilizumab is a humanized anti-IL-6Ra monoclonal antibody globally approved for management of various types of arthritis. IL-6 is an important cytokine in both acute and chronic inflammation. Tocilizumab binds to the IL-6 receptors, thus inhibiting inflammation by reducing circulating neutrophils, neutrophil infiltration, circulation of dendritic cells, and serum macrophage migration. Safety of tocilizumab intravenous and subcutaneous administration was reported with the most common adverse events being infections such as pneumonia and cellulitis. Elevated liver enzyme levels, neutropenia, and changes in lipid levels were reported. Serious adverse effects include myocardial infarction and stroke.[1]

Hyperinflammation contributes to the severity of COVID-19.[2] IL-6 is an important prognostic marker for survival of the disease. It is also independently associated with the severity and predictive outcome of ventilation and organ damage.[3] Recent WHO Therapeutic and COVID-19 Living Guideline strongly recommends the use of tocilizumab in severe or critical patients.

REVIEW METHODS

A systematic search was done from the date of last search May 18, 2021 until September 15, 2021 to check for new trials in the COVID-NMA living data. Trials found in the COVID-NMA were included. Search was done in Medline, Cochrane Library, Google scholar using free text, MeSH terms and advance search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2, and tocilizumab. Screening was done in various trial registries for ongoing trials. Preprint search was also done in medrxiv, chinaxiv and biorxiv. Randomized controlled trials on tocilizumab compared to placebo or standard of care on COVID-19 patients, regardless of severity were included.

RESULTS

Characteristics of included studies

Fifteen (15) randomized controlled clinical trials (RCTs) (N = 8,937) that evaluated the effectiveness of tocilizumab among confirmed hospitalized COVID-19 patients compared to placebo or standard of care were found. All of the trials reviewed were also included in the COVID-NMA Living Data which was last updated on September 15, 2021. Three (3) of the 15 trials were preprints. The summary on the characteristics of included studies can be found in Appendix 2.

Four (4) studies were multinational trials [5-8], while the rest were conducted in the United Kingdom [9], France [10,11], Italy [12], USA [13], China [14], Brazil [15], India [16], the Netherlands [17], Iran [18], and Dubai.[19] Study participants in all trials were suspected/confirmed COVID-19 patients, 18 years old and above, and with either presence of pulmonary infiltrates or requiring supplemental oxygen. Six (6) trials [7,10-13,18] excluded patients on mechanical ventilation at the start of the trial, while two (2) trials [10,11] enrolled critical patients admitted in the intensive care unit that were receiving respiratory or cardiovascular organ support. Four (4) trials included elevated laboratory markers such as C-reactive protein (CRP), d-dimer, and ferritin in their

inclusion criteria.[12-14,18] Standard of care varied per study but usually involved the administration of anticoagulants, steroids, or anti-viral drugs (e.g., darunavir/cobicistat, darunavir/ritonavir, lopinavir/ritonavir, or remdesivir).[5,8,12] Two (2) of the trials included steroids with tocilizumab as intervention.[11,19] All studies evaluated tocilizumab given via the intravenous route. There were no studies that evaluated tocilizumab given subcutaneously. There were only few moderate cases (not requiring oxygen) (121/ 8,937, 1.35%) that were included in these trials.

Overall Certainty of Evidence

Eleven (11) out of 15 trials were open label trials and there was an imbalance in the administration of steroids and anti-viral drugs as part of the standard of care among the participants of the studies. There were serious risk of bias, inconsistency, and imprecision in one important outcome (adverse events), however, given that the adverse events were not rated as critical outcomes to be included in the decision making by the panel, the overall quality of evidence is retained to be moderate. The risk of bias summary is shown in Appendix 4. The GRADE evidence summary is presented in Appendix 5.

Effectiveness Outcomes

The COVID-NMA project provided pooled analysis for clinical improvement, time to clinical improvement, time to death, adverse events, and serious adverse events (last updated July, 7, 2021).[20] Results on mortality and the initiation of mechanical ventilation were also pooled showing significant benefit in reducing these outcomes.

Mortality

Based on 14 RCTs (N = 8,489), tocilizumab reduced all-cause mortality at day 14 to day 90 follow-up compared to standard of care (RR 0.88, 95% CI 0.82-0.94, I^2=0%). Tocilizumab significantly reduced all-cause mortality at day 28 (RR 0.88, 95% CI 0.82-0.95, I^2=7%) but had no significant effect on all-cause mortality at day 90 (RR 0.88, 95% CI 0.76-1.02, I^2=0%). Pooled effect of tocilizumab based on co-administration of steroids also significantly reduced mortality however, it was noted to have borderline heterogeneity with RR 0.86, 95% CI 0.79-0.93, I^2= 43%, P=0.07.

Subgroup analyses on the effect of tocilizumab on mortality stratified according to oxygen requirement and co-administration of steroids were done (Appendix 5). Subgroup according to oxygen requirement did not show significant benefit across groups, including those requiring oxygen supplementation (RR 0.89, 95% CI 0.76-1.04, I^2=0%); those requiring non-invasive ventilation (RR 0.89, 95% CI 0.79-1.00, I^2=0%); and those requiring invasive mechanical ventilation (RR 0.98, 95% CI 0.82-1.16, I^2=0%). A subgroup analysis by co-administration of steroids demonstrated significant reduction in mortality among patients who were also given steroids (RR 0.80, 95% CI 0.73-0.88, I^2=17%) however, there was no significant benefit among patients who were not given steroids (RR 1.08, 95% CI 0.91-1.29, I^2=0%).

Clinical improvement

Eight (8) RCTs (N = 5,585) showed no significant difference in clinical improvement at day 28 among patients given tocilizumab compared to standard of care with borderline heterogeneity (RR 1.06, 95% CI 0.99-1.12, I^2=39.6%, p=0.07). There was a significantly shorter time to clinical improvement among those given tocilizumab (HR 1.25, 95% CI 1.14-1.38, I^2=9.9%).

Need for mechanical ventilation
There was significant reduction in the need for mechanical ventilation among patients given tocilizumab compared to standard of care (RR 0.78, 95% CI 0.68-0.89, I^2=0%; 9 RCTs).

Safety Outcomes
There was no significant difference in the risk for adverse events (RR 1.23, 95% CI 0.93-1.62, I^2=81.3%) and serious adverse events between the tocilizumab group and the control group (RR 0.92, 95% CI 0.77-1.08, I^2=0%), however, there is significant heterogeneity with the risk for adverse events. Common adverse events noted with tocilizumab were abnormal liver function tests, leukopenia, and neutropenia.[12-15] There was no evidence for increased risk for serious secondary infection.[5-7,10,13]

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Infectious Diseases Society of America (IDSA) (as of September 14, 2021)	Suggests the use of tocilizumab in adult hospitalized patients with progressive severe or critical COVID-19 who have elevated markers in addition to standard of care (i.e., steroids). Severe COVID-19 cases are patients with SpO2 ≤ 94% on room air, while critical cases are those on mechanical ventilation and ECMO *(Low certainty of evidence, Conditional recommendation*).[21]
US National Institutes of Health (NIH) (as of September 15, 2021)	Recommends the use of tocilizumab in combination with dexamethasone in hospitalized patients exhibiting rapid respiratory decompensation. These are COVID-19 patients that are: (1) admitted to an ICU unit within 24 hours and who require mechanical ventilation, non-invasive ventilator (NIV) or high-flow nasal cannula (HFNC) and (2) non-ICU patients but requiring NIV or HFNC AND have significantly increased markers of inflammation *(Moderate certainty of evidence, other randomized trials or subgroup analyses of randomized trials).[22]*
World Health Organization (WHO) (as of September 24, 2021)	Recommends treatment with the use of IL-6 receptor blocker (tocilizumab or sarilumab) in severe to critical COVID-19 patients, with recommendation to give both corticosteroids and IL-6 receptor blocker in the said patients. This is based on a high certainty of evidence for mortality and mechanical ventilation.[4]

RESEARCH GAPS

As of September 16, 2021, there are 18 ongoing clinical trials on tocilizumab for COVID-19 patients registered on *clinicaltrials.gov* and EU Clinical Trials Register. Four (4) of these trials have been completed and are awaiting results.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					
Benefits	Large (2)	Moderate (7)	Small	Uncertain			• Tocilizumab reduces all-cause mortality with significant reduction in mortality on subgroup analysis by co-administration of steroids • There was significant reduction in the need for mechanical ventilation
Harm	Large	Small (7)	Uncertain (2)				• Tocilizumab showed no significant difference in the risk for adverse events and serious adverse events between the 2 groups
Certainty of Evidence	High (1)	Moderate	Low (3)	Very low (5)			• The overall quality of evidence is very low due serious risk of bias, inconsistency and imprecision in one important outcome.
Balance of effects	Favors drug (9)	Does not favor drug	Uncertain				• Patients given tocilizumab had significant benefit in all-cause mortality and need for mechanical ventilation, with no significant increase in adverse events.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (4)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (9)	Moderate Cost	Negligible cost	Moderate savings	Large savings	• Cost of Php 28,830.84 for retail price of 400mg/20ml, 20ml vial; total drug regimen cost per patient per treatment course would be Php 57,661.68 • Issues on drug shortage and high demand
Certainty of evidence of required resources	No included studies (1)	Very low (1)	Low	Moderate (4)	High (3)		• The cost is regulated by Presidential Executive Order 104
Cost effectiveness	No included studies (5)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (3)			
Equity	Uncertain (2)	Reduced (3)	Probably no impact	Increased (4)			
Acceptability	Uncertain (3)	No	Yes (6)				
Feasibility	Uncertain (2)	No	Yes (7)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Tocilizumab	9/7/2021 5:09PM	16	13
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Tocilizumab	9/7/2021 9:05PM	24	12
COVID-NMA Initiative	Tocilizumab	9/7/2021 4:46PM	17	15
Google Scholar	Tocilizumab AND COVID AND randomized trial	9/7/2021 920PM	13	10
ClinicalTrials.gov	COVID-19 COVID-19 Pneumonia, Investigational Trials, Tocilizumab	9/15/2021 9:30PM	21	14
Chinese Clinical Trial Registry	COVID Tocilizumab	9/15/2021 9:40PM	3	0
EU Clinical Trials Register	COVID Tocilizumab	9/15/2021 9:50PM	6	4
Republic of Korea - Clinical Research Information Service	COVID Tocilizumab	9/15/2021 9:52PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	COVID Tocilizumab	9/15/2021 9:53M	0	0
CenterWatch	COVID Tocilizumab	9/15/2021 9:56PM	0	0
chinaxiv.org	COVID Tocilizumab	9/15/2021 10:01PM	1	0
Medrxiv.org	COVID Tocilizumab Filter: May 18-Sept 7	9/15/2021 10:23PM	5	5
Biorxiv.org	COVID Tocilizumab Filter: May 18-Sept 7	9/15/2021 1025	0	0

Appendix 3: Characteristics of Included Studies

Title/Author	Study Design	Country	Population	Intervention Group(s)	Control	Outcomes
Horby 2021 RECOVERY	Open label RCT	United Kingdom	Suspected or confirmed COVID-19 patients N = 4,116	Tocilizumab 8 mg/kg	Standard care	• All-cause mortality at day 28 • Time to discharge • Receipt of invasive mechanical ventilation • Use of non-invasive respiratory support • Time to successful cessation of invasive mechanical ventilation • Use of renal dialysis/hemofiltration • Major cardiac arrhythmia • Serious adverse events
Gordon 2020 REMAP-CAP	Adaptive RCT	United Kingdom, France, the Netherlands, Australia	ICU admitted critical COVID-19 patients AND receiving respiratory or cardiovascular organ support N = 755	Group 1: Tocilizumab 8 mg/kg Group 2: Sarilumab	Standard care	• Respiratory and cardiovascular organ support-free days • Survival • Time to ICU discharge • Time to hospital discharge • WHO scale at day 14 • Progression to invasive mechanical ventilation, ECMO or death • Serious adverse events
Hermine 2020	Open label RCT	France	Moderate, severe or critical COVID-19 patients with oxygen levels of 3 L/min or higher but without non-invasive ventilation (NIV) or mechanical ventilation (MV) N = 131	Tocilizumab 8 mg/kg	Usual care	• Mortality on day 4 and day 14 • Mechanical ventilation on day 4 and day 14 • Clinical status (WHO CPS) at day 7 and day 14 • Overall survival • Time to discharge • Time to oxygen supply independency • C-reactive protein levels • Adverse events
Rosas 2020 COVACTA	Double-blind, placebo controlled RCT	Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA	Severe COVID-19 patients N = 452	Tocilizumab 8 mg/kg	Placebo	• Clinical status at day 28 • Mortality • Ventilator free days • Time to improvement • Time to hospital discharge • Adverse events
Salama 2020	Double-blind, placebo controlled RCT	USA, Mexico, Kenya, South Africa, Peru, Brazil	Hospitalized COVID-19 pneumonia patients not on continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation. N = 388	Tocilizumab 8mg/kg	Placebo	• Invasive mechanical ventilation or ECMO • Mortality • Time to hospital discharge or readiness for discharge • Time to at least a two-category improvement in clinical status • Time to clinical failure
Salvarani 2020	Open-label RCT	Italy	Non-ICU COVID-19 patients. N = 126	Tocilizumab 8 mg/kg	Standard of care	• Clinical worsening at day 14: • Admission to ICU with mechanical ventilation • Death from any cause

						• PaO2/FIO2 ratio less than 150 mmHg
Stone 2020	Double-blind, placebo controlled RCT	USA	Confirmed COVID-19 patients not on oxygen above 10 L/minute N = 243	Tocilizumab 8 mg/kg	Placebo	• Mortality • Mechanical ventilation • Clinical worsening • Time to improvement • Time to death • Duration of supplemental O2 • Admission to ICU
Wang 2020	Open-label RCT	China	Moderate or severe COVID-19 patients with elevated IL-6. N = 65	Tocilizumab	Standard care	• Cure rate • Recovery rate of hypoxia over 14 days, • Worsening rate of hypoxia during hospitalization, • Duration of hospital stay, • Time to negative virus load.
Veiga 2021	Open-label RCT	Brazil	Severe or critical COVID-19 patients N = 129	Tocilizumab 8 mg/kg	Standard care	• Clinical status at Day 15 • All-cause mortality • In-hospital mortality • Sequential organ failure assessment score • Clinical status at day 8 and day 29 • Ventilator-free days within 29 days • Time to independence from supplemental oxygen • Duration of hospital stay
Soin 2021 (COVINTOC)	Open-label RCT	India	Moderate to severe Covid-19 patients Moderate – RR 15-30 AND SpO2 90-94% Severe- RR>30 OR SpO2 <90% OR ARDS OR septic shock N = 183	Tocilizumab 6 mg/ kg	Standard Care	• Clinical progression • Mortality • Clinical improvement • Time to clinical improvement • Ventilator free days • Organ failure free days • ICU admission • Time to hospital discharge • Time to negative result on RT-PCR • Adverse events • Serious adverse events
Rutgers 2021 ***(Pre-print)***	Open label RCT	The Netherlands	Hospitalized COVID 19 patients with the following conditions: Need for supplemental Oxygen Ferritin >2000 ug/l or doubling serum ferritin in 20-48 hours N = 354	Tocilizumab 8 mg/kg	Standard of care	• 30-day mortality • Duration of hospital stay • ICU admission • Duration of ICU stay • Duration of mechanical ventilation • Time to mechanical ventilation • Time to death
Talaschian 2021	Double blind RCT	Iran	COVID-19 patients with the following conditions:	Tocilizumab 8 mg/kg	Standard of care	• Clinical improvement • 28-day mortality • Time to improvement

			• Elevated CRP (>10 mg/L)/ IL 6 (> 18 pg/ml) / Lymphopenia (WBC< 1100/MCL) • O2 sat <93% or RR >24 • Not connected to mechanical ventilator • Not responding to standard COVID-19 treatment N = 40			
New Studies Added (as of Sept 15, 2021)						
Derde 2021 ***(Pre-print)***	Open label, Adaptive RCT	US, Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK	ICU admitted critical COVID-19 patient AND receiving respiratory or cardiovascular organ support N = 2,274	Group 1: Tocilizumab 8 mg/kg Group 2: Sarilumab Group 3: Anakinra Group 4: Interferon B1a	Standard care	• Respiratory and cardiovascular organ support-free days • Survival • In-hospital mortality 90 days • Time to ICU discharge • Time to hospital discharge
Hamed 2021	Open label RCT	Dubai	Hospitalized COVID-19 patients AND lung infiltrates >50% of lung fields within 48 hrs admission, O2 saturation <93% at rest on room air N = 76	Group 1: Methylprednisolone Group 2: Methylprednisolone and Tocilizumab	Historical control group	• All-cause mortality day 45 • Admission to ICU • Length of ICU stay • Invasive ventilation • Days on ventilation • Length of hospital stay
Hermine 2021 (CORIMUNO-TOCI-DEX) ***(Pre-print)***	Open label RCT	France	Moderate to severe COVID-19 patients requiring oxygen but without ventilation support, high flow or mech vent, WHO class 5 N = 453	Tocilizumab 8 mg/kg at Day 1 PLUS Dexamethasone 10 mg/d for 5 days and tapering up to 10 days	Dexamethasone 10mg/d for 5 days and tapering up to 10 days	• Survival without mechanical ventilation at day 14 • WHO-CPS progression • Time to oxygen supply independency • Time to hospital discharge • Adverse events

Appendix 4. Study Appraisal

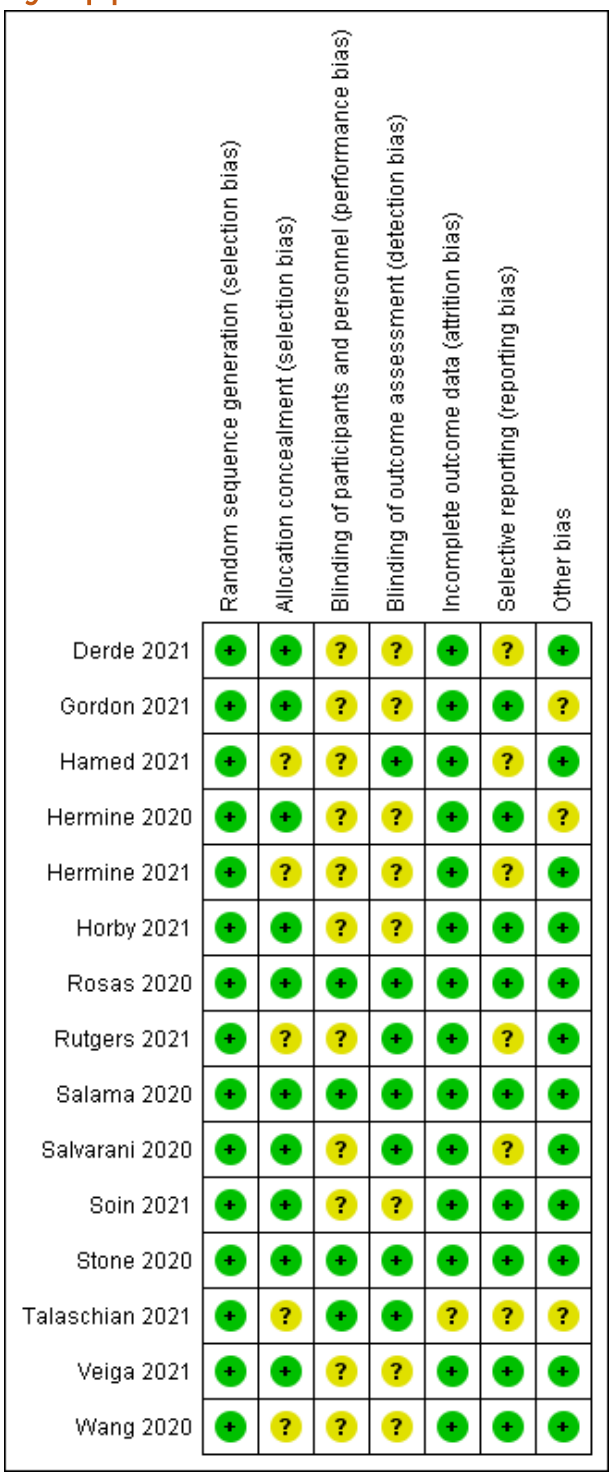

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): K. Relato; I. Cabaluna; A. Garcia
Question: Tocilizumab compared to standard of care in Covid-19
Bibliography: https://covid-nma.com/

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	SOC	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 14 days to 90 days)												
14	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	1214/4475 (27.1%)	1165/4014 (29.0%)	**RR 0.88** (0.82 to 0.94)	**35 fewer per 1,000** (from 52 fewer to 17 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical Improvement at Day 28												
8	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	1778/2952 (60.2%)	1434/2673 (53.6%)	**RR 1.06** (0.99 to 1.12)	**32 more per 1,000** (from 0 fewer to 70 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Time to Clinical Improvement												
7	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	2183 participants	1325 participants	-	**HR 1.25 higher** (1.14 higher to 1.38 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Need for mechanical ventilation												
9	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	342/2741 (12.5%)	408/2624 (15.8%)	**RR 0.78** (0.68 to 0.89)	**34 fewer per 1,000** (from 50 fewer to 17 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse Events												
8	Randomised trials	Serious [a]	Serious [b]	Not serious	Serious [c]	None	524/1033 (50.7%)	292/681 (42.9%)	**RR 1.23** (0.93 to 1.62)	**99 more per 1,000** (from 30 fewer to 266 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious Adverse Events												
10	randomised trials	serious [a]	not serious	not serious	serious [c]	none	241/1419 (17.0%)	164/1113 (14.7%)	**RR 0.92** (0.77 to 1.08)	**12 fewer per 1,000** (from 34 fewer to 12 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations
[a]. some concerns due to imbalance in the administration of steroids and antivirals
[b]. Heterogeneity: I2=81.3%
[c]. Wide confidence interval with possibility for benefit and harm.

Appendix 6. Forest Plots

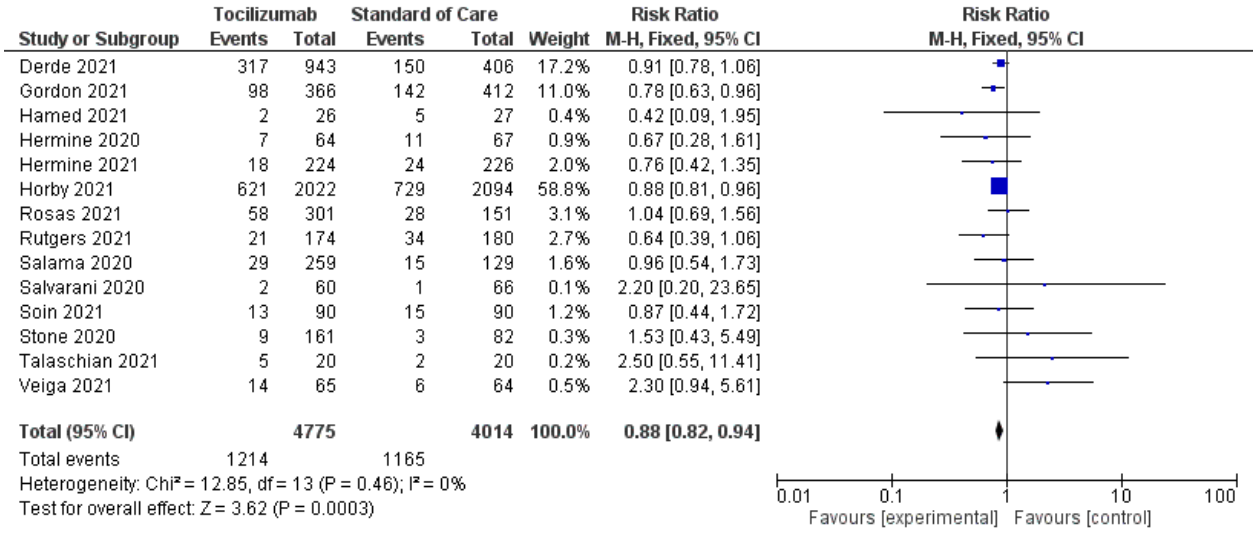

Figure 1. Pooled effect of tocilizumab on all-cause mortality (day 14 to day 90)

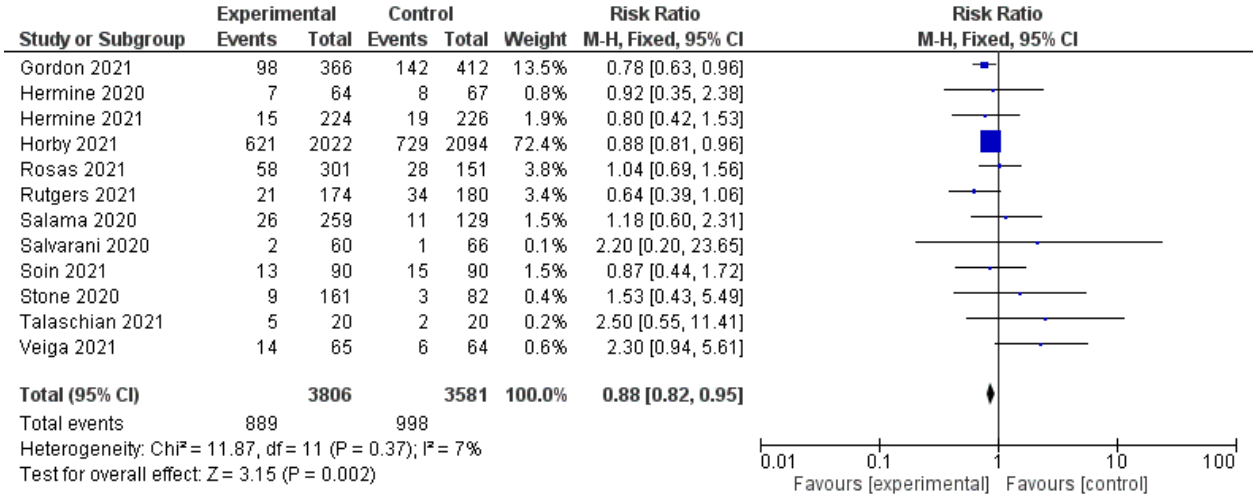

Figure 2. Pooled effect of tocilizumab on all-cause mortality day 28

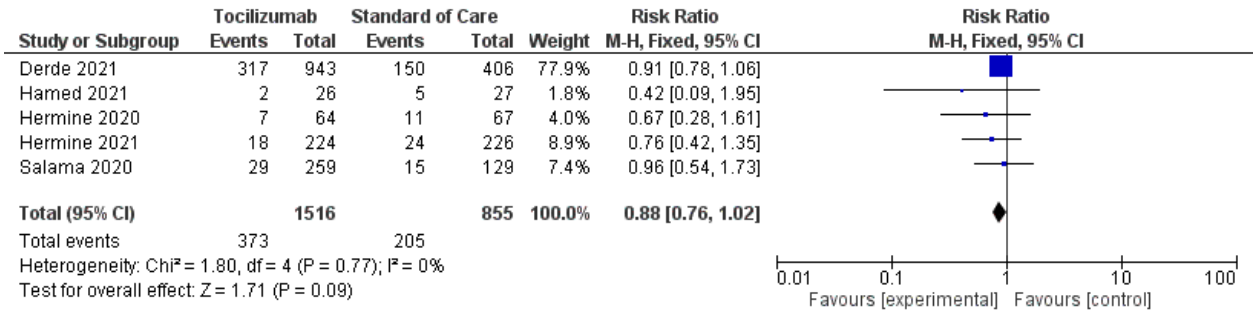

Figure 3. Pooled effect of tocilizumab on all-cause mortality day 90

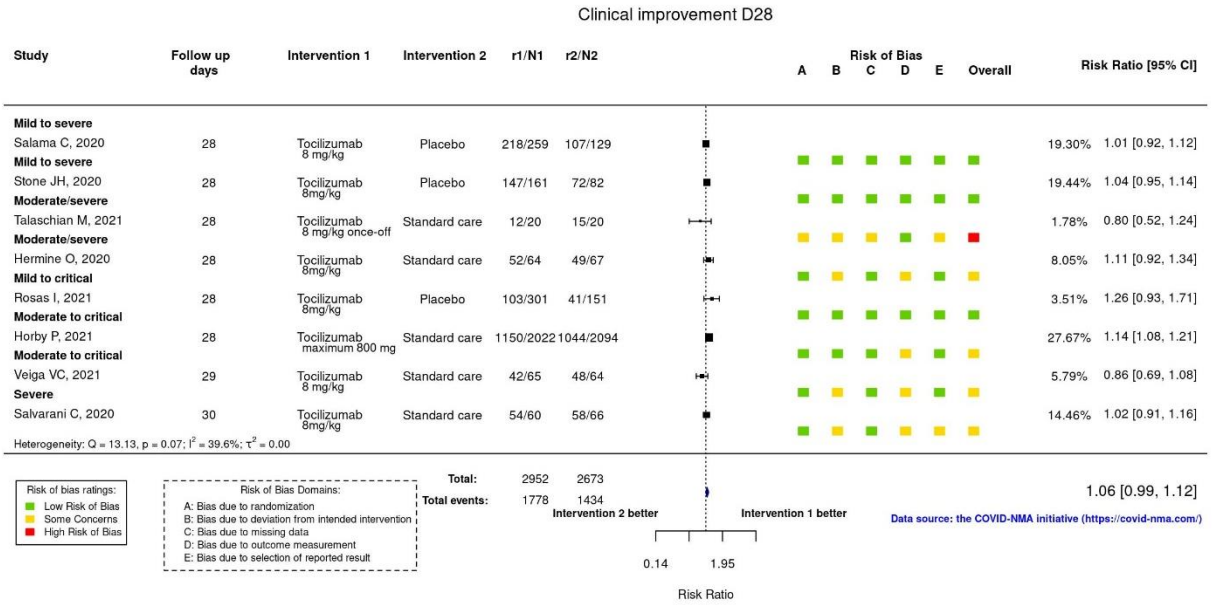

Figure 4. Pooled effect of tocilizumab on clinical improvement at day 28 (Source: covid-nma.com)

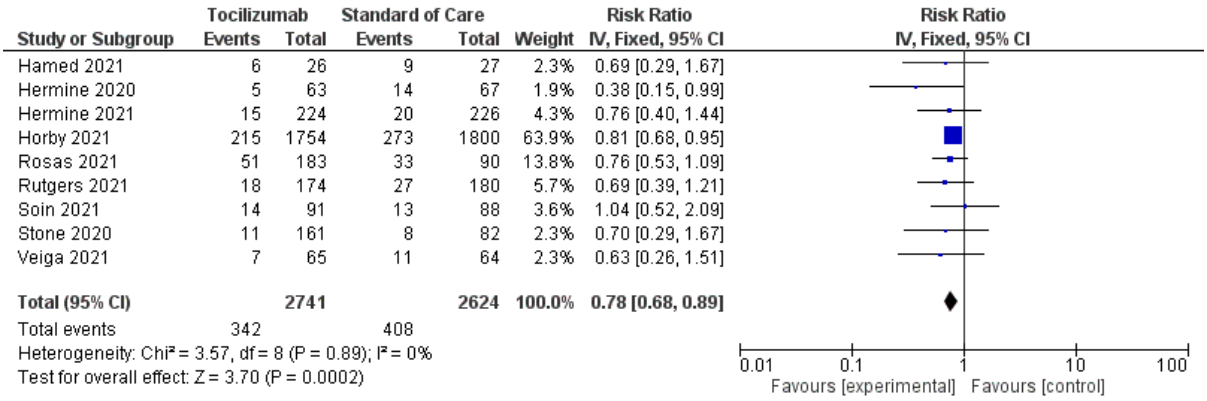

Figure 5. Pooled effect of tocilizumab on initiation of mechanical ventilation

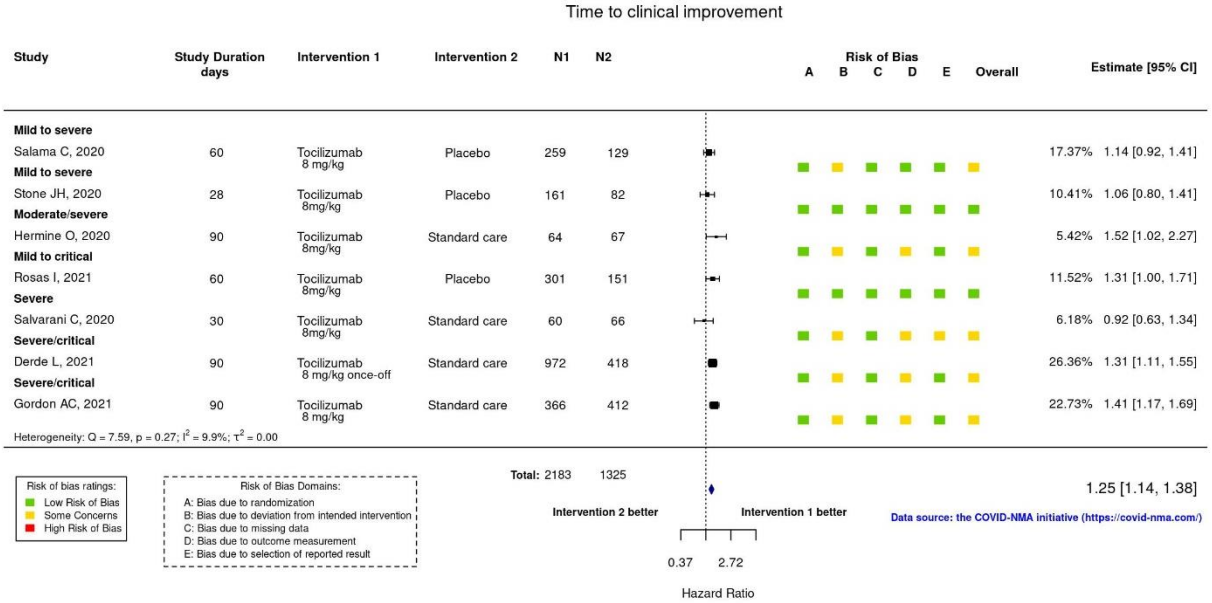

Figure 6. Pooled effect of tocilizumab on time to clinical improvement (hazard ratio) (Source: covid-nma.com)

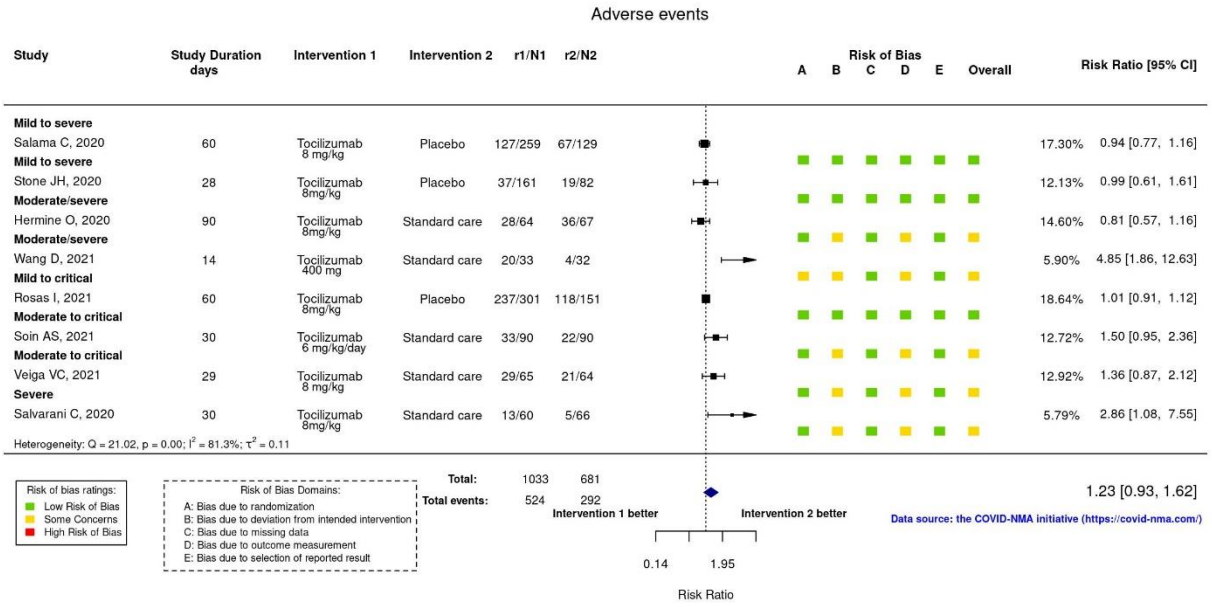

Figure 7. Pooled effect of tocilizumab on the incidence of adverse events (Source: covid-nma.com)

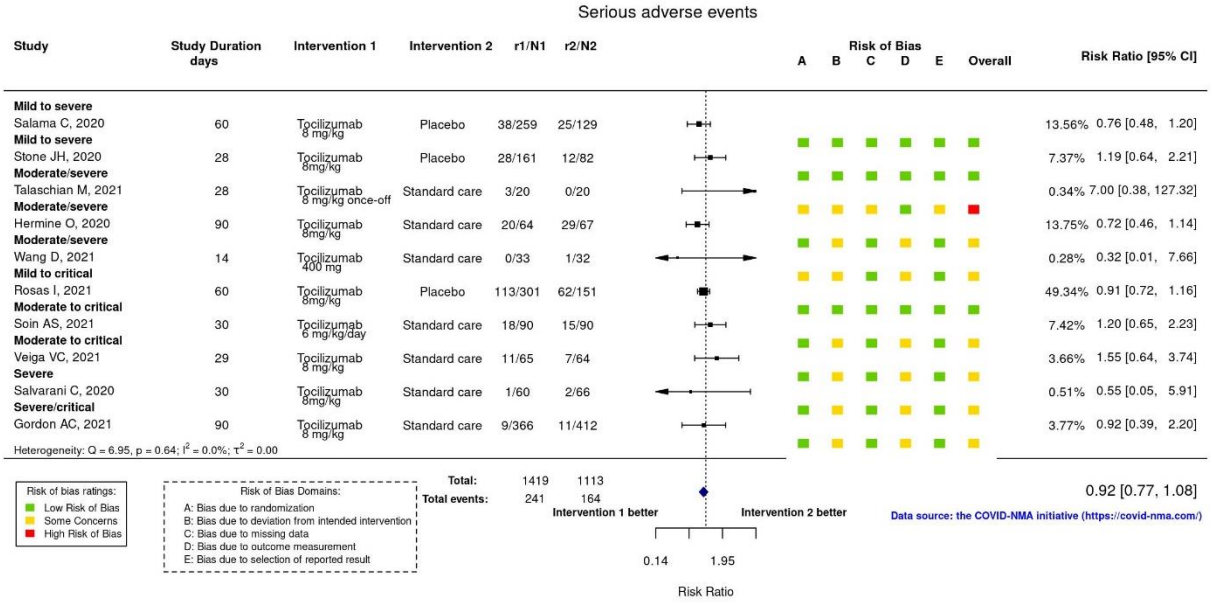

Figure 8. Pooled effect of tocilizumab on the incidence of serious adverse events (Source: covid-nma.com)

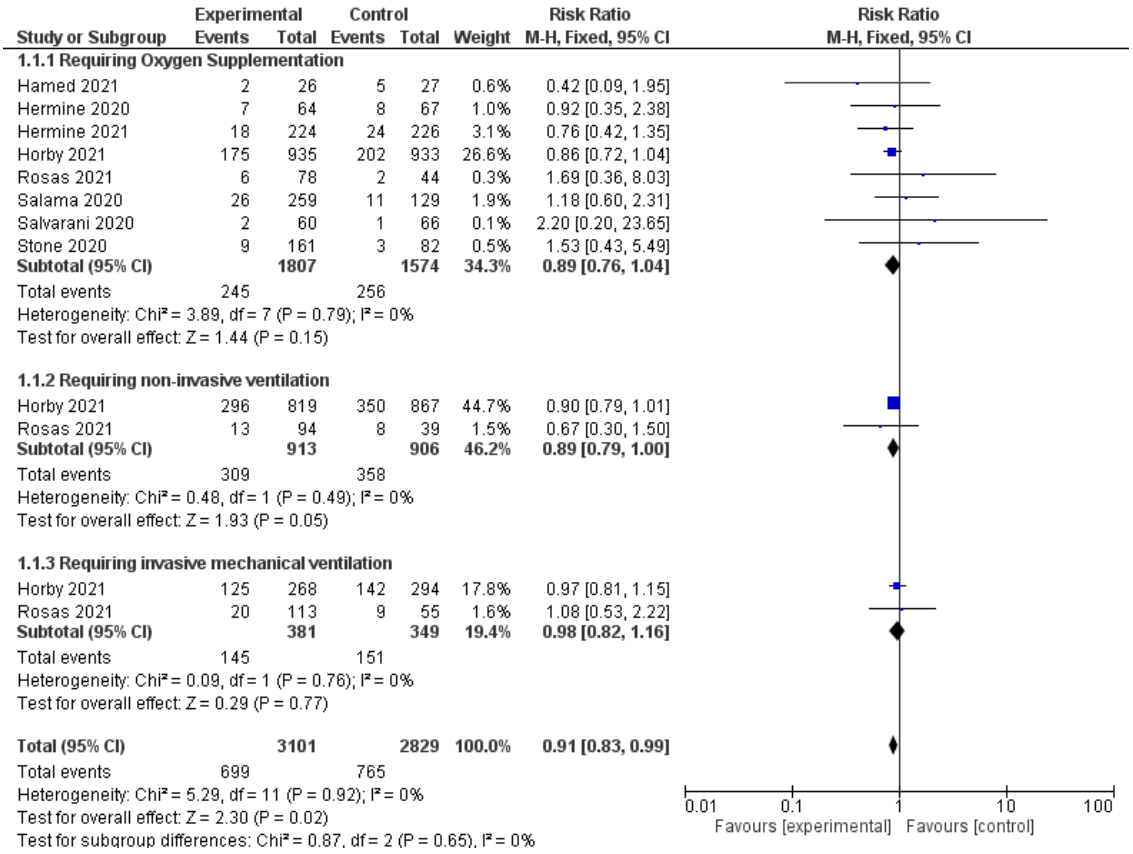

Figure 9. Pooled effect of tocilizumab on mortality according to oxygen requirement

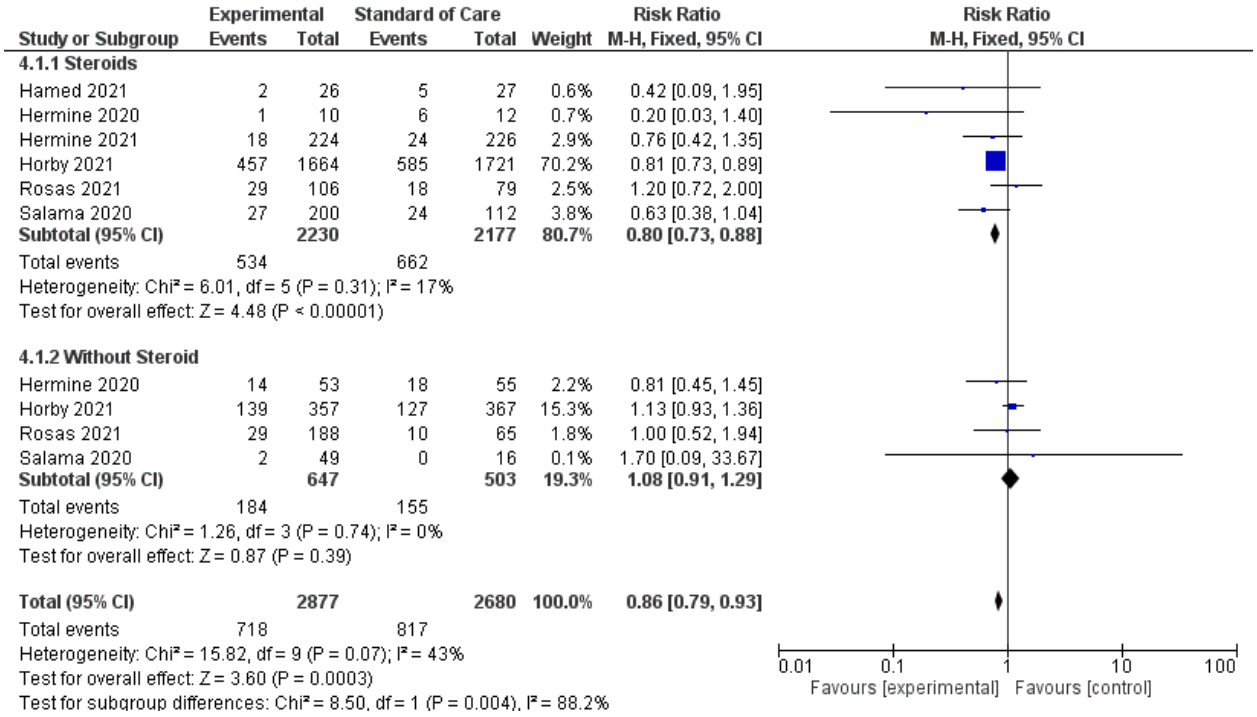

Figure 10. Pooled effect of tocilizumab on mortality with and without co-administration of steroids

Appendix 7. Pooled Results of Trials

Outcomes	Pooled Relative Risk	95% CI	Certainty of evidence (GRADE)
All-cause mortality (14 RCTs, N = 8,489)	0.88	0.82 to 0.94	Moderate
Clinical improvement D28 (8 RCTs, N = 5,625)	1.06	0.99 to 1.12	Moderate
Need for mechanical ventilation (9 RCTs, N = 5,365)	0.78	0.68 to 0.89	Moderate
Time to clinical improvement (Hazard ratio) (7 RCTs, N = 3,508)	1.25	1.14 to 1.38	Moderate
Adverse events (8 RCTs, N = 1,714)	1.23	0.93 to 1.62	Very Low
Serious adverse events (10 RCTs, N = 2,532)	0.92	0.77 to 1.08	Moderate

Appendix 8. Subgroup Analysis

	Pooled Relative Risk	95% CI	Certainty of Evidence
By oxygen requirement			
Requiring O2 supplementation (8 RCTs, N = 3,381)	0.89	0.76 to 1.04	Low
Requiring non-invasive ventilation (2 RCTs, N = 1,819)	0.89	0.79 to 1.00	Low
Requiring mechanical ventilation (2 RCTs, N = 730)	0.98	0.82 to 1.16	Low
By co-administration with steroids			
With steroids (6 RCTs, N = 4,407)	0.80	0.73 to 0.88	Moderate
Without steroids (4 RCTs, N = 1,150)	1.08	0.91 to 1.29	Low

Appendix 9. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Tocilizumab in COVID-19 Pneumonia (TOCIVID-19)	No age limit, COVID-19 confirmed by RT-PCR, hospitalized due to clinical/instrumental diagnosis of pneumonia, oxygen saturation ≤93% or requiring oxygen therapy or mechanical ventilation either non-invasive or invasive (intubated) (N = 402)	Experimental: Tocilizumab 8 mg/kg (up to a maximum of 800mg per dose). A second administration (same dose) can be given after 12 hours if respiratory function has not recovered, at discretion of the Investigator.	Primary: Lethality rate two weeks after registration	Single-arm, open-label, parallel cohort
2. Efficacy of Early Administration of Tocilizumab in COVID-19 Patients *Terminated*	>18 years old, RT-PCR confirmed COVID-19 patients, hospitalized due to clinical or instrumental diagnosis, presence of ARDS, with at least one of the ff: temperature of > 38C in the past two days, CRP >/= 10mg/dl, CRP increase of at least 2x the basal value (N = 126)	Experimental: Tocilizumab within 8 hours from entering the study plus standard of care; 8 mg/kg IV up to a maximum of 800mg with repetition of the same dosage after 12 hours Control: Standard of care	Primary: Entry into intensive care with invasive mechanical ventilation or death from any cause or clinical aggravation	Randomized parallel, open label
3. A Study to Investigate Intravenous Tocilizumab in Participants with Moderate to Severe COVID-19 Pneumonia (MARIPOSA) **Completed**	>18 years old, confirmed COVID-19 by RT-PCR Severe patients: SpO2 </= 93% or PaO2/FiO2 < 300 mmHg Moderate patients: CRP > 2 x upper limit of normal (ULN) is required	Experimental: Tocilizumab 4 mg/kg IV plus standard of care Active Comparator: Tocilizumab 8 mg/kg plus standard of care	Primary:Area Under the Curve from Day 0-28 (AUC0-d28) of Tocilizumab, Secondary: • Maximum Serum Concentration (Cmax) of Tocilizumab • Clearance (CL) of Tocilizumab • Volume of the Central Compartment (Vc) of Tocilizumab • Serum Concentration of C-reactive Protein (CRP) • Serum Concentration of Ferritin • Serum Concentration of Soluble Interleukin-6 Receptor • Serum Concentration of Interleukin-6 (IL-6)	Randomized, parallel, open label
4. A Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia (EMPACTA)	>18 years old, hospitalized COVID-19 pneumonia confirmed by RT-PCR and radiographic imaging, spO2 <94% while on ambient air (N = 388)	Experimental: Tocilizumab 8 mg/kg maximum dose 800mg plus standard of care Control: Placebo plus standard of care	Primary: Cumulative proportion of participants requiring mechanical ventilation by day 28	Randomized Parallel, Double-blind, Placebo-controlled
5. A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared with Remdesivir Plus Placebo in	>/= 12 years old, hospitalized with COVID-19 pneumonia confirmed by RT-PCR and evidenced by chest X-ray or CT scan Requiring > 6 L/min supplemental oxygen to maintain SpO2 > 93%	Experimental: Remdesivir plus Tocillizumab Control: Remdesivir plus Placebo	Primary: Time from randomization to hospital discharge or ready for discharge day 28	Randomized, parallel, doiuble-blind

Hospitalized Participants with Severe COVID-19 Pneumonia (REMDACTA) **Completed**	(N = 649)			
6. The Use of Tocilizumab in the Management of Patients Who Have Severe COVID-19 With Suspected Pulmonary Hyperinflammation	>/= 18 years old, RT-PCR positive, acute respiratory failure radiologic pneumonia, breathing spontaneously >50% Oxygen and MEWS score >7, if intubated PaO2/Fio2 </= 200 and PEEP >5 cm H2O (N = 500)	Experimental: Tocilizumab 8 mg/kg max 800mg Control: Placebo	Survival	Randomized, parallel, open label
7. Randomized, Unicentric, Open, Controlled Clinical Trial, in Phase III to Demonstrate the Effectiveness of Tocilizumab	18 -to 99 years old, bilateral pneumonia by SARS-COV-2 without response in 48 to 72 hours after starting the treatment according to local protocol, persistent elevated inflammatory markers (N = 60)	Experimental: Tocilizumab >75 kg = 600mg, <75kg = 400mg Control: Methylprednisolone 250mg IV for 3 days	Primary: Respiratory situation at 24 hours Secondary: Immune hyperactivation situation Mechanical ventilation In-hospital mortality	Randomized, parallel, open
8. Checkpoint Blockade in COVID-19 Pandemic (COPERNICO)	18 to 80 years old, confirmed COVID-19 with RT-PCR, or IgM, IgG, diagnostic confirmation of pneumonia on x-ray and CT scan, ARDS, SOFA score </= 3, total lymphocyte <0.8x106/mL, SpO2 </=92%, life expectancy of >10 years	Experimental: Tocilizumab 8 mg/kg plus Pembrolizumab 200mg Control: Standard of care	Primary: Percentage of patients with normalization of SpO2 ≥ 96% on room air	Randomized parallel, open-label
9. Low-dose Tocilizumab Versus Standard of Care in Hospitalized Patients With COVID-19 (COVIDOSE-2)	≥18 years old hospitalized, T ≥ 38 degrees C, positive test for active SARS-CoV-2 infection, radiographic evidence of infiltrates on chest radiograph (CXR) or computed tomography (CT) (N = 332)	Experimental sub study A: Tocilizumab 40mg Experimental sub study A: Tocilizumab 120mg Control A: Tocilizumab free standard of care Experimental sub study B: Tocilizumab 40mg Experimental sub study B: Tocilizumab 120mg Control B: Tocilizumab 400mg or 8mg/kg plus standard of care	Primary: Time to recovery	Randomized parallel, open label
10. COVID 19: Experimental use of tocilizumab (Roactemra®) in severe SARS-CoV-2 related pneumonia.	Positive COVID status as defined by positive RT-PCR, hospitalized patients aged ≥ 18 and ≤ 75 years old Signs of severe COVID-19 pneumonia (3 of the following): patient wheezing or unable to speak in full sentences while at rest/with minimal effort,	Experimental: Tocilizumab Control: Standard of care	Clinical status assessed using a 7-category ordinal scale at Day 28	Randomized open label

	respiratory rate >22, PaO2 <65 mmHg or SpO2 <90%, repeated chest imaging is significantly worsening despite being on standard of care, which may include anti-viral treatment, low dose steroids and antibiotics.			
11. A randomized clinical trial (IIIb) of eficacy of a single dose of Tocilizumab or a combination of Tocilizumab plus Vitamin D (single IM dose) for the treatment of the COVID-19 hyperimmune complication. Assessment of IL-6.	Moderate to severe COVID-19 patients (WHO severity scale 4-7) needing oxygen therapy At least 2 of the following: Dímer D> 1.500, CRP> 60 or Ferritin >800 Alternatively, IL-6 >40	Experimental: Tocilizumab plus Vitamin D3 2000 IU Control: Tocilizumab	Global survival rate	Randomized, open label
12. A prospective, randomized, double blinded placebo-controlled trial to evaluate the efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia (TOC-COVID)	≥ 18 years old, proof of SARS-CoV-2, severe respiratory failure: ambient air SpO2 ≤ 92% or need of ≥ 6L O2/min or NIV (non-invasive ventilation) or IMV (invasive mechanical ventilation)	Experimental: Tocilizumab Control: Placebo	Ventilator free days (d) (VFD) in the first 28 days after randomization	Randomized double-blind placebo-controlled
13. A multi-center, randomized, open-label study in patients with COVID-19 and respiratory distress not requiring mechanical ventilation, to compare standard-of-care with anakinra and tocilizumab treatment. The Immunomodulation-CoV Assessment (ImmCoVA) study	Age ≥18 years old, confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay < 3 days prior to screening SARS-CoV-2 infection with duration at least 7 days (as determined by onset of symptoms), 5 liters/minute of oxygen for at least 8 hours to maintain SpO2 at ≥93%, CRP > 70 mg/L with no non-SARS-Cov2 infections, Ferritin > 500 µg/L, at least two points on a scale of 0-3 where 1 point is awarded for each value of: lymphocytes < 1x 10(9)/L; D-dimer ≥ 0.5 mg/L and; Lactate Dehydrogenase ≥ 8 microkatal/L	Experimental: Anakinra and Tocilizumab Control: standard of care	Time to recovery [Time Frame: Day 1 through Day 29]	Randomized, open label
14. Trial of Tocilizumab for Treatment of Severe COVID-19: ARCHITECTS	Hospitalized with COVID-19 pneumonia, based on chest X-ray or CT scan AND Evidence of hyperinflammation: IL-6>40pg/mL (if available) OR CRP >2 mg/dL OR ferritin >2000 ng/mL AND iv. One or more of the following: impending need for requiring invasive or non-invasive mechanical ventilation OR shock requiring vasopressor (without evidence of bacterial / fungal infection) OR need for extracorporeal membrane oxygenation (ECMO) OR severe, refractor ARDS (PaO2/FiO2<200 mmHg)	Experimental: Tocilizumab Control: Placebo	Clinical status (on a 7-point ordinal scale) at day 28	Randomized, double blind Placebo control

15. CORIMUNO-19 - Tocilizumab Trial - TOCI (CORIMUNO-TOCI) 2	Patients included in the CORIMUNO-19 cohort Patients belonging to one of the 2 following groups: Group 1: Cases meeting all of the following criteria: Requiring more than 3L/min of oxygen, OMS/WHO progression scale = 5, No NIV or High flow Group 2: Cases meeting all of the following criteria Respiratory failure AND (requiring mechanical ventilation OR NIV OR High flow), WHO progression scale >=6, No do-not-resuscitate order (DNR order)	Experimental: Tocilizumab 8mg/kg day 1, if no response second injection Day 3 Control: Standard of care	Survival without needs of ventilator utilization WHO progression scale <=5 Cumulative incidence of successful tracheal extubation WHO progression scale <=7	Randomized, parallel open label
16. Treatment of COVID-19 Patients with Anti-interleukin Drugs (COV-AID)	Recent (≥ 6 days of flu-like symptoms or malaise yet ≤16 days of flu-like symptoms or malaise prior to randomization) infection with COVID-19. Confident COVID-19 diagnosis Presence of hypoxia signs of cytokine release syndrome Chest X-ray or CT scan showing bilateral infiltrates within last 2 days Admitted to specialized COVID-19 ward or an ICU ward taking care of COVID-19 patients Age ≥ 18 years old	Experimental: Anakinra, Siltuximab, Tocilizumab Control: Placebo and standard of care	Time to Clinical Improvement	Randomized open label
17. COVID-19: Salvage Tocilizumab as a Rescue Measures (COVISTORM) **Completed**	Hospitalized with COVID-19 disease Age >/= 18 years old SARS-CoV-2 NhO positive SpO2 </93% on ambient air or respiratory rate >30 /min Any 2 of the 4: P-IL-6 > 2 x ULN / P-ferritin > 2 x ULN / P-FIDD >1.5 mg/l / P- CRP >40 mg/l without obvious presence of bacterial infection (normal values: P -IL-6 <5.9 ng/l; P-ferritin, men 30-400 mikrog/l, women 13-150 mikrog/l ; P-FIDD (Fibrin degradation products, D-dimer) <0.5 mg/l; P-CRP <10 mg/l)	Experimental: Tocilizumab Control: Standard of care	Clinical status at day 28	Randomized Parallel Open Label
18. Efficacy of Tocilizumab in Modifying the Inflammatory Parameters of Patients With COVID-19 (COVITOZ-01) (COVITOZ-01) *Terminated*	> 18 years of age, mild-moderate SARS-CoV-2 pneumonia confirmed microbiologically ≤7 days before randomization, and presents: a. Basal oxygen saturation> 90% b. CURB-65 ≤1 c. PaO2 / FiO2≥300 or SatO2 / FiO2≥315 The patient is hospitalized or meets hospital admission criteria; the patient is not expected to enter the ICU or die in the next 24 hours.	Experimental 1: Tocilizumab single dose and standard of care Experimental 2: Tocilizumab two doses and standard of care Control: Standard of care	Change in IL-12 values in the 3 study groups from the start of treatment (D0) and on days D + 1 and D + 3	Randomized single group open label

Q10. Among patients with COVID-19, should baricitinib be used for treatment?

As of 21 October 2021

RECOMMENDATIONS

We suggest the use of baricitinib in addition to dexamethasone and remdesivir as treatment for hospitalized COVID-19 patients who require low-flow oxygen, high-flow oxygen, and non-invasive ventilation. *(Low certainty of evidence, Weak recommendation)*

There is insufficient evidence to recommend baricitinib as an alternative to tocilizumab as treatment for hospitalized COVID-19 patients. *(Very low certainty of evidence)*

Consensus Issues

The recommendation to give baricitinib in addition to dexamethasone and remdesivir was made based on 2 randomized controlled trials wherein baricitinib was given as an add-on therapy to dexamethasone and remdesivir among hospitalized patients with moderate to severe COVID-19. At present, dexamethasone, a systemic corticosteroid, is considered standard of care for patients requiring oxygen supplementation *(High quality of evidence; Strong recommendation),* while remdesivir may be considered as an additional therapy for patients who require oxygen supplementation but not on invasive mechanical ventilation *(Low quality of evidence, Conditional recommendation).* Although remdesivir is not currently considered standard care, there are studies that show possible synergistic effect in concurrently giving an anti-viral to shorten viral clearance plus an immunomodulator to address impending cytokine storm. Addition of baricitinib is recommended only for non-intubated patients (i.e., on low-flow oxygen, high-flow oxygen, and non-invasive ventilation).

As of writing, the available evidence on baricitinib is not as robust as tocilizumab, and there is only 1 retrospective observational study, which directly compared baricitinib versus tocilizumab. As such, there is insufficient evidence to make recommendations on whether baricitinib may be used as an alternative to tocilizumab. Strategies for conservation of tocilizumab is beyond the scope of the consensus panel, and may be discussed by the local expert group working on COVID-19 treatment algorithms.

PREVIOUS RECOMMENDATION

We suggest the use of baricitinib in combination with remdesivir in hospitalized COVID-19 patients requiring oxygen supplementation and who cannot take corticosteroids. *(Low quality of evidence; Conditional recommendation)*

There is insufficient evidence to recommend the use of baricitinib in combination with remdesivir and corticosteroids in hospitalized COVID-19 patients. *(Very low quality of evidence)*

There is no evidence to recommend the use of baricitinib alone in hospitalized COVID-19 patients.

Previous Consensus Issues
These recommendations were made in the context of dexamethasone being considered as a standard of care for severe or critical COVID-19 infection. The incremental benefit of giving baricitinib and remdesivir with dexamethasone remains to be a research gap.

Thus, there is insufficient evidence to recommend the use of baricitinib in combination with remdesivir and corticosteroids in hospitalized COVID-19 patients. Caution must be exercised in administering baricitinib in patients who are already taking steroids due to the likelihood of the occurrence of immunosuppression. Results showed that patients who received glucocorticoids had a higher risk of having serious or non-serious infections than those who did not.

Due to supply problems in recent months, baricitinib is currently being used locally to replace tocilizumab in regimens with both remdesivir and dexamethasone. However, using baricitinib for COVID-19 qualifies as off-label use as it is approved only for use in rheumatoid arthritis.

WHAT'S NEW IN THIS VERSION?
This version included data from 1 new randomized controlled trial (RCT).

KEY FINDINGS
The evidence on the use of baricitinib comes from 2 RCTs among hospitalized patients with moderate to severe COVID-19. Both studies found that there was a reduction in the all-cause mortalities, progression of oxygen use, and serious adverse events in the baricitinib group compared to the control group. However, there was no significant difference in the duration of hospitalization between the two groups.

INTRODUCTION
Baricitinib is an orally administered selective inhibitor of Janus kinase (JAK) 1 and 2 used in the management of rheumatoid arthritis. In vitro studies have shown that it can prevent the entry of SARS-CoV-2 virus to human cells and reduce the levels of cytokines (i.e., Interleukin-2, Interleukin-6, Interleukin-10, G-CSF, and IFN-Y) in COVID-19 patients.[1]

REVIEW METHODS
A systematic search was done from the date of the last search April 4, 2021 until September 6, 2021 using Medline, CENTRAL, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and baricitinib. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv, and biorxiv. Only randomized controlled trials that compared baricitinib against placebo or standard care were included in this review. Only randomized controlled trials were included. No limits were placed on age, COVID-19 severity, and dosing.

RESULTS
There are two (2) published studies that evaluate the use of baricitinib for treating hospitalized moderate to severe COVID-19 patients.[2,3] Both are Phase 3 trials that

had a total of 2,558 participants. One study compared baricitinib + remdesivir to remdesivir alone, with all study participants receiving standard supportive care. Glucocorticoids were given only for standard indications such as adrenal insufficiency, asthma exacerbation, laryngeal edema, septic shock, and acute respiratory distress syndrome, but not as a treatment for COVID-19.[2] The other study compared baricitinib to placebo, with all study participants receiving standard care including dexamethasone and remdesivir.[3] The studies reported the following outcomes: all-cause mortality by day 28, duration of hospitalization, and progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation or extracorporeal mechanical oxygenation (ECMO).[2,3] One study also reported the time to recovery and time to discharge.[2] The characteristics of the included studies may be found in Appendix 3.

The overall quality of evidence was rated low because of serious imprecision and inconsistency in one important outcome (adverse events). Appraisal of study quality showed no serious risk of bias in the included studies. The risk of bias summary is in Appendix 4. The GRADE evidence profile is in Appendix 5.

Pooled analysis showed a significant decrease in the all-cause mortality by day 28 in the baricitinib group among hospitalized COVID-19 patients compared to the control group (RR 0.64, 95% CI 0.50-0.82; I^2=0%). Both studies evaluated the severity of COVID-19 based on the National Institute of Allergy and Infectious Diseases Ordinal Scale (NIAID-OS) and simplified for clinical purposes (NIAID-OS score of 4: non-oxygen requiring, NIAID-OS score of 5: on low-flow oxygen, NIAID-OS score of 6: on high-flow oxygen or non-invasive ventilation, NIAID-OS score of 7: on invasive mechanical ventilation or ECMO). Subgroup analysis based on severity of the COVID-19 disease revealed that both low-flow oxygen requiring patients (RR 0.62, 95% CI 0.41-0.94; I^2=0%) and high-flow oxygen requiring patients or those on non-invasive ventilation (RR 0.59, 95% CI 0.42-0.85; I^2=0%) had reduced mortality compared to the control group. However, those not requiring oxygen (RR 0.27, 95% CI 0.03-2.39) and those on invasive mechanical ventilation or ECMO (RR 1.06, 95% CI 0.52-2.14) had no significant difference in mortality with the control group.

The progression of the use of oxygen to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO (combined endpoint) was significantly decreased in the baricitinib group versus control, although by a small margin (RR 0.87, 95% CI 0.76-0.98; I^2=4%). However, the duration of hospitalization was not significantly different between both treatment groups (MD -0.10 days, 95% CI -1.55 to 1.35; I^2=0%). One study reported no significant difference in the time to recovery of patients between both treatment groups (baricitinib group median 10 days, 95% CI 9-11, control group median 11 days, 95% CI 10-12; RR 1.11, 95% CI 0.99-1.24).[3]

Baricitinib versus tocilizumab

In a retrospective observational study, medical records of 60 patients were reviewed. The population included those with documented interstitial COVID-19 pneumonia with a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) of <300. These patients received baricitinib monotherapy (n = 12), tocilizumab monotherapy (n = 20), a combination of baricitinib and tocilizumab (n = 11) and neither of the 2 drugs (n = 17) aside from anti-virals such as remdesivir and other medications (hydroxychloroquine, azithromycin, and corticosteroids).[4] Appraisal of this study

showed serious risk of bias due to imbalance of prognostic factors with no statistical adjustments made. Summary of the risk of bias can be found in Appendix 4.

We compared the groups that received baricitinib only versus tocilizumab only. There was no significant difference in the number of days with symptoms between the 2 groups (MD -0.90, 95% CI -5.54 to 3.74), length of stay in the hospital (MD 0.90 days, 95% CI -1.82 to 3.62), and overall mortality (RR 0.83, 95% CI 0.18-3.88). However, there was significantly reduced need for ICU admission in the baricitinib only group versus the tocilizumab only group (RR 0.06, 95% CI 0-0.92). We also compared the groups that received baricitinib only versus combination baricitinib/tocilizumab. There was no significant difference in the number of days with symptoms (MD -2.10, 95% CI -6.97 to 2.77), length of stay in the hospital (MD -0.30 days, 95% CI -3.20 to 2.60), need for ICU admission (RR 0.13, 95% CI 0.01-2.30), and overall mortality (RR 0.61, 95% CI 0.12-3.00) between the 2 groups.

Safety

There were significantly less serious adverse events in the baricitinib group versus the control group (RR 0.79, 95% CI 0.67-0.94; I2=0%). The most common serious adverse events noted by the studies were development of serious infections, respiratory failure [2,3], and venous thromboembolic events.[3]

There was no significant difference found between the two groups for the number of adverse events (RR 0.91, 95% CI 0.75-1.10; I^2=84%). The most common adverse events noted in one study for the baricitinib group were decrease in glomerular filtration rate, decrease in hemoglobin, decrease in lymphocyte count, and decrease in blood glucose levels.[2]

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
US Food and Drug Administration (FDA)	Revised the Emergency Use Authorization (EUA) of baricitinib on July 2021. From the previous EUA, allowing the use of baricitinib only in combination with remdesivir, the revised EUA allows the use of baricitinib as monotherapy treatment for hospitalized moderate to severe COVID-19 patients on supplemental oxygen therapy.[5,6] The FDA recommends that baseline laboratory values (estimated glomerular filtration rate, liver enzymes and complete blood count) should be determined prior to administration of the drug to decide the suitability and dose for the patient.
National Institutes of Health (NIH) (as of October 7, 2021)	Recommends the use of baricitinib in addition to dexamethasone or remdesivir for patients who have rapidly increasing oxygen needs, require high-flow oxygen or non-invasive ventilation, and have increased inflammatory markers. However, they recommend against the use baricitinib for those who are stable enough for discharge and do not require supplemental oxygen.[9] Recommends against the use of baricitinib in combination with tocilizumab for the treatment of COVID-19. They stated insufficient evidence to recommend one drug over the other.[9]
Australian Guidelines (as of September 29, 2021)	Baricitinib should be considered for adults hospitalized with COVID-19 who require supplemental oxygen, high-flow oxygen and/or non-invasive ventilation.[10]
Infectious Diseases Society of America (IDSA) (as of October 1, 2021)	Suggests baricitinib rather than no baricitinib among hospitalized adults with severe COVID-19 (requiring supplemental oxygen, high-flow oxygen, or non-invasive ventilation) having elevated inflammatory markers but not on invasive mechanical ventilation.[11]
World Health Organization (WHO)	No recommendation on the use of baricitinib as treatment for COVID-19.[12]

RESEARCH GAPS

There are currently 10 ongoing clinical trials in *clinicaltrials.gov* on baricitinib for COVID-19 management. One trial (NCT04373044) was terminated after the release of the ACTT-2 data.[2] See Appendix 7 for details

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion: baricitinib vs control (N = 9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity
Benefits	Large (1)	Moderate (7)	Small	Uncertain	Varies (1)		• Significant reduction in all-cause mortality among hospitalized patients on low-flow oxygen (RR 0.62, 95% CI 0.41-0.94), high-flow oxygen or non-invasive ventilation (RR 0.59, 95% CI 0.42-0.85) but no difference in mortality among those not requiring oxygen or on invasive MV/ECMO • 1 panelist answered varies - clear benefit for those requiring oxygen while no benefit for those not requiring or already on invasive MV/ECMO
Harm	Large	Small (8)	Uncertain	No response			• Significantly less serious adverse events (RR 0.79, 95% CI 0.67-0.94)
Certainty of Evidence	High	Moderate (1)	Low (8)	Very low			• Low because of serious imprecision and inconsistency in one important outcome (adverse events)
Balance of effects	Favors drug (8)	Does not favor drug	Uncertain (1)				• Net potential benefit in all-cause mortality especially for those on low-flow oxygen, high-flow oxygen and non-invasive ventilation, as well as progression of oxygen use
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (4)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (1)	Moderate Cost (7)	Negligible cost	Moderate savings	Large savings (1)	• Php 19,380.48/14-day treatment course (Php 1,384.32 per 4mg tablet)
Certainty of evidence of required resources	No included studies	Very low	Low (3)	Moderate (3)	High (3)		• The cost is based on a DOH memorandum entitled OSEC-HTAC Recommendations on COVID-19 Investigational Drugs
Cost effectiveness	No included studies (4)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (4)			• None of the included trials assessed cost effectiveness.
Equity	Uncertain (2)	Reduced (3)	Probably no impact (1)	Increased (3)			
Acceptability	Uncertain (3)	No	Yes (5)	Varies (1)			
Feasibility	Uncertain (1)	No	Yes (7)	Varies (1)			

Additional considerations:

- There is need for more data on drug interactions and risk of immunosuppression

Table 2. Summary of initial judgements prior to the panel discussion: baricitinib vs tocilizumab (N=9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate (2)	Small (4)	Uncertain (2)	Trivial (1)		• No significant difference in the number of days with symptoms (MD -0.90, 95% CI -5.54-3.74), length of stay in the hospital (MD 0.90 days, 95% CI -1.82 to 3.62), and overall mortality (RR 0.83, 95% CI 0.18-3.88) • Significantly reduced need for ICU admission in the baricitinib only group versus the tocilizumab only group (RR 0.06, 95% CI 0-0.92).
Harm	Large (2)	Small (6)	Uncertain	Trivial (1)			• No severe adverse effects were documented in the baricitinib only and tocilizumab only group
Certainty of Evidence	High (1)	Moderate (2)	Low (3)	Very low (3)			• Very low – small retrospective observational study with serious risk of bias due to imbalance of prognostic factors with no statistical adjustments made
Balance of effects	Favors drug (6)	Does not favor drug (1)	Uncertain (2)				• When compared to tocilizumab, baricitinib showed no significant difference in harm or benefit in terms of reducing number of days with symptoms, length of hospital stay and all-cause mortality. • Although majority (6 out of 9) favored the drug prior to the panel discussion, the consensus panel eventually decided that there is currently insufficient evidence to base recommendations on whether baricitinib may be used as an alternative to tocilizumab
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Cost (7)	Negligible cost or savings (1)	Moderate savings (1)	Large savings	• Php 19,380.48 for a 14-day oral treatment course with baricitinib
Certainty of evidence of required resources	No included studies (1)	Very low	Low (1)	Moderate (4)	High (3)		• The cost is based on a DOH memorandum entitled OSEC-HTAC Recommendations on COVID-19 Investigational Drugs
Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison (2)	Favors the intervention (2)			• None of the included trials assessed cost effectiveness.
Equity	Uncertain (5)	Reduced (1)	Probably no impact (1)	Increased (2)			
Acceptability	Uncertain (6)	No	Yes (3)				
Feasibility	Uncertain (3)	No	Yes (6)				

Appendix 2. Search Yield and Results

Comparison 1: Baricitinib compared to standard of care or placebo

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (Baricitinib) Filters: from April 4, 2021 to September 1, 2021	Sep 6, 2021 9AM	51	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 AND (Baricitinib) Filters: from April 4, 2021 to September 1, 2021	Sep 6, 2021 915 AM	468	0
Google Scholar	Baricitinib AND COVID AND randomized trial	Sep 6, 2021 10 AM	15	2
COVID-NMA initiative	Baricitinib	Sep 6, 2021 1015 AM	2	0
ClinicalTrials.gov	COVID-19 AND baricitinib	Sep 6, 2021 1020 AM	21	0
Chinese Clinical Trial Registry	Baricitinib	Sep 6, 2021 1040 AM	2	0
EU Clinical Trials Register	Baricitinib	Sep 6, 2021 1045 AM	45	0
Republic of Korea - Clinical Research Information Service	Baricitinib	September 6, 2021 1050 AM	2	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Baricitinib	Sep 6, 2021 11 AM	27	0
CenterWatch	Baricitinib	Sep 6, 2021 1115 AM	0	0
chinaxiv.org	Baricitinib	Sep 6, 2021 1120 AM	0	0
Medrxiv.org	Baricitinib	Sep 6, 2021	22	1

	Filters: April 4, 2021 to September 6, 2021	1130 AM		
Biorxiv.org	Baricitinib Filters: April 4, 2021 to September 6, 2021	Sep 6, 2021 1145 AM	23	0

Comparison 2: Baricitinib compared to tofacitinib

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (Baricitinib) AND (Tocilizumab)	Sep 16, 2021 3PM	48	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 AND (Baricitinib) AND (Tocilizumab)	Sep 16, 2021 330PM	530	0
Google Scholar	Baricitinib AND COVID AND tocilizumab	Sep 16, 2021 4PM	1160	1
COVID-NMA initiative	Baricitinib AND tocilizumab	Sep 16, 2021 415 PM	2	0
ClinicalTrials.gov	Covid-19 AND baricitinib AND tocilizumab	Sep 16, 2021 430PM	1	0
Chinese Clinical Trial Registry	Baricitinib AND Tocilizumab	Sep 16, 2021 440 PM	0	0
EU Clinical Trials Register	Baricitinib AND Tocilizumab	Sep 16, 2021 445PM	0	0
Republic of Korea - Clinical Research Information Service	Baricitinib AND Tocilizumab	Sep 16, 2021 5PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Baricitinib AND Tocilizumab	Sep 16, 2021 515PM	0	0
CenterWatch	Baricitinib AND Tocilizumab	Sep 16, 2021 520 PM	0	0
chinaxiv.org	Baricitinib AND Tocilizumab	Sep 16, 2021 530 PM	0	0
Medrxiv.org	Baricitinib AND Tocilizumab	Sep 16, 2021 540 PM	0	0
Biorxiv.org	Baricitinib AND Tocilizumab	Sep 16, 2021 6PM	0	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
Baricitinib compared to standard of care				
Baricitinib plus Remdesivir for Hospitalized Adults with COVID-19 (ACTT-2) *Kalil AC et al. (USA)*	Hospitalized moderate to severe COVID-19 patients (N = 1,033) Duration of follow-up: 28 days	EXPERIMENTAL: Baricitinib (4mg tab daily for 14 days) + Remdesivir (20mg on first day then 10 mg/day for the next 9 days) CONTROL: Remdesivir (20mg on first day then 10 mg/day for the next 9 days)	PRIMARY: Time to recovery SECONDARY: Clinical status at day 15, time to improvement, time to discharge, number of days of receipt of supplemental oxygen, non-invasive ventilation or high-flow oxygen, and invasive ventilation or ECMO, incidence and duration of new use of oxygen, all-cause mortality, and adverse events	Randomized, double-blind, placebo-controlled
Efficacy and Safety of Baricitinib for the Treatment of Hospitalized Adults with COVID-19 (COV-BARRIER): A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Trial *Marconi VS et al., (Asia, Europe, USA, South America)*	Hospitalized moderate to severe COVID-19 patients (N = 1,525) Duration of follow-up: 28 days	EXPERIMENTAL: Baricitinib 4mg tablet + Standard of care CONTROL: Standard of care	PRIMARY: Proportion of patients who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation or death SECONDARY: All-cause mortality by day 28 and adverse events	Randomized, double-blind, placebo-controlled
Baricitinib compared to tocilizumab				
Experience with the use of baricitinib and tocilizumab monotherapy or combined, in patients with interstitial pneumonia secondary to Coronavirus COVID-19: A real-world study *Rosas J et al. (Spain)*	Hospitalized COVID-19 patients with documented interstitial pneumonia and PaO_2/FiO_2 <300 (N = 60) Duration of follow-up: 30 days	GROUP 1: Baricitinib monotherapy GROUP 2: Tocilizumab monotherapy GROUP 3: Combined baricitinib/tocilizumab GROUP 4: No baricitinib/tocilizumab	Days with symptoms Days of admission Severe adverse effects Admission to ICU Overall mortality since admission	Retrospective observational

Appendix 4. Study Appraisal

Figure 1. Risk of bias summary for baricitinib only versus standard of care/placebo studies

Table 1. Appraisal for the observational study (baricitinib versus tocilizumab)

Did the intervention in question precede the undesirable outcome?	Yes, the intervention (baricitinib) preceded the outcome
Were important prognostic factors balanced at the time of exposure? If not, were statistical adjustments made for these factors?	No, the baseline characteristics were different and patients were unmatched. There was no mention that statistical adjustments were made to compensate for the differences.
Were unbiased criteria used to determine exposure in all patients?	Yes, the patients received baricitinib, tocilizumab, both baricitinib and tocilizumab, or neither of the 2 drugs.
Were unbiased criteria used to detect the outcome in all patients?	Yes, outcomes were defined.
Was follow-up rate adequate?	Yes, there was no attrition rate since this is a retrospective study.

Appendix 5. GRADE Evidence Profile

Author(s): Isabella S. Ocampo, MD
Question: Baricitinib compared to Standard of care for COVID-19
Setting: In-hospital
Bibliography: 1. [Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021;384(9):795-807. 2. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021. doi:10.1016/S2213-2600(21)00331-3.

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baricitinib	Standard of care	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (over-all) (follow up: 28 days)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious [a]	None	86/1277 (6.7%)	137/1274 (10.8%)	**RR 0.63** (0.49 to 0.81)	**40 fewer per 1,000** (from 55 fewer to 20 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Duration of hospitalization (follow up: 28 days)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious [b]	None	1277	1274	-	MD **0.1 days lower** (1.55 lower to 1.35 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Progression of oxygen use (follow up: 28 days)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious [c]	None	328/1279 (25.6%)	379/1279 (29.6%)	**RR 0.87** (0.76 to 0.98)	**39 fewer per 1,000** (from 71 fewer to 6 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse events (follow up: 28 days)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious [c]	None	191/1265 (15.1%)	242/1270 (19.1%)	**RR 0.79** (0.67 to 0.94)	**40 fewer per 1,000** (from 63 fewer to 11 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events (follow up: 28 days)												
2	Randomised trials	Not serious	Serious [d]	Not serious	Serious [b]	None	602/1257 (47.9%)	661/1261 (52.4%)	**RR 0.91** (0.75 to 1.10)	**47 fewer per 1,000** (from 131 fewer to 52 more)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations
[a] There is a small number of events.
[b] There is a wide confidence interval.
[c] Upper limit of confidence interval crosses the threshold for meaningful benefit.
[d] There is significant heterogeneity.

Author(s): Isabella S. Ocampo, MD
Question: Baricitinib compared to Tocilizumab for COVID-19
Setting: In-hospital
Bibliography: Rosas J, Liano FP, Canto ML et al. Experience with the use of baricitinib and tocilizumab monotherapy or combined, in patients with interstitial pneumonia secondary to Coronavirus COVID19: A real-world study. Reumatol Clin. 2020. https://doi.org/10.1016/j.reuma.2020.10.009

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Days with symptoms (follow up: 30 days)									
1	Observational studies	Serious [a]	Not serious	Not serious	Serious [b]	None	There is no significant difference between baricitinib only versus tocilizumab only (MD -0.90, 95% CI -5.54 to 3.74) and baricitinib only versus combination baricitinib + tocilizumab (MD -2.10, 95% CI -6.97 to 2.77).	⊕◯◯◯ VERY LOW	CRITICAL
Length of hospital stay (follow up: 30 days)									
1	Observational studies	Serious [a]	Not serious	Not serious	Serious [b]	None	There is no significant difference between the baricitinib only versus tocilizumab only groups (MD 0.90 days, 95% CI -1.82 to 3.62) as well as the baricitinib only versus combination baricitinib + tocilizumab groups (MD -0.30 days, 95% CI -3.20 to 2.60).	⊕◯◯◯ VERY LOW	CRITICAL
Need for ICU admission (follow up: 30 days)									
1	Observational studies	Serious [a]	Not serious	Not serious	Serious [b]	None	There was significantly less ICU admissions in the baricitinib only group versus the tocilizumab only group though with minimal effect (RR 0.06, 95% CI 0-0.92) but there was no significant difference between the baricitinib only group versus the combination baricitinib + tocilizumab group (RR 0.13, 95% CI 0.01-2.30).	⊕◯◯◯ VERY LOW	CRITICAL
Overall mortality (follow up: 30 days)									
1	Observational studies	Serious [a]	Not serious	Not serious	Serious [b]	None	There was no significant difference between the baricitinib only versus tocilizumab only groups (RR 0.83, 95% CI 0.18-3.88) and the baricitinib only versus combination baricitinib + tocilizumab groups (RR 0.61, 95% CI 0.12-3.00).	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations
[a] There is a serious risk of bias due to imbalance of prognostic factors with no statistical adjustments made.
[b] There is a small sample size and wide confidence intervals.

Appendix 6. Forest Plots

Baricitinib versus standard of care

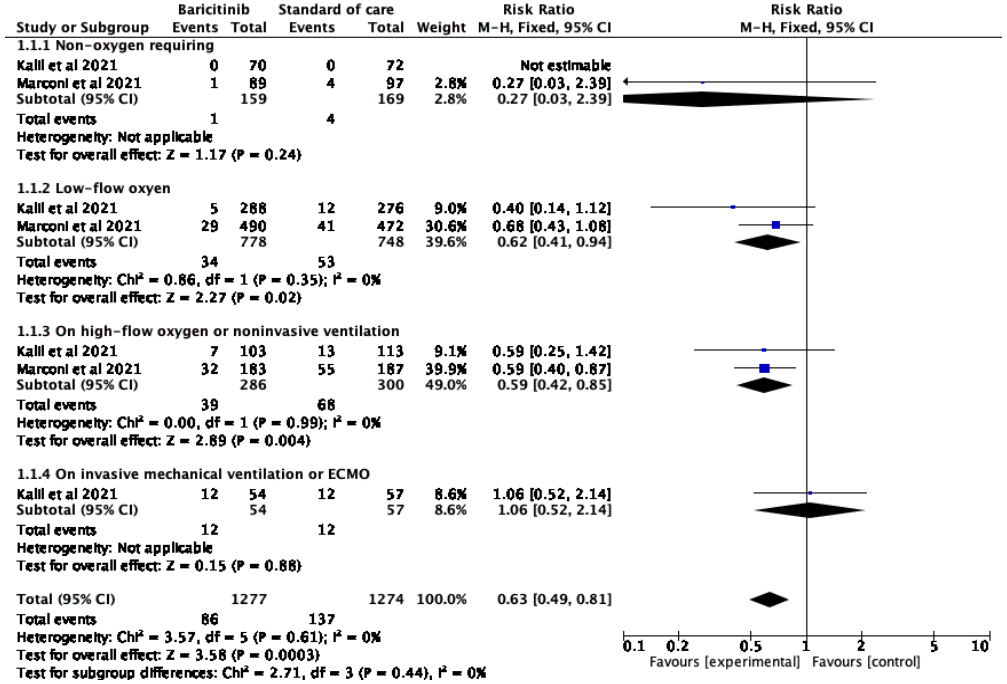

Figure 1. All-cause mortality by oxygen requirement

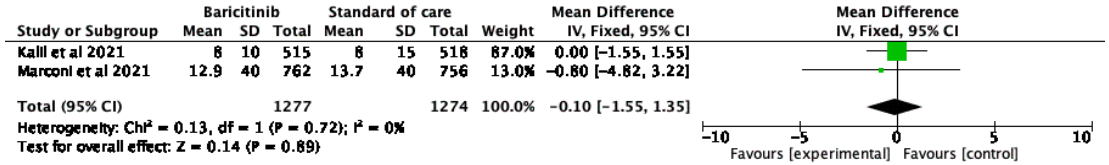

Figure 2. Duration of hospitalization

Figure 3. Progression of oxygen use

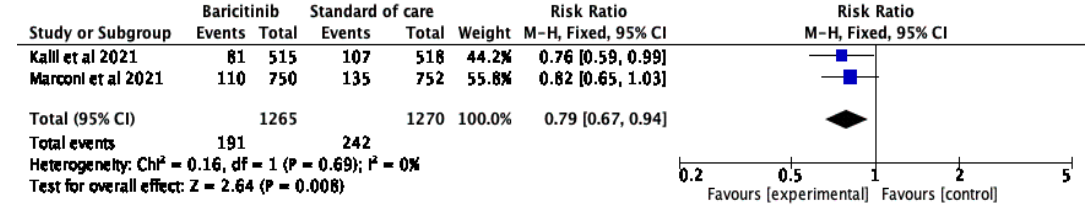

Figure 4. Serious adverse events

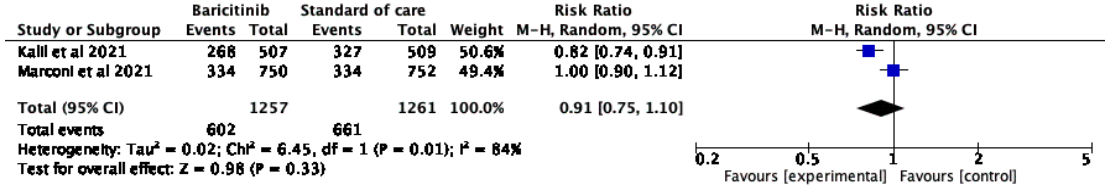

Figure 5. Adverse events

Appendix 7. Table of Ongoing Studies

Clinical Trial Identifier/Title	Participants	Interventions	Outcome
NCT04693026 Efficacy of Remdesivir and Baricitinib for the Treatment of Severe COVID 19 Patients	COVID-19 COVID-19 ARDS	Remdesivir + Baricitinib vs. Remdesivir + Tocilizumab	Time to Clinical Improvement (TTCI) Mortality Rate Duration of ICU stay Duration Total Hospital stay Rate of Daily Supplemental Oxygen Use Time to Clinical Failure
NCT04393051 Baricitinib Compared to Standard Therapy in Patients With COVID-19	COVID-19 Pneumonia	Baricitinib Oral Tablet vs. Standard of care	Need of invasive mechanical ventilation Mortality Time to invasive mechanical ventilation Time to independence from non-invasive mechanical ventilation Time to independence from oxygen therapy Time to improvement in oxygenation for at least 48 hours Length of hospital stay Length of ICU stay Instrumental response Proportion of adverse events
NCT04640168 Adaptive COVID-19 Treatment Trial 4 (ACTT-4)	COVID-19	Baricitinib and Remdesivir vs. Dexamethasone and Remdesivir	The proportion of subjects not meeting criteria for one of the following two ordinal scale categories at any time: 8) Death; 7) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) Change from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), creatinine, d-dimer concentration, glucose, hemoglobin, platelets, prothrombin time (PT), total bilirubin, white blood cell count (WBC) with differential Cumulative incidence of Grade 3 and 4 clinical and/or laboratory adverse events (AEs) Cumulative incidence of serious adverse events (SAEs) Days of invasive mechanical ventilation/ extracorporeal membrane oxygenation (ECMO) Days of non-invasive ventilation/high flow oxygen Days of supplemental oxygen Desirability of Outcome Ranking (DOOR) Duration of hospitalization Incidence of discontinuation or temporary suspension of study product administration 14-day mortality 28-day mortality Clinical status Time to an improvement of one category from baseline using an ordinal scale Time to an improvement of two categories from baseline using an ordinal scale Time to recovery
NCT04390464 Multi-arm Therapeutic Study in Pre-ICU Patients Admitted With COVID-19 - Repurposed Drugs (TACTIC-R)	COVID19	Ravulizumab vs. Baricitinib vs. Standard of care	Time to incidence of the composite endpoint of: Death, Mechanical ventilation, ECMO, Cardiovascular organ support, or Renal failure Change in clinical status from baseline Adverse events of special interest in each treatment arm Time to Sp02 >94% on room air Time to first negative SARS-CoV2 PCR Duration of oxygen therapy Duration of hospitalization

			All-cause mortality at day 28 Time to clinical improvement
NCT04381936 Randomised Evaluation of COVID-19 Therapy	Severe Acute Respiratory Syndrome	Lopinavir-Ritonavir Corticosteroid Hydroxychloroquine Azithromycin Convalescent plasma Tocilizumab Immunoglobulin Synthetic neutralising antibodies Aspirin Colchicine Baricitinib Anakinra Dimethyl fumarate Standard of care	All-cause mortality Duration of hospital stay Composite endpoint of death or need for mechanical ventilation or ECMO
NCT04832880 Factorial Randomized Trial of Remdesivir and Baricitinib Plus Dexamethasone for COVID-19 (the AMMURAVID Trial)	Confirmed COVID-19 patients on oxygen therapy or with documented cytokine storm	Dexamethasone + remdesivir Baricitinib + dexamethasone Remdesivir + baricitinib Standard of care (dexamethasone)	Prevention of very severe respiratory failure or mortality Prevention of mortality (Days 7, 14, 21, 28) Survival analysis Prevention of severe respiratory failure (Days 7, 14, 21, 28) Adverse events Reduction of requirement of tracheal intubation/ECMO Time to clinical improvement Time to discharge
EUCTR2020-001321-31-ES Prospective, phase II, randomized, open-label, parallel group study to evaluate the efficacy of hydroxychloroquine together with baricitinib, imatinib or early lopinavir / ritonavir in patients with SARS Cov2 pneumonia (COVID-19 HUF) - COVID-19 HUF	Confirmed COVID-19 patients with documented pneumonia	Hydroxychloroquine + baricitinib Hydroxychloroquine + imatinib Hydroxychloroquine + lopinavir/ritonavir Standard of care	Time to clinical improvement Adverse events
NCT04346147 Prospective, Phase II, Randomized, Open-label, Parallel Group Study to Evaluate the Efficacy of Baricitinib, Imatinib or Supportive Treatment in	Confirmed COVID-19 patients with documented pneumonia (radiologic or positive detection of SARS-CoV-2	Imatinib Baricitinib Supportive treatment	Time to clinical improvement Adverse events

Patients with SARS Cov2 Pneumonia	RNA in respiratory sample)		
NCT04321993 Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients	Patients with moderate to severe COVID-19 infection	Baricitinib vs Standard of care	Clinical status Length of time to clinical improvement Development of ARDS after treatment Time to clinical progression Duration of hospitalization and mechanical ventilation (if applicable) Adverse events
NCT04891133 European DisCoVeRy for Solidarity: An Adaptive Pandemic and Emerging Infection Platform Trial	Patients with moderate to severe COVID-19 infection	Baricitinib vs Placebo	Occurrence of death Occurrence of disease progression SpO2/FiO2-ratio Time to sustained recovery Time to first hospital discharge Viral clearance during hospitalization Adverse events

Q11. Among patients with COVID-19, should imatinib be used for treatment?

As of 8 November 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of imatinib among patients with COVID-19 infection. *(Low certainty of evidence)*

Consensus issues
Further trials are needed to recommend the use of imatinib for the treatment of COVID-19.

KEY FINDINGS

There is one (1) randomized controlled trial (RCT) that investigated the effect of imatinib compared to placebo as treatment for hospitalized patients with COVID-19 requiring supplemental oxygen. Imatinib was associated with significant reduction in the duration of mechanical ventilation and duration of intensive care unit (ICU) stay. However, there was no significant benefit for several outcomes such as mortality at day 28, need for ICU admission, need for mechanical ventilation, discontinuation of supplemental oxygen and mechanical ventilation, discontinuation of ventilation and supplemental oxygen in 48 hours, and duration of hospital admission. There was also no significant difference in the number of adverse events. The overall certainty of evidence was rated low; evidence was downgraded for serious risk of bias and imprecision due to wide confidence intervals and small number of events.

INTRODUCTION

Imatinib is an oral anti-cancer agent that inhibits the activity of some tyrosine kinases originally designed to treat Chronic Myeloid Leukemia.[1] Although imatinib was originally designed to inhibit the BCR-Abl fusion protein, it also inhibits several other kinases including c-Abl, Abl-related gene (Arg), c-kit, and platelet-derived growth factor receptor (PDGFR). These kinases are involved in regulating vascular permeability, suggesting that imatinib may have a potential role in attenuating inflammation and restoring vascular integrity in inflammatory leak syndrome.[2] Imatinib has also shown in vitro anti-viral properties against severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), which are phylogenetically related to SARS-CoV-2.[3]

Imatinib can be useful for treating pneumonia from SARS-CoV-2 infection, as it has shown promise in treating pulmonary diseases.[4] It improved the status of patients with pulmonary and systemic vascular leak.[5] Imatinib has been found to prevent pulmonary damage by reducing tissue edema and maintaining endothelial barrier integrity in murine models of acute inflammatory lung injury.[6]

REVIEW METHODS

A systematic search was done on September 10 to 11, 2021 using Medline, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and imatinib. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial

registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. Only randomized controlled trials that compared imatinib against placebo or standard of care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, need for mechanical ventilation, hospital length of stay, time to clinical improvement or recovery, improvement in radiographic findings, virologic clearance by PCR test, or adverse events. No limits were placed on age, COVID-19 severity, and dosing strategy of imatinib.

RESULTS

We found one (1) randomized double-blind, placebo-controlled trial that included a total of 400 COVID-19 patients in 13 hospitals followed-up for 28 days.[7] The study recruited hospitalized patients requiring supplemental oxygen administration and compared the use of imatinib with placebo in treating COVID-19, with all study participants receiving standard of care. The median age of the participants was 64 years and 69% were male. The characteristics of the included study are summarized in Appendix 3.

The overall certainty of evidence was rated low due to serious risk of bias and imprecision due to wide confidence intervals and small number of events. There were issues with selection and attrition bias. The risk of bias summary is shown in Appendix 4. The GRADE evidence summary is in Appendix 5.

There was no significant difference in the number of patients who discontinued supplemental oxygen and mechanical ventilation for more than 48 consecutive hours in the imatinib group and placebo group (RR 1.07, 95% CI 0.96,1.19). There was also no significant difference in the discontinuation of supplemental oxygen and mechanical ventilation (HR 1.07, 95% CI 0.62,1.84).

The imatinib group had significantly reduced risk of mortality at day 28 compared to the placebo group (RR 0.53, 95% CI 0.29, 0.96). However, there was no significant difference in mortality after adjustment for baseline imbalances (adjusted HR 0.52, 95% CI 0.26, 1.05). There was no significant difference in need for intensive care unit admissions (RR 1.13, 95% CI 0.74, 1.71) and need for mechanical ventilation (RR 0.98, 95% CI 0.76, 1.25; adjusted HR 1.02, 95% CI 0.80, 1.30).

The median duration of mechanical ventilation was significantly shorter for the imatinib group at 7 days (IQR 3-13) compared with the placebo group at 12 days (IQR 6-20), p-value = 0.008. The duration of hospital admission was not significantly different with a median of 7 days (IQR 4-11) for the imatinib group and 6 days (IQR 3-11) for the placebo group, p-value = 0.51. The median duration of ICU stay for the imatinib group was also significantly shorter at 8 days (IQR 5-13) compared to the placebo group at 15 days (IQR 7-21), p-value = 0.025.

Adverse events

The study also measured safety outcomes as occurrences of Grade 3, 4, and 5 adverse events (Grade 3 is categorized as severe or medically significant but not immediately life-threatening; Grade 4 means life-threatening consequences indicating urgent intervention; and Grade 5 is death). The number of adverse events did not differ significantly in the treatment and placebo arms (RR 1.06, 95% CI 0.85, 1.32). The most common Grade 3 adverse events were thromboembolic events, decrease

lymphocyte counts, alkalosis, and hyperglycemia while the most frequent Grade 4 adverse event was acute respiratory distress syndrome or ARDS.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Australian COVID-19 Guidelines (version 43.0, as of September 29, 2021)	The panel deems the evidence as insufficient to promote the use of imatinib outside of clinical trials, and is awaiting publication of additional studies before developing a recommendation.[10]
World Health Organization Living Guidelines (as of September 24, 2021)	No recommendations on imatinib as treatment for COVID-19.[11-13]
NIH COVID-19 Guidelines (as of October 7, 2021)	
Infectious Diseases Society of America (IDSA) Guidelines on Treatment and Management of Patients with COVID-19 (as of October 1, 2021)	

Imatinib is 1 of the 3 new medications included in the SOLIDARITY Plus Trial [14], which is currently ongoing in 52 countries.

RESEARCH GAPS

There are 11 studies registered in various clinical trial registries, 1 of which was prematurely ended due to undisclosed reasons. There are 2 studies evaluating intravenous imatinib and 6 studies involving the oral route. The doses of the treatment arms range from 200 to 800mg given for 14 to 21 days. The characteristics of ongoing studies are summarized in Appendix 6.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 6)

FACTORS	JUDGEMENT (N = 6)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					
Benefits	Large	Moderate (6)	Small	Uncertain			• Reduced risk of mortality at day 28 (RR 0.53, 95% CI 0.29-0.96) but no difference in mortality after baseline adjustment for imbalance (adjusted HR 0.52, 95% CI 0.26-1.05) • Shorter median duration of mechanical ventilation at 7 days (IQR 3-13) at 12 days (IQR 6-20), p-value = 0.008 • Median duration of ICU stay was shorter at 8 days (IQR 5-13) compared to the placebo group at 15 days (IQR 7-21), p-value = 0.025
Harm	Large	Small (4)	Uncertain (2)				• The number adverse events did not differ significantly in the treatment and placebo arms (RR 1.06, 95% CI 0.85-1.32).
Certainty of Evidence	High	Moderate (1)	Low (5)	Very low			• Low due to very serious issues with imprecision in 6 critical outcomes and a very small sample size
Balance of effects	Favors drug	Does not favor drug (5)	Uncertain (1)				• Imatinib was associated with significant benefit in mortality at day 28, duration of mechanical ventilation, and duration of intensive care unit (ICU) stay • No significant difference in the number of adverse events
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Cost (4)	Negligible cost	Moderate savings (2)	Large savings	• One 100mg tablet of imatinib costs Php 125.89 and the total cost of treatment per patient is Php 5,539.16 when given for 10 days
Certainty of evidence of required resources	No included studies	Very low (2)	Low (2)	Moderate (1)	High (1)		
Cost effectiveness	No included studies (4)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (3)	Reduced (1)	Probably no impact	Increased (2)			
Acceptability	Uncertain (5)	No	Yes (1)				
Feasibility	Uncertain (5)	No	Yes (1)				

Appendix 2. Search and Yield Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline https://pubmed.ncbi.nlm.nih.gov/	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND IMATINIB	Sept 11,2021	46	3
CENTRAL https://www.cochranelibrary.com/advanced-search	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND IMATINIB	Sept 10,2021	18 trials	11
Google Scholar	coronavirus, SARS COV 2,COVID-19, Imatinib	Sept 10,2021	407	2
COVID-NMA initiative https://covid-nma.com/	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 10,2021	1	1
ClinicalTrials.gov https://clinicaltrials.gov/	coronavirus, SARS COV 2,COVID-19, Imatinib	Sept 11,2021	6	6
Chinese Clinical Trial Registry http://www.chictr.org.cn/searchprojen.aspx	coronavirus, SARS COV 2 COVID-19, Imatinib	Sept 10,2021	0	0
EU Clinical Trials Register https://www.clinicaltrialsregister.eu/	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 11,2021	8	5
Republic of Korea – Clinical Research Information Service https://cris.nih.go.kr/cris/info/introduce.do?search_lang=E&lang=E	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 10,2021	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search https://rctportal.niph.go.jp/en/	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 10,2021	0	0
CenterWatch https://www.centerwatch.com/clinical-trials/listings/	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 10,2021	0	0
chinaxiv.org	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 10,2021	0	0
Medrxiv.org	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 11,2021	14	0
Biorxiv.org	coronavirus, SARS COV 2 COVID-19, Imatinib	Sept 11,2021	34	0

Appendix 3. Characteristics of Included Study

Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Imatinib in patients with severe COVID-19: A randomized, double blind, placebo controlled, clinical trial *Aman et al., 2021*	N = 400 18 years old and above Hospitalized patients with COVID-19 requiring supplemental oxygen Duration of follow-up: 28 days	Experimental: Imatinib 800mg loading dose (day 0) then 400mg once daily (days 1 to 9) Control: Placebo	Primary: Time to discontinuation of ventilation and supplemental oxygen for more than 48 hours Secondary: Mortality at 28 days, ICU admissions, length of ICU and hospital admission, and need for and duration of mechanical ventilation	Randomized Double-blind Placebo-controlled

Appendix 4. Study Appraisal

Aman et al. 2021

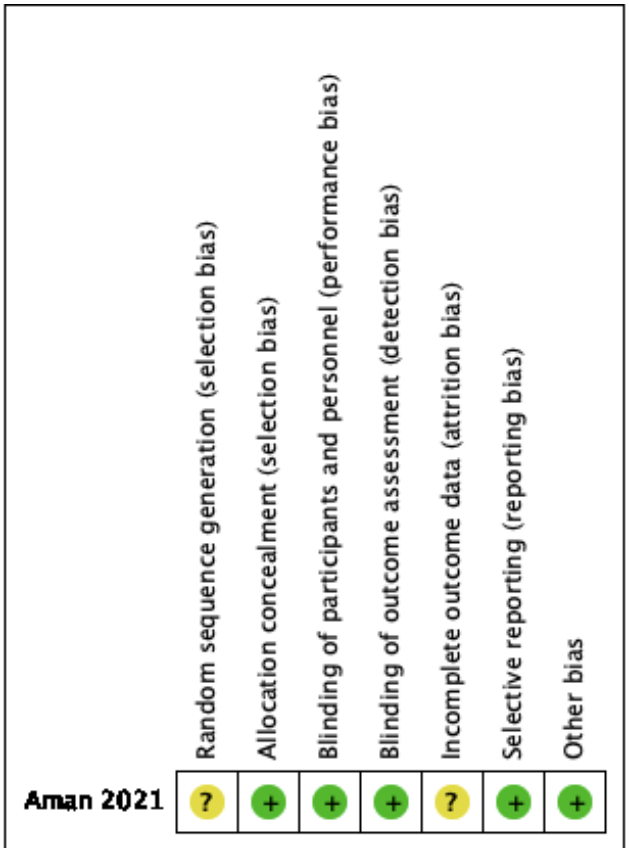

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Fides Roxanne M. Castor, MD
Question: Imatinib compared to Standard of Care or Placebo for Covid-19 Infection
Setting: In-hospital
Bibliography: Aman, J., Duijvelaar, E., Botros, L., Kianzad, A., Schippers, J., Smeele, P., Azhang, S., Bartelink, I., Bayoumy, A., Bet, P., Boersma, W., Bonta, P., Boomars, K., Bos, L., van Bragt, J., Braunstahl, G., Celant, L., Eger, K., Geelhoed, J., van Glabbeek, Y., Grotjohan, H., Hagens, L., Happe, C., Hazes, B., Heunks, L., van den Heuvel, M., Hoefsloot, W., Hoek, R., Hoekstra, R., Hofstee, H., Juffermans, N., Kemper, E., Kos, R., Kunst, P., Lammers, A., van der Lee, I., van der Lee, E., Maitland-van der Zee, A., Mau Asam, P., Mieras, A., Muller, M., Neefjes, E., Nossent, E., Oswald, L., Overbeek, M., Pamplona, C., Paternotte, N., Pronk, N., de Raaf, M., van Raaij, B., Reijrink, M., Schultz, M., Serpa Neto, A., Slob, E., Smeenk, F., Smit, M., Smits, A., Stalenhoef, J., Tuinman, P., Vanhove, A., Wessels, J., van Wezenbeek, J., Vonk Noordegraaf, A., de Man, F. and Bogaard, H., 2021. Imatinib in patients with severe COVID-19: a randomised, double-blind, placebo-controlled, clinical trial. The Lancet Respiratory Medicine, 9(9), pp.957-968.

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc with standard of care	Standard of care alone	Relative (95% CI)	Absolute (95% CI)		
Mortality (D28)												
1	Randomised trials	Serious [a]	Not serious	Not serious	Serious[b]	None	15/197 (7.6%)	27/188 (14.4%)	**HR 0.52** (0.26 to 1.05)	**66 fewer per 1,000** (from 104 fewer to 7 more)	⊕⊕◯◯ LOW	CRITICAL
Discontinuation of oxygen support/Mechanical Ventilation for >48 hours												
1	Randomised trials	Serious [a]	Not serious	Not serious	Serious[c]	None	160/197 (81.2%)	143/188 (76.1%)	**RR 1.07** (0.96 to 1.19)	**53 more per 1,000** (from 30 fewer to 145 more)	⊕⊕◯◯ LOW	CRITICAL
Admitted to the ICU												
1	Randomised trials	Serious [a]	Not serious	Not serious	Serious[c]	None	39/197 (19.8%)	33/188 (17.6%)	**RR 1.13** (0.74 to 1.71)	**23 more per 1,000** (from 46 fewer to 125 more)	⊕⊕◯◯ LOW	CRITICAL
Need for Intubation and Mechanical Ventilation												
1	Randomised trials	Serious [a]	Not serious	Not serious	Serious[c]	None	30/197 (15.2%)	26/188 (13.8%)	**HR 1.02** (0.80 to 1.30)	**3 more per 1,000** (from 26 fewer to 38 more)	⊕⊕◯◯ LOW	CRITICAL

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc with standard of care	Standard of care alone	Relative (95% CI)	Absolute (95% CI)	CERTAINTY	IMPORTANCE
Adverse Events												
1	Randomised trials	Serious [a]	Not serious	Not serious	Serious[c]	None	91/197 (46.2%)	82/188 (43.6%)	**RR 1.06** (0.85 to 1.32)	**26 more per 1,000** (from 65 fewer to 140 more)	⊕⊕◯◯ LOW	IMPORTANT
Duration of Mechanical ventilation												
1	Randomised trials	Serious [a]	Not serious	Not serious	Serious[b]	None	Median duration of mechanical ventilation was shorter for the imatinib group at 7 days (IQR 3-13) compared with the placebo group at 12 days (IQR 6-20) with a p value of 0.008				⊕⊕◯◯ LOW	IMPORTANT
Length of Hospital Admission												
1	Randomised trials	Serious [a]	Not serious	Not serious	Serious[b,d]	None	Median duration of hospital admission was 7 days (IQR 4-11) for the Imatinib group and 6 dyas (IQR3-11) for the placebo group with a p value of 0.51				⊕⊕◯◯ LOW	IMPORTANT
Duration of ICU admission												
1	Randomised trials	Serious [a]	Not serious	Not serious	Serious[b]	None	Median duration of ICU stay for the Imatinib group was shorter at 8days (IQR 5-13) compared to the placebo group at 15 days (IQR 7-21) with a p value of 0.025				⊕⊕◯◯ LOW	IMPORTANT

CI: confidence interval; **HR:** hazard Ratio; **RR:** risk ratio

Explanations

[a] selection and attrition bias
[b] only 1 study used, n =400
[c] wide confidence interval, only 1 study used, n =400
[d] p value not significant

Appendix 6. Characteristics of Ongoing Studies

Study Title	Patients (N)	Interventions	Outcomes	Method
1.Randomized Double-Blind Placebo-Controlled Trial on the Safety and Efficacy of Imatinib for Hospitalized Adults with COVID-19	Target N = 204 1. Hospitalized patients 2. ≥ 18 years of age 3. Positive RT-PCR assay for SARS-CoV-2 in the respiratory tract sample	Experimental: Imatinib oral 400mg daily for 14 days Control: Placebo oral tablet for 14 days	Improved Clinical status on an 8-category ordinal scale	Randomized Parallel assignment Open label
2. A Randomized, Double-blind, Multicentre 2-arm, Parallel-group, Placebo-controlled Study to Investigate the Efficacy and Safety of Intravenous Imatinib Mesylate in Reducing the Severity of Hypoxemic Respiratory Failure in Patients with Critical COVID-19 Receiving Standard of Care.	Target N = 84 1. ≥18 years 2. negative serum pregnancy test to confirm eligibility 3. SARS-CoV-2 infection confirmed by RT-PCR laboratory test 4. Moderate - severe ARDS 5.Requires intubation or is currently intubated and has been for ≤ 48 hours	Experimental: Intravenous imatinib mesylate Control: Intravenous placebo- matched	Change from baseline in Oxygen Saturation Index (OSI) at day 10	Randomized Parallel assignment Triple masking
3. Prospective, Phase II, Randomized, Open-label, Parallel Group Study to Evaluate the Efficacy of Baricitinib, Imatinib or Supportive Treatment in Patients With SARS-CoV-2 Pneumonia	N = 168 1. ≥ 18 years 2. Confirmed diagnosis Pneumonia COVID-19 3. ECOG functional state 0 or 1 4. Less than 10 days from onset of symptoms 5. No contraindication for medication 6. ECG QT < 440 ms males and < 460 ms females 7. Adequate liver, kidney and hematological function (or within the safety range to use these drugs)	Experimental: Imatinib 400mg Baricitinib 4mg Control: Supportive treatment	Primary Outcome: Clinical Improvement Secondary: Safety and Tolerability of treatments	Randomized Parallel assignment Open label
4. A Randomized, Double-blind, Placebo-controlled Study to Investigate the Safety and Efficacy of Intravenous Imatinib Mesylate (Impentri®) in Subjects with Acute Respiratory Distress Syndrome Induced by COVID-19	Target N = 90 1. Age ≥ 18 years 2. Moderate-severe ARDS, 3. PCR positive for SARS-CoV-2 within the current disease episode	Experimental: Intravenous imatinib mesylate Control: Intravenous placebo solution	Primary: Change in extravascular lung water index (EVLWi) between day 1 and day 4, measured by PiCCO catheter	Randomized Double-blind parallel-group placebo-controlled multi-centre
5. Imatinib for the Treatment of SARS-CoV-2 Induced Pneumonia: A Pilot Study	Target N = 30 1. Age ≥ 18 years 2. PCR positive for SARS-CoV-2 3. Hospitalized with moderate to severe respiratory symptoms as assessed by the Egyptian Ministry of Health National Guidelines	Experimental: Imatinib standard dose 400mg oral tablet once daily for 21 days + standard of care Imatinib low dose 200mg oral tablet once daily for 21 days + standard of care Control: Standard of care	Proportion of patients with COVID-19 pneumonia progressed to critical illness in need for invasive mechanical ventilation	Randomized Parallel assignment Open-label
6. A Randomized Non-Comparative Phase 2 Pilot Study Testing the value of Imatinib Besylate as an early treatment of COVID-19 Disease in aged hospitalized patents	Target N = 99 1. Age > 70 years 2. COVID-19 disease by SARS-CoV-2 RT-PCR 3. ≤ 7 days of COVID-19 disease 4. Non-severe COVID-19	Experimental: Imatinib 800 mg/day for 14 days Control: Standard of care	Prevention of severe COVID-19 disease in hospitalized aged patients. [Time Frame: 30 days] 30 day-mortality rate in aged patients hospitalized with COVID-19	Randomized Parallel assignment Open-label

7. COUNTER-COVID - Oral imatinib to prevent pulmonary vascular leak in COVID-19 – a randomized, double-blind, placebo controlled, clinical trial in patients with severe Covid19 disease	N = 386 1. Age > 18 years 2. Hospital admission with proven SARS-CoV-2 infection 3. Hypoxemic respiratory failure (SaO2 <94%, PaO2 <9kPa)	Experimental: Imatinib (oral) Control: Placebo	Time to liberation from ventilation and supplemental oxygen > 48 hours while being alive during a 28-day period after randomization	Randomized Controlled Parallel Double-blind
8. WHO SOLIDARITY Finland: The multicenter trial on the efficacy of different anti-viral drugs in SARS-CoV-2 infected patients (COVID-19)	N = 1,164 1. Age ≥ 18 years 2. Laboratory-confirmed SARS-2-CoV-2 infection 3. Admitted to the hospital ward or the ICU 4.No anticipated transfer within 72 hours to a non-study hospital	Experimental: Imatinib (oral) Artesunate Vs. Infliximab	In-hospital Mortality	Randomized Controlled Open label
9. Home treatment of elderly patients with symptomatic SARS-CoV-2 infection (COVID-19): a multiarm, multi-stage (MAMS) randomized trial to assess the efficacy and safety of several experimental treatments to reduce the risk of hospitalization or death (COVERAGE trial)	N = 1,057 1. Age ≥ 60 years old 2. Positive SARS-CoV-2 test on nasopharyngeal swab 3. Onset of symptoms < 5 days prior to swabbing 4. Valid, ambulatory person, fully capable of understanding the challenges of the trial 5. No hospitalization criteria 6. Covered by health insurance	Experimental: Imatinib 400mg Telmisartan 20mg Favipiravir 200mg Control: Vitamin supplements	Proportion of participants with an occurrence of hospitalization and/or death between D0 and D14 in each arm	Randomized Controlled Parallel Open
10. A proof of concept study testing the value of Imatinib in prevention of Covid 19 in aged patients Note: Prematurely ended	Target N = 382 Prevention of severe COVID-19: 1. Resident living in an open nurse home 2. Resident without symptom of COVID-19 3. No imatinib contra-indication Prevention of severe COVID-19: 1. Patient aged > 70y 2. Patient with a documented SARS-CoV-2 infection (if no test is available, suspected SARS-CoV-2 infection). 3. Initial phase (7 days) of COVID-19	Experimental: Imatinib oral Control: Standard follow-up	Prevention of SARS-CoV-2 infection Prevention of severe COVID-19 disease	Randomized Control Open trial

Q12. Among patients with COVID-19, should tofacitinib be used for treatment?

