PHILIPPINE COVID-19 LIVING CLINICAL PRACTICE GUIDELINES

As of January 2022

CRITICAL CARE and RESPIRATORY MANAGEMENT for COVID-19

EVIDENCE and RECOMMENDATIONS

Implementing Agency:

Institute of Clinical Epidemiology, National Institutes of Health
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Cooperating Agency:

Philippine Society of Microbiology and Infectious Diseases

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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.

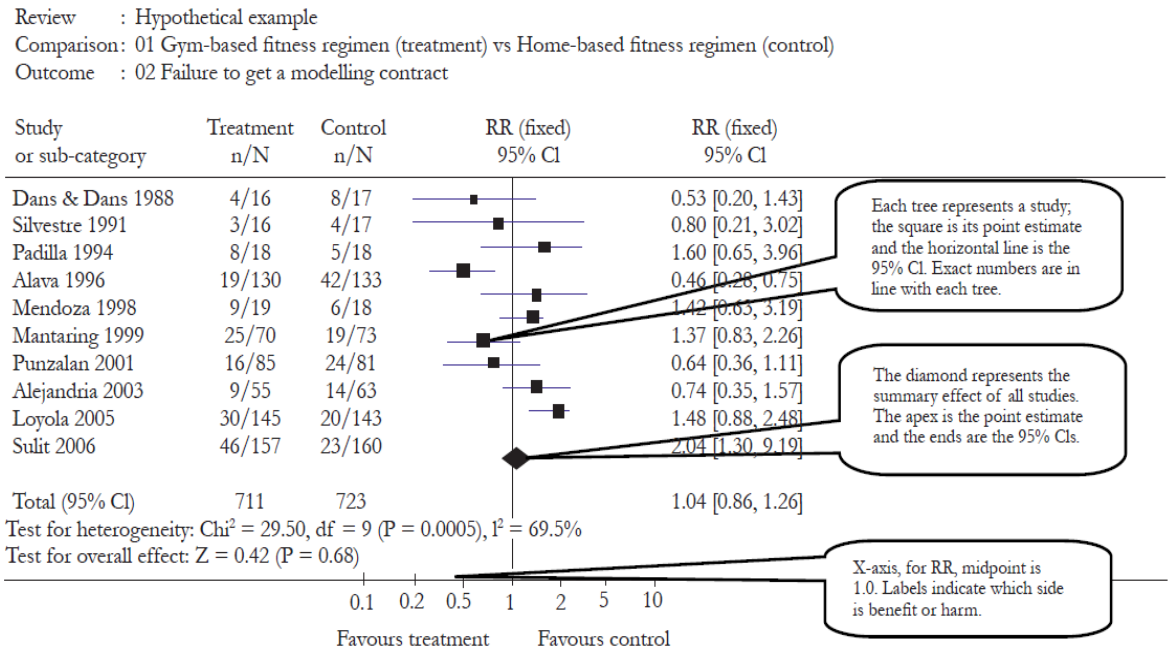


Figure 1. How to interpret forest plots

REFERENCE

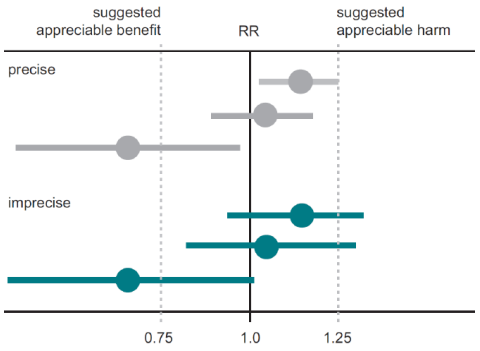
Dans, AL, et al. (2017). Painless Evidence-Based Medicine, 2nd Ed. UK: John Wiley & Sons Ltd.

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 critical care and respiratory management of COVID-19. The following key questions were addressed:

Q1. Should intravenous corticosteroids be used in COVID-19?

Q2. Should anticoagulation be used in treating patients diagnosed with COVID-19?

Q3. Should empiric antimicrobial coverage be given to patients with severe and critical COVID-19?

Q4. Should hemoperfusion be used in patients diagnosed with COVID-19?

Q5. Should a conservative fluid management strategy be used in mechanically ventilated adult COVID-19 patients?

Q6. Should side lying position be used in patients with severe to critical COVID-19? Should self-proning be used in non-intubated patients with severe COVID-19?

Q7. Should high flow nasal cannula be used for patients with COVID-19 and acute respiratory failure?

Q8. Should non-invasive ventilation be used over high flow nasal cannula for patients with severe and critical COVID-19?

Q9. Should lung protective ventilation, high PEEP and driving pressure-limited strategies be used in the management of adult patients with COVID-19-associated acute respiratory distress syndrome?

Q10. Should rapid sequence intubation or delayed sequence intubation be used for the management of COVID-19?

Q11. Should extracorporeal membrane oxygenation (ECMO) be used in the management of Acute Respiratory Distress Syndrome (ARDS) among COVID-19 patients?

Q12. Should hyperbaric oxygen therapy be used COVID-19 patients with hypoxemia?

Q13. Should sedation and neuromuscular blockade be done in mechanically ventilated patients with COVID-19-associated acute respiratory distress syndrome?

Q14. Should inhaled nitric oxide be used in patients with COVID-19?

Q15. Should etoposide be given among patients with severe COVID-19 pneumonia in cytokine storm?

Q16. Should pulmonary rehabilitation be done among long COVID patients with residual pulmonary symptoms to improve pulmonary function and quality of life?

Q17. Should pirfenidone versus nintedanib be used as therapy for post-COVID-19 pulmonary fibrosis?

Q1. Should intravenous corticosteroids be used in COVID-19?

As of 03 January 2022

RECOMMENDATIONS

We recommend the use of dexamethasone for up to 10 days among patients with severe and critical COVID-19. *(Moderate certainty of evidence; Strong recommendation)*

We recommend the use of 6 mg to 12 mg per day of dexamethasone among patients with severe and critical COVID-19. *(Moderate certainty of evidence; Strong recommendation)*

We recommend against the use of corticosteroids among mild and moderate (non-oxygen requiring) COVID-19 patients. *(Moderate certainty of evidence; Strong recommendation)*

We suggest that steroid therapy be initiated as soon as diagnosed or categorized as severe and critical COVID-19. *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues

The available data reviewed is still inconclusive to recommend high dose steroids for severe and critical COVID-19 patients. However, higher doses may still be considered since marginal benefit was found on ventilator-free days, cardiovascular-support free days, and renal replacement therapy-free days. Ideally, intravenous steroids are started for hospitalized patients but may be shifted to oral if deemed necessary or once able.

PREVIOUS RECOMMENDATION

We recommend the use of dexamethasone in patients with COVID-19 infection who require supplemental oxygenation (i.e., including high-flow device, non-invasive, invasive mechanical ventilation and ECMO). *(Moderate quality of evidence; Strong recommendation)*

We recommend against the use of systemic corticosteroids in patients with COVID-19 infection but not requiring oxygen supplementation. *(Moderate quality of evidence; Strong recommendation)*

Consensus Issues

Dexamethasone has a better pharmacokinetic profile (i.e., longer acting than hydrocortisone and methylprednisolone) and better anti-inflammatory effect as compared to other steroids with less corticoid effects (e.g., less water retention). Low-dose steroids (i.e., 6mg of dexamethasone) are preferred by physicians. As for other corticosteroids such as methylprednisolone and hydrocortisone, there is insufficient evidence to recommend its use in patients with COVID-19 infection who require supplemental oxygenation.

WHAT'S NEW IN THIS VERSION?

- This review update focused on the use of different corticosteroids on severe and critical COVID-19. Three new randomized controlled trials, which provided data on the use of methylprednisolone versus placebo, were added in this review.
- One randomized controlled trial comparing 12mg and 6mg dexamethasone showed no significant difference in all-cause mortality (RR 0.85, 95% CI 0.72-1.01; moderate certainty), life support-free days (MD 2.80 days, 95% CI -0.20-5.8; moderate certainty) and development of any adverse event (RR 0.84, 95% CI 0.60-1.18; moderate certainty).
- Seven cohort studies on the timing of administration of corticosteroids showed significant benefit when systemic corticosteroids were started early within 24 hours of diagnosis or categorization of severe to critical COVID-19 compared to non-early initiation beyond 24 hours (OR 0.68, 95% CI 0.51-0.92; I^2=0%; low certainty).

KEY FINDINGS

Fourteen randomized controlled trials (RCTs) provided data on the effect of different intravenous (IV) corticosteroids versus placebo or standard of care on all-cause mortality in severe and critical COVID-19 patients. Compared to placebo, only dexamethasone showed a statistically significant reduction in the risk of mortality. However, patients in this group had significantly longer duration of hospital stay. In terms of adverse events, no significant difference was found between the IV corticosteroids and control groups. No significant benefit on 28-day mortality and a tendency towards harm were observed when dexamethasone was given to COVID-19 patients who did not require oxygen therapy.

In comparing 12mg and 6mg dosing of dexamethasone, no significant differences were found in terms of all-cause mortality and life support-free days while marginal benefits in ventilator-free days, cardiovascular support-free days, and renal replacement therapy-free days were observed in the 12mg group. No significant difference in adverse events were observed between the two dosing regimens.

Seven retrospective cohort studies evaluated the effect in the timing of administration of different corticosteroids among severe and critical COVID-19 patients. Significant benefit was found only when systemic corticosteroids were started early within 24 hours of admission compared to non-early initiation beyond 24 hours. Mechanical ventilation was likewise significantly reduced when systemic corticosteroids were initiated within 24 hours of admission.

INTRODUCTION

The SARS-CoV-2 virus, the causative agent of COVID-19, is a highly transmissible and virulent organism responsible for the current global pandemic. Patients diagnosed with COVID-19, especially those ≥ 65 years old, who are smokers, and/or have comorbidities, are at risk for rapid deterioration and eventual need for hospital admission. This can be attributed to the body's inflammatory response which can release an excess of cytokines and inflammatory markers leading to organ damage such as acute respiratory distress syndrome (ARDS). Intravenous corticosteroids, a staple medication in the critical care setting, has been proven to have potent anti-inflammatory effects and has been used to treat other severe viral infections (e.g., SARS, MERS).[1] As it is a relatively affordable drug, it is readily accessible even in

low-income countries.[2] However, because of its serious side effects, such as immunosuppression, hyperglycemia, and fungal infection, due caution must be given when deciding to give this treatment. As hospitals and ICUs continue to admit COVID-19 cases, healthcare providers must further investigate the potential effects of IV corticosteroids on these patients.[1,3]. This review aims to evaluate the effectiveness and safety of intravenous corticosteroids in COVID-19 patients.

REVIEW METHODS

We searched Cochrane Library, PubMed, MEDLINE, Google Scholar, JSTOR, HERDIN, WHO ICTRP and ClinicalTrials.gov using a combined MeSH and free text search with the terms “SARS-CoV-2”, “COVID-19”, “severe”, “critical”, “intravenous”, “IV”, “systemic”, “dexamethasone”, “hydrocortisone”, “methylprednisolone”, “high dose”, “low dose”, “mortality”, “hospital length of stay”, “ICU length of stay”, “mechanical ventilation”, “organ support-free days” OR “adverse events”, “infection”, “superinfection”, “hyperglycemia”, and “gastrointestinal bleeding”. The study characteristics that were searched for were: Population – patients with severe or critical COVID-19; Intervention – IV corticosteroids; Comparator – standard care or placebo; Outcomes – mortality, length of hospital stay, length of ICU stay, organ support-free days, adverse events. Studies which recruited patients with moderately severe COVID-19 were included if the population was mixed with severely or critically ill patients. Randomized controlled trials were prioritized in the search; when none were found, non-randomized and observational studies were screened as well. When systematic reviews or meta-analyses were found, the individual studies were assessed for possible inclusion.

RESULTS

We found 16 RCTs which used different IV corticosteroids as treatment for COVID-19. A total of 3,004 COVID-19 patients with severe and critical illness were analyzed in this review.[4-19] The included studies either compared IV corticosteroid use with standard of care or placebo [4-17], compared two different IV corticosteroids [18], or compared different doses of the same IV corticosteroid.[19] The IV corticosteroids used were dexamethasone (4 RCTs)[5,7,11,13], hydrocortisone (3 RCTs)[4,6,14], methylprednisolone (8 RCTs)[7,8,10,12,15-18], and prednisolone (1 RCT).[9] Duration of use for each of the IV corticosteroids were reported (Range; Mean ± SD) as follows: DEX (10 days), HCT (7-14 days; 9.33 ± 3.3 days), MP (3-10 days; 5.25 ± 2.28 days), and PRDL (5 days). Characteristics of included studies are summarized in Appendix 3.

Type of Corticosteroids

Fourteen RCTs provided data on all-cause mortality. Results showed that there was a significant decrease in all-cause mortality in the corticosteroid groups (RR 0.87, 95% CI 0.78-0.97; I^2=14%; moderate certainty).[4-17]

Dexamethasone

Compared to placebo, only DEX group showed statistically significant benefit in decreasing the risk of mortality (RR 0.86, 95% CI 0.79-0.94; I^2=0%; moderate certainty)[2,4,8,10] and benefit in ventilator-free days (MD 2.26, 95% CI 0.2-2.38; moderate certainty).[5] However, patients in this group had significantly longer duration of hospital stay (MD 4.80 days, 95% CI 3.06-6.54; moderate certainty), and length of ICU stay (MD 4.2 days, 95% CI 3.26-5.14; high certainty).[11]

Other Corticosteroids: Hydrocortisone, Methylprednisolone, and Prednisolone
The HCT group (RR 0.85, 95% CI 0.50-1.44; I^2=51%; moderate certainty)[1,3,11], MP group (RR 0.82, 95% CI 0.59-1.16; I^2=38%; moderate certainty)[4,5,7,9,12,13], and PRDL group (RR 0.63, 95% CI 0.21-1.92; moderate certainty)[6] did not show any significant difference in terms of all-cause mortality. Likewise, COVID-19-related mortality did not differ significantly between the use of IV methylprednisolone corticosteroid and standard of care (RR 1.04; 95% CI 0.29-3.73; moderate certainty).[15]

Similarly, included studies which utilized HP, MP, and PRDL did not demonstrate significant difference for a majority of the other outcomes; namely, all-cause mortality in 28 days (HR 0.80, 95% CI 0.24-2.61; low certainty)[15], COVID-19-related mortality in 28 days (HR 0.96, 95% CI 0.24-3.84; low certainty)[15], clinical improvement in 28 days (HR 0.93, 95% CI 0.65-1.33; I^2=0%; low certainty)[15,16], ICU admission (RR 0.78, 95% CI 0.32-1.90; I^2=0%; low certainty)[9,16], need for endotracheal intubation (RR 0.69, 95% CI 0.40-1.18; I^2=0%; low certainty)[4,9], eventual extracorporeal membrane oxygenation (RR 0.96, 95% CI 0.14-6.64; moderate certainty)[4], and life support-free days (MD -12.68, 95% CI -40.28-14.92; I^2=95%; low certainty).[6,14] Regarding length of hospital stay, one study showed that patients given PRDL had significantly shorter stays when compared with the control group (MD -0.90 days, 95% CI -1.56 to -0.24; low certainty).[9] The pooled data for length of hospital stay did not show a significant difference between the MP group and the control group (MD -0.28 days, 95% CI -1.62-1.07; I^2=93%; low certainty).[9,12,15]

Overall Adverse Events
In terms of adverse events, there was no significant difference found between the IV corticosteroid and control groups (RR 0.95, 95% CI 0.86-1.05; I^2=0%; low certainty).[1,3-6,11] Specific adverse events such as development of nosocomial infection (RR 0.91, 95% CI 0.61-1.36; I^2=0%; low certainty)[4,8], shock (RR 0.17, 95% CI 0.01-3.32; low certainty)[8], need for insulin therapy (RR 1.20, 95% CI 0.99-1.46; moderate certainty)[9], and gastrointestinal symptoms (RR 0.91, 95% CI 0.47-1.78; I^2=0%; low certainty)[8,9] were likewise not significantly different between IV corticosteroids and control group or placebo.

Corticosteroids on Non-Oxygen-Requiring COVID-19 Patients
The RECOVERY Trial [13] provided a subgroup analysis on the mortality benefit of DEX among non-oxygen requiring COVID-19 patients. Result showed no 28-day mortality benefit and potential harm when DEX was given to COVID-19 patients who did not receive oxygen therapy at randomization (RR 1.19, 95% CI 0.92-1.55; moderate certainty).

Dosing of Corticosteroid: 12mg versus 6mg Dexamethasone
A multicenter, randomized controlled trial [19] assessed the effectiveness and safety of 12mg versus 6mg intravenous dexamethasone in 982 severe and critical COVID-19 patients. In this trial, 12mg dexamethasone (as intervention) was compared with the current standard dosing of 6mg (as control). Results showed marginal clinical benefit in terms of ventilator-free days (MD 1.00 day, 95% CI 0.21-1.79; high certainty), cardiovascular support-free days (MD 1.50 days, 95% CI 0.88-2.12; high certainty), and renal replacement therapy-free days (MD 1.10 days; 95% CI 0.66-1.54; high

certainty) with the use of the 12mg dosing regimen. No significant difference was found in terms of all-cause mortality (RR 0.85, 95% CI 0.72-1.01; moderate certainty) and life support-free days (MD 2.80 days, 95% CI -0.20-5.8; moderate certainty). Development of any adverse event (RR 0.84, 95% CI 0.60-1.18; moderate certainty), septic shock (RR 0.82, 95% CI 0.55-1.21; moderate certainty), and invasive fungal infection (RR 0.70, 95% CI 0.36-1.33; moderate certainty) were also not significantly different between 12mg and 6mg dosing regimens. However, a trend towards developing clinically significant gastrointestinal bleeding (RR 1.76, 95% CI 0.59-5.20; moderate certainty) was associated with the 12mg dosing regimen. Thus, current evidence still supports the use of the 6mg dosing regimen of dexamethasone on the basis of inconclusive effect on all-cause mortality and marginal clinical benefit in terms of organ support-free days with the use of the 12mg dosing regimen.

Timing of Administration of Corticosteroids

Seven retrospective cohort studies [20-26] were reviewed to evaluate the effect of timing of administration of different corticosteroids on in-hospital mortality, need for mechanical ventilation, and development of adverse events among severe and critical COVID-19 patients. Corticosteroids used in the studies were dexamethasone 8-16mg IV or PO, hydrocortisone 45-100mg IV, methylprednisolone 50mg IV, and prednisone 10-80mg PO. Duration of treatment from day of trial enrollment ranged from seven to ten days. Timing of initiation of corticosteroids was stratified into early versus non-early. Different cut-off times for early versus non-early or delayed initiation were used across seven studies. Two studies [20,21] provided data for ≤24 hours versus >24 hours, two studies [20,22] provided data for ≤48 hours versus >48 hours, three studies [20,23,24] provided data for ≤72 versus >72 hours, and one study [25] provided data for ≤120 hours versus >120 hours. Significant benefit was found only when systemic corticosteroids were started early within 24 hours of diagnosis of severe to critical COVID-19 or of admission compared to non-early initiation beyond 24 hours (OR 0.68, 95% CI 0.51-0.92; I^2=0%; low certainty).[20,21]

As initiation of systemic corticosteroids was further delayed at 48 hours (OR 0.98, 95% CI 0.78- 1.24; I^2=0%; low certainty)[20,22], 72 hours (OR 1.01, 95% CI 0.81-1.25; I^2=0%; low certainty)[23,26,27], and 120 hours (OR 1.06, 95% CI 0.72-1.56; very low certainty)[25] from admission, mortality benefit became inconclusive. Use of mechanical ventilation was likewise significantly reduced when systemic corticosteroids were initiated within 24 hours of admission (OR 0.24, 95% CI 0.07-0.87; low certainty).[26] In terms of adverse events, initiation of systemic corticosteroids within the first 72 hours of admission showed higher rate of developing hyperglycemia (OR 6.94, 95% CI 3.80-12.67; low certainty) but did not result in significant development of blood stream infection (OR 1.69, 0.83-3.47; very low certainty), and hospital-acquired or ventilator-associated pneumonia (OR 1.45, 0.82-2.57; very low certainty).[24]

SUMMARY OF CERTAINTY OF EVIDENCE

The certainty of evidence on the use of dexamethasone in severe and critical COVID-19 patients was downgraded to moderate certainty due to indirectness as one study [13] included patients who were given oral dexamethasone. The certainty of evidence on the use of dexamethasone in mild to moderate (non-oxygen) COVID-19 patients was downgraded to moderate certainty due to serious imprecision. For the use of hydrocortisone, methylprednisolone, and prednisolone, certainty of evidence was low

to moderate due to issues with blinding (in soft outcomes), inconsistency, indirectness, imprecision, and heterogeneity (see Appendix). Seven RCTs were either open-label trials or did not blind the personnel and the outcome assessors.[5,8-10,13-16] One RCT did not show the specific figures of the study results.[17] The data of two RCTs were extracted from the evidence review done by the WHO as their full articles could not be retrieved.[7] Certain outcomes, namely all-cause mortality (in HCT group)[4,6,14], length of hospital stay [9,11,12,15], and life support-free days [6,14] had significant heterogeneity (I^2>50%) in the pooled data.

In terms of dexamethasone dosing (12 mg versus 6 mg), certainty of evidence was downgraded to moderate certainty due to imprecision. Furthermore, publication bias may still be uncertain at this time as present evidence was based only on one published RCT. [19]

Cohort studies [20-26] which investigated the effect of timing of initiation of corticosteroids had very low overall certainty due to the inclusion of studies that lacked propensity matching and statistical adjustments on potential confounding variables, which had a serious impact on comparability between treatment groups.[24,25] As of 05 December 2021, no randomized controlled trial is currently available on this clinical question**.**

EVIDENCE TO DECISION

From our literature search, one cost-effectiveness analysis on the use of DEX (6mg oral or IV) was found. The study done in South Africa shows that even though there was a cost increase with the addition of DEX to standard care, its cost still fell below willingness to pay thresholds and approaches 100% cost-effectiveness for thresholds beyond $500.[27] Locally, IV corticosteroids remain to be an economically viable drug as the daily cost of medication is below the average daily wage in the Philippines (₱263.77).[28,29]

Table 1. IV Corticosteroid Prices based on The Philippine Drug Price Reference Index [29]

Drug	Sample Regimen	Unit Price	Price/Regimen
Dexamethasone	20 mg/day x 5 days + 10 mg/day x 5 days	₱39.88 per ampule (5 mg/mL,1 mL ampule)	₱1,196.4
Hydrocortisone	100 mg every 6 hours x 7 days	₱21.06 per vial (100 mg powder, vial)	₱589.68
Methylprednisolone	40 mg BID x 3 days + 20 mg TID x 3 days	₱289.93 per vial (40 mg, single dose vial)	₱3,189.23

Intravenous corticosteroids are some of the most readily available drugs globally.[30] The WHO has listed DEX and PRDL as essential medicines; in the Philippines, DEX, HCT, MP, and PRDL are similarly recognized in the national formulary.[30,31] These drugs were deemed highly acceptable by the WHO due to their ease of administration, relatively short courses, and generally benign safety profile.[30]

RECOMMENDATIONS FROM OTHER GROUPS

The WHO's guidelines for COVID-19 therapeutics recommend the use of IV corticosteroids for severe or critical COVID-19. While there was still insufficient evidence for its effects on COVID-19 outcomes at that time, the panel claimed that clinicians were more confident in its safety profile compared to novel drugs. As its adverse effects are more familiar and more predictable, these can be monitored

adequately by competent healthcare providers. For non-severe COVID-19, however, its use is not recommended as it was deemed unreasonable to obtain IV access just for corticosteroids.[30] Treatment guidelines published by the US National Institutes of Health specifically recommend the use of DEX for hospitalized patients requiring supplemental oxygen as there was no significant benefit found in patients on room air. In the absence of DEX, other IV corticosteroids are recommended as replacement (HCT, MP, Prednisone).[32]

RESEARCH GAPS

As of November 24, 2021, there are 14 ongoing RCTs on IV corticosteroid use for COVID-19 registered on ClinicalTrials.gov: 2 trials for IV corticosteroid vs. standard of care or placebo, five trials for two IV corticosteroids, five trials for different doses of the same IV corticosteroid, two trials for different timing of IV corticosteroid administration.

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Appendix 1. Evidence to Decision

Table 2. Summary of initial judgements prior to the panel discussion (N=6)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					• COVID-19 patients are at risk for ICU admission. IV corticosteroids are staple critical care medications that are easily accessible.
Benefits	Large (4)	Moderate (2)	Small	Uncertain			• Dexamethasone significantly decreased all-cause mortality in COVID-19 patients.
Harm	Large (2)	Small (4)	Uncertain	No response			• Adverse events are comparable between the IV corticosteroid group and the control group as well as between the different doses of Dexamethasone. • Incidence of hyperglycemia was significantly found in early initiation of corticosteroids (less than 72 hours). Development of blood stream infection, hospital-acquired pneumonia, and ventilator-acquired pneumonia were comparable between early and later initiation of corticosteroids.
Certainty of Evidence	High	Moderate (5)	Low (1)	Very low			• Low to very low
Balance of effects	Favors drug (6)	Does not favor drug	Uncertain				**Type and Dosing of Corticosteroids** • Favors IV Corticosteroids: All-cause Mortality, All-cause Mortality (Dexamethasone Group), Ventilator-free Days, WHO Ordinal Scale • Favors Control: Length of ICU Stay **Timing of Corticosteroids** • Favors Early Initiation at 24 hours of Admission: Decreased mortality and decreased odds of mechanical intubation
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Possibly NO important uncertainty or variability (6)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Cost (2)	Negligible cost (4)	Moderate savings	Large savings	• IV Corticosteroids are relatively affordable and easily accessible in most government hospitals.
Certainty of evidence of required resources	No included studies	Very low	Low	Moderate (6)	High		• Moderate • Cost-effectiveness analysis: high willingness-to-pay thresholds ($3015 per disability-adjusted life years).
Cost effectiveness	No included studies	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (5)			• The cost-effectiveness analysis favors the addition of Dexamethasone to standard care.
Equity	Uncertain	Reduced	Probably no impact (4)	Increased (2)			
Acceptability	Uncertain	No	Yes (4)				
Feasibility	Uncertain (1)	No	Yes (5)				

Appendix 2. Search Strategy & Results

Table 3A. Search Yield for Type and Dosing of Corticosteroids

#	Query	Results
1	"corticosteroids"	1,208,536
2	"intravenous" OR "IV" OR "systemic"	10,316,134
3	"dexamethasone" OR "hydrocortisone" OR "methylprednisolone"	960,504
4	"high dose" OR "low dose"	5,053,226
5	"SARS-CoV-2" OR "COVID-19"	4,611,326
6	"severe" OR "critical"	10,304,491
7	"mortality"	5,415,850
8	"hospital length of stay" OR "ICU length of stay" OR "mechanical ventilation" OR "organ support-free days" OR "adverse events" OR "infection" OR "superinfection" OR "hyperglycemia" OR "gastrointestinal bleeding"	4,115,119
9	#1 AND #2	763,571
10	#3 OR #9	930,619
11	#4 OR #10	1,024,552
12	#5 AND #6	3,647,875
13	#7 OR #8	3,021,395
14	#11 AND #12 AND #13	**20,339**

Figure 1A. PRISMA Flow Diagram for Type and Dosing of Corticosteroids

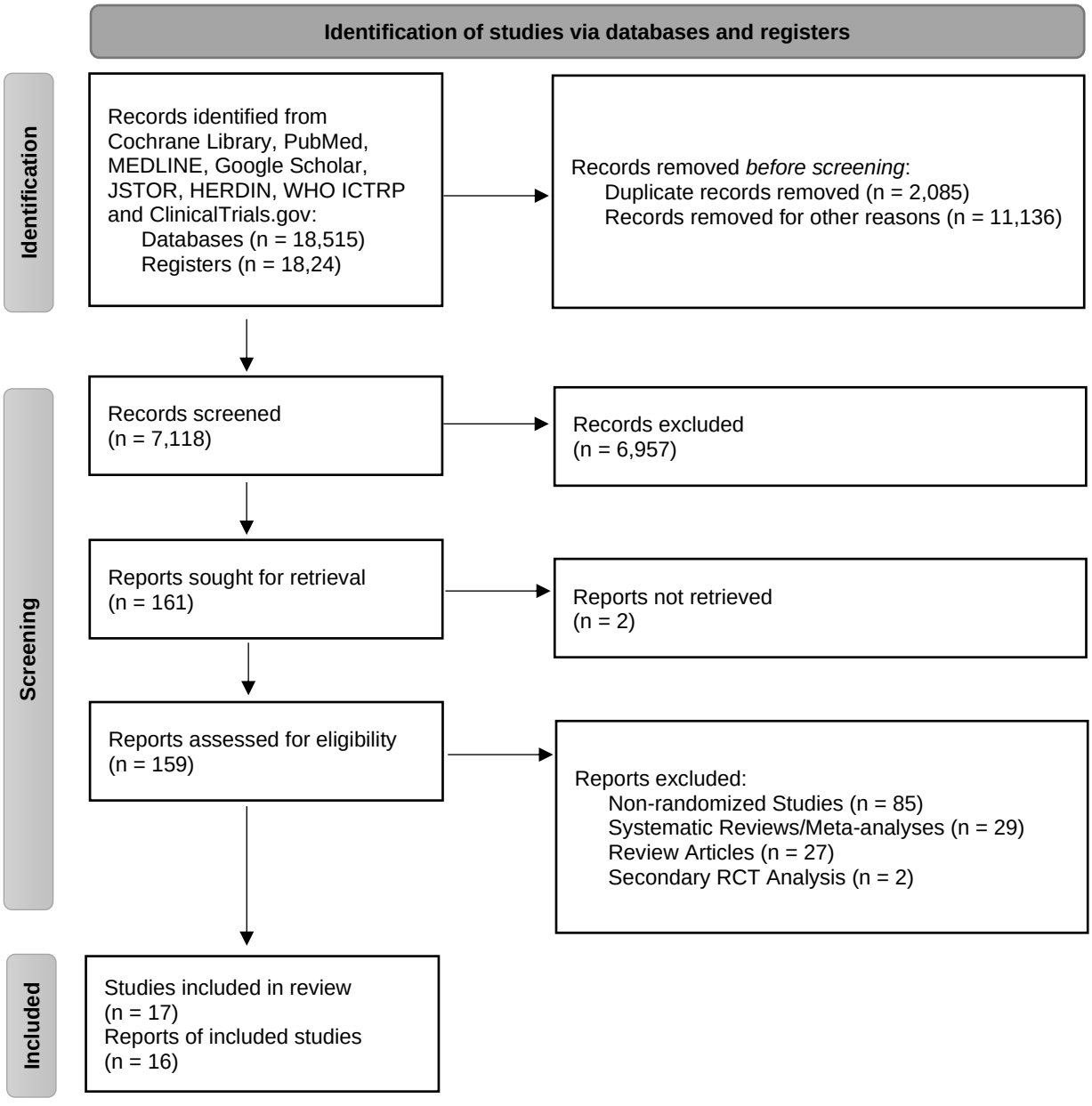
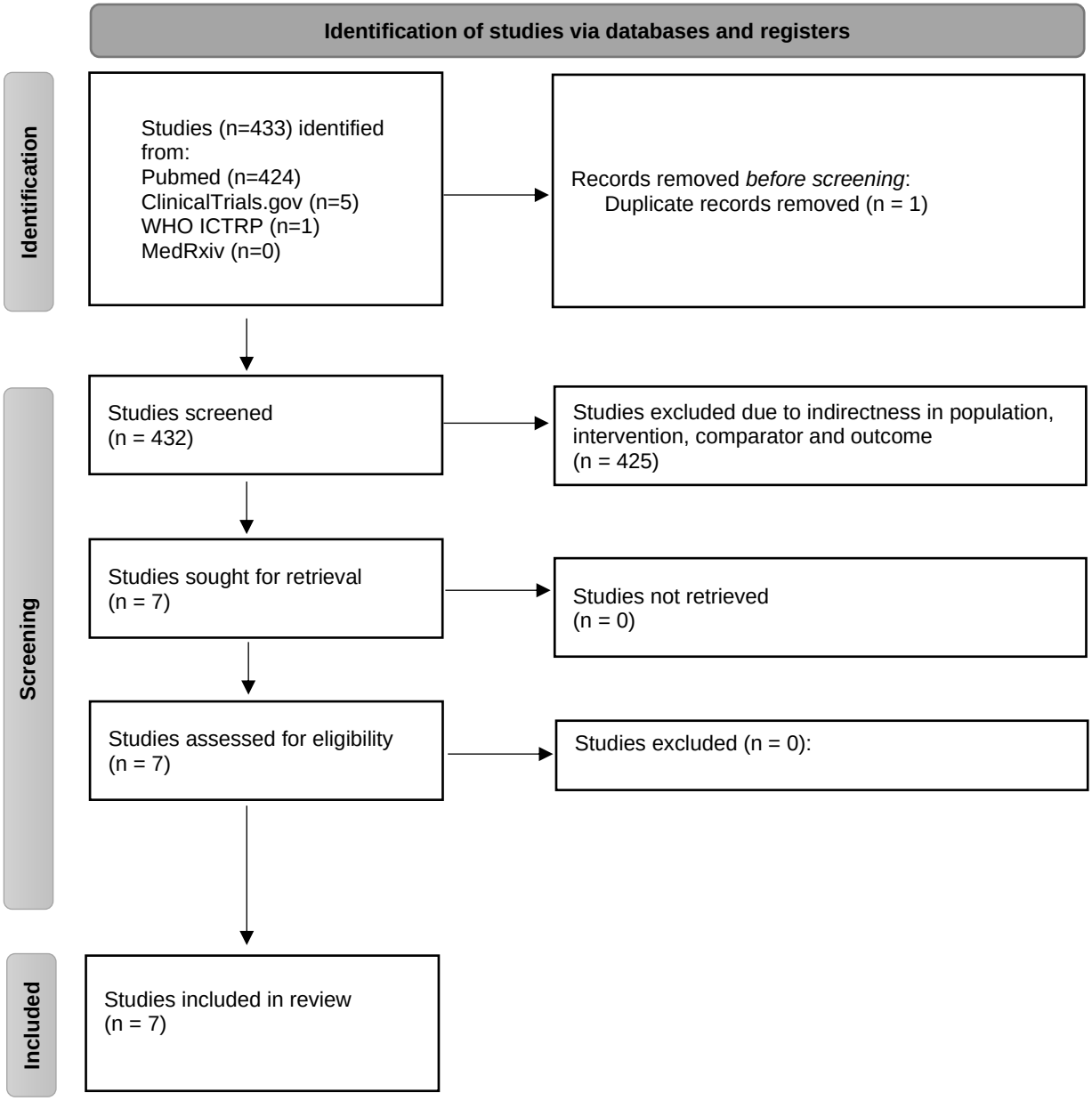


Table 3B. Search Yield for Timing of Corticosteroids

Search	Query	Results	Time
#6	Search: **((corticosteroids) AND (COVID-19)) AND ((early) OR (timing))** ("adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields]) AND ("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 "sars cov 2"[All Fields] OR "sars cov 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])) AND ("early"[All Fields] OR ("timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields])) **Translations** **corticosteroids:** "adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields] **COVID-19:** ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT])) **timing:** "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]	424	23:22:58
#5	Search: **(early) OR (timing)** "early"[All Fields] OR "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields] **Translations** **timing:** "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]	1,909,206	23:22:47
#4	Search: **timing** "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields] **Translations** **timing:** "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]	226,302	23:22:38
#3	Search: **early** "early"[All Fields]	1,730,924	23:22:29
#2	Search: **COVID-19** "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 "sars cov 2"[All Fields] OR "sars cov 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]) **Translations** **COVID-19:** ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT]))	202,271	23:22:04
#1	Search: **corticosteroids** "adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields] **Translations** **corticosteroids:** "adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields]	364,476	23:21:54

Figure 1B. PRISMA Flow Diagram for Timing of Corticosteroids



Appendix 3. Included Studies

Table 4A. Characteristics of Included Studies for Type and Dosing of Corticosteroids

Study ID	Patients (n)	Interventions	Outcomes	Method
CAPE COVID 2020	Critically-ill COVID-19 patients (n = 149)	Hydrocortisone (200 mg/day until day 7, then 100 mg/day x 4 days, then 50 mg/day x 3 days)	All-cause Mortality, Intubation Rate, ECMO Rate, Adverse Events, Nosocomial Infection	Multicenter Randomized Double-blind Trial
CoDEX 2020	COVID-19 patients with moderate to severe ARDS (n = 299)	Dexamethasone (20 mg/day x 5 days, then 10 mg/day x 5 days)	All-cause Mortality, Ventilator-free Days, SOFA Score	Multicenter Randomized Open-label Trial
COVID STEROID 2021	COVID-19 patients with severe hypoxia (n = 30)	Hydrocortisone (200 mg/day)	All-cause Mortality, Life Support-free Days, Adverse Events	Multicenter Randomized Blinded Trial
COVID STEROID 2 2021	COVID-19 patients with severe hypoxemia (n = 982)	Dexamethasone (12 or 6 mg/day)	All-cause Mortality, Life Support-free Days, Ventilator-free Days, Cardiovascular Support-free Days, Renal Replacement Therapy-free Days, Adverse Events	Multicenter Randomized Blinded Trial
DEXA-COVID 19 2020	COVID-19 patients with moderate to severe ARDS (n = 19)	Dexamethasone (20 mg/day × 5 days, then 10 mg/day × 5 days)	All-cause Mortality, Adverse Events	Multicenter Randomized Open-label Trial
Edalatifard 2020	patients with severe COVID-19 (n = 62)	Methylprednisolone (250 mg/day x 3 days)	All-cause Mortality, Adverse Events, Nosocomial Infection, Shock, GI Symptoms	Multicenter Randomized Single-blind Trial
Farahani 2020	COVID-19 patients with severe respiratory failure (n = 29)	Methylprednisolone (1000 mg/day x 3 days)	GCS	Single-center Randomized Double-blind Trial
Ghanei 2021	patients with severe COVID-19 (n = 336)	Prednisolone (25 mg/day)	All-cause Mortality, Length of Hospital Stay, Admission to ICU, Intubation Rate, Adverse Events, GI Symptoms	Multicenter Randomized Open-label Trial
GLUCOCOVID 2021	patients with severe COVID-19 (n = 64)	Methylprednisolone (40 mg BID x 3 days, then 20 mg TID x 3 days)	All-cause Mortality	Multicenter Randomized Open-label Trial
Jamaati 2021	COVID-19 patients with mild to moderate ARDS (n = 50)	Dexamethasone (20 mg/day x 5 days, then 10 mg/day x 5 days)	All-cause Mortality, Length of Hospital Stay, Length of ICU Stay, SOFA Score	Single-center Randomized Trial
Jeronimo 2021	patients with severe COVID-19 (n = 393)	Methylprednisolone (0.5 mg/kg/day)	All-cause Mortality, Length of Hospital Stay, Need for Insulin Therapy	Single-center Randomized Double-blind Trial

Ranjbar 2021	COVID-19 patients severe (n = 90)	Dexamethasone (6 mg/day) Methylprednisolone (2 mg/kg/day)	WHO Ordinal Scale	Single-center Randomized Triple-blind Trial
RECOVERY 2021	COVID-19 patients (n = 6,425)	Dexamethasone (6 mg/day x 10 days)	All-cause Mortality	Multicenter Randomized Open-label Trial
REMAP-CAP 2020	patients with severe COVID-19 (n = 379)	Hydrocortisone Fixed 7-day Course (50 mg or 100 mg every 6 hours) Hydrocortisone Shock-Dependent Course (50 mg or 100 mg every 6 hours when in shock)	All-cause Mortality, Life Support-free Days, Adverse Events	Multicenter Randomized Open-label Trial
Solanich 2021	patients with severe COVID-19 (n = 55)	Methylprednisolone (120 mg/day x 3 days)	All-cause Mortality, COVID-19-related Mortality, Time to Death (All-cause), Time to Death (COVID-19-related), Time to Clinical Improvement, Length of Hospital Stay	Single-center Randomized Open-label Trial
Steroids-SARI 2020	ICU-admitted COVID-19 patients (n = 47)	Methylprednisolone (40 mg every 12 hours × 5 days)	All-cause Mortality, Adverse Events	Single-center Randomized Open-label Trial
Tang 2021	COVID-19 patients with CT-confirmed pneumonia (n = 86)	Methylprednisolone (1 mg/kg/day)	All-cause Mortality, Time to Clinical Improvement, Admission to ICU	Multicenter Randomized Single-blind Trial

Table 4B. Characteristics of Included Studies for Timing of Corticosteroids

Study ID	Patients (n)	Interventions	Comparator	Outcomes
Bahl A, Johnson S, Chen NW. Timing of corticosteroids impacts mortality in hospitalized COVID-19 patients. Intern Emerg Med. 2021 Sep;16(6):1593-1603. doi: 10.1007/s11739-021-02655-6. Epub 2021 Feb 5. PMID: 33547620; PMCID: PMC7864133.[23]	Severe COVID-19 Hypoxia (n=615)	Timing: <24 Hours Timing: <48 Hours Timing: <72 Hours (n=371) Dexamethasone 8-16 mg IV/PO Hydrocortisone 45-100 mg IV Methylprednisolone 1-50 mg IV Prednisone 10-80 mg PO Plus Standard of Care	Timing: >24 Hours Timing: >48 Hours Timing: >72 Hours (n=244) Dexamethasone 8-16 mg IV/PO Hydrocortisone 45-100 mg IV Methylprednisolone 1-500 mg IV Prednisone 10-80 mg PO Plus Standard of Care	In-hospital Mortality
Sulaiman K, Al Juhani O, Korayen GB, Eljaaly K, Alhubaishi A, Al Harbi O, Badreldin HA, Al Yousif GA, Vishwakarma R, Altebainawi A, Albelwi S, Almutairi R, Almousa M, Alghamdi R, Alharbi A, Algami R, Akhani N, Al Hartin A, Alissa A, Al Homaid S, Al Qahtani K, Al Atassi A, Al Ghamdi G. Early Versus Late Use of Dexamethasone in Critically Ill Patients with COVID-19: A Multicenter, Cohort Study. ResearchSquare [Preprint]. 2021 Jul 26 [cited 2021 Nov 27]. Available from https://www.researchsquare.com/article/rs-349677/v1 [24]	Severe and critical COVID-19 (n=202)	Timing: <24 Hours *24 hours within ICU admission (n=101) Dexamethasone 6 mg Methylprednisolone Plus Standard of Care	Timing: >24 Hours *24 hours within ICU admission (n=101) Dexamethasone 6 mg Methylprednisolone Plus Standard of Care	In-hospital Mortality
Monedero P, Gea A, Castro P, Candela-Toha AM, Hernández-Sanz ML, Arruti E, Villar J, Ferrando C; COVID-19 Spanish ICU Network. Early corticosteroids are associated with lower mortality in critically ill patients with COVID-19: a cohort study. Crit Care. 2021 Jan 4;25(1):2. doi: 10.1186/s13054-020-03422-3. PMID: 33397463; PMCID: PMC7780210. [25]	Severe and critical COVID-19 (n=691)	Timing: <48 Hours (n=485) Dexamethasone Methylprednisolone Prednisone Plus Standard of Care	Timing: >48 Hours (n=206) Dexamethasone Methylprednisolone Prednisone Plus Standard of Care	In-hospital Mortality Adverse Events
Akhtar H, Khalid S, Rahman FU, Ali S, Afridi M, Khader YS, Hassan F, Akhtar N, Khan MM, Ikram A. Delayed admissions and efficacy of steroid use in patients with critical and severe COVID-19: an apprehensive approach. J Public Health (Oxf). 2021 Sep 27:fdab239. doi: 10.1093/pubmed/fdab239. [26]	Severe and critical COVID-19 (n=659)	Timing: <72 Hours (n=321) Cut off: 5 days from admission onset Type of steroid not specified Plus Standard of Care	Timing: >72 Hours (n=338) Type of steroid not specified Plus Standard of Care	In-hospital Mortality

Dupuis C, de Montmollin E, Buetti N, Goldgran-Toledano D, Reignier J, Schwebel C, Domitile J, Neuville M, Ursino M, Siami S, Ruckly S, Alberti C, Mourvillier B, Bailly S, Laurent V, Gainnier M, Souweine B, Timsit JF; OutcomeReaTM research network. Impact of early corticosteroids on 60-day mortality in critically ill patients with COVID-19: A multicenter cohort study of the OUTCOMEREA network. PLoS One. 2021 Aug 4;16(8):e0255644. doi: 10.1371/journal.pone.0255644. PMID: 34347836; PMCID: PMC8336847. [27]x	Severe and critical COVID-19 (n=303)	Timing: <72 Hours (n=66) Dexamethasone HSHC Methylprednisolone Prednisolone Plus Standard of Care	Timing: >72 Hours (n=237) Dexamethasone HSHC Methylprednisolone Prednisolone Plus Standard of Care	In-hospital Mortality Adverse Events Hyperglycemia Infection
Moreno A, Vargas C, Azocar F, Villarroel F, Cofré M, Oppliger H, Ríos F, Raijmakers M, Silva-Ayarza I, Beltrán C, Zamora F. Steroids and mortality in non-critically ill COVID-19 patients: a propensity score-weighted study in a Chilean cohort. Int J Infect Dis. 2021 Sep 20;112:124-129. doi: 10.1016/j.ijid.2021.09.038. Epub ahead of print. PMID: 34547488; PMCID: PMC8450146. [28]	Severe and critical COVID-19 (n=520)	Timing: <120 Hours (n=233) Initiation from start of symptoms: Early: 9 days (7-12) days Duration Early: 2-4 days Dexamethasone Methylprednisolone Prednisone Plus Standard of Care	Timing: >120 Hours (n=287) Initiation from start of symptoms: Non-Early: 10 days 10-16 days) Duration Early: 2-4 days Dexamethasone Methylprednisolone Prednisone Plus Standard of Care	In-hospital Mortality
Li Y, Zhou X, Li T, Chan S, Yiqi Y, Ai JW, Zhang H, Sun F, Zhang Q, Zhu L, Shao L, Xu B, Zhang W. Corticosteroid prevents COVID-19 progression within its therapeutic window: a multicentre, proof-of-concept, observational study, Emerg. Microbes Infect., 9:1, 1869-1877, DOI: 10.1080/22221751.2020.1807885 [29]	Severe to critical COVID-19 High risk for progressing to ARDS (n=68)	Timing: <24 Hours (n=47) Methylprednisolone 40-80 mg/day for 3 days then 20 mg/day with a total treatment period of less than 7 days Plus Standard of Care	Timing: >72 Hours (n=41) Methylprednisolone 40-80 mg/day for 3 days then 20 mg/day with a total treatment period of less than 7 days Plus Standard of Care	Need for Mechanical Ventilation

Appendix 4. Risk of Bias Assessment

Figure 2A. Risk of Bias Graph for Type and Dosing of Corticosteroids

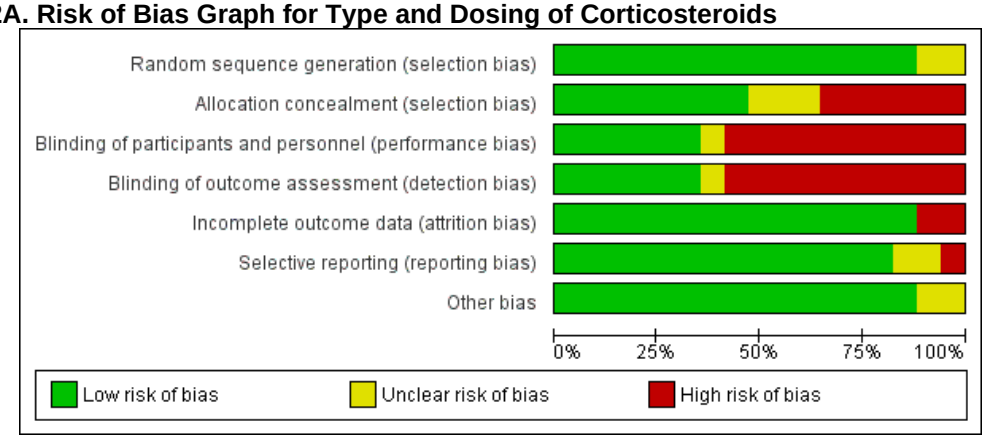


Figure 2B. Risk of Bias Summary for Type and Dosing of Steroids

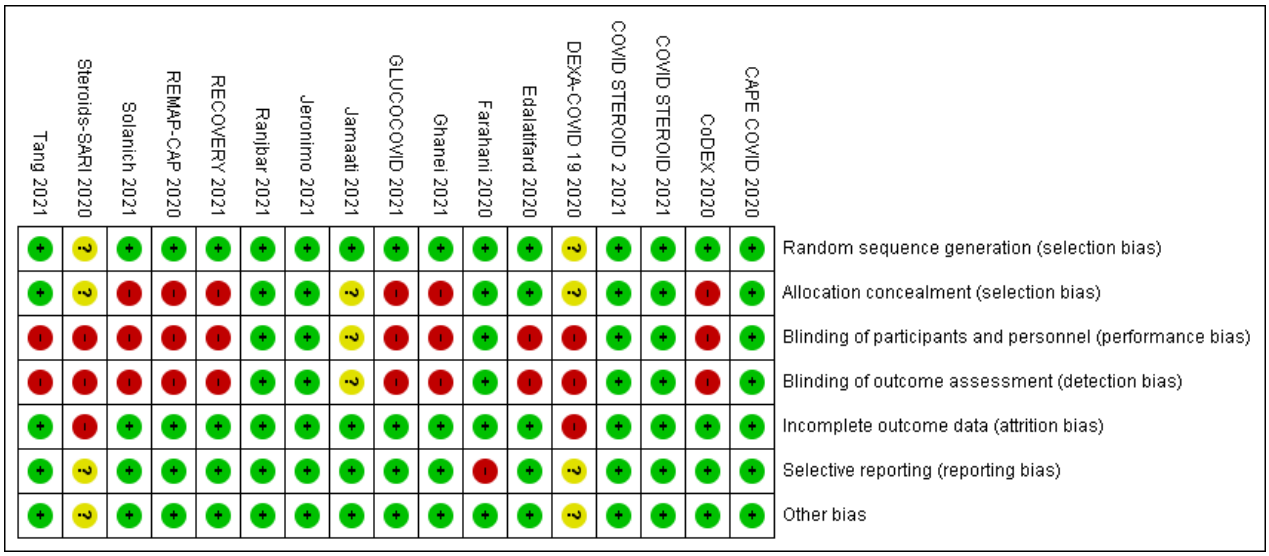


Figure 3A. Risk of Bias Graph for Timing of Corticosteroids

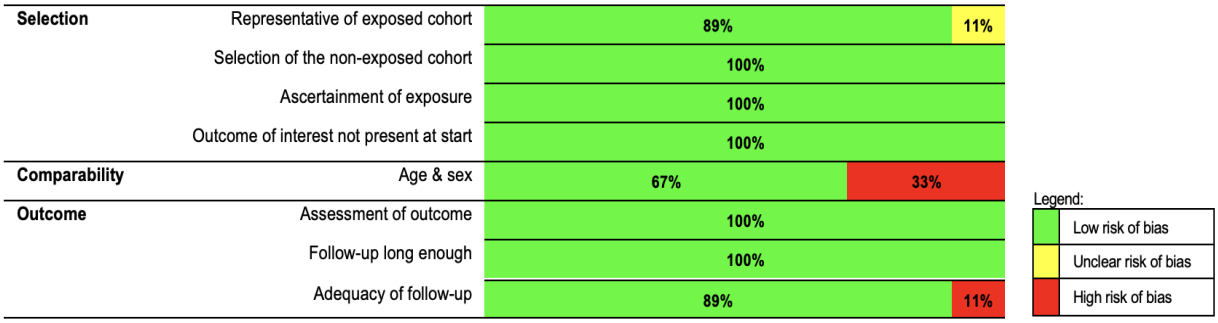


Figure 3B. Risk of Bias Summary for Timing of Corticosteroids Using Newcastle Ottawa Scale

		Akhtar 2021	Bahl 2021	Dupuis 2021	Hyun 2021	Li 2021	Monedero 2021	Moreno 2021	Sulaiman 2021
A	**Selection**								
	Representative of exposed cohort	+	+	+	+	+	+	+	+
	Selection of the non-exposed cohort from the same community as exposed cohort	+	+	+	+	+	+	+	+
	Ascertainment of exposure by secure record	+	+	+	+	+	+	+	+
	Demonstration that outcome of interest was not present at the start of the study	+	+	+	+	+	+	+	+
B	**Comparability**								
	Study controls for other variables	+	+	−	−	+	+	−	+
C	**Outcome**								
	Assessment of outcome	+	+	+	+	+	+	+	+
	Follow-up long enough for outcome to occur	+	+	+	+	+	+	+	+
	Complete follow up of all subjects accounted for	+	+	−	+	+	+	+	+

Legend:

+ Low risk of bias

? Unclear risk of bias

− High risk of bias

Appendix 5.1. GRADE Evidence Profile for Type and Dosing of Corticosteroids

Question: Should intravenous corticosteroids be used in COVID-19?
Patient or Population: Moderately to Critically-Ill COVID-19 Patients
Setting: In-patients Setting
Intervention: Intravenous Corticosteroids
Comparison: Standard Care or Placebo

Table 5. Summary of Findings Table (IV Corticosteroids vs. Standard Care or Placebo)

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV corticosteroids	Control	Relative (95% CI)	Absolute (95% CI)		
All-cause Mortality (All Corticosteroids)												
14	Randomized trials	Not serious	Not serious	Serious[c]	Not serious	None	703/2629 (26.7%)	1269/4230 (30.0%)	**RR 0.87** (0.78 to 0.97)	**39 fewer per 1,000** (from 66 fewer to 9 fewer)	⊕⊕⊕◯ MODERATE	
All-cause Mortality (Dexamethasone Group)												
4	Randomized trials	Not serious	Not serious	Serious[c]	Not serious	None	497/1786 (27.8%)	1079/3472 (31.1%)	**RR 0.86** (0.79 to 0.94)	**44 fewer per 1,000** (from 65 fewer to 19 fewer)	⊕⊕⊕◯ MODERATE	
All-cause Mortality (Hydrocortisone Group)												
3	Randomized trials	Not serious	Not serious	Not serious	Serious[d,e]	None	96/369 (26.0%)	56/188 (29.8%)	**RR 0.85** (0.50 to 1.44)	**45 fewer per 1,000** (from 149 fewer to 131 more)	⊕⊕⊕◯ MODERATE	
All-cause Mortality (Methylprednisolone Group)												
4	Randomized trials	Not serious	Not serious	Not serious	Serious[d]	None	106/357 (29.7%)	122/350 (34.9%)	**RR 0.82** (0.59 to 1.16)	**63 fewer per 1,000** (from 143 fewer to 56 more)	⊕⊕⊕◯ MODERATE	
All-cause Mortality (Prednisolone Group)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[d]	None	4/116 (3.4%)	12/220 (5.5%)	**RR 0.63** (0.21 to 1.92)	**20 fewer per 1,000** (from 43 fewer to 50 more)	⊕⊕⊕◯ MODERATE	
COVID-19-related Mortality												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[d,f,g]	None	4/27 (14.8%)	4/28 (14.3%)	**RR 1.04** (0.29 to 3.73)	**6 more per 1,000** (from 101 fewer to 390 more)	⊕⊕⊕◯ MODERATE	

Time to Death (All-cause)											
1	Randomized trials	Not serious	Not serious	Not serious	Serious[d]	None	27 participants	28 participants	**HR 0.80** (0.24 to 2.61)	--	⊕⊕⊕◯ MODERATE	
Time to Death (COVID-19-related)											
1	Randomized trials	Not serious	Not serious	Not serious	Serious[d]	None	27 participants	28 participants	**HR 0.96** (0.24 to 3.84)	--	⊕⊕⊕◯ MODERATE	
Time to Clinical Improvement											
2	Randomized trials	Serious[a]	Not serious	Not serious	Serious[d]	None	70 participants	71 participants	**HR 0.93** (0.65 to 1.33)	--	⊕⊕◯◯ LOW	
Length of Hospital Stay (Dexamethasone)											
1	Randomized trials	Not serious	Not serious	Not serious	Serious[f]	None	25	35	--	MD **4.80 day higher** (3.06 higher to 6.54 higher)	⊕⊕⊕◯ MODERATE	
Length of Hospital Stay (Methylprednisolone and Prednisolone)											
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[d,e]	None	337	406	--	MD **0.28 day lower** (1.62 lower to 1.07higher)	⊕⊕◯◯ LOW	
ICU Admission											
2	Randomized trials	Serious[a]	Not serious	Not serious	Serious[d]	None	7/159 (4.4%)	15/263 (5.7%)	**RR 0.78** (0.32 to 1.90)	**13 fewer per 1,000** (from 39 fewer to 51 more)	⊕⊕◯◯ LOW	
Length of ICU Stay											
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	25	25	--	MD **4.2 days more** (3.26 more to 5.14 more)	⊕⊕⊕⊕ HIGH	
Intubation Rate											
2	Randomized trials	Serious[a]	Not serious	Not serious	Serious[d]	None	10/132 (7.6%)	16/236 (6.8%)	**RR 0.69** (0.40 to 1.18)	**21 fewer per 1,000** (from 41 fewer to 12 more)	⊕⊕◯◯ LOW	
ECMO Rate											
1	Randomized trials	Not serious	Not serious	Not serious	Serious[d,g]	None	2/76 (2.6%)	2/73 (2.7%)	**RR 0.96** (0.14 to 6.64)	**1 fewer per 1,000** (from 24 fewer to 155 more)	⊕⊕⊕◯ MODERATE	
Life Support-free Days											
2	Randomized trials	Serious[a]	Not serious	Not serious	Serious[d]	None	294	115	--	MD **12.68 days fewer** (40.28 fewer to 14.92 more)	⊕⊕◯◯ LOW	

Ventilator-free Days												
1	Randomized trials	Serious [a]	Not serious	Not serious	Not serious	None	151	148	--	MD **2.26 days more** (0.2 more to 4.38 more)	⊕⊕⊕◯ MODERATE	
SOFA Score												
2	Randomized trials	Serious [a]	Not serious	Not serious	Serious [d]	None	152	145	--	MD **0.49 points lower** (2.18 lower to 1.2 higher)	⊕⊕◯◯ LOW	
Adverse Events												
7	Randomized trials	Serious [a,b]	Not serious	Not serious	Serious [d]	None	113/538 (21.0%)	168/461 (36.4%)	**RR 0.95** (0.86 to 1.05)	**18 fewer per 1,000** (from 51 fewer to 18 more)	⊕⊕◯◯ LOW	
Nosocomial Infection												
2	Randomized trials	Serious [a]	Not serious	Not serious	Serious [d]	None	29/110 (26.4%)	30/101 (29.7%)	**RR 0.91** (0.61 to 1.36)	**27 fewer per 1,000** (from 116 fewer to 107 more)	⊕⊕◯◯ LOW	
Shock												
1	Randomized trials	Serious [a]	Not serious	Not serious	Serious [d,f,g]	None	0/34 (0.0%)	2/28 (7.1%)	**RR 0.17** (0.01 to 3.32)	**59 fewer per 1,000** (from 71 fewer to 166 more)	⊕⊕◯◯ LOW	
Need for Insulin Therapy												
1	Randomized trials	Not serious	Not serious	Not serious	Serious [d]	None	103/173 (59.5%)	86/174 (49.4%)	**RR 1.20** (0.99 to 1.46)	**99 more per 1,000** (from 5 fewer to 227 more)	⊕⊕⊕◯ MODERATE	
Gastrointestinal Symptoms												
2	Randomized trials	Serious [a]	Not serious	Not serious	Serious [d]	None	12/148 (8.1%)	23/236 (9.7%)	**RR 0.91** (0.47 to 1.78)	**9 fewer per 1,000** (from 52 fewer to 76 more)	⊕⊕◯◯ LOW	

CI: Confidence interval; **HR**: hazard Ratio; **MD**: mean difference; **RR**: relative risk

Explanations

[a] Some included studies were open-label trials.
[b] Data from some RCTs were retrieved from a systematic review.
[c] One study used both oral and IV DEX.
[d] Confidence interval crossed the threshold.
[e] Pooled data showed significant heterogeneity.
[f] The study had low event rates within a small population.
[g] The result had a wide confidence interval.

Table 6. Summary of Findings Table (Dexamethasone 12 mg vs. 6 mg)

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dex 12mg	Dex 6mg	Relative (95% CI)	Absolute (95% CI)		
All-cause Mortality												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	157/490 (32.0%)	180/478 (37.7%)	**RR 0.85** (0.72 to 1.01)	**56 fewer per 1,000** (from 105 fewer to 4 more)	⊕⊕⊕◯ MODERATE	
Life Support-free Days												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	489	478	--	MD **2.8 days more** (0.2 fewer to 5.8 more)	⊕⊕⊕◯ MODERATE	
Ventilator-free Days												
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	491	480	--	MD **1 days more** (0.21 more to 1.79 more)	⊕⊕⊕⊕ HIGH	
Cardiovascular Support-free Days												
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	491	480	-	MD **1.5 days more** (0.88 more to 2.12 more)	⊕⊕⊕⊕ HIGH	
Renal Replacement Therapy-free Days												
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	491	480	-	MD **1.1 days more** (0.66 more to 1.54 more)	⊕⊕⊕⊕ HIGH	
Adverse Events												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	56/497 (11.3%)	65/485 (13.4%)	**RR 0.84** (0.60 to 1.17)	**21 fewer per 1,000** (from 54 fewer to 23 more)	⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **MD**: mean difference; **RR**: relative risk

Explanations

[a] Confidence interval crossed the threshold.

Appendix 5.2. GRADE Evidence Profile for Timing of Corticosteroids

Question: Should early versus non-early initiation of intravenous corticosteroids be used in COVID-19?
Patient or Population: Severe and critical COVID-19 patients
Setting: In-patients Setting
Intervention: Early Initiation of Corticosteroids
Comparison: Non-early Initiation of Corticosteroids

Table 7. Summary of Findings Table (Early versus Non-Early Initiation of Corticosteroids)

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early corticosteroids	Non-early corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Mortality (Intervention Cutoff: 24 Hours)												
2	Observational studies	Not serious	Not serious	Not serious	Not serious	None	107/307 (34.9%)	212/510 (41.6%)	**OR 0.68** (0.51 to 0.92)	**90 fewer per 1,000** (from 149 fewer to 20 fewer)	⊕⊕◯◯ LOW	CRITICAL
Mortality (Intervention Cutoff: 48 Hours)												
2	Observational studies	Not serious	Not serious	Not serious	Not serious	None	366/786 (46.9%)	223/520 (42.9%)	**OR 0.98** (0.78 to 1.24)	**5 fewer per 1,000** (from 59 fewer to 53 fewer)	⊕⊕◯◯ LOW	CRITICAL
Mortality (Intervention Cutoff: 72 Hours)												
3	Observational studies	Serious [a]	Not serious	Not serious	Not serious	None	380/758 (50.1%)	397/819 (48.5%)	**OR 1.01** (0.81 to 1.25)	**2 more per 1,000** (from 52 fewer to 56 more)	⊕⊕◯◯ LOW	CRITICAL
Mortality (Intervention Cutoff: 120 Hours)												
1	Observational studies	Not serious	Not serious	Not serious	Serious [b]	None	67/233 (28.8%)	79/287 (27.5%)	**OR 1.06** (0.72 to 1.56)	**12 more per 1,000** (from 61 fewer to 97 more)	⊕◯◯◯ VERY LOW	CRITICAL
Need for Mechanical Ventilation												
1	Observational studies	Not serious	Not serious	Not serious	Not serious	None	5/47 (10.6%)	7/21 (33.3%)	**OR 0.24** (0.07 to 0.87)	**226 fewer per 1,000** (from 300 fewer to 30 fewer)	⊕⊕◯◯ LOW	CRITICAL

Adverse Events: Hyperglycemia											
1	observational studies	not serious	not serious	not serious	not serious	none	46/66 (69.7%)	59/237 (24.9%)	**OR 6.94** (3.80 to 12.67)	**448 more per 1,000** (from 308 more to 599 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse Events: Blood Stream Infection											
1	observational studies	not serious	not serious	not serious	serious[b]	none	13/66 (19.7%)	30/237 (12.7%)	**OR 1.69** (0.83 to 3.47)	**70 more per 1,000** (from 19 fewer to 208 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse Events: Incidence of Hospital-Acquired Pneumonia and Ventilator Acquired Pneumonia											
1	observational studies	not serious	not serious	not serious	serious[b]	none	23/66 (34.8%)	70/237 (29.5%)	**OR 1.45** (0.82 to 2.57)	**83 more per 1,000** (from 40 fewer to 223 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD**: mean difference

Explanations

[a] Lack of propensity matching and statistical adjustment for potential confounders (Dupuis et al., 2021)

[b] Wide confidence interval

[c] Small population and small event rates

Appendix 6. Forest Plots

Figure 4. All-Cause Mortality Forest Plot for Type and Dosing of Corticosteroids

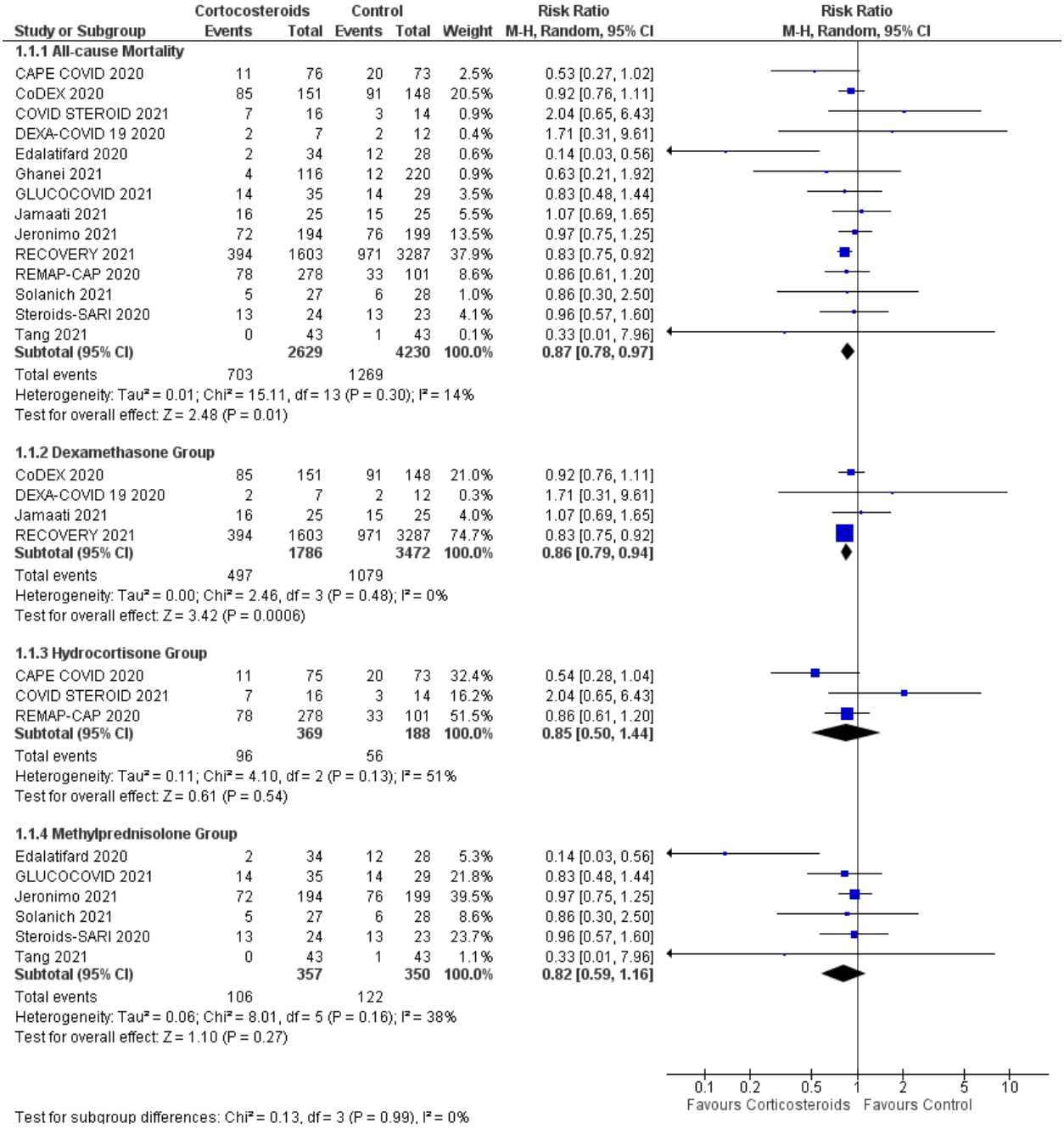


Figure 5. Time to Clinical Improvement Forest Plot for Type and Dosing of Corticosteroids

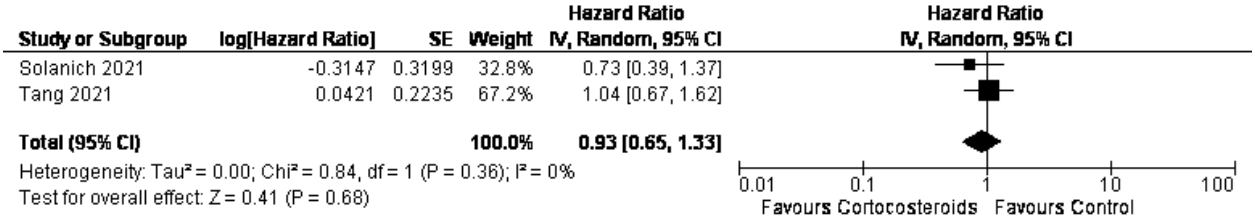


Figure 6. Length of Hospital Stay Forest Plot for Type and Dosing of Corticosteroids

Study or Subgroup	Corticosteroids Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ghanei 2021	5.5	3.1	116	6.4	2.3	179	37.6%	-0.90 [-1.56, -0.24]
Jeronimo 2021	10	1.7	194	9.3	1.5	199	40.4%	0.70 [0.38, 1.02]
Solanich 2021	13.9	3.5	27	14.9	3.9	28	22.0%	-1.00 [-2.96, 0.96]
Total (95% CI)			**337**			**406**	**100.0%**	**-0.28 [-1.62, 1.07]**

Heterogeneity: Tau² = 1.14; Chi² = 20.39, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 0.40 (P = 0.69)

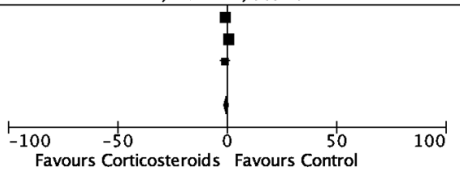


Figure 7. ICU Admission Forest Plot for Type and Dosing of Corticosteroids

Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ghanei 2021	5	116	13	220	78.3%	0.73 [0.27, 2.00]
Tang 2021	2	43	2	43	21.7%	1.00 [0.15, 6.78]
Total (95% CI)		**159**		**263**	**100.0%**	**0.78 [0.32, 1.90]**
Total events	7		15			

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)

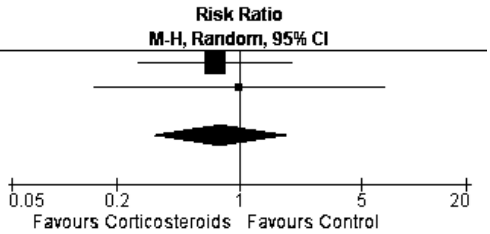


Figure 8. Intubation Rate Forest Plot for Type and Dosing of Corticosteroids

Study or Subgroup	Cortocosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CAPE COVID 2020	8	16	12	16	89.8%	0.67 [0.38, 1.17]
Ghanei 2021	2	116	4	220	10.2%	0.95 [0.18, 5.10]
Total (95% CI)		**132**		**236**	**100.0%**	**0.69 [0.40, 1.18]**
Total events	10		16			

Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)

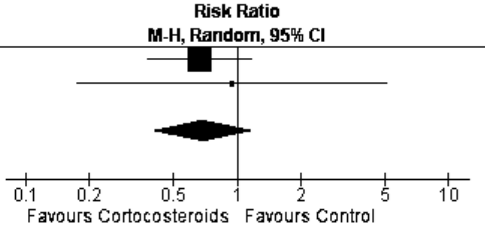


Figure 9. Life Support-free Days Forest Plot for Type and Dosing of Corticosteroids

Study or Subgroup	Cortocosteroids Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
COVID STEROID 2021	43.5	23	16	71	10.4	14	47.4%	-27.50 [-40.02, -14.98]
REMAP-CAP 2020	3.2	4.4	278	2.5	3.5	101	52.6%	0.70 [-0.16, 1.56]
Total (95% CI)			**294**			**115**	**100.0%**	**-12.68 [-40.28, 14.92]**

Heterogeneity: Tau² = 377.13; Chi² = 19.41, df = 1 (P < 0.0001); I² = 95%
Test for overall effect: Z = 0.90 (P = 0.37)

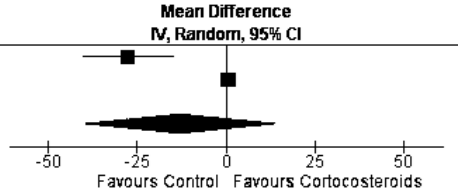


Figure 10. SOFA Score Forest Plot for Type and Dosing of Corticosteroids

Study or Subgroup	Cortocosteroids Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
CoDEX 2020	6.1	3.4168	127	7.5	3.3194	120	47.4%	-1.40 [-2.24, -0.56]
Jamaati 2021	4.73	0.65	25	4.4	0.52	25	52.6%	0.33 [0.00, 0.66]
Total (95% CI)			**152**			**145**	**100.0%**	**-0.49 [-2.18, 1.20]**

Heterogeneity: Tau² = 1.39; Chi² = 14.15, df = 1 (P = 0.0002); I² = 93%
Test for overall effect: Z = 0.57 (P = 0.57)

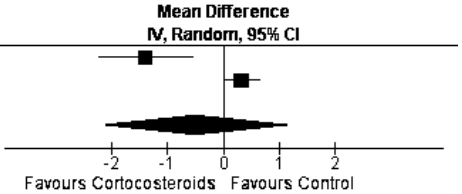


Figure 11. Adverse Events Forest Plot for Type and Dosing of Corticosteroids

Study or Subgroup	Cortocosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CAPE COVID 2020	28	75	30	73	6.2%	0.91 [0.61, 1.36]
COVID STEROID 2021	1	15	0	14	0.1%	2.81 [0.12, 63.83]
DEXA-COVID 19 2020	3	7	11	12	1.3%	0.47 [0.20, 1.12]
Edalatifard 2020	2	34	2	28	0.3%	0.82 [0.12, 5.48]
Ghanei 2021	47	105	101	210	15.5%	0.93 [0.72, 1.20]
REMAP-CAP 2020	9	278	1	101	0.2%	3.27 [0.42, 25.49]
Steroids-SARI 2020	23	24	23	23	76.3%	0.96 [0.86, 1.08]
Total (95% CI)		**538**		**461**	**100.0%**	**0.95 [0.86, 1.05]**
Total events	113		168			

Heterogeneity: Tau² = 0.00; Chi² = 4.58, df = 6 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.28)

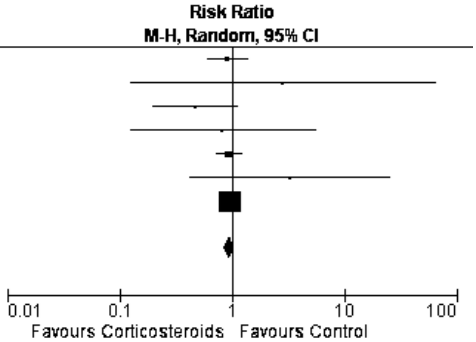


Figure 12. Nosocomial Infection Forest Plot for Type and Dosing of Corticosteroids

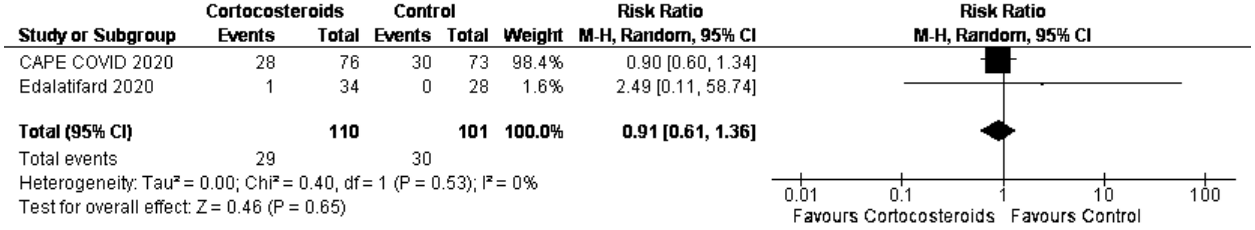


Figure 13. Gastrointestinal Symptoms Forest Plot for Type and Dosing of Corticosteroids

