PHILIPPINE COVID-19 LIVING CLINICAL PRACTICE GUIDELINES

As of January 2022

DIAGNOSIS and SCREENING of COVID-19

EVIDENCE and RECOMMENDATIONS

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Cooperating Agency:

Philippine Society of Microbiology and Infectious Diseases

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Department of Health
Disease Prevention and Control Bureau

Disclaimer

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

Contact Us

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

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Quick Guide on How to Interpret the Evidence

Evidence on Diagnosis

There are four conventional ways of determining how accurate a test is. These measures would be adequate if we are comparing the results of two tests using the method of 2 x 2 table.

1. ***Sensitivity (sn)*** refers to the proportion of persons with disease who correctly have a positive test.
2. ***Specificity (sp)*** refers to the proportion of persons with no disease who correctly have a negative test.
3. ***Positive predictive value (ppv)*** is the proportion of persons with a positive test who correctly turn out to have disease
4. ***Negative predictive value (npv)*** is the proportion of persons with a negative test who correctly turn out to have no disease

However, if we need to evaluate a test with multi-level results, we need a “2 x n” table and compute for ***likelihood ratio (LR)***. LR is a measure of how much the likelihood of the disease changes given a test result.

Table A1. Interpreting likelihood ratios (LRs)

Likelihood ratio	Likelihood of disease	Grade of likelihood
LRs > 1.0	INCREASE	LR < 3.0 (close to 1.0) – weakly positive LR = 3.0-10.0 – moderately positive LR 10.0 is strongly positive
LRs < 1.0	DECREASE	LR > 0.3 (close to 1.0) – weakly negative LR = 0.3-0.1 – moderately negative LR <0.1 – strongly negative