As of 21 October 2021

RECOMMENDATION

We suggest against the use of tofacitinib among hospitalized COVID-19 patients. *(Low certainty of evidence, Weak recommendation)*

Consensus Issues

The recommendation against the use of tofacitinib among hospitalized patients with COVID-19 was mainly due to the drug's safety issues. Although the study showed that there was benefit in reducing death or respiratory failure, particularly among patients on low-flow supplemental oxygen, patients who received tofacitinib were three times more likely to experience adverse events leading to treatment discontinuation. Furthermore, the US FDA and Health Canada issued safety alert on the use of tofacitinib due to increased risk of serious cardiovascular-related events (heart attack, stroke), cancer (lymphoma, lung cancer), thrombosis and death.

KEY FINDINGS

There is one (1) randomized controlled trial (RCT) that investigated the effect of tofacitinib compared to placebo as treatment for patients with COVID-19. Patients treated with tofacitinib had a significant reduction in death or respiratory failure. Tofacitinib did not show significant effect in all-cause mortality, need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO), cure (defined as resolution of fever, cough, or need for ventilatory/oxygen support), length of hospitalization, length of ICU stay, and duration of mechanical ventilation. There was no significant increase in serious adverse events and adverse events between the tofacitinib and placebo group. However, there was a significant increase in adverse events leading to treatment discontinuation for patients given tofacitinib compared to placebo, with increase in transaminase levels and lymphopenia being the most commonly reported adverse events. The very serious imprecision due to the limited number of events contributed to the downgrading of evidence to a low certainty of evidence.

INTRODUCTION

Tofacitinib is a Janus kinase (JAK) inhibitor that is used for adults with rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis, and for children with juvenile idiopathic arthritis. JAK pathways are involved in inflammatory gene expression and perpetuates an inflammatory cycle. Inhibition of JAK leads to an anti-inflammatory effect through decreased production of pro-inflammatory cytokines and increased production of anti-inflammatory cytokines.[1] Mortality in COVID-19 infection has been associated with a cytokine storm characterized by excessive production of proinflammatory cytokines.[2] The action of tofacitinib in inhibiting cytokine production provide the rationale for evaluating its use in COVID-19.

REVIEW METHODS

A systematic search was done using Medline, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections,

COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and tofacitinib. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. Only RCTs that compared tofacitinib against placebo or standard care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance or adverse events. No limits were placed on age, COVID-19 severity, and dosing strategy of tofacitinib. Subgroup analysis by disease severity, oxygen requirement, and age was planned.

RESULTS

The initial search yielded 86 articles. After review of search output, one (1) RCT was retrieved with a total of 289 participants that evaluated the use of tofacitinib in the treatment of hospitalized COVID-19 patients. This RCT was also included in the COVID-NMA Living Data.[3] Patients on non-invasive/invasive mechanical ventilation or ECMO, with history of thrombosis or current thrombosis, with known suppression or those with current cancer were excluded from the study. The treatment group received a dose of tofacitinib 10mg twice daily for 14 days or until hospital discharge, whichever was earlier. A reduced regimen of 5mg tofacitinib twice daily was administered for patients with estimated glomerular filtration rate of <50 mL/min/1.73m^2, moderate hepatic impairment or concomitant use of strong CYP3A4 or CYP2C1 inhibitors. The control group received placebo. All study participants received standard of care, including glucocorticoids, antibiotics, anticoagulants, and anti-viral agents. Concomitant use of other JAK inhibitors, biologic agents, immunosuppressants, interleukin-1 inhibitors, interleukin-6 inhibitors or CYP450 inducers were prohibited. Outcomes measured during the 28-day follow-up included death or respiratory failure, all-cause mortality, need for mechanical ventilation or ECMO, duration of hospital stay, duration of ICU stay, cure (defined as resolution of fever, cough, no use of ventilatory or oxygen support), hospital discharge, and serious adverse events. The characteristics of included studies are summarized in Appendix 3.

The overall quality of evidence was rated low because of very serious imprecision due to the small number of events and wide confidence intervals. Appraisal of study quality showed no serious risk of bias in the included study. The risk of bias summary is in Appendix 4. The GRADE evidence profile is in Appendix 5.

Result of the RCT showed significant reduction in death or respiratory failure among patients who received tofacitinib compared to placebo (RR 0.62, 95% CI 0.40-0.96). Subgroup analysis by severity showed trend towards benefit for patients not receiving supplemental oxygen (RR 0.71, 95% CI 0.21-2.00) and high-flow supplemental oxygen (RR 0.62, 95% CI 0.15-1.79); however, results did not reach statistical significance. There was significant benefit for patients on low-flow supplemental oxygen (RR 0.59, 95% CI 0.33-0.97).
Point estimates also showed trend towards benefit for all-cause mortality (RR 0.50, 95% CI 0.16-1.64) and need for mechanical ventilation or ECMO (RR 0.25, 95% CI 0.03-2.23); however, the wide confidence intervals preclude definite conclusions to be made.

There was no significant difference in cure, defined as resolution of fever, cough or need for ventilatory/oxygen support (RR 1.03, 95% CI 0.95-1.10). There was also no significant difference in median length of hospitalization (tofacitinib group 5.5 days, 95% CI 3.0-8.25; placebo group 6.0 days, 95% CI 3.0-11.0; subdistribution hazard ratio 1.18, 95% CI 0.94-1.48) and median length of ICU stay (tofacitinib group 5.0 days, 95% CI 3.0-11.0; placebo group 5.0 days, 95% CI 2.0-11.5; subdistribution hazard ratio 1.11, 95% CI 0.72-1.70), and duration of mechanical ventilation (median difference 1.00 days, 95% CI -7.0 to 7.0).

Adverse events

In terms of serious adverse events, the point estimate shows trend towards harm among those given tofacitinib compared to placebo. However, the wide confidence interval precludes definite conclusions to be made (RR 1.18, 95% CI 0.64-2.15). Among the serious adverse events of special interest, deep-vein thrombosis, acute myocardial infarction, ventricular tachycardia, and myocarditis occurred in 1 patient each in the tofacitinib group. In the placebo group, hemorrhagic stroke and cardiogenic shock occurred in 1 patient each.

The point estimate for adverse events also shows trend towards harm for tofacitinib; however, results were not statistically significant (RR 1.16, 95% CI 0.77-1.75). The most common adverse events were increase in aminotransferase levels, acute kidney injury, anemia, hyperglycemia, and lymphopenia. There was a significant increase in adverse events leading to treatment discontinuation in the tofacitinib group compared to the placebo group (RR 3.2, 95% CI 1.2-8.5). Increase in transaminase levels and lymphopenia were the most commonly reported adverse events leading to treatment discontinuation.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from other Groups

Regulatory Agency	Recommendation
Infectious Diseases Society of America (IDSA) (as of October 1, 2021)	Suggests the use of tofacitinib rather than no tofacitinib among hospitalized adults with severe COVID-19 (severe illness is defined as patients with SpO2 ≤94% on room air, including patients on supplemental oxygen or oxygen through a high-flow device, but not on non-invasive or invasive mechanical ventilation *(Low certainty of evidence; Conditional recommendation).* Patients treated with tofacitinib should be on at least prophylactic dose anticoagulant, and that these patients should not receive tocilizumab or other IL-6 inhibitor for treatment of COVID-19.[6]
National Institutes of Health (NIH) COVID-19 Guidelines (as of October 7, 2021)	Recommends tofacitinib for hospitalized COVID-19 patients as an alternative to baricitinib only when baricitinib is not available or not feasible to use *(Moderate recommendation).[*7]
Australian Guidelines for COVID-19 (as of September 29, 2021)	Does not recommend the use of tofacitinib for the treatment of COVID-19 outside of randomized trials *(Low certainty of evidence).[*8]
Surviving Sepsis Campaign Guidelines on COVID-19 (as of January 29, 2021)	No recommendation on tofacitinib for treatment of COVID-19.[9]
World Health Organization (WHO) (as of September 24, 2021)	No recommendation on tofacitinib for treatment of COVID-19.[10]

RESEARCH GAPS

There are five (5) studies in various clinical trial registries, of which 1 was withdrawn so that the investigators can pursue other COVID-19 related research. This review will be updated as soon as full results from these trials become available.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity
Benefits	Large	Moderate (4)	Small (3)	Uncertain (2)			• Significant reduction in death or respiratory failure (RR 0.62, 95% CI 0.40-0.96) • Significant benefit for patients on low-flow supplemental oxygen (RR 0.59, 95% CI 0.33-0.97)
Harm	Large (7)	Small (1)	Uncertain (1)				• Trend towards harm among those given tofacitinib compared to placebo, but wide confidence interval precludes definite conclusions to be made (RR 1.18, 95% CI 0.64-2.15) • Significant increase in adverse events leading to treatment discontinuation (RR 3.2, 95% CI 1.2-8.5)
Certainty of Evidence	High	Moderate	Low (8)	Very low (1)			• Low because of very serious imprecision due to the small number of events and wide confidence intervals
Balance of effects	Favors drug (3)	Does not favor drug (3)	Uncertain (3)				• There was variability prior to the panel discussion • However, the consensus panel eventually decided that the potential harm of giving tofacitinib outweighed its potential benefits
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (4)	Moderate Cost (5)	Negligible cost	Moderate savings	Large savings	• Php 22,799.00 per 14 day treatment course
Certainty of evidence of required resources	No included studies	Very low (1)	Low (4)	Moderate (2)	High (2)		• Based on published online rates of a Philippine drug store website
Cost effectiveness	No included studies (8)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention			• None of the included trials assessed cost effectiveness.
Equity	Uncertain (6)	Reduced (2)	Probably no impact	Increased (1)			
Acceptability	Uncertain (9)	No	Yes				
Feasibility	Uncertain (5)	No	Yes (4)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (tofacitinib OR tofacitinib[supplementary concept, Mesh])	September 11, 2021 11:00AM	44	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (tofacitinib) Filters: March 26, 2021 to August 28, 2021	September 11, 2021 11:15 AM	11	1
COVID-NMA Initiative	Tofacitinib	September 11, 2021 11:25 AM	1	1
Google Scholar	Tofacitinib AND COVID19 AND randomized trial	September 11, 2021 11:27 AM	30	1
ClinicalTrials.gov	Tofacitinib and COVID19	September 11, 2021 11:35 AM	6	4
Chinese Clinical Trial Registry	Tofacitinib	September 11, 2021 11:45 AM	11	0
EU Clinical Trials Register	Tofacitinib	September 11, 2021 11:50 AM	2	1
Republic of Korea - Clinical Research Information Service	Tofacitinib	September 11, 2021 11:52 AM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Tofacitinib	September 11, 2021 11:53 AM	25	0
CenterWatch	Tofacitinib and COVID	September 11, 2021 11:58 AM	1	1
WHO database COVID-19 studies	Tofacitinib	September 11, 2021 12:00 PM	8	2
chinaxiv.org	Tofacitinib	September 11, 2021 12:10 PM	0	0
Medrxiv.org	Tofacitinib and COVID	September 11, 2021 12:12 PM	29	0
Biorxiv.org	Tofacitinib and COVID	September 11, 2021 12:20 PM	16	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n)	Interventions	Outcomes	Method
Tofacitinib in Hospitalized Patients With COVID-19 Pneumonia *Guimaraes et al. 2021 (Brazil)*	N = 289 18 years and older with: ● Laboratory-confirmed SARS-CoV-2 infection as determined by RT-PCR ● Evidence of COVID-19 pneumonia assessed by radiographic imaging (CT or radiography) ● Hospitalized for less than 72 hours Exclusion criteria: ● Use of noninvasive or invasive mechanical ventilation or ECMO ● History of thrombosis or current thrombosis ● Known immunosuppression ● Current cancer Duration of follow-up: Up to 28 days after discharge	Experimental: Tofacitinib 10mg twice daily for 14 days or until hospital discharge (N = 144) Control: Placebo (N = 145)	Primary: Death or respiratory failure until Day 28 Secondary: all-cause mortality, scores of the NIAID ordinal scale of disease severity at day 14 and 28, need for mechanical ventilation or ECMO at day 14 and 28, duration of stay in the hospital, duration of stay in the ICU, cure (resolution of fever, cough, no use of ventilatory or oxygen support), hospital discharge at day 14 and 28, serious adverse events	Randomized, Double-blind, Placebo-controlled, Parallel-design Trial

Appendix 4. Study Appraisal

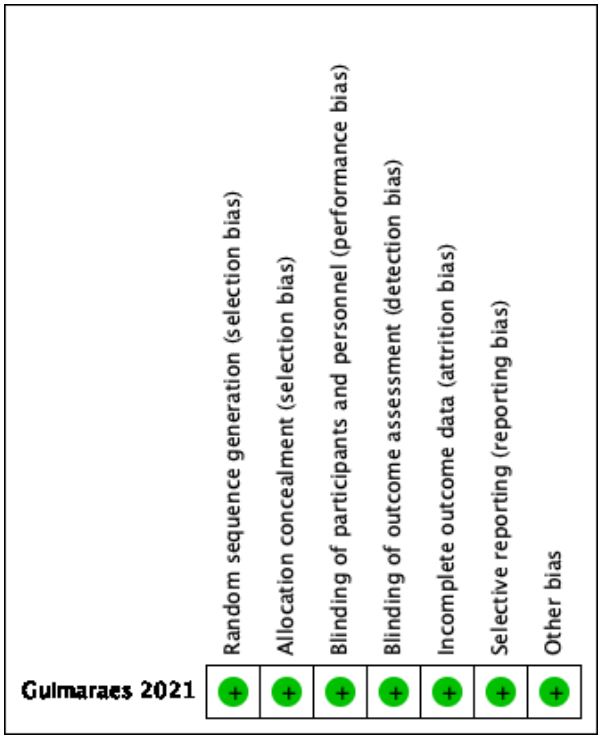

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: Tofacitinib compared to Placebo/Standard Care for COVID-19
Setting: Hospital setting
Bibliography: Guimaraes PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021;385:406-15.

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tofacitinib	Placebo/Standard care	Relative (95% CI)	Absolute (95% CI)		
Death or respiratory failure (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious [a]	None	26/144 (18.1%)	42/145 (29.0%)	**RR 0.63** (0.41 to 0.97)	**107 fewer per 1,000** (from 171 fewer to 9 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
All-cause mortality (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious [b]	None	4/144 (2.8%)	8/145 (5.5%)	**RR 0.49** (0.15 to 1.63)	**28 fewer per 1,000** (from 47 fewer to 35 more)	⊕⊕◯◯ LOW	CRITICAL
Progression to mechanical ventilation or ECMO (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious [b]	None	1/144 (0.7%)	4/145 (2.8%)	**RR 0.25** (0.03 to 2.23)	**21 fewer per 1,000** (from 27 fewer to 34 more)	⊕⊕◯◯ LOW	CRITICAL
Cure (resolution of fever, cough, or need for ventilatory/oxygen support) (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious [c]	None	134/144 (93.1%)	132/145 (91.0%)	**RR 1.03** (0.95 to 1.10)	**27 more per 1,000** (from 46 fewer to 91 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital discharge (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious [c]	None	134/144 (93.1%)	129/145 (89.0%)	**RR 1.05** (0.97 to 1.13)	**44 more per 1,000** (from 27 fewer to 116 more)	⊕⊕⊕◯ MODERATE	CRITICAL

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tofacitinib	Placebo/Standard care	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	very serious [b]	none	20/142 (14.1%)	17/142 (12.0%)	**RR 1.18** (0.64 to 2.15)	**22 more per 1,000** (from 43 fewer to 138 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events leading to treatment discontinuation												
1	Randomised trials	Not serious	Not serious	Not serious	serious [c]	none	16/142 (11.3%)	5/142 (3.5%)	**RR 3.2** (1.2 to 8.5)	**77 more per 1,000** (from 7 more to 264 more)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

[a] Upper boundary of 95% CI crosses threshold for meaningful effect

[b] Wide confidence interval, small number of events

[c] Small number of events

Appendix 6. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Tofacitinib for Treatment of Moderate COVID-19 NCT04415151	18 years and older with laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction, evidence of pneumonia assessed by radiographic imaging, and hospitalized	Experimental: Tofacitinib 10mg PO BID until return to their clinical baseline and then at 5mg PO BID for a total of 14 days Control: Placebo	Disease Severity (Time Frame: 14 days)	Randomized, double blinded, placebo-controlled study
2. Safety and Efficacy of Tofacitinib in Hospitalized Participants With COVID-19 Pneumonia Who Are Receiving Standard of Care Therapy NCT04412252 *Withdrawn to pursue other COVID-19 research*	18 years and older with laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction, evidence of pneumonia assessed by radiographic imaging	Experimental: Tofacitinib 10mg twice daily for 14 days Control: Placebo	Clinical status using ordinal scale (Time Frame: Day 28)	Randomized, Double-blind, Placebo-controlled, Parallel-group study
3. TOFAcitinib Plus Hydroxycloroquine vs Hydroxycloroquine in Patients With COVID-19 Interstitial Pneumonia (TOFACoV-2) NCT04390061	18 to 65 years old with SARS-CoV2 infection diagnosed by RT-PCR, hospital admission from less than 24 hours, P/F ratio >150 mmHg	Experimental: Tofacitinib 10mg twice daily + hydroxychloroquine 200mg thrice daily for 14 days Control: hydroxychloroquine 200mg thrice daily for 14 days	Prevention of severe Respiratory Failure requiring mechanical ventilation (Time Frame: 14 days)	Randomized, parallel assignment open label trial
4. Evaluation of use and right time identification to initiate Tofacitinib use in the treatment of moderate- severe COVID-19 infection CTRI/2021/06/034162	18 years and older with signs and symptoms consistent with COVID-19 infection confirmed with rapid antigen test (RAT) or RT- PCR and hospitalised with moderate or severe COVID-19 illness	Experimental: Tofacitinib 10mg BID on top of Standard Care for 10 days Control: Standard Care	All-cause mortality up to 28 days of follow-up	Open label randomised, controlled trial
5. Effectiveness evaluation of Tofacitinib plus Remdesivir in comparison with Remdesivir in the treatment of adult patients with severe COVID-19 A randomized double-blind placebo-included clinical trial IRCT20200329046892N2	All patients with severe COVID-19 admitted to the ICU of Razi Hospital in Rasht from March to June 2021	Experimental: Tofacitinib oral tablet 10mg daily + remdesivir IV 100mg daily for 14 days or hospital discharge Control: Placebo oral tablet daily + Remdesivir IV 100mg daily for 14 days or hospital discharge	The time required to improve clinical symptoms and paraclinical measures within 14 days of starting treatment	Double-blind, randomized clinical trial with parallel control group

Q13. Among patients with COVID-19, should leronlimab be used for treatment?

As of 28 October 2021

RECOMMENDATION

We suggest against the use of leronlimab as treatment for COVID-19 *(Very low certainty of evidence, Weak recommendation)*

Consensus Issues
The evidences of the review are now based on unpublished randomized controlled trials (previously from case series and a case study), however, similar to the previous consensus issue, the panel agreed that further trials are needed to recommend the use of leronlimab for the treatment of COVID-19.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of leronlimab as treatment for COVID-19 *(Very low certainty of evidence)*

Previous Consensus Issue
Further trials are needed to recommend the use of leronlimab for the treatment of COVID-19. The cost and accessibility of this drug must also be considered.

WHAT'S NEW IN THIS VERSION?

This version includes results of two (2) unpublished clinical trials (data obtained based on reports submitted to regulatory agencies).

KEY FINDINGS

Two (2) unpublished randomized controlled trial (RCTs) investigated the effect of leronlimab compared to placebo as treatment for patients with COVID-19. There was no significant benefit in the use of leronlimab in reducing mortality, length of hospital stay, resolution of clinical symptoms, and time to symptom resolution. There was no significant difference in serious adverse events and adverse events. The overall quality of evidence was rated very low because of serious risk of bias and very serious imprecision.

INTRODUCTION

Several molecules that play a role in determining diffuse tissue damage associated with cytokine release syndrome are upregulated in patients with COVID-19, especially in severe forms. Drugs inhibiting these molecules could be beneficial in reducing this exaggerated inflammatory response.[1] C-C chemokine receptor type 5 (CCR5) is expressed on the surface of white blood cells, especially T-CD4+ cells and mediates macrophage migration into areas of inflammation, favoring the release of inflammatory cytokines and amplification of the immune response. Leronlimab is a humanized monoclonal antibody inhibiting CCR5.[2]

REVIEW METHODS

A systematic search was done from the date of the last search April 5, 2021 until September 20, 2021 using Medline, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-

19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and leronlimab. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. Only randomized controlled trials that compared leronlimab against placebo or standard care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, or adverse events. No limits were placed on age, COVID-19 severity, hospitalization status, and dosing strategy of colchicine. Subgrouping by severity was planned.

RESULTS

Two (2) unpublished RCTs (N = 478) evaluated the use of leronlimab as treatment for patients with COVID-19 and compared it to placebo. One study is a Phase 2 RCT involving 84 patients with mild to moderate COVID-19. The second study is a Phase 2b/3 adaptive RCT involving 394 patients with severe or critical COVID-19. In both studies, leronlimab 700mg was given weekly for a total of 2 doses. Patients were followed up for 14 to 28 days. Outcomes measured included mortality, change in clinical status, duration of hospitalization, need for hospitalization, need for mechanical ventilation, need for oxygen support, and time to clinical resolution. The characteristics of included studies are shown in Appendix 2.

Data from these studies were from statements obtained from the U.S. Food and Drug Administration [3], and pharmaceutical reports. [4,5]. Appraisal of study quality was done based on data found on clinical trial registries. [6-8]

The overall quality of evidence was rated very low because of serious risk of bias and very serious imprecision due to the small number of events and wide confidence intervals. Appraisal of study quality showed serious risk of bias in the included studies due to concerns on reporting bias. The risk of bias summary is in Appendix 4. The GRADE evidence profile is in Appendix 5.

Mortality

Leronlimab did not show significant benefit in reducing mortality both for mild-moderate and severe-critical COVID-19 patients. Among the severe-critical COVID-19 patients, the relative risk (RR) was 0.96 (95% CI 0.64-1.45). The effect estimate for mild-moderate patients could not be computed due to inadequate data.[3]

Data from the pharmaceutical report on the subgroup of critically-ill COVID-19 (62 patients out of the 394 total patients) reported 78% efficacy of leronlimab compared to placebo on Day 7 mortality, 82% efficacy on Day 14 mortality, 50% on Day 21 mortality, and 31% on Day 28 mortality.[5] However, the US FDA cautions against reliance on this subgroup analysis especially in the context of a clinical trial that failed to show a benefit in the overall population.[3]

Other clinical outcomes

There was no significant difference in the length of hospital stay among the severe-critical COVID-19 patients (21.4 days in both the leronlimab and the placebo treatment groups).[3]

There was no significant benefit in resolution of clinical symptoms at day 3 among mild-moderate COVID-19 patients compared to placebo (RR 1.09, 95% CI 0.75-1.60).[4] Using the total clinical symptom score that ranges from 0 (no symptoms) to 12 (severe symptoms), the mean difference (MD) was -3.5 in the leronlimab group compared to MD -3.4 in the placebo group by Day 14.[3] However, using the National Early Warning Score 2, the pharmaceutical report noted significant benefit among patients given leronlimab compared to placebo in terms of proportion of patients with improved scores by Day 14 (RR 2.23, 95% CI 1.10-4.97).[4]

There was no significant benefit in time to symptom resolution and time to return to normal activity among mild-moderate COVID-19 patients.[3]

Adverse Events

There was no significant difference in adverse events (RR 0.68, 95% CI 0.40-1.14) and serious adverse events (RR 0.42, 95% CI 0.14-1.25) among the mild-moderate COVID-19 patients given leronlimab compared to placebo.[4] Among the severe-critical COVID-19 patients, the pharmaceutical report stated 21% less adverse events in the leronlimab arm compared to the placebo arm, and 3% less serious adverse events in the leronlimab arm compared to the placebo arm.[5]

RECOMMENDATIONS FROM OTHER GROUPS

No recommendations on leronlimab have been released by the US NIH (as of October 7), WHO (as of September 24), Australian Living CPG (as of September 29), and IDSA (as of October 1).[9-12]

RESEARCH GAPS

There are three (3) studies that were found in various clinical trial registries, of which 1 was marked completed but no results have been posted yet. This review will be updated as soon as published results from the included studies and results from these registered trials become available.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 8)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)					
Benefits	Large	Moderate	Small (5)	Uncertain (3)			• Leronlimab did not show significant benefit in reducing mortality both for mild-moderate and severe-critical COVID-19 patients.
Harm	Large	Small (5)	Uncertain (3)				• There was no significant difference in adverse events and serious adverse events • Among the severe-critical COVID-19 patients, there is 21% less adverse events and 3% less serious adverse events in the leronlimab arm
Certainty of Evidence	High	Moderate	Low (2)	Very low (6)			• Rated very low because of serious risk of bias and very serious imprecision due to the small number of events & wide confidence intervals.
Balance of effects	Favors drug	Does not favor drug (6)	Uncertain (2)				• There was no significant benefit in the use of leronlimab in reducing mortality, length of hospital stay, resolution of clinical symptoms, and time to symptom resolution.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain (8)	Large cost	Moderate Cost	Negligible cost	Moderate savings	Large savings	• No evidence • FDA granted Compassionate Special Permit
Certainty of evidence of required resources	No included studies (8)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (7)	Favors the comparison	Does not favor either the intervention or the comparison (1)	Favors the intervention			
Equity	Uncertain (7)	Reduced (1)	Probably no impact	Increased			
Acceptability	Uncertain (8)	No	Yes				
Feasibility	Uncertain (7)	No (1)	Yes				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (leronlimab) Filters: April 5, 2021 to September 20, 2021	September 20, 2021 9:00 PM	0	0
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (leronlimab) Filters: April 5, 2021 to September 20, 2021	September 20, 2021 9:15 PM	4	0
COVID-NMA Initiative	Leronlimab	September 20, 2021 9:30 PM	0	0
Google Scholar	Leronlimab and COVID (search in abstracts)	September 20, 2021 9:32 PM	7	1*
ClinicalTrials.gov	Leronlimab and COVID19	September 20, 2021 9:45 PM	5	5
Chinese Clinical Trial Registry	Leronlimab	September 20, 2021 9:50 PM	0	0
EU Clinical Trials Register	Leronlimab	September 20, 2021 9:51 PM	1	1
Republic of Korea - Clinical Research Information Service	Leronlimab	September 20, 2021 9:52 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Leronlimab	September 20, 2021 9:53 PM	0	0
CenterWatch	Leronlimab	September 20, 2021 9:54 PM	3	0
Cochrane COVID-19 study register	Leronlimab Filters: April 5, 2021 to September 20, 2021	September 20, 2021 9:40 PM	3	2
chinaxiv.org	Leronlimab	September 20, 2021 9:55 PM	0	0
Medrxiv.org	Leronlimab	September 20, 2021 9:56 PM	11	0
Biorxiv.org	Leronlimab	September 20, 2021 9:57 PM	3	0

**Report from pharmaceutical company*

Appendix 3. Characteristics of Included Studies

Study	Study Design	Population	Intervention	Comparison	Outcome
Clinical Trials					
NCT04343651 Study to Evaluate the Efficacy and Safety of Leronlimab for Mild to Moderate COVID-19 "CD10"	Phase 2 RCT	84 patients with mild to moderate symptoms of respiratory illness caused by coronavirus 2019 infection	Weekly doses of 700mg leronlimab (PRO 140) SQ	Placebo	Primary outcome: Clinical improvement as assessed by change in total symptom score (for fever, myalgia, dyspnea, and cough) [Time Frame: Day 14] Secondary outcomes: • Time to clinical resolution • Change from baseline in National Early Warning Score 2 (NEWS2) • Change from baseline in pulse oxygen saturation • Change from baseline in the patient's health status on a 7-category ordinal scale • Incidence of hospitalization • Duration (days) of hospitalization • Incidence of mechanical ventilation supply • Duration (days) of mechanical ventilation supply • Incidence of oxygen use • Duration (days) of oxygen use • Mortality rate • Time to return to normal activity
NCT04347239 Study to Evaluate the Efficacy and Safety of Leronlimab for Patients with Severe or Critical Coronavirus Disease 2019 (COVID-19) "CD12"	Phase 2b/3 adaptive RCT	394 patients with severe or critical symptoms of respiratory illness caused by coronavirus 2019 infection	Weekly doses of 700mg leronlimab (PRO 140) SQ	Placebo	Primary outcome: All-cause mortality at Day 28 Secondary outcomes: • All-cause mortality at Day 14 • Change in clinical status of subject at Day 14 (on a 7-point ordinal scale) • Change in clinical status of subject at Day 28 • Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Day 14

Appendix 4. Study Appraisal

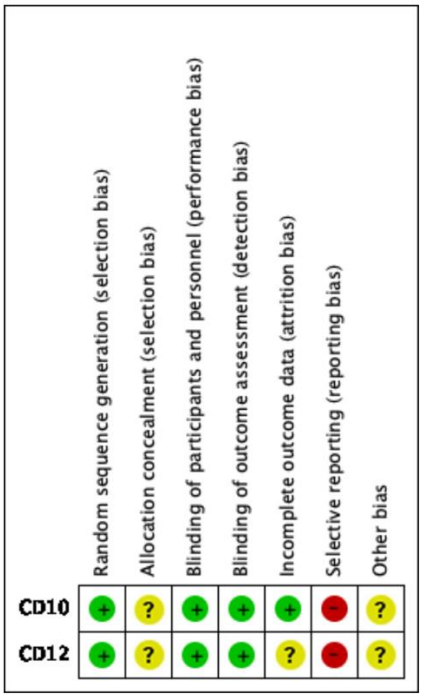

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: Leronlimab compared to Placebo for COVID-19
Bibliography: CD10 and CD12 trials

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Leronlimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 14 to 28 days)												
2	Randomised trials	Serious [a]	Not serious	Not serious	Very serious [b]	None	No significant benefit for mild-moderate patients. No significant benefit for severe-critical patients (RR 0.96, 95% CI 0.64-1.45)				⊕◯◯◯ VERY LOW	CRITICAL
Length of hospital stay												
1	Randomised trials	Serious [c]	Not serious	Not serious	Very serious [b]	None	263	131	-	MD = 0 days	⊕◯◯◯ VERY LOW	CRITICAL
Resolution of clinical symptoms Day 3												
1	Randomised trials	Serious [d]	Not serious	Not serious	Very serious [b]	None	35/56 (62.5%)	16/28 (57.1%)	**RR 1.09** (0.75 to 1.60)	**51 more per 1,000** (from 143 fewer to 343 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse events												
2	Randomised trials	Serious [a]	Not serious	Not serious	Very serious [b]	None	No significant difference among the mild-moderate COVID-19 patients (RR 0.42, 95% CI 0.14-1.25). Among the severe-critical COVID-19 patients, there was 3% less serious adverse events reported in the leronlimab arm compared to the placebo arm.				⊕◯◯◯ VERY LOW	CRITICAL
Adverse events												
2	Randomised trials	Serious [a]	Not serious	Not serious	Very serious [b]	None	No significant difference among the mild-moderate COVID-19 patients (RR 0.68, 95% CI 0.40-1.14). Among the severe-critical COVID-19 patients, there was 21% less adverse events reported in the leronlimab arm compared to the placebo arm				⊕◯◯◯ VERY LOW	IMPORTANT

[a] Issues with reporting bias in 2 studies, attrition bias in 1 study
[b] Wide confidence interval, small sample size and number of events
[c] Issues with reporting and attrition bias
[d] Issues with reporting bias

Appendix 6. Characteristics of Ongoing Studies

Study	Study Design	Population	Intervention	Comparison	Outcome	Estimated Completion Date
NCT04678830 COVID-19 Long-Haulers Study "CD15" Marked complete but no results posted	Phase 2 RCT	50 patients with prolonged symptoms (>6 weeks) caused by COVID-19	Weekly doses of 700mg leronlimab (PRO 140) SQ	Placebo	Primary outcome: Changes from baseline in daily COVID-19-related symptom severity score through Day 56. Secondary outcomes: ● Duration of COVID-19 associated symptoms from start of study treatment based on self-assessment using daily symptom diary ● Number of symptom-free days of COVID-19 associated symptoms that were present at the start of study treatment (Day 0) based on self-assessment using daily symptom diary ● Progression (or worsening) of COVID-19-associated symptoms through Day 56 compared to baseline ● Change from baseline in PROMIS® Fatigue Score at Days 28 and 56 ● Change from baseline in PROMIS® Cognitive Function Score at Days 28 and 56 ● Change from baseline in PROMIS® Sleep Disturbance Score at Days 28 and 56 ● Duration (days) of hospitalization during the treatment phase ● Incidence of hospitalization during the treatment phase ● Change from baseline in pulse oxygen saturation (SpO2) at Day 7, 14, 21, 28, 35, 42, 49, and 56 ● Incidence of treatment-related adverse events (TEAEs) ● Incidence and severity of treatment-emergent adverse events (TEAEs) ● Incidence of serious adverse events (SAEs) ● Incidence of TEAEs and SAEs leading to discontinuation of study medication.	July 23, 2021
NCT04901676 Leronlimab in Moderately Ill Patients With COVID-19 Pneumonia	Phase 3, Randomized, Double Blind, Placebo Controlled Trial	612 participants, 18 years and older, moderately ill patients with COVID-19, hospitalized, requiring supplemental oxygen or on non-invasive ventilation or high flow oxygen devices, evidence of pneumonia	Leronlimab subcutaneously once a week (up to 4 doses) until hospital discharge. The first dose will be of 700mg, followed by weekly doses of 350mg	Placebo	Primary outcome: Cumulative incidence of death or respiratory failure until day 28 Secondary outcomes: • Time to clinical recovery • Death or intubation until day 28 • Proportion of patients clinically recovered • All-cause mortality • Proportion of patients discharged alive • Clinical status • Length of hospital stay	February 2022

NCT04901689 Leronlimab in Patients with Coronavirus Disease 2019 (COVID-19) with Need for Mechanical Ventilation or Extracorporeal Membrane Oxygenation	Phase 3, Randomized, Double Blind, Placebo Controlled Trial	316 participants, 18 years and older, critically ill patients with COVID-19, Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) for less than 72 hours. Evidence of pneumonia	Leronlimab 700mg intravenously once a week (up to 4 doses) until hospital discharge	Placebo	<u>Primary outcome:</u> Cumulative proportion of clinical recovery <u>Secondary outcomes:</u> • Proportion of patients clinically recovered • All-cause mortality • Proportion of patients discharged alive • Clinical Status • Duration of invasive mechanical ventilation or ECMO • Length of hospital stay • Length of ICU stay	December 2021

Q14. Among patients with COVID-19, should infliximab be used for treatment?

As of 12 October 2021

RECOMMENDATION

We suggest against the use of infliximab among patients with COVID-19 infection *(Very low certainty of evidence, Weak recommendation)*

Consensus Issues
The recommendation against the use of infliximab among patients with COVID-19 was made based on a small, pre-print randomized controlled trial (n = 63), which did not show any benefit on mortality, hospital discharge within 28 days, and time to clinical improvement. The panel also emphasized that the infliximab arm of the study was prematurely terminated due to futility on interim analysis, explaining its small sample size.

KEY FINDINGS

There is one (1) pre-print randomized controlled trial (RCT) that reported the effect of infliximab compared to standard of care as treatment for patients with COVID-19. Results of the RCT showed no significant difference in mortality, hospital discharge in 28 days, and time to improvement in the WHO clinical progression scale. The RCT suffered from lack of allocation concealment, blinding, and poor comparability of treatment groups. It was also terminated prematurely due to futility. The very serious risk of bias and imprecision contributed to the downgrading of evidence to a very low certainty of evidence.

INTRODUCTION

Tumor necrosis factor (TNF) plays an important role in the pathogenesis of acute inflammatory reactions.[1] TNF, produced mainly by macrophages, activates signaling pathways that lead to the production of inflammatory cytokines (IL-1, IL-6) and chemokines (IL-8), inhibition of regulatory T-cells, and induction of apoptosis.[1] Infliximab is a TNF-alpha inhibitor approved for the treatment of various inflammatory conditions such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease.[1]

Among COVID-19 patients, levels of IL-6 and TNF-alpha are significantly elevated and are strong predictors of survival.[2-4] Anti-TNF therapy has also been shown to reduce the pathologic changes of viral pneumonia in preclinical studies.[5] These observations provide the rationale for anti-TNF therapy to reduce lung inflammation and improve clinical outcomes in COVID-19.[6]

REVIEW METHODS

A systematic search was done in Pubmed, Cochrane Library, and Google Scholar using free text and MeSH terms for coronavirus infections, novel coronavirus, COVID-19, SARS-CoV-2, and infliximab. Preprints were sought using the medrxiv, biorxiv, and chinarxiv databases. Ongoing studies were also searched including *clinicaltrials.gov*, EU Clinical Trials Register, Cochrane COVID-19 study register, and other trial registries. The COVID-NMA Initiative was also searched. Manual search of cross-referenced materials was also done.

All studies that compared infliximab to placebo or standard of care in treating patients with confirmed COVID-19 infection were included. Eligible studies should have at least one of the following outcomes: mortality, clinical deterioration, development of ARDS, need for mechanical ventilation or ECMO, need for ICU admission, ICU/hospital length of stay, time to clinical improvement/recovery, radiographic improvement, virologic clearance by RT-PCR test, and adverse effects. For this initial review, no limits were placed on disease severity, and age. Subgroup analysis by disease severity, oxygen requirement, and age was planned.

RESULTS

The initial search yielded 77 articles. After review of the search output, we retrieved 1 RCT with a total of 63 patients. The RCT is a pre-print and was done in UK. It involved hospitalized patients with features strongly suggestive of COVID-19 pneumonia, with or without a positive RT-PCR assay. Infliximab (single infusion of 5 mg/kg) as add-on to standard therapy was compared to standard therapy alone. Standard therapy included the administration of corticosteroids, tocilizumab, and remdesivir. Outcomes of interest were mortality, hospital discharge status at day 28, improvement in WHO clinical progression scale, and adverse events.[7] Appendix 3 summarizes the characteristics of the included studies.

The overall quality of evidence was rated very low because of very serious risk of bias and imprecision. The RCT suffered from lack of allocation concealment, blinding, and poor comparability of treatment groups with consequent selection, performance, and detection bias. During the course of recruitment, the RCT also changed one of its inclusion criterion from low oxygenation status to high CRP levels. The authors also changed the primary outcome during the recruitment phase from oxygenation status to CRP levels, stating that oxygenation status was not a viable outcome measure of sickness. On interim analysis, the infliximab arm of the RCT was discontinued due to futility.[7] The GRADE evidence profile is in Appendix 5.

Results of the RCT showed no significant difference in the use of infliximab compared to standard of care in reducing mortality (RR 0.94; 95% CI 0.28-3.17) and hospital discharge within 28 days (RR 1.17, 95% CI 0.85-1.62).[7] There was also no significant difference in the median time to improvement in the WHO clinical progression scale (infliximab group median 15 days, 95% CI 6-21; control group median 10 days, 95% CI 6-14).

Adverse events

There was no significant difference in the risk for adverse events (RR 1.00, 95% CI 0.66-1.51). The most common adverse events noted were hypoalbuminemia, elevated ferritin, azotemia, and leukocytosis.[7]

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendation from other Groups

Regulatory Agency	Recommendation
Australian Guidelines for COVID-19 (version 42.0)	Recommends the use of anti-TNF therapy (infliximab) as a third-line option in children and adolescents with Pediatric Inflammatory Multisystem Syndrome who do not respond to intravenous immunoglobulin and corticosteroids.[11] However, outside of this indication, no recommendation exists for infliximab use in COVID-19 infection.[11]
Surviving Sepsis Guidelines	No recommendation for infliximab as treatment in COVID-19 infection.[12]
Infectious Diseases Society of America (IDSA)	No recommendation for infliximab as treatment in COVID-19 infection.[13]
World Health Organization (WHO)	No recommendation for infliximab as treatment in COVID-19 infection.[14]
National Institutes of Health (NIH)	No recommendation for infliximab as treatment in COVID-19 infection.[15]

RESEARCH GAPS

There are six (6) ongoing studies registered in different trial registries. Five studies involve adults with severe COVID-19, while one study involves pediatric patients with MIS-C. Infliximab is either a sole intervention or part of a multi-arm treatment group involving other biological therapies such as abatacept, anakinra, cenicriviroc, gemtuzumab, namilumab, and tocilizumab. An update of this review will be done once results of these trials are available.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 8)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate	Small (5)	Trivial (1)	Uncertain (2)		• 1 small pre-print RCT (n = 63) showed that there was no significant difference in the use of infliximab compared to standard of care in reducing mortality (RR 0.94, 95% CI 0.28-3.17) and hospital discharge within 28 days (RR 1.17, 95% CI 0.85-1.62).
Harm	Large (1)	Small (5)	Trivial (1)	Uncertain (1)			• There was no significant difference in the risk for adverse events (RR 1.00, 95% CI 0.66-1.51).
Certainty of Evidence	High	Moderate	Low (2)	Very low (6)			• Very low because of very serious risk of bias and imprecision.
Balance of effects	Favors drug (1)	Does not favor drug (5)	Uncertain (2)				• Although infliximab showed no increase in harm, it had no significant effect on mortality, discharge status within 28 days, and time to clinical improvement. • One panelist also emphasized that recruitment was prematurely terminated due to futility on interim analysis, explaining the study's small sample size.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (8)	Moderate Cost	Negligible cost	Moderate savings	Large savings	• For a 5 mg/kg single infusion, 2-3 vials are needed per treatment course, amounting to Php 78,711 (biosimilar) –173,216.40 (Remicade)
Certainty of evidence of required resources	No included studies (1)	Very low (1)	Low (3)	Moderate (1)	High (2)		• Cost is from personal communication with local distributor and outpatient pharmacy of private hospital (available online)
Cost effectiveness	No included studies (3)	Favors the comparison (4)	Does not favor either the intervention or the comparison (1)	Favors the intervention			• None of the included trials assessed cost effectiveness.
Equity	Uncertain (3)	Reduced (1)	Probably no impact (2)	Increased (2)			
Acceptability	Uncertain (7)	No (1)	Yes				
Feasibility	Uncertain (5)	No (2)	Yes (1)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (“Infliximab” [Mesh] OR infliximab)	Sept. 1, 2021 9:00 PM	57	0
CENTRAL	{MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR MeSH descriptor: [COVID-19] OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND MeSH descriptor: [Infliximab] explode all trees OR infliximab	Sept. 1, 2021 9:45 PM	11	0
COVID-NMA Initiative	Infliximab	Sept. 1, 2021 10:00 PM	1	0
Google Scholar	Infliximab AND COVID	Sept. 1, 2021 10:30 PM	8	0
ClinicalTrials.gov	Infliximab AND COVID	Sept. 1, 2021 11:15 PM	8	0
Chinese Clinical Trial Registry	Infliximab AND COVID	Sept. 1, 2021 11:45 PM	0	0
EU Clinical Trials Register	Infliximab AND COVID	Sept. 1, 2021 11:50 PM	5	0
Republic of Korea - Clinical Research Information Service	Infliximab	Sept. 2, 2021 12:00 AM	4	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Infliximab	Sept. 2, 2021 12:15 AM	165	0
CenterWatch	Infliximab AND COVID-19	Sept. 2, 2021 12: 25 AM	2	1
Cochrane COVID-19 study register	Infliximab AND COVID-19	Sept. 2, 2021 12: 30 AM	55	6
chinaxiv.org	Infliximab	Sept. 1, 2021 10:43 PM	0	0
Medrxiv.org	Infliximab AND COVID	Sept. 1, 2021 10:45 PM	59	1
Biorxiv.org	Infliximab AND COVID	Sept. 1, 2021 11:00 PM	13	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Namilumab or infliximab compared to standard of care in hospitalized patients with COVID-19 (CATALYST): a phase 2 randomized adaptive trial [7] *Fisher et al, 2021 (UK)* *Pre-print*	N = 63* Patients ≥16 years old with a clinical picture strongly suggestive of COVID-19 pneumonia (with or without a positive RT-PCR) and CRP ≥ 40 mg/L Duration of follow-up: Up to 28 days after discharge	Experimental group 1: Namilumab 150mg Experimental group 2: Infliximab 5 mg/kg Control: Standard care	Primary outcome: change in CRP levels Secondary outcomes: WHO clinical progression scale, mortality, adverse events, and hospital discharge status at day 28	Randomized, open label

**For the infliximab arm and its corresponding control group*

Appendix 4. Study Appraisal

Study	Randomization	Allocation concealment	Similar baseline characteristics	Blinding (participants /personnel)	Blinding of outcome assessment	Intention-to-treat analysis	Adequate follow-up	Other trials
Fisher 2021	Yes	No	No	No	No	No	Yes	COVID diagnosis may be done through imaging only

* No p-value for baseline characteristics; number of confirmed COVID-19 patients higher in Infliximab arm; more patients in the control received Remdesivir

Appendix 5. GRADE Evidence Profile

Author(s): Daniel Y. Guevara, MD; Carol Tan-Lim, MD, MSc (clinical epidemiology)
Question: Infliximab compared to Standard care for COVID-19 infection
Setting: In-hospital
Bibliography: 1. Fisher B, et al. Namilumab or infliximab compared to standard of care in hospitalized patients with COVID-19 (CATALYST): a phase 2 randomized adaptive trial. preprint doi: https://doi.org/10.1101/2021.06.02.21258204 2. Farrokhpour M, et al. Infliximab and Intravenous Gammaglobulin in hospitalized severe COVID-19 patients in intensive care unit. Arch Iran Med. February 2021; 24 (2): 139-143 doi: 10.34172/aim.2021.22 3. Stallmach A, et al. Infliximab against severe COVID-19-induced cytokine storm syndrome with organ failure - a cautionary case series. Crit Care. 2020 Jul 17;24(1):444. doi: 10.1186/s13054-020-03158-0

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infliximab	Standard of care	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
1	Randomized trials	Very serious [a]	Not serious	Not serious	Serious [b]	None	4/29 (13.8%)	5/34 (14.7%)	**RR 0.94** (0.28 to 3.17)	**9 fewer per 1,000** (from 106 fewer to 319 more)	⨁◯◯◯ VERY LOW	CRITICAL
Hospital discharge status at 28 days (follow up: 28 days)												
1	Randomized trials	Very serious [a]	Not serious	Not serious	Serious [b]	None	22/29 (75.9%)	22/34 (64.7%)	**RR 1.17** (0.85 to 1.62)	**110 more per 1,000** (from 97 fewer to 401 more)	⨁◯◯◯ VERY LOW	CRITICAL
Time to improvement in WHO clinical progression scale												
1	Randomized trials	Very serious [a]	Not serious	Not serious	Serious [b]	None	No significant difference in median time to improvement in the WHO clinical progression scale (infliximab group median 15 days, 95% CI 6-21; control group median 10 days, 95% CI 6-14)				⨁◯◯◯ VERY LOW	IMPORTANT
Adverse events (follow up: 28 days)												
1	Randomized trials	Very serious [a]	Not serious	Not serious	Serious [b]	None	17/29 (58.6%)	20/34 (58.8%)	**RR 1.00** (0.66 to 1.51)	**0 fewer per 1,000** (from 200 fewer to 300 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

[a] Lack of allocation concealment, blinding, and poor comparability of treatment groups. Change in primary outcome done during the recruitment phase
[b] Wide confidence interval due to very small study size

Appendix 6. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
A Randomized, Controlled, Multicenter, Open Label Phase II Clinical Study to Evaluate Infliximab in the Treatment of Patients With Severe COVID-19 Disease (INFLIXCOVID)	Age ≥ 18 years with severe COVID-19 • Bipulmonary infiltrates • COVID inflammation score ≥ 10 • Ferritin ≥ 500 ng/mL • O2 sat ≤ 93% N = 88	Experimental: Infliximab 5 mg/kg (1 dose) Control: Standard of care	Primary outcome: 28-day mortality Secondary outcomes: • 90-day mortality • ARDS occurrence • Ventilation-free days • RRT-free days • Vasopressor-free days • ICU admission • ICU length of stay • Hospital length of stay • WHO COVID-19 progression scale • Incidence of cardiomyopathy • Health-related quality of life index • Changes in IL-6, Ferritin, lymphocyte count • Safety	Randomized parallel assignment, open label
Immune Modulators for Treating COVID-19 (ACTIV-1 IM)	Age ≥18 years with confirmed COVID-19 + one of the following: • Radiographic infiltrates • O2 sat ≤ 94% • O2 requiring (including MV, ECMO) N = 2,160	Experimental group 1: Infliximab 5 mg/kg (1 dose) + remdesivir Experimental group 2: Abatacept 10 mg/kg up too 1000mg (1 dose) + remdesivir Experimental group 3: Cenicriviroc 450mg LD (D1) then 150mg BID (D2-29) + remdesivir Control: Standard of care + matching placebo + remdesivir	Primary outcome: Time to recovery by day 29 Secondary outcomes: • Mortality rate • Number of patients hospitalized on MV • Clinical improvement (8-point clinical scale) • Decline in oxygen supplementation • Number of patients needing non-invasive ventilation/high flow O2 • Hospital length of stay • Changes in abnormal WBC counts • Adverse events	Randomized controlled trial

A randomised phase II proof of principle multi-arm multi-stage trial designed to guide the selection of interventions for phase III trials in hospitalised patients with COVID-19 infection (CATALYST)	Age ≥16 years with severe COVID-19 • O2 sat ≤ 94% • PF ratio ≤ 300 • Requiring MV N = 168	Experimental group 1: Gemtuzumab Ozogamicin (3 doses: D1, D5, D10) Experimental group 2: Namilumab Experimental group 3: Infliximab Control: Standard of care	Primary outcome: SpO2/FiO2 ratio Secondary outcomes: • Survival • Hospital discharge • Hospital length of stay • WHO progression scale • RR, Temp • CRP • Adverse events	Randomized controlled trial
Infliximab effectiveness in COVID-19 patients	Confirmed COVID-19 with O2 sat < 88%, high inflammatory markers N = 40	Experimental group: Infliximab 4 mg/kg (1 dose) Control: Matching placebo + usual care	Changes in: Blood oxygen levels, WBC count, ferritin, D-dimer, and CRP	Randomized controlled trial
MIS-C Comparative Effectiveness Study (MISTIC)	Age ≤20 years Current or recent COVID-19, suspected COVID-19 exposure with MIS-C N = 180	Experimental group 1: Infliximab 10 mg/kg (1 dose) Experimental group 2: Methylprednisolone 2 mg/kg IV or orally divided every 12 hours + steroid taper Experimental group 3: Anakinra 8 mg/kg/day IV or SQ (max dose: 100mg q6) Control: standard therapy (including IVIG) Allows for randomization to one of the two remaining arms if clinically warranted	Primary outcome: Treatment with lowest rate of second randomization Secondary outcomes: CRP reduction (50%), return of LV EF, and adverse events	Randomized parallel assignment, Open label

Q15. Among patients with COVID-19, should bevacizumab be used for treatment?

As of 12 October 2021

RECOMMENDATION

We suggest against the use of bevacizumab as treatment for COVID-19. (*Very low certainty of evidence Weak recommendation)*

Consensus Issues

Currently available evidence came from one small non-randomized clinical trial with only 27 patients in the treatment group and 26 patients in the external control cohort. Administration of bevacizumab led to net potential harm with unclear potential benefit in only 1 non-critical outcome (i.e., duration of oxygen support). Its cost and potential negative effect on equity, since the drug is also being used as treatment for lung cancer, were also considered by the consensus panel. At present, bevacizumab is not readily accessible due to its limited availability and large cost. Use of bevacizumab among COVID-19 patients when its benefit is still unclear, may lead to even greater difficulty for lung cancer patients to gain access to this drug

KEY FINDINGS

One (1) small non-randomized clinical trial investigated on the potential use of bevacizumab for treatment of COVID-19. The study showed that bevacizumab led to net potential harm with minimal potential benefit only in terms of duration of oxygen support. Evidence was inconclusive for hospital discharge. Adverse events in the bevacizumab group were elevation of liver enzymes (30%), reduced hemoglobin (19%), decreased platelet counts (15%), elevation of blood pressure (11%), elevated blood urea nitrogen (7%), and sepsis (7%).

INTRODUCTION

Bevacizumab is a humanized monoclonal antibody that acts as anti-vascular endothelial growth factor (VEGF) and is currently used for treatment of cancers. Its potential use in severe COVID-19 pneumonia has been explored since VEGF is a potent vascular permeability factor that induces vascular leakiness in COVID-19-infected lung tissues. VEGF results in plasma extravasation and pulmonary edema, which further increases tissue hypoxia. VEGF levels have been observed to be markedly elevated in patients with COVID-19. Blocking VEGF and the VEGF receptor (VEGFR)-mediated signaling would potentially improve oxygenation and anti-inflammatory response, thereby improving the clinical symptoms in patients with severe COVID-19.[1]

REVIEW METHODS

A systematic search was done from inception up to October 3, 2021 using Medline, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and bevacizumab. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. Clinical trials that compared bevacizumab against placebo or standard care were searched for in this review. Outcomes of interest included mortality, clinical

deterioration or improvement, improvement of radiographic findings, and adverse events. No limits were placed on age, COVID-19 severity, and dosing strategy.

RESULTS

One (1) published study investigated on the efficacy and tolerability of bevacizumab in patients with severe COVID-19 pneumonia.[1] The study is a single-arm, non-randomized, non-blinded, clinical trial which utilized an external control cohort. The treatment arm included 27 patients (13 from China and 14 from Italy) who were given a single 500mg dose of bevacizumab, with 1 dropout. The external control included 26 patients with severe COVID-19 from China and Italy who were admitted in the same center within a similar timeframe (±5 days). Data from the external cohort were collected retrospectively. Patients in the treatment and control groups received standard care, which included anti-viral drugs, hydroxychloroquine, antibiotics, steroids, anti-pyretics, and supportive care. The primary outcome reported was change in PaO2/FiO2 at days 1 and 7. Secondary outcomes included change in chest radiological imaging on day 7, oxygen-support status, discharge rate, and fever resolution during the 28-day follow-up.

The overall certainty of evidence was rated very low because of very serious risk of bias and imprecision. The study had serious risk of selection, performance, detection and reporting bias. The risk of bias summary is in Appendix 4. The GRADE evidence summary is in Appendix 5.

Compared to the control group, patients given bevacizumab had significant increase in PaO2/FiO2 values at day 1 (p-value = 0.0001) and day 7 (p-value = 0.0002) from baseline. Both Chinese and Italian cohorts showed a significant increase of PaO2/FiO2 values at day 1 post-bevacizumab treatment relative to the baseline values, whereas, at day 7, only the Italian cohort had significant increase in PaO2/FiO2 ratio. The bevacizumab group had significantly shorter duration of oxygen support (median 9 days, IQR 5-19 days) compared to control group (median 20 days, IQR 14-28; p-value = 0.003). There was no significant difference in hospital discharge (RR 1.42, 95% CI 0.86-2.34).

Of the eight patients in the treatment group who underwent chest CT scan, there was reported improvement in the total lesion areas (cm^3) and the lesion ratios (%) for both lungs at day 7 relative to baseline. There was observed rapid abatement of fever in 13 out of 14 febrile patients (93%) who had fever within 3 days after bevacizumab treatment.

Safety

Adverse events noted among patients given bevacizumab included elevation of liver enzymes (30%), reduced hemoglobin (19%), decreased platelet counts (15%), elevation of blood pressure (11%), elevated blood urea nitrogen (7%), and sepsis (7%). The following were observed in 1 study participant (4%) each: hemorrhagic urea, diarrhea, skin rash, muscle pains in the lower extremity, superficial phlebitis, and sinus tachycardia with atrial premature beats. Adverse events were not reported in the control group.

RECOMMENDATIONS FROM OTHER GROUPS

There are no recommendations on the use of bevacizumab in COVID-19 from the following organizations: NIH COVID-19 Treatment Guidelines (as of August 25, 2021) [2], Australian Guidelines for Clinical Care of People with COVID-19 (as of September 29, 2021) [3], Surviving Sepsis Campaign: Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU (as of March 2021) [4], Infectious Diseases Society of America Guidelines on Treatment and Management of Patients with Covid-19 (as of October 1, 2021) [5], and WHO Therapeutics and COVID-19 Living Guideline latest versions (as of September 24, 2021).[6]

RESEARCH GAPS

There are 4 ongoing randomized controlled trials evaluating the efficacy and safety of bevacizumab for severe to critical COVID-19 patients.

REFERENCES

1. Pang, Jiaojaio, et al. Efficacy and tolerability of bevacizumab in patients with severe COVID-19. Nature Communications (2021)12:814
2. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 30 August 2021
3. Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v43.0. Available at https://app.magicapp.org/#/guideline/5571. Accessed 5 October 2021
4. Surviving Sepsis Campaign: Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU: First Update, Accessed 30 August 2021 https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19
5. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 5.3.1. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 5 October 2021
6. World Health Organization. Therapeutics and COVID-19 Living Guidelines. 24 September 2021. Available at https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2. Accessed 5 October 2021
7. Maximum Retail Price for Medicines, Department of Health. https://www.doh.gov.ph. Accessed October 3, 2021
8. World Health Organization. WHO Handbook for Guideline Development. Geneva: World Health Organization; 2012

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 6)

FACTORS	JUDGEMENT (N = 6)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					
Benefits	Large	Moderate (1)	Small (2)	Uncertain (3)			• Shorter duration of oxygen support (median 9 days, IQR 5-19 days) compared to control group (median 20 days, IQR 14-28; p-value = 0.003) • There was no significant difference in hospital discharge (RR 1.42, 95% CI 0.86-2.34)
Harm	Large (2)	Small (2)	Uncertain (2)				
Certainty of Evidence	High	Moderate (1)	Low	Very low (5)			• Very low because of very serious risk of bias and imprecision. The study had serious risk of selection, performance, detection, and reporting bias.
Balance of effects	Favors drug	Does not favor drug (2)	Uncertain (4)				• Bevacizumab showed net potential harm with minimal benefit in clinical improvement in terms of oxygen support status and duration
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (6)	Moderate cost	Negligible cost	Moderate savings	Large savings	• Large cost; the maximum retail price of Bevacizumab 100mg/4 ml vial is Php 23,445.90 and the 400 mg/16 ml vial is Php 80,686.97 • The total cost of treatment per patient is Php 117,229.50
Certainty of evidence of required resources	No included studies (3)	Very low (1)	Low (1)	Moderate (1)	High		• The cost of bevacizumab was based from the published list of maximum retail price for medicines from the Department of Health
Cost effectiveness	No included studies (5)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (5)	Reduced (1)	Probably no impact	Increased			
Acceptability	Uncertain (4)	No	Yes (2)				
Feasibility	Uncertain (3)	No (3)	Yes				

Additional comments:

- Very small study, clinically important data such as mortality/clinical progression/prevention or shortening hospitalization is missing
- Basis is from 1 small non-randomized clinical trial investigation (27 patients); adverse effect includes sepsis

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (bevacizumab OR bevacizumab{Mesh})	October 2, 2021 6:00 pm	26	1
CENTRAL	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (bevacizumab OR bevacizumab{Mesh}	October 3, 2021 10:00 pm	8	1
COVID-NMA Initiative	Bevacizumab	October 3, 2021	0	0
Google Scholar	Bevacizumab AND COVID 19 AND randomized trial	October 2, 2021	1,260	1
ClinicalTrials.gov	Bevacizumab and COVID 19	October 3, 2021	4	4
Chinese Clinical Trial Registry	Bevacizumab and COVID	October 3, 2021	0	0
EU Clinical Trials Register	Bevacizumab and COVID	October 3, 2021	0	0
Republic of Korea - Clinical Research Information Service	Bevacizumab AND COVID	October 3, 2021	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Bevacizumab AND COVID	October 3, 2021	0	0
CenterWatch	Bevacizumab and COVID	October 3, 2021	0	0
Cochrane COVID-19 study register	Bevacizumab	October 3, 2021	15	0
chinaxiv.org	Bevacizumab	October 3, 2021	0	0
Medrxiv.org	Bevacizumab AND COVID	October 3, 2021	20	1
Biorxiv.org	Bevacizumab AND COVID	October 3, 2021	10	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n)	Interventions	Outcomes	Method
Efficacy and tolerability of bevacizumab in patients with severe COVID-19 *(Pang 2021)*	Bevacizumab group (n = 27): Patients aged 18 to 80 years old with a confirmed COVID-19 diagnosis and with respiratory distress: respiratory rate (RR) of ≥30 times/min, oxygen saturation (SpO_2) of ≤93% while they were breathing ambient air or a partial arterial oxygen pressure to the fraction of inspiration O_2 ratio (PaO_2/FiO_2) of >100 and ≤300 mmHg, and diffuse pneumonia confirmed by chest radiological imaging External control group (n = 26): Patients with severe COVID-19 from China and Italy who had complete data set available for PaO2/FiO2 and who were admitted in the same center within a similar timeframe (±5 days) Inclusion criteria was similar with bevacizumab group.	Bevacizumab 500mg single dose IV infusion	Primary outcome: Change in PaO2/FiO2 at days 1 and 7 Secondary outcomes: Change of chest radiological imaging on day 7, oxygen-support status, discharge rate, and change of fever symptom during the 28-day follow-up	Non-randomized controlled trial

Appendix 4. Study Critical Appraisal

1. Were the patients randomly assigned to treatment groups?	There was no randomization done. The control group is an external cohort and included patients were screened retrospectively.
2. Was the allocation concealed?	There was no allocation concealment.
3. Were baseline characteristics similar at the start of the trial?	Baseline characteristics were similar for both treatment and control groups.
4. Were the patients blinded to the treatment assignment?	There was no blinding.
5. Were the caregivers blinded to the treatment assignment?	There was no blinding.
6. Were the outcome assessors blinded to the treatment assignment?	There was no blinding.
7. Were all patients analyzed in the groups to which they were originally randomised?	Intention to treat analysis was not applicable.
8. Was the follow up rate adequate?	There was only 1 drop-out in the treatment group.

Appendix 5. GRADE Evidence Profile

Author: Maria Philina P. Villamor, MD, FPCP, FPCCP
Date: October 3, 2021
Question: Should Bevacizumab be used for treatment of COVID-19?
Setting: In-patients
Intervention: Bevacizumab
Comparison: Standard of care
Bibiliography: Pang, Jiaojaio, et al. Efficacy and tolerability of bevacizumab in patients with severe Covid-19. Nature Communications (2021)12:814

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab	Control	Relative (95% CI)	Absolute (95% CI)		
Improvement in oxygenation (assessed with: PaO2/FiO2 at Day 1 and Day 7)												
1	Non-randomised trial	Very serious[a]	Not serious	Not serious	Serious[b]	None	Compared to the control group, bevacizumab was associated with a significant increase in PaO2/FiO2 values at day 1 (p-value 0.0001) and day 7 (p-value 0.0002) from baseline.				⊕◯◯◯ VERY LOW	CRITICAL
Improvement in oxygen-support status (follow-up: 28 days)												
1	Non-randomised trial	Very serious[a]	Not serious	Not serious	Serious[b]	None	24/26 (92.3%)	16/26 (61.5%)	**RR 1.50** (1.09 to 2.07)	**308 more per 1,000** (from 55 more to 658 more)	⊕◯◯◯ VERY LOW	CRITICAL
Duration of oxygen support												
1	Non-randomised trial	Very serious[a]	Not serious	Not serious	Serious[b]	None	Significantly shorter duration of oxygen support for bevacizumab (median 20 days, IQR 14-28 for bevacizumab; median 9 days, IQR 5-19 days for control; p-value 0.003)				⊕◯◯◯ VERY LOW	CRITICAL
Adverse events												
1	Non-randomised trial	Very serious[a]	Not serious	Not serious	Serious[b]	None	Adverse events noted among patients given bevacizumab included elevation of liver enzymes (30%), reduced hemoglobin (19%), decreased platelet counts (15%), elevation of blood pressure (11%), elevated blood urea nitrogen (7%), and sepsis (7%). The following were observed in 1 study participant (4%) each: hemorrhagic urea, diarrhea, skin rash, muscle pains in the lower extremity, superficial phlebitis, sinus tachycardia with atrial premature beats.				⊕◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
[a] High risk of bias in selection bias, performance bias, detection bias, and reporting bias
[b] Small sample size

Appendix 6: Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Bevacizumab in Severe or Critical Patients with COVID-19 Pneumonia (NCT04257414)	Patients with severe or critical covid-19 N = 140	Experimental: Bevacizumab 7.5mg/kg + conventional therapy	The time from randomization to clinical improvement	Randomized controlled trial
2. **Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients CORIMUNO-19- BEVA Trial**	Adults with severe COVID-19 admitted in conventional units or ICU	Experimental: Bevacizumab Control: Standard of care	Oxygen saturation Adverse event ARDS Dyspnea Admission to ICU Mechanical ventilation Duration of hospital stay	Phase II Randomized controlled trial Parallel/cross-over
3. Pilot Study of Single Dose Bevacizumab as Treatment for Acute Respiratory Distress Syndrome (ARDS) in COVID-19 Patients	COVID-19 patients with ARDS who have previously received anti-viral and anti-inflammatory treatment	Experimental: Bevacizumab	Mortality	Phase II, multi-centered, randomized, open label, two-armed clinical trial
4. Trial Evaluating Efficacy and Safety of Bevacizumab (Avastin®/Zeribev®) in Patients With COVID-19 Infection, Nested in the Corimmuno-19 Cohort	Adult patients included in the CORIMUNO-19 cohort Hospitalized patients with no acute PE, no superimposed bacterial infection	Bevacizumab: 7.5 mg/kg (with a maximum of 750mg) on day 1 (D1) SOC: patients will receive the best of standard of care including corticosteroids, anticoagulant, antibiotics and tociluzimab	Primary Outcome: The time to recovery for a category 0 to 5 on the WHO Progression scale Secondary Outcomes: 1. Clinical status on the OMS Progression scale 2. Overall survival 3. Ventilator free days 4. High flow free days 5. Time to oxygen supply weaning 6. Changes in VEGF plasma levels 7. Comparison of the incidence of Grade 3 or 4 events 8. Proportion of Adverse Event	Randomized controlled trial Parallel/cross-over

Q16. Among patients with COVID-19, should ivermectin be used for treatment?

As of 6 December 2021

RECOMMENDATIONS

We recommend against the use of ivermectin for the treatment of patients with COVID-19 of any severity. *(Very low certainty of evidence; Strong recommendation)*

We suggest against the use of ivermectin combined with doxycycline for the treatment of patients with COVID-19. *(Very low certainty of evidence; Conditional recommendation)*

Consensus Issues

The review showed that ivermectin has no clear benefit for mortality and all other outcomes for patients with different disease severity, hence the panel made a general recommendation for all COVID-19 patients regardless of severity (mild, moderate, severe or critical).

This update provided additional evidence ivermectin did not differ significantly from placebo in terms of critical outcomes in the treatment of COVID-19. Hence, given the ongoing misuse and abuse of the drug, the panel unanimously voted for a strong recommendation against the use of ivermectin. Other considerations included issues on the pharmacologic property of the drug, given that the drug is registered for veterinary use, the need for higher doses, and concerns regarding adverse events. The panel also considered the issue on health equity wherein other medications for COVID-19 are available, hence resources should be allocated to these more effective and efficacious treatment with clear benefits. There are still a number of ongoing trials, including a local one, which will be considered once data is available.

There is no new evidence for ivermectin combined with doxycycline available, hence, no update was done and the previous recommendations were retained.

PREVIOUS RECOMMENDATION

We recommend against the use of ivermectin for the treatment of patients with severe and critical COVID-19. *(Very low certainty of evidence; Strong recommendation)*

We suggest against the use of ivermectin in the treatment of patients with mild-to-moderate COVID-19. *(Very low certainty of evidence; Conditional recommendation)*

We suggest against the use of ivermectin combined with doxycycline for the treatment of patients with COVID-19. *(Very low certainty of evidence; Conditional recommendation)*

Consensus Issues

The consensus panel noted that health equity may be decreased if budget will be allocated for ivermectin rather than efficacious medications and standard of care. The cost and availability of human grade ivermectin is another crucial consideration. The registered oral and parenteral preparations of ivermectin were registered for veterinary use only. Only the topical preparation of ivermectin is registered for human use. According to the Philippine

Food and Drug Administration, drugs that were registered for veterinary use should not be utilized for human consumption.

In this update, the consensus panel made a conditional recommendation against the use of ivermectin as a treatment for mild and moderate COVID-19 cases since the current available evidence shows no clear benefit in terms of mortality reduction and clinical outcomes. Studies that showed a potential mortality benefit had significant methodological limitations and had results that are inconsistent with those reported in other trials. For severe and critical COVID-19 cases, the consensus panel made a strong recommendation against the use of ivermectin as there are currently other treatments with established effectiveness. The panel also recognized that while the current data showed no statistical difference between ivermectin and control in terms of adverse events, there is still limited data regarding the adverse effects that may be observed when ivermectin is administered in high doses or in doses similar to those given in in vitro studies. Results from the ongoing randomized clinical trials are still needed to establish whether ivermectin is a safe and effective treatment for COVID-19.

NOTE: The Consensus Panel agreed to make separate recommendations for patients with different disease severity. These recommendations were made without considering the dose of ivermectin.

WHAT'S NEW IN THIS VERSION?

This version includes four (4) new randomized controlled trials (total of 16 RCTs; Abd-Elsalam, Biber, Kishoria, and Vallejos). Four studies were excluded from the current analysis (2 RCTs were retracted from preprint publication - Elgazzar and Samaha; 2 RCTs included COVID-19 unconfirmed patients - Niaee and Shabaznejad). Separate analyses for trials evaluating ivermectin alone and those evaluating ivermectin combination treatment were done.

KEY FINDINGS

There are 16 randomized controlled trials (RCTs) that investigated the effects of ivermectin as treatment for patients with COVID-19. No significant over-all mortality benefit was found. Subgroup analysis by disease severity also showed no significant benefit for low dose ivermectin. We cannot estimate the risk of benefit or harm associated with high dose ivermectin because no deaths were reported among the three included RCTs. Sensitivity analysis revealed that publication status and study quality did not influence our estimates.

Treatment with ivermectin was not significantly associated with clinical deterioration, need for mechanical ventilation, clinical improvement, reduction in hospital length of stay, time to symptom resolution, and virologic clearance. The risk for serious and non-serious adverse events was not significantly different among patients who received ivermectin. Our results agree with a recent Cochrane systematic review done in May 2021.

These results must be interpreted in the context of very low certainty of evidence. The certainty of evidence was downgraded due to varying degrees of risk of bias in most studies, inconsistency, and imprecision in several critical outcomes.

INTRODUCTION

Ivermectin is an anti-helminthic drug repurposed as a potential therapy for COVID-19 because of its anti-viral properties and immunomodulatory effects. In-vitro studies

show that ivermectin limits viral infection from SARS-CoV-2 by preventing viruses from suppressing the host's antiviral response. This action is through the inhibition of the importin alpha/beta-1 nuclear transport proteins that are utilized by viruses to promote infection.[1] As an immunomodulator, ivermectin may reduce cytokine secretion by inhibiting the translocation of nuclear transcription factor K-B and phosphorylation of mitogen activated protein (MAP) kinases. Ivermectin also prevents the entry of SARS-CoV-2 into the cell by disrupting the interaction between spike receptor binding domain and ACE2 cellular receptors.[2] Among mice exposed to lethal doses of lipopolysaccharide endotoxin, ivermectin was shown to improve survival and was associated with lower levels of tumor necrosis factor alpha, IL-1, and IL-6 inflammatory markers. Finally, an in-vitro experiment by Caly et al., showed that ivermectin may inhibit the replication of SARS-CoV-2 infected Vero/hSLAM cells with the addition of 5 μM ivermectin.[3] They found a 5000-fold reduction in viral RNA counts. These findings taken together sparked interest in the compassionate use of ivermectin ahead or outside of clinical trials.

Several systematic reviews have already been completed on ivermectin, with varying eligibility criteria and conflicting conclusions.[4-17] A recent Cochrane systematic review published in May 2021 found insufficient evidence to recommend ivermectin as prophylaxis or treatment for COVID-19.[7] However, to date, completed trials on ivermectin continue to be published and a number of trials are still ongoing.

REVIEW METHODS

A systematic search was done from the date of the last search May 3, 2021 until September 10, 2021. We included electronic databases (MEDLINE, Cochrane COVID-19 Study Register, and COVID-19 LOVE Evidence/Epistemonikos), preprint databases (MedRxiv, BioRxiv, and ChinaXiv), and trial registries (Chinese Clinical Trial Registry and WHO International Clinical Trials Registry). We also checked the included studies from other living guidelines and systematic reviews on COVID-19. References of published systematic reviews were also hand searched for studies. Reference lists from websites including IVMMeta were considered and included in the current review as long as they provided sufficient information to allow critical appraisal.[4-17] As appropriate, authors of potentially eligible studies for this review were contacted via email to obtain additional data. The full search strategy used for each source is detailed in Appendix 2.

Only randomized controlled trials that compared ivermectin against placebo or standard of care (SOC) among COVID confirmed patients were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, or adverse events. No limits were placed on age, COVID-19 severity, hospitalization status, and dosing strategy of ivermectin. Subgroup analysis by dose and disease severity was planned. For the outcome of clinical deterioration, subgroup analysis by admission to ICU, deterioration in WHO ordinal scale, progression in O2 support, and need for hospitalization were also planned. We performed sensitivity analysis to assess the robustness of the results when studies with serious risk of bias concerns were excluded. We excluded studies that included patients who were diagnosed with COVID-19 based on radiographic evidence but were negative for COVID-19 RT-PCR or COVID-19 antigen test.

RESULTS

The search yielded 574 records, of which 16 RCTs (N = 2,063) were included in this review. The trials were performed in Bangladesh [18,19], Spain [20], Pakistan [21,22], Egypt [23], Argentina [24,25], India [26-28], Turkey [29], Mexico [30], Brazil [31], Colombia [32], and Israel.[33] Sample sizes ranged from 24 to 501. Three of the 16 studies (16%) were still pre-prints.[21,30,33] Participants in the included studies had varying severity of COVID-19: 6 RCTs for mild [18,20,22,24,27,31], 7 RCTs for mild-to-moderate [19,21,23,25,26,28,33], 2 RCTs for severe [29,30], 1 RCTs for mixed non-severe and severe cases.[31] Different treatment regimens of ivermectin were used: 12 RCTs used low dose (200 mcg/kg or 12mg and lower) [18,19,21-24,27-30,32,33], 2 RCTs used high dose ivermectin (400-600 mcg/kg or 24mg or higher) [20,25], and 2 RCTs used mixed doses.[26,31] Eight studies were placebo-controlled [18,20,24,26,28,30,32,33], while 8 used the existing standard of care [19,21-23,25,27,29,31] in their country. The detailed characteristics of the included studies are summarized in Appendix 3.

The overall certainty of evidence was rated very low due to varying degrees of risk of bias in most studies, serious imprecision, and/or serious inconsistency in several outcomes. Risk of bias was rated very serious in 7/16 studies and serious in 5/16 studies, due to concerns with randomization, allocation concealment, and blinding of patients and outcome assessors. Only 4 trials [23,24,26,32] were appraised to have no serious risk of bias. At least 75% of all included studies had high risk for detection bias from unblinded assessors, performance bias from unblinded patients and investigators, and attrition bias from having incomplete outcome data. Appendix 4 provides details of the individual risk of bias ratings. Assessments of certainty of evidence per comparison are detailed in Appendix 5.

Mortality

Pooled analysis of 10 RCTs (N = 1,658) showed that ivermectin had no significant reduction in overall mortality among COVID-19 patients compared to placebo or standard of care (RR 0.73, 95% CI 0.42, 1.28; I^2 = 0%, for intention-to-treat analysis and for per-protocol analysis). Subgroup analysis by disease severity showed no significant reduction in mortality among those with mild (RR 1.05, 95% CI 0.27, 4.02, I^2 = 0%), mild to moderate (RR 0.43, 95% CI 0.08, 2.48, I^2 = 29%), and severe (RR 0.74, 95% CI 0.37, 1.48, I^2 = 0%).

Subgroup analysis by dose showed no significant difference in mortality among those given low-dose ivermectin compared to control (RR 0.73, 95% CI 0.42, 1.28, I^2 = 0%). For high dose ivermectin, we cannot estimate the risk of benefit or harm associated with treatment because no deaths were reported among the three included RCTs.
Sensitivity analysis by removing preprint studies from the analysis and excluding studies with serious risk of bias showed these had no significant influence on mortality (publication status, RR 0.69, 95% CI 0.36, 1.33; study quality, RR 0.90, 95% CI 0.33, 2.42).

Critical Clinical Outcomes

The effects of ivermectin were not significantly different from control for the following critical outcomes: clinical deterioration (RR 0.69, 95% CI 0.44, 1.09, I^2 = 0%), need for mechanical ventilation (RR 0.82, 95% CI 0.34, 1.99, I^2 = 0%), and clinical improvement (RR 1.05, 95% CI 0.94, 1.18, I^2 = 0%). Hospital length of stay was not significantly

different from the control (MD -0.48 days, 95% CI -2.48 to 1.52) with significant heterogeneity (I^2 = 72%; p=0.03).

Subgroup analysis for clinical deterioration showed no significant difference in the proportion of patients requiring admission to ICU (RR 0.85, 95% CI 0.27, 2.62), deterioration in WHO ordinal scale (RR 0.59, 95% CI 0.26, 1.30), and need for hospitalization (RR 0.72, 95% CI 0.39, 1.36). Based on one study (Ahmed), no events were reported for the outcome of progression in oxygen support.

Pooled results from 2 RCTs [19,26] showed that treatment with ivermectin was not significantly associated with a shorter time to symptom resolution (MD -0.53 days, 95% CI -1.50 to 0.44, I^2 = 0%). One larger study by Lopez-Medina (N = 398) also similarly reported no significant difference in time to symptom resolution (Hazard Ratio 1.07, 95% CI 0.87, 1.32).

Other Outcomes

Virologic clearance

Very low certainty of evidence from 11 RCTs showed no significant difference in virologic clearance from days 3 to 10 (RR 1.30, 95% CI 0.95, 1.79; I^2 = 89%; N = 621) between the ivermectin and control groups, but with significant heterogeneity. Subgroup analysis showed that regardless of disease severity (mild: RR 1.43, 95% CI 0.53, 3.83, I^2 = 96%; mild-moderate RR 1.14, 95% CI 0.86, 1.50, I^2 = 64%, and severe: RR 2.33, 95% CI 0.94, 5.82), ivermectin treatment had no significant influence on virologic clearance, however, still with significant heterogeneity.

Adverse events

Ivermectin was not significantly associated with an overall increased risk of any adverse events compared to control (RR 0.96, 95% CI 0.81, 1.15, I^2 = 8%; 12 RCTs). Subgroup analysis per dose showed no significant difference in adverse events with the use of high dose ivermectin (RR 1.03, 95% CI 0.61, 1.73, I^2 = 0%), and low-dose ivermectin (RR 0.97, 95% CI 0.75, 1.24, I^2 = 22%). Gastrointestinal symptoms such as epigastric pain, diarrhea and nausea, neurologic symptoms such as headache, agitation, confusion, and dizziness, were the most common side effects reported across studies.

There was no significant difference in serious adverse events (RR 0.78, 95% CI 0.24, 2.53, I^2 = 0%). Six serious adverse events related to ivermectin were reported: hyponatremia (N = 1; low dose, mild-moderate COVID) [25], multiorgan failure (N = 2; low dose, mild-moderate COVID) [32], and need for ventilatory support (N = 1; low and high dose, mild-moderate COVID).[31] Delirium-like behavior (N = 2; low dose, severe COVID) [29] was reported among patients who were tested to have mutations of either the MDR-1/ABCB1 or CYP3A4 genes affecting ivermectin metabolism.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
US-NIH (as of September 15, 2021) [34]	There are insufficient data for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19.
Infectious Diseases Society of America (IDSA) (as of September 6, 2021) [36]	Does not recommend the use of ivermectin outside of trials.
WHO Living Guideline on COVID-19 Therapeutics (as of September 24, 2021) [37]	Does not recommend using ivermectin in patients with COVID-19 except in the context of a clinical trial.
India COVID-19 Guidelines (as of May 15, 2021) [38]	Recommends against using ivermectin for treatment of patients with any severity of COVID-19 (non-severe, severe, critical). The group further stated that “its use may distract from use of other therapies for which there is better evidence, and that indiscriminate use might also reduce its availability for other conditions where its benefit is established, such as parasitic infections”.

The Cochrane systematic review published last May 2021 similarly reported no significant difference in the following the critical outcomes: mortality, adverse events, clinical deterioration, and need for mechanical ventilation.

RESEARCH GAPS

As of September 2021, there are at 81 ongoing clinical trials investigating the efficacy of ivermectin as treatment for COVID-19 that are listed in COVID-19 NMA database.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 8)

FACTORS	JUDGEMENT (N=8)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)					
Benefits	Large	Moderate (1)	Small (2)	Uncertain (5)			No significant benefit for over-all mortality (RR 0.73, 95% CI 0.42-1.28), clinical deterioration (RR 0.69, 95% CI 0.44, 1.09), need for mechanical ventilation (RR 0.82, 95% CI 0.34, 1.99), clinical improvement (RR 1.05, 95% CI 0.94, 1.18), and hospital length of stay (mean difference (MD -0.48 days, 95% CI -2.48, 1.52).
Harm	Large	Small (3)	Uncertain (5)				There are no significant differences in adverse events (RR 0.96, 95% CI 0.81, 1.15) and serious adverse events (RR 0.78, 95% CI 0.24, 2.53) between patients receiving ivermectin and placebo
Certainty of Evidence	High	Moderate	Low (2)	Very low (6)			The overall certainty of evidence was rated very low, downgraded due to varying degrees of risk of bias in most studies, inconsistency, and imprecision in several critical outcomes.
Balance of effects	Favors drug	Does not favor drug (5)	Uncertain (3)				Ivermectin showed no significant difference in over-all mortality, clinical deterioration, need for mechanical ventilation, clinical improvement, hospital length of stay, time to symptom resolution and virologic clearance, no difference with Aes and SAEs
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain (2)	Large cost	Moderate cost (4)	Negligible cost (2)	Moderate savings	Large savings	Cost is around P20-27 per tablet depending on concentration.
Certainty of evidence of required resources	No included studies (1)	Very low (2)	Low (1)	Moderate (3)	High (1)		Pricing information is taken from the website of Dr. Zen's Research, Inc. is a subsidiary of InnoGen Pharmaceuticals, Inc.
Cost effectiveness	No included studies (6)	Favors the comparison (2)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (4)	Reduced (2)	Probably no impact (2)	Increased			
Acceptability	Uncertain (6)	No (1)	Yes (1)				
Feasibility	Uncertain (4)	No (1)	Yes (3)				

Appendix 2. Search Strategy

Database	Search Strategy	Yield	Eligible
MEDLINE (PubMed)	“((("COVID-19" [Supplementary Concept] OR "COVID-19 Testing" OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccines" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2") OR ((19[tiab] OR 2019[tiab] OR "2019-nCoV" OR "Beijing" OR "China" OR "Covid-19" OR epidem*[tiab] OR epidemic* OR epidemy OR new[tiab] OR "novel"[tiab] OR "outbreak" OR pandem* OR "SARS-CoV-2" OR "Shanghai" OR "Wuhan") AND ("Coronavirus Infections"[Mesh] OR "coronavirus"[MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab] OR pneumonia-virus*[tiab]))) AND 2019/12/1:3000/12/31[PDAT]) AND ((ivermectin OR ivermectin[MeSH Terms])”	Sept 10: +270	34
Cochrane COVID-19 Study Register	“Ivermectin”	Sept 10: +70	23
MedRxiv	Advanced search: “Ivermectin AND COVID” with “match all” parameters	Sept 10: +142	14
BioRxiv	Advanced search: “Ivermectin AND COVID” with “match all” parameters	Sept 10: +51	0
ChinaXiv	Advanced search: “Ivermectin AND COVID” with “all fields” parameters	Sept 10: 0	0
Chinese Clinical Trial Registry	Under trial search (with more option), the search syntax “Ivermectin”, under intervention and “COVID-19”, under target disease was used	Sept 10: +1	0
WHO ICTRP	The search syntax “Ivermectin” was used. Results were filtered to “Restrict to COVID-19”	Sept 10: +7	6
Living Guidelines	Records were selected from three living guidelines (WHO Living Guidelines, Australian CPG, COVID-19 NMA)	Sept 10: +33	27

Appendix 3. Characteristics of Included Studies

Table 1. Ivermectin versus placebo or standard care (16 RCTs)

No.	Clinical Trial ID/ Title	Country	Study design	Population	Intervention	Comparator	Outcomes
1	Abd-Elsalam 2021 Clinical study evaluating the efficacy of Ivermectin in COVID-19 treatment: A randomized controlled study	Egypt	Open-label RCT (N=164)	Mild-moderate COVID-19 Age 20 to 65 years old	Oral Ivermectin, 12 mg once a day for 3 days. (n=82) Low dose Ivermectin	Standard care (n=82) Standard care: paracetamol, empiric antibiotics, oseltamivir if needed.	1. Mortality 2. Need for mechanical ventilation 3. Safety
2	Ahmed 2020 A five day course of Ivermectin for the treatment of COVID-19 may reduce the duration of illness.	Bangladesh	Double-blind RCT (N=76)	Mild COVID-19 Age 18 to 65 years hospitalized within the last 7 days; with either fever (≥37.5C); cough or sore throat; and diagnosed positive for SARS-CoV-2 by RT-PCR.	Oral Ivermectin, 12 mg once a day for 5 days. (n=22) Low dose Ivermectin	Placebo (n=22)	1. Mortality 2. Clinical deterioration 3. Duration of hospitalization 4. Remission of symptoms 5. Time to PCR negativity 6. Adverse effects
3	Beltran-Gonzalez 2021 Efficacy and safety of Ivermectin and hydroxychloroquine in patients with severe COVID-19	Mexico	Double-blind RCT (N=106)	Severe COVID-19 Mean age 53	Oral Ivermectin 12 or 18 mg according to weight (n=36) Low dose Ivermectin	Placebo (n=37)	1. Duration of hospitalization 2. Hospital discharge, n(%) 3. Discharged without respiratory deterioration or death, n(%) 4. Respiratory deterioration or death, n(%)
4	Biber 2021 Favorable outcome on viral load and culture viability using Ivermectin in early treatment of non-hospitalized patients with mild COVID-19 – A double-blind, randomized placebo-controlled trial.	Israel	Double-blind RCT (N=89)	Mild-moderate COVID-19 Age 18 years and older	Oral Ivermectin, 12 or 15 mg according to weight (n=47) Low dose Ivermectin	Placebo (n=42)	1. Viral clearance (repeat RT-PCR on D4,6,8,10)
5	Bukhari 2021 Efficacy of Ivermectin in COVID-19 patients with mild to moderate disease	Pakistan	Open-label RCT (N=100)	Mild-moderate COVID-19 Age 15 to 65 years	Oral Ivermectin 12 mg single dose at admission (n=50) Low dose Ivermectin	Standard care (n=50) Standard care: Vit C 500mg OD, Vit D3 200k IU once weekly, paracetamol 500mg	1. Viral clearance (days to RT-PCR negativity) 2. Adverse effects
6	Chaccour 2020	Spain	Double-blind RCT (N=24)	Mild COVID-19 Age 18 to 59 years	Oral Ivermectin, 400 mcg/kg, single dose (n= 12)	Placebo (n= 12)	1. Mortality 2. Clinical improvement

	The effect of early treatment with Ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot,double-blind, placebo-controlled, randomized clinical trial.			Outpatient setting. without comorbidities considered as risk factors to develop severe disease or COVID-19.	High dose Ivermectin		3. Virologic clearance: proportion of patients who become negative at day 7 and viral culture 4. Adverse effects
7	Chachar 2020 Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients	Pakistan	Open-label RCT (N=50)	Mild COVID-19 Age 18 to 75 years excluded severe COVID-19, with malignancy, chronic kidney disease, and liver cirrhosis	Oral Ivermectin, 12 mg on D0, then 12 mg after 12 hours, and 12 mg after 24 hours. (n=25) Low dose Ivermectin	Standard care (n=25) Standard care: conventional symptomatic treatment	1. Clinical improvement 2. Adverse effects
8	Kishoria 2020 Ivermectin as adjuvant to hydroxycholoroquine in patients resistant to standard treatment for sars-cov-2:results of an open-label randomized clinical study	India	Open-label RCT (N=32)	Mild COVID-19 Age 18 years and older Patients who remain positive after 6 days of standard care treatment.	Oral Ivermectin, 12 mg single dose on D1 (n=19) Standard care: HCQ 400 mg/tab twice a day for 5 days Paracetamol 500mg/tab prn, Vitamin C BID. Low dose Ivermectin	Standard care (n=13) Standard care: HCQ 400 mg/tab twice a day for 5 days Paracetamol 500mg/tab prn, Vitamin C BID.	1. Viral clearance D5 2. Hospital Discharge D5
9	Królewiecki 2020 Antiviral effect of high-dose Ivermectin in adults with COVID-19: a pilot randomised, controlled, open label, multicentre trial.	Argentina	Single-blind (outcome-assessor) RCT (N=45)	Mild-Moderate COVID-19 Age 18 to 69 years hospitalized patients not requiring ICU admission excluded patients with poorly controlled comorbidities	Oral Ivermectin, 600mcg/kg, once a day for 5 days (n=30) Co-Intervention: Standard care High dose Ivermectin	Standard care (n=15) Standard care: uncertain	1. Mortality 2. Clinical deterioration 3. Adverse effects
10	Lopez-Medina 2021 Effect of Ivermectin on time to resolution of symptoms among adults with mild COVID-19	Colombia	Double-blind RCT (N=476)	Mild COVID-19 Mean age 37 (range: 28-49)	Oral Ivermectin, 300 mcg/kg, once a day for 5 days (n=238) Low dose Ivermectin	Placebo (n=238)	1. Time to resolution of symptoms (D21); % patients with resolved symptoms 2. Clinical deterioration (% patient with clinical deterioration) 3. Fever since randomization 4. Escalation of care 5. Mortality

11	Mohan 2021 Ivermectin in mild and moderate COVID-19 (RIVETCOV): a randomized, placebo-controlled trial	India	Triple-blind RCT (N=157 mITT=125)	Mild-Moderate COVID-19 Age 18 years and older	Oral Ivermectin, 12 mg, single dose (n=40) Oral Ivermectin, 24 mg, single dose (n=40) Low dose and high dose Ivermectin	Placebo (n=45)	1. Mortality 2. Clinical deterioration 3. Progression to ventilation 4. Clinical improvement 5. Duration of hospitalization 6. Viral clearance 7. Adverse effects
12	Okumus 2021 The Effectiveness and Safety of Ivermectin as add-on Therapy in Severe COVID-19 Management	Turkey	Randomized open label (N=66)	Severe COVID-19 Age 18 years and older	Oral Ivermectin 200 mcg/kg, once a day for 5 days (n=30) Co-intervention: Standard care Low dose Ivermectin	Standard care (n=30) Standard care: Hydroxychloroquine, favipiravir and azithromycin (HFA) HCQ (2x400mg loading dose followed by 2x200mg, PO, 5 days), favipiravir (2x1600mg loading dose followed by 2x600mg maintenance dose, PO, total 5 days) and azithromycin (500mg 1st day loading dose, followed by 250mg/day, PO, total 5 days)	1. Mortality 2. Clinical improvement 3. Viral clearance D10 4. Adverse effects
13	Podder 2020 Outcome of Ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study	Bangladesh	Open-label RCT (N=62)	Mild-moderate COVID-19 Age 18 years and older	single dose of Ivermectin 200 mcg/kg on the day 1 of randomization (n=32) Low dose Ivermectin	Standard care (n=30) Standard care: symptomatic treatment which included antipyretics, cough suppressants, and capsule doxycycline (100 mg every 12 hours for seven days)	1. time needed for resolution of fever, cough, shortness of breath 2. time needed for full recovery from all symptoms 3. Viral clearance (repeat RT-PCR on day 10)
14	Pott-Junior 2021 Use of Ivermectin in the treatment of COVID-19: a pilot trial	Brazil	Open-label RCT (N=32)	Mild-severe COVID-19 Age 18 years and older	Ivermectin + SOC 100mcg/kg (n=6) 200mcg/kg (n=14) 400mcg/kg (n=7) Low and high dose Ivermectin	Standard care (n=4)	1. Viral clearance (% patients with 2 negative PCR tests w/in 7 days) 2. Adverse events
15	Ravikirti 2021 Ivermectin as a potential treatment for mild to moderate COVID-19 – A Double-blind randomized	India	Double-blind RCT (N=115)	Mild-Moderate COVID-19 Age 18 years and older	Oral Ivermectin 12mg on D1 and D2 (n=57)	Placebo (n=58) Standard care:	1. Mortality 2. Clinical deterioration 3. Progression to Ventilation 4. Clinical improvement 5. Viral Clearance

	placebo-controlled trial				Co-intervention: standard care Low dose Ivermectin	Hydroxychloroquine, steroids, enoxaparin, antibiotics, remdesivir, convalescent plasma, tocilizumab	
16	Vallejos 2021 Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo controlled trial	Argentina	Double-blind RCT (N=501)	Mild COVID-19 Age 18 years and older	Oral Ivermectin, 150-200mcg/kg, once a day for 2 days (n=250) Low dose Ivermectin	Placebo (n=251)	1. Clinical deterioration (need for hospitalization) 2. Mortality 3. Need for mechanical ventilation 4. Safety

Appendix 4. Methodological Quality Assessment of Included Studies

Table 1. Methodological quality assessment: Ivermectin vs. placebo/standard of care (17 RCTs)

Studies	Risk of bias	Random assignment	Allocation concealment	Similar baseline characteristics	Patients blinded	Caregivers blinded	Assessors blinded[1]	Intention-to-treat analysis	Adequate follow-up rate	Peer-reviewed
1. Abd-Elsalam*	**Not serious**	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
2. Ahmed	**Serious**	Yes	Unclear	Unclear	Yes	Yes	Unclear	No	Yes	Yes
3. Beltran-Gonzalez	**Very serious**	Yes	Unclear	No	Yes	Unclear	Unclear	Yes	Yes	No
4. Biber*	**Serious**	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
5. Bukhari	**Very serious**	Yes	Unclear	Yes	No	No	No	Yes	No	No
6. Chaccour	**Serious**	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
7. Chachar	**Serious**	Yes	No	Yes	No	No	No	Yes	Yes	Yes
8. Kishoria*	**Very serious**	Yes	Yes	Unclear	No	No	No	Yes	Yes	Yes
9. Królewiecki	**Serious**	Yes	Yes	Yes	No	No	No	Yes	No	Yes
10. Lopez-Medina	**Not serious**	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
11. Mohan	**Not serious**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Okumuş	**Very serious**	Yes	Unclear	Yes	No	No	No	Yes	No	Yes
13. Podder	**Very serious**	Yes	No	Yes	No	No	No	No	No	Yes
14. Pott-Junior	**Very serious**	Yes	Unclear	Unclear	No	No	No	Yes	No	Yes
15. Ravikirti	**Very serious**	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
16. Vallejos*	**Not serious**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

* New RCTs
Green: not serious; Yellow: serious; Red: very serious

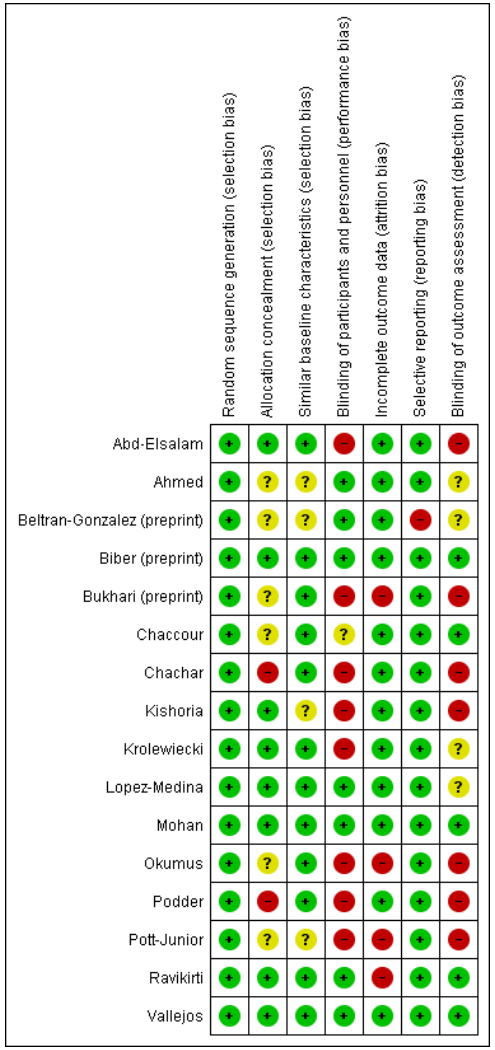


Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Appendix 5. Grade Evidence Profile

Author(s): MVASGJoson, HHGBayona, JJVBesa, DLROTating, MGCCruz
Question: Ivermectin compared to standard of care or placebo as treatment for COVID-19

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivermectin	Standard of care or placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
10[a]	Randomised trials	Serious[b]	Not serious	Not serious	Serious[c]	None	18/859 (2.1%)	27/799 (3.4%)	**RR 0.73** (0.42 to 1.28)	**9 fewer per 1,000** (from 20 fewer to 9 more)	⊕⊕◯◯ LOW	CRITICAL
Clinical deterioration												
7	Randomised trials	Not serious	Not serious	Not serious	Serious[c]	None	32/756 (4.2%)	41/697 (5.9%)	**RR 0.69** (0.44 to 1.09)	**18 fewer per 1,000** (from 33 fewer to 5 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Need for mechanical ventilation												
6	Randomised trials	Not serious	Serious[d]	Not serious	Serious[e]	None	10/547 (1.8%)	11/462 (2.4%)	**RR 0.82** (0.34 to 1.99)	**4 fewer per 1,000** (from 16 fewer to 24 more)	⊕⊕◯◯ LOW	CRITICAL
Clinical improvement (follow-up: 6-14 days)												
6	Randomised trials	Serious[f]	Not serious	Not serious	Not serious	None	239/469 (51.0%)	191/416 (45.9%)	**RR 1.05** (0.94 to 1.18)	**23 more per 1,000** (from 28 fewer to 83 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital length of stay (days)												
3	Randomised trials	Serious[g]	Serious[h]	Not serious	Serious[i]	None	142	143	-	MD **0.48 days lower** (2.48 lower to 1.52 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Time to symptom resolution (in days)												
3	Randomised trials	Very serious[j]	Serious[d]	Not serious	Not serious	None	**Pooled mean difference for Mohan 2020, Podder 2020:** MD -0.53 [-1.50, 0.44] days. **Lopez-Medina:** 10 days (IQR, 9-13) ivermectin group compared with 12 days (IQR, 9-13) placebo group. Hazard Ratio 1.07 [95%CI, 0.87 to 1.32]; *p* = .53 by log-rank test.				⊕◯◯◯ VERY LOW	IMPORTANT

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivermectin	Standard of care or placebo	Relative (95% CI)	Absolute (95% CI)		
Virologic clearance (negative RT-PCR) (follow-up: 3-10 days)												
11	Randomised trials	Very serious[k]	Serious[l]	Not serious	Serious[c]	None	215/341 (63.0%)	135/280 (48.2%)	**RR 1.30** (0.95 to 1.79)	**145 more per 1,000** (from 24 fewer to 381 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Adverse Events												
12	Randomised trials	Not serious[m]	Serious[n]	Not serious	Not serious	None	256/926 (27.6%)	239/842 (28.4%)	**RR 0.96** (0.81 to 1.15)	**11 fewer per 1,000** (from 54 fewer to 43 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious Adverse Events												
10	Randomised trials	Not serious	Very serious[o]	Not serious	Serious[p]	None	6/594 (1.0%)	4/509 (0.8%)	**RR 0.78** (0.24 to 2.53)	**2 fewer per 1,000** (from 6 fewer to 12 more)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

[a] Trials: Ahmed, Chaccour, Krolewiecki, Mohan, Ravikirti, Niaee, Lopez-Medina, Okumus, Abd-Elsalam, Beltran-Gonzalez, Vallejos, and Shahbaznejad; Okumus 2020 assessed mortality at D60

[b] Risk of bias downgraded by 1 level: some concerns regarding adequate randomization and deviations from intended interventions.

[c] Wide confidence interval containing 1.00

[d] Serious inconsistency due to different direction of effect of the included studies

[e] Wide confidence interval, few events

[f] Serious concern for bias over the clinical outcome measured since the study of Chachar, Kishoria, and Okmus are open-label in design.

[g] Very serious risk of bias in one study (Beltran-Gonzales)

[h] Results varied across 3 studies; High heterogeneity (I2 = 71%)

[i] wide confidence interval

[j] very serious risk of bias for Podder et al., 2020 - open-label in design

[k] Risk of bias downgraded by 2 levels: high risk of bias due to inadequate randomization and missing data, some concerns regarding deviations from intended interventions and selection of reported results. Serious concern for risk of bias due to high drop out in the study of Ravikirti.

[l] Some concern for inconsistency. I2 = 89%.

[m] Two studies with low risk of bias (Lopez-Medina and Vallejos) contributed to 83.3% of the overall effect. Risk of bias: not serious

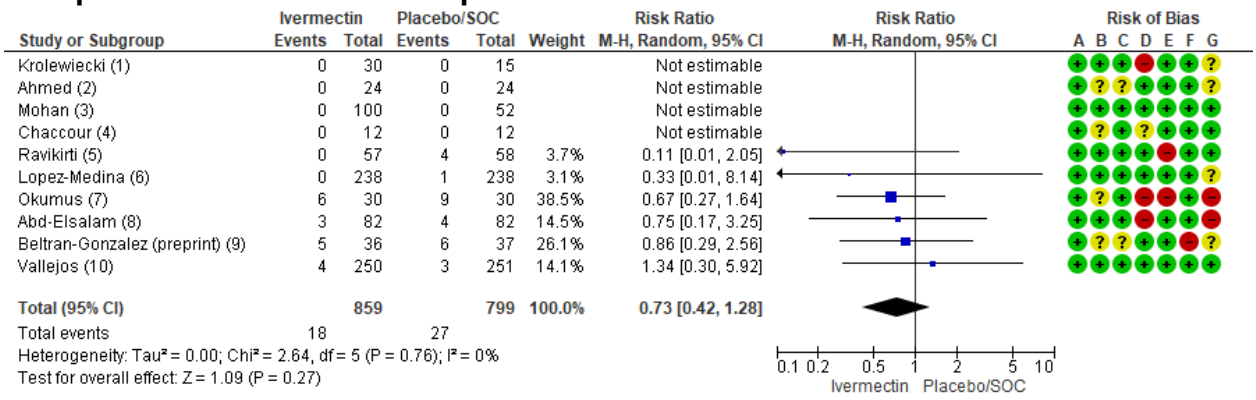
[n] There is some concern with the difference in ADR reporting between the RCTs

[o] Very serious inconsistency due to different direction of effect of the included studies.