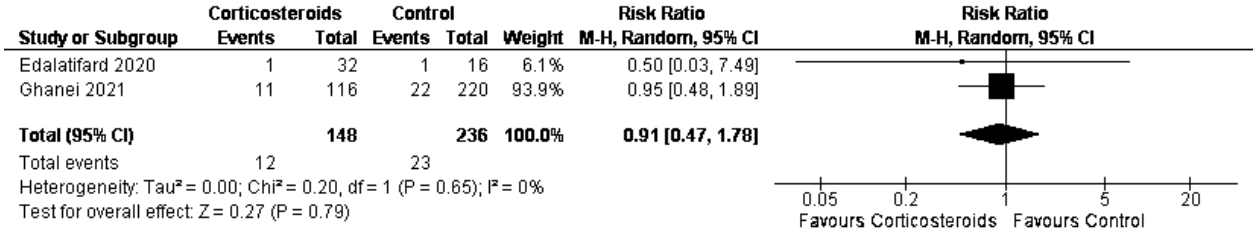


Figure 14. Mortality Forest Plot for Early versus Non-Early Initiation of Corticosteroids

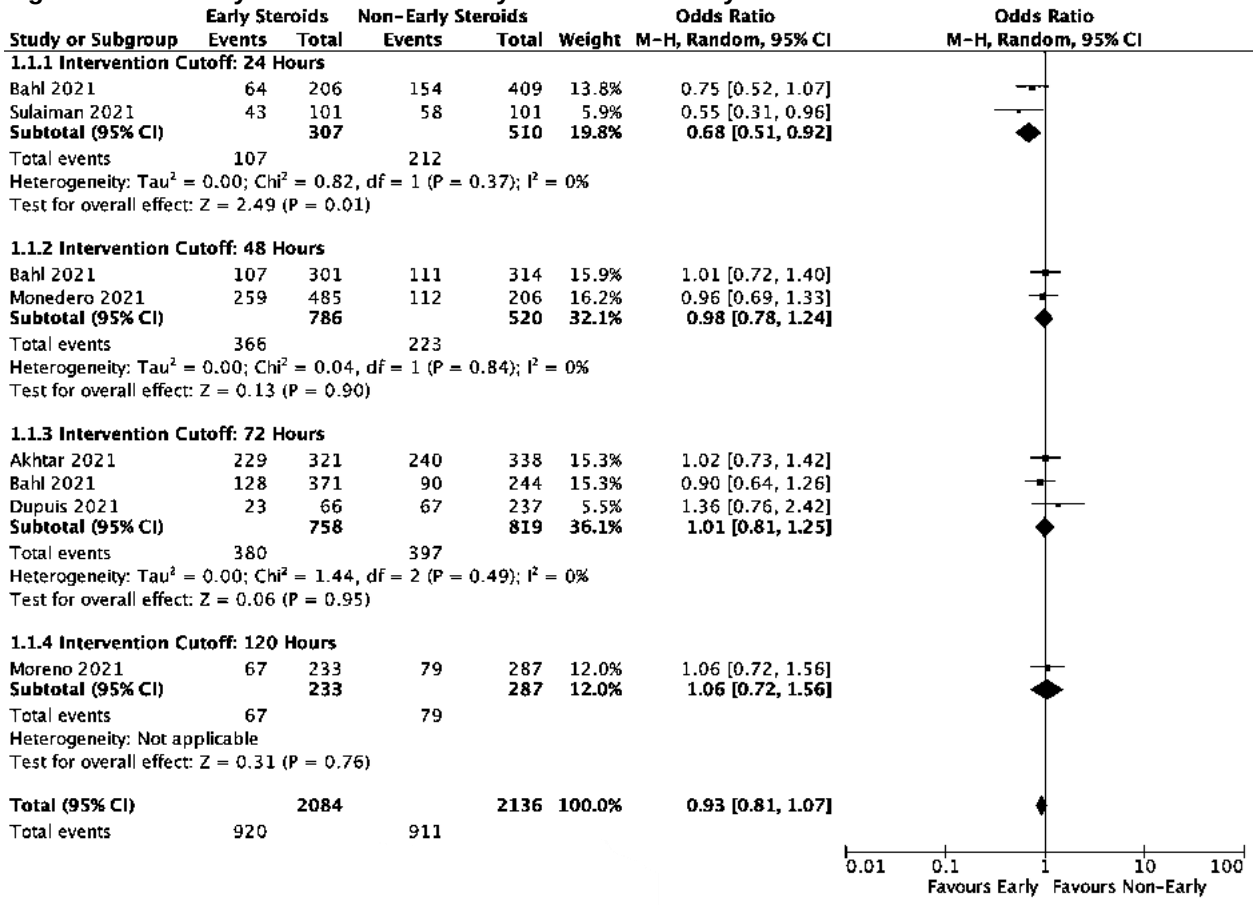


Figure 15. Need for Mechanical Ventilation Forest Plot for Early versus Non-Early Initiation of Corticosteroids

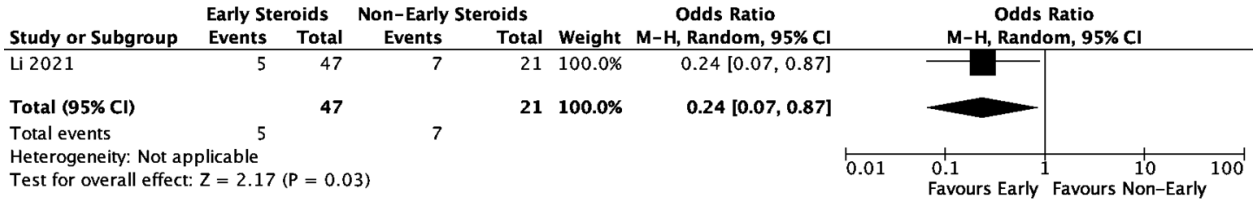


Figure 16. Adverse Events: Hyperglycemia Forest Plot for Early versus Non-Early Initiation of Corticosteroids

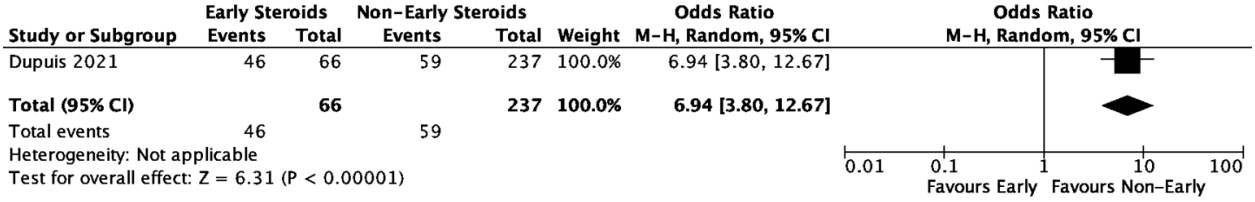


Figure 17. Adverse Events: Blood Stream Infection Forest Plot for Early versus Non-Early Initiation of Corticosteroids

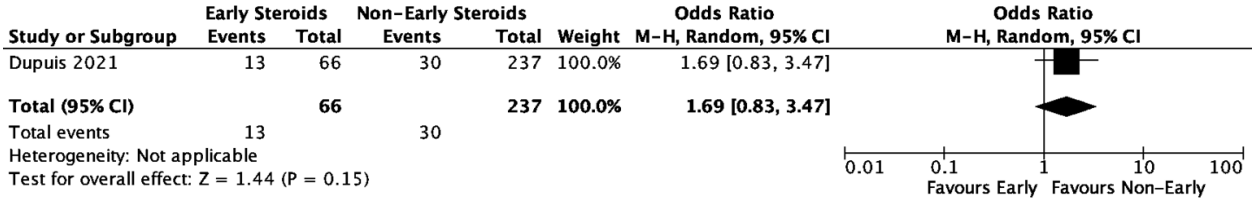
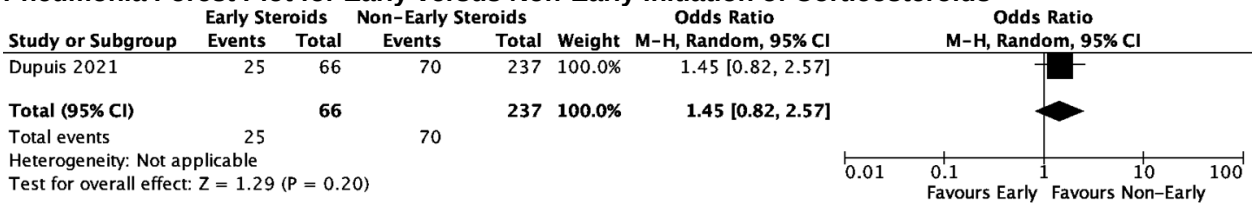


Figure 18. Adverse Events: Incidence of Hospital-acquired Pneumonia and Ventilator-acquired Pneumonia Forest Plot for Early versus Non-Early Initiation of Corticosteroids



Appendix 7. Table of Ongoing Studies

Table 8A. Characteristics of Ongoing Studies

Title (NCT Number)	Interventions	Characteristics	Population	Dates/ Location(s)
Dexamethasone Vs Methylprednisolone for the Treatment of Patients with ARDS Caused by COVID-19 (NCT04499313)	Dexamethasone Methylprednisolone	Multicenter Randomized Open-label Trial	20 to 80 years old with moderate to severe COVID-19 requiring hospitalization	August 5, 2020 – ongoing recruitment Bangladesh
Methylprednisolone vs. Dexamethasone in COVID-19 Pneumonia (MEDEAS RCT) (NCT04636671)	Methylprednisolone Dexamethasone	Single-center Randomized Open-label Trial	18 years and older with COVID-19 on oxygen support, CPAP, or NPPV	April 14, 2021 – ongoing recruitment Italy
Comparison Between Prednisolone and Dexamethasone on Mortality in Patients on Oxygen Therapy, With CoViD-19 (COPreDex) (NCT04765371)	Dexamethasone Prednisolone	Multicenter Randomized Open-label Trial	18 years and older with COVID-19 requiring oxygen therapy	March 3, 2021 – October 2023 France
Glucocorticoid Therapy in Coronavirus Disease COVID-19 Patients (NCT04780581)	Dexamethasone Methylprednisolone	Multicenter Randomized Open-label Trial	18 years and older with CT-confirmed COVID-19 requiring oxygen therapy	February 1, 2021 – December 31, 2021 Spain
RCT on the Efficacy of Dexamethasone Versus Methyl Prednisolone in Covid-19 Infected Patients with High Oxygen Flow (NCT05062681)	Dexamethasone Methylprednisolone	Single-center Randomized Single-blind Trial	18 years and older with COVID-19 on high oxygen flow therapy or positive pressure ventilation	September 15, 2021 – March 15, 2022 Egypt
Effect of Two Different Doses of Dexamethasone in Patients with ARDS and COVID-19 (REMED) (NCT04663555)	Dexamethasone (20 or 6 mg/day)	Phase II Single-center Randomized Open-label Trial	18 years and older with moderate or severe COVID-19	February 2, 2021 – March 31, 2023 Czech Republic
Higher vs. Lower Doses of Dexamethasone for COVID-19 and Severe Hypoxia (COVIDSTEROID2) (NCT04509973)	Dexamethasone (12 or 6 mg/day)	Multicenter Randomized Quadruple-blind Trial	18 years and older COVID-19 patients with severe hypoxia	August 27, 2020 – November 17, 2021 Denmark India Sweden Switzerland
Randomized Open Investigation Determining Steroid Dose (ROIDS-Dose) (NCT04834375)	Dexamethasone (0.2 mg/kg/day or 6 mg/day)	Single-center Randomized Open-label Trial	18 years and older COVID-19 patients with hypoxemia	March 19, 2021 – April 19, 2022 USA
The Efficacy of Different Hormone Doses in 2019-nCoV Severe Pneumonia (NCT04263402)	Methylprednisolone (< 40 or 40-80mg/day)	Single-center Randomized Single-blind Trial	18 years and older COVID-19 patients with severe pneumonia	February 1, 2020 – ongoing recruitment China
Efficacy of DEXamethasone in Patients with Acute Hypoxemic REspiratory Failure Caused by INfEctions (DEXA-REFINE) (NCT04545242)	Dexamethasone (6 mg/day or 20 mg/day x 5 days + 10 mg/day x 5 days)	Phase IV Multicenter Randomized Open-label Trial	18 years and older intubated and mechanically ventilated COVID-19 patients	February 8, 2021 – December 30, 2023 Spain
Timing of Corticosteroids in COVID-19 (NCT04530409)	Early-Dexamethasone Late-Dexamethasone	Phase IV Single-center Randomized Open-label Trial	18 years and older with mild or moderate severity COVID-19	February 10, 2021 – ongoing recruitment Egypt
DEXamethasone EARLY Administration in Hospitalized Patients with Covid-19 Pneumonia (EARLYDEXCoV2) (NCT04836780)	Early-Dexamethasone Late-Dexamethasone	Multicenter Randomized Open-label Trial	18 years and older COVID-19 patients with infiltrates on chest radiography or CT	June 10, 2021 – March 30, 2022 Spain

Evaluation of the Efficacy of High Doses of Methylprednisolone in SARS-CoV2 (COVID-19) Pneumonia Patients (NCT04673162)	Methylprednisolone + Dexamethasone Dexamethasone	Multicenter Randomized Quadruple-blind Trial	18 years and older with COVID-19 on non-invasive oxygen support	December 2020 (not yet recruiting) Italy
Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP) (NCT02735707)	Hydrocortisone (fixed duration vs. shock-dependent)	Multicenter Randomized Open-label Trial	18 years and older COVID-19 patients admitted to an ICU for severe community acquired pneumonia	October 12, 2020 – December 2023 USA Australia Belgium Canada Croatia Germany Hungary Ireland Netherlands New Zealand Portugal Romania Spain UK

Table 8B. Characteristics of Ongoing Studies

Title (NCT Number)	Interventions	Characteristics	Population	Dates/ Location(s)
Timing of Corticosteroids in COVID-19 (NCT04530409)	Early Administration of Dexamethasone given mild to moderate COVID-19 Late Administration of Dexamethasone during deterioration	Randomized Controlled Trial	Adults patients 18 years old and above with mild to moderate COVID-19	February 10, 2021 – August 15, 2021 (No results posted as of December 5, 2021) Cairo, Egypt

Q2. Should anticoagulation be used in treating patients diagnosed with COVID-19?

As of 26 October 2021

RECOMMENDATIONS

We recommend the use of prophylactic over therapeutic dose anticoagulation among hospitalized patients with moderate, severe or critical COVID-19 disease unless there are any contraindications. *(Low certainty of evidence; Strong recommendation)*

We recommend the use of standard dose prophylactic anticoagulation over intermediate dose prophylactic anticoagulation among hospitalized patients with COVID-19 disease unless there are any contraindications. *(Moderate certainty of evidence; Strong recommendation)*

Consensus Issues

A strong recommendation in favor of prophylactic dose anticoagulation was unanimously given despite the low certainty of evidence to give emphasis on preventing harm, as the risk of bleeding was significantly higher with therapeutic dose anticoagulation. It was further emphasized that the duration of anticoagulation, which was not directly addressed by the studies included in this review, should be individualized based on the patient's thromboembolic and bleeding risks.

PREVIOUS RECOMMENDATION

We suggest the use of prophylactic anticoagulation in patients admitted with COVID-19 infection, unless with contraindications. *(Very low quality of evidence; Conditional recommendation)*

We suggest the use of prophylactic dose anticoagulation over therapeutic anticoagulation in critically ill patients with COVID-19 infection. *(Low quality of evidence; Conditional recommendation)*

Previous Consensus Issues

The common dosing for prophylactic anticoagulation are: (1) enoxaparin – 40 mg; (2) heparin – 5000 units based on the studies that specified the dose. The frequency depends on the creatinine clearance of the patients. Relative contraindications to be considered prior to giving anticoagulation include active and clinically significant bleeding, severe bleeding diathesis, severe thrombocytopenia, major trauma, previous intracranial hemorrhage, recent invasive procedure and major trauma. The recommendations for critically ill patients may change once the results of big trials come out.

WHAT'S NEW IN THIS VERSION?

- A total of eight RCTs, seven of which are new, were reviewed to update the current recommendation on anticoagulation in COVID-19. The previous recommendation evaluated evidence from eight observational studies and one RCT.
- Similar recommendations are placed forward but are now based on moderate certainty of evidence. Subgroup analysis of moderate and critically ill patients was also done.

KEY FINDINGS

Eight randomized controlled trials (RCTs) were included in this review to compare therapeutic versus prophylactic anticoagulation and to compare intermediate dose versus standard dose prophylactic anticoagulation in COVID-19 patients. Quality of evidence ranged from very low to moderate due to issues regarding risk of bias, and imprecision due to underpowered population, and wide confidence intervals.

Comparing therapeutic and prophylactic anticoagulation (AC), there was no significant difference over-all in terms of mortality and organ support-free days among critically ill and stable patients. There was a significantly lower over-all incidence of venous thromboembolism (VTE) for therapeutic anticoagulation but there was significantly higher risk for major and minor bleeding for therapeutic anticoagulation considering all populations. However, no significant difference was seen in the incidence of VTE among critically ill patients. There was no significant difference in major bleeding among subgroups of critically ill and stable patients but the trend pointed to a higher incidence among those undergoing therapeutic anticoagulation. For minor bleeding, there was a significantly higher observed incidence among critically ill patients.

For the comparison of intermediate versus standard prophylactic anticoagulation dose among severely ill patients, there was no statistically significant difference in terms of mortality and incidence of venous thromboembolism. There was also no significant difference in terms of major and minor bleeding, but the trend showed higher incidence when given intermediate prophylactic dose anticoagulation.

INTRODUCTION

Microthrombi formation is a possible key mediator of organ dysfunction among COVID-19 patients. A relatively high prevalence rate of venous thromboembolic events (VTE) at 31%, including pulmonary embolism (PE), deep vein thrombosis (DVT), cerebrovascular accident (CVA) and myocardial infarction (MI), has been reported in a meta-analysis among ICU-admitted patients diagnosed with COVID-19.[1] Anticoagulants are the first line of therapy [2] in cases among the general population hence its possible role in decreasing COVID-19 morbidity and mortality is being investigated.

REVIEW METHODS

For this update, peer-reviewed and non-peer reviewed databases such as MEDLINE, Cochrane Library, MedRxIV, and BioRxIV databases were searched until September 10, 2021 with an updated search of ongoing RCTs done on October 10, 2021. Population included were confirmed COVID-19 patients, receiving any anticoagulation agent being used for treating VTE. Keywords used were 1) COVID-19 or SARS-CoV-2 [MeSH], and 2) anticoagulation [MeSH]. Studies with a non-randomized controlled design were excluded as well as studies using investigational or off-label anticoagulating agents. Two comparisons were made in this review: (1) prophylactic versus therapeutic dose anticoagulation and (2) intermediate versus standard dose prophylactic anticoagulation.

RESULTS

Summary of Characteristics of included studies

A total of eight (8) RCTs were included in this review, of which one was previously included in the initial recommendation. Observational studies were excluded in this update to generate better quality evidence provided by the RCTs. Of the eight included, six studies [3-8] compared therapeutic versus prophylactic anticoagulation doses while two RCTs [9,10] investigated intermediate dose prophylactic anticoagulation versus standard dose prophylactic anticoagulation. All studies included were open-label trials, however objective findings were used as primary outcomes; specifically, mortality, incidence of venous thromboembolism (VTE) and major and minor bleeding events.

Therapeutic versus prophylactic anticoagulation (6 RCTs)

Six RCTs investigated therapeutic versus prophylactic anticoagulation (n=4730). Two RCTs made this comparison among unstable patients [6,7] described as those admitted at the ICU, or who required oxygen support via high flow nasal cannula or mechanical ventilation, those on pressors, inotropes, or extracorporeal membrane oxygenation, and those unable to take oral medications. Meanwhile, two other RCTs made use of hospitalized patients with stable COVID-19 disease (moderate COVID-19 patients or those not requiring ICU-level care and not on high flow oxygen support).[4,5] The last two RCTs [3,8] investigated a mixed group population and outcomes were reported for the population as a whole and not based on disease severity, though one of these did a subgroup analysis of ICU-admitted and non-ICU patients only for the safety outcome of major bleeding and not for the efficacy outcomes.[8]

The studies made use of different anticoagulation agents mostly low molecular weight heparin (LMWH) (e.g. enoxaparin [3-8], tinzaparin [4-6], dalteparin [4-6,8]) with unfractionationated heparin (UFH) as an alternative for patients with low creatinine clearance (CrCl).[3-8] One study made use of oral rivaroxaban, a factor Xa inhibitor, as an alternative to enoxaparin in the therapeutic dose intervention group.[3] Given this, analysis to identify the best anticoagulation agent could not be done.

Five studies were open-label trials by design but outcome measures were objective findings (such as mortality and deep vein thrombosis). One study was able to blind the participants and outcome assessors; however, those that were directly involved in the care of the patients were not blinded. Therapeutic anticoagulants were given for 14 days in three RCTs [4,6,7], 28 [5] and 30 [3] days in two, and until hospital discharge or if with any indication to change in the other.[8] Meanwhile, prophylactic anticoagulation treatment was dependent on the treating physician for five RCTs [3-6, 8] and until discharge or day 28, whichever was shorter, for the other RCT.[7]

Major concerns for these studies included two RCTs which had populations not reaching their target sample size [5,7], hence had underpowered results as listed in the limitations of their work, while one did not employ intention to treat analysis, making their data also not consistent (i.e. different number of participants in different outcomes).[4] In addition, one study enrolled those with clinically proven high risk for thromboembolism, which may enhance the result of the intervention.[8] Since patients were already at high risk for thromboembolism, majority of the participants were already on anticoagulating agents (LMWH and UFH) even prior to randomization

(82.8% for therapeutic dose, 78.2% for prophylactic dose). No statistical adjustment was performed and no mention of the baseline dosage was made.

Efficacy outcomes
Pooled results for three efficacy outcomes were obtained from the studies: mortality, incidence of VTE, and organ support-free days.

Mortality was not significantly different between the therapeutic and prophylactic groups (RR 0.90, 95% CI 0.66-1.24, very low quality). This association was maintained in the subgroups of stable (RR 0.50, 95% CI 0.13-1.88, very low quality) and unstable patients (RR 0.84, 95% CI 0.37-1.87, moderate quality). There was noted significant heterogeneity over-all and even after subgroup analysis this heterogeneity was maintained. Possible source of heterogeneity is the treatment regimen and crossover of treatment which also contributed to the risk of bias. Downgrading of quality of evidence was based on the concerns for bias as stated above, inconsistent results and wide range effect estimate (see Appendix 4).

Incidence of VTE on the other hand was noted to be significantly less in the therapeutic group (RR 0.56, 95% CI 0.41-0.77, low quality). This observation was maintained for the subgroup of stable patients (RR 0.51, 95% CI 0.29-0.90, moderate quality) but among critically ill patients, there was no significant difference between the therapeutic and prophylactic groups (RR 0.96, 95% CI 0.44-2.13, moderate quality). Although a significant difference was noted in the pooled results, the individual results of the five RCTs showed no significant difference between the therapeutic and prophylactic group. Only the study that recruited those with high risk for thromboembolic events showed a significant benefit for the therapeutic dose group.

Organ support-free days did not differ significantly between the two groups as a whole (OR 1.11, 95% CI 0.79-1.56, low quality) based on three RCTs but subgroup analysis showed that stable patients receiving therapeutic anticoagulation had significantly longer organ support-free days as compared to those receiving prophylactic anticoagulation (OR 1.29, 95% CI 1.07-1.56, low quality). This trend was not observed among critically ill patients (OR 0.83, 95% CI 0.67-1.03, high quality) based on one RCT. High heterogeneity was observed in the overall pooled result but this was not seen in the subgroup effect estimate.

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Safety outcomes
Collectively, major bleeding was significantly higher among the therapeutic dose anticoagulation group compared to the prophylactic dose anticoagulation group (RR 1.82, 95% CI 1.18-2.82, low quality); however, subgroup analyses of the stable and unstable patients both showed no significant difference in incidence of major bleeding. It was noted though that the trend showed more events for the therapeutic group both in the stable (RR1.43, 95% CI 0.61-3.32, low quality) and unstable patients (RR 1.85, 95% CI 0.79-4.31, moderate quality). Minor bleeding events, defined as bleeding events warranting attention of a physician but not satisfying the criteria for major bleeding (BARC and ISTH criteria), was also noted to be significantly higher in the therapeutic group among the unstable patients (RR 2.74, 95% CI 1.03-7.26, moderate quality) and mixed population (RR 3.77, 95% CI 1.76-8.09, moderate quality). No data was available for stable patients.

Intermediate dose prophylactic anticoagulation versus standard dose prophylactic anticoagulation (2 RCTs)

Both RCTs compared the effect of intermediate (1mg/kg/day) and standard (40mg daily) prophylactic anticoagulation doses among patients with severe COVID-19 admitted at the ICU.[9,10] Both used enoxaparin, a LMWH as the primary agent of choice with dose adjustment as needed based on BMI (see Appendix 3). UFH was used in cases of severe renal injury. One study had concerns in the design since some participants (n= 37) were also allowed to participate in other COVID-19 trials [9], while the other study had low risk of bias.[10] Intervention was continued until hospital discharge or a clinically significant event warranted dose adjustment of the drug in one study, while it was continued until 30 days of follow-up in the other RCT regardless of the discharge status of the patient.

Efficacy outcomes

Pooled results from the two RCTs (n= 646) show no significant difference in terms of all-cause mortality (RR 1.0, 95% CI 0.78-1.28) and incidence of VTE (RR 1.03, 95% CI 0.52-2.02) between intermediate and standard dose anticoagulation.[9,10] Results are based on low quality of evidence due to some issues for risk of bias (participation in other clinical trials, significant difference in coadministration of azithromycin between treatment groups in one study) and wide confidence interval among all outcomes.

Safety outcomes

In terms of safety, there was no significant difference for major (RR 1.54, 95% CI 0.55-4.31) and minor (RR 1.62, 95% CI 0.67-3.91) bleeding events but there was a trend towards higher incidence among those receiving the intermediate anticoagulation dose (low quality of evidence). The INSPIRATION trial also reported similar ventilator-free days (p=0.50), ICU-length of stay (p=0.14), and number of patients discharged from ICU (OR 1.01, 95% CI 0.72-14.2) between the intermediate and standard dose group.

EVIDENCE TO DECISION

Different societies have advocated the use of prophylactic anticoagulation for those with increased risk of VTE from COVID-19 (see below). This recommendation also came from results of studies which were presented in this review. There is no study available directly discussing the cost of anticoagulation therapy in COVID-19; however, one study has demonstrated that in non-COVID-related critically-ill patients anticoagulation-associated major bleeding led to higher in-hospital mortality (adjusted OR 1.49, 95% CI 1.16-1.9), prolonged hospital stay (median of 11 days vs 6 days, p=0.02), and had higher expenses among those that survived. [11] This supports using the lowest acceptable dose that minimizes the risk of bleeding.

RECOMMENDATIONS FROM OTHER GROUPS

Listed below are recommendations for the use anticoagulation in COVID-19 from different notable societies/institutions.

Association/Institution (date last updated)	Recommendation
Australian Living CPG [12] (9/6/21)	Hospitalized patients with COVID-19 - VTE prophylaxis recommended (conditional recommendation) for moderate, severe and critical disease including pregnant and post-partum patients unless there is absolute contraindication (e.g. major risk for bleeding) - No additional indication for therapeutic anticoagulation dose based on current data and therefore should not be routinely offered - For pregnant and postpartum patients with moderate disease, should be continued for at least 14 days post discharge or until COVID-19 related morbidity has resolved. If with severe or critical disease, continued for at least 4 weeks post discharge or until morbidity has resolved
American Society of Hematology [13] (7/15/2021)	All hospitalized patients with COVID-19 - Prophylactic anticoagulation recommended unless risk of bleeding outweighs risk - LMWH recommended over UFH; if with contraindications to heparins, fondaparinux is recommended - Standard dose prophylaxis suggested over intermediate or therapeutic dose - Giving of anticoagulation after discharge suggested not to be given in the absence of any indication
National Institute of Health (NIH) [14] (2/11/2021)	Non-hospitalized patients with COVID-19 - Anticoagulation should not be initiated unless there are other indications or patient is participating in a clinical trial Hospitalized patients with COVID-19 - All non-pregnant adults recommended to receive prophylactic anticoagulation. There is insufficient evidence to support the use of higher than standard dose of AC outside of clinical trials - Pregnant patients with severe COVID-19 also recommended to receive prophylactic anticoagulation unless there is a contraindication - VTE prophylaxis after discharge is not recommended
World Health Organization (WHO) [15] (1/25/21)	Hospitalized patients with COVID-19 (conditional recommendation) - Standard dose prophylactic anticoagulation rather than higher prophylactic dose or therapeutic dose unless there is a warranted indication

RESEARCH GAPS

There is a uniform consensus among different organizations about the recommendation of using prophylactic dose anticoagulation among hospitalized COVID-19 patients. Current evidence however has yet to address which anticoagulating agent can best prevent VTEs while minimizing the risk of bleeding. There are currently 19 listed active ongoing studies, some of which are investigating not only LMWH but also other anticoagulating agents, among which are oral anticoagulants that are seen to cost less than injectable agents (Appendix 6). Another recommendation from some societies that still need further evidence is the duration of anticoagulation treatment after discharge from the hospital. Data on the incidence of DVTs post-recovery among previously hospitalized COVID-19 patients is still coming into light as part of the post-COVID symptoms.

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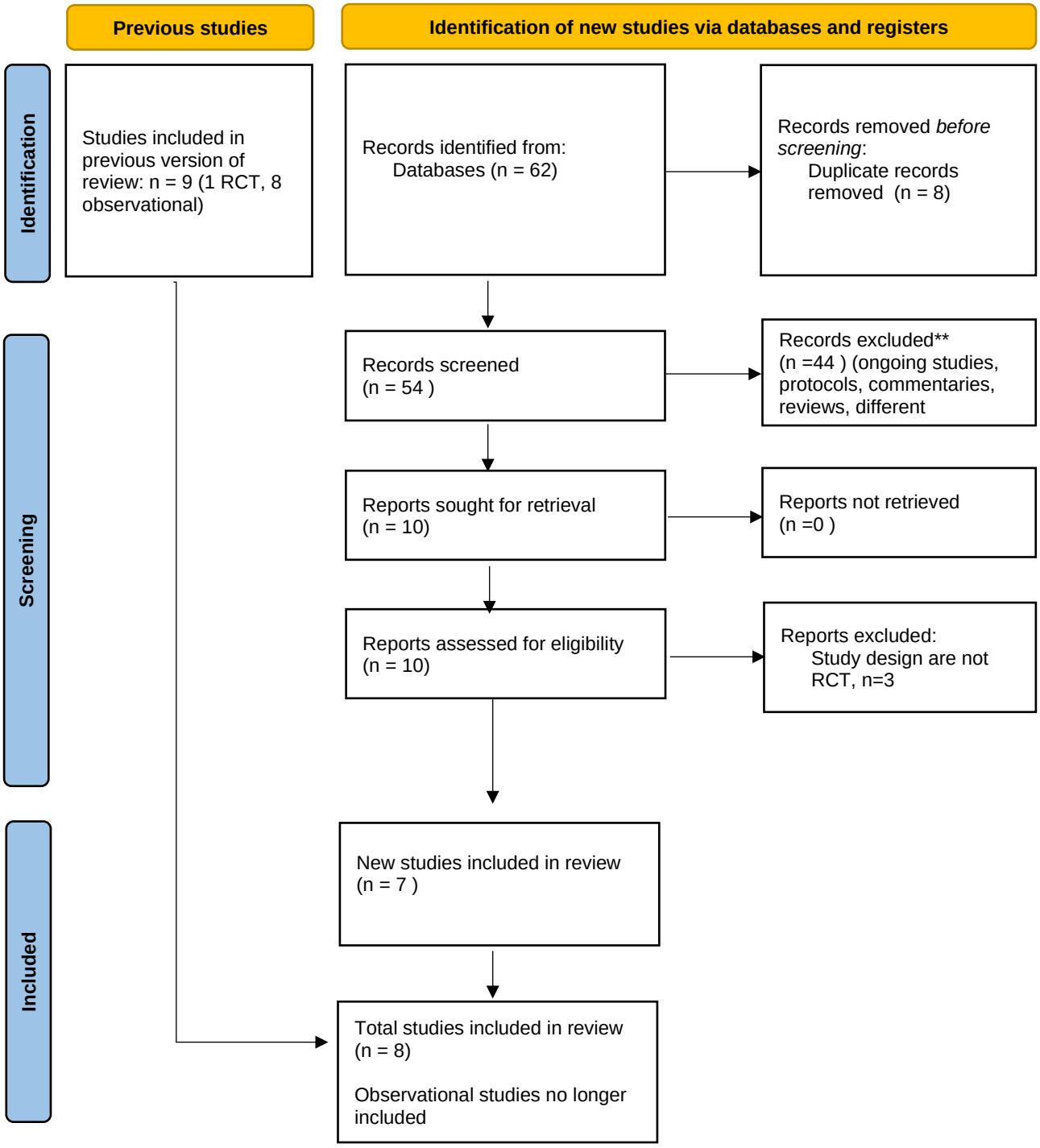
Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion: anticoagulation (N=10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)					• Relatively high prevalence rate of venous thromboembolic events (VTE) at 31% including pulmonary embolism (PE), deep vein thrombosis (DVT), cerebrovascular accident (CVA) and myocardial infarction (MI) has been reported in a meta-analysis among ICU-admitted patients diagnosed with COVID-19
Benefits	Large (2)	Moderate (5)	Small (3)	Uncertain			• <u>Therapeutic vs prophylactic AC:</u> No difference for mortality over-all and in subgroups analyze Favors therapeutic dose in terms of decreasing incidence of VTE overall and in stable and mixed population. No difference in unstable subgroup No difference over-all and in unstable group for organ support free days, with more organ0support free days in stable group • <u>Intermediate dose vs standard dose AC:</u> No benefit over the other for mortality and VTE
Harm	Large (3)	Small (7)	Uncertain	No response			• <u>Therapeutic vs prophylactic AC:</u> Major bleeding increased in therapeutic group overall, not significant but trend towards more incidence in the same group (stable and critical) Minor bleeding more in therapeutic • <u>Intermediate dose vs standard dose AC:</u> No benefit over the other for major and minor bleeding
Certainty of Evidence	High	Moderate (7)	Low (3)	Very low			• Very low to moderate
Balance of effects	Favors drug (6)	Does not favor drug (4)	Uncertain				• There is increased risk of possible harm (major and minor bleeding) for therapeutic anticoagulation dosing, and less incidence of VTE for the critically ill receiving this regimen, prophylactic anticoagulation dose is recommended. • Standard dose is shown to provide similar safety and harm outcomes as the intermediate dose.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (4)	No important uncertainty or variability (1)			
Resources Required	Uncertain (7)	Large cost (1)	Moderate Cost (2)	Negligible cost	Moderate savings	Large savings	
Certainty of evidence of required resources	No included studies (9)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (8)	Favors the comparison (1)	Does not favor either the intervention	Favors the intervention (1)			

			or the comparison			
Equity	Uncertain (7)	Reduced (1)	Probably no impact (1)	Increased (1)		
Acceptability	Uncertain (4)	No	Yes (6)			
Feasibility	Uncertain (3)	No	Yes (7)			

Appendix 2. Search Yield and Results



Appendix 3. Study Characteristics of Included Studies

Study ID	Study Design	Setting	Total population	Population	Intervention	Comparator	Outcomes
Perepu	multi-center, open-label RCT	three centers in the US	176	hospitalized adults with documented SEVERE COVID-19 (admitted to ICU and/or have laboratory evidence of coagulopathy) *exclusion: with indication for full dose AC, major bleeding, severe thrombocytopenia, current pregnancy, hx of acute venous/arterial thromobisis past 3 months, acute or chronic renal insufficiency (CrCl < 30)	intermediate dose enoxaparin 1mg/kg SC daily, fpr BMI < 30 0.5mg/kg SC twice dail for BMI > 30	standard prophylactic dose enoxaparin 40mg SC daily for BMI < 30 30 or 40mg SC BID for BMI > 30	all cause mortality at 30 days arterial/venous thromboembolism major bleeding minor bleeding
Sadeghipour (INSPIRATION)	open label RCT	10 academic centers in Iran	562	adult COVID-19 patients admitted to the ICU *exclusion: life expectancy < 24hrs, established indication for therapeutic AC, weigh less than 40kg, pregnancy, history of heparin induced thrombocytopenia, platelet less than 50, and overt bleeding	intermediate dose enoxaparin if CrCl >30 1mg/kg SC daily if wt <120kg or BMI<35 0.6mg/kg SC twice daily if wt?120kg or BMI .35 If CrCl 15-30 Enoxaparin 0.5mg/kg SC daily (at least 40mg) If CrCl<15 UFH 10,000U SC twice daily n= 276	standard prophylactic AC if CrCl >30 40mg SC daily if wt <120kg or BMI<35 40mg SC twice daily if wt?120kg or BMI .35 If CrCl 15-30 Enoxaparin 30mg SC daily If CrCl<15 UFH 5,000 U SC twice daily	COMPOSITE of mortality within 30 days, venous/arterial thrombosis and treatment with ECMO major bleeding severe thrombocytopenia
Lopes (ACTION)	multi-center, open-label RCT	31 hospitals in Brazil	615	hospitalised symptomatic COVID-19 patients (>18 years old) with elevated D-dimer concentration up to 14 days before randomisation *exclusion: indication for therapeutic AC, contraindications to rivaroxaban or heparin and high risk for bleeding	therapeutic AC oral rivaroxaban 15-20mg daily for stable patients OR initial SC enoxaparin (1mg/kg BID)/ IV unfractionated heparin (to achieve 0.3-0.7 IU/mL anti-Xa concentration) for clinically unstable patients followed by	prophylactic AC standard in-hospital enoxaparin, UFH, or fondaparinux for CrCl>30 if BMI < 40: enoxaparin 40mg SC daily, fondaparinux 2.5mg SC daily, UFH 5000U SC q8-12hrs if BMI >40 enoxaparin 60mg SC daily or 40mg SC BID, fondaparinux not	hierarchical composite of the ff: time to death duration of hospitalisation duration of supplemental O2 to day 30 major bleeding clinically significant non-major bleeding through D30

					oral rivaroxaban to day 30 n=311	recommended, UFH7500 U SC q8-12h if CrCl< 30 if BMI < 40: UFH 5000 SC U q8-12 If BMI >40 UFH 7500 U SC every8-12hours *may receive therapeutic dose if with clinical indication at the discretion of treating physician n=304	
Goligher (REMAP-CAP, ACTIV-4a, ATTACC)	open label, adaptive, multiplatform RCT	121 sites in 9 countries	1098	critically-ill patients with severe COVID-19 *exclusion- if admitted in ICU for 48hours or longer prior to randomisation OR admiited in hospital for 72 hours or longer, imminent risk of death, no commitment to organ support, high risk for bleeding, reeceiving dual antiplatelet therapy, has a non-covid indication for AC, or history of heparin sensitivity	therapeutic AC Enoxaparin 1mg/kg SC daily (CrCl >/30), 0.6mg/kg SC BID (w>120kg or BMI >35), 0.5mg/kg SC daily (CrCl 15-130), UFH 10000 units SC BID (CrCl </15) n= 534	prophylactic AC Enoxaparin 40mg SC daily (CrCl >/30), 40mg SC BID (weight >120, BMI > 35), 30mg SC daily (CrCl 15-30), UFH 5000 units SC twice daily (CrCl </15ml/min) n=564	organ support-free days up to 21 days (combined in-hospital death and number of days free of cardiovascular/respiratory organ support)
Lawler (REMAP-CAP, ACTIV-4a, ATTACC)	open label, adaptive, multiplatform RCT	121 sites in 9 countries	2219	hospitalized COVID-19 patients not receiving critical care management (as above) *exclusion- if >72 hrs since admission or inhospital confirmation of COVID-19 to randomisation, or >14 days since admission, discharge expected within 72 hrs, clinical indication for therepeutic AC, high risk of bleeding, or history of heparin sensitivity	therapeutic AC LMWH or UFH based on weight and CrCl dose dependent on local hospital policy or guidelines to treat VTE n=1171	prophylactic AC (either standard dose or intermediate dose prophylaxis) LMWH or UFH based on standard thrombopohylaxis dose n=1048	organ support-free days up to 21 days (combined in-hospital death and number of days free of cardiovascular/respiratory organ support)
Sholzberg (RAPID)	multi-center, open-label RCT	28 sites in 6 countries	465	moderately ill hositalised ward COVID-19 patients with elevated D-dimer within first five days of admission *exclusion- major bleeding risk, absolute indication for AC, any contraindication for use of heparin, pregnant, meet or imminent risk to develop component of primary outcome soon	therapeutic AC CrCl >30 if BMI < 40 enoxaparin1mg/kg SC q12 or 1.5mg/kg SC q24, dalteparin 200u/kg sc q 24 or 100u/kg q12,	Prophylactic AC CrCl >30 if BMI < 40 enoxaparin 40mg SC q24, dalteparin 5000 U q 24, Tinzaparin 4500U q24, Fondaparinux 2.5mg q24, UFH 5000u q8-12 If BMI >40	composite of death, invasive and non-invasive mechanical ventilation, ICU admission major bleeding

					Tinzaparin 175U/kg q24 UFH titrate to institution specific anti-Xa or aPTT values If BMI >40 Enoxaparin 1mg/kg q12, dalteparin 100u/kg q12, tinzaparin 175u/kg q24, UFH as above If CrCl< 30 Whether BMI >40 or < 40 UFH IV bolus to titrate to institution specific anti-Xa or aPTT values or LMWH as per institution-based BMI n= 228	enoxaparin 40mg SC q12, dalteparin 5000 U q 12, Tinzaparin 9000 U q24, Fondaparinux not recommended UFH 7500u q8 If CrCl< 30 BMI <40 UFH 5000 U Q8-q12 or LMWH as per institution-based BMI BMI > 40 UFH 7500 U q8 or LMWH as per institution-based BMI n= 237	
Lemos (HESACOVID)	open-label phase 2 RCT	single center in Brazil	20	COVID-19 patients with ARDS (by Berlin definition) requiring mechanical ventilation *exclusion- older than 85y/o, CrCl <10, advanced end organ diseases (liver, circulatory, renal), COPD requiring o2 at home, significant disability from stroke and other neurocognitive problems, pregnant, significant risk of bleeding, participating in other RCTs, with indication for therapeutic AC other than COVID	therapeutic AC SC enoxaparin adjusted for age and CrCl *if CrCl worsened during study, transitioned to UFH 24h after last dose of enoxaparin n=10	prophylactic (according to doctor's judgment) UFH 5,000 IU TID (weight <120kg), 7500 IU TID (>120kg) OR enoxaparin 40mg OD (w<120kg), 40mg BID (w>120kg) n=10	gas exchange over time (paO2/FiO2) at baseline, d7 and d14 time until weaning off MV, ventilator-free days
Spyropoulos (HEP-COVID)	Multi-center RCT	12 academic centers in US	253	Hospitalized non-pregnant adult COVID-19 patients with elevated D-dimer (>4x ULN) or sepsis induced coagulopathy score of 4 or greater AND requiring oxygen support *exclusion criteria: Indication for full dose AC or dual antiplatelet therapy, bleeding within the past month, active GI or intracranial cancer, bronchiectasis or pulmonary cavitation, hepatic dysfunction with elevated baseline INR, CrCl < 15, platelet < 25000,history of heparin-induced thrombocytopenia, and hypersensitivity to study drugs	Therapeutic AC SC enoxaparin 1 mg/kg BID or 0.5mg/kg SC BID (if CrCl 15-29) n= 129	Prophylactic AC (based on local standard) Standard dose Or intermediate dose Included UFH 22,500 BID-TID, enoxaparin 30-40mg SC OD-BID, or dalteparin 2500-5000 IU SC OD n=124	Venous or arterial thromboembolism, death, major bleeding

Study ID	Directness	Validity	Results	Main Issues	Risk of Bias
Perepu	Yes	Open label design, outcome assessors NOT blinded, more patients received azithromycin in treatment arm (possible confounding)	Intention to treat analysis and sensitivity analysis done	Enrolment in other clinical trials allowed	high
Sadeghipour (INSPIRATION)	Yes	Open label design, outcome assessors blinded	Intention to treat analysis and sensitivity analysis done	None	low
Lopes (ACTION)	Yes	Open label design, outcome assessors blinded	Intention to treat analysis and sensitivity analysis done	Used different types of anticoagulants in treatment arm (not just LMLWH)	moderate
Goligher (REMAP-CAP, ACTIV-4a, ATTACC)	Yes	Open label design, outcome assessors blinded	Intention to treat analysis and sensitivity analysis done	None	low
Lawler (REMAP-CAP, ACTIV-4a, ATTACC)	Yes	Open label design, outcome assessors not specified if blinded	Intention to treat analysis NOT done; sensitivity analysis done	Inconsistent counts in some outcomes (used different number of population)	high
Sholzberg (RAPID)	Yes	Open label design, outcome assessors blinded	Intention to treat analysis and sensitivity analysis done, did not reach sample size	Underpowered number of participants	moderate
Lemos (HESACOVID)	Yes	Open label design, outcome assessors blinded	Intention to treat analysis and sensitivity analysis done, small sample size, small outcome events	wide confidence intervals due to small event outcome and sample size	Moderate
Spyropoulos (HEP-COVID)	Yes	Participants and outcome assessors blinded, those with direct care not blinded. Population chosen were those that had high risk for VTE and thus would likely benefit for anticoagulation use	Intention to treat analysis done, for safety outcome data was presented among ICU-admitted and non-ICU admitted patient while for efficacy outcomes this was not done	Recruited population are those that would benefit use of AC, allowed recruitment of those using AC or antiplatelet prior to randomization (for both groups), not all outcomes had the same subgroup (no explanation why only done on safety outcome and not on efficacy outcome), For both groups anytime CrCl went down to < 15, AC is shifted to therapeutic dose UFH then shifted back to original assignment once CrCl increases to more than 15 however no analysis and mention of data regarding this	high

Appendix 4. Grade Evidence Profile

Therapeutic dose AC compared to prophylactic dose AC for hospitalised COVID-19 patients?

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 prophylactic dose AC	With therapeutic dose AC		Risk with prophylactic AC	Risk difference with therapeutic dose AC
Mortality- all population											
4730 (6 RCTs)	Very serious[a,b]	Serious[c]	Not serious	Serious[d]	None	⨁◯◯◯ Very low	363/2347 (15.5%)	351/2383 (14.7%)	**RR 0.90** (0.66 to 1.24)	155 per 1,000	**15 fewer per 1,000** (from 53 fewer to 37 more)
Venous Thromboembolism											
4730 (6 RCTs)	Very serious[a,b,e]	Not serious	Not serious	Not serious	None	⨁⨁◯◯ Low	98/2347 (4.2%)	55/2383 (2.3%)	**RR 0.56** (0.41 to 0.77)	42 per 1,000	**18 fewer per 1,000** (from 25 fewer to 10 fewer)
Organ support free days											
0 (3 RCTs)	Very serious[a,b]	Serious[c]	Not serious	Serious[f]	None	⨁◯◯◯ Very low			**OR 1.11** (0.79 to 1.56)	0 per 1,000	**1 fewer per 1,000** (from 2 fewer to 1 fewer)
Major bleeding											
4730 (6 RCTs)	Very serious[a,b]	Not serious	Not serious	Not serious	None	⨁⨁◯◯ Low	32/2347 (1.4%)	60/2383 (2.5%)	**RR 1.82** (1.18 to 2.82)	14 per 1,000	**11 more per 1,000** (from 2 more to 25 more)
Minor bleeding											
1793 (3 RCTs)	Serious[a]	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ Moderate	8/938 (0.9%)	30/855 (3.5%)	**RR 3.77** (1.76 to 8.09)	9 per 1,000	**24 more per 1,000** (from 6 more to 60 more)

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

Explanations

[a] different severity of disease
[b] differences in giving of intervention, such as shifting of kind of AC used, dose of AC used, etc
[c] concern over I2, wide range of effect estimate in included studies
[d] wide confidence interval
[e] two study recruited patients with high risk for VTE
[f] different result in studies, CI without overlap

Therapeutic dose AC compared to prophylactic dose AC for COVID-19 patients with critical illness?

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 prophylactic dose AC	With therapeutic dose AC		Risk with prophylactic AC	Risk difference with therapeutic dose AC
Mortality											
1118 (2 RCTs)	Not serious	Not serious	Not serious	Serious [a]	None	⨁⨁⨁◯ Moderate	205/574 (35.7%)	201/544 (36.9%)	**RR 0.84** (0.37 to 1.87)	357 per 1,000	**57 fewer per 1,000** (from 225 fewer to 311 more)
Venous Thromboembolism											
1118 (2 RCTs)	Not serious	Not serious	Not serious	Serious [a]	None	⨁⨁⨁◯ Moderate	12/574 (2.1%)	11/544 (2.0%)	**RR 0.96** (0.43 to 2.13)	21 per 1,000	**1 fewer per 1,000** (from 12 fewer to 24 more)
Major bleeding											
1201 (3 RCTs)	Not serious	Not serious	Not serious	Serious [a]	None	⨁⨁⨁◯ Moderate	13/612 (2.1%)	24/589 (4.1%)	**RR 1.85** (0.79 to 4.31)	21 per 1,000	**18 more per 1,000** (from 4 fewer to 70 more)
Minor bleeding											
1118 (2 RCTs)	Not serious	Not serious	Not serious	Serious [a]	None	⨁⨁⨁◯ Moderate	5/574 (0.9%)	14/544 (2.6%)	**RR 2.74** (1.03 to 7.26)	9 per 1,000	**15 more per 1,000** (from 0 fewer to 55 more)

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

Explanations

[a] wide confidence interval; one study has low population and event outcome

Therapeutic dose AC compared to prophylactic dose AC for COVID-19 patient with non-critical disease?

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 prophylactic dose AC	With therapeutic dose AC	Relative effect (95% CI)	Risk with prophylactic AC	Risk difference with therapeutic dose AC
Mortality											
2684 (2 RCTs)	Serious [a,b]	Serious [c]	Not serious	Serious [d]	None	⨁◯◯◯ Very low	104/1285 (8.1%)	90/1399 (6.4%)	**RR 0.50** (0.13 to 1.88)	81 per 1,000	**40 fewer per 1,000** (from 70 fewer to 71 more)
Venous Thromboembolism											
2684 (2 RCTs)	Serious [a,b]	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ Moderate	33/1285 (2.6%)	18/1399 (1.3%)	**RR 0.51** (0.29 to 0.90)	26 per 1,000	**13 fewer per 1,000** (from 18 fewer to 3 fewer)
Major bleeding											
2854 (3 RCTs)	Serious [a,b]	Not serious	Not serious	Serious [d]	None	⨁⨁◯◯ Low	15/1371 (1.1%)	26/ 1483 (1.8%)	**RR 1.43** (0.61 to 3.32)	11 per 1,000	**5 more per 1,000** (from 4 fewer to 25 more)
Minor bleeding											
1118 (2 RCTs)	Not serious	Not serious	Not serious	Serious [a]	None	⨁⨁⨁◯ Moderate	5/574 (0.9%)	14/544 (2.6%)	**RR 2.74** (1.03 to 7.26)	9 per 1,000	**15 more per 1,000** (from 0 fewer to 55 more)

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

Explanations

[a] one study with inconsistent event counts
[b] one study is underpowered (did not reach adequate sample size)
[c] concerns with I2, CI did not overlap
[d] wide confidence interval

Intermediate dose prophylactic AC compared to standard dose AC for severe COVID-19 patients?

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 prophylactic dose AC	With therapeutic dose AC	Relative effect (95% CI)	Risk with prophylactic AC	Risk difference with therapeutic dose AC
All-cause mortality at 30 days											
731 (2 RCTs)	Serious [a]	Not serious	Not serious	Serious [b]	None	⨁⨁◯◯ low	135/371 (36.4%)	132/360 (36.7%)	**RR 1.00** (0.78 to 1.28)	364 per 1,000	**0 fewer per 1,000** (from 80 fewer to 102 more)
Venous Thromboembolism											
731 (2 RCTs)	Serious [a]	Not serious	Not serious	Serious [b]	None	⨁⨁◯◯ low	16/371 (4.3%)	16/360 (4.4%)	**RR 1.03** (0.52 to 2.02)	43 per 1,000	**1 more per 1,000** (from 21 fewer to 44 more)
Major bleeding											
731 (2 RCTs)	Serious [a]	Not serious	Not serious	Serious [b]	None	⨁⨁◯◯ low	6/371 (1.6%)	9/360 (2.5%)	**RR 1.54** (0.55 to 4.31)	16 per 1,000	**9 more per 1,000** (from 7 fewer to 54 more)
Minor bleeding											
731 (2 RCTs)	Serious [a]	Not serious	Not serious	Serious [b]	None	⨁⨁◯◯ low	11/371 (3.0%)	18/360 (5.0%)	**RR 1.62** (0.67 to 3.91)	30 per 1,000	**18 more per 1,000** (from 10 fewer to 86 more)

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

Explanations

[a] one study allowed the participation of patients who are enrolled in other clinical trials (n= 37);

[b] wide confidence interval (>25% range on each side)

Appendix 5. Forest plots of comparisons of outcomes

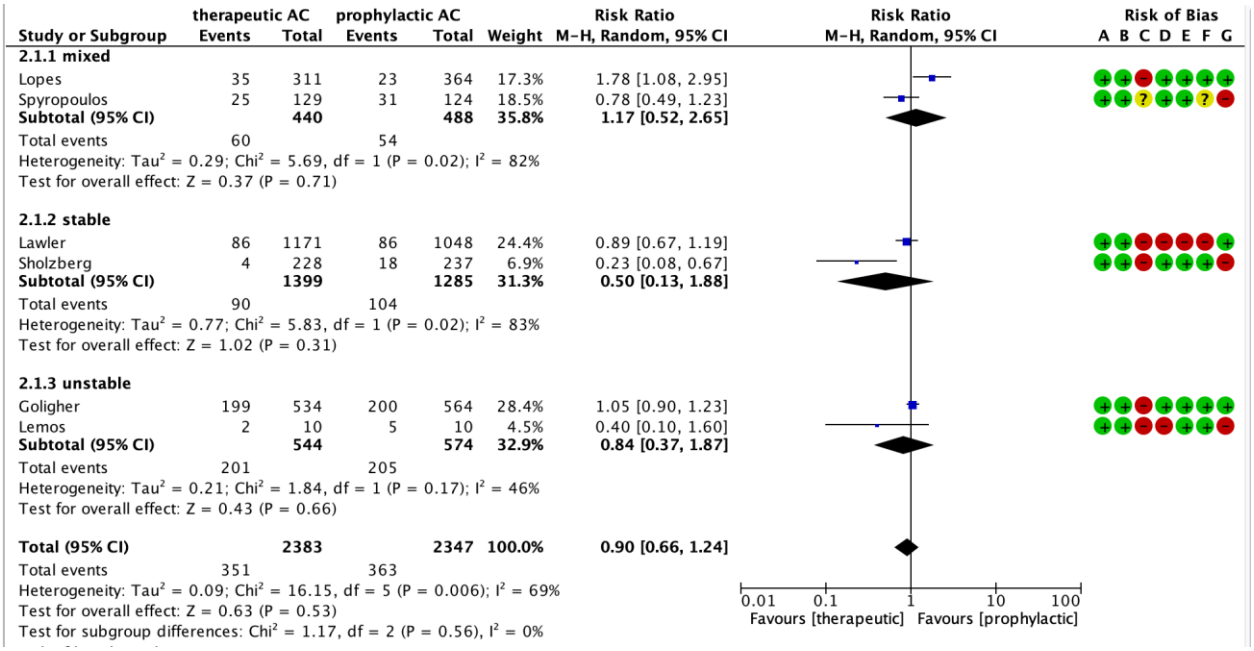


Figure 2. Risk of Mortality comparing therapeutic versus prophylactic AC

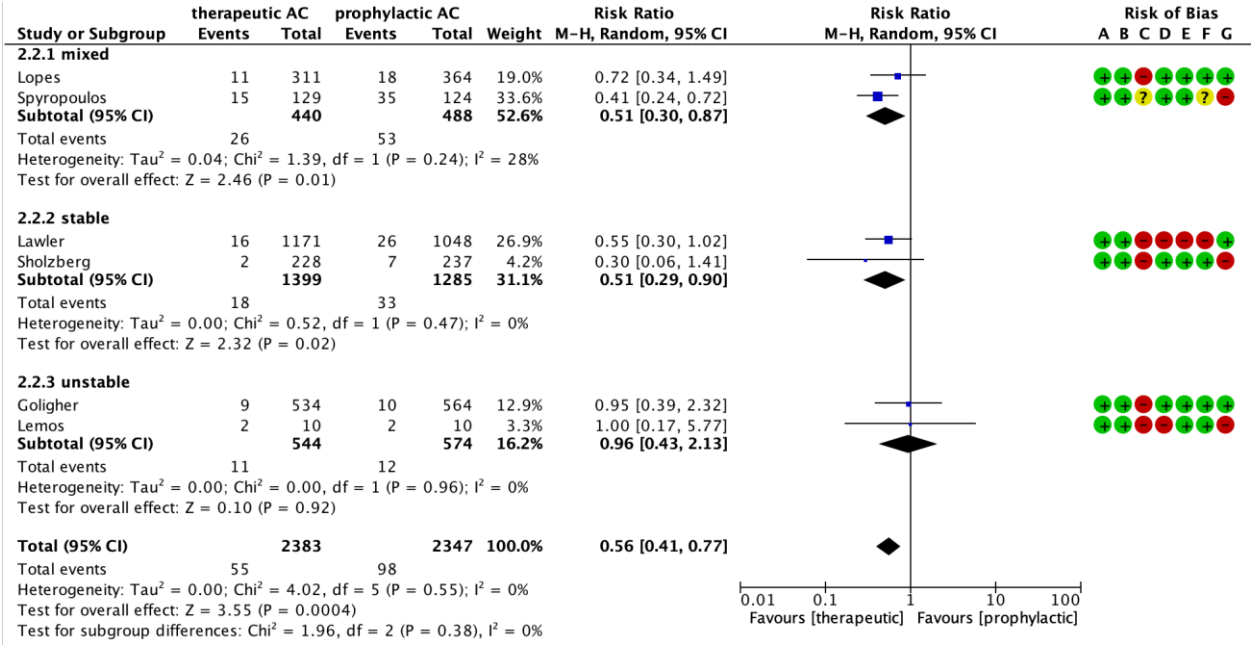


Figure 3. Comparing incidence of VTE in therapeutic versus prophylactic AC

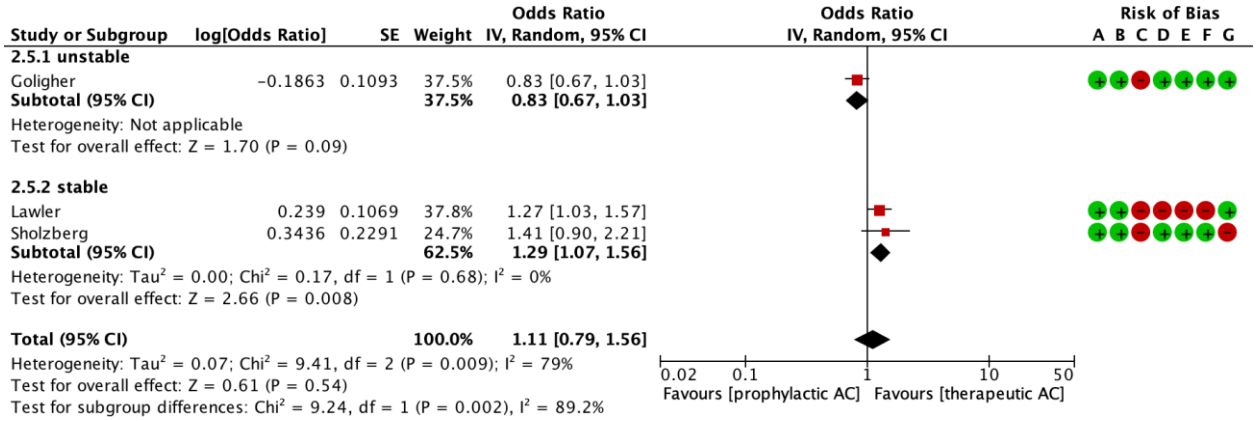


Figure 4. Comparing organ support-free days between therapeutic versus prophylactic AC

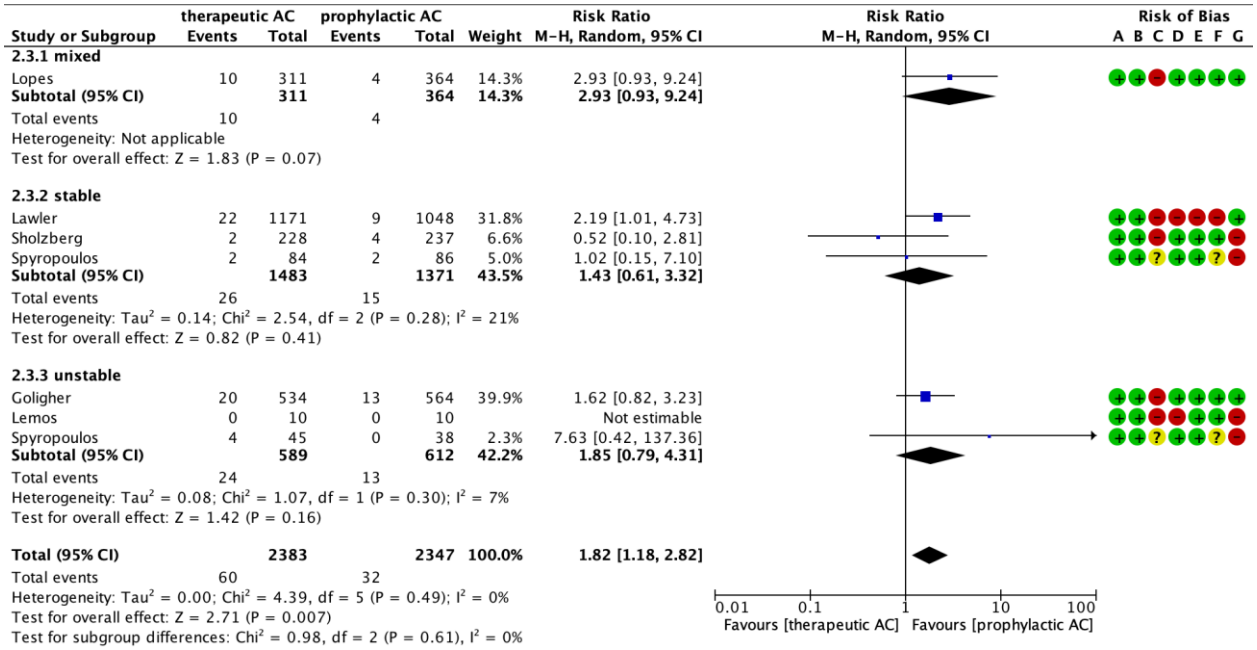


Figure 5. Comparing major bleeding risk between therapeutic versus prophylactic AC

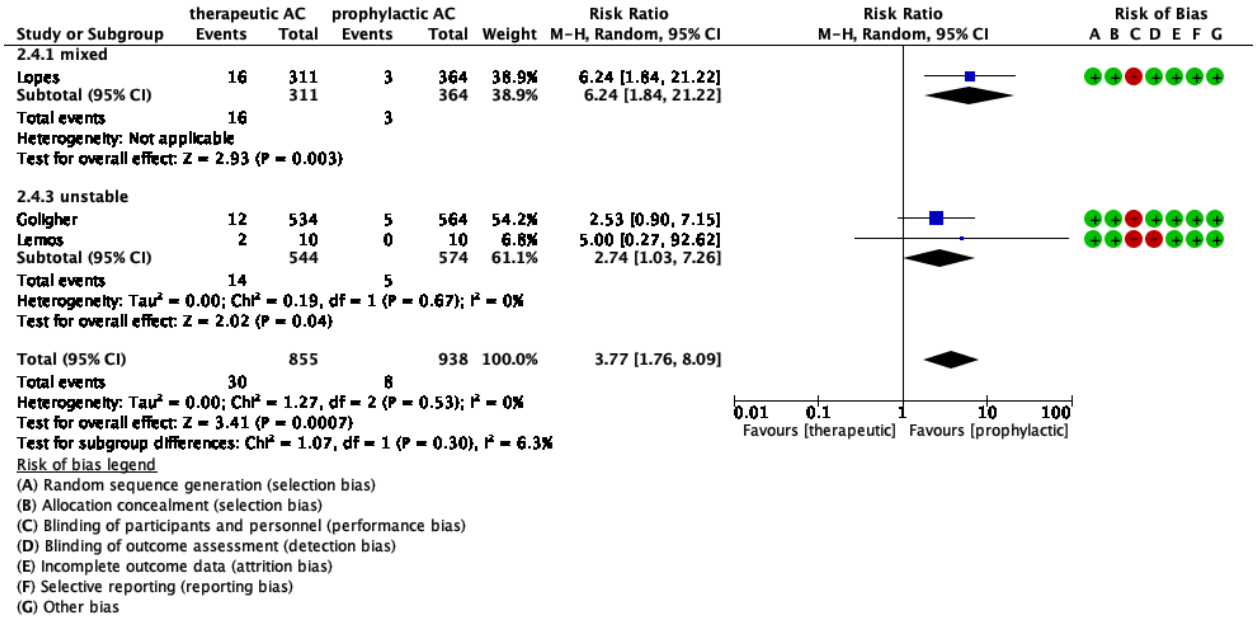


Figure 6. Comparing risk of minor bleeding between therapeutic versus prophylactic AC

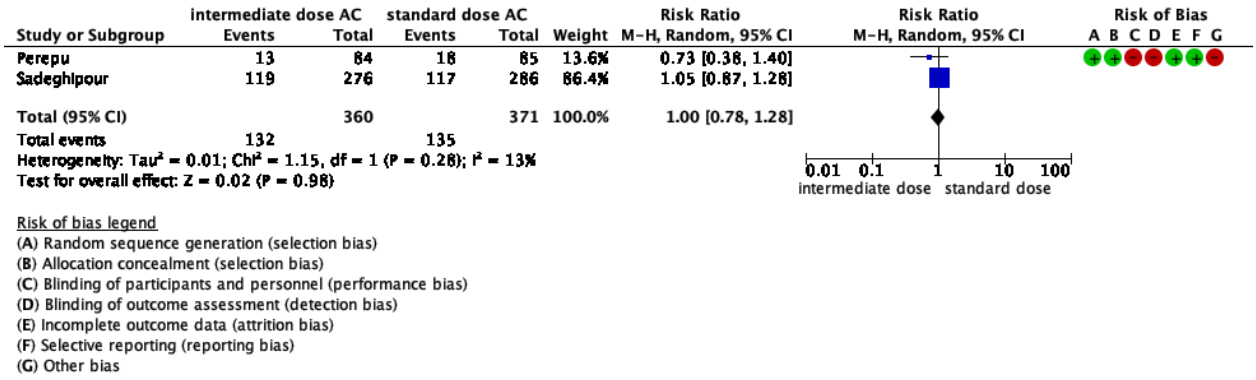


Figure 7. Comparison of risk of mortality between intermediate dose versus prophylactic dose AC

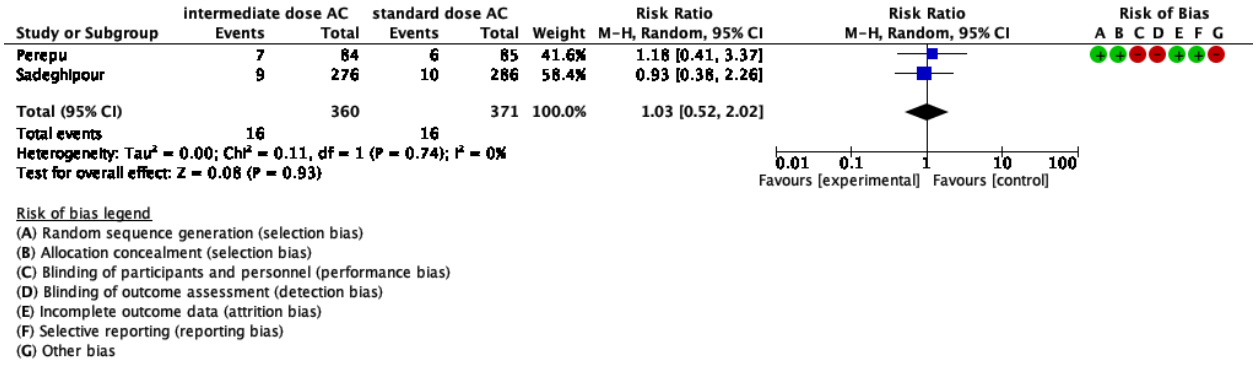


Figure 8. Comparison of incidence of VTE between intermediate dose versus prophylactic dose AC

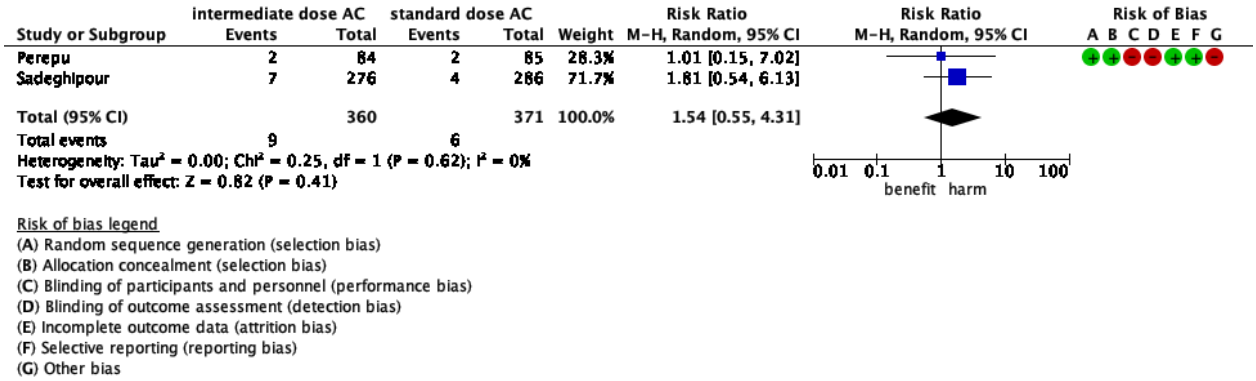


Figure 9. Comparison of risk of major bleeding between intermediate dose versus prophylactic dose AC

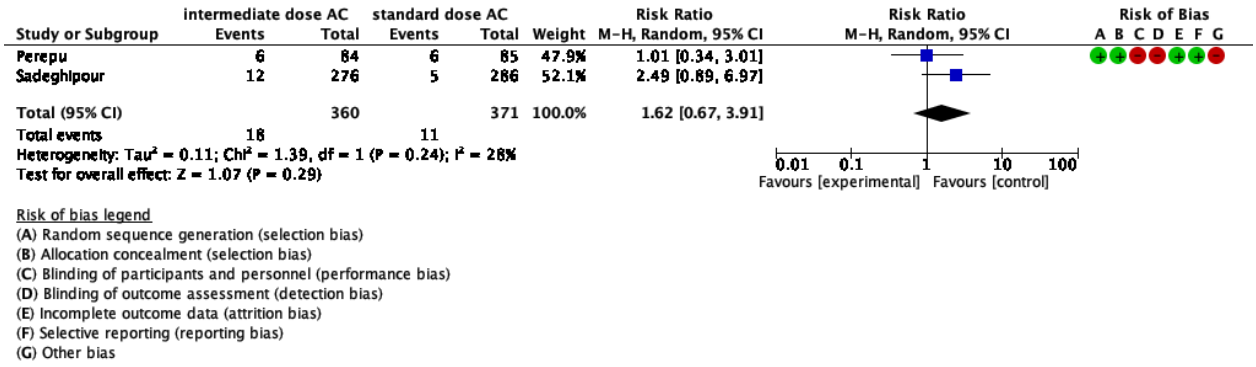


Figure 10. Comparison of risk of minor bleeding between intermediate dose versus prophylactic dose AC

Appendix 6. Study Characteristics of Ongoing Active Trials (n=19)

Title Identifier Expected completion date	Intervention	Comparator	Patients/population recruited	Outcome
ANTIcoagulation in severe COOVID-19 patients (ANTICOVID) December 1,2021 https://ClinicalTrials.gov/show/NCT04808882	Drug: Tinzaparin,Therapeutic anticoagulation	DrugTinzaparin, Low dose prophylactic anticoagulation Drug: Tinzaparin, High dose prophylactic anticoagulation	18 Years and older with severe COVID-19 pneumonia	All-cause mortality|Number of days to clinical improvement|Score on WHO Ordinal Scale|Number of days alive and free from supplemental oxygen at Day-28|Proportion of patients needing intubation at Day-28|Number of days alive and free from invasive mechanical ventilation at Day-28|Number of days alive and free from vasopressors at Day-28|Length of intensive care unit stay|Length of hospital stay|Quality of life and disability at assessed using a quality of life questionnaire|All-cause deaths|Proportion of patients with at least one thrombotic event at Day-28|D-dimers|Proportion of patients with at least one major bleeding event (MBE) at Day-28|Proportion of patients with at least one life-threatening bleeding event at Day-28|Proportion of patients with any bleeding event at Day-28|Proportion of patients with Heparin Induced Thrombocytopenia (HIT) at Day-28|7-points ordinal scale|Sepsis-Induced Coagulopathy Score (SCS)
Anticoagulation in Patients Suffering From COVID-19 Disease (The ANTI-CO Trial) March 28, 2021 (no posted results) https://ClinicalTrials.gov/show/NCT04445935	Bivalirudin Injection	standard anticoagulation with LMWH/UFH	18years to 99 years old with COVID-19 ARDS	P/F ratio Kidney function
Anticoagulation in Critically Ill Patients With COVID-19 (The IMPACT Trial) December 2022 https://ClinicalTrials.gov/show/NCT04406389	Therapeutic dose Drug: Enoxaparin sodium| Drug: Unfractionated heparin| Drug: Fondaparinux| Drug: Argatroban	Intermediate Dose Prophylaxis Drug: Enoxaparin sodium| Drug: Unfractionated heparin| Drug: Fondaparinux|	18 years old and older COVID-19 patients with critical illness	30-day mortality|Length of Intensive Care Unit (ICU) Stay in Days|Number of documented venous thromboembolism (VTE), arterial thrombosis (stroke, myocardial infarction, other) and microthrombosis events|Number of major and clinically relevant non-major bleeding events
Hamburg Edoxaban for Anticoagulation in COVID-19 Study (HERO-19) September 30, 2021 https://ClinicalTrials.gov/show/NCT04542408	Anticoagulation Agents (Edoxaban and/or high dose LMWH)	Drug: Low dose Low molecular weight heparin or Placebo	18 Years and older COVID-19 patients	Combined endpoint: all-cause mortality and/ or venous thromboembolism and/ or arterial thromboembolism|All-cause mortality|Mortality related to venous thromboembolism|Mortality related to arterial thromboembolism|Rate of venous and/ or arterial thromboembolism|Rate and length of mechanical ventilation|Length of initial stay at ICU after application of IMP|Rehospitalisation|Rate and length of renal replacement therapy|Cardiac arrest/ CPR
Effect of Anticoagulation Therapy on Clinical Outcomes in COVID-19 (COVID-PREVENT)	Drug: Rivaroxaban|	Standard Of Care (SOC)	18 Years and older COVID-19 patients	Composite endpoint of venous thromboembolism (DVT and/or fatal or non-fatal PE), arterial thromboembolism, new myocardial infarction, non-hemorrhagic stroke, all-cause mortality or progression to intubation and invasive ventilation|Development of disseminated intravascular coagulation (DIC) according to the ISTH criteria|Number of days requiring invasive ventilation|Number of days requiring

January 31, 2022 https://ClinicalTrials.gov/show/NCT04416048				non-invasive ventilation|Improvement on a seven-category ordinal scale recommended by the WHO as clinical improvement scale for patients with respiratory infections
Regional Anticoagulation Modalities in Continuous Venous Venous Hemodialysis in Patients With COVID-19 (CoV-Hep Study) August 2021 https://ClinicalTrials.gov/show/NCT04487990	Patients on continuous hemodialysis (blood flow 150 ml / min, dose of 30 ml / kg / h) receiving anticoagulation with sodium citrate at 4 mmol / l associated with unfractionated heparin at 10U / Kg / h.	Patients on continuous hemodialysis (blood flow 150 ml / min, dose of 30 ml / kg / h) receiving anticoagulation with sodium citrate at 4 mmol / l.	18 Years and older with acute kidney injury	Clotted dialyzers|Time-free of clotting|Number of dialyzers used|Pressure variation|Urea sieving|Downtime of dialysis
Safety and Efficacy of Therapeutic Anticoagulation on Clinical Outcomes in Hospitalized Patients With COVID-19 January 1, 2022 https://ClinicalTrials.gov/show/NCT04377997	Enoxaparin (therapeutic dose)	Standard dose anticoagulation	18 Years and older with cardiovascular disease	Number of patients with the composite efficacy endpoint of death, cardiac arrest, symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, or hemodynamic shock.|Number of patients with a major bleeding event according to the International Society on Thrombosis and Haemostasis (ISTH) definition
Intermediate or Prophylactic-Dose Anticoagulation for Venous or Arterial Thromboembolism in Severe COVID-19 (IMPROVE) April 2021 (recruiting) https://ClinicalTrials.gov/show/NCT04367831	Drug: Heparin SC| Drug: Enoxaparin/Lovenox Intermediate Dose	Enoxaparin Prophylactic Dose| Drug: Heparin Infusion|	18 years to 80 years old COVID-19 patients with venous or arterial thrombosis	Total Number of Patients with Clinically Relevant Venous or Arterial Thrombotic Events in ICU|Total Number of Patients with In hospital Clinically Relevant Venous or Arterial Thrombotic Events|ICU Length of Stay|Total Number of Patients with the Need for Renal Replacement Therapy in the ICU|Total Number of Patients with Major bleeding in the ICU|Hospital
FREEDOM COVID-19 Anticoagulation Strategy (FREEDOM COVID) March 2022	Drug: Enoxaparin (full dose) Drug: Apixaban	Drug: Enoxaparin (prophylactic dose)	18 years and older with COVID-19	Time to first event|Number of in-hospital rate of BARC 3 or 5|Number of participants with Myocardial infarction|Number of participants with Deep Vein Thrombosis|Number of participants requiring Ventilation|Number of All Death|Cause of Death|Number of participants with Stroke|Number of participants with Pulmonary Emboli|Number of participants with Systemic

https://ClinicalTrials.gov/show/NCT04512079				
Standard vs High Prophylactic Doses or Anticoagulation in Patients With High Risk of Thrombosis Admitted With COVID-19 Pneumonia (PROTHROMCOVID) July 31, 2021 https://ClinicalTrials.gov/show/NCT04730856	Drug: Tinzaparin (high dose)	Drug: Tinzaparin (standard dose)	18 years and older with COVID-19 related thrombosis	Reduction of suspicion of systemic thrombotic symptomatic events|Use of Mechanical ventilation|Progression on the WHO Progression Scale during follow-up.|Overall survival at 30 days.|Length of hospital stay (days)|Length of ICU stay (days)|Number of bleedings and adverse
Tenecteplase in Patients With COVID-19 December 2021 https://ClinicalTrials.gov/show/NCT04505592	Drug: Tenecteplase	Drug: Placebo	18 to 75years old with COVID-19 related ARDS	Number of participants free of respiratory failure|Number of occurrences of bleeding|Number of participants with in-hospital deaths at 14 days|Number of participants with death at 28 days|Number of ventilator-free days|Number of respiratory failure-free days|Number of vasopressor-free days|Vasopressor doses at 24 hours|Vasopressor doses at 72 hours|P/F ratio at 24 hours|P/F ratio at 72 hours|Number of ICU-free days|Hospital length of stay|Number of participants with new-onset renal failure|Number of participants with need for renal replacement therapy
Apixaban for PrOphyLaxis of thromboembolic Outcomes in COVID-19 (APOLLO) December 2021 https://ClinicalTrials.gov/show/NCT04746339	Drug: Apixaban	Drug: Placebo	18 years and older with COVID-19	Number of days alive and out of hospital or emergency department|Hospitalization due to bleeding|Hospitalizations for cardiopulmonary causes|All-cause hospitalization|All-cause death|Days free of venous thromboembolism|Major cardiovascular events (MACE)
Prevention of Arteriovenous Thrombotic Events in Critically-Ill COVID-19 Patients Trial (COVID-PACT) November 2021 https://ClinicalTrials.gov/show/NCT04409834	Drug: Unfractionated Heparin IV Drug: Enoxaparin 1 mg/kg|Drug: Clopidogrel|	Drug: Enoxaparin 40 Mg/0.4 mL Injectable Solution Drug: Unfractionated heparin SC|	18 years and older with COVID-19 critical illness	Venous or arterial thrombotic events|Key secondary endpoint: Clinically evident venous or arterial thrombotic events
Nebulized Heparin for COVID19-associated Acute Respiratory Failure March 31, 2022 https://ClinicalTrials.gov/show/NCT04842292	Drug: Heparin|	Drug: Placebo	18 to 80 years old COVID-19 patients	Mean PaO2/FiO2 ratio|Clinically Significant Bleeding|Incidence of venous thromboembolism
Australasian COVID-19 Trial ADAptive Platform Trial (ASCOT ADAPT) December 31, 2022	Drug: Nafamostat Mesilate|Biological: Hyperimmune Globulin|Drug: Enoxaparin|Drug:	Drug: Nafamostat Mesilate|Biological: Hyperimmune Globulin|Drug: Enoxaparin|Drug:	18 years and older COVID-19 patients	Death from any cause or requirement of new intensive respiratory support (invasive or non-invasive 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|Antiviral domain-specific outcome: Safety (Liver enzymes)|Antiviral

https://ClinicalTrials.gov/show/NCT04483960	Dalteparin|Drug: Tinzaparin	Dalteparin|Drug: Tinzaparin		domain-specific outcome: Safety (potassium)|Antiviral domain-specific outcome: Safety (sodium)|Antiviral domain-specific outcome: Safety (bleeding)|Antiviral domain-specific outcome: Safety (thrombophlebitis)|Antiviral domain-specific outcome: serious adverse reactions|Antibody domain-specific outcome: Serious treatment-related adverse events|Antibody domain-specific outcome: Haemolysis|Antibody domain-specific outcome: Confirmed arterial thrombosis|Antibody domain-specific outcome: Confirmed venous thrombosis|Anticoagulation domain-specific outcome: Confirmed deep venous thrombosis|Anticoagulation domain-specific outcome: Confirmed pulmonary embolus|Anticoagulation domain-specific outcome: Confirmed acute myocardial infarction|Anticoagulation domain-specific outcome: Confirmed ischemic cerebrovascular event|Anticoagulation domain-specific outcome: Major bleeding|Anticoagulation domain-specific outcome: Clinically relevant non-major bleeding|Anticoagulation domain-specific outcome: Heparin-induced thrombocytopenia (HIT)|Anticoagulation domain-specific outcome: Other confirmed thrombotic event
Low-Dose Tenecteplase in Covid-19 Diagnosed With Pulmonary Embolism December 31, 2021 https://ClinicalTrials.gov/show/NCT04558125	Tenetecplase	Placebo	18 to 75 years with COVID-19 related pulmonary embolism	Percent improvement in shock index (defined as heart rate divided by systolic blood pressure) 6 hours after the TNK/placebo bolus.|1. Clinical status at 24 hours after administration of TNK / placebo based upon 7-point scale.
Clinical Efficacy of Heparin and Tocilizumab in Patients With Severe COVID-19 Infection (HEPMAB) December 31,2021 https://ClinicalTrials.gov/show/NCT04600141	Drug: Tocilizumab|Drug: Heparin - Therapeutic dosage|	Drug: Tocilizumab| Drug: Heparin - Prophylactic dosage	18 years and older with COVID-19	Proportion of patients with clinical improvement|Hospital and ICU length of stay;|Duration of invasive mechanical ventilation|Duration of vasopressor use|Renal failure by AKIN criteria|Incidence of cardiovascular complications|Incidence of venous thromboembolism|Mortality
COVID-19 Positive Outpatient Thrombosis Prevention in Adults Aged 40-80 September 2021 https://ClinicalTrials.gov/show/NCT04498273	Drug: Apixaban 2.5 MG|Drug: Apixaban 5MG|Drug: Aspirin|	Drug: Placebo	40 to 80years old with mild COVID-19	Hospitalization for cardiovascular/pulmonary events
Hemostasis in COVID-19: an Adaptive Clinical Trial May 30,2022 https://ClinicalTrials.gov/show/NCT04466670	|Drug: Unfractionated heparin nebulized	Drug: acetylsalicylic acid	18 years and older with COVID-19	Hospital discharge - alive / death|Length of mechanical ventilation free days|Length of renal replacement therapy free days|Number of documented venous thromboembolism or arterial thrombosis

Q3. Should empiric antimicrobial coverage be given to patients with severe and critical COVID-19?