[p] imprecision due to small event rates

Appendix 6. Forest Plots

Comparison 1: Ivermectin vs. placebo or standard of care



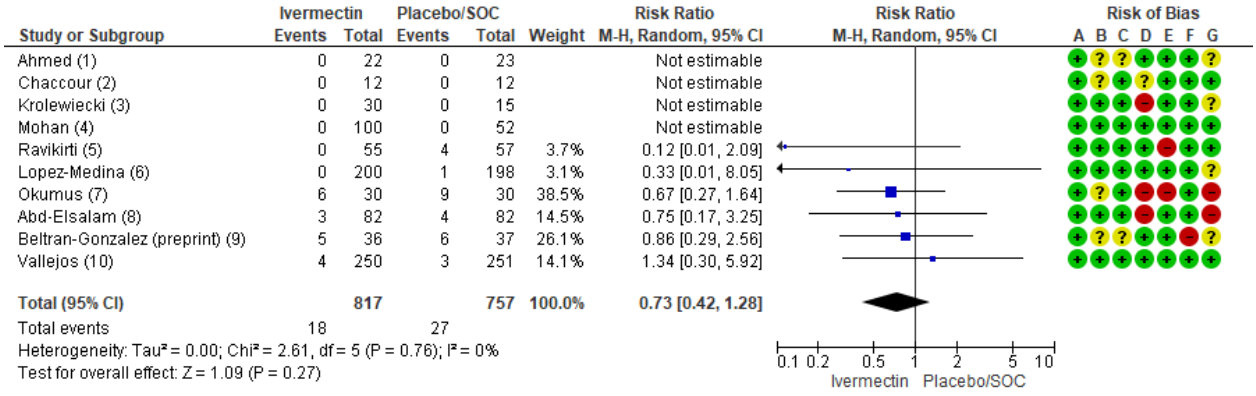
Footnotes

(1) IVM 600 mcg/kg x 5 days + SOC vs. SOC (unspecified)
(2) IVM 12 mg once daily x 5 days vs. placebo
(3) IVM 24mg single dose (arm1) or 12 mg single dose (arm2) vs. placebo
(4) IVM 400 mcg/kg (single dose) vs placebo
(5) IVM 12mg x 2 days + SOC; vs. placebo + SOC (HCQ, steroids, enoxaparin, antibiotics, remdesivir,
(6) IVM 300 mcg/kg 1x/day for 5 days vs. placebo
(7) IVM 200mcg/kg x 5 days vs. SOC (HCQ, AZT, favipiravir)
(8) IVM 12 mg once daily x 3 days vs. SOC
(9) IVM 12-18 mg/kg (unspecified duration) vs. placebo
(10) IVM 150-200mcg/kg oral x 2 days + SOC vs. placebo + SOC

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Similar baseline characteristics (selection bias)
(D) Blinding of participants and personnel (performance...
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.1. Mortality, overall (intention-to-treat)



Footnotes

(1) IVM 12 mg once daily x 5 days vs. placebo
(2) IVM 400 mcg/kg (single dose) vs. placebo
(3) IVM 600 mcg/kg x 5 days + SOC vs. SOC (unspecified)
(4) IVM 24mg single dose (arm1) or 12 mg single dose (arm2) vs. placebo
(5) IVM 12mg x 2 days + SOC; vs. placebo + SOC (HCQ, steroids, enoxaparin, antibiotics, remdesivir,
(6) IVM 300 mcg/kg 1x/day for 5 days vs. placebo
(7) IVM 200mcg/kg x 5 days vs. SOC (HCQ, AZT, favipiravir)
(8) IVM 12 mg once daily x 3 days vs. SOC
(9) IVM 12-18 mg/kg (unspecified duration) vs. placebo
(10) IVM 150-200mcg/kg oral x 2 days + SOC vs. placebo + SOC

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Similar baseline characteristics (selection bias)
(D) Blinding of participants and personnel (performance...
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.2. Mortality, overall (per protocol)

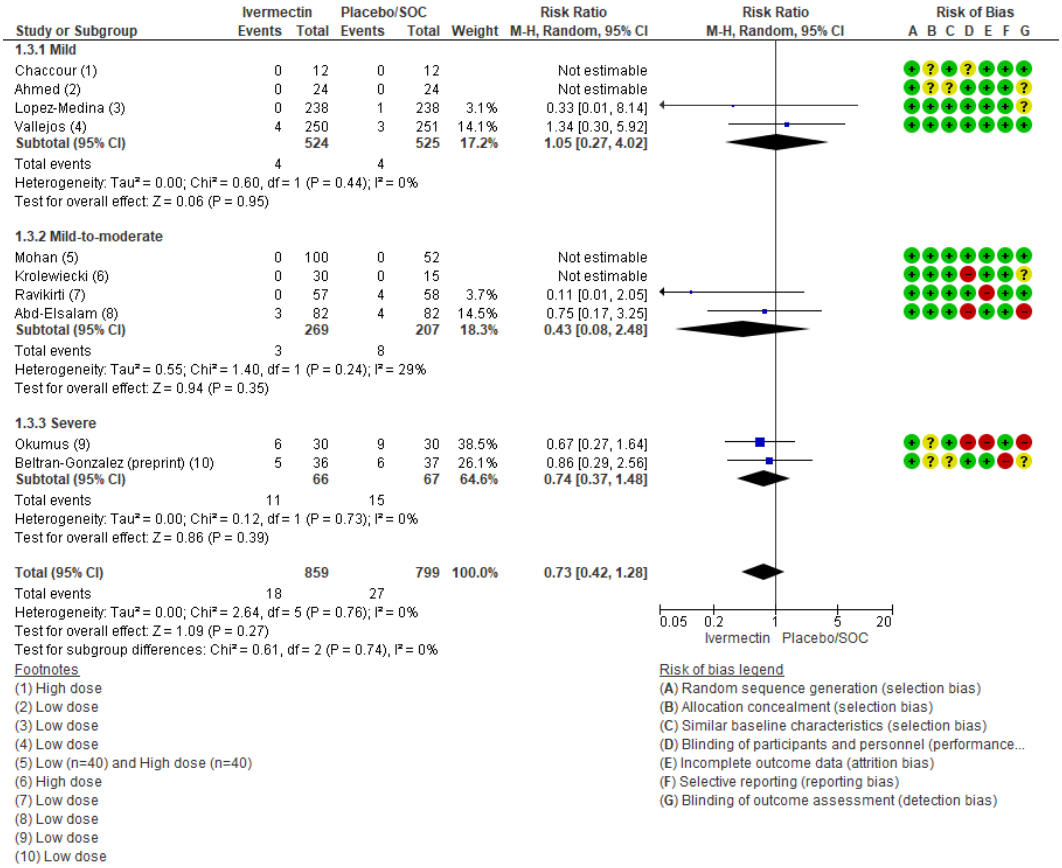


Figure 1.3. Mortality, by disease severity (ITT)

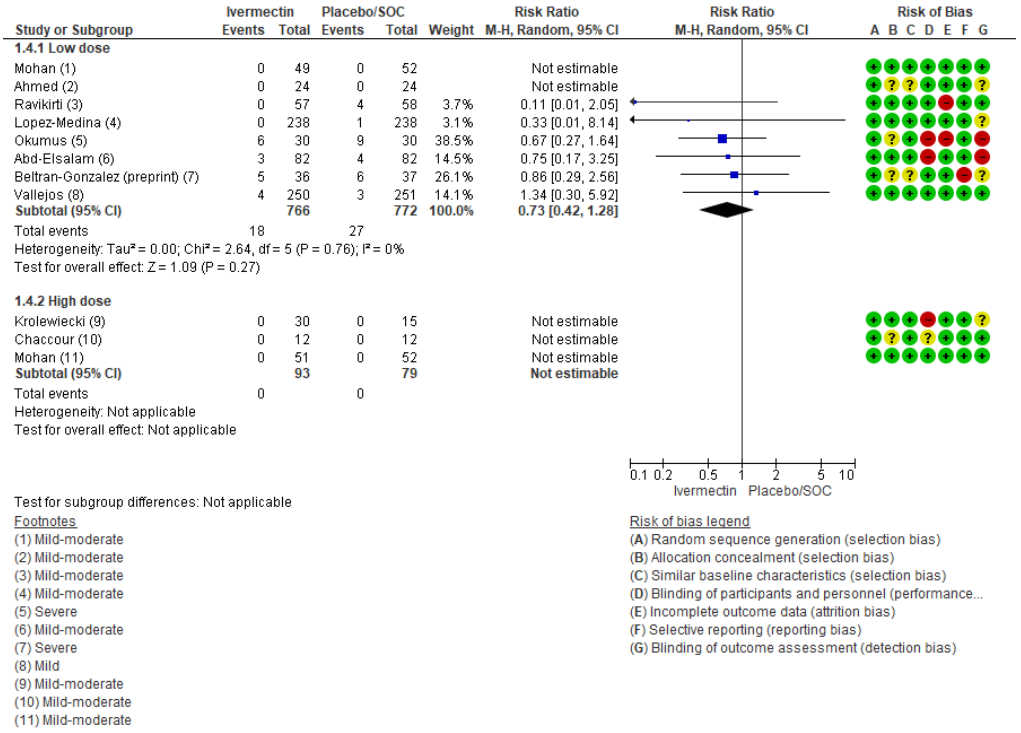


Figure 1.4. Mortality, by dose (ITT)

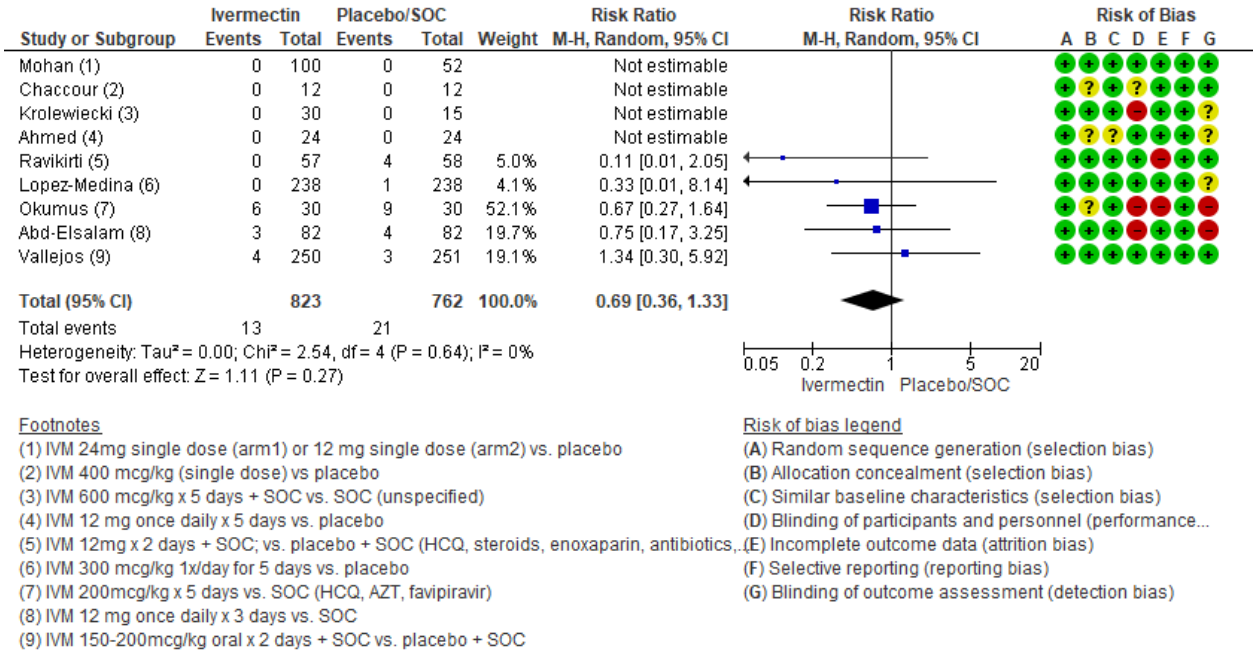


Figure 1.5. Mortality, by publication status (ITT)

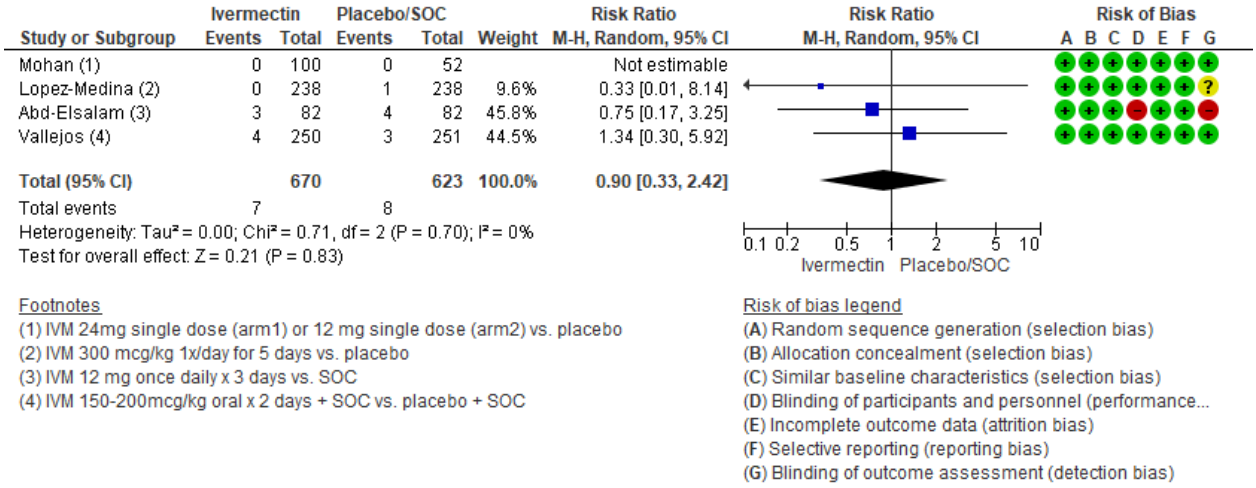


Figure 1.6. Mortality, by study quality (ITT)

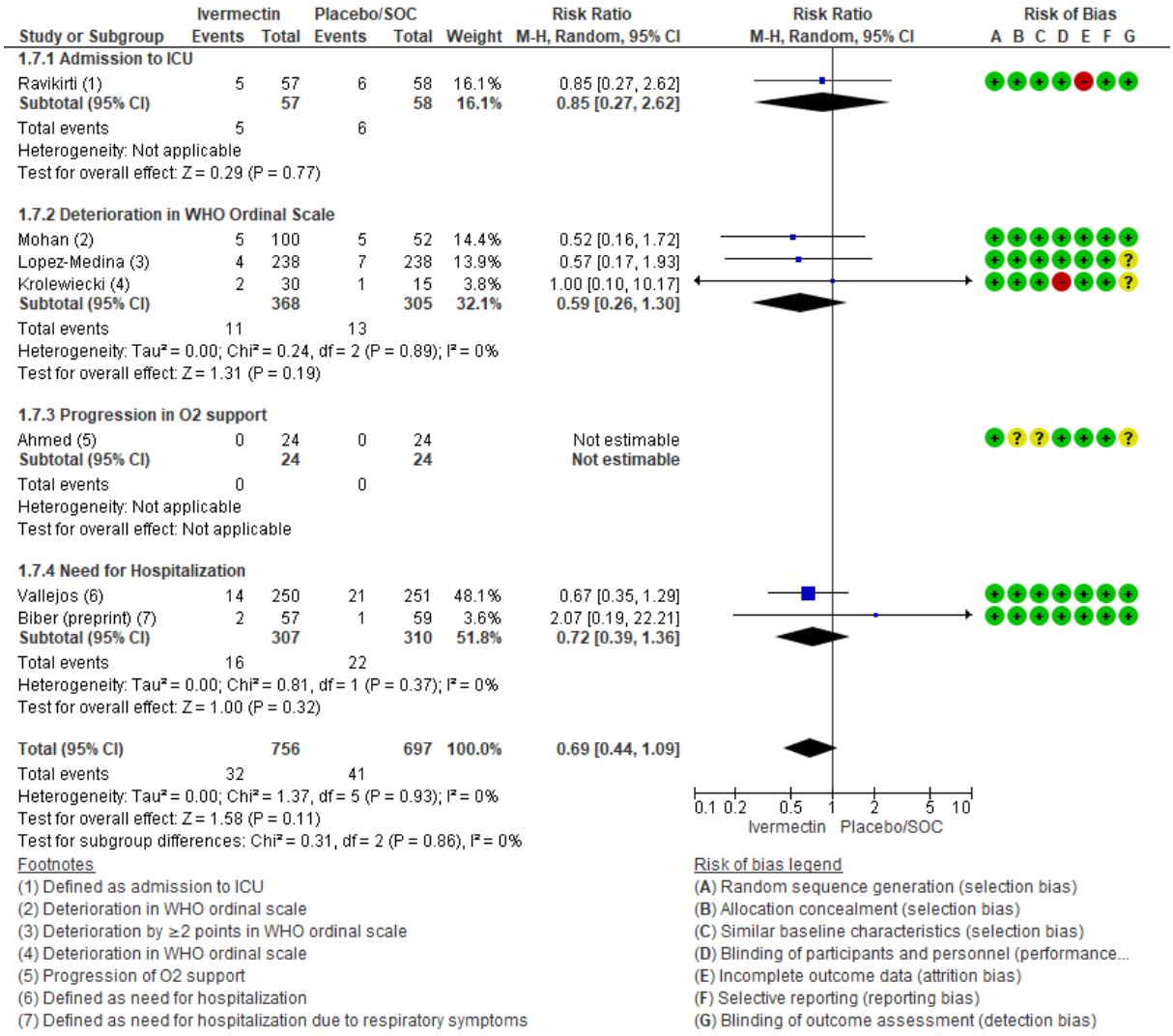


Figure 1.7. Clinical deterioration (ITT)

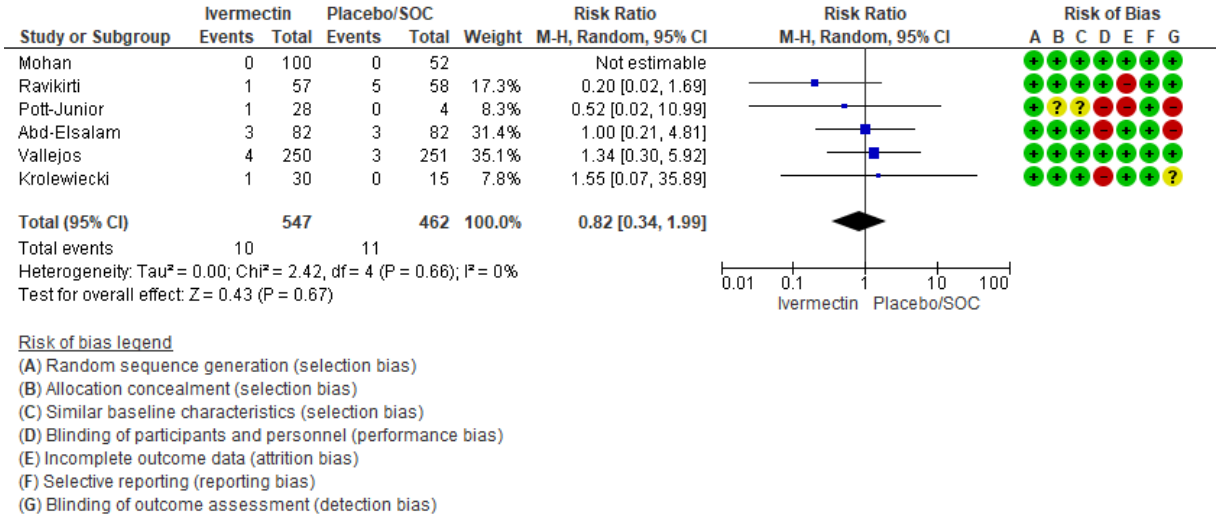


Figure 1.8. Need for mechanical ventilation (ITT)

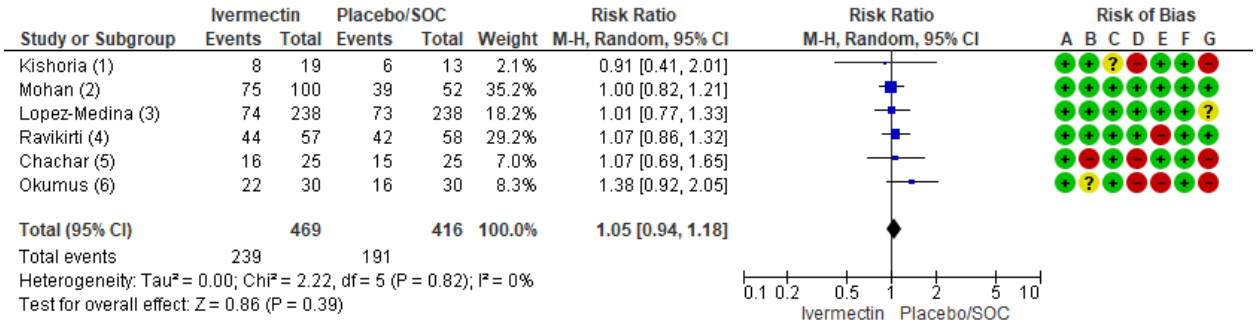


Figure 1.9. Clinical Improvement (ITT)

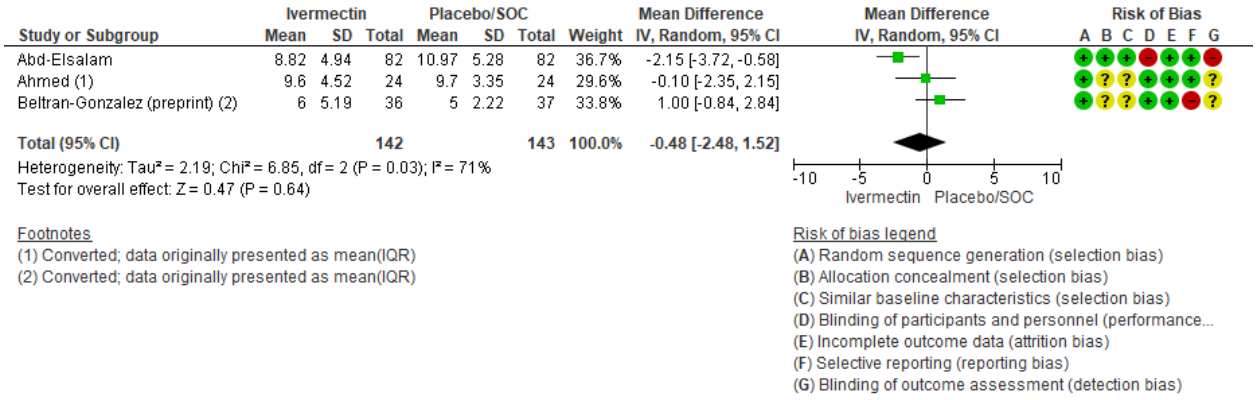


Figure 1.10. Hospital Length of stay (in days, ITT)

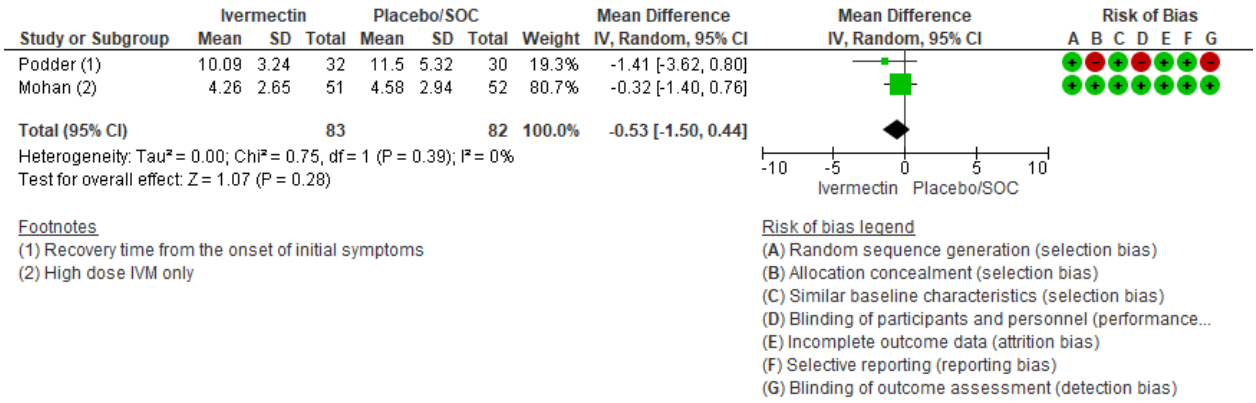


Figure 1.11. Time to symptom resolution (in days)

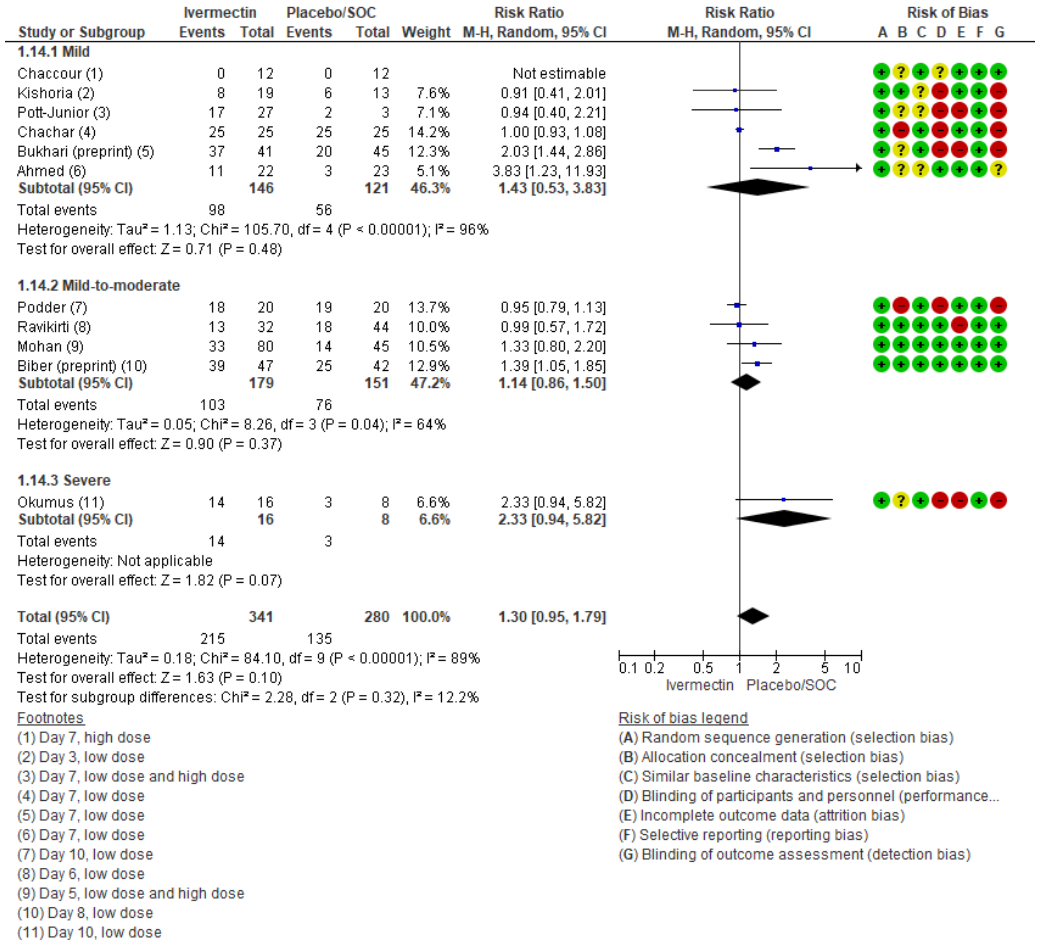


Figure 1.12. Virologic clearance

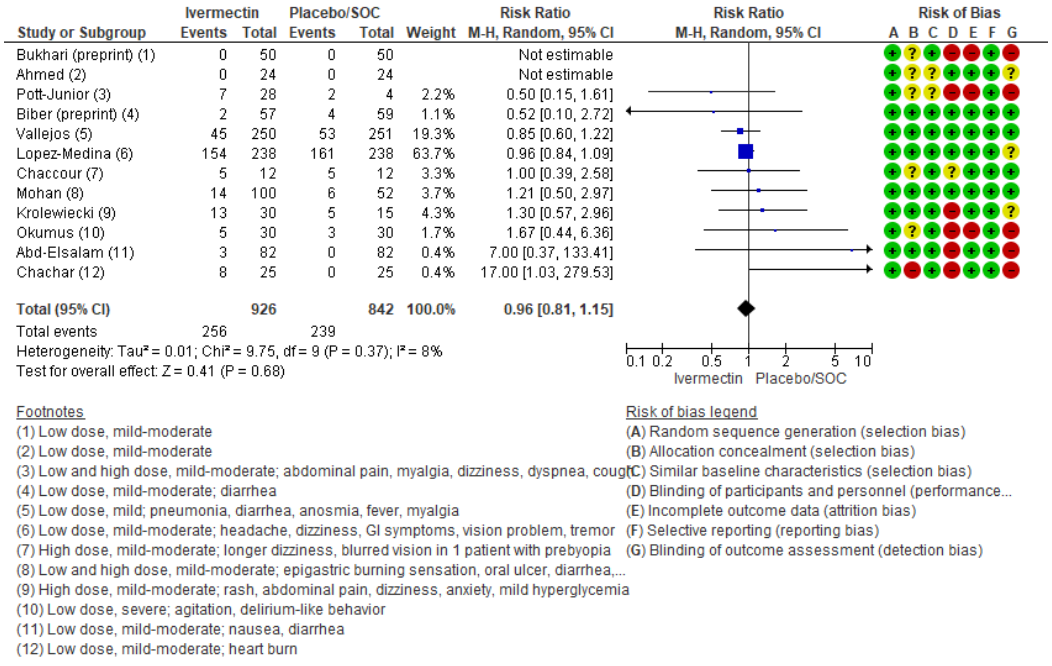


Figure 1.13. Any adverse events (ITT)

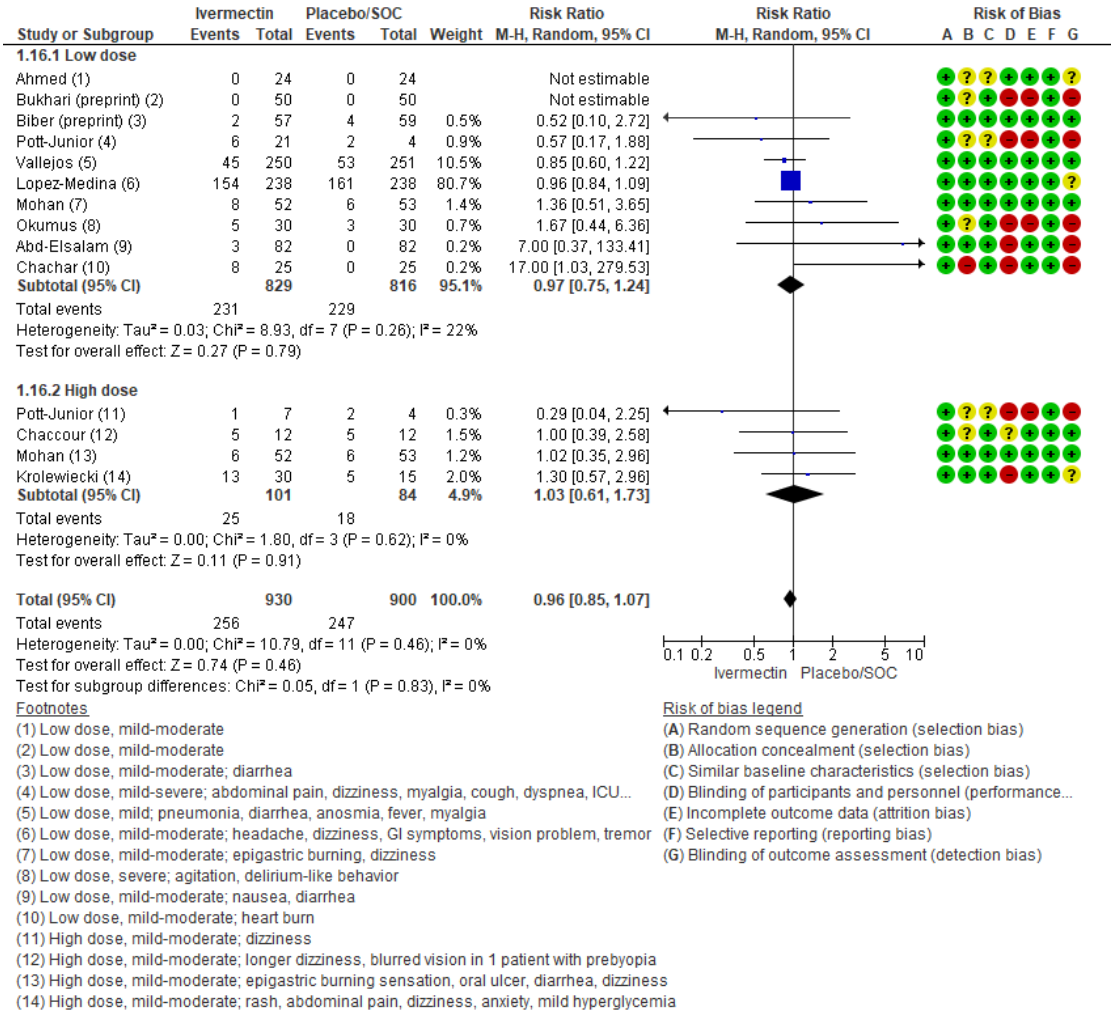


Figure 1.14. Any adverse events (by dose, ITT)

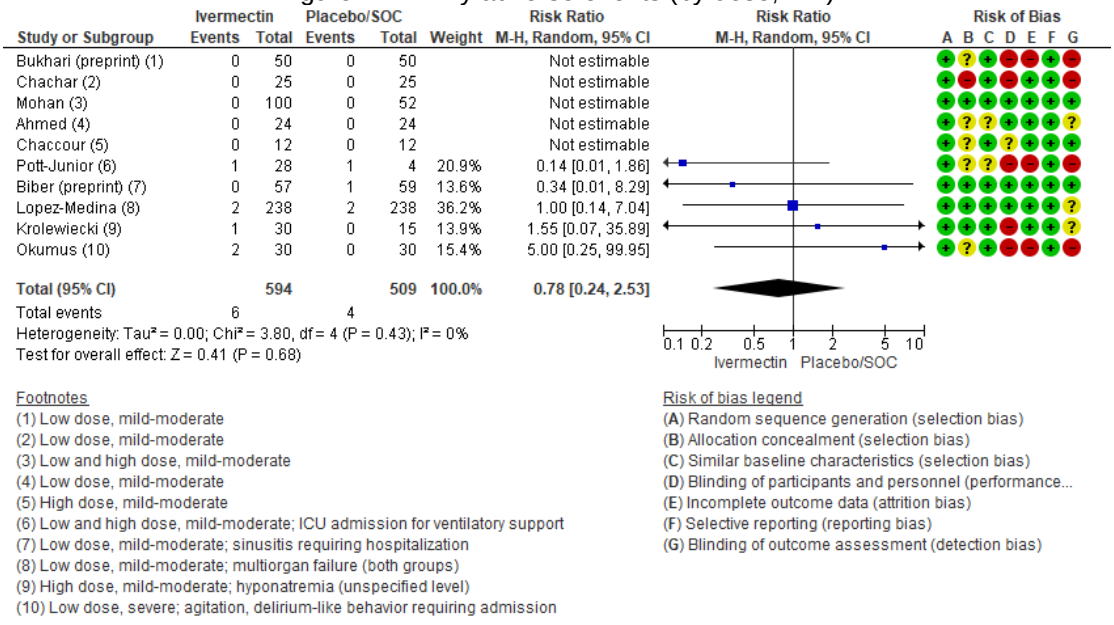


Figure 1.15. Serious adverse events (ITT)

Appendix 7. Summary of Results of this Review

Outcome	RCTs	Ivermectin	Control	Ivermectin vs. placebo/SOC	Interpretation	Certainty of evidence
Mortality (overall, ITT)	10 RCTs (n=1,718)	2.1% (18/859)	3.4% (27/799)	RR 0.73 [0.42, 1.28]	Inconclusive	⊕⊕◯◯ Low
Mortality based on disease severity						
Mortality (mild, ITT)	4 RCTs (n=1,049)	0.8% (4/524)	0.8% (4/525)	RR 1.05 [0.27, 4.02]	Inconclusive	⊕⊕⊕◯ Moderate
Mortality (mild-to-moderate, ITT)	4 RCTs (n=476)	1.1% (3/269)	3.8% (8/207)	RR 0.43 [0.08, 2.48]	Inconclusive	⊕⊕⊕◯ Moderate
Mortality (severe, ITT)	2 RCTs (n=133)	16.7% (11/66)	22.4% (15/67)	RR 0.74 [0.37, 1.48]	Inconclusive	⊕⊕◯◯ Low
Mortality (low dose, ITT)	8 RCTs (n=1,538)	2.3% (18/766)	3.5% (27/772)	RR 0.73 [0.42, 1.28]	Inconclusive	⊕⊕◯◯ Low
Clinical deterioration (ITT)	7 RCTs (n=1,453)	4.2% (32/756)	5.9% (41/697)	RR 0.69 [0.44, 1.09]	Inconclusive	⊕⊕⊕◯ Moderate
Need for mechanical ventilation (ITT)	6 RCTs (n=1,009)	1.8% (10/547)	2.4% (11/462)	RR 0.82 [0.34, 1.99]	Inconclusive	⊕⊕◯◯ Low
Clinical improvement (ITT)	6 RCTs (n=885)	51.0% (239/469)	45.9% (191/416)	RR 1.05 [0.94, 1.18]	Inconclusive	⊕⊕⊕◯ Moderate
Hospital length of stay (days, ITT)	3 RCTs (n=285)	8.8-9.6 vs 3.4-5.3 MD -0.48 [-2.48, 1.52]			Inconclusive	⊕◯◯◯ Very low
Time to symptom resolution (days, ITT)	3 RCTs (n=165)	4.3-10.1 vs 4.6-11.5 [a] MD -0.53 [-1.50, 0.44] 10 vs 12[b] HR 1.07 [0.87, 1.32]			Inconclusive	⊕◯◯◯ Very low
Virologic clearance (D3-10)	11 RCTs (n=621)	63.0% (215/341)	48.2% (135/280)	RR 1.30 [0.95, 1.79]	Inconclusive	⊕◯◯◯ Very low
Any adverse events (ITT)	12 RCTs (n=1,768)	27.6% (256/926)	28.4% (239/842)	RR 0.96 [0.81, 1.15]	Inconclusive	⊕⊕⊕◯ Moderate
Any adverse events (low dose, ITT)	10 RCTs (n=1,645)	27.9% (231/829)	28.1% (229/816)	RR 0.97 [0.75, 1.24]	Inconclusive	⊕⊕⊕◯ Moderate
Any adverse events (high dose, ITT)	4 RCTs (n=185)	25% (25/101)	21.4% (18/84)	RR 1.03 [0.61, 1.73]	Inconclusive	⊕⊕⊕◯ Moderate
Serious adverse events (ITT)[c]	10 RCTs (n=1,103)	1.0% (6/594)	0.8% (4/509)	RR 0.78 [0.24, 2.53]	Inconclusive	⊕◯◯◯ Very low

[a] Mohan 2021, Podder 2020
[b] Lopez-Medina 2021
[c] six serious adverse events

Appendix 8. Summary of Results of the Cochrane Review

(*Popp et al, 2021*)

Mild (out-patient)	RCTs	Ivermectin vs. placebo/SOC	
All-cause mortality (28 days)	2 RCT Chaccour, Lopez-Medina	RR 0.33 [0.01, 8.05]	⊕◯◯◯ Very low
Need for invasive ventilation (14 days)	1 RCT Lopez-Medina	RR 2.97 [0.12, 72.47]	⊕◯◯◯ Very low
Symptom resolution (up to 14 days)	1 RCT Lopez-Medina	RR 1.04 [0.89, 1.21]	⊕⊕◯◯ Low
Adverse events (28 days)	2 RCT Chaccour, Lopez-Medina	RR 0.95 [0.86, 1.05]	⊕⊕◯◯ Low
Viral clearance at D7	1 RCT Chaccour	RR 3.00 [0.13, 67.06]	⊕⊕◯◯ Low
Moderate to Severe (in patient)	**RCTs**	**Ivermectin vs. placebo/SOC**	
All-cause mortality (28 days)	2 RCTs Beltran-Gonzalez, Ravikirti	RR 0.60 [0.14, 2.51]	⊕◯◯◯ Very low
Need for invasive ventilation (28 days)	2 RCTs Beltran-Gonzalez, Ravikirti	RR 0.55 [0.11, 2.59]	⊕◯◯◯ Very low
Clinical improvement (28 days)	1 RCT Beltran-Gonzalez	RR 1.03 [0.78, 1.35]	⊕⊕◯◯ Low
Adverse events (28 days)	1 RCT Mohan	RR 1.21 [0.50, 2.97]	⊕◯◯◯ Very low
Duration of hospitalization	1 RCT Ahmed	MD -0.10 [-2.43 to 2.23]	⊕⊕◯◯ Low
Viral clearance at D7	2 RCTs Ahmed, Mohan	RR 1.82 [0.51, 6.48]	⊕◯◯◯ Very low

Q17. Among patients with COVID-19, should artesunate (artemisinin) be used for treatment?

As of 18 November 2021

RECOMMENDATION

We suggest against the use of artesunate, artemisinin or pyronaridine tetraphosphate + artesunate in the treatment of COVID-19. *(Very low certainty of evidence, Weak recommendation)*

Consensus Issues
There may be evidence on the in vitro effect of the drug. Despite being a new drug, we have a similar drug being used for malaria (Artemether-lumefantrine). However, given that the evidences available are very limited and the effect of drug is not yet clear, the panel unanimously suggests against the use of it. We need to wait for ongoing studies and more evidence for its use and effect on COVID 19.

KEY FINDINGS

There are three (3) randomized controlled trials (RCTs) that investigate the effect of artesunate (artemisinin) compared to varying standards of care or placebo as treatment for patients with COVID-19. Artesunate showed no significant difference in mortality, clinical deterioration, improvement in chest CT scan or X-ray, time to virologic clearance, and mild and moderate-to-severe adverse effects. Two (2) studies reported shorter time to clinical improvement for artesunate. The overall certainty of evidence was rated very low due to very serious imprecision, serious risk of bias, and in some outcomes, inconsistency and indirectness.

INTRODUCTION

Artemisinin and artesunate (one of its chemical derivatives), while known for anti-malarial properties, have demonstrated anti-inflammatory and in-vitro efficacy against viruses, including SARS-CoV-2.[1,2] Artemisinin and its derivative artesunate can inhibit the docking of the SARS-CoV-2 spike protein onto the human ACE2 receptor protein and TGF-β-dependent early steps in the infection process.[1] The combination of pyronaridine-artesunate has demonstrated in-vitro efficacy in inhibiting SARS-CoV-2 viral replication [2,3] (exact molecular mechanisms not elucidated). Consequently, the clinical benefits of this drug are currently being explored in human clinical trials.

REVIEW METHODS

A systematic search was done using Medline, Cochrane Library, Google Scholar, and CNKI with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and artemisinin, artesunate, or 青蒿素. The COVID-NMA Living Data was also checked, and ongoing studies in the NIH *clinicaltrials.gov* and various trial registries were also searched. Preprints were also searched using MedRxiv, ChinaXiv and BioRxiv. Other sources such as those directly given from the Republic of the Philippines Department of Health were used. Only randomized controlled trials that compared artesunate (artemisinin) against placebo or standard care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical

ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, or adverse events. No limits were placed on age, COVID-19 severity, and dosing strategy.

RESULTS

Three (3) randomized controlled trials (RCTs) with a total of 216 patients are included in this analysis. One RCT is published, one is a preprint, and another is unpublished (data obtained from a pharmaceutical report). All of these RCTs recruited mild-to-moderate RT-PCR confirmed COVID-19 patients.[4-6] Artemisinin was given differently in each RCT as follows: artemisinin [4], artesunate [5], and pyronaridine tetraphosphate / artesunate [6]. The comparator also varied widely across RCTs: standard of care (lopinavir/ritonavir 500mg + α-interferon 500) in one study [5], and placebo in another study [6]. In one RCT, the standard of care varied in three sites with remdesivir, prednisolone, low molecular weight heparin, and doxycycline in one site, azithromycin, dexamethasone in the second site, and ivermectin, doxycycline, and inhaled steroids in the third site.[4] Outcomes measured during the follow-up period of around 21 to 28 days included reducing mortality [6], clinical deterioration [6], time to clinical improvement or recovery [4,5], improvement in chest computed tomography (CT) or radiography (x-ray) [5], virologic clearance by polymerase chain reaction (PCR) test [5], and even mild and moderate-to-severe adverse effects.[4-6] The characteristics of included studies are summarized in Appendix 3.

The overall certainty of evidence was rated very low due to very serious imprecision, serious risk of bias, and in some outcomes, inconsistency and indirectness (from the use of other experimental drugs as control). The serious risk of bias was due issues with performance bias in all 3 studies; selection, detection, attrition bias, and reporting bias in 2 studies. The risk of bias summary is shown in Appendix 4. The GRADE evidence profile is in Appendix 5.

There was no significant difference in mortality between patients given artesunate and control (RR 0.35, 95% CI 0.01, 8.44; 1 RCT). Similarly, there was no significant difference in clinical deterioration (RR 0.42, 95% CI 0.09, 2.08; 1 RCT). One study reported significantly shorter time to clinical improvement among patients given artesunate compared to control (mean difference [MD] -1.51 days, 95% CI -2.74, -0.28 days). In another non-peer reviewed (pre-print) study, it also reported shorter time to clinical improvement for artesunate (MD -9 days, confidence interval could not be computed). However, results of the 2 studies could not be pooled due to inadequate data provided.

No significant difference in improvement in chest CT or X-ray (RR 0.67, 95% CI 0.17, 2.64) and time to virologic clearance (MD -5.37 days, 95% CI -11.97, 1.24) was noted between those given artesunate and control.

Adverse Events

There are no significant differences in mild adverse events (RR 0.81, 95%CI 0.62, 1.06; $I^2 = 0\%$) and moderate-to-severe adverse events (RR 0.85, 95% CI 0.37,1.95; $I^2 = 40\%$). Mild adverse events include nausea, muscle aches, fatigue, vomiting, diarrhea, transient mild rash, vertigo, and loss of appetite. Moderate-to-severe adverse events include AST and ALT elevation, QT interval prolongation, thrombocytopenia, bradycardia, and severe diarrhea.

RECOMMENDATIONS FROM OTHER GROUPS

There are currently no recommendations made by any other group on the use of artesunate for COVID-19, such as the National Institutes of Health, Infectious Disease Society of America, Australian Guidelines, World Health Organization Guidelines.[7-10]

RESEARCH GAPS

There are currently fourteen (14) ongoing RCTs (Appendix 7). This review will be updated as soon as full results from these trials become available.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS	JUDGEMENT (N = 9)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					
Benefits	Large	Moderate (1)	Small (6)	Uncertain (1)			• One study reported significantly shorter time to clinical improvement among patients given artesunate compared to control • Another study also reported shorter time to clinical improvement for artesunate
Harm	Large	Small (7)	Uncertain (2)				• There are no significant differences in mild adverse events and moderate-to-severe adverse events
Certainty of Evidence	High	Moderate	Low (1)	Very low (8)			• The overall quality of evidence was rated very low due to very serious imprecision, serious risk of bias, and in some outcomes, inconsistency and indirectness.
Balance of effects	Favors drug	Does not favor drug (4)	Uncertain (5)				• Artesunate showed no significant difference in mortality, clinical deterioration, improvement in chest CT scan or X-ray, time to virologic clearance, and mild and moderate-to-severe adverse effects.
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			
Resources Required	Uncertain (1)	Large cost	Moderate cost (4)	Negligible cost (2)	Moderate savings (2)	Large savings	• Cost is around 22.78-64 per 100mg capsule or Php 273-768 per patient • Not available in the market
Certainty of evidence of required resources	No included studies (1)	Very low (4)	Low (3)	Moderate (1)	High		• Sources are based on review articles, preliminary searches, and prices vary widely.
Cost effectiveness	No included studies (4)	Favors the comparison (2)	Does not favor either the intervention or the comparison (3)	Favors the intervention			
Equity	Uncertain (4)	Reduced (2)	Probably no impact (2)	Increased (1)			
Acceptability	Uncertain (7)	No	Yes (2)				
Feasibility	Uncertain (4)	No (1)	Yes (4)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (Artesunate OR Artemisinin)	September 15, 2021 9:00AM	60	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND artemisinin MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND artesunate	September 15, 2021 9:30AM	12	12
COVID-NMA Initiative	Artemisinin, Artesunate, Dihydroartemisinin	September 15, 2021 10:00AM	0	0
Google Scholar	Artemisinin OR Artesunate AND COVID AND randomized trial	September 15, 2021 10:10AM	30	0
ClinicalTrials.gov	Artemisinin and COVID19 Artesunate and COVID19	September 15, 2021 10:15AM	6	0
Chinese Clinical Trial Registry	Artemisinin Artesunate	September 15, 2021 10:20AM	3	0
CNKI	青蒿素, 青蒿素 新冠肺炎治疗	September 15, 2021 10:25AM	1	0
EU Clinical Trials Register	Artemisinin and COVID Artesunate and COVID	September 15, 2021 10:30AM	0	0

Republic of Korea - Clinical Research Information Service	Artemisinin Artesunate	September 15, 2021 10:30AM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Artemisinin Artesunate	September 15, 2021 10:30AM	0	0
CenterWatch	Artemisinin and COVID Artesunate and COVID	September 15, 2021 10:30AM	0	0
chinaxiv.org	Artemisinin Artesunate	September 15, 2021 10:30AM	1	0
Medrxiv.org	Artemisinin Artesunate	September 15, 2021 10:35AM	64	1
Biorxiv.org	Artemisinin and COVID Artesunate and COVID	September 15, 2021 10:50AM	20	0
Files from Republic of the Philippines Department of Health	N/A	N/A	N/A	4

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Targeting TGF-β pathway with COVID-19 Drug Candidate ARTIVeda/PulmoHeal Accelerates Recovery from Mild-Moderate COVID-19 *Trieu et al., 2021 (India)* [2] *Pre-print*	N = 60 **Patients 21-60 years old with RT-PCR confirmed COVID-19 infection, mild to moderate, without any requirement of oxygen therapy or assisted ventilation** <u>Duration of follow-up:</u> Not defined, but based on results estimated to be at around 28 days	EXPERIMENTAL: Artemisinin 500 mg capsule PO (duration not indicated) + Standard of Care* CONTROL: Standard of Care* *Standard of Care varies: • Site 1: Remdesivir, prednisolone, low molecular weight heparin, and doxycycline • Site 2: Azithromycin, dexamethasone • Site 3: Ivermectin, doxycycline, and inhaled steroids	PRIMARY time to recovery, clinical improvement (WHO score)	Randomized Parallel Open-label
Clinical trial on Artesunate in the treatment of COVID-19 *Lin et al., 2020 (China)* [3]	N = 43 **Patients 25-85 years old with RT-PCR confirmed COVID-19 infection, mild to moderate** <u>Duration of follow-up:</u> Not defined, but based on results estimated to be at least 21 days	EXPERIMENTAL: Artesunate was 60 mg twice a day for 10 days CONTROL: Standard of Care (Lopinavir/Ritonavir 500 mg + α-interferon 500×104 U nebulized inhalation for 10 days)	PRIMARY Time to significant improvement in symptoms; Time of throat swab virus nucleic acid turning negative; Adverse drug reactions; Number of days of hospitalization to evaluate the efficacy	Randomized parallel
A Multi-center, Randomized, Double-blind, Parallel, Placebo-Controlled, Phase II Clinical Trial to Evaluate Efficacy and Safety of Pyramax in Mild to Moderate COVID-19 Patients [4] *Shin Poong Pharm. Co., Ltd. 2021 (South Korea)* [4] *Unpublished*	N = 113 **Patients with RT-PCR confirmed COVID-19 infection, mild to moderate** <u>Duration of follow-up:</u> Not defined, but based on results estimated to be at around 28 days	EXPERIMENTAL: Pyramax (Pyronaridine tetraphosphate 180 mg/Artesunate 60 mg) CONTROL: Placebo	PRIMARY (1) Proportion of patients at a given time with non-viable virus / viral clearance; (2) Clinical deterioration; (3) Drug-related adverse events	Randomized double blind Parallel Double-blind Placebo-controlled

Appendix 4. Study Appraisal

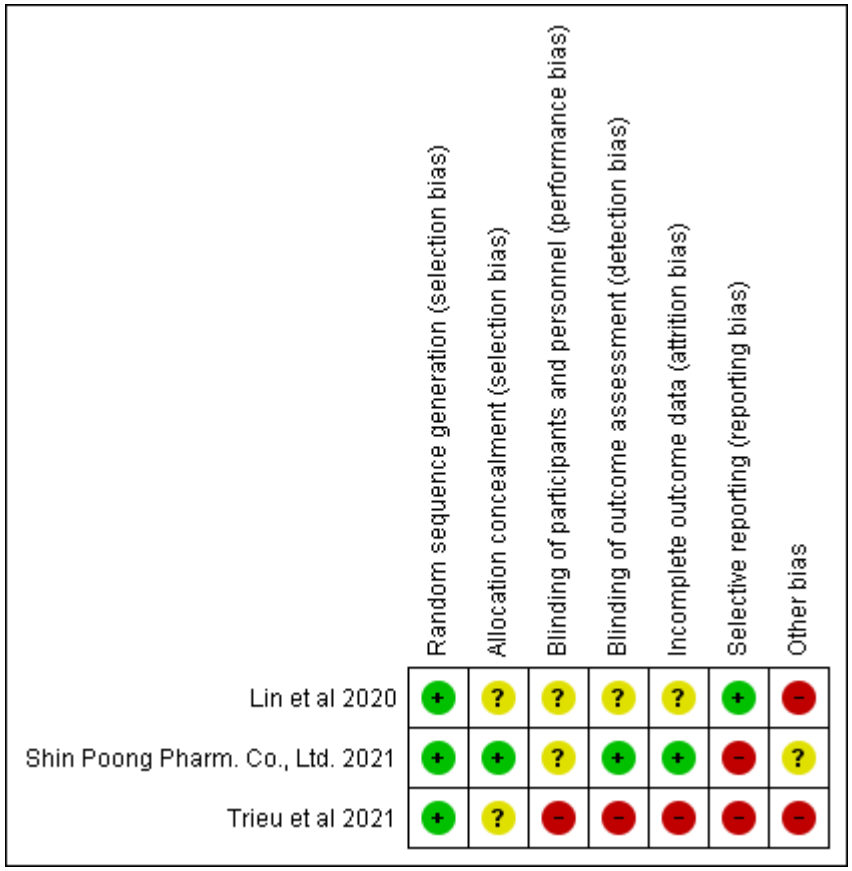

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Dy, Louie
Question: Artemisinin (Artesunate) compared to Placebo or Standard of Care (SOC) for patients with confirmed COVID-19 infection
Setting: Hospital setting
Bibliography: Trieu V, Saund S, Rahate P, Barge V, Nalk K, Windlass H et al. Targeting TGF-β pathway with COVID-19 Drug Candidate ARTIVeda/PulmoHeal Accelerates Recovery from Mild-Moderate COVID-19. 2021;.Lin, Wu, Xie et al. Clinical trial on Artesunate in the treatment of COVID-19. Chinese Critical Care Medicine. 2020;.Shin Poong Pharm. Co., Ltd. A Multi-center, Randomized, Double-blind, Parallel, Placebo-Controlled, Phase Ⅱ Clinical Trial to Evaluate Efficacy and Safety of Pyramax in Mild to Moderate COVID-19 Patients. South Korea; 2021.

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Artemisinin (Artesunate)	Placebo or standard of care	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 28 days)												
1	Randomised trials	Serious [a]	Not serious	Not serious	Very serious [b]	None	0/55 (0.0%)	1/58 (1.7%)	**RR 0.35** (0.01 to 8.44)	**11 fewer per 1,000** (from 17 fewer to 128 more)	⊕◯◯◯ VERY LOW	CRITICAL
Clinical Deterioration (follow-up: 28 days)												
1	Randomised trials	Serious [a]	Not serious	Not serious	Very serious [b]	None	2/55 (3.6%)	5/58 (8.6%)	**RR 0.42** (0.09 to 2.08)	**50 fewer per 1,000** (from 78 fewer to 93 more)	⊕◯◯◯ VERY LOW	CRITICAL
Time to Clinical Improvement or Recovery												
2	Randomised trials	Very serious [c]	Serious [d]	Serious [e]	Very serious [f]	None	One study reported median 1.51 days lower (2.74 lower to 0.28 lower). Another study reported median 9 days lower.				⊕◯◯◯ VERY LOW	CRITICAL
Adverse Effects (Mild) (follow-up: 14-28 days)												
3	Randomised trials	Very serious [a,c]	Not serious	Serious [e]	Very serious [b]	None	49/112 (43.8%)	56/104 (53.8%)	**RR 0.81** (0.62 to 1.06)	**102 fewer per 1,000** (from 205 fewer to 32 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Adverse Effects (Moderate-Severe) (follow-up: 14-28 days)												
3	Randomised trials	Very serious [a,c]	Not serious	Serious [e]	Very serious [b]	None	9/112 (8.0%)	12/104 (11.5%)	**RR 0.85** (0.37 to 1.95)	**17 fewer per 1,000** (from 73 fewer to 110 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

[a]. Details on how blinding of participants and outcome assessors was not clearly elaborated; selective reporting

[b]. Wide confidence interval with a relatively small sample size

[c]. Serious risk of bias from performance and detection bias (unblinded of participants or outcome assessors) in 2 studies, incomplete outcome data and selective reporting in 1 study

[d]. Mean difference and median difference of the 2 studies vary widely

[e]. Control groups include experimental drugs

[f]. Small sample size

Appendix 6. Forest Plots

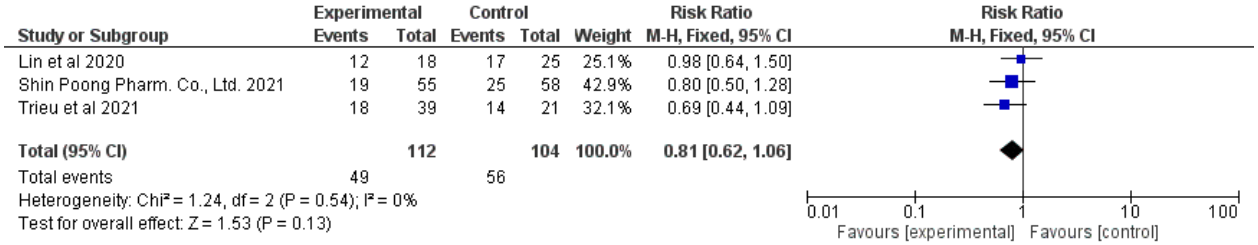

Figure 1. Adverse Effects (Mild)

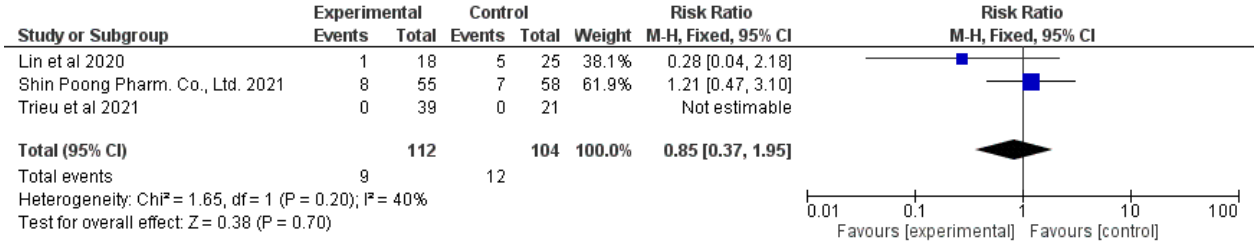

Figure 2. Adverse Effects (Moderate-to-Severe)

Appendix 7. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. A Prospective, Randomized, Multi-center, Open label, Interventional Study to Evaluate the Safety and Efficacy of Artemisinin 500 mg capsule in Treatment of Adult Subjects with COVID-19	Patients with mild to moderate COVID-19 (age 19 to 44 years) + exclusion criteria (refer to link: https://trialsearch.who.int/?TrialID=CTRI/2020/09/028044)	Experimental: Artemisinin + standard of care Control: Standard of care	Clinical improvement, clinical progression, and adverse events	Randomized, open-label trial
2. A Study to Evaluate the Safety and Efficacy of Artemisinin- a Herbal Supplement on COVID-19 Subjects	Patients with confirmed, mild to moderate COVID-19 (≥18 to 60 years of age, + exclusion criteria, please refer to link: https://clinicaltrials.gov/ct2/show/NCT05004753)	Experimental: Artemisinin 500mg and Standard of Care (which includes dexamethasone) Control: Standard of care (which may include cexamethasone)	Clinical improvement, worsening, mortality, duration of supplemental oxygen, duration of ICU stay, duration of hospitalization, ventilator free days, days on ventilation	Open label, prospective, multi-center, comparative, interventional study
3. A Study to Evaluate the Safety and Efficacy of OT-101+Artemisinin in Hospitalized COVID-19 Subjects	Patients with severe COVID-19 (WHO COVID-19 Clinical Improvement Ordinal Scale 5 - non-invasive ventilation or high flow oxygen, or 6 - intubation and mechanical ventilation); more information: https://clinicaltrials.gov/ct2/show/record/NCT04801017	Experimental: OT-101 (TGF β2 specific synthetic 18 mer phosphorothioate antisense oligodeoxynucleotide) plus artemisinin and standard of care Control: Placebo + artemisinin + standard of care	Clinical improvement, worsening, mortality, duration of supplemental oxygen, duration of ICU stay, duration of hospitalization, ventilator free days, days on ventilation	Randomized, double blind, placebo-controlled study
4. A Prospective, Randomized, Multi-center, Open label, Interventional Study to Evaluate the Safety and Efficacy of Artemisinin 500 mg capsule in Treatment of Adult Subjects with COVID-19	Patients with mild to moderate COVID-19 (age 19 to 44 years) + exclusion criteria (refer to link: https://trialsearch.who.int/?TrialID=CTRI/2020/09/028044)	Experimental: Artemisinin + standard of care Control: Standard of Care	Clinical improvement, clinical progression, adverse events	Randomized, open-label trial
5. A Prospective, Randomized, Multi-center, Open label, Interventional Study to Evaluate the Safety and Efficacy of Artemisinin 500 mg capsule in Treatment of Adult Subjects with COVID-19	Patients with mild to moderate COVID-19 (age 19 to 44 years) + exclusion criteria (refer to link: https://trialsearch.who.int/?TrialID=PACTR202012892855610)	Experimental: Artemisinin + standard of care Control: Standard of care	Clinical improvement, clinical progression, adverse events	Randomized, open-label trial
6. Effect of Hesperidin,Artemisinin-Artemisia annua, Noscapine, N-acetylcysteine, Resveratrol supplements and high dose of vitamin C on treatment, clinical symptoms of non-hospitalization and hospitalization patients with symptomatic COVID-19	Patients with confirmed COVID-19 (age 12 years old and above) + exclusion criteria (refer to link: https://trialsearch.who.int/?TrialID=IRCT20181030041504N1)	Experimental: Artemisinin, IV vitamin C, noscapine, hesperidin, N-acetylcysteine Control: Standard of care	CBC, CRP, ESR, LDH< lung involvement, Na, K, Ca, weakness and nausea	Randomized, double-blind, non-placebo-controlled trial
7. Clinical trial of the use of Annual SZ drug in the treatment of patients with Covid-19 disease in Emam Hosein hospital in Tehran.	Patients with confirmed COVID-19 (age 16 to 70 years old); more information: https://trialsearch.who.int/?TrialID=IRCT20181030041504N1	Experimental: Artemisinin + azithromycin Control: Hydroxychloroquine + keltra + lopinavir-ritonavir + azithromycin	Blood oxygen level, coughs, CRP, fever, HRCT score	Randomized, open-label, non-placebo-controlled trial

8. A randomized controlled trial for the efficacy and safety of artemisinin-pipequine tablets in the treatment of the mild and common type novel coronavirus pneumonia (COVID-19) patients whose nCoV Nucleic acid did not turn negative after treated by hydroxychloroquine and Abidor	Patients with confirmed COVID-19, mild to moderate (age 2 to 65 years old), excluding pregnant women, liver and kidney disease, blood diseases, ECG with prolonged QT; more information: https://trialsearch.who.int/?TrialID=ChiCTR2000032915	Experimental: Artemisinin-Piperaquine Control: Symptomatic treatment with non-antiviral drugs	Tolerance, viral load, routine blood and immunological examination, liver and kidney function tests, myocardial enzymes, ECG, urinalysis, body temperature, pulse, respiratory rate, blood pressure, CT examination of the lungs	Randomized controlled trial
9. A Phase II, Open label controlled clinical study designed to evaluate the effect of ArtemiC in patients diagnosed with COVID-19.	Patients with confirmed COVID-19, admitted to controlled facility or hospital (age 18 years old and above) + exclusion criteria (pregnancy, critically ill, autoimmune disease, uncontrolled diabetes; refer to link: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=52515)	Experimental: ArtemiC medical nasal spray (artemisinin, curcumin, frankincense, vitamin C) Control: Standard of care	Time to clinical improvement, adverse drug events, time until negative PCR, proportion of participants with normalization of fever, COVID-19 related survival, incidence and duration of mechanical ventilation, incidence of ICU stay, duration of ICU stay, duration of time on supplemental oxygen	Randomized, placebo-controlled trial
11. A Phase II, Controlled Clinical Study Designed to Evaluate the Effect of ArtemiC in Patients Diagnosed With COVID-19	Patients with confirmed COVID-19, admitted to controlled facility or hospital (age 18 years old and above) + exclusion criteria (pregnancy, critically ill, autoimmune disease, uncontrolled diabetes; refer to link: https://clinicaltrials.gov/ct2/show/NCT04382040)	Experimental: ArtemiC medical nasal spray (artemisinin, curcumin, frankincense, vitamin C) Control: Placebo (oromucosal medical spray)	Time to clinical improvement, adverse drug events, time until negative PCR, proportion of participants with normalization of fever, COVID-19 related survival, incidence and duration of mechanical ventilation, incidence of ICU stay, duration of ICU stay, duration of time on supplemental oxygen	Randomized, placebo-controlled trial
12. Evaluating the Efficacy of Artesunate in Adults with Mild Symptoms of COVID-19	Patients with mild to moderate COVID-19, no risk factors, not on other medications (age 18 to 60 years) + exclusion criteria (refer to link: https://clinicaltrials.gov/ct2/show/record/NCT04387240)	Experimental: Artemisinin Control: Placebo	Clinical improvement, worsening, mortality, duration of supplemental oxygen, duration of ICU stay, duration of hospitalization, ventilator free days, days on ventilation	Randomized, double blind, placebo-controlled study
13. No title yet; study by Shin Poong Pharma Co. Ltd. In South Africa	Symptomatic COVID-19 outpatients self-reported symptoms of COVID-19 of up to 72 hours duration who tests positive for SARS-CoV-2	Experimental: SOC + artesunate-amodiaquine; SOC + pyronaridine-artesunate; SOC + favipiravir + nitazoxanide; SOC + sofosbuvir / daclatasvir Control: Standard of care (SOC)	Virologic clearance on Day 7, clinical improvement, adverse events, mortality	Randomized, single center, open-label Placebo-controlled
14. No title yet; study by Shin Poong Pharma Co. Ltd. In the Philippines	Mild to severe COVID-19 patients (can be modified depending on stage 1 results)	[Stage 1: open-label] - Pyramax only (20 patients) [Stage 2: randomized, double-blinded, placebocontrolled] - Experimental: Pyramax - Control: Placebo	Clinical improvement, virologic clearance on Day 7, adverse events, mortality	Randomized, multicenter, 2 stages (stage 1: open-label/ stage 2: double-blinded)

Q18. Among patients with COVID-19, should colchicine be used for treatment?

As of 8 November 2021

RECOMMENDATION

We suggest against the use of colchicine in the treatment of COVID-19 patients. (*Low certainty of evidence, Weak recommendation)*

Consensus Issues

The addition of a large multicenter trial (RECOVERY trial) still showed that colchicine led to net potential harm (significant increase in adverse events) with no significant benefit in terms of all-cause mortality, clinical improvement (defined as hospital discharge) within 28 days, need for hospitalization, need for mechanical ventilation, and need for hemodialysis or hemofiltration. Hence, the consensus panel decided to maintain the previous recommendation against the use of colchicine in patients with COVID-19, regardless of hospitalization status.

PREVIOUS RECOMMENDATION

We suggest against the use of colchicine in the treatment of COVID-19 *(Low certainty of evidence; Conditional recommendation)*

Previous Consensus Issues

Current evidence showed significantly more adverse events (e.g., pulmonary embolism, gastrointestinal effects, nausea, rash, and most commonly diarrhea) with no significant clinical benefit in COVID-19 patients treated with colchicine compared to those receiving placebo or standard of care. Results from ongoing studies such as the ACT Trial are needed to better assess the effectiveness of colchicine as a treatment for COVID-19.

WHAT'S NEW IN THIS VERSION?

This version includes data from one (1) large multicenter randomized controlled trial (RECOVERY trial).

KEY FINDINGS

Five (5) randomized controlled trials (RCTs) investigated the effect of colchicine compared to standard of care as treatment for patients with COVID-19. Colchicine showed net potential harm (significant increase in adverse events) with no significant benefit in all-cause mortality, need for mechanical ventilation, clinical improvement (defined as hospital discharge) within 28 days, need for hospitalization, and need for hemodialysis or hemofiltration. One large RCT reported that colchicine did not significantly shorten duration of hospitalization, while 2 smaller RCTs reported significantly shorter duration of hospitalization (data could not be pooled due to inadequate data provided). All studies had risk of bias issues as there were concerns in allocation concealment, blinding, attrition and selective reporting of outcome. The serious risk of bias and issues with inconsistency and imprecision in one critical outcome contributed to the downgrading of evidence to very low certainty of evidence.

INTRODUCTION

Colchicine is an anti-inflammatory agent currently being used for gout, familial Mediterranean fever, Behcet's syndrome, and pericarditis.[1,2] Colchicine has a unique anti-inflammatory property with a prolonged anti-inflammatory effect even after discontinuation.[1] Its primary mechanism of action is tubulin disruption leading to subsequent down regulation of multiple inflammatory pathways and modulation of innate immunity.[3] This anti-inflammatory mechanism may potentially have an effect on the clinical course of the patient with COVID-19 in terms of developing pneumonia and other lung complications.[4] In a recent, good quality systematic review on colchicine and adverse events, colchicine was shown to increase gastrointestinal adverse events specifically diarrhea, but was not shown to increase rate of liver, sensory, muscle, infectious or hematologic adverse events or death.[5]

REVIEW METHODS

A systematic search was done from the date of the last search March 26, 2021 until August 28, 2021 using Medline, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and colchicine. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv, and biorxiv. Only randomized controlled trials that compared colchicine against placebo or standard of care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, or adverse events. No limits were placed on age, COVID-19 severity, hospitalization status, and dosing strategy of colchicine. Subgrouping by severity was planned.

RESULTS

We found five (5) RCTs that included a total of 16,113 COVID-19 patients. These RCTs were also included in the COVID-NMA Living Data (The COVID-NMA Initiative 2021).[6] One RCT from Canada recruited out-patients (non-hospitalized) with mild disease [4], 2 RCTs from Brazil [7] and Greece [8] recruited hospitalized patients with moderate to severe disease, 1 RCT from Iran (pre-print) [9] had patients with unclear disease severity, and 1 large multicenter RCT from UK, Indonesia and Nepal that involved hospitalized patients with mild to critical disease severity.[10] Standard of care used across these studies varied as they followed their respective local guidelines at the time the studies were conducted, namely placebo [4], azithromycin and hydroxychloroquine (HCQ) [7,8], HCQ [9], and corticosteroids, remdesivir, and tocilizumab which were used in the newly added large multicenter RCT (RECOVERY trial).[10] The dose of colchicine varied from 0.5 to 1 mg/day, while the duration of treatment with colchicine ranged from 6 to 27 days. Outcomes measured during the follow-up period of approximately 21 to 30 days included all-cause mortality [4,7-10], need for mechanical ventilation [4,8,10], clinical improvement (hospital discharge) within 28 days [4,10], need for hospitalization [4], duration of hospitalization [7,9,10], and adverse events [4,7,8]. The characteristics of included studies are summarized in Appendix 3.

The overall quality of evidence was rated very low because of serious risk of bias in the included studies, as well as issues with inconsistency and imprecision in 1 critical outcome. Of the 5 included studies, 2 studies had serious risk of performance and detection bias due to lack of blinding.[8,10] One study [4] had issues with selection and attrition bias, one study [7] had issues with attrition and reporting bias, and one study [9] had issues with selection, performance, detection and reporting bias. The risk of bias summary is shown in Appendix 4. The GRADE evidence profile is in Appendix 5.

Based on five (5) RCTs, colchicine did not show any significant difference compared to standard care in reducing all-cause mortality (RR 1.00, 95% CI 0.93-1.07; I^2=0%). Subgroup analysis by hospitalization status showed no significant difference in all-cause mortality among hospitalized patients (RR 1.00, 95% CI 0.93-1.08) and non-hospitalized patients (RR 0.56, 95% CI 0.19-1.67) given colchicine compared to control. Subgroup analysis according to disease severity showed no significant results for mild disease (RR 0.56, 95% CI 0.19-1.67), moderate-to-severe disease (RR 0.22, 95% CI 0.04-1.29), and mild to critical disease (RR 1.18, 95% CI 0.99-1.40). Subgroup analysis by age similarly showed no significant results for those <70 years old (RR 1.02, 95% CI 0.91-1.15), 70 to 80 years old (RR 0.98, 95% CI 0.87-1.10), and 80 years and older (RR 1.04, 95% CI 0.93-1.17).

There was no significant difference in clinical improvement, defined as hospital discharge, within 28 days (RR 0.99, 95% CI 0.97-1.01; I^2=0%; 2 RCTs). Colchicine did not significantly reduce the number of patients needing mechanical ventilation (RR 0.68, 95% CI 0.29, 1.60; I^2=74%; 3 RCTs), hospitalization (RR 0.80, 95% CI 0.62-1.03; 1 RCT), and hemodialysis or hemofiltration (RR 1.07, 95% CI 0.88-1.29; 1 RCT).

Three RCTs reported on duration of hospitalization. One large RCT reported no significant benefit in duration of hospitalization with a median of 10 days vs. 10 days, with a range of 5 to >28 for colchicine and control groups (N = 11,340).[10] Two smaller studies reported significantly shorter duration of hospitalization (mean 6.3 vs. 8.1 days, p = 0.001, n =100; median 7 days [IQR 5-9] vs. 9 days [IQR 7-12]; p = 0.003, n = 38).[7,9] Data could not be pooled due to inadequate data provided.

Adverse events

Three (3) studies showed that serious adverse events were reduced among patients given colchicine group compared to control group but only by a small margin (RR 0.78, 95% 0.61-0.99; I^2=0). Subgroup analysis by hospitalization status showed no significant difference for hospitalized patients (RR 0.58, 95% CI 0.15-2.27) and non-hospitalized patients (RR 0.78, 95 % CI 0.61-1.00). The reported serious adverse events included pneumonia, pulmonary embolism, myocardial infarction, and dehydration.

There were significantly more adverse events among patients who received colchicine (RR 1.55, 95% CI 1.37-1.75; I^2=0%; 2 RCTs). The most common was diarrhea. Other adverse events included abdominal pain, nausea, and rash. Subgroup analysis by hospitalization status showed that this effect was more evident among non-hospitalized patients with mild disease (RR 1.56, 95% CI 1.38-1.76) than those hospitalized with moderate to severe disease (RR 1.30, 95% CI 0.62-2.71).

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
NIH Covid-19 Guidelines (as of October 7, 2021)	Recommends against the use of colchicine for the treatment of hospitalized patients with COVID-19. *(Strong recommendation)* No recommendation either for or against the use of colchicine for non-hospitalized patients with COVID-19 was made due to insufficient evidence.[11]
Australian COVID-19 Guidelines (as of September 29, 2021)	Does not recommend the use of colchicine for the treatment of COVID-19 outside of randomized trials.[12]
Surviving Sepsis Campaign Guidelines (as of January 29, 2021)	No statement on the recommendation of colchicine as treatment for COVID-19. (13-15)
Infectious Diseases Society of America (as of October 1, 2021	
World Health Organization (WHO) Living Guidelines (as of September 24, 2021)	

RESEARCH GAPS

There are 42 studies registered in various clinical trial registries. Of the 42 studies, 1 was suspended already due to results of the RECOVERY trial [10] showing that further recruitment would not provide conclusive proof of worthwhile benefit, 1 was withdrawn due to lack of funding, 6 are marked as completed but no results have been posted yet, and 34 are still ongoing. Furthermore, the ACT trial (Anti-Coronavirus Therapies to Prevent Progression of COVID-19, a Randomized Trial) is currently recruiting study subjects in the Philippines. This review will be updated as soon as full results from these trials become available.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate	Small (5)	Uncertain (3)	Trivial (1)		• Colchicine did not show any significant difference compared to standard care in reducing all-cause mortality (RR 1.00, 95% CI 0.93-1.07; I^2=0%) and clinical improvement, defined as hospital discharge, within 28 days (RR 0.99, 95% CI 0.97-1.01; I2=0%, 2 RCTs). • Colchicine did not significantly reduce the number of patients needing mechanical ventilation (RR 0.68, 95% CI 0.29, 1.60; I^2=74%, 3 RCTs), hospitalization (RR 0.80, 95% CI 0.62-1.03, 1 RCT), and hemodialysis or hemofiltration (RR 1.07, 95% CI 0.88-1.29, 1 RCT).
Harm	Large (4)	Small (3)	Uncertain (1)	Varies (1)			• 3 studies showed that serious adverse events were reduced among patients given colchicine group compared to control group but only by a small margin (RR 0.78, 95% 0.61-0.99; I^2=0). • There were significantly more adverse events among patients who received colchicine (RR 1.55, 95% CI 1.37-1.75; I^2=0%, 2 RCTs).
Certainty of Evidence	High	Moderate (1)	Low (3)	Very low (5)			• The overall quality of evidence was rated very low because of serious risk of bias in the included studies, as well as issues with inconsistency and imprecision in 1 critical outcome.
Balance of effects	Favors drug (2)	Does not favor drug (7)	Uncertain				• Colchicine showed net potential harm (significant increase in adverse events) with no significant benefit in all-cause mortality, need for mechanical ventilation, clinical improvement
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Cost	Negligible cost (8)	Moderate savings	Large savings (1)	• 1 colchicine 500 mcg tablet is Php 2.25 • Total cost is around 47.25-56.25
Certainty of evidence of required resources	No included studies (2)	Very low	Low (1)	Moderate (3)	High (3)		• The cost is based on the 2020 Philippine Drug Reference Index
Cost effectiveness	No included studies (6)	Favors the comparison (3)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (2)	Reduced (2)	Probably no impact (4)	Increased (1)			
Acceptability	Uncertain (5)	No (3)	Yes (1)				
Feasibility	Uncertain (2)	No (1)	Yes (6)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (colchicine OR colchicine{Mesh}) Filters: March 26, 2021 to August 28, 2021	August 28, 2021 11:00AM	55	0
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (colchicine OR MeSH descriptor: [Colchicine] explode all trees Filters: March 26, 2021 to August 28, 2021	August 28, 2021 11:30AM	21	0
COVID-NMA Initiative	Colchicine	August 28, 2021 11:30AM	5	1
Google Scholar	Colchicine AND COVID AND randomized trial	August 28, 2021 8:00PM	26	0
ClinicalTrials.gov	Colchicine and COVID19	August 28, 2021 10:00PM	27	5
Chinese Clinical Trial Registry	Colchicine	August 28, 2021 10:30PM	8	0
EU Clinical Trials Register	Colchicine and COVID	August 28, 2021 10:35PM	5	2
Republic of Korea - Clinical Research Information Service	Colchicine	August 28, 2021 10:45PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Colchicine	August 28, 2021 10:50PM	26	0
CenterWatch	Colchicine and COVID	August 28, 2021 11:00PM	3	1
Cochrane COVID-19 study register	Colchicine Filters: March 26, 2021 to August 28, 2021	August 28, 2021 1:00 PM	40	14
chinaxiv.org	Colchicine	August 28, 2021 11:10PM	1	0
Medrxiv.org	Colchicine Filters: March 26, 2021 to August 28, 2021	August 28, 2021 11:12PM	28	1
Biorxiv.org	Colchicine and COVID	August 28, 2021 11:20PM	19	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Colchicine for community-treated patients with COVID-19 (COLCORONA): A phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicenter trial *Tardif et al. 2021 (Canada, USA, Brazil)* [4]	N = 4488 Non-hospitalized patients with COVID-19 diagnosed by polymerase chain reaction (PCR) testing or clinical criteria at least 40 years of age <u>Duration of follow-up:</u> Approximately 30 days	EXPERIMENTAL: Colchicine (0.5mg twice daily for 3 days and once daily thereafter) CONTROL: Placebo	PRIMARY: Composite of death or hospitalization due to COVID-19 infection SECONDARY: Components of the composite primary endpoint; need for mechanical ventilation, serious adverse events, and non-serious adverse events	Randomized Parallel Double-blind
Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial *Lopes et al., 2021 (Brazil)* [7]	N = 75 Individuals hospitalized with moderate or severe forms of COVID-19 diagnosed by RT-PCR in nasopharyngeal swab specimens and lung CT scan involvement compatible with COVID-19 pneumonia, older than 18 years <u>Duration of follow-up:</u> Up to 26 days	EXPERIMENTAL: Colchicine 0.5mg 3x daily for 5 days, then 0.5mg 2x daily for 5 days plus standard care CONTROL: Standard of care (azithromycin, hydroxychloroquine (HCQ), unfractionated heparin, methylprednisolone)	PRIMARY: Time of need for supplemental oxygen, time of hospitalization, need for admission and length of stay in ICU, death rate and causes of mortality SECONDARY: Adverse events	Randomized placebo-control double blind
Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized with Coronavirus Disease 2019 The GRECCO-19 Randomized Clinical Trial *Deftereos et al., 2020 (Greece)* [8]	N = 110 Hospitalized adult patients diagnosed with SARS-CoV-2 infection by RT-PCR <u>Duration of follow-up:</u> 21-25 days	EXPERIMENTAL: Colchicine administration (1.5-mg loading dose followed by 0.5mg after 60 min and maintenance doses of 0.5mg twice daily) with standard medical treatment CONTROL: Standard medical treatment (azithromycin, HCQ)	PRIMARY: Time to deterioration by 2 points on a 7-grade clinical status scale (WHO R&D Blueprint Ordinal Clinical Scale), ranging from able to resume normal activities to death SECONDARY: Need for mechanical ventilation, all-cause mortality, adverse events.	Randomized parallel
The Impact of Colchicine on the COVID-19 Patients: A Clinical Trial Study *Salehzadeh et al. 2020 (Iran)* [9] *Pre-print*	N = 100 Pulmonary involvement seen in CT-Scan compatible with COVID-19 and Positive PCR of COVID-19. <u>Duration of follow-up:</u> 21 to 30 days	EXPERIMENTAL: HCQ + colchicine 1mg OD CONTROL: HCQ + placebo	PRIMARY: Length of hospitalization; symptoms and co-existed disease SECONDARY Mortality and morbidity, re-admission, and symptoms	Randomized double blind Placebo control

Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial *Horby et al. 2021* *(UK, Indonesia, Nepal)* [10] *Preprint*	N = 11,340 Clinically suspected or laboratory confirmed SARS-CoV-2 infection among patients admitted in a hospital Duration of follow-up: 28 days	EXPERIMENTAL: Colchicine 1mg after randomization followed by 500mcg 12 hours later and then 500mcg twice daily for 10 days in total or until discharge CONTROL: Usual care (corticosteroids, remdesivir, and tocilizumab)	PRIMARY: Mortality SECONDARY: Time to discharge from hospital, invasive mechanical ventilation non-invasive respiratory support, time to successful cessation of invasive mechanical ventilation, use of renal dialysis or hemofiltration, cause-specific mortality, and serious adverse reactions	Randomized controlled trial

Appendix 4. Study Appraisal

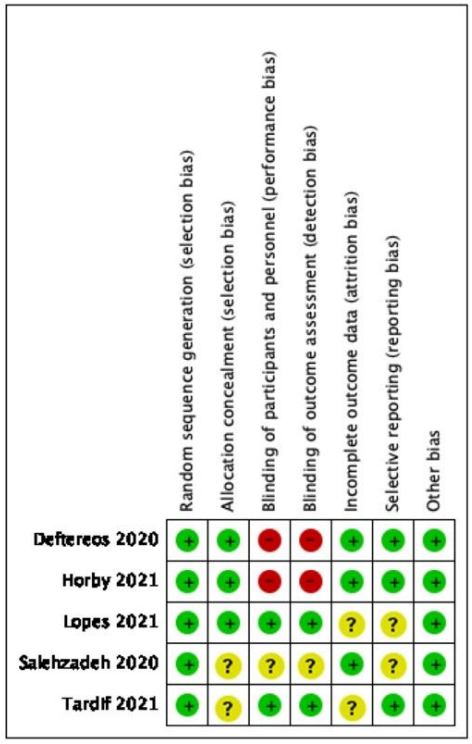

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: Colchicine compared to Placebo or Standard Care for COVID-19
Setting: out-patient and in-hospital

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CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Placebo/Standard of care	Relative (95% CI)	Absolute (95% CI)	CERTAINTY	IMPORTANCE
All-cause mortality (follow up: 1 month)												
5	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	1180/7989 (14.8%)	1206/8124 (14.8%)	**RR 1.00** (0.93 to 1.07)	**0 fewer per 1,000** (from 10 fewer to 10 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Need for mechanical ventilation (follow up: 1 month)												
3	Randomised trials	Serious [b]	Serious [c]	Not serious	Serious [d]	None	271/6106 (4.4%)	255/6269 (4.1%)	**RR 0.68** (0.29 to 1.60)	**13 fewer per 1,000** (from 29 fewer to 24 more)	⊕◯◯◯ VERY LOW	CRITICAL
Clinical improvement (discharge from hospital) within 28 days												
2	Randomised trials	Serious [e]	Not serious	Not serious	Not serious	None	3936/5648 (69.7%)	4064/5767 (70.5%)	**RR 0.99** (0.97 to 1.01)	**7 fewer per 1,000** (from 21 fewer to 7 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Need for hospitalization (follow up: 1 month)												
1	Randomised trials	Serious [f]	Not serious	Not serious	Serious [d]	None	101/2235 (4.5%)	128/2253 (5.7%)	**RR 0.80** (0.62 to 1.03)	**11 fewer per 1,000** (from 22 fewer to 2 more)	⊕⊕◯◯ LOW	CRITICAL
Need for hemodialysis or hemofiltration												
1	Randomised trials	Serious [g]	Not serious	Not serious	Serious [d]	None	212/5570 (3.8%)	203/5683 (3.6%)	**RR 1.07** (0.88 to 1.29)	**3 more per 1,000** (from 4 fewer to 10 more)	⊕⊕◯◯ LOW	CRITICAL

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Placebo/Standard of care	Relative (95% CI)	Absolute (95% CI)		
Duration of hospitalization (follow up: 1 month)												
3	Randomised trials	Serious [h]	Not serious	Not serious	Not serious	None	Colchicine was not associated with significantly shorter duration of hospitalization with a median of 10 vs 10 days, range 5 to >28 for both groups, n=11,340, Horby 2021). Two studies reported significantly shorter duration of hospitalization (mean 6.3 vs 8.1 days, p=0.001, n=100, Salehzadeh 2020; median 7 days [IQR 5-9] vs 9 days [IQR 7-12], p=0.003, n=38, Lopes 2020)				⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse events (follow up: 1 month)												
3	Randomised trials	Serious [i]	Not serious	Not serious	Serious [d]	None	111/2329 (4.8%)	144/2344 (6.1%)	**RR 0.78** (0.61 to 0.99)	**14 fewer per 1,000** (from 24 fewer to 1 fewer)	⊕⊕◯◯ LOW	CRITICAL
Adverse events (follow up: 1 month)												
2	Randomised trials	Serious [j]	Not serious	Not serious	Not serious	None	554/2273 (24.4%)	353/2290 (15.4%)	**RR 1.55** (1.37 to 1.75)	**85 more per 1,000** (from 57 more to 116 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

Explanations

[a]. Two studies with overall high risk of bias and 3 studies with overall some risk of bias
[b]. Issues on performance and detection bias (Defteros 2020 and Horby 2021), selection and attrition bias (Tardif 2021)
[c]. Significant heterogeneity (I2>50%)
[d]. Wide confidence interval
[e]. Issues on performance and detection bias (Horby 2021), attrition and reporting bias (Lopes 2021)
[f]. Issues on selection and attrition bias (Tardif 2021)
[g]. Issues on performance and detection bias (Horby 2021)
[h]. Issues on performance and detection bias (Horby 2021), selection, performance, detection and reporting bias (Salehzadeh 2020) and attrition and reporting bias (Lopes 2020)
[i]. Issues on selection and attrition bias (Tardif 2021), attrition and reporting bias (Lopes 2020), performance and detection bias (Deftereos 2020)
[j]. Issues on selection and attrition bias (Tardif 2021), attrition and reporting bias (Lopes 2020)

Appendix 6. Forest Plots

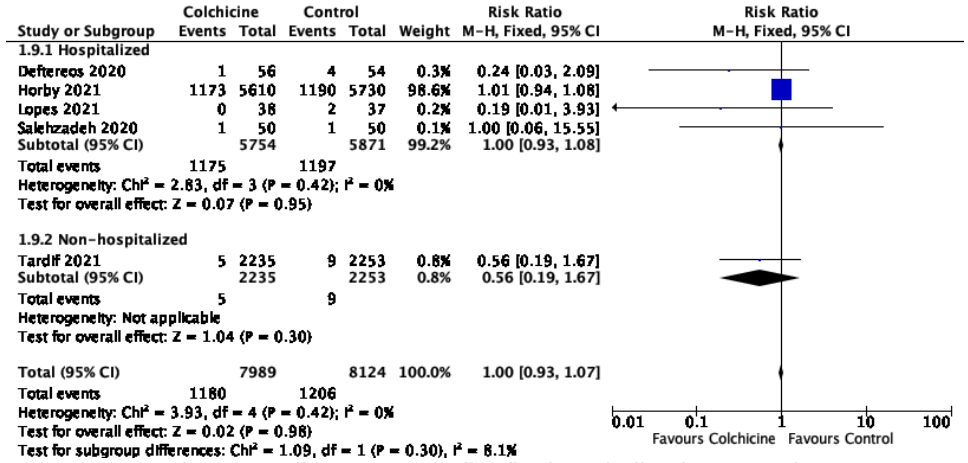

Figure 1. All-cause mortality (by hospitalization status)

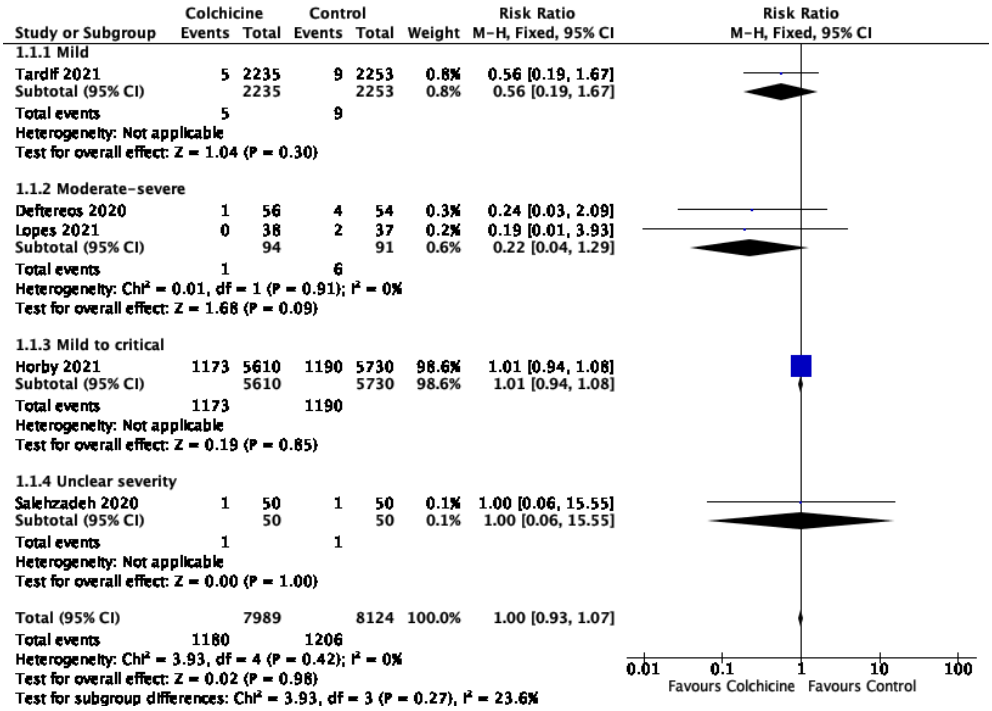

Figure 2. All-cause mortality (by severity)

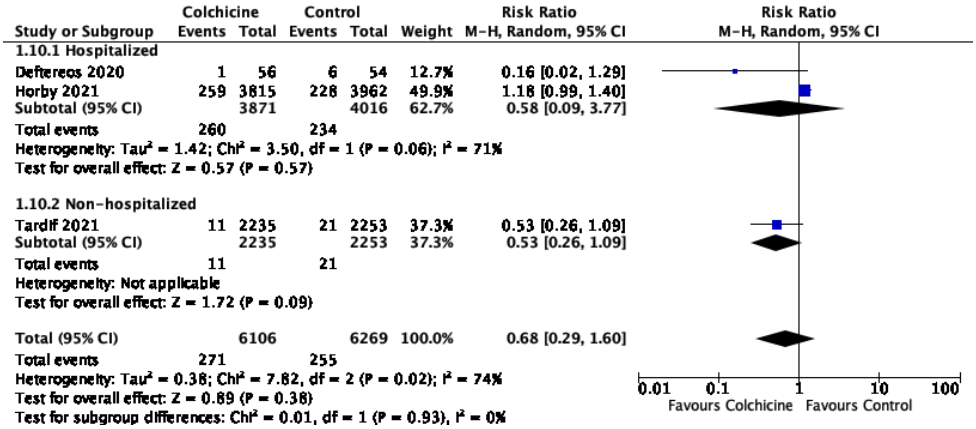

Figure 3. Need for Mechanical Ventilation

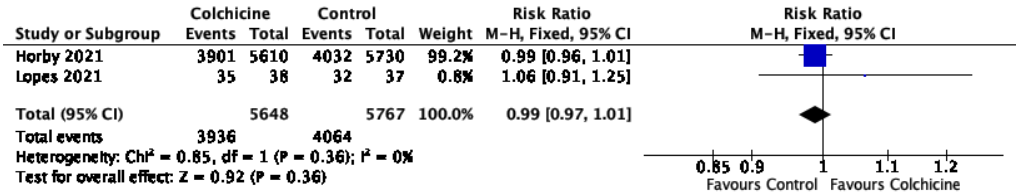

Figure 4. Clinical improvement (hospital discharge) within 28 days

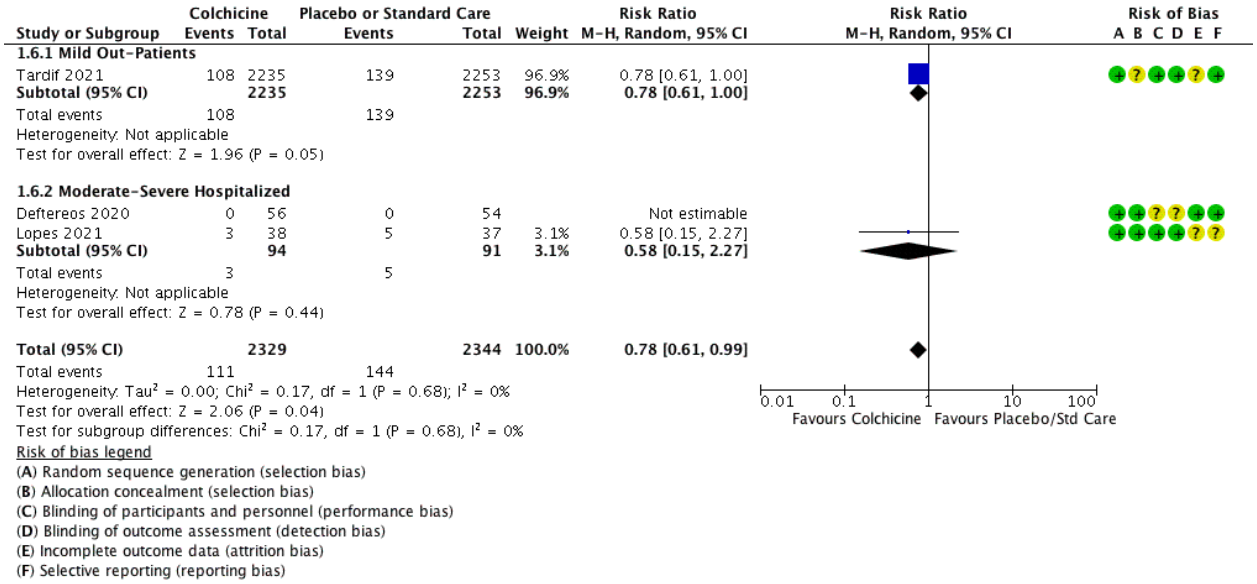

Figure 5. Serious Adverse Events

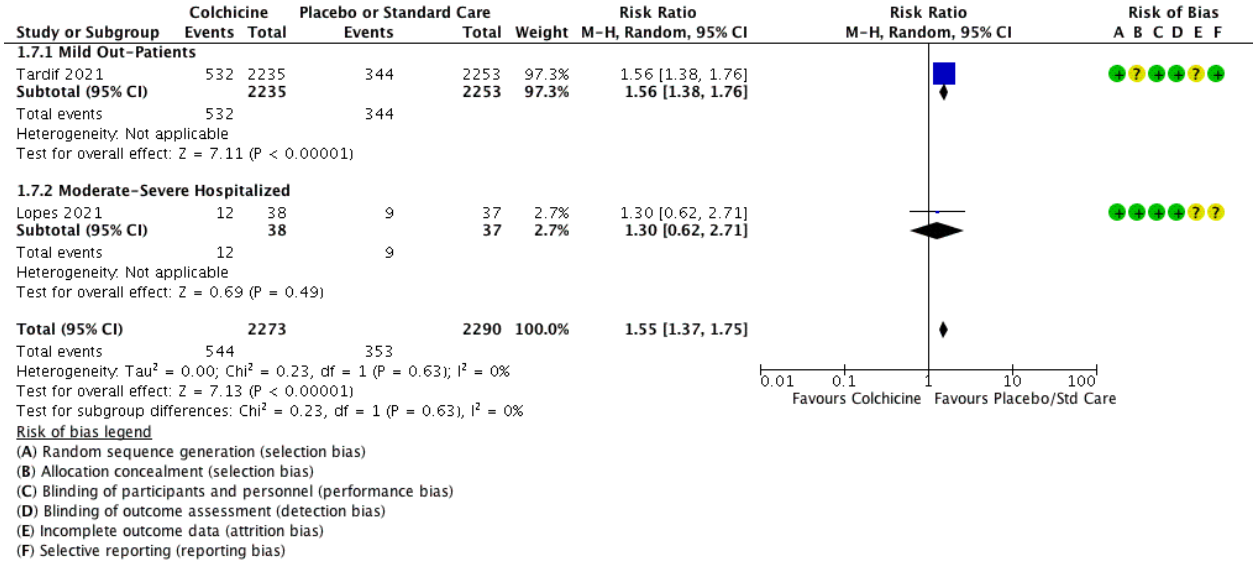

Figure 6. Adverse events

Appendix 7. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Colchicine / Statins for the Prevention of COVID-19 Complications (COLSTAT) Trial	18 years and older with clinical or definitive diagnosis of COVID-19 by PCR test, admitted to the hospital (non-ICU) within 48h to hospital admission	Experimental: Standard of Care (SOC) and colchicine + rosuvastatin rosuvastatin 40mg daily and colchicine 0.6mg twice for 3 days and then 0.6mg daily during hospitalization Control: SOC during hospitalization determined by the primary care team during hospitalization.	Severity of COVID measured by WHO Scores 5-8	Randomized; parallel assignment, open label
2. Treatment With Colchicine of Patients Affected by COVID-19: A Pilot Study	18 years or older Virological diagnosis of SARS-CoV-2 infection (real-time PCR), hospitalized due to clinical/instrumental diagnosis of pneumonia	Experimental: Colchicine plus current care Control: Current care	Primary: Rate of entering critical stage (respiratory failure requiring mechanical ventilation; Patients combined with other organ failure need ICU monitoring and treatment; death)	Randomized; parallel assignment, open label
3. Study to Investigate the Treatment Effect of Colchicine in Patients With COVID-19 *Withdrawn due to no funding*	18 to 65 years old SARS-CoV-2 infection confirmed by PCR admitted in the hospital in the previous 48 hours, with clinical status 3, 4 or 5 of WHO classification.	Experimental: SOC plus colchicine Control: SOC	Primary: Changes in the patients' clinical status through the 7 points ordinal scale WHO R&D Blueprint expert group	Randomized, controlled, open-label
4. Randomized, Open-Label, Controlled Trial of Colchicine to Reduce Cardiac Injury in Hospitalized COVID-19 Patients (COLHEART-19) *Suspended due to RECOVERY trial results*	Age above 18 years old Confirmed COVID-19 infection by polymerase chain reaction with cardiac injury	Experimental: colchicine plus current care Control: Current care	Primary: Composite of all-cause mortality, need for mechanical ventilation, or need for mechanical circulatory support	Randomized, parallel assignment, open-label
5. Preemptive Therapy with Colchicine in Patients Older Than 60 Years with High Risk of Severe Pneumoniae Due to Coronavirus SARS-Cov-2 (COVID-19)	At least two high-risk criteria, diagnosis of COVID-19 infection in the last 72 hours and confirmed by PCR Patients in outpatient follow-up or institutionalized in senior centers/residences	Experimental: Colchicine plus symptomatic treatment. Control: Symptomatic treatment	Primary: Death, need for hospitalization	Randomized, parallel assignment, open-label
6. Effects of Standard Protocol Therapy with or Without Colchicine in COVID-19 Infection: A Randomized Double Blind Clinical Trial	Patients >18 years old with nasopharyngeal swab confirmed COVID-19 PCR, CT involvement compatible with COVID, Fever and Dyspnea without hypoxemia.	Experimental: Colchicine 1.5mg loading then 0.5mg BID plus SOC Control: SOC, vitamin C, thiamine, selenium, omega-3 Vit A, Vit D, azithromycin, ceftriaxone, Kaletra	Primary: increasing inflammatory status (CRPxN/R ratio change); Clinical deterioration by the WHO definition including change in fever or O2 Saturation; RT-PCR viral load; change in CT severity involvement index	Randomized Parallel assignment Double blind

Study Title	Patients (n)	Interventions	Outcomes	Method
7. Effectiveness and Safety of Medical Treatment for SARS-CoV-2 (COVID-19) in Colombia: A Pragmatic Randomized Controlled Trial	Age 18 years or over Positive RT-PCR for COVID-19 or high suspicion of SARS covid 19	Experimental 1: Emtricitabine 200mg + tenofovir 300mg Experimental 2: Colchicine 0.5mg every 12 hours for 14 days + rosuvastatin: 40mg / day for 14 days Experimental 3: Emtricitabine 200mg + tenofovir 300 mg + colchicine: 0.5mg every 12 hours for 14 days + rosuvastatin: 40 mg/day for 14 days Control: Standard treatment	Primary: Mortality, cumulative incidence on day 28 Number of participants that develop severe adverse events related to the treatment	Randomized Parallel assignment Open label
8. Phase 2/3, Randomized, Open Study to Compare the Efficacy and Safety of Colchicine and Glucocorticoids Compared With the Standard of Treatment for Moderate/Severe COVID-19 in a Fragile and Vulnerable Population, Admitted to a Geriatric Hospital Unit or in a Transitional Care Center	At least 65 years old and admitted to the Geriatrics Unit of the Internal Medicine Service (Hospital Clínic de Barcelona) or to a transitional care center Clinical diagnosis compatible with COVID-19, moderate to severe	Experimental: Colchicine plus prednisone Control: Standard treatment	Primary: Reduction of mortality on day 28	Randomized Parallel assignment Open label
9. Efficacy and Safety of Edoxaban and or Colchicine for Patients With SARS-CoV-2 Infection Managed in the Out of Hospital Setting	18 years and older Patients with laboratory confirmed SARS-CoV-2 infection (under RT PCR) who are managed at home or in another out-of-hospital setting.	Experimental 1: Edoxaban Experimental 2: Colchicine at 0.5mg twice daily for the first 3 days and then once daily to day 14 Experimental 3: Edoxaban and colchicine Control: No edoxaban colchicine	Primary: SARS-CoV-2 clearance rates, death or hospitalization at day 14	Randomized Factorial assignment Open label
10. The ECLA PHRI COLCOVID Trial. Effects of Colchicine on Moderate/High-risk Hospitalized COVID-19 Patients (COLCOVID) **(Marked as completed; results still for posting)**	Age ≥18 years, suspected COVID-19, admitted in hospital	Experimental: Colchicine Control: Standard of care	Primary: Need for intubation for mechanical ventilation, death	Randomized Parallel assignment Open label
11. Prospective-randomized Adaptive Study, With Active Control to Evaluate the Efficacy and Safety of Interleukin (IL)-17 Inhibitor	18 years and older, positive PCR test for SARS-CoV-2, with pneumonia confirmed by chest imaging	Experimental 1: IL-17 inhibitor (ixekizumab) Experimental 2: IL-2 (aldesleukin)	Primary: Ordinal scale of seven World Health Organization (WHO) categories	Randomized Parallel assignment Open label

Study Title	Patients (n)	Interventions	Outcomes	Method
Treatment Versus Low Doses of IL-2 Versus Indirect IL-6 Inhibitor in Hospitalized Patients With Severe Forms of COVID-19 (STRUCK Trial)		Experimental 3: Colchicine 0.5mg every 8 hours for 3 days (PO), followed by 4 weeks 0.5mg twice daily. Control: Standard treatment		
12. Open-label (Unblinded) Randomization to Treatment of Colchicine Plus Current Care Per Institution Treating Physicians vs. Current Care Per Institution Treating Physicians (Control Arm)	18 to 99 years old, Covid-19 positive hospitalized patients with cardiac injury	Experimental: Colchicine (0.6mg BID x 30 days) plus current care	Primary: Composite of all-cause mortality; need for mechanical ventilation; Need for mechanical circulatory support	Randomized Parallel assignment Open label
13. Double-blind, Placebo-controlled Clinical Trial of the Use of Colchicine for the Management of Patients With Mild and Severe SARS-Cov2 Infection	18 to 70 years old, Diagnosed with COVID-19 with mild or severe disease Must receive in-hospital care at the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran	Experimental: Colchicine 1mg, 1 ½ pill in day 1 and ½ pill BID during 10 days in both mild and severe COVID-19 Control: Placebo	Primary: Number of patients with improvement in body temperature, myalgia, arthralgia	Randomized Parallel assignment Double blind Placebo controlled
14. Colchicine to Counteract Inflammatory Response in COVID-19 Pneumonia (ColCOVID-19)	Positive nasopharyngeal swab for COVID-19 Asymptomatic or pauci-symptomatic, aged ≥ 70 years and/or with clinical risk factors for poor outcome Symptomatic with respiratory or systemic symptoms, however clinically stable	Experimental: Colchicine 1mg (or 0.5mg in CKD)/day + standard of care Control: Standard care	Primary: Time to clinical improvement or live discharge from the hospital (whichever comes first)	Randomized Parallel assignment Open label
15. Colchicine Versus Ruxolitinib and Secukinumab In Open Prospective Randomized Trial	18 years and older COVID-19 with the mild and severe course	Experimental 1: Colchicine 0.5mg twice a day during the first 3 days and then 0.5mg daily if weight < 86 kg or 0.5mg twice a day if weight > 85kg for 7 days Experimental 2: Ruxolitinib Experimental 3: Secukinumab Control: Standard therapy	Primary: CAS COVID 19 measures clinical and laboratory parameters in 7 domains: respiratory rate, body temperature, Sp02 without support oxygen, ventilation, C-reactive protein, d -dimer	Randomized Parallel assignment Open label
16. Impact of Colchicine in Hospitalized Colombian Patients With COVID-19	18 years and older Laboratory-confirmed SARS-CoV-2 infection: infection confirmed with nasopharyngeal swab by positive RT PCR in the last 48 hours. Hospital admission for COVID-19 in the previous 48 hours.	Experimental: Colchicine plus standard treatment Colchicine 1.5mg orally on the first day, followed by 0.5mg every 12 hours on days 2 to 7, and continuing with 0.5mg per day until completing 14 days Control: Standard treatment	Primary: Number of participants who die or require transfer to intensive care unit	Randomized Parallel assignment Open label

Study Title	Patients (n)	Interventions	Outcomes	Method
17. Colchicine in Moderate-severe Hospitalized Patients Before ARDS to Treat COVID-19 (the COMBAT-COVID-19 Pilot Study)	18 to 100 years old, hospitalized and requiring medical care for COVID-19, with significant COVID-19 symptom or judged to be at high risk of progression to severe COVID-19 infection	Experimental: Colchicine Control: Usual care	Primary: Percentage of Patients requiring supplemental oxygen beyond 8L nasal cannula	Randomized Parallel assignment Open label
18. Anti-Coronavirus Therapies to Prevent Progression of COVID-19, a Randomized Trial	Outpatient trial: Symptomatic and laboratory-confirmed diagnosis of COVID-19, age ≥18 years. High risk: either age ≥70 or one of the following: male; obesity (BMI ≥30); chronic cardiovascular, respiratory or renal disease; active cancer; diabetes.	Experimental 1: Colchicine 0.6mg twice daily for 3 days, then 0.6mg once daily for 25 days (total 28 days) Experimental 2: Interferon Beta Experimental 3: Aspirin (ASA) Experimental 4: Rivaroxaban 2.5 mg Control: Usual care	Primary: Outpatient trial - hospitalization or death Inpatient trial - invasive mechanical ventilation or death	Randomized parallel group factorial Open-label
19. Colchicine in Moderate Symptomatic COVID-19 Patients: Double Blind, Randomized, Placebo Controlled Trial to Observe the Efficacy (COLCOVIDBD) **(Marked as completed; results still for posting)**	18 years and older (+) RT-PCR for SARS CoV-2, moderate symptoms	Experimental: Colchicine Starting dose of 1.2mg of colchicine (2 tablets of 0.6mg) single or 12 hourly divided doses, after that, they will take colchicine 0.6mg daily for 13 days. Control: Placebo plus standard care	Primary: Clinical deterioration, defined as the time from randomization to a deterioration of two points on a Seven-category ordinal scale.	Randomized parallel assignment triple blind
20. Clinical Outcome of Patients With COVID-19 Pneumonia Treated With Corticosteroids and Colchicine in Colombia **(Marked as completed; results still for posting)**	18 years and older, hospitalized for Covid-19 Pneumonia, confirmed positive by nasopharyngeal RT-PCR SARS-Cov2	Experimental 1: Dexamethasone Experimental 2: Colchicine at a dose of 0.5mg every 12 hours for 7 to 14 days	Primary: death	Case-crossover
21. Administration of Colchicine Plus Standard Treatment vs. Standard Therapy, in Hospitalized Patients With COVID-19, Within the First 48 Hours, and no Severity Criteria **(Marked as completed; results still for posting)**	18 years and older SARS-CoV-2 infection confirmed by PCR Admitted in the hospital in the previous 48 hours, with clinical status 3, 4 or 5 of WHO classification	Experimental: Colchicine plus standard care Control: Standard care	Primary: Changes in the patients' clinical status through the 7 points ordinal scale WHO R&D Blueprint expert group; Changes in IL-6 concentrations	Randomized parallel assignment open label
22. Colchicine for the Treatment of Hyperinflammation	Patient hospitalized for COVID pneumonia19 (microbiological confirmation and chest X-ray	Experimental: Colchicine 0.5-1mg Control: Other medicinal products	Primary: Support compound with CPAP / BiPAP, ICU admission, invasive ventilation or death	Randomized Open label controlled

Study Title	Patients (n)	Interventions	Outcomes	Method
associated with Pneumonia due to COVID-19	compatible with pneumonia are required); Hyperinflammation			
23. Randomized clinical trial for the treatment of moderate to severe cases of COVID-19 with Chloroquine and Colchicine	Moderate or severe forms of COVID-19; 18 years or older;	Experimental: Chloroquine and colchicine 0.5mg TID for 5 days Control: Chloroquine and placebo	Primary: Number of days needing supplemental oxygen; number of days from the admission to discharge; ICU admission due to clinical deterioration; death	Randomized controlled, parallel double-blind
24. Randomized open-blind controlled trial to study the benefit of Colchicine in Patients with COVID-19 **(Marked as completed; results still for posting)**	Age over 18 years, infection confirmed by SARS-CoV-2 by RT-PCR, Hospital admission in the previous 48 hours for clinical involvement in groups 3, 4 or 5 of the WHO clinical scale.	Experimental: Colchicine 0.5mg plus standard care Control: Standard care	Primary: Ordinal 7-point clinical evaluation scale (WHO R&D Blueprint expert group)	Randomized open-blind controlled
25. Adding Colchicine to the Antiretroviral Medication - Lopinavir/ Ritonavir (Kaletra) in Hospitalized Patients with Non-Severe COVID-19 Pneumonia: A Structured Summary of a Study Protocol for a Randomized Controlled Trial	Hospitalized patients with positive nasopharyngeal swab for COVID-19 infection (RT - PCR) and lung computed tomography scan involvement compatible with COVID-19 pneumonia	Experimental: Lopinavir/Ritonavir (Kaletra) + colchicine 1.5mg loading then 0.5mg twice daily orally Control: Lopinavir/Ritonavir (Kaletra)	Primary: Time for clinical improvement and lung CT score changes 14 days after treatment	Randomized Double blind
26. Impact of Colchicine on the Clinical Outcome of COVID-19 and the Development of Post-COVID-19 Pulmonary Fibrosis: Randomized Controlled Clinical Trial	Patients who are confirmed to have COVID-19 clinically, radiologically and PCR Age above 18 years old	Experimental: Colchicine group Control: Local standard protocol	Primary: Clinical status, Pulmonary fibrosis at week 2 and day 45	Randomized Controlled Clinical Trial
27. Effectiveness of Colchicine Among Patients With COVID-19 Infection **(Marked as completed; results still for posting)**	Patients diagnosed clinically or by RT-PCR and/ or lung involvement by computed tomography scan compatible with COVID-19 Between 18 year and 70 years, body weight > 50 kg	Experimental: Colchicine group Control: Usual care	Primary: Need for supplemental oxygen, length of hospital stay, need for invasive mechanical ventilation, death rate	Randomized open label clinical trial

Study Title	Patients (n)	Interventions	Outcomes	Method
28. Investigator initiated study to evaluate the effect of Marketed Colchicine 0.5mg given along marketed Aspirin 75mg with SOC and Marketed aspirin 75mg with SOC on COVID-19 patients	40 to 80 years old Positive oropharyngeal/nasal swab RT-PCR with moderate symptoms	Experimental: Colchicine 0.5mg with aspirin 75mg with SOC Control: Aspirin 75mg with SOC	Primary: Symptomatic improvement through the NEWS score and 8-point ordinal score	Randomized, parallel/crossover trial
29. Evaluation of the colchicine tablet efficacy as an adjuvant therapy for patients with mild to moderate COVID-19	**Patients with COVID-19, mild to moderate**	Experimental: Colchicine 1mg tablet daily for two weeks. Control: Placebo	Primary: clinical response to treatment, adverse reaction, fever	Randomized, parallel/crossover trial
30. Double Blind Randomized Clinical Trial of Use of Colchicine Added to Standard Treatment in Hospitalized Patients with COVID-19 Infection (CORONACOLCHI)	**Acute symptoms compatible with SARS-CoV-2 infection, microbiologically confirmed infection by SARS-CoV-2, .> 18 years, admitted**	Experimental: Colchicine for 2 weeks orally added to the standard treatment of COVID-19 Control: Placebo for 2 weeks orally added to standard COVID-19 treatment	Primary: Death, need for mechanical ventilation or respiratory distress	Double Blind Randomized Clinical Trial
31. A Clinical Trial to Assess the Efficacy, Safety and tolerability of Colchicine for COVID-19 Disease Treatment in Indian Patients	**40 to 65 years old, confirmed diagnosis of at least moderate COVID-19 symptoms**	Experimental: Colchicine 0.5mg tablets plus standard of care Control Standard of care	Primary: Time to clinical improvement of 2-points on WHO 8-point ordinal scale	Randomized, parallel/crossover trial
32. Efficacy of Colchicine in Treatment of COVID-19	Patients with COVID-19 with moderate to severe respiratory failure admitted to ICU wards	Experimental: Methylprednisolone pulse therapy and colchicine (2mg stat then 1mg daily) with standard treatment Control group: Standard treatment (dexamethasone, interferon beta1, remdesivir)	Primary: Respiratory distress	Randomized, parallel/crossover trial
33. Will treatment with a drug named colchicine be useful in treating Corona virus infection in kidney failure patients who are on regular dialysis?	**Patients with end stage kidney disease who are on maintenance hemodialysis with SARS-CoV-2 infection**	Experimental: Colchicine and Standard of care Control: Standard of care	Primary: Time to deterioration by 2 points on the WHO clinical progression scale	Randomised, parallel/crossover trial

Study Title	Patients (n)	Interventions	Outcomes	Method
34. Effect of colchicine in treatment of COVID-19	Age 18 to 70 years old with COVID-19 in the last 24 to 48 hours, candidate for hospitalization **COVID-19 patients hospitalized with hospital indications according to the guidelines**	Experimental: 0.5mg of colchicine until the third day and 12 days later 1mg plus standard treatment Control: Standard treatment	Primary: Clinical symptoms, pulmonary infiltration findings on CT scan.	Randomised, parallel/crossover trial
35. Efficacy and safety of colchicine on clinical improvement in patients with COVID-19: A randomized, double blind clinical trial	Over the age of 18 with a diagnosis of COVID-19 based on clinical criteria or PCR and had clinical symptoms of COVID-19 within two weeks	Experimental: Interferon beta 1 b plus remdesivir with colchicine at 2mg as loading dose then 1 mg daily for 7 days. Control: Interferon beta 1 b and remdesivir	Primary: Blood oxygen saturation, fever recovery, respiratory rate, adverse effects	Randomized, parallel/crossover trial
36. The Effectiveness of Pentoxifylline and Colchicine in the Treatment of COVID-19	Hospitalized patients suspected with COVID-19 infection, SpO2 less than 93%, respiratory symptoms, older than 40 years	Experimental: Pentoxifylline group receiving 400mg every 12 hours plus colchicine ½ mg every day in addition to the standard treatment Control group: Standard treatment	Primary: Duration of hospitalization.	Randomized, parallel/crossover trial
37. Efficacy of colchicine in the treatment of COVID-19 patients	At least 18 years of age, confirmation of COVID-19 with RT-PCR in the last 24 hours, outpatient	Experimental: Colchicine 0.5mg tablets for the first 3 days, twice a day, and then for the next 27 days, once a day, with standard treatment (famotidine, cetirizine, N-acetylcysteine, bromhexine, naproxen, and fluticasone spray) Control: Placebo and standard treatment	Primary: Death, hospitalization, severe illness.	Randomized, parallel/crossover trial
38. Colchicine in combination with infliximab compared with infliximab in the treatment of patients with COVID-19	Patients with the common type of Novel Coronavirus Pneumonia (NCP) (at high risk) and other severe cases of newly diagnosed coronavirus pneumonia between the ages of 18 and 85 with an increase in IL-6 levels	Experimental: Infliximab + standard treatment + colchicine Control group: Infliximab + standard treatment	Primary: Clinical symptoms, pulmonary CT scan changes	Randomized, parallel/crossover trial
39. Impact of Colchicine to Improve long-COVID-19 or ARDS Outcomes	Aged 18 years and older, hospitalized with confirmed COVID-19 respiratory infection by swab-positive PCR with hypoxia	Experimental: Colchicine 0.5mg tablet twice daily + standard of care Control: Standard of care	Primary: Death at 6 months and end of study, maximum oxygen requirement, COVID-19 WHO score	Randomized, parallel/crossover trial
40. Colchicine in COVID-19: a Pilot Study (COLVID-19)	Virological diagnosis of SARS-CoV-2 infection (real-time PCR), Hospitalized due to clinical/instrumental diagnosis of pneumonia	Experimental: Colchicine plus current care Control: Current care alone	Primary Outcome Rate of entering the critical stage with any of the following: respiratory failure and requires mechanical ventilation; organ failure; need ICU admission; death	Randomized, parallel/crossover trial

Study Title	Patients (n)	Interventions	Outcomes	Method
41. Impact of Colchicine and Low-dose Naltrexone on COVID-19 (COLTREXONE)	Requiring admission to Methodist or Regions Hospital due to laboratory-confirmed COVID-19, only up to moderate COVID-19 disease	Experimental: Colchicine-Only Arm Experimental: Colchicine and Naltrexone ("Combined") Arm Experimental: Naltrexone-Only Arm No Intervention: Standard of Care Arm	Primary: Progression of COVID-19 from "moderate" classification to "severe/critical"	Randomized Open Label Trial
42. A randomization, multicentric, open-label, controlled, clinical trial to investigate the effectiveness of early colchicine administration in patients over 70 years of age with high risk of developing severe pulmonary complications associated with coronavirus sars-cov2 pneumonia (COVID-19) COLCHI-COVID	At least 70 years old, Diagnosis of COVID-19 infection within the last 24 hours and confirmed by PCR, in outpatient follow-up, with at least two high-risk criteria	Experimental: Colchicine Control: Not clearly stated	Primary: Death or requires hospitalization	Randomization, multicentric, open-label, controlled, clinical trial

Q19. Among patients with COVID-19, should interferon be used for treatment?

As of 6 December 2021

RECOMMENDATION

We recommend against the use of interferon in the treatment of COVID-19 patients. *(Very low certainty of evidence, Strong recommendation)*

Consensus Issues
Recent review included more participants (close to 6,000) yet, interferon still did not show any clear benefit for all-cause mortality and other critical outcomes. There is a need to emphasize the potential harm and side effects of the drug as well as its high cost.

PREVIOUS RECOMMENDATION

We suggest against the use of interferon in the treatment of hospitalized patients with moderate to critical COVID-19. *(Very low certainty of evidence; Weak recommendation)*

Previous consensus issues
Current evidence shows no significant benefit with using interferon for treating COVID-19 infections. The high cost this drug must be considered

WHAT'S NEW IN THIS VERSION?

Six (6) new RCTs (Bhushan 2021, Pandit 2021, Ader 2021, Darazam 2021, Khalil 2021, and Rahmani 2020) were included in this update.

KEY FINDINGS

Nine (9) published randomized controlled clinical trials (RCTs) (N = 5,957) investigated the efficacy and safety of interferon in the treatment of COVID-19 compared to standard of care and/or placebo. Results showed significant benefit on viral negative conversion among patients given interferon, however, there was inconclusive evidence in terms of the critical outcomes such as all-cause mortality, clinical improvement, need for mechanical ventilation, progression to severe disease, ICU admission, adverse events, and serious adverse events.

INTRODUCTION

Interferons are used for treatment and control of multiple sclerosis, viral hepatitis and some hematologic malignancies. Type I interferon (IFN-I) includes interferon alpha and beta.[1] IFN-I response is the first line defense against viral infection. Evasion of interferon response leads to viral transmission, replication and infection. Interferons modulate the response of the immune system to viruses.[2] An in-vitro study showed that IFN-I reduced viral replication, antigen expression, and viral load in SARs-CoV-2 [3], hence these are under investigation as a potential treatment for individuals with COVID-19.

REVIEW METHODS

A systematic search was done from the date of the last search on March 30, 2021 until November 5, 2021. Search was done in Medline, Cochrane Library, and Google scholar using free text, MeSH terms and advanced search using the term coronavirus

infections, COVID-19, severe acute respiratory syndrome coronavirus 2, and interferon. Trials found in the COVID-NMA were included. Screening with ongoing trials was done in various trial registries. Medrxiv, chinaxiv, and biorxiv were searched for preprints. RCTs on interferon as treatment for COVID-19 compared to placebo were included. No limits were placed on age, severity and dose. In order to compute for confidence interval, we imputed 1 if a study had no event in the treatment arm.

RESULTS

Characteristics of included studies

Nine (9) published randomized controlled clinical trials (RCTs) (N = 5,957) investigated the effectiveness of interferon among confirmed COVID-19 patients compared to placebo and/or standard of care. All the trials reviewed were also included in the COVID-NMA Living Data.[4-12] Appendix 3 summarizes the characteristics of the included studies.

The severity of the patients included were as follows: mild 1,156 (19.41%), moderate 4,259 (71.4%), moderate to severe 60 (1.01%), and severe 482 (8.09%). Five (5) studies compared interferon beta-1b to standard of care and/or placebo.[4-8] One study compared the effectiveness of interferon beta-1a plus hydroxychloroquine, lopinavir/ritonavir to interferon beta-1b plus hydroxychloroquine, lopinavir/ritonavir and to standard of care hydroxychloroquine, lopinavir/ritonavir.[9] One study compared the effectiveness of interferon beta-1b to standard of care in the treatment of COVID-19 [10], while, two (2) studies compared the effectiveness of PEG-interferon alpha-2b compared to standard of care in the treatment of COVID-19.[11-12] The standard of care included in the studies are hydroxychloroquine, lopinavir/ritonavir, atazanavir/ritonavir, remdesivir, steroids, IVIg, steroids, antibiotics, antipyretics, anticoagulants, and oxygen supplementation depending on the national clinical management guidelines. In three (3) RCTs [4,5,11], 1,078 patients in the IFN arm and 1,144 patients in the control group were given glucocorticoids.

Overall certainty of evidence

The overall certainty of evidence was rated very low due to very serious risk of bias, serious inconsistency, and imprecision in 4 critical outcomes (all-cause mortality, need for mechanical ventilator, clinical improvement, and serious adverse events). The included studies had a very serious risk of bias due to issues on performance bias, detection bias, attrition bias, and reporting bias. Seven out of nine trials were open label trials. The risk of bias summary is shown in Appendix 4. The GRADE evidence summary is in Appendix 5.

Outcomes

Interferon showed significant benefit on one of the important, but not critical outcome, viral negative conversion (RR 1.30, 95% CI 1.14, 1.49; I^2 = 0%; 2 RCTs, 290 participants). However, interferon showed no significant benefit compared to standard of care and/or placebo in all-cause mortality (RR 1.06, 95% CI 0.91, 1.23; I^2 = 48%; 9 RCTs, 5,957 participants), need for mechanical ventilation (RR 0.97, 95% CI 0.82, 1.14; I^2 = 0%; 4 RCTs, 4,307 participants), clinical improvement (RR 1.02, 95% CI 0.98, 1.06; I^2 = 52%; 6 RCTs, 1,732 participants), progression to severe disease (RR 0.57, 95% CI 0.23, 1.42; 1 RCT, 98 participants), ICU admission (RR 0.77, 95% CI 0.59, 1.00; I^2 = 46%; 2 RCTs, 126 participants), and duration of hospitalization (MD

2.55, 95% CI -0.92 to 6.02; 1 RCT, 81 participants). Results on all cause mortality and clinical improvement also showed borderline heterogeneity.

Subgroup analyses on the effect of interferon on mortality were stratified according to types of interferon used and severity (Appendix 5). Subgroup according to types of interferon used did not show significant benefit across groups, including those given interferon beta-1a (RR 0.91, 95% CI 0.61, 1.36; I^2 = 53%; 6 RCTs, 5,571 participants); those given interferon beta-1b (RR 0.51, 95% CI 0.23, 1.12; I^2 = 0%; 2 RCTs, 96 participants); and those given interferon alpha-2a (RR 2.01, 95% CI 0.36, 11.30; I^2 = 0%; 2 RCTs, 290 participants). Subgroup on interferon beta-1a had borderline heterogeneity (p = 0.06).

Subgroup analysis by severity did not show significant benefit across groups, including those patients belonging to mild to severe (RR 1.12, 95% CI 0.95, 1.33; I^2 = 0%; 3 RCTs, 5,167 participants), moderate (RR 2.10, 95% CI 0.40, 11.14; I^2 = 0%; 2 RCTs, 290 participants), moderate to severe (RR 0.76, 95% CI 0.51, 1.14; 3 RCTs, 254 participants), and severe (RR 0.33, 95% CI 0.07, 1.53; 1 RCT, 66 participants). Results of the moderate to severe subgroup had significant heterogeneity (p = 0.04; I^2 = 68%).

Safety

The rates of adverse events among patients receiving interferon (RR 1.13, 95% CI 0.93, 1.38; I^2 = 53%; p = 0.06) did not differ from those not receiving interferon. There was no significant difference in serious adverse events in interferon (RR 0.91, 95% CI 0.71, 1.18; I^2 = 78%; p = 0.001) compared to standard of care/placebo. Both adverse events and serious adverse events presented with heterogeneity. Adverse events reported were chest pain, asthenia, myalgia, headache, nausea, vomiting, hypersensitivity reaction, cough, decreased oxygen saturation, diarrhea, lymphopenia, and pruritus. Serious adverse events reported included acute kidney injury, nosocomial infection, septic shock, deep vein thrombosis, arrhythmia, respiratory failure, and hepatic failure.

All relevant forest plots for the analyses above are found in Appendix 6.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
US-NIH Guidelines as of October 27, 2021 [13]	Recommends against the use of interferons for the treatment of patients with severe or critical COVID-19, except in a clinical trial (*Strength of recommendation is AIII*) and states that there are insufficient data to recommend either for or against the use of interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.
Australian Guideline on COVID-19 as of November 3, 2021 [14]	Recommends against the use interferons the treatment of COVID-19 except in the context of randomized trials. *(Moderate priority recommendation and will be updated when new evidence becomes available*)
WHO Living Guidelines as of September 24, 2021 [15]	No statement on the use of interferons for the treatment of COVID-19.
Infectious Diseases Society of America (IDSA) as of November 18, 2021 [16]	

RESEARCH GAPS

As of November 5, 2021, there are 23 ongoing trials on interferon alpha and interferon beta registered on *clinicaltrials.gov*, EU Clinical Trials Register, and WHO International Clinical Trials Registry Platform (Appendix 9). One of the trials was terminated, two trials are already on Phase 3 and two trials are on Phase 4.

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Appendix 1. Evidence to Decision Table

Table 1. Summary of initial judgements prior to the panel discussion (N = 5)

FACTORS	JUDGEMENT (N = 5)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (1)	Yes (4)					
Benefits	Large	Moderate	Small (5)	Uncertain			Interferon showed no significant benefit compared to standard of care and/or placebo in all-cause mortality (RR 1.06, 95% CI 0.91-1.23), need for mechanical ventilation (RR 0.97, 95% CI 0.82-1.14), clinical improvement (RR 1.02 95% CI 0.981.06), progression to severe disease (RR 0.57, 95% CI 0.23-1.42), ICU admission (RR 0.77, 95% CI 0.59-1.00), and duration of hospitalization (MD 2.55, 95% CI -0.92 – 6.02). Interferon showed significant benefit on one of the important, but not critical outcome, viral negative conversion (RR 1.30, 95% CI 1.14-1.49).
Harm	Large (1)	Small (2)	Uncertain (2)				Interferon showed no significant difference in the risk for adverse events (RR 1.13, 95% CI 0.93-1.38) and serious adverse events (RR 0.91, 95% CI 0.71-1.18).
Certainty of Evidence	High	Moderate	Low (2)	Very low (3)			The overall certainty of evidence rated very low due to very serious risk of bias, serious inconsistency and imprecision in 4 critical outcomes.
Balance of effects	Favors drug	Does not favor drug (3)	Uncertain (2)				Interferon showed no potential harm since there is no significant difference in the adverse event and serious adverse event. With the balance favoring benefit in the viral negative conversion.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (5)	Moderate Cost	Negligible cost	Moderate savings	Large savings	Large cost amounting to P19,144.55 to P463,650.00 for the total cost of treatment per patient
Certainty of evidence of required resources	No included studies (5)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (4)	Reduced (1)	Probably no impact	Increased			
Acceptability	Uncertain (3)	No (2)	Yes				
Feasibility	Uncertain (2)	No (2)	Yes (1)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Interferon AND randomized	10/31/2021 3:20PM	188	12
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND MeSH descriptor: [Interferons] explode all trees	10/31/2021 5:05PM	60	17
COVID-NMA Initiative	Interferon	10/30/2021 4:30PM	18	8
Google Scholar	allintitle: interferon AND "COVID 19" custom range: 2020-2021	11/5/2021 4:37PM	117	8
ClinicalTrials.gov	COVID-19 COVID-19 Pneumonia, Investigational Trials, Interferon	11/5/2021 8:30PM	44	16
Chinese Clinical Trial Registry	Advanced: COVID, randomly sampling, interferon	11/5/2021 9:40PM	0	0
EU Clinical Trials Register	COVID AND Interferon	11/5/2021 9:44PM	7	1
Republic of Korea - Clinical Research Information Service	COVID AND Interferon	11/5/2021 9:46PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	COVID AND Interferon	11/5/2021 9:47PM	0	0
CenterWatch	COVID AND Interferon	11/5/2021 9:48PM	0	0
WHO International Clinical Trials Registry Platform	COVID AND Interferon (Filter 01/01/2021 to 11/05/2021)	11/5/2021 9:54PM	53	14
chinaxiv.org	COVID Interferon	11/5/2021 10:41PM	0	0
Medrxiv.org	COVID AND Interferon AND Randomized Filter: April 10-November 11	11/5/2021 10:47PM	180	1
Biorxiv.org	COVID AND Interferon AND Randomized Filter: April 10-November 11	11/5/2021 11:21PM	251	0

Appendix 3. Characteristics of Included Studies

Title/Author	Study design	Country	Population	Intervention Group(s)	Control	Outcomes
Pan 2020 WHO Solidarity Trial Consortium N = 4,100	Adaptive Open-label RCT	30 countries Albania, Austria, Belgium, Finland, France, Ireland, Italy, Lithuania, Luxembourg, North Macedonia, Norway, Spain, Switzerland, Argentina, Brazil, Colombia, Honduras, Peru, Egypt, India, Indonesia, Kuwait, Lebanon, Malaysia, Pakistan, Philippines, Saudi Arabia, South Africa	Hospitalized COVID-19 patients Mild to severe	Interferon β-1a 44µg 3 doses subcutaneous over a period of 6 days OR 10µg intravenously daily for 6 days	Standard care	All-cause mortality Need for mechanical ventilation
Davoudi-Monferad 2020 N = 81	Open-label RCT	Iran	Confirmed covid-19 patients, >50% bilateral opacities on CT scan, <90% O2, hypotension, renal failure secondary to COVID-19, neurologic disorder 3 secondary to COVID-19, Thrombocytopenia Moderate to severe	Interferon β-1a 44µg/ml subcutaneously 3x a week for 2 consecutive weeks	Standard of care	All- cause mortality Clinical Improvement Time to clinical improvement Duration of hospitalization Duration of ICU stay Duration of mechanical ventilation Serious Adverse Events Adverse Events
Monk 2021 UK N = 98	Randomized, double-blind placebo-controlled, phase 2	UK	Confirmed COVID-19 patients Mild to severe	SNG001 (recombinant Interferon β-1a) 6 MIU via nebulizer once daily for up to 14 days	Placebo	All- cause mortality Clinical Improvement Progression to severe COVID-19 Serious Adverse Events Adverse Events
New Added Studies (As of November 5, 2021)						
Ader 2021 DisCoVeRy N = 293	Open-label Adaptive RCT	France	Hospitalized confirmed COVID-19 patients, pulmonary rales or crackels, O2 sat ≤94% or requiring supplemental oxygen Moderate to severe	IFN β-1a 44 µg subcutaneously on days 1, 3 and 6 PLUS Lopinavir/ritonavir PLUS standard of care	Standard of care	Clinical improvement Day 15 Clinical improvement Day 29 Time to clinical improvement All-cause mortality Day 29 Adverse events Serious Adverse events
Kalil 2021 N = 969	Randomized, double-blind placebo-controlled	Japan, Mexico, Singapore, South Korea, USA	Hospitalized confirmed COVID-19 patients one of the following criteria of lower respiratory tract infection: radiographic infiltrates on imaging, SpO2 ≤94%, or requiring O2 supplementation Mild to severe	Interferon beta-1a 44 µg 4 doses PLUS Remdesivir	Placebo PLUS Remdesivir	Time to clinical recovery day 28 Clinical improvement Time to clinical improvement Duration of supplemental oxygen Duration of hospitalization All-cause mortality Adverse event Serious adverse event

Darazam 2021 COVIFERON N = 60	Open-label RCT	Iran	Confirmed COVID-19 patients with RTPCR and CT scan, SpO2 ≤93% OR RR ≥24 on ambient air and acute symptoms (≤14 days) Moderate to severe	Experimental 1: IFN β-1a 44 µg subcutaneous day 1, 3 and 6 PLUS Hydroxychloroquine+ Lopinavir/ritonavir Experimental 2: IFN β-1b subcutaneous 0.25mg (8 MIU) PLUS Hydroxychloroquine+ Lopinavir/ritonavir	Hydroxychloroquine +Lopinavir/Ritonavir	Time to clinical improvement All-cause mortality day 21 Need for mechanical ventilation Adverse event Serious adverse event
Rahmani 2020	Open-label RCT	Iran	Confirmed COVID-19 patient with clinical signs/symptoms of pneumonia, SpO2 ≤93% or Pao2/FiO2 <300 SpO2/FiO2 < 315 and lung involvement in chest imaging Severe	IFN β-1b 250mcg subcutaneously every other day for two consecutive weeks	Standard of care	Time to clinical improvement ICU admission Need for mechanical ventilation Duration of hospitalization All-cause mortality
Bhushan 2021 N = 250	Open-label RCT	India	Confirmed COVID-19 patient, Moderate SpO2 90-94% RR ≥24, Pneumonia without signs of severe pneumonia Moderate	PEG IFN α2b 1µg/kg, Subcutaneous, single dose PLUS standard of care	Standard of care	Clinical improvement Viral negative conversion Need for supplemental oxygen Need for mechanical ventilation Time to resolution of symptoms Adverse events
Pandit 2021 N= 40	Open-label RCT (Phase II)	India	Confirmed COVID-19 patient, Moderate SpO2 90-94% RR15-30, Pneumonia without signs of severe pneumonia CRP < 16mg/L, IL-6 <100 pg/ml, D-dimer < 2 µg/ml, interferon γ, ferritin, TNF-α, IL-1β> upper limit of normal Moderate	PEG IFN α2b 1µg/kg, Subcutaneous, single dose PLUS standard of care	Standard of care	Clinical improvement Adverse events Need for supplemental oxygen Need for mechanical ventilation Duration of hospitalization Viral negative conversion

Appendix 4. Study Appraisal

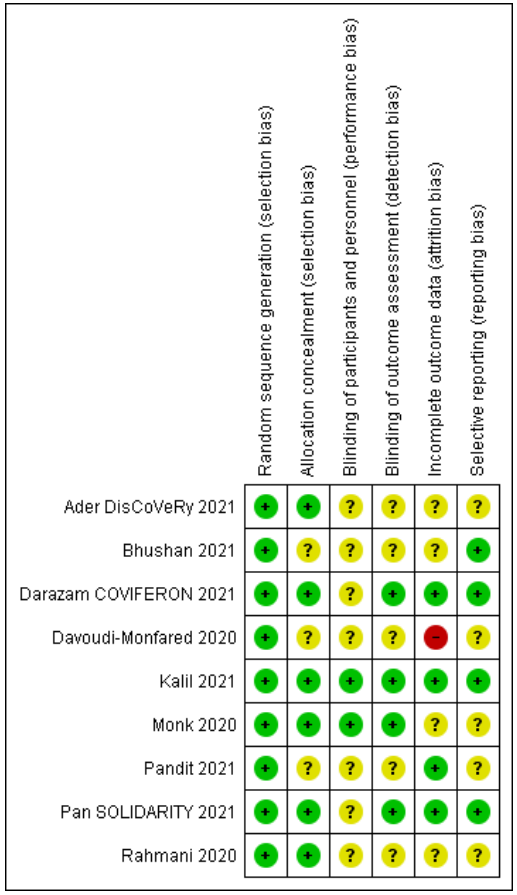

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Katherine O. Relato

Question: Interferon compared to Standard of Care for COVID-19

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon	Standard of care	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
9	Randomised trials	Very serious[a,b]	Not serious	Not serious	Serious[c]	None	306/2985 (10.3%)	282/2972 (9.5%)	**RR 1.06** (0.91 to 1.23)	**6 more per 1,000** (from 9 fewer to 22 more)	⊕◯◯◯ VERY LOW	CRITICAL
Need for mechanical ventilation												
4	Randomised trials	Very serious[a,b]	Not serious	Not serious	Serious[c]	None	240/2165 (11.1%)	240/2142 (11.2%)	**RR 0.97** (0.82 to 1.14)	**3 fewer per 1,000** (from 20 fewer to 16 more)	⊕◯◯◯ VERY LOW	CRITICAL
Clinical Improvement												
6	Randomised trials	Very serious[a,b]	Serious[d]	Not serious	Serious[c]	None	693/862 (80.4%)	683/870 (78.5%)	**RR 1.02** (0.98 to 1.06)	**16 more per 1,000** (from 16 fewer to 47 more)	⊕◯◯◯ VERY LOW	CRITICAL
Progression to severe disease												
1	Randomised trials	Serious[b]	Not serious	Not serious	Serious[c,e]	none	6/48 (12.5%)	11/50 (22.0%)	**RR 0.57** (0.23 to 1.42)	**95 fewer per 1,000** (from 169 fewer to 92 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events												
6	Randomised trials	Very serious[a,b]	Serious[f]	Not serious	Serious[c]	None	373/862 (43.3%)	315/869 (36.2%)	**RR 1.13** (0.93 to 1.38)	**47 more per 1,000** (from 25 fewer to 138 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Serious adverse events												
5	Randomised trials	Very serious[a,b]	Serious[g]	Not serious	Serious[c]	None	236/762 (31.0%)	234/739 (31.7%)	**RR 0.91** (0.71 to 1.18)	**28 fewer per 1,000** (from 92 fewer to 57 more)	⊕◯◯◯ VERY LOW	CRITICAL

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon	Standard of care	Relative (95% CI)	Absolute (95% CI)		
Duration of hospitalization												
1	Randomised trials	Very serious[a,b]	Not serious	Not serious	Serious[c]	None	42	39	-	MD **2.55 days higher** (0.92 lower to 6.02 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Viral negative conversion												
2	Randomised trials	Serious[a]	Not serious	Not serious	Not serious	None	119/140 (85.0%)	98/150 (65.3%)	**RR 1.30** (1.14 to 1.49)	**196 more per 1,000** (from 91 more to 320 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
ICU admission												
2	Randomised trials	Serious[a]	Not serious	Not serious	Serious[c,e]	None	43/73 (58.9%)	38/53 (71.7%)	**RR 0.77** (0.59 to 1.00)	**165 fewer per 1,000** (from 294 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

[a] performance and detection bias
[b] attrition and reporting bias
[c] wide confidence interval with possibility for benefit and harm
[d] I2=52%
[e] small number of events does not reach optimal information size
[f] I2=53%
[g] I2=78%

Appendix 6. Forest Plots

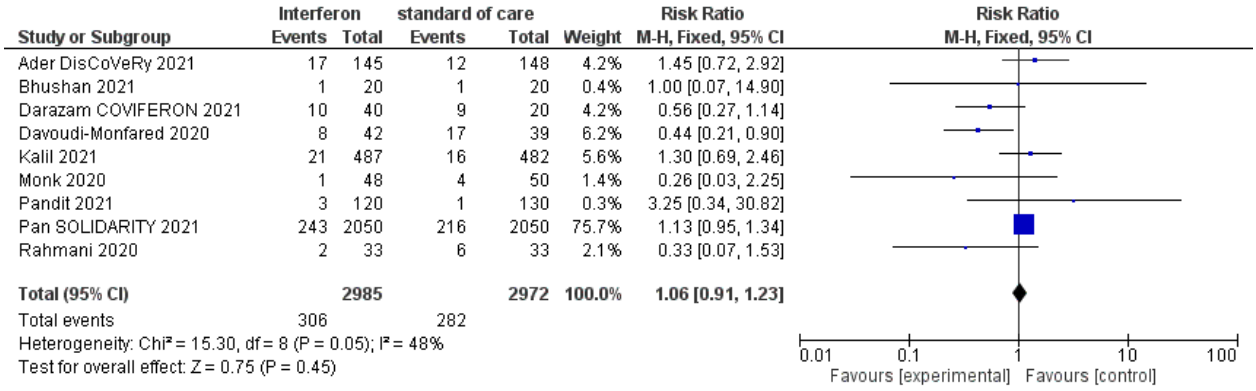

Figure 1.1. All-cause mortality

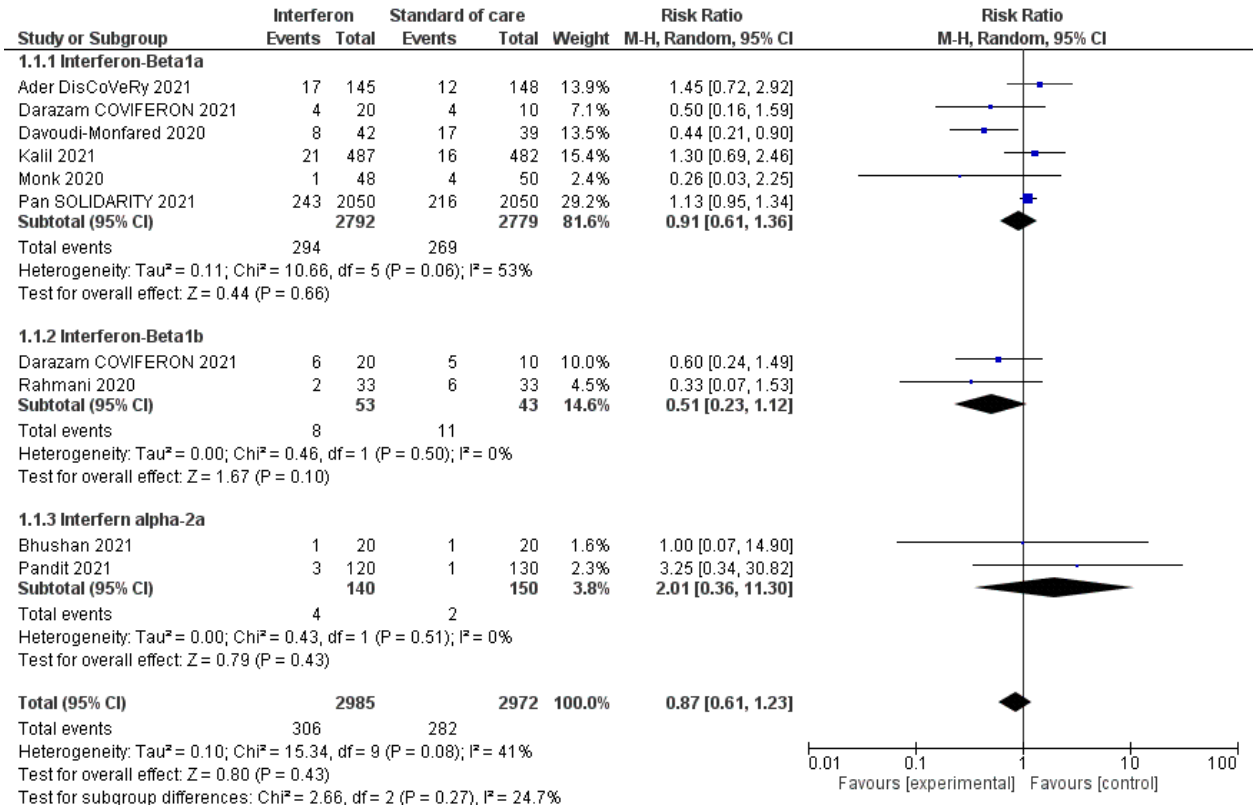

Figure 1.2 All-cause mortality subgroup based on types of interferon

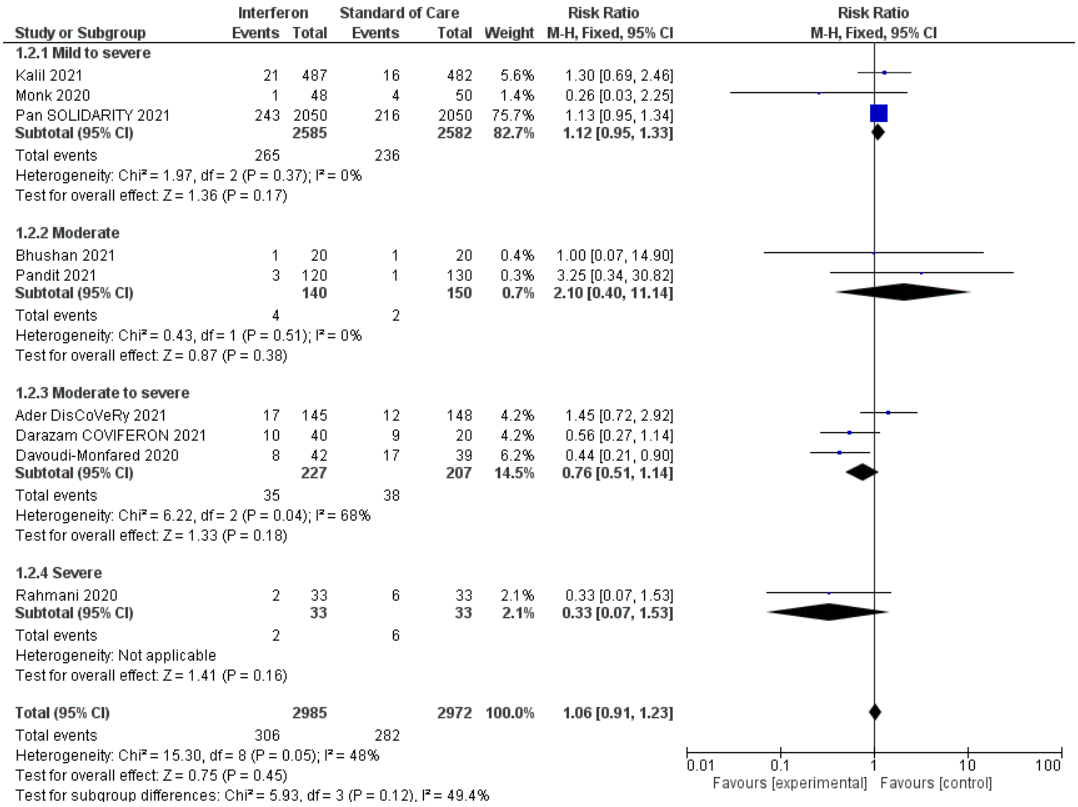

Figure 1.3 All-cause mortality subgroup based on severity

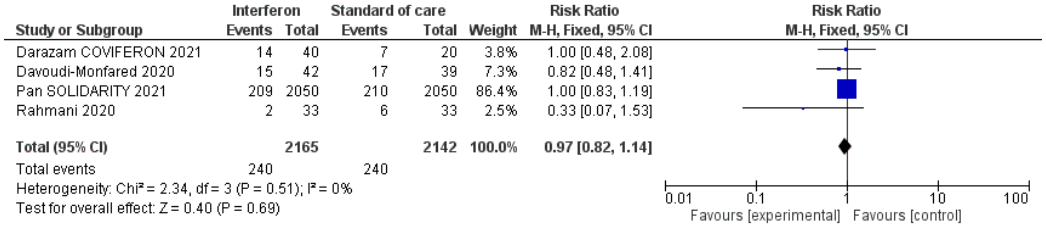

Figure 2. Need for mechanical ventilation

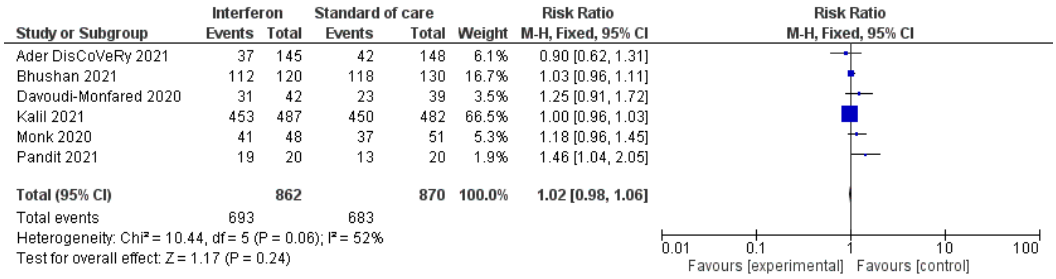

Figure 3. Clinical Improvement

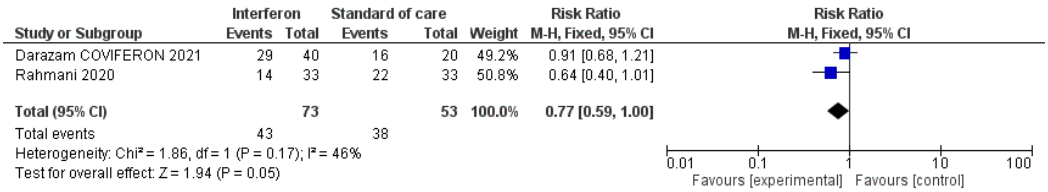

Figure 4. ICU admission

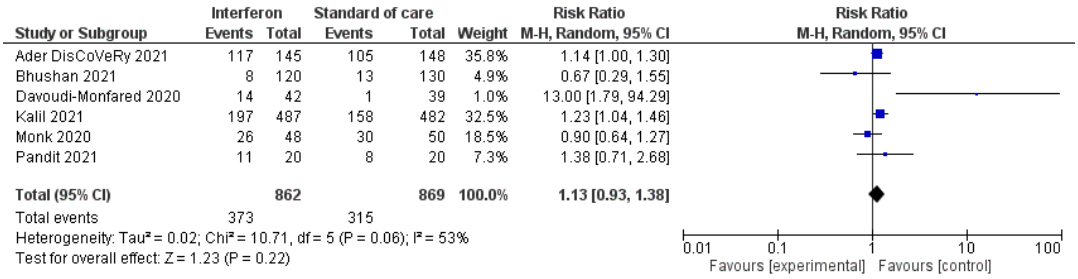

Figure 5. Adverse events

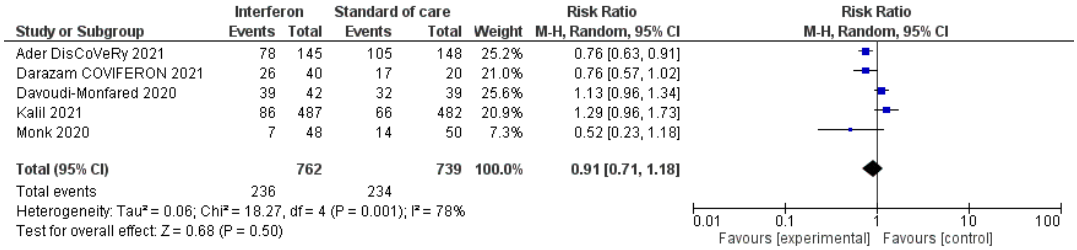

Figure 6. Serious Adverse Events

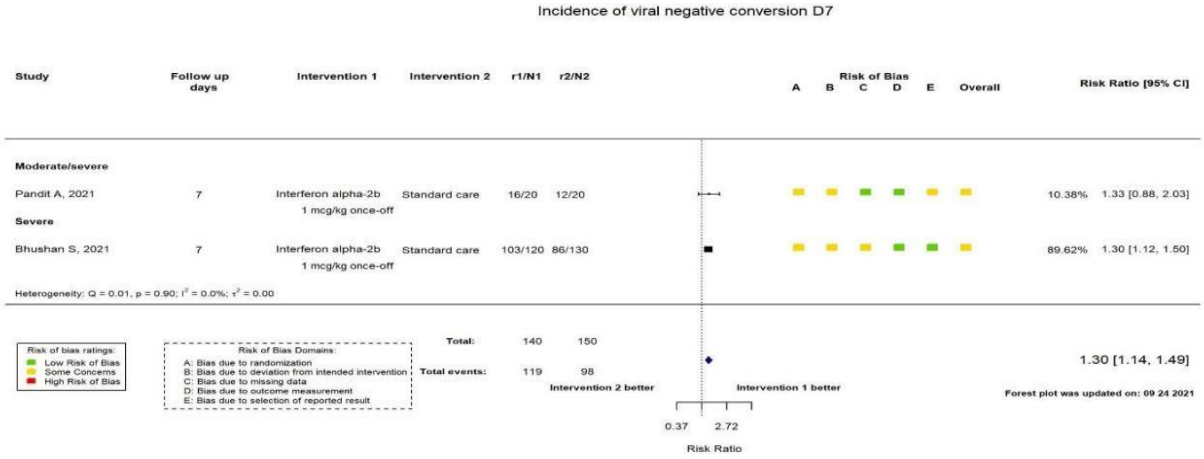

Figure 7. Viral negative conversion

Appendix 7. Pooled Results of Trials

Outcome	Pooled/ Relative Risk	95% CI	Certainty of evidence (GRADE)
All-cause mortality (9 RCTs, N = 5,957)	1.06	0.91 to 1.23	Very Low
Need for mechanical ventilation (4 RCTs, N = 4,307)	0.97	0.82 to 1.14	Very Low
Clinical improvement (6 RCTs, N = 1,732)	1.02	0.98 to 1.06	Very Low
Progression to severe disease (1 RCT, N = 98)	0.57	0.23 to 1.42	Low
Serious adverse event (5 RCTs, N = 1,501)	0.91	0.71 to 1.18	Very Low
Adverse events (6 RCTs, N = 1,731)	1.13	0.93 to 1.38	Very Low
Duration of hospitalization (1 RCT, N = 81)	MD= 2.55	-0.92 to 6.02	Very Low
ICU admission (2 RCTs, N = 126)	0.77	0.59 to 1.00	Low
Viral negative conversion (2 RCTs, N = 290)	1.30	1.14 to 1.49	Moderate

Appendix 8. Subgroup Analysis

	Pooled Relative Risk	95% CI	Certainty of Evidence
By type of Interferon			
Interferon beta-1a (6 RCTs, n = 5,581)	0.91	0.61 to 1.36	Very Low
Interferon beta-1b (2 RCTs, n = 106)	0.51	0.23 to 1.12	Low
Interferon alpha-2a (2 RCTs, n = 290)	2.01	0.36 to 11.30	Low
By severity			
Mild to severe (3 RCTs, n = 5,167)	1.12	0.95 to 1.33	Low
Moderate (2 RCTs, n = 290)	2.10	0.40 to 11.14	Low
Moderate to severe (3 RCTs, n = 254)	0.76	0.51 to 1.14	Very Low
Severe (1 RCT, n = 66)	0.33	0.07 to 1.53	Low

Appendix 9. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. IFN-beta 1b and Remdesivir for COVID19 Recruiting Phase 2	≥18 years hospitalized for confirmed SARS-CoV-2 infection with one of the following criteria: age 65 years or above, radiological evidence of pneumonia, oxygen desaturation <94% on room air, comorbidity including hypertension, diabetes, cardiovascular diseases, chronic obstructive lung disease, chronic liver diseases, chronic kidney diseases, malignancy, haematological diseases, rheumatological diseases, immunocompromised hosts and obesity (BMI > 30) (n=100)	Experimental: Interferon- beta 1b (16 million IU) and remdesivir 200mg IV day 1 then 100mg daily day 2-5 Control: Remdesivir 200mg IV day 1 then 100mg daily day 2-5	Primary: Clinical improvement (30 day)	Randomized, parallel, open label
2. Dual Therapy with Interferon Beta-1b and Clofazimine for COVID-19 Recruiting Phase 2	18 years or above hospitalized for virologic confirmed SARS-CoV-2 infection (n=81)	Experimental 1: Interferon beta-1b (16 million IU) SC day 1-3 and Clofazamine PLUS standard of care Experimental 2: Clofazamine PLUS standard of care Control: Standard of care	Primary: Clinical alleviation of symptoms (7 days)	Randomized parallel, open label
3. Clinical Study for the Treatment with Interferon-ß-1a (IFNß-1a) of COVID-19 Patients (INTERCOP) Terminated	Hospitalized with confirmed swab RT-PCR detection of SARS-CoV-2, X-ray and/or CT diagnosed pneumonia, Age >=18 years, Clinical status defined as 3, 4 or 5 on the 7-point ordinal scale (n=56)	Experimental: Interferon beta-1a SC 12 million IU 3 times a week at least 48 hrs apart for 2 weeks Control: Standard of care	Primary: Time to negative conversion of SARS-CoV-2 nasopharyngeal swab (day 29)	Randomized, parallel, open label
4. IFN Beta-1b and Ribavirin for Covid-19 Recruiting Phase 2	≥18 years hospitalized for confirmed SARS-CoV-2 infection. (n=96)	Experimental: Interferon beta-1b 16 million IU and Ribavirin PLUS standard of care Control: Standard of care	Primary: Clinical symptoms alleviation (7 days)	Randomized Parallel, open label
5. Inhaled Interferon α2b for the Treatment of Coronavirus Disease	Male subjects aged 18-50 years;In good state of health, determined by medical history, physical exam, and normal Active SARS-CoV-2 infection demonstrated by positive polymerase chain reaction (PCR) ≤ 5 days at enrollment;	Experimental 1a: Nebulized Interferon alpha 2b 2.5 million IU every 12 hours during 10 days Experimental 1b:	Primary: Treatment-emergent adverse events in healthy subjects [Time Frame: At the end of Phase 1 (11 days)	Randomized, parallel, open label

19 (COVID-19) (IN2COVID) Recruiting Phase 2	Symptomatic of mild or moderate COVID-19 for ≤ 5 days at enrollment (n=168)	Nebulized Interferon alpha 2b 5 million IU every 12 hours during 10 days Control Part 1: Placebo Experimental 2: nebulized Interferon alpha 2b 5 million IU every 12 hours for 10 days Control Part 2: Placebo	Change in perception of health status measured by EQ VAS in COVID-19 patients (28 days)	
6. Interferon Beta 1a in Hospitalized COVID-19 Patients (IB1aIC) Enrolling by invitation Phase 4	Age ≥ 50, COVID-19 Confirmed Cases, Tympanic Temperature of ≥37.5 AND at least one of the following: Cough, Sputum production, nasal discharge, myalgia, headache or fatigue) on admission, Time of onset of the symptoms should be acute (Days ≤ 10), SpO2 ≤ 88%, Respiratory Rate ≥ 24 (n=40)	Experimental: Interferon-β 1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine Control: Lopinavir / Ritonavir + Single Dose of HydroxychloroquinePlacebo	Primary: Time to clinical improvement (14 days)	Randomized, parallel, double-blind, placebo-controlled
7. Trial of Inhaled Anti-viral (SNG001) for SARS-CoV-2 (COVID-19) Infection Active, not recruiting Phase 2	A. Hospital setting: positive virus test for SARS-CoV-2, ≥18 years of age, admitted to hospital due to the severity of their COVID 19 disease, B. Home setting: positive virus test for SARS-CoV-2, ≥50 years of age at the time of consent, non-hospitalized patients from high-risk groups, defined as ≥65-years of age, or ≥50 years of age and with any risk factors (n=820)	Experimental: SNG001(interferon beta) inhalation using the I-neb device. Control: Placebo	Primary: Ordinal Scale for Clinical Improvement	Randomized, parallel, double-blind placebo-controlled
8. Pegylated Interferon - α2b With SARSCoV- 2 (COVID-19) Active not recruiting Phase 2	Male or non-pregnant females, ≥18 years of age at the time of enrolment. Has laboratory-confirmed SARS-CoV-2 infection, with SpO2 > 93% and respiratory rate <30 breaths/min,illness of any duration, and at least one of the following: Radiographic infiltrates by imaging, clinical assessment (evidence of rales/crackles or other clinical symptoms on exam) (n=40)	Experimental: Pegylated Interferon-α2b 1 mcg/kg on day 1 and day 8 after safety evaluations PLUS standard of care Control: Standard of care	Primary: Change in Clinical status of subject on a 7-point	Randomized parallel, open-label
9. Efficacy and Safety of IFN-α2β in the Treatment of Novel Coronavirus Patients Not yet recruiting Early Phase 1	Age ≥ 18 years; Clinically diagnosed patients with new type of coronavirus pneumonia, including: in accordance with the criteria for suspected cases, have one of the following etiology evidence: RT-PCR, Sequencing of viral genes in respiratory specimens or blood specimens, highly homologous to known new coronavirus. The time interval between the onset of symptoms and random enrollment is within 7 days (n=328)	Experimental: Recombinant human interferon α1β 10ug Bid was administered by nebulization for 10 days plus standard of care Control: Standard of care	Primary: Incidence of side effects	Randomized parallel, open label

10. Human Intravenous Interferon Beta-Ia Safety and Preliminary Efficacy in Hospitalized Subjects with CoronavirUS (HIBISCUS) Recruiting Phase 2	Age ≥18 years, Positive SARS-CoV-2 test by PCR, Admission to hospital with respiratory symptoms of COVID-19 requiring hospital care and oxygen supplementation (≤ 8L/min), Symptom onset no more than 7 days prior to hospital arrival (n=140)	Experimental: IFN beta-1a 10 µg as an IV bolus for 6 days while hospitalised Control: Dexamethasone	Clinical status at Day 14 (first day of study drug is Day 1) as measured by WHO 9-point ordinal scale	Randomized, parallel, double-blind
11. Treatment of COVID-19 by Nebulization of Inteferon Beta 1b Efficiency and Safety Study (COV-NI) Recruiting Phase 2	≥ 18 years old, confirmed SARS-CoV-2 infection as determined by PCR < 96 h (at initial diagnosis or persistent carriage <96 h), Hospitalized patient with COVID-19 requiring oxygen therapy, And targeting in phase B: under oxygen therapy such as nasal cannula/mask or non-invasive ventilation with paO2/FiO2 > 200 mmHg, hospitalized for less than 7 days, patients with symptoms for less than 10 days or RT-PCR (<96h) with Cycle Threshold < 25	Experimental: Inhaled interferon (9.6 MUI x2/d for 48 hours, then 9.6 MUI x1/d for 8 to 16 days or discharge), in addition to standard care. Control: Placebo	Oxygen requirement score at day 0 Oxygen requirement score at day 15 Variation oxygen requirement score between day 0 and day15	Randomized, double-blind
12. Public Health Emergency: SOLIDARITY TRIAL Philippines Active not recruiting	Age ≥18 hospitalized with: probable or confirmed COVID-19 regardless of severity, Not already receiving any of the study drugs, without known allergy or contraindications to any of the study drugs (in the view of the physician responsible for their care), and without anticipated transfer within 72 hours to a non-study hospital.	Experimental 1: Remdesivir with SoC Experimental 2: Hydroxychloroquine with Soc Experimental 3: Lopinavir/Ritonavir with SoC Experimental 4: Acalabrutinib with SoC Experimental 5: Interferon beta-1a with SoC Control: Standard of care	Primary: All-cause mortality	Randomized parallel, adaptive open label
13. Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP) Recruiting Phase 4	Adult patient admitted to an ICU for severe CAP within 48 hours of hospital admission with: symptoms or signs or both that are consistent with lower respiratory tract infection AND radiological evidence of new onset consolidation Up to 48 hours after ICU admission, receiving organ support with one or more of: Non-invasive or Invasive ventilatory support; receiving infusion of vasopressor or inotropes or both	Experimental 1: Interferon B1a 10 ug IV bolus once daily for 6 days or until ICU discharge Others: Hydrocortisone, Ceftriaxone, Moxifloxacin/Levofloxacin, Piperacillin-tazobactam, Ceftaroline, Amoxicillin-clavulanate, Macrolide, Oseltamivir, Lopinavir/ritonavir, Hydroxychloroquine, anakinra, tocilizumab, sarilumab, vitamin c, therapeutic anticoagulation	Primary: All-cause mortality Days alive and not receiving organ support in ICU	Randomized Factorial open label
14. Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial (CATCO)	≥ 18 years of age, laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or Hospitalized at a participating centre (n= 440)	Experimental 1: Interferon Beta 1a plus standard supportive care Experimental 2: Remdesivir plus standard supportive care	Primary: all-cause mortality	Randomized, parallel, open label

Recruiting Phase 2		Control: Standard supportive care		
15. Study to Assess Efficacy and Safety of Inhaled Interferon-β Therapy for COVID-19 (SPRINTER) Recruiting Phase 3	Admitted to hospital due to the severity of their COVID-19, Positive virus test for SARS-CoV-2, Require oxygen therapy via nasal prongs or mask (WHO OSCI score of 4)	Experimental: inhaled interferon B (SNG001) once daily Control: Placebo	Primary: Time to hospital discharge Time to recovery	Randomized, Parallel, Placebo controlled, double blind
15. World Health Organization (WHO) COVID-19 Solidarity Trial for COVID-19 Treatments (SOLIDARITY) Not yet recruiting Phase 3	Consenting adults (age ≥18) hospitalized with definite COVID-19	Experimental 1: Remdesivir Experimental 2: Acalabrutinib Experimental 3: Interferon B1a IV 10 ug once daily for 6 days if oxygen dependent or subcutaneously at 44 ug Day 1, Day 3, and Day 6 Control: Standard of Care	Primary: all-cause mortality	Randomized parallel open label
16. Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease 2019 (COVID-19) Trial (ACTCOVID19) Recruiting Phase 3	Symptomatic and laboratory-confirmed diagnosis of COVID-19, ≥18 years old, high risk: either age ≥70 or one of the following: male; obesity (BMI ≥30); chronic cardiovascular, respiratory or renal disease; active cancer; diabetes; Within 7 days (ideally 72 hours) of diagnosis, or worsening clinically	Experimental 1: Colchicine Experimental 2: ASA Experimental 3: Rivaroxaban Experimental 4: Interferon Beta 0.25mg days 1, 3, 5, 7 Control: Standard of care	Primary: Outpatients: Hospital Admission or Death Inpatients: Invasive mechanical ventilation or mortality	Randomized, parallel, open-label
17. Efficacy and safety of Interferon beta-1-a in mild to moderate COVID-19 Recruiting	COVID-19, based on reverse transcriptase-polymerase chain reaction (rt-PCR), patients with mild to moderate COVID-19 within 48 hours of the onset of the symptoms	Experimental: Interferon B-a 12 million units SC very other day for 3 doses plus acetaminophen and antihistamine Control: Acetaminophen and antihistamine	Primary: BNody temp, DBP, level O2 saturation, PR, RR SBP	Randomized, Open label, parallel
18 Evaluation of the effect of interferon beta-1b in the treatment of COVID-19 Recruiting	Individuals over 18 years of age whose covid-19 disease has been confirmed by PCR test and clinically severely ill, o2sat below 90% despite receiving oxygen, severe bilateral pulmonary involvement	Experimental: Hydroxychloroquine and Kelatra with interferon beta-one B (at a dose of 250 micrograms or 8 million subcutaneously every other day Control: Hydroxychloroquine and kelatra	Primary: Changes in liver enzyme, oxygen saturation, respiratory rate, duration of hospitalization, LDH levels, Moratlity rate	Randomized, open label, parallel

19. Using interferon to treat COVID-19 Recruiting	Adult over 18 years, Clinical diagnosis of COVID-19	Experimental 1: Interferon beta plus standard of care Experimental 2: Interferon alpha plus standard of care Control: Standard of care plus placebo	Primary: Blood gas level, body temperature, respiratory rate, FiO2	Randomized, placebo controlled, double-blind
20. Efficacy evaluation of inhalation therapy (nasal spray) of Interferon Beta-1a in hospitalized Covid-19 patients Recruiting	Patients who have Covid-19 based on the CT-scan or RT-PCR findings, Hospitalized patients, age between 20-65	Experimental: Interferon B1a nasal spray every 6 hours for 7 days and standard of care Control: Placebo	Primary: Viral negative conversion	Randomized, double blind placebo controlled
21. Investigating the efficacy and safety of Interferon Beta1a nasal spray in controlling the symptoms of patients with COVID-19 Recruiting	18 years old or more, clinical symptoms (dry cough, shortness of breath, fever) confirm COVID-19; confirmed diagnosis of COVID-19, less than 7 days have passed since the onset of symptoms.	Experimental: Interferon Beta 1a nasal spray 1 puff in each nostril every 6 hours, for 14 days Control: Standard of care	Primary: Clinical improvement	Randomized, open label, parallel
22. Interferon beta 1b in COVID-19 Recruiting	All adult patients with highly suspected or confirmed COVID-19 who are candidate for hospitalization and starting therapeutic regimen with lopinavir/ritonavir and hydroxychloroquine	Experimental: Hydroxychloroquine, lopinavir/ritonavir and interferon beta 1b Control: Lopinavir/ritonavir hydroxychloroquine	Primary: Clinical improvement	Randomized, open label parallel
23. Efficacy of dexamethasone, IV-IG and Interferone beta for treatment of patients with severe COVID-19 Recruiting	Age 18-70 years Sever COVID19 disease with the following criteria: SPpO2 below 90% and respiratory rate higher 24 per minute; Involvement of more that 50% of lung in CT-scan	Experimental: IVIg, Dexamethasona and Interferone beta Control: Standard of care	Primary: Oxygen improvement	Randomized, open label, parallel

Q20. Among patients with COVID-19, should fluvoxamine be used for treatment?

As of 8 November 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of fluvoxamine among COVID-19 patients. (*Low certainty of evidence)*

Consensus Issues
Current evidence showed that although fluvoxamine appeared to reduce the need for emergency room visit or hospitalization, there was inconclusive evidence in terms of other critical outcomes such as all-cause mortality, clinical deterioration, adverse events, and serious adverse events. The sample size of the two randomized controlled trials may still be too small to reach a level of significance, precluding any recommendation to be made. As of writing, there are 9 ongoing clinical trials, results of which may further elucidate on fluvoxamine's effectiveness in the treatment of COVID-19.

KEY FINDINGS

Two (2) published randomized controlled trials (RCTs) (N = 1,649) investigated on the effectiveness of fluvoxamine compared to placebo among confirmed symptomatic non-hospitalized COVID-19 patients compared. Results showed significant reduction in emergency room visits and the need for hospitalization. There was inconclusive evidence in terms of other critical outcomes such as all-cause mortality, clinical deterioration, viral negative conversion, adverse events, and serious adverse events.

INTRODUCTION

Fluvoxamine is a selective serotonin re-uptake inhibitor used to treat obsessive compulsive disorder. The anti-viral and anti-inflammatory roles of fluvoxamine have been recently studied. The potential role of fluvoxamine on the treatment of COVID-19 include a decrease in serotonin levels leading to decreased platelet aggregation, reduced mast cell degranulation thus reducing cytokine release, interference in the lysosomal activity and entry of the virus, inhibition of hyperinflammation by sigma-1 receptor affinity, and mitigation of inflammation by increasing melatonin.[1]

Common adverse reactions associated with fluvoxamine include nausea, insomnia, somnolence, headache, asthenia, dizziness, dry mouth, and vomiting. It should also be used with caution when used with other serotonergic drugs to avoid serotonin syndrome.[2]

REVIEW METHODS

A systematic search was done last October 10, 2021 to check for trials in COVID-NMA living data. Trials found in the COVID-NMA were included. Search was done in Medline, Cochrane Library, and Google scholar using free text, MeSH terms and advance search using the terms coronavirus infections, COVID-19 severe acute respiratory syndrome coronavirus 2, and fluvoxamine. Ongoing trials screening was done in various trial registries. Medrxiv, chinaxiv and biorxiv was also searched for preprints. RCTs on fluvoxamine as treatment for COVID-19 compared to placebo were

included. No limits were placed on age, severity and dose. In order to compute for confidence interval, we imputed 1 if a study has no event in the treatment arm.

RESULTS

Two (2) published RCTs (N = 1,649) evaluated the effectiveness of fluvoxamine among confirmed symptomatic non-hospitalized COVID-19 patients compared to placebo. Both trials reviewed were also included in the COVID-NMA Living Data.[3,4]

Appendix 3 summarizes the characteristics of the included studies. One study was done in the US [3] and the other was done in Brazil.[4] Study participants in both trials included confirmed COVID-19 symptomatic patients aged 18 years old and above. One of the studies [4] specified at least one co-morbidity in the inclusion criteria. Both studies excluded patients being referred for hospitalization at the start of the study.

The overall quality of evidence was rated low due to very serious imprecision on one critical outcome (clinical deterioration) and serious imprecision and inconsistency on another critical outcome (serious adverse events). Both trials have no serious risk of bias. The risk of bias summary is shown in Appendix 4. The GRADE evidence summary is in Appendix 5.

Fluvoxamine significantly reduced the need for hospitalization (RR 0.75, 95% CI 0.57-0.99; I^2 48%; 2 RCTs, 1,649 participants) [3,4] and the need for emergency room visits (RR 0.73, 95% CI 0.62-0.86; 1 RCT, 1,497 participants) among symptomatic COVID-19 patients compared to placebo.[4] However, fluvoxamine had no benefit on all-cause mortality (RR 0.69, 95% CI 0.38-1.27) [4], clinical deterioration at day 15 (RR 0.70, 95% CI 0.00-1.21) [3], and viral negative conversion at day 7 (RR 0.70, 95% CI 0.48-1.04) compared to placebo.[4]

Safety

There was no significant difference on adverse events (RR 1.00, 95% CI 0.77-1.29) and serious adverse events (RR 0.49, 95% CI 0.10-2.27) between fluvoxamine and placebo. Common adverse events reported were loss of sense of smell, fatigue, body aches, cough, subjective fever, and loss of appetite. Serious adverse events reported were dehydration, exacerbation of COVID-19, respiratory failure, and pneumonia.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
US-NIH Guidelines as of October 7, 2021 [5]	There is insufficient evidence to recommend either for or against the use of fluvoxamine for the treatment of COVID-19.
Australian Guideline on COVID-19 as of October 8, 2021 [6]	Fluvoxamine for the treatment of COVID-19 should only be used in research settings.
WHO Living Guidelines [7]	No statement on the use of fluvoxamine for the treatment of COVID-19.
Infectious Diseases Society of America (IDSA) [8]	

RESEARCH GAPS

As of October 10, 2021, there are nine (9) ongoing trials on fluvoxamine registered on *clinicaltrials.gov* and EU Clinical Trials Register. One trial is already completed and awaiting results (Appendix 8).

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 7)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (7)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate	Small (5)	Uncertain (2)	Trivial		• Fluvoxamine significantly reduced the need for hospitalization (RR 0.75, 95% CI 0.57-0.99; 2 RCTs, 1,649 participants) and need for emergency room visits (RR 0.73, 95% CI 0.62-0.86; 1 RCT, 1,497 participants) among symptomatic COVID-19 patients compared to placebo. • However, fluvoxamine had no benefit on all-cause mortality (RR 0.69, 95% CI 0.38-1.27), clinical deterioration at day 15 (RR = 0.70, 95% CI 0.00-1.21), and viral negative conversion at day 7 (RR 0.70, 95% CI 0.48-1.04) compared to placebo.
Harm	Large	Small (4)	Uncertain (3)	Varies			• There was no significant difference on adverse events (RR 1.00, 95% CI 0.77-1.29) and serious adverse events (RR 0.49, 95% CI 0.10-2.27) between fluvoxamine and placebo
Certainty of Evidence	High	Moderate (1)	Low (4)	Very low (2)			• The overall quality of evidence is rated low due to very serious imprecision on one critical outcome(clinical deterioration) and serious imprecision and inconsistency on another critical outcome (serious adverse events)
Balance of effects	Favors drug (3)	Does not favor drug (2)	Uncertain (2)				• There appears to be trend towards benefit (need for hospitalization, need for ER visit) without significant harm • There is still inconclusive evidence in terms of other critical outcomes (all-cause mortality, clinical deterioration, adverse events and serious adverse events)
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate cost (7)	Negligible cost	Moderate savings	Large savings	• The local price of fluvoxamine is at P75.25 for 50mg/tab. Taken orally, two to three times a day for 10 to 15 days at a maximum dose of 300 mg/day. • The total cost of treatment per patient would be P 6,772.50
Certainty of evidence of required resources	No included studies (3)	Very low (2)	Low (1)	Moderate (1)	High		• The cost of fluvoxamine was quoted from a private tertiary hospital's drug price list available online
Cost effectiveness	No included studies (4)	Favors the comparison (1)	Does not favor either the intervention or the comparison (2)	Favors the intervention			
Equity	Uncertain (3)	Reduced (1)	Probably no impact (1)	Increased (2)			
Acceptability	Uncertain (5)	No	Yes (2)				
Feasibility	Uncertain (3)	No	Yes (4)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Fluvoxamine	October 9, 2021 8:47 PM	30	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Fluvoxamine	October 9, 2021 9:29 PM	13	10
COVID-NMA Initiative	Fluvoxamine	October 9, 2021 9:18 PM	2	2
Google Scholar	Fluvoxamine AND COVID-19 AND “randomized trial” Custom range: year 2020-2021	October 9, 2021 10:47PM	108	2
ClinicalTrials.gov	COVID-19, COVID-19 Pneumonia, Investigational Trials, Fluvoxamine	October 9, 2021 11:09 PM	7	7
Chinese Clinical Trial Registry	COVID, Fluvoxamine, Randomly Sampling	October 9, 2021 11:24 PM	0	0
EU Clinical Trials Register	COVID AND Fluvoxamine	October 9, 2021 11:25 PM	1	1
Republic of Korea - Clinical Research Information Service	COVID, fluvoxamine, investigational	October 9, 2021 11:29 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	COVID AND Fluvoxamine	October 9, 2021 11:30 PM	0	0
CenterWatch	COVID AND fluvoxamine	October 9, 2021 11:32 PM	0	0
WHO database COVID-19 studies	COVID AND fluvoxamine	October 9, 2021 11:38 PM	16	2
chinaxiv.org	COVID AND fluvoxamine	October 9, 2021 11:40 PM	0	0
Medrxiv.org	COVID AND fluvoxamine	October 9, 2021 11:44 PM	18	1
Biorxiv.org	COVID AND fluvoxamine	October 9, 2021 11:46 PM	13	0

Appendix 3. Characteristics of Included Studies

Title/Author	Study design	Country	Population	Intervention Group(s)	Control	Outcomes
Lenze 2020	Double-blind, placebo-controlled, randomized trial	United States of America	≥18 years old, outpatient, confirmed, symptomatic (N = 152)	Fluvoxamine 50mg, then 100mg twice daily for 2 days, then 100mg 3 times daily through day 15	Placebo	• Clinical deterioration • Clinical Status on 7-point scale • Adverse event • Serious adverse events
Reis 2021 TOGETHER Trial	Adaptive Placebo controlled randomized trial	Brazil	≥18 years old, with acute symptomatic confirmed COVID-19, at least one additional criterion for comorbidity (N = 1,497)	Fluvoxamine 100mg twice daily for 10 days	Placebo	• Extended emergency room observation • Hospitalization • Viral clearance • Time to clinical improvement • Number of days with respiratory symptoms • Time to hospitalization • Clinical deterioration • All-cause mortality • Days in hospital or mechanical ventilator • Adverse events

Appendix 4. Study Appraisal

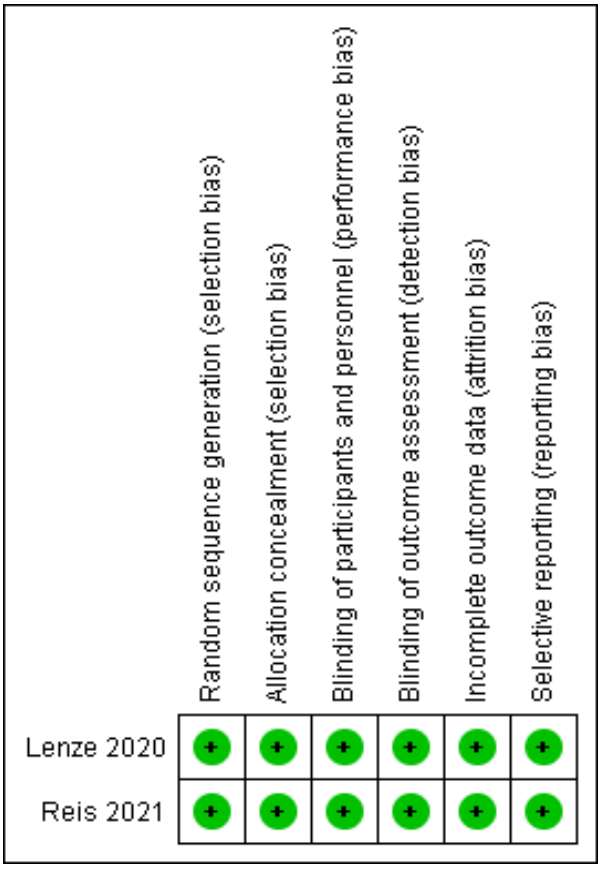

Figure 1. Risk of bias summary table

Appendix 5: GRADE Evidence Profile

Author(s): K. Relato; S.
Question: Fluvoxamine compared to standard of care in COVID-19
Bibliography: https://covid-nma.com/

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluvoxamine	Standard of care alone	Relative (95% CI)	Absolute (95% CI)	CERTAINTY	IMPORTANCE
Clinical Deterioration												
1	Randomised trials	Not serious	Not serious	Not serious	Vvery serious[a,b,c]	None	1/80 (1.3%)	7/72 (9.7%)	**RR 0.07** (0.02 to 1.02)	**85 fewer per 1,000** (from – fewer to 17 more)	⊕⊕◯◯ LOW	CRITICAL
All-cause mortality at Day 28												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[c]	None	17/741 (2.3%)	25/756(3.3 %)	**RR 0.69** (0.38 to 1.27)	**10 fewer per 1,000** (from 21 fewer to 9 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Need for hospitalization												
2	Randomised trials	Not serious	Not serious	Not serious	Serious[c]	None	76/821 (9.3%)	103/828 (12.4%)	**RR 0.75** (0.57 to 0.99)	**31 fewer per 1,000** (from 53fewer to 1 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Emergency room visit												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	180/741 (24.3%)	251/756 (33.2%)	**RR 0.73** (0.62 to 0.86)	**90 fewer per 1,000** (from 126 fewer to 46 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Viral Negative Conversion												
1	Randomised trials	Not serious	Not serious	Not serious	Serious [c]	None	40/741 (5.4%)	57/756 (7.5%)	**RR 0.70** (0.48 to 1.04)	**23 fewer per 1,000** (from 39 fewer to 3 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Adverse Events												

2	Randomised trials	Not serious	Not serious	Not serious	Serious[c]	None	103/821(12.5.0%)	104/828 (12.6%)	**RR 1.00** (0.77 to 1.29)	**0 fewer per 1,000** (from 29 fewer to 36 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious Adverse Events												
2	Randomised trials	Not serious	Serious [d]	Not serious	Serious [c]	None	78/821 (9.5%)	102/828(12.3.7%)	**RR 0.49** (0.10 to 2.27)	**63 fewer per 1,000** (from 111fewer to 156 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanation

[a] small number of events does not reach optimal information size

[b] low sample size

[c].wide confidence interval with possibility for benefit and harm.

[d] I^2 = 60%

Appendix 6. Forest Plots

Figure 1. Need for hospitalization

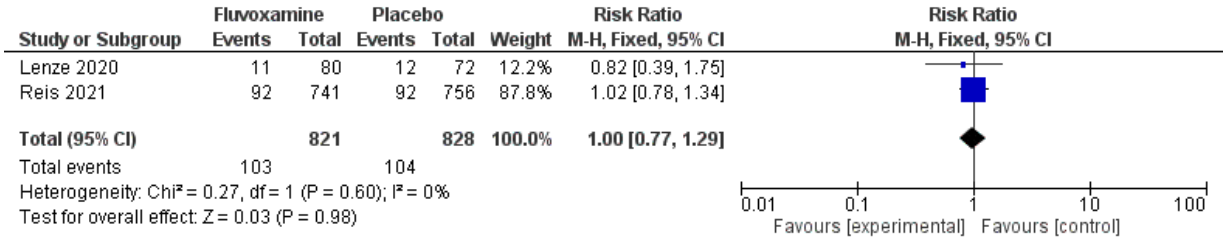

Figure 2. Adverse Events

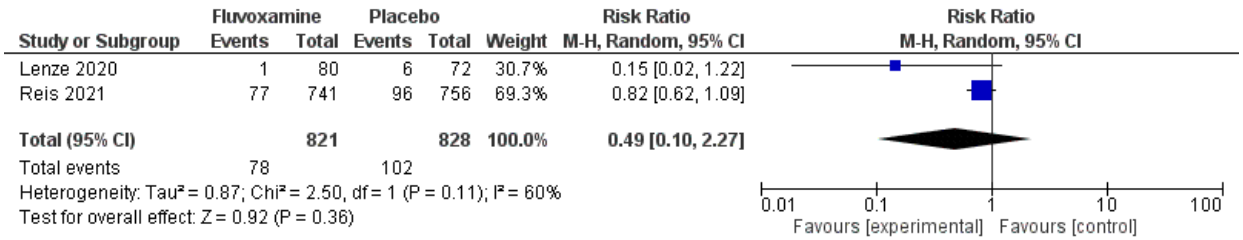

Figure 3. Serious Adverse Events

Appendix 7. Pooled Results of Trials

Outcome	Pooled/ Relative Risk	95% CI	Certainty of evidence (GRADE)
Clinical Deterioration (1 RCT, N = 152)	0.07	0.00 to 1.21	Low
All-cause mortality (1 RCT, N = 1497)	0.69	0.38 to 1.27	Moderate
Need for hospitalization (2 RCTs, N = 1649)	0.75	0.57 to 0.99	Moderate
Emergency Room visit (1 RCT, N = 1497)	0.73	0.62 to 0.86	High
Viral Negative Conversion (1 RCT, N = 1497)	0.70	0.48 to 1.04	Moderate
Adverse events (2 RCTs, N = 1649)	1.00	0.77 to 1.29	Moderate
Serious adverse events (2 RCTs, N =1649)	0.49	0.10 to 2.27	Low

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Appendix 8. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Effect of fluvoxamine medicine on cytokine level of COVID-19 patients, hospitalized in ICU ward **Completed awaiting result**	Hospitalized in ICU due to COVID-19	Experimental: Fluvoxamine 50mg daily up to 300mg/week Control: Standard of care	Primary: CRP, ESR, IL-6 level upon discharge from ICU	Randomized control open label
2. Fluvoxamine for Adults With Mild to Moderate COVID-19 Suspended	Laboratory-confirmed SARS-CoV-2 patients who have mild to moderate symptoms related to COVID-19	Experimental: Fluvoxamine 50mg then 100mg twice daily until discharge or for approximately 10 days Control: Placebo	Primary: Time to clinical deterioration	Randomized placebo-control single blind
3. Fluvoxamine for Early Treatment of Covid-19 (Stop Covid 2) Recruitment completed	>/= 30 years old, not currently hospitalized, proven SARS-CoV-2 positive, currently symptomatic, one of the following risk factors for clinical deterioration: age≥40, racial/ethnic group African-American, Hispanic, or Native American or 1+ of the following medical conditions which increased risk for developing moderate-severe COVID illness: obesity, hypertension, diabetes, heart disease, lung disease, immune disorder	Experimental: Fluvoxamine 50mg once daily then 100mg twice daily approximately 15 days Control: Placebo	Primary: Time to clinical deterioration	Randomized placebo controlled double-blind
4. Repurposed Approved and Under Development Therapies for Patients With Early-Onset COVID-19 and Mild Symptoms Recruiting	>/=18 years old, flu-Like symptoms < 07 days, at least ONE enhancement criteria: 50 years; Diabetes mellitus, Systemic arterial hypertension, cardiovascular diseases, Symptomatic lung disease, Fever > 38 C at baseline, Obesity, Transplanted patients, chronic kidney disease, Immunosuppressed patients/ using corticosteroid therapy, Patients with a history of cancer Patients with important limitation of daily activities, positive rapid test for SARS-CoV2 antigen performed on occasion of the screening or patient with a positive SARS-CoV2 diagnostic test within 07 days of the onset of symptoms.	Experimental: Group 1: Fluvoxamine 100mg twice daily through day 9 Group 2: Doxazosin Group 3: Ivermectin Group 4: Peg INF lambda Group 5: Peg INF Beta Control: Placebo	Primary: Need for emergency care and clinical worsening 28 days Need for hospitalization	Randomized double blind placebo controlled
5. Effect of Combined Fluvoxamine with Favipiravir versus Favipiravir Monotherapy in Prevention of Clinical Deterioration among mild to moderate COVID-19 patients Monitoring by Telemedicine in Virtual Clinic: Open-label Randomized Controlled Trial *Not yet recruiting*	>/= 18 years old, confirmed COVID-19 with 1 or more of the symptoms, Asymptomatic COVID-19, accept to perform chest CT, Nasopharyngeal swab or oropharyngeal swab detected ORF1 a/b gene E gene from SARS-CoV-2 PCR with Ct value, does not meet WHO criteria for hospitalization	Experimental: Fluvoxamine 100mg daily for 10 days plus Favipavir Control: Favipavir	Primary: Clinical deterioration	Randomized open-label
6. Fluvoxamine Administration in Moderate SARS-CoV-2 (COVID-19) Infected Patients	18-70 years of age, Hospitalized patients with confirmed SARS-CoV-2 by PCR, Moderate cases (each of the followings met): showing dyspnea but not manifest respiratory distress, respiratory rate 22-29 / min; oxygen saturation at rest > 93%;	Experimental: Fluvoxamine 200mg daily over 74 days Control: Placebo	Primary: Time to clinical recovery	Randomized double blind placebo-controlled

Recruiting	with or without the need for oxygen supplementation; pneumonia on medical imaging with pulmonary infiltrates occupying ≤ 50% of the lung-fields			
7. A randomized, double-blind, placebo-controlled, adaptive-design study to assess the safety and efficacy of daily 200 mg fluvoxamine as add-on therapy to standard of care in moderate severity COVID-19 patients *Recruiting*	18-80 years of age, hospitalized patients with confirmed SARS-CoV-2, Moderate cases (at least one of the following criteria is met): dyspnea/tachypnea, respiratory rate 22-29 / min; with the need for oxygen supplementation; pulmonary infiltrates on medical imaging	Experimental: Fluvoxamine 50mg Control: Placebo	Primary: Time to clinical recovery	Randomized double blind placebo-controlled
8. ACTIV-6: COVID-19 Study of Repurposed Medications Recruiting	Age ≥ 30 years old, Confirmed SARS-CoV-2 infection within 10 days of screening, Two or more current symptoms of acute infection for ≤7 days: fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, new loss of sense of taste or smell	Experimental: Group 1: Ivermectin Group 2: Fluvoxamine 50mg twice daily for 10 days Group 3 Fluticasone Control: Placebo	Primary: Number of hospitalizations Number of deaths Number of symptoms	Randomized double blind placebo controlled
9. COVID-OUT: Early Outpatient Treatment for SARS-CoV-2 Infection (COVID-19) *Recruiting*	30 to 85 years old, positive RT PCR within 3 days, no known history of confirmed SARS-CoV-2 infection, BMI >= 25kg/m2, GFR>45ml/min within 2 weeks for patients >75 years old, or with history of heart, kidney, or liver failure.	Experimental: Group 1: Metformin Group 2: Ivermectin Group 3: Fluvoxamine 50mg twice daily for 14 days Group 4: Fluvoxamine and Metformin Group 5: Metformin and Ivermectin Control: Placebo	Primary: Decreased oxygenation Emergency department utilization	Randomized double blind placebo-controlled

Q21. Among patients with COVID-19, should bamlanivimab in combination with etesivimab be used for treatment?

As of 12 October 2021

RECOMMENDATION

We suggest the use of bamlanivimab and etesevimab combination therapy as treatment for mild to moderate, non-hospitalized COVID-19 patients with at least 1 risk factor* for progression to severe disease. *(Low certainty of evidence, Weak recommendation)*

*Risk factors for severe COVID-19: age ≥65 years, body-mass index ≥35 kg/m^2, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions

Consensus Issues

The panel favoured the use of bamlanivimab and etesevimab among non-hospitalized COVID-19 patients who are at risk for severe disease, based on the results of 2 randomized controlled trials that showed net potential benefit in terms of COVID-19 related hospitalizations and all-cause mortality, reduction in total symptom score, and number of days to symptom resolution, with no significant difference in terms of adverse events. Concern regarding the drug's effectivity against variants was raised by one of the panelists. As of writing, the drug has no emergency use authorization from the Philippine FDA, thus may only be used in the context of clinical trials.

PREVIOUS RECOMMENDATION

We recommend against the use of bamlanivimab monotherapy as treatment for COVID-19 infection *(Very low quality of evidence; Strong recommendation)*

We suggest against the use of bamlanivimab/etesevimab in the treatment of non-hospitalized COVID-19 patients with mild-to-moderate COVID-19 at high risk of progression to severe disease *(Low quality of evidence; Conditional recommendation)*

Previous Consensus Issues

Bamlanivimab as monotherapy or in combination with etesevimab showed no significant benefit as treatment for COVID-19. Further studies are needed to show the effectiveness of bamlanivimab in the treatment of COVID-19 infection. In addition, the current cost of bamlanivimab remains high with an approximate cost of Php 60,000 to 120,000 per dose. Recommending its use will possibly promote inequity especially in remote areas. Its local availability should also be considered.

WHAT'S NEW IN THIS VERSION?

This version includes one (1) new study (results of a phase 3 randomized controlled trial).

KEY FINDINGS

The evidence on the use of bamlanivimab + etesevimab combination comes from two (2) randomized controlled trials (RCT) among non-hospitalized patients with COVID-19. Both studies found that there was a significant reduction in COVID-19 related hospitalizations, all-cause mortalities, symptom resolution, and reduction in viral load among the participants who received the bamlanivimab + etesevimab cocktail compared to placebo. There was no significant difference in adverse events between the two groups.

INTRODUCTION

Neutralizing monoclonal antibodies are being studied as a way to boost the immune response to SARS-CoV-2. The investigational neutralizing IgG1 monoclonal antibody bamlanivimab (LY-CoV555; Lilly) was shown to bind to the receptor binding domain of the spike protein of SARS-CoV-2 viruses, which blocks attachment of the virus to the human ACE2 receptor.[1] Etesevimab (LY3832479 or LU-CoV016) is another potent monoclonal antibody that binds to a different epitope of the spike protein of SARS-CoV-2 viruses. Preclinical studies have shown that etesevimab may be able to neutralize even the emerging variants thus, the combination of the 2 drugs may prove to be an effective treatment against COVID-19 and the predominant variants. [2,3]

REVIEW METHODS

A systematic search was done from the date of the last search April 7, 2021 until September 3, 2021 using Medline, CENTRAL, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and bamlanivimab or etesevimab. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. Only randomized controlled trials that compared a combination of bamlanivimab and etesevimab against placebo or standard care were included in this review. No limits were placed on age, COVID-19 severity, and dosing.

RESULTS

The initial search yielded 66 articles. After review of search output, we retrieved 2 published studies that evaluated the use of combination bamlanivimab + etesevimab in COVID-19. One was a Phase 2/3 trial [4], while the more recently published trial was a Phase 3 trial.[5] The dose used in both studies was a single dose of bamlanivimab 2800mg + etesevimab 2800mg administered intravenously.

These 2 studies had a total of 1,303 participants. Both studies included non-hospitalized COVID-19 confirmed participants.[4,5] One study included non-hospitalized COVID-19 patients with ≥1 risk factor for severe COVID-19, including age ≥65 years, body-mass index ≥35 kg/m^2, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions.[5] Both studies reported the following outcomes: COVID-19 related hospitalization and all-cause mortalities, resolution of COVID-19 symptoms, and adverse events. The characteristics of the included studies are summarized in Appendix 3.

The overall quality of evidence was rated low because of serious imprecision and inconsistency in one important outcome (adverse events). Appraisal of study quality showed no serious risk of bias in the included studies. The risk of bias summary is in Appendix 4. The GRADE evidence profile is in Appendix 5.

Pooled analysis showed significant decrease in the COVID-19 related hospitalizations and all-cause mortalities (combined endpoint) among COVID-19 patients who received the combination bamlanivimab + etesevimab compared to placebo (RR 0.28, 95% CI 0.15-0.53; I^2=0%). One study reported a reduction in mean total symptom score from baseline to day 11 in the bamlanivimab + etesevimab group compared to placebo (MD -0.6 points, 95% CI -1.18 to -0.03). The total symptom score ranges from 0 to 24 points based on 8 symptom domains (cough, shortness of breath, feeling feverish, fatigue, body aches and pain, sore throat, chills, and headache), with higher points correlating with more severe symptoms.[4] The other study recorded a 1-day decrease in the number of days to symptom resolution also in the bamlanivimab + etesevimab group compared to the control group (experimental group median 8 days, 95% CI 7-8 days vs. control group 9 days, 95% CI 8-10 days; p=0.007).[5]

Safety

There was no significant difference in adverse events (RR 0.87, 95% CI 0.49-1.57; I^2=75%) and serious adverse events (RR 1.09, 95% CI 0.40-2.93; I^2=0%) in the experimental group compared to placebo. The most common adverse effects mentioned were nausea, rash/pruritus [4,5], dizziness [5], diarrhea [5], and hypertension.[5] The serious adverse event noted in the combination bamlanivimab + etesevimab group for one study was a urinary tract infection, deemed unrelated to COVID-19 by the investigators.[4] The other study did not mention the serious adverse events encountered.[5]

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from other Groups

Regulatory Agency	Recommendation
US Food and Drug Administration (FDA) (as of September 2, 2021)	Revoked the Emergency Use Authorization (EUA) of bamlanivimab monotherapy as treatment for mild-to-moderate COVID-19 due to the emergence of Gamma (P.1), Beta (B.1351) and Delta (B.1.617.2) variants that have shown resistance to this drug, resulting in treatment failure.[7] Etesevimab remains active in neutralizing the Alpha, Beta and Delta variants.[8] Maintained the EUA for the bamlanivimab + etesevimab cocktail for states in which the combined frequency of the variants resistant to the cocktail is less than 5%. The resistance rates are being closely monitored by the CDC. The cocktail is approved for use in all 50 states at a dose of bamlanivimab 700mg + etesevimab 1400mg.[9,10]
National Institutes of Health (NIH) (as of September 15, 2021)	Recommends bamlanivimab 700mg + etesevimab 1400mg for treating non-hospitalized mild-to-moderate COVID-19 patients who are at high risk for progression to severe disease in regions where the combined frequency of potentially resistant variants is low.[11]
Infectious Diseases Society of America (IDSA) (as of August 25, 2021)	Recommends the administration of a lower dose than the clinical trials of bamlanivimab 700mg + etesevimab 1400mg for those with mild-to-moderate COVID-19 symptoms who are at risk for progression to severe disease (*Moderate certainty of evidence; Conditional recommendation).*[12]

Australian Guidelines (as of August 26, 2021)	Recommends against the use of bamlanivimab + etesevimab combination therapy due to the resistance of several variants against bamlanivimab.[13]
World Health Organization (WHO)	No recommendation on the use of bamlanivimab + etesevimab combination in the treatment of COVID-19.[14]

RESEARCH GAPS

There are currently six (6) ongoing randomized clinical trials on bamlanivimab + etesevimab as treatment for COVID-19 (Appendix 7).

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large (2)	Moderate (6)	Small (2)	Uncertain			• Pooled analysis of the 2 RCTs showed significant decrease in the COVI related hospitalizations and all-cause mortalities (combined endpoint) (RR 0.28 CI 0.15-0.53, I2=0%).
Harm	Large (1)	Small (8)	Uncertain (1)				• No significant difference in adverse events (RR 0.87, [0.49-1.57]) and serious adverse events ((RR 1.09, [0.40-2.93]) vs placebo
Certainty of Evidence	High	Moderate (2)	Low (8)	Very low			• Low because of serious imprecision and inconsistency in one important outcome (adverse events).
Balance of effects	Favors drug (9)	Does not favor drug (1)	Uncertain				• There is net potential benefit in terms of COVID-19 related hospitalizations and all-cause mortalities, reduction in total symptom score and number of days to symptom resolution, with no significant difference in terms of adverse events. • 1 panelist believed that there is still inadequate evidence to favor the drug, particularly with regards to its effectivity against variants.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (5)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (10)	Moderate Cost	Negligible cost	Moderate savings	Large savings	• $2,100 or PHP 105,000 for a single course (1 dose bamlanivimab + etesevimab IV)
Certainty of evidence of required resources	No included studies (1)	Very low	Low (7)	Moderate	High (2)		• There is low certainty of evidence on the cost of bamlanivimab + etesevimab treatment. • The cost was derived from foreign news websites (Forbes, PMLive).
Cost effectiveness	No included studies (6)	Favors the comparison	Does not favor either the intervention or the comparison (1)	Favors the intervention (3)			• None of the included trials assessed cost effectiveness.
Equity	Uncertain (3)	Reduced (3)	Probably no impact	Increased (4)			
Acceptability	Uncertain (7)	No	Yes (3)				
Feasibility	Uncertain (6)	No (1)	Yes (3)				

Additional Considerations / Comments:

- The drug currently has no emergency use authorization from the Philippine FDA, thus may only be used in the context of clinical trials.
- There is need for more data on the drug's effectivity against variants

Appendix 2. Characteristics of Included Studies

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR COVID19 OR COVID 19 OR COVID-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (Bamlanivimab) Filters: from April 7, 2021 to September 1, 2021	September 3, 2021 2PM	66	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR COVID19 OR COVID 19 OR COVID-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 AND (Bamlanivimab) Filters: from April 7, 2021 to September 1, 2021	September 3, 2021 830 PM	6	1
Google Scholar	Bamlanivimab AND etesevimab AND COVID AND randomized trial	September 3, 2021 840 PM	369	2
COVID-NMA initiative	Bamlanivimab and etesevimab	September 3, 2021 9 PM	4	2
ClinicalTrials.gov	COVID19 AND bamlanivimab	September 3, 2021 915 PM	14	0
Chinese Clinical Trial Registry	Bamlanivimab	September 3, 2021 920 PM	0	0
EU Clinical Trials Register	Bamlanivimab	September 3, 2021 930 PM	2	0
Republic of Korea - Clinical Research Information Service	Bamlanivimab	September 3, 2021 940PM	0	0
Japan Primary Registries	Bamlanivimab	September 3, 2021 945PM	0	0

Network/ NIPH Clinical Trials Search				
CenterWatch	Bamlanivimab	September 3, 2021 950PM	4	0
chinaxiv.org	Bamlanivimab	September 3, 2021 955PM	0	0
Medrxiv.org	Bamlanivimab Filters: April 7, 2021 to September 3, 2021	September 3, 2021 10PM	2	0
Biorxiv.org	Bamlanivimab Filters: April 7, 2021 to September 3, 2021	September 3, 2021 1010PM	3	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
Effect of Bamlanivimab as Monotherapy or in Combination with Etesevimab on Viral Load in Patients with Mild to Moderate COVID-19: A Randomized Clinical Trial *Gottlieb et al., USA*	Non-hospitalized confirmed COVID-19 patients with mild to moderate symptoms (N = 268)* Duration of follow-up: 29 days	EXPERIMENTAL: Bamlanivimab 2800mg + Etesevimab 2800mg IV CONTROL: Placebo IV	PRIMARY: Change in SARS-CoV-2 log viral load at day 11 SECONDARY: Time to viral clearance, clinical recovery, COVID-19 related hospitalization or all-cause death, adverse events	Randomized, double-blind, placebo-controlled
Bamlanivimab plus Etesevimab in Mild or Moderate COVID-19 *Dougan et al., USA*	Ambulatory confirmed COVID-19 patients with ≥1 risk factor for severe COVID-19 (N = 1,035) Duration of follow-up: 29 days	EXPERIMENTAL: Bamlanivimab 2800mg + Etesevimab 2800mg IV CONTROL: Placebo IV	PRIMARY: COVID-19 related hospitalization or all-cause death SECONDARY: Time to sustained patient-reported resolution of symptoms, reduction in viral load, time to viral clearance, adverse events	Randomized, double-blind, placebo-controlled

**For the bamlanivimab + etesevimab + placebo groups only*

Appendix 4. Study Appraisal

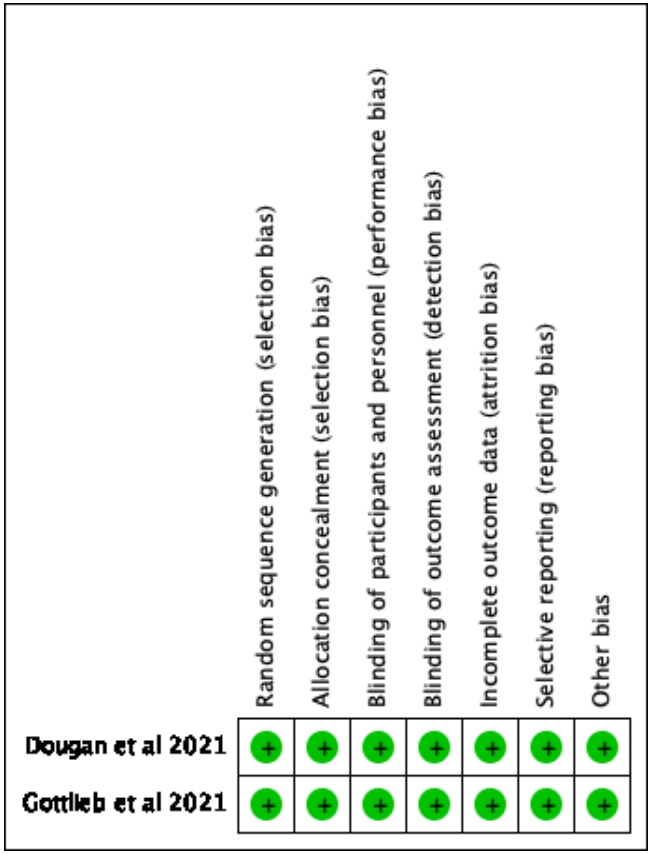

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Isabella S. Ocampo, MD
Question: Bamlanivimab + Etesevimab compared to Placebo for COVID-19
Setting: Outpatient
Bibliography: 1. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. JAMA - J Am Med Assoc. 2021;325(7):632-644. doi:10.1001/jama.2021.0202 2. Dougan M, Nirula A, Azizad M et al. Bamlanivimab plus Eteseviman in Mild or Moderate Covid-19. N Engl J Med. 2021. doi:10.1056/NEJMoa2102685.

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bamlanivimab + Etesevimab	Standard of care alone	Relative (95% CI)	Absolute (95% CI)		
Covid-19 related hospitalization and all-cause mortalities (follow up: 29 days)												
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	12/630 (1.9%)	45/673 (6.7%)	**RR 0.28** (0.15 to 0.53)	**48 fewer per 1,000** (from 57 fewer to 31 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Number of days to sustained patient-reported Covid-19 symptom resolution (follow up: 29 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	There was a reduction in the number of days to symptom resolution (8 days in bamlanivimab + etesevimab group [95% CI: 7-8] vs 9 days in placebo group [95% CI: 8-10]; p=0.007).				⊕⊕⊕⊕ HIGH	CRITICAL
Change in mean total symptom score from baseline (follow up: 11 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious [a]	None	4.37	3.8	-	MD **0.6 lower** (1.18 lower to 0.03 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse events (follow up: 29 days)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious [c]	None	8/630 (1.3%)	8/673 (1.2%)	**RR 1.09** (0.40 to 2.93)	**1 more per 1,000** (from 7 fewer to 23 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events (follow up: 29 days)												
2	Randomised trials	Not serious	Serious [b]	Not serious	Serious [c]	None	88/630 (14.0%)	102/673 (15.2%)	**RR 0.87** (0.49 to 1.57)	**20 fewer per 1,000** (from 77 fewer to 86 more)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations
[a] The upper limit of the CI is clinically insignificant
[b] There is considerable heterogeneity
[c] There is a wide confidence interval

Appendix 6. Forest Plots

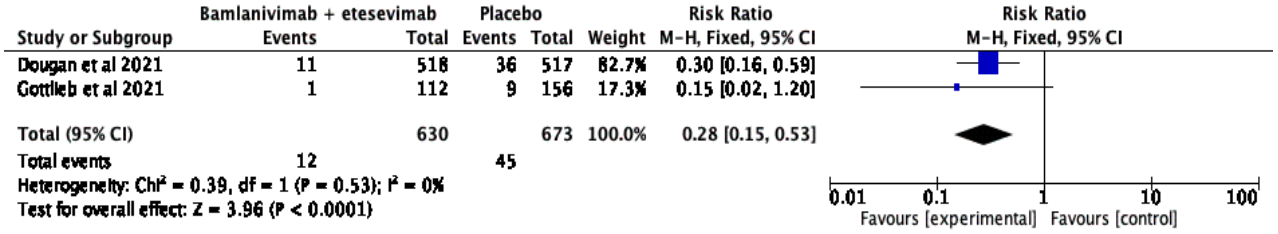

Figure 1. Effect of bamlanivimab + etesevimab compared to placebo on COVID-19 related hospitalizations and all-cause mortalities

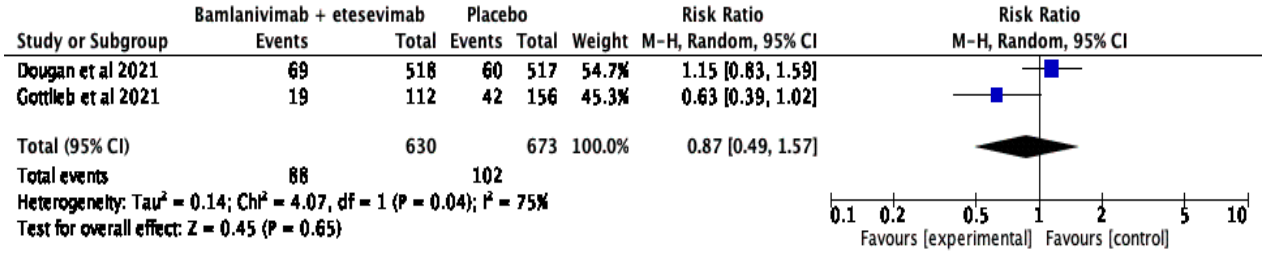

Figure 2. Effect of bamlanivimab + etesevimab compared to placebo on adverse events

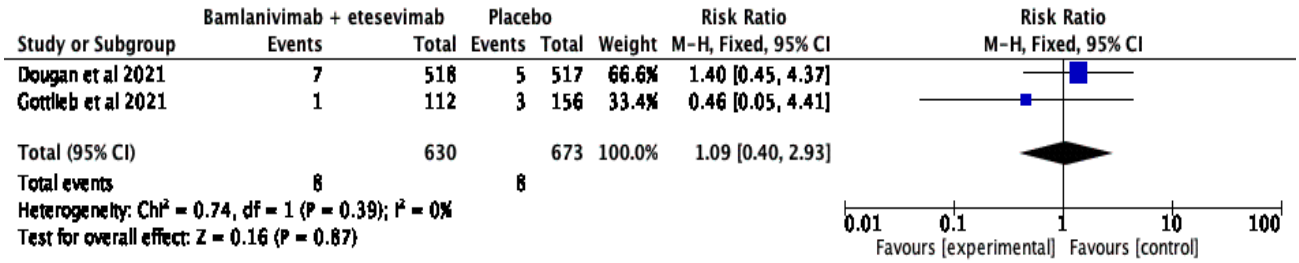

Figure 3. Effect of bamlanivimab + etesevimab compared to placebo on serious adverse events

Appendix 7. Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Population	Intervention	Outcome	Completion
NCT04790786 UPMC OPTIMISE-C19 Trial, a COVID-19 Study (OPTIMISE-C19)	Randomized, open-label, parallel assignment	COVID-19 confirmed patients	Bamlanivimab vs casirivimab + imdevimab vs. bamlanivimab + etesevimab	Alive and free from hospitalization 28 days after initial participation	December 2022
NCT04427501 A Study of LY3819253 (LY-CoV555) and LY3832479 (LY-CoV016) in Participants With Mild to Moderate COVID-19 Illness (BLAZE-1)	Randomized, double blind, sequential assignment	Confirmed COVID-19, non-hospitalized with mild to moderate symptoms	Bamlanivimab vs. bamlanivimab + etesevimab vs. placebo	Percentage of patients who experience COVID-related hospitalization or death from any cause up to 29 days from baseline; change from baseline to day 11 in viral load; adverse events	June 24, 2022
NCT04497987 A Study of LY3819253 (LY-CoV555) and LY3832479 (LY-CoV016) in Preventing SARS-CoV-2 Infection and COVID-19 in Nursing Home Residents and Staff	Randomized, double-blind, parallel assignment	Resident or facility staff in a skilled nursing or assisted living facility with at least one confirmed case of SARS-CoV-2	Bamlanivimab vs. bamlanivimab + etesevimab vs. placebo	Percentage of participants with COVID-19 within 21 days of detection	May 20, 2021
NCT04634409 A Study of Immune System Proteins in Participants With Mild to Moderate COVID-19 Illness	Randomized parallel assignment	Confirmed COVID-19, Not hospitalized with mild to moderate symptoms	Bamlanivimab + etesevimab vs. bamlanivimab vs. placebo	Percentage of participants with SARS-CoV-2 viral load greater than 5.27	October 13, 2021
EudraCT 2021-002612-31 Adaptive, randomized, placebo-controlled trial to evaluate the efficacy of monoclonal antibodies in outpatients with mild or moderate COVID-19	Randomized, placebo-controlled trial	Adult patients with mild confirmed COVID-19	Bamlanivimab + etesevimab vs. casirivimab + imdevimab vs. placebo	Prevention of disease progression (need for oxygen therapy supplementation, hospitalization and/or death)	Not mentioned
EudraCT 2021-004035-88 A randomized, open-label, active controlled, parallel group, multicenter phase 3 study to evaluate the efficacy and tolerability of bamlanivimab and etesevimab, casirivimab and imdevimab, and sotrovimab versus standard of care in patients with mild to moderate COVID-19 disease	Randomized, open-label, parallel assignment	Patients with mild to moderate confirmed COVID-19 infection	Bamlanivimab + etesevimab vs. casirivimab + imdevimab vs. sotrovimab vs. placebo	Prevention of disease progression (hospitalization in intensive care unit, peripheral oxygen saturation ≤92%, oxygen desaturation ≤4%)	Not mentioned

Q22. Among patients with COVID-19, should casirivimab-imdevimab be used for treatment?

As of 20 December 2021

RECOMMENDATIONS

We suggest the use of casirivimab-imdevimab as treatment for symptomatic, non-hospitalized patients with at least 1 risk factor* for severe COVID-19. (*Moderate certainty of evidence, Weak recommendation)*

We recommend against casirivimab-imdevimab as treatment for hospitalized COVID-19 patients. (*Low certainty of evidence, Strong recommendation)*

There is insufficient evidence to recommend casirivimab-imdevimab as treatment for asymptomatic COVID-19 patients. *(Low certainty of evidence)*

**Risk factors: age >50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions.*

Consensus Issues

Addition of 2 new pre-print randomized controlled trials (RCTs) still showed that casirivimab and imdevimab cocktail is beneficial for symptomatic, non-hospitalized COVID-19 patients with at least 1 risk factor for progression to severe disease. Although there was moderate certainty of evidence, the recommendation was weak due to inconclusive evidence on all-cause mortality, large cost, need for emergency room visit for drug administration and close monitoring and equity considerations. At present, the drug is only available in private tertiary hospitals.

The evidence remained inconclusive for hospitalized COVID-19 patients. The previous update included 1 pre-print RCT (RECOVERY trial), which on subgroup analysis showed that casirivimab-imdevimab appeared to have benefit in terms of all-cause mortality, need for mechanical ventilation, and clinical recovery among hospitalized patients who were seronegative at baseline (negative for serum SARS-CoV-2 antibodies). However, addition of 1 (one) new pre-print RCT showed trend towards benefit in clinical recovery only. The panel maintained the previous recommendation against the use of casirivimab-imdevimab cocktail among hospitalized COVID-19 patients because of uncertain balance of effects in this specific subset of patients and both RCTs are still pre-print. As of writing, there are 8 ongoing clinical trials on casirivimab-imdevimab, 2 of which are among hospitalized patients. Results of these trials may further elucidate on the cocktail's effectiveness in the treatment of hospitalized COVID-19 patients.

Lastly, the only available study for asymptomatic, non-hospitalized COVID-19 patients is a small pre-print RCT with low certainty of evidence. The panel deemed that current evidence is still insufficient to make any recommendations for this subset of patients.

PREVIOUS RECOMMENDATIONS

We suggest casirivimab + imdevimab as treatment for non-hospitalized patients with at least 1 risk factor* for severe COVID-19. (*Moderate quality of evidence; Weak recommendation)*

We recommend against casirivimab + imdevimab as treatment for hospitalized COVID-19 patients. (*Moderate quality of evidence; Strong recommendation)*

*Risk factors: age >50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions.

Previous Consensus Issues

Administration of casirivimab + imdevimab to non-hospitalized COVID-19 patients should be under the supervision of a licensed physician and in a facility capable of monitoring and managing adverse reactions. Patients should be closely monitored during and after drug administration. The recommendation to give casirivimab + imdevimab to non-hospitalized COVID-19 patients who are at risk for severe disease was weak because the evidence was from 1 study only, cost considerations and need for emergency room visit for drug administration and monitoring.

The pre-print study (RECOVERY trial) did not show any benefit in giving casirivimab + imdevimab to hospitalized patients in general, but showed benefit only for seronegative patients. However, this subgroup analysis was only post-hoc or exploratory in nature. Hence, the consensus panel recommended against its use among hospitalized COVID-19 patients until further research confirms this finding.

WHAT'S NEW IN THIS VERSION?

This version includes data from four (4) new pre-print randomized clinical trials.

KEY FINDINGS

Six (6) RCTs evaluated the efficacy of casirivimab-imdevimab cocktail as treatment for patients with COVID-19. Among non-hospitalized patients given casirivimab-imdevimab, there was a significant reduction in combined end-point of need for invasive mechanical ventilation or death, COVID-19-related medically-assisted visits, duration of symptoms, and serious adverse events. However, evidence was largely inconclusive for hospitalized patients and asymptomatic, non-hospitalized patients. There was trend towards benefit in clinical recovery among hospitalized seronegative patients (negative for serum SARS-CoV-2 antibodies at baseline), but not for seropositive patients (positive for serum SARS-CoV-2 antibodies at baseline). There was no benefit in all-cause mortality regardless of hospitalization status.

INTRODUCTION

COVID-19 hypoxemia has been theorized to be related to an immune hyperresponsiveness to viral infection. With recent studies showing high viral titers among hospitalized patients with hypoxemia, it is hypothesized that treatments that effectively reduce viral load could prevent complications and death resulting from COVID-19 infection.[1,2] One such treatment that has shown favorable effects from in vitro studies is casirivimab-imdevimab, an antibody cocktail containing two non-competing SARS-CoV-2 neutralizing human IgG1 antibodies (casirivimab

[REGN10933] and imdevimab [REGN10987]). By targeting the receptor-binding domain of the SARS-CoV-2 spike protein, viral entry into human cells through the angiotensin-converting enzyme 2 (ACE2) receptor is prevented.[3,4]

REVIEW METHODS

A systematic search was done from the date of the last search September 1, 2021 until November 26, 2021 using Medline, CENTRAL, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and REGEN-COV or REGN-COV2 or casirivimab. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv, and biorxiv. Only randomized controlled trials that compared REGEN-COV against placebo or standard care were included in this review. Only randomized controlled trials were included. No limits were placed on age, COVID-19 severity, and dosing. Preplanned subgroup analysis on dosing, severity and serologic status were conducted.

RESULTS

A total of 231 related articles were found using Medline, CENTRAL, COVID-NMA initiative, and Google Scholar, however no new articles met our inclusion criteria. Four pre-prints were found using Medrxiv.org.[7-10] These studies evaluated the use of casirivimab-imdevimab as treatment for COVID-19 patients and were added to the previous 2 studies.[5-6]

The 6 studies included a total of 18,785 COVID-19 confirmed patients.[5-10] One of the pre-prints studied casirivimab-imdevimab as treatment for inpatient adult patients with COVID-19 who required little to no oxygen supplementation. These patients were enrolled in 1 of 4 cohorts: little to no oxygen support (cohort 1 and cohort 1a), high-intensity oxygen (cohort 2), and mechanical ventilation (cohort 3). However, due to low sample size, cohorts 2 and 3 were discontinued. These patients were randomized to receive intravenous (IV) 2400mg casirivimab-imdevimab, IV 8000mg casirivimab-imdevimab or placebo. Standard of care treatments for COVID-19 were permitted.[7]

Another pre-print studied the use of casirivimab-imdevimab as treatment for asymptomatic close contacts of a COVID-19 index case who are at least 12 years of age and tested positive for COVID-19 within 96 hours of exposure. These participants received a subcutaneous (SC) dose of 1200mg casirivimab-imdevimab or placebo.[8]

The 2 other pre-prints are Phase 1/2 trials that included non-hospitalized COVID-19 patients. One of these is a dose-ranging study that included the following interventions: IV 300mg casirivimab-imdevimab, IV 600mg casirivimab-imdevimab, IV 1200mg casirivimab-imdevimab, IV 2400mg casirivimab-imdevimab, SC 600mg casirivimab-imdevimab, and SC 1200mg casirivimab-imdevimab.[9] The second is part of the seamless Phase 1/2/3 trial of the published study.[10]
The overall quality of evidence was rated moderate because of serious risk of bias. The serious risk of bias was due to issues in attrition, allocation concealment, performance bias, and reporting bias. The risk of bias summary is found in Appendix 4. The GRADE evidence profile is in Appendix 5.

All-cause mortality was not significantly different between the casirivimab-imdevimab group and the placebo group regardless if non-hospitalized (RR 0.33, 95% CI 0.07-1.63) [5] or hospitalized (RR 0.81, 95% CI 0.56-1.17; I^2 = 75%).[6-7]
Among asymptomatic, non-hospitalized patients, there was no difference between the experimental and control groups in reducing the number of COVID-related medically assisted visits (MAVs) (RR 0.08, 95% CI 0.00-1.40). The same study found trend towards benefit in terms of development of symptomatic COVID-19 infection among patients given casirivimab-imdevimab versus placebo (RR 0.69, 95% CI 0.47-1.00).[8]

Among symptomatic non-hospitalized patients, there was a significant reduction in the combined end-point of need for invasive mechanical ventilation or death in the casirivimab-imdevimab group versus the control (RR 0.40, 95% CI 0.32-0.51).[5] Subgroup analysis according to dose showed benefit in the casirivimab-imdevimab 1200mg IV dose group (RR 0.40, 95% CI 0.24-0.66) and the 2400mg IV dose group (RR 0.45, 95% CI 0.33-0.61), but not in the 8000mg IV dose group (RR 0.74, 95% CI 0.48-1.12). There was a significant reduction in the number of COVID-related MAVs defined as consult at the emergency room, urgent care or hospitalization in the experimental group compared to the placebo group (RR 0.34, 95% CI 0.26-0.46; I^2 = 7%).[5,10] In one study, there was also a significant decrease in the duration of COVID-19 symptoms (MD -4.00 days, 95% CI -4.24 to -3.76) and in the duration of hospitalization, regardless of dose in the experimental group versus the control group (8.6 days in 2400mg group versus 10 days in control, 7 days in 1200mg group versus 8.4 days in control).[5]

Among hospitalized patients, there was no significant difference between the casirivimab-imdevimab group versus the placebo group in terms of need for invasive ventilation or death (RR 0.85, 95% CI 0.62-1.16; I^2 = 76%).[6-7] Post hoc subgroup analysis by serologic status showed no difference in reducing all-cause mortality among seronegative patients (RR 0.64, 95% CI 0.36-1.15; I^2 = 79%) [6-7] as well as among seropositive patients (RR 1.07, 95% CI 0.94-1.22).[6] There was also no difference in reducing the need for invasive mechanical ventilation or death among seronegative patients (RR 0.70, 95% CI 0.46-1.08; I^2 = 74%) [6-7] and among seropositive patients (RR 1.10, 95% CI 0.97-1.24).[6] However, in one study, the duration of hospitalization among seronegative patients was also shortened by 4 days in the experimental group versus the control group (13 days versus 17 days).[6]

Safety
Overall, there was a significant reduction in the number of serious adverse events (SAEs) in the experimental group versus the control group, regardless of dose (RR 0.52, 95% CI 0.37-0.74; I^2 = 76%) or route of administration (RR 0.51, 95% CI 0.29-0.90; I^2 = 77%). However, based on hospitalization status there is significant reduction in SAEs for the non-hospitalized patients in the experimental group versus the control group (RR 0.35, 95% CI 0.25-0.49; I^2 = 0%) but no significant results for the hospitalized patients (RR 1.15, 95% CI 0.56-2.36; I^2 = 96%). The most common serious adverse events noted were development of COVID-19 pneumonia.[5,7,8] In one study, the investigators noted that the 2 SAEs in the experimental group were miscarriages in the first trimester, both considered unrelated to the study drug or COVID-19. One participant was a primigravida and the other was a patient with significant medical history of abortions.[9] The most common adverse events were infusion-related reactions.[5,7]

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Australian Guidelines (updated November 26, 2021)	Conditional recommendation using casirivimab plus imdevimab in the following situations: • Within 7 days of symptom onset in adult outpatients and pregnant or breastfeeding women who are outpatients with mild COVID-19 who have one or more risk factors for disease progression • Seronegative adults hospitalized with moderate to critical COVID-19, including pregnant or breastfeeding women Recommends against the use of casirivimab plus imdevimab in the following situations: • For mild or asymptomatic COVID-19 patients and for seropositive hospitalized patients, including seropositive pregnant or breastfeeding women • For seropositive children and adolescents hospitalized with moderate to critical COVID-19 Consensus recommendation to consider using, in exceptional circumstances, casirivimab plus imdevimab within 7 days of symptom onset in children and adolescents aged 12 years and over and weighing at least 40 kg with mild COIVD-19 who are at high risk of deterioration.[9]
Japanese rapid/living recommendations on drug management for COVID-19: Updated guidelines (updated October 22, 2021)	Recommends for the use of casirivimab plus imdevimab administration to patients with mild COVID-19 who do not require oxygen supplementation. No clear recommendation on casirivimab plus imdevimab administration to patients with moderate COVID-19 requiring oxygen supplementation/hospitalization an those with severe COVID-19 requiring mechanical ventilation or intensive care.[10]
India Covid Guidelines (updated October 8, 2021)	Conditional recommendation for the use of casirivimab plus imdevimab in the following situations: • Within 10 days of symptom onset for those with mild COVID-19 with 1 or more risk factors for progression to severe disease [12] • For hospitalized patients requiring oxygen support in the early illness (<7 days of symptoms) with no detectable COVID-19 antibodies [11] Strongly recommend against the use of casirivimab plus imdevimab in the following situations: • For patients with moderate, severe or critical COVID-19 who are seropositive [11] • For patients with mild COVID-19 with no risk factors for progression to severe disease [12] • For Asymptomatic patients [13]
National Institutes of Health (NIH) Guidelines (updated October 19, 2021)	Recommends the use of casirivimab plus imdevimab for non-hospitalized patients at high risk of clinical progression.[14]
World Health Organization (WHO) Guidelines (updated September 24, 2021)	Conditional recommendation for the use of casirivimab plus imdevimab as treatment for patients with non-severe COVID-19 who are at highest risk of hospitalization. Conditional recommendation for the use of casirivimab plus imdevimab as treatment for patients with severe or critical COVID-19 with seronegative status.[15]
Infectious Diseases Society of America (updated October 1, 2021)	Suggests the use of casirivimab + imdevimab for non-hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease.[14]

RESEARCH GAPS

There are currently eight (8) ongoing randomized clinical trials on casirivimab-imdevimab as treatment for COVID-19 (Appendix 6).