As of 15 April 2021

RECOMMENDATION

We recommend against the use of antibiotics in patients with severe and critical COVID-19 infection, unless with suspicion of secondary bacterial co-infection. For patients on empiric antibiotics, they should be assessed daily for the need for discontinuation, continuation or escalation based on clinical and laboratory parameters. *(Very low certainty of evidence; Strong recommendation)*

Consensus Issues

Despite the low quality of evidence available, the panel voted for a strong recommendation against the routine use of antibiotics due to concerns on antimicrobial resistance.

KEY FINDINGS

Very low quality of evidence from one retrospective observational report was found on the use of empiric antimicrobials for COVID-19. Early administered antibiotics did not significantly impact mortality or delayed hospital acquired infections in critically ill patients with COVID-19.

INTRODUCTION

COVID-19 may be indistinguishable from other acute bacterial infections. This has led to frequent administration of empiric antimicrobials which in turn raised concern for its overuse. Latest systematic reviews and meta-analysis noted pooled prevalence of 71-72% of empiric antimicrobial use among COVID-19 cases despite a low pooled prevalence of 6-8% of bacterial co-infection among COVID-19 cases [1,2,3]. Antibiotic overuse may trigger emergence and transmission of multidrug-resistant bacteria and onset of adverse reactions such as Clostridium difficile infections which may add to further to morbidity and mortality. Thus, recommendations from different societies emphasized that antibiotic stewardship programmes should be put into place or continue among COVID-19 patients.

REVIEW METHODS

Comprehensive literature in PubMed, MedRxiv and Cochrane Library up to January 31, 2021 using the search terms COVID-19, antimicrobials, antibiotics, and bacterial coinfection yielded 12 studies. Upon doing a full text-analysis, 11 studies were excluded because of the following: 1) did not include severe/critical cases, 2) comparison group includes another set of antibiotics, 3) intervention included antimicrobials used as treatment and not for routine bacterial co-infection coverage and 4) did not compare antibiotics vs no antibiotics group. The remaining study is an article published as a letter to the editor which reported the findings of their observational study[4]. The author was contacted thru email and he disclosed that they did not write issue a full- text article for the said study.

RESULTS

Characteristics of Included Studies and methodologic quality

The article reported the findings of a retrospective observational study done in Switzerland which included 48 intubated intensive care unit patients with COVID-19, where 19 were given antibiotics before ICU admission. The intervention was empiric antibiotics coverage before ICU admission versus no antibiotics, with the most frequently used antibiotic as amoxicilin/clavulanate (n=13). Outcome measures include mortality and incidence of delayed healthcare associated infections (HCAI) (Appendix – Table 1). Methodologic quality cannot be adequately assessed since the report only gave key findings and limited discussion.

Summary of results of included studies

Mortality was similar between the two groups (24% without antibiotics versus 26% with antibiotics, p = 0.86). There was no significant difference in the number of delayed HCAI during ICU stay was observed between the antibiotics and the no antibiotics groups. HCAI investigated were ventilator associated pneumonia, urinary tract infection, candidemias, cathter related blood stream infection, and colitis.

RECOMMENDATIONS FROM OTHER GROUPS

The US-NIH [5], in their latest guideline update last February 2021, they gave a strong recommendation via expert opinion, that empiric antimicrobials should not be given in the absence of another indication and its use must be assessed daily in order to minimize the adverse consequences of unnecessary antimicrobial therapy. This was consistent with WHO [6] update in January 2021 and PSMID guideline [7] in July 2020.

RESEARCH GAPS

There is one retrospective cohort study listed in ClinicalTrials.gov. The status is active but not recruiting and estimated completion date was February 28, 2021[8] (Appendix – Table 3).

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Appendix 1. Characteristics of Included Studies

First Author- Year- Site	Type of Study	Characteristics of population	Sample Size	Antibiotic used	Outcome
Buetti, Niccolo 2020 Switzerland	Retrospective Study	Intubated ICU COVID 19 patients Median age was 66.6, 33% were female	58	Co-amoxiclav, etc Did not enumerate all the antibiotics used	Differences in mortality, VAP, CRBSIs, UTI

Appendix 2. GRADE Evidence Profile

Empiric antimicrobial coverage compared to no empiric antimicrobial coverage for COVID-19 severe and critical cases
Patient or population: COVID-19 severe and critical cases
Setting: Philippines
Intervention: empiric antimicrobial coverage
Comparison: no empiric antimicrobial coverage

Outcome Nº of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
Mortality No of participants: 48 (1 observational study)	**RR 1.09** (0.40 to 2.94)	24.1%	**26.3%** (9.7 to 71)	**2.2% more** (14.5 fewer to 46.8 more)	⊕◯◯◯ VERY LOW	Inconclusive

*__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; **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 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

Appendix 3. Table of Ongoing Studies

Study Setting	Study Type	Population	Intervention	Comparator	Outcome/s	Status	Estimated Completion date
Utility of Empiric Antibiotics for Non-intubated Novel Coronavirus Diseases 2019 Patients NCT04674410 United States	Retrospective Cohort	Adult patients admitted to hospital with diagnosis of COVID-19 present-on -admission or positive RT-PCR test sampled on admission who were given antibiotics	Empiric Antibiotics	Adult patients admitted to hospital with diagnosis of COVID-19 present-on - admission or positive RT-PCR test sampled on admission who were not given antibiotics	Primary Outcome: In-Hospital Mortality or discharge to hospice Secondary Outcomes: Rates of Mechanical Ventilation, Rates of C. difficile infection, Length of stay for survivors, Rates of ICU Admission ,Rates of Acute Kidney Injury, Days free of antibiotics,Rates of secondary infections due to antibiotic resistant pathogens	Active, not recruiting	February 28, 2021

Q4. Should hemoperfusion be used in patients diagnosed with COVID-19?

As of 01 December 2021

RECOMMENDATION

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

Consensus Issues
No randomized controlled trials were available for review and the observational studies included did not adjust for confounders. With the available sparse evidence, the use of hemoperfusion can be suggested in COVID-19 patients with clinical deterioration despite standard medical therapy (including Tocilizumab). However, there is no consensus among experts in the panel on the use of hemoperfusion in COVID-19. Clinical trials are needed to be able to identify and evaluate the balance of benefits, harm, and cost for an invasive mode of treatment such as hemoperfusion especially since immunotherapy has been made available for the management of COVID-19.

PREVIOUS RECOMMENDATION

There is insufficient evidence on the use of hemoperfusion at this time among patients with COVID-19 infection. *(Very low quality of evidence)*

Consensus Issues
None raised during the panel meeting

WHAT'S NEW IN THIS VERSION?

Two retrospective cohort studies on the use of hemoperfusion in patients with COVID-19 were included in this updated review.

KEY FINDINGS

Presently, no randomized clinical trials have been published to provide data on the use of hemoperfusion in patients with COVID-19. Two retrospective cohort studies showed statistically significant benefit in terms of mortality. Improvement in some clinical parameters such as respiratory rate, heart rate, and peripheral oxygen saturation, and selected markers such as C-reactive protein, erythrocyte sedimentation rate, and serum ferritin levels were also significantly observed among COVID-19 patients who received hemoperfusion. However, the benefits in clinical and laboratory parameters failed to translate to more clinically important outcomes such as decrease in the length of hospital and intensive care unit stay. Moreover, the studies were of very low certainty of evidence being non-clinical trials.

INTRODUCTION

Hemoperfusion utilizes a device with specialized filters to remove pathogens and cytokines from the blood. The EUPHRATES Trial done in North America among patients with septic shock compared the mortality rate of patients who received hemoperfusion using polymixin B filters from those who received sham hemoperfusion. The trial found that there was no significant difference in the mortality

rate between the two groups and a higher incidence of adverse effects was observed in the treatment group.[1] A meta-analysis on the use of polymixin B immobilized hemoperfusion in patients with sepsis and septic shock reported a decrease in mortality rate only for less severe septic patients but the same conclusion could not be made for patients with severe sepsis or refractory septic shock.[2] Several case series and case reports demonstrated decreased serum concentration levels of inflammatory markers and cytokine levels, specifically IL-6.[3-16] Decrease in inflammatory markers were documented in these studies but improvement in mortality rate was inconsistent. Since patients with severe COVID-19 have been documented to have elevated serum concentrations of cytokines, hemoperfusion was theorized to improve clinical outcomes by decreasing these cytokine levels.

REVIEW METHODS

The PubMed for MEDLINE database, US NIH ClinicalTrials.gov, and WHO International Clinical Trials Registry were searched on 14 September 2021 using the search terms “hemoperfusion” and “COVID-19” or “SARS-COV-2”. Literature reviews, editorials, case reports, and case series were excluded. Abstracts and full texts were reviewed.

RESULTS

In the systematic search for relevant articles, method filter for randomized clinical trials was applied but no published randomized controlled trial articles comparing the use of hemoperfusion to standard of care were found. Two retrospective cohort studies [17,18] compared the effect of hemoperfusion among COVID-19 patients. Patients were divided into two groups, the patients in the intervention group received hemoperfusion with standard of care while the control group received standard of care alone. There were 48 patients in the study of Soleimani and colleagues [17], with 24 patients in each intervention group. There were 128 patients in the study of Darazam and co-workers [18]. In the latter study, 73 patients who received standard of care were matched in terms of age, sex, and oxygen saturation with 55 patients who then received standard of care and hemoperfusion.

In the study of Soleimani, the difference in mortality rate of COVID-19 patients who received standard of care (8/24, 33.33%) compared to those who received hemoperfusion (5/24, 20.83%) was not statistically significant (RR 0.63, 95% CI 0.28-1.64). On the other hand, the lower mortality rate of COVID-19 patients who received hemoperfusion (n=37/55) compared to those who received standard of care alone (n=65/74) was statistically significant in the Darazam study (RR 0.76, 95% CI 0.62-0.92). Pooled analysis showed reduction in mortality was significantly observed in the hemoperfusion group (RR 0.74, 95% 0.60-0.91; I^2=0%; Low certainty).

Hospital length of stay was inconsistent in the two studies. In the study by Soleimani et al., hospital length of stay was not statistically significant between the two groups. Patients who received hemoperfusion and standard of care stayed for 19.21 ± 11.66 days while those who received standard of care without hemoperfusion stayed for 17.83 ± 8.99 days (MD 1.38 days, 95% CI -4.49-7.25). In the study by Darazam, patients who received hemoperfusion stayed hospitalized for a significantly longer duration with a median length of stay of 12 days compared to the standard of care group who had a median length of stay of only 8 days ($p<0.001$).

Peripheral oxygen saturation and C-reactive protein (CRP) levels significantly improved among patients who received hemoperfusion compared to those who only received standard of care. The peripheral oxygen saturation of patients who received standard of care improved from 89.75% ± 5.58% to 92.94% ± 2.70% while those who received hemoperfusion improved from 80.73% ± 12.74% to 91.68% ± 7.12% (MD 7.76, 95% CI 2.71-12.81).[1] Similar results were found in the Darazam study where patients who received hemoperfusion had higher median peripheral oxygen saturation 80% compared to those who received standard of care alone with a median peripheral oxygen level of 64% ($p<0.001$).[2] The change in CRP levels was also statistically significant between the two groups. CRP decreased from 85.38 ± 56.74 mg/dL to 45.21 ± 47.41 mg/dL in patients who received standard of care while CRP decreased from 160.96 ± 80.12 mg/dL to 67.08 ± 54.77 mg/dL in those who received hemoperfusion (MD -53.8, 95% CI -97.98 to -9.62).[1] In the Darazam study, CRP was also found to be lower in the hemoperfusion group with a median CRP level of 19.9 mg/dL compared the standard of care group with a median CRP level of 59 mg/dL ($p<0.001$).[2]

Other laboratory parameters did not show any statistically significant difference between those who received hemoperfusion and those who received standard of care alone. Erythrocyte sedimentation rate (MD -14.34 mm/hr, 95% CI -34.38-5.7; $p=0.168$), fibrinogen levels (MD -54.92 mg/dL, 95% CI -229.02-338.86; $p=0.564$), and serum ferritin levels (MD -327.54 ng/mL, 95%CI -715.38-60.3; $p=0.081$).[1]

OTHER FACTORS IN EVIDENCE TO DECISION

The latest PhilHealth coverage for critical COVID-19 pneumonia is PhP 786,384.00.[19] The amount covers the use of renal replacement therapy and hemoperfusion. The cost per unit of a hemoperfusion filter ranges from PhP 23,500 to PhP 32,250. While it seems to be within the allocated PhilHealth coverage, other costs that come with the hospitalization for critical COVID-19 patients like mechanical ventilation and intensive care unit care will accumulate and likely exceed PhilHealth coverage. However, if hemoperfusion is done early to avoid cytokine storm or prior to needing mechanical ventilation, the intervention may be beneficial [20] and may decrease hospital costs. Therefore, while hemoperfusion may be a good adjunct for managing critical COVID-19 patients, cost effectiveness should also be considered with its use. At present, there are no data on equity, acceptability, and feasibility of hemoperfusion among COVID-19 patients.

RECOMMENDATIONS FROM OTHER GROUPS

There are no recommendations on the use of hemoperfusion from the WHO Living Clinical Practice Guidelines [21], the NIH COVID-19 Treatment Guidelines [22] and the Infectious Disease Society of America COVID-19 Guidelines.[23] The 2020 Clinical Practice Guidelines for Sepsis and Septic Shock in adults in the Philippines [24] and the 2021 Surviving Sepsis Campaign [25] recommended against the use of hemoperfusion in non-COVID patients with sepsis and septic shock.

RESEARCH GAPS

High-quality randomized clinical trials are still needed to provide data on critical and important clinical outcomes on the use of hemoperfusion in COVID-19 patients.

Currently, there are ten ongoing clinical trials published in the WHO International Clinical Trials Registry and the US National Library of Medicine ClinicalTrials.gov on the use of hemoperfusion among COVID-19 patients.[26-35]

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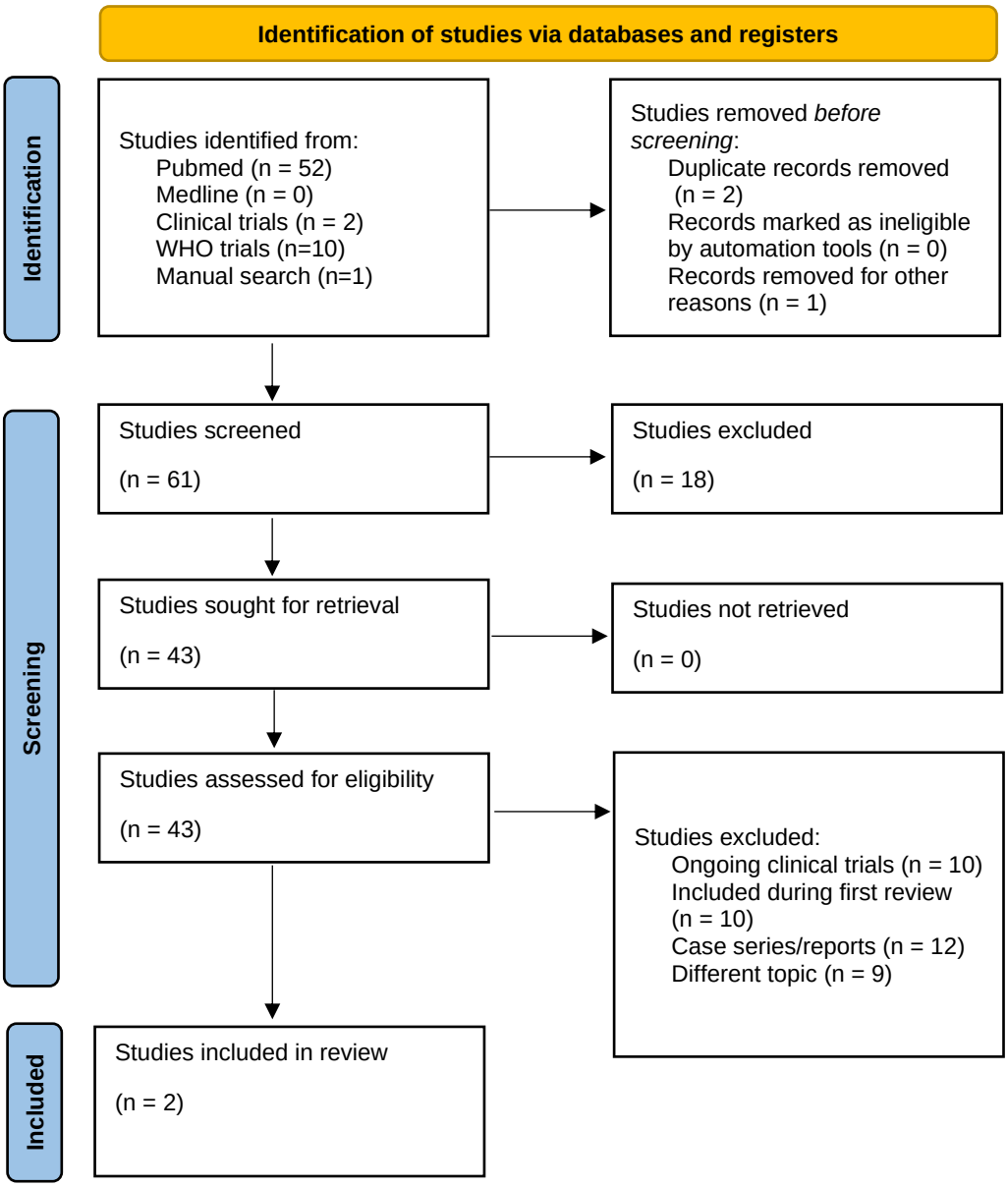
Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					• Management options that can decrease mortality rate and length of hospital stay can help improve disease outcome and decrease overall hospital cost.
Benefits	Large	Moderate (1)	Small (3)	Uncertain (3)			• There are no randomized controlled trials as of this writing that has proven substantial benefits from using hemoperfusion in COVID-19 patients though results from observational studies and case series/reports have documented improved clinical outcomes. • One observational study has documented improved mortality rate and need for mechanical ventilation among patients who received hemoperfusion.
Harm	Large (1)	Small (4)	Uncertain (2)				• No documented harm on the patients.
Certainty of Evidence	High	Moderate	Low (4)	Very low (3)			• No completed RCTs available yet.
Balance of effects	Favors drug (1)	Does not favor drug (3)	Uncertain (3)				
Values	Important uncertainty or variability	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability (1)			
Resources Required	Uncertain	Large cost (5)	Moderate Cost (2)	Negligible cost	Moderate savings	Large savings	• The cost per unit of a hemoperfusion filters ranges from PhP 23,500 to PhP 32,250
Certainty of evidence of required resources	No included studies	Very low (2)	Low (1)	Moderate (2)	High (2)		
Cost effectiveness	No included studies (5)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (3)	Reduced (3)	Probably no impact	Increased (1)			
Acceptability	Uncertain (1)	No	Yes (6)				
Feasibility	Uncertain (1)	No (1)	Yes (5)				

Appendix 2. Search Yield and Results



Appendix 3. Table of Included Studies

Study Characteristics of Included Studies (2)

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
The effect of Hemoperfusion on Outcome, Clinical and Laboratory findings of Patients with Severe COVID-19: A Retrospective Study Soleimani 2021	Retrospective Cohort	Kashan, Iran	48 Standard of care 24 Hemoperfusion 24	- severe COVID-19 - positive PCR, positive chest CT scan - admitted in the ICU Inclusion At least 2 - RR >30 cpm - SPO2 <85% - intermittent fever At least 3 - PaO2 <60 mmHg - PaO2/FiO2 <200 - CRP >60mg/dl - Ferritin >2000 - elevated D dimer - Fibrinogen <150 mg/dl - bicytopenia (PC <100,000; Hgb <9g/dl; lymphocyte <1100/ul Lab results done 1 day before and 72 hours after HP	Hemoperfusion plus conventional antiviral therapies During inflammatory phase 3 sessions with HA330 and HA280 for 4 hours	Standard of care (conventional antiviral therapies)	Mortality rate Hospital Length of stay After Hemoperfusion: Breathing rate, heart rate decreased, significant increase in SpO2, significant decrease in CRP
Efficacy of Hemoperfusion in Severe and Critical Cases of COVID-19 Darazam, 2021	Single-center, matched control retrospective study	Tehran, Iran	128 Standard treatment 73 Hemoperfusion 55	- > 18 yo - Positive for COVID-19 RT PCR - Positive chest CT scan (diffuse bilateral pulmonary opacities without effusion) - SPO2 < 86% or RR > 30bpm - Respiratory failure not fully explained by cardiac failure or fluid overload - Within 1 week of a known clinical insult or new/worsening respiratory symptom - Hopitalization days <14 days from signs and symptom onset (T>37.8, cough, shortness of breath, nasal congestion/discharge, myalgia/arthralgia, diarrhea/vomiting, headache, fatigue)	Hemoperfusion plus standard treatment	Standard treatment	Mortality rate Duration of hospitalization Intubation length SPO2 (peripheral oxygen saturation) Arterial blood gas Complete blood count C reactive protein

Appendix 4. GRADE Evidence Profile

Author(s): Erika A. Crisostomo, MD, Vaneza Leah Espino MD, Christopher G. Manalo MD
Question: Should hemoperfusion be used in patients diagnosed with COVID-19 infection?
Setting: Hospitalized COVID-19 patients
Bibliography: Soleimani A, Taba SMM, Hasibi Taheri S, Loghman AH, Shayestehpour M. The effect of hemoperfusion on the outcome, clinical and laboratory findings of patients with severe COVID-19: a retrospective study. New Microbes New Infect. 2021 Nov;44:100937. doi: 10.1016/j.nmni.2021.100937. Epub 2021 Sep 2. PMID: 34490065; PMCID: PMC8410636.

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hemoperfusion	Standard of care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	Observational studies	Not serious	Not serious	Not serious	Not serious	None	42/79 (53.2%)	73/98 (74.5%)	**RR 0.74** (0.60 to 0.91)	**194 fewer per 1,000** (from 298 fewer to 67 fewer)	⊕⊕◯◯ Low	CRITICAL
Hospital Length-of-Stay (assessed with: Days)												
1	Observational studies	Not serious	Not serious	Not serious	Serious[a]	None	24	24	-	MD **1.38 days higher** (4.49 lower to 7.25 higher)	⊕◯◯◯ Very low	CRITICAL
Change in Oxygen Saturation (assessed with: %)												
1	Observational studies	Not serious	Not serious	Not serious	Not serious	None	24	24	-	MD **7.76 % higher** (2.71 higher to 12.81 higher)	⊕⊕◯◯ Low	IMPORTANT
Change in C-Reactive Protein (assessed with: mg/dL)												
1	Observational studies	Not serious	Not serious	Not serious	Not serious	None	24	24	-	MD **53.8 mg/dL lower** (97.98 lower to 9.62 lower)	⊕⊕◯◯ Low	IMPORTANT
Change in Erythrocyte Sedimentation Rate (assessed with: mm/hour)												
1	Observational studies	Not serious	Not serious	Not serious	Serious[a]	None	24	24	-	MD **14.34 mm/hour lower** (34.38 lower to 5.7 higher)	⊕◯◯◯ Very low	IMPORTANT

Change in Fibrinogen Levels (assessed with: mg/dL)												
1	Observational studies	Not serious	Not serious	Not serious	Serious[a]	None	24	24	-	MD **54.92 mg/dL higher** (229.02 lower to 338.86 higher)	⊕◯◯◯ Very low	IMPORTANT
Change in Ferritin Levels (assessed with: ng/mL)												
1	Observational studies	Not serious	Not serious	Not serious	Serious[a]	None	24	24	-	MD **327.54 ng/mL lower** (715.38 lower to 60.3 higher)	⊕◯◯◯ Very low	IMPORTANT

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

Explanations

[a] Confidence interval crosses line of no effect

Appendix 5. Risk of Bias Assessment

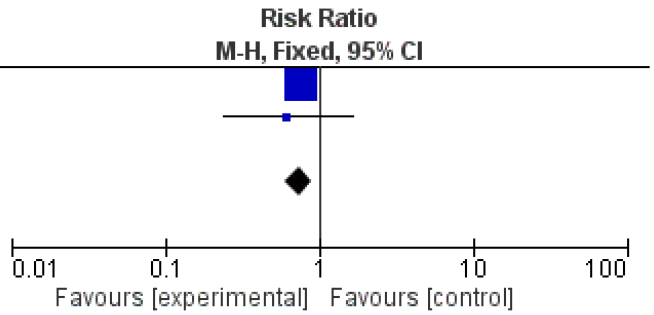
Newcastle-Ottawa Quality Assessment For Cohort Studies		
	Soleimani	Darazam
Selection		
Representative of the exposed cohort	Truly representative	Truly representative
Selection of the non-exposed cohort	Draw from the same community as the exposed cohort	Draw from the same community as the exposed cohort
Ascertainment of exposure	Secure record	Secure record
Demonstration that outcome of interest was not present at the start of the study	No	No
Comparability	The study controls age, sex, marital status	The study controls age, sex, marital status
Outcome		
Assessment of outcome	Record linkage	Record linkage
Was follow-up long enough for outcomes to occur	Yes	Yes
Adequacy of follow up	All subjects were accounted for	All subjects were accounted for
	Fair quality	Fair quality

Appendix 6. Forest Plot

Study or Subgroup	Hemoperfusion Events	Total	Standard treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Darazam 2021	37	55	65	73	87.5%	0.76 [0.62, 0.92]
Soleimani 2021	5	24	8	24	12.5%	0.63 [0.24, 1.64]
Total (95% CI)		**79**		**97**	**100.0%**	**0.74 [0.60, 0.91]**
Total events	42		73			

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%

Test for overall effect: Z = 2.83 (P = 0.005)



Appendix 7. Table of Ongoing Studies

Study Characteristics of Ongoing Studies (10)

Title Identifier Expected Completion Date	Intervention	Comparator/ Control	Patients/ Population Recruited	Outcomes
Evaluating the Use of Polymixin B Cartridge Hemoperfusion for Patients with Spepptic Shick and COVID 19 Clinical trials First posted April 20, 2020 Last update August 28, 2020 WHO trials Identifier: NCT04352985 Date of Registration: 04/15/20	Hemoperfusion using Toraymyxin PMX-20R cartridge	Standard medical care	- 18 years and older - Hypotension needing vasopressor support - received minimum of 30ml/kg intravenous fluid resuscitation in 24 hours - documented or suspected infection - Multi organ dysfunction score of more than 9 - endotoxin activity assay 0.6-0.9 units - at least 1 (needing positive pressure ventilation via invasive support, thrombocytopenia platelet less than 150,000; acute oliguria <0.5ml/kg/hr - positive COVID	Not indicated
Registry of CytoSorb Therapy in COVID-19 ICU Patients (CTC REGISTRY): Registry of Patient-level Clinical Data on CytoSorb Hemoadsorption Provided Via Integration of the CytoSorb Device Into Extracorporeal Membrane Oxygenation (ECMO), Continuous Renal Replacement Therapy (CRRT), or Hemoperfusion Extracorporeal Circuits in COVID-19 Clinical trials First posted May 18, 2929 Last update May 20, 2021 Estimated completion date October 2022 WHO trials Identifier: NCT04391920 Date of Registration: 12/05/20	Hemoperfusion using CytoSorb 300ml device	Standard medical care	- 18 years and older - COVID confirmed	ICU mortality Duration of ECMO after start of CytoSorb Duration of MV after CytoSorb Duration of pharmacologic hemodynamic support after CytoSorb Change in serum concentrations of inflammatory markers after CytoSorb Change in PaO2/FiO2 ratio after CytoSorb
Investigating the hemoperfusion effect on the recovery of hospitalized patients with severe COVID-19 symptoms in Imam Khomeini Hospital, Urmia; a before-after pilot study Identifier: IRCT20180625040232N7 Date of Registration: 11/30/20	Hemoperfusion	Conventional medical treatment	- COVID confirmed patients not responding to conventional therapies - lung involvement more than 50% on Chest CT scan - SpO2 <88% despite oxygen support - no age limit	Respiratory status Improvement in SpO2
Comparison of therapeutic effects of hemoperfusion in intubated and non-intubated patients with respiratory failure caused by the COVID-19 Identifier: IRCT20200608047686N2 Date of Registration: 11/19/21	Hemoperfusion	Standard medical care	- 18 years and older - COVID confirmed - Respiratory failure from COVID	Length of hospital stay

Exploratory study on the efficacy and safety of Direct hemoperfusion using polymyxin B-immobilized polystyrene column (PMX-DHP) for COVID-19 patients - X-CODE Identifier: JPRN-jRCTs032200131 Date of Registration: 09/28/20	Hemoperfusion using Toraymyxin PMX 20R filter	Standard medical care	- COVID confirmed - 16 years or older - requiring oxygen supplementation	Improvement in the following - P/F ratio - oxygen supplementation
Effect of hemoperfusion on short-term outcome of critically ill COVID-19 patients admitted to ICU Identifier: IRCT20091012002582N22 Date of Registration: 08/08/20	Hemoperfusion using cytosorb	Standard medical care - lung protective strategies - Antiviral, corticosteroids - given enteral or parenteral nutrition as tolerated	- 18 to 75 years - COVID confirmed - no active bleeding - no irreversible disease - Pulmonary involvement more than 50%	Mechanical ventilation duration ICU length of stay Mortality
Efficacy of Blood Purification Techniques on Acute Respiratory Distress Syndrome (ARDS) in COVID-19 Pneumonia Identifier: IRCT20150107020592N29 Date of Registration: 06/21/20	Continuous renal replacement therapy with anti complement filter 3x/week Hemoperfusion 3x/week	Standard medical care	- 18 years and older - COVID confirmed - PaO2/FiO2 ratio <150 IL-6 more than 100 pg/ml	IL-6 Mortality Oxygenation
CytoSorb Device Into Extracorporeal Membrane Oxygenation (ECMO), Continuous Renal Replacement Therapy (CRRT), or Hemoperfusion Extracorporeal Circuits in COVID-19 ICU Patients Identifier: NCT04391920 Date of Registration: 05/12/2020	Hemoperfusion using CytoSorb 300	Standard medical care	- 18 years and older - COVID confirmed	ICU mortality
Treatment of COVID-19-induced cytokine storm with filter hemoperfusion HA330 Identifier: IRCT20200317046797N5 Date of Registration: 04/19/20	Hemoperfusion using HA330 filter	Standard medical care	- 18 to 65 years - COVID confirmed - PaO2/FiO2 <200 mmHg - more than 50% incolvement of pulmonary fields in chest CT scan - Respiratory rate more than 30 cpm - SpO2 <90%	Mortality rate Need for intubation Period of hospitalization
Efficacy of HA330 Hemoperfusion in Critically Ill Patients with Severe COVID-19 Identifier: TCTR20200409006	Hemoperfusion using HA330	Standard medical care	- 18 years and older - COVID confirmed - ICU admission - IL-6 more than 400 pg/ml	28 day mortality Clinical improvement

Date of Registration: 04/09/20				
To evaluate the effectiveness of hemoperfusion in patients with severe coronavirus disease 2019 (COVID-19) Identifier: IRCT20150704023055N2 Date of Registration: 04/03/20	Hemoperfusion using HA280 and HA230	Standard medical care	- 18 years and older - COVID confirmed - PaO2/FiO2 <200 mmHg - PaCO2 >50, pH <7.35 - SpO2 <88%	Improvement of general condition IL-6 serum concentration

Q5. Should a conservative fluid management strategy be used in mechanically ventilated adult COVID-19 patients?

As of 05 March 2021

RECOMMENDATION

We suggest the use of conservative fluid management rather than liberal fluid management strategy in mechanically ventilated adult COVID-19 patients with acute respiratory distress syndrome who have been adequately resuscitated*.
(Low certainty of evidence; Weak recommendation)
**without tissue hypoperfusion and fluid responsiveness*

Consensus Issues
The recommendation of initiating a conservative fluid management strategy should be employed in adequately resuscitated and hemodynamically stable mechanically ventilated patients with acute respiratory distress syndrome. Studies included in the evidence review for this clinical question excluded patients with hemodynamic instability or those with more than minimal requirement for vasopressors for septic shock. It should be emphasized that fluid resuscitation for septic shock should be prioritized in order to optimize adequate perfusion and hemodynamic stability. Fluid responsiveness should also be adequately assessed as conservative fluid management strategy must not be initiated until patient is deemed fluid or volume unresponsive.

KEY FINDINGS

Analysis of four randomized controlled trials, which included 1,106 hemodynamically stable mechanically ventilated patients with acute respiratory distress showed a trend towards decreased risk of mortality in the conservative fluid management strategy group. Furthermore, the use of conservative fluid management strategy resulted in significantly increased ventilator-free days, significant decrease in the length of intensive care unit stay and duration of mechanical ventilation. In terms of adverse events, the use of conservative fluid management strategy showed no significant difference in renal failure-free days and need for renal replacement therapy. The overall quality of studies included in this analysis was found to have moderate risk of bias with common issues on selection, performance, and reporting bias.

INTRODUCTION

Current guidance on ideal fluid-management strategy in COVID-19-associated acute respiratory distress syndrome (CARDS) is not yet well established but is comparably modelled from other typical causes of acute respiratory distress syndrome (ARDS) such as sepsis, aspiration pneumonitis, infectious pneumonia, and trauma [1,2] Pulmonary involvement during COVID-19 infection can rapidly worsen and may result to significant morbidity and mortality [3]. A recent global literature survey reported that ARDS develop in approximately 33% of hospitalized COVID-19 confirmed patients with an observed mortality rate of 45% [4]. Along with ARDS and respiratory failure, the clinical course of critically ill patients with COVID-19 is further complicated by cardiac dysfunction [4,5]. A multicenter retrospective cohort study published a 51% incidence of myocardial injury in severe COVID-19 infection [6]. The complex interaction of pathophysiologic mechanisms that involve worsening pulmonary infiltrates and edema in the setting of ARDS and cardiac dysfunction in COVID-19

infection becomes a fundamental consideration for optimal and safe fluid-management strategy.

REVIEW METHODS

Two reviewers independently conducted search and screening using free text and MeSH terms of these keywords: "conservative fluid management," "fluid management strategy," "acute respiratory distress syndrome," using MEDLINE through PubMed and the Cochrane CENTRAL Database. Ongoing trials were included in the search thru ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. Potential data from on-going trials were also searched thru the COVID-19 Open Living Evidence Synthesis (https://covid-nma.com/) and the Living Evidence on COVID-19 (https://zika.ispm.unibe.ch/assets/data/pub/search_beta/)
Studies related to the following were included: (1) mechanically ventilated patients with acute respiratory distress syndrome, (2) conservative fluid management strategy compared to liberal fluid management strategy, (3) systematic reviews, randomized controlled trials, (4) outcomes included mortality, mechanical ventilator-free days, renal failure-free days, and the risk for renal replacement therapy.

RESULTS

In 2016, a high-quality systematic review and meta-analysis evaluated the efficacy and safety of conservative or deresuscitative fluid-management strategy (dry approach) compared to liberal fluid-management strategy (wet approach) in patients with ARDS and sepsis [7]. In this systematic review, conservative or deresuscitative fluid-management strategy utilized restricted intravenous crystalloid administration, intravenous furosemide bolus and infusion together with intravenous albumin, and continuous renal replacement therapy targeting a negative fluid balance. The liberal fluid-management strategy, on the other hand, utilized intravenous crystalloid administration, furosemide bolus and infusion without albumin, and continuous renal replacement therapy targeting a higher (or less negative to positive) fluid balance than the conservative or deresuscitative group. The conservative or deresuscitative fluid-management group had a significantly negative fluid balance (SMD -0.72; 95% CI -1.06, -0.38; p<0.0001) compared to liberal fluid-management group (Hu et al. 2014; Wiedemann et al., 2006). Subgroup analysis of four randomized controlled trials [8,9,10,11], which included 1,106 hemodynamically stable mechanically ventilated patients with ARDS showed a trend towards decreased risk of mortality in the conservative or deresuscitative group (RR 0.90; 95% CI 0.74, 1.09; p=0.27). However, the difference in the risk of mortality did not achieve statistical significance. In the same subgroup analysis, the use of conservative or deresuscitative fluid-management strategy resulted to significantly increased ventilator-free days (MD, 2.49 days; 95% CI 1.15, 3.82; p=0.0003) compared to liberal fluid-management [9,11]. One small trial [8] showed significant decrease in the length of intensive care unit stay (MD, -3.00; 95% CI -5.20, -0.80; p=0.008) and in the duration of mechanical ventilation (MD, -2.51; 95% CI -4.66, -0.36; p=0.02) in the conservative or deresuscitative group. In terms of adverse events, the largest trial [9] in the subgroup analysis showed no significant difference in renal failure-free days (MD, 0.30; 95% CI -1.08, 1.68; p=0.67) and need for renal replacement therapy (RR 0.72; 95% CI 0.51, 1.01; p=0.06). The overall methodological quality of the clinical trials included in this analysis was low. The level of evidence was downgraded due to indirectness of evidence and imprecision of results.

RECOMMENDATIONS FROM OTHER GROUPS

Currently, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine suggest using conservative fluid strategy over liberal fluid strategy for mechanically ventilated adults with COVID-19 and ARDS. The recommendation was weak due to low-quality evidence. Likewise, the World Health Organization Living Guidance also suggest the use of conservative fluid management strategy for ARDS without tissue hypoperfusion. Both external recommendations were published as of January 2021.

RESEARCH GAPS

At present, no ongoing clinical trials are investigating on the effect of conservative fluid management strategy among mechanically ventilated adult COVID-19 patients with acute respiratory distress syndrome.

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Appendix 1: Characteristics of Included Studies

Table 1. Summary of included randomized controlled trials

Study & Setting	Population (n=1106)	Interventions		Outcomes
		Conservative Fluid-Management Strategy (n=557)	Liberal Fluid-Management Strategy (n=549)	
Hu et al., 2014 China	Mechanically ventilated patients with ARDS (n=29)	Diuretics + CRRT Mean Daily Fluid Balance Over Study Period: -1.6 mL/kg/d	Diuretics + CRRT Mean Daily Fluid Balance Over Study Period: -0.5 mL/kg/d	60-day Mortality ICU Length-of-stay Duration of Mechanical Ventilation
Martin et al., 2002 USA	Mechanically ventilated patients with ARDS (n=37)	Furosemide Infusion + Albumin Mean Daily Fluid Balance Over Study Period: -47.6 mL/kg/d	Placebo Mean Daily Fluid Balance Over Study Period: -22.4 mL/kg/d	30-day Mortality
Martin et al., 2005 USA	Mechanically ventilated patients with ARDS (n=40)	Furosemide Infusion + Albumin Mean Daily Fluid Balance Over Study Period: -15.7 mL/kg/d	Furosemide Infusion + Placebo Mean Daily Fluid Balance Over Study Period: -4.3 mL/kg/d	30-day Mortality Mechanical ventilator-free days
Martin et al., 2006 USA & Canada	Mechanically ventilated patients with ARDS (n=1000)	Fluid boluses + Diuretics guided by filling pressures CVP<4 mmHg Mean Daily Fluid Balance Over Study Period: -0.3 mL/kg/d	Fluid boluses + Diuretics guided by filling pressures CVP>10 mmHg Mean Daily Fluid Balance Over Study Period: 14.3 mL/kg/d	60-day Mortality Mechanical ventilator-free days Renal failure free days Renal Replacement Therapy

ARDS: Acute respiratory distress syndrome using American-European Consensus Definition

Adapted from Silversides JA, Major E, Ferguson AJ, Mann EE, McAuley DF, Marshall JC, Blackwood B, Fan E. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive Care Med. 2017 Feb;43(2):155-170. doi: 10.1007/s00134-016-4573-3. Epub 2016 Oct 12. PMID: 27734109.

Appendix 2: GRADE Evidence Profile

Author(s): Dr. Christopher G. Manalo, Dr. Cary Amiel G. Villanueva
Question: Among mechanically ventilated adult COVID-19 patients with acute respiratory distress syndrome, does conservative fluid strategy reduce mortality and improve patient outcomes?
Setting: Intensive Care Unit
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	Conservative fluid strategy	Liberal fluid strategy	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	randomised trials	not serious	not serious	serious [a]	serious [b]	none	142/557 (25.5%)	156/549 (28.4%)	**RR 0.90** (0.74 to 1.09)	**28 fewer per 1,000** (from 74 fewer to 26 more)	⨁⨁◯◯ LOW	CRITICAL
Mechanical Ventilator-free Days												
2	randomised trials	not serious	not serious	serious [a]	not serious	none	523	517	-	MD 2.49 days higher (1.15 higher to 3.82 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Renal Failure-free Days												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	503	497	-	MD 0.3 days higher (1.08 lower to 1.68 higher)	⨁⨁◯◯ LOW	IMPORTANT
Renal Replacement Therapy (Dialysis to Day 60)												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	51/503 (10.1%)	70/497 (14.1%)	**RR 0.72** (0.51 to 1.01)	**39 fewer per 1,000** (from 69 fewer to 1 more)	⨁⨁◯◯ LOW	IMPORTANT

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

Explanations
[a] Indirect evidence from a different study population (i.e., non-COVID and inclusion of trauma patients)
[b] The confidence interval crosses the line of no effect

Appendix 3: Forest Plots

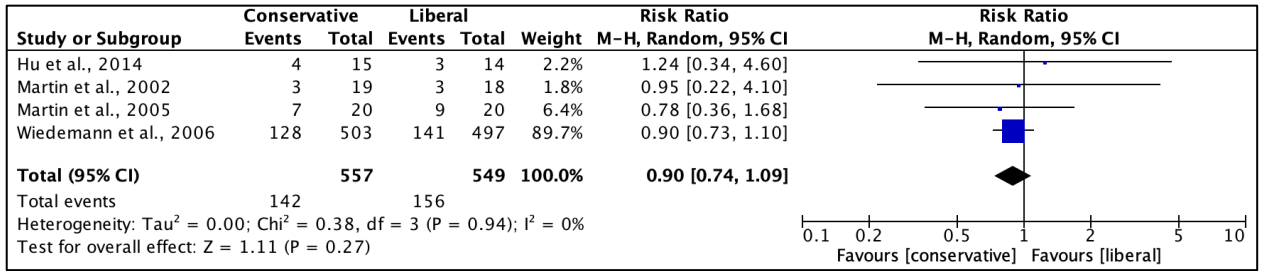

Figure 1. Forest plot for mortality

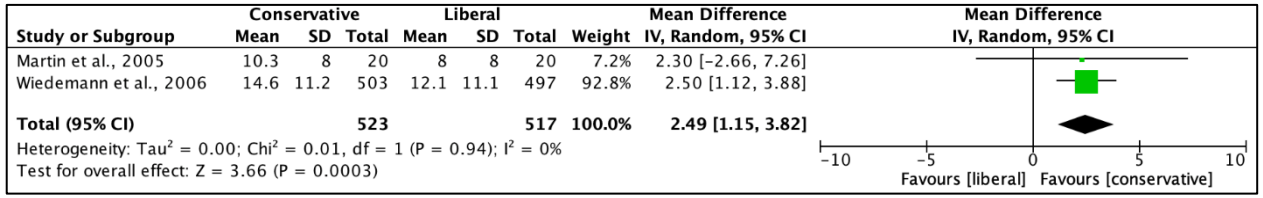

Figure 2. Forest plot for mechanical ventilator-free days

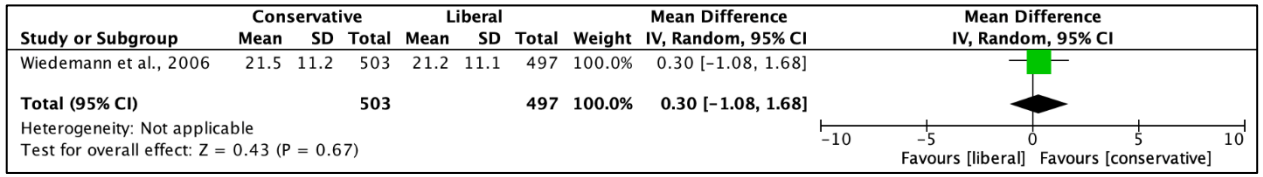

Figure 3. Forest plot for renal failure-free days

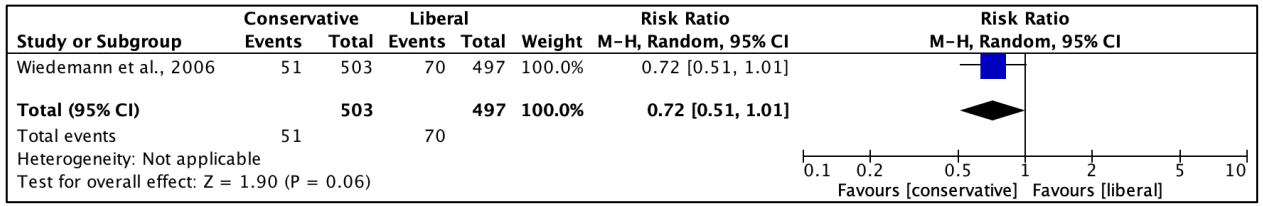

Figure 4. Forest plot for renal replacement therapy at Day 60

Q6.1. Should side lying position be used in patients with severe to critical COVID-19?

Q6.2. Should self-proning be used in non-intubated patients with severe COVID-19?

As of 26 October 2021

RECOMMENDATIONS

We suggest self-proning position in non-intubated patients with severe and critical COVID-19 (*Very low certainty of evidence; Weak recommendation)*

Consensus Issues
Self-proning in non-intubated patients with severe and critical COVID-19 was suggested despite the lack of significant benefit in terms of mortality, need for endotracheal intubation, and need for intensive care unit stay on the basis that self-proning may still offer some benefit on improving oxygenation citing theoretical effect and personal experience, and taking into consideration the existing recommendations made by various international guidelines as well.

There is insufficient evidence to recommend the use of side lying in non-intubated patients with severe and critical COVID-19 *(Very low certainty of evidence)*

Consensus Issues
There was very limited evidence to recommend side lying for the same subset of patients, although it was recognized that there may be some benefit. This intervention will depend on the physician's prerogative in situations where self-proning is not possible. Potential harms such as patient discomfort and risk of accidental removal of peripheral lines and endotracheal tubes and the need for additional healthcare workers to perform proning in sedated and mechanically ventilated patients should be considered for both patient and health care worker in attempting this intervention.

PREVIOUS RECOMMENDATION

We suggest self proning to improve oxygenation status of non-intubated hospitalized patients with COVID-19 infection requiring oxygen supplementation. *(Very low quality of evidence; Conditional recommendation)*

Previous Consensus Issues
Self-proning is recommended for patients with COVID-19 infection who are not qualified to be intubated. Based on the studies, self proning has no impact on mortality and intubation.

WHAT'S NEW IN THIS VERSION?

As of September 20, 2021, 4 new randomized controlled trials (RCTs) were available for review to evaluate proning in COVID-19 patients. Recommendation for proning is maintained based on very low quality of evidence with a conditional recommendation.

KEY FINDINGS

Among non-intubated severe patients with COVID 19 with oxygen saturation of at least 90% and oxygen requirement of less than 6 liters per minute, pooled results of 4 randomized controlled trials showed no difference in the duration of proning and outcomes such as mortality, need for intubation and the need for intensive care.

A case series of five patients with COVID-19 associated ARDS showed that side lying accompanied with Positive End Expiratory Pressure (PEEP) titration provided a statistically significant benefit by decreasing the incidence of overdistension and lung collapse. Adverse events were not reported.

The certainty of evidence for both side lying and proning are very low due to serious risk of bias, substantial heterogeneity and imprecision.

INTRODUCTION

Positioning maneuvers such as proning and side lying have been proven to provide benefit in patients with Acute Respiratory Distress Syndrome (ARDS).[1] However, whether these benefits extend to patients with severe to critical COVID-19 is still under clinical investigation. Proning position results in improvement in ventilation-perfusion mismatching in patients with ARDS. Despite studies explaining the proposed pathophysiologic basis for COVID ARDS (CARDS) such as intravascular thrombosis and loss of lung perfusion regulation, retrospective studies have provided some evidence of benefit for positioning maneuvers in severe and critical patients.[2-4]

REVIEW METHODS

A comprehensive literature search was done (date of last search: September 20, 2021) for the 2 clinical questions using Medline, Cochrane Library, Google Scholar and clinicaltrials.gov with the following keywords: “lateral positioning”, “side lying” “lateral decubitus”, “proning”, “prone positioning” “prone position” and “COVID-19” “SARS-COV2”. All studies that resulted from the search were reviewed and appraised. Randomized controlled trials and available meta-analysis relating to side lying and proning were included.

RESULTS

Proning

A total of 34 RCTs were screened and evaluated at the time of the search. Of these, only four RCTS (Rosen et al., Kharat et al., Jayakumar et al., and Taylor et al.)[6-9] were found to have completed and published results on proning and COVID-19 while the other 30 RCTs were still in the process of recruitment, final manuscript review or publishing. There were no RCTs available for the use of proning in intubated COVID-19 patients.

Patients included in the studies were adults greater than 18 years old, diagnosed with COVID-19, admitted in the ICU [8] and medical wards [6,7,9], with oxygen saturation of at least 90% [7-9] and oxygen requirement of <6 liters per minute.[7-9] Exclusion criteria were similar among all studies which included pregnant women, patients who were unable to perform proning, those with hemodynamic instability and those who were in need of immediate intubation.

Different protocols on proning were used in the included studies and ranged from 6 to 48 hours. The study of Taylor et al., Kharat et al. and Jayakumar et al. instructed patients on how to perform self-proning (not specified) and were advised to undergo proning for at least 48 hours, 12 hours and 6 hours respectively. On the other hand, the study by Rosen et al. provided illustrations and instructed patients to do self-proning for at least 16 hours. All four studies had assigned teams of nurses and physicians for evaluation and monitoring of patients with no mention of self-monitoring. Similar outcomes were identified such as need for intensive care, mortality and need for intubation. The study of Jayakumar et al. provided data on the effect of proning on oxygenation by measuring the PaO2/FiO2 ratio after 2 hours, which was found to be statistically not significant (p value=0.3). Other outcomes such as change in PaO2, change in SpO2 and change in ROX index were not evident in the studies.

Need for intubation

Three randomized controlled trials [6,8,9] with very low evidence have been evaluated in terms of patients needing intubation. The study of Rosen et al. reported their primary outcome of patients on proning needing intubation at 33% while rates taken from Taylor et al. and Jayakumar et al. were at 0 and 20% respectively. A subgroup analysis was done based on duration of proning, which showed no difference between patients who underwent self-proning for 16 hours or more (RR 1.0, 95% CI 0.53-1.90) and those who underwent self-proning for less than 6 hours (RR 1.0, 95% CI 0.56-1.77*).*

Mortality

Three studies evaluated mortality as an outcome in patients who underwent proning. The studies of Rosen et al., Taylor et al. and Jayakumar et al. reported a mortality rate of 17%, 0% and 10% respectively. On subgroup analysis, there were no significant differences in mortality for patients who did self-proning for 16 hours or more (RR 2.17, 95% CI 0.58-8.03) and self-proning for 6 hours or less (RR 1.50, 95% CI 0.27-8.34).

Need for Intensive Care

All of the four RCTS evaluated the effect of proning and the need for intensive care. Two studies (Rosen et al. and Taylor et al.) who had proning for >16 hours had rates of 75% and 29% respectively while patients who underwent proning for <12 hours (Jayakumar et al. and Kharat et al.) had rate of 13% and 10% respectively. Results from both subgroups with different durations of proning (>16 hours RR 0.96, 95% CI 0.61-1.51 and <12 hours RR 1.58, 95% CI 0.98-2.54) showed no significant difference in the patient's need for intensive care.

Side Lying

A total of six studies were screened to review the evidence of side lying in COVID-19. Of the six studies, two were excluded due to the unavailability of outcomes and three were RCTS that were on the process of recruiting participants. The identified and available study was a case series published in 2021 which included five patients on mechanical ventilation.[5] Patients included in the study were adults aged 44-85 years old with COVID-19 associated ARDS, who were mechanically ventilated, sedated, and paralyzed. Lung overdistension and collapse were evaluated using Electrical Impedance Tomography (EIT) accompanied with Positive End Expiratory Pressure (PEEP) titration in 5 patients, initially on supine followed by side lying, as determined by the more aerated lung which would then be positioned down. Lung overdistension and collapse were measured before and after positioning (supine to targeted lateral

position) with decremental PEEP titration. Results from this study revealed a statistically significant effect of decreasing overdistension accompanied with PEEP titration in the right lung ($p < 0.0005$) when in side lying and prevention of lung collapse in the left lung [at PEEP 14 ($p = 0.034$), at PEEP 10 ($p = 0.028$), at PEEP 8 ($p = 0.019$), and at PEEP 6 cmH2O ($p = 0.007$)]. No statistical significance was observed in right lung collapse and left lung overdistension. There was no data available for outcomes on mortality, Intensive Care Unit (ICU) admission, initiation of anti-inflammatory treatment and length of hospital stay.

EVIDENCE TO DECISION

There is still scarce data on the use of proning and side lying in the management of severe to critical COVID-19 patients. Retrospective cohort studies and other RCTS would recommend these maneuvers but some are still uncertain on its benefit on management.

One of the most common disadvantages of doing proning position especially in intubated patients is the need for a team of health workers to carefully position patients into proning, taking into consideration the discomfort and the risk of removing peripheral lines and tubes.[10, 11]

RECOMMENDATIONS FROM OTHER GROUPS

Four guidelines on the management of COVID-19 were identified. Their recommendations are summarized in the table below.

Group/Society/Network	Year	Recommendation	Level of Evidence/Strength of Recommendation
American Thoracic Society [12]	2020	For patients with refractory hypoxemia due to progressive COVID-19 pneumonia (ARDS), we suggest prone ventilation	Conditional Recommendation
World Health Organization [13]	2021	We suggest awake prone positioning of severely ill patients hospitalized with COVID-19 requiring supplemental oxygen (includes high-flow nasal oxygen) or non-invasive ventilation (conditional, low certainty evidence).	Conditional Recommendation
European Respiratory Society [14]	2021	Prone positioning may improve oxygenation in non-intubated patient with acute hypoxemic respiratory failure and is widely used for mechanically ventilated patients with COVID-19.	Very Low Conditional Recommendation
National Institutes of Health [15]	2021	For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation	CIIa
		The Panel recommends against using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation	AIII
		For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation	BIIa

RESEARCH GAPS

There is still limited data on the use of proning and side lying in the management of severe to critical COVID -19 patients. As of now, RCTS are in the process of recruitment and data collection and may further contribute to provide evidence in the management of COVID-19.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion: side lying, proning (N = 8)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)					• Despite studies explaining the proposed pathophysiologic basis for COVID ARDS (CARDS) such as intravascular thrombosis and loss of lung perfusion regulation, retrospective studies have provided some evidence of benefit in severe and critical patients
Benefits	Large (3)	Moderate (1)	Small (2)	Uncertain (2)			• One observational study provided a significant decrease in overdistension and lung collapse in mechanically ventilated patients accompanied with PEEP titration. Proning: no significant difference in terms of need of intubation, need for intensive care and mortality regardless of duration of proning
Harm	Large	Small (8)	Uncertain				Reported adverse effects during proning: pressure ulcers, vomiting and cardiac arrest. Other harms observed in studies were removal of peripheral lines and possible removal of the endotracheal tube in intubated patients.
Certainty of Evidence	High	Moderate (2)	Low (2)	Very low (4)			
Balance of effects	Favors drug (4)	Does not favor drug (1)	Uncertain (3)				• There were no significant difference in terms of need of intubation, mortality and need for intensive care in COVID-19 patients who underwent proning.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability (1)			
Resources Required	Uncertain (3)	Large cost (1)	Moderate Cost (2)	Negligible cost (2)	Moderate savings	Large savings	
Certainty of evidence of required resources	No included studies (4)	Very low (1)	Low (2)	Moderate (1)	High		
Cost effectiveness	No included studies (3)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (5)			
Equity	Uncertain (3)	Reduced	Probably no impact (3)	Increased (2)			
Acceptability	Uncertain (1)	No	Yes (7)				
Feasibility	Uncertain (1)	No	Yes (7)				

Appendix 2. Search Yield and Results

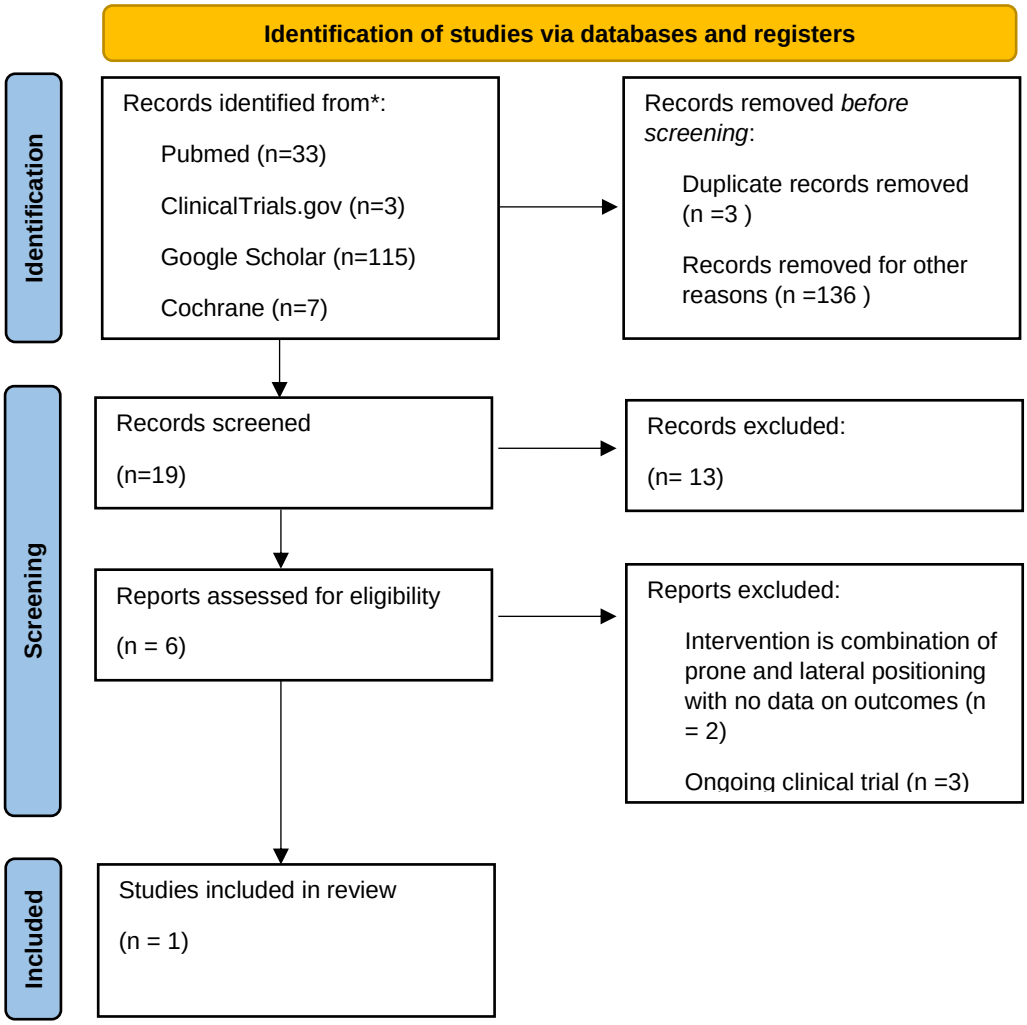

Figure 1: PRISMA flow diagram of Search Yield results for side lying

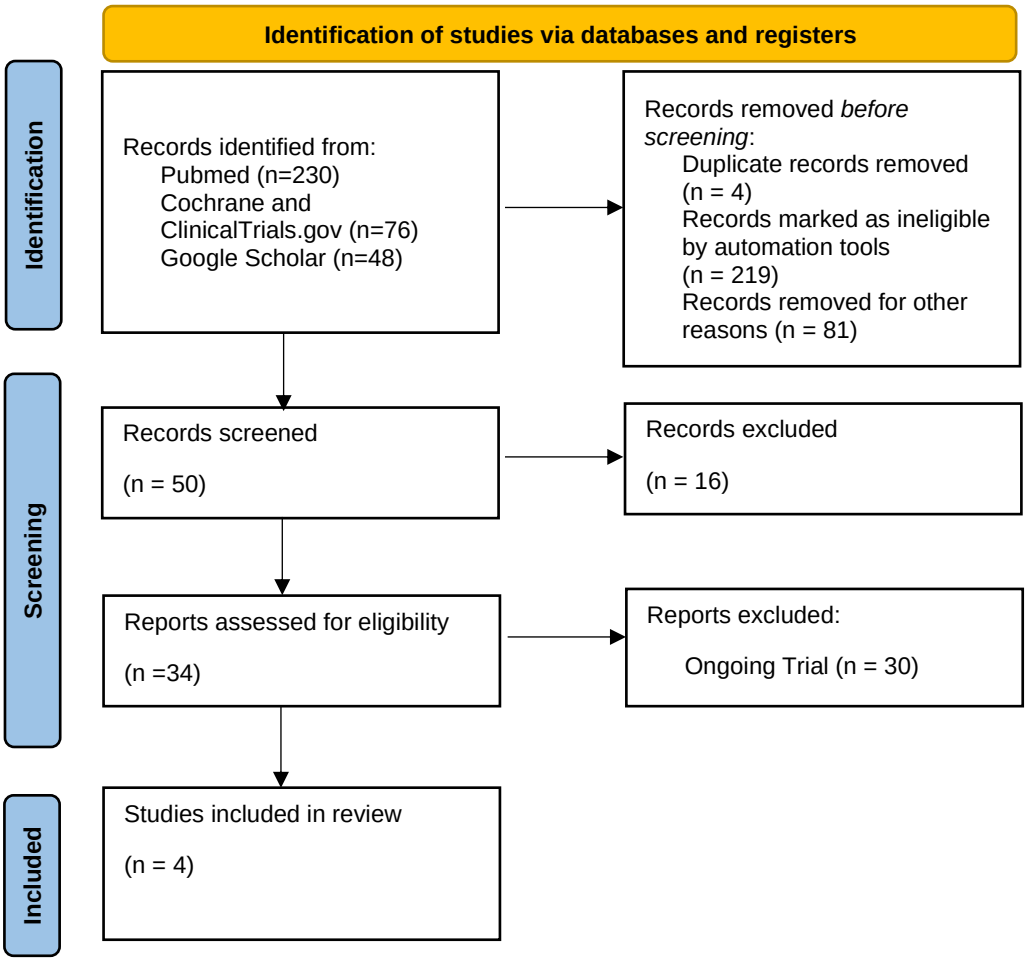

Figure 2: PRISMA flow diagram of Search Yield results for proning

Table 2. Detailed search strategy for side lying

#	Query	Results
	Pubmed	
1	((lateral positioning) OR (lateral decubitus positioning)) OR (side lying)	39,946
2	((("COVID-19" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccine" [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])	176,657
3	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	4,520,121
4	(((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]	202,510
5	#1 AND #2	33
6	#1 AND #2 AND (#3 OR #4)	4
	COCHRANE	
1	((lateral positioning) OR (lateral decubitus positioning)) OR (side lying)	1444
2	COVID-19 OR SARS-COV2 OR nCOV-2019 OR Coronavirus OR Coronavirus of 2019	7401
3	(randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups)	1538615
4	(((systematic review OR systematic literature review OR systematic scoping review OR systematic narrative review OR systematic qualitative review OR systematic evidence review OR systematic quantitative review OR systematic meta-review OR systematic critical review OR systematic mixed studies review OR systematic mapping review OR systematic cochrane review OR systematic search and review OR systematic integrative review) NOT comment NOT (protocol OR protocols)) NOT MEDLINE) OR (Cochrane Database Syst Rev AND review) OR systematic review	33327
5	#1 AND #2	7
6	#5 AND (#3 OR #4)	7 (2 cochrane reviews, 5 trials)
	Clinical trials.gov	
1	COVID 19 AND lateral positioning AND trials	3
	Google Scholar	
1	Allintitle: positioning AND COVID	115

Table 3. Detailed search strategy for proning

#	Query	Results
Pubmed		
1	((prone positioning) OR (proning)) OR (proning position) OR (prone)	85,169
2	((("COVID-19" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccine" [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])	176,657
3	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	4,520,121
4	(((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]	202,510
5	#1 AND #2	1,332
6	#1 AND #2 WITH filter (Clinical Trial, Randomized Controlled Trial)	11
COCHRANE		
1	((prone positioning) OR (proning)) OR (proning position) OR (prone)	1,974
2	COVID-19 OR SARS-COV2 OR nCOV-2019 OR Coronavirus OR Coronavirus of 2019	7401
3	#1 AND #2	74 (5 Cochrane Reviews, 69 Trials) Cross Referenced with Clinicaltrials.gov*
Google Scholar		
1	allintitle: prone OR proning OR prone positioning OR prone position AND COVID	48

Appendix 3. Characteristics of Included Studies

Table 4. Study Characteristics of Included Studies for Side Lying (n=1)

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Targeted lateral positioning decreases lung collapse and overdistension in COVID-19-associated ARDS Micek 2021	Prospective observational study	Brazil	5	Patients with COVID-19 associated ARDS in the first days of mechanical ventilation ARDS by Berlin Criteria	Targeted lateral position defined by selecting the less aerated lung to be positioned up and the more aerated lung to be positioned down. During all the procedures, the patients were deeply sedated and under muscle paralysis		Regional overdistension and collapse

Table 5. Study Characteristics of Included Studies for Proning (n=4)

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/Control	Outcomes
Awake prone positioning in patients with hypoxemic respiratory failure due to COVID-19: the PROFLO multicenter randomized clinical trial Rosen et.al 2021	Prospective multicenter, open-label, parallel arm, randomized clinical superiority trial	Sweden	75	Adults ≥ 18 years old - SARS-CoV-2 reverse transcription polymerase chain reaction tests on naso- or oropharyngeal swabs - hypoxemic respiratory failure, -HFNO or NIV for respiratory support - PaO2/FiO2-ratio ≤ 20 kPa or corresponding values of SpO2 and FiO2	at least 16h Awake Prone Positioning (APP) per day Prone and semi-prone posi- tioning was allowed During in-hospital transportation, oxygenation by face mask and positioning appropriate for adequate monitoring and safety was allowed	APP was not encouraged but could be prescribed by the attending clinician at his/her discretion.	• Primary outcome ○ Intubation within 30 days after enrollment • Secondary outcome ○ Duration of APP ○ Use of NIV ○ Time of NIV for patients included with HFNO ○ use of vasopressors/inotropes ○ CRRT,ECMO ○ Ventrilator-free days ○ Days free of NIV/HFNO for patients not intubation ○ Hospital and ICU length of stay ○ 30 day mortality ○ WHO ordinal scale for clinical improvement at day 7, 30 ○ Adverse events
Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomized controlled trial	Single-centre cluster randomized	Geneva, Switzerland	27	patients aged ⩾18 years on low-flow oxygen therapy (defined as 1–6 L·min−1)	self-proning for 12 h per day as an addition to usual care for 24 h	Usual care consisted of 1) oxygen titration with nasal cannula according to our	The pre-specified **primary outcome** was oxygen needs assessed by nasal cannula oxygen flow at 24 h.