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 5)

FACTORS	JUDGEMENT (N = 5)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					
Benefits	Large	Moderate (1)	Small (1)	Uncertain (3)			• Asymptomatic: trend towards benefit in development of symptomatic COVID-19 infection (RR 0.69, 95% I 0.47-1.00); no benefit in reducing COVID-related MAV (RR 0.08, 95% CI 0.00-1.40), • Symptomatic, non-hospitalized: significant reduction in need for invasive mechanical ventilation or death (RR 0.40, 95% CI 0.32-0.51), number of COVID-related MAV (RR 0.34, 95% CI 0.26-0.46), duration of COVID-19 symptoms (MD -4.00 days, 95% CI -4.24, -3.76), duration of hospitalization • Hospitalized: no benefit in need for invasive ventilation or death
Harm	Large	Small (2)	Uncertain (3)				• Non-hospitalized: less serious adverse effects (RR 0.35, 95% CI 0.25-0.49) • Hospitalized: no significant difference in serious adverse effects (RR 1.15, 95% CI 0.56-2.36)
Certainty of Evidence	High	Moderate (1)	Low (4)	Very low			• Serious risk of bias due to issues in attrition, allocation concealment, performance bias, and reporting bias
Balance of effects	Favors drug (3)	Does not favor drug (1)	Uncertain (1)				• Net potential benefit only for symptomatic, non-hospitalized patients who are at risk for developing severe disease.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (5)	Moderate cost	Negligible cost	Moderate savings	Large savings	• Cost is PHP 28,615 per single dose infusion (2 vials of 300mg casirivimab + 300mg imdevimab/5mL) • Additional cost for ER and doctor's fees may vary across different hospitals
Certainty of evidence of required resources	No included studies (1)	Very low (1)	Low (3)	Moderate	High		• Local cost is from personal communication with the private hospitals
Cost effectiveness	No included studies (4)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (1)			

Equity	Uncertain (2)	Reduced (2)	Probably no impact (1)	Increased		
Acceptability	Uncertain (4)	No (1)	Yes			
Feasibility	Uncertain (5)	No	Yes			

Additional Comments:

- Specify specific subgroups (eg. severity and site of care)
- Put uncertain on benefits and harms since different subgroups (hospitalized vs non hospitalized have different benefits and harm

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (Casirivimab) Filters: from September 1, 2021 to November 26, 2021	November 26, 2021 9:30 AM	34	0
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 AND (REGEN-COV) OR (REGN-COV2) OR (Casirivimab) Filters: from September 1, 2021 to November 26, 2021	November 26, 2021 10:30 AM	0	0
Google Scholar	Casirivimab AND imdevimab AND COVID AND randomized trial	November 26, 2021 11:30 AM	191	2
COVID-NMA initiative	REGEN-COV REGN-COV2 Casirivimab	November 26, 2021 2:00 PM	6	0
ClinicalTrials.gov	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	November 27, 2021 1:30 PM	18	0
Chinese Clinical Trial Registry	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:00 PM	0	0
EU Clinical Trials Register	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	November 27, 2021 2:10 PM	2	0
Republic of Korea - Clinical Research Information Service	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:15 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:20 PM	4	0
CenterWatch	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:10 PM	7	0
chinaxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:15 PM	0	0
Medrxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:20 PM	64	4
Biorxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2 AND COVID-19	November 27, 2021 2:45 PM	60	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
REGEN-COV Antibody Cocktail Clinical Outcomes Study in COVID-19 Outpatients *Weinrich et al. (USA);*	Ambulatory confirmed COVID-19 patients with ≥1 risk factor for severe COVID-19 (n = 4,057) Duration of follow-up: Approximately 29 days	EXPERIMENTAL: Casirivimab-imdevimab 1200mg cocktail IV Casirivimab-imdevimab 2400mg cocktail IV Casirivimab-imdevimab 8000mg cocktail IV CONTROL: Placebo	PRIMARY: COVID-19 related hospitalization or all-cause death SECONDARY: Time to symptom resolution, adverse events	Randomized, double-blind, placebo-controlled
Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial *Horby et al., United Kingdom); pre-print*	Confirmed COVID-19 patients admitted to the hospitals already participating in the RECOVERY trial (n = 11,464) Duration of follow-up: 28 days	EXPERIMENTAL: Casirivimab-imdevimab 8000mg cocktail IV CONTROL: Standard of care	PRIMARY: All-cause mortality SECONDARY: Discharge alive from hospital, use of invasive ventilation among patients, serious adverse events	Randomized, open-label, controlled
REGEN-COV for Treatment of Hospitalized Patients with Covid-19 *(Somersan-Karakaya et al., USA); pre-print*	Hospitalized COVID-19 patients with little to no oxygen support (n = 1336) Duration of follow-up: 29 days	EXPERIMENTAL: Casirivimab-imdevimab 2400mg cocktail IV Casirivimab-imdevimab 8000mg cocktail IV CONTROL: Placebo	PRIMARY: Time-weighted average (TWA) daily change from baseline viral load until day 7, progression of disease (need for invasive mechanical ventilation or death) SECONDARY: All-cause mortality, discharge from/readmission to hospital, safety	Randomized, double-blinded, placebo-controlled trial
Subcutaneous REGEN-COV Antibody Combination in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial *(O'Brien et al., USA); pre-print*	Asymptomatic individuals at least 12 years of age with known exposure to COVID-19, tested positive for COVID-19 at baseline (n = 314) Duration of follow-up: 28 days	EXPERIMENTAL: Casirivimab-imdevimab 1200mg cocktail SC CONTROL: Placebo	PRIMARY: Development of COVID-19 symptoms SECONDARY: Duration of COVID-19 symptoms, number of weeks of high viral load, safety	Randomized, double-blind, placebo-controlled trial
Phase 2 Dose-Ranging Study of the Virologic Efficacy and Safety of the Combination	Non-hospitalized COVID-19 patients without risk factors for developing severe COVID-19 (n = 815)	EXPERIMENTAL: Casirivimab-imdevimab 300mg cocktail IV Casirivimab-imdevimab 600mg cocktail IV	PRIMARY: TWA daily change from baseline in viral load from day 1 to 7	Randomized, double-blind, placebo-controlled, parallel-

COVID-19 Antibodies Casirivimab and Imdevimab in the Outpatient Setting *(Portal-Celhay et al., USA); pre-print*	<u>Duration of follow-up:</u> 4 months	Casirivimab-imdevimab 1200mg cocktail IV Casirivimab-imdevimab 2400mg cocktail IV Casirivimab-imdevimab 600mg cocktail SC Casirivimab=-imdevimab 1200mg cocktail SC CONTROL: Placebo	SECONDARY: Virologic efficacy, safety and tolerability, REGEN-COV concentrations in serum over time, safety	group, dose-ranging trial
REGEN-COV Antibody Cocktail in Outpatients with Covid-19 (*Weinrich et al., USA); pre-print*	Non-hospitalized COVID-19 patients (n = 799) <u>Duration of follow-up:</u> 29 days	EXPERIMENTAL: Casirivimab-imdevimab 2400mg cocktail IV Casirivimab-imdevimab 8000mg cocktail IV CONTROL: Placebo	PRIMARY: TWA change in viral load from baseline through day 7 SECONDARY: At least 1 COVID-19-related medically-attended visit (MAV), safety	Randomized, double-blind, placebo-controlled trial

Appendix 4. Study Appraisal

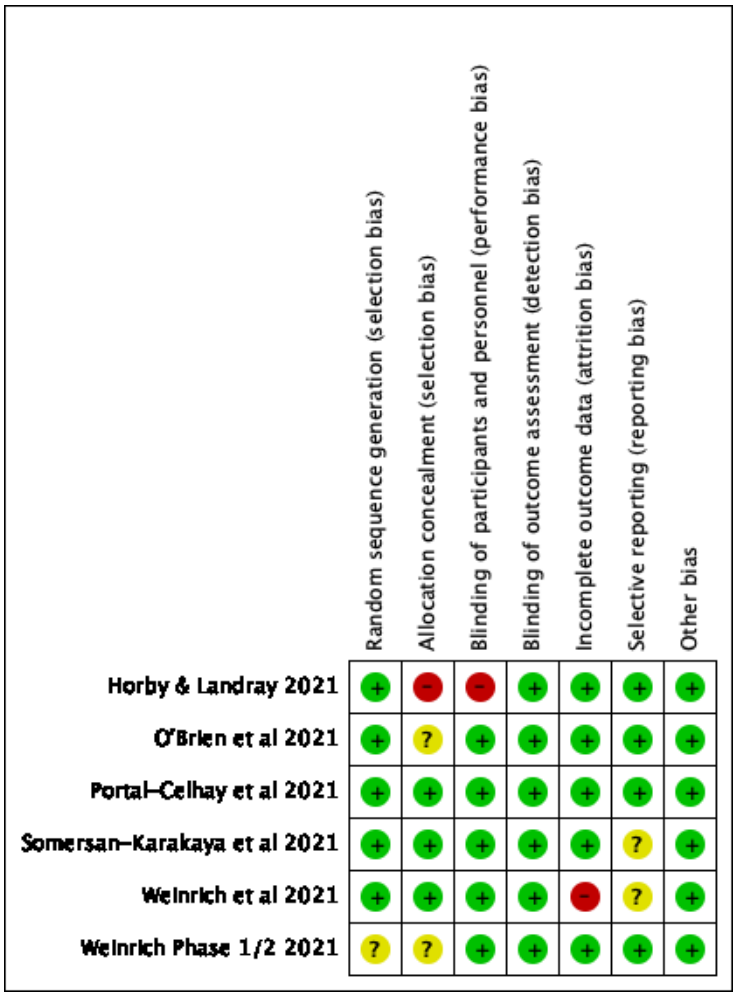

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 treatment
Setting: **A**symptomatic non-hospitalized
Bibliography: [1,2]

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab + Imdevimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
At least 1 COVID-related MAV (asymptomatic non-hospitalized) (follow-up: 28 days)												
1	randomized trial	not serious	not serious	not serious	very serious[a,b]	none	0/100 (0.0%)	6/104 (5.8%)	**RR 0.08** (0.00 to 1.40)	**53 fewer per 1,000** (from -- to 23 more)	⨁⨁◯◯ LOW	CRITICAL
Duration of COVID-19 symptoms (asymptomatic non-hospitalized) (follow-up: 28)												
1	randomized trial	not serious	not serious	not serious	not serious	none	The duration of symptoms was 4.9 days less in the experimental group versus the control (MD -4.9 days, 95% CI -5.74, -4.06).				⨁⨁⨁⨁ HIGH	CRITICAL
Serious adverse events (asymptomatic non-hospitalized) (follow-up: 28 days)												
1	randomized trial	not serious	not serious	not serious	very serious[a,b]	none	0/155 (0.0%)	4/156 (2.6%)	**RR 0.11** (0.01 to 2.06)	**23 fewer per 1,000** (from 25 fewer to 27 more)	⨁⨁◯◯ LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
[a] Wide confidence intervals
[b] Fragility of events

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 treatment
Setting: Symptomatic, non-hospitalized
Bibliography: [1,2]

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab + Imdevimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (symptomatic non-hospitalized) (follow-up: 29 days)												
1	Randomized trial	Not serious	Not serious	Not serious	Very serious[a,b]	None	2/2716 (0.1%)	6/2682 (0.2%)	**RR 0.33** (0.07 to 1.63)	**1 fewer per 1,000** (from 2 fewer to 1 more)	⊕⊕◯◯ LOW	CRITICAL
Need for invasive mechanical ventilation or death (outpatient) (follow-up: 29 days)												
1	Randomized trial	Not serious	Not serious	Not serious	Not serious	None	89/2716 (3.3%)	218/2682 (8.1%)	**RR 0.40** (0.32 to 0.51)	**49 fewer per 1,000** (from 55 fewer to 40 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
At least 1 COVID-related medically-assisted visit (symptomatic non-hospitalized) (follow-up: 29 days)												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	66/3150 (2.1%)	178/2913 (6.1%)	**RR 0.34** (0.26 to 0.46)	**40 fewer per 1,000** (from 45 fewer to 33 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Duration of hospitalization (outpatient) (follow-up: 29 days)												
1	Randomized trial	Not serious	Not serious	Serious	Very serious[b,c]	None	Among those hospitalized, the duration of hospitalization was shorter in the experimental group versus the control group regardless of dose (8.6 days in 2400mg group vs 10 days in placebo group; 7 days in 1200mg group vs 8.4 days in placebo group).				⊕◯◯◯ VERY LOW	IMPORTANT
Duration of symptoms in days (symptomatic non-hospitalized) (follow-up: 28 days)												
1	Randomized trial	Not serious	Not serious	Not serious	Not serious	None	2091	2089	-	mean **4 days lower** (4.24 lower to 3.76 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse events (outpatient) (follow-up: 29 days)												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	56/4361 (1.3%)	84/2261 (3.7%)	**RR 0.35** (0.25 to 0.49)	**25 fewer per 1,000** (from 28 fewer to 19 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
[a] Wide confidence intervals
[b] Fragility of events
[c] No mentioned confidence intervals

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 treatment
Setting: Hospitalized

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab + Imdevimab	Placebo	Relative (95% CI)	Absolute (95% CI)	CERTAINTY	IMPORTANCE
All-cause mortality (inpatient) (follow-up: 28 days)												
2	Randomized trials	Not serious	Serious[b]	Not serious	Serious[a]	none	1003/5643 (17.8%)	1071/5339 (20.1%)	**RR 0.81** (0.56 to 1.17)	**38 fewer per 1,000** (from 88 fewer to 34 more)	⊕⊕◯◯ LOW	CRITICAL
Need for invasive mechanical ventilation or death (inpatient) (follow-up: 28 days)												
2	Randomized trials	Not serious	Serious[b]	Not serious	Serious[a]	none	1171/5360 (21.8%)	1209/5035 (24.0%)	**RR 0.85** (0.62 to 1.16)	**36 fewer per 1,000** (from 91 fewer to 38 more)	⊕⊕◯◯ LOW	CRITICAL
Duration of hospitalization (inpatient) (follow-up: 29 days)												
1	Randomized trial	Serious [c]	Not serious	Serious[d]	Serious[e]	none	Among hospitalized seronegative patients, the median duration of hospitalization was 4 days shorter in the experimental group versus control (13 days vs 17 days).				⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse events (inpatient) (follow-up: 29 days)												
2	Randomized trials	Serious [c]	Not serious	Not serious	Serious[a]	none	460/3132 (14.7%)	277/2381 (11.6%)	**RR 1.15** (0.56 to 2.36)	**17 more per 1,000** (from 51 fewer to 158 more)	⊕⊕◯◯ LOW	CRITICAL
Serious adverse events (outpatient) (follow-up: 29 days)												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	56/4361 (1.3%)	84/2261 (3.7%)	**RR 0.35** (0.25 to 0.49)	**25 fewer per 1,000** (from 28 fewer to 19 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
[a] Wide confidence intervals
[b] High heterogeneity
[c] Open label study
[d] Only mentioned for seronegative patients
[e] No mentioned confidence intervals

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 treatment
Setting: Seronegative hospitalized
Bibliography: [1,2]

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab + Imdevimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (seronegative hospitalized) (follow-up: 29 days)												
2	Randomized trials	Not serious	Serious[b]	Not serious	Serious[a]	None	420/1993 (21.1%)	475/1680 (28.3%)	**RR 0.64** (0.36 to 1.15)	**102 fewer per 1,000** (from 181 fewer to 42 more)	⊕⊕◯◯ LOW	CRITICAL
Need for invasive mechanical ventilation or death (seronegative hospitalized) (follow-up: 29 days)												
2	Randomized trials	Serious[c]	Serious[b]	Not serious	Serious[a]	None	524/1959 (26.7%)	573/1644 (34.9%)	**RR 0.70** (0.46 to 1.08)	**105 fewer per 1,000** (from 188 fewer to 28 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
[a] Wide confidence intervals
[b] High heterogeneity
[c] Open label study

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 treatment
Setting: Seropositive hospitalized
Bibliography: [1,2]

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab + Imdevimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (seropositive hospitalized) (follow-up: 29 days)												
1	Randomized trial	Not serious	Not serious	Not serious	Serious[a]	None	411/2636 (15.6%)	383/2636 (14.5%)	**RR 1.09** (0.95 to 1.26)	**13 more per 1,000** (from 7 fewer to 38 more)	⊕⊕◯◯ MODERATE	CRITICAL
Need for invasive mechanical ventilation or death (seropositive hospitalized) (follow-up: 29 days)												
1	Randomized trial	Serious[b]	Not serious	Not serious	Serious[a]	None	456/2449 (18.6%)	415/2450 (16.9%)	**RR 1.10** (0.97 to 1.24)	**17 more per 1,000** (from 5 fewer to 41 more)	⊕⊕◯◯ LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
[a] Wide confidence intervals
[b] Open label study

Appendix 6. Forest Plots

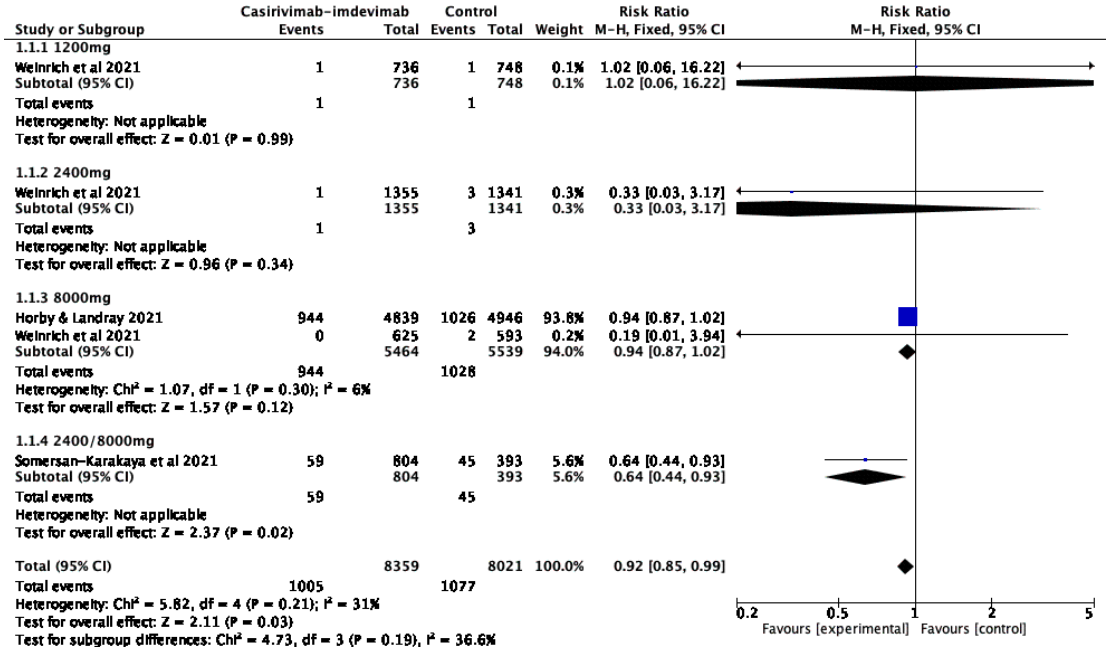

Figure 2. All-cause mortality by dose

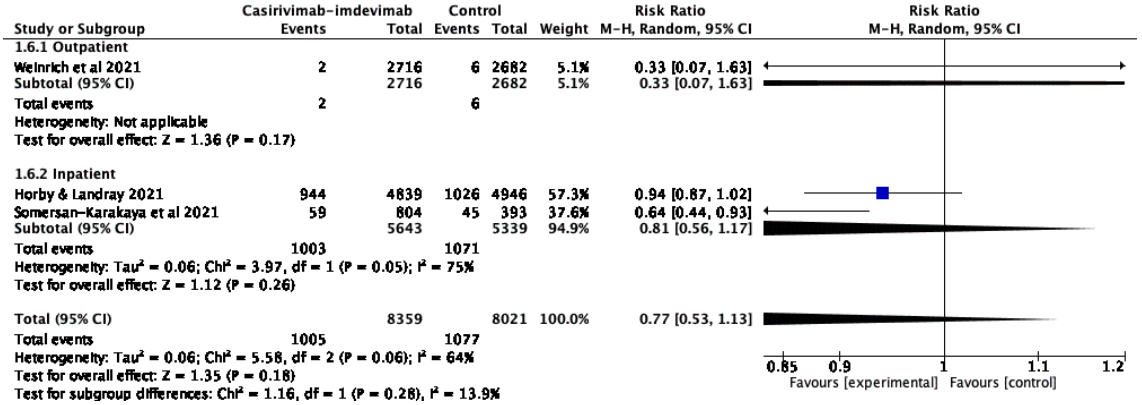

Figure 3. All-cause mortality by hospitalization status

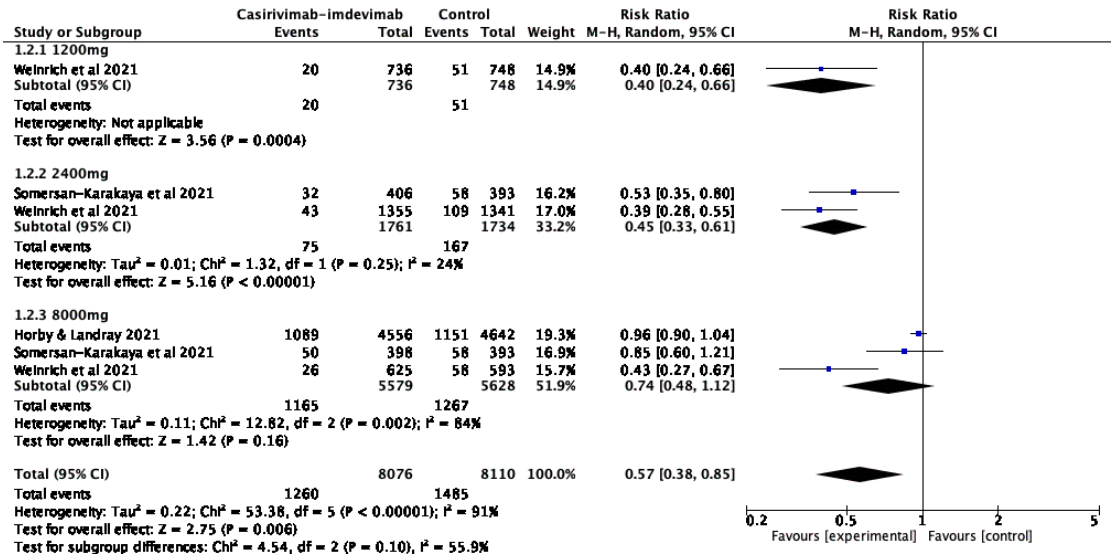

Figure 4. Need for invasive mechanical ventilation or death by dose

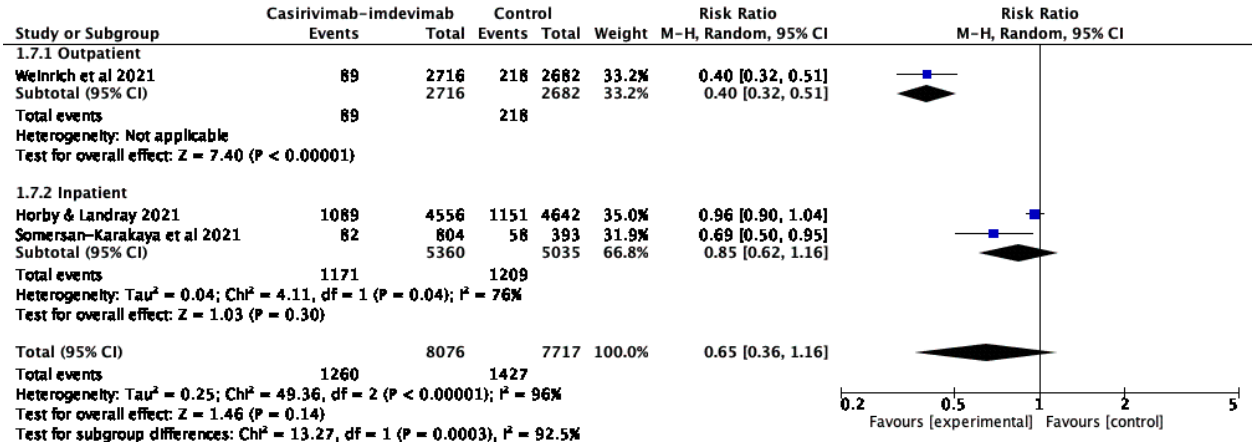

Figure 5. Need for invasive mechanical ventilation or death by hospitalization status

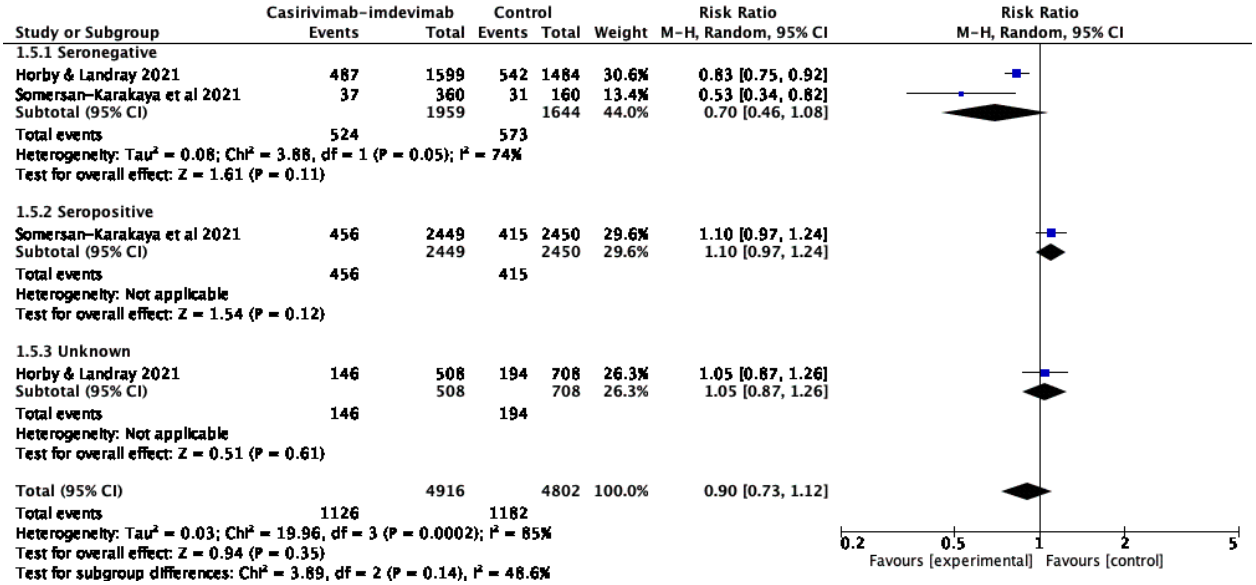

Figure 6. Need for invasive mechanical ventilation by antibody status

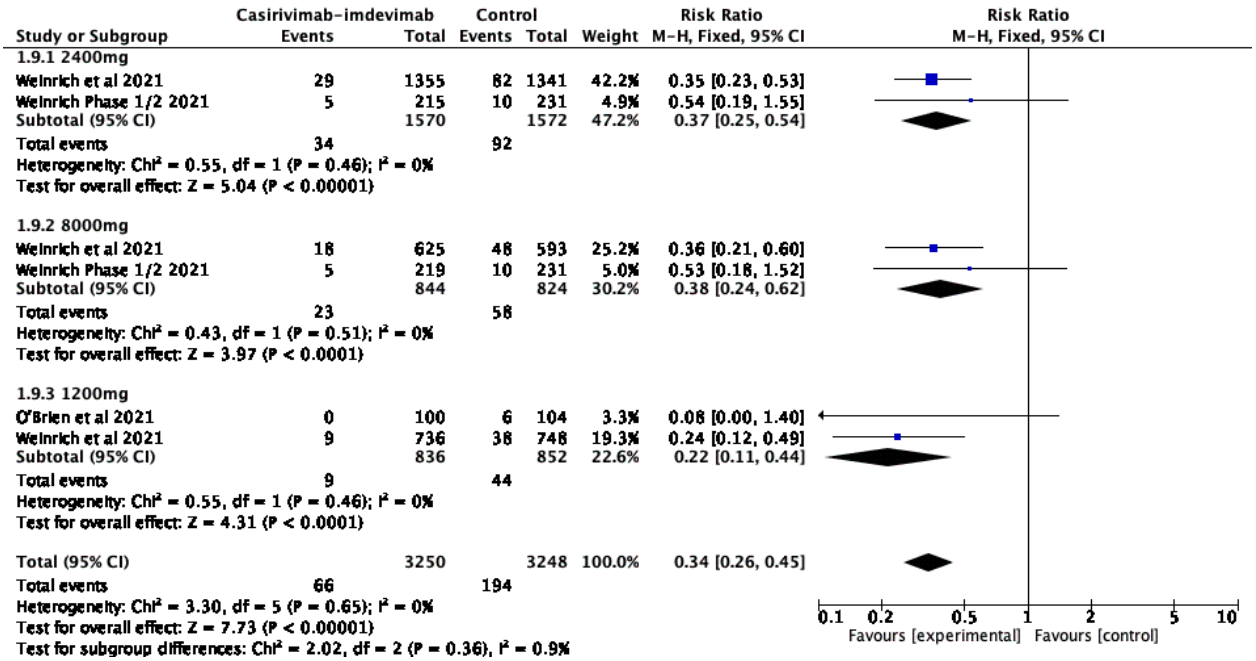

Figure 7. At least 1 COVID-related MAV by dose

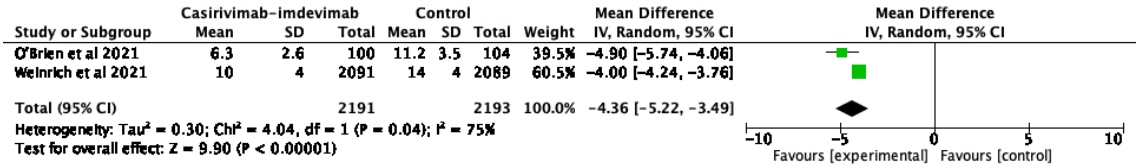

Figure 8. Duration of COVID-19 symptoms in days

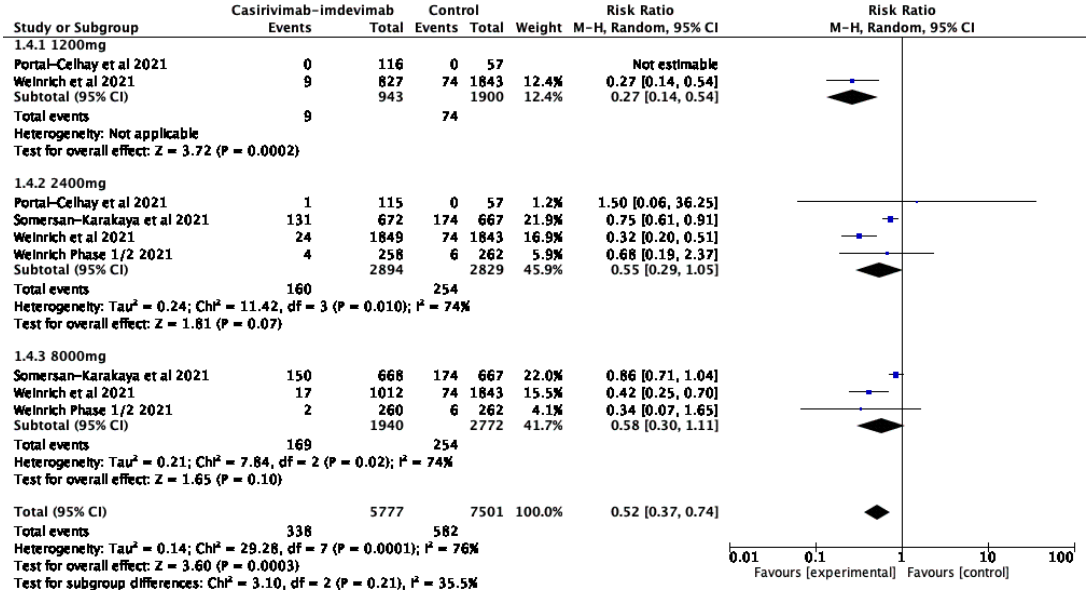

Figure 9. Serious adverse events by dose

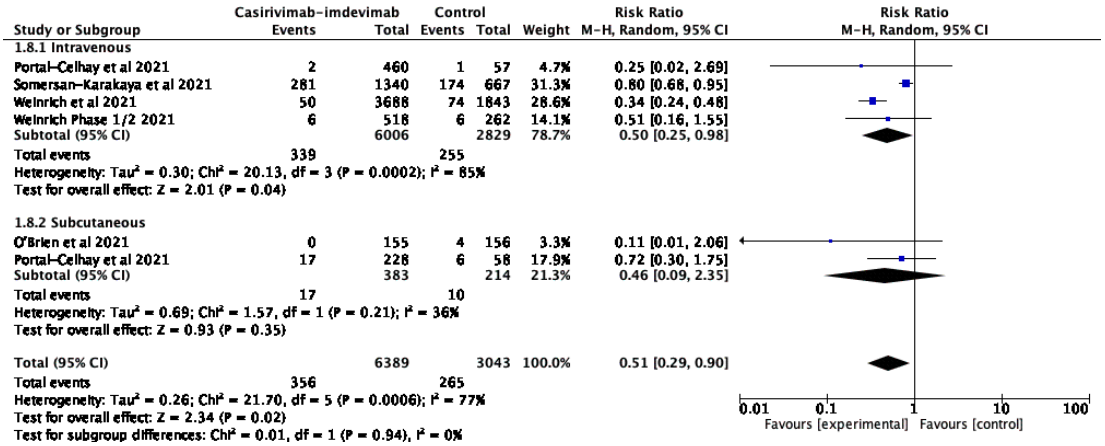

Figure 10. Serious adverse events by route of administration

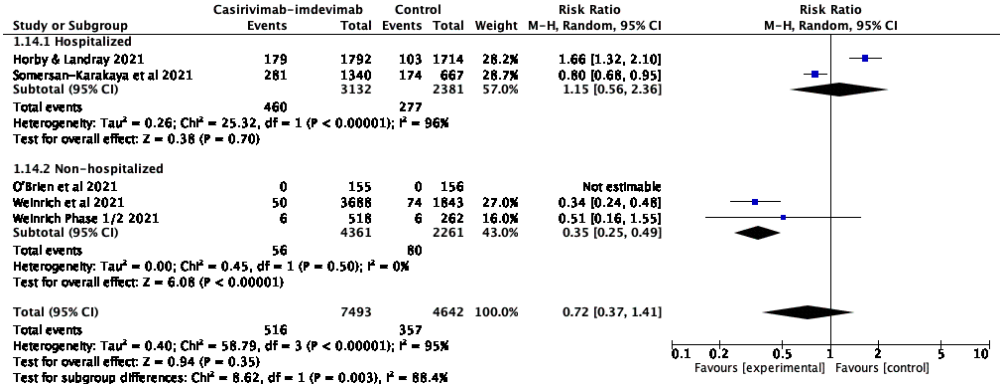

Figure 11. Serious adverse events by hospitalization status

Appendix 7. Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT0458410 ACTIV-2: A Study for Outpatients with COVID-19	Randomized control trial	USA	Mild to moderate COVID-19 positive patients	Experimental 1: Bamlanivimab IV Experimental 2: BRII-196/BRII-198 IV Experimental 3: AZD7442 IV Experimental 4: SNG001 inhalation Experimental 5: AZD7442 IM Experimental 6: Camostat PO Experimental 7: BMS 986414 + BMS 986413 SC Experimental 8: SAB-185 IV Experimental 9: Casirivimab + imdevimab IV Control: Placebo IV	Prevention of disease progression	Dec 25, 2023
EudraCT 2021-002612-31 Adaptive, randomized, placebo-controlled trial to evaluate the efficacy of monoclonal antibodies in outpatients with mild or moderate COVID-19	Randomized controlled trial	Italy	COVID-19 positive patients ≥94% O2 saturation on room air with onset of COVID-19 symptoms no more than 4 days prior to the study drug administration	Bamlanivimab + etesevimab vs. placebo Casirivimab + imdevimab vs. placebo	COVID-19 disease progression (hospitalization, need for supplemental oxygen therapy at home or death) within 14 days of randomization	Not mentioned
EudraCT 2021-004035-88 A randomized, open-label, active controlled, parallel group, multicenter phase 3 study to	Randomized controlled trial	Italy	Mild to moderate COVID-19 positive patients	Bamlanivimab + etesivimab vs. casirivimab + imdevimab vs. sotrovimab vs. standard of care	Disease progression (hospitalization in intensive care unit, oxygen desaturation ≥4% or peripheral	Not mentioned

evaluate the efficacy and tolerability of Bamlanivimab and Etesivimab, Casirivimab and Imdevimab, and Sotrovimab versus Standard of Care in patients with mild to moderate COVID-19 disease					oxygen saturation ≤92%) during the 30-day follow-up period, adverse events	
NCT05092581 A Phase 1b, Open-Label, Single Dose Study Assessing the Pharmacokinetics, Safety, Tolerability and Efficacy of Intravenous Anti-Spike(s) SARS-CoV-2 Monoclonal Antibodies (Casirivimab+Imdevimab) for the Treatment of Pediatric Patients Hospitalized Due to COVID-19	Randomized controlled trial	USA	Hospitalized children (up to 17 years old) with COVID-19	Casirivimab + imdevimab vs placebo	Concentrations of casirivimab+imdevimab in serum over time, proportion of patients with treatment-emergent SAEs, proportion of patients with infusion-related reactions, proportion of patients with hypersensitivity reactions, incidence of anti-drug antibodies to casirivmab+imdevimab over time, incidence of neutralizing antibodies to casirivimab+imdevimab over time	June 9, 2023
NCT04840459 Use of Monoclonal Antibodies (Bamlanivimab and Casirivimab+Imdevimab) for the Treatment of Mild to Moderate COVID-19 in Non-Hospitalized Setting	Randomized controlled trial	USA	Non-hospitalized COVID-19 positive patients ages 12 years and older weighing at least 40 kg who are at "high risk" for progressing to severe COVID-19 and/or hospitalization	Bamlanivimab vs. casirivimab-imdevimab vs. placebo	Disease progression (hospitalization), time to symptom resolution	January 31, 2022
NCT04748588 Canadian Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of Nosocomial Acquired COVID-19 Patients	Randomized controlled trial	Canada	Nosocomially-acquired hospitalized COVID-19 patients	Casrivimab-imdevimab vs. bamlanivimab vs. sotrovimab	Proportion of patients requiring mechanical ventilation or not surviving to hospital discharge, in-hospital death, need for mechanical ventilation, need for new intensive care admission, need	March 31, 2023

					for new oxygen administration	
NCT04790786 The UPMC Optimizing Treatment and Impact of Monoclonal antIbodies Through Evaluation for COVID-19 Trial (UPMC OPTIMISE-C19)	Randomized controlled trial	USA	COVID-19 positive patients eligible for mAB under FDA EUA	Bamlanivimab vs. Casirivimab-imdevimab vs. Bamlanivimab-etesevimab vs. Sotrovimab vs. placebo	Survival, all-location mortality, all-cause mortality, organ-support free days,	February 2022
NCT05081388 A Phase 1/2/3 Adaptive Sudy to Evaluate the Safety, Tolerability, and Efficacy of REGN14256+Imdevimab for the Treatment of COVID-19 Patients Without Risk Factors for Progression to Severe Disease	Randomized controlled trial	USA	Mild to moderate COVID-19 patients without co-morbidities	Casirivimab vs. imdevimab vs. casirivimab + imdevimab vs. placebo	Treatment emergent adverse events, injection-site reactions, hypersensitivity reactions, time-weight average daily change from baseline in viral load, time to COVID-19 symptom resolution	November 10, 2022

Q23. Among patients with COVID-19, should regdanvimab be used for treatment?

As of 20 December 2021

RECOMMENDATION

We suggest against the use of regdanvimab for the treatment of mild to moderate COVID-19. *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues

Very limited evidence (2 small randomized controlled trials, one of which is still a pre-print) support the use of regdanvimab in treatment of mild to moderate COVID-19. Although regdanvimab showed potential benefit in terms of clinical recovery at Day 14 and Day 28, the evidence was inconclusive for other critical outcomes such as all-cause mortality, need for hospitalization, or clinical deterioration. Clinical recovery among patients with moderate to severe symptoms at baseline was defined as improvement of symptoms and not necessarily complete resolution of symptoms. Concern regarding the effect of possible publication bias on subjective outcomes such as clinical recovery was raised, since currently available studies were both funded by regdanvimab's manufacturing company. Hence, the panel suggested against use of regdanvimab considering its limited evidence, potentially large cost, and availability of treatment alternatives with more robust evidence that has shown benefit on more objective outcomes (e.g., all-cause mortality and need for hospitalization) among patients with mild to moderate COVID-19.

KEY FINDINGS

Two (2) randomized controlled trials (RCTs) evaluated the efficacy of regdanvimab as treatment for patients with COVID-19. The overall certainty of evidence was very low because of serious risk of bias, imprecision, and high probability of publication bias. Among patients with mild to moderate COVID-19 infection, regdanvimab showed minimal potential benefit in terms of clinical recovery at Day 14 and Day 28. There was inconclusive evidence in terms of other critical outcomes such as all-cause mortality, need for hospitalization, and oxygen therapy requirement. There was no significant difference in adverse events between patients treated with regdanvimab compared to placebo.

INTRODUCTION

Regdanvimab or CT-P59 is a recombinant human monoclonal immunoglobulin G1 antibody, which has shown potent neutralizing activity against SARS-CoV-2 isolates. It binds to the receptor binding domain (RBD) of the virus' spike protein, thereby preventing viral entry into human cell via the angiotensin-converting enzyme 2 (ACE2) receptor and subsequent viral replication.[1]

REVIEW METHODS

We conducted a literature search for studies published from 2019 to December 5, 2021. Databases searched were Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL), Epistemonikos, and Google Scholar with a combined MeSH and free text search using the terms Regdanvimab OR CT-P59 AND COVID-19 OR coronavirus. Registries for ongoing or completed clinical trials were also searched (*clinicaltrials.gov*, ISRCTN registry, and World Health Organization International

Clinical Trials Registry Platform). We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv, and biorxiv. References of all studies were reviewed to identify other studies. Only randomized controlled trials that compared regdanvimab against placebo or standard of care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, or adverse events. No limits were placed on age, COVID-19 severity, hospitalization status, and dosing strategy of regdanvimab. Subgrouping by severity was planned.

RESULTS

Of the 137 records identified from the search, 2 RCTs with total of 345 participants were included in this review. The first RCT is a Phase 1 trial involving healthy subjects and COVID-19 patients with mild infection. Only patients with mild COVID-19 infection were included in this review.[2] The second RCT is a pre-print Phase 2/3 trial of the earlier study, which enrolled COVID-19 patients with mild to moderate infection.[3] Both trials were funded by the manufacturing company of regdanvimab. Comparing with placebo, the Phase 1 trial [2] used three doses of regdanvimab (20 mg/kg, 40 mg/kg, and 80 mg/kg), while the Phase 2/3 trial [3] used two doses (40 mg/kg and 80 mg/kg), all given as one dose of IV infusion. The characteristics of studies are reported in Appendix 3.

The overall certainty of evidence was assessed to be very low due to serious risk of bias, imprecision in some critical outcomes, and probability of publication bias. Publication bias was considered for all outcomes because the only trials available were sponsored by the manufacturing company of regdanvimab. The risk of bias summary is shown in Appendix 4. The GRADE evidence profile is in Appendix 5.

Based from 2 RCTs, which enrolled patients with mild-moderate COVID-19 infection, regdanvimab showed a trend towards benefit in terms of clinical recovery at Day 14 for both 40mg/kg (RR 1.23, 95% CI 1.02-1.47; $I^2 = 0$) and 80mg/kg (RR 1.25, 95% CI 1.04-1.49; $I^2 = 0$). Clinical recovery was defined as all symptoms being absent or mild for $\geq$ 24 hours. A patient has clinical recovery if symptoms scored as moderate or severe at baseline became mild or absent at recovery. A patient has clinical recovery if symptoms scored as mild or absent at baseline became absent at recovery. At Day 7, 40mg/kg dose showed trend towards benefit (RR 1.46, 95% CI 1.08-1.97; $I^2 = 0$), whereas the result was inconclusive for 80mg/kg (RR 1.34, 95% CI 0.98-1.81; $I^2 = 0$). There was no benefit at Day 7 and 14 for 20mg/kg dose. There was no significant difference in terms of time to recovery among those with mild COVID-19 infection given regdanvimab, for both 40 mg/kg (MD -1.9 days, 95% -4.96 to 1.15; $I^2 = 0$) and 80 mg/kg (MD -1.58 days, 95% -4.29 to 1.14; $I^2 = 0$) compared to placebo.[2,3]

Based from 1 RCT, regdanvimab showed a trend towards benefit in terms of clinical recovery at Day 28 for both 40 mg/kg (RR 1.22, 95% CI 1.06-1.42) and 80mg/kg (RR 1.2, 95% CI 1.03-1.4).[3]

The median time to recovery was shorter among patients with moderate COVID-19 infection who were given regdanvimab 40mg/kg (5.73 days, 95% CI 4.13-7.33) and 80mg/kg (7.3 days, 95% CI 5.58-10.72) compared to placebo (10.81 days, 95% CI 6.81-not calculable). There is insufficient data to conclude whether these differences were statistically significant. Subgroup analysis showed that for moderate infection and patients aged $\geq$ 50 years old, the median time to recovery was 6.64 days (95% CI 4.13-11.94) for 40 mg/kg dose, 7.29 days (95% CI 5.54-12.33) for 80 mg/kg dose, and 12.97 days(95% CI 6.81-not calculable) for placebo.[3]

None of the patients with mild COVID-19 infection were hospitalized or required oxygen therapy. Regdanvimab did not significantly reduce the need for hospitalization among patients with mild to moderate COVID-19 infection compared to placebo, for both 40mg/kg (RR 0.45, 95% CI 0.14-1.42) and 80mg/kg (RR 0.56, 95% CI 0.19-1.6). Likewise, there was no significant difference in terms of oxygen therapy requirement among those given regdanvimab 40mg/kg (RR 0.45, 95% CI 0.14-1.42) and 80mg/kg (RR 0.44, 95% CI 0.14-1.4) compared to placebo. Subgroup analyses considering only patients aged $\geq$ 50 years old with moderate infection still showed inconclusive results on need for hospitalization or oxygen therapy for both 40mg/kg dose (RR 0.32, 95% CI 0.09-1.08) and 80mg/kg dose (RR 0.42, 95% CI 0.14-1.26).[3]

Mean change in viral titers (log_{10} copies/ml) measured from baseline up to 7 days following treatment showed trend towards benefit among patients given regdanvimab 20mg/kg (MD -2.11, 95% CI -3.97 to -0.25), but not among those given 40mg/kg (MD -0.76, 95% CI -2.57 to 1.05) or 80mg/kg (MD -1.29, 95% CI -2.78 to 0.19).[2]

Safety

There was no significant difference in adverse events between patients treated with regdanvimab compared to placebo (RR 0.91, 95% CI 0.65-1.29; $I^2 = 0$). Most adverse events were mild. There was no incidence of anaphylaxis nor life-threatening adverse events. There was no evidence of dose-related increase in toxicity. There was no occurrence of any adverse event causing discontinuation of treatment.[2,3]

In the Phase 1 trial, adverse events reported included diarrhea (13.3% of patients given regdanvimab), flank pain (6.6%), insomnia (6.6%), productive cough (6.6%), palpitations (6.6%), dysphagia (6.6%), Candida infection (unspecified location, 6.6%), increased ALT (13.3%), and increased blood creatine phosphokinase (6.6%). One patient had grade 3 hepatocellular injury (6.6%). One patient (6.6%) had baseline obesity and hypertriglyceridemia and had worsening of hypertriglyceridemia after being given regdanvimab. However, the investigators stated that all the adverse events were considered unrelated to the study drug.[2]

In the Phase 2/3 trial, the most frequently reported adverse event was hypertriglyceridemia but the number of patients affected was not reported. One patient had infusion-related reaction, described as fever and dyspnea, which resolved on the same day after paracetamol and oxygen therapy.[3]

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Australian COVID-19 Guidelines (as of November 26, 2021) [4]	Recommends against the use of monoclonal antibody regdanvimab for the treatment of COVID-19 outside of randomized trials with appropriate ethical.
NIH COVID-19 Guidelines (as of October 19, 2021)	No statement on the recommendation of regdanvimab as treatment for COVID-19.[5-8]
Surviving Sepsis Campaign Guidelines (as of January 29, 2021)	
Infectious Diseases Society of America (as of November 18, 2021	
World Health Organization (WHO) Living Guidelines (as of September 24, 2021)	
Korean Society of Infectious Diseases/National Evidence-based Healthcare Collaborating Agency Guidelines (as of June 18, 2021) [11]	Anti-SARS-CoV-2 monoclonal antibody may be considered in patients with mild to moderate COVID-19 who are at high risk of progression to severe COVID-19. (*Low level of evidence; Grade of recommendation: B, conditional)* Anti-SARS-CoV-2 monoclonal antibody is not recommended for patients with severe COVID-19. These treatments may be considered for clinical trials of patients with severe COVID-19 requiring supplemental oxygen but not high flow oxygen or invasive mechanical ventilation. *(Low level of evidence; Grade of recommendation: C, not recommended)* Anti-SARS-CoV-2 monoclonal antibody pertains to bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab, and regdanvimab.

RESEARCH GAPS

There is one (1) ongoing study on regdanvimab, also funded by the manufacturer. It is a Phase 2/3, randomized, parallel-group, placebo-controlled, double-blind study, which aimed to evaluate the efficacy and safety of regdanvimab in combination with standard of care, in patients hospitalized with COVID-19.[3] It has already completed recruitment as of October 20, 2021, but results were not published yet. As of writing, there are no independent trials studying the efficacy of regdanvimab for COVID-19 infections.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 5)

FACTORS	JUDGEMENT (N = 5)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					
Benefits	Large	Moderate	Small (2)	Uncertain (3)			• Regdanvimab showed trend towards benefit in terms of clinical recovery at Day 14 and Day 28. • Inconclusive evidence in terms of other critical outcomes such as all-cause mortality, need for hospitalization, and oxygen therapy requirement.
Harm	Large	Small (2)	Uncertain (3)				• No significant difference in adverse events between patients treated with regdanvimab compared to placebo (RR 0.91, 95% CI 0.65-1.29) • Adverse events: hypertriglyceridemia, increased ALT, 1 infusion-related (fever, dyspnea), cough, diarrhea
Certainty of Evidence	High	Moderate	Low (2)	Very low (3)			• Very low due to serious risk of bias, imprecision in some critical outcomes, and high probability of publication bias
Balance of effects	Favors drug	Does not favor drug (1)	Uncertain (4)				• Minimal net potential benefit (in terms of clinical recovery), with no significant harm
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (4)	Moderate cost (1)	Negligible cost	Moderate savings	Large savings	• Regdanvimab is currently not available in the Philippines. • Its estimated cost is PHP 25,000 / course
Certainty of evidence of required resources	No included studies (5)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (4)	Favors the comparison	Does not favor either the intervention or the comparison (1)	Favors the intervention			
Equity	Uncertain (3)	Reduced (2)	Probably no impact	Increased			
Acceptability	Uncertain (5)	No	Yes				
Feasibility	Uncertain (2)	No (3)	Yes				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	(regdanvimab OR CT-P59 OR (regdanvimab[tiab]) OR (CT-P59[tiab])) AND (((COVID-19[MeSH Terms]) OR (coronavirus[MeSH Terms])) OR ((COVID-19 [tiab]) OR (coronavirus [tiab]))) AND (((((((COVID-19[MeSH Terms]) OR (coronavirus[MeSH Terms])) OR (sars-cov-2[MeSH Terms])) OR (nCoV [tiab])) OR (COVID-19)) OR (COVID-19 [tiab])) OR (coronavirus [tiab])) OR (SARS-CoV-2 [tiab]))	Dec 5, 2021	11	1
CENTRAL	(regdanvimab OR CT-P59) AND (COVID-19 OR SARS-Cov-2 OR coronavirus)	Dec 5, 2021	1	1
Google Scholar	Regdanvimab OR CT-P59 AND COVID-19 OR SARS-Cov-2	Dec 5, 2021	109	5
COVID-NMA initiative	Regdanvimab OR CT-P59	Dec 5, 2021	10	0
ClinicalTrials.gov	Regdanvimab OR CT-P59	Dec 4, 2021 10:00 AM	1	1
Chinese Clinical Trial Registry	Regdanvimab OR CT-P59	Dec 4, 2021 10:05 AM	0	0
EU Clinical Trials Register	Regdanvimab OR CT-P59	Dec 4, 2021 10:10 AM	0	0
Republic of Korea - Clinical Research Information Service	Regdanvimab OR CT-P59	Dec 4, 2021 10:15 AM	1	1
Japan Primary Registries Network/ NIPH Clinical Trials Search	Regdanvimab OR CT-P59	Dec 4, 2021 10:20 AM	0	0
CenterWatch	Regdanvimab OR CT-P59	Dec 4, 2021 10:25 AM	0	0
chinaxiv.org	(Regdanvimab OR CT-P59) AND (COVID-19 OR SARS-Cov-2)	Dec 5, 2021	0	0
Medrxiv.org	(Regdanvimab OR CT-P59) AND COVID-19	Dec 5, 2021	4	0
Biorxiv.org	(Regdanvimab OR CT-P59) AND COVID-19	Dec 5, 2021	13	0

Appendix 3. Characteristics of Included Studies

Author	Study Design	Country	Population	Intervention	Control	Outcomes
Kim et al. 2021	RCT	South Korea, Romania	Part 1.1: Age 19 to 55 years, without SARS-CoV-2 infection, weigh ≥50 kg, BMI 18-29.9 (not included in this review) Part 1.2: Age 18-70 years, with mild SARS-Cov-infection (based on WHO) diagnosed by RT PCR, with O2 sats >94%, and symptom onset within 7 days before drug administration	Regdanvimab at 3 doses (20 mg/kg, 40 mg/kg and 80 mg/kg) as IV infusion, single dose	Placebo (0.9% NaCl)	Adverse events, vital signs, ECG, physical exam, laboratory tests, radiography; Pharmacokinetics; Incidence of antidrug antibodies (ADA); Time to clinical recovery; Proportion of patients with clinical recovery up to day 14
Eom et al. 2021 (pre-print)	RCT	South Korea, Romania, Spain, USA	Age ≥ 18 years, with SARS-Cov-2 infection diagnosed by rapid SARS-Cov-2 test or RT-PCR, with O2 sats >94%, mild to moderate infection (based on WHO), and symptom onset within 7 days before drug administration	Regdanvimab at 2 doses (40 mg/kg and 80 mg/kg) as IV infusion, single dose	Matching placebo	Time to conversion to negative RT PCR; Time to clinical recovery; Proportion of patients with clinical recovery; Proportion of patients requiring hospitalization, oxygen therapy, mechanical ventilation, ICU admission, or rescue therapy; All cause mortality; Proportion of patients with conversion to negative RT PCR

Appendix 4. Study Appraisal

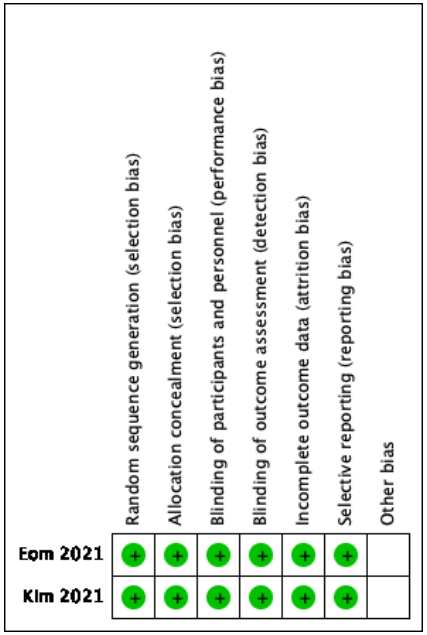

Fig. 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Furqaan Lim, April Padua-Zamora
Question: Should Regdanvimab be used to treat patients with COVID-19?
Setting: South Korea, Romania
Bibliography: Kim JY, Jang YR, Hong JH, et al. Safety, Virologic Efficacy, and Pharmacokinetics of CT-P59, a Neutralizing Monoclonal Antibody Against SARS-CoV-2 Spike Receptor-Binding Protein: Two Randomized, Placebo-Controlled, Phase I Studies in Healthy Individuals and Patients With Mild SARS-CoV-2 Infection. 18 Aug 2021. Available from https://doi.org/10.1016/j.clinthera.2021.08.009

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regdanvimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mean change in viral titers (20 mg/kg Regdanvimab)												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected[a]	5	3	-	MD **2.11 lower** (3.97 lower to 0.25 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Mean change in viral titers (40 mg/kg Regdanvimab)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	5	3	-	MD **0.76 lower** (2.57 lower to 1.05 higher)	⊕⊕◯◯ LOW	IMPORTANT
Mean change in viral titer (80 mg/kg Regdanvimab)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	5	3	-	MD **1.29 lower** (2.78 lower to 0.19 higher)	⊕⊕◯◯ LOW	IMPORTANT
Time to recovery, mild infection (20 mg/kg Regdanvimab)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[c]	Publication bias strongly suspected[a]	5	3	-	MD **0.82 lower** (8.69 lower to 7.05 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Clinical recovery at day 7 (20 mg/kg Regdanvimab)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	4/5 (80.0%)	2/3 (66.7%)	**RR 1.20** (0.48 to 2.99)	**133 more per 1,000** (from 347 fewer to 1,000 more)	⊕⊕◯◯ LOW	IMPORTANT

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regdanvimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical recovery at day 14 (20 mg/kg Regdanvimab)												
1	Randomised trials	Not serious	Not serious	N ot serious	Very serious[c]	Publication bias strongly suspected[a]	5/5 (100.0%)	2/3 (66.7%)	**RR 1.47** (0.66 to 3.25)	**313 more per 1,000** (from 227 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	IMPORTANT

Author(s): Furqaan Lim, April Padua-Zamora
Question: Should Regdanvimab be used to treat patients with COVID-19?
Setting: South Korea, Romania, Spain, USA
Bibliography: Eom, JS, Ison M, Streinu-Cercel A, et al. Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebocontrolled trial in outpatients with mild-to-moderate
SARS-CoV-2 infection. 15 March 2021. Available from https://www.researchsquare.com/article/rs-296518/v1

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regdanvimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical recovery at day 28 (40 mg/kg Regdanvimab)												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected[a]	83/95 (87.4%)	70/98 (71.4%)	**RR 1.22** (1.06 to 1.42)	**157 more per 1,000** (from 43 more to 300 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Clinical recovery at day 28 (80 mg/kg Regdanvimab)												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected[a]	79/92 (85.9%)	70/98 (71.4%)	**RR 1.20** (1.03 to 1.40)	**143 more per 1,000** (from 21 more to 286 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Requirement for hospitalization (40 mg/kg Regdanvimab) for mild-moderate infection												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	4/101 (4.0%)	9/103 (8.7%)	**RR 0.45** (0.14 to 1.42)	**48 fewer per 1,000** (from 75 fewer to 37 more)	⊕⊕◯◯ LOW	CRITICAL
Requirement for oxygen therapy (40 mg/kg Regdanvimab) for mild-moderate infection												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	4/101 (4.0%)	9/103 (8.7%)	**RR 0.45** (0.14 to 1.42)	**48 fewer per 1,000** (from 75 fewer to 37 more)	⊕⊕◯◯ LOW	CRITICAL

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regdanvimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Requirement for hospitalization or oxygen therapy (40 mg/kg Regdanvimab) for moderate infection												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	4/62 (6.5%)	9/57 (15.8%)	**RR 0.41** (0.13 to 1.25)	**93 fewer per 1,000** (from 137 fewer to 39 more)	⨁⨁◯◯ LOW	CRITICAL
Requirement for hospitalization or oxygen therapy (40 mg/kg Regdanvimab) for moderate infection, age≥50 years												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	3/40 (7.5%)	9/38 (23.7%)	**RR 0.32** (0.09 to 1.08)	**161 fewer per 1,000** (from 216 fewer to 19 more)	⨁⨁◯◯ LOW	CRITICAL
Requirement for hospitalization (80 mg/kg Regdanvimab) for mild-moderate infection												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	5/103 (4.9%)	9/103 (8.7%)	**RR 0.56** (0.19 to 1.60)	**38 fewer per 1,000** (from 71 fewer to 52 more)	⨁⨁◯◯ LOW	CRITICAL
Requirement for oxygen therapy (80 mg/kg Regdanvimab) for mild-moderate infection												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	publication bias strongly suspected[a]	4/103 (3.9%)	9/103 (8.7%)	**RR 0.44** (0.14 to 1.40)	**49 fewer per 1,000** (from 75 fewer to 35 more)	⨁⨁◯◯ LOW	CRITICAL
Requirement for hospitalization or oxygen therapy (80 mg/kg Regdanvimab) for moderate infection												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	publication bias strongly suspected[a]	5/63 (7.9%)	9/57 (15.8%)	**RR 0.50** (0.18 to 1.41)	**79 fewer per 1,000** (from 129 fewer to 65 more)	⨁⨁◯◯ LOW	CRITICAL
Requirement for hospitalization or oxygen therapy (80 mg/kg Regdanvimab) for moderate infection, age≥50 years												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	publication bias strongly suspected[a]	4/40 (10.0%)	9/38 (23.7%)	**RR 0.42** (0.14 to 1.26)	**137 fewer per 1,000** (from 204 fewer to 62 more)	⨁⨁◯◯ LOW	CRITICAL
Requirement for mechanical ventilation (80 mg/kg Regdanvimab)												
1	Randomised trials	Not serious	Not serious	Not serious	very serious[c]	publication bias strongly suspected[a]	1/103 (1.0%)	0/103 (0.0%)	**RR 3.00** (0.12 to 72.80)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regdanvimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Requirement for rescue therapy (40 mg/kg Regdanvimab)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	7/101 (6.9%)	15/103 (14.6%)	**RR 0.48** (0.20 to 1.12)	**76 fewer per 1,000** (from 117 fewer to 17 more)	⊕⊕◯◯ LOW	CRITICAL
Requirement for rescue therapy (80 mg/kg Regdanvimab)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	11/103 (10.7%)	15/103 (14.6%)	**RR 0.73** (0.35 to 1.52)	**39 fewer per 1,000** (from 95 fewer to 76 more)	⊕⊕◯◯ LOW	CRITICAL

Author(s): Furqaan Lim, April Padua-Zamora
Question: Should Regdanvimab be used to treat patients with COVID-19?
Setting: South Korea, Romania, Spain, USA
Bibliography:

1) Kim JY, Jang YR, Hong JH, et al. Safety, Virologic Efficacy, and Pharmacokinetics of CT-P59, a Neutralizing Monoclonal Antibody Against SARS-CoV-2 Spike Receptor-Binding Protein: Two Randomized, Placebo-Controlled, Phase I Studies in Healthy Individuals and Patients With Mild SARS-CoV-2 Infection. 18 Aug 2021. Available from https://doi.org/10.1016/j.clinthera.2021.08.009
2) Eom, JS, Ison M, Streinu-Cercel A, et al. Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebocontrolled trial in outpatients with mild-to-moderate SARS-CoV-2 infection. 15 March 2021. Available from https://www.researchsquare.com/article/rs-296518/v1

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regdanvimab	Standard of care alone	Relative (95% CI)	Absolute (95% CI)		
Time to recovery, mild infection (40 mg/kg Regdanvimab)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	43	49	-	MD **1.9 lower** (4.96 lower to 1.15 higher)	⊕⊕◯◯ LOW	IMPORTANT
Time to recovery, mild infection (80 mg/kg Regdanvimab)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	45	49	-	MD **1.58 lower** (4.29 lower to 1.14 higher)	⊕⊕◯◯ LOW	IMPORTANT
Clinical recovery at day 7 (40 mg/kg Regdanvimab)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	57/100 (57.0%)	39/101 (38.6%)	**RR 1.46** (1.08 to 1.97)	**178 more per 1,000** (from 31 more to 375 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Clinical recovery at day 7 (80 mg/kg Regdanvimab)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	Publication bias strongly suspected[a]	51/97 (52.6%)	39/101 (38.6%)	**RR 1.34** (0.98 to 1.81)	**131 more per 1,000** (from 8 fewer to 313 more)	⊕⊕◯◯ LOW	IMPORTANT
Clinical recovery at day 14 (40 mg/kg Regdanvimab)												
2	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[a]	78/100 (78.0%)	64/101 (63.4%)	**RR 1.23** (1.02 to 1.47)	**146 more per 1,000** (from 13 more to 298 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

Clinical recovery at day 14 (80 mg/kg Regdanvimab)												
2	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[a]	77/97 (79.4%)	64/101 (63.4%)	**RR 1.25** (1.04 to 1.49)	**158 more per 1,000** (from 25 more to 310 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total adverse events												
2	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	68/230 (29.6%)	35/113 (31.0%)	**RR 0.91** (0.65 to 1.29)	**28 fewer per 1,000** (from 108 fewer to 90 more)	⊕⊕◯◯ LOW	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

[a] Limited trials available are sponsored by manufacturing company

[b] The outcome has imprecision because the results include the line of null effect and has a wide confidence interval.

[c] The outcome includes the line of null effect and has a very wide confidence interval.

Appendix 6. Forest Plots

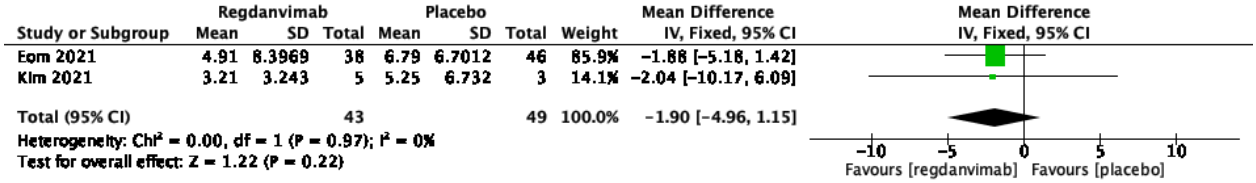

Figure 1. Time to recovery (40 mg/kg regdanvimab vs placebo)

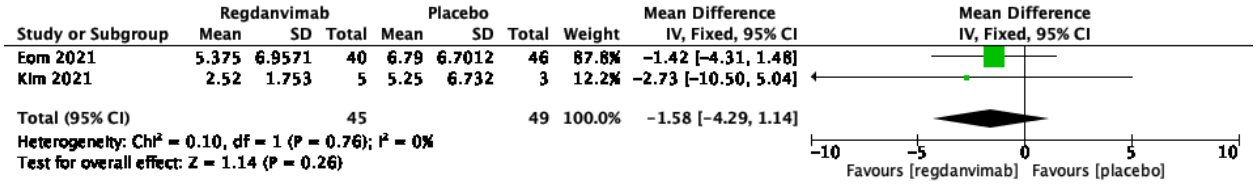

Figure 2. Time to recovery (80 mg/kg regdanvimab vs placebo)

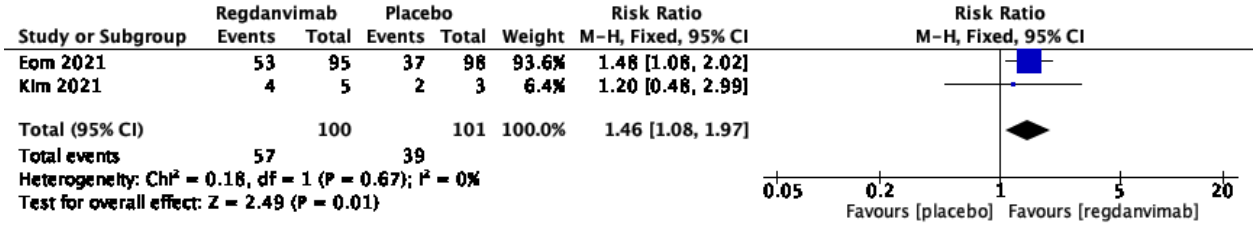

Figure 3. Patients with clinical recovery at day 7 (40 mg/kg regdanvimab vs placebo)

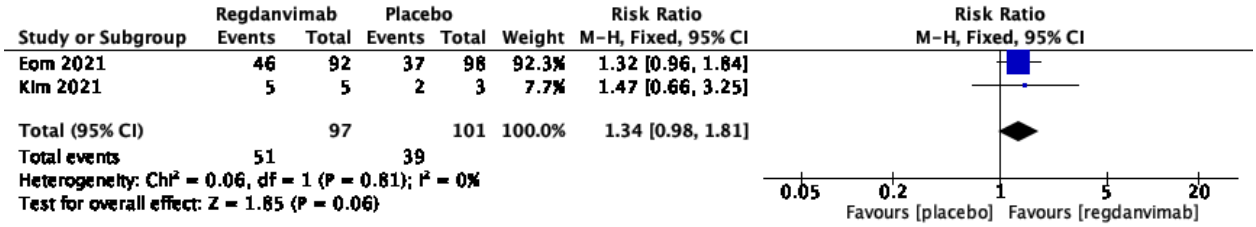

Figure 4. Patients with clinical recovery at day 7 (80 mg/kg regdanvimab vs placebo)

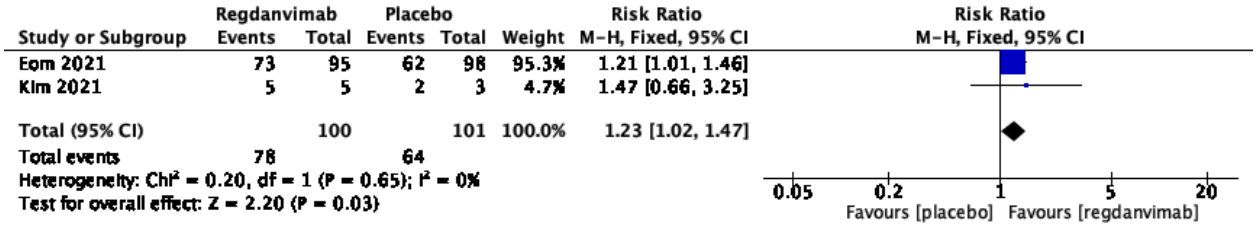

Figure 5. Patients with clinical recovery at day 14 (40 mg/kg regdanvimab vs placebo)

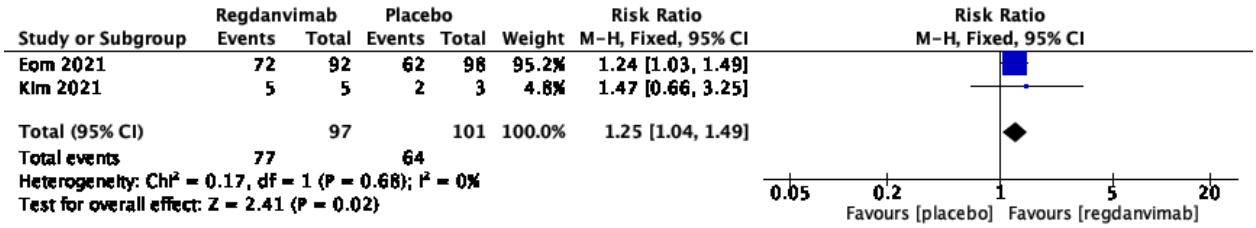

Fig. 6. Patients with clinical recovery at day 14 (80 mg/kg regdanvimab vs placebo)

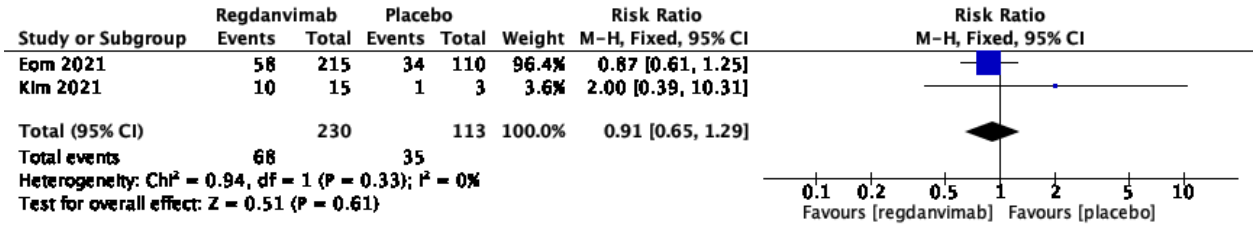

Fig. 7. Adverse events in patients (all doses of regdanvimab vs placebo)

Appendix 7. Ongoing Studies

Randomized Controlled Trials

Study ID	Setting	Title	Intervention	Control	Outcomes
NCT0460 2000	Multi-country (unspecified)	A Phase 2/3, Randomized, Parallel-group, Placebo-controlled, Double-Blind Study to Evaluate the Efficacy and Safety of CT-P59 in Combination with Standard of Care in Outpatients with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection	Regdanvimab	Placebo	Effect of CT-P59 on clinical symptoms requiring hospitalization, oxygen therapy, or mortality

Q24. Among patients with COVID-19, should convalescent plasma be used for treatment?

As of 18 November 2021

RECOMMENDATION

We recommend against the use of convalescent plasma in patients with COVID-19 infection. *(Moderate certainty of evidence, Strong recommendation)*

Consensus Issues
Serious adverse events and progression to respiratory distress/respiratory failure were re-rated and still considered as critical outcomes. However, the panel unanimously voted to give more value to the effect of convalescent plasma on all-cause mortality, clinical improvement, and need for invasive ventilation and ICU admission, hence, the over-all certainty of evidence was retained as moderate.

Recommendation remains strong given that convalescent plasma is no different from placebo in terms of efficacy, clinical outcomes, and harm; yet there is a lot to consider in terms of cost, value preferences, equity, and feasibility.

PREVIOUS RECOMMENDATION

We recommend against the use of convalescent plasma in patients with COVID-19 infection. *(Moderate certainty of evidence; Strong recommendation)*

Previous Consensus Issues
None were raised during panel meetings.

WHAT'S NEW IN THIS VERSION?

Eight (8) new randomized controlled trials have been added to this review.

KEY FINDINGS

There are 22 randomized controlled trials (RCTs) that compared the effect of convalescent plasma therapy against placebo and/or standard of care among confirmed COVID-19 patients. Pooled estimates of critical patient outcomes (i.e., all-cause mortality) on the use of convalescent plasma were not statistically significant. Exploratory subgroup analysis done for all-cause mortality by age, severity of disease, and timing of administration did not show any statistically significant benefit except for the subgroup of early administration (defined as within 3 days of hospitalization) of high-level titers of convalescent plasma (RR 0.42, 95% CI 0.21, 0.86; I^2 = 0%; 4 RCTS, n = 376).

The incidence of adverse and serious adverse events (e.g., transfusion-related events) were not significantly different between the convalescent plasma group and those given standard care or placebo. The over-all certainty of evidence was retained as moderate.

INTRODUCTION

The use of convalescent plasma for passive immunity has been shown to be safe and effective in reducing viral load with consequent decreases in cytokines in a diverse range of viral diseases, such as the Spanish flu (1915), type A flu (H1N1, 2009-2010),

avian flu (H5N1), Ebola virus, Zika virus, Middle East Respiratory Syndrome (MERS-CoV), and Severe Acute Respiratory Syndrome (SARS), specifically in the case of SARS-CoV-1.[1-7]

Convalescent plasma contains neutralizing antibodies that may aid in more rapid clearance of SARS-CoV-2 through accelerated viral clearance and blunting of the pro-inflammatory profile with decreases in IL-6, IL-10, and tumor necrosis factor-α as proposed mechanisms evaluated during those other epidemics.[3] The results of a study by Cheng in 2005 and a meta-analysis by Mair-Jenkins in 2015 support the usefulness of passive immunization using convalescent plasma to treat the disease and also suggests that the use of convalescent plasma is more effective if administered before day 14 following the onset of the disease.[8]

Majority of studies on convalescent plasma documented minimum risk factors or side effects with the latest efficacy studies demonstrating inconclusive results [9] and therefore immediate studies should target convalescent plasma preparations with high titer levels of anti–SARS-CoV-2 antibodies given early in the disease course with comparative research studies that involve the determination of antibody titers to demonstrate efficacy.

REVIEW METHODS

A systematic search was done on Medline, Cochrane Library, and Google Scholar until September 11, 2021 with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and convalescent plasma. The COVID-NMA Living Data was also checked and a search for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries was done. Preprints using medrxiv, chinaxiv and biorxiv were also searched. Only randomized controlled trials that compared convalescent plasma against placebo or standard care were included in this review. Outcomes of interest included mortality, clinical improvement, time to clinical improvement/resolution of symptoms, progression to respiratory distress or failure, duration of hospitalization, need for ICU admission, viral clearance, time to viral clearance, and adverse events or serious adverse events. Planned subgroup analysis was done for severity, time of administration of titer plasma, and oxygen support as needed.

RESULTS

There are 22 (17 published and 5 preprints) RCTs [10-32] comparing the effect of convalescent plasma therapy against placebo/fresh frozen plasma and/or standard of care among confirmed COVID-19 patients (n = 17, 251). Pooled estimates from the meta-analysis of the Living COVID-NMA and other eligible studies from the search yield were adopted for the outcomes reported.

Trials were conducted in different countries and different centers including two studies in Argentina [10,11], and USA [24, 30], three studies in India [12,13,18], and one study each in Bahrain [14], China [15], Netherlands [16], Spain [17], United Kingdom [20], Italy [22], Egypt [23], Germany [25], Chile [28], Uganda [29], Iraq [31], and Brazil [32]. There were 3 multicenter trials, one study conducted in Brazil and USA [21], one conducted in Canada, Brazil, and USA [26], and one conducted in Australia, Canada, UK and USA [27]. The summary of characteristics of included studies can be found in Appendix 3.

There were inconsistencies and imprecision in some critical outcomes and majority of the studies had serious risk of bias due to concerns with performance, detection, selection, and attrition bias. Serious adverse events and progression to respiratory distress/respiratory are considered as critical outcomes, however, the panel unanimously voted to give more value to the effect of convalescent plasma on all-cause mortality, clinical improvement and need for invasive ventilation and ICU admission. Hence, the over-all certainty of evidence was retained as moderate. The risk of bias summary is in Appendix 4. The GRADE evidence summary is in Appendix 5.

Overall, pooled estimates showed that the use of convalescent plasma in terms of all patient-centric outcomes did not reach statistical significance except for viral clearance at day 7 (RR 1.59, 95% CI 1.06, 2.37; 6 RCTs) but with substantial heterogeneity (I^2 = 61%) and the subgroup analysis by time of administration for all-cause mortality, which showed significant benefit when high level titers of convalescent plasma are given early (within 3 days of hospitalization) to patients (RR 0.42, 95% CI 0.21, 0.86; I^2 = 0%; 4 RCTs, n = 376).

Outcomes

Pooled estimates from 21 RCTs (n = 17,221) did not show significant difference in all-cause mortality between those who received the convalescent plasma versus those who received standards of care (RR 0.96, 95% CI 0.87, 1.06; I^2 = 17%). Likewise, pooled estimates for the remaining outcomes, namely duration of hospitalization (MD -1.42 days, 95% CI -4.5, 1.65; I^2 = 91%; 4 RCTs), time to clinical improvement/resolution of symptoms (MD -0.90 days, 95% CI -2.20, 0.41; I^2 = 95%; 3 RCTs), clinical improvement (RR 1.06, 95% CI 0.98, 1.15; p=0.07, I^2 = 41%; 12 RCTs), progression to respiratory distress/failure (RR 0.85, 95% CI 0.68, 1.07; I^2 = 19%; 9 RCTs), need for invasive ventilation (RR 1.00, 95% CI 0.91, 1.09; I^2 = 0%; 8 RCTs), need for ICU admission (RR 0.74, 95% CI 0.33, 1.66; I^2 = 38%; 2 RCTs), time to viral clearance (MD -0.76 days, 95% CI -6.73, 5.21 higher; I^2 = 90%; 2 RCTs) were not statistically beneficial. Most of these outcomes (duration of hospitalization, time to clinical improvement/resolution of symptoms, clinical improvement, time to viral clearance) had significant heterogeneity.

Sensitivity analysis excluding preprint studies revealed no significant difference in the all of the outcomes: all-cause mortality (RR 0.96, 95% CI 0.83, 1.12, I^2 = 17%), clinical improvement (RR 1.05, 95% CI 0.97, 1.14), progression to respiratory distress/failure (RR 0.88, 95% CI 0.68-1.07) need for invasive ventilation (RR 0.99 95% CI 0.74, 1.06), and duration of hospitalization (MD -0.73 days, 95% CI -4.4, 2.94, I^2 = 94%). Results of the sensitivity analysis are similar results with the over-all analysis, except for the outcome on viral clearance at day 7 where it initially showed benefit in the over-all analysis but not on the sensitivity analysis (RR 1.59, 95% CI 0.98, 2.57).

Subgroup Analysis

For the outcome of all-cause mortality, exploratory subgroup analysis was done according to severity of disease, age, oxygen support, and time of administration of high-level plasma titers. Subgroup analysis done for patients with mild disease severity (RR 0.86, 95% CI 0.49, 1.52; I^2 = 12%), moderate to severe disease severity (RR 1.03, 95% CI 0.84, 1.25; I^2 = 0%), moderate to critical disease severity (RR 0.95, 95% CI

0.84, 1.08; I^2 = 52%), severe/critical disease severity (RR 0.89, 95% CI 0.63, 1.25; I^2 = 39%) did not show statistically significant benefit in the use of convalescent plasma versus standard of care or placebo.

Subgroup analysis done by age demonstrated no statistically significant benefit in the use of convalescent plasma versus standard of care and/or placebo for both aged 50 years old and above (RR 0.88, 95% CI 0.70, 1.10; I^2 = 15%) and aged 60 years old and above (RR 0.96, 95% CI 0.90, 1.03; I^2 = 0%). Sensitivity analysis excluding preprints on aged 50 years old and above (RR 0.94, 95% CI 0.80, 1.10; I^2 = 5%) yielded a similar result.

Subgroup analysis done for oxygen support showed that the use of convalescent plasma was not significantly beneficial compared to standard of care and/or placebo for both non-oxygen requiring patients (RR 0.83, 95% CI 0.60, 1.14; n = 907, I^2 = %), patients on supplemental oxygen (RR 0.89, 95% CI 0.59, 1.32; I^2 = 40%), and patients on invasive ventilation (RR 0.88, 95% CI 0.45, 1.73; I^2 = 68%).

Subgroup Analysis by Time of Administration of High Titer Convalescent Plasma

Subgroup analysis by time of administration revealed that high level titers of convalescent plasma given early (within 3 days of hospitalization) to patients showed significant benefit compared to standard of care (RR 0.42, 95% CI 0.21, 0.86; I^2 = 0%, 4 RCTs, n = 376). There was no benefit noted for those given within 7 days (RR 0.98, 95% CI 0.65, 1.48; n = 5,931), and for those given within 14 days (RR 0.81, 95% CI 0.57, 1.17; n = 6,036) from onset of symptoms or hospitalization.

Characteristics of studies included in the early (within 3 days of hospitalization) subgroup were reviewed. Of the 4 RCTs, 1 was a double-blind placebo-controlled trial and 3 are open-label. These were conducted in different countries namely Argentina, Netherlands, Spain, and Iraq. The trials in Argentina and Netherlands only included patients aged ≥ 65 years and aged ≥ 55 years respectively, while the trials in Spain and Iraq included a wider age range of patients aged 45 to 76 years and 32 to 74 years respectively. One study involved mild COVID-19 patients, 1 study involved mild to moderate patients, 1 involved moderate to critical disease and 1 enrolled critically ill patients. In all the trials, transfusion was done within 3 days from hospitalization.

Safety

The incidence of adverse events (e.g., transfusion-related events) was not significantly different between the convalescent plasma group compared to those given standard of care and/or placebo (RR 1.11, 95% CI 0.98, 1.25; I^2 = 0%, n = 1,147). The proportions of serious adverse events were also not significantly different between the two groups (RR 1.19, 95% CI 0.93, 1.51; p=-.02, I^2 = 54%). Adverse events reported include cardiovascular (sinus bradycardia, tachycardia, arrhythmia, hypertension, hypotension); respiratory (dyspnea, hypoxia, pneumonia); neurologic (headache, dizziness); hematologic (bleeding, thrombosis, thrombocytopenia, leukocytosis, anemia); gastrointestinal (elevated liver enzymes, diarrhea, abdominal pain, nausea); and metabolic (fever, chills, hyperglycemia, electrolyte disturbances e.g., hyperkalemia, hypokalemia, hypernatremia). Serious adverse events reported include cardiovascular (sinus bradycardia, arrhythmia, hypotension, ventricular tachycardia, syncope, volume overload); neurologic (cerebral bleed, cerebral infarct); respiratory

(dyspnea, hypoxia, pneumonia, pulmonary hemorrhage, acute respiratory distress syndrome (ARDS), respiratory failure); hematologic (anemia, hemolysis, site hematoma); renal (acute kidney injury (AKI)); gastrointestinal (GI hemorrhage); and multi-organ failure. In majority of the studies, frequency of adverse events and serious adverse events was similar in both the convalescent plasma and the control groups. Transfusion-related events reported include febrile reaction, allergic reaction, transfusion associated dyspnea, transfusion associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI). Most of the transfusion-related complications were non-fatal and had complete recovery after treatment except in a trial in India wherein mortality in 3 participants (1%) was assessed as possibly related to CP transfusion.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Surviving Sepsis Campaign Guidelines (as of March 2021)	Recommends against the use of convalescent plasma for adults with severe or critical COVID-19 outside of clinical trials (*Low certainty of evidence, Weak recommendation).*[33]
NIH COVID-19 Treatment Guidelines (as of September 15, 2021)	• Recommends against the use of low-titer COVID-19 convalescent plasma for the treatment of COVID-19. *(Strong recommendation*) • Recommends against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients who do not have impaired immunity that are mechanically ventilated. *(Strong recommendation)* • Recommends against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients without impaired immunity who do not require mechanical ventilation, except in a clinical trial. *(Strong recommendation)* • For hospitalized patients with COVID-19 who have impaired immunity, there is insufficient evidence for the panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19. • There is also insufficient evidence for the panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in patients who are not hospitalized, except in a clinical trial.[34]
Infectious Diseases Society of America (as of August 25, 2021)	Suggests against COVID-19 convalescent plasma among patients hospitalized with COVID-19 *(Conditional recommendation, Low certainty of evidence)* and recommends COVID-19 convalescent plasma among ambulatory patients with mild-to-moderate COVID-19 only in the context of a clinical trial.[35]
Australian Guidelines (as of September 6, 2021)	Recommends against the use convalescent plasma for the treatment of COVID-19.[36]

RESEARCH GAPS

As of September 11, 2021, there are 93 ongoing clinical trials on convalescent plasma therapy registered. This review will be updated as soon as full results from these trials become available.

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Appendix 1. Evidence to Decision

FACTORS	JUDGEMENT (n=9)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					
Benefits	Large	Moderate (2)	Small (7)	Uncertain			• Viral clearance at D7 (non-critical outcome) was significantly beneficial
Harm	Large (1)	Small (8)	Uncertain				• The incidence of adverse and serious adverse events was not significantly different between 2 groups
Certainty of Evidence	High	Moderate (1)	Low (1)	Very low (7)			• It is rated very low due to serious risk of bias, inconsistency and imprecision in some critical outcomes
Balance of effects	Favors drug (2)	Does not favor drug (3)	Uncertain (4)				• Convalescent plasma showed net potential benefit [significantly beneficial for Viral clearance at D7and early (within 3 days) high titer plasma administration and beneficial but not statistically significant for all the remaining patient outcomes]and with no significant adverse events and serious adverse events reported.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability (1)			
Resources Required	Uncertain	Large cost (8)	Moderate cost (1)	Negligible cost	Moderate savings	Large savings	• One patient needs 2 aliquots. 1 aliquot is Php 28,000. • Total cost per patient is Php 56,000 (2 x 28,000/aliquot).
Certainty of evidence of required resources	No included studies (1)	Very low (2)	Low	Moderate (6)	High		• The cost is based on the UP-PGH Laboratory rate.
Cost effectiveness	No included studies (7)	Favors the comparison (1)	Does not favor either the intervention or the comparison (1)	Favors the intervention			
Equity	Uncertain (6)	Reduced	Probably no impact (1)	Increased (2)			
Acceptability	Uncertain (8)	No	Yes (1)				
Feasibility	Uncertain (4)	No (3)	Yes (2)				

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	("Coronavirus Infections"[MeSH Terms] OR "Coronavirus"[MeSH Terms] OR ("Coronavirus"[MeSH Terms] OR "Coronavirus"[All Fields] OR "coronaviruses"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR ("novel"[All Fields] AND "Coronavirus"[All Fields]) OR "novel coronavirus"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "ncov"[All Fields]) OR "COVID-19"[Supplementary Concept] OR ("COVID-19"[MeSH Terms] OR "COVID-19"[All Fields] OR "covid19"[All Fields]) OR ("COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("Coronavirus"[MeSH Terms] OR "Coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) OR ("COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("Coronavirus"[MeSH Terms] OR "Coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sars2"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sars 2"[All Fields]) OR ("SARS"[All Fields] AND "COV2"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[All Fields])) AND (("convalesce"[All Fields] OR "convalesced"[All Fields] OR "convalescence"[MeSH Terms] OR "convalescence"[All Fields] OR "convalescences"[All Fields] OR "convalescent"[All Fields] OR "convalescents"[All Fields] OR "convalescing"[All Fields]) AND ("plasma"[MeSH Terms] OR "plasma"[All Fields] OR "plasmas"[All Fields] OR "plasma s"[All Fields])) AND (("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "random"[All Fields] OR "randomization"[All Fields] OR "randomized"[All Fields] OR "randomisation"[All Fields] OR "randomisations"[All Fields] OR "randomise"[All Fields] OR "randomised"[All Fields] OR "randomising"[All Fields] OR "randomizations"[All Fields] OR "randomize"[All Fields] OR "randomizes"[All Fields] OR "randomizing"[All Fields] OR "randomness"[All Fields] OR "randoms"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields] OR "trial s"[All Fields] OR "trialed"[All Fields] OR "trialing"[All Fields] OR "trials"[All Fields]))	9/6/21 23:36:39	176	15
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {Convalescent Plasma} AND {Randomized trial}	9/8/21	134	17

COVID-NMA Initiative	Convalescent plasma	9/9/21	22	22
Google Scholar	{Coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {Convalescent Plasma} AND {Randomized trial}	9/10/21	7860	20
ClinicalTrials.gov	Coronavirus AND Convalescent plasma	9/9/21	45	11
Chinese Clinical Trial Registry	Coronavirus AND Convalescent plasma	9/10/21	473	0
EU Clinical Trials Register	Coronavirus AND Convalescent plasma	9/10/21	5	0
Republic of Korea - Clinical Research Information Service	Coronavirus AND Convalescent plasma	9/9/21	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Coronavirus AND Convalescent plasma	9/9/21	2	0
CenterWatch	Coronavirus AND Convalescent plasma	9/9/21	22	0
WHO database COVID-19 studies	Convalescent plasma	9/11/21	72	9
chinaxiv.org	Coronavirus AND Convalescent plasma	9/11/21	0	0
Medrxiv.org	Coronavirus AND Convalescent plasma	9/11/21	758	7
Biorxiv.org	Coronavirus AND Convalescent plasma	9/11/21	413	0

Appendix 3. Characteristics of Included Studies

Study ID	Participants	Sample Size	Comparisons		Design	Outcomes
			Treatment 1	Treatment 2		
ChiCTR2000029757 Li L, JAMA, 2020	Patients with COVID-19 (severe to critical) admitted to 7 centers in China	N = 103	Convalescent plasma	Standard care	RCT	All-cause mortality D28, Clinical improvement D28, Incidence of viral negative conversion at D7, Adverse events, Serious adverse events, Time to clinical improvement, Time to death
NCT04342182 Gharbharan A, medRxiv, 2020	Patients with COVID-19 (moderate-critical) admitted to 14 centers in the Netherlands	N = 86	Convalescent plasma	Standard care	RCT	All-cause mortality D28, Clinical improvement D28, Serious adverse events
NCT04345523 Avendano-Sola C, medRxiv, 2020	Patients with confirmed COVID-19 (moderate) admitted to 14 centers in Spain	N = 81	Convalescent plasma	Standard care	RCT	All-cause mortality D28, WHO Progression score level 7 or above at D28, Serious adverse events, Time to clinical improvement
CTRI/2020/04/024775 PLACID Agarwal A, BMJ, 2020	Patients with confirmed COVID-19 (mild to severe) admitted to 39 centers in India.	N = 464	Convalescent plasma	Standard care	RCT	All-cause mortality D28, Incidence of viral negative conversion at D7
NCT04346446 Bajpai M, medRxiv, 2020	Patients with confirmed COVID-19 (severe) admitted to a single center in India	N = 31	Convalescent plasma	Fresh frozen plasma	RCT	All-cause mortality D28, Improvement in O2 saturation at D7, Need for MV within 7 days, Duration of Hospital stay, ICU stay, Adverse events, Serious adverse events
NCT04356534 AlQahtani M, medRxiv, 2020	Patients with confirmed COVID-19 (severe) admitted to 2 centers in Bahrain	N = 40	Convalescent plasma	Standard care	RCT	All-cause mortality D28, Clinical improvement D28, Need for ventilation, Length of stay
NCT04479163 Libster R, N Engl J Med, 2021	Patients with confirmed COVID-19 (mild) admitted to multiple centers in Argentina	N = 160	Convalescent plasma (high titer)	Placebo	RCT	All-cause mortality, Adverse events, Serious adverse events

NCT04383535 PlasmAr Simonovich VA, N Engl J Med, 2020	Patients with confirmed COVID-19 (severe) admitted to 12 centers in Argentina	N = 334	Convalescent plasma	Placebo	RCT	All-cause mortality D28, Clinical improvement D28, WHO Progression score level 7 or above at D28, Adverse events, Serious adverse events, Time to clinical improvement, Time to WHO progression score level 7 or above, Time to death
CTRI/2020/05/025209 Ray Y, medRxiv, 2020	Patients with confirmed COVID-19 (severe) admitted to a single center in India	N = 80	Convalescent plasma	Standard care	RCT	All-cause mortality D28, Time to death, duration of hospital stay
NCT04530370 Salman OH, Egypt J Anaesth, 2020	Patients with confirmed COVID-19 (severe) admitted to a single center in Egypt	N = 30	Convalescent plasma	Standard care	RCT	Incidence of viral negative conversion at D7
NCT04381936; EudraCT 2020-001113-21; ISRCTN5018967 Horby P, (RECOVERY) medRxiv, 2021	Patients with suspected or confirmed COVID-19 (mild-moderate-severe-critical) admitted to 177 centers in the UK.	N = 11,558	Convalescent plasma (high titer)	Standard care	RCT	All-cause mortality D28, Clinical improvement D28
NCT04359810 O Donnell M, medRxiv, 2021	Patients with confirmed COVID-19 (mild-critical) admitted to 5 centers in Brazil and USA	N = 223	Convalescent plasma	Control plasma	RCT	All-cause mortality D28, WHO Progression score level 7 or above at D28, Adverse events, Serious adverse events, Time to clinical improvement
Pouladzadeh 2021	Patients with specified COVID-19 symptoms (less than 7 days since the onset of the symptoms) and severe disease.	N = 60	Convalescent plasma	Standard care	RCT	2month mortality after admission; length of in-hospital stay (LOS), 2-month mortality after admission, the improvement in the 8-point WHO severity score, and the frequency of CP therapy-related side effects
Bennett-Guerrero 2021	Patients hospitalized with a confirmed diagnosis of COVID-19 infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription polymerase chain reaction (PCR) testing.	N = 74	Convalescent plasma	Standard care	RCT	Total number of ventilator-free days from randomization to day 28; All-cause mortality through 9- days post randomization; WHO ordinal scale; Immune response

Koerper 2021	Patients with (1) SARSCoV-2 infection confirmed by PCR (bronchoalveolar lavage, sputum, nasal and/or pharyngeal swap); (2) age ≥ 18 years and ≤ 75 years and (3) severe disease	N = 105	Convalescent plasma	Standard care	RCT	Treatment success (dichotomous composite outcome of survival and no longer requiring ventilation support or ICU treatment and no tachypnea (i.e., respiratory rate <30 breaths/minute) on day 21; time to clinical improvement and the frequency and severity of adverse events (AE); all-cause mortality
NCT04348656 Begin, P (CONCOR-1) July 2021	Patients aged >16 in Canada or >18 years of age in the United States and Brazil who were admitted to the hospital ward with confirmed COVID-19 and who required supplemental oxygen.	N = 921	Convalescent plasma (high titer and low titer)	Standard care	RCT	Composite of intubation or death by day 30; time to intubation or death; ventilator-free days by day 30; in-hospital death by day 90; time to in-hospital death; death by day 30; length of stay in critical care and hospital; need for extracorporeal membrane oxygenation; need for renal replacement therapy; convalescent plasma associated adverse events; occurrence of ≥3 grade adverse events by day 30
Estcourt June 2021 Preprint	Patients aged 18 years or older with confirmed SARS-CoV-2 infection admitted to hospital and classified as moderately or severely ill, equivalent to severely or critically ill respectively, as per the World Health Organization (WHO) case definitions in Australia, Canada, UK and USA.	N = 2,011	Convalescent plasma (high titer)	Standard care	RCT	Respiratory and cardiovascular organ support-free days up to day 21; 28-day survival; 90-day survival; progression to invasive mechanical ventilation, extra corporeal mechanical oxygenation (ECMO) or death; intensive care and hospital length-of-stay; and World Health Organization ordinal scale at day 14; All-cause mortality at 28 days; Serious treatment-related adverse events; Serious Adverse Events (SAE)
Balcells March 2021	Patients over 18 years old who were hospitalized in an academic medical center in Santiago Chile with COVID-19 symptoms present at enrollment and confirmed with a positive SARS-CoV-2 real-time PCR	N = 58	Convalescent plasma	Standard of care and deferred plasma	RCT	Composite of mechanical ventilation, hospitalization for >14 days, or death; time to respiratory failure; days of mechanical ventilation; hospital length of stay; mortality at 30 days; and SARS-CoV-2 real-time PCR clearance rate

Kirenga Aug 2021	Patients with documented SARS-CoV-2-positive RT-PCR irrespective of severity performed at the trial laboratory of Makerere University Department of Immunology and Molecular Biology in Uganda	N = 136	Convalescent plasma + SOC	Standard of care	RCT	Time to viral clearance; time to symptom resolution, clinical status on the modified WHO Ordinal Clinical Scale for clinical improvement (≥1-point increase) and progression to severe/critical condition (defined as oxygen saturation (SPO2 < 93% or needing oxygen)
Korley Aug 2021	Multicenter trial (21 States in the US) of patients 50 years of age or older or had one or more risk factors for disease progression, with SARS-CoV-2 infection as confirmed by nucleic acid assay, with an onset of symptoms within 7 days before enrollment and patient's condition was stable for outpatient treatment without new supplemental oxygen	N = 511	Convalescent plasma (high titer)	placebo	RCT randomized, multicenter, single-blind trial)	Disease progression within 15 days after randomization; worst severity of illness on an 8-category ordinal scale, hospital-free days within 30 days after randomization, and death from any cause
Rasheed 2020	Critically-ill COVID-19 patients affected by pneumonia and residing in Respiratory Care Units (RCU) in Baghdad, Iraq	N = 49	Convalescent plasma + SOC	Standard of care	RCT	Recovery or death, length of stay in hospital, and improvement in the clinical course of the disease
Sekine 2021	Patients admitted to the hospital in Porto Alegre, Brazil (severe or critically ill) 18 yo or older, with confirmed COVID 19 infection, less than 15 days of initial symptoms onset and severe respiratory disease (defined by the presence of at least one of the following: respiratory rate >30 breaths per minute in room air; oxygen saturation (O2) ≤93% in room air; arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≤ 300; need for supplemental O2 to maintain O2 saturation >95%; need for supplemental O2 by high flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation)	N=160	Convalescent plasma + SOC	Standard of care	RCT	Clinical improvement 28 days after enrolment; RT PCR for SARS-CoV-2 from nasal and oropharyngeal swab at day 7 from enrolment or hospital discharge (if earlier than 7 days); clinical status assessed using the 6-level ordinal scale and all-cause mortality at days 14 and 28 after enrolment; time to hospital discharge and days alive and free of supplemental oxygen support (non-survivors and patients requiring oxygen support at day 28 were assigned as 0 supplemental oxygen support free-days) within 28 days from enrolment; Sequential Organ Failure Assessment (SOFA) score and National Early Warning Score 2 (NEWS) 2 on day 7 after enrolment; and length of invasive ventilatory support (for those who received mechanical ventilation)

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Appendix 4. Methodological Assessment of Included Studies

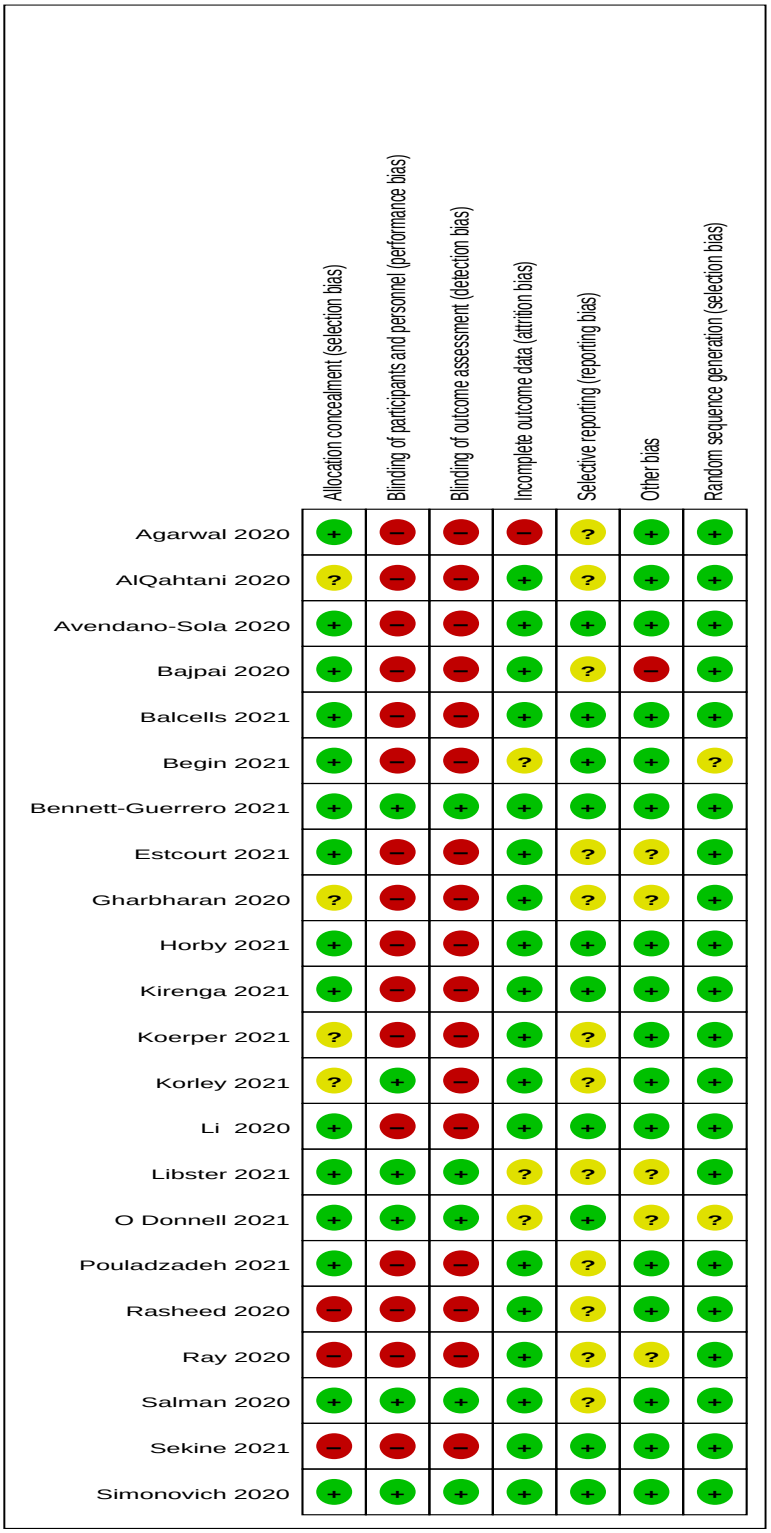

Figure 1. Risk of bias summary table

.

Appendix 5. GRADE Evidence Summary

Author(s): Liza Marie Bejemino, MD
Question: Convalescent plasma compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19
Setting: Worldwide
Bibliography: Convalescent Plasma versus Standard of Care for COVID 19 Infection. Cochrane Database of Systematic Reviews.

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Convalescent Plasma	Standard of care alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
21	Randomized trials	Serious [a]	Not serious	Not serious	Not serious	None	2113/8985 (23.5%)	1982/8236 (24.1%)	**RR 0.96** (0.87 to 1.06)	**10 fewer per 1,000** (from 31 fewer to 14 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Duration of hospitalization												
4	Randomized trials	Serious [b]	Serious [c]	Not serious	Serious [d]	None	108	109	-	MD 1.42 lower (4.50 lower to 1.65 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Time to Clinical Improvement or Resolution of Symptoms												
3	Randomized trials	Serious [e]	Serious [c]	Not serious	Serious [d]	None	128	130	-	MD 0.90 lower (2.20 lower to 0.41 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Clinical Improvement												
12	Randomized trials	Serious [a]	Not serious	Not serious	Not serious	None	4446/6721 (66.2%)	4240/6482 (65.4%)	**RR 1.06** (0.98 to 1.15)	**39 more per 1,000** (from 13 fewer to 98 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Need for Invasive Ventilation												
8	Randomized trials	Serious [a]	Not serious	Not serious	Not serious	None	792/6611 (12.0%)	754/6377 (11.8%)	**RR 1.00** (0.91 to 1.09)	**0 fewer per 1,000** (from 11 fewer to 11 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Progression to Respiratory Distress/Respiratory Failure												
9	Randomized trials	Serious [a]	Not serious	Not serious	Serious [d]	None	173/1030 (16.8%)	189/904 (20.9%)	**RR 0.85** (0.68 to 1.07)	**31 fewer per 1,000** (from 67	⊕⊕◯◯ LOW	CRITICAL

										fewer to 15 more)		
Need for ICU admission												
2	Randomized trials	Not serious	Not serious	Not serious	Serious [d]	None	125/308 (40.6%)	69/186 (37.1%)	**RR 0.74** (0.33 to 1.66)	**96 fewer per 1,000** (from 249 fewer to 245 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse Events												
7	Randomized trials	Serious [e]	Not serious	Not serious	Serious [d]	None	319/673 (47.4%)	170/474 (35.9%)	**RR 1.11** (0.98 to 1.25)	**39 more per 1,000** (from 7 fewer to 90 more)	⊕⊕◯◯ LOW	IMPORTANT
Serious Adverse Events												
13	randomized trials	serious [e]	serious [c]	not serious	serious [d]	none	441/8284 (5.3%)	220/7539 (2.9%)	**RR 1.19** (0.93 to 1.51)	**6 more per 1,000** (from 2 fewer to 15 more)	⊕◯◯◯ VERY LOW	CRITICAL

Appendix 6: Forest Plots

	Convalescent Plasma		Standard Care or Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Agarwal 2020	34	235	31	229	4.5%	1.07 [0.68, 1.68]	
AlQahtani 2020	1	20	2	20	0.2%	0.50 [0.05, 5.08]	
Avendano-Sola 2020	0	38	4	43	0.1%	0.13 [0.01, 2.26]	
Bajpai 2020	3	15	1	16	0.2%	3.20 [0.37, 27.49]	
Balcells 2021	5	28	2	30	0.4%	2.68 [0.56, 12.71]	
Begin 2021	141	614	63	307	11.0%	1.12 [0.86, 1.46]	
Bennett-Guerrero 2021	14	59	4	15	1.1%	0.89 [0.34, 2.31]	
Estcourt 2021	401	1078	347	909	28.4%	0.97 [0.87, 1.09]	
Gharbharan 2020	6	43	11	43	1.2%	0.55 [0.22, 1.34]	
Horby 2021	1399	5795	1408	5763	37.4%	0.99 [0.93, 1.05]	
Kirenga 2021	10	69	8	67	1.3%	1.21 [0.51, 2.89]	
Koerper 2021	8	53	14	52	1.6%	0.56 [0.26, 1.22]	
Korley 2021	5	257	1	254	0.2%	4.94 [0.58, 42.00]	
Li 2020	8	52	12	51	1.5%	0.65 [0.29, 1.47]	
Libster 2021	2	80	4	80	0.4%	0.50 [0.09, 2.65]	
O Donnell 2021	19	150	18	73	2.8%	0.51 [0.29, 0.92]	
Pouladzadeh 2021	3	30	5	30	0.6%	0.60 [0.16, 2.29]	
Rasheed 2020	1	21	8	28	0.3%	0.17 [0.02, 1.23]	
Ray 2020	10	40	14	40	2.1%	0.71 [0.36, 1.41]	
Sekine 2021	18	80	13	80	2.3%	1.38 [0.73, 2.63]	
Simonovich 2020	25	228	12	106	2.3%	0.97 [0.51, 1.85]	
Total (95% CI)		**8985**		**8236**	**100.0%**	**0.96 [0.87, 1.06]**	
Total events	2113		1982				

Heterogeneity: Tau² = 0.01; Chi² = 24.09, df = 20 (P = 0.24); I² = 17%

Test for overall effect: Z = 0.79 (P = 0.43)

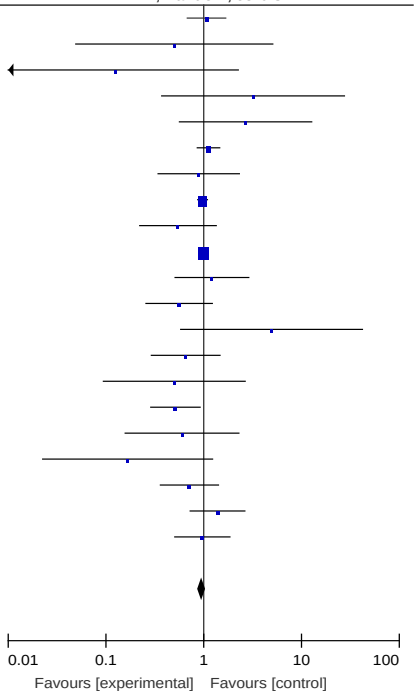

Figure 1. Forest plot of comparison: 1 Convalescent Plasma Versus Control, Outcome: 1.1 All-cause mortality

	Convalescent Plasma		Standard Care or Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Agarwal 2020	34	235	31	229	8.8%	1.07 [0.68, 1.68]	
AlQahtani 2020	1	20	2	20	0.4%	0.50 [0.05, 5.08]	
Balcells 2021	5	28	2	30	0.9%	2.68 [0.56, 12.71]	
Begin 2021	141	614	63	307	18.8%	1.12 [0.86, 1.46]	
Bennett-Guerrero 2021	14	59	4	15	2.3%	0.89 [0.34, 2.31]	
Gharbharan 2020	6	43	11	43	2.6%	0.55 [0.22, 1.34]	
Horby 2021	1399	5795	1408	5763	41.7%	0.99 [0.93, 1.05]	
Kirenga 2021	10	69	8	67	2.8%	1.21 [0.51, 2.89]	
Korley 2021	5	257	1	254	0.5%	4.94 [0.58, 42.00]	
Li 2020	8	52	12	51	3.2%	0.65 [0.29, 1.47]	
Libster 2021	2	80	4	80	0.8%	0.50 [0.09, 2.65]	
O Donnell 2021	19	150	18	73	5.8%	0.51 [0.29, 0.92]	
Pouladzadeh 2021	3	30	5	30	1.2%	0.60 [0.16, 2.29]	
Rasheed 2020	1	21	8	28	0.6%	0.17 [0.02, 1.23]	
Salman 2020	0	0	0	0		Not estimable	
Sekine 2021	18	80	13	80	4.8%	1.38 [0.73, 2.63]	
Simonovich 2020	25	228	12	106	4.8%	0.97 [0.51, 1.85]	
Total (95% CI)		**7761**		**7176**	**100.0%**	**0.96 [0.83, 1.12]**	
Total events	1691		1602				

Heterogeneity: Tau² = 0.01; Chi² = 18.14, df = 15 (P = 0.26); I² = 17%

Test for overall effect: Z = 0.48 (P = 0.63)

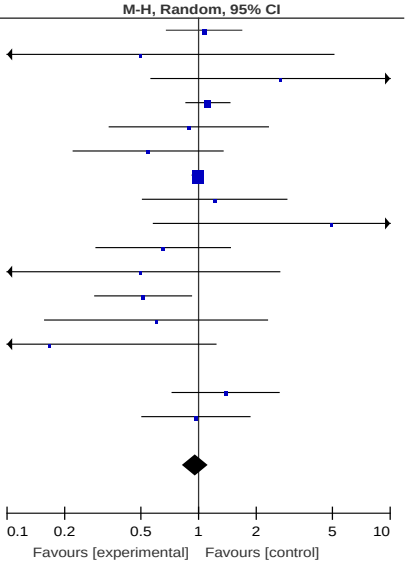

Figure 1a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.18 All-cause Mortality (Sensitivity Analysis)

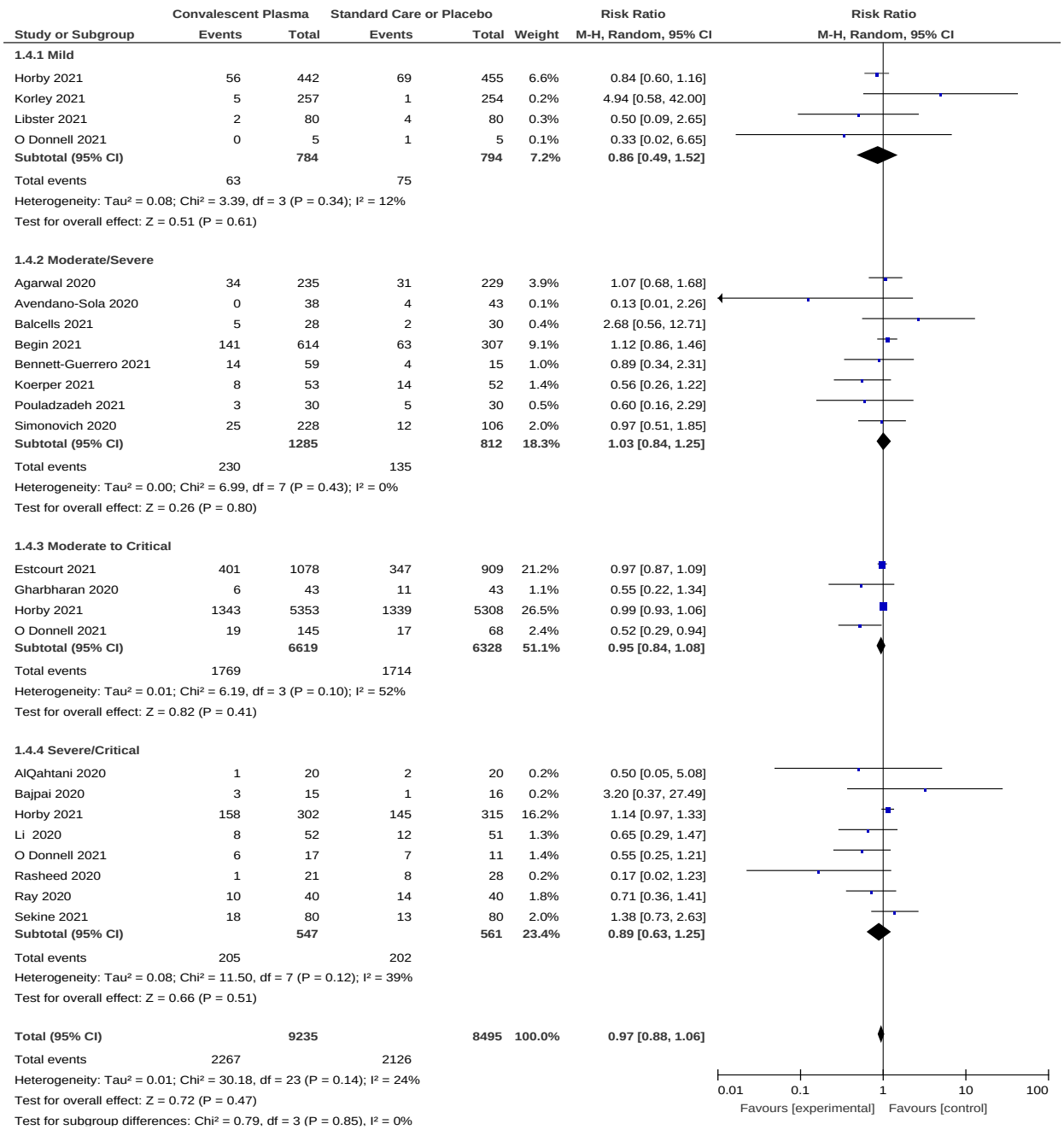

Figure 2. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.4 All-cause Mortality (by severity)

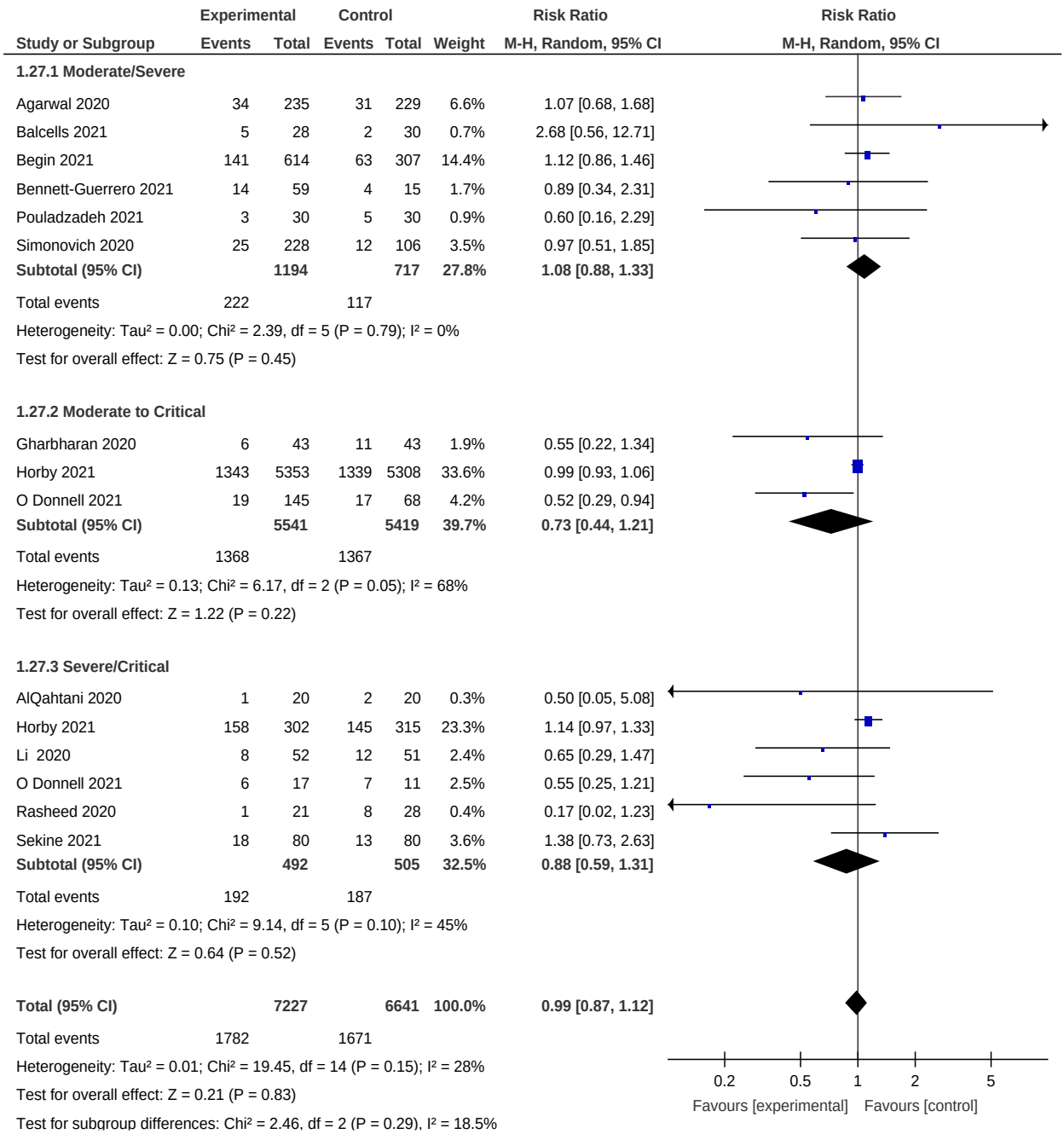

Figure 2a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.27 Mortality (Sensitivity Analysis on Severity)

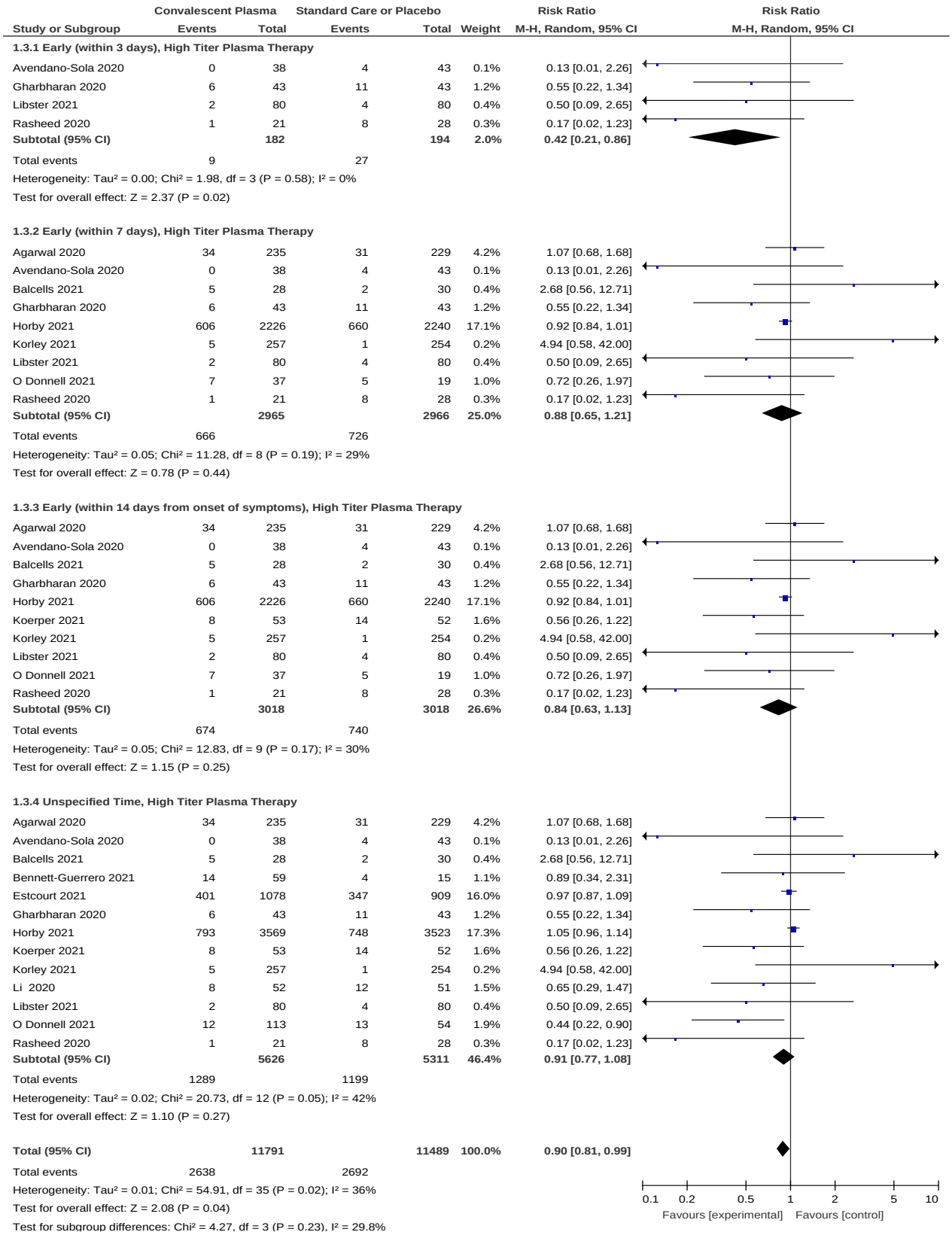

Figure 3. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.2 All-Cause Mortality (Time of administration of High Titer Plasma)

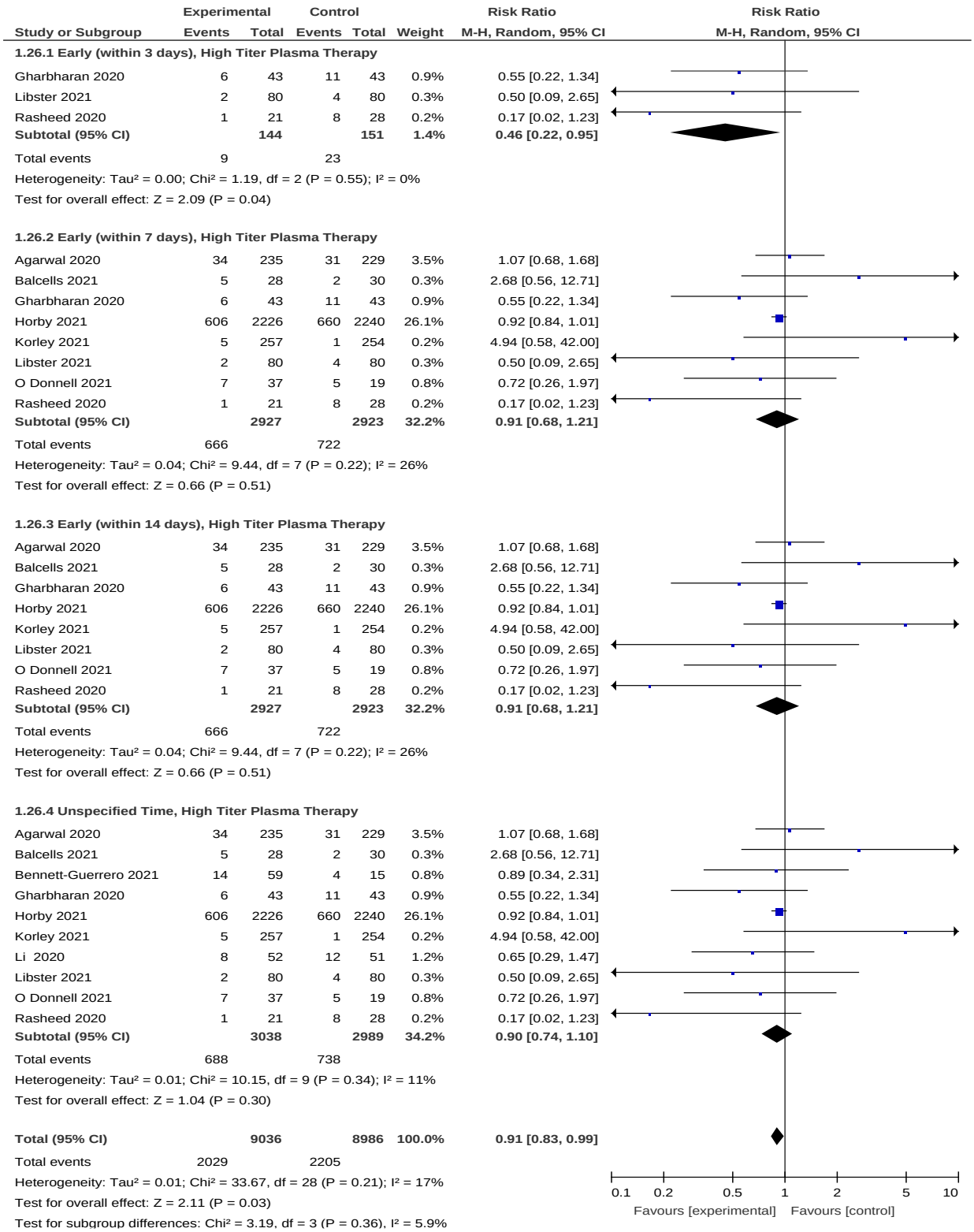

Figure 3a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.26 Mortality (Sensitivity Analysis on Time of Administration of High Titer Plasma)

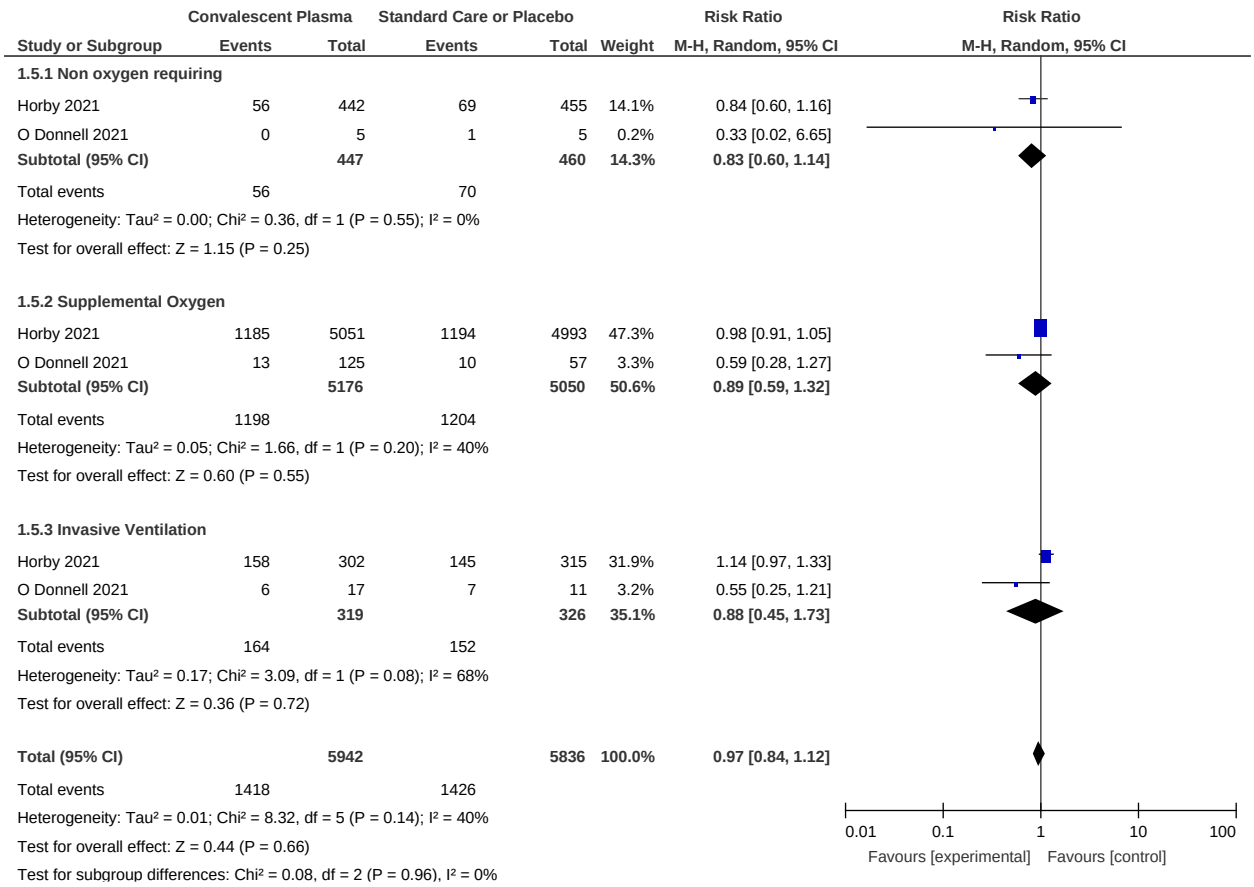

Figure 4. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.5 All-cause Mortality (by oxygen support)

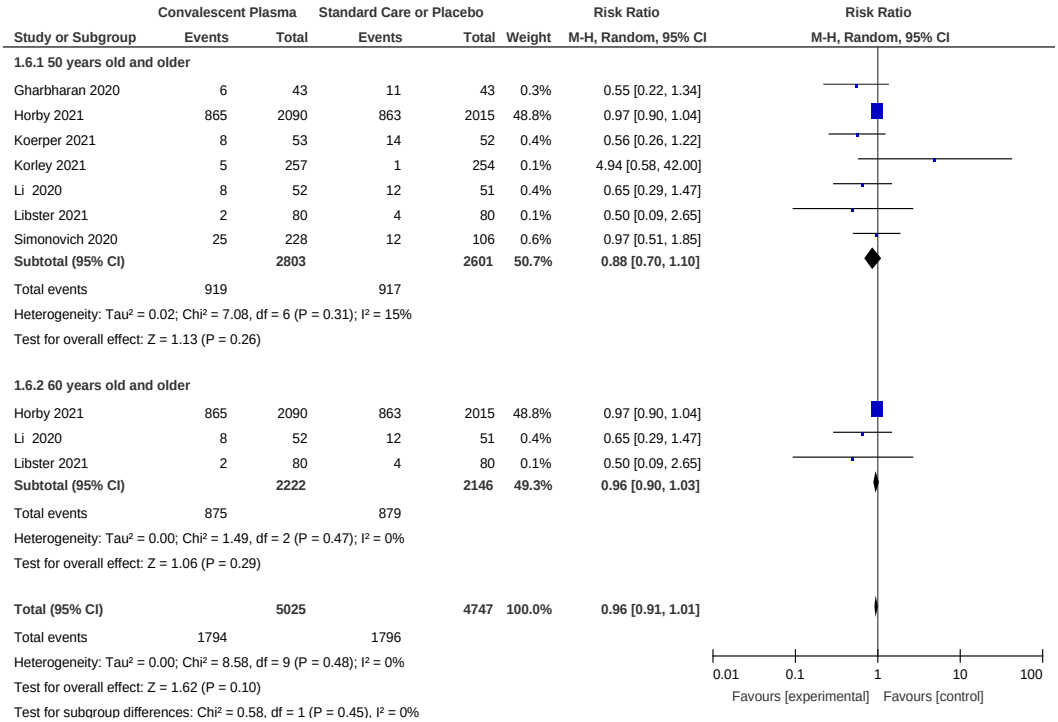

Figure 5. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.6 All-cause Mortality (by Age)

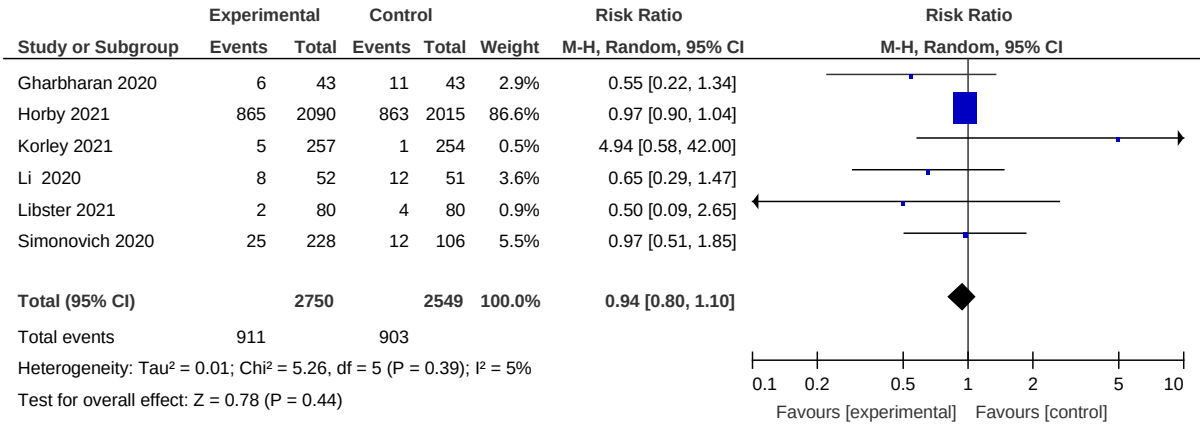

Figure 5a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.28 Mortality (Sensitivity of Aged 50 years old and above)

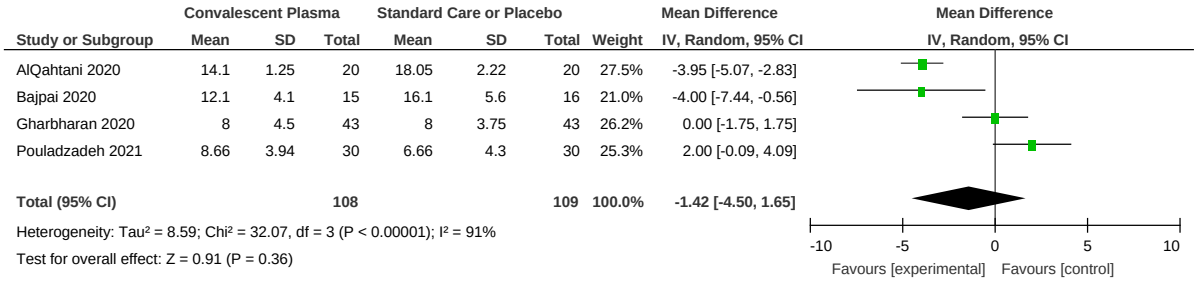

Figure 6. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.7 Duration of hospitalization

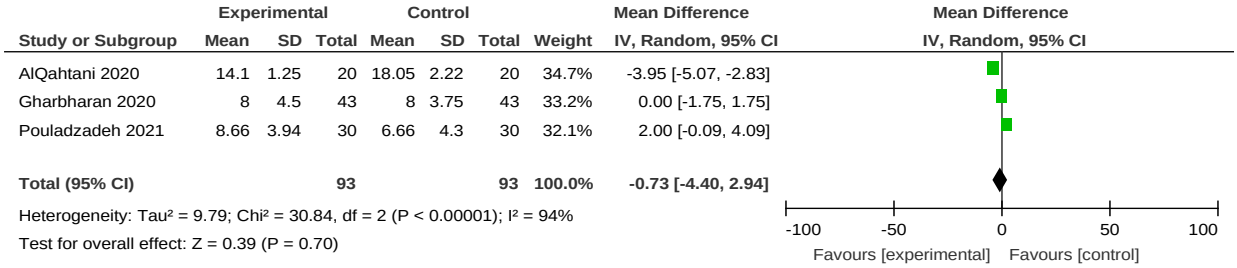

Figure 6a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.20 Duration of Hospitalization (Sensitivity Analysis)

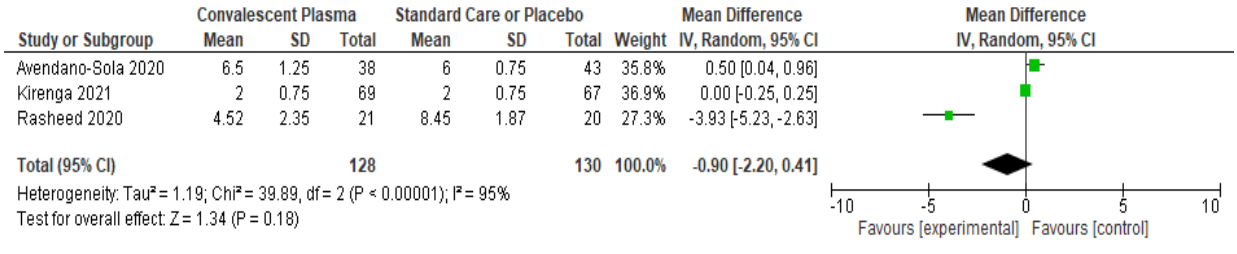

Figure 7. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.8 Time to Clinical Improvement or Resolution of Symptoms

Study or Subgroup	Convalescent Plasma Events	Total	Standard Care or Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Agarwal 2020	140	235	119	229	13.0%	1.15 [0.97, 1.35]
AlQahtani 2020	19	20	18	20	11.8%	1.06 [0.88, 1.26]
Bennett-Guerrero 2021	12	20	3	20	0.5%	4.00 [1.33, 12.05]
Gharbharan 2020	25	43	25	43	4.2%	1.00 [0.70, 1.43]
Horby 2021	3850	5795	3846	5763	28.5%	1.00 [0.97, 1.02]
Koerper 2021	23	53	17	52	2.3%	1.33 [0.81, 2.18]
Li 2020	27	52	22	51	3.3%	1.20 [0.80, 1.81]
O Donnell 2021	108	150	48	73	10.6%	1.09 [0.90, 1.33]
Pouladzadeh 2021	16	30	8	30	1.3%	2.00 [1.01, 3.95]
Salman 2020	6	15	2	15	0.3%	3.00 [0.72, 12.55]
Sekine 2021	49	80	52	80	8.0%	0.94 [0.74, 1.19]
Simonovich 2020	171	228	80	106	16.1%	0.99 [0.87, 1.13]
Total (95% CI)		**6721**		**6482**	**100.0%**	**1.06 [0.98, 1.15]**
Total events	4446		4240			

Heterogeneity: Tau² = 0.01; Chi² = 18.63, df = 11 (P = 0.07); I² = 41%

Test for overall effect: Z = 1.46 (P = 0.15)

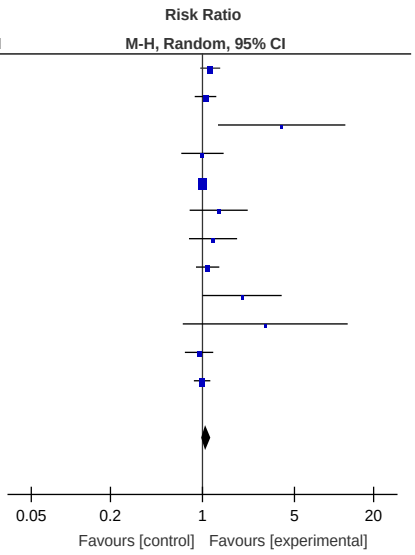

Figure 8. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.9 Clinical Improvement.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Agarwal 2020	140	235	119	229	13.3%	1.15 [0.97, 1.35]
AlQahtani 2020	19	20	18	20	12.1%	1.06 [0.88, 1.26]
Bennett-Guerrero 2021	12	20	3	20	0.5%	4.00 [1.33, 12.05]
Gharbharan 2020	25	43	25	43	4.2%	1.00 [0.70, 1.43]
Horby 2021	3850	5795	3846	5763	29.3%	1.00 [0.97, 1.02]
Li 2020	27	52	22	51	3.4%	1.20 [0.80, 1.81]
O Donnell 2021	108	150	48	73	10.9%	1.09 [0.90, 1.33]
Pouladzadeh 2021	16	30	8	30	1.3%	2.00 [1.01, 3.95]
Salman 2020	6	15	2	15	0.3%	3.00 [0.72, 12.55]
Sekine 2021	49	80	52	80	8.2%	0.94 [0.74, 1.19]
Simonovich 2020	171	228	80	106	16.5%	0.99 [0.87, 1.13]
Total (95% CI)		**6668**		**6430**	**100.0%**	**1.05 [0.97, 1.14]**
Total events	4423		4223			

Heterogeneity: Tau² = 0.01; Chi² = 17.38, df = 10 (P = 0.07); I² = 42%

Test for overall effect: Z = 1.31 (P = 0.19)

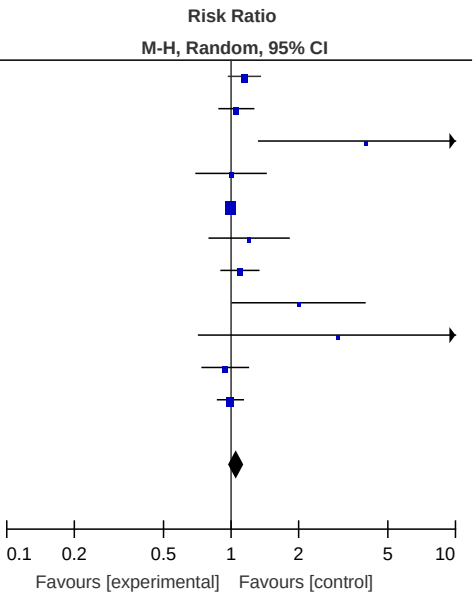

Figure 8a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.22 Clinical Improvement (Sensitivity Analysis)

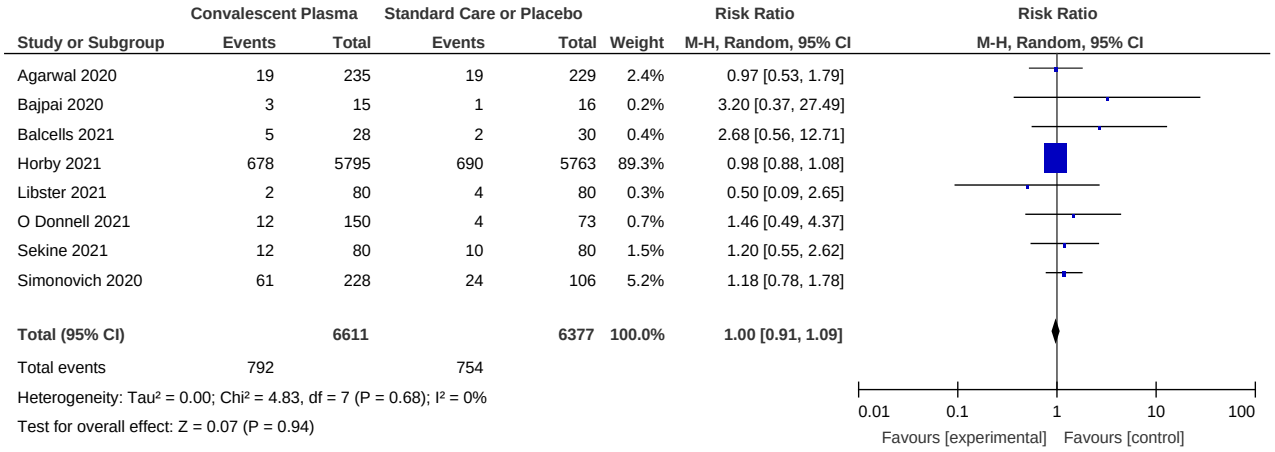

Figure 9. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.10 Need for Invasive Ventilation.

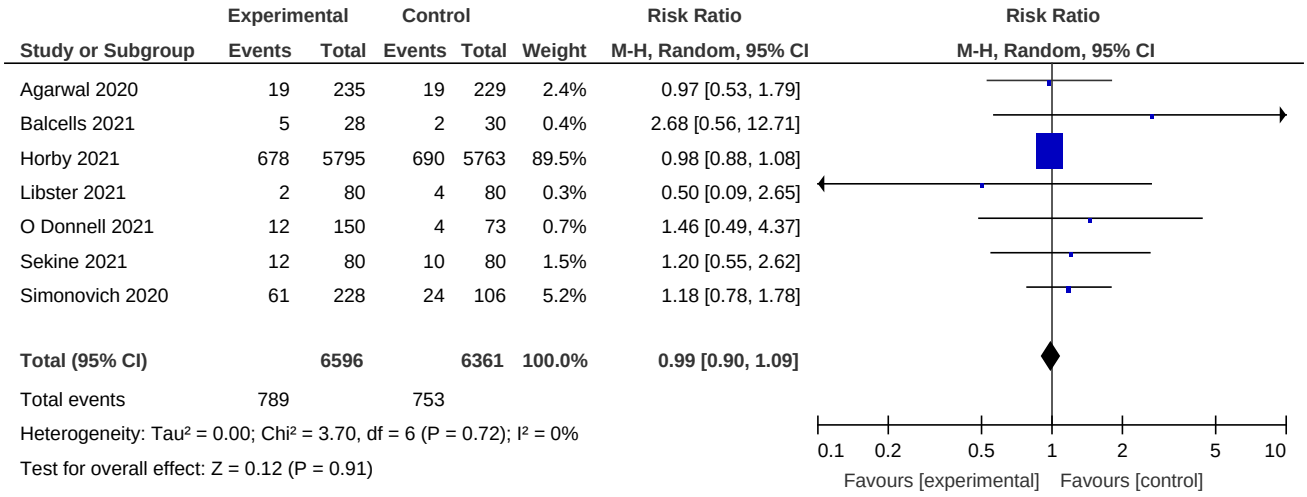

Figure 9a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.23 Need for Invasive Ventilation (Sensitivity Analysis)

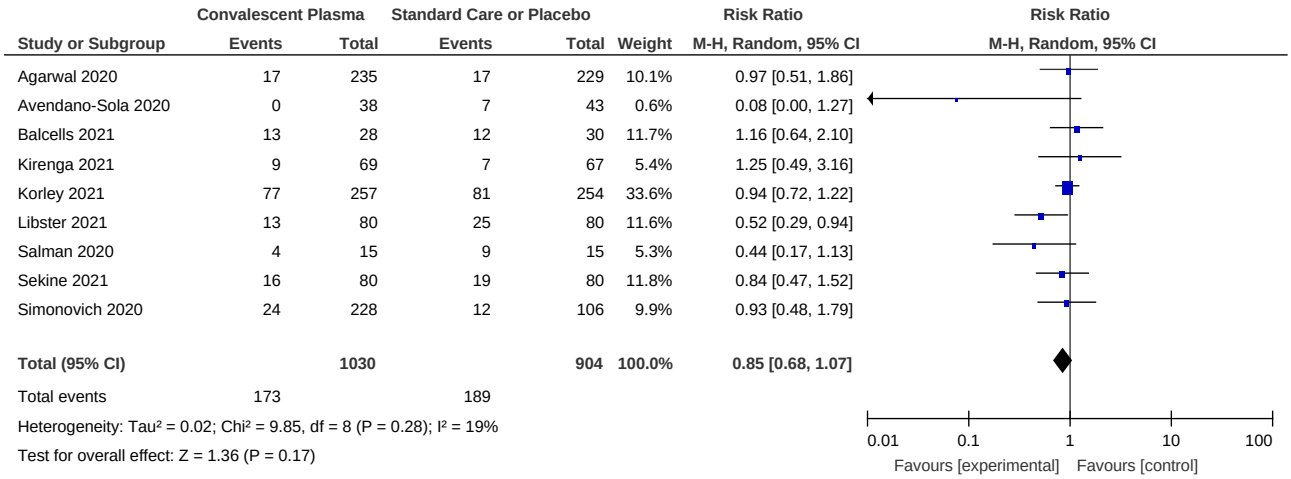

Figure 10. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.11 Progression to Respiratory Distress/Respiratory Failure

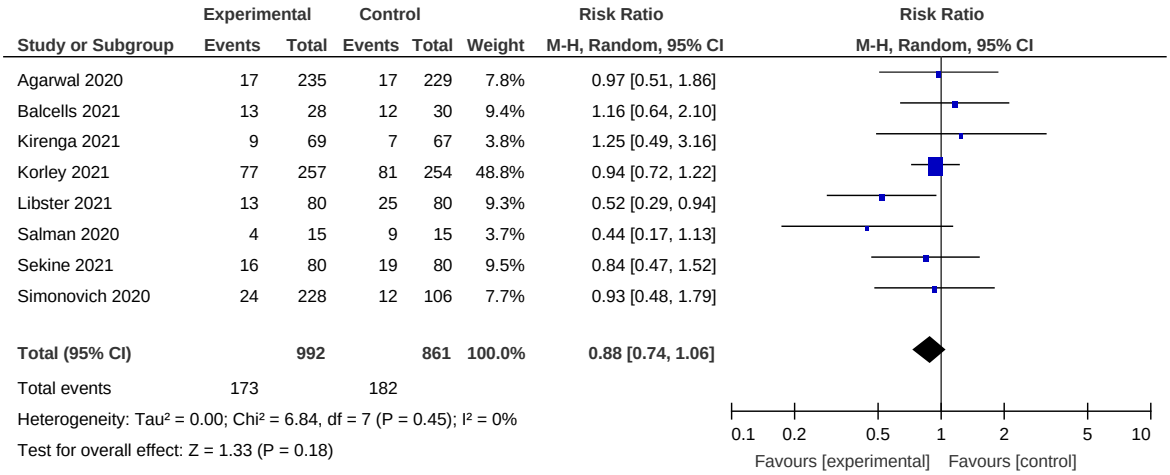

Figure 10a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.24 Progression to Respiratory Distress/Respiratory Failure (Sensitivity Analysis)

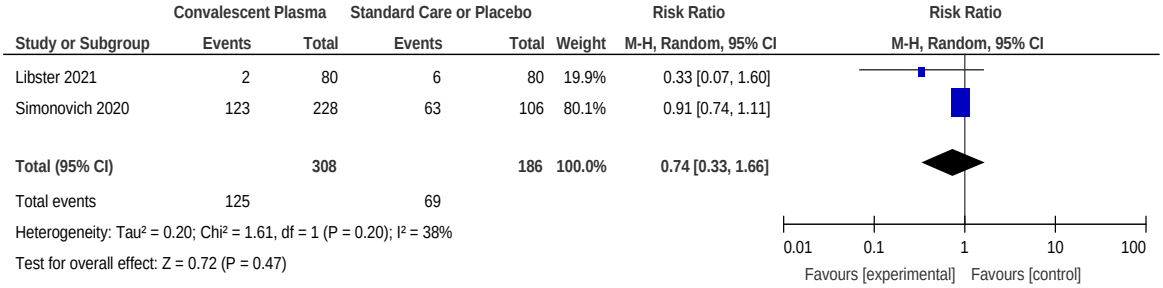

Figure 11. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.12 Need for ICU admission

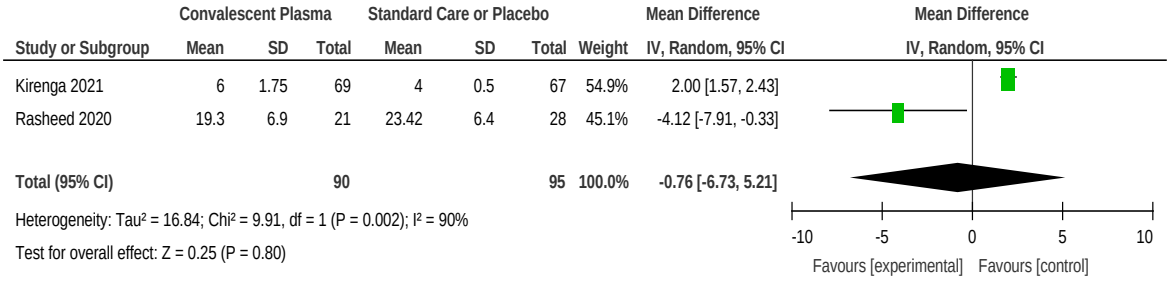

Figure 12. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.13 Time to Viral Clearance

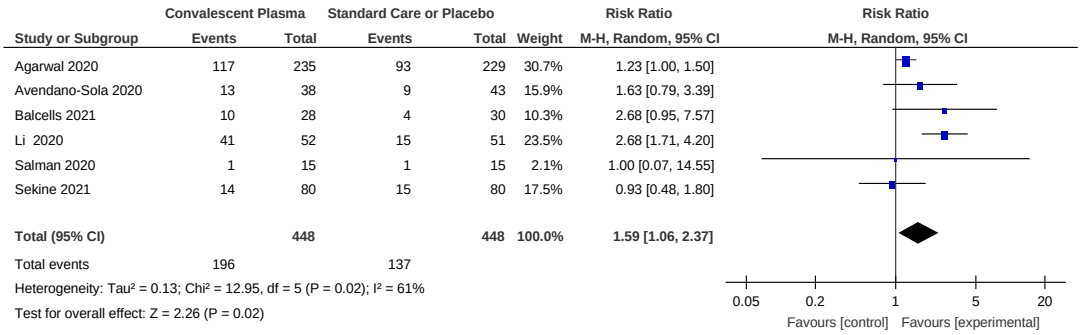

Figure 13. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.14 Viral Clearance D7

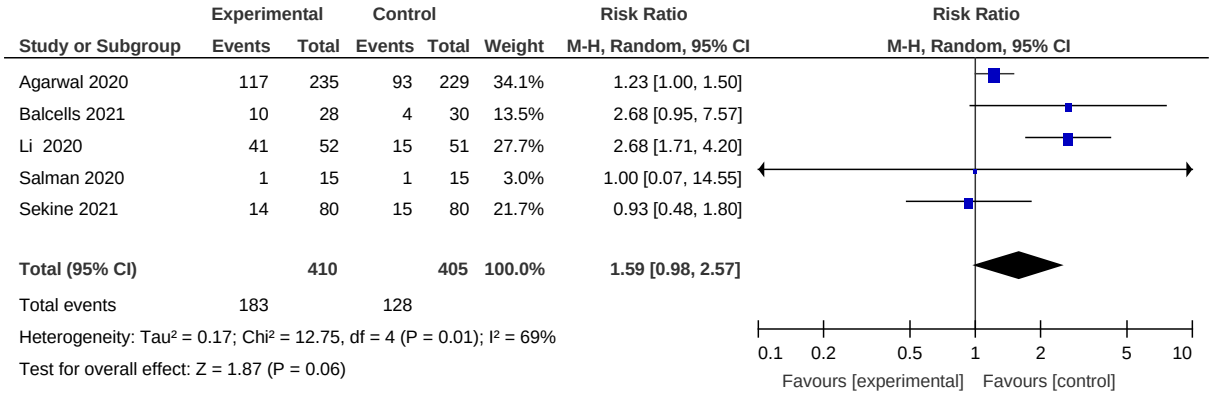

Figure 13a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.25 Viral Clearance D7

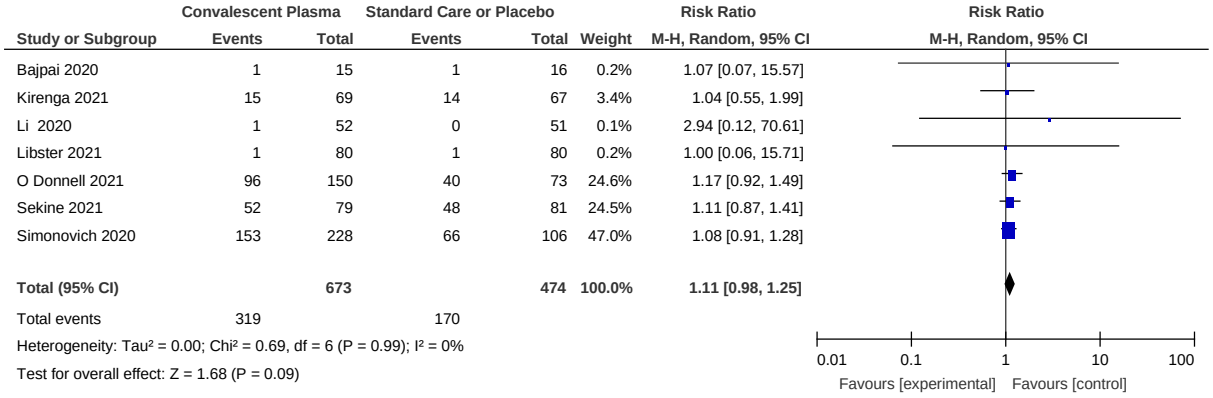

Figure 45. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.15 Adverse Events

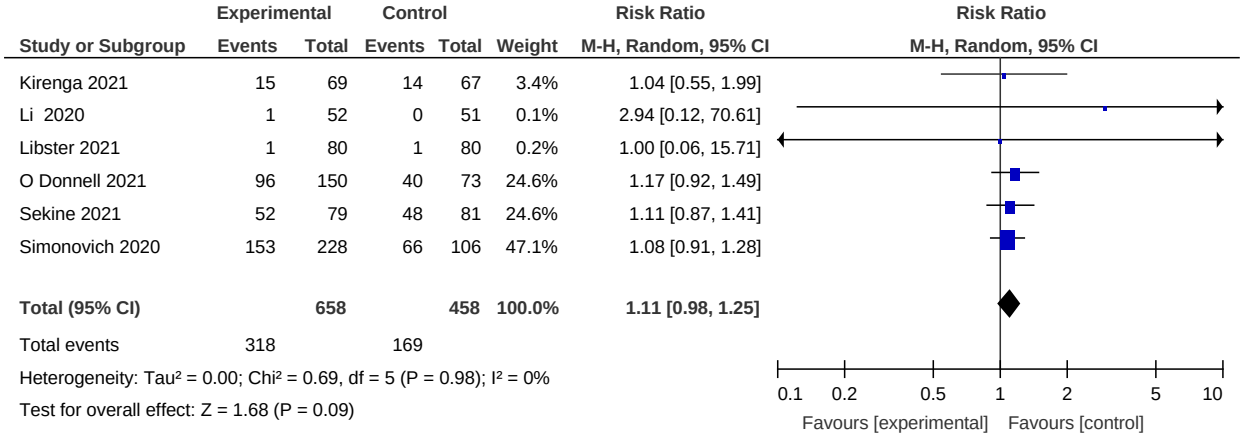

Figure 14a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.29 Adverse Events (Sensitivity Analysis)

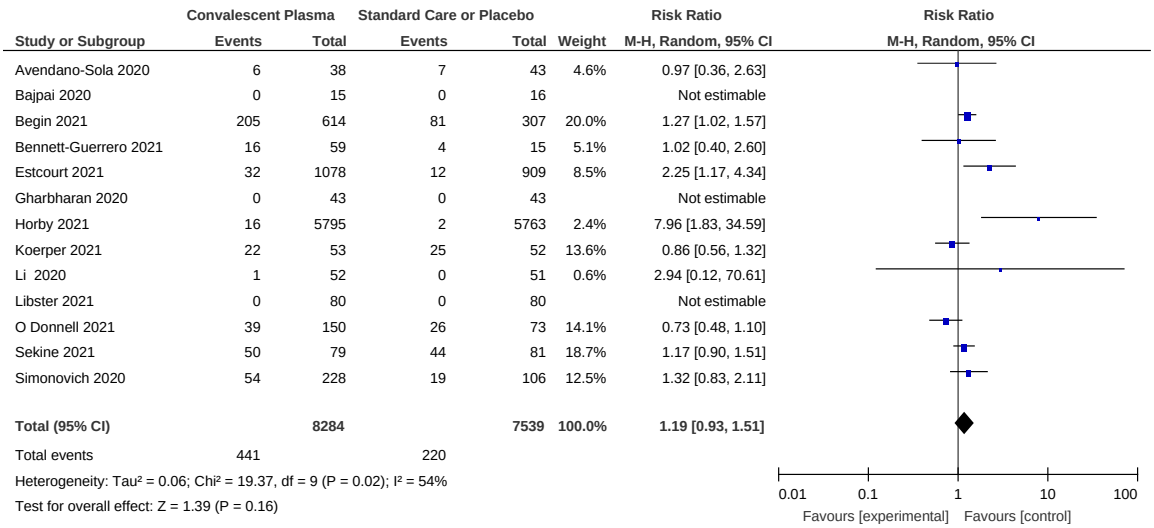

Figure 15. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.11 Serious Adverse Event

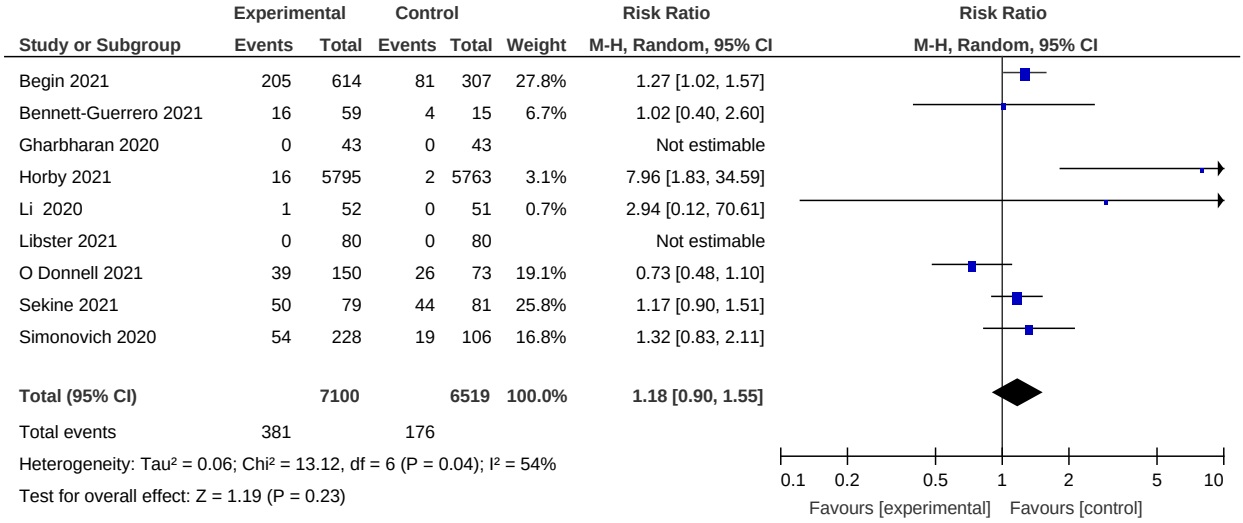

Figure 15a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.30 Serious Adverse Events (Sensitivity Analysis)

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Appendix 7: Characteristics of Ongoing Studies

	Title	Population	Interventions	Characteristics	Outcome Measures
1	COVID-19 Convalescent Plasma (CCP) Transfusion	18 Years and older (Adult, Older Adult)	Biological: COVID Convalescent Plasma Study	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Change in PaO2/FiO2 after CCP transfusion Change in pulse oximetry status after CCP transfusion Change in aO2 after CCP transfusion Change in respiratory rate after CCP transfusion Change in intubation status after CCP transfusion Change in Sequential Organ Failure Assessment (SOFA) Change in 8-point ordinal clinical deterioration scale Length of ICU/hospital stay Development of plasma transfusion reactions Development of immune complex disorders Change in anti CoV-2 IgM and IgG levels.
2	Convalescent Plasma for Treating Patients With COVID-19 Pneumonia Without Indication of Ventilatory Support	Child, Adult, Older Adult	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Area under the curve of SARS-COV-2 viral load obtained from nasopharyngeal and /or oropharyngeal swabs Assessment of clinical improvement using an Ordinal Severity Scale Evaluate oxygen saturation Evaluate oxygen supplementation Assess respiratory rate Evaluate the PaO2 / FiO2 ratio (for patients on mechanical mechanisms) Length of hospital stay Length of stay in intensive care Assess the rate of orotracheal intubation Change in the profile of cytokines/chemokines in both groups
3	PERUCONPLASMA: Evaluating the Use of Convalescent Plasma as Management of COVID-19	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Transfusion-related Serious Adverse Events All-cause in-hospital mortality Length of hospital stay Length of ICU stay Need of invasive mechanical ventilation Duration of mechanical ventilation Clinical Improvement at 14 days
4	Convalescent Plasma for Treatment of COVID-19: An Exploratory Dose Identifying Study	18 Years and older (Adult, Older Adult)	•Biological: SARS-CoV-2 convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Number and proportion of patients with progression to ventilation or sustained requirement of supplementary oxygen therapy Adverse events Dose of plasma needed to clear viremia Clearance of viremia Fever and symptoms Inflammatory parameters Antibody response to SARS-CoV-2
5	Efficacy of Convalescent Plasma Therapy in the Early Care of COVID-19 Patients.	18 Years to 90 Years (Adult, Older Adult)	Drug: Transfusion of SARS-CoV-2 Convalescent Plasma Drug: Transfusion of standard Plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Survival time without needs of a ventilator Morbidity Mortality Length of stay Effect on viral pharyngeal specimen clearance Effect on viral blood specimen clearance Effect on hemostasis disorders

					Kinetics of appearance of neutralizing antibodies Transfusion endotheliopathy effect Transfusion biological Inflammation effect Transfusion hemovigilance Decrease in the consumption of antibiotics
6	Convalescent Plasma as Adjunct Therapy for COVID-19	18 Years to 60 Years (Adult)	Biological: Convalescent plasma treatment	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	The mortality in COVID-19 patients treated with convalescent plasma Change in clinical status category in CP receiving patients Duration of hospitalization Duration of mechanical ventilation Duration of ICU stay Change in lung image radiography in CP receiving patients Change in inflammatory parameters in CP receiving patients Change in coagulation parameters in CP receiving patients Change in viral load in CP receiving patients Changes in anti-SARS-CoV-2 antibody levels in CP receiving patients
7	Treatment of Patients With COVID-19 With Convalescent Plasma	18 Years and older (Adult, Older Adult)	Biological: convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Time elapsed until clinical improvement or hospital discharge Acute adverse events Clinical Status Duration of clinical events SARS-CoV-2 in nasopharyngeal swab IgG, IgM and IgA titers for SARS-CoV-2 Neutralizing antibodies
8	Treatment With Investigational Convalescent Plasma and Measure Antibody Levels in Patients Hospitalized With COVID-19	18 Years and older (Adult, Older Adult)	Drug: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Prevention	Correlation between the NAb dose titer in the convalescent plasma and change or lack of change when comparing pre-treatment and day one NAb titers to inpatients with documented COIVD-19 infection Rapid deterioration as evidenced by increase in ordinal or news score within 4 hours of transfusion Number of participants with clearance of viral shedding of SARSCoV-2 in nasopharyngeal or nasal samples
9	Convalescent Plasma as Treatment for Acute Coronavirus Disease (COVID-19)	18 Years to 80 Years (Adult, Older Adult)	Biological: SARS-CoV-2 convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Disease progression Adverse events (AE) Time to resolution of fever and symptoms Clearance of viraemia Inflammatory parameters Antibody response to SARS-CoV-2
10	Convalescent Plasma as Treatment for Hospitalized Subjects With COVID-19 Infection	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	For patients hospitalized for COVID-19 but not intubated Primary objective for patients with COVID-19 already intubated Duration of hospitalization Duration of mechanical ventilation Time to symptoms resolution Overall survival Rate of virologic clearance by nasopharyngeal swab at day 10 Impact of donor titers level on efficacy Impact of donor titers level on safety Recipient Anti-SARS-CoV2 titer assessment on days 0 (pre-infusion),3,10,30, 60

11	Evaluating the Efficacy of Convalescent Plasma in Symptomatic Outpatients Infected With COVID-19	18 Years and older (Adult, Older Adult)	Biological: CCP	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Time to Resolution of Symptoms SAEs within 24 hours of plasma infusion Decrease in Inflammatory Markers Hospitalization within 28 days
12	Convalescent Plasma for the Treatment of Patients with Severe COVID-19 Infection	18 Years and older (Adult, Older Adult)	Procedure: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Survival Clinical improvement (i.e., percentage of patients not fulfilling the criteria for severe disease)
13	Convalescent Plasma as Treatment for Subjects with Early COVID-19 Infection	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma Other: Best Supportive Care	Allocation: Randomized Intervention Model: Crossover Assignment Masking: None (Open Label) Primary Purpose: Treatment	Hospitalization Rate Time to symptoms resolution Overall survival Rate of virologic clearance by nasopharyngeal swab at 2 and 4 weeks Rate of nasopharyngeal swab positivity in donors •Rate of donor titers level Impact of donor titers level on efficacy Patients' anti-SARS-CoV2 titer assessment preinfusion for the Treatment group, at 2 weeks, 4 weeks, and 2 months.
14	Convalescent Plasma as a Possible Treatment for COVID-19	40 Years and older (Adult, Older Adult)	Biological: Convalescent plasma Biological: Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Oxygen supplementation 28-day and in-hospital mortality rate Number of participants transferred to the Intensive Care Unit (ICU) Number of participants intubated Length of hospital stay in days Type of respiratory support C-reactive Protein (CRP) Lymphocyte count •Length or respiratory support required, in days Lactate dehydrogenase (LDH)
15	Convalescent Plasma as Adjunctive Therapy for Hospitalized Patients With COVID-19	19 Years and older (Adult, Older Adult)	Drug: Anti-SARS-CoV-2 convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Incidence of serious adverse events Quick SOFA (qSOFA) score Cardiopulmonary arrest ICU mortality ICU length of stay Hospital mortality Hospital length of stay Dialysis-free days Vasopressor-free days ICU-free days
16	Safety and Efficacy of Convalescent Plasma Transfusion for	18 Years and older (Adult, Older Adult)	Biological: convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Severity and death Adverse events that require study treatment interruption Time to clinical improvement Antibodies against SARS-CoV-2 Disease progression 1 Disease progression 2

	Patients With COVID-19				Time on mechanical ventilation Number of days with fever Adverse events attributed to the study intervention
17	Convalescent Plasma Transfusion in Severe COVID-19 Patients in Jamaica	18 Years to 65 Years (Adult, Older Adult)	Biological: Convalescent Plasma Infusion	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Mortality Viral load Antibody titre for Immunoglobulin (IgG) antiSARS-CoV-2 antibody Antibody titre for Immunoglobulin A (IgA) antiSARS-CoV-2 antibody Procalcitonin titres Interleukin 6 (IL-6) D-dimer C-reactive protein Ferritin Length of ICU admission Days to recovery
18	Statistical and Epidemiological Study Based on the Use of Convalescent Plasma for the Management of Patients With COVID-19	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Care Provider) Primary Purpose: Treatment	All-cause mortality Side effects Length of stay in Intensive Care Unit (ICU) Length of stay in hospitalization Days of mechanical ventilation •Inflammatory biomarkers (d-dimer) Inflammatory biomarkers (c-reactive protein) Inflammatory biomarkers (lactate dehydrogenase) Inflammatory biomarkers (ferritin)
19	Anti-COVID-19 Convalescent Plasma Therapy	18 Years and older (Adult, Older Adult)	Biological: anti-SARS-CoV-2 convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Changing of viral load of SARS-CoV2 Changes in immunoglobulin G COVID-19 antibody titer Changes at the cytokine pattern Intensive Care Unit Admission Length of hospital stay Duration of mechanical ventilation Clinical Status Mortality
20	Convalescent Plasma for Treatment of COVID-19: An Open Randomized Controlled Trial	18 Years and older (Adult, Older Adult)	Biological: SARS-CoV-2 convalescent plasma •Other: Standard of care	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	COVID-19 related mortality within 28 days COVID-19 related mortality within 60 days Requirement of invasive ventilation or Pao2/ FiO2 # 70 for # 12 hours in the case of patients not eligible for intensive care Adverse events Dose of plasma needed to clear viremia Time to clearance of viremia
21	Application of Convalescent Plasma in the Treatment of SARS CoV-2 Disease (COVID-19) With Evaluation of Therapy Effectiveness	18 Years and older (Adult, Older Adult)	Biological: COVID-19 convalescent plasma treatment	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Death, for any reason For patients with respiratory support, the time to take one's own breath (extubation) Stay in the intensive care unit (ICU) Time to disconnect CPAP respiratory support Time to elimination of SARS-Cov-2 (RT-PCR) Time to serological response (anti-SARS-COv-2 antibodies)

22	Efficacy of Convalescent Plasma to Treat COVID-19 Patients, a Nested Trial in the CORIMUNO-19 Cohort	18 Years and older (Adult, Older Adult)	Drug: Transfusion of COVID-19 convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Survival without needs of ventilator utilization or use of immunomodulatory drugs WHO progression scale #6 Severe adverse events WHO progression scale Overall survival Time from randomization to discharge Time to oxygen supply independency Survival without needs of ventilator utilization Survival without use of immunomodulatory drugs
23	Convalescent Plasma in the Early Treatment of High-risk Patients With SARS-CoV-2 (COVID-19) Infection	18 Years to 99 Years (Adult, Older Adult)	Biological: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Determine the therapeutic efficacy (response rate) of convalescent plasma infusion in patients at high risk for mortality when infected by SARS-CoV-2 (COVID-19). Determine the immunologic effects of convalescent plasma infusion Absolute lymphocyte count (10*3/uL) Creatinine kinase (mg/dL) C-reactive protein (mg/dl) D-Dimer (ng/ml FEU) Interleukin-6 (pg/ml) Ferritin (ng/mL)
24	Therapeutic Plasmapheresis in Critically Ill Adult Patients With COVID-19 Confirmed Diagnosis	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	In-hospital mortality Incidence of renal replacement therapy Incidence of adverse events
25	Assessment of Efficacy and Safety of Therapy With COVID-19 Convalescent Plasma in Subjects with Severe COVID-19 (IPCO)	18 Years and older (Adult, Older Adult)	Biological: COVID-19 convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Change in SOFA score from Baseline Visit Assessment of impact of immune therapy with COVID-19 convalescent plasma on markers for ARDS due to severe COVID-19 infection Assessment of impact of immune therapy with COVID-19 convalescent plasma on short-term all-cause mortality Assessment of impact of immune therapy with COVID-19 convalescent plasma on oxygen supply in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on oxygen demand in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on Duration of Oxygen supply in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on PEEP in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on FiO2 in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on driving pressure in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on Duration of invasive mechanical Ventilation in patients with ARDS due to severe COVID-19

26	Convalescent Plasma for Early Treatment of COVID-19	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma (anti-SARS-CoV-2 plasma) Biological: Control (albumin 5%)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor) Primary Purpose: Treatment	Rate of Severe Disease Rate of measurable anti-SARS-CoV-2 titers Rate of SARS-CoV-2 PCR Positivity Duration of SARS-CoV-2 PCR Positivity Levels of SARS-CoV-2 RNA
27	Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Overall mortality until discharge from the hospital or a maximum of 60 days after admission whichever comes first Impact of 300ml convP therapy on hospital days •Impact of 300ml convP on weaning from oxygen therapy Impact of 300ml convP on overall mortality in patients admitted to the ICU within 24 hours after admission Difference in the effect of convP on mortality in patients with a duration of symptoms less or more the median duration of symptoms in the study population Impact of 300ml convP therapy on ICU days in patients admitted to the ICU within 24 hours after admission Impact of plasma therapy on the decrease in SARS-CoV2 shedding from airways Impact of CTL and NK cell immunity on the likelihood of being protected from immune serum transfer Safety of convP therapy Change of the 8-point WHO COVID19 disease severity scale on day 15
28	Convalescent Plasma in ICU Patients With COVID-19-induced Respiratory Failure	18 Years and older (Adult, Older Adult)	Biological: Multiple Doses of AntiSARS-CoV-2 convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Proportion of subjects who consent to the study and receive at least one dose of convalescent plasma Overall survival of patients in the ICU receiving at least once dose of convalescent plasma for Covid-19-induced respiratory failure
29	Standard or Convalescent Plasma in Patients with Recent Onset of COVID-19 Respiratory Failure	18 Years and older (Adult, Older Adult)	Drug: Standard Therapy Protocol (STP) Other: STP + Standard Plasma (SP) •Other: STP + COVID-19 Convalescent Plasma (CP)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor) Primary Purpose: Treatment	30-days survival Ventilator free survival 6-months survival •Incidence of complications Days in intensive care units (ICU) Positivity for Immunoglobulin G to SARS-Cov-2 Clearance of viral load •Sequential Organ Failure Assessment (SOFA) score Any variation from Standard Therapy Protocol
30	Convalescent Plasma for COVID-19 Patients (CPCP)	18 Years to 75 Years (Adult, Older Adult)	Biological: Convalescent Plasma as Therapy for Covid-19 patients	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Change in mortality Change in requirement for mechanical ventilation Change in the duration of mechanical ventilation Incidence of Treatment-Emergent Adverse Events
31	Open-label Treatment of Severe Coronavirus Disease 2019 (COVID-19) With	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma transfusion	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Change is clinical status Transfusion related events SOFA score at days 0, 7, 14, 21, 28 Length of Hospital Stay Supplemental oxygen Mechanical Ventilation Change in mechanical ventilation status

	Convalescent Plasma				Mortality Change in inflammatory markers
32	Experimental Use of Convalescent Plasma for Passive Immunization in Current COVID-19 Pandemic in Pakistan in 2020	18 Years to 55 Years (Adult)	Other: convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label)	Change in COVID-19 severity status
33	Convalescent Plasma in the Treatment of Covid-19	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma from COVID-19 donors Biological: Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Safety (SAE) Rate of intubation Number of participants initiating systemic corticosteroids Hospital stay Mortality ICU stay Ventilator days Severity of respiratory failure Viral load Antibody measurements
34	Potential Efficacy of Convalescent Plasma to Treat Severe COVID-19 and Patients at High Risk of Developing Severe COVID-19	18 Years to 85 Years (Adult, Older Adult)	Other: convalescent plasma from recovered COVID-19 donors	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	ICU length of stay Safety of convalescent plasma & Serious adverse reactions. Number of days on mechanical ventilation 30 days of mortality Days to clinical recovery
35	Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications	18 Years to 85 Years (Adult, Older Adult)	Drug: Convalescent Plasma Other: Standard Care Therapy	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Composite measure of the avoidance of – 1 Progression to severe ARDS (P/F ratio 100) and 2 All-cause Mortality at 28 days Time to symptom resolution-Fever, Shortness of Breath, Fatigue Hospital length of stay Change in SOFA pre and post transfusion Duration of respiratory support required a. Duration of Invasive Mechanical Ventilation b.Duration of Non-Invasive Radiological improvement Adverse events (AE) associated with transfusion To measure the change in RNA levels (Ct values) of SARS-CoV-2 from RT-PCR [Time Frame: Days 0, 1, 3, and 7 after transfusion] Levels of bio-markers pre and post transfusion Need of Vasopressor use
36	Convalescent Plasma as Potential Therapy for Severe COVID-19 Pneumonia	18 Years and older (Adult, Older Adult)	Biological: COVID19 convalescent plasma infusion	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	28 days survival Efficacy of plasma infusion according to antibodies levels in the infuse bags Clinical efficacy of plasma infusion according to frame time from symptoms onset and hospitalization Change in clinical WHO ordinal scale from 1 to 10 points

37	Effectiveness and Safety of Convalescent Plasma in Patients With High-risk COVID-19 Age: 18 Years and older (Adult, Older Adult) Study Completion: February 2021		Biological: SARS-CoV-2 convalescent plasma treatment Other: Standard care	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Treatment	Mortality Adverse events ICU admission Mechanical ventilation ICU length Reduction of D Dimer LDH reduction Reduction of Troponin level Decrease in ferritin level Decrease in procalcitonin level
38	Early Convalescent Plasma Therapy for High-risk Patients With COVID-19 in Primary Care (the CoV-Early Study)	50 Years and older (Adult, Older Adult)	Biological: ConvP Biological: FFP	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Highest disease status Percentage of deaths Percentage of hospital admissions Percentage of ICU admissions Disease duration in days of symptoms Age and clinical frailty score
39	Convalescent Plasma (PC) and Human Intravenous Anti-COVID-19 Immunoglobulin (IV Anti COVID-19 IgG) in Patients Hospitalized for COVID-19.	18 Years and older (Adult, Older Adult)	Biological: COVID-19 convalescent plasma Biological: Anti-COVID-19 human immunoglobulin Drug: Standard (specific) therapy for COVID-19	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Admission to ICU and/or mechanical ventilation Length of hospital stay Neutralizing antibody (IgG) titers against COVID-19 Safety - Adverse events Death
40	Convalescent Plasma in the Treatment of Covid-19	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Number of days in need of oxygen Number of days before discharge from hospital Mortality within 3 months Number of days before need of assisted ventilation
41	Convalescent Plasma for the Treatment of COVID-19 (Coronavirus Disease 2019)	18 Years and older (Adult, Older Adult)	Biological: COVID 19 Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Cumulative incidence of serious adverse events related to the treatment intervention Mortality at Day 28 post-hospital admission Length of hospital stay Length of supplemental oxygen requirement Length of mechanical ventilation requirement Length of ICU stay
42	COVID19-Convalescent Plasma for Treating Patients With Active Symptomatic COVID 19	15 Years and older (Child, Adult, Older Adult)	Biological: Convalescent Plasma from COVID-19 donors	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	In-hospital mortality secondary to COVID-19 among patients treated with convalescent plasma Safety of the use of convalescent plasma from COVID 19 donors Mortality at 30 days, 90 days, 6 months and 1 year In-hospital Mortality COVID-19 related compared with non-treated population according to Chilean official reports Number of days of hospitalization in high complexity facilities after convalescent plasma use

	Infection (FALPCOVID)				Number of days of hospitalization in intensive care unit after convalescent plasma use Number of days of mechanical ventilatory support in patients after convalescent plasma use Total number of days of mechanical ventilatory support Total number of hospitalization days in patients treated with convalescent plasma Number of hospitalization days in patients after treatment with convalescent plasma
43	Convalescent Plasma Therapy in Severe COVID-19 Infection	16 Years and older (Child, Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Proportion of In-hospital mortality Time to death Fever Respiratory distress Saturation of oxygen Blood pressure Oxygen requirement C-reactive Protein Ferritin SGPT
44	Assessment of the Effect of Convalescent Plasma Therapy in Patients With Life-threatening COVID19 Infection	21 Years to 70 Years (Adult, Older Adult)	Biological: Convalescent Plasma Drug: Standard of Care	Allocation: Randomized Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Duration of hospitalization/Recovery status
45	Use of Convalescent Plasma for COVID-19 Study	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Arms 1 & 2: number of critical and severe COVID-19 infected patients who are transfused with convalescent plasma result in lower death rates than the reported fatality rate Arms 1 & 2: number of critical and severe COVID-19 infected patients who survive the infection Arm 3: number of high risk COVID-19 infected patients who are transfused with convalescent plasma result in lower incidence of progression to severe or critical disease than the reported case rate Arm 4: number of health care providers who are at risk to exposure to COVID-19 who are transfused with convalescent plasma result in lower incidence of developing COVID-19 infection than the reported case rate
46	Convalescent Plasma for COVID-19 Patients	18 Years to 75 Years (Adult, Older Adult)	Biological: Convalescent COVID 19 Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Evaluate the safety Change in requirement for mechanical ventilatory support
47	COVID-19 Convalescent Plasma Treatment in SARSCoV-2 Infected Patients	15 Years to 85 Years (Child, Adult, Older Adult)	Drug: COVID-19 Convalescent Plasma	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Time to clinical improvement All-cause mortality

48	Convalescent Plasma for the Treatment of Severe SARS-CoV-2 (COVID-19)	18 Years and older (Adult, Older Adult)	Drug: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Intrahospital mortality from any cause Length of hospital stay Free time for ventilatory support on day 60 Overall survival at day 60 since hospitalization Cumulative incidence of adverse events: transfusion reactions (fever, flare), TRALI (transfusion-associated lung injury), TACO (transfusion-related circulatory overload), transfusion- related infections
49	COVID-19 (VA CURES-1)	18 Years and older (Adult, Older Adult)	Drug: Convalescent Plasma Other: Masked Saline Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Proportion of participants developing acute hypoxemic respiratory failure or all-cause death Time (in days) to recovery Time (in days) to death or respiratory failure Proportion of patients who died from any cause, had respiratory failure, or required humidified heated high-flow nasal cannula (HHHFNC) at 15 Lpm Time (in days) to death or respiratory failure or HHHFNC at 15 Lpm Subject 28-day all-cause mortality Time to an improvement of one category using an ordinal scale Time to an improvement of two categories using an ordinal scale Participant's clinical status by ordinal scale Mean change in the ordinal scale
50	Therapeutic Use of Convalescent Plasma in the Treatment of Patients with Moderate to Severe COVID-19	18 Years and older (Adult, Older Adult)	Biological: COVID-19 convalescent plasma (CCP) plus standard of care (SOC) Biological: Standard of care (SOC) plus placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Clinical Improvement Adverse Events of special interest Serious Adverse Events Survival Invasive mechanical ventilation Disease severity Time to outcomes of interest Length of stay measures SARS-CoV PCR Inflammatory markers
51	CONTAIN COVID-19: Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma Other: Saline solution	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment	Score on the WHO 11-point ordinal scale for clinical improvement at 14 days Score on the WHO 11-point ordinal scale for clinical improvement at 28 days
52	CONVALESCENT PLASMA FOR ILL PATIENTS BY COVID-19	16 Years and older (Child, Adult, Older Adult)	Biological: convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Clinical improvement Improvement in tomographic image Test positivity for COVID-19 Early and late complications associated to convalescent plasma Days at ICU
53	Convalescent Plasma for COVID-19	18 Years to 75 Years (Adult, Older Adult)	Biological: Blood plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Titers of anti-SARS-CoV-2 antibodies in the plasma derived from convalescent donors Change in titers of anti-SARS-CoV-2 antibodies in patients' plasma Change in inflammatory cytokines concentration (e.g., IL-6, HMGB1) Viral load decay in the recipient after plasma transfusion with semiquantitative assessment of nasopharyngeal swabs Number of patients with improvement in the 7- points Ordinal Scale

					Proportion of patients with adverse events, severity of adverse events
54	Human Convalescent Plasma for High-Risk Children Exposed or Infected With SARS-CoV-2 (COVID-19)	1 Month to 18 Years (Child, Adult)	Biological: Anti-SARS-CoV-2 Human Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Safety of treatment with high-titer anti-SARSCoV-2 plasma as assessed by adverse events Proportion of subjects with disease worsening event Pharmacokinetics of anti-SARS-CoV-2 antibodies as defined by changes in antibody titers Proportion of subjects with a natural antibody response to SARS-CoV-2 infection
55	Effectiveness and Safety of Convalescent Plasma Therapy on COVID-19 Patients with Acute Respiratory Distress Syndrome	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma Drug: Standard of care	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	All-cause mortality Length of stay in intensive care unit Duration of mechanical ventilation Body temperature (degree in Celsius) The Sequential Organ Failure Assessment (SOFA) Score PAO2/FIO2 ratio C-Reactive Protein (CRP) in mg/L D-Dimer in ng/mL Procalcitonin in ng/mL Interleukin 6 (IL-6) in pg/mL
56	A Study of COVID 19 Convalescent Plasma in High-Risk Patients with COVID 19 Infection	16 Years and older (Child, Adult, Older Adult)	Drug: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Survival Rate
57	Preemptive Use of Convalescent Plasma for High-risk Patients With COVID-19	18 Years and older (Adult, Older Adult)	Drug: SARS-CoV-2 convalescent plasma	Allocation: Non-Randomized Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Prevention	Proportion of patient that progress to WHO 8 ordinal scale # 4 (oxygen requirement) Proportion of death Proportion of patients with cleared nasopharyngeal viral load
58	Clinical Study for Efficacy of Anti-Corona VS2 Immunoglobulins Prepared from COVID19 Convalescent Plasma Prepared by VIPS Mini-Pool IVIG Medical Devices in Prevention of SARS-CoV-2 Infection in High-Risk Groups as Well as Treatment of Early Cases of COVID19 Patients	21 Years to 50 Years (Adult)	Other: hyper immunoglobulins containing anti-Corona VS2 immunoglobulin	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Efficacy of COVID19 hyper immunoglobulins for patients Efficacy of COVID19 hyper immunoglobulins for high-risk groups Safety of anti-SARS-CoV-2 hyper immunoglobulins assessed by percentage of adverse events

59	Efficacy of Reinforcing Standard Therapy in COVID-19 Patients with Repeated Transfusion of Convalescent Plasma	18 Years and older (Adult, Older Adult)	Other: Convalescent Plasma with antibody against SARS-CoV-2. Other: Standard treatment for COVID-19	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	WHO clinical progression scale Lung X-ray Concomitant medication assessment Hematimetry Activated partial thromboplastin time Fibrinogen level Fragment D-dimer assessment Glomerular Filtration Rate assessment Ferritin blood assessment C-reactive protein assessment
60	A Study Evaluating the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 Plasma in Hospitalized Patients With COVID-19 Infection	18 Years and older (Adult, Older Adult)	Biological: anti-SARS-CoV-2 convalescent plasma	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Overall Mortality within 60 days Length of ICU stay during current admission for COVID
61	COPLA Study: Treatment of Severe Forms of COronavirus Infection with Convalescent PLAsma plasma	18 Years and older (Adult, Older Adult)	Biological: Convalescent	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Lung injury Overall survival Adverse reactions to plasma
62	Efficacy of Convalescent Plasma in Patients with COVID-19 Treated with Mechanical Ventilation	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma Other: Standard of Care	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Vital status Day 90 mortality Number of ventilator-free days at day 28 Number of renal replacement therapy free days at day 28 Number of vasopressors free-days at day 28 Use of ECMO before day 28 Value of the SOFA score at days 7, 14 and 28 Changes in SOFA scores (delta SOFA) over 7, 14 and 28 days Assessment of the SARS-CoV-2 viral load Blood C-reactive protein (CRP) concentration
63	Convalescent Plasma to Limit SARS-CoV-2 Associated Complications	18 Years and older (Adult, Older Adult)	Biological: SARS-CoV-2 convalescent plasma Biological: Plasma from a volunteer donor	Allocation: Randomized Intervention Model: Parallel Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Cumulative incidence of hospitalization or death prior to hospitalization Cumulative incidence of treatment-related serious adverse events Cumulative incidence of treatment-related grade 3 or higher adverse events Change in serum SARS-CoV-2 antibody titers Time to SARS-CoV-2 Polymerase Chain Reaction (PCR) negativity
64	Convalescent Plasma Therapy for COVID-19 Patients	15 Years to 80 Years (Child, Adult, Older Adult)	Biological: convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Clinical outcome after plasma therapy Clinical response to treatment

65	Passive Immunity Trial for Our Nation to Treat COVID-19 in Hospitalized Adults	18 Years and older (Adult, Older Adult)	Biological: pathogen reduced SARSCoV-2 convalescent plasma Biological: Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor) Primary Purpose: Treatment	COVID-19 7-point Ordinal Clinical Progression Outcomes Scale All-location, all-cause 14-day mortality All-location, all-cause 28-day mortality Survival through 28 days Time to hospital discharge through 28 days COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 3 COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 8 COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 29 Oxygen-free days through Day 28 •Ventilator-free days through Day 28
66	Convalescent Plasma for Treatment of COVID-19 Patients with Pneumonia	18 Years and older (Adult, Older Adult)	Drug: High-Titer Anti-SARS-CoV-2 (COVID 19) Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Transfer to ICU 28-day mortality Cumulative incidence of serious adverse events Rates and duration of SARS-CoV-2 Serum of plasma antibody titer to SARS-CoV-2 Cellular and humoral immune response Supplemental oxygen free days Ventilator free days ICU free days Sequential organ failure assessment score
67	Efficacy and Safety of Novel Treatment Options for Adults With COVID-19 Pneumonia	18 Years and older (Adult, Older Adult)	Biological: Convalescent anti-SARSCoV-2 plasma Other: Infusion placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	All-cause mortality or need of invasive mechanical ventilation Frequency of adverse events Frequency of severe adverse events Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status Ventilator-free days Organ failure-free daysDuration of ICU stay Mortality rate Length of hospital stay Duration of supplemental oxygen
68	Donated Antibodies Working Against nCoV	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma Drug: Standard of care	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Patients requiring mechanical ventilation or death Clinical status of subject at day 15 and day 30 (on a 10-point "WHO progression" ordinal scale)
69	Investigating Effect of Convalescent Plasma on COVID-19 Patients Outcome: A Clinical Trial	30 Years to 70 Years (Adult, Older Adult)	Biological: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Mortality changes in day 10 Mortality changes in day 30 Changes of C-reactive protein Changes of Interleukin 6 Changes of tumor necrosis factor-# Changes of PaO2/FiO2 Ratio Changes of CD3 Changes of CD4 Changes of CD8 Changes of CD4/CD8 ratio

70	Plasma Exchange (PLEX) and Convalescent Plasma (CCP) in COVID-19 Patients with Multiorgan Failure	18 Years and older (Adult, Older Adult)	Procedure: Plasma exchange and convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Alive at Day 90 Day 8 serious adverse events Day 28 all-cause mortality Days alive without life support at day 90
71	Hyperimmune Plasma in Patients With COVID-19 Severe Infection	18 Years to 60 Years (Adult)	Other: plasma hyperimmune Drug: standard therapy	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Decrease in mortality Lymphocytes PCR levels vs control PCR levels vs before treatment AB levels and clinical improvement Inflammatory cytokines vs controls Inflammatory cytokines vs before treatment
72	Inactivated Convalescent Plasma as a Therapeutic Alternative in Patients COVID-19	18 Years and older (Adult, Older Adult)	Drug: Inactivated convalescent plasma Drug: Support treatment	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Investigator) Primary Purpose: Treatment	Mortality reduction in CoViD-19 patients treated with inactivated convalescent plasma + support treatment Clinical evolution Clinical evolution by seven-parameter ordinal scale Multi-organ failure progression Change in hemoglobin concentration Change in blood cell count Change in serum creatinine level Change in aspartate aminotransferase level Change in alanin aminotransferase level Change in bilirubin level
73	Reconvalescent Plasma/Camostat Mesylate Early in SARS-CoV-2 Q-PCR (COVID-19) Positive High-risk Individuals	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma Drug: CamostatMesilate Drug: Placebo for CamostatMesilate Other: Standard of Care (SoC)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	WHO ordinal COVID-19 scale up to day 28 Cumulative number WHO categories 4b-8 Cumulative number WHO categories 3-4a Not hospitalized All-cause mortality Reinfection Secondary sclerosing cholangitis (SSC) Chronic pulmonary disease as sequelae from COVID-19 patients with remdesivir treatment COVID-19 WHO status of patients at start of remdesivir treatment
74	COVID-19 Convalescent Plasma as Prevention and Treatment for Children with Underlying Medical Conditions	1 Month to 17 Years (Child)	Biological: anti-SARS-CoV-2 human convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Cumulative incidence of Grade 3 and Grade 4 adverse events Cumulative incidence of serious adverse events Proportion of participants with disease worsening event Serum concentration at baseline, Day 7, Day 14, and Day 28 for anti-SARS-CoV-2 antibodies Percentage of participants with a natural antibody response to SARS-CoV-2 infection
75	Convalescent Plasma to Stem Coronavirus (CSSC-001)	18 Years and older (Adult, Older Adult)	Biological: Anti- SARS-CoV-2 Plasma Biological: SARS-CoV-2 non-immune Plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator)	Efficacy of treatment at Day 28 Safety of treatment with high-titer Anti- SARSCoV-2 plasma versus control - 1

				Primary Purpose: Treatment	Safety of treatment with high-titer Anti- SARSCoV-2 plasma versus control - 2 Cumulative incidence of disease severity
76	Convalescent Plasma Collection and Treatment in Pediatrics and Adults	31 Days and older (Child, Adult, Older Adult)	Biological: Convalescent Plasma 1 Unit Biological: Convalescent Plasma 2 Units Other: Standard of Care	Allocation: Non-Randomized Intervention Model: Sequential Assignment Masking: None (Open Label) Primary Purpose: Treatment	Survival Incident of treatment-Emergent Adverse Events [Safety and Tolerability] Morbidity reduction Reduced Length of Stay in hospital Reduced Length of Stay on Advance Respiratory Support
77	COVID-19 Plasma in Treatment of COVID-19 Patients	18 Years to 80 Years (Adult, Older Adult)	Biological: Convalescent COVID 19 Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Reduce mortality Reduce requirement for mechanical ventilation Reduce the duration of mechanical ventilation Review of treatment related adverse events.
78	Hyperimmune Plasma for Patients With COVID-19	18 Years and older (Adult, Older Adult)	Other: treated with hyperimmune plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Death Time to extubation Length of intensive care unit stay Length of hospitalization Immune response Viral load
79	Randomized Evaluation of COVID-19 Therapy	Child, Adult, Older Adult	Drug: Lopinavir-Ritonavir Drug: Corticosteroid Drug: Hydroxychloroquine Drug: Azithromycin Biological: Convalescent plasma Drug: Tocilizumab Biological: Immunoglobulin Drug: Synthetic neutralising antibodies Drug: Aspirin Drug: Colchicine and 5 more	Allocation: Randomized Intervention Model: Factorial Assignment Masking: None (Open Label) Primary Purpose: Treatment	All-cause mortality Duration of hospital stay Composite endpoint of death or need for mechanical ventilation or ECMO
80	Anti-COVID-19 Hyperimmune Intravenous Immunoglobulin (C-IVIG) Therapy for Severe COVID-19 Patients	18 Years and older (Adult, Older Adult)	Biological: Anti COVID-19 Intravenous Immunoglobulin (C-IVIG)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Participant) Primary Purpose: Treatment	28-day Mortality Immediate and serious adverse event during hospital stay Clinical Status of follow-up days according to 7- Category Ordinal Scale Change in C-Reactive Protein (CRP) levels Change in interleukin 6 (IL-6) Change in anti-SARS-CoV-2 antibody levels Change in Horowitz index Change in radiological findings
81	Plasma Rich Antibodies from Recovered Patients from COVID19	18 Years to 80 Years (Adult, Older Adult)	Other: Antibody-Rich Plasma from COVID-19 recovered patient	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Viral COVID-19 clearance Decrease of radiological abnormalities Clinical improvement
82	Study Testing Convalescent Plasma vs Best Supportive Care	18 Years and older (Adult, Older Adult)	Biological: high-titer anti-Sars-CoV-2 plasma Other: oxygen therapy	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Reduction in oxygen and ventilation support

83	Efficacy and Safety of Recovered Covid 19 Plasma Transfusion to Covid 19 Severly Ill Patients Age: 18 Years and older (Adult, Older Adult) Study Completion: September 1, 2020		Biological: recovered COVID-19 patients' plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Patients' response to recovered COVID-19 plasma (RCP) during 5 days after transfusion Satisfactory outcome (two or more of the following 4 conditions/ or otherwise unsatisfactory): 1. respiratory frequency < 30/min, 2. Sustain blood oxygen saturation ≥93% on room air, 3. partial pressure of arterial oxygen to fraction of inspired oxygen ratio > 300 mmHg, 4. Regression of pulmonary infiltrates occupying less than 50% of both lungs.
84	plasmApuane CoV-2: Efficacy and Safety of Immune Covid-19 Plasma in Covid-19 Pneumonia in Non-ICU Patients	18 Years and older (Adult, Older Adult)	Biological: immune plasma	Allocation: N/A Intervention Model: Sequential Assignment Masking: None (Open Label) Primary Purpose: Prevention	ICU admission Administration of O2 Hospital mortality Immune plasma infusion adverse reaction
85	Convalescent Antibodies Infusion in Critically Ill COVID-19 Patients	18 Years and older (Adult, Older Adult)		Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Number of mechanical ventilation days Survival Shift to Continuous Positive Airway Pressure (CPAP) ventilation Referral to a sub-intensive care unit or discharge Viral titer Anti-COVID-19 IgG antibodies Anti-COVID-19 IgM antibodies C5a concentration C3a concentration Serum C5b-9 concentration
86	Convalescent Antibodies Infusion in COVID-19 Patients	Years and older (Adult, Older Adult)	Biological: Anti-coronavirus antibodies (immunoglobulins) obtained with DFPP form convalescent patients	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Time to weaning of oxygen support Chest XR or CT scan evaluation Survival, Viral titer Anti-COVID-19 IgG antibodies Anti-COVID-19 IgM antibodies C5a concentration C3a concentration Serum C5b-9 concentration Marker of complement activation Serum IL-6 levels
87	Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-	18 Years and older (Adult, Older Adult)	Drug: Fixed-duration Hydrocortisone Drug: Shock-dependent hydrocortisone Drug: Ceftriaxone Drug: Moxifloxacin or Levofloxacin	Allocation: Randomized Intervention Model: Factorial Assignment Masking: None (Open Label) Primary Purpose: Treatment	All-cause mortality Days alive and not receiving organ support in ICU ICU Mortality ICU length of stay Hospital length of stay Ventilator free days Organ failure free days

	Acquired Pneumonia		Drug: Piperacillin-tazobactam Drug: Ceftaroline Drug: Amoxicillin-clavulanate Drug: Macrolide administered for 3-5 days Drug: Macrolide administered for up to 14 days Drug: Five-days oseltamivir and 20 more		Health-related Quality of life assessment Proportion of intubated patients who receive a tracheostomy Destination at time of hospital discharge Readmission to the index ICU during the index hospitalization World Health Organization 8-point ordinal scale outcome
88	Study to Evaluate the Safety and Efficacy of XAV-19 in Patients With COVID-19 Induced Moderate Pneumonia	18 Years and older (Adult, Older Adult)	Drug: XAV-19 Drug: Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Phase 2a: XAV-19 antibody titers Phase 2a: Adverse events of XAV-19 Phase 2b: To evaluate the efficacy of XAV-19 + standard-of-care (Soc) therapy compared with placebo + Soc therapy for treatment of COVID-19 assessed by the proportion of patients who die or develop respiratory failure between baseline and Day 15. Phase 2a: Pharmacokinetic analysis Phase 2a: Antibody titer between the two groups Phase 2a: Supplemental oxygen Phase 2a: Evaluation of Transfer to intensive care Phase 2a: Normalization of Fever Phase 2a: Biomarkers Phase 2a: Hospital length of stay
89	Selenium as a Potential Treatment for Moderately-ill, Severely-ill, and Critically-ill COVID-19 Patients.	18 Years and older (Adult, Older Adult)	Drug: Selenium (as Selenious Acid) Other: Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment	Mean change in the ordinal scale Rate of hospital discharges or deaths Clinical status using ordinal scale Time to an improvement of one category using an ordinal scale Change in National Early Warning Score (NEWS) from baseline Cumulative incidence of serious adverse events (SAEs) Duration of hospitalization Incidence of new oxygen use Duration of new oxygen use Incidence of new non-invasive ventilation or high flow oxygen use
90	Australasian COVID-19 Trial (ASCOT) ADAptive Platform Trial	Years and older (Adult, Older Adult)	Drug: NafamostatMesilate Biological: Hyperimmune Globulin Drug: Enoxaparin Drug: Dalteparin Drug: Tinzaparin	Allocation: Randomized Intervention Model: Factorial Assignment Masking: None (Open Label) Primary Purpose: Treatment	Death from any cause or requirement of new intensive respiratory support (invasive or noninvasive ventilation) or vasopressor/inotropic support Time to clinical recovery WHO 8-point ordinal outcome scale All-cause mortality Days alive and free of hospital Days alive and free of invasive or non-invasive ventilation Shortness of breath Quality of life Antiviral domain-specific outcome: Viral clearance Antiviral domain-specific outcome: Viral load
91	Exchange Transfusion Versus Plasma from Convalescent Patients with	18 Years to 65 Years (Adult, Older Adult)	Biological: exchange blood transfusion from normal donor Biological: plasma from convalescent patients with COVID-19	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Improvement of condition Change in organs function with PFS and OS

	Methylene Blue in Patients With COVID-19		Drug: Methylene Blue 5 MG/ML		
92	Clinical Trial to Evaluate the Efficacy of Treatment with Hyperimmune Plasma Obtained from Convalescent Antibodies of COVID-19 Infection	18 Years to 80 Years (Adult, Older Adult)	Biological: Hyperimmune plasma Drug: Standard of care for SARSCoV-2 infection	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Safety: Incidence of Adverse Events and Serious Adverse Events grade 3 and 4, related to the product under investigation or the administration procedure, graduated according to the common toxicity criteria scale (CTCAE). Efficacy: Death from any cause Efficacy: Need for mechanical ventilation Efficacy: Any of the following analytical data after 72h of randomization. Efficacy: SOFA scale # 3 after 72 hours of randomization or an increase of 2 points or more from the basal level Efficacy: Mortality on days 14 and 28 Efficacy: Proportion of patients who required mechanical ventilation Efficacy: Proportion of patients who develop analytical alterations Efficacy: Cure / clinical improvement (disappearance or improvement of signs and symptoms of COVID-19) in the cure test. Efficacy: PCR negative for SARS-CoV-2
93	Early Use of Hyperimmune Plasma in COVID-19	18 Years and older (Adult, Older Adult)	Other: hyperimmune plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Clinical improvement (efficacy) Ventilation WHO (World Health Organization) scale SOFA (Sequential Organ Failure Assessment) score Naso-pharyngeal swab SARS-CoV2 P/F Thrombosis Curarization Complication kidney

Appendix 8. Characteristics of Studies in the Early (within 3 days of hospitalization), High Titer Plasma

Study ID	Participants	Settings & Sample Size	Comparisons		Design	Outcomes	Patient and Study Characteristics								
			Treatment	Control			Age (mean ±SD — yr)	Sex	Time from hospitalization to randomization/ transfusion	Time from Symptom Onset to Randomization/ Transfusion	Comorbidity	Severity	Oxygen support/ Respiratory support	Standard of care treatment given	Adverse Events/ Serious Adverse events
NCT04479163 Libster R, N Engl J Med, 2021	Patients with confirmed COVID-19 (mild; had at least one of each sign and symptom in the following two categories for less than 48 hours: a temperature of at least 37.5 C, unexplained sweating or chills; and dry cough, dyspnea, fatigue, myalgia, anorexia, sore throat, dysgeusia, anosmia, rhinorrhea) admitted to multiple centers in Argentina	Argentina (N = 160)	Convalescent plasma (1:1000 titer) (N=80)	Placebo (0.9% Normal Saline) (N=80)	RCT (double blind, placebo controlled)	All-cause mortality, Adverse events, Serious adverse events	CP: 76.4±8.7; Placebo: 77.9±8.4	CP: Male: 26/80 (32%), Female: 54/80 (68%); Placebo: Male: 34/80 (42%), Female: 46/80 (58%)	Within 24 hours	Within 72 hours (CP: 39.6±13.9 (in hrs), Placebo: 38.3±14.3 (in hrs))	Hypertension for which treatment was being received: CP: 62/80 (78%), Placebo: 52/80 (65%); Diabetes for which treatment was being received: CP: 23/80 (29%), Placebo: 13/79 (16%); Obesity: CP: 4/80 (5%), Placebo: 8/79 (10%); COPD for which treatment was being received: CP: 2/80 (2%), Placebo: 5/79 (6%); Cardiovascular disease: CP: 14/80 (18%), Placebo: 7/79 (9%); Chronic renal failure: CP: 1/80 (1%), Placebo: 3/79 (4%); At least one primary coexisting condition: CP: 69/80 (86%), Placebo: 62/80 (78%)	Mild	not requiring supplemental oxygen; baseline oxygen saturation at room air: CP: 96.1±1.6, Placebo: 96.1±1.7	None mentioned	No solicited adverse events were observed.
NCT04342182	Patients with COVID-19 (moderate-critical) admitted to 14	Netherlands (N=86)	Convalescent plasma (media	Standard care (N=43)	RCT (open-label)	All-cause mortality D28, Clinical improve	CP: median 61, IQR (56–	CP: Male: 29 (67%), Femal	median: 2 days (IQR 1–3)	median: 10 days (IQR 6–15)	Diabetes mellitus: CP: 13 (30%), SOC: 8 (19%); Hypertension: CP: 11 (26), SOC: 11 (26%); Cardiac: CP: 9 (21%),	Moderate - critical	hospitalized with no oxygen: CP: 7 (16%), SOC: 1 (2%); Hospitalized	None mentioned	No plasma-related serious adverse

Gharbharan A, medRxiv, 2020	centers in the Netherlands		n PRNT 50 (640, IQR 320–1280)) + SOC (N=43)			ment D28, Serious adverse events	70); SOC: median 63, IQR (55–77)	e: 14 (33%); SOC: Male: 33 (77%), Female: 10 (23%)			SOC: 11 (26%); Pulmonary: CP: 12 (28%), SOC: 11 (26%); Cancer: CP: 5 (12%), SOC: 3 (7%); Immunodeficiency: CP: 5 (12%), SOC: 6 (14%); chronic kidney disease: CP: 1 (2%), SOC: 6 (14%); Liver cirrhosis: CP: 1 (2%), SOC: 0		with Oxygen support or NIV: CP: 31 (72%), SOC: 34 (79%); Hospitalized with invasive ventilation (MV): CP: 5 (12%), SOC: 8 (19%)		events were observed
NCT04345523	Patients with confirmed COVID-19 [moderate (Pneumonia (CXR) or O2sat ≤94%] admitted to 14 centers in Spain	Spain (N=81)	Convalescent plasma (VMNT-ID50: median titer 1:292, IQR 238-451) (N=38)	Standard of care (43)	RCT (open-label)	All-cause mortality D28, WHO Progression score level 7 or above at D28, Serious adverse events, Time to clinical improvement	60.8 ±15.5	Male: 44 (54.3%); Female: 37 (45.7%)	within 3 days	(8.0 (6.0-9.0) (Median time (IQR) from symptom onset to randomization — days)	Diabetes mellitus: CP: 12 (31.6%), SOC: 5 (11.6%); Hypertension: CP: 20 (52.6%), SOC: 12 (27.9%); Cardiovascular disorder: CP: 6 (15.8%), SOC: 9 (20.9%); Chronic lung disease: CP: 2 (5.35), SOC: 8 (18.6%); chronic kidney disease: CP: 2 (5.35), SOC: 2 (4.7%); Immunodeficiency: CP: 2 (5.3%), SOC: 5 (11.6%)	Mild to Moderate	Not requiring supplemental oxygen: CP: 10 (26.32%), SOC: 13 (30.23%), Total: 23 (28.40%); Requiring supplemental oxygen by mask or nasal prongs: CP: 28 (73.68%), SOC: 30 (69.77%), Total: 58 (71.60%)	Hydroxychloroquine: CP: 34 (89.47%), SOC: 36 (83.72%), Total: 70 (86.42%); Lopinavir-ritonavir: CP: 15 (39.47%), SOC: 19 (44.19%), Total: 34 (41.98%); Azithromycin: CP: 24 (63.16%), SOC: 26 (60.47%), Total: 50 (61.73%); Remdesivir: CP: 1 (2.63%), SOC: 3 (6.98%), Total: 4 (4.94%); Glucocorticoid therapy: CP: 21 (55.26%), SOC: 25 (58.14%), Toatal: 46 (56.79%); Tocilizumab: CP: 10 (26.32%), SOC: 13 (30.23%), Total: 23 (28.40%); Low Molecular Weight Heparin:	Sixteen serious or grade 3-4 AE were reported in 13 patients, 6 in the CP group and 7 in the SOC group. Two CP infusion-related AE and suspected TRALI were reported. In both cases, TRALI was ruled out after full assessment. Both patients recovered without sequelae. None of the remaining events (n=14) were considered to be related to the CP. Five of the patients with reported

														CP: 27 (71.05%), SOC: 33 (76.74%), Total: 60 (74.07%)	severe AE died due to their underlying disease (4 deaths within the study, 1 death after the end of the study, all in the SOC group). The remaining patients recovered without sequelae.
Avendano-Sola C, medRxiv, 2020															
Rasheed 2020	Critically-ill COVID-19 patients aged ≥18-year-old affected by pneumonia with SpO2 <90% in resting state at their first 3 days in RCU receiving O2 or on ventilators at their early stages of admission to RCU before developing full-blown Acute Respiratory Distress Syndrome (ARDS) or respiratory and/or multiple	Iraq (N=49)	Convalescent plasma (IgG index ≥1.25 as measured by ELISA; to ensure getting CP with the highest titers of antibodies) + SOC (N=21)	Standard of care (N=28)	RCT (open-label)	Recovery or death, length of stay in hospital, and improvement in the clinical course of the disease	CP: 55.66 ± 17.83, SOC: 47.82 ± 15.36	Not mentioned	within 3 days	CP: 14.80 ± 7.46, SOC: 16.57 ± 5.99	Diabetes mellitus: CP: 8 (38%), SOC: 9 (32%); Hypertension: CP: 7 (33%), SOC: 10 (36%); heart disease: CP: 5 (24%), SOC: 5 (18%); Obesity: CP: 10 (48%), SOC: 11 (39%); Cancer: CP: 3 (14%), SOC: 5 (18%)	early-stage (no more than 3 days in ICU) critically ill COVID-19 patients before developing full-blown ARDS or respiratory and/or multiple organ failure	With oxygen support or on ventilators	Hydroxychloquine 200 mg twice per day for at least 10 days + azithromycin once 500 mg/day loading dose, followed by 250 mg once per day for 5 days + oxygen therapy + methylprednisolone 40 mg per day after admission to RCU]	No adverse events except that 1 patient developed mild skin redness and itching that lasted for 1 hour after CP; resolved by antihistamine injection

	organ failure and residing in Respiratory Care Units (RCU) in Baghdad, Iraq														

Q25. Should intravenous immunoglobulin (IVIG) be used in the treatment of patients with COVID-19 infection?

As of 18 May 2021

RECOMMENDATION

We suggest against the use of intravenous immunoglobulin as treatment for moderate to severe COVID-19. (*Very low certainty of evidence, Weak recommendation*)

Consensus Issues
A conditional/weak recommendation was made while waiting for the results of the 31 ongoing trials.

KEY FINDINGS

Four RCTs (n=277) that were of low to very low quality found that the use of intravenous immunoglobulin (IVIg) did not significantly reduce mortality or risk of mechanical ventilation among patients with moderate to severe COVID-19. However, one very low quality RCT found higher incidence of virologic clearance as assessed by negative RT PCR with the use of IVIg. There was also no significant increase risk of adverse events with its use in COVID-19.

INTRODUCTION

The acute respiratory distress syndrome of COVID-19 has been described as being driven by pro-inflammatory markers. The use of IVIg has been proposed as a treatment for COVID-19 due to its anti-inflammatory and immunomodulatory effects and its wide use in inflammatory and infectious diseases as well.[1] However, observational studies on the use of IVIg for severe COVID-19 show conflicting results. Hence we evaluated randomized control trials investigating the effectiveness of IVIg for COVID-19.

REVIEW METHODS

We performed a systematic literature search in online databases such as MEDLINE and CENTRAL. Additional searches in MedRxiv and WHO ICTRP were also done to look for articles awaiting publication and ongoing clinical trials, respectively. We used search terms such as “intravenous immunoglobulin,” “intravenous immune globulin,” “normal human immunoglobulin,” “human normal immunoglobulin,” “IVIg,” and “COVID-19.” References from review articles were also manually searched for additional articles.

RESULTS

The initial search from all the databases retrieved 331 references. After removal of duplicates, letters, commentaries, narrative reviews, and studies not meeting the inclusion criteria, we retrieved four full text articles.

Four RCTs compared the use of IVIg in various doses among 277 patients with moderate to severe COVID-19 (Appendix 1). The study by Gharebaghi et al. [4] compared IVIg against placebo while the three other RCTs [5–7] compared it to standard care. Pooled analysis of these three RCTs found no significant effect on mortality (RR 0.91 [95% CI 0.56, 1.46]) or need for mechanical ventilation (RR 0.79

[95% CI 0.53, 1.18]). However, the use of IVIg was associated with a higher chance of virologic clearance (RR 3.8 [95% CI 2.3, 6.3]). [5] There was also no increase in the risk of adverse events with the use of IVIg. [5,6]

In terms of length of hospital stay, two studies demonstrated a longer duration of hospitalization with the use of IVIg (median duration 2 to 3 days) [4,7] while the study by Raman et al., [5] showed a shorter mean length of hospital stay by 10 days (SD 5). Pooled analysis on the length of hospital stay showed a mean difference of -1.9 days (-2.8 to -0.9) which we considered as inconclusive.

The studies investigating the use of IVIg in COVID-19 were limited by high risk of unclear allocation concealment, and lack of intention to treat analysis. In addition, the studies were of small sample size leading to serious risk of imprecision (see Appendix 2).

RECOMMENDATIONS FROM OTHER GROUPS

The Surviving Sepsis Campaign Guidelines suggest against the routine use of standard IV immunoglobulin in critically-ill adults with COVID-19 (updated March 2021). [8]

Clinical practice guidelines from WHO, IDSA, US NIH, UK NHS, American Thoracic Society/European Respiratory Society, and the Australian Living Guideline made no recommendation on the use of intravenous immunoglobulin as treatment for COVID-19.

The US NIH however, did evaluate the use of SARS-COV2 specific immunoglobulins and found no sufficient evidence to support its use pending results of clinical trials.

ONGOING STUDIES

There are currently 31 ongoing randomized clinical trials in different phases investigating the effect of various forms of immunoglobulin as treatment for COVID-19 patients (Appendix 3).

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Appendix 1. Characteristics of Included Studies

Title/Author	Study design	Sample Size	Population	Intervention Group(s)	Control	Outcomes
Gharebaghi et al 2020	RCT	59	patients with severe COVID-19 who did not respond to initial treat-ments, ARDS	4 vials of 5g IVIg x 3 days	placebo	In-hospital mortality
Tabarsi et al	RCT	84	Severely ill COVID-19 pstients	400 mg/Kg daily for three doses	Standard of care	invasive mechanical ventilation and oxygenation, the need for admission to the Intensive Care Unit (ICU), and the mortality rate
Sakoulas et al	RCT, open label	34	Moderate to severe COVID-19	500 mg/kg daily for 3 days	Standard of care	Need for mechanical ventilation, length of hospital stay, length of ICU stay
Raman et al 2021	RCT open label	100	Moderate COVID-19	400 mg/kg daily for 5 days	Standard of care	Number of days hospitalized, time to clinical improvement, duration of mechanical ventilation, 28-day mortality, proportion of patients with negative RT PCR (day 14, 28)

Appendix 2: GRADE Evidence Profile

Author(s): Macalalad-Josue, Faltado

Question: Intravenous immunoglobulin compared to placebo or standard of care for COVID-19

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intravenous immunoglobulin	Placebo or standard of care	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 30 days)												
3	Randomised trials	Very serious [a,b,c]	Serious [d,e]	Not serious	Not serious	None	31/149 (20.8%)	32/128 (25.0%)	**RR 0.91** (0.56 to 1.46)	**22 fewer per 1,000** (from 110 fewer to 115 more)	⨁◯◯◯ VERY LOW	CRITICAL
Need for mechanical ventilation												
3	Randomised trials	Serious [a,b]	Serious [e,f]	Not serious	Serious [g]	None	35/118 (29.7%)	36/99 (36.4%)	**RR 0.79** (0.53 to 1.18)	**76 fewer per 1,000** (from 171 fewer to 65 more)	⨁◯◯◯ VERY LOW	CRITICAL
Length of hospital stay (follow up: 28 days; assessed with: number of days; Scale from: 1 to 28)												
3	Randomised trials	Serious [a,b]	Very serious [h]	Not serious	Serious [g]	None	132	111	-	MD **1.9 days lower** (2.83 lower to 0.94 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Incidence of virologic clearance (assessed with: negative RT PCR)												
1	Randomised trials	Serious [a,b,c]	Not serious	Not serious	Very serious [g,i]	None	46/50 (92.0%)	12/50 (24.0%)	**RR 3.83** (2.33 to 6.32)	**679 more per 1,000** (from 319 more to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Adverse events												
2	Randomised trials	Serious [a,b]	Serious [e]	Not serious	Serious [g]	None	15/67 (22.4%)	12/67 (17.9%)	**RR 1.25** (0.65 to 2.39)	**45 more per 1,000** (from 63 fewer to 249 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

[a] unclear allocation concealment ; [b] lack of blinding; [c] reporting bias (lack of intention-to-treat analysis) ; [d] different comparator ; [e] different doses ; [f] heterogeneity I2=58% ; [g] small sample size ; [h] heterogeneity I2=99% [i] wide confidence interval

Appendix 3. Characteristics of Ongoing Studies

TrialID	Scientific title	Countries	Condition	Intervention	Control	Primary outcome
ACTRN12620001249943	Intravenous immunoglobulin rich in neutralising antibodies to SARS-CoV-2 as a passive immunity modality in healthy individuals : an open label, active control Phase 1/2 Study to investigate the safety profile and to characterise the pharmacokinetics of COVID-19 complementary plasma and hyperimmune intravenous immunoglobulin G specific to SARS-CoV-2.	Australia	healthy adults	Hyperimmune intravenous immunoglobulin G specific to SARS-CoV-2		safety, tolerability and pharmacokinetic (PK) profile
ChiCTR2000030841	Treatment of Acute Severe COVID-19 With Immunoglobulin From Cured COVID-19 Patients	China	COVID-19	Experimental group:Immunoglobulin of cured patients	gamma-Globulin;	Time to Clinical Improvement (TTCI);
CTRI/2020/06/026222	A Phase II Safety and Efficacy Study on prognosis of Moderate Pneumonia in COVID-19 patients with Regular Intravenous Immunoglobulin Therapy	India	healthy adults	Immunoglobulin and standard of care	Azithromycin ,lopinavir/ritonavir, piperacillin - tazobactam	Number of days to clinical improvement. <br/ > It is defined as no. of days from initiation of treatment day to discharge day on a six-category ordinal scale Timepoint: 0-28 days
CTRI/2020/11/028779	A phase I, open label, parallel, randomised trial to assess the safety and efficacy of SARS-CoV-2 Equine Antiserum Immunoglobulin (Purified F(ab)2 fragment) in hospitalised COVID-19 patients with moderate disease in addition to standard of care. - None	India	healthy adults	SARS-CoV-2 Antiserum Immunoglobulins (Purified F(ab)2 fragment	Standard care	Proportion of patients with treatment-emergent adverse events including infusion related reactionsTimepoint: Day 0 Through Day 28
CTRI/2021/01/030824	An Open-Label, Randomized, Controlled, Multicenter Study to evaluate the Efficacy and Safety of COVID-19 Hyperimmunoglobulin in Patients with COVID-19	India	COVID-19	Hyperimmunoglobulin 50 mg/kg	Standard care	Mean change in 8 point ordinal scale in clinical improvement from baseline to day 8Timepoint: Day 8
EUCTR2020-001570-30-FR	Interest of early treatment with polyvalent immunoglobulins in the management of respiratory distress syndrome associated with SARS-CoV-2 infections_COVID-19 - ICAR (IgIV in Covid-related ARds)	France	COVID-19	ClairYg 50mg/ml	Placebo	Survival without invasive ventilatory assistance
EUCTR2020-001768-27-FR	"Study Of The Efficiency Of Normal Human Immunoglobulins (Ivig) In Patients Aged 75 Years And Over Covid-19 With Severe Acute Respiratory Failure"	France	elderly patients with moderate to severe COVID-19	Immunoglobulines Humaines Normales	Standard care	Mortality

EUCTR2020-002542-16-GB NCT04546581	An International Multicenter, Adaptive, Randomized Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability and Efficacy of Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin for the Treatment of Adult Hospitalized Patients at Onset of Clinical Progression of COVID-19 - Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC)	United States; Portugal; Nigeria; Greece; Thailand; Spain; Israel; United Kingdom;France; Mexico; Argentina; Belgium; Poland; Denmark; Peru; Germany; Japan	COVID-19	Anti-COVID-19 Hyperimmune Globulin (Human)	Placebo	All-cause mortality through Day 28.Change in National Early Warning Score (NEWS) from baseline at Day 3
EUCTR2020-005410-18-PL	Multicentre, randomized, double-blind, placebo-controlled, non-commercial clinical trial to evaluate the efficacy and safety of specific anti-SARS-CoV-2 immunoglobulin in the treatment of COVID-19	Poland	COVID-19	anti SARS-CoV-2 immunoglobulin	Placebo	No oxygen supplementation required on Day 7 and 14 from the start of the therapy
IRCT20151227025726N20	Evaluating the efficacy and safety of intravenous immunoglobulin (IVIG) in COVID-19 patients	Iran (Islamic Republic of)	COVID-19	IVIG (Biotest) 400 mg/Kg for 3 doses + hydroxychloroquine 200 mg twice daily + Lopinavir/Ritonavir 200-50 mg 2 Tab twice daily for 7 days	hydroxychloroquine 200 mg twice daily + Lopinavir/ Ritonavir 200-50 mg 2 Tab twice daily for 7 days.	Need for mechanical ventilation.
IRCT20200310046736N1	Comparison of The Therapeutic Effect of Convalescent Plasma and Plasma-derived Immunoglobulin-enriched solution on COVID-19 Patients: A Clinical Trial Study	Iran (Islamic Republic of)	critical COVID-19	Plasma-derived Immunoglobulin-enriched solution {IV, 0.2 _0.4 g/kg/day	routine care	complete remission of clinical signs of disease
IRCT20200317046797N3	To evaluate the effectiveness of intravenous immunoglobulin (IVIG) for the treatment of COVID-19-induced cytokine storm	Iran (Islamic Republic of)	moderate to severe COVID-19	IVIG for 2 days (100-200 mg twice a day)	HCQ, Kaletra	Mortality rate.;Need for intubation
IRCT20200325046859N1	Evaluation of the efficacy of intravenous immunoglobulin (IVIg) in patients with severe COVID-19 (Before intubation phase) who have not	Iran (Islamic	COVID-19	0.4-0.5/g/kg/day of IVIg in 3-5 doses	Standard care	fever, heart rate, respiratory rate, Chest CT scan, WBC

	responded to treatment with the standard three-drug protocol (hydroxychloroquine / chloroquine + lupinavir / ritonavir + ribavirin)	Republic of)				
IRCT20200413047056N1	Comparison between the efficacy of intravenous immunoglobulin and convalescent plasma in improving the condition of patients with COVID-19: A randomized clinical trial	Iran (Islamic Republic of)	COVID-19	IVIg (400mg/kg/d)	Standard care	Lung involvement in X-ray and CT-scan
IRCT20200418047116N1	Effect of Intravenous immunoglobulin (IVIG) versus Kaletra (lopinavir and ritonavir) tablets in patients with acute respiratory infection (COVID-19): A clinical trial studies	Iran (Islamic Republic of)	COVID-19	IVIg 400 mg/kg/day in 3 doses	Lopinavir/ritonavir	Pulmonary manifestations (Chest CT)
KCT0005649	A prospective, open-label, randomized, multi-center, phase 2a study to evaluate the dose response, efficacy and safety of Hyper-Ig (Hyper-immunoglobulin) GC5131 in Patients with COVID-19	Korea, Republic of	COVID-19	Hyper-immunoglobulin GC5131	Standard care	Percentage of subjects whose scores decreased by 2 points or reach level 1 or 2 by 9-ordinal scale
NCT04261426	A Randomized, Open-label, Controlled, Single-center Study to Evaluate the Efficacy of Intravenous Immunoglobulin Therapy in Patients With Severe 2019- nCoV Pneumonia		COVID-19	Intravenous Immunoglobulin	Standard care	Clinical improvement based on the 7-point scale;Lower Murray lung injury score;Lower Murray lung injury score
NCT04264858	An Exploratory Clinical Study on the Treatment of Acute Severe 2019-nCoV Pneumonia With Immunoglobulin From Cured 2019-nCoV Pneumonia Patients	China	COVID-19	Intravenous Immunoglobulin of cured patients	gamma-globulin	Time to Clinical Improvement (TTCI)
NCT04350580	Value of Early Treatment With Polyvalent Immunoglobulin in the Management of Acute Respiratory Distress Syndrome Associated With SARS-CoV-2 Infections	France, Mexico	Acute Respiratory Distress Syndrome; COVID-19	Intravenous Immunoglobulin	Placebo	Ventilator-free days
NCT04395170	A Randomized, Multicenter Clinical Trial to Evaluate the Efficacy and Safety of the Use of Convalescent Plasma (PC) and Human Intravenous Anti COVID-19 Immunoglobulin (IV Anti COVID-19 IgG) in Patients Hospitalized for COVID-19.	Colombia	COVID-19	Anti-COVID-19 human immunoglobulin	Standard care	Admission to ICU and/or mechanical ventilation
NCT04403269	"Study Of The Efficiency Of Normal Human Immunoglobulins (Ivig) In Patients Aged 75 Years And Over Covid-19 With Severe Acute Respiratory Failure" Geronimo 19	France	elderly with severe COVID-19	IVIg (0.8 g / kg by IV infusion)		Mortality
NCT04411667	Randomized Open Label Study of Standard of Care Plus Intravenous Immunoglobulin (IVIG) Compared to Standard of Care Alone in the Treatment of COVID-19 Infection	United States	COVID-19	IVIG (Octagam) 0.5g/kg IVPB actual body weight daily x 3 days	Standard care	Mechanical Ventilation

NCT04500067	An Open-label Multicenter Randomized Trial to Evaluate the Efficacy of Bioven, Manufactured by Biopharma Plasma, LLC, in Complex Therapy of Patients With Pneumonia Induced by COVID-19 / SARS-CoV-2	Ukraine	COVID-19	IVIG 0,8-1,0 g/kg once a day for 2 days	Standard care	Period duration (in days) to clinical improvement
NCT04514302	Pilot Study to Evaluate Safety and Efficacy of Anti-SARS-CoV-2 Equine Immunoglobulin F(ab')2 Fragments (INOSARS) in Hospitalized Patients With COVID-19	Mexico	COVID-19	Anti-SARS-CoV-2 equine immunoglobulin fragments (INOSARS)	Placebo	Proportion of patients with improvement in clinical status
NCT04521309	Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) Antibodies Based Intravenous Immunoglobulin (IVIG) Therapy for Severe and Critically Ill COVID-19 Patients	Pakistan	severe COVID-19	SARS-CoV-2 antibody based IVIG therapy	Standard care	28 Days mortality
NCT04548557	Intravenous Immunoglobulins for the Treatment of Covid-19 Patients: a Clinical Trial	Pakistan	Covid19	Biological: intravenous immunoglobulin therapy		In hospital days;14 day mortality
NCT04555148	A Prospective, Open-label, Randomized, Multi-center, Phase 2a Study to Evaluation the Dose Response, Efficacy and Safety of Hyper-Ig (Hyper-immunoglobulin) GC5131 in Patients With COVID-19	Korea, Republic of	Covid19	hyperimmunoglobulin GC5131	Placebo	Ordinal scale outcome
NCT04573855	Treatment With Anti-Sars-Cov-2 Immunoglobulin In Patients With Covid-19: A Phase I / Ii Study	Covid19		Anti-SARS-CoV-2 immunoglobulin	Standard care	Clearence of viral RNA evaluated by RT-PCR;Rate of adverse events.
NCT04661839	A Phase 1, Double-blind, Randomized, Placebo-controlled Study to Evaluate Safety and Pharmacokinetics of Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) Investigational Product (COVID-HIGIV) Administered as a Single Dose or a Repeat Dose Regimen to Healthy Adults	United States	healthy adults	COVID-HIGIV	Placebo	adverse events
NL9379	A Phase I-II study of virus neutralizing antibodies against SARS-CoV-2. A focus on convalescent plasma and hyperimmune anti-SARS-CoV2 immunoglobulines	The Netherlands	COVID-19	Nanogam plus (IVIG-therapy containing anti-SARS-CoV-2 antibodies)		Pharmacokinetics

Q26. Should mesenchymal stem cell therapy be used in the treatment of patients with COVID-19 infection?