Kharat et. Al 2021	controlled trial			through nasal cannulas to obtain a SpO2 level of 90–92%.		institutional recommendations to target SpO2 values between 90% and 94%.	**Secondary outcomes** were the SpO2/FiO2 ratio (defined as SpO2 percentage divided by the FiO2) at 24 h; respiratory and heart rate at 24 h; patient trajectory (transfer to critical care unit); potential intervention-related adverse effects as defined by neck pain, position-related discomfort and gastroesophageal reflux
Standard Care Versus Awake Prone Position in Adult Nonintubated Patients with Acute Hypoxemic Respiratory Failure Secondary to COVID-19 Infection—A Multicenter Feasibility Randomized Controlled Trial Jayakumar et.al, 2021	Multicenter feasibility randomized controlled trial	India	60	18 years of age and requiring 4 or more liters per minute (LPM) of supplemental oxygen to maintainSpO2 92% PaO2/FiO2 ratio between 100 and 300 mmHg (mild to moderate ARDS) with PaCO2 <45mmHg Patients with AHRF and Hemodynamic hemodynamic shock requiring <0.1mcg/kg/min of norepinephrine were also considered for inclusion.	lie prone for a minimum of 6 hours in a day (cumulative)	Patients randomized to standard care were allowed to change their position as per their comfort (supine, semi sitting, sitting or lateral). If patients in the standard arm wished to lie prone for comfort, this was allowed.	Primary outcome measure proportion of patients adhering to the protocol in each group Secondary outcomes proportion of patients requiring escalation of respiratory support in either group; number of hours prone and maximum hours of continuous prone positioning in a day; length of stay in the ICU; ICU mortality; adverse events; reasons for not lying prone
Awake prone positioning strategy for non-intubated Hypoxic Patients with COVID-19: A pilot trial with embedded implementation evaluation Taylor, et. al 2021	Pragmatic, two-arm parallel cluster RCT and a qualitative study	North Carolina, USA	40	positive for SARS-CoV-2 within 7 days or were suspected to have COVID-19 pneumonia, room air oxygen saturation,93% or oxygen requirement of 3 liters per minute or greater without the need for mechanical ventilation.	Awake Prone Positioning Strategy (APPS) Patients were encouraged to sustain the prone position as long as possible but were allowed to return to the supine position as necessary	Usual Care	• The primary outcome • Establish outcomes relative to successful implementation of a future definitive RCT. • Specific research outcomes • nadir oxygen saturation to fraction of inspired oxygen (S/F) ratio • Time spent with S/F ratio less than 315 • Receipt of intensive care, greater than 6 L/min • Oxygen support • Intubation • Hospital length of stay • Hospital mortality

Appendix 4. Study Appraisal

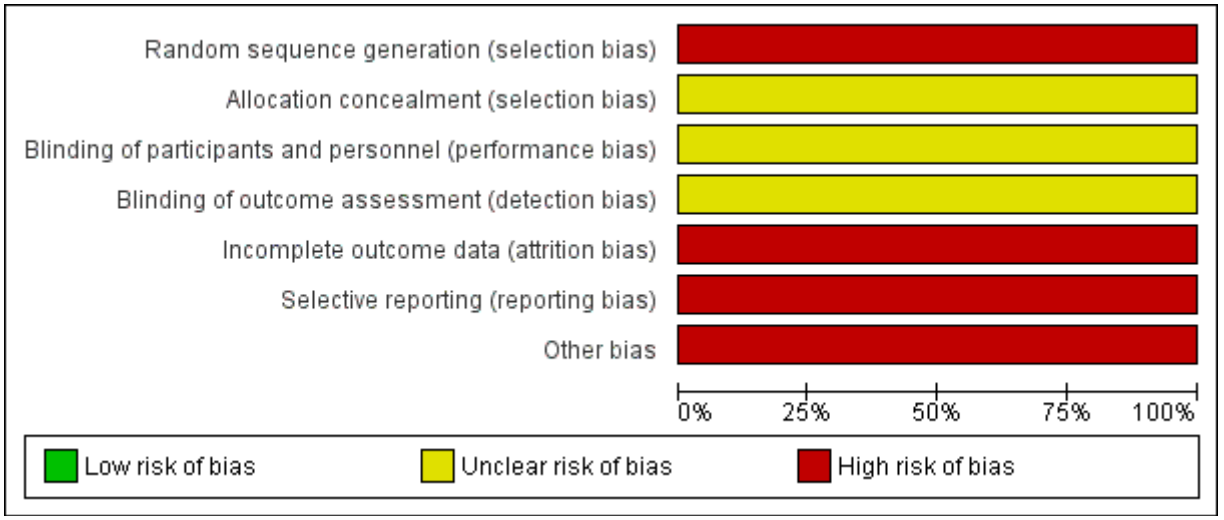

Figure 3. Risk of Bias (Micek et. al 2021) in side lying in patients with severe to critical COVID 19

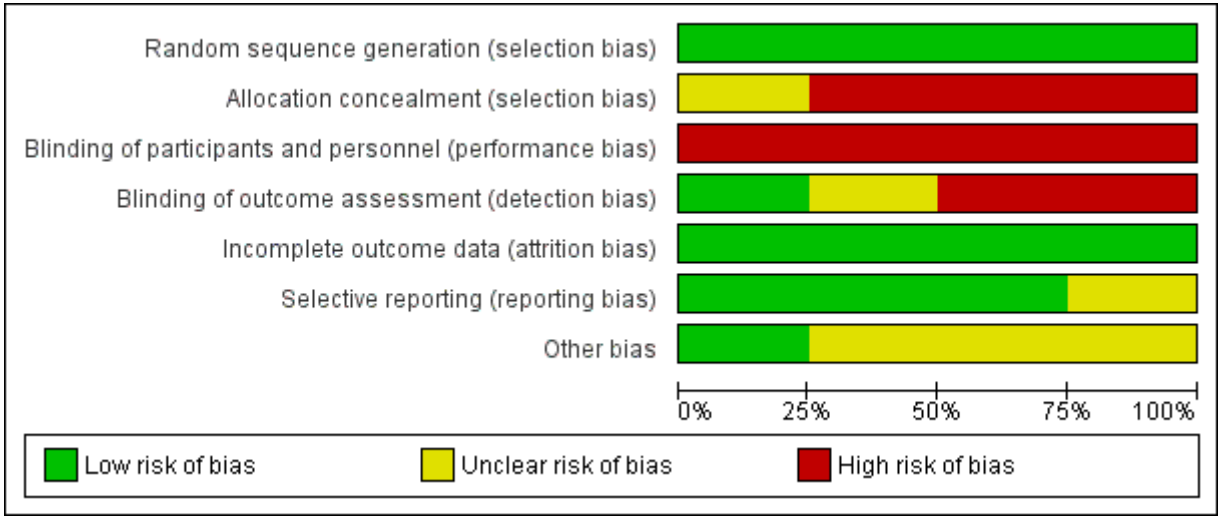

Figure 4. Risk of Bias (Rosen et. al, Taylor et. al, Kharat et. al, Jayakunar et. al 2021) in proning in non inubated severe patients with COVID -19

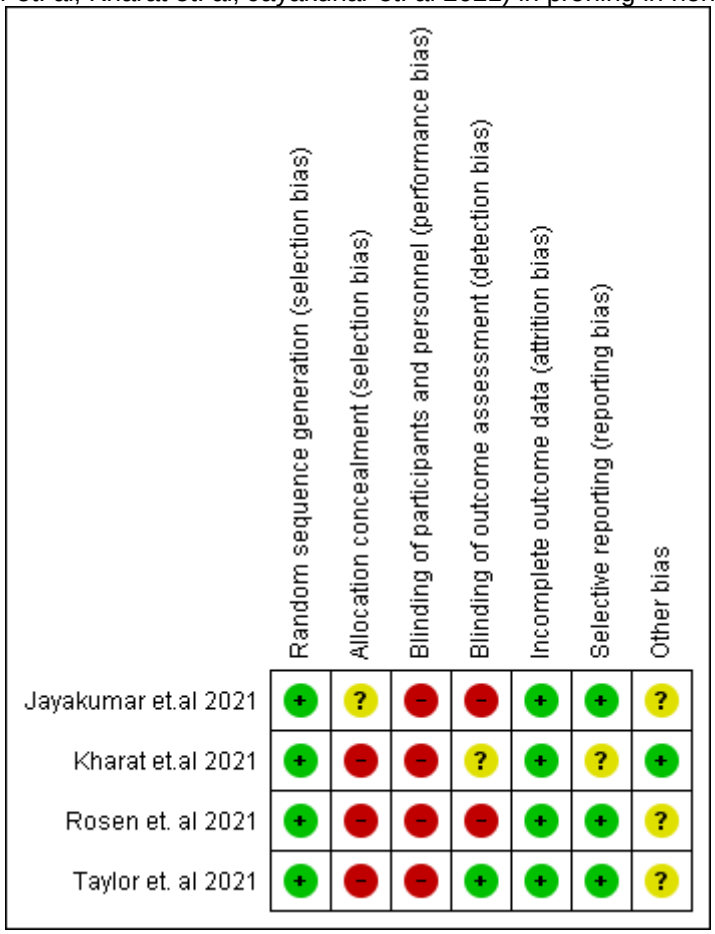

Figure 5. Risk of Bias Summary of included studies for proning

Appendix 5. GRADE Evidence Profile

Table 6. GRADE Evidence Profile for side lying

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Regional overdistension									
1	Observational studies	Serious [a]	Very serious [b]	Not serious	Very serious [c]	None	There was a marginal two-way interaction between position and PEEP (p= 0.073). The main effect of position showed a statistically significant difference in the % of overdistension within the right lung: less overdistension along the PEEP titration in targeted lateral (right down) than supine position (p=0.005) there was no statistically significant differences for position and overdistension of the left lung	⊕◯◯◯ VERY LOW	CRITICAL
Lung Collapse									
1	Observational studies	Serious [a]	Very serious [b]	Not serious	Very serious [c]	None	There was a statistically significant two-way interaction between position and PEEP (p=0.014) in the percent of collapse within the left lung: less collapse along the PEEP titration was found within the left lung in targeted lateral (right down) than supine position there was no statistically significant differences for right lung collapse on lateral position	⊕◯◯◯ VERY LOW	CRITICAL

Explanations

[a] inadequate control of confounding factors

[b] effect size was not available

[c] total population was only at 5

Table 7. GRADE evidence for prone positioning

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone positioning	Supine positioning	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	Randomized trials	Serious [a]	Serious [b]	Serious [c]	Serious [d]	None	9/93 (9.7%)	41/82 (50.0%)	**RR 1.89** (0.67 to 5.36)	**445 more per 1,000** (from 165 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	
Need for Intensive Care												
4	Randomized trials	Serious [a]	Serious [b]	Serious [c]	Serious [d]	None	56/103 (54.4%)	46/99 (46.5%)	**RR 1.14** (0.81 to 1.62)	**65 more per 1,000** (from 88 fewer to 288 more)	⨁◯◯◯ VERY LOW	
Need for intubation												
3	randomized trials	serious [a]	serious [b]	serious [c]	serious [d]	none	16/93 (17.2%)	17/82 (20.7%)	**RR 1.00** (0.56 to 1.77)	**0 fewer per 1,000** (from 91 fewer to 160 more)	⨁◯◯◯ VERY LOW	

Explanations

[a] personnel and outcome assessors were not blinded

[b] downgrade by 1 due to substantial heterogeneity

[c] no reported outcomes on Change in PF RATIO, PaO2, SpO2 and ROX index

[d] downgraded due to a wide confidence interval

Appendix 6. Forest Plots

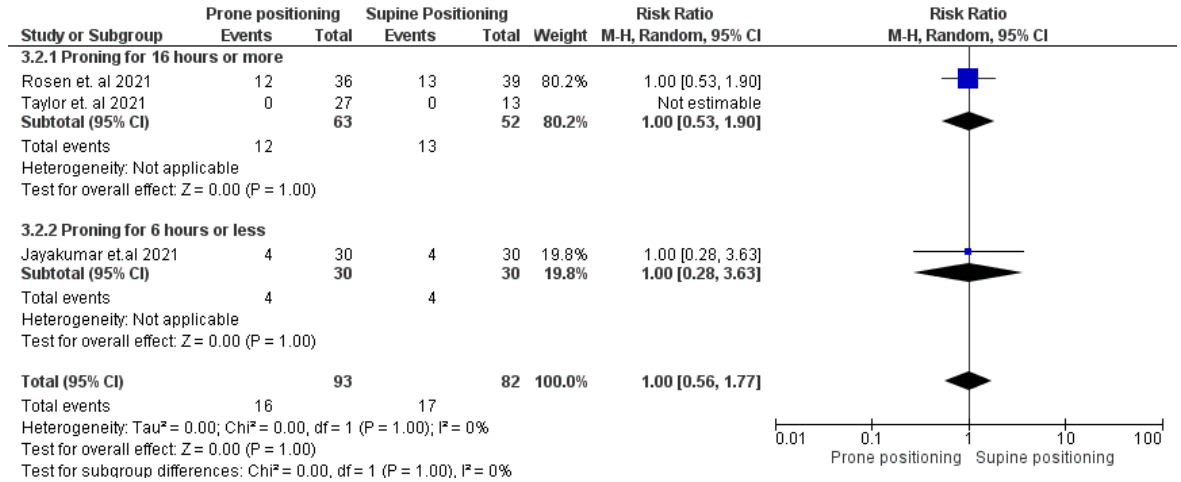

Figure 6. Forest Plot on the outcome of proning and need for intubation

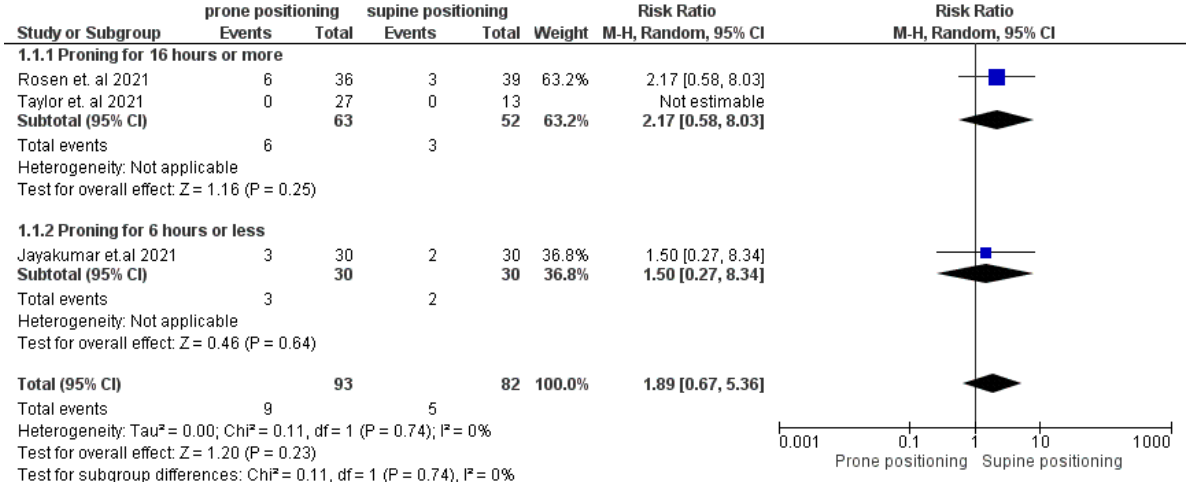

Figure 7. Forest plot on the outcome of proning and mortality

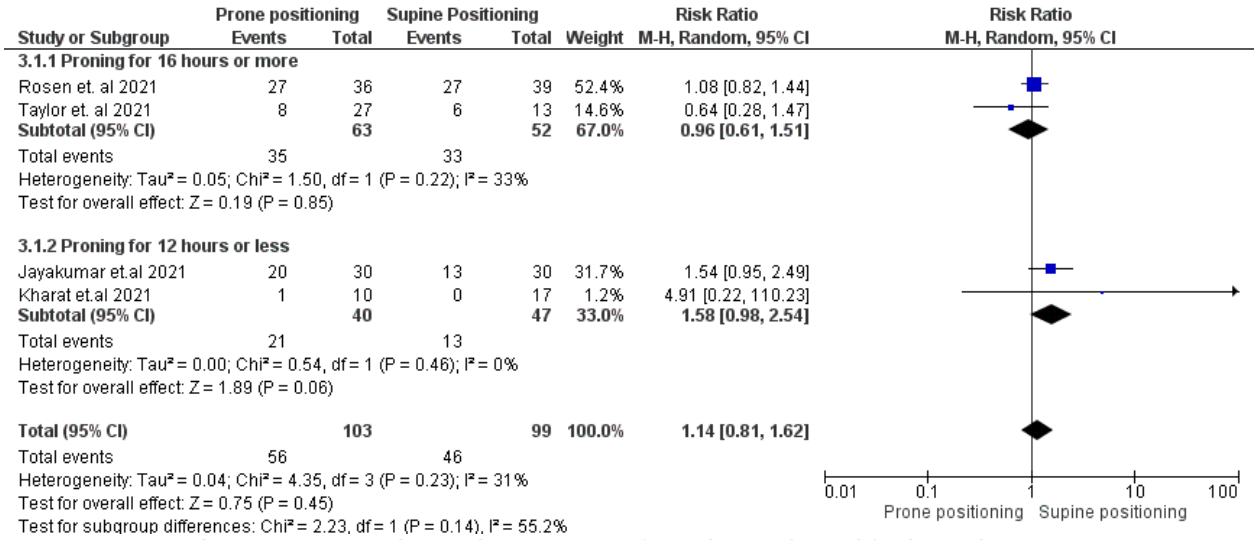

Figure 8. Forest Plot on the outcome of proning and need for intensive care

Appendix 7. Characteristics of Ongoing Studies

Table 8. Study Characteristics of Ongoing studies for side lying (n=3)

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
Immediate effect of prone and side lying position on oxygen saturation in patients with COVID 19- A Randomised Controlled Trial Main ID: CTRI/2021/03/031939	Prone position after doing Diaphragmatic breathing exercises, thoracic expansion exercise Lateral Position after doing Diaphragmatic breathing exercises, thoracic expansion exercise patients will adopt the position (supine) after breathing exercises for 1 hour. Frequency - 1 session per day The patient's face could be placed on either side and patients were allowed to adjust their position for comfort.	Supine Position after doing Diaphragmatic breathing exercises, thoracic expansion exercise and patients will adopt the position (supine) after breathing exercises for 1 hour. Frequency - 1 session per day	NOT YET RECRUITING Patients who required additional oxygen supplementation (HFNC) Age group of >30 years both male and female	Spo2Timepoint: 1 hour
Awake Prone Position Versus Repeated Position Change in Moderate to Severe COVID-19 patients: A Pilot Randomized Controlled Trial Main ID: CTRI/2020/07/026532	Repeated Position Change: One hour right lateral, two hours prone and one hour left lateral	Awake Prone Positioning: Awake Prone Positioning for 4h in patients presented with shortness of breath	NOT YET RECRUITING Adult patients (aged between 18 and 75y) with laboratory confirmed diagnosis of COVID-19 pneumonia, self-reported symptom of shortness of breath patients,	Primary Outcome • compare repeated positioning with 4h continuous prone positioning in terms of self-reported dyspnea in a 10- point visual analogue scale Time point: 4hour since randomization Secondary Outcome • oxygenation status (room air oxyhemoglobin saturation or PaO2/FiO2 ratio in arterial blood gas) • requirement of rescue therapy (high flow nasal oxygen) in both the groups. • hemodynamic variables in both the groups. • requirement of mechanical ventilation within 24h in both the groups. • the change in respiratory rate in both the groups. • Timepoint: 4 hour since randomization • Secondary ID(s)
NCT04475068 Feasibility and Physiological Effects of a Postural Recruitment Maneuver in Patients With Acute	Lateral Position (left and right lateral decubitus) patients will be sedated deeply with sedatives and opioids and paralyzed.		Patients > 18 years of age Patients with moderate-to-severe ARDS as per the Berlin definition	• Effects of a postural recruitment maneuver in lung aeration • Lung aeration measured by ultrasound reaeration score, ranges from 0 (all regions are well aerated) to 36 (all regions are consolidated).

Respiratory Distress Syndrome Due to COVID-19 Infection	Patients will be evaluated in 5 positions sequentially: 1) Supine 2) Left lateral 3) Supine 4) Right lateral 5) Supine. Each step will last 30 minutes. Aeration measured by Electric Impedance Tomography (EIT) and lung ultrasound, distribution of the lung ventilation and perfusion measured by EIT, ventilator and hemodynamic parameters, esophageal pressure, and blood gas analysis will be recorded at the end of each step. Continuous monitoring of blood pressure, heart rate and saturation of arterial blood (SpO2) will be carried out during all steps of the protocol to assess the tolerance to the procedure.		Infection due to COVID-19 Body mass index (BMI) ≤ 35 kg /m^2. Exclusion Criteria:	• Effects of a postural recruitment maneuver in distribution of ventilation • Distribution of ventilation measured by EIT (distribution and changes in the impedance in AU, arbitray units) • Effects of a postural recruitment maneuver in gas exchange • Gas exchange measured by blood gas analysis (PaO2, PaCO2, in mmHg) and capnography (end-tidal CO2, in mmHg) • Effects of a postural recruitment maneuver in respiratory mechanics • Respiratory mechanics measured by esophageal balloon (esophageal pressure, transpulmonary pressure, in cmH2O) • Effects of a postural recruitment maneuver in hemodynamic • Hemodynamic data measured by invasive arterial monitoring (mean arterial pressure, in mmHg) Secondary outcome • Feasibility of a postural recruitment maneuver • Oxygenatory tolerance evaluated with pulse oximeter (arterial oxygen saturation, in percentage)

Table 9. Study characteristics of ongoing studies for proning (n=30)

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes

NCT04424797
 	
Prone Positioning on Admission for Hospitalized COVID-19 Pneumonia Protocol
 	
Estimated completion date
July 31, 2022
	The Prone Experimental Group will position patient in approximately 15-degree reverse trendelenburg and prone using pillows for comfort. The participant will be asked to rotate to prone positioning every 2 hours while awake and encourage to sleep prone overnight as possible with a goal of 10-12 hours daily.	The Standard Supine Control Group will utilize standard oxygen (O2) device in supine position at approximately 30-60 degrees to target peripheral capillary oxygen saturation (SpO2) >90% and the participant or nurse will document time in non-supine position.	• Patients >18 years old and above
			• Patients admitted to the hospital floor with primary diagnosis of confirmed COVID-19 pneumonia and respiratory failure requiring greater than or equal to 2 Liters(L) Nasal Cannula (NC) to maintain SpO2>90%
			• Ability to independently change positions in bed
			• Able to tolerate prone positioning
				Primary Outcome
				• Incidence of intubation
				
				Secondary Outcome
				• Maximum oxygen
				  ○ Measure of maximum oxygen requirements
				• Length of Stay
				  ○ Measured in days of hospitalization
				• Ventilator-free days
				  ○ Measured in days not on a ventilator

				• Treatment failure of prone positioning due to worsening SpO2 status while prone
				  ○ Whether or not the participant met treatment failure descriptions
				• Mortality
				  ○ Whether or not the participant died while hospitalized

ACTRN12620000740998
 	
A Randomised Controlled Trial of Early Prone Positioning to Improve Oxygenation in Non-Intubated Adults Admitted to Intensive Care with COVID-19
 	
Estimated completion date: no data
 	
Not yet recruiting
	lying prone for up to 12 hours a day in a prone position
	
	no minimum time been period of proning and no restriction on participants positioning outside of the 'intervention' periods.
	
	If this duration is not tolerated for an individual patient, staff will trial a variety of comfort measures
	
	The intervention will continue for 72 hours (a maximum of 36 hours prone).
	
	If a participant is unable to tolerate a 12h/day prone position as above
	
	Step 1 - Trial 3 x 3hr sessions/9 hours a day
	Step 2 - If needing longer breaks not prone - Trial 2 x 4hr sessions/8 hours a day
	Step 3 - Trial 2 x 3hr sessions/6 hours a day
	Step 4 - 3 x 2 hour sessions/6 hours a day
	Step 5 - 2 x 2 hours sessions/4 hours a day
	Step 6 - Abandon proning, document in EMR why proning was abandoned
			• Adults, over the age of 18
			• COVID-19 Diagnosis Confirmed – either by PCR or as per any unit policy changes that may be applied during the enrolment period
			• Admitted to Intensive Care
			• Any severity of disease (As defined by National COVID 19 Clinical Evidence Taskforce "Australian Guidelines for the clinical care of people with COVID-19" assessable at https://covid19evidence.net.au).
			• For patients with severe disease, the treating intensivist must be consulted prior to randomisation (see exclusion criterion #2)
			• Willing and able to tolerate prone positioning (A pre-enrollment screening test to ensure they can tolerate the position and can maneuver into & out of the prone position with minimal assistance from their usual care staff only.)
			• Prior informed consent has been obtained from the patient
				Primary Outcome
				• Oxygen Saturations in the blood
				  ○ Difference in average gradient of the PaO2:FiO2 (PF ratio) in the prone and control groups over the trial period (72 hours).
				  ○ Calculated by pulse oximetry recordings and oxygen delivery method
				
				Secondary Outcome(s)
				• Median number of hours spent prone per day during trial period in the intervention group
				  ○ Number of adverse events in the prone group compared to control, as collected by staff survey, and any other incidence of adverse events brought to the attention of investigators.

CTRI/2020/06/025804 Effectiveness of awake self proning strategy in COVID-19: An open-labelled randomized controlled trial Not yet recruiting	:The COVID-19 patient will be asked to be in prone position and its effect on improvement of their blood oxygenation will be seen using a finger saturation probe.	The COVID-19 patient will be lying supine or sitting and its effect on improvement of blood oxygenation will be seen using a finger saturation probe	• >18 years of age • Diagnosed as COVID-19 positive by RT- PCR • Oxygen saturation < 94% as assessed by pulse oximeter or requiring oxygen support • Can communicate and self-prone	Primary outcomes (Phase 1 study): • Oxygen saturation measured using by pulse oximeter at 0, 10, 20, 30, 40 minutes Primary Outcomes (Phase 2 study): • Need for endotracheal intubation and mechanical ventilation measured at discharge or death • Mortality up to 30 days after enrolment

				• Oxygen saturation measured using by pulse oximeter at 0, 10, 20, 30, 40 minutes Primary Outcomes (Phase 2 study): • Need for endotracheal intubation and mechanical ventilation measured at discharge or death • Mortality up to 30 days after enrolment Secondary Outcome (For phase 2 study): • Time to endotracheal intubation/ventilation measured using hospital record at discharge. • Duration of requirement of oxygen support measured using clinical proforma at patient discharge • Duration of hospital stay measured using using hospital record at discharge
CTRI/2020/12/029587 Efficacy of awake prone positioning with high flow nasal cannula versus prone positioning with non-rebreathing mask in COVID-19 patients. A prospective comparative study. Not yet recruiting	Awake prone position with high flow nasal cannula: Oxygen will be given through high flow nasal oxygen at flows of 60 L/min and FiO2 adjusted to obtain oxygenation (SpO2 â?¥92%). A minimum of 8 hours of prone positioning per day shall be encouraged.	Awake prone positioning with non-rebreathing mask: Patient will receive high flow oxygen@10 to 15 liter/min with non-rebreathing mask to maintain adequate oxygenation ((SpO2 â?¥92%). All patients shall be encouraged prone positioning in this group also	Adult Confirmed COIVD19 positive patients admitted to ICU for acute hypoxemic respiratory failure. Acute hypoxemic respiratory failure defined by respiratory rate â?¥25 breaths/min, and PaO2/FiO2 â?¤300 mm Hg while spontaneously breathing under standard oxygen therapy.	Primary Outcome • rates of intubation between the two groups at 28 days Secondary Outcome • arterial oxygen partial pressures after 1 hour, 6 hours, 12 hours and then every 24 hours after enrolment. • intubation free ICU stay of patients. • percentage of patients who required non-invasive ventilation at 28 days
NCT04547283 Awake-Prone Positioning Strategy for Hypoxic Patients With COVID-19: A Pilot Randomized Controlled Trial COMPLETED Not yet published No results	Clinical team guidance on prone positioning of patients	No clinical team recommendation, patients will remain in their natural choice of position	18 Years old and above hospitalized patients with positive COVID testing during hospitalization or 7 days prior OR Hospitalized with suspected COVID pneumonia room air oxygen saturation <93% or oxygen requirement > or equal to 3 Liters per minute	Primary Outcome Measures: • Average S/F ratio • Average oxygen saturation to fraction of inspired oxygen ratio • Time spent with S/F ratio < 315 • Time spent with oxygenation saturation to fraction of inspired oxygen ratio less than 315 Secondary Outcome Measures • Highest oxygen support • Highest level of supplemental oxygen required • Number of patients requiring ICU admission during study

				• Number of patients requiring ICU admission during study period • Number of patients requiring ICU admission during hospitalization • Number of patients requiring ICU admission during hospitalization • Number of patients experiencing who die prior to discharge • Number of patients who die prior to hospital discharge • Number of patients requiring intubation • Number of patients requiring intubation • Hospital length of stay • Number of days from hospital admission to discharge
NCT04359797 Pragmatic Trial Exploring Impact of Patient Positioning in the Management of Patients Infected With COVID-19: Supine vs. Prone COMPLETED Not yet published No results	prone position for as much time as is tolerable during hospitalization.	remain in their natural choice of position, which is anticipated to favor a supine, semi-recumbent position.	18 years old and above patients admitted to VUMC who test positive for COVID-19 and require supplemental oxygen, but are not yet mechanically ventilated.	Primary Outcome Measures: • Modified WHO Ordinal Scale • The highest level of support on the 5th day after enrollment according to the following scale adjusted for patient status at enrollment according to the same scale and ranked by mean FIO2 within each category, as appropriate. • Death • ECMO • Mechanical ventilation (ranked by mean FIO2) • Non-invasive ventilation such as BiPAP (ranked by mean FIO2) • High flow nasal cannula, • Standard nasal cannula (titrated by L/min up to 15 L/min) or face mask (ranked by mean FIO2) • Room air Secondary Outcome Measures • FIO2

NCT04350723 Awake Prone Position in Hypoxemic Patients With Coronavirus Disease 19 (COVI-PRONE): A Randomized Clinical Trial (COVI-PRONE) Recruiting	The oxygen mask or NIPPV or HFNC will be initiated at the treating team's discretion. The patient will be observed for 15 minutes to ensure that: SPO2 > 90% and the patient is tolerating oxygen mask or NIPPV or HFNC treatment. Proning once SPO2 >90% Procedure: Awake Proning The duration of proning will be a total of 8-10 hours with 1-2 hours break in supine position.	The patient will receive usual care without proning at the discretion of the treating team. The oxygen mask or NIPPV or HFNC will be initiated, the choice of starting oxygen mask versus NIPPV versus HFNC will be up to the treating team	Adults ≥ 18 years of age. Suspected or confirmed COVID-19. Hypoxemia on room air (SPO2<90%), and oxygen requirement ≥ 0.4 FiO2 (i.e. ≥ 40% oxygen). Bilateral or unilateral chest infiltrates on x-ray as interpreted by the treating team. Admitted to the ICU or an acute care bed where hemodynamic and respiratory monitoring is feasible.	Primary Outcome Measures: • Endotracheal intubation Secondary Outcome Measures: • Mortality • Invasive mechanical ventilation free days • Non-invasive ventilation free days • ICU length of stay • Hospital length of stay • Change in oxygenation • Complications from proning,
NCT04395144 Randomized-controlled Trial of HFNC Alone vs HFNC and Awake Self-proning for Treatment of Severe COVID-19 Completed Not yet published No results	Prone positioning of patients on nasal high-flow oxygen therapy Procedure: Awake Prone Positioning Patients will receive instruction to remain in prone position as long and as often as possible, up to 16h/24h	Standard decubitus positioning of patients on nasal high-flow oxygen therapy Patients will not receive any special instructions with regards to proning.	COVID-19, either confirmed by SARS-CoV-2 assay, or clinically suspected, with results of the assay pending; Lung infiltrates documented on chest X-ray or chest CT-scan; Significant respiratory distress that requires treatment with HFNO.	Primary Outcome Measures: • Rate of Therapeutic failure, defined as a combined outcome of rate of intubation or death Secondary Outcome Measures: • Intubation rate • Mortality • Days spent on mechanical ventilation • Days spent in the ICU • Hospital stay (in days) Other Outcome Measures: • Time in prone position • Total time spent in prone position, as recorded by nursing or respiratory therapists • Oxygenation (SpO2/FiO2 ratio) • Daily evolution of oxygenation
CTRI/2020/12/029898 Self-prone positioning to reduce the need for ventilatory support in COVID-19 patients- a randomized controlled trial Not yet recruiting	The intervention group (group P) will be instructed to lie prone for a session of at least two hours and a total duration of 12 hours in a day.	The control group participants will receive the conventional treatment for COVID-19	Suspected (presenting with dyspnea, fever, cough) or confirmed COVID-19 positive having SpO2 â?¥90% with FiO2 â?¤0.6.	Primary Outcome • Requirement of ventilatory support Secondary Outcome • oxygen requirement, oxygen saturation, requirement of ICU admission, duration of hospital stay and adverse effects of prone position.
CTRI/2021/03/031939 Immediate effect of prone and side lying position on oxygen saturation in patients with COVID	Prone position after doing Diaphragmatic breathing exercises, thoracic expansion exercise	Supine Position after doing Diaphragmatic breathing exercises, thoracic expansion exercise: Frequency - 1 session per day	Both male& female patients with covid 19. Patients who are willing to participate in the study.	Primary Outcome Spo2Timepoint: 1 hour

19- A Randomised Controlled Trial Not yet recruiting	Lateral Position after doing Diaphragmatic breathing exercises, thoracic expansion exercise: Frequency - 1 session per day		Patients with definite diagnosis of COVID-19 Patients who required additional oxygen supplementation (HFNC) Age group of >30 years both male and female	
CTRI/2020/07/026532 Awake Prone Position Versus Repeated Position Change in Moderate to Severe COVID-19 patients: A Pilot Randomized Controlled Trial Not yet recruiting	Repeated Position Change: One hour right lateral, two hours prone and one hour left lateral	Awake Prone Positioning for 4h in patients presented with shortness of breath	Adult patients (aged between 18 and 75y) with laboratory confirmed diagnosis of COVID-19 pneumonia,	Primary Outcome • repeated positioning with 4h continuous prone positioning in terms of self-reported dyspnea in a 10- point visual analogue scale Secondary Outcome • oxygenation status (room air oxyhemoglobin saturation or PaO2/FiO2 ratio in arterial blood gas) • requirement of rescue therapy (high flow nasal oxygen) in both the groups. • hemodynamic variables in both the groups. • requirement of mechanical ventilation within 24h in both the groups. • change in respiratory rate in both the groups.
NCT04760561 Effects of Self-prone Positioning on Oxygenation and Physiological Outcomes Among Awake Non-intubated Patients With COVID-19 Not yet recruiting	Each patient in the intervention group will be helped into the prone position and encouraged to stay in the prone position as long as tolerated (at least 1 hour). Self-prone position will be performed 45 minutes up to 1 hour after meals to avoid gastrointestinal side effects. The patient will be maintained in prone position until the patient becomes too tired and uncomfortable to keep that position.	conventional positioning interventions provided by the critical care nurses, which will not include self-prone positioning.	Aged 18-75 years old Awake non-intubated spontaneously breathing patients Confirmed diagnosis of severe COVID-19; manifesting as dyspnea with respiratory rate ≥ 30 breaths/min, pulse rate ≥ 100 beats/min, oxygen saturation ≤93%, or partial pressure of arterial oxygen (PaO2) to fraction of inspired oxygen (FiO2) ratio ≤ 150 mmHg. Positive RT-PCR for SARS-CoV-2 from analysis of nasopharyngeal, oropharyngeal swab, or tracheal secretion specimens and with chest X-ray showing bilateral infiltrations	Primary Outcome Measures: • Oxygenation: arterial oxygen pressure/fractional inspired oxygen PaO2/FiO2 ratio mmHg. • SpO2: Peripheral oxygen saturation • ROX: combination of the ratio of oxygen saturation measured by pulse oximetry to fraction of inspired oxygen and respiratory rate ([SpO2/FiO2]/respiratory rate) • PaO2mmHg: Partial pressure of oxygen within arterial blood • PCO2mmHg: The partial pressure of carbon dioxide within arterial blood • SaO2 • pH • Respiratory Rate (RR) (bpm) • Heart Rate (HR) (bpm)

			or chest computerized tomographic (CT) images showing exudation or consolidation. Requiring supplemental oxygen (nasal cannula, non-invasive CPAP, non-rebreathing face mask) Capable of adopting a prone posture independently.	• Blood Pressure (BP) mmHg • Positive response to prone Secondary Outcome Measures: • Prone position adverse events • respiratory distress, dyspnea, use of accessory respiratory muscles, oxygen desaturation SpO2≤70%, hypotension SBP≤90 mmHg, vomiting, aspiration, musculoskeletal pain, discomfort, facial edema, pressure ulcers and accidental withdrawal of catheters, tubes and/or drainages.
NCT04391140 Effectiveness of Prone Positioning Combined With High-flow Nasal Cannula for Patients With COVID-19 Induced ARDS Recruiting	Combination of prone position and HFNC HFNC set to a SpO2 of 90-95% combined with prone position. At least 2 sessions of 30 minutes or more will be performed daily.	HFNC set for a SpO2 90-95% if unless indication for intubation is present.	COVID-19 pneumonia according to the diagnostic criteria in effect at the time of inclusion or very strongly suspected. Patient treated by nasal high flow. Moderate or severe ARDS: Informed consent.	Primary Outcome Measures : • Therapeutic failure death or intubation Secondary Outcome Measures: • Feasibility and safety of prone position in HFNC patients • Comfort measurement using a visual-analog scale. • Presence of complications related with prone position and the use of high-flow nasal cannula: • Skin ulcers. • Intravascular lines displacement • HFNC related events (hot air feeling, nasal lesions) • Efficacy of prone position in HFNC patients • Evolution of the oxygenation (SpO2/FiO2) in prone position. Efficacy • Length of HFNC therapy • Length of ICU stay • Length of mechanical ventilation (in those who require intubation) • ICU and hospital mortality
IRCT20160126026217N4 Investigation of the effects of prone position on respiratory status, hemodynamics, hospital stay and transfer to intensive care unit in patients with Covid-	In this group, participants will be in the prone position for 90 minutes for the first time. After evaluating the initial outcomes, the participant will be asked to be in the prone position for 6 to 8 hours until the clearance time, and then the secondary outcomes will be evaluated.	In this group, participants will be in their usual position for 90 minutes for the first time, after evaluating the initial outcomes, the participant will be asked to be in his usual positions until the time of discharge, and then the secondary outcomes will be evaluated.	All patients with COVID-19 based on standard diagnosed test and had at least one respiratory symptom Age between 18 and 65 years Willing to participate in the study	Primary Outcomes • Breath shortness. • Heart rate • Mean blood pressure. • Oxygen saturation. • Respiratory rate. Secondary Outcomes

19: A randomized controlled clinical trial Pending Recruiting Status				• Hospital stay • Mortality rate of patients. • Percentage of patients transferred to the intensive care unit.
NCT04363463 Impact of Prone Position in Patients Under Spontaneous Breathing on Intubation or Non-invasive Ventilation or Death Incidence During COVID-19 Acute Respiratory Distress Recruiting Estimated Completion Date: August 2022	Two sessions minimum of prone position over the day. With a total objective of at least 2h30 of cumulated duration over the day. The objective is to spend as much time as possible in prone position if the patient tolerates it well.	semi-seated in bed or seated in a chair during the day. The prone position is not allowed during the day (it is allowed at night if it is the natural sleeping position).	Patients aged from 18 to 85 years old with COVID-19 documentation Undergoing oxygen therapy (nasal cannula, medium or high concentration mask or high flow nasal oxygen therapy) Able to move to PP by him/herself or with minimal assistance Written consent Hospitalized in COVID medical department for less than 72 hours	Primary Outcome Measures: • Percent age of patients who will have endotracheal intubation or non-invasive ventilation at two pressure levels and/or die, in each of the 2 randomization groups. • Endotracheal intubation or non-invasive ventilation (NIV) with two pressure levels • And/or death Secondary Outcome Measures: • Duration in days for the change of 2 points on the WHO ordinal scale • Rate (%) of intubation and invasive ventilation in the 2 randomization groups. • Rate (%) of non-invasive ventilation at two pressure levels in the 2 randomization groups • Duration of oxygen therapy in the 2 randomization groups. • Duration of hospitalization in the 2 randomization groups. • Hospital mortality and mortality at D28 in the 2 randomization groups • Rate (%) of need for transfer to intensive care unit • Rate (%) of use of non-invasive ventilation at two pressure levels, intubation throughout the entire stay when the stay is longer than 28 days. • Compare the impact of the use of non-invasive ventilation and intubation on the entire hospital stay when the hospital stay is longer than 28 days between the two groups.
ISRCTN54917435 Awake prone positioning with high flow nasal cannula in critically ill COVID-19 patients	prone position or semi-recumbent position with the head of the bed elevated to 30 degrees with the target of 16 hours per day and night.	Patients are neither prohibited nor encouraged and may be prescribed by the treating physician at their discretion. All other treatment or interventions for all included patients will follow ordinary local	Age 18 year or older Admission to a hospital with confirmed or strongly suspected COVID-19 infection	Primary Outcome • Rate of intubation for mechanical ventilation support, recorded in EHR at inclusion and once if applied. Secondary Outcome(s)

COMPLETED Not yet published No results	Follow-up is at 2 months after the end of inclusion.	guidelines at the present hospital and are not affected by the study protocol.	Hypoxic respiratory failure defined as a PaO2/FiO2 ratio = 20 kPa (150 mmHg) and/or a FiO2 of = 0.5 to reach a SpO2 of 94% for more than 1 hour Oxygen supplementation (ongoing or planned) with high flow nasal cannuale or noninvasive ventilating support	• Time in prone position (pp); every time the patient changes position the timepoint will be recorded in a preprinted protocol (CRF) or the PDMS if available, total time measured once per day and night in hospital • Need for vasoactive drugs, day and time for start, change of infusion rate or stop of vasopressor infusion, recorded in PDMS or EHR, evaluated once per day and night in hospital • Days on ventilator support, day and time of intubation and start of ventilator support, day and time of extubation and end of ventilator support, recorded in PDMS or EHR, checked once a day in hospital • In-hospital and ICU length of stay: timepoint recorded in the EHR when enrolled and discharge at hospital/ICU • Rate of complications reported in a preprinted protocol (CRF) every 24th hour after inclusion • 7- and 30-day mortality: day and time of death recorded in the EHR, checked once within a month after discharge from the hospital • Clinical improvement measured using WHO ordinal scale at baseline, day 7 and day 30
IRCT20151020024625N12 Comparison of prone and supine position on oxygenation of patients with COVID-19 with acute hypoxemia treated using reservoir mask COMPLETED Not yet published No results	Patients who need to continuous oxygen therapy by reserve bag will be placed in a prone position for one hour, every three hours up to three days.	Patients who need to continuous oxygen therapy by reserve bag will be placed in a supine position	Confirmed COVID-19 based on PCR test PaO2/FiO2 ratio between 150-300	• Arterial blood oxygen saturation level
IRCT20210316050722N1 Evaluation of pulmonary rehabilitation and prone position on respiratory parameters in patients with COVID-19 admitted	The second group of standard treatment measures of the state oxygen protocol with a normal mask + 2 hours of prone position + 15 minutes of lung rehabilitation.	Control group: Group 1 will only receive the standard treatments recommended in the national protocol.	Covid-positive patients admitted to non-specialized wards From 18 to 75 years old	• Spo2. Timepoint: 30 and 60 minutes after being in the prone position and also 60 minutes after the patient is in the supine position

to non- specialized ward of Hajar hospital of Shahrekord; a double blind randomized clinical trial Recruiting	Intervention group: Group 3 standard treatment measures of the state oxygen protocol with reservoir mask + 2 hours of prone position + 15 minutes of lung rehabilitation.		Non-intubated and supported by oxygen therapy, No bed sores on shoulders, knees, and face, Estimated weight less than 100 kg	
NCT04358939 Evaluation of Prone Position in Conscious Patients on Nasal High-flow Oxygen Therapy for COVID-19 Disease Induced Acute Respiratory Distress Syndrome COMPLETED not yet published No results	Prone positioning of patients on nasal high-flow oxygen therapy with usual care the objective is to spend as much time as possible, up to 16 hours and beyond in prone position every 24 hours. At least two sessions of at least 30 minutes each must be performed daily.	Patients on nasal high-flow oxygen therapy with usual care and positioned in supine	Adult patient with COVID-19 pneumonia according to the diagnostic criteria in effect at the time of inclusion or very highly suspected. Patient treated with nasal high-flow Mild, moderate or severe ARDS: bilateral radiological opacities not fully explained by effusions, atelectasis or nodules; acute hypoxemia with worsening within the previous 7 days, not fully explained by left ventricular failure; PaO2/FiO2 ratio < 300 mmHg (or equivalent SpO2/FiO2). Covered by or having the rights to French social security Informed Consent	Primary Outcome Measures: • Therapeutic failure within 14 days of randomization Secondary Outcome Measures: • Therapeutic failure within 28 days of randomization • Timeframe of intubation or death • Evolution of oxygenation (PaO2/FiO2 ratio or SpO2/FiO2 surrogate) over the 14 days following randomization • Evolution of the SpO2/FiO2 ratio during the first prone session • Evolution of the ROX index during the first prone session • Evolution of the World Health Organization disease severity score of COVID • Patient comfort before, during and after the first prone position session • Occurrence of skin lesions on the anterior surface of the body • Displacement of invasive devices during reversals • Days of nasal High-Flow therapy use in the general population, in non-intubated patients and in intubated patients • Days spent in the intensive care unit and in the hospital • Mortality in the intensive care unit and in the hospital • Ventilator-free-days within 28 days of randomization
NCT04477655 Prone Positioning in Non-intubated Patients With Severe COVID-19: a Randomized Controlled Trial	Patients will be asked to remain in prone position throughout the day as long as possible, with breaks according to tolerance.	Prone positioning will be allowed as a rescue therapy. Oxygen therapy through high flow nasal cannula (HFNC). Inspired fraction of oxygen will be titrated to	Adult patients with confirmed COVID-19, and requirement of a fraction of inspired oxygen (FiO2) ≥30% through high-flow nasal cannula (HFNC) to maintain a capillary saturation of ≥90%	Primary Outcome Measure: • Intubation rate Secondary Outcome Measures : • Total hours of prone position at day • Total number of prone sessions at day

COMPLETED Not yet published No results	Patients will be asked to remain in prone position or lateral decubitus throughout the day as long as possible.	maintain a capillary saturation of ≥92%		• Hours of the longest prone session each day • Change in oxygenation 1-hour after first prone session • Change in the ROX-index 1-hour after first prone session • Total days of prone positioning • Adverse effects of prone positioning therapy • Mechanical ventilation days • Intensive care unit length of stay • Hospital length of stay • Hospital mortality
NCT04366856 PROne Positioning in coVID-19 Oxygeno-dependent Patients in Spontaneous Ventilation (PROVID Study) Recruiting	the interventional group will be suggested to spend at least 6 hours a day in prone position	the control group will get no instruction regarding positioning	Laboratory-confirmed SARS-CoV-2 infection as determined by PCR and/or CT scan showing typical radiological findings (ground glass abnormalities) Need for O2 3L/min to get an SpO2 higher or equal to 95%. Patient able to understand and to get in prone position themself No therapeutic limitation	Primary Outcome Measures: • Proportion of patients who meet one or both following criteria: need for intubation (for mechanical ventilation), occurrence of death during hospital stay. Secondary Outcome Measures: • Proportion of patients admitted to ICU (for patients included out of ICU) • Days alive and free from non invasive ventilation (NIV) or high flow nasal canula oxygen delivery (HFNC) (for those neither under NIV or HFNC at the time of study inclusion) • Days alive and out of ICU • Maximum oxygenotherapy rate during hospital stay
NCT04347941 Awake Prone Positioning to Reduce Invasive VEntilation in COVID-19 Induced Acute Respiratory failurE (APPROVE-CARE) Recruiting	16 hours per day in Prone Positioning with 45 minutes breaks for meals	Standard of care. Prone positioning may be administered as a rescue therapy	Suspected or confirmed COVID19 infection Bilateral Infiltrates on CXR SpO2 <94% on FiO2 40% by either venturi facemask or high flow nasal cannula RR <40 Written informed consent	Primary Outcome Measures: • The effect of prone positioning on requirement for invasive mechanical ventilation in patients with COVID 19 induced respiratory failure Secondary Outcome Measures: • Length of time tolerating prone positioning • PaO2/FiO2 measured before prone positioning • PaO2/FiO2 ratio after 1 hours of prone positioning • SpO2/FiO2 ratio measured before prone positioning

				• SpO2/FiO2 ratio after 1 hours of prone positioning • Number requiring increase in ventilatory assistance (CPAP+BIPAP+IMV etc) • Work of breathing assessment (Respiratory distress scale) • Changes in bioimpedance measures of lung edema in patients in PP • Use of awake prone positioning as a rescue intervention in control patients
NCT04667286 Awake Pronation for Covid-19 Treatment Recruiting	Oxygen via a Venturi mask in order to keep an oxygen saturation between 92 and 96% plus PP for a minimum of 10 hrs a day	Oxygen via a Venturi mask in order to keep an oxygen saturation between 92 and 96%	confirmed COVID-19 infection using PCR Acute Respiratory Failure (200 <PaO2/FiO2 <300) and respiratory rate < 30 atti/min O2 therapy initiated <72 hrs informed consent	Primary Outcome Measures: • number of day free of ventilatory support Secondary Outcome Measures: • changes in respiratory pattern • daily changes in the ratio SaO2/FiO2 • dyspnea • comfort during PP Other Outcome Measures: • number of hours on PP
NCT04477655 Prone positioning in non-intubated patients with COVID-19 associated acute respiratory failure, the PRO-CARF trial	remain in a prone position throughout the day as long as possible, with breaks according to tolerance	prone positioning will be allowed as a rescue therapy. Staff intensivists will monitor the patient's status in both groups on a 24/7 basis. All other treatment will be unchanged and left to the attending physicians	all adult patients admitted to the COVID-19 unit who test positive for COVID-19 by PCR-test and in need for oxygen are eligible for inclusion. fraction of inspired oxygen ≥30% for an oxygen capillary saturation of ≥90%.	• Endotracheal intubation rate for mechanical ventilation at 28 days.
NCT04589936 Prone Position to Improve Oxygenation in COVID-19 Patients Outside Critical Care (PRONE-COVID)	Patient will first lay supine for a given time period, followed by lateral position on either side, then prone position, lastly return to supine position. Participants are anticipated to stay in prone position for a minimum of 30min to a maximum of 2 hours depending on tolerability.	Patient will first lay supine for a given time period, followed by lateral position on either side, then prone position, lastly return to supine position. Participants are anticipated to stay in prone position for a minimum of 30min to a maximum of 2 hours depending on tolerability. Participants will be guided in how to independently position themselves and rotate through the cycle of positions.	Have confirmed or suspected COVID-19 or non-COVID pneumonia (confirmed with radiological changes) FiO2 ≥24% or requiring basic respiratory support (supplementary oxygen via face mask, nasal cannula, venturi, non-rebreathe bag) to achieve clinical target SpO2 (e.g. SpO2 92-96%), ensuring patient is on appropriately titrated oxygen to be within this range. Be able to provide informed consent	Primary Outcome Measures • Peripheral Oxygen saturation (FiO2) Secondary Outcome Measures: • PaO2 :FiO2 ratio calculated from formulae • Respiratory rate measured with Masimo device • Heart rate measured with Masimo device • Blood pressure measured with Masimo device • Patient reported severity of breathlessness on a continuous linear

			Communicate and cooperate with the procedure Rotate and adjust position independently No anticipated airway issues	scale of 0 to 10cm (10cm being the most severe) • Patient tolerability of prone position on a continuous linear scale of 0 to 10cm (10cm being the most unacceptable) • Investigator experience of delivering prone positioning • To assess patient's peripheral oxygen saturation
NCT04427969 Early Prone Position on Coronavirus Disease 2019 Pneumonia (Prone Position)	Behavioral: prone position to lay in prone position at least 12 hour in a day at ICU	patient who only get conventional oxygen therapy as respiratory supply	Patients who developed acute respiratory failure due to coronavirus disease 2019 pneumonia received conventional oxygen therapy with reservoir mask oxygen at the stage of admission to the intensive care unit older than 18 years old	Primary Outcome Measure: • intensive care unit stay • short term mortality Secondary Outcome Measure • blood gases
NCT04325906 Early PP With HFNC Versus HFNC in COVID-19 Induced Moderate to Severe ARDS	Proning + HFNC	HFNC only no proning	COVID-19 induced adult ARDS patients admitted to the medical ICU PaO2/FiO2 is less than 200mmHg or FIO2 ≥ 0.4 is required to maintain SpO2 at 88-93% on HFNC treatment	Primary Outcome Measure: • Treatment failure • Intubation rate Secondary Outcome Measures: • Efficacy of PP
NCT04344587 Awake Prone Position for Early Hypoxemia in COVID-19 (APPEX-19)	Self-proning A recommendation to "prone" while lying in bed (4 times for 1-2 hours each during the day and at night every 24 hours). A reminder to keep track of the time spent in 1) prone position, 2) lying flat on back, 3) lying on side, 4) sitting up, and 5) standing or walking	Usual Care	Assigned to or admitted to a COVID-19 ward team at a participating site (these teams only admit patients who are under investigation for COVID-19 or who have confirmed COVID-19 infection) via the emergency department (ED) within the last 24 hours Have access to their own functioning smartphone in the hospital room English or Spanish-speaking Ability to read simple instructions and answer simple written questions	• Change in respiratory status • Length of time in each positio • Reports of dyspnea, discomfort • Length of hospital stay • Invasive mechanical ventilation • ARDS diagnosis • Loss of IV access as a consequence of turning • Hospital mortality
NCT04383613 Prone Positioning for Patients on General Medical Wards With COVID19 (COVID-PRONE)	The intervention is prone positioning (i.e., instructing a patient to lie on their stomach while they are in bed) for 7 days or until the first of study hospital discharge or not requiring supplemental oxygen for >24 hours or study outcome.	Standard of care Not specifically instructed to lie on their stomach	Patients ≥ 18 years of age COVID-19 infection is suspected by the treating clinician or confirmed by diagnostic test Able to lie on their stomach with verbal instruction	• All-cause mortality (4 weeks) • Invasive or non-invasive mechanical ventilation need for FiO2 of 60% or more

			Requiring supplemental oxygen less than or equal to 50% FiO2 Capable to make treatment related decisions Hospitalized in the last 48 hours with suspected or confirmed COVID-19 infection or diagnosed for nosocomial infection in the last 48 hours during their hospital stay	
KCT0005258 The effect of prone positioning on non-intubated patients with postoperative acute respiratory failure	Prone positioning at least 12 hours in prone positioning group position change q 2hr(within 45 degree of Lt or Rt decubitus position change). dexmedetomidine continuous infusion if RASS > +1, target : light sedation	supine positioning and keep going management of respiratory failure	adult patients (18 years and older) with acute respiratory failure - 30 minutes after applying High flow nasal cannula(FiO2 0.5, flow 50L) - > PaO_2< 150㎜Hg, $PaCO_2$< 50㎜Hg	• Intubation rate within 7 days • Lung ultrasound reaeration score • PaO_2/FiO_2 ratio \ • Mechanical ventilation (MV) duration • ventilator-free days • tracheostomy rate • ICU, 30 days, 90 days mortality • Complication related to prone positioning • sedative

Q7. Should high flow nasal cannula be used for patients with COVID-19 and acute respiratory failure?

As of 01 December 2021

RECOMMENDATION

We suggest the use of high flow nasal cannula for patients with severe to critical COVID-19 who do not respond to conventional oxygen therapy (low flow nasal cannula/face mask). *(Low certainty of evidence; Weak recommendation)*

Consensus Issues

The use of high flow nasal cannula should only be considered when patients fail to respond to low flow nasal cannula or face mask. It is not intended to be the immediate first line respiratory support for COVID-19 patients. It was initially promoted due to its capability to deliver high oxygen concentration, particularly when coupled with the potential harm or risk of viral aerosolization with non-invasive ventilation. The comparison of the efficacy of high flow nasal cannula and non-invasive ventilation is discussed in a separate review.

PREVIOUS RECOMMENDATION

We suggest the use of high-flow nasal cannula oxygenation over non-invasive ventilation (e.g., helmet CPAP, mask NIV) in patients with COVID-19 infection and acute hypoxemic respiratory failure who do not respond to conventional oxygen therapy. *(Very low quality of evidence; Conditional recommendation)*

Consensus Issues

The use of HFNC over conventional oxygen therapy (i.e., nasal cannula, venture mask or non-rebreather mask) is not congruent to usual clinical practice. The use for HFNC is preferred for patients who are not doing well with the conventional oxygen therapy. In addition, the trial employing severe COVID-19 patients, used HFNC even if it is not yet needed at the time.

WHAT'S NEW IN THIS VERSION?

One new pre-print randomized controlled trial was included for review to evaluate the use of high flow nasal cannula therapy in COVID-19 patients. The previous recommendation was reviewed from one randomized controlled trial and four retrospective cohort studies.

In this updated review, the recommendation for the use of high flow nasal cannula therapy is upgraded to low certainty of evidence.

KEY FINDINGS

Two randomized controlled trials comparing the use of high flow nasal cannula (HFNC) versus conventional oxygen therapy (COT) in COVID-19 patients with acute respiratory failure showed significant improvement of PaO_2/FiO_2 ratio among patients who received HFNC. However, no significant benefit was found in terms of 30-day mortality, length of hospital stay, length of intensive care unit stay, and eventual tracheal intubation and intensive care unit admission. Certainty of evidence was low

because of unclear to high-risk of selection and detection bias, and imprecision in most of the critical outcomes.

INTRODUCTION

Deaths from COVID-19 infections have been cited as the 5th most common cause of mortality among Filipinos in a recent report released by the Philippine Statistics Authority on the 1st half of 2021.[1] Acute respiratory failure has been one of the common complications in patients with COVID-19 leading to invasive mechanical ventilation. Descriptive studies done locally have reported that the most common complications in the subset of patients were from respiratory failure.[2,3] Physiological effects of high flow nasal cannula (HFNC) therapy has been shown to improve oxygenation in patients with respiratory failure compared to conventional oxygen therapy.[4] The interest in using high flow nasal cannula is based on its ability to be well tolerated among patients and its features to deliver higher concentrations of oxygen at a constant rate. [5-7]

REVIEW METHODS

A comprehensive literature search was done as of 07 November 2021 on the use of HFNC in COVID-19 using Medline, Cochrane Library, Google Scholar, clinicaltrials.gov, and medRxiv (pre-prints) with the following keywords: “high flow nasal cannula”,“COVID-19,” and “SARS-COV2”. All search yields were reviewed and appraised. Randomized controlled trials relating to the use of HFNC in COVID-19 associated acute respiratory failure were included.

RESULTS

A total of 15 journal articles were reviewed to evaluate the evidence of HFNC therapy in COVID-19 associated respiratory failure. Of the 15 studies, ten articles were still in the process of recruitment and finalizing the publication manuscript. Only one article presented the study protocol but with no results posted as of search date. Two systematic reviews on the use of HFNC therapy were found but these articles did not fulfill the population criteria and only included acute respiratory failure not secondary to COVID-19. The remaining two studies, one of which was included in the initial evidence review, were both randomized controlled trials that satisfied the criteria for this evidence review. There were no RCTS that evaluated HFNC versus non-invasive ventilation in COVID-19 associated respiratory failure.

Two RCTs by Teng et al. [8] and Perkins et al. [9] done in China and the United Kingdom included all adult patients 18 years of age and above, diagnosed with severe to critical COVID-19 with acute respiratory failure and having peripheral oxygen saturations of less than 94%. Pregnant patients, patients for immediate intubation, and patients with chronic pulmonary and/or cardiac conditions were excluded from the studies. Teng et al. provided the initial HFNC settings used in the study: temperature of 37^{o}C, flow rate at 50 liters per minute, and fraction of inspired oxygen at 50%. HFNC therapy was delivered continuously for 72 hours to maintain peripheral oxygen saturation of 93% or higher. On the other hand, the HFNC settings in the study of Perkins et al. were titrated based on clinical judgement of the trial physicians.

The study of Perkins et al. also studied the efficacy of Continuous Positive Airway Pressure (CPAP) with Conventional Oxygen Therapy (COT) in reducing critical

outcomes such as tracheal intubation, critical care unit admission and 30-day mortality. Findings showed benefit in decreasing the incidence of tracheal intubation (RR 0.66, 95% CI 0.47-0.93) but no difference in decrease in 30-day mortality (RR 0.91, CI 0.59-1.39). There were also no statistical benefits of using CPAP with regard to the length of ICU (MD1.01, 95% CI -0.1.11-3.14) and hospital stay (MD 1.25, 95% CI -1.36-3.97).

In the study by Teng et al., PaO_2/FiO_2 ratio was assessed on the 6th, 24th, and 72nd hour from HFNC initiation. Compared to COT, HFNC significantly improved PaO_2/FiO_2 on the 6th hour (MD 30.50 mmHg, 95% CI 23.29-37.71; p<0.00001), 24th hour (MD 34.90 mmHg, 95% CI 28.61-41.19; p<0.00001), and 72nd hour (MD 34.52 mmHg, 95% CI 29.25-39.79; p<0.00001). Only the HFNC therapy group significantly improved PaO_2/FiO_2 ratio of >300 mmHg at the 24th and 72nd hours. Only the trial by Perkins et al. provided data on 30-day mortality, need for tracheal intubation, and admission to critical care unit between HFNC and COT. No statistically significant difference was found in 30-day mortality (RR 0.94, 95% CI 0.71-1.25; p=0.67), need for tracheal intubation (RR 0.98, 95% CI 0.83-1.15; p=0.77), and admission to critical care unit (RR 1.05, 95% CI 0.93-1.17; p=0.45). Pooled results showed that length of intensive care unit stay (MD -0.21 days, 95% CI -2.00-1.59; p=0.82) and overall hospital stay (MD -0.49 days, 95% CI -3.52-2.54; p=0.75) were also statistically similar for both groups.

OTHER FACTORS IN EVIDENCE TO DECISION

Since the start of the COVID-19 pandemic, the country has been acquiring several HFNC machines which have been distributed to several hospitals across the country with more concentration on private and government hospitals in Metro Manila. An estimated 1,318 HFNC machines were acquired and distributed for use as of March 2021.[10-12] The use of HFNC in patients with acute hypoxemic respiratory failure has been tolerated by most patients compared to other forms of oxygen delivery devices; however, some adverse events with its use have been reported such as hemodynamic instability, pneumothorax and pneumomediastinum.[7,9]

RECOMMENDATIONS FROM OTHER GROUPS

Five Guidelines on the management of COVID-19 were identified. Their recommendations are summarized in the table below:

Group/Society/Network	Year	Recommendation	Level of Evidence/Strength of Recommendation
The Australian and New Zealand Intensive Care Society (ANZICS) [13]	2020	High flow nasal oxygen (HFNO) therapy (in ICU): HFNO is a recommended therapy for hypoxia associated with COVID-19 disease, as long as staff are wearing optimal airborne PPE	None stated
European Respiratory Journal [14]	2021	We suggest HFNC or non-invasive CPC delivered through either a helmet or a face-mask for patients with COVID-19 and hypoxemic acute respiratory failure without an immediate indication for invasive mechanical ventilation	Very Low Quality Conditional Recommendation
National Institutes of Health [15]	2020	For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula	BIIa

		(HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV)	
World Health Organization [16]	2021	In selected patients with COVID-19 and mild ARDS, a trial of HFNO, non-invasive ventilation – continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) may be used.	Conditional Recommendation
Society of Critical Care Medicine [17] Surviving Sepsis Campaign	2021	For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, we suggest using HFNC over conventional oxygen therapy.	Weak Recommendation
		In adults with COVID-19 and acute hypoxemic respiratory failure, we suggest using HFNC over NIPPV	Weak Recommendation

RESEARCH GAPS

Despite the agreement of different international societies in recommending the use HFNC among patients with COVID-19, there is still paucity of high-quality clinical trials determining its effectiveness in preventing invasive mechanical ventilation and improving critical and clinically important outcomes. Ten trials which are currently ongoing may provide better evidence whether the use of HFNC is beneficial or detrimental.

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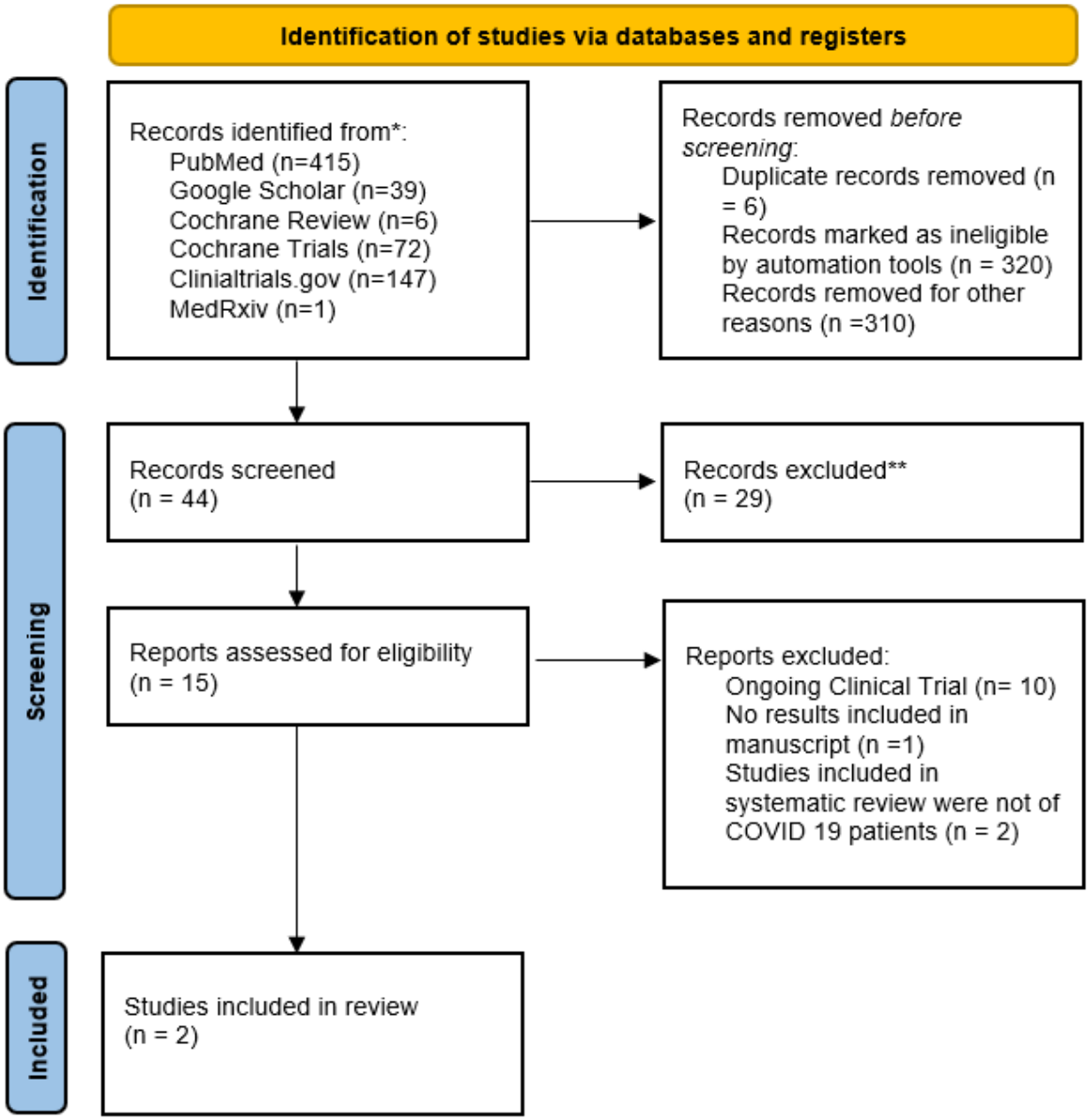
Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (7)					
Benefits	Large (3)	Moderate	Small (4)	Uncertain			• Significant improvement in PaO2/FiO2 on the 6th hour (MD 30.50 mmHg; 95% CI 23.29, 37.71; p<0.00001), 24th hour (MD 34.90 mmHg; 95% CI 28.61, 41.19; p<0.00001), and 72nd hour (MD 34.52 mmHg; 95% CI 29.25, 39.79; p<0.00001). • Only the HFNC therapy group significantly improved PaO_2/FiO_2 ratio of >300 mmHg at the 24th and 72nd hours
Harm	Large	Small (2)	Uncertain (5)				• No evidence
Certainty of Evidence	High	Moderate	Low (7)	Very low			
Balance of effects	Favors drug (5)	Does not favor drug	Uncertain (2)				• The use of HFNC in patients with acute hypoxemic respiratory failure has been tolerated by most patients compared to other forms of oxygen delivery devices, however, some adverse events with its use have been reported such as hemodynamic instability, pneumothorax and pneumomediastinum
Values	Important uncertainty or variability	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability (4)	No important uncertainty or variability (1)			
Resources Required	Uncertain	Large cost (2)	Moderate Cost (5)	Negligible cost	Moderate savings	Large savings	• The country has been acquiring several HFNC machines which have been distributed to several hospitals across the country with more concentration on private and government hospitals in Metro Manila. (1 billion peso funding for 2,550 HFNC machines)
Certainty of evidence of required resources	No included studies (6)	Very low (1)	Low	Moderate	High		
Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (2)			
Equity	Uncertain (7)	Reduced	Probably no impact	Increased			
Acceptability	Uncertain (1)	No	Yes (6)				
Feasibility	Uncertain	No	Yes (7)				• As of March 24, there are 1,318 HFNC machines available in hospitals in Metro Manila.

Appendix 2. PRISMA Flow Diagram



Appendix 3. Characteristics of Included Studies

Study ID Title Author	Study Design	Setting/Country	Total number of Patients Included	Population	Intervention	Comparator/Control	Outcomes
The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia Teng et. Al (2020)	Randomized controlled trial	Fuyang, China	22	Age >28 years Met the diagnostic criteria for patients with evere COVID-19	Admitted to ICU HFNC oxygen therapy machine model: Optiflow PT101AZ Parameters: Temp 37 oC Flow Rate: 50LPM Oxygen concentration 50% Parameters were adjusted according to blood oxygen saturation level (SpO2), blood gas and tolerance, maintaining SpO2 above 93 Duration of continuous treatment for all patients was >72 hours	Conventional Oxygen therapy: Admitted to ICU Nasal catheter or common mask (including venturi and oxygen storage mask) Initial O2 absorption flow at 5lpm (adjusted according to the condition of SpO2 above 93%) Duration of treatment >72 hours *All patients were given Lopinavir/ritonavir tablets and interferon alpha as antiviral treatment for regulation of gastrointestinal flora and protection of organ function	• Comparison of HR, RR and PaO2/FiO2 at each time point between 2 groups • Comparison of infection indexes between two groups before and after oxygen therapy • Comparison of length of ICU stay and total length of hospitalizarion between thr two groups
An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19 Perkins et. Al (2021) (PREPRINT)	Parallel group, open-label, three-arm, adaptive, randomized controlled trial	London, United Kingdom	1259	Adults >18 years old hospitalized with COVID-19 Acute respirator failure defined as SpO2 of <94% despite receiving a fraction of inspired oxygen of at least 0.4 Deemed suitable for tracheal intubation of treatment escalation was required	Participants randomized to High Flow Nasal Cannula started treatment as soon as possible	Conventional oxygen therapy (via face mask or nasal cannulae)	Primary Outcome • Composite outcome of tracheal intubation or mortality within 30-days of randomization Secondary Outcomes • Incidence of tracheal intubation and mortality at 30 days • Time to tracheal intubation • Duration of invasive mechanical ventilation • Time to death • Mortality • Incidence of intensive care unit admission • Length of stay

Appendix 4. Risk of Bias Assessment of Included Studies

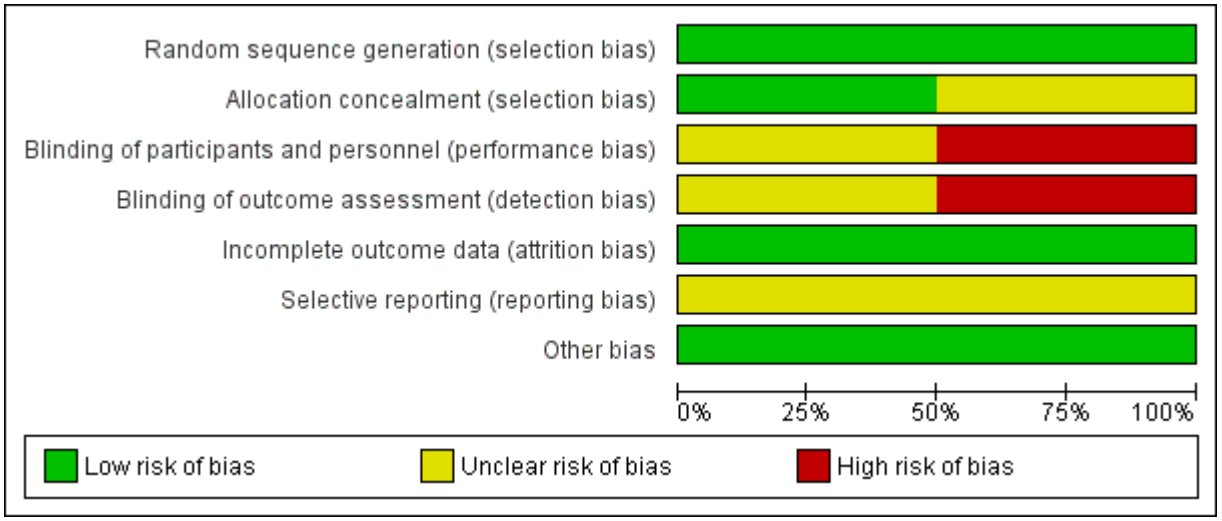


Figure 3.1 Risk of Bias Graph of Included Studies

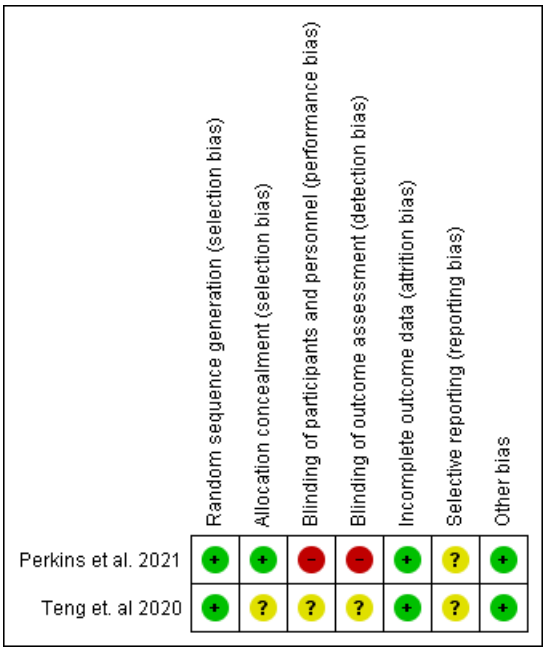


Figure 3.2 Risk of Bias Summary of Included Studies

Appendix 5. Forest Plots of Pooled Results

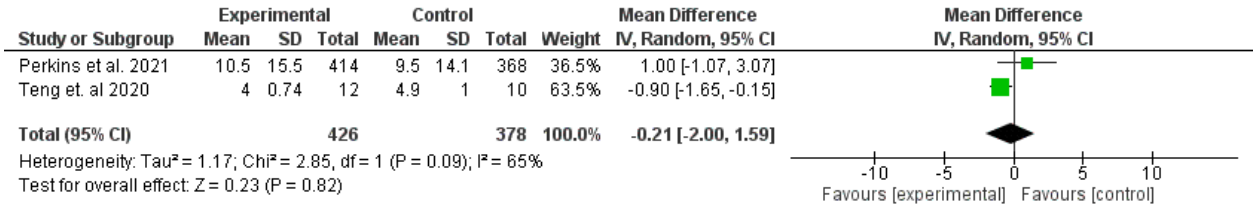


Figure 4.1 Forest plot for Intensive Care Unit Length of Stay

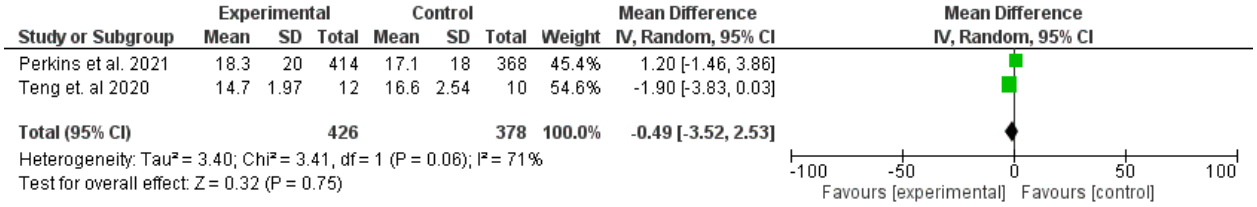


Figure 4.2 Forest plot for Overall Hospital Length of Stay

Appendix 6. GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HFNC	COT	Relative (95% CI)	Absolute (95% CI)		
30-day Mortality												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[a]	None	78/415 (18.8%)	74/370 (20.0%)	**RR 0.94** (0.71 to 1.25)	**12 fewer per 1,000** (from 58 fewer to 50 more)	⊕⊕⊕◯ Moderate	CRITICAL
Tracheal Intubation												
1	Randomised trials	Serious[b]	Not serious	Not serious	Not serious	None	169/414 (40.8%)	154/368 (41.8%)	**RR 0.98** (0.83 to 1.15)	**8 fewer per 1,000** (from 71 fewer to 63 more)	⊕⊕⊕◯ Moderate	CRITICAL
Critical Care Unit Admission												
1	Randomised trials	Serious[b]	Not serious	Not serious	Not serious	None	253/416 (60.8%)	214/368 (58.2%)	**RR 1.05** (0.93 to 1.17)	**29 more per 1,000** (from 41 fewer to 99 more)	⊕⊕⊕◯ Moderate	CRITICAL
ICU Length of Stay												
2	Randomised trials	Serious[b]	Not serious	Not serious	Serious[c]	None	428	380	-	MD **0.21 days lower** (2 lower to 1.59 higher)	⊕⊕◯◯ Low	IMPORTANT
Hospital Length of Stay												
2	Randomised trials	Serious[b]	Not serious	Not serious	Serious[c]	None	428	380	-	MD **0.49 days lower** (3.52 lower to 2.54 higher)	⊕⊕◯◯ Low	IMPORTANT
PaO2/FiO2 at 6 hours												
1	Randomised trials	Serious[b]	Not serious	Not serious	Not serious	None	12	10	-	MD **30.5 mmHg higher** (23.29 higher to 37.71 higher)	⊕⊕⊕◯ Moderate	IMPORTANT

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HFNC	COT	Relative (95% CI)	Absolute (95% CI)		
PaO2/FiO2 at 24 hours												
1	Randomised trials	Serious[b]	Not serious	Not serious	Not serious	None	12	10	-	MD **34.9 mmHg higher** (28.61 higher to 41.19 higher)	⊕⊕⊕◯ Moderate	IMPORTANT
PaO2/FiO2 at 72 hours												
1	Randomised trials	Serious[b]	Not serious	Not serious	Not serious	None	12	10	-	MD **34.52 mmHg higher** (29.25 higher to 39.79 higher)	⊕⊕⊕◯ Moderate	IMPORTANT

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

Explanations

[a] Risk estimates cross line of no effect

[b] Unclear to high-risk selection and performance bias

[c] Mean difference estimates cross line of no difference

Appendix 7: Characteristics of Ongoing Clinical Trials

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
High-Flow Nasal Therapy Versus Conventional Oxygen Therapy in Patients With COVID-19: A Randomized Controlled Trial (The COVID-HIGH Trial) NCT04655638 Expected completion date: October 2021	High flow nasal therapy	Conventional oxygen therapy	Inclusion Criteria: • Age ≥ 18 years old • Tested positive for SARS-CoV-2 using real-time reverse transcriptase PCR (RT-PCR) nasopharyngeal swabs • Clinical signs of acute respiratory infection and radiological evidence of pneumonia • Hospital admission in any ward or Emergency Department within 48 h • SpO2 ≤ 92% or PaO2/FiO2 < 300 in room air and need for oxygen therapy according to clinical judgment, at the screening	Primary Outcome Measures : • Proportion of patients needing escalation of treatment during hospital stay [Time Frame: 28 days] • Proportion of patients needing escalation of treatment (i.e. noninvasive ventilation - including CPAP - or intubation). Secondary Outcome Measures : • Proportion of patients needing intubation during hospital stay [Time Frame: 28 days] • Proportion of patients who receive CPAP during hospital stay [Time Frame: 28 days] • Proportion of patients who receive continuous positive airway pressure during hospital stay • Proportion of patients who receive NIV during hospital stay [Time Frame: 28 days] • Proportion of patients undergone noninvasive ventilation (e.g. BiLevel, PSV) • Proportion of patients admitted to intensive care unit during hospital stay [Time Frame: 28 days] • Proportion of patients who terminate the study protocols for improvement [Time Frame: 28 days] • Length of stay in hospital [Time Frame: 28 days] • Time to escalation of treatment to CPAP/NIV during hospital stay [Time Frame: 28 days] • Time to escalation of treatment to intubation/invasive ventilation during hospital stay [Time Frame: 28 days] • Length of stay in ICU [Time Frame: 28 day] • Days free from CPAP/NIV during hospital stay [Time Frame: 28 days] • Ventilator-free days during hospital stay [Time Frame: 28 days] • Oxygen-free days during hospital stay [Time Frame: 28 days] • 28-day mortality [Time Frame: 28 days from hospital admission] • 60-day mortality [Time Frame: 60 days from hospital admission] • Hospital mortality [Time Frame: 28 days] • Treatment interruption due to intolerance during study treatment [Time Frame: 28 days] • Dyspnea score (BORG scale) during hospital stay [Time Frame: 28 days] [0= no dyspnea to 10= severe dyspnea] - daily collection • National Early Warning Score 2 (NEWS2) during hospital stay [Time Frame: 28 days]

				Daily collection of Six simple physiological parameters that form the basis of the scoring system: respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion, temperature. A score is allocated to each parameter, with the magnitude of the score reflecting how extremely the parameter varies from the norm. The score is then aggregated and uplifted by 2 points for people requiring supplemental oxygen to maintain their recommended oxygen saturation. Range of values: 0 (best) - 23 (worst) points. • ROX index during hospital stay [Time Frame: 28 days] SpO2/FiO2/Respiratory rate - daily collection
A Trial of High-Flow Nasal Cannula vs. Conventional Oxygen Therapy in Patients With SARS-CoV-2-Related Acute Respiratory Failure: the HiFlo-COVID Trial NCT04609462 Completed: February 2021 – no results posted	High flow nasal cannula	Conventional oxygen therapy	Inclusion Criteria: • Adults > 18 years. • Emergency or ICU admission with suspected/confirmed SARS-CoV-2 infection. • Moderate/severe acute respiratory failure: • PaO2/FiO2 < 200. • Use of accessory muscles. • Breathing rate > 25 x minute. • Have a progression < 6 hours since meeting the definition of moderate/severe acute respiratory failure secondary to suspected/confirmed SARS-CoV-2 infection.	Primary Outcome Measures : 1. Intubation rate [Time Frame: 28 days]. 2. Clinical recovery [Time Frame: 28 days] Modified 7-point ordinal scale: An ordinal scale of 7 points where 1= Ambulatory/no limitation of activities and 7= Death. Low scores denote a better outcome and high scores denote a worse outcome. Time to reduction in scale score will be measured (daily scale scoring). Secondary Outcome Measures : 1. Proportion of patients with requirement of early mechanical ventilation. [Time Frame: 7 and 14 days] 2. Mechanical ventilation-free days [Time Frame: 28 days] 3. Renal replacement therapy-free days [Time Frame: 28 days] 4. Length of ICU stay [Time Frame: 28 days] 5. Length of hospital stay [Time Frame: 28 days] 6. All-cause day-28 mortality [Time Frame: 28 days] 7. Proportion of serious adverse events [Time Frame: 28 days] 8. Proportion of bacterial - fungal infections [Time Frame: 28 days]
Comparison of High Flow Nasal Cannula (HFNC), Face-mask Non-Invasive Ventilation (NIV) & Helmet NIV in COVID-19 ARDS Patients NCT04715243 Estimated Study completion date: December 30, 2021	Intervention 1: high flow nasal cannula Intervention 2: helmet NIV	Face-mask NIV	Inclusion Criteria: • > 18 years of age • confirmed COVID-19 • Within 48 hours of presentation in the emergency department, high dependency area or intensive care unit (ICU) • ARDS according to Berlin definition (P/F < 300) or O2 saturation < 90% or RR > 30/min) in room air • Standard oxygen therapy at flow rate < 15L/min x 60 minutes	Primary Outcome Measures : 1. Rate of endotracheal intubation [Time Frame: within the study period with an average of one month.] Secondary Outcome Measures : 1. Hospital mortality [Time Frame: 90 days from the hospital mortality.] 2. Hospital length of stay [Time Frame: Throughout the study completion. An average of 90 days.] 3. Ventilator free days [Time Frame: Throughout the study completion. An average of 90 days.]