As of 29 May 2021

RECOMMENDATION

There is insufficient evidence to recommend using umbilical cord-derived mesenchymal stem cell therapy among adults with severe COVID-19 (PaO2/FiO2 ratio ≤ 300 mmHg). *(Very low certainty of evidence)*

Consensus Issues
Although the current available evidence shows benefit in terms of mortality and time to clinical improvement, no recommendation was made due to the small sample size of the included studies. Further, more patients in the mesenchymal stem cell (MSC) therapy arm received co-interventions (i.e., remdesivir and corticosteroids) compared to the control arm which may have overestimated the true effect of MSC

KEY FINDINGS

We found 3 randomized controlled trials (RCTs) evaluating the effectiveness and safety of mesenchymal stem cell (MSC) therapy in COVID-19 treatment. One RCT was at high risk of bias while the remaining 2 RCTs were of moderate quality. Validity issues included unclear allocation concealment, lack of blinding and incomplete outcome reporting. Based on very low quality evidence, umbilical cord-derived MSC (UC-MSC) therapy reduces mortality and hastens clinical improvement in adults with severe COVID-19. Limited by small sample sizes, adverse events were not significantly different between MSC and control groups.

INTRODUCTION

Cell-based therapies including MSC, natural killer cells and dendritic cells have been proposed as investigational treatment for COVID-19 [1]. MSCs, which may be isolated from bone marrow, adipose and umbilical cord tissue, are multipotent cells that can attenuate inflammatory responses and induce regeneration [2]. Early-stage clinical trials in acute respiratory distress syndrome and chronic obstructive pulmonary disease have demonstrated the apparent safety of MSC therapy and their potential to reduce inflammatory markers like C-reactive protein [2]. However, stem cell therapy is more expensive compared to other anti-COVID-19 medications and may cost around $4,000 to $8,000 without cell culture expansion in developed countries [1].

At least four hospitals in the Philippines have experience with stem cell therapy [4]. Locally, a single-center case series of patients with severe COVID-19 and cytokine response syndrome found that UC-MSC infusion was well-tolerated. Most patients concurrently received steroids (10/11) and remdesivir (9/11). Hydroxychloroquine and intravenous immunoglobulin (IVIg) were given to one patient each. Seven (63.6%) enrolled patients were eventually discharged [3].

This review sought to summarize the available evidence on the clinical effectiveness and safety of MSC therapy in treating adults with COVID-19.

REVIEW METHODS

An electronic search was conducted on several databases (MEDLINE through PubMed and Cochrane Library), preprint servers (medRxiv, bioRxiv, ChinaXiv) and clinical trial registries (ClinicalTrials.gov, WHO ICTRP, ChiCTR) until April 24, 2021 using the following terms and their variations: mesenchymal stem cell transplantation, mesenchymal stem cells, COVID-19 and SARS-CoV-2. MeSH terms were also used whenever available. No language restrictions were applied. We also searched the COVID-19 Living NMA initiative's Living Synthesis of Published Trials for studies involving stem cells on May 14, 2021.

Randomized controlled trials (RCTs) investigating the use of mesenchymal stem cells (MSC) derived from any source in treating adult patients with COVID-19 were included. Outcomes included mortality, endotracheal intubation or invasive mechanical ventilation, length of hospital stay, time to clinical improvement and safety. Systematic reviews were used to identify additional studies that may potentially be eligible.

Dichotomous endpoints were presented as relative risks (RR). Continuous outcomes were reported as presented by the respective study authors. Meta-analyses using random-effects models using Review Manager 5.4.1 (The Cochrane Collaboration 2020) were performed for outcomes similarly reported by multiple studies. Subgroup analyses according to disease severity and stem cell origin were planned but not pursued due to limited available data.

RESULTS

Characteristics of Included Studies

We found 3 RCTs (n = 148) comparing MSC therapy with placebo or standard care in severe COVID-19 patients with P_aO_2/FiO_2 ratio ≤ 300 mmHg (Appendix 1) [5-7]. Two studies were conducted in China [5,7] while another was performed in the United States [6]. All trials used UC-MSC delivered via intravenous infusion. The dose was either fixed ($100 \pm 20 \times 10^6$ cells each for 2 doses [6] or 4.0×10^7 cells each for three doses [7]) or determined by weight (2×10^6 cells/kg single dose [5]).

Quality of evidence

The quality of evidence for effectiveness and safety outcomes was very low (Appendix 2). Across all outcomes, we downgraded one to two levels due to issues with study quality (allocation concealment, blinding and attrition). We also downgraded for imprecision in most outcomes due to the small sample sizes and wide interval estimates.

One RCT was judged to be at high risk of bias because of unclear allocation concealment and lack of blinding [5]. There were also more participants in the treatment group with respiratory rates above 24 breaths/min (91.67% vs. 68.97%, p = 0.231) suggesting that they may have been worse off. The remaining 2 RCTs were of moderate quality: one trial limited to a modified intention-to-treat analysis (1 patient was randomized to receive MSC therapy but was excluded due to withdrawal of consent) [7] while re-inclusion could be performed to generate the intention-to-treat population for mortality in the another [6]. In the latter study, allocation sequence concealment was unclear and differences in co-interventions probably favored the

MSC arm (more treatment group patients received remdesivir [75% vs. 58.3%] and corticosteroids [83.3% vs. 75%]).

Mortality
Three RCTs (n = 148, with re-inclusion of one excluded death in Lanzoni 2021) reported mortality at 28 or 31 days from the first infusion. UC-MSC therapy significantly reduced the risk of death in severe COVID-19 patients: RR 0.25 (95% CI 0.07 to 0.86, I^2 = 0%; Appendix 3, Figure 1).

Invasive mechanical ventilation
Only one randomized trial (n = 100) reported the incidence of endotracheal intubation [7]. MSC appears to be non-inferior to placebo in avoiding mechanical ventilation (0% vs. 11.4%; RR 0.06 [95% CI 0 to 1.09]; Appendix 3, Figure 2). The wide confidence intervals are largely a function of the small sample size.

Length of hospital stay
Duration of hospital stay was provided in one RCT (n = 100) [7]. Although the treatment group patients appeared to have shorter hospital stays (median [IQR]: 20.00 days [16.00, 24.00] vs. 24.00 days [20.00, 26.50]), the difference was not statistically significant (p = 0.054).

Time to clinical improvement
UC-MSC therapy appeared to hasten clinical improvement according to 2 studies (n = 48) [5,6]. Clinical improvement, which was defined as hospital discharge or a decline in two categories of a seven-point ordinal scale of clinical status, was achieved about five days earlier with treatment (median [IQR]: 9.00 days [6.00, 13.00] vs. 14.00 days [9.50, 21.00], p = 0.006) in one study [5] In another RCT of similar size, time to recovery (i.e., discharge or no longer requiring COVID-19-related medical care) was more favorable in the MSC arm: HR 0.2891 (95% CI: 0.088 to 0.948) [6].

Adverse events
Adverse reactions associated with treatment were reported in 3 RCTs (n = 165) [5-7]. A study which reported adverse events for patients receiving MSC but made no explicit mention for the comparison group was assumed to have zero events in the control arm [5].

In 2 RCTs (n = 141), the risk of developing any adverse event did not significantly differ between MSC and control groups (RR 0.95 [95% CI 0.67 to 1.34; Appendix 3, Figure 3). The most common side effects recorded were laboratory derangements, e.g., increased lactate dehydrogenase and alanine aminotransferase [7].

Only one trial (n = 24) reported infusion-associated adverse events within 6 hours of administration (RR 1.00 [95% CI 0.07, 14.2]) [6]. Bradycardia requiring an increase in vasoactive agent dose occurred in one patient who received UC-MSC while another patient in the placebo group experienced cardiac arrest.

As for serious adverse events (n = 124, 2 studies), the likelihood did not differ significantly between treatment and control groups (RR 0.36 [95% CI 0.08 to 1.57]; Appendix 3, Figure 4). In one RCT, pneumothorax developed in a patient who received UC-MSC [5].

RECOMMENDATIONS FROM OTHER GROUPS

The U.S. National Institutes of Health (21 Apr 2021) [8] COVID-19 Treatment Guidelines Panel recommends against using MSCs for COVID-19 treatment except within clinical trials. They cited that the U.S. Food and Drug Administration (FDA) has not yet approved any MSC product for COVID-19 treatment, and that there is limited data on MSCs in COVID-19.

RESEARCH GAPS

There are 5 completed RCTs that used MSCs in COVID-19 patients from the United States, China and Russia and Indonesia. However, their results have yet to be published.

There are at least another 59 ongoing randomized trial investigating MSCs or exosomes in COVID-19 treatment (Appendix 4). The MSCs, sourced from umbilical cord, bone marrow or adipose tissue, are given singly or in combination with another drug (e.g., ruxolitinib). These trials are conducted in the United States, Germany, France, Spain, Mexico, Brazil, Australia, Colombia, China, Russia, Indonesia, Iran and Pakistan.

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Appendix 1. Characteristics of Included Studies

Study ID Design	Sample Size	Population / Setting	Intervention/s	Control	Outcomes
Shu 2020 RCT	41	Patients with severe COVID-19 (PaO2/FiO2 ≤ 300 mHg)	hUC-MSC: 2 doses x 10^6 cells/kg MSCs (The Jiangsu Cell Tech Medical Research Institute and The Jiangsu Cell Tech Biotechnology Co.) suspended in 100 mL normal saline IV infusion	Placebo *Standard care included supplemental oxygen, abidor/oseltamivir, antibiotics, glucocorticoids	Mortality at D28 Length of hospital stay Time to clinical improvement Adverse events
Lanzoni 2021 RCT	24	Patients ≥ 18 years with COVID-19 ARDS (PaO2/FiO2 ratio < 300 mmHg)	UC-MSC: Intravenous infusions (IV) of 100 ± 20 x 10^6 UC-MSC* each, in vehicle solution containing Human Serum Albumin (HSA) and heparin, two doses within 72 +/- 6 hours apart *Culture-expanded from a previously established and characterized Master Cell Bank (MCB) derived from the subepithelial lining of a UC, collected from a healthy term delivery (kindly provided by Jadi Cell and Amit Patel, MD)	Two infusions of vehicle solution containing HSA and heparin	Mortality at D31 (D28 after last infusion) Time to recovery Serious adverse events Infusion-associated adverse events
Shi 2021 RCT	100 (modified intention-to-treat)	Patients with severe COVID-19 (PaO2/FiO2 ≤ 300 mHg)	UC-MSC: 4.0 x 10^7 cells (VCANBIO Cell & Gene Engineering Corp, Tianjin, China) each infusion on days 0, 3 and 6 after randomization	Placebo	Mortality at D28 Invasive mechanical ventilation Adverse events (Grades 1-2, Grades 3-4)

Appendix 2. GRADE Evidence Profile

Mesenchymal stem cell therapy compared to control for adults with COVID-19

CERTAINTY ASSESSMENT							SUMMARY OF FINDINGS				
							Study event rates			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With control	With mesenchymal stem cell therapy	Relative effect (95% CI)	Risk with control	Risk difference with mesenchyme stem cell therapy
Mortality (follow up: range 28 days to 31 days)											
148 (3 RCTs)	Very serious [a]	Not serious	Not serious	Serious [b]	None	⨁◯◯◯ VERY LOW	10/59 (16.9%)	2/89 (2.2%)	**RR 0.29** (0.09 to 0.88)	169 per 1,000	**120 fewer per 1,000** (from 154 fewer to 20 fewer)
Invasive mechanical ventilation											
100 (1 RCT)	Serious [c]	Not serious	Not serious	Very serious [d]	None	⨁◯◯◯ VERY LOW	4/35 (11.4%)	0/65 (0.0%)	**RR 0.06** (0.00 to 1.09)	114 per 1,000	**107 fewer per 1,000** (from -- to 10 more)
Length of hospital stay											
100 (1 RCT)	Serious [c]	Not serious	Not serious	Very serious [e]	None	⨁◯◯◯ VERY LOW	In one RCT (n = 100), the duration of hospital stay was not significantly different between MSC and control groups (median [IQR]: **20.00 days [16.00, 24.00] vs. 24.00 days [20.00, 26.50], p = 0.054**).				
Time to clinical improvement											
48 (2 RCTs)	Very serious [a]	Not serious	Not serious	Serious [b]	None	⨁◯◯◯ VERY LOW	Clinical improvement was achieved earlier with MSC therapy than control in one RCT (n = 24, median [IQR]: **9.00 days [6.00, 13.00] vs. 14.00 days [9.50, 21.00], p = 0.006**). In another RCT (n = 24), time to recovery was more favorable in the MSC arm: **HR 0.2891 (95% CI: 0.088 to 0.948)**.				
Any adverse event											
124 (2 RCTs)	Very serious [a]	Not serious	Not serious	Very serious [d]	None	⨁◯◯◯ VERY LOW	8/47 (17.0%)	3/77 (3.9%)	**RR 0.36** (0.08 to 1.57)	170 per 1,000	**109 fewer per 1,000** (from 157 fewer to 97 more)
Serious adverse events											
141 (2 RCTs)	serious [f]	not serious	not serious	very serious [d]	none	⨁◯◯◯ VERY LOW	21/64 (32.8%)	37/77 (48.1%)	**RR 0.95** (0.67 to 1.34)	328 per 1,000	**16 fewer per 1,000** (from 108 fewer to 112 more)

CERTAINTY ASSESSMENT							SUMMARY OF FINDINGS				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With mesenchymal stem cell therapy		Risk with control	Risk difference with mesenchyme stem cell therapy
Infusion-associated adverse events											
24 (1 RCT)	serious [g]	not serious	not serious	very serious [d]	none	⨁◯◯◯ VERY LOW	1/12 (8.3%)	1/12 (8.3%)	**RR 1.00** (0.07 to 14.20)	83 per 1,000	**0 fewer per 1,000** (from 77 fewer to 1,000 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

[a] Downgraded twice due to unclear allocation concealment, unequal baseline characteristics between groups, lack of blinding and exclusion of a patient that was randomized

[b] Downgraded once due to small sample size

[c] Downgraded once due to attrition (exclusion of a patient that was randomized)

[d] Downgraded twice due to wide confidence interval and small sample sizes

[e] Downgraded twice due to significant overlaps in confidence intervals (difference likely due to chance) and small sample size

[f].Downgraded once due to issues on allocation concealment and attrition (exclusion of a patient that was randomized)

[g] Downgraded once due to unclear allocation concealment

Appendix 3. Forest Plots

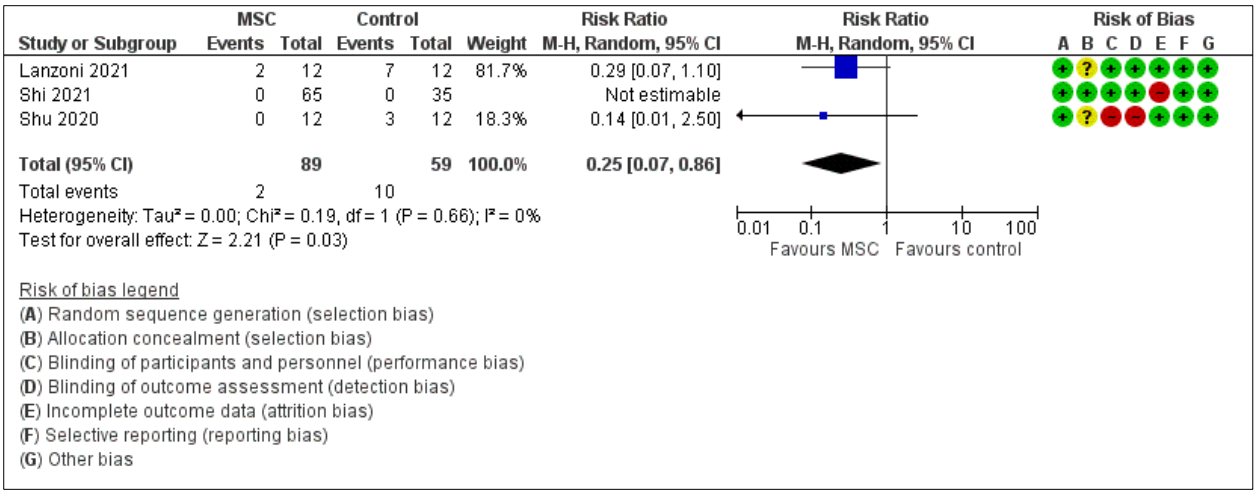

Figure 1. Forest plot for mortality

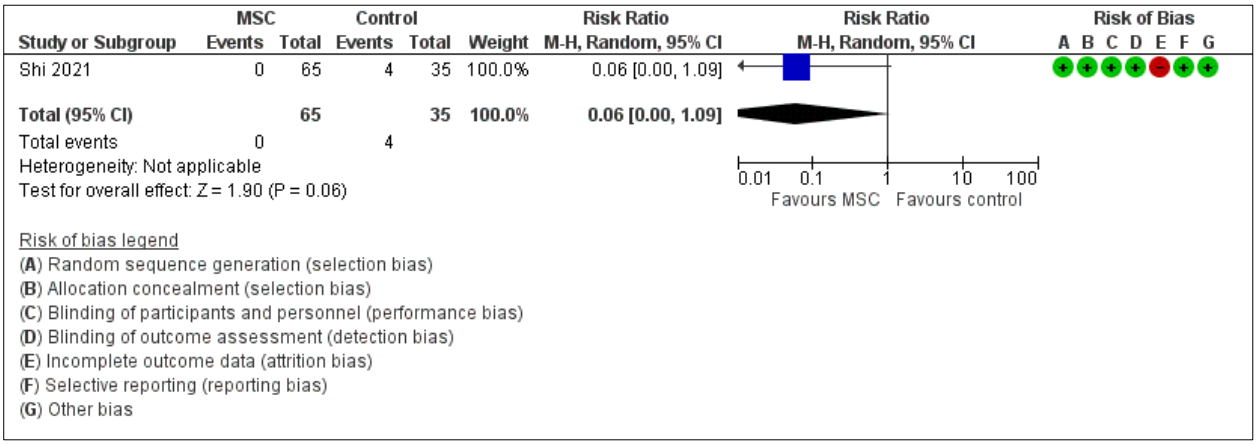

Figure 2. Forest plot for invasive mechanical ventilation

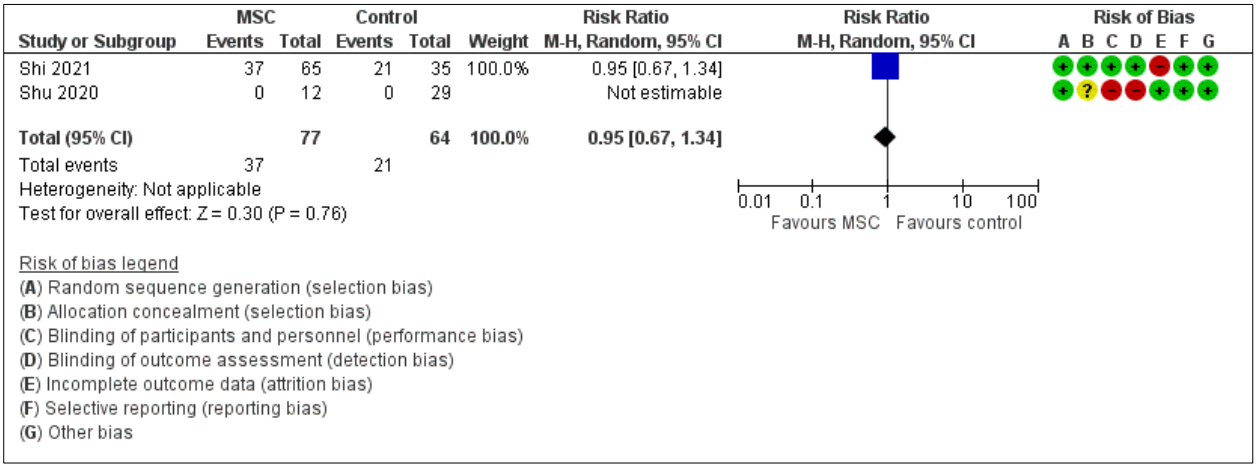

Figure 3. Forest plot for patients with any adverse event

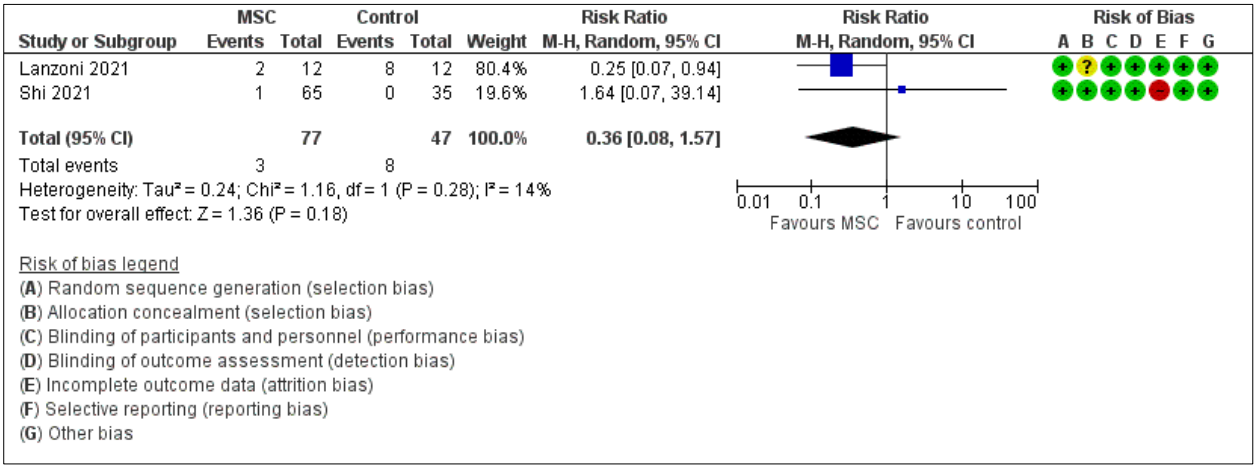

Figure 4. Forest plot for patients with serious adverse events

Appendix 4. Characteristics of Ongoing Studies

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
IRCT20190717044241N3 Iran (Islamic Republic of)	COVID-19	Intervention 1: Intervention group: Patients with coronavirus 19 who undergo mesenchymal stem cell transplantation at a rate of 2 million per kilogram body weight (based on IBW) through peripheral blood (IV)on days 0, 3, and 6. Intervention 2:	Control group: Participants with COVID19 receiving routine and placebo treatment (based on IBW) intravenously on days 0, 3, and 6.	Clinical response. Timepoint: 28 days-From the time of cell injection until the 28th day. Method of measurement: clinical observation by Infectious Diseases Specialist.;O2 saturation. Timepoint: Since the injection of the cell; 0,3,6 days. Method of measurement: ventilator. Inflammation cytokines. Il-6 & Il-10. Timepoint: On days 0,3,6,14 - from the time of cell injection. Method of measurement: Assay by the Elisa.;CD4 and CD8 markers. Timepoint: On days 0,3,6,14 - from the time of cell injection. Method of measurement: Flow Cytometry.;Evaluation of lung function. Timepoint: On days 0,14 - from the time of cell injection. Method of measurement: CT scan of the lungs.
IRCT20200426047206N2 Iran (Islamic Republic of)	COVID-19 disease. Severe Acute Respiratory Syndrome coronavirus;RA01.0	Intervention 1: Intervention group: This group receiving mesenchymal stem cells. In this group, patients are received 1 million Umbilical core-derived MSCc/BW by intravenous injection (provided by volunteer donors at Fatemieh Hospital) (Through the catheter and the Central vein and from the superior vena cava vein). Also, in addition to cell therapy, Other routine treatments (The last national protocol for COVID-19 treatment) will be given to patients according to the physician's supervision.The umbilical cord will be provided by volunteer donors at Fatemieh Hospital and after that will be cultured and expanded in the cleanroom of Hamadan University of Medical Sciences	Intervention 2: Control group: Receiving routine therapies (The last national protocol for COVID-19 treatment) (without stem cell).	Patient respiratory status. Method of measurement: Using CT scan image, physical examination, oxygen saturation percentage.;Inflammatory factors. Timepoint: Before and two week after intervention. Method of measurement: Elisa.
ISRCTN33578935 Germany	Hypercytokinemia in patients with COVID-19 and severe respiratory distress syndrome (SARS) due to CoV-2 infection Infections and Infestations	Intervention Intravenous infusion of purified exosomes, XoGloÂ®, which are isolated, neonatal, mesenchymal stem cell-derived extracellular vesicles at a dose of 0.2 mg/kg each in a total of 15ml on day 1 and day 3.	Control: 15ml of saline, i.v. on Day 1 and Day 3	1. Safety and adverse events measured using i.v. administration of 0.2mg/kg of placental, mesenchymal stem cell-derived exosome preparations (KTA 100,= XoGloÂ®) at day 1 and day 3 2. Improved respiration measured using PaO2/FiO2 at day 1, 2, and onwards daily 3. Mechanical ventilator and vasopressors treatment-free days (number of days that a patient is alive and free from mechanical ventilation and vasopressors) over 28 days. 4. Percentage of patients alive and free of mechanical ventilation at Day 29 5. Ventilator free days (VFD) over 28 days. VFD are defined as one point for each day during the measurement period that are both alive and free of mechanical ventilation. 6. Percentage of patients alive and free of vasopressors at Day 29 7. Vasopressor treatment-free days over 28 days defined as one point for each day during the measurement period that subjects are both alive and free of vasopressors. 8. Time to end of invasive mechanical ventilation 9. Time to end of invasive and/or non-invasive mechanical ventilation

				10. Time to end of vasopressors treatment 11. sVP-ARDS-COVID-19 Clinical Response at Day 14 assessed as follows: 11.1 Cure: complete resolution of pneumonia signs and symptoms present at baseline, no new symptoms or complications attributable to the pneumonia 11.2. Non-response: any of the following: 11.2.1. Failure related to pneumonia: Persistence/progression of baseline signs/symptoms of pneumonia; or baseline radiographic abnormalities after at least 2 days of treatment; or development of new pulmonary/extra pulmonary findings consistent with active infection, or development of new pulmonary infection or extrapulmonary infection requiring antimicrobial therapy; or persistence/progression of baseline signs/symptoms of severe sepsis; or development of new signs/symptoms of severe sepsis; or death due to sepsis 11.2.2. Failure unrelated to pneumonia: Any other cause of clinical response failure than in the investigator's judgement is unrelated to the index pneumonia (myocardial infarction, pulmonary thromboembolism, sepsis of urinary origin, etc.). 11.2.3. Indeterminate: extenuating circumstances precluding classification to one of the above 12. Clinical response at Day 8-10 and Day 29 or early discontinuation: 12.1. Time to sVP-ARDS-COVID-19 cure 12.2. Duration of antiviral treatment 12.3. Rate of pneumonia recurrence/reinfection after clinical cure 12.4. Pneumonia recurrence is defined as a new acute clinical episode of pneumonia, after clinical cure of the episode that qualified the patient for the study, based on the presence of two relevant signs (fever, tachypoea, leukocytosis, or hypoxemia) and radiographic findings of new pulmonary infiltrates or clinically significant worsening of previous ones. If a pathogen isolated in the recurrent episode is phenotypically different from the one isolated in the previous episode this will be considered as reinfection. 13. Time to recurrence/reinfection of pneumonia after clinical cure at sVP-ARDS-COVID-19 clinical response assessments. 14. Survival 28-day all-cause mortality 15. 28-day sVP-ARDS-COVID-19-associated mortality 16. Survival at Day 7, 14, 29, and 90 visits 17. Time to death 18. Time to discharge from ICU 19. Time to discharge from hospital 20. Length of stay in ICU and hospital after randomization 21. Number of ICU-free days over 28 days 22. Changes in Sepsis-related Organ Failure 23. Assessment score daily during stay at ICU 24. Changes on chest X-ray assessed at Screening, and then as medically required with at least one CXR per sVP-ARDS-COVID-19 clinical response assessment until clinical cure from Day 1 to Day 28 and for pneumonia recurrence/reinfection assessment. 25. Evolution of partial pressure of oxygen/fraction inspired oxygen (PaO2/FiO2) daily until Day 7

				26. Need of mechanical ventilation or need for non-invasive ventilation 12 hours after the second XoGlo infusion 27. Use of rescue antibiotics i.e. addition or change of antibiotic treatments due to the occurrence of antibiotic resistance posterior to microbiology results at baseline or insufficient efficacy during the course of the study 28. Cell responses on Day 0 Pre-dose and Days 7, 14 and 29 or early discontinuation: 28.1. Cell proliferative capacity in the presence and absence of stimulation 28.2. Cell activation status (phenotype pro/anti-inflammatory monocytes, pro/antiinflammatory T cells, HLADR, CD69) 28.3. Secretion assay of peripheral blood mononuclear cells in response to stimulation 28.4. Evaluation of RNA expression profiles of blood leukocytes on Screening, Day 0 Post-dose, Day 2, Day 3 Post-dose and Days 7 and 14 or early discontinuation (only if early termination [ET] is before V9 [Day 14]). 28.5. Evaluation of plasma concentrations of biomarkers on Screening, Day 0 Post-dose, Day 2, Day 3 Post-dose, and Days 7 and 14 or early discontinuation (only if ET is before V9 [Day 14]) 28.6. Protein biomarkers may include, but are not restricted to: TNF-a, IL-1, IL-6, IL-8, IL-10, IL-17, soluble triggering receptor expressed on myeloid cells 1, C-reactive protein, plasminogen activator inhibitor-1, protein C, sE selectin, angiopoietin-1, and angiopoietin-2, troponin-I
IRCT20160809029275N1 Iran (Islamic Republic of)	Covid-19 disease. Severe Acute Respiratory Syndrome coronavirus;RA01.0	Intervention 1: Intervention group: Group receiving mesenchymal stem cells. In this group, patients in 3 times (1, 3 and 6 days) are received 1 million Umbilical core-derived MSCc/BW by intravenous injection (Through the catheter and the Central vein and from the superior vena cava vein). Also, in addition to cell therapy,Other common treatments will be given to patients according to the physician's supervision.Mesenchymal Stem cells had an ISCT standard and were given from a healthy donor. Blood samples were given from patients on days 0, 2, and 7, as well as 14 days after the second injection and patients will follow for 20 days (in terms of clinical and immunological parameters).It should be noted that of all patients at the beginning of the study conscious consent form will be received	Intervention 2: Control group: Receiving common therapies (without stem cell). In this group, patients are received other common treatments including antiviral drugs and etc In accordance with the physician's opinion and do not receive stem cells.	Respiratory symptoms and pulmonary function in patients. Timepoint: In onset of study and days 2, 7 and 14 after the second injection. Method of measurement: Using CT scan image , physical examination , Oxygen saturation Percentage.;Evaluation of IFN-?,IL4,TGF-ÃŸ,IL1-ÃŸ , IL-6 and TNF-a cytokine levels in patients blood. Timepoint: In onset of study and days 2, 7 and 14 after the second injection. Method of measurement: Using Elisa kits.;Cell markers and populations. Timepoint: In onset of study and days 2, 7 and 14 after the second injection. Method of measurement: Using Flow cytometery technique.
NCT04444271 Pakistan	COVID-19	Drug: Mesenchymal stem cells	Other: Placebo	Overall survival Clinical improvement;Time of COVID19 PCR negativity;Radiological improvement (day 15 and day 30 assessment);days required to discharge from hospital
ACTRN12620000612910 Australia	COVID-19;	Treatment: Other- Mesenchymoangioblast-derived mesenchymal stem cells (CYP-001	Control group: standard of care in ICU. The active agent in CYP-001 is allogeneic mesenchymoangioblast-	To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in intensive care units (ICU), based on improvements in P/F ratio compared to controls. This outcome is defined as a trend in trajectory of

		Intervention group: Mesenchymoangioblast-derived mesenchymal stem cells (CYP-001) at a dose of 2 million cells/kg (up to a maximum of 200 million cells) by IV infusion on two occasions (Day 1 and Day 3) PLUS standard of care in ICU	derived mesenchymal stem cells (MCA-derived MSCs), which are produced using the proprietary Cymerusâ„¢ platform technology. Cymerus refers to the process of generating cell-based products from intermediate cells, MCAs, which in turn are derived from induced pluripotent stem cells or iPSCs. The iPSCs used in the Cymerus process were derived from blood donated by a fully-consented healthy adult donor, and were reprogrammed using a transgene-free, viral-free and feeder-free technique	P/F ratio between groups by day 7. P/F ratio is collected from ventilatory support data combined with arterial blood gas measures[By day 7 in the study (within days 1-7). P/F ratio will be collected as per routine standard collection of data to inform respiratory function (at least 4 hourly when relevant) plus every 15 minutes during cell adminstration and 1, 2, 3, 4 and 5 hours after];To assess the safety and tolerability of CYP-001 in adults with COVID-19 being treated in ICU measured by the incidence and severity of treatment-emergent adverse events (including events related with reactions to cryoprotectant; fever read from digital thermometer, allergy, olfactory/taste disturbances), safety laboratory evaluations (immunology screen with full blood examination) and vital signs (including significant fluctuations from clinically acceptable BP, and HR and SaO2 levels measured via pulse oximetry)[Up to day 28 in the study. On days 0-7 this will be collected routinely in standard care (at least 4-hourly) plus every 15 minutes during cell administration and 1, 2, 3, 4 and 5 hours after, then daily after day 8] To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in ICU, measured by changes in blood inflammatory marker, C-reactive protein[Up to day 7 after patient enrolment in study, collected as part of standard care pathology analysis occurring daily];To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in ICU, based on changes in physiological indices of respiratory dysfunction (including exploratory measures of P/F ratio, respiratory rate, oxygenation index (OI), respiratory compliance, positive end-expiratory pressure (PEEP), fever monitoring, ICU length of stay, ventilator free days (VFDs)) from data collected routinely in standard care (i.e. records of extubation, reintubation) up to day 28. [Up to day 28 after patient enrolment in study, collected as per routine standard collection of data to inform respiratory function (at least 4 hourly when relevant) and at the same intervals as P/F ratio];To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in ICU, based on proportional differences between groups on the Clinical Improvement Scale[Assessed on day 28 after patient enrolment in study, based on health and hospitalisation status];To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in ICU, based on proportional differences between groups in Quality of Life and Disability assessments measured by the 36-Item Short Form Survey (SF-36)[Assessed on day 28 after patient enrolment in study];To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in ICU, based on proportional differences between groups in Quality of Life and Disability assessments measured by the Standardised Mini-Mental State Examination (SMMSE)[Assessed on day 28 after patient enrolment in study]
IRCT20200421047150N1 Iran (Islamic Republic of)	COVID-19	Intervention 1: Intervention group: In this group, umbilical cord Whartonâ€™s jelly mesenchymal stem cells are infused at an initial dose of 0.5-2 milion/ kg. This process is performed on the first, third and sixth days. This intervention is done along with other standard treatments for this type of	Intervention 2: Control group: This group, like the intervention group, will receive all standard medication according to national and international guidelines, depending on the severity of COVID-19. But on the first, third and	Death. Timepoint: Up to 28 days after starting the study. Method of measurement: Patient observation and evaluation of vital signs. Evaluation of Pneumonia Severity Index. Timepoint: Up to 28 days. Method of measurement: PSI.;Evaluation of oxygen supply index. Timepoint: Discharge from ICU. Method of measurement: Pulse Oximeter.;Improve pneumonia evaluated by CT scan. Timepoint: After the second and third infusions. Method of measurement: CT scan.;+ CD4 + / CD8 ratio.

		patients, varying in severity of COVID-19 Infectious, and in accordance with national and international guidelines.	sixth day, placebo (normal saline) is infused.	Timepoint: Before the first injection and after the third injection. Method of measurement: Flow cytometry.;Counting of CD3 +, CD4 + and CD8 + T cells. Timepoint: Before the first injection and after the third injection. Method of measurement: Flow cytometry.;Lymphocyte count. Timepoint: Until the marker is normalized. Method of measurement: CBC.;Procalcitonin. Timepoint: Until the marker is normalized. Method of measurement: Blood sample.;C- Reactive protein. Timepoint: 28 days or until the marker is normalized. Method of measurement: Blood sample.
IRCT20200413047063N1 Iran (Islamic Republic of);Iran (Islamic Republic of)	Acute Respiratory Distress Syndrome of COVID-19. COVID-19;U07.1	Intervention 1: Intervention group:Intervention group: The intervention group 1, Patients will receive three doses of MSCs. Two doses of 100Ã—10e6 (Â±10%) cells will intravenously infuse as a normally dropped single dose over 10-12 minutes at the infusion speed of 4-5 mL/minute in day 0 and day 2 and day 4.	Intervention 2: Control group: Patients will receive conventional therapy.	Adverse events assesment. Timepoint: At the same time of each intervention, 24 hours after each intervention, on days 6, 7, 14 and 28 after the first intervention. Method of measurement: Number of participants with treatment-related adverse events as assessed by CTCAE v4.0.;Blood oxygen saturation. Timepoint: At Baseline, simultaneously with each intervention and on days 5, 6, 7, 14 after the first intervention. Method of measurement: Evaluation of Pneumonia Improvement. Biomarkers concentrations in plasma. Timepoint: At baseline, 7, 14, 28 days after the first intervention. Method of measurement: Biochemical examination.;Respiratory efficacy. Timepoint: From baseline to day 7. Method of measurement: Evaluated by the increase in PaO2/FiO2 ratio.;Intensive care unit-free days. Timepoint: Up to day 8. Method of measurement: Number of day.;Change in clinical symptoms. Timepoint: At Baseline, simultaneously with each intervention and on days 5, 6, 7, 14 after the first intervention. Method of measurement: Evaluation of Pneumonia Improvement.
NCT04348435 United States	COVID-19	Drug: HB-adMSCs	Drug: Placebo	Incidence of hospitalization for COVID-19;Incidence of symptoms associated with COVID-19 Absence of upper/lower respiratory infection;Leukocyte differential;C Reactive protein;TNF alpha;IL-6;IL-10;Glucose;Calcium;Albumin;Total protein;Sodium;Total carbon dioxide;Potassium;Chloride;BUN;Creatinine;Alkaline phosphatase;Alanine aminotransferase;Total bilirubin;white blood cells;red blood cells;hemoglobin;hematocrit;mean corpuscular volume;mean corpuscular hemoglobin;mean corpuscular hemoglobin concentration;red cell distribution width;neutrophils;Lymphs;Monocytes;Eosinophils;Basophils;Absolute neutrophils;Absolute lymphs;Absolute monocytes;Absolute eosinophils;Absolute basophils;Immature granulocytes;Platelets;Prothrombin time;INR;SF-36;PHQ-9
IRCT20200217046526N2 Iran (Islamic Republic of);Iran (Islamic Republic of)	Acute Respiratory Distress Syndrome of COVID-19.	Intervention 1: Intervention group: The intervention group 1, Patients will receive three doses of MSCs. Two doses of 100Ã—10e6 (Â±10%) cells will intravenously infuse as a normally dropped single dose over 10-12 minutes at the infusion speed of 4-5 mL/minute in day 0 and day 2	Intervention 2: The intervention group 3, Patients will receive two doses of MSCs intravenously and EVs. Two doses of 100Ã—10e6 (Â±10%) MSCs will intravenously infuse as a normally dropped single dose over 10-12 minutes at the infusion speed of 4-5 mL/minute in day 0 and day 2. In days 4 and 6, the patients will receive two times the infusion of MSCs-EVs.	Adverse events assesment. Timepoint: At the same time of each intervention, 24 hours after each intervention, on days 6, 7, 14 and 28 after the first intervention. Method of measurement: Number of participants with treatment-related adverse events as assessed by CTCAE v4.0.;Blood oxygen saturation. Timepoint: At Baseline, simultaneously with each intervention and on days 5, 6, 7, 14 after the first intervention. Method of measurement: Evaluation of Pneumonia Improvement. Biomarkers concentrations in plasma. Timepoint: At baseline, 7, 14, 28 days after the first intervention. Method of measurement: Biochemical examination.;Respiratory efficacy. Timepoint: From baseline to day 7. Method of measurement: Evaluated by the increase in PaO2/FiO2

			Intervention 3: Control group: Patients will receive conventional therapy.	ratio.;Intensive care unit-free days. Timepoint: Up to day 8. Method of measurement: Number of day.;Change in clinical symptoms. Timepoint: At Baseline, simultaneously with each intervention and on days 5, 6, 7, 14 after the first intervention. Method of measurement: Evaluation of Pneumonia Improvement.
NCT04341610 Denmark	COVID-19	Drug: allogeneic adipose-derived mesenchymal stromal cell	Placebo: saline	Changes in clinical critical treatment index Days of respirator treatment;Improvement of clinical symptoms including duration of fever and respiratory need;Mortality;Marker of Immunological function -CD4+ and CD8+ T cell count;C-reactive protein and leucocyte;Cytokine profile;Glomerular Filtration Rate;Duration of hospitalization
IRCT20140528017891N8 Iran (Islamic Republic of)	COVID-19. Severe Acute Respiratory Syndrome coronavirus;RA01.0	Intervention 1: Intervention group: In this group, mesenchymal stem cells will be injected at an initial dose of 0.5-1 milion/ kg. This process will be performed on the first, third and sixth days. This intervention will be done along with other treatments for this type of patients, varying in severity of COVID Infectious, and in accordance with national and international guidelines. Mesenchymal Stem Cell is GMP-approved by SinaCell	Intervention 2: Control group:This group, like the intervention group, will receive all routine medication according to national and international guidelines, depending on the severity of COVID-19. But on the first, third and sixth day, placebo (normal saline) will be injected.	Death. Timepoint: Up to 28 days after starting the study. Method of measurement: Patient observation and evaluation of vital signs. Evaluation of Pneumonia Severity Index. Timepoint: Up to 28 days. Method of measurement: PSI.;Evaluation of oxygen supply index. Timepoint: Discharge from ICU. Method of measurement: Pulse Oximeter.;C-Reactive protein. Timepoint: 28 days or until the marker is normalized. Method of measurement: Blood sample.;Procalcitonin. Timepoint: Until the marker is normalized. Method of measurement: Blood sample.;Lymphocyte count. Timepoint: Until the marker is normalized. Method of measurement: CBC.;Counting of CD3 +, CD4 + and CD8 + T cells. Timepoint: Before the first injection and after the third injection. Method of measurement: Flow cytometry.;+ CD4 + / CD8 ratio. Timepoint: Before the first injection and after the third injection. Method of measurement: Flow cytometry.;Improve pneumonia evaluated by CT scan. Timepoint: After the second and third infusions. Method of measurement: CT scan.
NCT04346368 China	Coronavirus Disease 2019 (COVID-19)	Biological: BM-MSCs	Biological: Placebo	Changes of oxygenation index (PaO2/FiO2);Side effects in the BM-MSCs treatment group Clinical outcome;Hospital stay;CT Scan;Changes in viral load;Changes of CD4+, CD8+ cells count and concentration of cytokines;Rate of mortality within 28-days;Changes of C-reactive protein
NCT04429763	COVID-19	Biological: Umbilical cord derived mesenchymal stem cells	Biological: Placebo	Clinical deterioration or death
NCT04315987 Brazil	COVID-19 Pneumonia	Biological: NestaCell	Biological: Placebo	Change in Clinical Condition|Rate of mortality within 10-days|Change of Clinical symptoms - respiratory rate|Hypoxia|PaO2 / FiO2 ratio|CD4+ and CD8+ T cell count|Changes of blood oxygen|Side effects in the treatment group|Complete blood count, cardiac, hepatic and renal profiles;
NCT04336254 China	COVID-19	Biological: allogeneic human dental pulp stem cells (BSH BTC & Utooth BTC)	Other: Intravenous saline injection (Placebo)	TTCI|Lung lesion|Immune function|Time of SARS-CoV-2 clearance|Blood test|SPO2|RR|Body temperature|Side effects in the treatment group|C-reactive protein (mg/L)
NCT04611256 Mexico	Covid19	Biological: MSC	Drug: Control	Change form baseline in Arterial oxygen saturation|Days to clinical improvement|Change Form Baseline in C reactive protein at 25 days|Change Form Baseline Immune cells: CD3+, CD4+, CD8+, CD16+, CD19+, and CD56+ lymphocytes|Change Form Baseline in pro-inflammatory cytokines: IL-1Î², IL- 2, TNF-Î±, ITN-Î³, IL-4, IL-6, IL-10|Change Form Baseline in Immunoglobulins; IgA, IgG, IgM, and IgE.
NCT04288102 China	Corona Virus Disease	Biological: UC-MSCs	Saline with albumin	Change in lesion proportion (%) of full lung volume from baseline to day 28.|Change in lesion proportion (%) of full lung volume from baseline to day 10 and 90|Change in consolidation lesion proportion (%) of full lung

*Completed	2019(COVID-19)			volume from baseline to day 10, 28 and 90.|Change in ground-glass lesion proportion (%) of full lung volume from baseline to day 10, 28 and 90.|Pulmonary fibrosis - related morphological features in CT scan at day 90 a. cord-like shadow b. honeycomb-like shadows c. interlobular septal thickening d. intralobular interstitial thickening e. pleural thickening|Lung densitometry: Change in total voxel 'weight' in lesion area voxel 'weight'=voxel density (in HU) Ã— voxel volume (in voxel)|Lung densitometry: volumes histogram of lung density distribution (<-750, -750~-300, -300~50, >50) at day 10, 28 and 90.|Time to clinical improvement in 28 days.|Oxygenation index(PaO2/FiO2)|Duration of oxygen therapy(days)|Blood oxygen saturation|6-minute walk test|Maximum vital capacity (VCmax)|Diffusing Capacity (DLCO)|mMRC (Modified Medical Research Council) dyspnea scale|Changes of absolute lymphocyte counts and subsets from baseline to day 6, 10, 28 and 90.|Changes of cytokine/chemokine levels from baseline to day 6, 10, 28 and 90.|Adverse events|Serious adverse events|All-cause mortality
NCT04366271 Spain	COVID	Biological: Mesenchymal cells	Drug: Standard of care	Mortality due to lung involvement due to SARS-CoV-2 virus infection at 28 days of treatment|Mortality due to lung involvement due to SARS-CoV-2 virus infection at 14 days of treatment|Mortality from any cause at 28 days|Days without mechanical respirator and without vasopressor treatment for 28 days|Patients alive without mechanical ventilation and without vasopressors on day 28|Patients alive and without mechanical ventilation on day 14|Patients alive and without mechanical ventilation on day 28|Patients alive and without vasopressors on day 28|Days without vasopressors for 28 days|Patients cured at 15 days|Incidence of Treatment-Emergent Adverse Events
NCT04371601 Fujian, China	COVID-19 Pneumonia	Mesenchymal stem cells	Drug: Oseltamivir	Changes of oxygenation index (PaO2/FiO2) ,blood gas test|Detection of TNF-Î± levels, IL-10 levels|Detection of immune cells that secret cytokines, including CXCR3+, CD4+, CD8+, NK+ cells, and regulatory T cells (CD4 + CD25 + FOXP3 + Treg cells).|Changes of c-reactive protein and calcitonin
NCT04366323 Spain	Sars-CoV2	Drug: allogeneic and expanded adipose tissue-derived MSCs	No intervention	Safety of the administration of allogeneic mesenchymal stem cells derived from adipose tissue assessed by Adverse Event Rate|Efficacy of the administration of allogeneic mesenchymal stem cells derived from adipose tissue assessed by Survival Rate
NCT04625738	COVID19 ARDS	Biological: Ex vivo expanded Wharton's Jelly Mesenchymal Stem Cells	Biological: Placebo	PaO2 / FiO2 ratio|respiratory function evolution|respiratory assistance|organ failures 1|organ failures 2|organ failures 3|duration of intensive care|Cause of death|respiratory morbidity (TDM, functional respiratory measures)|viral load|Anti-HLA antibody rate|immediate hypersensitivity reactions|thromboembolic adverse events 1|thromboembolic adverse events 2|infectious adverse events
NCT04273646 China	2019 Novel Coronavirus Pneumonia|COVID-19	Biological: UC-MSCs	Drug: Placebo	Pneumonia severity index|Oxygenation index (PaO2/FiO2)|Side effects in the UC-MSCs treatment group|28-days survival|Sequential organ failure assessment|C-reactive protein|Procalcitonin|Lymphocyte count|CD3+, CD4+ and CD8+ T celll count|CD4+/CD8+ratio
NCT04348435 United States	COVID-19	Drug: HB-adMSCs	Drug: Placebos	Incidence of hospitalization for COVID-19|Incidence of symptoms associated with COVID-19|Absence of upper/lower respiratory infection|Leukocyte differential|C Reactive protein|TNF alpha|IL-6|IL-10|Glucose|Calcium|Albumin|Total protein|Sodium|Total carbon

				dioxide|Potassium|Chloride|BUN|Creatinine|Alkaline phosphatase|Alanine aminotransferase|Total bilirubin|white blood cells|red blood cells|hemoglobin|hematocrit|mean corpuscular volume|mean corpuscular hemoglobin|mean corpuscular hemoglobin concentration|red cell distribution width|neutrophils|Lymphs|Monocytes|Eosinophils|Basophils|Absolute neutrophils|Absolute lymphs|Absolute monocytes|Absolute eosinophils|Absolute basophils|Immature granulocytes|Platelets|Prothrombin time|INR|SF-36|PHQ-9
NCT04339660 China	COVID-19	Biological: UC-MSCs	Other: Placebo	The immune function (TNF-alpha, IL-6)|Blood oxygen saturation|Rate of mortality within 28-days|Size of lesion area by chest imaging|CD4+ and CD8+ T cells count|Peripheral blood count recovery time|Duration of respiratory symptoms (fever, dry cough, difficulty breathing, etc.)|COVID-19 nucleic acid negative time
NCT04629105 United States	ARDS, Human|Covid19	Biological: Longeveron Mesenchymal Stem Cells (LMSCs)	Other: Placebo	Incidence of Treatment-Emergent Serious Adverse Events|Number of Participants with Abnormal Clinical Significant Laboratory Values in Hematology.|Number of Participants with Changes in Echocardiography Overall Assessment|Number of Participants with Changes to overall assessment of Electrocardiogram|Time to recovery of Sp02|Number of Participants with Abnormal Clinical Significant Lab Values in the Blood Chemistry testing.|Number of Participants with Abnormal Clinical Significant Lab Values in the Coagulation.|Number of Participants with Abnormal Clinical Significant Lab Values in the Urinalysis|Immunity|Change in Imaging via X-ray|Change in Imaging via Computerized Tomography
NCT04753476 Indonesia	Covid-19|Cytokine Storm	Biological: Injection of Secretome-MSCs	Drug: Standard treatment of Covid-19	Change in patients clinical manifestation|Need for a ventilator|Duration of using a ventilator|Length of stay|Routine blood profile|CRP|D-dimer|Blood Gas Analisis (BGA)|Photo thorax|Survival
NCT04428801	COVID-19	Biological: autologous adipose-derived stem cells	Placebo	Tolerability and acute safety of AdMSC infusion by assessment of the total number of AEs/SAEs related and non-related with the medication|The overall proportion of subjects who develop any AEs/SAEs related and non-related with the AdMSC infusions as compared to the control group|COVID-19 incidence rates in both the study and control groups|The proportion of subjects who are infected by SARS-Cov-2 measured by PCR or other nuclear level-based SARS-Cov-2 virus testing in respiratory tract specimens (oropharyngeal samples) collected by oropharyngeal swab using the CDC standard method.|The proportion of subjects who are infected by SARS-Cov-2 virus develop symptoms including mild, classic, severe and critical sever cases between study group and control group.|Change of proportion of subjects who are infected by SARS-Cov-2 and develop IgM/IgG antibodies against SARS-Cov-2 between study group and control group.|Change of lymphocyte count in white blood cell counts from the baseline|Change of PaO2 arterial blood gases from the baseline|Compare the proportion of subjects who develop severe COVID-19 pneumonia cases for both study and control groups|COVID-19 mortality rates for both study and control groups|Change of C-reactive protein (CRP) (mg/L) from the baseline|Change of D-dimer (mg/L) from the baseline|Change of Procalcitonin (ug)/L from the baseline|Change of pro-

				type B natriuretic peptide (pro-BNP) (pg/mL) from the baseline|Change of Bilirubin (mg/dL) from the baseline|Change of Creatinine (mg/dL) from the baseline|Change in blood test values for cytokine panels (IL-1Î², IL-6, IL-8, IL-10, TNFÎ±) from the baseline|The proportion of subjects from SARS-CoV-2 RT-PCR positive to negativity in respiratory tract specimens (oropharyngeal samples) collected by oropharyngeal swab using the CDC standard method. as compared to control group|Quantifying viral RNA in stool for baseline and final follow-up.
NCT04728698 United States	Covid19|ARDS	Drug: COVI-MSC	Drug: Placebo	Mortality at Day 28|Mortality at Days 60 and 90|Number of ventilator-free days|Improvement in oxygenation|SOFA score at Day 28
NCT04457609 Indonesia	COVID|Pulmonary Infection|Sars-CoV2	Biological: Umbilical Cord Mesenchymal Stem Cells	Drug: Oseltamivir Drug: Azithromycin	Clinical improvement: Presence of dyspnea|Clinical improvement: presence of sputum|Clinical improvement: fever|Clinical improvement: ventilation status|Clinical improvement: blood pressure|Clinical improvement: heart rate|Clinical improvement: respiratory rate|Clinical improvement: oxygen saturation|General laboratory outcome from leukocyte level|General laboratory outcome from lymphocytes level|General laboratory outcome from blood pH|General laboratory outcome from blood level of CO2|General laboratory outcome from blood base excess level|General laboratory outcome from blood oxygen partial pressure|General laboratory outcome from blood level of HCO3|General laboratory outcome from blood level of O2 saturation|General laboratory outcome from level of CRP|General laboratory outcome from level of SGOT/SGPT (AST/ALT)|General laboratory outcome from the level of ureum/creatinine level|General laboratory outcome from the level of eGFR|General laboratory outcome from the level of sodium|General laboratory outcome from the level of potassium|General laboratory outcome from the level of chloride|Changes in procalcitonin level|General laboratory outcome from albumin level|General laboratory outcome from total bilirubin level|Changes in D-Dimer level|Changes in fibrinogen level|Cardiac changes from troponin level|Cardiac changes from NT proBNP level|Changes in Leukemia Inhibiting Factor|Changes in level of IL-6|Changes in level of IL-10|Changes in level of vascular endothelial growth factor (VEGF)|Changes in level of ferritin|Changes in level of CXCR3|Changes in level of CD4|Changes in level of CD8|Changes in level of CD56|Radiologic Improvement from Chest X-Ray/CT Scan
NCT04490486 United States	COVID-19|Acute Respiratory Distress Syndrome|Corona Virus Infection	Biological: UCMSCs	Other: Placebo	Percent of participants with treatment related Serious Adverse Events (SAE)|Change in inflammatory marker levels|Change in systemic inflammatory marker levels|COVID-19 Viral Load|Change in SOFA score|Change in electrolytes levels|Change in LDH levels|Number of subjects discharged from the ICU|Percentage of participants with less requirement for vasoactive agents|Rate of Mortality|Percentage of participants with changes in immune marker expression|Percentage of participants with changes in radiologic findings|Percentage of participants with less pneumonia symptoms
NCT04366063 Royan Institute, Tehran, Iran, Islamic Republic of	Covid-19	Two MSC infusion Two MSC infusion plus two extracellular vehicles	Conventional therapy	Adverse events assessment|Blood oxygen saturation|Intensive care unit-free days|Clinical symptoms|Respiratory efficacy|Biomarkers concentrations in plasma

NCT04573270 United States *Completed	Covid19|Prophylaxis	Biological: PrimePro (MSC)	Other: Placebo	Survival Rates|Contraction Rates
NCT04355728 United States *Completed	Corona Virus Infection|ARDS|ARDS, Human|Acute Respiratory Distress Syndrome|COVID-19	Biological: Umbilical Cord Mesenchymal Stem Cells + Heparin along with best supportive care.	Other: Vehicle + Heparin along with best supportive care	Incidence of pre-specified infusion associated adverse events|Incidence of Severe Adverse Events|Survival rate after 90 days post first infusion|Ventilator-Free Days|Change in Oxygenation Index (OI)|Plat-PEEP|Sequential Organ Failure Assessment (SOFA) Scores|Small Identification Test (SIT) scores|Troponin I levels|C-Reactive Protein levels|Arachidonic Acid (AA)/Eicosapentaenoic Acid (EPA) Ratio|D-dimer levels|25-Hydroxy Vitamin D levels|Alloantibodies levels|Blood white cell count|Platelets count
NCT04362189 United States	COVID-19	Drug: HB-adMSC	Drug: Placebo	Interleukin-6|C Reactive protein|Oxygenation|TNF alpha|IL-10|Return to room air (RTRA)|EKG qt interval|Leukocyte differential|Glucose|Calcium|Albumin|Total protein|Sodium|Total carbon dioxide|Potassium|Chloride|BUN|Creatinine|Alkaline phosphatase|Alanine aminotransferase|Total bilirubin|White blood cells|Red blood cells|Hemoglobin|Hematocrit|Mean corpuscular volume|Mean corpuscular hemoglobin|Mean corpuscular hemoglobin concentration|Red cell distribution width|Neutrophils|Lymphs|Monocytes|Eosinophils|Basophils|Absolute neutrophils|Absolute lymphs|Absolute monocytes|Absolute eosinophils|Absolute basophils|Immature granulocytes|Platelets|Prothrombin time|INR|NK cell surface antigen (CD3-CD54+)|CD4+/CD8+ ratio|Myoglobin|Troponin|Creatinine kinase MB|Serum ferritin|Adverse events|7-point ordinal scale|D-dimer|Chest X-ray|CT scan|PCR test for SARS-CoV-2
NCT04565665 United States	COVID-19 Infection|COVID-19-Associated Acute Respiratory Distress Syndrome|Hematopoietic and Lymphoid Cell Neoplasm|Malignant Solid Neoplasm|Symptomatic COVID-19 Infection Laboratory-Confirmed	Biological: Mesenchymal Stem Cell	Standard of care	Incidence of composite serious adverse events (Phase I)|Patients alive without grade 3, 4 infusional toxicity (Phase II)|Patients alive with grade 3 or 4 infusional toxicity (Phase II)|Patients not alive (Phase II)|Proportion of successfully extubated patients who present intubated on ventilator support (Phase I)|Rate of successful progression to intubation in patients who require supplemental oxygen but who are otherwise able to breathe without assistance (Phase I)|Overall survival rate (Phase I)|Survival rate in patients who present intubated on ventilator support (Phase I)|Survival rate in patients who require supplemental oxygen but who are otherwise able to breathe without assistance (Phase I)|Clinical parameters (Phase I)|Oxygenation parameters (Phase I)|Respiratory parameters (Phase I)|Laboratory markers (Phase I)|Hospitalization stay (Phase I)|Intensive care unit stay (Phase I)|Incidence of infusion-related adverse events (Phase I)

NCT04535856 Indonesia *Completed	Covid19|Corona Virus Infection|SAR	Drug: allogeneic mesenchymal stem cell	Other: Placebo	Incidence of TEAE* in Treatment group|Survival rate|Duration of hospitalization|Clinical improvement Ordinal scale|Clinical improvement National EWS|Clinical improvement Oxygenation index|Clinical improvement Lung involvement change|Clinical improvement Inflammation markers change
NCT04390152 Colombia	Acute Respiratory Distress Syndrome	Drug: Wharton's jelly derived Mesenchymal stem cells.	Drug: Hydroxychloroquine, lopinavir/ritonavir or azithromycin and placebo (standard therapy)	Intergroup mortality difference with treatment|Number of patients with treatment related adverse events|Difference in days of mechanical ventilation between groups|Median reduction of days of hospitalization|Median reduction of days of oxygen needs|Difference between "Sequential Organ Failure Assessment" score between groups|Difference between median Murray score between groups|Difference in APACHE II score between groups|Difference in lymphocyte count between groups|Changes in C reactive protein concentration between groups|Changes in D dimer concentration|Changes in ferritin concentration|Changes in lactate dehydrogenase concentration|Impact on interleukin 6 concentrations between groups.|Impact on interleukin 8 concentrations between groups.|Impact on interleukin 10 concentrations between groups.|Impact on tumor necrosis factor alpha concentrations between groups.
NCT04494386United States	Covid19|Corona Virus Infection|SARS-CoV Infection|ARDS|Coronavirus	Biological: Umbilical Cord Lining Stem Cells (ULSC)	Other: Placebo (carrier control)	Incidence of Dose Limiting Toxicity (DLT)|Incidence of Dose Limiting Toxicity (DLT), suspected adverse reaction (SAR), or serious adverse event (SAE)|Treatment-emergent adverse events (AE) and serious adverse events (SAE)|Levels of COVID-19 related ARDS as defined by the Berlin Definition of ARDS|Changes from baseline pulse oximetric saturation SpO2/FiO2 ratio or arterial oxygen pressure pAO2/FiO2 ratio|Number of ventilator-free days (VFD)|Changes in Complete Blood Count (CBC) with differential from baseline|Changes in levels of blood glucose (mg/dL) from baseline|Changes in levels of sodium (mEq/L) from baseline|Changes in levels of potassium (mEq/L) from baseline|Changes in levels of blood urea nitrogen (BUN; mg/dL) from baseline|Changes in levels of alanine transaminase (ALT; U/L) from baseline|Change in Urinalysis (UA) from baseline
NCT04377334 Germany	ARDS|COVID-19	Biological: MSC	No intervention	lung injury score|D-dimers|phenotype|pro-resolving lipid mediators|cytokines|chemokines|Survival|extubation|lymphocyte subpopulations|SARS-CoV-2-specific antibody titers|complement molecules (C5-C9)
NCT04345601 United States	Sars-CoV2|Acute Respiratory Distress Syndrome|COVID-19	Biological: Mesenchymal Stromal Cells	Other: Supportive Care	Treatment-related serious adverse events (tSAEs)|Change in clinical status at day 14
NCT04397796 United States	COVID	Biological: BM-Allo.MSC	Biological: Placebo	Incidence of AEs|Mortality|Death|Number of ventilator-free days|Improvement of one category|7-point ordinal scale|NEWS|NEWS of â‰¤ 2|Sequential Organ Failure Assessment (SOFA)|Oxygen|Hospitalization|Incidence of SAEs
NCT04390139 Spain	COVID-19|SARS-CoV	Drug: XCEL-UMC-BETA (Wharton-Jelly mesenchymal stromal cells)	Other: Placebo	All-cause mortality at day 28|Safety of WJ-MSC|Need for treatment with rescue medication|Need and duration of mechanical ventilation|Ventilator

	2|Adult Respiratory Distress Syndrome			free days|Evolution of PaO2 / FiO2 ratio|Evolution of the SOFA index|Evolution of the APACHE II score|Duration of hospitalization|Evolution of markers of immune response (leucocyte count, neutrophils)|Feasibility of WJ-MSC administration|Evolution of disease biomarker: polymerase chain reaction (RT-PCR)|Evolution of disease biomarker: lactate dehydrogenase (LDH)|Evolution of disease biomarker: D-dimer|Evolution of disease biomarker: Ferritin
NCT04780685 United States	Covid19 with ARDS	Biological: hMSC via IV administration	Placebo Comparator: Lactated Ringer's Solution	Survival|Number of patients with treatment-related adverse events as assessed by CTCAE v4.0
NCT04798716 United States	Covid19|Novel Coronavirus Pneumonia|Acute Respiratory Distress Syndrome	Drug: MSC-exosomes delivered intravenously every other day on an escalating dose: (2:4:8)	Drug: MSC-exosomes delivered intravenously every other day on an escalating dose (8:4:8) Drug: MSC-exosomes delivered intravenously every other day (8:8:8)	Measure and report the number of participants with treatment-related-adverse events as assessed by CTCAE v4.0; for patients receiving ARDOXSOâ„¢, perinatal MSC-derived exosome therapy.|Tabulate and report the number of IMV days for patients receiving ARDOXSOâ„¢ perinatal MSC-derived exosome therapy.|Analyze and report organ failure, associated with ICU mortality in participants confirmed with SARS-CoV2 infection, receiving ARDOXSOâ„¢ as an interventional exosome therapy.|Record and analyze respiratory measures (Berlin Score/PEEP) following treatment regime.
NCT04392778 Turkey	Covid19|Pneumonia|Multiple Organ Failure|Corona Virus Infection	Biological: MSC Treatment	Biological: Saline Control	Clinical improvement|Lung damage improvement|Sars-Cov-2 viral infection laboratory test|Blood test
NCT04537351 Australia	Covid19 with Acute Respiratory Distress Syndrome	Biological: CYP-001	Standard of care	Trend in trajectory of PaO2/FiO2 ratio (P/F ratio) between groups|Incidence and severity of treatment-emergent adverse events|Change in C-reactive protein (CRP) levels|Proportional differences between groups on the Clinical Improvement Scale|Changes in P/F ratio|Changes in respiratory rate|Changes in oxygenation index|Changes in respiratory compliance (the change in lung volume per unit change in transmural pressure gradient)|Changes in positive end-expiratory pressure|Ventilator-free days|Proportional differences between groups on the SF-36|Proportional differences between groups on the mini mental state examination
NCT04398303	COVID-19 Pneumonia	Biological: ACT-20-MSC|Biological: ACT-20-CM	Biological: Placebo	Mortality at day 30|Ventilated Subjects - Ventilator Free Days|Ventilated Subjects - Improvement in Ventilator Settings|High-Flow O2 Support Subjects - Step-Down O2 Therapy|High Flow O2 Support Subjects - Respiration Rate|Both Ventilated and High-Flow O2 Support Subjects - ICU-Free Days|Both Ventilated and High-Flow O2 Support Subjects - Pulmonary Function Improvement|Both Ventilated and High-Flow O2 Support Subjects - Increased Berlin Score
NCT04361942 Hospital Universitario Rio Hortega, Valladolid, Spain	COVID-19 Pneumonia	Biological: Mesenchymal Stromal Cells	Other: Placebo	Proportion of patients who have achieved withdrawal of invasive mechanical ventilation|Rate of mortality|Proportion of patients who have achieved clinical response|Proportion of patients who have achieved radiological responses
NCT03042143 Belfast Health and Social Care Trust,	COVID-19 with Acute Respiratory	Biological: Human umbilical cord derived CD362 enriched MSCs	Biological: Placebo (Plasma-Lyte 148)	Oxygenation index (OI)|Incidence of Serious Adverse Events (SAEs)|Oxygenation index|Sequential Organ Failure Assessment (SOFA) score|Respiratory compliance (Crs)|Partial pressure of arterial oxygen to

Royal Hospitals, Belfast, Northern Ireland, United Kingdom	Distress Syndrome			the fraction of inspired oxygen ratio (P/F ratio)|Driving Pressure|Extubation and reintubation|Ventilation free days at day 28|Length of ICU and hospital stay|28-day and 90-day mortality
NCT04437823 Pakistan	Coronavirus Infection, moderate to severe	Biological: Intravenous Infusions of Stem Cells	Standard of care	Safety and efficacy assessment of infusion associated adverse events|Chest Radiograph or Chest CT Scan|COVID-19 Quantitative Real Time PCR|Sequential Organ Failure Assessment (SOFA) Score|Rate of mortality|Clinical Respiratory Changes
NCT04602442 Russian Federation	Covid19|SARS-CoV-2 PNEUMONIA|COVID-19	Drug: EXO 1 inhalation Drug: EXO 2 inhalation	Drug: Placebo inhalation	Number of participants with non-serious and serious adverse events during trial|Number of participants with non-serious and serious adverse during inhalation procedure|Time to clinical recovery (TTCR)|SpO2 concentration changes|Chest Imaging Changes|Blood biochemistry (CRP)|Procalcitonin concentration|Ferritin concentration|Creatinine concentration|Urea concentration
NCT04371393 United States	Acute Respiratory Distress Syndrome|COVID	Biological: Remestemcel-L MSC + standard of care	Drug: Placebo + standard of care	Number of all-cause mortality|Number of days alive off mechanical ventilatory support|Number of adverse events|Number of participants alive at day 7|Number of participants alive at day 14|Number of participants alive at day 60|Number of participants alive at day 90|Number of participants alive at 12 Months|Number of participants with resolution and/or improvement of ARDS|Severity of ARDS|Length of stay|Readmissions|Length of Stay in Intensive Care Unit|Clinical Improvement Scale|Change in plasma hs-CRP concentration|Change in serum hs-CRP concentration|Change in IL-6 inflammatory marker level|Change in IL-8 inflammatory marker level|Change in TNF-alpha inflammatory marker level|Pulmonary symptoms
NCT04491240 Russian Federation *Completed	Covid19|SARS-CoV-2 PNEUMONIA|COVID-19	Drug: EXO 1 inhalation Drug: EXO 2 inhalation	Drug: Placebo inhalation	Number of Participants With Non-serious and Serious Adverse Events During Trial|Number of Participants With Non-serious and Serious Adverse During Inhalation Procedure|Time to Clinical Recovery (TTCR)|SpO2 Concentration|C-reactive Protein|Lactic Acid Dehydrogenase (LDH)
NCT04333368France	Severe Acute Respiratory Syndrome Coronavirus 2|Severe Acute Respiratory Distress Syndrome	Biological: Umbilical cord Wharton's jelly-derived MSC	NaCl 0.9%	Respiratory efficacy evaluated by the increase in PaO2/FiO2 ratio from baseline to day 7 in the experimental group compared with the placebo group|Lung injury score|Oxygenation index|In-hospital mortality|Mortality|Ventilator-free days|Number of days between randomization and the first day the patient meets weaning criteria o Number of days between randomization and the first day the patient meets PaO2/FiO2 > 200 (out of a prone positioning session)|Cumulative use of sedatives|Cumulative duration of use of sedatives|Cumulative duration of use of neuromuscular blocking agents (other than used for intubation)|Cumulative use of neuromuscular blocking agents (other than used for intubation)|ICU-acquired weakness and delirium|Treatment-induced toxicity rate and adverse events up to day 28|Quality of life at one year (EQ5D-3L quality of life questionnaire)|Measurements of plasmatic cytokines (IL1, IL6, IL8, TNF-alpha, IL10, TGF-beta, sRAGE, Ang2) level|Anti-HLA antibodies plasmatic dosage
NCT04299152	Severe Acute Respiratory Syndrome	Combination Product: Stem Cell Educator-Treated Mononuclear Cells Apheresis	Conventional treatment	Determine the number of Covid-19 patients who were unable to complete SCE Therapy|Examine the percentage of activated T cells after SCE therapy by flow cytometry|Assess the percentage of Th17 cells after SCE

	(SARS) Pneumonia			therapy by flow cytometry|Chest imaging changes by computed tomography (CT) scan of the chest|Quantification of the SARS-CoV-2 viral load by real time RT-PCR
NCT04466098 United States	COVID-19 Pneumonia with Acute Respiratory Distress Syndrome, Moderate or Severe	Biological: Mesenchymal stromal cells	Placebo	Incidence of grade 3-5 infusional toxicities and predefined hemodynamic or respiratory adverse events related to the infusion of MSC|Incidence of a reduction in one or more biomarkers of inflammation by day 7|Trend changes in PaO2:FiO2 ratio|Trend changes in Mean Airway Pressure|Trend changes in peak pressure|Trend changes in plateau pressure|Trend changes in Positive end-expiratory airway pressure (PEEP)|Incidence of mortality|Number of ICU-free days|Number of days alive and ventilator free composite score 3|Change in acute lung injury (ALI) score 2|Incidence of serious adverse events|Number of days alive off supplemental oxygen
NCT04445220 United States	COVID-19 with acute kidney injury and receiving or planned to receive renal replacement therapy in < 24 hours	Biological: SBI-101 (Extracorporeal Mesenchymal Stromal Cell Therapy)	Standard of care	Safety and tolerability as measured by incidence of IP-related serious adverse events
ChiCTR2000029580 China	COVID-19	Ruxolitinib combined with mesenchymal stem cell	Routine treatment	Safety
ChiCTR2000030088 China	COVID-19 with respiratory failure	IV injection of Wharton's Jelly mesenchymal stem cells (1×10^6/kg), cell suspension volume: 40ml	IV 40ml saline	Nucleic acid test via throat secretion Ground glass on CT scan
ChiCTR2000030173 China	COVID-19	Umbilical cord mesenchymal stem cells	Conventional treatment	Pulmonary function Chest radiograph Chest CT scan findings
ChiCTR2000030138	COVID-19 pneumonia	Intravenous injection of human umbilical cord mesenchymal stem cells (UC-MSC)	Placebo + routine treatment	Clinical index

Q27. Among patients with COVID-19, should inhaled corticosteroids be used for treatment?

As of 18 November 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of inhaled corticosteroids in treatment of non-hospitalized COVID-19 patients. *(Very low certainty of evidence)*

Consensus Issues

Current evidence shows that inhaled corticosteroids (i.e., budesonide and ciclesonide) had benefit for subjective outcomes such as self-reported recovery on day 14 and day 28/30. However, evidence was inconclusive in terms of objective outcomes such as mortality, emergency room visit, need for hospitalization, duration of hospitalization, and clinical improvement (as evaluated by an assessor). Self-reported recovery may be biased since participants are not blinded, hence a more objective marker of clinical status such as oxygen saturation is more reliable. Only 1 study explicitly excluded patients with asthma or chronic obstructive pulmonary disease (COPD), and the perceived positive effect may have been due to improvement of asthma or COPD and not COVID infection. As of writing, there are 13 ongoing clinical trials, results of which may further elucidate on the effectiveness of inhaled corticosteroids in the treatment of COVID-19.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of inhaled corticosteroids as treatment for non-hospitalized patients with mild to moderate COVID-19 infection. *(Very low certainty of evidence)*

Previous consensus issues

Further studies are needed to determine the effectiveness of inhaled corticosteroids for the treatment of COVID-19 infection. Inhaled corticosteroids can be used to provide symptomatic relief for other concomitant conditions such as asthma and COPD

WHAT'S NEW IN THIS VERSION

Two (2) randomized controlled trials (RCTs) were added to this review.

KEY FINDINGS

Four (4) randomized controlled trials (RCTs) investigated the effectiveness of inhaled corticosteroids for the treatment of COVID-19. Use of inhaled corticosteroids (e.g., budesonide and ciclesonide) among non-hospitalized patients with mild to moderate COVID-19 demonstrated benefit only for subjective outcomes such as self-reported clinical recovery or improvement at day 14 and day 28/30 but not for objective outcomes such as mortality, need for hospitalization, emergency room visit, and duration of hospitalization. There was no significant difference in serious adverse events and adverse events.

INTRODUCTION

Systemic corticosteroids have demonstrated efficacy against COVID-19 in several studies, probably through decreasing SARS-CoV-2 infection-associated inflammation

and have been used for the treatment of COVID-19. One of the major causes of COVID-19-related deaths is acute respiratory distress syndrome which can be attributed to an exaggerated immune response.[1] COVID-19 is postulated to elicit inflammatory cytokine secretion, not only from alveolar macrophages but also from alveolar epithelial type 2 cells leading to the assumption that immunosuppression should be largely directed towards the lungs.[2] Inhaled corticosteroids (ICS) have been used to treat asthma and chronic obstructive pulmonary disease (COPD) by reducing lung inflammation, which led to the premise that ICS may have the potential to protect against severe SARS-CoV-2 infection.[3] Furthermore, administration of corticosteroids via inhalation could effectively reduce inflammation in the lungs with fewer systemic side effects. Two reviews of inhaled corticosteroids for COVID-19 showed no clear evidence on whether use of ICS had adverse or beneficial outcomes in COVID-19 patients.[4,5]. In-vitro studies implied that inhaled glucocorticoid use reduced the replication of SARS-CoV-2 in airway epithelial cells. Furthermore, inhaled glucocorticoids may lead to the downregulation of angiotensin-converting enzyme 2 (*ACE2*) and transmembrane serine protease 2 (*TMPRSS2*) expression, which are both necessary for viral entry.[6] Studies showed that nebulized budesonide improved oxygenation and significantly reduced inflammatory markers (tumor necrosis factor-α, interleukin 1β [IL-1β], and IL-6) in patients with acute respiratory distress syndrome.[7] The anti-inflammatory effect of ciclesonide can be attributed to its blocking effect on PAK1 (RAC/CDC42-activated kinase 1), which is necessary in inflammation.[8] The activity of fluticasone propionate is attributed to the inhibition of cytokine-induced production of pro-inflammatory proteins leading to the suppression of inflammatory mediators and reducing the number of mast cells and lymphocytes.[9] Apart from their anti-inflammatory effects, in-vitro studies showed that ciclesonide and mometasone have antiviral effects and suppressed the replication of SARS-CoV-2 and MERS-CoV.[10]

REVIEW METHODS

A systematic search was done in Medline, Cochrane Library, and Google Scholar from October 9, 2021 to October 13, 2021 using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome, coronavirus 2 or SARS-CoV-2, budesonide, ciclesonide, fluticasone, mometasone, beclomethasone, flunisolide, inhalational steroid, inhalational corticosteroid, inhaled steroid, and inhaled corticosteroid. The COVID-NMA Living Data was also searched and a search for ongoing studies in the WHO clinical trial registry, NIH *clinicaltrials.gov,* and various trial registries was done. Medrxiv, chinaxiv and biorxiv were also searched for preprints. Only randomized controlled trials were included in this review. Outcomes of interest included hospitalization, emergency department visit, mortality, clinical recovery or improvement, and adverse events.

RESULTS

Four (3 published and 1 preprint) RCTs [11-14] compared the effect of inhaled corticosteroid against placebo and/or standard of care among confirmed COVID-19 patients (n = 2,463). Two trials were conducted in the UK [11,12], and 2 multicenter trials were conducted in the US [14] and South Korea.[13] Two studies evaluated inhaled budesonide [11,12], while 2 studies evaluated inhaled ciclesonide.[13,14] Three studies [11,12,14] included patients with chronic respiratory disease [e.g., bronchial asthma and chronic obstructive pulmonary disease (COPD)] who were not

on maintenance medication of inhaled corticosteroids or not currently using inhaled corticosteroids during the time of the trial. One study [13] however, excluded patients diagnosed with bronchial asthma and COPD. Appendix 3 summarizes the characteristics of included studies in this review.

The overall methodological quality of evidence was rated very low due to serious risk of bias (performance, detection, and attrition), and imprecision in majority of the critical outcomes (e.g., hospitalization, death, self-reported clinical recovery, and serious adverse events). The risk of bias summary is in Appendix 4. The GRADE evidence summary is in Appendix 5.

Pooled estimates of objective outcomes, namely hospitalization/death (RR 0.82, 95% CI 0.62-1.08; I^2 = 0%; n = 2,256, 2 RCTs), hospitalization/emergency department visit (RR 0.36, 95% CI 0.11-1.20; I^2 = 73%; n = 2,132, 3 RCTs), mortality (RR 0.74, 95% CI 0.28-1.99; n = 1,856, 1 RCT), hospitalization (RR 0.85, 95% CI 0.64-1.15; n = 1,856, 1 RCT) and duration of hospitalization (MD -0.25 days, 95% CI -0.75 to 0.25; I^2 = 0%; n = 1,917, 2 RCTs) did not reach statistical significance.

In terms of subjective outcomes, inhaled corticosteroids showed statistically significant benefit in self-reported clinical recovery/improvement at day 14 (RR 1.18, 95% CI 1.10-1.27; I^2 = 0%, n = 2,463, 4 RCTs) and day 28/30 (RR 1.10, 95% CI 1.04-1.16, I^2 = 0%; n = 2,317, 3 RCTs) compared with placebo and/or standard of care. There was benefit in self-reported clinical recovery at day 14 (RR 1.15, 95% CI 1.07-1.24; n = 2,402, 3 RCTs) and at day 28/30 (RR 1.09, 95% CI 1.03-1.15; n = 2,256, 2 RCTs). However, there was no significant benefit for self-reported clinical recovery/improvement at day 7 (RR 1.07, 95% CI 0.95-1.20; I^2 = 0%; n = 2,317, 3 RCTs) and self-reported clinical recovery at day 7 (RR 1.08, 95% CI 0.95-1.22; I^2 = 0%; n = 2,256, 3 RCTs). The findings were inconclusive for clinical improvement at day 7 (RR 0.94, 95% CI 0.60 to 1.47; n = 61, 1 RCT) as well as clinical improvement at day 14 (RR 1.38, 95% CI 0.92-2.07; n = 61, 1 RCT) and did not reach statistical significance but showed potential towards benefit for the outcome clinical improvement at day 28/30 (RR 1.20, 95% CI 0.99-1.46; n = 61, 1 RCT). Time to self-reported clinical recovery/improvement also demonstrated to be statistically beneficial for inhaled corticosteroids (MD -1.72 days, 95% CI -3.28 to -0.17; n = 2,402, 3 RCTs) but with substantial heterogeneity (I^2 = 91%).

Pooled estimate for viral eradication at day 14 (RR 6.45, 95% CI 0.89-46.60; n = 51, 1 RCT) did not reach statistical significance but showed potential towards benefit. The forest plots are shown in Appendix 6.

Sensitivity analysis excluding the preprint study still showed statistically significant benefit for the following outcomes: time to self-reported clinical recovery/improvement (MD -2.04 days, 95% CI -4.0 to -0.08, I^2 = 94%; n = 2,002, 2 RCTs), self-reported clinical recovery/improvement at day 14 (RR 1.19, 95% CI 1.10-1.28; I^2 = 0%; n = 2,063, 3 RCTs), self-reported clinical recovery/improvement at day 28/30 (RR 1.09, 95% CI 1.03-1.17; I^2 = 3%; n = 1,917, 2 RCTs), self-reported clinical recovery at day 14 (RR 1.15, 95% CI 1.07-1.25; I^2 = 0%; n = 2,002, 2 RCTs), and self-reported clinical recovery at day 28 (RR 1.08, 95% CI 1.02 to 1.15, n=1,856, 1 RCT). Sensitivity analysis excluding the preprint study for self-reported clinical recovery at day 7 (RR 1.16, 95% CI 1.06-1.27; n = 1,856, 1 RCT) showed statistically significant benefit.

Sensitivity analysis excluding the preprint study for the rest of the outcomes including hospitalization/death (RR 0.78, 95% CI 0.57-1.08; n = 1,856, 1 RCT), hospitalization/emergency department visit (RR 0.46, 95% CI 0.11-1.93; n = 1,732, 2 RCTs), duration of hospitalization (MD -0.25 days, 95% CI -0.75 to 0.25; n = 1,917, 2 RCTs) and self-reported clinical recovery/improvement at day 7 (RR 1.07, 95% CI 0.95-1.21; n=1,917, 2 RCTs) was similar with primary analysis and remained statistically insignificant.

Safety

There was no significant difference in the incidence of adverse events (RR 2.31, 95% CI 0.35-15.07; I^2 = 59%; n = 607, 3RCTs) and serious adverse events (RR 0.68, 95% CI 0.12-3.70; n = 1,856, 1 RCT) between the inhaled corticosteroids and standard of care or placebo group. Sensitivity analysis excluding the preprint study for the outcome adverse events showed potential towards harm, although results did not reach statistical significance (RR 7.64, 95% CI 0.98-59.34; I^2 = 0%; n = 207, 2 RCTs). Reported adverse events included headache, dizziness, nausea, bruising, odynophagia, sore throat, dry mouth, and oral candidiasis. The adverse events were non-fatal and self-limiting with full recovery upon cessation of the inhaled corticosteroid. Serious adverse events were reported in only one study (PRINCIPLE trial) but these serious adverse events requiring hospital admission were not specified in the trial.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Canadian Thoracic Society (CTS) (as of October 15, 2021)	Recommends the use of inhaled corticosteroids as regular maintenance and exacerbation management for asthma and chronic obstructive pulmonary disease (COPD) be continued according to current treatment guidelines. They do not recommend the use of a nebulizer unless absolutely necessary (no other alternative available).[15-17]
UK NICE (as of April 16, 2021)	
Public Health Agency of Canada (PHAC) (as of December 22, 2020)	
British Thoracic Society (as of October 4, 2021)	Recommends the use of inhaled corticosteroids as regular maintenance and exacerbation management for asthma and chronic obstructive pulmonary disease (COPD) be continued according to current treatment guidelines and supports the use of nebulizers, claiming that there is no evidence supporting an increased risk of viral transmission.[18]
Australian Guideline (as of October 21, 2021)	Conditionally recommends inhaled corticosteroid (budesonide) for treating patients with confirmed COVID-19 who do not require oxygen but have 1 or more risk factors for disease progression and recommends the use of inhaled or oral steroids for the management of people with co-existing asthma or chronic obstructive pulmonary disease (COPD) and COVID-19 as one would normally do for viral exacerbation of asthma or COPD but do not recommend the use of a nebulizer.[19]
Philippine Society for Microbiology and Infectious Diseases (PSMID) (as of July 20, 2020)	Do not recommend the use of inhaled corticosteroid (ICS) as treatment nor for prophylaxis against COVID-19 pending the results of ongoing studies.[20]

US-NIH (as of August 25, 2021)	No recommendation on the use of inhaled corticosteroids for the treatment of COVID-19.
World Health Organization (WHO) (as of September 21, 2021)	
Infectious Diseases Society of America (IDSA) (as of October 1, 2021)	
American Thoracic Society and European Respiratory Society	

RESEARCH GAPS

As of October 13, 2021, there are 13 ongoing clinical trials on inhaled corticosteroids registered (Appendix 6).

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 4)

FACTORS	JUDGEMENT (N = 4)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (4)					
Benefits	Large	Moderate (2)	Small (2)	Uncertain			• Inconclusive in terms of objective outcomes: mortality, hospitalization/death, hospitalization/ER visit, duration of hospitalization • Benefit in self-reported clinical recovery/improvement at day 14 (RR 1.18, 95% CI 1.10-1.27) and day 28/30 (RR 1.10, 95% CI 1.04-1.16)
Harm	Large	Small (2)	Uncertain (2)				• No significant difference in adverse events (RR 2.31, 95% CI 0.35-15.07; I^2 = 59%; n = 607, 3RCTs) and serious adverse events (RR 0.68, 95% CI 0.12-3.70; n = 1,856, 1 RCT)
Certainty of Evidence	High	Moderate	Low (4)	Very low			• Serious risk of bias (performance, detection, and attrition), and imprecision in majority of the critical outcomes (e.g., hospitalization, death, self-reported clinical recovery, and serious adverse events)
Balance of effects	Favors drug (3)	Does not favor drug	Uncertain (1)				• Net potential benefit in terms of subjective (self-reported) outcomes, with no significant harm
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (1)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate cost (4)	Negligible cost	Moderate savings	Large savings	• Budesonide 800 mcg/dose 2x a day for 14 days = Php 1,862.00 to Php 12,091.24 (nebule), Php 796.32 to 1,422.00 (dry powder inhaler) • Ciclesonide 160 mcg/dose 2x a day for 14 to 30 days = Php 6,641.37 to 14,231.50
Certainty of evidence of required resources	No included studies	Very low (1)	Low	Moderate (2)	High (1)		• Prices were from the 2020 Philippine Drug Price Reference Index, the DOH Memorandum (9/9/2020) on suggested retail price, and Amazon Pharmacy.
Cost effectiveness	No included studies (4)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (2)	Reduced (1)	Probably no impact (1)	Increased			
Acceptability	Uncertain (3)	No	Yes (1)				
Feasibility	Uncertain (1)	No	Yes (3)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields] OR ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "ncov"[All Fields])) AND ("budesonide"[All Fields] OR "ciclesonide"[All Fields] OR "fluticasone"[All Fields] OR "mometasone"[All Fields] OR "beclomethasone"[All Fields] OR "flunisolide"[All Fields] OR "inhalational steroid"[All Fields] OR "inhalational corticosteroid"[All Fields] OR "inhaled steroid"[All Fields] OR "inhaled corticosteroid"[All Fields])	10/9/21 5:55:16 AM	124	3
CENTRAL	(Coronaviridae Infections OR Coronavirus OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-20 AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") AND Randomized trial	10/12/21	100	3
COVID-NMA Initiative	Corticosteroids	10/12/21	2	2
Google Scholar	{Coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {Inhaled Corticosteroid} AND {Randomized trial}	10/12/21	706	3
ClinicalTrials.gov	Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid")	10/12/21	29	3
Chinese Clinical Trial Registry	Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid")	10/13/21	1	0
EU Clinical Trials Register	Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid")	10/13/21	291	1
Republic of Korea - Clinical Research Information Service	Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid")	10/13/21	2	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid")	10/13/21	2	0
CenterWatch	Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid")	10/13/21	420	0

WHO database COVID-19 studies	("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid")	10/13/21	389	3
chinaxiv.org	Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid")	10/13/21	0	0
Medrxiv.org	Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid")	10/13/21	101	4
Biorxiv.org	Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid")	10/13/21	18	0

Appendix 3. Characteristics of Included Studies

Study ID	Participants	Sample Size	Comparisons		Design	Outcomes
			Intervention	Control		
Ramakrishnan S, et al, 2021 (STOIC Trial)	Adults aged older than 18 years with symptoms of COVID-19 (new onset cough and fever or anosmia, or both) within 7 days in Oxfordshire, UK	N = 146	Budesonide (N = 73)	Usual care (N = 73)	Randomized, open-label, parallel-group, phase 2 clinical trial	The primary endpoint was COVID-19-related urgent care visits, including emergency department assessment or hospitalization The secondary outcomes were self-reported clinical recovery (symptom resolution), viral symptoms measured using the Common Cold Questionnaire (CCQ) and the InFLUenza Patient Reported Outcome Questionnaire (FLUPro), body temperature, blood oxygen saturations, and SARS-CoV-2 viral load
Yu LM, et al, 2021 (PRINCIPLE Trial)	People in the community in the UK aged at least 65 years, or at least 50 years with comorbidities, and had ongoing symptoms from PCR-confirmed or suspected COVID-19 (in accordance with the UK National Health Service definition of high temperature, new, continuous cough, or change in sense of smell or taste) which had started within the previous 14 days	N = 2530 SARS-CoV-2-positive participants (787 in the budesonide group, 1,069 in the usual care group, and 974 receiving other treatments)	Budesonide (N = 787)	Usual care (N = 1,069)	Multicenter, open-label, multi-arm, randomized, controlled, adaptive platform trial	The coprimary endpoints are time to first self-reported recovery and hospital admission or death related to COVID-19, within 28 days; Secondary outcomes include a binary outcome of early, sustained recovery (recovered by day 14 and remains recovered until day 28), time to sustained recovery (date participant first reports recovery and subsequently remains well until 28 days), daily rating of 1–10 of how well participants feel, time to initial alleviation of symptoms (date symptoms first reported as minor or none), time to sustained alleviation of symptoms (date symptoms first reported as minor or none and subsequently remain minor or none until 28 days), time to initial reduction of severity of symptoms (date symptom severity reported at least one grade lower), contacts with health services, hospital assessment without admission, oxygen administration, intensive care unit admission, mechanical ventilation, adherence to study treatment, WHO-5 Well-Being Index and reports of new household infections; Serious adverse events other than the coprimary outcome of hospital admission or death related to COVID-19 were measured in all trial groups

Song JY, et al, 2021	Patients (aged ≥19 years) with mild-to-moderate COVID-19, confirmed by quantitative reverse transcription polymerase chain reaction (qRT-PCR), were enrolled in the study within 3 days of diagnosis or within 7 days from symptom onset (6 hospitals in South Korea)	N = 61	Ciclesonide group (N = 35)	Standard care group (N = 26)	Randomized, open-label, multicenter clinical trial	Primary endpoint was the SARS-CoV-2 eradication rate based on qRT-PCR on day 14 of study enrollment. SARS-CoV-2 eradication was defined as negative conversion of two consecutive negative results of qRT-PCR Secondary endpoints were as follows: SARS-CoV-2 eradication rate based on qRT-PCR at days 7 and 10 from study enrollment; rate of clinical improvement (resolution of all systemic and respiratory symptoms) at days 7, 10, and 14 from study enrollment; rate of clinical failure within 28 days; safety/tolerability of ciclesonide
Clemency, B, et al, 2021	Participants were eligible for inclusion if, at the time of enrollment, they (1) were at least 12 years of age, (2) had a positive SARS-CoV-2 molecular or antigen diagnostic sample obtained in the previous 72 hours, (3) were not hospitalized or under consideration for hospitalization, (4) had an oxygen	N = 400	Ciclesonide (N = 197)	Placebo (N = 203)	Phase III, multicenter, double-blind, randomized controlled trial	The primary endpoint was time to alleviation of all COVID-19 related symptoms (cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell) by Day 30 Secondary endpoints included subsequent emergency department visits or hospital admissions for reasons attributable to COVID-19.

	saturation of at least 93% on room air, (5) were able to demonstrate successful use of an MDI, and (6) had at least one of the following symptoms of COVID: fever, cough, or dyspnea (10 centers in the US)					

Appendix 4. Methodological assessment of included studies

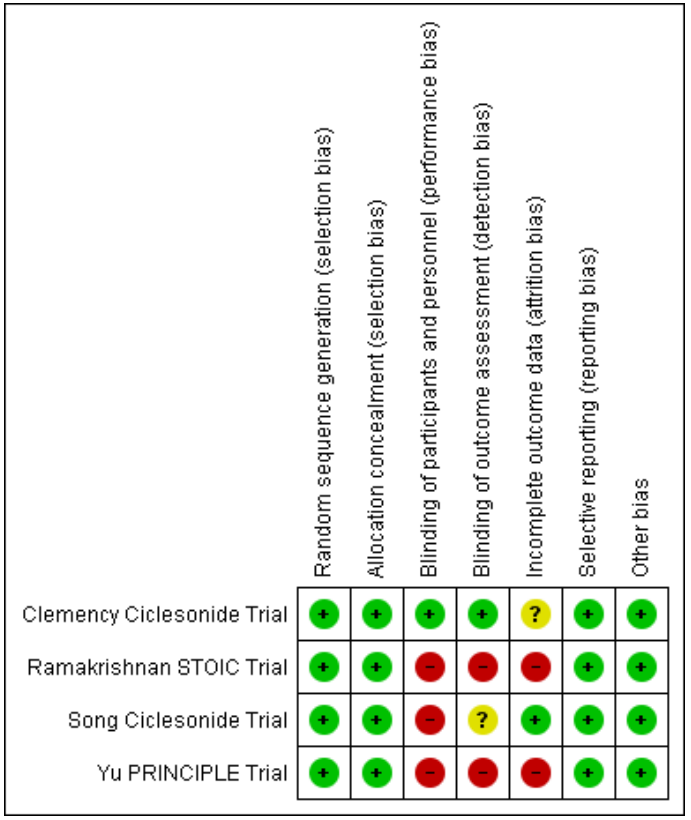

Figure 1. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study

Appendix 5. GRADE Evidence Summary

Question: Inhaled Corticosteroids compared to Standard Care and/or Placebo for COVID 19 infection

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled corticosteroids	Standard care	Relative (95% CI)	Absolute (95% CI)		
Hospitalization/Death												
2	Randomised trials	Serious [a]	Not serious	Not serious	Serious [b]	None	75/984 (7.6%)	123/1272 (9.7%)	**RR 0.82** (0.62 to 1.08)	**17 fewer per 1,000** (from 37 fewer to 8 more)	⊕⊕◯◯ LOW	CRITICAL
Hospitalization/Emergency Department Visit												
3	Randomised trials	Serious [c]	Serious [d]	Not serious	Serious [b]	None	92/1057 (8.7%)	132/1075 (12.3%)	**RR 0.36** (0.11 to 1.20)	**79 fewer per 1,000** (from 109 fewer to 25 more)	⊕◯◯◯ VERY LOW	CRITICAL
Clinical Recovery/Clinical Improvement D7												
3	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	319/1019 (31.3%)	385/1298 (29.7%)	**RR 1.07** (0.95 to 1.20)	**21 more per 1,000** (from 15 fewer to 59 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Clinical Recovery/Clinical Improvement D14												
4	Randomised trials	Serious [c]	Not serious	Not serious	Not serious	None	619/1092 (56.7%)	664/1371 (48.4%)	**RR 1.18** (1.10 to 1.27)	**87 more per 1,000** (from 48 more to 131 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Clinical Recovery/Clinical Improvement D28/D30												
3	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	739/1019 (72.5%)	860/1298 (66.3%)	**RR 1.10** (1.04 to 1.16)	**66 more per 1,000** (from 27 more to 106 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse Events												
3	Randomised trials	Serious [c]	Serious [d]	Not serious	Serious [b]	None	30/305 (9.8%)	29/302 (9.6%)	**RR 2.31** (0.35 to 15.07)	**126 more per 1,000** (from 62 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious Adverse Events												
1	Randomised trials	Serious [a]	Not serious	Not serious	Serious [b]	None	2/787 (0.3%)	4/1069 (0.4%)	**RR 0.68** (0.12 to 3.70)	**1 fewer per 1,000** (from 3 fewer to 10 more)	⊕⊕◯◯ LOW	CRITICAL

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled corticosteroids	Standard care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	Randomised trials	Serious [a]	Not serious	Not serious	Serious[b]	None	6/787 (0.8%)	11/1069 (1.0%)	**RR 0.74** (0.28 to 1.99)	**3 fewer per 1,000** (from 7 fewer to 10 more)	⊕⊕◯◯ LOW	CRITICAL
Hospitalization												
1	Randomised trials	Serious [a]	Not serious	Not serious	Serious[b]	None	66/787 (8.4%)	105/1069 (9.8%)	**RR 0.85** (0.64 to 1.15)	**15 fewer per 1,000** (from 35 fewer to 15 more)	⊕⊕◯◯ LOW	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

[a] Risk of bias downgraded by 1 level: some concerns regarding performance and attrition bias.
[b] Imprecision was downgraded by 1 level due to the wide confidence interval
[c] Risk of bias downgraded by 1 level: some concerns regarding performance, detection and attrition bias.
[d] Inconsistency was downgraded by 1 level due to substantial heterogeneity

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled corticosteroids	Standard care	Relative (95% CI)	Absolute (95% CI)		
Time to Clinical Recovery/Clinical Improvement												
3	Randomised trials	Serious [b]	Serious[c]	Not serious	Not serious	None	1057	1345	-	MD 1.72 lower (3.28 lower to 0.17 lower)	⊕⊕◯◯ LOW	IMPORTANT
Duration of Hospitalization												
2	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	822	1095	-	MD 0.25 lower (0.75 lower to 0.25 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Viral Eradication D14												
1	Randomised trials	Serious [d]	Not serious	Not serious	Very serious[e]	none	10/31 (32.3%)	1/20 (5.0%)	**RR 6.45** (0.89 to 46.60)	**273 more per 1,000** (from 6 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

[a] Risk of bias downgraded by 1 level: some concerns regarding performance and attrition bias.
[b] Risk of bias downgraded by 1 level: some concerns regarding performance, detection and attrition bias.
[c] Inconsistency was downgraded by 1 level due to substantial heterogeneity
[d] Risk of bias downgraded by 1 level: some concerns regarding performance bias.
[e] Imprecision was downgraded by 2 level due to the very wide confidence interval

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled corticosteroids	Standard care	Relative (95% CI)	Absolute (95% CI)		
Self-reported Clinical Recovery D7												
2	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	300/984 (30.5%)	370/1272 (29.1%)	**RR 1.08** (0.95 to 1.22)	**23 more per 1,000** (from 15 fewer to 64 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Self-Reported Clinical Recovery D14												
3	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	582/1057 (55.1%)	647/1345 (48.1%)	**RR 1.15** (1.07 to 1.24)	**72 more per 1,000** (from 34 more to 115 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Self-Reported Clinical Recovery D28/D30												
2	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	705/984 (71.6%)	839/1272 (66.0%)	**RR 1.09** (1.03 to 1.15)	**59 more per 1,000** (from 20 more to 99 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Clinical Improvement D7												
1	Randomised trials	Serious [b]	Not serious	Not serious	Serious [c]	None	19/35 (54.3%)	15/26 (57.7%)	**RR 0.94** (0.60 to 1.47)	**35 fewer per 1,000** (from 231 fewer to 271 more)	⊕⊕◯◯ LOW	CRITICAL
Clinical Improvement D14												
1	Randomised trials	Serious [b]	Not serious	Not serious	Serious [c]	None	26/35 (74.3%)	14/26 (53.8%)	**RR 1.38** (0.92 to 2.07)	**205 more per 1,000** (from 43 fewer to 576 more)	⊕⊕◯◯ LOW	CRITICAL
Clinical Improvement D28/D30												
1	Randomised trials	Serious [b]	Not serious	Not serious	Not serious	None	34/35 (97.1%)	21/26 (80.8%)	**RR 1.20** (0.99 to 1.46)	**162 more per 1,000** (from 8 fewer to 372 more)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

[a] Risk of bias downgraded by 1 level: some concerns regarding performance, detection and attrition bias.

[b] Risk of bias downgraded by 1 level: some concerns regarding performance bias.

[c] Imprecision was downgraded by 1 level due to the wide confidence interval

Appendix 6. Forest Plots

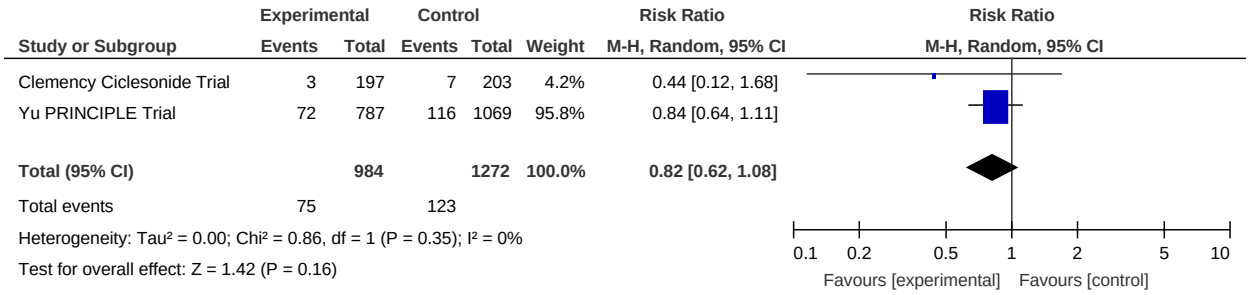

Figure 1a. Hospitalization/Death

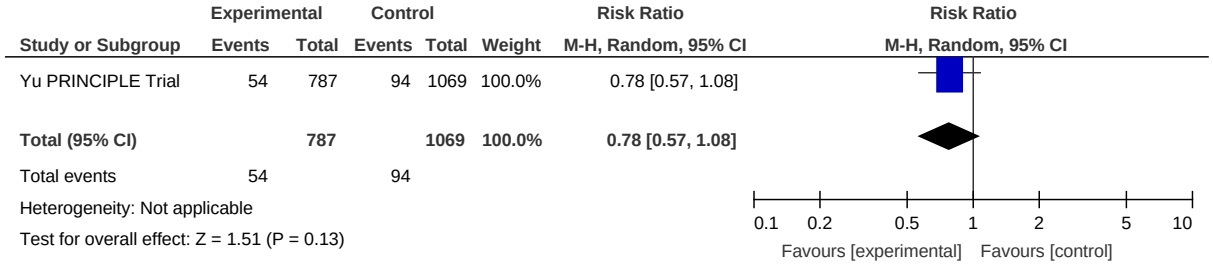

Figure 1b. Hospitalization/Death (Sensitivity Analysis excluding preprint)

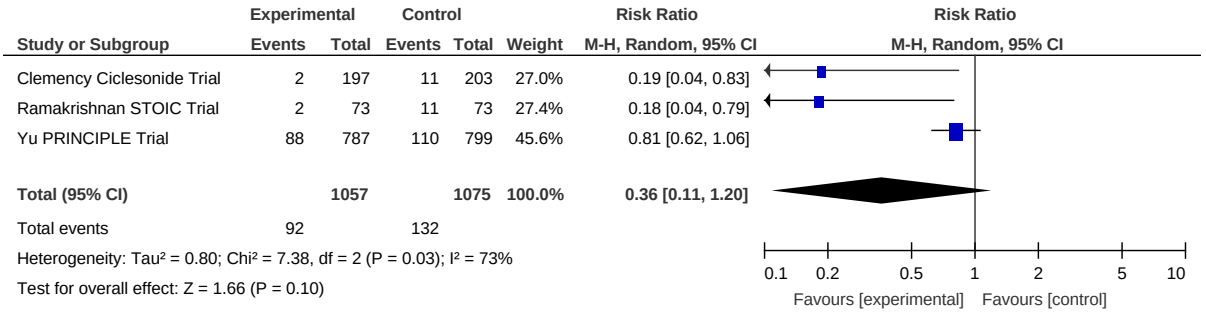

Figure 2a. Hospitalization/Emergency Department Visit

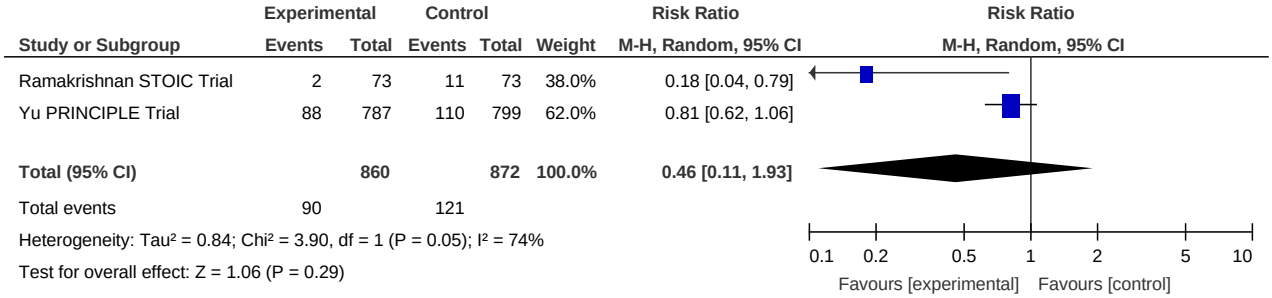

Figure 2b. Hospitalization/Emergency Department Visit (Sensitivity Analysis excluding preprint)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Clemency Ciclesonide Trial	18.25	5.8	197	19.25	6.5	203	30.4%	-1.00 [-2.21, 0.21]
Ramakrishnan STOIC Trial	7.25	2.5	73	8.25	2.8	73	33.4%	-1.00 [-1.86, -0.14]
Yu PRINCIPLE Trial	11.9	4	787	14.9	5	1069	36.2%	-3.00 [-3.41, -2.59]
Total (95% CI)			**1057**			**1345**	**100.0%**	**-1.72 [-3.28, -0.17]**

Heterogeneity: Tau² = 1.70; Chi² = 23.31, df = 2 (P < 0.00001); I² = 91%

Test for overall effect: Z = 2.17 (P = 0.03)

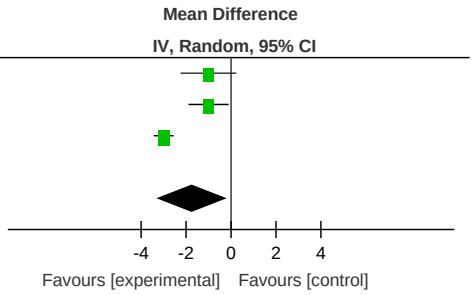

Figure 3a. Time to Clinical Recovery/Clinical Improvement

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ramakrishnan STOIC Trial	7.25	2.5	73	8.25	2.8	73	48.1%	-1.00 [-1.86, -0.14]
Yu PRINCIPLE Trial	11.9	4	787	14.9	5	1069	51.9%	-3.00 [-3.41, -2.59]
Total (95% CI)			**860**			**1142**	**100.0%**	**-2.04 [-4.00, -0.08]**

Heterogeneity: Tau² = 1.88; Chi² = 16.90, df = 1 (P < 0.0001); I² = 94%

Test for overall effect: Z = 2.04 (P = 0.04)

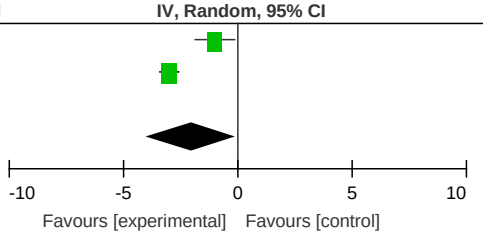

Figure 3b. Time to Clinical Recovery/Improvement (Sensitivity Analysis excluding preprint)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Clemency Ciclesonide Trial	28	197	29	203	6.3%	0.99 [0.62, 1.61]
Song Ciclesonide Trial	19	35	15	26	7.3%	0.94 [0.60, 1.47]
Yu PRINCIPLE Trial	272	787	341	1069	86.4%	1.08 [0.95, 1.23]
Total (95% CI)		**1019**		**1298**	**100.0%**	**1.07 [0.95, 1.20]**
Total events	319		385			

Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 2 (P = 0.80); I² = 0%

Test for overall effect: Z = 1.05 (P = 0.30)

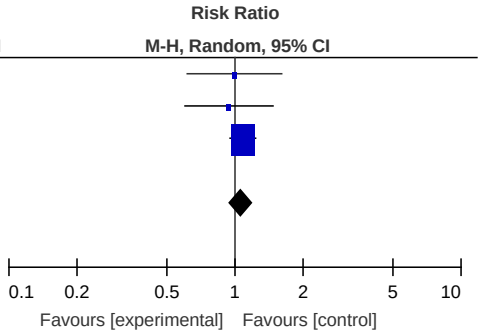

Figure 4a. Clinical Recovery/Clinical Improvement Day 7

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Song Ciclesonide Trial	19	35	15	26	7.8%	0.94 [0.60, 1.47]
Yu PRINCIPLE Trial	272	787	341	1069	92.2%	1.08 [0.95, 1.23]
Total (95% CI)		**822**		**1095**	**100.0%**	**1.07 [0.95, 1.21]**
Total events	291		356			

Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.55); I² = 0%

Test for overall effect: Z = 1.09 (P = 0.28)

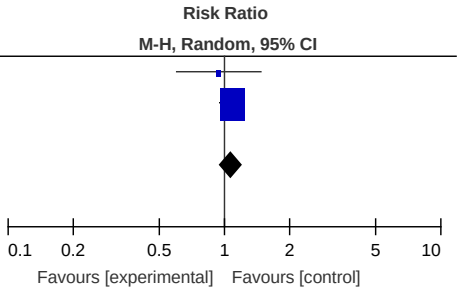

Figure 4b. Clinical Recovery/Clinical Improvement Day 7 (Sensitivity Analysis excluding preprint)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Clemency Ciclesonide Trial	28	197	29	203	6.8%	0.99 [0.62, 1.61]
Yu PRINCIPLE Trial	272	787	341	1069	93.2%	1.08 [0.95, 1.23]
Total (95% CI)		**984**		**1272**	**100.0%**	**1.08 [0.95, 1.22]**
Total events	300		370			

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%

Test for overall effect: Z = 1.16 (P = 0.25)

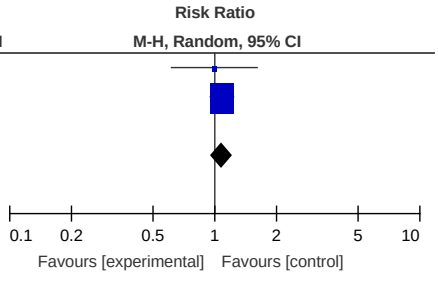

Figure 4c. Self-Reported Clinical Recovery Day 7

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Yu PRINCIPLE Trial	446	787	522	1069	100.0%	1.16 [1.06, 1.27]
Total (95% CI)		**787**		**1069**	**100.0%**	**1.16 [1.06, 1.27]**
Total events	446		522			

Heterogeneity: Not applicable

Test for overall effect: Z = 3.37 (P = 0.0008)

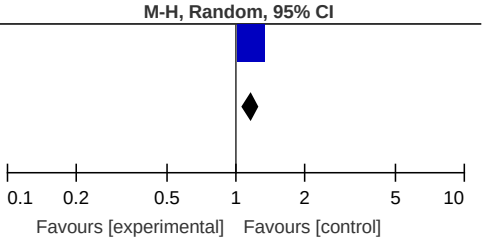

Figure 4d. Self-Reported Clinical Recovery D7 (Sensitivity Analysis)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Clemency Ciclesonide Trial	81	197	76	203	9.4%	1.10 [0.86, 1.40]
Ramakrishnan STOIC Trial	55	73	49	73	13.0%	1.12 [0.91, 1.38]
Song Ciclesonide Trial	26	35	14	26	3.4%	1.38 [0.92, 2.07]
Yu PRINCIPLE Trial	446	787	522	1069	74.3%	1.16 [1.06, 1.27]
Total (95% CI)		**1092**		**1371**	**100.0%**	**1.16 [1.07, 1.25]**
Total events	608		661			

Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 3 (P = 0.80); I² = 0%

Test for overall effect: Z = 3.81 (P = 0.0001)

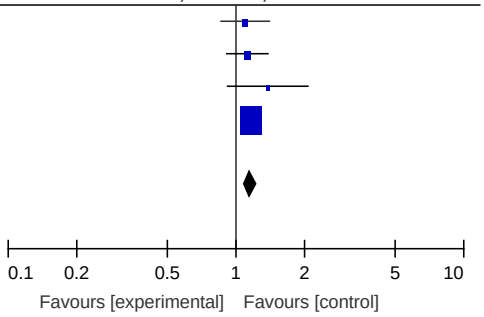

Figure 5a. Clinical Recovery/Clinical Improvement Day 14.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ramakrishnan STOIC Trial	55	73	49	73	14.3%	1.12 [0.91, 1.38]
Song Ciclesonide Trial	26	35	14	26	3.7%	1.38 [0.92, 2.07]
Yu PRINCIPLE Trial	446	787	522	1069	82.0%	1.16 [1.06, 1.27]
Total (95% CI)		**895**		**1168**	**100.0%**	**1.16 [1.07, 1.26]**
Total events	527		585			

Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 2 (P = 0.67); I² = 0%

Test for overall effect: Z = 3.76 (P = 0.0002)

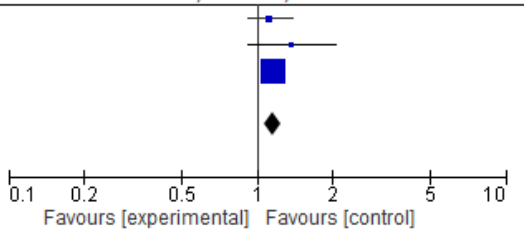

Figure 5b. Clinical Recovery/Improvement Day 14 (Sensitivity Analysis excluding preprint)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Clemency Ciclesonide Trial	81	197	76	203	9.7%	1.10 [0.86, 1.40]
Ramakrishnan STOIC Trial	446	787	522	1069	76.9%	1.16 [1.06, 1.27]
Yu PRINCIPLE Trial	55	73	49	73	13.4%	1.12 [0.91, 1.38]
Total (95% CI)		**1057**		**1345**	**100.0%**	**1.15 [1.07, 1.24]**
Total events	582		647			

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 2 (P = 0.89); I² = 0%

Test for overall effect: Z = 3.59 (P = 0.0003)

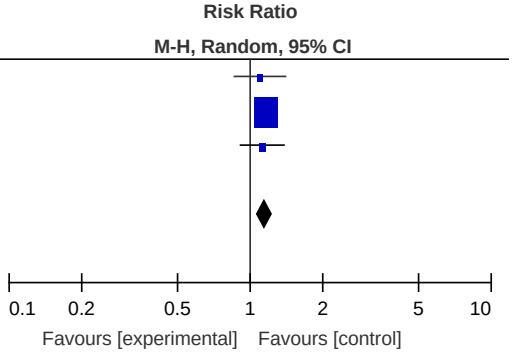

Figure 5c. Self-Reported Clinical Recovery Day 14

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ramakrishnan STOIC Trial	55	73	49	73	14.8%	1.12 [0.91, 1.38]
Yu PRINCIPLE Trial	446	787	522	1069	85.2%	1.16 [1.06, 1.27]
Total (95% CI)		**860**		**1142**	**100.0%**	**1.15 [1.07, 1.25]**
Total events	501		571			

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%

Test for overall effect: Z = 3.53 (P = 0.0004)

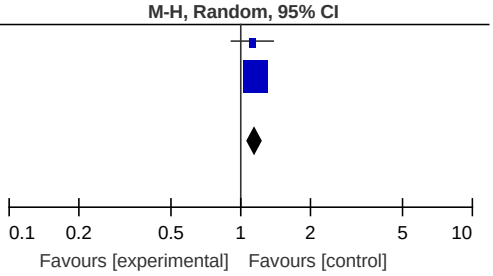

Figure 5d. Self-Reported Clinical Recovery D14 (Sensitivity Analysis)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Clemency Ciclesonide Trial	139	197	129	203	15.2%	1.11 [0.97, 1.27]
Song Ciclesonide Trial	34	35	21	26	7.5%	1.20 [0.99, 1.46]
Yu PRINCIPLE Trial	566	787	710	1069	77.3%	1.08 [1.02, 1.15]
Total (95% CI)		**1019**		**1298**	**100.0%**	**1.10 [1.04, 1.16]**
Total events	739		860			

Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 2 (P = 0.59); I² = 0%

Test for overall effect: Z = 3.33 (P = 0.0009)

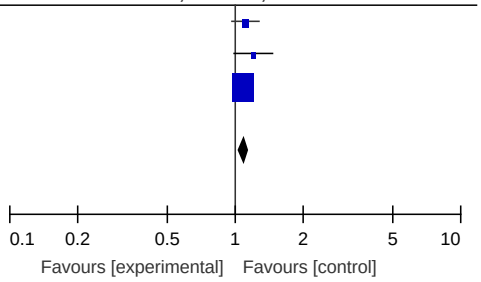

Figure 6a. Clinical Recovery/Clinical Improvement Day 28/Day 30

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Song Ciclesonide Trial	34	35	21	26	10.2%	1.20 [0.99, 1.46]
Yu PRINCIPLE Trial	566	787	710	1069	89.8%	1.08 [1.02, 1.15]
Total (95% CI)		**822**		**1095**	**100.0%**	**1.09 [1.03, 1.17]**
Total events	600		731			

Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%

Test for overall effect: Z = 2.80 (P = 0.005)

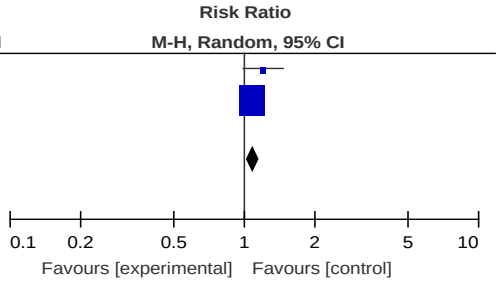

Figure 6b. Clinical Recovery/Clinical Improvement Day 28/30 (Sensitivity Analysis excluding preprint)

.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Clemency Ciclesonide Trial	139	197	129	203	16.4%	1.11 [0.97, 1.27]
Yu PRINCIPLE Trial	566	787	710	1069	83.6%	1.08 [1.02, 1.15]
Total (95% CI)		**984**		**1272**	**100.0%**	**1.09 [1.03, 1.15]**
Total events	705		839			

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%

Test for overall effect: Z = 2.94 (P = 0.003)

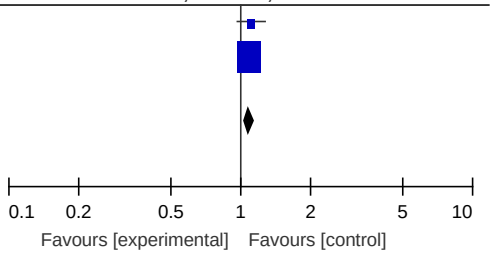

Figure 6c. Self-Reported Clinical Recovery Day 28/30

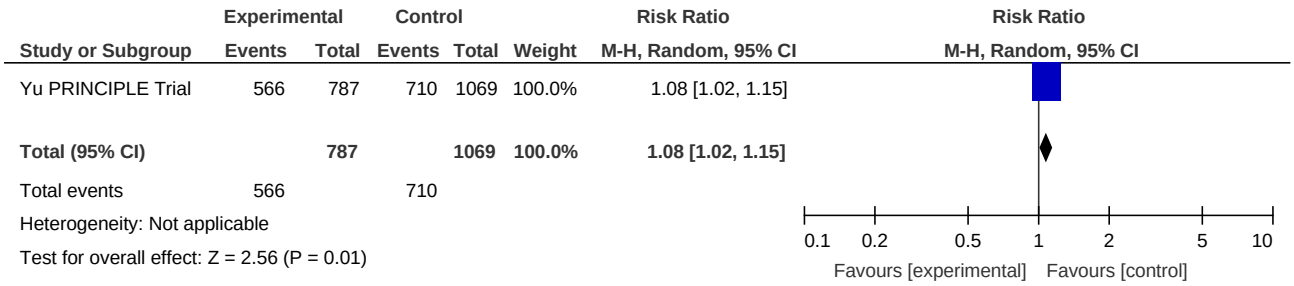

Figure 6d. Self-Reported Clinical Recovery D28/D30 (Sensitivity Analysis)

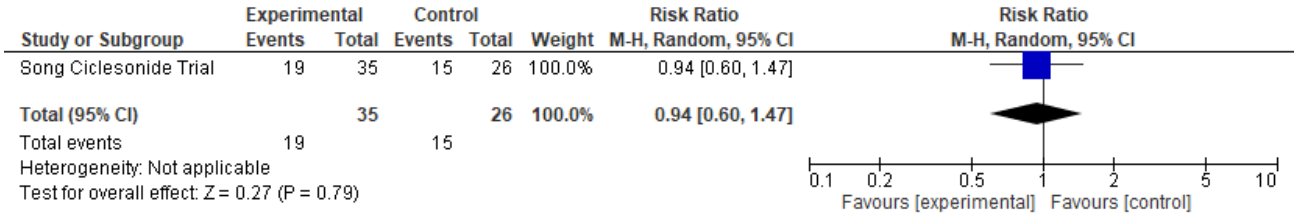

Figure 7. Clinical Improvement D7

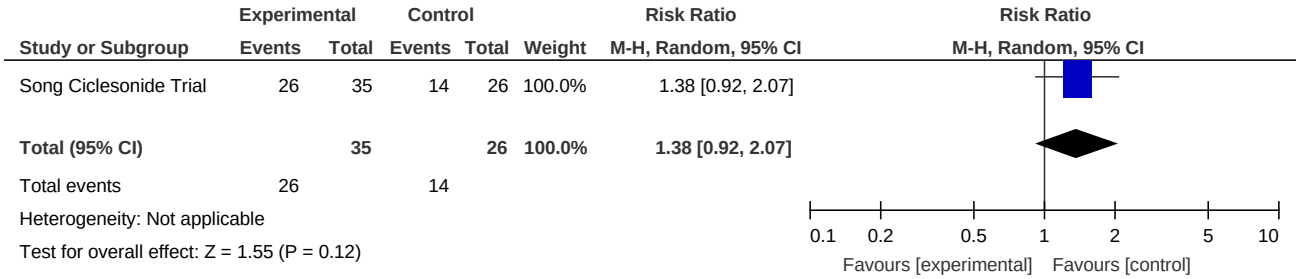

Figure 8. Clinical Improvement D14

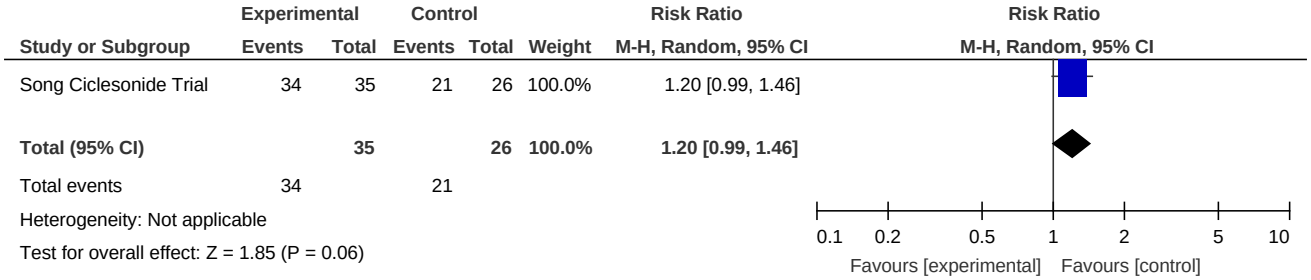

Figure 9. Clinical Improvement D28/D30

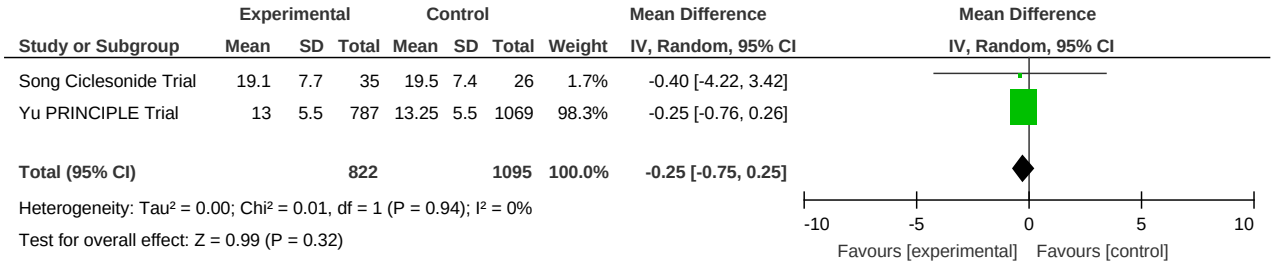

Figure 10. Duration of Hospitalization

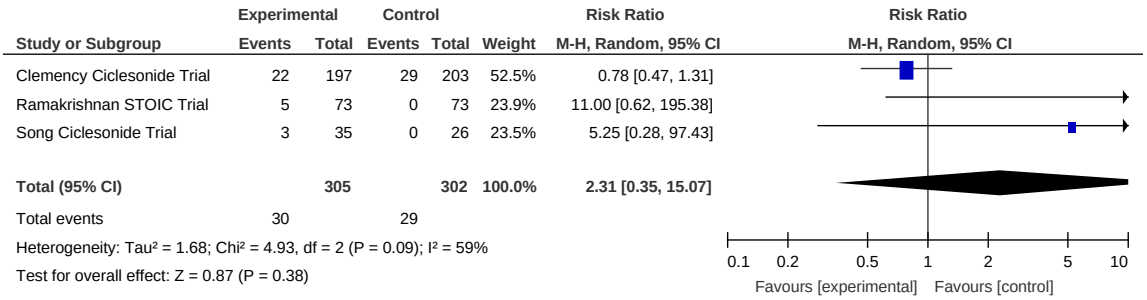

Figure 11a. Adverse Events

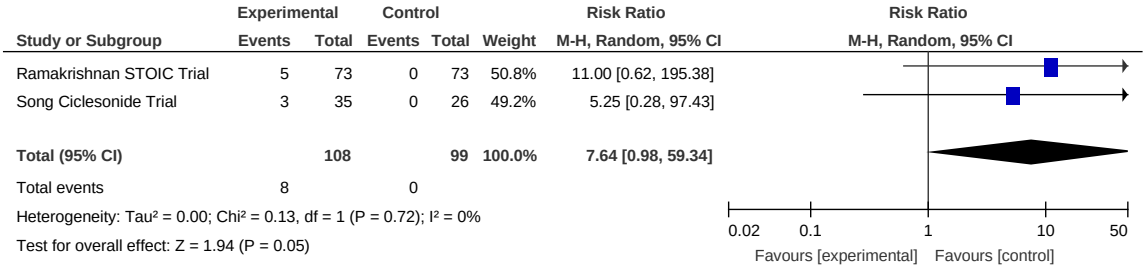

Figure 11b. Adverse Events (Sensitivity Analysis excluding preprint)

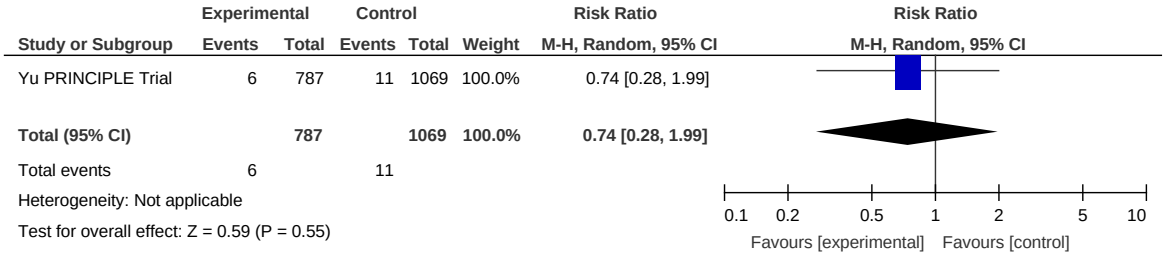

Figure 12. Mortality

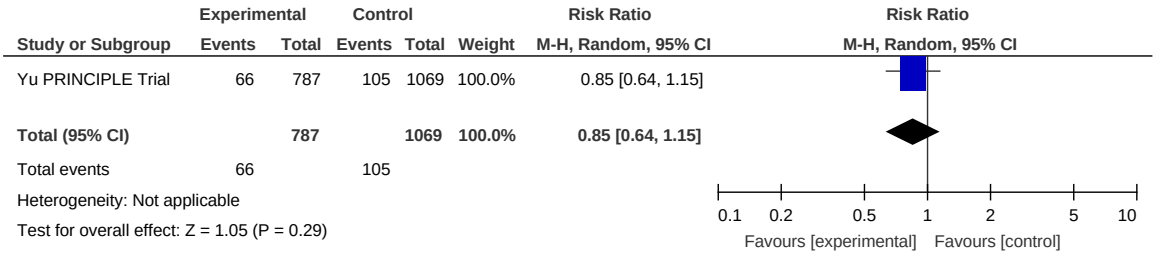

Figure 13. Hospitalization

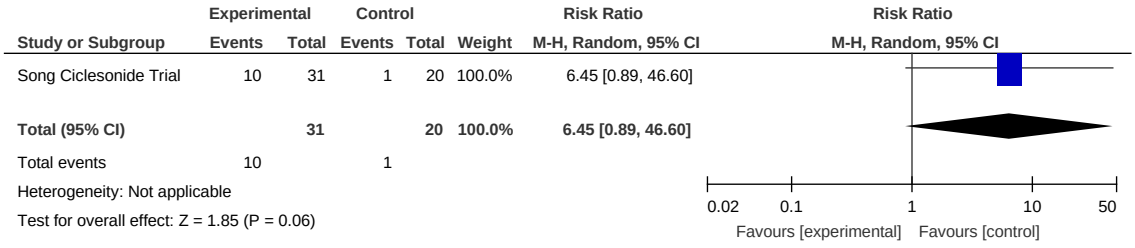

Figure 14. Viral Eradication Day 14

Appendix 7. Characteristics of Ongoing Studies

	Title	Population	Interventions	Characteristics	Outcome Measures
1	Arformoterol/Budesonide for COVID-19 NCT05055414	19 years and older (Adult, Older Adult)	UI030	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Time to Clinical Improvement on World Health Organization (WHO) Ordinal Scale World Health Organization (WHO) Ordinal Scale for Clinical Improvement World Health Organization (WHO) Ordinal Scale change Clinical cure rate
2	Fluticasone in Covid Treatment (FLOT) NCT05054322	18 years and older (Adult, Older Adult)	Fluticasone Propionate	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Incidence of adverse outcomes Duration of isolation based on WHO's criteria The incidence of patients with oxygen saturation by pulse oximetry (SpO2) < 94%; Self-reported recovery rate
3	Efficacy of Nebulized Lidocaine, Salbutamol and Beclomethasone Plus Salbutamol in the COVID-19 Patient with ARDS on Non-Invasive Ventilation: Randomized Controlled Trial NCT04979923	18 to 70 years old (Adult, Older Adult)	Lidocaine, Salbutamol, Beclomethasone	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Care Provider) Primary Purpose: Supportive Care	Cough suppression Correction of hypoxia
4	Efficacy of Inhaled Therapies in the Treatment of Acute Symptoms Associated with COVID-19 NCT04937543	18 years and older (Adult, Older Adult)	Inhaled beclometasone, inhaled beclomethasone / formoterol / glycopyrronium	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Proportion of patients in preventing the use of health resources in patients Airway obstruction Small airway obstruction
5	Early Treatment of Vulnerable Individuals with Non-Severe SARS COV 2 Infection NCT04920838	18 years and older (Adult, Older Adult)	Nitazoxanide and Ciclésonide Telmisartan 20mg oral tablet Paracetamol	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	SpO2 >/= 93% within 14 days Death within 14 days Death within 28 days Occurrence of at least one grade 3 or 4 clinical or biological adverse event within 14 days Number of hospitalizations due to severe progression
6	ACTIV-6: COVID-19 Study of Repurposed Medications NCT04885530	30 years and older (Adult, Older Adult)	Ivermectin Fluvoxamine Fluticasone Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Care Provider) Primary Purpose: Treatment	Number of hospitalizations as measured by patient reports. Number of deaths as measured by patient reports Number of symptoms as measured by patient reports Change in COVID Clinical Progression Scale Number of hospitalizations as measured by patient reports Number of Symptom Resolutions as measured by patient reports Change in Quality of Life (QOL) as measured by the PROMIS-29 Composite score of hospitalizations, urgent care visits, and emergency room visits as measured by patient reports

7	Inhaled Ciclesonide for Patients with COVID-19 NCT04435795	18 years and older (Adult, Older Adult)	Normal Saline intranasal and placebo inhaler Ciclesonide Ciclesonide nasal	Allocation: Randomized Intervention Model: Factorial Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Proportion of participants with no symptoms of cough, fever or dyspnea Overall feeling Improvement in dyspnea Visual Analog scale for Cough Hospitalization for SARS-CoV-2 Changes in Promis dyspnea characteristics scale Change in dyspnea severity Promis scale Incidence of new oxygen use Mortality Anxiety Sleep Disturbance
8	Inhalation of Ciclesonide for Patients with COVID-19: A Randomized Open Treatment Study (HALT COVID-19) NCT04381364	18 years and older (Adult, Older Adult)	Ciclesonide Inhalation Aerosol	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Duration of received supplemental oxygen therapy Treatment with systemic corticosteroids Invasive mechanical ventilation or all-cause death (key secondary outcome) All-cause death Invasive mechanical ventilation Remaining dyspnea symptoms Time from inclusion to initiation of treatment with systemic corticosteroids
9	A Study of the Safety and Efficacy of Ciclesonide in the Treatment of Non-Hospitalized COVID-19 Patients NCT04377711	12 to 100 years old (Child, Adult, Older Adult)	Ciclesonide Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment	Time to alleviation of COVID-19- related symptoms by Day 30 Percentage of patients with hospital admission or death by day 30 All-cause mortality by day 30 COVID-19-related mortality by day 30 Percentage of patients with subsequent emergency department visit or hospital admission for reasons attributable to COVID-19 by day 30 Percentage of patients with alleviation of COVID-19-related symptoms defined as symptom-free for a continuous period of more than 24 hours (ie, later than 3 AM/PM assessments) by day 7, by day 14, and by day 30 Time to hospital admission or death Change from baseline in oxygen saturation levels Change from baseline in COVID-19 viral load in nasopharyngeal sample at day 30
10	Trial of COVID-19 Outpatient Treatment in Individuals with Risk Factors for Aggravation NCT04356495	50 years and older (Adult, Older Adult)	Dietary Supplement: Vitamins Telmisartan Ciclesonide Interferon #-1b	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Pilot Phase: Proportion of participants who had a Grade 3 or 4 adverse event Efficacy phase: Death Efficacy phase: oxygen therapy Efficacy phase: hospitalization Proportion of hospitalizations, overall and by cause, in each group Death and causes of death Proportion of intensive care hospitalizations, overall and by cause, in each group Proportion of participants with negative SARS-CoV-2 RT-PCR Hematological markers evolution Inflammatory markers evolution and 6 more
11	Inhaled Corticosteroid Treatment of COVID 19 Patients with Pneumonia NCT04355637	18 to 79 years old (Adult, Older Adult)	Inhaled budesonide	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Proportion of patients in both arms fulfilling the criteria for treatment failure ICU admission ICU refusal Occurrence of complications Lactate dehydrogenase (LDH) C-Reactive Protein (CRP) Ferritin D-dimer

					Leukocyte counts
12	Evaluation of Efficacy of Levamisole and Formoterol+Budesonide in the Treatment of COVID-19 NCT04331470	15 to 100 years old (Child, Adult, Older Adult)	Levamisole Pill + Budesonide+Formoterol inhaler Lopinavir/Ritonavir + hydoxychloroquine	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor) Primary Purpose: Treatment	Clear chest CT-scan PCR test Physical statues of patient
13	Protective Role of Inhaled Steroids for COVID-19 Infection NCT04331054	18 to 75 years old (Adult, Older Adult)	Usual practice + Symbicort Rapihaler Usual practice	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Time (in days) to clinical improvement within 30 days after randomization Mortality rate at D30 Time (in days) from randomization to death Number of days alive outside ICU within 30 days Number of days alive free of invasive or non-invasive ventilation within 30 days Number of days alive with oxygen therapy within 30 days Maximal oxygen rate within 30 days Difference between PaO2/FiO2 ratio at randomization and at Day 7 (or at the time of stopping oxygen therapy or discharge if occurs before Day 7) Number of days alive outside hospital within 30 days Use of antibiotics for respiratory (proved or suspected) infection within 30 days Difference between CRP levels at randomization and at Day 7 (or at the time of discharge if occurs before Day 7) Safety outcomes included events that occurred during treatment, serious adverse events, and premature discontinuation of treatment.

Q28. Should steam inhalation be used in the treatment of patients with COVID-19 infection?

As of 12 March 2021

RECOMMENDATION

We recommend against the use of steam inhalation in the treatment of COVID-19. *(Very low certainty of evidence, Strong recommendation)*

Consensus Issues
The panel strongly recommended against the use of steam inhalation as prevention and treatment for COVID-19 inspite of the very low quality of evidence because it was recognized that the potential for harm outweighs the benefit.

KEY FINDINGS

Based on two single arm observational studies with high risk of bias, there is currently only very low quality evidence showing the possible benefit of steam inhalation in the prevention of developing symptomatic COVID-19 among exposed healthy individuals and reducing symptoms and number of days to negative SARS-COV-2 RT-PCR test of COVD-19 confirmed individuals. Meanwhile, there are indirect evidence highlighting the significant adverse effects of steam inhalation among individuals using it for symptomatic relief from the colds.

INTRODUCTION

Steam inhalation is a traditional practice used as a home remedy for treating common colds. It is thought to provide relief by loosening mucus, opening up the nasal passage, reducing mucosal inflammation and inhibiting viral replication by heat inactivation. Published articles supporting its use are varying but a systematic review published in Cochrane showed no association between symptomatic relief, reduction of clinical severity and having a positive viral culture from nasal washings from the common colds and use of steam inhalation [1]. The Philippines has a diverse culture and is known for certain populations having strong beliefs in traditional medicine sometimes choosing these over scientifically sound treatment options, hence this review.

REVIEW METHODS

We searched for articles investigating the use of steam inhalation (I) in the prevention of COVID-19 (O) among healthy individuals (P).

We performed a systematic literature search in online databases such as MEDLINE, CENTRAL, and Google Scholar. Additional searches in MedRxiv, clinicaltrials.gov, and WHO ICTRP were also done to look for articles awaiting publication and ongoing clinical trials, respectively. We used search mesh terms for “steam inhalation,” “steam treatment,” “prevention,” “prophylaxis” and “COVID-19.” References from review articles were also manually searched for additional articles.

Results

We found one prospective observational study investigating steam therapy for prevention and treatment of COVID-19 and one single-arm interventional study as treatment of COVID-19 [2,3].

As prevention

An observational study investigated the role of steam inhalation for the prevention and treatment of COVID-19 [2]. In this study, one group composed of asymptomatic healthcare workers who were exposed to COVID-19 patients either through direct contact or travel were advised to take in steam at least twice daily for five minutes (n=25). None of the participants developed any symptoms throughout the follow-up duration (14 days to 2 months). There was, however, no control group in this study. There was also no mention of whether the participants were tested for COVID-19,the adherence to the intervention or if they received any other treatment, used other personal protective equipment, and how symptoms were assessed (self-reported or with an independent assessor); hence, this study had a high risk for bias.

As treatment

In the same study a second group of people (n=80) composed of patients and healthcare workers) were observed. These were COVID-19 confirmed cases who had mild to moderate symptoms. They were given steam inhalation for five minutes every three hours. Outcome assessed was regression of symptoms and number of days to having a negative COVID-19 test. For this group, patients having mild symptoms recovered in a mean of 3 days while those having moderate symptoms recovered in 7 to 10 days. Test for COVID-19 became negative after 10 days for 65 (81%) of the participants, 14 days for 78 of them (97.5%) and 18 days for everyone to have negative result. Issues with this study include no mention of concurrent treatment, no mention if patients were admitted, total number of days steam inhalation was given, their adherence to steam inhalation, at what day of illness intervention was started. It also had no control group.

Another study investigated ten asymptomatic and pauci-asymptomatic healthcare professionals who tested positive for COVID-19 (N=10) [3]. Steam inhalation was given for at least twenty minutes either by 4 cycles of 5 minutes or 5 cycles of 4 minutes within one hour. The study excluded three from the final pool but monitoring was continued. Among the 7, all tested negative after only one day of steam inhalation, with 4 patients having no symptoms after 5 days while three had still some symptoms but with improvement. This study poses a high risk of bias because there was no control and blinding, no mention of what day of illness the intervention was started, no mention of adherence of participants to the intervention. Moreover, three of the participants did self-swabbing which could have affected yield of the samples. The three excluded participants also happened to be the ones who had a positive test for COVID-19 on repeat testing which adds to the bias of the result of the study.

Safety

There is no mention of safety from the two included studies. However, a published narrative report in the Lancet [4] describes an increase in incidence of scald burn among the pediatric population due to the increased use of steam inhalation for COVID-19 (from average of two scald burn per year from steam inhalation to six cases for just one month). As indirect evidence, a meta-analysis [1] also described that those who received steam inhalation for common colds had a significant higher risk for adverse events (N=65, OR 4.73 95% CI 1.46-15.30) which included nasal and lip irritation, increase in congestion, lightheadedness and general discomfort.

RECOMMENDATIONS FROM OTHER GROUPS

There are no recommendations from other groups on the use of steam inhalation for COVID-19.

ONGOING STUDIES

Currently, there is one registered clinical trial that will investigate the effect of steam inhalation as a treatment for COVID-19. Recruitment of participants is ongoing and the estimated primary completion of the study is registered on October 2021.

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Appendix 1. Characteristics of included studies

Authors	Country	Population	Intervention	Control	Outcomes	Results
La Marca (Italy)	Single center open label interventional study	Asymptomatic or pauci-symptimatic (2-3 mild to moderate symptoms) healthcare professionals working at a Hospital with positive rhinopharyngeal swab Exclusion criteria for enrolment a history of pre-existing allergies and/or asthma, ongoing drug therapies against SARS-CoV-2, and individuals with multiple symptoms consistent with COVID infection.	Steam inhalation for at least 20 minutes (either 4 cycles of 5 minutes or 5 cycles of 4 minutes) within 1 hour. temperature of boiled water was maintained at 55-65 C in the first 4-5minutes after initiation of boiling	None	Reduction of viral shedding after 4 days (at elast 6 cycle threshold measured with RT PCR) Complete virus elimination after 4 days	n=10 (3 patients met exclusion criteria) 1/7 asymptomatic all throughout 6/7 improvement of symptoms after end of study period - 3 improvement of all symptoms - 2 persistent anosmia and ageusia - 1 mild muscle pain and nasal congestion 7/7- tested negative on RT-PCR
Pawar	Prospective observational	Group 1: asymptomatic healthcare workers exposed to COVID-19 either thourgh travel or direct contact (n= 25) group 2: mild or moderate COVID-19 PCR confirmed patients (n=80 patient and health care workers) Severe patients excluded	Inhalation of steam twice daily, either through ordinary steamers or by boiling of water - Grp 1: 5mins byt nasal route BID (no mention of duration of treatment) - Grp 2: 5mins every 3 hours	None	RT PCR result after 5 days of steam inhalation, and until COvID was negative for two consecutive tests symptom pattern	No patients in group 1 developed symptoms (14 days to 2 months follow-up) Group 2 regression of symtptoms - for mild symptoms, mean of 3 days to return to normal - for moderate symptoms, 7-10 days to return to normal COVID-19 test - after 10 days since start: 65/80 turned negative (81%) - after 14 days since start: 78/80 turned negative (97.5%) - after 18 days since start: 80/80 turned negative (100%)

Appendix 2. GRADE Evidence Profile

Question: Should steam inhalation compared to no steam inhalation for COVID-19 treatment
Setting: COVID-19 confirmed patients

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recovery									
2	Observational studies	Very serious [a]	Not serious	Not serious	Not serious	Publication bias strongly suspected [b]	In one study, patients having mild symptoms recovered in a mean of 3 days while those having moderate symptoms recovered in 7 to 10 days in the other study, all seven had recovered after five days	⨁◯◯◯ VERY LOW	IMPORTANT
Time to negative RT-PCR									
2	Observational studies	Very serious [a]	Not serious	Not serious	Not serious	Publication bias strongly suspected [b]	Test for COVID-19 became negative after 10 days for 65 (81%) of the participants, 14 days for 78 of them (97.5%). in the other study, all included participants became negative after one day of steam inhalation	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations
[a] no mention of how symptoms was monitored (self monitoring or independent assessor), no mention of participants' adherence to the protocol and at what day of ilneess the intervention was given
[b] limited presentation of data

Appendix 3. Characteristics of Ongoing Studies

	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04743349 Steam Inhalations in COVID-19 Patients (Steam-COVID)	recruiting	Study Start: January 26,2021 Primary Completion: October 31, 2021	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: single (Outcome Assessor) •Primary Purpose: Treatment	Italy	Adults confirmed to have SARS-Cov-2 within 48 hrs of enrolment and only have no or mild symptoms	Steam inhalation	No steam inhalation	Reduction in viral shedding, clinical outcome, negativization rate

Q29. Should virgin coconut oil (VCO) be used in the treatment of patients with COVID-19 infection?

As of 20 February 2021

RECOMMENDATION

There is no evidence to recommend the use of VCO as treatment among patients with COVID-19 infection.

Consensus Issues

It is important to note that this recommendation is strictly for the use of VCO in the treatment of COVID-19 infection and should not be confused with another living recommendation pertaining to the use of VCO in the adjunctive treatment of COVID-19.

The ongoing clinical trial for VCO is not yet registered with the local Food and Drug Administration, hence, the evidence that will be generated cannot be used as an additional indication for the marketing purpose of VCO.

KEY FINDINGS

To date, there is no available completed clinical trial directly investigating effectiveness or safety of virgin coconut oil as an adjunct treatment for COVID-19 patients of any age or disease severity. Indirect evidence was noted from two studies of VCO on other viruses such as human immunodeficiency viruses.

INTRODUCTION

Virgin coconut oil contains chemical compounds that were thought to have antiviral and anti-inflammatory properties. In one local news [1], VCO was reported to decrease the C-reactive protein of patients with probable COVID-19.

REVIEW METHODS

We searched for evidence from December 14 to December 26, 2020 using any or combinations of all of the following keywords in free text or MeSH terms in databases listed in General Methods and one local database: “virgin coconut oil,” “lauric acid,” “COVID-19,” “SARS-CoV-2,” “2019-nCov,” “coronavirus,” “COVID.”

RESULTS

To date, there is no available completed clinical trial directly investigating effectiveness or safety of virgin coconut oil as an adjunct treatment for COVID-19 patients of any age or disease severity. Indirect evidence was noted from two studies of VCO on other viruses such as human immunodeficiency viruses.

VCO showed anti-HIV properties in two underpowered clinical trials. In a study in the Philippines, Dr. Conrado Dayrit [1] studied effect of VCO in viral load after three and six months among 15 patients with HIV infection who were randomized into three groups of VCO forms: two different doses of monolaurin in capsule and coconut oil. Only three out of 15 patients had significant decrease in viral load at the end of the study. [1, 2]

In Indonesia, another study was done among 40 HIV-positive patients without antiretroviral treatment randomized into VCO and non-VCO group. No significant difference was found in $CD4^+$ T lymphocyte count (indicator of HIV disease progression) after treatment. [2]

Dr. Fabian Dayrit has published a concept paper [3] on VCO and explained the VCO's antiviral property. First, lauric acid and monolaurin in VCO can disintegrate the cell membrane of the virus. Second, they can also stop the progression to late stage in the Junin virus' cycle of replication. Lastly, capric acid and lauric acid can prevent binding of viral proteins to the cell membrane of the host.

RECOMMENDATIONS FROM OTHER GROUPS

Currently there are no clinical practice guidelines that recommend the use of VCO as treatment for COVID-19.

RESEARCH GAPS

Two on-going trials are investigating effects of VCO among patients infected with the COVID-19 [4-6].

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Q30. Among patients with COVID-19, should Lianhua be used for treatment?

As of 06 December 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of Lianhua in the treatment of patients with non-severe COVID-19. *(Very low certainty of evidence)*

Consensus Issues

Although the recent review showed some benefit on the symptomatic treatment (clinical deterioration), the panel considered that the uncertainties on the quality of the evidence outweigh the trend in benefit. First, the subset of patients (percentage of mild and moderate cases) were not clearly stated in the included studies. This may actually affect the trend towards benefit since patients with mild COVID are expected to improve and have shorter time to recovery. Second, the definition of outcomes, particularly total symptom recovery may be too lax as it accounted only for at least one of the major symptoms. The panel also considered that since this is a regulated drug, there are uncertainties about the reported harm (expected adverse effects from ephedra such as hypertension and tachycardia was not assessed in the study procedures or reported in the results) and serious adverse events (unclear if the reported events were transient nor how severe the cases were). There are also inconsistencies in the direction of the clinical outcomes. While there is some benefit seen in reducing clinical deterioration, no definite benefit was seen in terms of clinical improvement of individual symptoms.

PREVIOUS RECOMMENDATION

We recommend against the use of Lianhua as treatment in patients with mild to moderate COVID-19. *(Very low certainty of evidence; Strong recommendation)*

Previous Consensus Issues

The consensus panel considered the evidence from the presented trials to be of very low certainty, with only marginal benefit in terms of rate of recovery and time to symptom recovery and inconclusive evidence for harm due to imprecise confidence intervals. The accessibility issue and potential harm the drug might cause should be considered. Lianhua is currently a drug regulated by the Philippine Food and Drug Administration as it contains ephedra, a controlled substance. As a result, Lianhua could not be sold over-the-counter and may only be prescribed by physicians holding an S2 license. The ephedra content of Lianhua was reported by some physicians to be potentially harmful especially in patients with cardiovascular disease.

WHAT'S NEW IN THIS VERSION

This review includes 3 additional RCTs (total of 5 included studies).

KEY FINDINGS

Five (5) randomized controlled trials investigated the effect of Lianhua compared to standard of care as treatment for patients with COVID-19. Lianhua showed significant

benefit in preventing clinical deterioration or progression to severe disease among patients with non-severe COVID 19. There was no significant benefit in mortality, and day-14 improvement in fever, cough and fatigue. There was no significant difference in adverse events or serious adverse events between the Lianhua and control group. The overall certainty of evidence was rated very low due to very serious risk of bias and serious imprecision in some critical outcomes.

INTRODUCTION

Since COVID-19 was declared a pandemic in early March 2020, various potential pharmacologic therapies including traditional Chinese medicine (TCM) have been extensively explored. Lianhua Qingwen (LHQW), a classical Chinese medical preparation officially recorded in the 2015 edition of the *Chinese Pharmacopoeia*, has been used in the SARS outbreak of 2002-2003 in China.[1] Recent *in vitro* studies have shown its effectiveness against SARS-CoV-2 through inhibition of replication, modification of viral morphology, and exertion of anti-inflammatory activity.[2] Specifically, a network pharmacologic analysis has shown that it regulates TFs or miRNAs of ACE2.[3] Furthermore, blocking of SARS-CoV-2 binding with ACE2 receptors were observed in vitro in *Lonicera japonica*, *Forsythia suspensa*, and *Rheum palmatum*, which are some of the plant components of Lianhua.[4]

A systematic review and meta-analysis of five studies published in September 2020 (including RCTs and observational studies) on the use of Lianhua against COVID-19 pneumonia showed benefit in terms of improvement of flu-like symptoms, shortness of breath, pulmonary imaging, shorter healing period, and lesser conversion to severe cases.[5] This review presents clinical studies on the efficacy and safety of Lianhua against COVID-19.

REVIEW METHODS

Databases including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane COVID-19 Study Register, LitCOVID, CenterWatch, China National Knowledge Infrastructure (CNKI), ChinaXiv.org, MedRxiv.org, BioRxiv.org, *clinicaltrials.gov*, Japan Primary Registries Network/ NIPH Clinical Trials Search, Republic of Korea - Clinical Research Information Service (CRIS), Chinese Clinical Trial Registry (ChiCTR), LitCOVID, WHO Clinical Trials International Clinical Trials Registry Platform (ICTRP), COVID-NMA Initiative COVID-19 Open Living Evidence Synthesis, EU Clinical Trials Register, WHO Therapeutics and COVID-19 Living Guideline, COVID-19 Local Evidence Database, and HERDIN Plus were searched for studies from the date of the last search June 11, 2021 to October 28, 2021. For PubMed, the following search terms were used: coronavirus infections, COVID-19, severe acute respiratory syndrome, coronavirus 2 or SARS-CoV-2, lianhua qingwen, lianhua, lianhua qingwen capsules, or lianhua capsules. Only randomized controlled trials were included. There is no language restriction in the included studies. The reference list of systematic reviews, meta-analyses, and clinical practice guidelines were reviewed for possible additional studies. Review articles and other study designs were excluded.

RESULTS

Characteristics of included studies

Five (5) RCTs were included in this review.[6,10-13] All RCTs were conducted in China. One RCT [6] was identified in the CNKI database, but only the abstract can be retrieved despite maximal efforts. Data from this study was obtained from three systematic reviews [7-9], with 2 reviews appraised to be of high certainty and one to be of moderate certainty using the AMSTAR 2 tool.

The 5 studies included a total of 896 adult patients without severe COVID-19. The standard of care used in these studies was based on the recommendations on the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)", which included anti-virals, oxygen therapy, and/or symptomatic treatments. Four (4) studies used Lianhua Qingwen thrice daily: 2 as capsule and 2 as granules.[6,10-12] One study used Lianhua Qingke granules twice daily.[13] Outcomes reported were clinical deterioration, day-14 symptom improvement (fever, cough, and fatigue), improvement in chest CT scan, and serious drug-related adverse events. The characteristics of included studies are summarized in Appendix 3.

The overall certainty of evidence was rated very low due to very serious risk of bias and serious imprecision in some critical outcomes. The very serious risk of bias was due to unclear treatment allocation in 4 studies, issues with performance and detection bias in all 5 studies (4 studies were open-label, 1 study did not report if it was blinded), and issues with incomplete outcome data in 1 study [6]. One study also had some concerns for other bias due to lack of description on how the outcomes were measured.[6] The risk of bias summary is in Appendix 5. The GRADE evidence profile is in Appendix 6.

Effectiveness Outcomes

Mortality

Only one study with very low certainty of evidence with 295 participants reported on mortality.[12] Yu et al., reported 2 deaths in the comparator arm and 1 in the Lianhua arm yielding inconclusive results (RR 0.50, 95% CI 0.05-5.49).

Clinical deterioration

Data from 5 RCTs (N = 814) showed a significant benefit in preventing clinical deterioration or progression to severe disease in favor of Lianhua (RR 0.55, 95% CI 0.36 to 0.82; I^2 = 0%). Of the 5 studies, only one study with very serious risk of bias showed a significant decrease in the risk of clinical deterioration.

Cure rate

Only one study (N = 284) with low certainty of evidence reported on cure rate.[10] In the study, cure rate is defined as having met all of the following criteria: recovery of body temperature for more than 3 days, symptom recovery, marked improvement in the chest CT images, and two consecutive negative SARS-CoV-2 RNA tests (at least one day apart). This study reported that Lianhua compared to standard care resulted in a slight increase in cure rate (RR 1.19, 95% CI 1.03-1.38).

Symptom improvement

There were 3 studies that reported symptom improvement using various outcomes. Only cough, fatigue, and fever improvement on day 14 were similarly reported in 2 studies [11,13], while the rest of the outcomes could not be pooled.

Pooled analysis from 2 studies with very low certainty of evidence on day-14 improvement of the following symptoms showed no significant difference between Lianhua arm and the control arm: cough (RR 1.09, 95% CI 0.65 to 1.81; I^2 = 86%), fatigue (RR 1.11, 95% CI 0.92 to 1.34; I^2 = 0%), and fever (RR 1.00, 95% CI 0.90 to 1.11; I^2 = 0%).[11,13] One study reported that day-14 total symptom recovery was slightly higher in the Lianhua arm (RR 1.11, 95% CI 1.01 to 1.22).[10]

One study reported improvement of other symptoms such as loss of appetite, nausea and vomiting, diarrhea, sore limbs, chest tightness and shortness of breath at day 7 and day 14.[11] At day 7, there was no significant benefit in loss of appetite (RR 0.86, 95% CI 0.64 to 1.16), nausea and vomiting (RR 0.80, 95% CI 0.62 to 1.03), diarrhea (RR 1.00, 95% CI 0.69 to 1.45), sore limbs (RR 1.26, 95% CI 0.88 to 1.81), and shortness of breath (RR 1.18, 95% CI 0.77 to 1.82), among those given Lianhua and control. Similarly, there was no significant benefit at day 14 in loss of appetite (RR 0.95, 95% CI 0.87 to 1.07), nausea and vomiting (RR 0.93, 95% CI 0.82 to 1.07), diarrhea (RR 1.00, 95% CI 1.00 to 1.00), sore limbs (RR 1.05, 95% CI 0.81 to 1.36), and chest tightness and shortness of breath (RR 0.97, 95% CI 0.73 to 1.29).[11]

Based on one study, there was no significant improvement in day 14 hoarseness (RR 1.31, 95% CI 0.62-2.80) and sore throat (RR 1.00, 95% CI 1.00-1.00) among those given Lianhua and control. There was significant improvement of sputum expectoration at day 14 among those given Lianhua compared to control (RR 1.66, 95% CI 1.04-2.64).[13]

One study reported symptom improvement as a continuous variable (mean difference for symptom scores), with the symptom score ranging from 1 (no symptom) to 4 (severe symptoms). Results showed statistically significant improvement in symptom scores for fever (MD -0.48, 95% CI -0.61 to -0.35), fatigue (MD -0.28, 95% CI -0.39 to -0.17), cough (MD -1.10, 95% CI -1.26 to -0.94), sore throat (MD -1.40, 95% CI -1.54 to -1.26). and chest pain (MD -0.37, 95% CI -0.55 to -0.19). [12]

One study showed significant shorter median time to recovery of total symptoms (HR 1.72, 95% CI 1.33 to 2.22), fatigue (HR 1.78, 95% CI 1.04 to 2.05), and cough (HR 1.71, 95% CI 1.3 to 2.23) in the Lianhua arm. There was no trend towards benefit in time to recovery for fever (HR 1.39, 95% CI 1.0 to 1.94),[10]

Improvement in chest CT scan

The pooled result from 3 studies [10,12,13] with low certainty of evidence showed significant improvement in chest CT scan in patients given Lianhua (RR 1.22, 95% CI 1.10 to 1.35; I^2 = 31%). One [12] out of the 3 studies defined improvement as a minimum of 30% decrease in lesion size while the rest defined it as reduction of infiltration, lesion site, or density of ground glass opacities in chest CT scan.[12,13]

Viral clearance

There was no significant difference in the conversion rate of SARS-CoV-2 viral assay (RR 1.08, 95% CI 0.94 to 1.24) and time to negative conversion (MD -0.42 days, 95% CI -1.51 to 0.67; p = 0.45).

Safety Outcomes

Pooled estimate from three studies with very low certainty of evidence reported no significant difference in total adverse events (RR 0.87, 95% CI 0.70-1.10; I^2 = 0%).[6,10,12] Adverse events reported in both the Lianhua and control group included abnormal liver function, renal dysfunction, headache, nausea, vomiting, and loss of appetite.

Two studies with very low certainty of evidence reported zero serious adverse event in both experimental and control arms.[10,12]

Expected adverse effects from ephedra such as hypertension and tachycardia was not mentioned as an outcome to be measured in the methodology, nor reported in the results in any of the studies.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendation from Other Groups

Regulatory Agency	Recommendation
National Institutes of Health (as of October 19, 2021) [14]	No recommendations on the use of Lianhua for the treatment of COVID-19.
World Health Organization (as of September 24, 2021) [15]	
Infectious Diseases Society of America (as of October 15, 2021) [16]	
Australian Clinical Evidence Taskforce (as of October 21, 2021) [17]	
National Health Commision & State Administration of Traditional Chinese Medicine Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (as of March 4, 2020)	Recommend Lianhua Qingwen capsules to be used during medical observation as treatment of fatigue and fever. [18-20]
Diagnosis and Treatment Protocol for COVID-19 of the National Health Commission (as of August 18, 2020)	
Rapid Advice Guideline for the Diagnosis and Treatment of 2019-nCoV by the China International Exchange and Promotive Association for Medical and Healthcare (CPAM) (as of February 6, 2020)	
CPAM & Chinese Research Hospital Association (CRHA) (as of September 4, 2020)	Recommends the use of Lianhua to treat patients with mild or moderate COVID-19 with conventional therapy and suggested that Lianhua granules/capsules 6 g/1.4g be taken orally, thrice daily for 14 days.[21]
Expert Consensus on Guidance and Prevention Strategies for Hospital Pharmacists and Pharmacy Workfoce by the Chinese Pharmaceutical Association (CPA)	Recommends the use of Lianhua capsule, 4 capsules orally, thrice daily or Lianhua granules, 1 packet orally, thrice daily to detoxify and remove lung hotness.[22] CPA mentioned common adverse reactions such as gastrointestinal symptoms, rash, and pruritus and advised patients with hypertension

	and heart disease, patients with severe chronic diseases such as liver disease, diabetes, and kidney disease, patients with spleen deficiency and loose stools, children, pregnant women, lactating women, elderly to take Lianhua with caution and under physician guidance of physicians. Long term use is discouraged.[22]
International Trusthworthy Traditional Chinese Medicine Recommendations (TCM Recs) Working Group (as of October 11, 2021)	Suggests against the use of Lianhua Qingke granules in addition to western medicine for mild and moderate COVID-19 patients. However, the guideline only based its recommendation on one RCT.[23]

RESEARCH GAPS

There are 5 ongoing registered RCTs (ChiCTR2000029433 for suspected cases, ChiCTR2100042066 for asymptomatic cases, NCT04433013 and ChiCTR2100042069 for mild COVID-19, and ChiCTR2100042068 for severe cases). Three are still ongoing recruitment while 2 are pending or no recruitment yet.

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Appendix 1. Evidence to Decision

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					
Benefits	Large	Moderate (2)	Small	Uncertain (3)			Lianhua had no significant effect in the mortality, however, it can prevent clinical deterioration or progression to severe disease among patients with non-severe COVID 19.
Harm	Large	Small (3)	Uncertain (2)	Varies			No significant differences in terms of adverse events or serious adverse events from the Lianhua group compared to standard of care.
Certainty of Evidence	High	Moderate (1)	Low (2)	Very low (2)			The overall certainty of evidence was rated very low due to very serious risk of bias and serious imprecision in some critical outcomes.
Balance of effects	Favors drug (1)	Does not favor drug (2)	Uncertain (4)				
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate cost	Negligible cost (4)	Moderate savings (1)	Large savings	Lianhua would cost P288.00/box with 24 capsules per box. Most recommended regimen (Lianhua cap TID for 14 days) will cost P504.00 (P36/day). On August 7, 2020, the FDA approved its use only for symptomatic relief but not for COVID-19 treatment
Certainty of evidence of required resources	No included studies (3)	Very low (1)	Low (1)	Moderate	High		
Cost effectiveness	No included studies (4)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (4)	Reduced	Probably no impact	Increased (1)			
Acceptability	Uncertain (4)	No	Yes (1)				
Feasibility	Uncertain (3)	No	Yes (2)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	((“COVID-19”) OR (“severe acute respiratory syndrome coronavirus 2”) OR (“2019-nCoV”) OR (“SARS-CoV-2”) OR (“corona virus disease 2019”)) AND ((lianhua) OR (lianhua qingwen) OR (lianhua capsule) OR (lianhua qingwen capsule))	10/28/21, 2:10 am	46	10
CENTRAL	“COVID-19” and “lianhua”	10/27/21, 11 pm	12	5
Cochrane COVID-19 Study Register	“COVID-19” and “lianhua”	10/27/21, 11:45 pm	12	2
COVID-NMA Initiative	Filter: “lianhua”	10/28/21, 1:12 am	0	0
LitCOVID	“COVID-19” and “lianhua”	10/28/2021, 12:15 am	10	4
China National Knowledge Infrastructure	“COVID-19” and “lianhua”	10/28/2021, 1: 37 am	40	8
HERDINPlus	“COVID-19” and “lianhua”	10/28/21, 12:10 am	0	0
ClinicalTrials.gov	Condition or disease: COVID-19 Other terms: Lianhua	10/27/21, 8 pm	1	1
Chinese Clinical Trial Registry	Target disease: COVID-19 Intervention: lianhua	10/27/21, 11:05 pm	3	0
EU Clinical Trials Register	“COVID-19” and “lianhua”	10/27/21, 11:17 pm	0	0
Republic of Korea – Clinical Research Information Service	“COVID-19” and “lianhua”	10/27/21, 11:42 pm	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	“COVID-19” and “lianhua”	10/28/2021, 1:03 am	0	0
CenterWatch	Filter: COVID-19 I am looking for: lianhua	10/27/21, 11:27 pm	0	0
WHO International Clinical Trials Registry Platform (ICTRP)	“COVID-19” and ‘lianhua”	10/27/21, 11:30 pm	5	3
chinaxiv.org	“COVID-19” and “lianhua”	10/28/21, 1:04 am	0	0
Medrxiv.org	“COVID-19” and “lianhua”	10/28/21, 1:05 am	10	0
Biorxiv.org	“COVID-19” and “lianhua”	10/28/21, 1:10 am	7	0
Google Scholar	“Clinical Study of Lianhua Qingwen Capsule in the Treatment of Corona Virus Disease 2019”	10/28/2021, 12:50 am	4	3
CiteSeerX	“Clinical Study of Lianhua Qingwen Capsule in the Treatment of Corona Virus Disease 2019”	10/28/2021, 12:53 am	2	0

Appendix 3. Characteristics of Included Studies

Author	Study design	Population (n)	Inclusion criteria	Exclusion criteria	Intervention	Outcomes
Chen et al, 2021 [6]	Single site, randomized, controlled, two arms	Diagnosed cases of COVID-19 (n = 60)	Mild COVID-19 cases and ordinary cases of new COVID-19 pneumonia	Severe or critically ill patients	Control group: conventional treatment (symptomatic and supportive treatment plus interferon alfa, lopinavir or ritonavir) Experimental: conventional treatment + Lianhua Qingwen capsule, 4 caps thrice a day for 10 days	Clinical deterioration rate, nucleic acid conversion time, adverse events
Hu K et al 2020 [10]	Multicenter, randomized controlled, open-label	Patients more than 18 years old. with COVID-19 (n = 284)	Laboratory-confirmed cases with COVID-19; being symptomatic (either having fever, coughing, or fatigue) plus radiologic abnormalities consistent with pneumonia; patients aged 18 years or greater of either sex.	Respiratory tract bacterial infections due to primary or secondary immunodeficiency, congenital respiratory malformation, congenital heart disease, gastroesophageal reflux, and lung malformation; asthma or other chronic airway diseases needing maintenance therapy, acute respiratory tract bacterial infection (i.e., bronchiectasis, tonsillitis, bronchitis, rhinosinusitis, otitis media), severe pulmonary interstitial diseases; severe pneumonia needing mechanical ventilation; severe systemic diseases (i.e., malignancy, autoimmune	Routine treatment; Lianhua (4 capsules, thrice daily) plus routine treatment (oxygen therapy, antiviral medications, symptomatic therapies)	Primary endpoint: rate of symptom recovery Secondary endpoint: time to symptom recovery, rate of and time to recovery of individual symptoms, proportion of patients with improvement on chest CT, proportion of patients with clinical cure, timing and rate of conversion of SARS-CoV-2 RNA assay, adverse events

				diseases, liver or renal diseases) or surgeries (splenectomy, organ transplantation) that in the judgement of the investigators could affect the assessment of efficacy; women during pregnancy or lactation; participation in clinical trials within 3 months; known allergies to the investigational medications; other conditions judged by the investigators.		
Xiao et al, 2020 [11]	Single site, randomized, controlled, non-blinded, three arms	Diagnosed cases of COVID-19 (n = 182)	Diagnosed cases of COVID-19 meeting the diagnostic criteria; 18–85 years old, regardless of sex; provided informed consent.	Clear evidence of bacterial infection; severe primary diseases, such as heart, kidney, lung, endocrine, blood, metabolism, or gastrointestinal tract diseases, which may affect the patient's participation in the trial or affect the outcome of the study; family history of mental illness or previous mental illness; allergies or multiple drug allergies; pregnant or lactating women	6g of Lianhua Qingwen granules thrice a day + Western medicine; one bag of Huoxiang Zhengqi dropping pills twice a day + one bag of Lianhua Qingwen granules thrice a day + Western medicine; Western medicine	Main outcome measure: clinical symptom improvement and disappearance rates after 14 days of treatment secondary outcome: proportion of patients who progressed to severe status
Yu et al, 2020 [12]	Single site randomized, controlled	Diagnosed COVID-19 adult inpatients from February 17 to March 6, 2020 (n = 295)	1) All meet the diagnostic criteria of COVID-19 in the "Diagnosis and Treatment Plan for Pneumonia of Novel Coronavirus Infection (Sixth Edition)", and are either mild (with mild	Severe or critically ill patients; Severe heart, liver and kidney dysfunction; Severe diseases that may affect the outcome of the patient; Pregnant or breastfeeding women; HIV infection	Control group: arbidol + moxifloxacin + ambroxol Experimental group: Lianhua Qingwen Granules (6 g, thrice daily, for 7 days) +	Aggravation rate, mortality rate, improvement of chest CT, adverse events

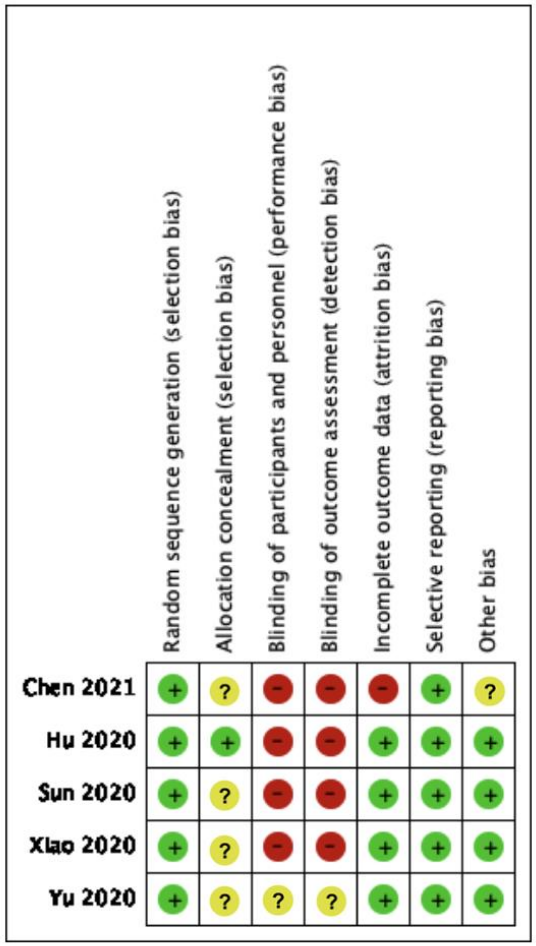
			symptoms and no pneumonia on imaging) or common (with Symptoms such as fever and respiratory tract, and imaging shows the presence of pneumonia); 2) 18 to 75 years old; 3) voluntarily signed the informed consent form		arbidol + moxifloxacin + ambroxol	
Sun et al 2020 [13]	Randomized, controlled two arms	COVID-19 patients over 18 years of age	Patients over 18 years of age diagnosed with new coronavirus pneumonia with cough symptoms		Lianhua Qingke granules (twice daily) vs. conventional (lopinavir or ritona, interferon alfa plus symptomatic and supportive treatment	Aggravation rate, mortality rate, improvement of chest CT, adverse events

Appendix 4. Summary of Evidence

Outcomes	Basis	Relative Effect (95% CI)	Difference (95% CI)	Interpretation	Overall Certainty of Evidence
CRITICAL OUTCOMES					
Mortality	1 RCT (n = 295)	RR 0.50 (0.05-5.49)	**7 fewer per 1,000** (from 13 fewer to 61 more)	Inconclusive	Very Low[1]
Clinical Deterioration	5 RCT (n = 814)	RR 0.55 (0.36-0.82)	**62 fewer per 1,000** (from 88 fewer to 25 fewer)	Benefit	Low
Clinical cure	1 RCT (n = 284)	RR 1.19 (1.03 – 1.38)	**126 more per 1,000** (from 20 more to 252 more)	Tendency towards benefit	Low
Time to symptom recovery	1 RCT (n = 284)	HR 1.72 (1.33-2.22)	--	Benefit	Low
Total symptom recovery, Day 14	1 RCT (n = 284)	RR 1.11 (1.01-2.22)	**91 more per 1,000** (from 8 more to 181 more)	Tendency towards benefit	Very Low[1]
Fever Improvement, Day 14	2 RCT (n = 51)	RR 1.00 (0.90-1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	Equivalent	Very Low[1]
Cough Improvement, Day 14	2 RCT (n = 123)	RR 1.09 (0.65-1.81)	**72 more per 1,000** (from 64 fewer to 271 more)	Inconclusive	Very Low[1]
Fatigue Improvement, Day 14	2 RCT (n = 86)	RR 1.11 (0.92-1.34)	**88 more per 1,000** (from 280 fewer to 648 more)	Inconclusive	Very Low[1]
Serious adverse events	2 RCT (n = 579)	RR 1.00 (0.14-7.07)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Inconclusive	Very Low[2]
OTHER NON-CRITICAL OUTCOMES					
Chest CT scan improvement	3 RCT (n = 636)	RR 1.22 (1.10-1.35)	**141 more per 1,000** (from 64 more to 224 more)	Benefit	Low
Negative conversion time	2 RCT (n = 341)	MD -0.42 day (-1.51 to 0.67)	**0.42 day lower** (1.51 lower to 0.67 higher)	Inconclusive	Low
Conversion rate of SARS-CoV 2 viral assay	1 RCT (n = 284)	RR 1.08 (0.94-1.24)	**57 more per 1,000** (from 43 fewer to 171 more)	No difference	Very Low[1]
Adverse events	3 RCT (n = 456)	RR 0.87 (0.70-1.10)	**35 fewer per 1,000** (from 80 fewer to 27 more)	Inconclusive	Very Low[1]

[1]very serious risk of bias, serious imprecision
[2]very serious risk of bias, very serious imprecision

Appendix 5. Methodological Assessment of Included Studies



Appendix 6. GRADE Evidence Profile

Author(s): Joey Tabula, Timothy Hudson David Culasino Carandang
Question: Lianhua plus SOC compared to SOC for COVID-19
Bibliography:

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CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lianhua plus SOC	Standard of care alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1 [1]	Randomised trials	Very serious [a,b]	Not serious	Not serious	Serious [c]	None	1/147 (0.7%)	2/148 (1.4%)	**RR 0.50** (0.05 to 5.49)	**7 fewer per 1,000** (from 13 fewer to 61 more)	⊕◯◯◯ VERY LOW	CRITICAL
Clinical Deterioration												
5 [1,2,3,4,5]	Randomised trials	Very serious [a,b]	Not serious	Not serious	Not serious	None	30/407 (7.4%)	56/407 (13.8%)	**RR 0.55** (0.36 to 0.82)	**62 fewer per 1,000** (from 88 fewer to 25 fewer)	⊕⊕◯◯ LOW	CRITICAL
Clinical cure												
1 [4]	randomised trials	very serious [b]	not serious	not serious	not serious	None	112/142 (78.9%)	94/142 (66.2%)	**RR 1.19** (1.03 to 1.38)	**126 more per 1,000** (from 20 more to 252 more)	⊕⊕◯◯ LOW	CRITICAL
Time to symptom recovery												
1 [4]	randomised trials	very serious [b]	not serious	not serious	not serious	None	7 days vs 10 days, HR 1.72, (1.33 to 2.22), p<0.01	⊕⊕◯◯ LOW	CRITICAL	**90 fewer per 1,000** (from 126 fewer to 46 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Total symptom recovery, Day 14											
1 [4]	randomised trials	very serious [b]	not serious	not serious	serious [d]	None	130/142 (91.5%)	117/142 (82.4%)	**RR 1.11** (1.01 to 1.22)	**91 more per 1,000** (from 8 more to 181 more)	⊕◯◯◯ VERY LOW	CRITICAL
Fever improvement, Day 14											
2 [1,3]	randomised trials	very serious [a,b]	not serious	not serious	serious [c]	None	28/28 (100%)	23/23 (100%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⊕◯◯◯ VERY LOW	CRITICAL
Cough improvement, Day 14											
2 [1,3]	randomised trials	very serious [a,b]	Very serious [e,f]	not serious	serious [c]	None	54/64 (84.4%)	47/59 (79.7%)	**RR 1.09** (0.65 to 1.81)	**72 more per 1,000** (from 64 fewer to 271 more)	⊕◯◯◯ VERY LOW	CRITICAL
Fatigue improvement, Day 14											
2 [1,3]	randomised trials	very serious [a,b]	Not serious	not serious	serious [c]	None	41/46 (89.1%)	32/40 (80.0%)	**RR 1.11** (0.92 to 1.34)	**88 more per 1,000**	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects											
3 [1,4,5]	randomised trials	very serious [a,b]	not serious	not serious	serious [c]	None	74/137 (23.3%)	85/319 (26.6%)	**RR 0.87** (0.70 to 1.1)	**35 fewer per 1,000** (from 80 fewer to 27 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Serious adverse effects											
2 [1,4]	randomised trials	very serious [a,b]	not serious	not serious	very serious [c,g]	None	0/289 (0.0%)	0/290 (0.0%)	**RR 1.00** (0.14 to 7.07)[h]	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio; **MD:** Mean difference

Explanations

[a] Unclear allocation concealment
[b] Lack of blinding
[c] CI is not on the same side
[d] Lower or upper limit of CI very close to 1
[e] Minimal or no overlap of confidence intervals
[f] Substantial heterogeneity
[g] No event rate
[h] Computed via imputing values

Appendix 7. Forest Plots

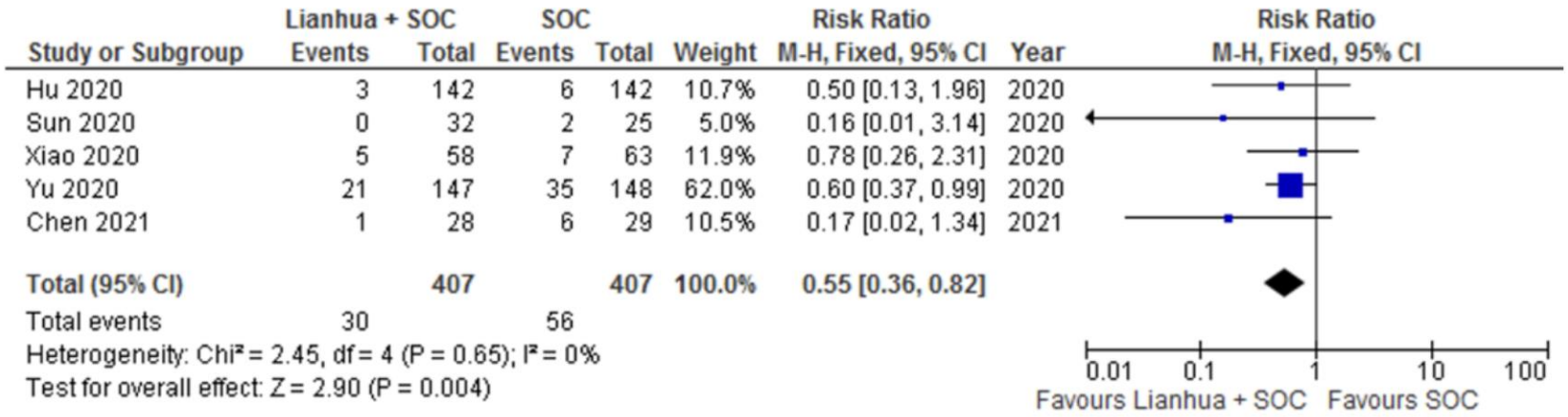

Figure 1. Clinical Deterioration

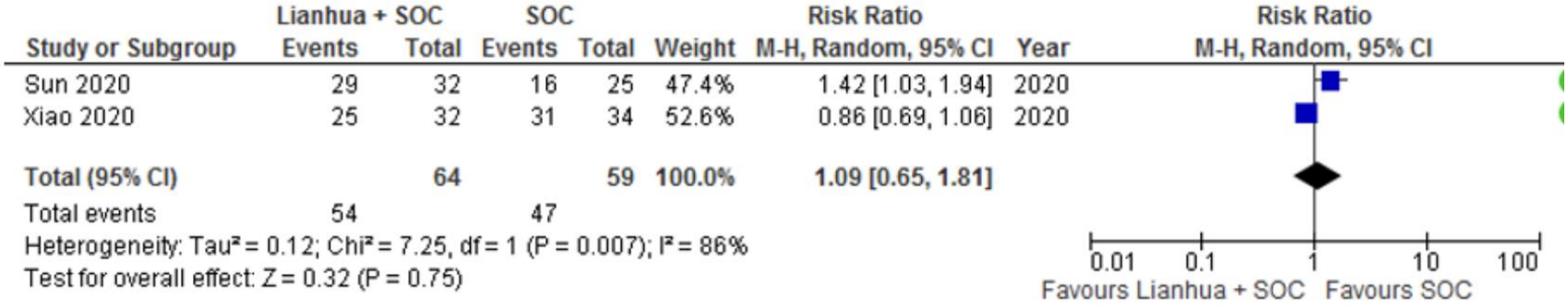

Figure 2. Day-14 cough improvement

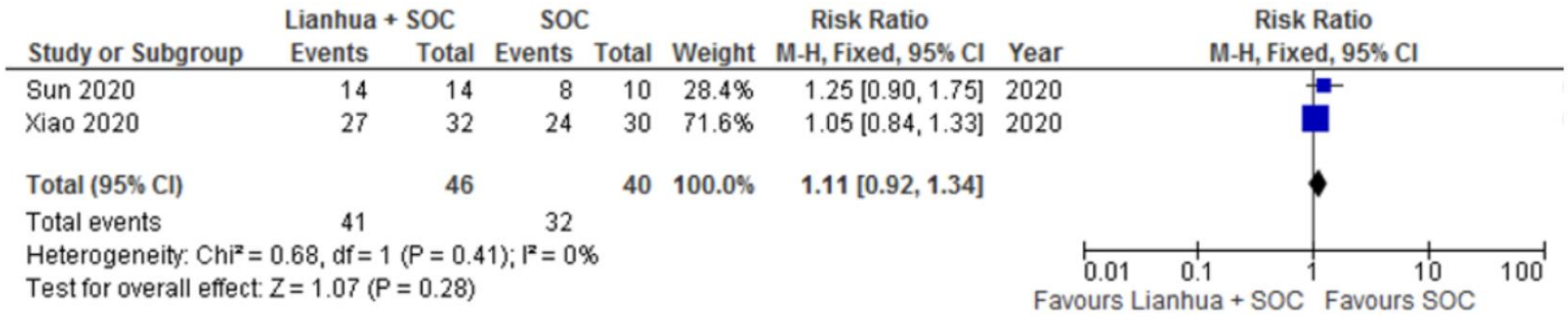

Figure 3. Day-14 fatigue improvement

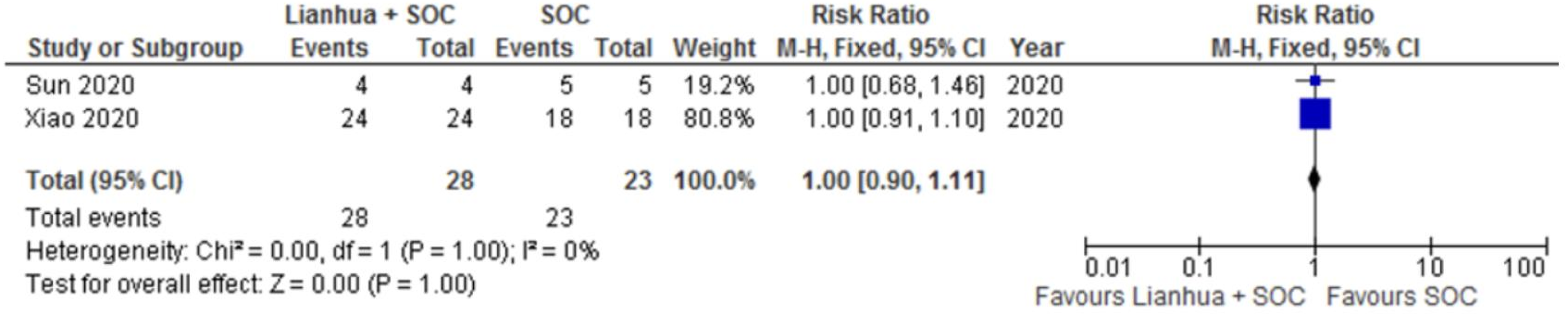

Figure 4. Day-14 fever improvement

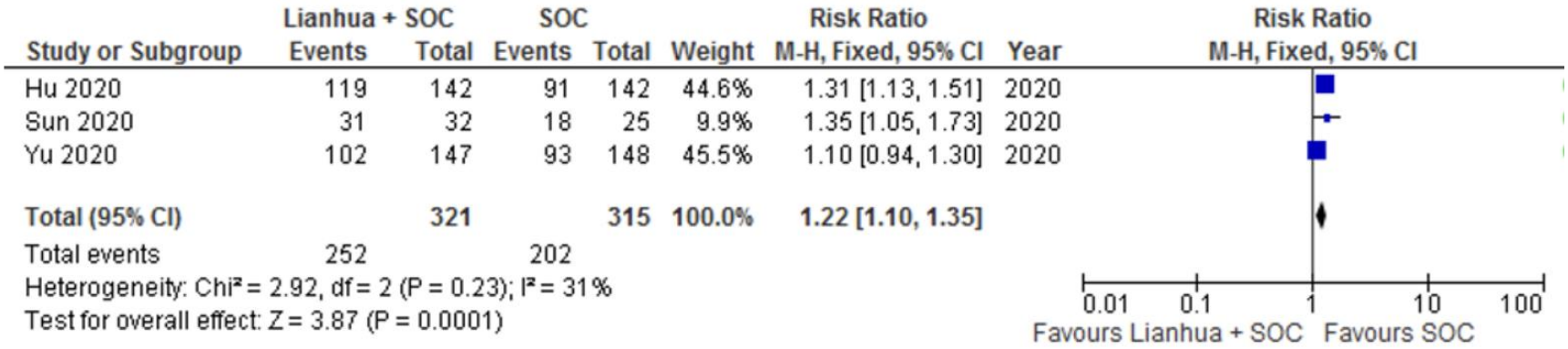

Figure 5. Chest CT improvement

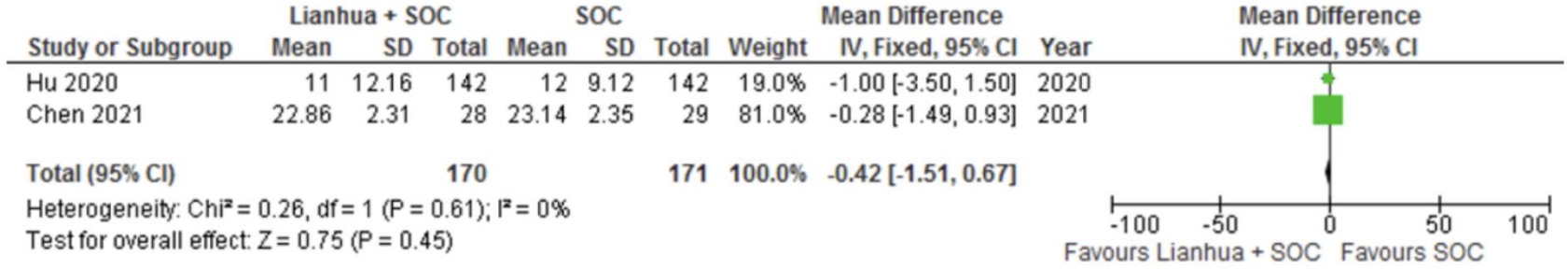

Figure 6. Negative Conversion Time

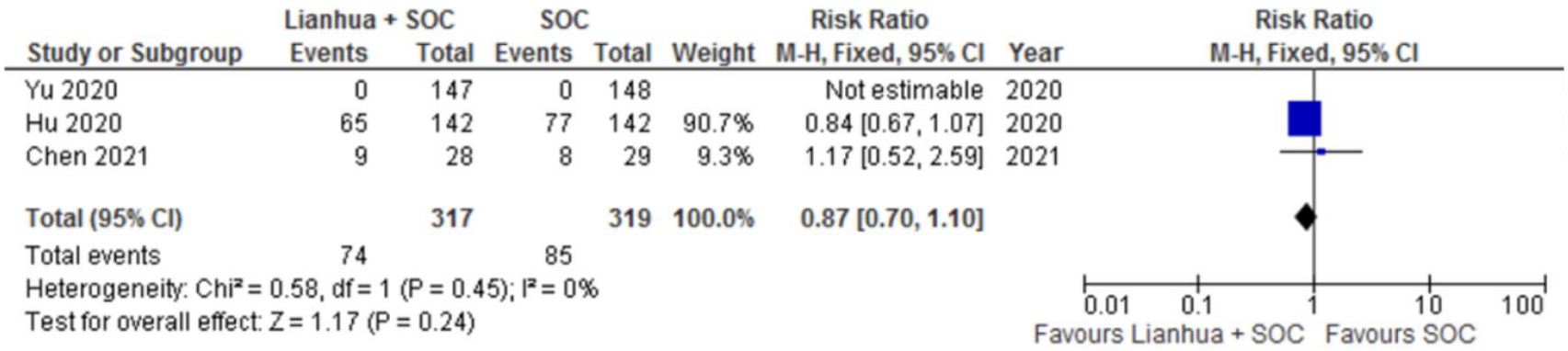

Figure 7. Adverse Events

Appendix 8. Characteristics of Ongoing Studies

Title	Population	Interventions	Characteristics	Outcome Measures
ChiCTR2000029433 A randomized, open-label, blank-controlled, multi-center clinical study for Lian-Hua Qing-Wen Capsule/Granule in the treatment of suspected novel coronavirus pneumonia	Symptomatic (any of the ff: fever, cough, fatigue) patients ≥ 18 years old	Routine treatment + Lianhua Qingwen 4 caps/1 bag TID	N = 240 Equally divided to both arms Allocation: Randomized Intervention Model: Parallel Assignment Masking: none	Primary: clinical symptoms recovery rate and recovery time Secondary: single symptom disappearance rate and main symptom disappearance time, proportion of aggravation during treatment, rate of CT improvement, disease recovery rate, routine blood test, biochemical indicators
ChiCTR2100042066 A randomized, open-label, blank-controlled, multi-center clinical study for Lian-Hua Qing-Wen Capsule/Granule in the treatment of asymptomatic patients with novel coronavirus pneumonia	Asymptomatically infected patients discovered through pathogenic testing ≥ 18 years old	Lian-Hua Qing-Wen Capsule/Granule	N = 120 Equally divided to both arms Allocation: Randomized Intervention Model: Parallel Assignment Masking: none	Primary: Time and rate of nucleic acid turning negative Secondary: clinical symptom and severity Clinical symptoms appearance time and proportion Proportion of mild and common cases diagnosed duting isolation/observation period
NCT04433013 A Randomized Controlled Trial Assessing the Efficacy of Lianhua Qingwen as an Adjuvant Treatment in Patients with Mild Symptoms of COVID-19	Symptomatic (≥1 symptom) patients ≥ 21 years old with confirmed COVID-19 by pathogenic testing	LHQW capsules 4 capsules, TID	N = 300 Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor	Primary: Proportion of participants who test negative for COVID-19 Secondary: Time taken in days for relief of clinical symptoms, proportion of participants with mild symptoms of COVID-19 progressing to moderate or severe illness, proportion of participants who test positive for COVID-19 with Ct value>30
ChiCTR2100042069 A randomized, open-label, blank-controlled, multi-center clinical study for Lian-Hua Qing-Ke Tablets in the treatment of COVID-19 patients with mild and common-type	Symptomatic (any of the ff: fever, cough, fatigue) patients ≥ 18 years old with confirmed COVID-19 by pathogenic testing	Routine treatment + Lian-Hua Qing-Ke tablets	N = 120 Equally divided to both arms Allocation: Randomized Intervention Model: Parallel Assignment Masking: none	Primary: clinical symptoms recovery rate and recovery time Secondary: single symptom disappearance rate and main symptom disappearance time, changes in color, quality, and quantity of sputum in patients with expectoration, proportion of aggravation during treatment, rate of CT improvement, disease recovery rate, time and rate of coronavirus becoming negative
ChiCTR2100042068 A randomized, open-label, blank-controlled, multi-center clinical study for Lian-Hua Qing-Ke Tablets in the treatment of severe novel coronavirus pneumonia	Patients ≥18 years old with confirmed COVID-19 by pathogenic testing and severe COVID-19 pneumonia	Routine treatment + Lian-Hua Qing-Ke tablets	N = 20 Equally divided to both arms Allocation: Randomized Intervention Model: Parallel Assignment Masking: none	Primary: time to clinical improvement (censored at Day 28) Secondary: improvement time of clinical symptoms, changes of oxygenation index in blood gas analysis, duration of mechanical ventilation, duration of supplemental oxygen, time to RT-PCR negativity, all-cause mortality

Appendix 9. Characteristics of the systematic reviews retrieved through citation search

Study and Impact Factor	Country of authors	Cochrane review or not?	Is funding present?	Is there prospective registration or protocol publication?	Number of included studies in the review	Total sample size (number of participants included)	Are meta-analyses done?	Intervention	Comparison	Outcomes
Wang et al., 2021 IF: 4.4	China	No	No	Yes	25 RCTs	2,222	Yes	Chinese medicine interventions alone or combined with other treatments	Placebo, standard medication treatment, and usual care	Primary: improved clinical cure and the negativity of the SARS-CoV-2 nucleic acid test Secondary: 1) clinical deterioration, 2) incidence of unfavorable clinical events of acute respiratory distress syndrome (ARDS), mechanical ventilation, and intensive care unit (ICU) admission, 3) death 4) time to fever clearance, 5) duration of hospital stay, and 6) chest imaging improvement
Shi et al., 2021 IF: 3.885	China	No	Yes	Yes	19 RCTs 29 observational with control arm	2,696 – CHM 2,008 - SOC	Yes	CHM + standard pharmacotherapy.	standard pharmacotherapy alone or standard pharmaco-therapy plus placebo	Primary: GI symptom improvement and liver function Secondary: Sggravation of COVID-19, time to viral assay conversion
He et al., 2021 IF: N/A; preprint	China	No	No	Yes	6 RCTs 3 case control	1,163	Yes	Lianhua Qingwen + western medicine	Western medicine alone	Clinical effective rate, chest CT disappearance rate of fever, cough, and fatigue, duration of fever; progress into severe clinical disease; adverse events.

*CHM – Chinese herbal medicine

*Chinese medicine interventions include Chinese medicine formulas (e.g., Qingfei Paidu decoction, Huashi Baidu formula, and Xuanfei Baidu formula), Chinese patented medicine (e.g., Jinhua Qinggan granule and Lianhua Qingwen capsule), and Chinese medicine injections (e.g., Xuebijing and Xiyanping injections)

* Frontiers in Pharmacology

* International Union of Biochemistry and Molecular Biology (IUBMB) Life

Appendix 10. Evaluation of the systematic reviews retrieved using AMSTAR-2 tool

AMSTAR 2 Questions	Wang et al., 2021	Shi et al., 2021	He et al., 2021
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y	Y	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y	Y	Y
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Y	Y	N
4. Did the review authors use a comprehensive literature search strategy?	Y	Y	PY
5. Did the review authors perform study selection in duplicate?	Y	Y	Y
6. Did the review authors perform data extraction in duplicate?	Y	Y	Y
7. Did the review authors provide a list of excluded studies and justify the exclusions?	PY	PY	PY
8. Did the review authors describe the included studies in adequate detail?	Y	Y	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y	PY	Y
10. Did the review authors report on the sources of funding for the studies included in the review?	N	N	N
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Y	Y	Y
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y	Y	N
13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Y	Y	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y	Y	Y
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y	Y	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Y	Y	Y
Rate of overall confidence	High	High	Moderate

Q31. Should famotidine be used in the treatment of patients with COVID-19 infection?

As of 30 May 2021

RECOMMENDATION

We suggest against the use of famotidine in the treatment of COVID-19. *(Very low certainty of evidence, Weak recommendation)*

Consensus Issues
No issue was raised during the consensus panel meeting.

KEY FINDINGS

Very low-quality evidence from seven retrospective cohort studies was found on the use of famotidine for the treatment of COVID-19. There was no significant reduction in the risk of mortality, mechanical ventilation, and composite outcome of mortality or mechanical ventilation. However, there was a significant increase in the risk of the composite outcome of mortality, mechanical ventilation, and intensive care unit admission. Adverse events were not examined in these retrospective cohort studies.

INTRODUCTION

Famotidine is a histamine H2 receptor antagonist and inverse agonist currently being used as alternative treatment for gastroesophageal reflux disease (GERD), hypersecretory disorders, non-ulcer dyspepsia, and benign gastric and duodenal ulceration. The H2 receptor, aside from its well-known role in gastric secretion, is also expressed by mast cells, which release pro-inflammatory cytokines that promote lung damage [1] and increase in number in the alveoli of severe acute coronavirus-2 (SARS-CoV-2)-infected patients. [2] It has recently become a drug of interest in the treatment of coronavirus disease 2019 (COVID-19). The mechanism of action for famotidine in this regard is currently unclear; however, it has been shown to inhibit neither (SARS-CoV-2) proteases nor SARS-CoV-2 infection and replication in cultured cells [1,3] and may instead act through direct H2 receptor inhibition [1]. This study investigated the effect of famotidine compared to placebo or standard-of-care treatment in influencing clinical outcomes of patients with confirmed COVID-19.

METHODS

A database search of MEDLINE and Cochrane CENTRAL with a combination of free-text and MeSH terms including "COVID-19" and "famotidine" was done to search for randomized controlled trials, cohort studies, systematic reviews, and meta-analyses that report the effect of famotidine compared to placebo or standard of care in the management of COVID-19 patients. Preprints were obtained by searching the medRxiv, bioRxiv, and ChinaXiv databases, and ongoing clinical trials were searched in ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, and the Chinese Clinical Trials Registry. These were supplemented by searches in the COVID-NMA living database and the COVID-19 Living Evidence Database, the latter of which includes articles from Embase. The final search date was on May 2, 2021.

No restrictions on patient COVID-19 severity status, treatment outcome, country, or language were. Studies that were not original research, in-vitro studies, case-control studies and case series, studies combining famotidine with another drug, and those

that compare famotidine to treatments that are not placebo or standard of care were excluded.

Included studies were appraised for risk of bias using the Newcastle-Ottawa Scale for cohort studies [4]. Data extracted included country, study design, patient profile, sample size (famotidine and non-famotidine groups), patient age and sex ratio, primary outcome, and reported hazard ratio (HR) or odds ratio (OR). Whenever possible, the review used HR and OR estimates reported after adjustment of study groups to minimize the risk of bias due to confounders [5]. All data were analyzed using Review Manager 5.4 (Cochrane Collaboration).

RESULTS

Characteristics of included studies

Seven studies were obtained following the database search, with a total sample size of 42,459 (Appendix 1). All studies used data retrospectively obtained from either a single-center database [6,7] or a database spanning multiple centers [8-12]. A total of 4022 patients (median = 519, range 23-1623) were enrolled in the famotidine group, and 38437 (median = 1536, range 795-24404) in the non-famotidine group.

Methodological quality

Four studies (57%) had a Newcastle-Ottawa score of 9/9 [6,10-12], while three studies (43%) had a score of 8/9 [7-9], indicating low risk of bias across the included studies. Three studies [8-9,12] did not conclusively demonstrate that the specified treatment outcomes were not present at the start of the study, while one [7] did not specify the length of follow-up for recruited patients.

Efficacy and safety

Four categories of efficacy outcomes were reported by the included studies: 1) mortality, 2) need for mechanical ventilation (MV), 3) a composite of mortality or MV, and 4) a composite of mortality, MV, and ICU admission (Appendix 1**)**. Pooled estimates were not obtained for outcome categories with multiple studies as they reported both HR and OR. Four studies reported HR or OR for all-cause mortality [7,9-11]; of these, one study reported that famotidine significantly reduced the risk of mortality [7], while three reported no effect [9-11]. One study [9] reported data for MV only, with an aOR of 0.469 (95% CI 0.228-0.965). Three studies [6,9-10] reported HR or OR for a composite of death or MV; two studies reported a significant decrease in risk with famotidine [6,9], although their sample sizes were small compared with the third study, which reported no effect [10]. Two studies [8,12] reported HR for a composite of mortality, MV, and ICU admission; of these, one study reported no effect for famotidine [8], although the second study, which used the same database but with an expanded search date range, reported a significant decrease in risk [12]. Adverse events were not examined in these retrospective cohort studies.

Table 1. Effect size of famotidine per outcome category.

STUDY ID	FAMOTIDINE	NO FAMOTIDINE	EFFECT SIZE (95% CI)	ASSOCIATION
IN-HOSPITAL MORTALITY				
Mather 2020	83	795	aOR 0.366 (0.155-0.862)	No effect
Mura 2021	563	816	aOR 0.73 (0.57-0.94)	Decreased risk
Shoaibi 2020	1623	24404	aHR 1.03 (0.89-1.18)	No effect
Yeramaneni 2020	1127	6031	aOR 1.59 (0.94-2.71)	No effect
MECHANICAL VENTILATION				
Mather 2020	83	795	aOR 0.469 (0.228-0.965)	Decreased risk
COMPOSITE OF MORTALITY AND MECHANICAL VENTILATION				
Freedberg 2020	84	1536	aHR 0.43 (0.21-0.88)	Decreased risk
Mather 2020	83	795	aOR 0.469 (0.228-0.965)	Decreased risk
Shoaibi 2020	1623	24404	aHR 1.03 (0.95-1.15)	No effect
COMPOSITE OF MORTALITY, MECHANICAL VENTILATION, AND ICU ADMISSION				
Cheung 2021	23	929	aOR 1.34 (0.24-6.06)	No effect
Zhou 2020	519	3926	aHR 1.81 (1.28-2.58)	Increased risk

**aOR – adjusted odds ratio; aHR – adjusted hazards ratio*

RECOMMENDATIONS FROM OTHER GROUPS

The Infectious Disease Society of America released a guideline on famotidine for hospitalized patients dated June 2020. Based on one non-randomized study, the society recommends against famotidine use for the sole purpose of treating COVID-19 outside the context of a clinical trial [13].

RESEARCH GAPS

Data from randomized controlled trials (RCTs) are needed to determine the efficacy of famotidine in treating COVID-19. To this end, 4 clinical trials, including 3 RCTs, are currently being run (Appendix 3).

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Appendix 1. Characteristics of Included Studies

STUDY ID	COUNTRY	STUDY DESIGN	PATIENT PROFILE	SAMPLE SIZE		PATIENT AGE AND SEX RATIO	FAMOTIDINE EXPOSURE	CO-INTERVENTIONS	PRIMARY OUTCOME	NEWCASTLE-OTTAWA SCORE
				FAMOTIDINE	NON-FAMOTIDINE					
Cheung 2021	Hong Kong	Multi-center retrospective cohort study	Adult patients diagnosed with COVID-19 from January 1 to May 10, 2020	23	929	N/A	N/A	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, statins, prednisolone	Severe disease, defined as: 1) Critical complication (respiratory failure, septic shock, and/or multiple organ dysfunction) 2) Ventilatory support 3) ICU admission 4) Mortality	8
Freedberg 2020	United States	Single-center retrospective cohort study	Patients testing positive for SARS-CoV-2 within 72 h after hospital admission	84	1536	Mean age 67 +/- 16 years 54.7% male, 45.3% female	PO (72%) IV (28% of total): 10 mg/d (17%), 20 mg/d (47%), 40 mg/d (35%) Median dose: 136 mg, 5.8 days	N/A	Death or intubation by hospital day 30	9
Mather 2020	United States	Multi-center retrospective cohort study	COVID-19-positive patients requiring hospital admission	83	795	55.7% female, 44.3% male	66.3% intake during admission only, 28.9% before and during admission, 4.8% before admission only PO (83% of total): 20 mg/d (95.2%), 40 mg/d (4.8%) IV (17% of total): 20 mg/2 mL solution Median inpatient dose: 80 mg, 4 d	Hydroxychloroquine, azithromycin, remdesivir, corticosteroids	In-hospital mortality, mechanical ventilation, intubation-free survival	8
Mura 2021	Multinational (30 countries)	Single-center retrospective cohort study	Patients with severe COVID-19 requiring ventilatory support	563	816	N/A	N/A	N/A	All-cause mortality	8
Shoaibi 2020	United States	Multi-center retrospective cohort study	Hospitalized adult patients with COVID-19	1623	24404	N/A	On the day of admission: 20 mg (73.29%), 40 mg (20.59%) 63.6% PO, 39.04% IV, 1.4% both	N/A	Mortality, or combination of mortality and intensive services (mechanical ventilation, tracheostomy or ECMO)	9

Yeramaneni 2020	United States	Multi-center retrospective cohort study	Hospitalized patients with COVID-19	1127	6031	Mean age 57.9 +/- 19.3 years 50.9% female, 49.1% male 44.6% white, 25.2% black	PO or IV within 24 h of admission	Azithromycin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, remdesivir, tocilizumab, corticosteroids	All-cause mortality by hospital day 30	9
Zhou 2020	Hong Kong	Multi-center retrospective cohort study	Adult patients diagnosed with COVID-19 from January 1 to August 22, 2020	519	3926	Median age 44.8 years 50% male, 50% female	Famotidine group = median age 60.4, 46.62% male Non-famotidine group = median age 42.3, 50.61% male		Need for ICU admission, intubation, or death	8

Appendix 2. GRADE Summary of Evidence

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	famotidine	no famotidine	Relative (95% CI)	Absolute (95% CI)		
In-hospital mortality												
4	observational studies	not serious	serious [a]	not serious	serious [b]	none	Two studies (Mather et al, Mura et al) reported decreased odds, while two studies (Shoaibi et al, Yeramaneni et al) reported no change in risk or odds.				⨁◯◯◯ VERY LOW	
Mechanical ventilation												
1	observational studies	not serious	not serious	not serious	not serious	none	18/83 (21.7%)	221/795 (27.8%)	**OR 0.469** (0.228 to 0.965)	**125 fewer per 1,000** (from 197 fewer to 7 fewer)	⨁⨁◯◯ LOW	
In-hospital mortality and mechanical ventilation												
3	observational studies	not serious	not serious	not serious	serious [b]	none	Two studies (Freedberg et al, Mather et al) reported decreased odds or risk, while one study (Shoaibi et al) reported no change in odds.				⨁◯◯◯ VERY LOW	
In-hospital mortality, mechanical ventilation, and ICU admission												
2	observational studies	not serious	not serious	not serious	serious [b]	none	One study (Zhou et al) reported increased risk, while the other (Cheung et al) reported no change in odds.				⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. One study (Mura 2020) included only patients with severe disease requiring ventilatory support, while the others included hospitalized patients only.

b. Narrative synthesis conducted, estimates not precise.

Appendix 3. Characteristics of Ongoing Trials

Clinical Trial Identifier (Location)	Official Title	Methodology	Outcome Measures	Population	Estimated Date of Completion
NCT04724720 United States	A Randomized, Double-Blind, Comparative Trial of the Safety and Efficacy of Famotidine vs Placebo for the Treatment of Non-Hospitalized Symptomatic Adults With COVID-19	Randomized, Double-Blind Comparative Placebo Controlled Trial	**Primary outcome:** Cumulative incidence of symptom resolution [Time Frame: Day 28] **Secondary outcomes:** Cumulative incidence of symptom resolution [Time Frame: Day 60] Relative change of symptoms Assessment of serious adverse events Clinical improvement Improvement in peripheral oxygen saturation Mortality Comparative proportions of hospitalized patients Change in systemic inflammation (CRP, procalcitonin, ferritin	56 non-hospitalized symptomatic adults with COVID-19	December 2021
NCT04565392 United States	Proof-of-concept Randomized Placebo-controlled Trial of Famotidine for Outpatients With COVID-19	Parallel double-blind placebo-controlled interventional trial	**Primary outcomes:** Clinical course binary outcome Serious adverse events **Secondary outcomes:** 30- and 60-day follow-up of: Time to symptomatic recovery Self-check list of 18 COVID-19 symptoms Patient's global impression of change Adverse events	150 adult patients with COVID-19 symptoms	January 31, 2022
NCT04834752 South Korea	Effect of Histamine 2 Receptor Antagonist (H2RA) and Proton Pump Inhibitor (PPI) on the Positivity Rates and Clinical Outcomes of Coronavirus Disease-19 (COVID-19).	Multi-center retrospective cohort study	**Primary outcomes:** COVID-19 test positivity Mortality at 60 days **Secondary outcomes**: ICU admission rate Mechanical ventilator application rate Oxygen support application rate Rates of vasopressor and inotrope use	400000 adult patients testing for COVID-19	December 31, 2021
IRCT20200509047364N2 Iran	The effect of Famotidine on the improvement of patients with COVID-19	Randomized single-blind comparative placebo clinical trial	Respiratory rate Oxygen saturation state Lung infiltration status LDH, CRP levels Lymphocyte, platelet counts Patient temperature Length of hospitalization Length of ICU admission	20 confirmed COVID-19 patients	N/A

Q32. Should ibuprofen be used in the treatment of patients with COVID-19 infection?

As of 5 March 2021

RECOMMENDATION

We recommend against the use of ibuprofen as treatment in patients with COVID-19 infection. *(Very low certainty of evidence, Strong recommendation)*

Consensus Issues
It is important to note that this recommendation is strictly for the use of ibuprofen in the treatment of COVID-19 infection and should not be confused with another living recommendation pertaining to the effect of the concurrent use of ibuprofen with other COVID-19 outcomes.

Although direct evidence of very low quality suggests a trend towards benefit, there was indirect evidence of possible harm. The benefit that was seen from the first study might not be solely because of ibuprofen given that other patients were given other medications. The severity of COVID-19 infection was not also specified in the first study and it was assumed that it included patients of all severity (i.e., mild, moderate, severe) since the information were taken from electronic health records of different hospitals.

KEY FINDINGS

Currently, there are no randomized controlled trials that assessed the efficacy of ibuprofen as a treatment for COVID-19. Based on the two observational studies (one retrospective cohort and one case series) that have not been peer-reviewed, there is limited evidence that ibuprofen treatment could improve COVID-19 symptoms and outcomes.

INTRODUCTION

The 2019-nCOV belongs to a family of viruses with positive-sense single stranded RNA genome with a lipid envelope in its structure [1]. Ibuprofen in vitro has demonstrated viricidal activity against enveloped viruses [2]. Several studies have demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) including ibuprofen can alter adherence, degranulation and phagocytosis and production of reactive oxygen species (ROS) by polymorphonuclear neutrophils (PMNs). In addition, treatment with ibuprofen, flurbiprofen, and indomethacin led to a significantly reduced migration of leukocytes and volume of exudates in acute pleural effusion [3-6]. Moreover, NSAIDs could also reduce local release of pro-inflammatory cytokines through the effect on cyclooxygenases [7-11]. Its anti-inflammatory effects led to the hypothesis that ibuprofen could aid in the treatment of cytokine storm.

REVIEW METHODS

Eligible articles were appraised using the Painless Evidence-Based Medicine book by Dans et al. evaluating directness, validity and applicability using the following:

Population	COVID-19 patients
Intervention/Exposure	Ibuprofen
Comparison	Usual standard of care or placebo
Outcomes	Clinical Improvement (i.e. decrease in hospitalization rate, decrease in duration of hospital stay, decreased oxygen requirement, decrease in mortality rate)
Methodological filter	Randomized controlled trials (RCT), observational clinical studies, systematic review and meta-analysis available, case series

RESULTS

Characteristics of included studies

A retrospective cohort study done by Castro et. Al. [12] identified common pharmacotherapies associated with reduced COVID-19 morbidity using electronic health records. They included 7,360 patients from six hospitals in Massachusetts, USA. Data of the patients including medication exposure were obtained from electronic health records in the one year to 30 days prior to presentation to the emergency department. The primary outcome was hospitalization among COVID-19 positive patients and the secondary outcomes were intensive care unit (ICU) admission and death among those COVID-19 patients who were hospitalized.

After adjusting for age, sex, race, ethnicity, site and Charlson score, ibuprofen was one of the prescribed medications associated with lower hospitalization rate (odds ratio (OR) 0.73; 95% confidence interval (CI), 0.64 to 0.84). Furthermore, ibuprofen was also associated with a significantly decreased odds of requiring ICU (OR, 0.70; 95% CI, 0.56 to 0.86), and mortality (OR, 0.73; 95% CI; 0.56 to 0.96). No adverse events were reported in the study.

The observational nature of this study makes it difficult to ascertain if it was ibuprofen intake that caused such reductions in hospitalization, ICU admission and mortality. Patients were not randomized hence other confounders that could not be controlled could have led to these effects. Also, the investigators only extracted data through electronic health records and actual intake of the medications could not be assured. Moreover, they only noted intake of the medications from one year to 30 days prior to the presentation and not while the patients were having COVID-19 infection. This study is a pre-print version and not peer reviewed.

A case series done by Kelleni et al [13] included 17 COVID-19 confirmed or suspected Egyptian patients who were living in the Kingdom of Saudi Arabia (KSA). Among the 17 patients were 7 males, 5 females, 2 pregnant patients and 3 pediatric patients. The author used his own treatment protocol that includes nitazoxanide, azithromycin and ibuprofen or diclofenac which were given in different combinations as dictated by his own judgment. He also allowed some of the patients to have concurrent intake of vitamin C and zinc and any other food supplements. He classified all of these patients as improved, however, there was no specific criteria for the improvement in symptoms and he based it on patients' subjective feeling of improvement as well as lysis of fever, resolution of sore throat, dyspnea, cough and diarrhea. He also noted improvement in the lymphocyte and neutrophil counts. In this case series, there was no report of adverse drug reactions. This study has a lot of biases. This is a non-randomized

controlled study hence, the improvement noted in these patients could just be due to chance. Patients included in the study seemed to have mild to moderate severity of infection and they could have improved even without giving the medications. The exposure to treatment was also based on the author's judgment. In addition to this, the patients and the outcome assessor which is also the author were not blinded so there could also be performance bias and observer bias. The author included patients who were not tested for COVID-19 and just assumed that they were infected based on exposure and symptoms so we cannot ascertain if they really had COVID-19 infection. Also, there was no individual description of cases written in the report. This study is a pre-print version and not peer reviewed

Indirect evidence for harm

A systematic review was done by Philipsborn et. al. among patients with viral respiratory infection exposed to NSAIDs. Studies on (1) patients of any age;(2) with viral respiratory infections or conditions commonly caused respiratory viruses; and, (3) exposed to systemic NSAIDS of any kind reporting on acute severe adverse events, acute healthcare utilization, explicit quality of life measures and long-term survival were included. They searched MEDLINE, EMBASE, WHO-COVID Database, Scopus and references of existing reviews and included studies. A total of 87 eligible studies were included (72 RCTs, 7 cohort, 3 case-cross-over studies, 3 non RCTs, 1 case-control study and 1 case series) with a total of 172,831 patients and median follow up of 3 days. They were not able to identify any study on COVID-19, SARS or MERS that meets the eligibility criteria. Data extraction and quality assessment of included studies were done by one author only. They used tools Assess Risk of Bias for Case Control Studies, Cochrane risk of Bias tool and GRADE.

In one retrospective cohort study among 683 adults, the effects of NSAID on mortality in critically ill adults with influenza during the 2009/2010H1N1 influenza pandemic are unclear (adjusted RR (aRR): 0.9, 95%CI: 0.5 to 1.6). The confidence interval is wide and includes the possibility of a negative, null or positive effect. This evidence was graded as very low certainty.

Two case cross-over studies in 9793 patients with myocardial infarction and 29,518 patients with ischaemic or haemorrhagic stroke assessed effects on cardiovascular events, and showed higher ORs for the combined exposure to NSAIDs and acute respiratory infection than acute respiratory or NSAIDs alone. For ischemic stroke, the risk associated with NSAID use and ARI episode reported aOR=2.27 (95% CI: 2.00 to 2.58); for hemorrhagic stroke it was aOR=2.28 (95% CI: 1.71 to 3.02), and for myocardial infarction the risk associated with NSAID use and ARI episode was aOR=3.41 (95% CI: 2.80 to 4.16). Other adverse events noted in 28 RCTs and two cohort studies included nausea, dyspepsia, urticaria, syncopation, pneumonia, meningitis, peritonsillar abscess, abdominal pain, drowsiness and lightheadedness.

Among critically-ill children with H1N1 influenza, there was an unclear effect of NSAIDs on mortality (aRR 1.5, 95% CI: 0.7 to 3.2; very low certainty evidence). Other adverse events noted among children with viral respiratory infection given NSAIDs were empyema and gastrointestinal bleeding. This study has not been peer-reviewed. This was considered indirect evidence because the patients in this study had other viral respiratory infections and not COVID-19. In addition to this the exposure of interest was NSAID in general and not ibuprofen. As to reproducibility, only one author

did the data extraction and quality assessment. There is also a note of selection bias because they only included articles with study designs most capable of detecting rare severe adverse events. There is also channeling bias in the studies included wherein patients who are critically ill and with more severe symptoms were more likely to be given NSAIDS which could have contributed to the results.

There were no RCTs found in the search but only two observational studies which were pre-print and not peer reviewed. One systematic review on the use of ibuprofen on patients with viral respiratory infection included showed possible harm. This was considered indirect because the study did not include patients with MERS, SARS and COVID. The results of these studies were of very low certainty.

RECOMMENDATIONS FROM OTHER GROUPS

Currently there are no clinical practice guidelines that recommend the use of ibuprofen as treatment for COVID-19.

RESEARCH GAPS

There are currently 5 ongoing clinical trials. (refer to Appendix 4).

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Appendix 1. Characteristics of Included Studies

Author, Year	Patients (n)	Intervention	Comparator	Outcomes
Castro et al, 2020	COVID-19 confirmed patients (n=7,360)	Pharmacotherapies identified to be used among patients with COVID-19 including iburpofen	no Ibuprofen	Ibuprofen was one of the prescribed medications associated with lower hospitalization rate (odds ratio (OR), 0.73; 95% confidence interval (CI), 0.64 to 0.84). Furthermore, ibuprofen was also associated with a significantly decreased odds of requiring ICU (OR, 0.70; 95% CI, 0.56 to 0.86) and mortality (OR, 0.73; 95% CI; 0.56 to 0.96).
Kelleni et al. 2020	COVID-19 patients confirmed/suspected n=17)	Nitazoxanide/Azithromycin/Ibuprofen or diclofenac	none	There was note of improvement and decrease in duration of symptoms. There was an increase in lymphocyte counts and decrease in neutrophil count

Appendix 2: GRADE Evidence Profile

Summary of findings:

Ibuprofen compared to Placebo or usual care for COVID-19

Patient or population: COVID-19
Setting:
Intervention: Ibuprofen
Comparison: Placebo or usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo or usual care	Risk with Ibuprofen				
Hospitalization follow up: 4 months	527 per 1,000	**449 per 1,000** (417 to 484)	**OR 0.73** (0.64 to 0.84)	7360 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	
ICU admission	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 0.70** (0.56 to 0.86)	7360 (1 observational study)	⨁◯◯◯ VERY LOW [a,b,c]	
Mortality	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 0.73** (0.56 to 0.96)	7360 (1 observational study)	-	
Resolution of symptoms	All patients improved			17 (1 observational study)	⨁◯◯◯ VERY LOW [d,e]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The data were extracted only from electronic health record hence actual intake of medications were not assured. No mention on the severity of cases and the reasons for admission were based only on the physicians' clinical judgment. They did not indicate whether the exposure to medication was during the time when the patients were infected with COVID-19.
b. the exposure to the medication was 1 year to 30 days prior to the patient presenting at the emergency department
c. Confounding by indication
d. The author combined ibuprofen with other medications, no strict protocol with regards to treatment which the author based on his own judgments. Patients and outcome assessors were not blinded
e. the author included patients who were not confirmed cases of COVID-19 (i.e. no RT PCR done and only based it on symptoms plus exposure of patients

Appendix 3: Summary of Findings Table (Indirect Evidence)

Outcomes	Effect Estimate	95% Confidence Interval	Basis	Certainty of evidence
Mortality	RR, 0.90	0.50 to 1.60	1 retrospective registry based cohort study (683)	Uncertain, Very Low[ab]
Ischemic Stroke	RR, 2.27	2.00 to 2.58	1 case-crossover study (23,618)	Harmful, Very Low[ab]
Hemorrhagic Stroke	RR, 2.28	1.71 to 3.02	1 case-crossover study (5,900)	Harmful, Very Low[ab]
Myocardial infarction	RR, 3.41	2.80 to 4.16	1 case-crossover study (5,900)	Harmful, Very Low[ab]

a. studies included for this comparison were non randomized
b. downgraded by 1 level for imprecision

Appendix 4. Characteristics of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome
NCT04500639 Do Common Medications Alter the Course of COVID-19?	Observational, Case Control Propective Study	Canada	Patients tested for COVID-19	not provided	Ibuprofen exposure for symptom management
NCT04382768 Extended Compassionate Use Program (UCA) With Inhalational Ibuprofen in Patients With Acute Respiratory Pathology, Mediated by COVID-19	Interventional Open label Single group Assignment	Argentina	Patients with COVID-19	Inhaled ibuprofen and standard of care plus lipid ibuprofen 200mg	Primary outcome: 1. Time to clinical improvement 2. Change to Negativization of the swab Secondary Outcome: 1. Change in length of hospital stay 2. duration of ventilation 3. critical care stay 4. Average score in National Early Warning (NEWS2) 5. Time from first dose to conversion to normal or mild pneumonia 6. Antibiotic requirement 7. Glucocorticoids requirement 8. Incidence of adverse event 9. Incidence of serious adverse event 10. Number of deaths from any cause at 28 days 11. Lymphocyte count
NCT04334629 Lipid Ibuprofen Versus Standard of Care for Acute Hypoxemic Respiratory Failure Due to COVID-19: a Multicentre, Randomised, Controlled Trial (LIBERATE)	Randomized, double blind, parallel assignment	United Kingdom	Adult patients with confirmed COVID-19 infection	Ibuprofen and Standard of Care	Primary Outcome: 1. Disease Progression 2. Time to Mechanical Ventilation Secondary Outcome: 1. Overall survival 2. Reduction in proportion of patients who require ventilation 3. Reduction in length of Critical Care stay 4. Reduction in length of Hospital stay 5. Modulation of serum pro- and anti-inflammatory cytokines 6. Reduction in duration of ventilation 7. Increase in ventilator-free days
NCT04383899 Role of Ibuprofen and Other Medicines on Severity of Coronavirus Disease 2019 (COVID-19) Infections: a Case-control Study	Case Control	France	Patients with COVID-19	Case and Control using a questionnaire	Describe and quantify medications used prior to admission associated with worse infection in COVID-19


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