A randomised controlled trial of high flow nasal oxygen versus non rebreathing oxygen face mask therapy in acute hypoxemic respiratory failure CTRI/2020/12/029803 *Not yet recruiting*	Intervention 1: high flow nasal cannula	Conventional oxygen therapy	All adult patients aged 18 years and above diagnosed as acute hypoxemic respiratory failure with covid positive status	Treatment failure
Randomized Controlled Trial to evaluate the effectiveness of HFNC and standard non-rebreathing mask for oxygen therapy in moderate category COVID 19 pneumonia CTRI/2021/01/030829 *Not yet recruiting*	High flow nasal cannula	Standard non-rebreathing mask	Adult patients with COVID-19 pneumonia	Time to progression to severe disease PaO2/FiO2 ratio, patient tolerance & acceptability will be assessed and Length of hospital stay will be recorded
COMPARISON USE OF HIGH-FLOW NASAL CANNULA AND NON INVASIVE VENTILATION IN PATIENTS WITH COVID-19: A RANDOMIZED COMPARATIVE STUDY CTRI/2020/11/029356 *Not yet recruiting*	High flow nasal cannula vs NIV	High flow nasal cannula vs NIV	Patients with COVID-19 rtPCR positive who requires HFNO and NIV as first line therapy	Reduction in respiratory distress signs like decrease in respiratory rate and increase in saturation SpO2 90%. Improvement in hemodynamic stability such as Heart rate, respiratory rate and blood pressure mprovement in chest x-ray/High Resolution Computerised Tomography. ICU stay and outcome of HFNO and NIV. Incidence of failed HFNO and NIV who needs intubation
Efficacy of awake prone positioning with high flow nasal cannula versus prone positioning with non-rebreathing mask in COVID-19 patients. A prospective comparative study CTRI/2020/12/029587 *Not yet recruiting*	Awake prone positioning with high flow nasal cannula	Awake prone positioning with non-rebreathing mask	Adult Confirmed COIVD19 positive patients admitted to ICU for acute hypoxemic respiratory failure	Intubation rates Intubation-free ICU stay Time to require NIV
n adult patients with known or suspected COVID-19, does the use of Continuous Positive Airway Pressure (CPAP) or high-flow nasal oxygen (HFNO), compared with standard care reduce mortality or need for tracheal intubation? ISRCTN16912075	Arm 1: Continuous positive airway pressure (CPAP), administered according to local protocol/guidelines. Administration will be left to clinical discretion.	Arm 3: Standard care. Standard oxygen therapy according to local protocol/guidelines	Current participant inclusion criteria as of 04/05/2021: 1. Adults =18 years 2. Hospital inpatient with suspected or proven COVID-19 3. FiO2 =0.4 and SpO2 =94% 4. Plan for escalation to intubation if needed	Composite outcome comprising tracheal intubation or mortality within 30 days. Mortality will be reported from hospital records up until discharge and tracked after discharge. Intubation will be obtained from hospital data Current secondary outcome measures as of 04/05/2021: All outcome measures are assessed at up to 30-days or hospital discharge, whichever is later, and obtained from hospital records unless otherwise specified.

Ongoing recruitment	Arm 2: High flow nasal oxygen (HFNO) will be administered according to local protocol/guidelines. Administration will be left to clinical discretion.			1. Intubation rate 2. Time to intubation 3. Time to death (mortality), obtained from hospital record or other source 4. Mortality in critical care (level 2/3) 5. Mortality during hospital stay 6. Mortality at 30 days, obtained from hospital record or other source 7. Length of stay in critical care (level 2/3) 8. Length of stay in hospital 9. Duration of invasive ventilation 10. Admission to ICU
Evaluation of the effectiveness of high flow nasal cannula (HFNC) oxygen delivery in comparison with non-invasive ventilation (NIV) in patients with COVID-19 IRCT20160516027929N8 *Recruitment status completed, but no available results*	HFNC	NIV	Adults with COVID-19 pneumonia	Partial pressure of carbon dioxide. Timepoint: Before the intervention, 24 hours after the intervention and 48 hours after the intervention. Oxygen saturation
High flow nasaloxygen versus Continuous Positive Airway Pressure Helmet Evaluation: A Randomized Crossover Trial in COVID-19 Pneumonia NCT04381923 Estimated study completion date: December 15, 2022	HFNO (active comparator, arm 1)	Helmet CPAP (active comparator, arm 2)	Adult patients with confirmed COVID-19 with an Sp02 < 92% on ≥ 6 liters NC admitted to a Penn Medicine advanced respiratory unit. An advanced respiratory unit is a unit capable of non-invasive respiratory support such as an ICU or intermediate care unit.	Ventilator-free days ICU and hospital length of stay Intubation Renal replacement therapy Mortality

Q8. Should non-invasive ventilation be used over high flow nasal cannula for patients with severe and critical COVID-19?

As of 03 January 2022

RECOMMENDATION

We suggest the use of either high flow nasal cannula or non-invasive positive pressure ventilation in COVID-19 patients with hypoxemic respiratory failure in the absence of any indication for emergent invasive mechanical ventilation. *(Low certainty of evidence; Weak recommendation)*

Consensus Issues

The risk of aerosolization using non-invasive ventilation was not discussed in the identified studies, but case series and reports have suggested minimal risk for health care workers. Standard operating procedure includes the use of filters in the expiratory limb tubing for non-invasive ventilation and use of face masks for patients on high flow nasal cannula. Physicians must be cognizant of the indications for intubation such as continued and progressive deterioration, and signs of respiratory failure.

KEY FINDINGS

Two randomized controlled trials were evaluated to compare the effect of non-invasive ventilation (NIV) and high flow nasal cannula (HFNC) oxygenation in improving clinical outcomes in COVID-19 patients with respiratory failure. Direct comparison of NIV in the form of helmet and face mask CPAP with HFNC in 218 COVID-19 patients with hypoxemia showed that reduction in mortality and need for endotracheal intubation were inconclusive. Certainty of evidence was low due to serious risk of bias and serious imprecision. Indirect mixed treatment comparison of NIV in the form of helmet CPAP and HFNC among COVID-19 patients with hypoxemia also showed no significant difference in terms of in-hospital mortality, need for mechanical ventilation, intensive care unit admission, and length of hospital stay.

INTRODUCTION

Non-invasive ventilation (NIV) has been one of the options in managing patients with acute respiratory failure. It decreases the need to escalate to invasive mechanical ventilation; however, its use in COVID-19 is still under investigation. Devices such as continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BiPAP) can provide Positive End Expiratory Pressure (PEEP), which aids in decreasing inspiratory effort. Compared to HFNC, mask and helmet CPAP are able to provide higher levels of PEEP which can contribute to decreasing the incidence of invasive mechanical intubation.[1] A systemic review that included 31 journal articles and 5136 participants with different non-COVID-related etiologies of respiratory failure evaluated whether HFNC was superior to NIV in preventing mortality. The result did not reach statistical significance and there was no difference between the two interventions in terms of length of hospital stay and the occurrence of adverse events such as barotrauma.[2] The practice of placing patients on non-invasive ventilation such as CPAP and BiPAP has not been widely used, with a recorded prevalence of 10% and 5.9% of patients in the United Kingdom and in the Philippines respectively.[3,4] Studies on non-COVID patients have demonstrated that HFNC or NIV offer physiological benefit for patients requiring respiratory support. [2] However,

clinically beneficial improvement in patient outcomes such as prevention of invasive mechanical ventilation and reduction of mortality and their association with the use of NIV or HFNC among COVID-19 patients with respiratory failure remains to be unanswered. This review aims to evaluate the effectiveness of NIV compared with HFNC among COVID-19 patients with respiratory failure.

REVIEW METHODS

A comprehensive literature search was done as of 07 December 2021 on the use of NIV compared to HFNC in COVID-19 using Medline, Cochrane Library, Google Scholar, clinicaltrials.gov, and medRxiv (pre-prints) with the following keywords: “CPAP”, “non-invasive ventilation”, “high flow nasal cannula”, “COVID-19”, and “SARS-COV2”. All search yields were reviewed and appraised. Randomized controlled trials comparing NIV with HFNC in COVID-19 and respiratory failure were included.

RESULTS

Direct Comparison of NIV versus HFNC

Two randomized controlled trials compared NIV and HFNC among COVID-19 patients with hypoxemic respiratory failure.[5,6] The trials enrolled 218 adult patients admitted to the intensive care unit (ICU). One study [5] randomized patients to either NIV (as helmet CPAP) or HFNC while the other study [6] randomized patients to either NIV (as facemask or helmet CPAP) or HFNC. Both studies reported clinical outcomes such as mortality, need to shift to invasive mechanical ventilation, and clinical improvement. Pooled analysis showed that reduction in mortality was inconclusive (RR 1.28, 95% CI 0.77-2.12; moderate certainty). Certainty of evidence was downgraded to moderate due to serious imprecision. The need for mechanical ventilation between the two intervention groups was likewise inconclusive (RR 0.96, 95% CI 0.32-2.92; low certainty). Certainty of evidence was downgraded to low due serious risk of bias because of the lack of participant and study personnel blinding, and serious imprecision. In one RCT [6], no statistically significant improvement in median respiratory rate (NIV at 24 breaths per minute versus HFNC at 24 breaths per minute; p=0.57), median oxygen saturation (NIV at 96% versus HFNC at 96%; p=0.52) and median PF ratio (NIV at 153.60 versus HFNC at 118.33; p=0.10) were found at 24 hours after initiation of NIV or HFNC.

Indirect Comparison of NIV and HFNC versus Conventional Oxygen Therapy (COT)

One randomized controlled trial [7] compared NIV (as facemask CPAP) to COT and HFNC to COT in 1272 adult COVID-19 patients with acute respiratory failure defined as peripheral oxygen saturation of 94% or below despite receiving oxygen support with fraction of inspired oxygen of at least 40%. Indirect mixed treatment comparison to determine the effect of NIV compared with HFNC showed higher ranking probability for NIV but inconclusive difference in terms of in-hospital mortality (RR 0.93, 95% CrI 0.57-1.49; moderate certainty), need for invasive mechanical ventilation (RR 0.82, 95% CrI 0.53-1.27; low certainty), ICU admission (RR 0.84; 95% CrI 0.61-1.11; low certainty), and length of hospital stay (MD -2.03, 95% CrI -6.27-2.13; low certainty). Findings in this indirect comparison were concordant with the results reported in the above randomized controlled trials [5,6] which directly compared NIV and HFNC. Certainty of evidence for in-hospital mortality was downgraded to moderate due to imprecision while certainty of evidence for need for mechanical ventilation, ICU

admission, and overall length of hospital stay were downgraded to low due to lack of blinding and imprecision.

EVIDENCE TO DECISION

There is still insufficient evidence and a scarce amount of published randomized controlled trials on the effect of NIV in COVID-19. Though there is promising evidence on and benefits from the use of helmet CPAP, it is still unavailable in the Philippines and is only accessible in countries such as the United States and United Kingdom among others. Infection control issues such as aerosol generation in NIV is also a concern especially for healthcare workers. While the use of a helmet CPAP has minimal aerosol generation as long as there are no leaks [8-10], the use of a face mask CPAP may produce aerosols at the exhalation ports and also if there are air leaks on the face. Placement of filters in the expiratory tubing may mitigate aerosol leak without affecting the patient's breathing.[11] Adverse events may also occur in patients on NIV. Among the most common serious adverse events seen in patients on CPAP were pneumothorax and pneumomediastinum, the incidence of which has been reported at approximately 3-4%.[5,12]

RECOMMENDATIONS FROM OTHER GROUPS

Four Guidelines on the use of NIV in COVID-19 were identified. Their recommendations are summarized in the table below:

Group/Society or Network	Year	Recommendation	Level of Evidence/Strength of Recommendation
European Respiratory Journal [12]	2020	We suggest HFNC or non-invasive CPAP delivered through either a helmet or a face-mask for patients with COVID-19 and hypoxemic acute respiratory failure	Conditional Recommendation Very Low Certainty of Evidence
National Institutes of Health [13]	2021	In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure and for whom HFNC is not available	BIIa
World Health Organization [14]	2021	In selected patients with COVID-19 and mild ARDS, a trial of HFNO, non-invasive ventilation – continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) may be used	Conditional recommendation
Surviving Sepsis Campaign [15]	2020	In adults with COVID-19 and acute hypoxemic respiratory failure, if HFNC is not available and there is no urgent indication for endotracheal intubation, we suggest a trial of NIPPV with close monitoring and short-interval assessment for worsening of respiratory failure	Weak
		We were not able to make a recommendation regarding the use of helmet NIPPV compared with mask NIPPV. It is an option, but we are not certain about its safety or efficacy in COVID-19	No recommendation

RESEARCH GAPS

More clinical trials comparing NIV with HFNC are needed to establish conclusive benefits especially on clinically important outcomes such as the reduction in mortality and reduction in mechanical ventilation. Furthermore, studies on the aerosol-generating effects associated with the use if NIV, which may increase transmission of infection to healthcare workers, should also be included as a safety outcome. Currently, there are 3 ongoing randomized controlled trials, which may further elucidate and provide evidence on its use and safety in preventing mortality.

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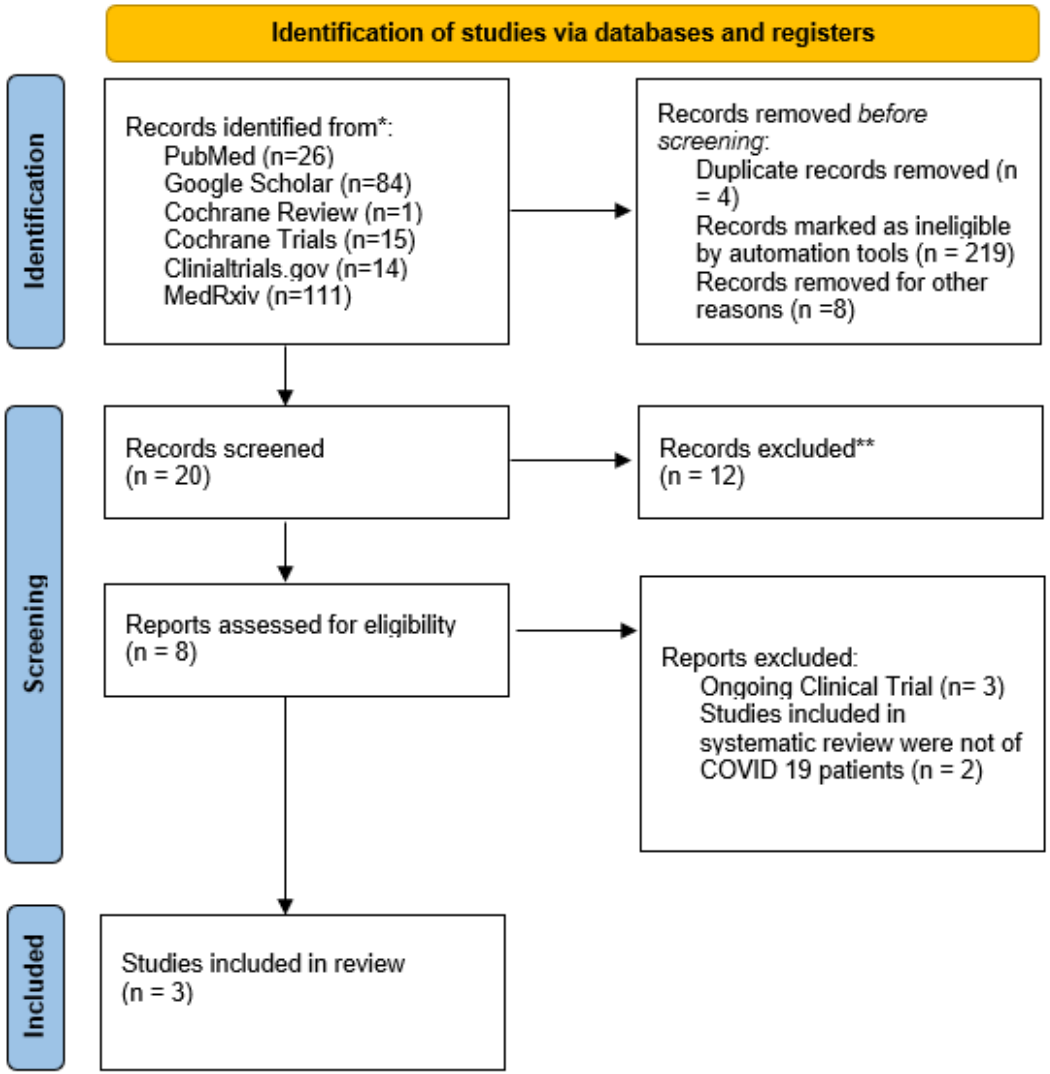
Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					• Non-invasive ventilation has been one of the options in managing patients with acute respiratory failure. It decreases the need to escalate to invasive mechanical ventilation, however, its use in COVID-19 is still under investigation.
Benefits	Large (2)	Moderate (3)	Small	Uncertain			• No significant difference in mortality with the use of NIV compared to HFNC, invasive mechanical ventilation rate. • No statistically significant improvement in median respiratory rate (NIV at 24 breaths per minute versus HFNC at 24 breaths per minute; p=0.57), median oxygen saturation (NIV at 96% versus HFNC at 96%; p=0.52) and median PF ratio (NIV at 153.60 versus HFNC at 118.33; p=0.10) were found at 24 hours after initiation of NIV or HFNC.
Harm	Large (1)	Small (2)	Uncertain (2)	No response			• Concerns: Infection control measures such as aerosol generation in NIV. • The use of a helmet CPAP has minimal aerosol generation as long as there are no leaks. • Adverse events on NIV: pneumothorax and pneumomediastinum reported at approximately 3-4%.
Certainty of Evidence	High	Moderate (1)	Low (4)	Very low			• Certainty of evidence was low due the risk of bias and imprecision
Balance of effects	Favors drug (1)	Does not favor drug (1)	Uncertain (3)				
Values	Important uncertainty or variability	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain (3)	Large cost	Moderate Cost (2)	Negligible cost	Moderate savings	Large savings	
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 (2)	Reduced (1)	Probably no impact (1)	Increased (1)			
Acceptability	Uncertain (2)	No	Yes (3)				
Feasibility	Uncertain (3)	No	Yes (2)				

Appendix 2. PRISMA Flow Diagram

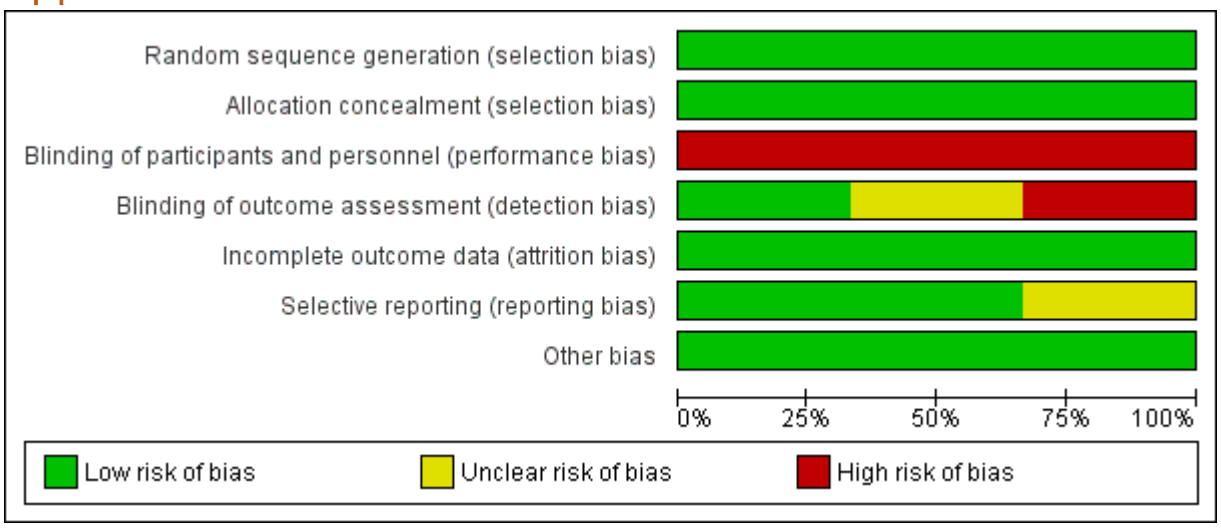


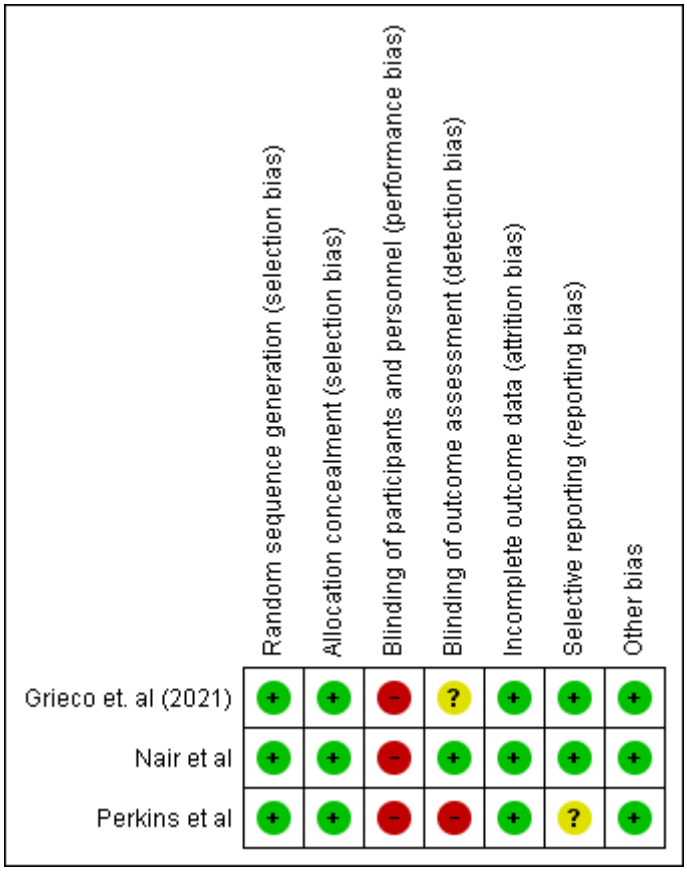
Appendix 3. Characteristics of Included Studies

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/Control	Outcomes
Effect of Helmet Noninvasive Ventilation VS High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients with COVID_19 and Moderate to Severe Hypoxemic Respiratory Failure The HENIVOT Randomized Clinical Trial Grieco et. al March 2021	Investigator-initiated 2-group open label, multicenter randomized clinical trial	Italy	N = 109	All adult patients admitted in the intensive care units with acute hypoxemic respiratory failure and diagnosed with COVID-19 Inclusion Criteria: PaO2/FiO2 equal or below 200 Partial pressure of arterial carbon dioxide equal to or lower than 45 mmHg Absence of history of chronic respiratory failure or moderate to severe cardiac insufficiency (NYHA >II or LV ejection fraction of <50%) Exclusion Criteria: Acute exacerbation of chronic pulmonary disease Kidney failure	Non-invasive ventilation was delivered by a compressed gas-based ventilator connected to the helmet through a bi-tube circuit Initial pressure support between 10 and 12 cm H2) eventually increased to ensure a peak inspiratory flow ot 100L//min Positive ed expiratory pressure between 10 and 12 cm H2) and FiO2 titrated to obtain SpO2 between 92 and 98%	High flow nasal cannula for 48 hours Gas flow initially set at 60L/min and decreased in case of intolerance, FIO2 titrated to obtain peripheral oxygen saturation as mea sured by pulse oximetry (SpO2) between 92% and 98%, and humidification chamber was set at 37 °C or 34 °C according to the patient's comfort.	Primary Outcome Number of days free of respirator support within 28 days after enrollment Secondary outcome: proportion of patients who required endotracheal intubation within 28 days from study enrollment, number of days free of invasive mechanical ventilation at days 28 and 60 Intensive care unit mortality In hospital mortality 28 and 60 day mortality Intensive care unit length of stay and hospital length of stay 90-day mortality Quality of life after 6 and 12 hours
Comparison of High-Flow Nasal Cannula and Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure due to Severe COVID-19 Pneumonia Nair et al September 2021	Single-center, prospective randomized controlled trial	India	n= 109	Adult patients 18-75 years old Severe COVID-19 pneumonia presenting with fever, cough, respiratory distress with frequency >30 breaths/min and/or room air SpO2 <90%	NIV with either mask/helmet device connected to an ICU ventilator with the setting of Pressure support of 10-20 cmH2O adjusted to obtain an expired tidal volume of 7-10 mL/kg of PBW and PEEP 5-10 cm H2O and FiO2 0.5-1 titrated to target SpO2 >94%	HFNC with large bore binasal prongs and high flow heated humidifier device. Initial flow set up was at 50lpm and FiO2 of 1.0 The flow and FiO2 were adjusted between 30-60lpm and 0.5-1.0 to maintain SpO2 of >94%	Primary Outcome: Early intubation rate Proportion of subjects requiring invasive mechanical ventilation at 48 hours of ICU admission Secondary Outcome Late intubation rate Early improvement in oxygenation In hospital mortality Proportion of patients requiring awake prone positioning

An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19 Perkins et. Al (2021) (PREPRINT)	Parallel group, open-label, three-arm, adaptive, randomized controlled trial	London, United Kingdom	1259	Adults >18 years old hospitalized with COVID-19 Acute respiratory failure defined as SpO2 of <94% despite receiving a fraction of inspired oxygen of at least 0.4 Deemed suitable for tracheal intubation of treatment escalation was required	Participants randomized to High Flow Nasal Cannula started treatment as soon as possible	Conventional oxygen therapy (via face mask or nasal cannulae)	Primary Outcome Composite outcome of tracheal intubation or mortality within 30-days of randomization Secondary Outcomes Incidence of tracheal intubation and mortality at 30 days Time to tracheal intubation Duration of invasive mechanical ventilation Time to death Mortality Incidence of intensive care unit admission Length of stay

Appendix 4. Risk of Bias Assessment of Included Studies





Appendix 5. Forest Plots

Study or Subgroup	NIV Events	NIV Total	HFNC Events	HFNC Total	Weight	Risk Ratio M-H, Random, 95% CI
Grieco 2021	13	54	14	55	41.6%	0.95 [0.49, 1.82]
Nair 2021	25	54	16	55	58.4%	1.59 [0.96, 2.63]
Total (95% CI)		**108**		**110**	**100.0%**	**1.28 [0.77, 2.12]**
Total events	38		30			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 1.53$, df = 1 (P = 0.22); $I^2 = 35\%$
Test for overall effect: Z = 0.97 (P = 0.33)

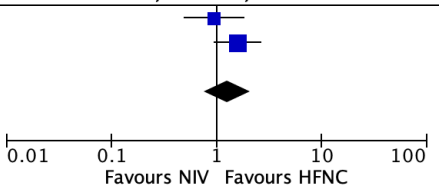


Figure 5-1 Forest plot for In-hospital Mortality

Study or Subgroup	NIV Events	NIV Total	HFNC Events	HFNC Total	Weight	Risk Ratio M-H, Random, 95% CI
Grieco 2021	15	54	28	55	50.2%	0.55 [0.33, 0.90]
Nair 2021	25	54	15	55	49.8%	1.70 [1.01, 2.85]
Total (95% CI)		**108**		**110**	**100.0%**	**0.96 [0.32, 2.92]**
Total events	40		43			

Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 9.50$, df = 1 (P = 0.002); $I^2 = 89\%$
Test for overall effect: Z = 0.07 (P = 0.94)

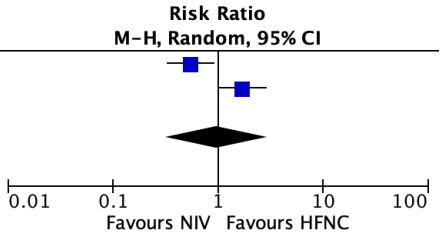


Figure 5-2 Forest plot for Need for Invasive Mechanical Ventilation

Appendix 6. League Tables for Bayesian Indirect Comparison

Table 6-1 League Table for In-hospital Mortality

Treatment effects for all studies: comparison of all treatment pairs.

	COT	HFNC	NIV
COT	COT	0.93 (0.67, 1.29)	0.86 (0.61, 1.21)
HFNC	1.08 (0.78, 1.49)	HFNC	0.93 (0.57, 1.49)
NIV	1.16 (0.82, 1.64)	1.07 (0.67, 1.75)	NIV

Treatment effects are expressed as relative risk (RR) with 95% credible intervals (95% CrI)

Table 6-2 League Table for Invasive Mechanical Intubation

Treatment effects for all studies: comparison of all treatment pairs.

	COT	HFNC	NIV
COT	COT	0.98 (0.73, 1.33)	0.81 (0.59, 1.11)
HFNC	1.02 (0.75, 1.37)	HFNC	0.82 (0.53, 1.27)
NIV	1.24 (0.9, 1.7)	1.22 (0.79, 1.88)	NIV

Treatment effects are expressed as relative risk (RR) with 95% credible intervals (95% CrI)

Table 6-3 League Table for ICU Admission

Treatment effects for all studies: comparison of all treatment pairs.

	COT	HFNC	NIV
COT	COT	1.04 (0.86, 1.26)	0.88 (0.72, 1.07)
HFNC	0.96 (0.79, 1.16)	HFNC	0.84 (0.64, 1.11)
NIV	1.14 (0.94, 1.39)	1.19 (0.9, 1.56)	NIV

Treatment effects are expressed as relative risk (RR) with 95% credible intervals (95% CrI)

Table 6-4 League Table for Length of Stay

Treatment effects for all studies: comparison of all treatment pairs.

	COT	HFNC	NIV
COT	COT	1.17 (-1.75, 4.18)	-0.84 (-3.79, 2.06)
HFNC	-1.17 (-4.18, 1.75)	HFNC	-2.03 (-6.27, 2.13)
NIV	0.84 (-2.06, 3.79)	2.03 (-2.13, 6.27)	NIV

Treatment effects are expressed as relative risk (RR) with 95% credible intervals (95% CrI)

Appendix 7. GRADE Evidence Profile

Table 7-1. GRADE Profile Table (Direct Comparison)

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	HFNC	Relative (95% CI)	Absolute (95% CI)		
In hospital mortality												
2	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	None	38/108 (35.2%)	30/110 (27.3%)	RR 1.28 (0.77 to 2.12)	76 more per 1,000 (from 63 fewer to 305 more)	⊕⊕⊕◯ Moderate	CRITICAL
Need for intubation												
2	Randomised trials	Serious [a]	Not serious	Not serious	Serious[b]	None	40/108 (37.0%)	43/110 (39.1%)	RR 0.96 (0.32 to 2.92)	16 fewer per 1,000 (from 266 fewer to 751 more)	⊕⊕◯◯ Low	CRITICAL

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

Explanations
[a] Lack of patient blinding
[b] Wide confidence interval

Table 7-2. GRADE Profile Table (Indirect Mixed Treatment Comparison)

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	HFNC	Relative (95% CI)	Absolute (95% CI)		
In hospital mortality												
	Randomised trials	Not serious	Not serious	Not serious	Serious[a]	None	**RR 0.93** (0.57 to 1.49)				⊕⊕⊕◯ Moderate	CRITICAL
Need for Invasive Mechanical Intubation												
	Randomised trials	Serious [b]	Not serious	Not serious	Serious[a]	None	**RR 0.82** (0.53 to 1.27)				⊕⊕◯◯ Low	CRITICAL
Intensive Care Unit Admission												
	Randomised trials	Serious [b]	Not serious	Not serious	Serious[a]	None	**RR 0.84** (0.61, 1.11)				⊕⊕◯◯ Low	CRITICAL
Length of Hospital Stay (DAYS)												
	Randomised trials	Serious [b]	Not serious	Not serious	Serious[a]	None	**MD -2.03** (-6.27 to 2.13)				⊕⊕◯◯ Low	IMPORTANT

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

Explanations
[a] Wide confidence interval
[b] Lack of patient blinding

Appendix 8. Characteristics of Ongoing Clinical Trials

Title Identifier Expected Completion Date	Intervention	Comparator/ Control	Patients/Population Recruited	Outcomes
Comparison of High Flow Nasal Cannula (HFNC), Face-mask Non-Invasive Ventilation (NIV) & Helmet NIV in COVID-19 ARDS Patients (NIV COVID19) NCT04715243 **Ongoing Recruitment** **Estimated completion date: December 2021**	HFNC	NIV	Inclusion Criteria: ● > 18 years of age ● confirmed COVID-19 ● Within 48 hours of presentation in the emergency department, high dependency area or intensive care unit (ICU) ● ARDS according to Berlin definition (P/F < 300) or O2 saturation < 90% or RR > 30/min) in room air ● Standard oxygen therapy at flow rate < 15L/min x 60 minutes	Primary Outcome Measures : • Rate of endotracheal intubation [Time Frame: within the study period with an average of one month.] ○ The patient will be randomly assigned to one of the treatment arms. Then the patient will be followed up for one month for the primary outcome which is endotracheal intubation. Secondary Outcome Measures : • Hospital mortality [Time Frame: 90 days from the hospital mortality.] ○ Number of patients who survived compared to who died in each intervention • Hospital length of stay [Time Frame: Throughout the study completion. An average of 90 days.] ○ total number of days patients remain in the hospital as inpatient in each intervention • Ventilator free days [Time Frame: Throughout the study completion. An average of 90 days.] ○ number of days patients remain off intervention (invasive or non-invasive)
High Flow Nasal Oxygen Versus Continuous Positive Airway Pressure Helmet Evaluation: A Randomized Crossover Trial in COVID-19 Pneumonia ***COVIDNOCHE Trial (HFNO Versus CPAP Helmet) in COVID-19 Pneumonia (COVIDNOCHE)*** NCT04381923 **Not yet recruiting** **Estimated study completion: December 2022**	HFNC	Hemet CPAP	Inclusion Criteria: ● Adult patients with confirmed COVID-19 with an Sp02 < 92% on ≥ 6 liters NC admitted to a Penn Medicine advanced respiratory unit. An advanced respiratory unit is a unit capable of non-invasive respiratory support such as an ICU or intermediate care unit.	Primary Outcome Measures : • Ventilator-Free Days (VFD) [Time Frame: 28 days] ○ VFD is the number of days alive and free of mechanical ventilation in the first 28 days after study enrollment. Death before 28 days will be assigned a VFD equal to 0 to penalize non-survival. In cases of repeated intubation and extubation, periods free from invasive ventilation and lasting at least 24 consecutive hours will be calculated and summed. Timing of intubation and extubation will be captured in hours, and the number of hours a patient received invasive ventilation will be used to calculate duration of ventilation. Secondary Outcome Measures : 1. ICU and Hospital Length of Stay [Time Frame: 28 days]

				Days spent in the ICU and hospital after time of enrollment 2. Intubation [Time Frame: 28 days] Incidence and time to intubation in days after the time of enrollment 3. Renal Replacement Therapy (RRT) [Time Frame: 28 days] Incidence of RRT after the time of enrollment 4. Mortality [Time Frame: 28 days, 90 days] Death from any cause during after the time of enrollment
Comparison of efficacy of HighFlow Nasal Cannula with Continuous Positive Airway Pressure in prevention of Invasive mechanical ventilation in COVID 19 patients with Acute Respiratory Distress Syndrome in Critical Care Unit- A Randomized Control Study - COVID HFNC CTRI/2021/04/032501 **Not yet recruiting** **Estimated completion date:**	HFNC	NIV	Inclusion criteria: All COVID -19 positive patients (by RT-PCR) with paO2/Fio2 (P/F) â?? 150 to 250, with good sensorium, stable hemodynamics and pH > 7.2	Primary outcome: To compare the efficacy of High Flow Nasal Cannula and Non Invasive Ventilation - Continuous Positive Airway Pressure in reducing need for invasive mechanical ventilation in patients with ARDS in COVID-19.Timepoint: 24 hours Secondary outcome: Ability of ROX index to identify COVID 19 patients on HFNC requiring invasive mechanical ventilation.Timepoint: 24 hours Ability to alleviate dyspnoea as assessed by modified Borg scaleTimepoint: 24 hours Patientâ’s compliance to therapy - comfort / noise level, ability to proneTimepoint: 24 hours

Q9. Should lung protective ventilation, high PEEP and driving pressure-limited strategies be used in the management of adult patients with COVID-19-associated acute respiratory distress syndrome?

As of 19 February 2021

RECOMMENDATIONS

We suggest the use of a lung protective ventilation strategy (tidal volume 4-8 mL/kg predicted body weight and plateau pressure less than 30 cmH2O) in patients with COVID-19 infection and ARDS. *(Very low certainty of evidence; Weak recommendation)*

There is insufficient evidence to recommend the use of a higher PEEP strategy. We suggest to individualize PEEP or employ a PEEP strategy based on respiratory mechanics (i.e., compliance) in patients with COVID-19 infection. *(Low certainty of evidence)*

There is insufficient evidence to recommend a driving pressure limited strategy in patients with COVID-19 infection. We suggest to keep the driving pressure ≤ 14 cmH2O. *(Low certainty of evidence)*

Consensus Issues

During the early stages of the disease, COVID-19 ARDS may not be the same as the usual ARDS. In COVID-19-related ARDS, compliance can be high or normal even in patients with very low PaO2/FiO2 ratios. In these cases, the lungs are not recruitable and the use of high levels of PEEP will not lead to better oxygenation.

As the respiratory mechanics (compliance) in COVID-19 ARDS are not uniformly correlated with the severity of the hypoxemia, it is best to individualize PEEP based on compliance and driving pressure rather than titrating PEEP based on the severity of the PaO2/FiO2 ratio. Thus, a higher PEEP strategy (using the high PEEP/ FiO2 table) for moderate to severe ARDS is not recommended for all patients with COVID 19 infections, due to possible complications such as barotrauma.

We suggest titrating lung volumes (tidal volume 4-8 ml/kg predicted body weight) and PEEP to maintain the plateau pressure less than 30 and to have the lowest driving pressure. A driving pressure of < 14cm H20 is recommended. The driving pressure is the difference between the plateau pressure and the PEEP, or tidal volume over the respiratory system compliance.

KEY FINDINGS

There were no clinical trials evaluating the (1) effectiveness and harms of lung protective ventilation strategy and high PEEP strategies in patients with COVID-19-associated ARDS; (2) effectiveness and harms of higher PEEP versus lower PEEP strategies in conjunction with LTVV in patients with COVID-19-associated ARDS; and, (3) effectiveness and harms of a driving pressure-limited strategy in patients with COVID-19 and ARDS.

Lung Protective Ventilation
Higher tidal volume was associated with the same or higher risk of 28-day mortality but there was no significant difference in ventilator-free days in multivariable models. A smaller case study also showed that barotrauma cases were observed to have significantly lower V_T than the controls. These studies provided very low quality of evidence for this component of the review question.

Higher PEEP and Low Tidal Volume Ventilation
Higher PEEP was not associated with differences in 28-day mortality nor ventilator-free days in adults with COVID-19-related ARDS. A case-control study showed that PEEP was not statistically significantly different between patients with and without barotrauma. These studies provided low quality of evidence for this component of the review question.

Driving Pressure
There was no significant difference in 28-day mortality, in-hospital mortality, mechanical ventilation-free days, hospital stay and barotrauma were observed. These studies provided low quality of evidence for this component of the review question.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is characterized by lung inflammation and non-hydrostatic proteinaceous pulmonary edema. [1] The Berlin definition established in 2012 is widely used to identify ARDS in practice: occurrence within 7 days of a known clinical insult or worsening respiratory symptoms with PaO2/FiO2 ≤ 300 mmHg in a patient receiving a positive end-expiratory pressure (PEEP) of at least 5 cmH2O, and bilateral radiographic opacities not entirely explained by heart failure or volume overload. Unlike usual ARDS, two COVID-19 pneumonia phenotypes were initially proposed: An L-type (low elastance / high compliance, low ventilation-to-perfusion ratio, low lung weight, low recruitability) and an H-type (high elastance / low compliance, high right-to-left-shunt, high lung weight, high recruitability). [7] Gattinoni and colleagues recommended that intubated and deeply sedated L-type patients, if hypercapneic, can be ventilated with tidal volumes (VT) up to 8-9 mL/kg because of their high compliance. The H phenotype was to be treated similar to typical severe ARDS. [7] However, CARDS management remains controversial. Emerging evidence suggest that the features and respiratory mechanics of CARDS and non-COVID-19 ARDS are comparable. [2,6] Many experts still recommend low tidal volume ventilation (6 mL/kg predicted body weight [PBW]) and keeping plateau pressure (Pplat) below 30 cmH2O in patients with CARDS. [2, 6]

REVIEW METHODS

Five clinical practice guidelines with recommendations on mechanical ventilation management were found on electronic search (MEDLINE through PubMed, CENTRAL, ChinaXiv, MedRxiv, BioRxiv, ClinicalTrials.gov, ChiCTR, WHO ICTRP) on December 26, 2020. Quality was assessed using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument. Two guidelines were judged to be of high quality and suitable for adapting (Australian Guidelines for the Clinical Care of People with COVID-19[1], 95%, and the Surviving Sepsis Campaign [SSC] [2], 78%) over others (US National Institutes of Health [3], 69%, National Health Service England [4], 62%, Chinese Medical Association [5], 29%). The evidence profiles from the Australian Guidelines and the SSC were adapted as indirect evidence.

RESULTS

There were two observational studies on intubated adult patients with COVID-19 and ARDS which reported V_T, plateau pressure and PEEP parameters and the development of clinical outcomes (mortality, ventilator-free days, barotrauma including pneumothorax). [6,7] The small sample sizes (n = 553 and n = 20) preclude generalizability, while selection bias (single-center study at an ARDS referral center) and missing outcome data (23 of 553 patients) pose a significant risk of bias.

Indirect evidence comes from one RCT and two systematic reviews in patients without COVID-19. One systematic review of 9 RCTs investigated low VT strategies (V_T 4-8 mL/kg and/or Pplat < 30 cmH2O) against non-volume-limited strategies (VT 10-15 mL/kg) in ARDS patients. [9] This review is of moderate quality as inclusion criteria for ARDS was unclear (lung injury score or Berlin criteria) and gray literature was not sought. All but one RCT had low risk of bias.

Higher vs. lower PEEP strategies were compared in a high-quality individual-patient data meta-analysis (IPDMA) conducted with patients ≥ 16 years of age with acute lung injury (PaO_2/FiO_2 ≤ 300 mmHg and > 200 mmHg) or ARDS (PaO_2/FiO_2 ≤ 200 mmHg) according to the American-European Consensus (3 RCTs, n = 2,299). All patients were ventilated with a target V_T < 8 mL/kg PBW and Pplat ≤ 30 cmH2O except in the higher PEEP arm of one study (Pplat ≤ 40 cmH2O; n = 476). High PEEP was based on the ARDSNet $PEEP/FiO_2$ table except in one trial where a maximum PEEP that maintained Pplat ≤ 30 cmH2O was given.

A small but high-quality multicenter RCT (n = 31) compared a driving pressure-limited strategy versus conventional ARDSNet protocol in ARDS prior to the COVID-19 pandemic. [17] Patients with ARDS who met the 2011 Berlin criteria were randomized to either driving pressure-limited strategy group (V_T 4-8 mL/kg PBW to target ΔP 10 cm H2O) or control group (V_T 6 mL/kg PBW, Pplat <= 30 cmH2O and ARDSNet low-PEEP table). Apart from patients in the driving pressure-limited group being slightly younger (mean 45.1 vs. 51.9 years) and having a higher proportion of females and septic shock (56.2% vs. 40%), most baseline characteristics were similar between intervention arms.

Lung Protective Ventilation

Direct Evidence

There were no clinical trials evaluating the effectiveness and harms of lung protective ventilation strategy and high PEEP strategies in patients with COVID-19-associated ARDS.

In the PRoVENT-COVID study, a multicenter retrospective cohort study conducted in the Netherlands on adults with COVID-19-related ARDS (n = 553), patients received a median tidal volume of 6.3 mL/kg PBW (IQR 5.7 to 7.1), PEEP of 14 (IQR 11 to 15) and driving pressure of 14 (IQR 11.2 to 16.0). [13] Plateau pressure was not reported. Higher tidal volume was associated with the same or higher risk of 28-day mortality (OR 1.28, 95% CI 1.00-1.64) but no significant difference in ventilator-free days (MD -0.73 days, 95% CI -1.52 to 0.06) in multivariable models. No cut-off values for tidal volume were stated.

A much smaller case-control study looked at the incidence of barotrauma among invasively ventilated COVID-19 patients (n = 20) meeting the Berlin definition for ARDS. [14] Of the 8 cases (40%) that developed barotrauma (pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema), 6 patients received low tidal volume ventilation (V_T ≤ 8 mL/kg and Pplat < 30 cmH2O). The barotrauma cases were observed to have significantly lower V_T (median 5.4 vs. 11.7 mL/kg PBW, p = 0.005) and Pplat (median 27 vs. 32 cmH2O, p = 0.01) than the controls. Notably, patients with barotrauma had low lung compliance (median 30 cmH2O/mL) and may have confounded outcomes in this retrospective study.

Indirect Evidence

There are several studies on lung protective ventilation to avoid ventilator-associated lung injury in the ARDS literature prior to the COVID-19 pandemic. In one systematic review [15], the low tidal volume group had a mean V_T of 6.8 +/- 1.2 mL/kg while the control group had a mean V_T of 11.4 +/- 1.1 mL/kg. When trials with a high PEEP co-intervention were excluded in the primary analysis (7 RCTs, n = 1,481), mortality was not significantly reduced (RR 0.87, 95% CI 0.70 to 1.08, **Appendix 3**). Moderate heterogeneity (I^2 = 46%) may be attributed to differences in determining the primary endpoint (in-hospital, 28-day and 60-day mortality) and severity of lung injury. No significant differences were noted in terms of barotrauma (RR 0.96, 95% CI 0.67 to 1.37; 3 RCTs) and ventilator-free days (MD -0.03 days, 95% CI -5.88 to 5.95; 2 RCTs). Furthermore, an a priori sensitivity analysis which also included studies with LTVV and high PEEP (“open lung” approach) (9 RCTs, n = 1,629) found a significantly greater reduction in mortality with low tidal volume protocols versus controls (RR 0.80, 95% CI 0.66 to 0.98, I2 = 46%).

Higher PEEP and Low Tidal Volume Ventilation

Direct Evidence

We found no clinical trials evaluating the effectiveness and harms of higher PEEP versus lower PEEP strategies in conjunction with LTVV in patients with COVID-19-associated ARDS.

In the observational PRoVENT-COVID study (n = 553), higher PEEP was not associated with 28-day mortality (OR 1.08, 95% CI 0.85-1.39) nor ventilator-free days (MD –0.73 days, 95% CI –1.52 to 0.06) in adults with COVID-19-related ARDS. [13] No cut-off value for higher PEEP was stated.

Meanwhile, a case-control study with COVID-19 patients and ARDS (n = 20) found that PEEP was not statistically significantly different between patients with and without barotrauma (14 vs. 15 cmH2O, p = 0.80). [14]

Indirect Evidence

In an IPDMA on ALI/ARDS patients with PaO2/FiO2 ≤ 300 mmHg receiving LTVV (V_T median 6.5 vs. 6.4 mL/kg PBW and Pplat median 27 vs. 24 cmH2O on day 7), a higher PEEP strategy significantly reduced ICU mortality (RR 0.87, 95% CI 0.78 to 0.97) but not hospital mortality (RR 0.94, 95% CI 0.86 to 1.04). [16] Days with unassisted breathing (MD 0.64 days, -0.12 to 1.39) and development of pneumothorax (RR 1.19, 95% CI 0.89 to 1.60) were not significantly different. In a preplanned subgroup analysis of ARDS patients with PaO2/FiO2 ≤ 200 (i.e. moderate and severe ARDS in the Berlin definition), a higher PEEP strategy significantly reduced ICU mortality (RR 0.85, 95% CI 0.76 to 0.95) and was non-inferior to a lower PEEP strategy for hospital mortality (RR 0.90, 95% CI 0.81 to 1.00). The intervention group had a mean PEEP of 10.8

cmH2O (SD 5.0) while the control group had a mean PEEP of 7.8 cmH2O (SD 3.3) on day 7.

Driving Pressure

Direct Evidence

There were no clinical trials evaluating the effectiveness and harms of a driving pressure-limited strategy in patients with COVID-19 and ARDS.

Indirect Evidence

In one RCT on non-COVID-19 ARDS, primary endpoint of ΔP in the first three days was higher in the driving pressure-limited group (MD 4.6 cmH2O, 95% CI 2.8 to 6.5). [17] The driving pressure-limited group had slightly lower tidal volumes (mean 4.5 vs. 5.7 mL/kg PBW, $p < 0.001$) but PEEP was not significantly lower (mean 8.1 vs. 9.0 cmH2O, $p = 0.31$) on the third day from randomization. No significant differences in 28-day mortality (RR 1.31, 95% CI 0.53 to 3.25, calculated using EpiCalc), in-hospital mortality (RR 0.82, 95% CI 0.40 to 1.70) nor barotrauma were observed. Mechanical ventilation-free days (MD 1.5 days, 95% CI -4.5 to 18.5), ICU stay (MD 3.9, 95% CI -6.9 to 18.7) and hospital stay (MD 2.0, 95% CI -10.5 to 22.3 were also not significantly different.

RECOMMENDATIONS FROM OTHER GROUPS

The SSC 2020 guidelines recommend using low tidal volume ventilation (V_T 4-8 mL/kg of PBW) over higher tidal volumes (V_T > 8 mL/kg) in mechanically ventilated adults with COVID-19 and ARDS. [9] The SSC guideline panel gave a strong recommendation for low tidal volume ventilation considering the moderate magnitude of benefit, low cost, and feasibility of intervention.

In addition, the SSC 2020 also recommended using low tidal volume ventilation (V_T 4-8 mL/kg of PBW) in mechanically ventilated adults with COVID-19 and ARDS. [9] Both the Australian Living Guidelines 2020 (consensus recommendation) and the SSC 2020 (weak recommendation) favor a higher PEEP strategy (PEEP > 10 cm H2O) for mechanically ventilated adults with COVID-19 and moderate to severe ARDS. [8-9] These recommendations were based on indirect evidence from the non-COVID-19 population.

RESEARCH GAPS

There are at least 3 ongoing clinical trials investigating management of mechanical ventilator settings and pressures (PEEP, transpulmonary pressure) in adults with COVID-19 (Appendix 4).

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Appendix 1. Characteristics of Included Studies

Author Study Design	Population / Setting	Intervention/s	Control	Outcomes
Botta 2020 Retrospective cohort study	Adult patients intubated for COVID-19-related respiratory failure with ARDS Netherlands	Various mechanical ventilator settings	-	Primary: Main ventilator settings during the first 4 days (VT, PEEP, respiratory system compliance, driving pressure) Others: Ventilator-free days at day 28, duration of ventilation, ICU and hospital length of stay, 28-day mortality, 29-day mortality
Udi 2020 Case-control study	COVID-19 patients on mechanical ventilation with ARDS (Berlin definition) treated at a medical ICU Germany	Mechanical ventilator settings in the last 24 hours prior to barotrauma	-	Incidence of barotrauma / VILI defined as presence of pneumothorax, pneumomediastinum or pneumopericardium in the absence of preceding intervention with risk of pulmonary complications
Walkey SR of 9 RCTs	Adult patients with ARDS	Volume-limited strategy (VT 4-8 mL/kg)	Traditional methods of ventilation (VT 10-15 mL/kg)	Primary: Mortality within 28 days Secondary: New organ failures, ventilator-free days, barotrauma,
Briel 2010 IPDMA of 3 RCTs	Critically ill patients > 16 years with ALI or ARDS (American-European Consensus definition) with TV < 8 mL/kg PBW	High PEEP	Low PEEP	Primary: Hospital mortality at 60 days Secondary: Death before ICU discharge, pneumothorax with need for chest tube drainage within 28 days, death following pneumothorax with need for chest tube drainage, time-to-unassisted breathing within the first 28 days, days with unassisted breathing between day 1 and day 28, use of rescue therapy, death following rescue therapy, use of neuromuscular blockers, vasopressors and corticosteroids
Romano 2020 RCT	ARDS patients with $\Delta P \geq 13$ cmH2O Brazil	Driving pressure-limited strategy (ΔP 10 cmH2O)	Volume-controlled or pressure-support mode with VT 6 mL/kg PBW and Pplat ≤ 30 cmH2O	Primary: ΔP on days 1-3 Secondary: Adherence to study procedures, rate of $\Delta P \leq 13$ cmH2O, rate of ventilation with VT within target, mean PEEP, mean VT, mean static compliance of the respiratory system, mean Pplat, mean ΔP, mean RR, death in the first 28 days, in-hospital death, ICU death, barotrauma within the first 7 days

Appendix 2: GRADE Evidence Profile

A. LUNG PROTECTIVE VENTILATION

Lung protective ventilation compared to non-volume-limited strategy for COVID-19-associated ARDS

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 non-volume limited streategy	With lung protective ventilation		Risk with non-volume limited strategy	Risk difference with lung protective ventilation
28-day mortality (direct)											
553 (1 observational study)	Serious [a]	Not serious	Not serious	Serious [b]	None	⨁◯◯◯ VERY LOW	In one study on adults with COVID-19-related ARDS, higher tidal volume was associated with the same or higher risk of 28-day mortality (**OR 1.28, 95% CI 1.00-1.64**).				
Ventilator-free days (direct)											
553 (1 observational study)	Serious [a]	Not serious	Not serious	Serious [b]	None	⨁◯◯◯ VERY LOW	In one study on adults with COVID-19-related ARDS, there was no significant difference in ventilator-free days (**MD 0.73 days less, 95% CI 1.52 days less to 0.06 days more**) in multivariable models .				
Ventilator-free days (indirect)											
1481 (7 RCTs)	Not serious	Not serious	Serious [c]	Serious [b]	None	⨁⨁◯◯ LOW	296/732 (40.4%)	252/749 (33.6%)	**RR 0.87** (0.70 to 1.08)	404 per 1,000	**53 fewer per 1,000** (from 121 fewer to 32 more)
Major bleeding											
977 (2 RCTs)	Not serious	Not serious	Serious [c]	Serious [b]	None	⨁⨁◯◯ LOW	487	490	-		MD **0.03 days lower** (5.88 lower to 5.95 higher)
Barotrauma (indirect)											
1029 (3 RCTs)	Not serious	Not serious	Serious [c]	Serious [b]	None	⨁⨁◯◯ LOW	55/513 (10.7%)	53/516 (10.3%)	**RR 0.96** (0.67 to 1.37)	107 per 1,000	**4 fewer per 1,000** (from 35 fewer to 40 more)

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

Explanations

[a] Downgraded for serious risk of bias (unable to determine baseline characteristics in each group, missing outcome data)

[b] Downgraded for imprecision (wide confidence interval)

[c] Downgraded for indirectness (non-COVID-19 population)

B. HIGHER PEEP WITH LTVV

Higher PEEP with LTVV compared to lower PEEP with LTVV for COVID-19 associated ARDS

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 lower PEEP with LTVV	With higher PEEP with LTVV		Risk with lower PEEP with LTVV	Risk difference with higher PEEP with LTVV
Hospital mortality (indirect)											
2299 (3 RCTs)	Not serious	Not serious	Serious [a]	Serious [b]	None	⨁⨁◯◯ LOW	409/1163 (35.2%)	374/1136 (32.9%)	**RR 0.94** (0.86 to 1.04)	352 per 1,000	**21 fewer per 1,000** (from 49 fewer to 14 more)
ICU mortality (indirect)											
2299 (3 RCTs)	Not serious	Not serious	Serious [a]	Not serious	None	⨁⨁⨁◯ MODERATE	381/1163 (32.8%)	324/1136 (28.5%)	**RR 0.87** (0.78 to 0.97)	328 per 1,000	**43 fewer per 1,000** (from 72 fewer to 10 fewer)
Pneumothorax (indirect)											
2299 (3 RCTs)	Not serious	Not serious	Serious [a]	Serious [b]	None	⨁⨁◯◯ LOW	75/1163 (6.4%)	87/1136 (7.7%)	**RR 1.19** (0.89 to 1.60)	64 per 1,000	**12 more per 1,000** (from 7 fewer to 39 more)
Ventilator-free days (indirect)											
2299 (3 RCTs)	Not serious	Not serious	Serious [a]	Serious [b]	None	⨁⨁◯◯ LOW	1163	1136	-	The median ventilator-free days (indirect) was **11** days	MD **0.64 days more** (0.12 fewer to 1.39 more)
Minor bleeding											
1793 (3 RCTs)	Serious[a]	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ Moderate	8/938 (0.9%)	30/855 (3.5%)	**RR 3.77** (1.76 to 8.09)	9 per 1,000	**24 more per 1,000** (from 6 more to 60 more)

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

Explanations

[a] Downgraded for indirectness (non-COVID-19 population)

[b] Downgraded for imprecision (wide confidence interval)

C. DRIVING PRESSURE

Driving pressure-limited ventilation compared to non-driving pressure-limited ventialtion for COVID-19-associated ARDS

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 non-driving pressure-limited ventialtion	With driving pressure-limited ventilation	Relative effect (95% CI)	Risk with non-driving pressure-limited ventialtion	Risk difference with driving pressure-limited ventilation
28-day mortality (indirect)											
31 (1 RCT)	Not serious	Not serious	Serious [a]	Serious [b]	None	⨁⨁◯◯ LOW	5/15 (33.3%)	7/16 (43.8%)	**RR 1.31** (0.53 to 3.25)	333 per 1,000	**103 more per 1,000** (from 157 fewer to 750 more)
In-hospital mortality (indirect)											
31 (1 RCT)	Not serious	Not serious	Serious [a]	Serious [b]	None	⨁⨁◯◯ LOW	8/15 (53.3%)	7/16 (43.8%)	**RR 0.82** (0.40 to 1.70)	533 per 1,000	**96 fewer per 1,000** (from 320 fewer to 373 more)
Barotrauma (indirect)											
31 (1 RCT)	Not serious	Not serious	Serious [a]	Serious [b]	None	⨁⨁◯◯ LOW	0/15 (0.0%)	1/16 (6.3%)	not estimable	0 per 1,000	
Ventilation-free days (indirect) (follow up: 28 days)											
31 (1 RCT)	Not serious	Not serious	Serious [a]	Serious [b]	None	⨁⨁◯◯ LOW	15	16	-	The median ventilation-free days (indirect) was **11** days	MD **1.5 days higher** (4.5 lower to 18.5 higher)
Hospital stay (indirect)											
31 (1 RCT)	Not serious	Not serious	Serious [a]	Serious [b]	None	⨁⨁◯◯ LOW	15	16	-	The median hospital stay (indirect) was **21.4** days	MD **2 days higher** (10.5 lower to 22.3 higher)

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

Explanations

[a] Downgraded for indirectness (non-COVID-19 population)

[b] Downgraded for imprecision (wide confidence interval)

Appendix 3. Forest Plot

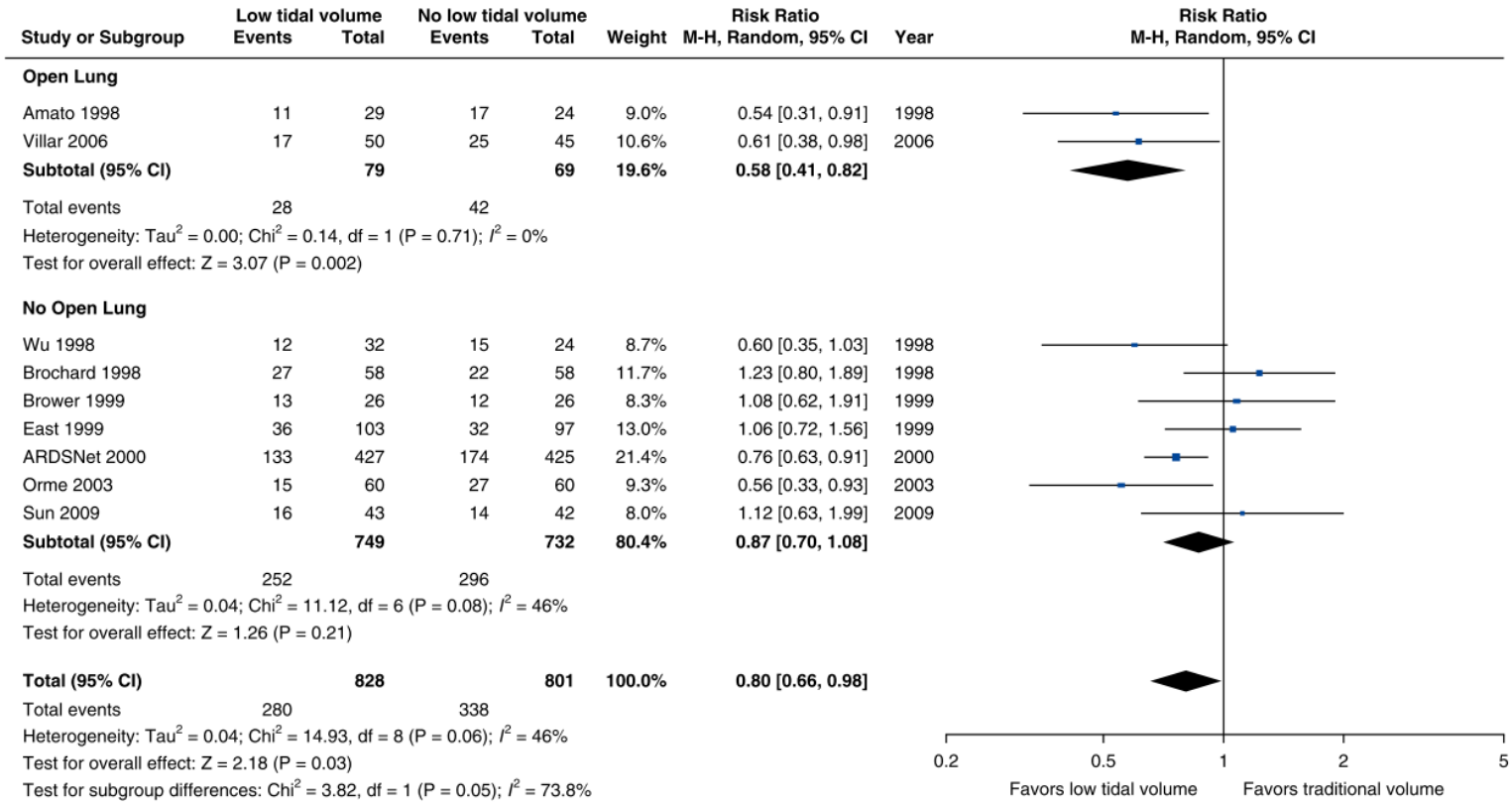

Figure 1. Forest plot for mortality comparing low tidal volume or pressure-limited ventilation strategy versus control (Adapted from Walkey 2017)

Appendix 4. Characteristics of Ongoing Studies

Study	Population / Setting	Intervention/s	Outcomes	Status [1]
NCT04497454 Mechanical Ventilation Strategy for Coronavirus Disease 2019 (COVID-19) - COVEN Study RCT	Patients 18 years and older on mechanical ventilation with ARDS (Berlin definition) caused by SARS-COV2 infection: Brazil	EIT-Group (Pressure-controlled ventilation with maintain driving pressure < 16 cmH2O) vs. ARDSNet protocol (Volume-controlled ventilation)	Average daily Modified Lung injury score until day 28 High oxygen dependence free days until day 28 [Time Frame: 28 days] Mechanical ventilation free days until day 28 [Time Frame: 28 days] Incidence of shock or barotrauma [Time Frame: 28 days] Incidence of acute renal failure requiring renal replacement therapy [Time Frame: 28 days] 28-day mortality [Time Frame: 28 days]	Recruiting Estimated study completion: December 1, 2021
Transpulmonary Driving Pressure in ARDS COVID19 Patients / TRANSPULMONARY-COVID19 Prospective cohort	Patients 18-90 years old with SARS-CoV-2 and mechanical ventilation requirement France	Transpulmonary pressure	Duration of mechanical Ventilation Number of Participants with during of Acute respiratory distress syndrome [Time Frame: 1 day] Length of stay in intensive care unit [Time Frame: 1 day] Mortality [Time Frame: 1 day] number of patients with pulmonary complications [Time Frame: 1 day] Number of Participants with pulmonary stress and strain [Time Frame: 1 day]	Estimated study completion: December 31, 2021
CTRI/2020/05/025071 Driving pressure guided positive end expiratory pressure (PEEP) strategy Vs physician guided PEEP (ARDSnet protocol) in mechanical ventilation for Acute respiratory distress syndrome (ARDS) in COVID-19 patients: a prospective randomised controlled trial RCT	All adult patients > 16 years of age of either sex fulfilling WHO case definition of COVID-19 positive with ARDS (Berlin Criteria) needing invasive mechanical ventilation India	Lowest driving pressure-guided PEEP vs. Conventional lung protective ventilation strategy (ARDSnet protocol)	Difference in the area under the curve (adjusted to survival time) for Murray's lung injury score between the two groups in the first 4 days. Difference in following parameters between the two groups- PaO2/FiO2 (P/F) ratio pH, pCO2, base excess, lactate Plateau pressure, static compliance SOFA score Vasopressor requirement Need for sedation and neuromuscular blockade Reintubation Rates Number of days of ventilation and number of ventilator free days Number of ICU days and number of ICU free days Incidence of pneumothorax Mortality at day 7, day 14 and day 28.	Not yet recruiting

Q10. Should rapid sequence intubation or delayed sequence intubation be used for the management of COVID-19?

As of 19 Fberuary 2021

RECOMMENDATION

We suggest the use of rapid sequence intubation for COVID-19 patients to reduce infection among healthcare workers performing the procedure *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues

There is no direct comparison between rapid sequence intubation (RSI) and delayed sequence intubation (DSI). RSI does not pertain to the timing of intubation but rather it pertains to the sequence of events.

RSI helps prevent the aerosolization of COVID-19 particles and is safer for the healthcare workers performing RSI. RSI is done rapidly and prevents further deterioration of patients who are in need of oxygen supplementation. However, there is a potential to develop hypoxemia among patients who have undergone RSI. RSI is commonly done locally except in patients with collapsed airways. Depending on the condition, RSI may be modified to suit the patients' needs. On the other hand, delayed sequence intubation (DSI) is generally much safer for patients because it ensures that the procedure is not conducted haphazardly (patients are pre-oxygenated and sedatives and neuromuscular blockers are administered). In addition, RSI is also recommended by the other societies except for agitated patients. Additional costs for anesthesia must be considered in performing RSI.

KEY FINDINGS

There were no studies directly comparing rapid sequence intubation (RSI) and delayed sequence intubation (DSI). For each modality, there were very low quality evidence, which had limitations in study design and indirectness. Both RSI and DSI improved the post-intubation oxygen saturations of the patients. The study on RSI reported that 10.4% of the patients died within 24 hours of intubation. On the other hand, the study on DSI reported no deaths within an unspecified time period. The study on RSI reported cardiac arrest in 2% of the patients and pneumothorax in 5.9% of the patients post intubation. Conversely, the study on DSI reported that none of the patients had cardiac arrest post intubation within an unspecified time period. The study on RSI reported that there was no evidence of cross infection in the anesthesiologists who intubated the COVID-19 patients.

INTRODUCTION

The study by Weissman et al., concluded that among the aerosol-generating procedures, performing endotracheal intubation is especially hazardous. The said study included a systematic literature review and meta-analysis that evaluated transmission of SARS coronavirus 1 (SARS-CoV-1) to health care personnel in association with exposure to aerosol-generating procedures such as bag ventilation. This meta-analysis found a significantly increased odds ratio of 6.6 in the exposed group. [1] On the other hand, the study by El-Boghdadly reported that 10.7% of clinicians in the study reported subsequent confirmed COVID-19 diagnosis or development of symptoms requiring a period of self-isolation following intubation of a

patient with known or suspected COVID-19 infection. Additionally, multivariate analysis in the study showed no significant association between intubation techniques or other demographic characteristics. [2]

In patients with COVID-19 disease, there is also a high risk of aerosol spread of the virus during airway management procedures. Rapid sequence intubation (RSI) involves pre-oxygenating and rapidly rendering the patients unconscious to facilitate emergency endotracheal intubation. This avoids the use of mask ventilation and thereby minimizes the risk for aerosol formation during intubation. Because of the reduced risk of aerosol formation, this method of intubation has been recommended by most groups [3].

However, patients presenting with acute respiratory failure due to COVID-19 can be agitated and uncooperative due to hypoxia, making adequate preoxygenation very challenging. For this group of patients, delayed sequence intubation (DSI) technique, which consists of the administration of sedatives that preserve spontaneous ventilation in order to provide preoxygenation, has been a valuable technique [3].

REVIEW METHODS

The authors searched for articles using PubMed, Medrxiv, Cochrane Library, UptoDate, and free search using the keywords: Rapid Sequence Intubation OR Delayed Sequence Intubation OR Intubation AND COVID-19 (search limit up to March 8, 2021). The authors included studies that investigated the effects of rapid sequence intubation versus delayed sequence intubation . There were no restrictions on age, sex, race and co-morbidities. The authors excluded studies that investigated the effects of early and delayed intubation and studies that investigated the effects of using a barrier box

RESULTS

Characteristics of Included Studies

The comprehensive literature search yielded 11 studies, to which 9 studies were excluded. A retrospective observational case series [4] of 202 COVID-19 patients provided direct evidence on RSI. Before tracheal intubation, most patients showed hypoxemia, tachypnea, hypotension, tachycardia, and unconsciousness. These patients underwent modified RSI. Outcomes investigated include succes rates of intubation, mortality rate and adverse events.

The other study, a case series, provided indirect evidence on DSI. 62 non-COVID adult patients with altered mental status were included, who were not predicted by clinicians to have an anatomically difficult airway requiring awake intubation. Delayed sequence intubation was performed on patients who remained uncooperative after maximal attempts of traditional means of preoxygenation. Outcomes investigated include mortality rate, oxygen saturations pre and post intubation and adverse events [5].

Overall summary of Methodological Quality

Both studies [4,5] had serious risk of bias due to very low sample size and lack of comparison group to establish the efficacy of the mode of intubation. The study by Weingart et al is also considered as indirect evidence for DSI in COVID-19 [5], and had unclear duration of follow-up. All these downgrade the quality of evidence to very low.

Summary of Results of Included Studies
No studies were found that directly compared the outcomes of RSI vs DSI. However, there were two studies that measured the effects of RSI and DSI separately. The difference in the population could have influenced the estimates in the studies.

Oxygen Saturations
The study on RSI reported a decrease in the number of hypoxemic patients before and after intubation. Before intubation, 152/202 (75.2%) had hypoxemia while 36/202 (17.82%) had hypoxemia post intubation. [4] On the other hand, the study on DSI reported a mean increase of 8.9% (95% CI 6.4%- 10.9%) in the oxygen saturation after the patients were intubated. Additionally, the authors reported that only 2/62 had a decreased post-intubation oxygen saturation. [5]

Mortality Rates
The study on RSI reported that 21/201 of the patients (10.4%) died within 24 h after rapid sequence intubation. [4] On the other hand, the study on DSI reported 0/62 deaths after delayed sequence intubation. However, the time period for mortality rate on the study on DSI was not explicitly stated. [5]

Serious adverse effects
The study on RSI reported that 4/202 (2%) had cardiac arrest post-intubation but all four patients were successfully resuscitated. Additionally, they also reported that 12/202 (5.9%) of the patients had pneumothorax post-intubation. [4] On the other hand, the study on DSI reported that none (0/62) of the patients had cardiac arrest post-intubation. Again, the time period for this outcome was not explicitly stated. [5]

Success rates
The study on RSI reported first time and overall intubation success rates were 89% and 100%, respectively. It is worth noting that the intubators were all anesthesiologists which could have contributed to the high success rates. [4] The study on DSI did not include success rates of intubation

Infection rates
The study on RSI reported that none of the anesthesiologists developed COVID-19 infection 14 days after the procedure. It is important to note that all the anesthesiologists wore at least a level 3 PPE which could have also minimized the risk of infection. After confirmed negative PCR test results, the anesthesiologists were cleared to return to work in the hospital again for the next 14-day duty shift. [4] The study on DSI did not investigate the infection rates following the procedure

RECOMMENDATIONS FROM OTHER GROUPS

The expert panel of airway management in Chinese Society of Anaesthesiology, experts from Departments of Anesthesiology and Pain Medicine and Physiology in Ontario, Canada and the Difficult Airway Society, the Association of Anaesthetists the Intensive Care Society, the Faculty of Intensive Care Medicine and the Royal College of Anaesthetists all recommend the use of RSI [6,7,8]. Furthermore, the Chinese Society of Anaesthesiology specifically recommended modified RSI [6]. Common modifications of RSI in practice include but not limited to the following: omitting the placement of an esophageal tube; supine positioning; titrating the dose of induction agent; use of propofol, ketamine, midazolam or etomidate to induce anesthesia; use

of high dose rocuronium as a neuromuscular blocking agent and omitting cricoid pressure. However, the exact modification was not explicitly stated by the Chinese Society of Anaesthesiology. On the other hand, the experts from Departments of Anesthesiology and Pain Medicine and Physiology recommend modified RSI if the patient has very high alveolar–arterial gradient and is unable to tolerate 30 seconds of apnea or has a contraindication to a neuromuscular-blocking drug [7].

The Difficult Airway Society, the Association of Anaesthetists the Intensive Care Society, the Faculty of Intensive Care Medicine and the Royal College of Anaesthetists suggest the use DSI for agitated patients [8].

RESEARCH GAPS

Currently, there are no ongoing studies investigating the effects of RSI and DSI listed in the NIH- U.S NLM's *ClinicalTrials.gov* and Cochrane Library.

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Appendix 1. Characteristics of Included Studies

First Author- Year- Site	Type of Study	Characteristics of population	Intervention	Comparator	Outcome
Yao, Wenlong 2020 China	Retrospective observational case series	202 COVID-19 patients confirmed via RT-PCR,testing for viral ribonucleic acid in respiratory samples, in combination with chest CT findings. Patients were predominantly males (67%) and aged 65 yr or more (63%). Forty-five (22%) patients had a predicted anatomically difficult airway, and all patients were anticipated to have physiologically difficult airway as a result of severe hypoxaemia.	Modified Rapid Sequence Intubation	None	Overall intubation success, adverse events during intubation, physical status after intubation, ventilation and adverse events including all cause mortality rate and incidence of pneumothorax
Weingart, Scott 2015 United States and Denmark	Prospective observational study	62 Patients were undergoing emergency airway management. Patients were aged 18 years or older, spontaneously breathing, and not predicted by clinicians to have an anatomically difficult airway requiring awake intubation. Delayed sequence intubation was performed on patients who remained uncooperative after maximal attempts of traditional means of preoxygenation.	Delayed Sequence Intubation	None	The primary outcome was the difference in oxygen saturations after maximal attempts at preoxygenation before delayed sequence intubation compared with saturations just before intubation. Secondary outcomes included the number of patients with pre–delayed sequence intubation saturations likely to progress to critical desaturation and their post–delayed sequence intubation saturations, the number of successful nasogastric tube placements in patients who would not tolerate attempts at this procedure during their pre-intubation preparations, and the number of successful denitrogenations Complications were also evaluated including pre–muscle relaxant apnea, peri-intubation emesis, and peri-intubation cardiac arrest or mortality (within 3 hours of intubation).

Appendix 2. GRADE Evidence Profile

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rapid sequence intubation		Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	Observational studies	Serious [a]	Not serious	Not serious	Not serious	None	21/202 (10.4%)				⊕◯◯◯ Very Low	
Hypoxemia during intubation												
1	Observational studies	Serious [a]	Not serious	Not serious	Not serious	None	175/202 (86.6%)				⊕◯◯◯ Very Low	
Hypotension during intubation												
1	Observational studies	Serious [a]	Not serious	Not serious	Not serious	None	36/202 (17.8%)				⊕◯◯◯ Very Low	
Cardiac arrest post-intubation												
1	Observational studies	Serious [a]	Not serious	Not serious	Not serious	None	4/202 (2.0%)				⊕◯◯◯ Very Low	
Pneumothorax post-intubation												
1	Observational studies	Serious [a]	Not serious	Not serious	Not serious	None	12/202 (5.9%)				⊕◯◯◯ Very Low	

CI: confidence interval

Explanation:
[a] low sample size and lack of comparison group to establish the efficacy of the mode of intubation

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Delayed sequence intubation	-	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	Observational studies	Very serious [a]	Not serious	Serious [b]	Not serious	None	0/62 (0.0%)	0/0	Not estimable		⊕◯◯◯ Very Low	
Oxygen Desaturations Post-intubation												
1	Observational studies	Very serious [a]	Not serious	Serious [b]	Not serious	None	2/62 (3.2%)	0/0	Not estimable		⊕◯◯◯ Very Low	
Cardiac Arrest												
1	Observational studies	Very serious [a]	Not serious	Serious [b]	Not serious	None	0/62 (0.0%)	0/0	Not estimable		⊕◯◯◯ Very Low	

CI: confidence interval

Explanation:
[a] very low sample size and lack of comparison group to establish the efficacy of the mode of intubation
[b] population does not include COVID-19 patients

Q11. Should extracorporeal membrane oxygenation (ECMO) be used in the management of Acute Respiratory Distress Syndrome (ARDS) among COVID-19 patients?

As of 03 January 2022

RECOMMENDATION

We suggest the use of Extracorporeal Membrane Oxygenation (ECMO) for judiciously selected COVID-19 patients with severe Acute Respiratory Distress Syndrome (ARDS) based on the ELSO criteria. *(Very low certainty of evidence; Weak recommendation)*

PREVIOUS RECOMMENDATION

We suggest the use of VV-ECMO for judiciously selected COVID-19 patients with severe ARDS based on the ELSO criteria *(Very low quality of evidence; Conditional recommendation)*

Consensus Issues

VV-ECMO is not indicated for all severe COVID-19 patients with ARDS. The general guidelines for the use of ECMO among non-COVID patients must be followed given that there are no guidelines for the use of ECMO among patients with COVID-19. Likewise, standard selection criteria, indications and contraindications should be followed in recommending the use of ECMO. The protocol for the treatment of severe ARDS must be followed. VV-ECMO is used once other modalities (e.g., proning, mechanical ventilation and lung protective strategies) did not work and the patients are qualified for ECMO.

There is a limited number of ECMO machines that are locally available. In addition, manipulation of this machine requires manpower, training and additional medical equipment. The use of ECMO must be judicious due to the considerable concern on the high cost and local availability of ECMO. ECMO is also used for the treatment of ARDS caused by leptospirosis and cytokine adsorption among COVID patients. The use of ECMO is included in the COVID fund and it costs around Php 2,000,000.00 per day, however, the costs are not fully covered. The results of ongoing trials are needed to show that the use of ECMO is effective and safe among patients with COVID-19 infection.

WHAT'S NEW IN THIS VERSION?

Four cohort studies on the use of extracorporeal membrane oxygenation (ECMO) among patients with critical COVID-19 or COVID-19 acute respiratory distress syndrome (ARDS) were included in this review update.

KEY FINDINGS

Four cohort studies on the use of ECMO in adult patients with critical COVID-19 or COVID-19 ARDS were reviewed in this evidence update. Pooled results from four studies showed inconclusive mortality benefit with the use ECMO versus standard of care. In one study, occurrence of procedure-related infection reported as a serious adverse event was significantly associated with ECMO therapy. The certainty of evidence is very low because of the risk of bias attributed to lack of randomized

studies, inconsistency due to significant heterogeneity, and imprecision due to small study sample sizes.

INTRODUCTION

In patients with COVID-19 acute respiratory distress syndrome (ARDS), severe hypoxemia complicated by respiratory or circulatory failure may persist despite optimal mechanical ventilation strategies.[1] Extracorporeal Membrane Oxygenation (ECMO) is indicated for patients with acute severe cardiac or respiratory failure with high mortality risk.[2] Initiation of ECMO in cases of COVID-19 ARDS refractory to mechanical ventilation and salvage therapy (such as prone positioning or nitric oxide) may lead to improvement in oxygenation and decrease in mechanical power through a homogeneous ultraprotective ventilation strategy.[3,4] Current practice takes into consideration referring patients with COVID-19 ARDS refractory to lung-protective ventilation for ECMO initiation. However, several practical concerns such as institutional ECMO capability, trained personnel availability, and costs should be considered prior to its initiation. Latest guidance from Philippine COVID-19 Living Clinical Practice Guidelines suggested the use of ECMO for judiciously selected COVID-19 patients with severe ARDS based on very low certainty of evidence. Given the evidence gap and local resource limitations on the use of ECMO, this review aims to update and summarize current literature on outcomes associated with the use of ECMO among COVID-19 patients with severe ARDS.

REVIEW METHODS

An exhaustive literature search was conducted in PUBMED, Cochrane Library, clinicaltrials.gov and MedRxiv (for pre-print articles) databases for articles relating to the use of ECMO in patients with COVID-19. The following keywords were used in the search: “extracorporeal membrane oxygenation”, “acute respiratory distress syndrome”, “COVID-19” and “cohort”. No restrictions were applied as to the language or date of publication. The retrieved titles and abstracts were screened for possible inclusion. Studies which determined the use of ECMO on COVID-19 ARDS or critical COVID-19 and its outcomes in terms of mortality and/or adverse events were retrieved for full-text review. Irrelevant studies which did not address the PICO question, case reports, case series, systematic reviews, and commentary articles were excluded. Four full-text articles were reviewed and included in the qualitative and quantitative analysis. The PRISMA Flow Diagram [5] is shown in Figure 1 (see Appendix 2). The quality of the included studies was evaluated based on the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort Studies.[6]

RESULTS

Four cohort studies compared a total of 1,301 adult patients with critical COVID-19 and COVID-19 ARDS who received ECMO and standard of care with 16,548 adult patients with critical COVID-19 and COVID-19 ARDS who received standard of care alone without ECMO therapy [7-10]. In three studies [7-9], venovenous ECMO (VV-ECMO) was used. In one study, [10] the type of ECMO therapy used was not explicitly specified. The studies were done in China [7,8] and the USA [9,10]. Characteristics of included studies are presented in detail in Table 2 (see Appendix 3). The general methodological quality of the included studies was assessed to be of good quality based on the NHLBI quality assessment tools.

All-Cause Mortality

Pooled analysis from four cohort studies [7-10] showed inconclusive reduction in all-cause mortality with the use of ECMO (RR 0.70, 95% CI 0.47-1.07; I2=95%; very low certainty). In two studies [7,10], younger age was found to have lower mortality rates. The cohort study by Cheng and coworkers [7] demonstrated that in-hospital mortality among patients with critical COVID-19 placed on ECMO was significantly lower compared to patients who were not placed on ECMO and received standard of care (RR 0.84, 95% CI 0.71-0.99; low certainty). In this study, patients who were placed on ECMO were significantly younger compared to those who did not receive ECMO (58 versus 66 years old, p<0.003). Similarly, the cohort study by Nguyen and colleagues [10] reported that in-hospital mortality was found to increase with age. Patients under 30 years old who received ECMO had the lowest in-hospital mortality (34/125, 25.2%). In-hospital mortality rates were higher in the 31-50 (232/550, 42.2%) and 51-64 (234/440, 53.2%) age groups. Patients aged 65 years old and above had the highest in-hospital mortality rate (42/57, 73.7%).

Other Outcomes: Length of Hospital Stay, & Direct Cost

The mean length of stay was longer for ECMO (37.1±24.9 days) versus the non-ECMO (23.1 ±18.8 days) group (MD 14.0 days, 95% CI 12.51-15.49; low certainty). Direct hospitalization cost was likewise higher in the ECMO group ($138,403 ±99,173) compared to the non-ECMO ($48,419 ± 44,799) group (MD $89,984.00, 95% CI $84,117.34-95,850.66; low certainty).[10]

Adverse Events

In the study by Cheng et al. [7], the presence of bacterial co-infections was observed in 34/74 patients (45.9%) compared to 26/94 patients (27.7%) among those who received ECMO and those who received standard of care, respectively (RR 1.66, 95% CI 1.10-2.50; very low certainty).[7] On the other hand, Li et al. [8] reported that of the 34 patients with COVID-19 who were placed on ECMO, bleeding at different sites (intracranial, gastrointestinal, pulmonary or airway) was observed in 26/34 patients (76.4%), infections in eight patients, and pneumothorax in four cases. The study did not provide a comparison of the adverse events for the non-ECMO group.

Summary of Certainty of Evidence

The GRADE evidence profile is shown in Appendix 4. The certainty of evidence was very low because of the risk of bias attributed to non-randomized study designs, inconsistency due to significant heterogeneity, and imprecision. Significant heterogeneity may be attributed to several clinical factors such as patients' age, duration of ECMO therapy, duration of mechanical ventilation prior to ECMO initiation, differences in institutional ECMO protocols, and co-interventions (see Appendix 5).

At present, a nationwide cohort study on the use of ECMO as a therapeutic option in severe COVID-19 is being conducted in France [11]. The characteristics of this study are shown in Table 3 (see Appendix 6). No ongoing clinical trials were identified at the time of this review.

EVIDENCE TO DECISION

In dedicated ECMO referral institutions, patients with severe COVID-19 ARDS who are not clinically responding to optimal lung protective ventilation may safely be initiated on ECMO.[4] However, hospital capability should be considered prior to

ECMO initiation.[12] Cost of ECMO initiation and daily use should also be considered. The average direct cost for adult COVID-19 patients who were managed with ECMO therapy was $138,403.00.[10] Thus, practical considerations should include the availability and capacity of medical centers equipped with facilities and specialized personnel or teams for ECMO and the financial limitations for patients and their families.

RECOMMENDATIONS FROM OTHER GROUPS

According to the Extracorporeal Life Support Organization (ELSO) guidelines for ECMO use in COVID-19, contraindications for ECMO use should become more stringent as ECMO capacity diminishes. Based on the ELSO guidelines, ECMO should not be initiated for patients with end-stage chronic organ failure without anticipated recovery and who are not candidates for durable device or transplant, in severe acute multiple organ failure with anticipated death despite ECMO support, and in severe acute neurologic injury with poor prognosis for recovery. Potential additional contraindications also include long invasive mechanical duration of more than 10 days, patient or surrogate refusal of blood products, inability to receive systemic anticoagulation, ongoing cardiopulmonary resuscitation, significant underlying comorbidities, advanced age, and immunocompromised condition." [12]

The World Health Organization (WHO) living guidance on COVID-19 recommended that in settings with adequate ECMO resources and expertise, a consideration of referring patients with refractory hypoxemia for initiation of ECMO should be made.[13]

The Australian guidelines on COVID-19 gave a conditional recommendation on the use of ECMO for adult patients with critical COVID-19. The decision regarding ECMO initiation should consider the preferences and values of the patients as well as the benefits and risks associated with this form of invasive and resource-intensive treatment [14].

RESEARCH GAPS

Presently, there are no randomized controlled trials on the use of ECMO for patients with critical COVID-19. There is also a lack of evidence on long-term clinical outcomes, including pulmonary function, of patients who were successfully discharged after ECMO therapy.

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Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					• Initiation of ECMO in cases of COVID-19 ARDS refractory to mechanical ventilation and salvage therapy may lead to improvement in oxygenation.
Benefits	Large (1)	Moderate (2)	Small (1)	Uncertain (1)			• Reduction in all-cause mortality (RR 0.70; 95% CI 0.47, 1.07; I2=95%; Very Low Certainty)
Harm	Large (2)	Small (1)	Uncertain (2)	No response			• The presence of bacterial co-infections was observed in 34/74 patients (45.9%) compared to 26/94 patients (27.7%) who received ECMO and those who received standard of care, respectively (RR1.66, 95% CI 1.10, 2.50) Cheng et al. [7]
Certainty of Evidence	High	Moderate	Low (2)	Very low (3)			• Very low: risk of bias attributed to lack of randomized studies, inconsistency due to significant heterogeneity, and imprecision due to small study sample sizes.
Balance of effects	Favors drug (5)	Does not favor drug	Uncertain				
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	• Direct hospitalization cost was higher in the ECMO group ($138,403 ±99,173) compared to the non-ECMO ($48,419 ± 44,799) group (MD $89,984.00; 95% CI $84,117.34,95,850.66; Low Certainty) [10]
Certainty of evidence of required resources	No included studies	Very low (1)	Low (3)	Moderate (1)	High		
Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (1)	Reduced (2)	Probably no impact	Increased (2)			
Acceptability	Uncertain (2)	No	Yes (3)				
Feasibility	Uncertain (5)	No	Yes				

Appendix 2. Search Yield and Results

SEARCH Strategy for Extracorporeal Membrane Oxygenation in COVID-19
Date of Last Search: 09 November 00:38H

Search	Query	Results	Time
#8	Search: **((extracorporeal membrane oxygenation) AND ((COVID-19) OR (SARS-CoV-2))) AND (cohort)** ("extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields]) AND ("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])) AND ("cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields] OR "cohort s"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields]) **Translations** **extracorporeal membrane oxygenation:** "extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] **COVID-19:** ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT])) **SARS-CoV-2:** "sars-cov-2"[MeSH Terms] OR "sars-cov-2"[All Fields] OR "sarscov 2"[All Fields] **cohort:** "cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields] OR "cohort's"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields]	253	10:59:09
#7	Search: **cohort** "cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields] OR "cohort s"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields] **Translations** **cohort:** "cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields] OR "cohort's"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields]	2,553,504	10:36:23
#5	Search: **(extracorporeal membrane oxygenation) AND ((COVID-19) OR (SARS-CoV-2))** ("extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields]) AND ("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])) **Translations** **extracorporeal membrane oxygenation:** "extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] **COVID-19:** ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-	1,019	10:36:09

	cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT])) **SARS-CoV-2:** "sars-cov-2"[MeSH Terms] OR "sars-cov-2"[All Fields] OR "sarscov 2"[All Fields]		
#6	Search: **(extracorporeal membrane oxygenation) AND ((COVID-19) OR (SARS-CoV-2))** Filters: **Randomized Controlled Trial** (("extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields]) AND ("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])))) AND (randomizedcontrolledtrial[Filter]) **Translations** **extracorporeal membrane oxygenation:** "extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] **COVID-19:** ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT])) **SARS-CoV-2:** "sars-cov-2"[MeSH Terms] OR "sars-cov-2"[All Fields] OR "sarscov 2"[All Fields]	10	10:36:06
#4	Search: **(COVID-19) OR (SARS-CoV-2)** "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]) **Translations** **COVID-19:** ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT])) **SARS-CoV-2:** "sars-cov-2"[MeSH Terms] OR "sars-cov-2"[All Fields] OR "sarscov 2"[All Fields]	194,768	10:34:58
#3	Search: **SARS-CoV-2** "sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[All Fields] **Translations** **SARS-CoV-2:** "sars-cov-2"[MeSH Terms] OR "sars-cov-2"[All Fields] OR "sarscov 2"[All Fields]	121,387	10:34:50
#2	Search: **COVID-19** "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]) **Translations** **COVID-19:** ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19	194,745	10:34:42

	Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT]))		
#1	Search: **extracorporeal membrane oxygenation** "extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] **Translations** **extracorporeal membrane oxygenation:** "extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields]	18,102	10:34:31

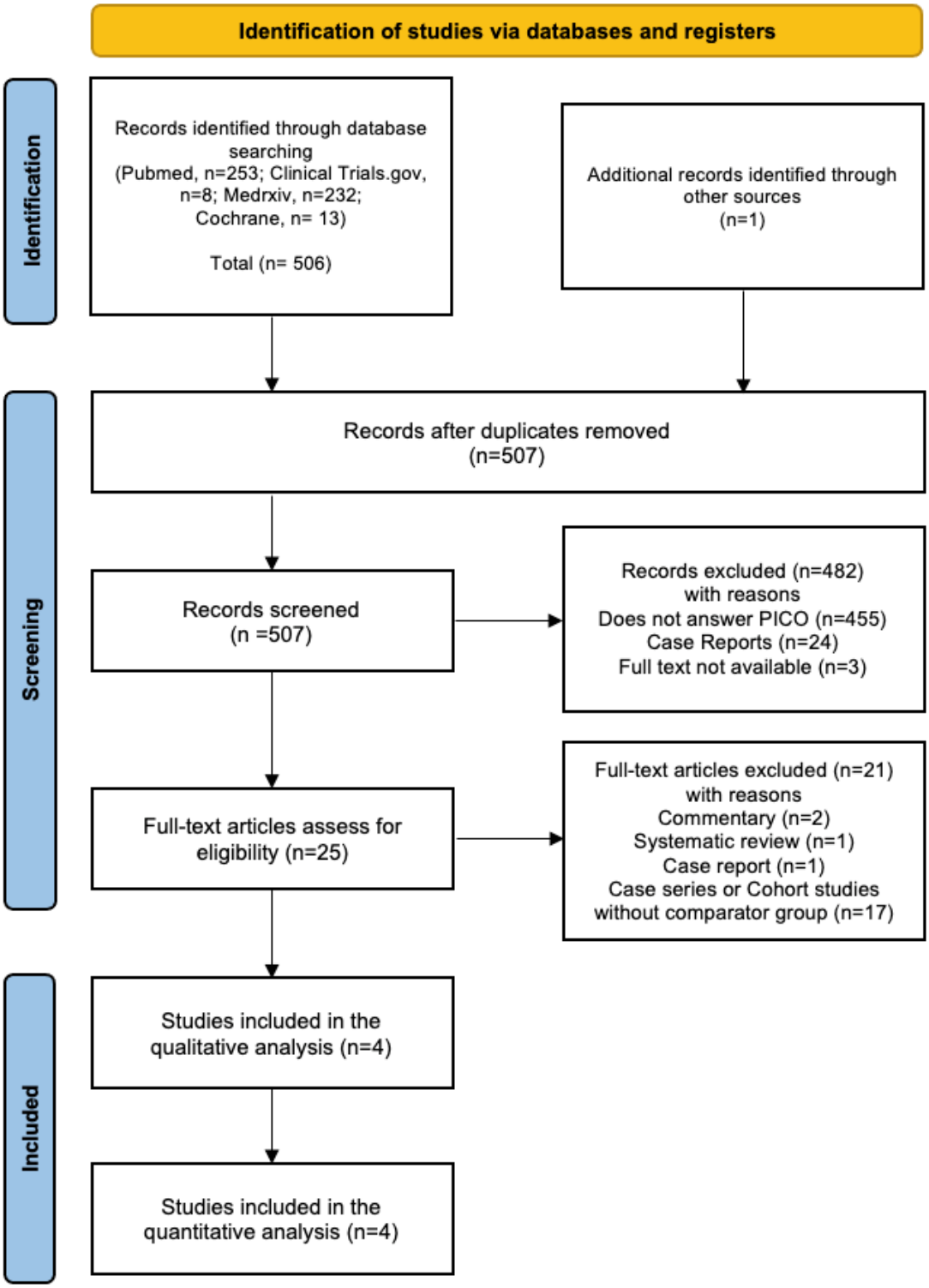

Figure 1. PRISMA Flow Diagram

Appendix 3. Characteristics of Included Studies

Table 2. Study Characteristics of Included Studies (n=21)

Study ID Title Author	Study Design	Setting/ Country	Population	Intervention	Comparator/ Control	Outcomes
Cheng 2021 [7]	Retrospective Cohort	Wuhan, China	Patients with critical COVID-19	VV ECMO (n=74)	Standard of Care + No ECMO (n=94)	**Mortality** In-hospital mortality ECMO=53/74 (71.6%) Non-ECMO=80/94 (85.1%) **Length of Stay** Length of Hospital Stay ECMO=32 (16-45) days Non-ECMO= 21.5 (12-34) Length of ICU stay ECMO=21 (12.75-33) Non-ECMO=15 (5-30) **Adverse events** Co-Infection ECMO=34/74 Non-ECMO=26/94 RR=1.4530 95% CI 0.9362, 2.2549 P=0.0957
Li 2021 [8]	Retrospective Cohort	Wuhan, China	patients with critical COVID-19	VV ECMO (n=34)	Conventional Ventilatory Support (n=31)	**Mortality** In-hospital mortality ECMO=20/34 (58.8%) Non-ECMO=29/31 (93.5%
Mustafa 2021 [9]	Prospective Cohort with Propensity-Matching	Illinois, USA	Patients with Critical COVID-19	VV ECMO(n=80)	Maximum Ventilatory Alone (MVA; n=80)	**Mortality** Overall mortality ECMO=20/80 (25%) MVA=59/80 (93.5%) Discharged alive ECMO=54/80 (67.5%) MVA=21/80 (26.3%)
Nguyen 2021 [10]	Retrospective Cohort	California, USA	Patients with COVID-19 ARDS	ECMO (n=1113)	Standard of Care + No ECMO (n=16,343)	**Mortality** In-hospital mortality ECMO=497/1113 (44.7%) No ECMO=6191/16,343 (37.9%) **Length of Hospital Stay** Mean Hospital LOS ECMO=37.1±24.9 Non-ECMO=23.1±18.8 Cost ECMO=$138,403 ±99,173 No ECMO=$48,419 ± 44,799

Appendix 4. GRADE Evidence Profile

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECMO	SOC	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	Observational studies	Serious [a]	Serious[b]	Not serious	Serious[b]	None	590/1301 (45.3%)	6359/16548 (38.4%)	**RR 0.70** (0.47 to 1.07)	**115 fewer per 1,000** (from 204 fewer to 27 more)	⨁◯◯◯ Very low	CRITICAL
Mean Length of Stay												
1	Observational studies	Serious [a]	Not serious	Not serious	Not serious	None	1113	16343	-	MD **14 days higher** (12.51 higher to 15.49 higher)	⨁⨁◯◯ Low	CRITICAL
Direct Cost												
1	Observational studies	Serious [a]	Not serious	Not serious	Not serious	None	1113	16343	-	MD **89984 USD higher** (84117.34 higher to 95850.66 higher)	⨁⨁◯◯ Low	CRITICAL
Adverse Events: Bacterial Infection												
1	Observational studies	Serious [a]	Not serious	Not serious	Serious[c]	None	34/74 (45.9%)	26/94 (27.7%)	**RR 1.66** (1.10 to 2.50)	**183 more per 1,000** (from 28 more to 415 more)	⨁◯◯◯ Very low	CRITICAL

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

Explanations

[a] non-randomized studies

[b] significant heterogeneity

[c] small sample sizes / optimal information size not met

Appendix 5. Forest Plot

Study or Subgroup	ECMO Events	ECMO Total	Standard of Care Events	Standard of Care Total	Weight	Risk Ratio M-H, Random, 95% CI
Cheng 2021	53	74	80	94	26.4%	0.84 [0.71, 0.99]
Li 2021	20	34	29	31	24.2%	0.63 [0.47, 0.85]
Mustafa 2021	20	80	59	80	21.9%	0.34 [0.23, 0.51]
Nguyen 2021	497	1113	6191	16343	27.4%	1.18 [1.10, 1.26]
Total (95% CI)		**1301**		**16548**	**100.0%**	**0.70 [0.47, 1.07]**
Total events	590		6359			

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 59.88$, df = 3 ($P < 0.00001$); $I^2 = 95\%$

Test for overall effect: Z = 1.65 (P = 0.10)

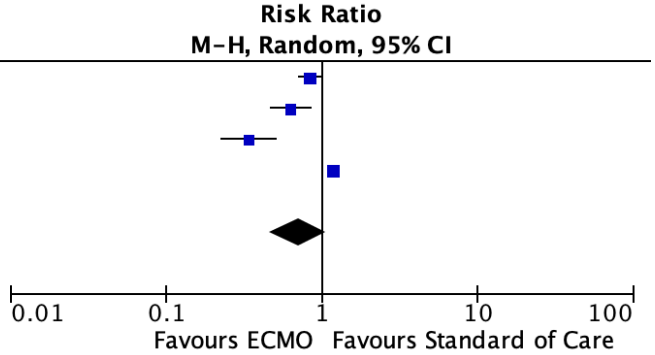

Figure 2. Forest Plot of Pooled Studies on Mortality among patients with COVID-19 who were placed on ECMO versus Standard of Care

Appendix 6. Study Characteristics of Ongoing Studies

Title Identifier Expected Completion Date	Intervention	Comparator/ Control	Patients/Population Recruited	Outcomes
Extracorporeal Membrane Oxygenation (ECMO) as a Therapeutic Option in Severe Form of COVID-19: a Nationwide Cohort Study France NCT04397588 [11] Ongoing recruitment	VV or VA ECMO	None	All COVID-19 patients, adults or children, Tested positive by RT-PCR for SARS-CoV2 (nasopharyngeal swabs, sputum, endotracheal aspiration, bronchoalveolar lavage or stool sample) and / or with a diagnosis made on chest CT findings, Supported by venovenous or venoarterial ECMO	Primary Outcome Measures : 1. Hospital mortality (Time Frame: up to 90 days) Secondary Outcome Measures : 1. Mortality Day 28 2. Mortality Day 90 3. Ventilator-free days 4. Intensive care unit-free days 5. Hospital-free days

Q12. Should hyperbaric oxygen therapy be used in COVID-19 patients with hypoxemia?

As of 01 December 2021

RECOMMENDATION

We suggest against the use of hyperbaric oxygen therapy for the management of COVID-19 patients with hypoxemia due to insufficient evidence. *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues

The potential for the use of hyperbaric oxygen therapy in COVID-19 is recognized based on some reported benefit and minimal harm. However, its large cost and limited availability are important factors to consider especially since the noted benefits are based on a singular trial with very low certainty of evidence. More clinical trials are thus needed before recommending its use in patients with COVID-19.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of hyperbaric oxygen therapy for the management of COVID-19 patients *(Very low quality of evidence)*

Consensus Issues

The high cost of hyperbaric oxygen therapy must be considered before recommending its use for the treatment of COVID-19 infection. There is also limited availability of hyperbaric oxygen therapy machines in the Philippines. Its use may applied in the context of a clinical trial. The results of ongoing studies are needed to show the use of hyperbaric oxygen therapy for the treatment of COVID-19 infection.

WHAT'S NEW IN THIS VERSION?

We included one new open-label randomized controlled trial which looked at mostly surrogate outcomes. There is still insufficient evidence to recommend use of Hyperbaric Oxygen Therapy (HBOT) in COVID-19 patients with hypoxemia.

KEY FINDINGS

Two interventional studies (non-randomized and randomized controlled trials) were included in this review update on the use of hyperbaric oxygen therapy (HBOT) among COVID-19 patients with hypoxemia. HBOT appears to have a tendency towards benefit in reducing need for mechanical ventilation (HR 0.26, 95% CI 0.07-0.98) and in increasing the proportion of patients successfully weaned from oxygen support (RR 6.33, 95% CI 2.15-18.62). The effects of HBOT on mortality, oxygen saturation, and clinical improvement scores were inconclusive given the wide confidence intervals. The intervention appears generally safe with only a few minor adverse events including claustrophobia (RR 1.60, 95% CI of 0.07-38.20) and ear pain (RR 4.81, 95% CI of 0.27-86.47) reported. The overall certainty of evidence was low because of non-randomization, imprecision, and presence of possible confounders.

INTRODUCTION

Hyperbaric oxygen therapy (HBOT) refers to modalities used to deliver intermittent supplemental oxygen in airtight vessels with controlled pressures of compressed air. The addition of high pressure allows the elevation in arterial oxygen tension beyond that which can be reached with conventional (i.e., normobaric) 100% oxygen supplementation alone. Apart from its direct effect on enhancing oxygen diffusion in hypoxic tissues, the high arterial oxygen tension is suggested to have indirect cell-signaling effects on the downregulation of inflammation.[1] For these reasons, the use of HBOT in COVID-19 has been investigated in clinical trials to counteract the hypoxemic and pro-inflammatory states seen in severe cases.[2]

REVIEW METHODS

A literature search was performed across PubMed, Scopus, WHO ICTRP, MedRxiv, and ClinicalTrials.gov on October 26, 2021, as an update to a previous search done on March 8, 2021. Included studies were those which investigated the use of hyperbaric oxygen therapy in COVID-19 patients requiring oxygen supplementation. Keywords used in the systemic search for relevant articles were “hyperbaric oxygenation”, hyperbaric oxygen therapy”, “HBOT”, “COVID-19”, “coronavirus disease”, and “SARS-CoV-2 infection”. Observational studies and review articles were excluded. Full search strategy is presented in Appendix 2.

RESULTS

The updated literature search yielded 78 new records after removal of duplicates. Screening of titles and abstracts followed by appraisal of individual full text articles resulted in the inclusion of one new trial. Compared to the previous non-randomized prospective trial included in the original review, the new study in this update provides better methodological quality as a randomized controlled trial.

The two studies included were both deemed to have serious risk for bias, the first for non-randomization and the other for having an open-label study design. Certainty of evidence was very low for the non-randomized trial by Gorenstein and colleagues [3] (n = 80) owing to wide confidence intervals leading to the inconclusive interpretation of results, and also since the results presented were still part of an interim analysis. Meanwhile, certainty of evidence for the randomized controlled trial by Petrikov and coworkers [4] (n = 90) was low due to lack of blinding and indirectness.

Only one study looked at mortality and need for ventilation.[3] Mortality was shown to be lower in the group which received HBOT (Perry/Baromed) 2.0 ATA for 90min daily for up to 5 sessions (2/20, 10%) compared to propensity-matched controls which received standard of care (16/60, 22%). After adjusting for possible confounders, the effect of HBOT on inpatient mortality appears inconclusive (HR 0.37, 95% CI 0.10-1.37). In the same trial, the need for mechanical ventilation was lower in the HBOT group (2/20, 10%) compared to the control group (18/60, 30%). Based on very low-quality evidence, HBOT appears to have a tendency towards benefit in terms of reducing need for mechanical ventilation (HR 0.26, 95% CI 0.07-0.98).

The other study [4] showed more patients being successfully weaned from respiratory support among those given intermittent sessions of HBOT (Sechrist 2800) 1.4-1.6 ATA for 40min a day (19/24, 79.2%) compared to those who received standard of care

alone (3/24, 12.5%).[4] HBOT appears to have definite benefit in terms of increasing the rate of weaning from respiratory support (RR 6.33, 95% CI 2.15-18.62) based on moderate certainty of evidence. In the same study, mean improvement in oxygen saturation measured at day 1 and day 14 was found to be significant in the HBOT group (MD 4.20, 95% CI 1.98-6.42) but not in the control group (MD 0.80, 95% -1.46-3.06). Comparing mean oxygen saturation at day 14 between HBOT and control, significant improvement was found only in the HBOT group (MD 2.70, 95% CI 0.72-4.68). Certainty of evidence for this outcome was assessed to be low because of indirectness as the analysis included both hypoxemic and non-hypoxemic patients. Analysis of clinical scores at baseline and after day 10 showed significant improvement in the HBOT group when compared to standard of care using the National Early Warning Score 2 (NEWS2) Score (MD -2.80, 95% CI -3.84 to -1.76) and the WHO Ordinal Scale for Clinical Improvement (OSCI) Score (MD -0.90, 95% CI -1.26 to -0.54) based on low certainty of evidence. Minor adverse events associated with HBOT included claustrophobia (RR 1.60, 95% CI 0.07-38.20) and ear pain (RR 4.81, 95% CI 0.27-86.47).[4]

EVIDENCE TO DECISION

Access to hyperbaric chamber therapy remains limited in the Philippines. Some institutions which offer outpatient sessions charge Php 1,500- 6,500 per session. Further well-powered studies may be needed to justify the cost of five to eight sessions of HBOT as therapy for COVID-19. Nevertheless, given the current published data on its efficacy and safety, it may be applied in the context of a clinical trial or for compassionate use.

RECOMMENDATIONS FROM OTHER GROUPS

There has been no follow up to the position statement released by Undersea and Hyperbaric Medical Society and American College of Hyperbaric Medicine which was last updated on August 22, 2020.[5] The said document did not give specific recommendations for or against the use of HBOT among patients with COVID-19, but rather advocated for well-designed clinical trials on the topic and encouraged well-documentation whenever it is used off-protocol. There are still no recommendations on the use of HBOT in COVID-19 treatment guidelines from the World Health Organization, United of States National Institutes of Health, and Infectious Disease Society of America to date.[6–8]

RESEARCH GAPS

Previous clinical trials on HBOT done among non-COVID patients have attempted sham treatment (i.e., being placed in an airtight container at 1.2 ATA) as control in an attempt to remove a possible placebo effect of being placed inside a chamber. Randomized clinical trials with hard outcomes such as mortality and need for mechanical ventilation are still ongoing. Since the initial review on this topic, three new trials have been registered, one study has been terminated, and one has been completed but with unreleased results. We currently await the results of ten clinical trials which may potentially change the consensus decision on the use of this therapy for COVID-19.

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Appendix 1. Evidence to Decision

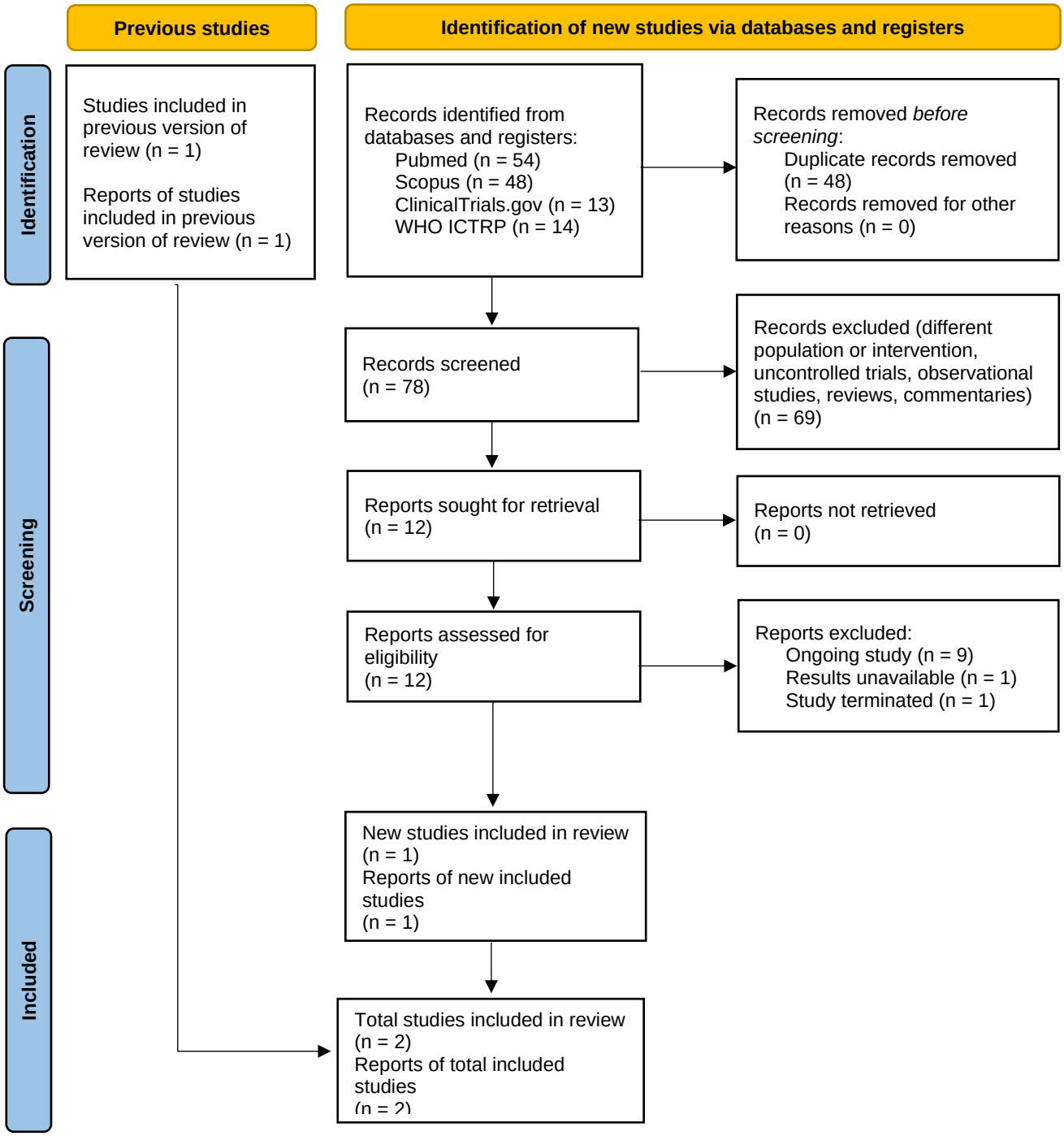
Table 1. Summary of initial judgements prior to the panel discussion (N=7)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					• Conventional respiratory support for patients with low oxygen saturation are effective in improving hypoxemia; but a number of patients still progress to need mechanical ventilation.
Benefits	Large (1)	Moderate (1)	Small (4)	Uncertain (1)			• HBOT appears to have significant benefit in terms of increasing rates of weaning from respiratory support, increasing oxygen saturation, and improving clinical scores.
Harm	Large	Small (7)	Uncertain				• There are reports of minor adverse events (2-7%) such as claustrophobia and ear pain. No major adverse events were directly attributed to HBOT.
Certainty of Evidence	High	Moderate	Low (5)	Very low (2)			
Balance of effects	Favors drug (3)	Does not favor drug (2)	Uncertain (2)				• Potential benefits outweigh harms, however cost, which was not mentioned in both studies, must be considered in our context.
Values	Important uncertainty or variability (5)	Possibly important uncertainty or variability (1)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (6)	Moderate Cost (1)	Negligible cost	Moderate savings	Large savings	• The cost of a session ranges from Php 1,500 to 6,000. The protocols used in most studies cited use 5 to 8 sessions. The direct cost is estimated to be between Php 7,500 to 48,000.
Certainty of evidence of required resources	No included studies (6)	Very low	Low (1)	Moderate	High		
Cost effectiveness	No included studies (2)	Favors the comparison (2)	Does not favor either the intervention or the comparison (2)	Favors the intervention (1)			
Equity	Uncertain (1)	Reduced (5)	Probably no impact	Increased (1)			
Acceptability	Uncertain (3)	No (3)	Yes (1)				
Feasibility	Uncertain (2)	No (4)	Yes (1)				

Appendix 2. Search Yield and Results

Database or Register	Query String	Total Results	Studies Included in Previous Review	New Studies
Pubmed (database)	("COVID-19"[Mesh] OR (COVID-19)) AND ("hyperbaric oxygenation"[MeSH Terms] OR hyperbaric oxygen therapy OR HBOT)	55	1	54
Scopus (database)	TITLE-ABS-KEY(Hyperbaric Oxygen Therapy OR Hyperbaric Oxygenation OR HBOT) AND (COVID-19 OR Coronavirus disease OR SARS-CoV-2 Infection)	49	1	48
ClinicalTrials.gov (register)	(Hyperbaric Oxygen Therapy OR Hyperbaric Oxygenation OR HBOT) AND (COVID-19 OR Coronavirus disease OR SARS-CoV-2 Infection)	141	1	13
WHO ICTRP (register)	(Hyperbaric Oxygen Therapy OR Hyperbaric Oxygenation OR HBOT) AND (COVID-19 OR Coronavirus disease OR SARS-CoV-2 Infection)	15	1	14
MedRxiv	Hyperbaric oxygen AND COVID	0	0	0

Appendix 3. Prisma Flow Diagram



Appendix 4. Characteristics of Included Studies

Study ID	Study Design	Setting	Population	Intervention	Comparator	Outcomes
Gorenstein 2020	Non-randomized trial with propensity matched controls	New York, United States	COVID-19 patients with room air SpO2 <93% (n = 80) Excluded: pregnant, had pneumothorax, had positive troponin	HBOT (Perry/ Baromed) 2.0 ATA for 90 min daily for up to 5 sessions in addition to standard of care	Propensity matched controls (based on risk factors for poor outcomes) admitted during the same period	Primary: mortality Secondary: need for mechanical ventilation, days on mechanical ventilation
Petrikov 2021	Open-label randomized controlled trial	Moscow, Russia	COVID-19 patients (n = 90) with moderate to severe disease severity assessed by chest CT Excluded: did not consent	HBOT (Sechrist 2800) 1.4-1.6 ATA for 40 min in addition to standard of care	Standard of care	Primary: SpO2 Secondary: clinical improvement scores (NEWS, OSCI) markers of oxidative stress (MDA, OCP, and apoptosis of lymphocytes)

SpO2, peripheral capillary oxygen saturation; **CT**, computed tomography; **HBOT**, hyperbaric oxygen therapy; **ATA**, standard atmosphere unit; **NEWS**, national early warning score; **OSCI**, ordinal scale for clinical improvement; **MDA**, serum malone dialdehyde; **OCP**, open circuit potential.

Appendix 5. GRADE Evidence Profile

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hyperbaric oxygen therapy	Normobaric oxygen therapy or SOC	Relative (95% CI)	Absolute (95% CI)	CERTAINTY	IMPORTANCE
Mortality (follow-up: 16 days; assessed with: Inhospital mortality within the study period)												
1	Observational studies	Serious[a]	Not serious	Not serious	Serious[b]	None	2/20 (10.0%)	13/60 (21.7%)	**Adjusted HR 0.37** (0.10 to 1.37)	**-- per 1,000** (from -- to --)	⊕◯◯◯ Very low	
Need for mechanical ventilation (follow-up: 16 days; assessed with: Required mechanical ventilation within the study period)												
1	Observational studies	Serious[a]	Not serious	Not serious	Serious[c]	None	2/20 (10.0%)	18/60 (30.0%)	**Adjusted HR 0.26** (0.07 to 0.98)	**-- per 1,000** (from -- to --)	⊕◯◯◯ Very low	
Successful weaning from respiratory support (follow-up: 10 days; assessed with: Need for respiratory support (3-6 l/min oxygen support or noninvasive ventilation or high flow oxygen therapy) on day 4 and day 10 of admission)												
1	Randomised trials	Serious[d]	Not serious	Not serious	Not serious	None	19/24 (79.2%)	3/24 (12.5%)	**RR 6.33** (2.15 to 18.62)	**666 more per 1,000** (from 144 more to 1,000 more)	⊕⊕⊕◯ Moderate	
Change in oxygen saturation (follow-up: 14 days; assessed with: peripheral oxygen saturation measured at different point intervals)												
1	Randomised trials	Serious[d]	Not serious	Serious	Not serious	None	96.1	93.4	-	MD +**2.7 % SpO2** (+0.72 to +4.68)[e]	⊕⊕◯◯ Low	
Clinical improvement score (National Early Warning Score 2) (follow-up: 10 days; assessed with: Differences in summary scores based on respiratory rate, oxygen saturation, systolic blood pressure, heart rate, level of consciousness, temperature and supplemental oxygen dependency on day 4 and day 10 of admission; Scale from: 0 to 20)												
1	Randomised trials	Serious[d]	Not serious	Serious[f]	Not serious	None	3.2	0.7	-	MD -**2.8 score** (-3.8 to -1.76)[g]	⊕⊕◯◯ Low	
Clinical improvement score (Ordinal Scale for Clinical Improvement) (follow-up: 10 days; assessed with: Differences in scores based on functionality on day 4 and day 10 of admission; Scale from: 1 to 8)												
1	Randomised trials	Serious[d]	Not serious	Serious[f]	Not serious	None	1.2	0.2	-	MD -**0.9 score** (-1.26 to -0.54)[h]	⊕⊕◯◯ Low	
Minor adverse events (claustrophobia) (follow-up: 14; assessed with: Proportion of patients who reported claustrophobia during the study duration)												
1	Randomised trials	Serious[d]	Not serious	Serious[f]	Not serious	None	1/57 (1.8%)	0/30 (0.0%)	**RR 1.60** (0.07 to 38.20)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low	

Minor adverse events (ear pain) (assessed with: Proportion of patients who reported ear pain during the study duration)												
1	Randomised trials	Serious[d]	Not serious	Serious[f]	Not serious	None	4/57 (7.0%)	0/30 (0.0%)	**RR 4.81** (0.27 to 86.47)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low	

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

Explanations

[a]. non-randomized study

[b]. unadjusted subdistribution hazard ratio for time to death was 0.42 (p-value = 0.24, 95% CI of 0.10 to 1.79); adjusted subdistribution hazard ratio for inpatient mortality was 0.37 (p-value = 0.14, 95% CI of 0.10 to 1.37)

[c]. unadjusted subdistribution hazard ratio for time to mechanical ventilation was 0.30 (p-value = 0.09, 95% CI of 0.07 to 1.23); adjusted subdistribution hazard ratio for time to mechanical ventilation was 0.26 (p-value = 0.046, 95% CI of 0.07 to 0.98)

[d]. open-label trial

[e]. MD for HBOT +4.20 (95% CI 1.98, 6.42; p=0.0002), MD for Control +0.80 (95% CI -1.46, 3.06; p=0.70), MD for HBOT vs Control +2.70 (95% CI 0.72, 4.68; p=0.007

[f]. patients who did and did not require supplemental oxygen were both included in the analysis

[g]. MD for HBOT -3.20 (95% CI -4.23, -2.17; p<0.00001), MD for Control +0.70 (95% CI -0.46, 1.86; p=0.24), MD for HBOT vs Control -2.80 (95% CI -3.84, -1.76; p<0.00001)

[h]. MD for HBOT -1.20 (95% CI -1.54, -0.86; p<0.00001), MD for Control -0.20 (95% CI -0.60, 0.20; p=0.33), MD for HBOT vs Control -0.90 (95% CI -1.26, -0.54; p<0.00001)

Appendix 6. Table of Ongoing Studies

Study ID	Study Design	Population	Intervention	Comparator	Outcomes
Hyperbaric Versus Normobaric Oxygen Therapy for COVID-19 Patients (NCT04500626)	Randomized Controlled Trial	Adult COVID-19 patients in requiring 21%<FIO2≤100% to maintain saturation by pulse oximetry (SpO2) ≥90%	HBOT 2.0 ATA x 75 min	Normobaric oxygenation	7-level COVID scale, hospital LOS, days with O2 supplementation, daily O2 flow values, ICU admission, ICU LOS, days on MV or NIV, major thrombotic events, sleep quality, fatigue, mortality, adverse events attributed to HBOT
Hyperbaric Oxygen for COVID-19 Patients With Moderate to Severe Hypoxemia (NCT04619719)	Randomized Controlled Trial	Adult COVID-19 patients with moderate to severe hypoxemia defined by a baseline supplemental oxygen requirement of 6 liters or higher within 24 h before enrollment	HBOT 2 ATA x 90 min x up to 5 treatments in addition to standard of care	Standard of care	Death from any cause 60 days after, time to mechanical ventilation, persistent symptoms, pulmonary function abnormality
Hyperbaric Oxygen Therapy (HBOT) as a Treatment for COVID-19 (COVID-19) Infection (NCT04343183)	Randomized Controlled Trial	Adult COVID-19 patients, O2 <90%, pO2 55-70	HBOT	Standard of care	Decrease incidence of intubation by 30% or greater, decrease renal injury
Hyperbaric Oxygen Therapy Effect in COVID-19 RCT (NCT04358926)	Randomized Controlled Trial	Adult COVID-19 patients, room Air SpO2 <94% or PaO2/FiO2<300mmHg, at least one risk factor for bad prognosis of COVID-19	HBOT 2.2 ATA x 60 min x 8 sessions in 4 days	Standard of care	SpO2, early warning score, CRP, WBC, IL-1, IL-2, IL-6, IL-10, TNF-a, PCT, ferritin, symptoms, IgM and IgG seroconversion, FEV1/FVC, time to recovery, requiring MV, time to negative PCR, mortality rate, barotrauma events
Hyperbaric Oxygen Therapy in Non-ventilated COVID-19 Patients (HBOT) (NCT04409886)	Randomized Controlled Trial	Adult COVID-19 patients, room Air SpO2 <94% or PaO2/FiO2<300mmHg, at least one risk factor for bad prognosis of COVID-19	HBOT	None	PaO2/FiO2 (oxygenation index)
Management by Hyperbaric Oxygen Therapy of Patients with Hypoxaemic Pneumonia with SARS-CoV-2 (NCT04344431)	Randomized Controlled Trial	Adult COVID-19 patients need to maintain an oxygen flow rate less than or equal to 6 liters / min to obtain saturation by pulse oximetry (SpO2) greater than or equal to 92% or arterial gas with value PaO2 greater than 60mmHg	HBOT 1 session per day in addition to standard treatment	None	Time to normalized O2 requirement, hospital LOS, O2 needed, days on MV, mortality

Safety and Efficacy of Hyperbaric Oxygen for ARDS in Patients with COVID-19 (NCT04327505)	Randomized Controlled Trial	Adult COVID-10 patients with PaO2/FiO2 (PFI) below 200 mmHg and at least two risk factors for increased morbidity/mortality	HBOT 1.6-2.4 ATA 30-60 min	Standard of care	ICU admission, mortality, time-to-intubation, time-to-ICU, inflammatory response, OS
Compassionate Use of Hyperbaric Oxygen Therapy (NCT04386265)	Prospective observational	Adult COVID-19 patients	HBOT	None	Need for mechanical ventilation in COVID-19 patients, adverse events associated with HBOT
Effecacy and Safety of Hyperbaric Oxygen Therapy to Patients with Novel Coronavirus Pneumonia (COVID-19) (ChiCTR2000032011)	Randomized Controlled Trial	Adult COVID-19 patients meeting severe criteria: RR >30 bpm, SpO2 ≤93%, PaO2/FiO2 ≤300, significant progression of pulmonary lesions within 24-48 h on imaging	HBOT 1.5 ATA group and HBOT 2.5 ATA group	Standard of care	Oxygenation index, activity endurance, IL-6, blood routine biochemical indicators, lung CT, microparticle, CRP
Hyperbaric Oxygen Therapy for Hospitalized Patients with COVID-19 (U1111-1253-2793)	Randomized Controlled Trial	Adult COVID-19 patients with hypoxemia defined as SaO2 less than or equal to 94%	HBOT 2.0 ATA daily for 5 days	Hyperbaric chamber 1.2 ATA daily for 5 days	Number of days to defervescence, reduction in cough, SpO2, PpO2, days to respiratory improvement, mortality, outpatient treatment days

Q13. Should sedation and neuromuscular blockade be done in mechanically ventilated patients with COVID-19-associated acute respiratory distress syndrome?

As of 03 January 2022

RECOMMENDATIONS

We suggest light over deep sedation in COVID-19 patients who are mechanically ventilated and who are anxious or agitated. *(Very low certainty of evidence; Weak recommendation)*

We suggest against the routine use of neuromuscular blockade in mechanically ventilated patients with COVID-19 associated respiratory distress syndrome. *(Low certainty of evidence; Weak recommendation)*

Consensus Issues

Light sedation for mechanically ventilated COVID-19 patients has been suggested to help in managing agitation and anxiety. Certain patients, however, who are on paralytics and prone position, as well as those who exhibit ventilator asynchrony must be considered for deep sedation. On the other hand, routine neuromuscular blockade is not recommended unless there are indications for paralysis: as supportive management to facilitate lung protective strategies or prone ventilation.

KEY FINDINGS

There are currently no available randomized clinical trials testing for the effect of sedation and neuromuscular blockade in COVID-19 patients with acute respiratory distress syndrome (ARDS). Only indirect evidence from eight studies (two randomized clinical trials (RCTs) on the use of sedation versus no sedation in mechanically ventilated patients and six RCTs on the use of neuromuscular blockade agent (NMBA) compared to light sedation alone or placebo with or deep sedation in mechanically ventilated patients with moderate to severe ARDS) showed no significant benefit in 90-day mortality, length of hospital stay, and ventilator free-days. In terms of adverse events, major thromboembolic complications were significantly observed among mechanically ventilated patients on sedation while the incidence of delirium, accidental extubation, and ventilator-associated pneumonia did not significantly differ. The use of NMBA in moderate-to-severe ARDS showed significant reduction in 28- and 90-day mortality, improvement in PaO2/FiO2 ratio at 72 hours when compared to a deep sedation strategy without NMBA. Likewise, the use of NMBA reduced the risk of barotrauma and pneumothorax compared to no NMBA.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a life-threatening condition that complicates a variety of critical illnesses, including sepsis, pneumonia, and trauma.[1] The Coronavirus Disease 2019 ARDS (COVID-19 ARDS) has some distinguishing features that includes progressive pulmonary infiltrates and hyperinflammatory response resulting in severe refractory hypoxemia, which poses a major challenge in ventilatory management. [2,3] In critically ill patients, sedatives are frequently administered to relieve anxiety, reduce the stress of being mechanically ventilated,

and prevent agitation-related harm. On the other hand, the routine use of neuromuscular blocking agents is not recommended unless indicated as supportive therapy to facilitate lung protective ventilation or prone ventilation.[4,5]. This review aims to evaluate the effects of sedation and neuromuscular blockade among mechanically ventilated COVID-19 patients with moderate to severe ARDS.

REVIEW METHODS

We performed a systematic literature search to identify relevant studies in PubMed, Cochrane Library, WHO trial Registry, and ClinicalTrial.gov databases up to November 19, 2021. Our search strategy combined concepts related to Sedation, Paralysis, COVID-19 and acute respiratory distress syndrome (i.e., “Mechanical Ventilation”, “Severe Pneumonia”, “Sedation”, “ARDS”, “respiratory distress syndrome”, “ICU”, “Randomized Trial”, and “neuromuscular blockade”). In addition, MeSH and free text search were done for the following terms: sedation, neuromuscular blockade, paralysis, ICU, mechanical ventilation, COVID-19, and acute respiratory distress syndrome. We also reviewed the references listed in each identified study and manually searched the related articles to identify all eligible studies and minimize any potential publication bias. No language or journal type restriction was applied.

RESULTS

Sedation in Mechanically Ventilated Patients

Characteristics of Study Population, Interventions, and Comparators

The population, drugs used, and methodology process were similar in the two (2) studies included for sedation. Both trials were conducted to investigate whether a plan of no sedation in patients receiving mechanical ventilation would result in a better survival outcome than a plan of light sedation with daily interruption. In both studies, included patients were 18 years of age or older, had undergone endotracheal intubation within 24 hours before screening, and were expected to receive mechanical ventilation for more than 24 hours. Upon inclusion, the patients were randomly assigned in a 1:1 ratio to a plan of no sedation (non-sedation group) or to light sedation with daily interruption (sedation group).[6,7] Patients in the non-sedation group did not receive any sedatives but could receive bolus doses of morphine for analgesia while the patients in the sedation/control group received intravenous morphine in bolus doses (2.5 or 5mg) as needed, and were sedated with an infusion of propofol (20 mg/mL) titrated to reach a Ramsay score of 3–4. Ramsay Sedation Scale scores range from 1 [anxious, restless] to 6 [unresponsive], with a score of 2 indicating that the patient is cooperative and oriented. The Ramsay score was recorded every 2–3 h to ensure correct titration of the sedative infusion. Every day, sedation was interrupted until the patients were awake, starting the day after enrolment. After 48 hours, the sedative was changed to an infusion of midazolam (1 mg/mL) titrated to a Ramsay score of 3–4.[6,7] Once the ventilator settings reached an FiO2 of 40% and a positive end-expiratory pressure of 5 cm H2O, the administration of sedatives were stopped.

Mortality

Two studies [6,7] were included in evaluating the effect of sedation in 813 mechanically ventilated patients. In both studies, patients were randomly assigned in a 1:1 ratio to a plan of no sedation or to light sedation with daily interruption within 24 hours after intubation. Pooling of the results showed that among mechanically ventilated patients, the 90-day mortality outcome (RR 1.00, 95% CI 0.70-1.43; I^2=59%;

very low certainty), ventilator free days (MD -1.07, 95% CI -3.05-0.91; low certainty), and length of ICU stay (MD -0.34, 95% CI -6.15-5.47; low certainty), did not differ significantly between the two groups. Significant heterogeneity in mortality could have been introduced by differences in the study population in terms of cause of respiratory failure and sedation protocols. Certainty of evidence for mortality was downgraded to very low due to indirectness of the study population, inconsistency, and imprecision, while certainty of evidence for ventilator-free days and ICU length of stay were downgraded to low due to indirectness of the study population and imprecision.

Adverse Events

Two randomized controlled trials reported adverse events between sedation and non-sedation treatment groups. Among the reported adverse events, major thrombotic events were significantly observed among patients who received sedation (RR 9.94, 95% CI 1.28-77.26; moderate certainty).[6] Delirium (RR 0.34, 95% CI 0.12-1.02; low certainty) [7], extubation (RR 0.66, 95% CI 0.26-1.66; I^2=0%; low certainty) [6,7], need for reintubation in 24 hours (RR 1.49, 95% CI 0.62-3.57; low certainty) [7], and incidence of ventilator-associated pneumonia (RR 1.11, 95% CI 0.40-3.09; low certainty) [7] were not significantly different between sedation and non-sedation treatment groups. Certainty of evidence for major thrombotic events was downgraded to moderate due to indirectness while certainty of evidence for the rest of the reported adverse events was downgraded to low due to indirectness and imprecision.

Use of Neuromuscular Blockade in Mechanically Ventilated Patients with ARDS

Characteristics of Study Population, Interventions, and Comparators

The studies included for NMBA met all of the following criteria: (1) the design was a parallel group RCT; (2) the population was adults with ARDS of any severity; (3) the intervention included any continuous NMBA infusion, at any dose or duration, compared to placebo or no continuous NMBA infusion but allowing the use of as needed NMBA boluses; and (4) outcomes included any of the following: mortality at 28 days, ICU discharge, or hospital discharge; long-term outcomes, ICU-acquired weakness; duration of mechanical ventilation; ventilator-free days (VFDs); ICU or hospital length of stay; barotrauma; or changes in oxygenation wherein PaO2/FiO2 ratio is specified.[8-13]

Four studies were conducted in France, and one was conducted in China, while the most recent study (PETAL/ROSE Trial), the largest RCT investigating NMBAs effect on ARDS thus far, was conducted in the United States. In all 6 studies, no significant differences were noted between the baseline characteristics of the treatment and control groups.[8-13] Four studies used a 48-hour infusion of cisatracurium [8,9,12,13] whereas the other two studies did not pre-specify a duration for NMBA infusions.[10,11] Weight-based dosing of cisatracurium was used in two of the studies [8,9] and a fixed high dose was used in three studies (15mg bolus, followed by a continuous infusion of 37.5mg per hour).[10,11,13] The study from China was the only included trial which used vecuronium, utilizing maintenance doses without boluses being reported: 0.05 mg/kg/h and 1 μg/ kg/min.[11]

The interventions used in the control arm varied between studies: three studies used a 48-hour infusion of placebo (normal saline) with deep sedation [8-10], an additional two studies did not describe the control they used [11,13], and one study used light sedation in the control group.[12] All experimental groups received deep sedation on

top of the assigned NMBA. Deep sedation was defined as a Ramsay score of 6 while light sedation was defined by a score on the Richmond Agitation–Sedation Scale of 0 or −1 (scores range from 4 [combative] to −5 [unresponsive], with a score of 0 indicating that the patient is alert and calm), a score on the Riker Sedation–Agitation Scale of 3 or 4 (scores range from 1 [unresponsive] to 7 [dangerous agitation], with a score of 4 indicating that the patient is calm and cooperative), or a score on the Ramsay Sedation Scale of 2 or 3 (scores range from 1 [anxious, restless] to 6 [unresponsive], with a score of 2 indicating that the patient is cooperative and oriented).[12,14]

In the study done by Guervilly et al., severe ARDS patient whose PaO2/FiO2 ratio was less than 100 did not get randomization but received open label NMBA infusion as per study protocol, only patients with PaO2/FiO2 ratio between 100 to 150 were randomized.[7] Most studies excluded patients with recent NMBA use prior to enrolment. In terms of neuromuscular blockade monitoring, three studies used nerve stimulators to monitor train of four (TOF) with NMBA dose adjustment accordingly. The other three studies were carried out with fixed NMBA dose. ROSE trial specifically mentioned that the reason for using a fixed dose was to replicate the dosing regimen used in the (ACURASYS) trial and to facilitate adherence to the trial protocol.[12,13] All the studies used lung protective ventilation with low tidal volume with an aim of keeping plateau pressure ≤30cmH2O. ROSE Trial used high PEEP strategy with a baseline PEEP at around 12cmH2O at enrolment.[12] ACURASYS and ROSE trials allowed any rescue therapy, and no statistical difference was found between the intervention group and control group.[12,13]

Mortality

Pooled results of studies which used deep sedation on both its control and intervention groups [8-11,13] showed that the use of NMBA infusion was associated with lower 28-day mortality (RR 0.63, 95% CI 0.49–0.82; I^2=0%; moderate certainty), a lower 90-day mortality (RR 0.72, 95% CI 0.58–0.91; I^2=0%; moderate certainty), and a lower ICU mortality (RR 0.70, 95% CI 0.55-0.89; I^2=0; moderate certainty).

The ROSE trial [12], the largest trial to date, which also applied the latest recommendation for the use of light sedation in mechanically ventilated patients in their control arm, reported no mortality benefit associated with NMBA use at 90 days regardless of ARDS severity or duration (RR 0.99, 95% CI 0.86-1.15; moderate certainty). There are a number of factors that might have contributed to the differences in results. In the ROSE/PETAL Trial, the subjects who were randomized to NMBAs received deep sedation, but for subjects in the control arm, light sedation was targeted and daily sedation interruptions were encouraged. Second, a high-PEEP strategy was utilized, which has been associated with improved recruitment and decreased lung stress and atelectrauma. Lastly, the mean time to inclusion for subjects in ROSE was earlier compared to the other five RCTs. The median time to randomization for subjects enrolled in ROSE was 6.8 to 8.2 hours compared to 21 to 22 hours in the other studies.

Improvement in Oxygenation

Improvement in oxygenation was assessed via change in the PaO2/FiO2 ratio evaluated at 48 and 72 hours of NMBA infusion. Three of the included studies [8,9,12] evaluated the effect of NMBA to oxygenation after 48 hours while four studies

measured PaO2/FiO2 changes after 72 hours.[8,9,12,13] Pooled results showed no significant improvement in oxygenation after 48 hours (MD 22.2, 95%CI -4.47-48.88; I^2=64%; very low certainty). Significant benefit was observed with the PaO2/FiO2 ratio improvement after 72 hours (MD 12.9, 95% CI 3.88-21.92; I^2=32%; low certainty). Some of the proposed mechanisms leading to improvement in oxygenation include improved ventilator synchrony, decreased work of breathing, facilitation of lung protective strategy, better lung recruitment, and improved lung compliance.[15,16]

Duration of Mechanical Ventilation and Ventilator-free Days

Three of the studies (n=431) reported on the duration of mechanical ventilation.[8,9,13] Results showed no significant difference in the duration of mechanical ventilation among those given NMBA compared to those who were not given NMBA (MD -1.21 days, 95% CI -4.23-1.81; I^2=0%; low certainty). A similar trend was observed in the pooled analysis for ventilator-free days which also showed no significant difference between the NMBA and control groups (MD 0.68 days, 95% CI -0.86-2.22; I^2=32%; low certainty).

Adverse Events

Pooled data on adverse events showed a decrease in the risk of barotrauma (RR 0.55, 95% CI 0.35-0.85; I^2=0%; moderate certainty) and pneumothorax (RR 0.46, 95% CI 0.28-0.77; I^2=0%; moderate certainty) in the NMBA group. Barotrauma was defined as new-onset pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele larger than 2cm in diameter. These may be due to the increase in lung compliance and decrease in ventilatory desynchrony between the machine and the patient.[8,9,12,13] Certainty of evidence was downgraded to moderate due to indirectness of the study population.

Four of the included studies [8,9,12,13] reported on adverse events. The PETAL trial reported most of the adverse events in the pooled data.[12] Pooled analysis on the development of any adverse event showed no significant difference between those who were given NMBA infusion compared to control group (RR 1.63, 95% CI 0.97-2.71; I^2=0%; low certainty). Adverse events observed were methemoglobinemia, complete heart block, atrial fibrillation, cardiac arrest, SVT, ventricular tachycardia, new-onset pneumonia, hyperkalemia, intracranial hemorrhage, cerebrovascular accident, aspiration, hypotension, and superficial venous thrombosis. Certainty of evidence was downgraded to low due to indirectness of the study population and imprecision.

ICU-acquired weakness up to 28 days from randomization was also assessed and was evaluated with the use of the Medical Research Council (MRC) scale, a previously validated scale that assesses three muscle groups in each arm and leg.[8,9,12,13] The score for each muscle group ranged from 0 (paralysis) to 5 (normal strength), with the overall score ranging from 0 to 60.[2] The definition of ICU-acquired paresis was an MRC score of less than 48.[2] The pooled results did not show a significant difference in the rate of ICU-acquired weakness with NMBA infusion (RR 1.15, 95% CI 0.95-1.39; I^2=0%; low certainty). Certainty of evidence was downgraded to low due to indirectness of the study population and imprecision.

RECOMMENDATIONS FROM OTHER GROUPS

There are currently no guidelines regarding sedation and neuromuscular blockade specific for this patient population. At present, sedation regimens for COVID-19 ARDS patients are based on the standard guidelines in treating patients with “classic” or “pre-COVID” ARDS.

As per Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) in Adult Patients in the ICU 2018, using light sedation in critically ill, mechanically ventilated adults is suggested in order to relieve anxiety, reduce the stress of being mechanically ventilated, and prevent agitation-related harm *(conditional recommendation, low quality of evidence).*[17]

As of Surviving Sepsis Guidelines 2021, continuous NMBA infusion did not improve mortality when compared with a light sedation strategy with as needed NMBA boluses (RR 0.99, 95% CI 0.86−1.15). On the other hand, continuous NMBA infusion reduced mortality when compared to deep sedation with as needed NMBA boluses (RR 0.71, 95% CI 0.57−0.89).[18] Since cisatracurium is the only agent recorded to have been studied in large RCTs, it is then the preferred agent to use. In summary, it is recommended for adults with sepsis induced moderate-severe ARDS to use intermittent NMBA boluses over NMBA continuous infusion.[18]

In an ICM-RPG for the use of neuromuscular blocker by Alhazzani 2020, the panel issued one recommendation and two suggestions regarding the use of NMBA in ARDS. The current evidence does not support the early routine use of NMBA infusion in all adults with ARDS. It favors avoiding an NMBA infusion for patients who are ventilated using a lighter sedation strategy. But, for patients who require deep sedation to facilitate lung protective ventilation, prone positioning, and neuromuscular blockade, an infusion of an NMBA is a reasonable option; limiting its use to 48hrs is recommended.[19]

As for local guidelines issued by the Clinical Practice Guidelines for Sepsis and Septic Shock in Adults in the Philippines 2020, the use of either continuous or intermittent sedation in mechanically-ventilated patients with sepsis or septic shock is recommended *(conditional recommendation, low quality of evidence)* as an adjunct to short-acting non-benzodiazepine sedatives (e.g. dexmedetomidine and propofol) in order to address agitation and the need for adequate sedation to achieve protocol-based sedation targets *(conditional recommendation, low quality of evidence).* With regard to NMBA use, local guidelines recommend its early use preferably within 48 hours of ARDS diagnosis in moderate to severe ARDS *(weak recommendation, very low quality of evidence).*[20]

RESEARCH GAPS

The data specific for patients with COVID-19 with ARDS are limited, derived mainly from observational studies and clinical experiential accounts. A randomized clinical trial, if possible, is needed to further assess and evaluate optimal components of care (i.e., use of sedation and neuromuscular blockade) in this particular patient population. Though their condition is similar to “traditional” ARDS, the differences in other

processes might affect the final outcome when studied strictly among the said population.

ONGOING TRIALS

There are four registered clinical trials in ClinicalTrials.gov as of November 20, 2021 (see Appendix 6), one of which is a randomized clinical trial comparing the effect of neuromuscular blockade with sedation vs sedation alone in intubated COVID-19 patients with ARDS but is yet to begin recruitment. The remaining three trials are related to inhaled sedatives and its possible utilization in COVID-19 ARDS patients. Two of the three trials have completed their data collection but no published article is presently available. Other than this, one registered randomized clinical trial was found comparing sedation vs non sedation in mechanically ventilated patients. No published results are available at present.

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Appendix 1. Evidence to Decision

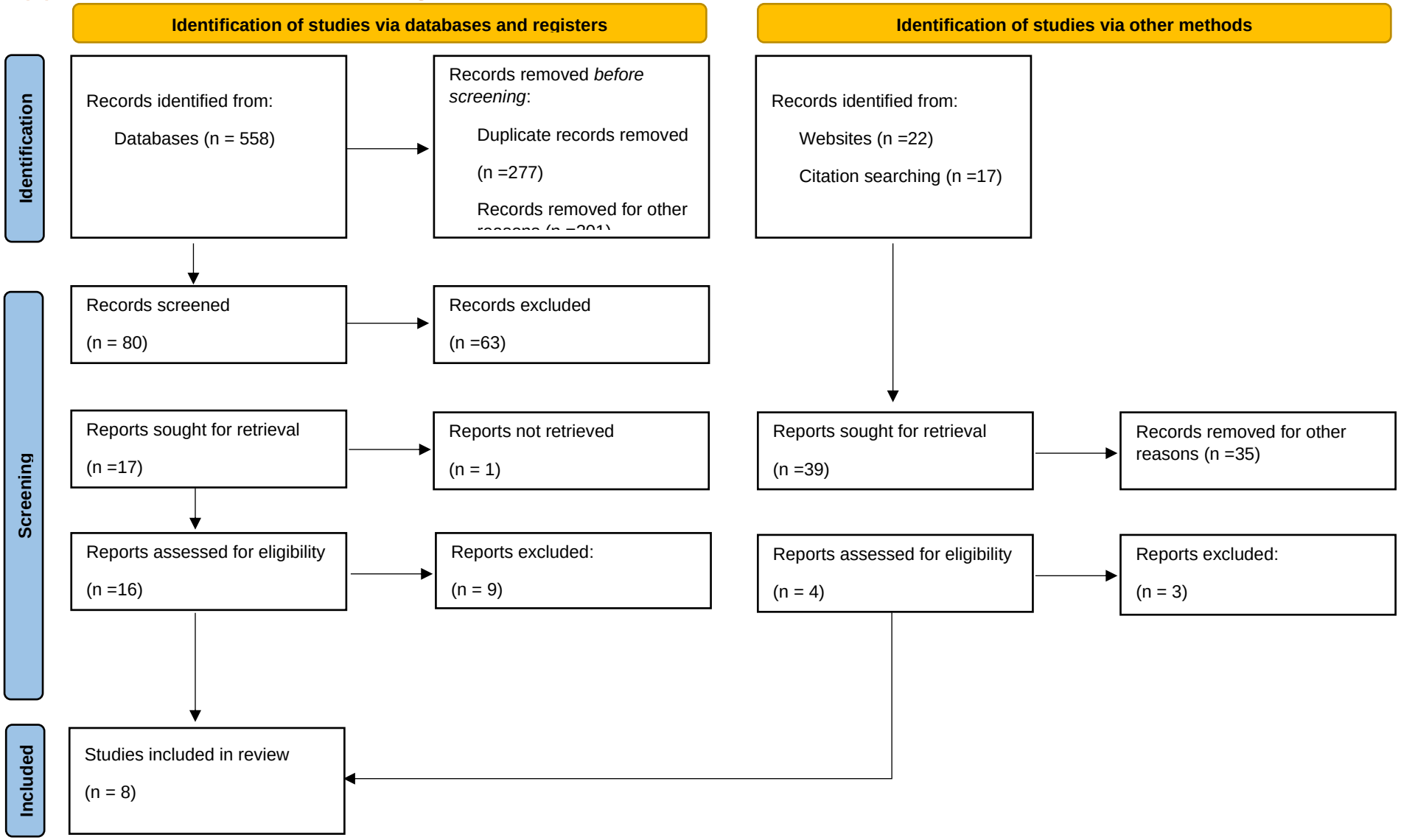
Table 1. Summary of initial judgements prior to the panel discussion: sedation (N=5)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					• Critically ill patients with ARDS may require sedation and neuromuscular blockade as supportive therapy to alleviate patient anxiety and improve tolerance, and as therapeutic measures to improve ventilatory synchrony and oxygenation without contributing to adverse outcomes
Benefits	Large	Moderate (1)	Small (2)	Uncertain (2)			• No significant difference in: the 90-day mortality outcome (RR 1.00; 95% CI 0.70, 1.43; I2=59%; Very Low Certainty), ventilator free days (MD -1.07; 95% CI -3.05, 0.91; Low Certainty), and length of ICU stay (MD -0.34; 95% CI -6.15, 5.47; Low Certainty).
Harm	Large (3)	Small (1)	Uncertain (1)	No response			• Reported adverse events: major thrombotic events was significantly observed among patients who received sedation (RR 9.94; 95% CI 1.28, 77.26; Moderate Certainty)
Certainty of Evidence	High	Moderate	Low (1)	Very low (4)			• Very low due to indirectness in study population, inconsistency, and imprecision
Balance of effects	Favors drug (1)	Does not favor drug (3)	Uncertain (1)				
Values	Important uncertainty or variability (4)	Possibly important uncertainty or variability (1)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain (4)	Large cost (1)	Moderate Cost	Negligible cost	Moderate savings	Large savings	
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 (0)	Reduced (1)	Probably no impact (4)	Increased			
Acceptability	Uncertain (1)	No (4)	Yes (0)				
Feasibility	Uncertain	No	Yes (5)				

Table 2. Summary of initial judgements prior to the panel discussion: neuromuscular blockade (N=5)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					• Critically ill patients with ARDS may require sedation and neuromuscular blockade as supportive therapy to alleviate patient anxiety and improve tolerance, and as therapeutic measures to improve ventilatory synchrony and oxygenation without contributing to adverse outcomes
Benefits	Large	Moderate (5)	Small	Uncertain			• A lower 28-day mortality (RR 0.63; 95% CI 0.49–0.82; I^2=0%; Moderate Certainty), a lower 90-day mortality (RR 0.72; 95% CI 0.58–0.91; I^2=0%; Moderate Certainty), and a lower ICU mortality (RR 0.70; 95% CI 0.55-0.89, I^2=0; Moderate Certainty). • Significant benefit was observed with the PaO2/FiO2 ratio improvement after 72 hours (MD 12.9; 95% CI 3.88, 21.92; I^2=32%; Low Certainty).
Harm	Large (3)	Small (2)	Uncertain	No response			• Decreased risk of barotrauma (RR 0.55; 95% CI 0.35, 0.85; I^2=0%; Moderate Certainty) and pneumothorax (RR 0.46; 95% CI 0.28, 0.77; I^2=0%; Moderate Certainty) in the NMBA group
Certainty of Evidence	High	Moderate	Low (5)	Very low			• Certainty of evidence was low due to indirectness in study population, and imprecision
Balance of effects	Favors drug (5)	Does not favor drug	Uncertain				
Values	Important uncertainty or variability	Possibly important uncertainty or variability (1)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability (2)			
Resources Required	Uncertain (5)	Large cost	Moderate Cost	Negligible cost	Moderate savings	Large savings	
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 (1)	Reduced (1)	Probably no impact (3)	Increased			
Acceptability	Uncertain	No	Yes (5)				
Feasibility	Uncertain	No	Yes (5)				

Appendix 2. PRISMA Flow Diagram



Appendix 3. Characteristics of Included Studies

3.1 Study Characteristics of Included Studies on Sedation (n=2)

Study ID Title Author	Study Design	Setting/Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcome Monitored or Observed	Result
Olsen et.al.[9] (2020) DOI: 10.1056/NEJMoa1906759 Non sedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients	Randomized Clinical Trial, open label	Multicenter 5 in Denmark; 2 in Norway; 1 in Sweden	n= 700	• 18 years of age or older • Underwent endotracheal intubation within 24 hours before screening • Expected to receive mechanical ventilation for more than 24hours	Non sedation	Interrupted sedation (Using Propofol for the first 48hours followed by midazolam infusion thereafter)	**Primary outcome**: 1. all-cause mortality at 90 days after randomization. **Secondary outcomes:** 1. Number of days until death up to 90 days after randomization 2. Number of thromboembolic events (pulmonary embolus or deep vein thrombosis) 3.Number of days free from coma or delirium 4. The highest score on the Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (RIFLE) 5. Length of stay in the ICU 6. The number of days without mechanical ventilation	• 48 patients (42.4%) in the non sedation group had died and 130 patients (37.0%) in the sedation group • Number of days until death up to 90 days was 13 days (interquartile range, 6 to 27) in the non sedation group and 12 days (interquartile range, 5 to 28) in the sedation group • A major thromboembolic event (pulmonary embolus or deep-vein thrombosis) within 90 days after randomization occurred in 1 patient (0.3%) in the non sedation group and in 10 patients (2.8%) in the sedation group • The number of days free from coma or delirium was 27 in the non sedation group and 26 in the sedation group • The highest measured RIFLE score within 28 days after randomization was 2 in both groups • All other secondary outcomes did not differ significantly between the trial groups: Length of stay in the ICU (13 vs 14) and Median number of days without mechanical ventilation (20 vs 19).
Strom et. al.[12] (2010) DOI: 10.1016/S0140-6736(09)62072-9 A Protocol of No Sedation for Critically Ill	Randomized Clinical Trial, open label	Single Center; Denmark	n=113	• 18 years of age or older • Underwent endotracheal intubation within 24 hours before screening • Expected to receive mechanical ventilation for more than 24hours	Non sedation	-interrupted sedation (Using Propofol for the first 48hours followed by midazolam infusion thereafter)	**Primary outcome**: 1. Number of days without mechanical ventilation in a 28-day period **Secondary outcomes:** 1. Length of stay in the ICU (28 days) 2. Length of stay in the hospital (90 days)	• The no sedation strategy was associated with a significantly higher number of days without ventilation • Length of stay in the intensive care unit was significantly shorter in the no sedation group than in the sedation group, with a difference of 9·7 days • Length of hospital stay was substantially shorter in the no sedation group than in the sedation group, with a difference of 24 days

Patients Receiving Mechanical Ventilation: A Randomised Trial							3. Mortality in the ICU (28 days) 4. Mortality in the Hospital (90 days) 5. Occurrences of need for CT or MRI brain scans 6. Number of accidental removal of endotracheal tube 7. Number of ventilator-associated pneumonia 8. Incidence of delirium	• No difference was recorded in the occurrence of complications between both groups: ○ Accidental removal of the endotracheal tube (n=7 vs n=6; p=0·69); ○ Need for CT or MRI brain scans (n=5 vs n=8; p=0·43); ○ Ventilator-associated pneumonia (n=6 vs n=7; ○ p=0·85) ○ Need for intubation again within 24 h (n=7 vs n=11; p=0·37). ○ Delirium was recorded in 11 (20%) patients in the no sedation group and 4 (7%) in the sedation group (p=0·04)

3.2 Study Characteristics of Included Studies on Neuromuscular Blockade (n=6)

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcome Monitored or Observed	Result
Gainnier et. al.[5] (2004) DOI: 10.1097/01.CCM.0000104114.72614.BC Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome	Randomized Clinical Trial	Multicenter (4), France	n=56	• Adult patients >18 years old • Intubated <48hrs • AECC definition of ARDS; PaO2/FIO2 ratio ≤150; PEEP≥5 cm H20	NMBA infusion (Cisatracurium) for 48hrs + Deep sedation [Midazolam and Sufentanil]	Standard of care (Deep Sedation) [Midazolam and Sufentanil] + Placebo (Sodium chloride 0.9%)	**Primary outcome:** 1. f PaO2/FIO2 ratio (p 0.021) **Secondary outcome:** 1. Decrease in positive end-expiratory pressure 2 Adverse events	• Patients randomized to the NMBA group had a higher PaO2/FIO2 at 48, 96, and 120 hrs. • A decrease in positive end-expiratory pressure (p0.036) was found in the NMBA group. • Only one patient (from the control group) developed pneumothorax
Forel et. al.[4] (2006) DOI: 10.1097/01.CCM.0000239435.87433.0D. Neuromuscular blocking agents decrease inflammatory response in patients presenting	Randomized Clinical Trial	Multicenter (3), France	n=32	• Adult patients >18 years old • Intubated <48hrs • AECC definition of ARDS; PaO2/FIO2 ratio ≤150; PEEP≥5 cm H20	NMBA infusion (Cisatracurium) for 48hrs + Deep sedation [Midazolam and Sufentanil]	Standard of care (Deep Sedation) [Midazolam and Sufentanil] + Placebo (Sodium chloride 0.9%)	**Primary outcome**: 1. Effects of a 48-hr period of NMBA infusion on pulmonary and systemic inflammatory response (measured by IL-6, IL-8, IL-1B) **Secondary outcome:**	• At 48 hrs, pulmonary concentrations of IL-1 (p 0.005), IL-6 (p 0.038), and IL-8 (p 0.017) were lower in the NMBA group as compared with the control group. • A decrease over time in IL-6 (p 0.05) and IL-8 (p 0.003) serum concentrations in the NMBA group. • Sustained improvement in PaO2/FIO2 ratio in the NMBA group (p < .001).

with acute respiratory distress syndrome							1.Improvement in oxygenation, measured with the PaO2/FIO2 ratio	
Papazian et. al.[11] ACURASYS (2010) DOI: 10.1056/NEJMoa1005372 Neuromuscular blockers in early acute respiratory distress syndrome	Randomized Clinical Trial	Multicenter (20), France (Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	n=340	• Adult patients >18 years old • Intubated <48hrs • AECC definition of ARDS; PaO2/FIO2 ratio ≤150; PEEP≥5 cm H20	NMBA infusion (Cisatracurium) for 48hrs + Deep sedation [Midazolam, Propofol, Ketamine, and Sufentanil]	Standard of care (Deep Sedation) [Midazolam, Propofol, Ketamine, and Sufentanil] + Placebo	**Primary outcome**: 1.Reduction of the mortality rate of ARDS patients at d90 **Secondary outcome:** 1. Mortality at day 28, day 60, day 180 and ICU mortality 2. Ventilator-free days and alive at day 28 and day 60 3. Exposure time to FIO2 > 80% or PEEP > 10 cmH2O during the first 7 days 4. Sedatives and analgesics requirements during the first 7 days 5.Organ failure-free days and alive at day 28 6.Incidence of barotrauma 7.Incidence of critical illness neuromyopathy 8.Incidence of ventilator-associated pneumonia 9.Quality of life at day 180	The hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, was 0.68 (95% confidence interval [CI], 0.48 to 0.98; P=0.04), after adjustment for both the baseline PaO2:FIO2 and plateau pressure and the Simplified Acute Physiology II score. The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group (P=0.08). Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo (P=0.05). The rate of ICU-acquired paresis did not differ significantly between the two groups
Lyu et. al. [7] (2014) DOI: 10.3760/cma.j.issn.2095-4352.2014.05.008 Clinical study of early use of neuromuscular blocking agents in patients with severe sepsis and acute respiratory distress syndrome	Randomized Clinical Trial	Single Center, China	n=96	• Adult patients >18 years old • Severe sepsis • Intubated • Moderate to severe ARDS (Berlin Criteria) • PaO2/FiO2<200	NMBA infusion (Vecuronium) for 48hrs + Deep sedation	Standard of care (Deep Sedation)	**Primary outcome**: 1. 21-day mortality rate **Secondary outcomes:** 1.acute physiology and chronic health evaluation II (APACHEII) score 2.Sequential organ failure assessment (SOFA) 3.Arterial oxygenation index (PaO2/FiO2) 4.Central venous oxygen saturation (ScvO2) 5.Arterial blood lactate (Lac) 6.C-reactive protein (CRP) levels at 48 hours after treatment	• For both moderate and severe ARDS group, there were no statistically significant difference in APACHEII score, SOFA score, PaO2/FiO2, ScvO2, Lac and CRP *before* treatment between two groups. • 48hrs *after* treatment APACHEII score, SOFA score, PaO2/FiO2, ScvO2, and Lac were significantly improved in *severe* ARDS group compared with control group, while the value of CRP showed no significant difference • 21-day mortality in treatment group was significantly lower than that in control group • In moderate ARDS group, the clinical parameters were improved in both groups except for CRP at 48 hours *after* treatment

								• The 21-day mortality rate in the treatment group was slightly lower than that in the control group but showed no statistically significant difference.
Guervilly et. al.[6] (2016) DOI: 10.1007/s00134-016-4653-4 Effects of neuromuscular blockers on transpulmonary pressures in moderate to severe acute respiratory distress syndrome	Randomized Clinical Trial	Multicenter (2), France	n=24	• Adult patients >18 years old • Intubated <48hrs • ARDS Berlin definitions. • PaO2/FiO2≤150, • PEEP≥5 cm H20	NMBA infusion (Cisatracurium) for 48hrs + Deep sedation [Midazolam, Ketamine, and Sufentanil]	Standard of care (Deep Sedation) [Midazolam, Ketamine, and Sufentanil]	**Primary outcome**: 1. To assess the effects of a 48-h infusion period of NMBA on respiratory mechanics (Pplat, total PEEP, driving pressure, inspiratory and expiratory PL and ΔPL) in moderate to severe ARDS. **Secondary outcome:** 1. To assess and compare the percentages of positive expiratory PL during the 48 h of the study	• NMBA infusion was associated with an improvement in oxygenation in both moderate and severe ARDS, accompanied by a decrease in both • plateau pressure and total positive end-expiratory pressure • The mean inspiratory and expiratory PL were higher in the moderate ARDS group receiving NMBA than in the control group • No change was observed in either driving pressure or ΔPL related to NMBA administration.
PETAL [8] (2019) DOI: 10.1056/NEJMoa1901686 Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome	Randomized Clinical Trial	Multicenter (48), USA Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	N=1,006	ARDS, PaO2/FiO2≤150 PEEP≥8 cm H2O, Criteria met in <48 hours	NMBA infusion (Cisatracurium) for 48hrs + Deep sedation	Standard of care (Light Sedation)	**Primary outcome**: 1. Hospital Mortality to Day 90 [Time Frame: 90 days after randomization] **Secondary outcomes:** 1. Mean Ventilator Free Days to Day 28 2. Mean Organ Failure Free Days to Day 28 3. ICU Free Days to Day 28 4. Mean Hospital Free Days to Days 28 5. Katz Activities of Daily Living (ADL)/Lawton Instrumental Activities Of Daily Living Scale (IADL) [3mos,6mos,12mos] 6. EuroQol (EQ-5D-5L): Health Related Quality of Life. [3mos, 6mos, 12mos] 7. PTSS-14: Post-traumatic Stress-like Symptoms Scores >/= 45. [3mos,6mos,12mos] 8. MoCA-Blind: Montreal Cognitive Assessment [3mos,6mos,12mos]	• The trial was stopped at the second interim analysis for futility. • At 90 days, 213 patients (42.5%) in the intervention group and 216 (42.8%) in the control group had died before hospital discharge (between group difference, −0.3 percentage points; 95% confidence interval, −6.4 to 5.9; P=0.93). • In the hospital, patients in the intervention group were less physically active and had more adverse cardiovascular events than patients in the control group. -There were no consistent between-group differences in end points as assessed at 3, 6, and 12 months.

Appendix 4. Risk of Bias Table

Study	Sequence Generation	Allocation Concealment	Blinding	Withdrawal; loss to follow-up	Selective outcome reporting	Free of other bias	Overall risk of bias
Gainnier et. al. (2004)	Low risk	Low risk Centralized	Low risk Nurses aware of assignment; infusion covered by sheet.	Low risk None	Low risk None	Low risk None	Low
Forel et. al. (2006)	Low risk	Low risk Centralized	Low risk Nurses aware of assignment; infusion covered by sheet.	Low risk None	Low risk None	Low risk None	Low
Papazian et. al. (2010)	Low risk	Low risk Centralized, using undisclosed block sizes	Low risk Blinding of patients, clinicians, evaluators, invstigators, analysts	Low risk None	Low risk None	Low risk None	Low
Lyu et. al. (2014)	Low risk	Unclear risk Not reported	High risk Probably only patients blinded	Unclear risk Not reported	High risk Incomplete reporting	High risk Unclear	High
Guervilly et. al. (2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low
Rose (2019)	Low risk	Low risk Process not specifically explained	Low risk Primary end point unblinded. Uncertainty about In-hospital assessors of end points being unaware of treatment group, but all post-discharge end points were assessed by trial personnel who were unaware of the group assignment.	Low risk	Low risk	Low risk Although trial was topped early for futility it included a very large number of events	Low

Appendix 5. GRADE Evidence Profile

5.1 GRADE PROFILE: Sedation vs Non Sedation

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sedation	No sedation	Relative (95% CI)	Absolute (95% CI)		
90-Day Mortality												
2	Randomised trials	Not serious	Serious[a]	Serious[b]	Serious[c]	None	157/409 (38.4%)	168/404 (41.6%)	RR 1.00 (0.70 to 1.43)	0 fewer per 1,000 (from 125 fewer to 179 more)	⨁⨁◯◯ Low	CRITICAL
Length of ICU Stay												
2	Randomised trials	Not serious	Not serious	Serious[b]	Serious[c]	None	409	404	-	MD 0.34 lower (6.15 lower to 5.47 higher)	⨁⨁◯◯ Low	IMPORTANT
Ventilator Free Days												
2	Randomised trials	Not serious	Not serious	Serious[b]	Serious[c]	None	409	404	-	MD 1.07 lower (3.05 lower to 0.91 higher)	⨁⨁◯◯ Low	IMPORTANT
Adverse Event: Delirium												
1	Randomised trials	Not serious	Not serious	Serious[b]	Serious[c]	None	4/58 (6.9%)	11/55 (20.0%)	**RR 0.34** (0.12 to 1.02)	**132 fewer per 1,000** (from 176 fewer to 4 more)	⨁⨁◯◯ Low	CRITICAL
Adverse Event: Extubation												
2	Randomised trials	Not serious	Not serious	Serious[b]	Serious[c]	None	7/409 (1.7%)	11/404 (2.7%)	**RR 0.66** (0.26 to 1.66)	**9 fewer per 1,000** (from 20 fewer to 18 more)	⨁⨁◯◯ Low	CRITICAL
Adverse Event: Major Thrombotic Event (Pulmonary Embolism & Deep Vein Thrombosis)												
1	Randomised trials	Not serious	Not serious	Serious[b]	Not serious	None	10/351 (2.8%)	1/349 (0.3%)	**RR 9.94** (1.28 to 77.26)	**26 more per 1,000** (from 1 more to 219 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse Event: Reintubation												
1	Randomised trials	Not serious	Not serious	Serious[b]	Serious[c]	None	11/58 (19.0%)	7/55 (12.7%)	**RR 1.49** (0.62 to 3.57)	**62 more per 1,000** (from 48 fewer to 327 more)	⨁⨁◯◯ Low	CRITICAL
Adverse Event: Ventilator-Associated Pneumonia												
1	Randomised trials	Not serious	Not serious	Serious[b]	Serious[c]	None	7/58 (12.1%)	6/55 (10.9%)	**RR 1.11** (0.40 to 3.09)	**12 more per 1,000**	⨁⨁◯◯ Low	CRITICAL

										(from 65 fewer to 228 more)		

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

Explanations

[a] Significant heterogeneity (I^2>50%)

[b] Study population were mechanically ventilated patients with ARDS but of non-COVID etiology

[c] Risk estimates crossed the line of no effect

5.2. GRADE PROFILE: Neuromuscular Blockade vs Standard of Care (Sedation Only)

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 SOC	With NMBA		Risk with SOC	Risk difference with NMBA
Duration of Mechanical Ventilation											
431 (3 RCTs)	Not serious	Not serious	Serious[b]	Not serious	None	⨁⨁⨁◯ Moderate	208	223	-	The mean duration of Mechanical Ventilation was **-1.21**	MD **1.21 lower** (4.23 lower to 1.81 higher)
Mortality Outcome by Level of Sedation (Light) at 90 days											
1006 (1 RCT)	Not serious	Not serious	Serious[b]	Serious[c]	None	⨁⨁◯◯ Low	216/505 (42.8%)	213/501 (42.5%)	**RR 0.99** (0.86 to 1.15)	428 per 1,000	**4 fewer per 1,000** (from 60 fewer to 64 more)
Mortality Outcome by Level of Sedation (Deep) at t 90 days											
431 (3 RCTs)	Not serious	Not serious	Serious[b]	Not serious	None	⨁⨁⨁◯ Moderate	98/208 (47.1%)	76/223 (34.1%)	**RR 0.72** (0.58 to 0.91)	471 per 1,000	**132 fewer per 1,000** (from 198 fewer to 42 fewer)
Mortality Outcome at 21-28days											
503 (5 RCTs)	Not serious	Not serious	Serious[b]	Not serious	None	⨁⨁⨁◯ Moderate	98/245 (40.0%)	65/258 (25.2%)	**RR 0.63** (0.49 to 0.82)	400 per 1,000	**148 fewer per 1,000** (from 204 fewer to 72 fewer)
ICU Mortality											

455 (4 RCTs)	Not serious	Not serious	Serious[b]	Not serious	None	⊕⊕⊕◯ Moderate	98/221 (44.3%)	73/234 (31.2%)	**RR 0.70** (0.55 to 0.89)	443 per 1,000	**133 fewer per 1,000** (from 200 fewer to 49 fewer)
Improvement in Oxygenation after 48hours (assessed with: PaO2/FiO2)											
821 (3 RCTs)	Not serious	Serious[a]	Serious[b]	Serious[c]	None	⊕◯◯◯ Very Low	394	427	-	The mean improvement in Oxygenation after 48hours was **0**	MD **22.2 higher** (4.47 lower to 48.88 higher)
Improvement in Oxygenation after 72hours (assessed with: PaO2/FiO2)											
1011 (4 RCTs)	Not serious	Not serious	Serious[b]	Serious[c]	None	⊕⊕◯◯ Low	469	542	-	The mean improvement in Oxygenation after 72hours was **0**	MD **12.9 higher** (3.88 higher to 21.92 higher)
Ventilator Free Days (Day 28)											
1437 (4 RCTs)	Not serious	Not serious	Serious[b]	Serious[c]	None	⊕⊕◯◯ Low	713	724	-	The mean ventilator Free Days (Day 28) was **0**	MD **0.68 higher** (0.86 lower to 2.22 higher)
Barotrauma											
1437 (4 RCTs)	Not serious	Not serious	Serious[b]	Not serious	None	⊕⊕⊕◯ Moderate	52/713 (7.3%)	29/724 (4.0%)	**RR 0.55** (0.35 to 0.85)	73 per 1,000	**33 fewer per 1,000** (from 47 fewer to 11 fewer)
Pneumothorax											
1401 (3 RCTs)	Not serious	Not serious	Serious[b]	Not serious	None	⊕⊕⊕◯ Moderate	45/695 (6.5%)	21/706 (3.0%)	**RR 0.46** (0.28 to 0.77)	65 per 1,000	**35 fewer per 1,000** (from 47 fewer to 15 fewer)
ICU Acquired Weakness											
714 (4 RCTs)	Not serious	Not serious	Serious[b]	Serious[e]	None	⊕⊕◯◯ Low	115/351 (32.8%)	136/363 (37.5%)	**RR 1.15** (0.95 to 1.39)	328 per 1,000	**49 more per 1,000** (from 16 fewer to 128 more)
Adverse Events											

1437 (4 RCTs)	Not serious	Not serious	Serious[b]	Serious[f]	None	⊕⊕◯◯ Low	22/713 (3.1%)	36/724 (5.0%)	**RR 1.63** (0.97 to 2.71)	31 per 1,000	**19 more per 1,000** (from 1 fewer to 53 more)

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

Explanations

[a] Significant heterogeneity (I2>50%)

[b] The population included in the studies are Non-Covid ARDS patients. Based on latest studies, there are some considered differences between the pathology of Non- Covid and Covid ARDS which may change the actual results if the said population was studied.

[c] CI included both small benefit and harm

[d] Downgraded by 1 due to serious imprecision. CI included extreme benefit and harm

[e] CI included substantial harm and trivial benefit.

[f] The CI included both substantial harm and small benefit. Also, the number of events is small (n=58).

Appendix 6. Characteristics of Ongoing Studies

6.1 Study Characteristics of Ongoing Studies on Sedation and Neuromuscular Blockade on COVID-19 patients (n=4)

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
Comparison for the Effect of Neuromuscular Blocking Agents Versus Sedation Alone on Severe ARDS Patients Due to COVID-19 NCT04922814 August 1, 2022	**Experimental:** Muscle relaxant group (group B) They will receive muscle relaxation treatment for at least 48 hours. Cisatracurium will be given. Short term infusions up to 24 hours will be given in a dose rate of 2-3 mic/Kg/min followed by intervallic shots of 2-5 mg.	**Control:** No Intervention (Group A) Only sedation for mechanically ventilated COVID patients	• 18 Years to 75 Years • With Severe ARDS: • PaO2/FiO2 <200, resistant hypoxemia and tachypnoea (RR > 40 breath/minute) • Not relieved by high frequency nasal canula or CPAP. • Need for invasive mechanical ventilation (uncooperative) • ***NOT YET RECRUITING***	**Primary Outcome Measures:** • PaO2/FiO2: Ratio of arterial oxygen pressure in milliliters mercury to fraction of inspired oxygen at same time within the arterial blood gas **Secondary Outcome Measures:** • Change in lung mechanics • SOFA score • Measurement of tissue perfusion: • Monitoring of Alveolar - Arterial Oxygen difference • 28 days survival • Recording risk factors • Recording complications
Sevoflurane Sedation in COVID-19 ARDS Patients to Reduce Lung Injury: a Randomized Controlled Trial NCT04355962 July 16, 2021 *(Final data collection date for primary outcome measure)* (No results posted yet)	**Experimental**: Sevoflurane Sedation Sedation with sevoflurane (etSevo 0.5-1.5 Vol %) for 48 hours in patients with COVID-19 ARDS	**Control:** Intravenous No use of sevoflurane, but current intravenous sedation at discretion of the ICU physician in charge, e.g. with propofol, fentanyl, midazolam and dexmedetomidine	• Male and female patients • 18 to 85 years • -Positive SARS-CoV-2 test or CTscan suspected of COVID-19 ARDS • -On sedation and mechanical ventilation in ICU	**Primary Outcome Measures:** • Composite outcome of death rate (rate of patients that did not survive) • Organ failure rate (rate of patients surviving with persistent organ dysfunction) at day 28 **Secondary Outcome Measures:** • The effect of sevoflurane • Plasma Inflammatory markers • Length of stay at hospital • Sex-related differences in complications
Inhaled Sedation in COVID-19-related Acute Respiratory Distress Syndrome (ISCA): an International Research Data Study in the Recent Context of Widespread Disease Resulting From the 2019 (SARS-CoV2) Coronavirus Pandemics (COVID-19)NL8523 NCT04383730 April 30, 2021 *(Final data collection date for primary outcome measure)* (No results posted yet)	**Experimental:** Inhaled sedation	**Control:** Intravenous sedation	• >18years old • Admitted in ICU requiring invasive mechanical ventilation • Suspected or confirmed COVID19	**Primary Outcome Measures:** • Number of days off the ventilator **Secondary Outcome Measures:** • All-cause mortality • Ventilator-free days • ICU-free • Number of days alive and not in the ICU from inclusion to day 28 • Duration of invasive mechanical ventilation • Duration of controlled mechanical • Physiological measures of lung function • Development of complications • Duration of vasopressor • Duration of renal replacement therapy

				• Duration (in days) of any adjuvant therapies • Number of days with continuous neuromuscular blockade • Type of sedation practices
SedAting With Volatile Anesthetics Critically Ill COVID-19 Patients in ICU: Effects On Ventilatory Parameters And Survival. Multicentre Open-label, Pragmatic, Randomized Controlled Trial and a Parallel Prospective (Non-randomized) Cohort Study NCT04415060 June 15, 2023	**Experimental:** Inhaled - volatile anesthetic The ICU patient will be randomized to either Isoflurane or Sevoflurane, whichever is available at the hospital. Dosage will be modified as per health care team guidance for the best treatment of the participant. **Interventions:** Drug: Isoflurane Inhalant Product Drug: Sevoflurane inhalant product	**No Intervention:** Standard Care The ICU patient will be randomized to standard of care, which is any IV sedation supplied by the hospital. Dosage will be modified as per health care team guidance for the best treatment of the participant. **No Intervention:** Non-randomized ICU patients who cannot be randomized will receive inhaled or IV sedation as per available in their unit. This is done to try to obtain the maximum amount of information available from the patients present to our ICUs.	• ≥ 18 years of age; • Mechanically ventilated • Receiving IV sedation by infusion or bolus for ≤72 hours to facilitate mechanical ventilation • Proven or suspected (under investigation) COVID-19 infection	**Primary Outcome Measures:** • Hospital Mortality • Ventilator-Free • ICU-Free Days • Participant Quality of Life at 3 and 12 months after discharge **Secondary Outcome Measures:** • Median Daily Oxygenation • Delirium and Coma Free Days • Adjunctive ARDS therapies • Hospital-Free Days • Disability • Cost Utility Analysis • Quality of Life

6.2 Study Characteristics of Ongoing Studies on Sedation on NON COVID patients (n=1)

Title Identifier Expected Completion Date	Intervention	Control Intervention: Comparator/Control	Patients/Population Recruited	Outcomes
Non-sedation versus sedation with a daily wake-up trial in critically ill patients receiving mechanical ventilation (NONSEDA Trial): study protocol for a randomised controlled trial NCT00196768 June 2018 *(Final data collection date for primary outcome measure)* (No results posted yet)	**Experimental:** The experimental group will not receive sedatives. Patients are thoroughly and repeatedly informed by the staff of where they are, what has happened, and what type of treatment they are going to receive.	**Control:** The control group will be sedated with continuous infusion of sedatives to Ramsay score 3 to 4. The first 48 hours the patients will be sedated with propofol, after 48 hours midazolam will be used.	-Endotracheally intubated within the last 24 hours -Expected time on ventilator >24 hours as estimated by the attending physician -Age ≥18 years	**Primary Outcome Measures:** -All-cause mortality at 90 days after randomization **Secondary Outcome Measures:** -Days until death throughout the total observation period -Coma- and delirium-free days -Highest RIFLE score days until discharge from the intensive care unit (within 28 days) -Days until the participant is without mechanical ventilation (within 28 days); and) -Proportion of patients with a major cardiovascular outcome. Explorative outcomes: -All cause mortality at 28 days after randomization -Days until discharge from the intensive care unit -Days until the participant is without mechanical ventilation -Days until discharge from the hospital - Incidence of organ failure

Appendix 7. Forest Plots

A. SEDATION IN MECHANICALLY VENTILATED PATIENTS

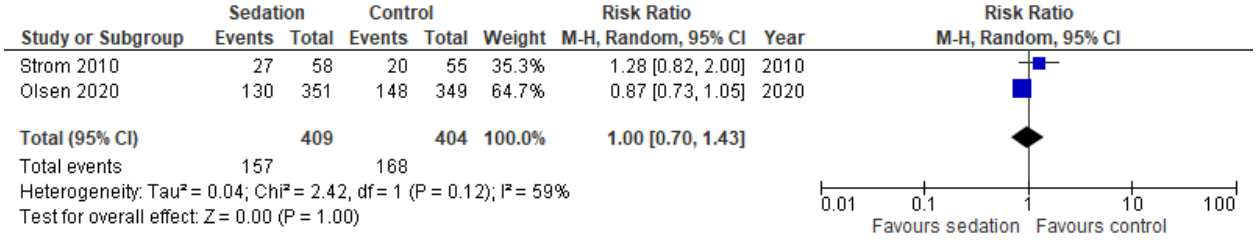


Figure 1. 90-day Mortality Outcome for Sedation versus No Sedation

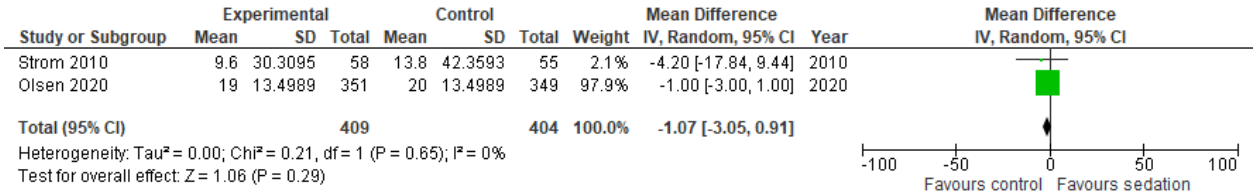


Figure 2. Ventilator Free Days for Sedation versus No Sedation

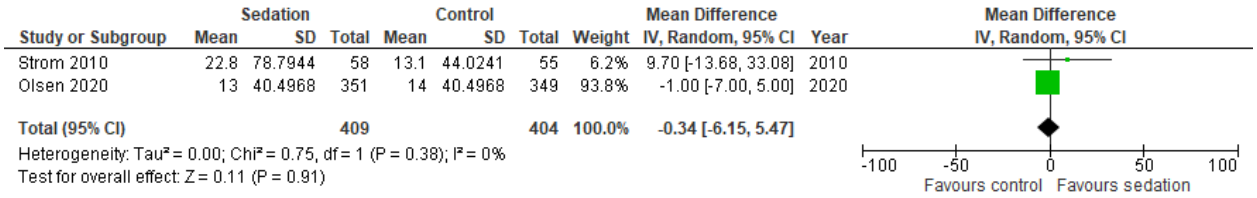


Figure 3. Length of ICU Stay for Sedation versus No Sedation

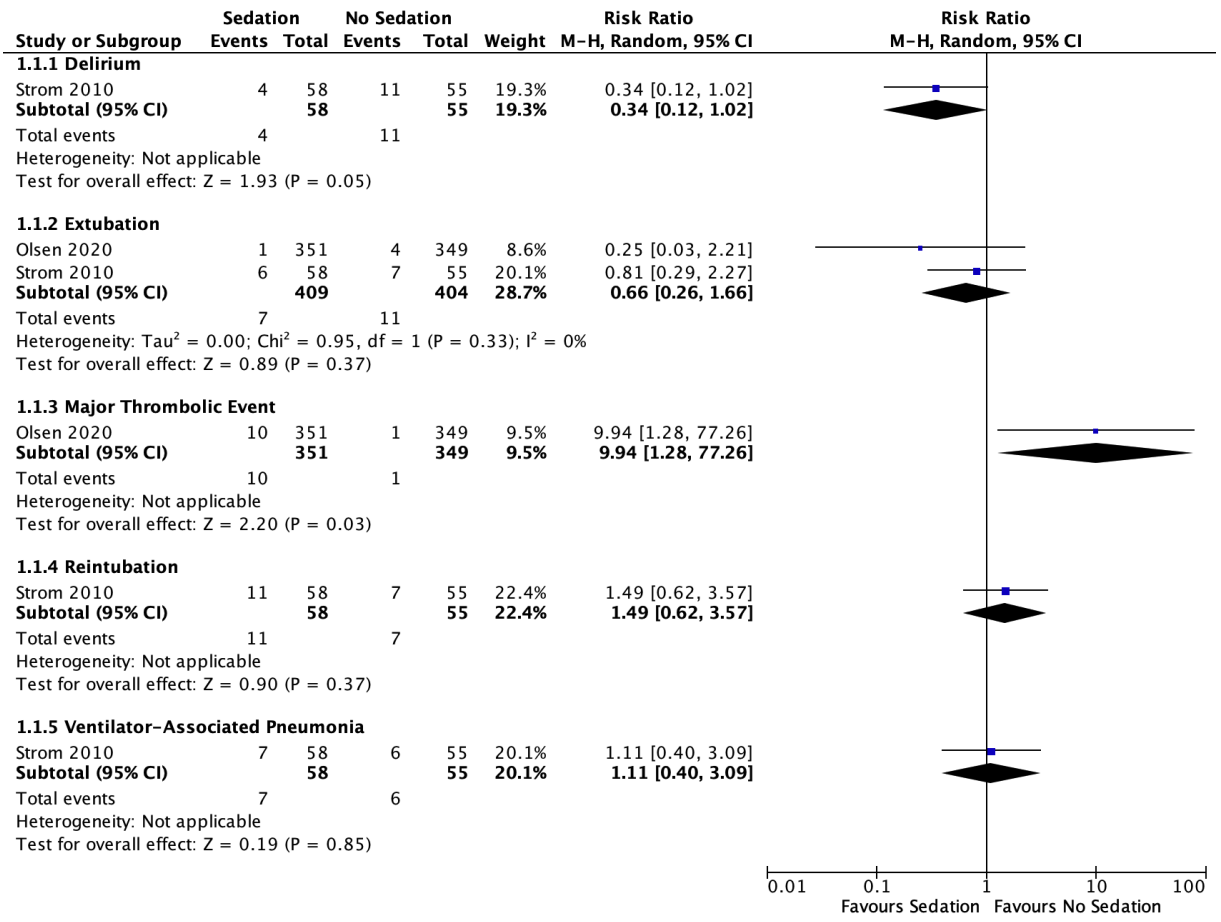


Figure 4. Adverse Events for Sedation versus No Sedation

B. NMBA IN MECHANICALLY VENTILATED PATIENTS WITH ARDS

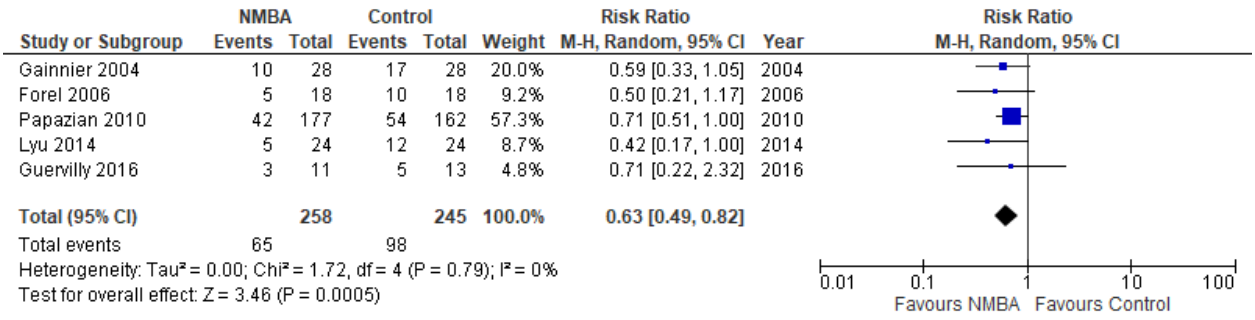


Figure 5. Mortality at 21-28 days

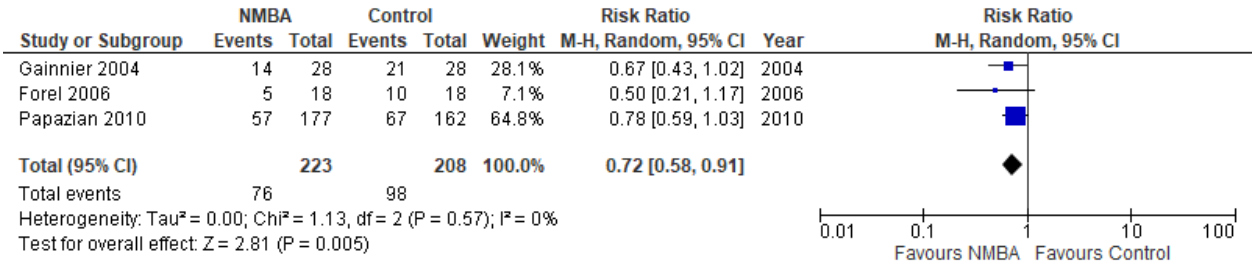


Figure 6. Mortality at 90 days

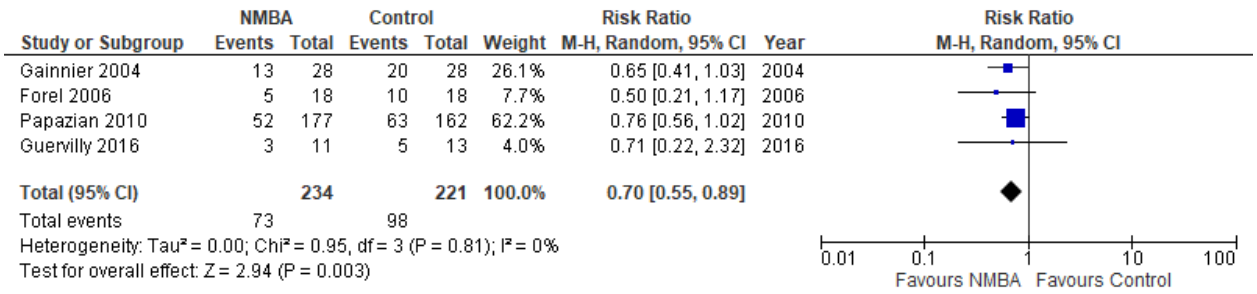


Figure 7. ICU Mortality

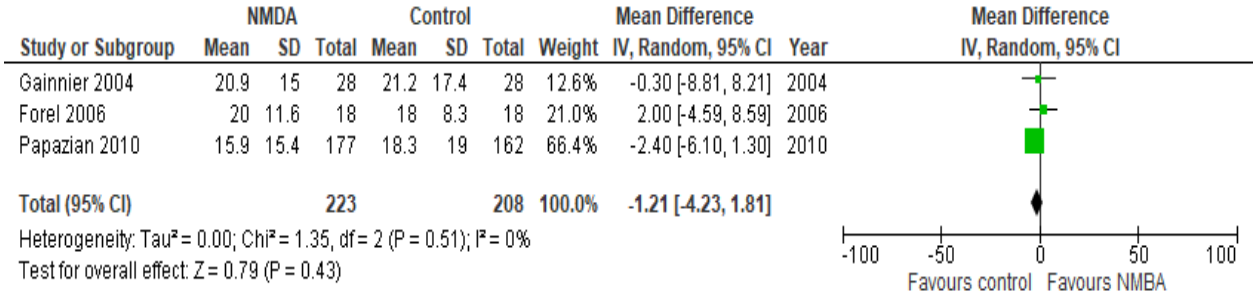


Figure 8. Duration of Mechanical Ventilation

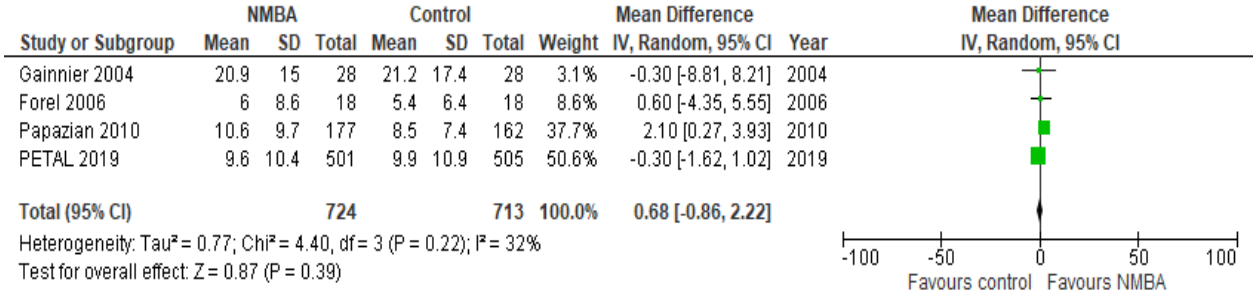


Figure 9. Ventilator Free Days at day 28

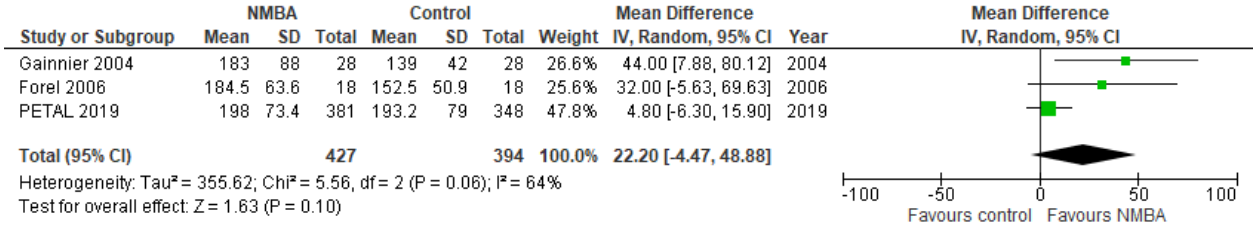


Figure 10. PaO_2/FiO_2 Changes after 48 hours

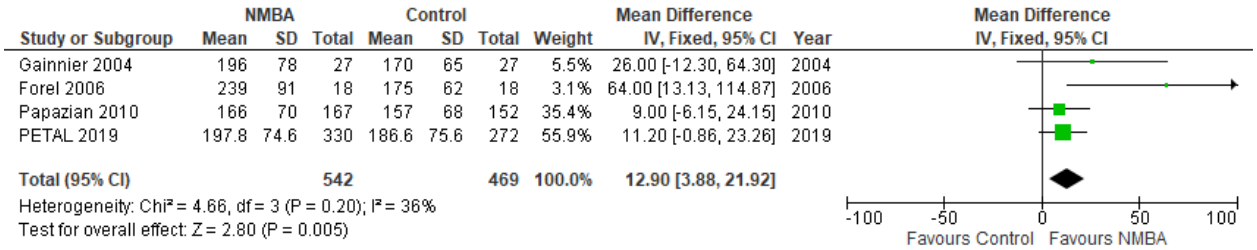


Figure 11: PaO_2/FiO_2 Changes after 72hours

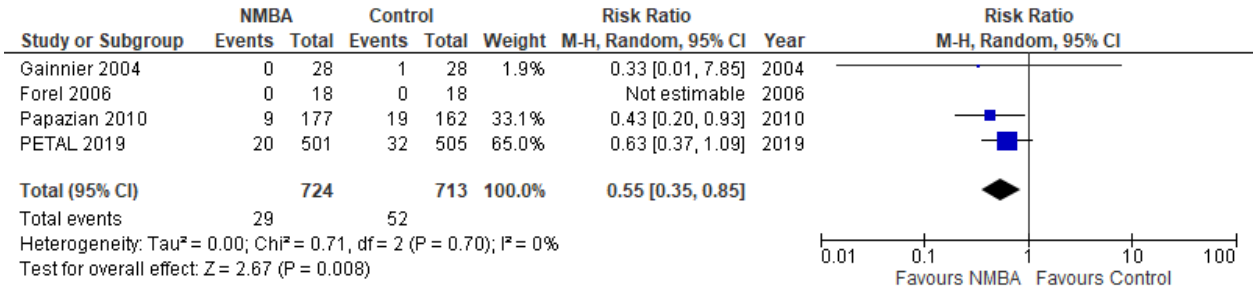


Figure 12. Barotrauma

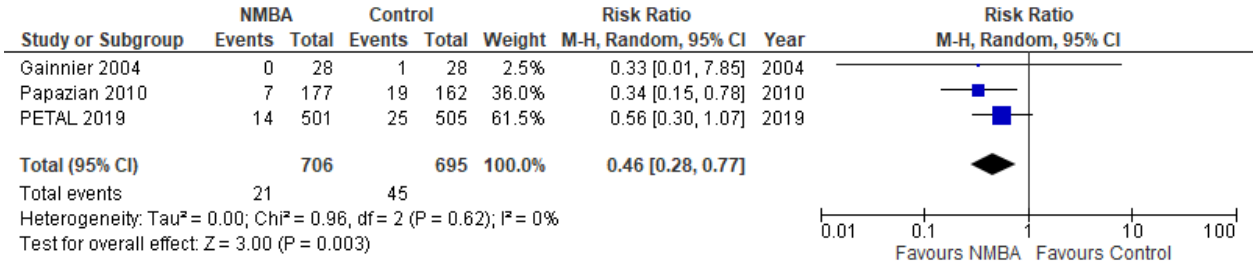


Figure 13. Pneumothorax

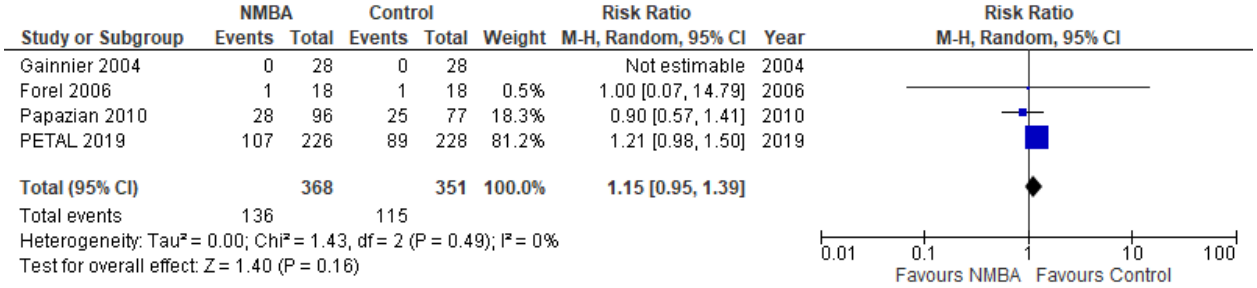


Figure 14. ICU Acquired Weakness

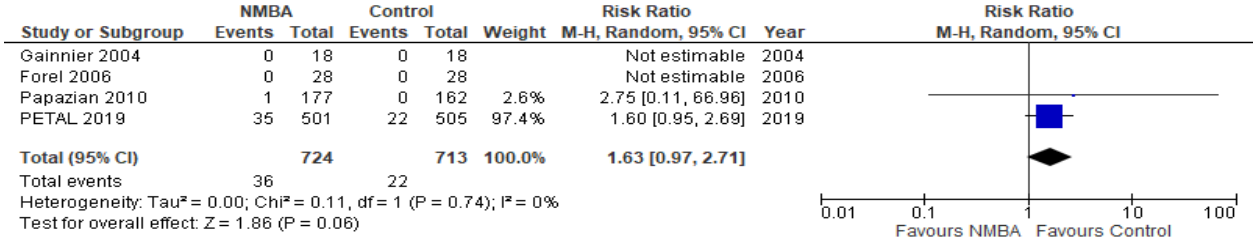


Figure 15. Adverse Events

Appendix 8. Other Tables

Table 7. Adverse Events with NMBA infusion

System/Disorder	Event	Severity	Intervention	Control	Overall
Blood/lymphatic	Methemoglobinemia	Serious	2	0	2
Cardiac	Complete atrioventricular block	Serious	1	0	1
	Atrial fibrillation (paroxysmal)	Non-Serious	1	0	1
	Atrial fibrillation w/ rapid vent response	Serious	1	0	1
	Bradycardia	Serious	1	0	1
		Non-Serious	1	0	1
	Cardiac arrest	Serious	6	2	8
		Non-Serious	0	2	2
	Cardiac arrhythmia (NOS)	Non-Serious	1	0	1
	3rd degree atrioventricular block	Serious	0	1	1
	Myocardial infarction	Serious	1	1	2
	Serious prolonged bradycardia	Non-Serious	1	0	1
	Tachycardia	Non-Serious	1	0	1
	Supraventricular tachycardia	Serious	1	0	1
	Torsades De Pointe	Serious	1	0	1
	Vasovagal reaction	Non-Serious	0	1	1
	Ventricular tachycardia	Serious	2	0	2
Gastrointestinal	Ileus	Non-Serious	0	1	1
General	Death *	Serious	1	0	1
Infection	Pneumonia	Non-Serious	0	1	1
Injury	Paralysis awareness	Non-Serious	1	0	1
Metabolism/nutrition	Hyperkalemia	Serious	0	1	1
Musculoskeletal	Myopathy	Non-Serious	1	0	1
Nervous system	Intracranial bleed	Serious	0	1	1
	Cerebral infarction	Serious	1	1	2
	Cerebrovascular accident	Serious	1	0	1
	Brain hemorrhage	Serious	1	1	2
	Polyneuropathy	Serious	0	1	1
	Seizure	Serious	1	0	1
	Stroke	Serious	3	1	4
	Subarachnoid hemorrhage	Serious	0	1	1
	Subdural effusion	Serious	1	0	1
Respiratory tract	Aspiration	Serious	0	1	1
		Non-Serious	0	1	1
	Airway obstruction	Serious	1	0	1
Vascular disorders	Hematoma	Serious	0	1	1
	Retroperitoneal hemorrhage	Non-Serious	0	1	1
	Hypotension	Serious	1	1	2
		Non-Serious	6	2	8
	Superficial venous thrombosis	Non-Serious	1	0	1

Q14. Should inhaled nitric oxide be used in patients with COVID-19?

As of 26 October 2021

RECOMMENDATION

We recommend against the use of nitric oxide among patients with COVID-19. *(Low certainty of evidence; Strong recommendation)*

Consensus Issues
A strong recommendation against the use of nitric oxide was unanimously given on the basis of low certainty of currently available evidence (non-peer reviewed pre-print article with small population and imprecision of effect estimates) to justify its use and the high cost of the intervention.

KEY FINDINGS

One open-label randomized controlled trial showed that the administration of inhaled nitric oxide as an adjunct to standard-of-care among hospitalized patients with moderate COVID-19 infection had no significant difference in 28-day mortality, need for mechanical ventilation, intensive care unit length of stay, hospital length of stay, viral clearance, and two-point WHO Ordinal Scale improvement when compared to standard-of-care alone. The incidence of methemoglobinemia was also not significantly different among patients who were given inhaled nitric oxide compared to those who received standard-of-care. The certainty of evidence was low due to lack of allocation concealment and serious imprecision of effect estimates.

INTRODUCTION

COVID-19 is an ongoing pandemic from the SARS-COV-2 virus. While vaccines have been made available to protect against the deadly disease, to date, there has been no specific drug identified to treat the infection as it continues to spread around the globe. Nitric oxide (NO), a free radical that has bronchodilator and vasodilator effects, has been shown to inhibit viral replication and inactivate viruses as previous studies from the 2004 SARS-CoV infection demonstrated.[1,2] In addition, NO plays a key role in vascular function and regulating the inflammatory cascade which, when excessively activated, can lead to acute respiratory distress syndrome (ARDS) and acute lung injury (ALI).[3,4] Knowing its pathophysiology and its potential role in mitigating viral infections, NO is currently being suggested as a potential therapy for severe and critical COVID-19 patients.

REVIEW METHODS

A search was done through PubMed of available studies to search for the best evidence of the role of nitric oxide in COVID-19 patients. The following search terms were used: “inhaled nitric oxide”, “therapy”, “COVID 19 treatment”. A total of 30 studies were retrieved after data search. After duplicates were removed, a total of 28 studies were screened with 7 articles excluded after title/abstract screening due to different primary outcome of interest (pulmonary hypertension reversal), use of another intervention on top of inhaled nitric oxide (veno-venous ECMO) and population of interest (mild COVID patients treated in OPD setting). After review of inclusion criteria, a total of 8 studies were included in the final review and a randomized controlled trial was included in the final evidence summary.

RESULTS

A single randomized control trial [5] was included in the final evidence review (n = 25, low certainty of evidence). The study was a phase II open label, randomized controlled trial done in a tertiary hospital in India. A total of 29 patients with moderate COVID (SpO_2 <94%, Respiratory Rate> 24) were enrolled with 25 patients completing the trial (treatment group = 14, control group = 11). Inhaled nitric oxide (iNO) was given via pulse in a crescendo-decrescendo pattern twice daily for 3 consecutive days. Primary outcome was decline in viral load, and cycle threshold was measured pre-, during and post-treatment.

Mortality and need for invasive mechanical ventilation

A total of 4 patients died in the control group (4/11, 36%) while none died in the iNO group. Moreover, 4 other patients in the control group also required mechanical ventilation.

Other important outcomes

Longitudinal analysis of viral loads collected on days 0, 3, 5, 7 and 10 show reduction in viral load in the iNO group with increased viral efficiency compared to the control group, which was not statistically significant (RR 1.37, 95% CI 0.96-1.97; p> 0.05 at Day 7). Other important outcomes including average length of ICU stay (MD -2.08 days, 95% CI -5.75-1.59; p>0.05), average length of hospital stay (MD -2.29 days, 95% CI -8.99-4.41; p>0.05), viral load decline at 7 days (RR 1.37, 95% CI 0.96-1.97; p >0.05) and 2 point improvement in WOS at 7 days were also not significant between the two groups (RR 1.05, 95% CI 0.74-1.49, p >0.05). None of the patients administered iNO demonstrated increase methemoglobin >3% throughout treatment.

ONGOING STUDIES

There are currently 10 ongoing randomized clinical trials [6-15] registered in the clinicaltrials.gov assessing the efficacy of inhaled nitric oxide for COVID-19 among adult patients.

EVIDENCE TO DECISION

A study evaluating the cost effectiveness of inhaled nitric oxide in pediatric ICU patients was done in 2015 showing that the direct cost was $100 per hour regardless of dose without a statistically significant difference in mortality.[17] In the Philippines, nitric oxide is used as a biomarker of inflammation and is measured as fraction of exhaled nitric oxide (FeNO).[19] In the Philippines, FeNO has been studied for obstructive lung diseases.[20, 21] No local studies to date evaluate cost, feasibility and efficacy of FeNO for COVID-19 patients.

RECOMMENDATIONS FROM OTHER GROUPS

The Society of Critical Care Medicine recommends against the routine use of iNO in patients with COVID 19 pneumonia.[16] Instead, they recommend a trial of iNO only in mechanically ventilated patients with severe COVID ARDS and hypoxemia despite other rescue strategies. Meanwhile, the Philippine Society for Microbiology and Infectious Diseases states that there is no current evidence to support its use for patients with COVID-19.[18]

RESEARCH GAPS

Most studies on the utility of inhaled nitric oxide are observational studies and clinical trials are still ongoing to assess efficacy and safety of the intervention for COVID-19 patients.[6-15]

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Appendix 1. Evidence to Decision

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

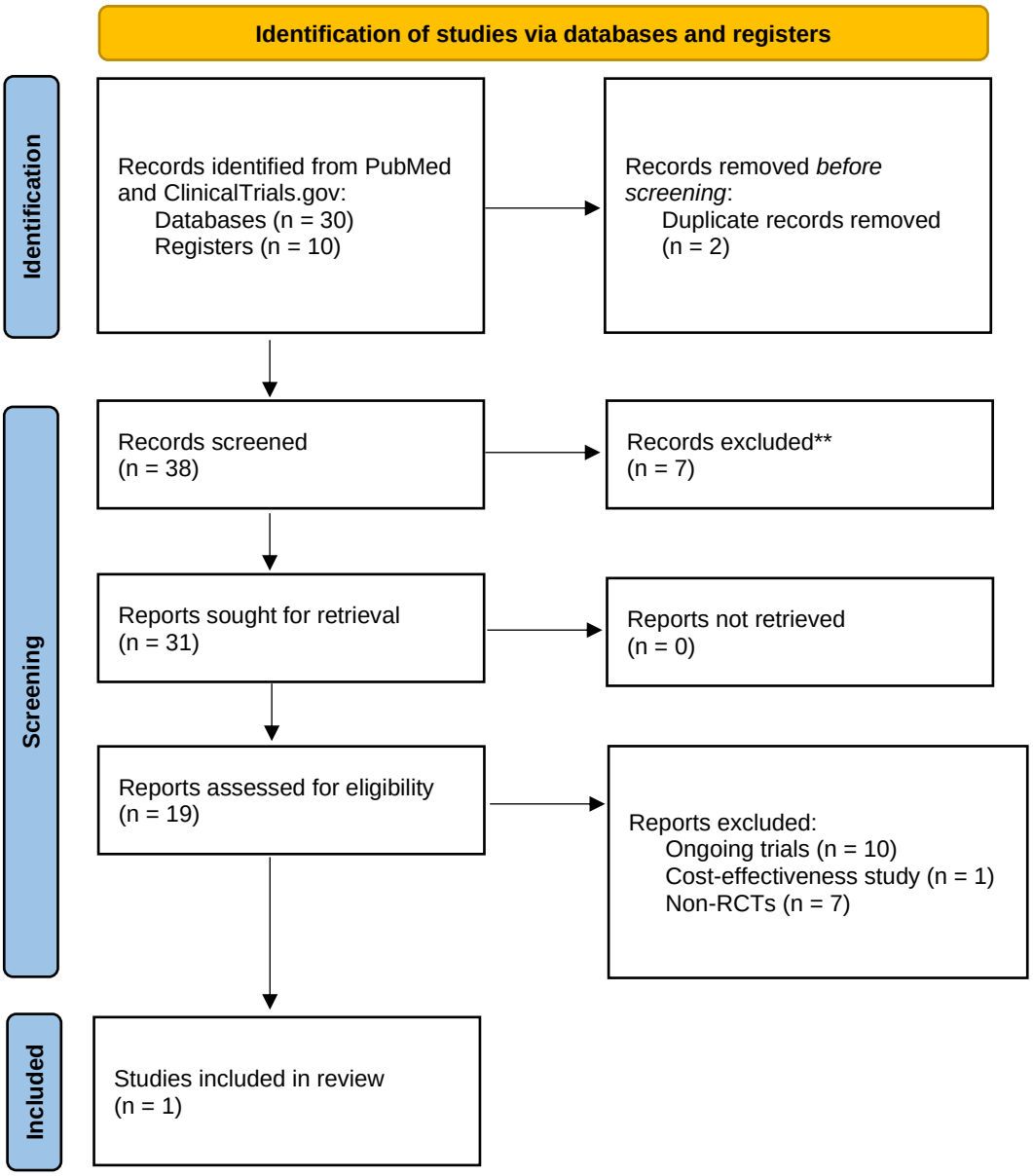
FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					• NO plays a key role in vascular function and regulating inflammatory cascade which when excessively activated can lead to acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) [3,4].
Benefits	Large	Moderate (2)	Small (3)	Uncertain (4)			• Significant reduction in viral load in iNO group (p <0.002, n = 23) • Outcome of improvement ≥ 2 points in the WHO ordinal scale (WOS) for severe acute respiratory infections was also observed in the iNO group. • SOFA, total length of stay in the ICU and hospital were insignificant between the two groups.
Harm	Large	Small (7)	Uncertain	No response			• None of the patients administered iNO demonstrated increase methemoglobin > 3% throughout treatment.
Certainty of Evidence	High	Moderate	Low (7)	Very low (2)			
Balance of effects	Favors drug	Does not favor drug	Uncertain (6)				• Limited RCTs evaluating the efficacy and safety of inhaled nitric oxide for COVID-19
Values	Important uncertainty or variability	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability	No important uncertainty or variability			• No research evidence found
Resources Required	Uncertain (1)	Large cost (5)	Moderate Cost (3)	Negligible cost	Moderate savings	Large savings	• Direct cost was $100/h regardless of dose without a statistically significant difference in mortality [17].
Certainty of evidence of required resources	No included studies (5)	Very low (4)	Low	Moderate	High		• Cost is based on economic burden of disease from a study in 2015 from pediatric ICU patients. No studies were retrieved on adult patients during the evidence review.
Cost effectiveness	No included studies (8)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (7)	Reduced	Probably no impact	Increased			
Acceptability	Uncertain (7)	No (2)	Yes				
Feasibility	Uncertain (6)	No	Yes				

Appendix 2. Search Yield and Results

Hand searching, Google Scholar and PUBMED

Search	Query	Results
#4	#1 AND #2 AND #3 **((inhaled nitric oxide AND therapy [MeSH]) AND (COVID 19 treatment [MeSH])) AND (inhaled nitric oxide AND COVID 19)**	30
#3	**inhaled nitric oxide AND COVID 19** ("administration, inhalation"[MeSH Terms] OR ("administration"[All Fields] AND "inhalation"[All Fields]) OR "inhalation administration"[All Fields] OR "inhalant"[All Fields] OR "inhalability"[All Fields] OR "inhalable"[All Fields] OR "inhalants"[All Fields] OR "inhalated"[All Fields] OR "inhalation"[MeSH Terms] OR "inhalation"[All Fields] OR "inhal"[All Fields] OR "inhalations"[All Fields] OR "inhale"[All Fields] OR "inhaled"[All Fields] OR "inhaling"[All Fields] OR "inhalational"[All Fields] OR "inhalative"[All Fields] OR "inhalatively"[All Fields] OR "inhalent"[All Fields] OR "inhaler s"[All Fields] OR "inhales"[All Fields] OR "nebulizers and vaporizers"[MeSH Terms] OR ("nebulizers"[All Fields] AND "vaporizers"[All Fields]) OR "nebulizers and vaporizers"[All Fields] OR "inhalator"[All Fields] OR "inhalators"[All Fields] OR "inhaler"[All Fields] OR "inhalers"[All Fields]) AND ("nitric oxide"[MeSH Terms] OR ("nitric"[All Fields] AND "oxide"[All Fields]) OR "nitric oxide"[All Fields]) AND ("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 "sars cov 2"[All Fields] OR "sars cov 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]))	70
#2	**COVID 19 treatment [MeSH]** ("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 "sars cov 2"[All Fields] OR "sars cov 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])) AND "therapeutics"[MeSH Terms]	23,147
#1	**inhaled nitric oxide AND therapy [MeSH]** ("administration, inhalation"[MeSH Terms] OR ("administration"[All Fields] AND "inhalation"[All Fields]) OR "inhalation administration"[All Fields] OR "inhalant"[All Fields] OR "inhalability"[All Fields] OR "inhalable"[All Fields] OR "inhalants"[All Fields] OR "inhalated"[All Fields] OR "inhalation"[MeSH Terms] OR "inhalation"[All Fields] OR "inhal"[All Fields] OR "inhalations"[All Fields] OR "inhale"[All Fields] OR "inhaled"[All Fields] OR "inhaling"[All Fields] OR "inhalational"[All Fields] OR "inhalative"[All Fields] OR "inhalatively"[All Fields] OR "inhalent"[All Fields] OR "inhaler s"[All Fields] OR "inhales"[All Fields] OR "nebulizers and vaporizers"[MeSH Terms] OR ("nebulizers"[All Fields] AND "vaporizers"[All Fields]) OR "nebulizers and vaporizers"[All Fields] OR "inhalator"[All Fields] OR "inhalators"[All Fields] OR "inhaler"[All Fields] OR "inhalers"[All Fields]) AND ("nitric oxide"[MeSH Terms] OR ("nitric"[All Fields] AND "oxide"[All Fields]) OR "nitric oxide"[All Fields]) AND "therapeutics"[MeSH Terms]	3,975

Search Yield and Results



PRISMA 2020 Flow Diagram

Appendix 3. Characteristics of Included Studies

(1) – Randomized Controlled Trial

Study ID	Study Design	Setting	Population	Intervention	Comparator	Outcomes
Moni M et al. 2021 A feasibility trial to evaluate the composite efficacy of inhaled nitric oxide in the treatment of COVID-19 pneumonia: impact on viral load and clinical outcomes	RCT	India	COVID confirmed with moderate symptoms (sPO2 <94% and RR > 24)	inhaled nitric oxide given in pulse for 3 days	standard of care	Primary outcome: Viral load Secondary outcomes: 28 day all cause mortality, need for invasive ventilation, length of hospital/ICU stay, change in SOFA score, methemoglobin levels > 3%

Appendix 4. Characteristics of Excluded Studies

(7) – Observational studies

Study ID	Study Design	Setting	Population	Intervention	Comparator	Outcomes
Longobardo A et al. 2021 Inhaled nitric oxide produces minimal improvement in oxygenation in COVID-19 related ARDS	Retrospective case control (single center)	London, UK (ICU)	ICU patients with ARDS COVID and non COVID	inhaled nitric oxide given to COVID 19 patients in ARDS (n = 27)	inhaled nitric oxide patients given to non-COVID 19 patients in ARDS (n = 20)	- Improvement in PaO2:FiO2 ratio - Conclusion: more than half of patients with refractory hypoxemia secondary to COVID 19 ARDS did not show increase PF ratio in response to iNO; response much lower compared to cohort with non-COVID ARDS
Safaee F et al. 2021 Inhaled nitric oxide is a safe and effective respiratory treatment in spontaneous breathing hospitalized patients with COVID-19 pneumonia	Interventional study (single arm) comment: RCT protocol but did not reach target patients	Massachusetts, USA	Symptomatic non-intubated adults admitted for COVID 19	inhaled nitric oxide + standard of care iNO twice daily at 160 ppm for 30 mins x 14 days (n = 29)	no comparator	- Mortality, need for invasive ventilation, time to clinical recovery, hospital length of stay, viral shedding - Conclusion: acute improvement of systemic oxygenation in hypoxemic patients and reduced respiratory rate
Tavazzi G et al. 2020	Interventional study	Pavia, Italy	COVID-19 mechanically	inhaled nitric oxide + standard of care	no comparator	- Improvement in hypoxemia and hemodynamic parameters

Inhaled nitric oxide in patients admitted to intensive care unit	(single arm)		ventilated patients with refractory hypoxemia (ARDS)	iNO at 25 ppm for 30 minutes (n = 16)		- Conclusion: iNO did not improve oxygenation in COVID-19 patients with refractory hypoxemia
Benjamin G et al. 2020 Potential for personalized application of inhaled nitric oxide in COVID-19 pneumonia	Interventional study (single arm)	London, UK	COVID-19 mechanically ventilated patients with refractory hypoxemia (ARDS)	inhaled nitric oxide + standard of care iNO at 20 ppm for an average of 146.4 hours (n = 35)	no comparator	- Improvement in hypoxemia (PF ratio) - Conclusion: iNO may be helpful in patients with COVID-19 with refractory hypoxemia
Lotz C et al. 2020 Effects of inhaled nitric oxide in COVID-19 induced ARDS – is it worthwhile?	Retrospective observational study	Wurzburg, Germany	COVID-19 mechanically ventilated patients with refractory hypoxemia (ARDS)	inhaled nitric oxide + standard of care iNO at 20 ppm x 15-30 mins for as long as deemed necessary (n = 7)	no comparator	- Hemodynamics, hypoxemia - Conclusion: non-significant pulmonary vasodilation with significant improvement in arterial oxygenation
Ferrari M et al. 2020 Inhaled nitric oxide in mechanically ventilated patients with COVID-19	Interventional study (single arm)	Milan, Italy	COVID-19 mechanically ventilated patients with refractory hypoxemia (ARDS)	inhaled nitric oxide + standard of care iNO at 20 ppm x 30 mins – continue as deemed necessary if with initial improvement in hypoxemia after 30 mins (n = 10)	no comparator	- Improvement in hypoxemia - Conclusion: No significant improvement in arterial oxygenation
Abou-Arab et al. 2020 Inhaled nitric oxide for critically ill COVID-19 patients	Interventional study (single arm)	Amiens, France	COVID-19 mechanically ventilated patients with refractory hypoxemia (ARDS)	inhaled nitric oxide + standard of care iNO at 10 ppm x 30 mins (n = 34)	no comparator	- Improvement in respiratory parameters (PEEP, respiratory compliance, driving pressures, PF ratio) - Conclusion: 65% response rate to iNO administration

Appendix 5. Characteristics of Ongoing Studies (10)

Study ID	Study Design	Setting	Population	Intervention	Comparator	Outcomes
Inhaled nitric oxide for preventing progression in COVID-19 (NO-COVID-19)	RCT	USA	COVID-19 confirmed with high risk for mortality	iNO	standard of care	- Prevention of progressive systemic de-oxygenation
High dose inhaled nitric oxide for COVID-19 patients	RCT	Toronto, Canada	COVID-19 critical patients	iNO	standard of care	- Viral load and ICU admission
Nitric oxide inhalation therapy for COVID-19 infections in ED (NO COV-ED)	RCT	USA	COVID-19 patients in ED	iNO	standard of care	- Inpatient hospitalization, rates of intubation, rates of mortality
NO prevention of COVID-19 for healthcare providers	RCT	USA	healthcare workers in COVID-19 areas	iNO	no intervention	- COVID-19 diagnosis, RT PCR positive test, total number of quarantine days
Nitric oxide gas inhalation in severe acute respiratory syndrome in COVID-19 (NOSARSCOVID)	RCT	USA	hypoxic COVID-19 confirmed patients	iNO	standard of care	- Improvement in oxygenation, mortality
Nitric oxide gas inhalation therapy for mild/moderate COVID-19 (NoCOVID)	RCT	USA	COVID-19 confirmed with mild to moderate illness	iNO	standard of care	- Reduction in the incidence of patients with mild/moderate COVID-19 requiring invasive ventilation
Inhaled NO for the treatment of COVID-19 caused by SARS-COV-2 (US trial)	RCT	USA	COVID-19 confirmed patients with sPO2 <93% on room air	iNO	standard of care	- Time to deterioration
Nitric oxide therapy for COVID-19 patients with oxygen requirement	RCT	Russia	COVID-19 confirmed patients needing oxygen support	iNO	standard of care	- Change in methemoglobin levels, improvement in oxygenation, time to clinical recovery
Prevent viral exposure and transmission study: a SARS-COV2 PEP study	RCT	USA	non-confirmed COVID patients with exposure to known COVID positive patients	iNO	standard of care	- Incidence of newly confirmed COV-2 infection in previously uninfected household members
A study to assess efficacy and safety of RESP301 plus standard of care to standard of care alone in hospitalized participants with COVID 19	RCT	United Kingdom	COVID-19 confirmed patients	iNO	standard of care	- Proportion of participants who progress using WHO ordinal scale by day 14, desaturation

Appendix 6. GRADE Evidence Profile

Author(s): Mithi Kalayaan Zamora MD, Vaneza Leah Espino MD, Christopher G. Manalo MD
Question: Inhaled NO compared to standard of care for COVID-19 infection
Setting: Hospitalized COVID-19 patients

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled NO	SOC	Relative (95% CI)	Absolute (95% CI)		
28-day Mortality												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	0/14 (0.0%)	4/11 (36.4%)	RR 0.0889 (0.0053 to 1.4935)	**331 fewer per 1,000** (from 362 fewer to 179 more)	⨁⨁◯◯ Low	CRITICAL
Need for Mechanical Ventilation												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	0/14 (0.0%)	4/11 (36.4%)	RR 0.0899 (0.0053 to 1.4935)	**331 fewer per 1,000** (from 362 fewer to 179 more)	⨁⨁◯◯ Low	CRITICAL
Average Intensive Care Unit Length-of-Stay (assessed with: Days)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	14	11	-	MD 2.08 days lower (5.75 lower to 1.59 higher)	⨁⨁◯◯ Low	IMPORTANT
Average Hospital Length-of-Stay (assessed with: Days)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	14	11	-	MD 2.29 days lower (8.99 lower to 4.41 higher)	⨁⨁◯◯ Low	IMPORTANT
Viral Clearance at Day 7 (N-Gene) (assessed with: CT Value >35)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	12/12 (100.0%)	8/11 (72.7%)	RR 1.3750 (0.9575 to 1.9746)	**273 more per 1,000** (from 31 fewer to 709 more)	⨁⨁◯◯ Low	IMPORTANT
Viral Clearance at Day 7 (ORF1ab) (assessed with: CT value>35)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	12/12 (100.0%)	10/11 (90.9%)	RR 1.1000 (0.9125 to 1.3260)	**91 more per 1,000** (from 80 fewer to 296 more)	⨁⨁◯◯ Low	IMPORTANT
Incidence of Methemoglobin Levels >3%												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	0/14 (0.0%)	0/11 (0.0%)	RR 0.8000 (0.0171 to 37.4368)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	IMPORTANT

Two-point Improvement in WOS at Day 7											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	2/14 (14.3%)	2/11 (18.2%)	RR 1.0476 (0.7374 to 1.4884)	**9 more per 1,000** (from 48 fewer to 89 more)	⊕⊕◯◯ Low	IMPORTANT
Two-point Improvement in WOS at Day 14											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	11/14 (78.6%)	4/11 (36.4%)	RR 2.1607 (0.9438 to 4.9465)	**422 more per 1,000** (from 20 fewer to 1,000 more)	⊕⊕◯◯ Low	IMPORTANT

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

Explanations

[a] Lack of allocation concealment

[b] Confidence interval crosses line of no effect

Q15. Should etoposide be given among patients with severe COVID-19 pneumonia in cytokine storm?

As of 15 April 2021

RECOMMENDATION

We recommend against the use of etoposide among patients with COVID-19 pneumonia in cytokine storm *(Very low certainty of evidence; Strong recommendation)*

Consensus Issues

There is not enough high-quality evidence to show that etoposide is useful for the management of COVID-19 patients with pneumonia in cytokine storm. There are significant adverse events with the use of etoposide, namely: alopecia, nausea, vomiting, myelosuppression, acute hypersensitivity reactions, hepatotoxicity, hypotension from rapid infusion, and secondary malignancies.

KEY FINDINGS

Very low quality evidence was found on the use of etoposide as treatment for severe COVID-19: one case series and one case report. The case series showed an improvement in PaO2-FiO2 ratio (PFR) post-treatment of etoposide. Among the 14 patients studied in both studies, three patients expired while ten patients improved and were subsequently discharged. Adverse effects of etoposide include alopecia, gastrointestinal symptoms, acute hypersensitivity reactions, myelosuppression, and rarely, secondary malignancies such as acute myelocytic leukemia.

INTRODUCTION

Clinical and laboratory findings in secondary hemophagocytic lymphohistiocytosis (sHLH) are due to upregulations in pro-inflammatory cytokines. Incidentally, many of the criteria for the diagnosis of sHLH (fever, splenomegaly, cytopenias affecting at least 2 lineages, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in biopsy, elevated plasma ferritin, low or absent NK-cell activity, and elevated sCD25R) are found in moderately-severe to severe COVID-19 and are predictors of COVID-19 mortality. [1] Etoposide, a topoisomerase II inhibitor, is the standard of care for sHLH and aims to target cytokine storm [1] as well as inhibit hyperactivation of inflammatory monocyte-derived macrophages seen in patients with COVID-19 [2].

REVIEW METHODS

Electronic search through PubMed, Cochrane Library Database, ChinaXiv, MedRxiv, BioRxiv, Clinicaltrials.gov, ChiCTR, Living Evidence on COVID-19 (https://zika.ispm.unibe.ch/assets/data/pub/search_beta/) was done from March 17-22 2020. Studies evaluating the effects of etoposide on patients with severe COVID-19 pneumonia were searched using the keywords COVID-19, SARS-CoV-2 and etoposide. Databases such as Cochrane Library Database, ChinaXiv, MedRxiv, BioRxiv, Clinicaltrials.gov, ChiCTR yielded 0 results. Advanced search in PubMed was done and the following search term: ((COVID-19) OR (SARS-CoV-2)) AND (etoposide), yielded 16 studies. Electronic search through Living Evidence on COVID-19 yielded the same results. After screening of titles and abstracts, 2 studies were retrieved and included.

RESULTS

Both studies by Montero-Baladia et al. [4] and Patel et al. [5] reported the effects of etoposide among patients with severe COVID-19 infection. (Appendix 1 and 4). The case series by Montero-Baladia et al. included adults with COVID-19 ARDS and with biochemical alterations suggestive of severe inflammation (ferritin >1000ng/mL and/or IL-6 >50pg/mL). Other interventions given to the patients included oxygen support, lopinavir-ritonavir, antimicrobials, methylprednisolone, interleukin inhibitors (tocilizumab, anakinra), orotracheal intubation, mechanical ventilation, prone positioning, prophylactic enoxaparin and therapeutic anticoagulation if needed. Meanwhile, the case report by Patel et al. reported a 66-year old female diagnosed with severe COVID-19 pneumonia and met four of the eight criteria for the diagnosis of HLH. Other interventions included orotracheal intubation, mechanical ventilation, sarilumab (as part of a trial), anakinra, intravenous immunoglobulin, antimicrobials, bivalirudin, acyclovir, cotrimoxazole and dexamethasone. Patients in both studies were given etoposide doses of 50-150mg/m^2 weekly for 1-2 doses.

The major limitation of the two studies is its study design. Other limitations include the lack of a control group for the studies, the small population (n=14), lack of standardized dosing and frequency of etoposide and a history of varied interventions prior to and concurrent with etoposide among patients.

In the case series by Montero-Baladia, et al., mean PFR among the patients studied improved by 164% after treatment with etoposide, from a mean PFR of 110$\pm$40 prior to etoposide, to a mean PFR of 290$\pm$131 post-treatment. Combining both studies of Montero- et al. and Patel, et al., out of the 14 patients, five patients needed mechanical ventilation (three of which were already mechanically ventilated prior to treatment with etoposide), ten patients fully recovered and were discharged, while three patients died (including two patients who died due to thrombotic complications). Four patients had adverse effects: three patients had cytopenias of at least two cell lineages with two of the patients having concomitant infections while one patient had mild elevation in transaminases. [4, 5]

Similar to other chemotherapeutic agents, common minor adverse effects occur in 20-30% of patients and include alopecia (8-66%), gastrointestinal symptoms such as nausea and vomiting (31-43%), and anorexia (10-13%). Myelosuppression is a major adverse effect and is a common dose-limiting factor, with leukopenia occurring in 60-91% of cases and thromboycytopenia in 22-41%. Other major and less common adverse effects (in 1-10% of cases) include acute hypersensitivity reactions in <1%, such as flushing, bronchospasm, cyanosis, hypertension or hypotension. Hepatotoxicity in <3% and hypotension from rapid infusion of the drug in 1-2% of cases also occur. Lastly, etoposide treatment has also been shown to cause secondary malignancies such as acute myelocytic leukemia in some case reports. [6, 7]

RECOMMENDATIONS FROM OTHER GROUPS

As of writing, none of the existing COVID-19 guidelines from National Institutes of Health, Infectious Diseases Society of America, Philippine Society for Microbiology and Infectious Diseases, Philippine Academy of Family Physicians and Australian Living CPG recommended etoposide as treatment for COVID-19.

RESEARCH GAPS

There is one ongoing study on the effect of etoposide in severe COVID-19 pneumonia which is expected to be completed by June 2022. [Appendix 3].

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Appendix 1. Characteristics of Included Studies

Study	Study Design	Population Characteristics	Intervention	Other Interventions	Outcomes reported
Montero-Baladia, et al., Sep 2020, Spain	Case Series	n=13 Patients with COVID-19, >18years old with biochemical alterations suggestive of severe hyper-inflammation*, ARDS	Etoposide: 50 – 150 mg/m^2 x 1-2 doses	Oxygen support, lopinavir-ritonavir, anti-microbials, methylpredniso-lone, interleukin inhibitors (tocilizumab, anakinra), orotracheal intubation, mechanical ventilation, prone positioning, prophylactic enoxaparin, therapeutic anticoagulation if needed	Improvement in PFR, Need for mechanical ventilation, recovery and discharge, mortality, adverse events
Patel, et al., Jan 2021, USA	Case report	n=1 66F diagnosed with COVID-19, with T2DM, hypertension, hyperlipidemia Mechanically ventilated Met 4 / 8 criteria for HLH	Etoposide: 50mg/m^2 once a week x 2 doses	Orotracheal intubation, mechanical ventilation, sarilumab (as part of a trial), anakinra, IVIg, antimicrobials, bivalirudin, acyclovir, cotrimoxazole, dexamethasone	Decline in biomarkers, liberation from ventilator, improvement in condition to allow for discharge, adverse effects

***ARDS**: Acute respiratory distress syndrome; **HLH**: Hemophagocytic lymphohistiocytosis; **IVIg**: Intravenous immunoglobulin; **PFR**: arterial oxygen partial pressure to fractional inspired oxygen ratio; **T2DM**: Type 2 Diabetes Mellitus*

**Peak ferritin > 500ng/mL and one or more of the following: LDH > 500U/L, d-dimer >1000 ng/mL, CRP > 100mg/L, or white blood count >15k/microlitre*

Appendix 2. GRADE Evidence Profile

Certainty assessment							Impact	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Mortality									
2	Observational studies	Very serious [a]	Not serious	Not serious	Not serious	None	Among 14 patients with severe COVID-19 who were given etoposide, 3 patients died due to thrombotic complications.	⊕◯◯◯ VERY LOW	
Rate of mechanical ventilation									
2	Observational studies	Very serious [a]	Not serious	Not serious	Not serious	None	Among 14 patients with severe COVID-19 who were given etoposide, 5 were on invasive mechanical ventilation. Of note, however is that 3 of the 5 patients were already on invasive mechanical ventilation prior to treatment of etoposide.	⊕◯◯◯ VERY LOW	
Discharge Rate									
2	Observational studies	Very serious [a]	Not serious	Not serious	Not serious	None	Among 14 patients with severe COVID-19 who were given etoposide, 10 patients were discharged from the hospital.	⊕◯◯◯ VERY LOW	
PFR									
1	Observational studies	Very serious [a]	Not serious	Not serious	Not serious	None	Mean PFR among the patients studied improved by 164% after treatment with etoposide, from a mean PFR of 110±40 prior to etoposide, to a mean PFR of 290±131 post-treatment	⊕◯◯◯ VERY LOW	

CI: Confidence interval

Explanations

[a] There was no comparison group for the studies, with a small population of patients included.

Appendix 3. Table of Ongoing Studies

Study	Study Design	Sample Size (n)	Inclusion Criteria	Dose of Etoposide	Comparison	Outcomes reported
Sloan & Jose, 2020-2022, USA	Randomized, open-label phase II study	64	>18years old with evidence of cytokine storm* Two Cohorts: (a) intubated due to COVID-19, (b) evidence of progressive respiratory failure (requiring >4L/min of supplemental oxygen to maintain O2 saturation of > 92%) without intubation	150 mg/m^2 on Days 1 and 4	Standard of care	Primary: Change in pulmonary status Secondary: Change in ferritin levels, change in CRP, change in d-dimer, change in WBC count, incidence of serious adverse events, overall survival, length of hospitalization, duration of ventilation, ventilator free days, improvement in arterial oxygen partial pressure to fractional inspired oxygen

**Defined as peak ferritin > 10,000ng/mL OR peak ferritin >500ng/mL and one or more of the following at any time during hospital stay: LDH > 500U/L, d-dimer >1000ng/mL, CRP > 100ng/mL, or WBC > 15k/uL.*

Appendix 4. Clinical and laboratory characteristics and outcomes of patients given etoposide in the included studies

Characteristic	Montero-Baladia													Patel
	1	2	3	4	5	6	7	8	9	10	11	12	13	
Age	56	41	63	79	60	70	55	57	64	58	79	73	42	66
Sex	M	M	M	M	F	M	M	F	M	M	M	M	M	F
Dose of etoposide (mg/m^2)	80	80	100	50	100	100	150	150	150	150	50	50	174	50
Total number of doses	1	1	2	1	2	1	2	2	2	2	2	1	1	2
PFR Pre Etoposide	150	94	150	73	98	96	112	63	52	174	63	118	154	ND
PFR post-etoposide	430	452	435	ND	200	445	287	120	160	321	180	120	340	ND
Oxygen support*	NI	NI	NI	I	I	NI	S	NI	I	S	I	NI	S	I
Outcome**	D	D	D	DNR	M	D	D	D	D	D	H	M	D	D
Hospital stay (days)	15	15	13	11	13	14	7	20	5	5	15	14	32	ND
Cyopenia > 2 lines	No	No	No	No	Yes	No	No	No	Yes	No	No	Yes	No	No
Infections	No	No	No	No	Enteroco-ccus	No	No	No	HSV1	No	No	No	No	UTI, VAP, PCP

**Oxygen support: NI: Noninvasive; I: Invasive; S: Spontaneous*
***Outcome: D: Discharged; M: Mortality; H: Still hospitalized by completion of the study; DNR: Do not resuscitate directive signed by representative ND: No data available; PCP: Pneumocystis carinii pneumonia; PFR: arterial oxygen partial pressure to fractional inspired oxygen ratio; UTI: Urinary tract infection; VAP: Ventilator associated pneumonia*

Q16. Should pulmonary rehabilitation be done among long COVID patients with residual pulmonary symptoms to improve pulmonary function and quality of life?

As of 19 February 2021

RECOMMENDATION

We recommend individualized pulmonary rehabilitation with pre-intervention medical clearance for long COVID patients who show residual respiratory symptoms *(Moderate certainty of evidence; Strong recommendation)*

Consensus Issues

The panel recommends that the start and duration of pulmonary rehabilitation of each patient should be individualized depending on the assessment of a pulmonologist. Studies showed that the assessment of pulmonary rehabilitation among long COVID patients should start at least 6 months after their hospital admission and last for as long as 6 weeks. However, recommendations on when the assessment for pulmonary rehabilitation should start differ across professional medical societies. An international task force with representation from the European Respiratory Society and the American Thoracic Society recommends that the assessment should be done 6-8 weeks after hospital discharge in order to identify patients who will have residual symptoms. In addition, pulmonary rehabilitation for other disease conditions lasts for 6-9 weeks.

KEY FINDINGS

We found one randomized controlled trial that investigated the effect of pulmonary rehabilitation (PR) among long COVID patients with residual respiratory symptoms. The study was found to have a moderate risk of bias due to absence of blinding for both patients and outcome assessors and unclear allocation process. They also enrolled only participants above 65 years of age. Based on moderate quality of evidence, pulmonary function tests of those who received pulmonary rehabilitation significantly improved. Quality of life and anxiety scales also significantly differed between groups, with improvement noted in the PR group compared to no PR. There was no significant difference for depression and activities of daily living between groups and within groups before and after the intervention. The RCT did not report any adverse events; indirect evidence from PR done on COPD patients likewise showed no to low number of adverse events which did not hinder the feasibility and safety of the procedure of pulmonary rehabilitation.

INTRODUCTION

COVID-19 patients suffer long term effects after the acute phase of the infection, a condition now known as long COVID. Other terms referred to this condition are post-acute COVID-19 syndrome, post-acute sequelae of COVID and long-haul or long-tail COVID. This group includes patients suffering from symptoms four to twelve weeks after the acute phase (ongoing symptomatic COVID-19) and those suffering symptoms for >12 weeks past the onset of infection (post-COVID-19 syndrome) [1]. Pulmonary rehabilitation (PR) is a multidisciplinary approach used in improving functional status of patients who are suffering/suffered pulmonary diseases such as interstitial lung disease, chronic obstructive pulmonary disease and even SARS infection [2,3].

REVIEW METHODS

We searched for articles that investigated long COVID patients (P) who underwent respiratory rehabilitation (I) to improve patients' pulmonary function and quality of life (O). We performed a systematic literature search in online databases such as MEDLINE, Cochrane, and Google Scholar. Additional searches in MedRxiv, BioRxiv, clinicaltrials.gov , and WHO ICTRP were also done to look for articles awaiting publication and ongoing clinical trials, respectively. We used mesh terms for "long COVID," "post-COVID," "respiratory rehabilitation," and "pulmonary function". References from review articles were also manually searched for additional articles. We also performed a free search. Letters, narrative reviews, and case reports were excluded. Studies that did pulmonary rehabilitation while patient is still admitted at the ICU were also excluded.

RESULTS

Efficacy

Our initial search yielded 215 articles from which we obtained one randomized control trial (RCT) which fit our inclusion criteria. Liu et. Al. [4] investigated the effect of pulmonary rehabilitation which included respiratory muscle training, cough exercise, diaphragmatic training, stretching exercise and home exercise among long COVID patients at least 6 months after their hospital admission (N= 76, intervention group n= 38). Participants were all above 65 years old and those who received the intervention underwent their regimen once a day for ten minutes, with two sessions per week for 6 weeks.

Primary outcome was the respiratory function reported as forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, and diffuse lung capacity for carbon monoxide (DLCO) pre-PR and six weeks post-PR. (Table 1). Patients receiving PR had statistically significant improvement in all pulmonary function tests compared to the control group, as well as post-PR pulmonary parameters compared to pre-PR. Among the secondary outcomes, those who received PR had significant improvement in quality of life (assessed using the Short Form-36 questionnaire) compared to those who did not (p value <0.05 among all eight domains: (physical health, body role function, physical pain, general health, energy, social function, emotional role function, mental health). Anxiety and depression scores improved post-intervention in the PR group, but only the anxiety scores were statistically significant within and between the groups compared. Activities of daily living (ADL) assessed using the Functional Independence Measure (FIM) on the other hand showed no significant difference among and between groups pre and post-PR.

This RCT was appraised to have a moderate risk of bias because blinding was not possible for the participants. Outcome assessors were also not blinded and the allocation process was not mentioned. This study is also limited by the population, which investigated only patients aged 65 years or older.

Table 1. Differences among those who received pulmonary rehabilitation (PR) and no PR (reported as mean difference, 95% CI, p-value)

	PR vs no PR	Control (pre vs 6 wks after)	PR (pre vs 6 wks after)
FEV1 (MD in L)	-0.18 (95%CI -0.31 to -0.05, p <0.05)	0.13 (0.02 to 0.24, p=0.02)	0.34 (0.26 to 0.42, p <0.05)
FVC(MD in L)	-0.28 (-0.48 to -0.08, p<0.05)	0.31 (0.07 to 0.55, p=0.01)	0.57 (0.34 to 0.80, p <0.05)
FEV1/FVC (MD %)	-6.96 (-9.81 to -4.11, p <0.05)	0.79 (-2.0 to 3.58, p =0.564)	7.7 (4.87 to 10.55, p<0.05)
TLCO (MD %)	-15.1 (-20.98 to -9.22, p <0.05)	2.3 (-3.51 to 8.11, p =0.43)	17.8 (12.4 to 23.2, p <0.05)
Exercise capacity (6min walk test,m)	-55.1 (-90.4 to -19.77, p <0.05)	1.5 (-33.73 to 36.73, p=0.93)	49.6 (14.2 to 85, p <0.05)
ADL (FIM)	-0.5 (-5.3 to 4.35, p =0.84)	-0.4 (-5.16 to 4.36, p=0.87)	0.2 (-5.32 to 5.73, p =0.07)
Quality of life (FIM)	Across 8 domains, significant improvement within groups, and in between groups after 6 weeks, p<0.05		
Anxiety	7.5 (4.38 to 10.6, p<0.05)	-0.9 (-4.26 to 2.46 p=0.6)	-8.9 (-12.22 to -5.58, p<0.05)
Depression	1.3 (-1.68 to 4.2, p=0.39)	-0.1 (-3.39 to 3.19, p=0.95)	-1.9 (-5.09 to 1.29, p=0.24)

Safety

Liu et al. did not report adverse events in their study. Indirect evidence showed PR to be generally safe and feasible. He et al. reported that no adverse events were observed in the conduct of their RCT comparing PR versus no PR for the improvement of dyspnea, endurance capacity, and health-related quality of life in patients with chronic obstructive pulmonary disease (COPD) in acute exacerbation [5]. Pleguezuelos et al., used limb warm-up and aerobic exercises in their study for PR, reported two major complications (defined as warranting discontinuation of PR), both in patients with previous hypertension, diabetes and dyslipidemia: acute coronary syndrome in a 71-year-old patient, and a debut of cardiac arrythmia in a 60-year-old patient. They reported the incidence of major complications as 2.7/10,000 hours of PR (n=291). Minor complications were noted: three individuals with acute low back pain and two with increased sensation of dyspnea (incidence of 6.5/10 000 hours) of physical exercise [6].

RECOMMENDATIONS FROM OTHER GROUPS

The WHO recommends that patients who experience persistent symptoms or disability after discharge from the hospital should be screened for physical, mental and cognitive impairments, and those deemed to have rehabilitation needs should be given such, tailored to the needs of individual patients [5]. No specific recommendation or guideline was further provided. An international task force composed of a European Respiratory society and the American Thoracic Society recommends assessment of respiratory function and exercise capacity 6 to 8 weeks after hospital discharge and provide those in need with a comprehensive individualized rehabilitation program including pulmonary rehabilitation if necessary [6]. An Indian Society recommends different respiratory exercises for post-COVID patients 3-6 weeks after discharge depending on the severity of the patient's COVID-19 infection [7]. Exercises should include respiratory exercise endurance, strength training, energy conservation and patient education.

RESEARCH GAPS

There are currently nine registered ongoing clinical trials that investigate the effect of respiratory exercises among previously admitted COVID-19 patients.

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Appendix 1. Characteristics of Included Studies

Authors	Country	Population	Intervention	Control	Outcomes
Liu 2020	China	Previously admitted COVID-19 patients aged >65 years old recruited 6 months after the onset of infection	Respiratory rehabilitation 2 sessions per week for 6 weeks, each session held once a day for 10 minutes	No respiratory rehabilitation	Respiratory function (FEV1, FVC, FEV1/FVC, DLCO)

Appendix 2. GRADE Evidence Profile

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulmonary rehabilitation	No rehabilitation	Relative (95% CI)	Absolute (95% CI)		
FEV1												
1	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	none	38	38	-	MD 0.18 higher (0.05 higher to 0.31 higher)	⊕⊕⊕◯ MODERATE	
FVC												
1	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	38	38	-	MD 0.28 higher (0.08 higher to 0.28 higher)	⊕⊕⊕◯ MODERATE	
FEV1/FVC												
1	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	38	38	-	MD 6.96 higher (4.11 higher to 9.81 higher)	⊕⊕⊕◯ MODERATE	
DLCO												
1	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	38	38	-	MD 15.1 higher (9.22 higher to 20.98 higher)	⊕⊕⊕◯ MODERATE	
6min walk test												
1	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	38	38	-	MD 55.1 higher (19.77 higher to 90.4 higher)	⊕⊕⊕◯ MODERATE	
functional independence measure												
1	Randomised trials	Serious [a]	Not serious	Not serious	Not serious	None	38	38	-	MD 0.5 higher (4.35 lower to 5.3 higher)	⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **MD:** Mean difference

Explanations

[a] allocation concealment unclear, no blinding

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	Organization of Pulmonary Rehabilitation of Post-COVID-19 patient with sequelae (REHABCOVID) NCT04634318	Recruiting	Study start: December 10,2020 Estimated primary completion: December 2021	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	France	Known COVID-19 patient who have atleast one post-COVID-19 sequelae	Respiratory tele-rehabilitation program	Respiratory Rehabilitation program	6min walk test 1min sit to stand test Dyspnea and fatigue evaluation Anxiety and depression evaluation
2	Implementation of a respiratory physiotherapy program in post covid-19 patient through tele-assistance NCT04678700	Recruiting	Start date: March 1, 2021 Estimated primary completion: June 1, 2021	Allocation: Randomized Intervention Model: Parallel Assignment Intervention Model Description: Experimental study composed of an intervention group and a control group The control group will receive the intervention after finishing the intervention with the experimental group. Masking: None (Open Label) Primary Purpose: Treatment	Spain	Patients with COVID-19 in the recovery period who still have subjective dyspnea	Chest physiotherapy modules	No physotherapy	Euroqil-5d quality of life tool Dyspnea scale Borg Anxiety Scale
3	SingStrong: Strong Lungs through song long covid study NCT04810065	Recruiting	Start: March 29, 2021 Estimated completion: July 2021	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Ireland	Previously diagnosed COVID-19 patient with residual symptoms of shortness of breath, disordered breathing, or reduced exercise tolerance	Biweekly hour-long breathing and singing classes	none	COVID-19 Yorkshire Rehab Screen DePaul Symptom Questionnaire
4	Long term functional outcomes of COVID-19 patients treated by rehabilitation services via telehealth NCT04385901	Completed but no result posted yet	Start date: May 19,2020 Completion: February 2021 (no result posted)	Allocation: Non-Randomized Intervention Model: Parallel Assignment Intervention Model Description: Patients receiving care through the program developed by the University of Missouri Healthcare system will, if willing, return for follow up testing and be compared against a matched group that did not receive the rehabilitative treatment to see if there are short or long term differences. Masking: Double (Investigator, Outcomes Assessor) Purpose: treatment	USA	Coid-19 confirmed in the previous 6 months	Therapy intervention including speech therapy, occupational therapy, strength exercise, pulmonary strengthening and breathing exercises	Standard of care	Change in 6minute walk test Change in Qulaity of life (SF-36) Change in peak flow meter test Change in strength testing

5	Breathing Exercise After COVID-19 Pneumonia NCT04771598	Not yet recruiting	Start date: February 25, 2021 Estimated completion date: June 30, 2021	Allocation: Randomized Intervention Model: Parallel Assignment Intervention Model Description: Randomised Controlled Study Masking: None (Open Label) Primary Purpose: Supportive Care	Turkey	Known COVID-19 patients with residual dyspnea 2 months after the diagnosis of COVID-19	Respiratory exercises	Breathing exercises	Pulmonary function tests (FEV1, FVC. FEV1/FVC, MVV) 6 min walking test
7	Effects of Respiratory muscle training in people who have had COVID-19 disease NCT04734561	Not yet recruiting	Start date: February 8,2021 Primary completion: July 30,2022	Allocation: Randomized Intervention Model: Parallel Assignment Intervention Model Description: double-blind randomized controlled clinical trial Masking: Double (Participant, Outcomes Assessor) Primary Purpose: Treatment	Spain	Discharged COVID-19 patients who has been diagnosed n the last 3 months	Inspiratory and expiratory muscle training group	none	Health-related quality of life Exercise tolerance Maximum respiratory pressures Inspiratory muscle endurance Forced spirometry Cognitive scale assessment Psychological assessment Upper and lower limb muscle strength
8	Home-based respiratory physiotherapy and telephone-based psychological support in severe covid-19 patients (WAYRA) NCT04649736	Recruiting	Start date: Octiber 26,2020 Estimated completion: March 30,2021	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Treatment	Peru	50-75yr old previously diagnosed COVID-19 patients	Respiratory rehabilitation	No rehabilitation	6min walk distance Respiratory questionnaire PHQ-9 Anxiety assessment scale QoL assessment (SF36) Pulmonary function tests (FEV,FVC) PTSD assessment
9	The effect of chest physiotherapy on respiratory capacity and the rate of respiratory gas exchange during walking on the treadmill in patients with COVID-19 after the recovery stage IRCT20160808029264N9	Recruiting	Start date: 9/20/2020 Expected end date: 6/20/2021	Randomized clinital trial, parallel group assignmen, double-blinded phase 2 study	Iran	35-55 years old previously hospitalized COVID-19 patients diagnosed in the past past 1-2months	Chest physiotherapy intervention with exercises and postural/movement rehabilitation	No rehabilitation, will receive intervention after the study period	Tidal volume, residual volume, FEV1, FVC

Q17. Should pirfenidone versus nintedanib be used as therapy for post-COVID-19 pulmonary fibrosis?

As of 26 October 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of pirfenidone or nintedanib among patients with post-COVID-19 pulmonary fibrosis *(Very low certainty of evidence)*

Consensus Issues

Evidence to support this recommendation is indirect as the studies included do not involve patients with post-COVID-19 pulmonary fibrosis. This is due to the paucity of available data on the use of pirfenidone and nintedanib in this population. There is no strong evidence to favor one anti-fibrotic agent over the other except for less side effects with nintedanib. Both drugs are costly, with annual expenses amounting to approximately Php 4.3M and Php 2.4M for pirfenidone and nintedanib, respectively. This may increase the inequity of treatment among those who cannot afford these drugs.

KEY FINDINGS

Limited evidence is available on the use of pirfenidone or nintedanib among patients with post-COVID-19 fibrosis, most of which are from published case reports. There are no clinical trials or observational studies among this group of patients which directly compare both anti-fibrotic agents, nor are there studies comparing each drug individually to placebo. Indirect evidence from prospective and retrospective cohort studies on the use of pirfenidone versus nintedanib among non-COVID patients with idiopathic pulmonary fibrosis showed no difference in mortality rate, respiratory-related hospitalizations, acute exacerbation of pulmonary fibrosis and percent predicted forced vital capacity (FVC%) at 6 and 12 months of treatment; higher frequency of diarrhea and transaminitis with nintedanib; and a higher rate of discontinuation due to adverse events with pirfenidone.

INTRODUCTION

Post-COVID-19 fibrosis is currently a recognized sequela of COVID-19 disease associated with fibrotic-like changes in the lung tissue with both viral and immune-mediated mechanisms involved.[8,9] The anti-fibrotic agents, pirfenidone and nintedanib, are well-tolerated and approved for use in idiopathic pulmonary fibrosis (IPF) and other progressive fibrosing lung disease regardless of underlying pathology.[10,11] A network meta-analysis comparing pirfenidone and nintedanib to placebo revealed that both drugs effectively reduce lung function decline in the first year of treatment as demonstrated by the change from baseline FVC [pirfenidone vs placebo: mean difference 0.12 L (95% CI 0.03 - 0.21 L); nintedanib vs placebo: mean difference 0.11 L (95% CI 0.00 - 0.22 L). [12] The same network meta-analysis showed that treatment with pirfenidone was associated with a lower risk for decline in FVC% predicted by ≥10% over 1 year (OR 0.58, 95% CI 0.4 - 0.88) and reduced all-cause mortality (HR 0.52, 95% CrI 0.28 -0.93) when compared with placebo.[12] No difference was seen between nintedanib and placebo in terms of these parameters. The role of these drugs in the treatment of post-COVID-19 pulmonary fibrosis is still unknown.

REVIEW METHODS

An electronic search for published studies (PubMed, Cochrane Library, Herdin) and ongoing trials (Clinicaltrials.gov Registry, International Clinical Trials Registry Platform) was conducted using the free text and MeSH terms of the following key words: “pirfenidone,” “nintedanib,” “post-COVID-19 pulmonary fibrosis,” “COVID-19” and “pulmonary fibrosis” until September 19, 2021. Due to paucity of published studies on the use of these interventional drugs in COVID-19 patients, observational and controlled trials among non-COVID-19 patients with pulmonary fibrosis were included. Case reports, case series, reviews and letters were excluded.

RESULTS

Summary of Characteristics of included studies

There were no randomized controlled trials nor observational studies found comparing pirfenidone to nintedanib, nor either drug with placebo, among patients with post-COVID-19 pulmonary fibrosis. However, indirect evidence from seven observational studies were found, screened, and included in the analysis.[1-7] One out of the seven studies had a prospective cohort design [4], while the rest were retrospective cohort studies. Five studies included patients with idiopathic pulmonary fibrosis (IPF) [1-4,6], while one study included those with IPF and pulmonary fibrosis from other etiologies such as nonspecific interstitial pneumonia, chronic hypersensitivity pneumonitis and connective tissue disease-associated interstitial lung disease.[5] The total number of participants across all studies was 2226 with an age range of 32-97 years old. Follow-up varied from 9-24 months. All studies did a head-to-head comparison between pirfenidone and nintedanib, with one study including in their analysis a control group that received neither drug.

Overall summary of methodological quality

Only two [3,4] out of the seven included studies adjusted their analysis for possible confounding bias inherent in observational studies. Additionally, these studies only indirectly address the research question because of the absence of COVID-19 infection among the participants. Hence, overall quality of evidence is very low.

Summary of results of included studies

Mortality Rate

Three studies reported mortality rate with follow-up range of 9 to 24 months.[2-4] A pooled analysis of mortality rate showed a trend favoring pirfenidone but results were not significant (RR 0.86, 95% CI 0.73-1.02; I^2 = 14%).

Rate of respiratory-related hospitalizations

Only the study by Belhassen et al. [3] reported respiratory-related hospitalizations as an outcome. It included 804 patients on pirfenidone and 509 on nintedanib with a follow-up of 3 years. Unadjusted incidence rate was 27 per 100 person-years and 30.7 per 100 person-years for those on pirfenidone and nintedanib, respectively. The cumulative incidence of the event at one year was 22.85% vs 27.46%, and at 3 years was 48.26% vs 43.62% for pirfenidone and nintedanib, respectively. The adjusted HR was 1.3 (95% CI 1.0-1.7).

Acute exacerbations

Two studies reported the incidence of acute exacerbations of pulmonary fibrosis [5,6] with a follow-up of 10 months to 3 years. The study by Galli et al. included patients

with IPF and pulmonary fibrosis of other etiologies. Their results showed that 16.3% and 10.5% of subjects experienced an acute exacerbation among those on pirfenidone and nintedanib, respectively (p=0.37). Mean time to first exacerbation was 294 days with pirfenidone and 247 days with nintedanib (p=0.72).[5] The study by Isshiki et al. included solely those with IPF. This study reported the cumulative incidence rate of acute exacerbations at 1-, 2- and 3-years in pirfenidone and nintedanib groups to be 5.1% vs 18.6%, 20.4% vs 25.3% and 22.6% vs 29.6%, respectively. The data on 1-year cumulative incidence rate was used in the pooled analysis of this review. The cumulative incidence rate of acute exacerbations was significantly lower in those on pirfenidone than nintedanib (p=0.035). A sub-group analysis on patients who started either drug as first-line therapy showed similar accumulated acute exacerbation of idiopathic pulmonary fibrosis incidence rates (p=0.136).[6] Pooled analysis showed no difference in the incidence of acute exacerbations of pulmonary fibrosis between both groups (RR 0.71, 95% CI 0.41-1.26; p=0.24) although there was note of significant heterogeneity (I^2=86%) probably due to the difference in populations.

Adverse events

Adverse events were reported by four studies.[2-5] Pooled analysis showed the following: there was no significant difference in risk for anorexia (RR 1.45, 95% CI 0.62-3.41; p=0.39), nausea or vomiting (RR 0.91, 95% CI 0.58-1.43; p=0.67), and rash (RR 2.87, 95% CI 0.97-8.56; p=0.06) between the two groups; whereas there was a significantly higher risk for diarrhea (RR 0.13, 95% CI 0.07-0.24; p<0.00001) and transaminitis (RR 0.25, 95% CI 0.08-0.79; p=0.02) among those taking nintedanib compared to pirfenidone. Discontinuation of the drug due to adverse events [2,3,5] was higher in the pirfenidone group (RR 1.18, 95% CI 1.05-1.31; p=0.004). Significant heterogeneity was observed in the data on diarrhea (I^2=65%) and discontinuation due to adverse events (I^2=70%) likely due to the differences in populations and study designs.

ONGOING STUDIES

There were 10 ongoing studies identified: 2 studies directly comparing pirfenidone vs nintedanib among COVID-19 patients [13-14]; 3 studies on nintedanib versus placebo among COVID-19 patients [15-17]; 4 studies on pirfenidone versus placebo among COVID-19 patients [18-21]; and 1 randomized controlled trial comparing pirfenidone vs nintedanib among patients with pulmonary fibrosis not associated with COVID-19.[22] Primary outcomes are change in FVC [13,15-20, 22], and the change in HRCT and arterial blood gas.[14,18,20,21]

EVIDENCE TO DECISION

Cost	Mean duration of treatment in the abovementioned included studies is 12 months. Pirfenidone 267mg tablet costs Php 1323 per tablet and is given as three tablets three times a day (9 tablets/day) as maintenance dose [23]: Php 1323/tablet x 9 tablets/day x 30 days/month x 12 months = Php 4,286,520 Nintedanib 150mg tablet costs Php 3279 per tablet given as one tablet twice a day (2 tablets/day) [24]: Php 3279/tablet x 2 tablets/day x 30 days/month x 12 months = Php 2,360,880

	A cost-effectiveness analysis study by Rinciog et al. [25] compared the two drugs (Pirfenidone 267mg three times a day vs Nintedanib 150mg twice a day) in the treatment of IPF in Belgium. There were similar survival and progression outcomes in both groups, as well as the total QALY (Pirfenidone 3.318 vs Nintedanib 3.353). Over a patient's lifetime, treatment with nintedanib accumulated lower overall costs than pirfenidone (€102,315 vs €113,313). This includes cost of the drug (Pirfenidone €88.32/day vs Nintedanib €79.21/day), patient monitoring of liver panel tests (€48.39 every 3 months), oxygen use (€775.82 every 3 months), cost related to acute exacerbations (€6,649.50) and adverse events, and palliative care costs (€3,783.61 for the last 30 days of life).
Availability	Both drugs are available at a private tertiary hospital in Metro Manila
Patient's Values or Preferences; Social Impact	No evidence
Factors to Impact Acceptability or Compliance	Higher rate of discontinuation of pirfenidone than nintedanib due to adverse events among patients with pulmonary fibrosis not related to COVID-19 (pooled RR 1.18, 95% CI 1.05-1.31; p=0.004) [2,3,5]

RECOMMENDATIONS FROM OTHER GROUPS

In the Swiss Recommendation for Long COVID, the committee settled on awaiting evidence from the ongoing RCTs that evaluate the efficacy and safety of pirfenidone and nintedanib among patients with post-COVID-19 fibrosis. However, they agreed that anti-fibrotic drugs may be given if an underlying progressive interstitial lung disease such as idiopathic pulmonary fibrosis is incidentally identified.

RESEARCH GAPS

There is still a paucity of data on the use of these anti-fibrotic agents in the setting of post-COVID-19 pulmonary fibrosis although many trials are underway.

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Appendix 1. Evidence to Decision

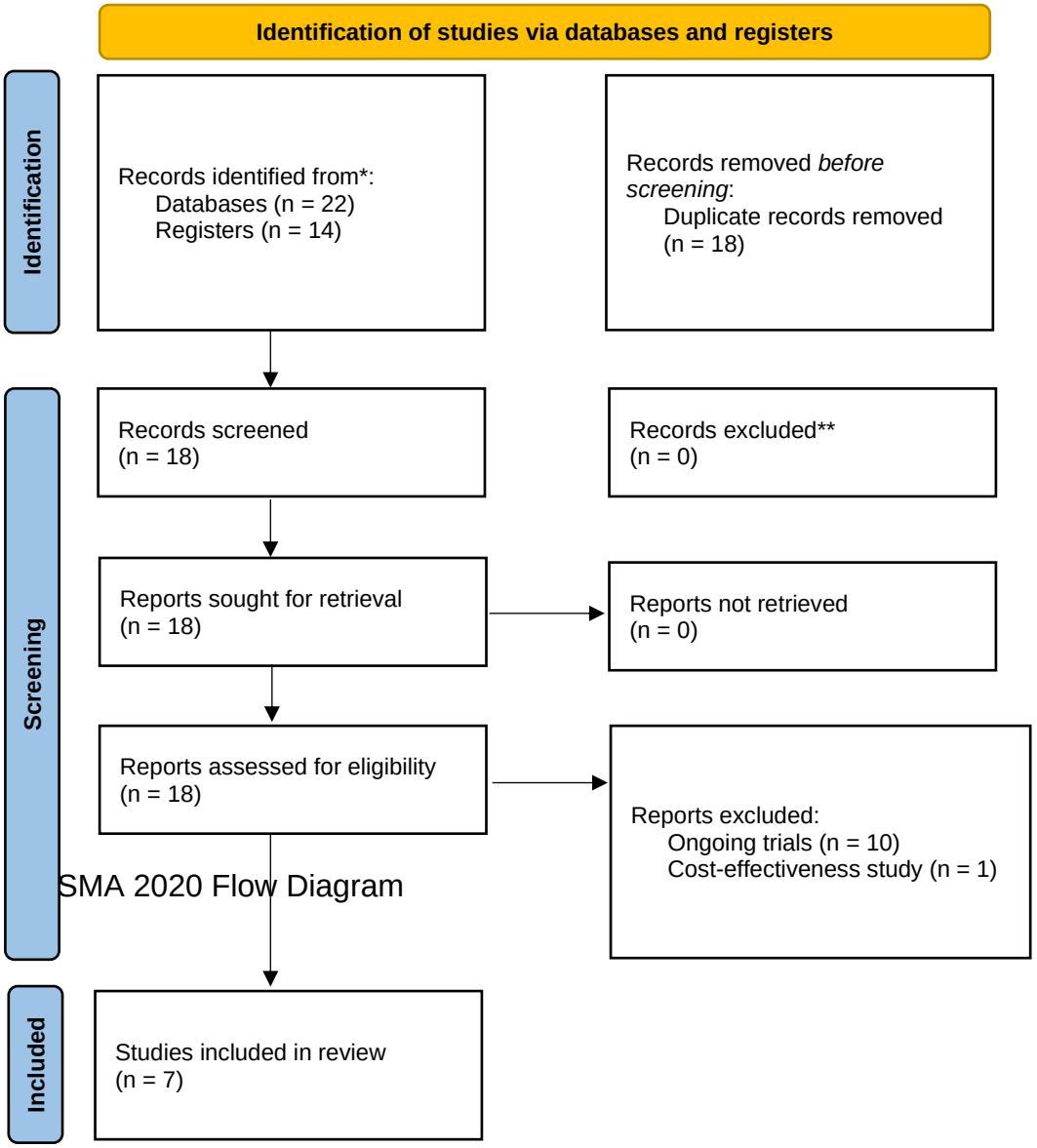
Table 1. Summary of initial judgements prior to the panel discussion: pirfenidone vs nintedanib (N = 9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					• There is paucity of evidence on the incidence and prognosis of post-COVID-19 pulmonary fibrosis. However, given the high prevalence of COVID-19 infection, this complication will likely have major health effects at the population level
Benefits	Large	Moderate	Small (3)	Uncertain (6)			No difference between the two drugs in terms of: • Mortality rates (RR 0.86 [0.73, 1.02] p=0.08) • Rate of respiratory-related hospitalizations (RR 1.11 [0.98, 1.25] p=0.10) • Acute exacerbations (RR 0.71 [0.41, 1.26] p=0.24) • FVC% predicted at 6 (mean difference 3.19 [-3.38, 9.76] p=0.34) • 12 months of treatment (mean difference1.00 [-10.54, 12.54] p=0.87

Harm	Large (2)	Small (5)	Uncertain (2)	No response			• Slight increase in frequency of: (among those taking Nintedanib)
							  ◦ Diarrhea (RR 0.13 [0.07, 0.24 p<0.00001])
							  ◦ Transaminitis (RR 0.25 [0.08, 0.79] p=0.02)
							• Higher rate of discontinuation due to adverse events (RR 1.18 [1.05, 1.31] p=0.004) with pirfenidone.
							• No difference in rates of anorexia (RR 1.45 [0.62, 3.41 p=0.39]), nausea/vomiting (RR 0.91 [0.58, 1.43] p=0.67) and rashes (RR 2.87 [0.97, 8.56] p=0.06)

Certainty of Evidence	High (1)	Moderate	Low (4)	Very low (4)			• Observational and involved non-COVID patients with pulmonary fibrosis
Balance of effects	Favors drug	Does not favor drug (5)	Uncertain (4)				
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability (2)			
Resources Required	Uncertain (3)	Large cost (5)	Moderate Cost (1)	Negligible cost	Moderate savings	Large savings	• Pirfenidone 267mg tab: Php 1323/tab - Php 4,286,520 (12 mo) • Nintedanib 150mg tab: Php 3279/tab - Php 2,360,880 (12mo) • Similar survival and progression outcomes in both groups, total QALY (Pirfenidone 3.318 vs Nintedanib 3.353). • Over a patient's lifetime, treatment with nintedanib accumulated lower overall costs than pirfenidone (€102,315 vs €113,313).
Certainty of evidence of required resources	No included studies (6)	Very low	Low (2)	Moderate (1)	High		
Cost effectiveness	No included studies	Favors the comparison (5)	Does not favor either the intervention or the comparison (4)	Favors the intervention			
Equity	Uncertain (5)	Reduced (2)	Probably no impact	Increased (2)			
Acceptability	Uncertain (7)	No (1)	Yes (1)				
Feasibility	Uncertain (4)	No (3)	Yes (2)				

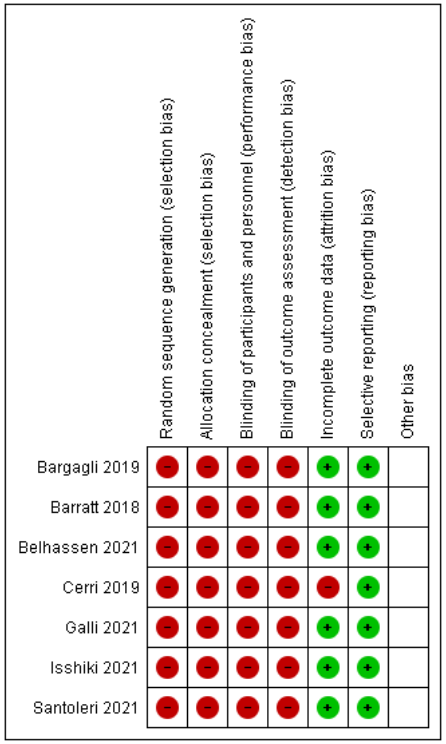
Appendix 2. Search Yield and Results



Appendix 3. Table of Included Studies (7)

Study ID	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Bargagli 2019	Retrospective cohort	Italy	82	Patients with IPF	Pirfenidone	Nintedanib	• FVC, FEV1, TLC, DLCO Percentages of predicted at time 0, after 6 months and 12 months
Barratt 2018	Retrospective cohort	England	164	Patients with IPF	Pirfenidone	Nintedanib	Treatment emergent adverse events: • Adverse drug events • Discontinuation of therapy due to disease progression (decline in percent predicted FVC of 10% or more within any 12-month period) • Death
Belhassen 2021	Retrospective cohort	France	1313	Patients with IPF	Pirfenidone	Nintedanib	• All-cause mortality • Acute respiratory-related hospitalization • Treatment discontinuation at 12 months
Cerri 2019	Prospective cohort	Italy	142	Patients with IPF	Pirfenidone or Nintedanib	No treatment	Primary outcomes: • Changes in lung function parameters (FVC and DLCO) in 24 months • Side effects Secondary outcomes: • Rate of disease progression [Reduction in FVC ≥10% of predicted and/or diffusion capacity (DLCO) ≥15% of predicted] • Mortality rate at 6, 12, 18 and 24 months
Galli 2021	Retrospective cohort	Philadelphia, USA	186	Patients with IPF and PF from other causes	Pirfenidone	Nintedanib	Primary outcome: • Drug discontinuation as a result of an adverse drug event Secondary outcomes: • Time to drug discontinuation • Adverse events • Clinical outcome • Adverse event • Severe bleeding events • MI • Acute exacerbation of pulmonary fibrosis
Isshiki 2021	Retrospective cohort	Japan	195	Patients with IPF	Pirfenidone	Nintedanib	• Acute exacerbation of idiopathic pulmonary fibrosis
Santoleri 2021	Retrospective cohort	Italy	144	Patients who picked up pirfenidone and nintedanib from hospital pharmacy at least twice	Pirfenidone	Nintedanib	• Adherence and persistence of treatment at 1 and 2 years • FVC and DLCO at 6 and 12 months • Gender-Age-Physiology (GAP) Index

Appendix 4. Study Appraisal



Risk of Bias Summary: review authors' judgements about each risk of bias item for each included study.

Appendix 5. GRADE Evidence Profile

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	P	N	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	Observational studies	Serious [a]	Not serious	Serious [b]	Serious [d]	None	255/997 (25.6%)	174/586 (29.7%)	**RR 0.86** (0.73 to 1.02)	**42 fewer per 1,000** (from 80 fewer to 6 more)	⨁◯◯◯ VERY LOW	
Respiratory-related hospitalizations												
1	Observational studies	Not serious	Not serious	Serious [b]	Serious [d]	None	388/804 (48.3%)	222/509 (43.6%)	**RR 1.21** (0.96 to 1.51)	**47 more per 1,000** (from 10 fewer to 103 more)	⨁◯◯◯ VERY LOW	
Acute exacerbation												
2	Observational studies	Serious [a]	Not serious	Serious [b]	Serious [d]	None	28/260 (10.8%)	18/121 (14.9%)	**RR 0.71** (0.41 to 1.26)	**43 fewer per 1,000** (from 88 fewer to 39 more)	⨁◯◯◯ VERY LOW	
FVC % Predicted at 6 months of treatment												
2	Observational studies	Serious [a]	Not serious	Serious [b]	Serious [d]	None	94	57	-	MD **3.19 higher** (3.38 lower to 9.76 higher)	⨁◯◯◯ VERY LOW	
FVC % Predicted at 12 months of treatment												
1	Observational studies	Serious [a]	Not serious	Serious [b]	Serious [d]	None	42	27	-	MD **1 higher** (10.54 lower to 12.54 higher)	⨁◯◯◯ VERY LOW	
Discontinuation due to Adverse event												
3	Observational studies	Serious [a]	Serious [c]	Serious [b]	Serious [d]	None	505/1048 (48.2%)	260/615 (42.3%)	**RR 1.18** (1.05 to 1.31)	**76 more per 1,000** (from 21 more to 131 more)	⨁◯◯◯ VERY LOW	
Anorexia												
3	Observational studies	Serious [a]	Not serious	Serious [b]	Serious [d]	None	22/322 (6.8%)	6/134 (4.5%)	**RR 1.45** (0.62 to 3.41)	**20 more per 1,000** (from 17 fewer to 108 more)	⨁◯◯◯ VERY LOW	
Nausea/Vomiting												
3	Observational studies	Serious [a]	Not serious	Serious [b]	Serious [d]	None	44/322 (13.7%)	21/134 (15.7%)	**RR 0.91** (0.58 to 1.43)	**14 fewer per 1,000** (from 66 fewer to 67 more)	⨁◯◯◯ VERY LOW	

Diarrhea												
3	Observational studies	Serious [a]	Serious [c]	Serious [b]	Not serious	None	12/322 (3.7%)	40/134 (29.9%)	**RR 0.13** (0.07 to 0.24)	**260 fewer per 1,000** (from 278 fewer to 227 fewer)	⊕◯◯◯ VERY LOW	
Transaminitis												
3	Observational studies	Serious [a]	Not serious	Serious [b]	Not serious	None	4/322 (1.2%)	7/134 (5.2%)	**RR 0.25** (0.08 to 0.79)	**39 fewer per 1,000** (from 48 fewer to 11 fewer)	⊕◯◯◯ VERY LOW	
Rash												
2	Observational studies	Serious [a]	Not serious	Serious [b]	Serious [d]	None	23/207 (11.1%)	3/85 (3.5%)	**RR 2.87** (0.97 to 8.56)	**66 more per 1,000** (from 1 fewer to 267 more)	⊕◯◯◯ VERY LOW	

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

Explanations

[a] observational studies, did not adjust for confounding
[b] patients included have pulmonary fibrosis not due to COVID-19
[c] unexplained inconsistency and heterogeneity, with point estimates widely different (I^2 > 70%)
[d] CI crosses null value (RR = 1)
[e] Range from negative/lower to positive/higher

Appendix 6. Forest Plots

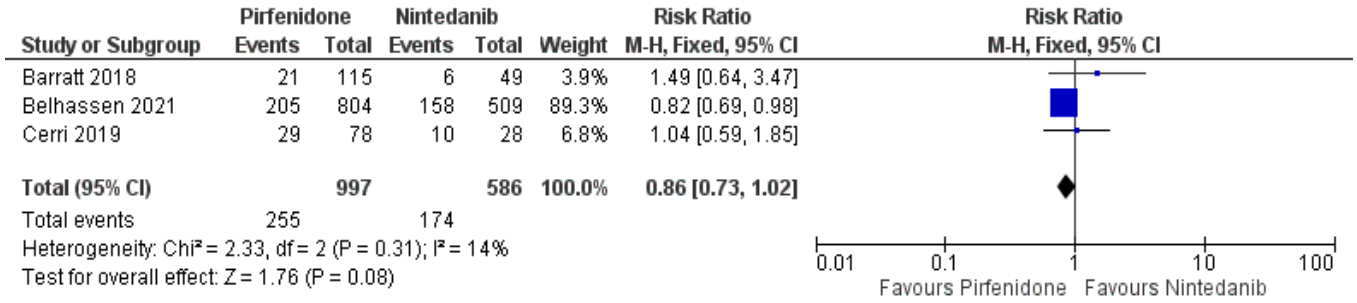


Figure 1. Mortality rate

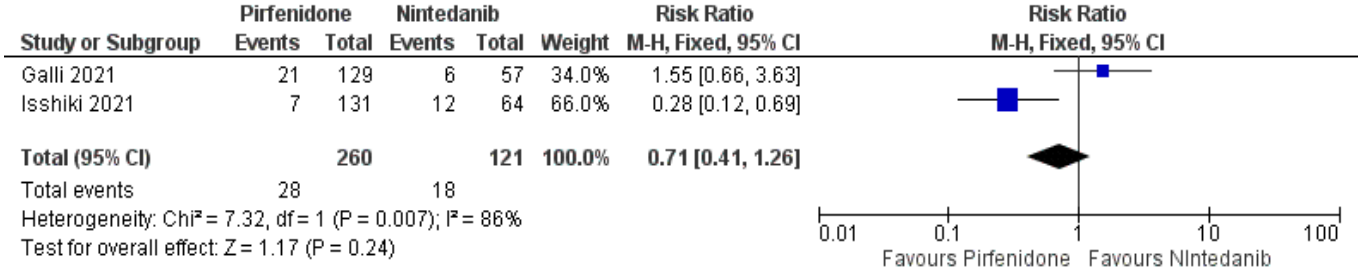


Figure 2. Acute exacerbations of pulmonary fibrosis

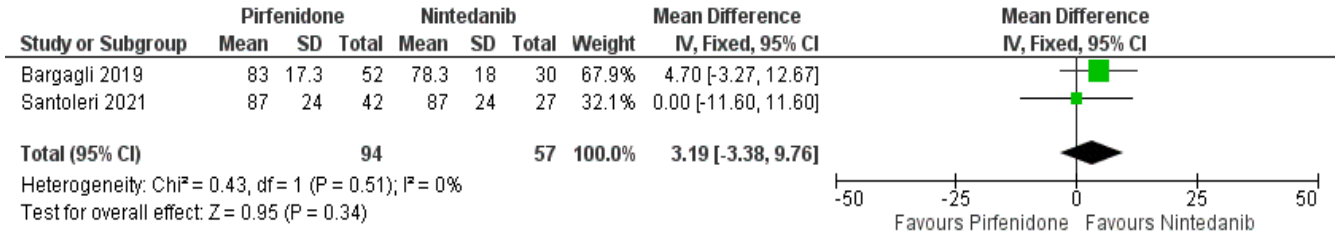


Figure 3. FVC% predicted at 6 months of treatment

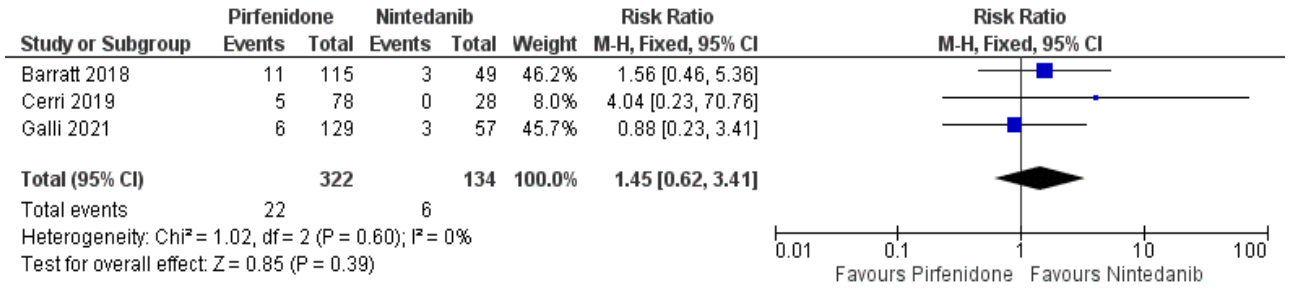


Figure 4. Adverse event: Anorexia

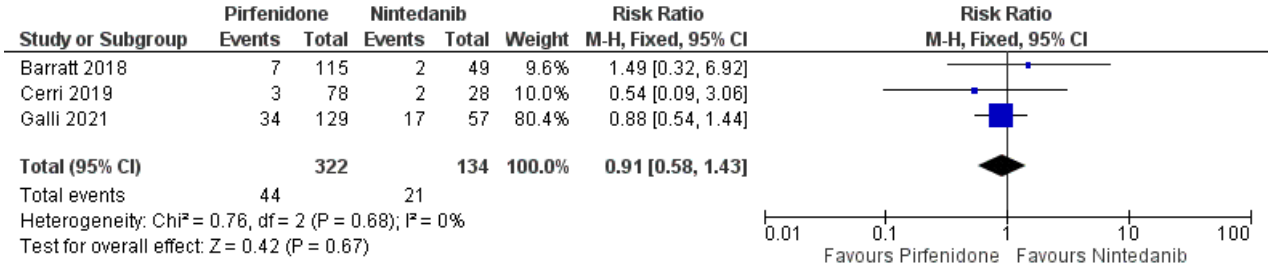


Figure 5. Adverse event: Nausea/Vomiting

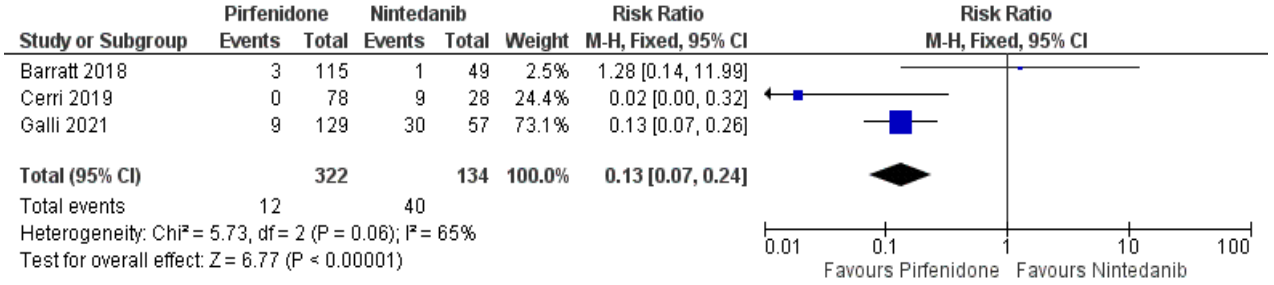


Figure 6. Adverse event: Diarrhea

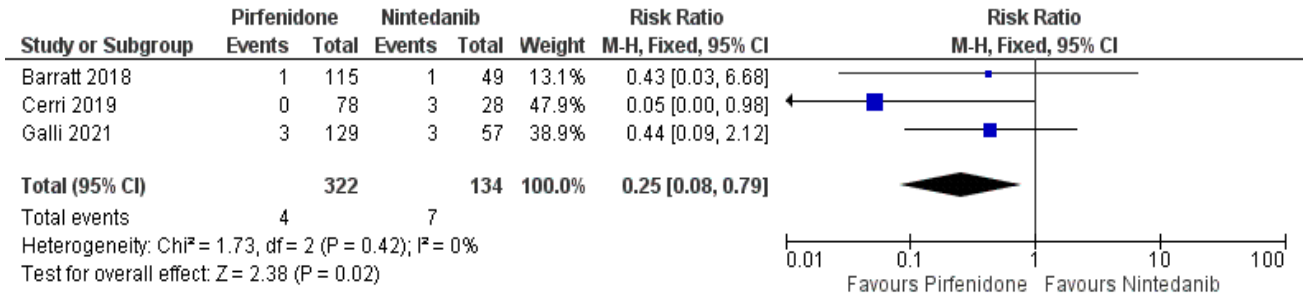


Figure 7. Adverse event: Transaminitis

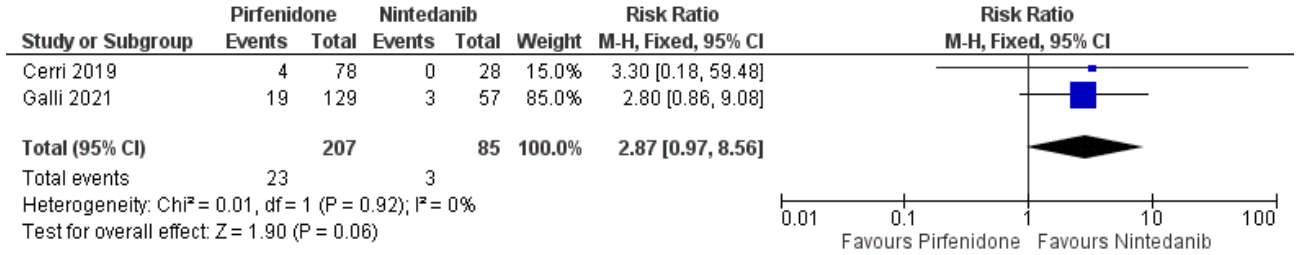


Figure 8. Adverse event: Rash

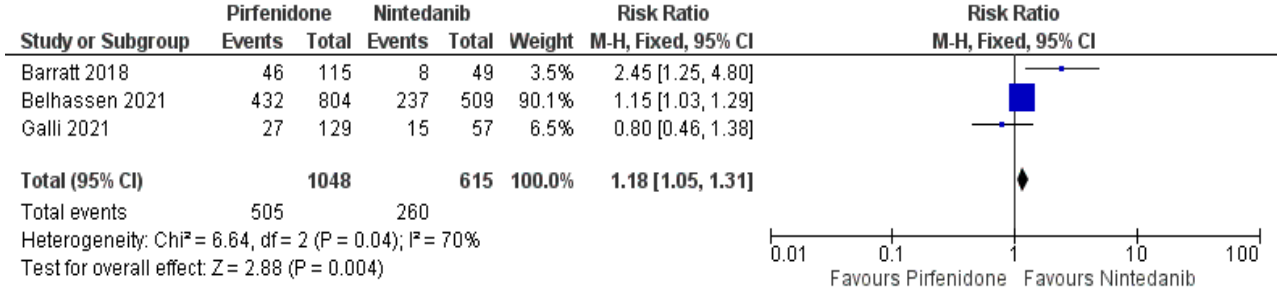


Figure 9. Discontinuation due to adverse events

Appendix 7. Characteristics of Ongoing Studies (10)

Title Identifier Expected Completion Date	Intervention	Comparator/ Control	Patients/Population Recruited	Outcomes
A Study of the Efficacy and Safety of Pirfenidone vs. Nintedanib in the Treatment of Fibrotic Lung Disease After Coronavirus Disease-19 Pneumonia (PINCER) NCT04856111 December 31, 2021	Pirfenidone	Nintedanib	Inclusion Criteria: 1. Age above 18 years 2. Diagnosed to have COVID-19 by means of a real-time reverse transcription polymerase chain reaction (rRT-PCR) test performed on a respiratory (upper or lower respiratory) sample or positive IgM antibody test or a rapid antigen test with consistent clinicoradiologic findings within the previous 4 months 3. Persistent respiratory symptoms 4. Having post-COVID parenchymal involvement >10% of the lung parenchyma on visual inspection of the scans with the presence of radiologic signs of fibrosis, or having persistent reticulation or persistent consolidation despite a trial of glucocorticoids for a minimum period of 4 weeks after discharge for the acute COVID-19 illness Exclusion Criteria: 1. Pregnant or lactating women 2. Having absolute contraindication for pirfenidone or nintedanib 3. Known patient with diffuse lung disease prior to the diagnosis of COVID	Primary Outcome: 1. Change in the forced vital capacity (FVC) Secondary Outcome: 1. Proportion of subjects with improvement or stabilization (improvement or a <10% relative decline in FVC from the baseline value) 2. Proportion of subjects with a good composite response (< mMRC grade 2 breathlessness with ≥10% improvement in FVC with an O_2 saturation >92% during and after exertion) 3. Change in dyspnea score on modified Medical Research Council scale 4. Severity of dyspnea on the Functional Assessment of Chronic Illness Therapy - Dyspnea-10 item 5. Change in resting oxygen saturation 6. Proportion of subjects with oxygen desaturation on exercise testing 7. Percentage change in the six-minute walk distance 8. Proportion of participants who need rescue treatment 9. Change in health-related quality of life using the Short Form-36 questionnaire 10. Change in respiratory health status using the King's Brief ILD questionnaire 11. Changes in HRCT scores using the modified Salisbury system 12. Proportion of subjects who develop adverse effects due to either study drug 13. Predictors of response to antifibrotic agents, pirfenidone and nintedanib
Nintedanib Vs Pirfenidone in management of Covid19 related lung abnormality CTRI/2020/12/029814 (Expected Completion Date not indicated)	Nintedanib	Pirfenidone	Inclusion criteria: 1. All cases of COVID-19 pneumonia who were diagnosed as COVID positive >15 days back or antibody positive and continue to be breathless symptomatically, have SPo2 <96%, CT-severity score >10 and CORADS-4/5/6 Exclusion criteria: 1. Patients having other interstitial lung diseases. 2. Patient having CKD or creatinine clearance <30 and CLD with deranged LFT will be excluded. 3. Not fulfilling the criteria for study 4. Not giving consent for study.	Primary outcome: 1. Improvement in CT-severity score 2. Improvement in Arterial Blood Gas. Secondary outcome: 1. Improvement in 6-Minute Walk Distance
Efficacy and Safety of Nintedanib Ethanesulfonate Soft Capsule in the Treatment of Pulmonary Fibrosis in Patients With Moderate to Severe COVID-9(COVID 19) : a	Nintedanib	Placebo	Inclusion Criteria: 1. 18-70 years old (including 18 and 70 years old), regardless of gender; 2. Infection with new coronavirus pneumonia confirmed by throat swab nucleic acid test.	Primary Outcomes: 1. Changes in forced vital capacity (FVC) Secondary Outcomes: 1. Changes in carbon monoxide dispersion (DLco%) 2. Changes in the six-minute walk test (6MWT)

Single-center, Randomized, Placebo-controlled Study NCT04338802 ChiCTR2000031453 August 1, 2020			3. CT examination of patients with multiple fibrotic shadows in both lungs; 4. Blood routine, liver, and kidney functions are within the controllable range: 5. Signed informed consent. Exclusion Criteria: 1. Previous history of chronic bronchitis, emphysema, interstitial lung disease or pulmonary heart disease; 2. Combining with other serious diseases 3. Active peptic ulcer 4. Pregnancy and lactation 5. Mental illness or cannot cooperate effectively 6. Researcher judges uncomfortable to participate in trial	3.Changes in High resolution CT score
Early Nintedanib Deployment in COVID-19 Interstitial Fibrosis (ENDCOV-I) NCT04619680 April 2024	Nintedanib 150 mg PO twice a day, taken with food	Placebo equivalent given twice a day	Inclusion Criteria: 1. Willing and able to provide written informed consent 2. Subjects Age > 18 3. Initial SARS-CoV-2 infection confirmed by PCR test or positive serologies 4. Fibrosis found on CT scan 5. Required one of the following after diagnosis with SARS-CoV-2: supplemental oxygen by nasal cannula, high flow oxygen, non invasive ventilation such as CPAP or BIPAP, or mechanical ventilation 6. Are 30 days from onset of initial SARS-CoV-2 symptoms 7. Forced Vital Capacity less than 80% predicted based on ATS/ERS criteria or DLCO<60% 8. Women of childbearing potential who agree to use of highly effective contraception during treatment and for three months following the last dose of nintedanib Exclusion Criteria: 1. Co-administration of other investigational agents against COVID-19 2. Active SARS-CoV-2 infection based on clinical judgment 3. Currently Pregnant or Breast Feeding 4. Current Use of Prednisone or equivalent > 10 mg/daily 5. Use of full dose anticoagulation therapy or high dose anti platelet drug therapy at screening (6. History of myocardial infarction within past 90 days 7. Life threatening bleed 8. Hemodynamic instability or shock 9. Superimposed pulmonary bacterial infection 10. Pre-existing interstitial lung disease 11. Active Hep A/B/C hepatitis as measured with PCR for viral load and/or serologies	Primary Outcome: 1. Change in Forced Vital Capacity (FVC) Secondary Outcome: 1. Deaths due to respiratory cause 2. Chest CT visual score 3. St. George's Respiratory Questionnaire (SGRQ) at 90 and 180 days 4. King's Brief Interstitial Lung Disease (KBILD) at 90 and 180 days 5. Leicester Cough Questionnaire (LCQ) at 90 and 180 days 6. Short Form (SF) 36 Health Survey at 90 and 180 days 7. Hospital Anxiety and Depression Scale (HADS) at 90 and 180 days 8. Number of participants with Increase in liver transaminases (AST and ALT) > 3 times the upper limit of normal at 90 and 180 days 9. Number of participants with Thrombotic events at 90 and 180 days 10. Number of participants with 10% weight loss over 90 and 180 days 19. Number of participants with GI events at 90 and 180 days and anti-motility agents

			12. Pre-existing liver disease: Including Abnormal Laboratory Liver Function: 13. Creatinine clearance <30 ml/min or currently on hemodialysis 14. Inability to tolerate orally administered medication	
Nintedanib for the Treatment of SARS-Cov-2 Induced Pulmonary Fibrosis (NINTECOR) NCT04541680 EUCTR2020-002114-40-FR December 2021	Nintedanib	Placebo	Inclusion Criteria: 1. History of hospitalization for COVID-19 infection documented with positive PCR or positive serology in the previous 2 to 12 months 2. Lung opacities on HRCT involving more than 10% of the lung volume, with fibrotic features 3. DLCO≤ 70% of the predicted value Exclusion Criteria: 1. Pre-existing lung disorder with abnormal HRCT (including COPD, lung cancer, or pulmonary fibrosis) 2. Laboratory parameter thresholds: ● renal insufficiency (Creatinine clearance <30 ml/min) ● Total bilirubin > 1.5 above the upper limit of the normal range (ULN), ● Aspartate or alanine aminotransferase (AST or ALT) >3 × ULN 3. Recent surgery with wound healing in progress (<7days) 4. Underlying chronic liver disease 5. Significant pulmonary arterial hypertension (PAH) 6. History of cardiovascular diseases, any of the following: ● Severe hypertension, uncontrolled under treatment (≥160/100 mmHg), within 6 months of Visit 1 ● Myocardial infarction within 6 months ● Unstable cardiac angina within 6 months 7. Bleeding risk 8. Alcohol or drug abuse 9. Ongoing or past antifibrotic treatment with pirfenidone or nintedanib 10. Hypersensitivity to nintedanib, peanut or soya or to any of the excipients of the specialty Ofev® 11. Patients not able to understand and follow study procedures 12. No written informed consent from the patient 13. Absence of affiliation to the French social security 14. Participation in another interventional research	Primary Outcome: 1. Decline in forced vital capacity (FVC) over 12 months Secondary Outcome: 1. Rate of decline of DLCO over 12 months 2. 6MWT at 12 months 3. Change in HRCT fibrosis score and HRCT fibrosis extension at inclusion and 12 months 4. Change in the total score on the St. George's Respiratory Questionnaire at 12 months 5. Change in the Dyspnea score (Multidimensional Dyspnea Profile and mMRC score) at 3, 6, 9 and 12 months 6. Change in Hospital Anxiety and Depression score at 3, 6, 9 and 12 months 7. Change in Biomarker assay (KL-6, NT-proBNP, CRP, D-dimers) at 12 months 8. Pulmonary hypertension prevalence 9. Association between genetic susceptibility (MUC5B polymorphism) and lung fibrosis in COVID-19 survivors 10. Incidence of clinical or biological adverse events with nintedanib versus placebo over 12 months
A Randomized, Open-label Study to Evaluate the Efficacy and Safety of Pirfenidone in Patients	Pirfenidone	No Intervention	Inclusion Criteria: 1. Age ≥ 18 years.	Primary Outcome: 1. Lesion area of chest CT image at 4 weeks 2. Absolute change in pulse oxygen from baseline

With Severe and Critical Novel Coronavirus Infection NCT04282902 June 1, 2020			2. Clinically diagnosed patients with new type of coronavirus pneumonia Exclusion Criteria: 1. AST and ALT> 1.5 x ULN 2. Bilirubin> 1.5 x ULN 3. Creatinine clearance rate calculated by Cockcroft-Gault formula at visit 1 <30 mL / min; 4. Patients with potential chronic liver disease 5. Previous treatment with nintedanib or pirfenidone 6. Received other research drug treatment within 1 month or 6 half-lives 7. IPF diagnosis based on ATS / ERS / JRS / ALAT 2011 guidelines (P11-07084); 8. Significant pulmonary hypertension (PAH) 9. Other clinically significant lung abnormalities considered by the investigator; 10. Major extrapulmonary physiological limitations 11. Cardiovascular diseases, any of the following diseases: Severe hypertension within 6 months, uncontrollable after treatment (≥160 / 100 mmHg); myocardial infarction within 6 months; unstable angina within 6 months; 12. History of severe central nervous system (CNS) events; 13. Known trials Drug allergies; 14. Other diseases that may interfere with the testing process or as judged by the investigator 15. Women who are pregnant, breastfeeding, or planning pregnancy in this trial 16. Unable to understand or follow the trial procedures,	3. Absolute change in blood gas from baseline 4. Absolute change in total score of King's brief questionnaire for interstitial Absolute change in total score of King's brief questionnaire for interstitial pulmonary disease (k-bild) from baseline at week 4 Secondary Outcome: 1. Time to death within 4 weeks due to respiratory problems 2. Time to disease progression or death within 4 weeks 3. Blood lymphocyte count 4. Absolute change in viral nucleic acid from baseline 5. Change in Dyspnea score 6. Changes in blood inflammatory indexes 7. Absolute change in cough scores for pulmonary fibrosis survival symptoms from baseline
Phase-II Randomized Clinical Trial to Evaluate the Effect of Pirfenidone Compared to Placebo in Post-COVID19 Pulmonary Fibrosis NCT04607928 August 1, 2021	Pirfenidone	Placebo	Inclusion Criteria: 1. Age > 18 years 2. Signed Informed Consent Form 3. Ability to comply with the study protocol in the opinion of the Investigator 4. Confirmation of SARS-COV2 infection in previous weeks which induced severe pneumonia and ARDS, with subsequent torpid recovery and/or incipient clinical-radiological signs of pulmonary fibrosis. 5. HRCT with fibrotic radiological changes of at least 5% after recovery from the acute process 6. Be able to understand the information given and sign the informed consent 7. For women or men of childbearing age who are not sterile, a commitment to use non-hormonal contraception during the 24-week treatment period will be required.	Primary Outcome: 1. Change from Baseline in % in forced vital capacity (FVC) 2. Change in % fibrosis in high resolution computed tomography (HRCT) of the lung Secondary Outcome: 1. Maintenance of stability or functional improvement FVC . 2. Decreased oxygen requirement for physical activity 3. Improved exercise capacity (> 50 meter improvement or less decrease in% oxygen saturation) 4. Hospitalizations (general and due to respiratory problems) 5. Visits to the Emergency or Day Hospital for 6. Lung transplantation 7. Death

			Exclusion Criteria: 1. Use of systemic steroids) at doses greater than 15 mg/day one month prior to randomization. 2. Severe or moderate myopathy that may associate a decrease of FVC. 3. Severe or life-limiting chronic disease prior to COVID19 infection 4. Treatment with pirfenidone or nintedanib prior to Covid19 5. Concomitant treatment with significant interactions with pirfenidone 6. Participation in any other investigational trial throughout the study 7. Active smoking. 8. Relevant blood alterations in the analysis made during the screening period: ● Total bilirubin > 2 ULN ● AST/SGOT or ALT/SGPT > 2.5 ULN ● Alkaline phosphatase >3.0 ULN ● Creatinine Clearance <40 mL/min, calculated by the Cockcroft-Gault formula 9. Pregnancy or lactation 10. Concomitant treatments that can cause severe digestive problems. 11. Gastric surgery in the last 3 months 12. Inability to complete required visits. 13. Previous intolerance or allergy to pirfenidone or hypersensitivity to any of its excipients. 14. History of angioedema	
Pirfenidone for coronavirus disease 2019 (COVID-19) related pulmonary fibrosis: A placebo-controlled randomized controlled trial CTRI/2021/03/032199 (Expected Completion Date not indicated)	Pirfenidone	Placebo	Inclusion criteria: 1. History of COVID-19 illness diagnosed by RT-PCR/Rapid antigen/ Truenaat of throat or nasopharyngeal swab at least 8 weeks prior 2. Persistent respiratory symptoms or persistent hypoxemia (SpO2 <94% on room air) or oxygen desaturation on exercise AND Has evidence of pulmonary fibrosis on HRCT performed at least 8 weeks after COVID-19 diagnosis 3. Provides written informed consent for evaluation and treatment as per study protocol Exclusion criteria: 1. Patients not providing consent for participation in the study 2. FEV1/FVC ratio < 0.80 3. Active smokers	Primary outcome: 1. The change in Forced Vital Capacity (FVC) (% predicted) at 6 months Secondary outcomes: 1. Change in diffusion capacity for carbon mono-oxide (DLCO) at 3 and 6 months 2. Change in total lung capacity at 3 and 6 months 3. Adverse events during therapy 4. Change in high resolution computed tomography (HRCT) at 3 months 5. Change in Six-minute walk distance at 3 and 6 months 6. Change in dyspnea on modified borg dyspnea scale 7. Change in FVC at 3 months

			4. Any active malignancy/ malignancy within past 2 years 5. Severe hepatic impairment 6. Use of immunosuppressant drugs (except corticosteroids and tocilizumab) within last 6 weeks	
A Randomized Phase-II Clinical Trial to Evaluate to Effect of Pirfenidone compared with Placebo in Pulmonary Fibrosis Post-COVID 19 (FIBRO-COVID) EUCTR2020-002518-42-ES (Expected Completion Date not indicated)	Pirfenidone	Placebo	Inclusion criteria: 1. Age > 18 years 2. Signed Informed Consent Form 3. Ability to comply with the study protocol in the opinion of the Investigator 4. Confirmation of SARS-COV2 infection in previous weeks which induced severe pneumonia and ARDS, with subsequent torpid recovery and/or incipient clinical-radiological signs of pulmonary fibrosis. 5. HRCT with fibrotic radiological changes of at least 5% after recovery from the acute process 6. Be able to understand the information given and sign the informed consent 7. For women or men of childbearing age who are not sterile, a commitment to use non-hormonal contraception during the 24-week treatment period will be required. Exclusion criteria: 1. Use of systemic steroids (at doses greater than 15 mg/day one month prior to randomisation. 2. Severe or moderate myopathy that may associate a decrease of FVC. 3. Severe or life-limiting chronic disease prior to COVID19 infection 4. Treatment with pirfenidone or nintedanib prior to Covid19 5. Concomitant treatment with significant interactions with pirfenidone 6. Participation in any other investigational trial throughout the study 7. Active smoking. 8. Relevant blood alterations in the analysis made during the screening period: ● Total bilirubin > 2 ULN ● AST/SGOT or ALT/SGPT > 2.5 ULN ● Alkaline phosphatase >3.0 ULN ● Creatinine Clearance <40 mL/min, calculated by the Cockcroft-Gault formula 9. Pregnancy or lactation 10. Concomitant treatments that can cause severe digestive problems. 11. Gastric surgery in the last 3 months. 12. Inability to complete required visits.	Primary Outcomes: 1. % change in FVC 2. Radiological change in % of pulmonary fibrosis (Chest HRCT) 3. Percentage of patients who improve functionally (=10% change in FVC) and radiologically (% of fibrotic signs in chest HRCT) Secondary outcomes: 1. % of cases with progression of pulmonary fibrosis 2. Death or lung transplant (transplant free-survival time) 3. Improvement in quality of life 4. Hospitalizations or urgent visits of respiratory cause 5. Semi-annual rate of change in % FVC 6. HRCT Chest Fibrotic Score 7. Incidence of drug-associated adverse events (nature, seriousness, severity, frequency, causality, clinical consequence and time since drug onset) 8. Discontinuation of treatment. 9. % of cases with progression of pulmonary fibrosis 10. Exercise capacity 11. Decreased oxygen requirement for physical activity 12. Improvement in quality of life (difference in final K-BILD score greater than 5) 13. Lung transplant or death

			13. Previous intolerance or allergy to pirfenidone or hypersensitivity to any of its excipients. 14. History of angioedema	
The comparison of the efficacy and safety of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis JPRN-UMIN000020682 (Expected Completion Date not indicated)	Pirfenidone	Nintedanib	Inclusion criteria: 1. Idiopathic pulmonary fibrosis Exclusion criteria: 1. Coexisting lung cancer 2. Acute exacerbation of idiopathic pulmonary fibrosis 3. Severe cardiac or hepatic diseases 4. Pulmonary arterial hypertension 5. Sarcoidosis and respiratory infection, 6. Cannot perform pulmonary function test 7. Pregnant women 8. Use of prednisone greater than 20mg/day and immunosuppressives during the preceding 3 months 9. Patients who participated in other clinical trials in the last 3 months, the patients who are judged inappropriate for this study	Primary Outcome(s) 1. The change in vital capacity from baseline to months 12 Secondary Outcome(s) 1. Dyspnea 2. KL-6 3. SP-D 4. %DLCO 5. Changes in the lowest peripheral oxygen saturation during the 6-minute walk test 6. Arterial blood gas 7. The reduction of ground-glass and reticular opacities 8. Echocardiogram 9. Bronchoalveolar lavage 10. First occurrence of acute exacerbation 11. The development of lung cancer 12. Survival at 12 months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