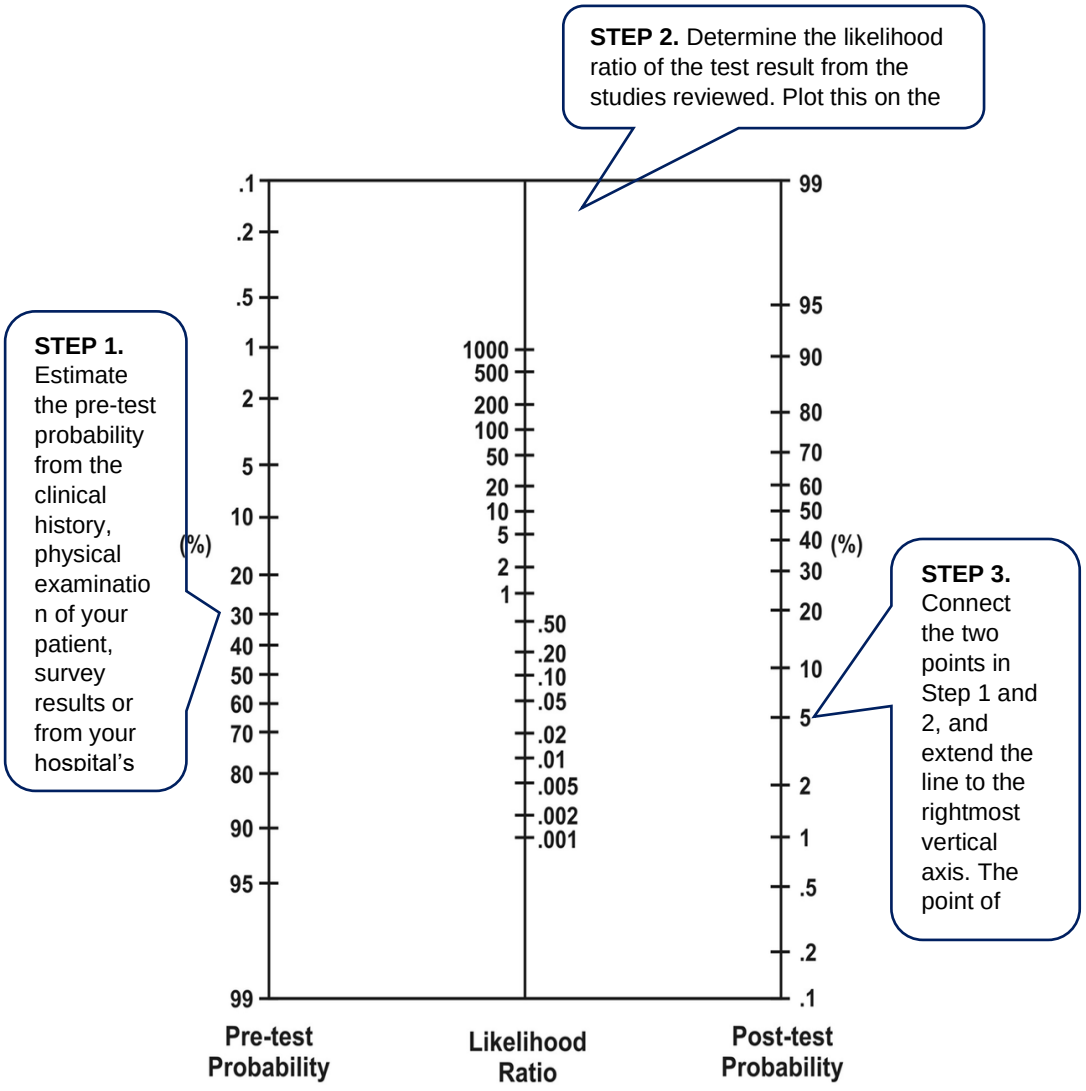


Figure A1. Using Bayes nomogram for estimating post-test probability

Evidence on Screening Program

The criteria for evaluating screening programs are:

1. The burden of illness must be high.
2. The tests must be accurate.
3. Early treatment must be more effective than late treatment.
4. Diagnostic tests and early treatment must be safe.
5. The cost of screening strategy must be commensurate to the potential benefit.

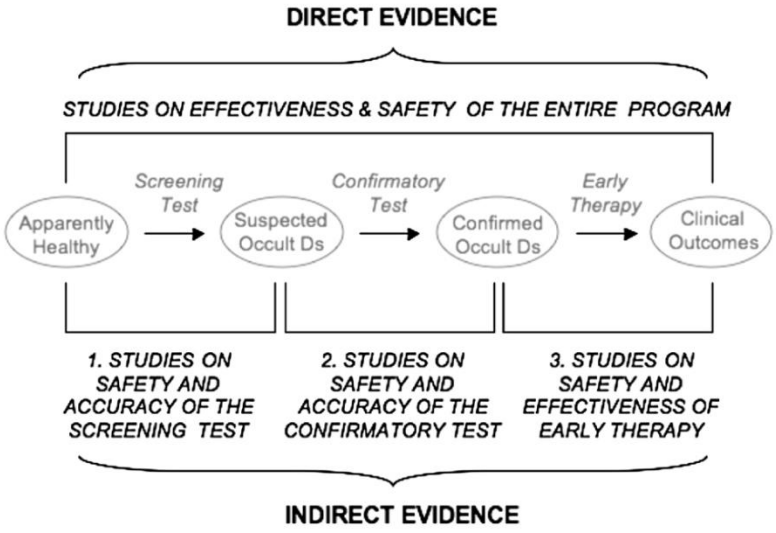


Figure A2. Admissible evidence for evaluation of a screening program[1]

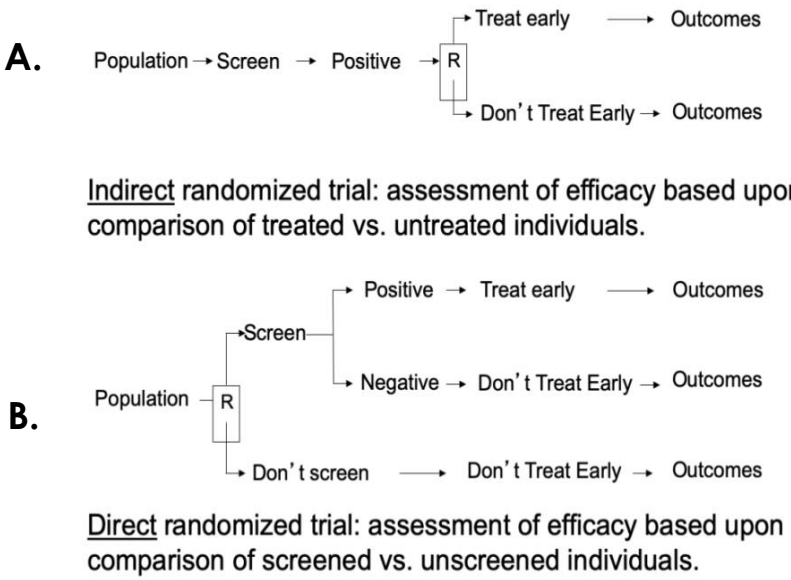


Figure A3. Indirect (A) and direct (B) trials of the effectiveness of screening[1]

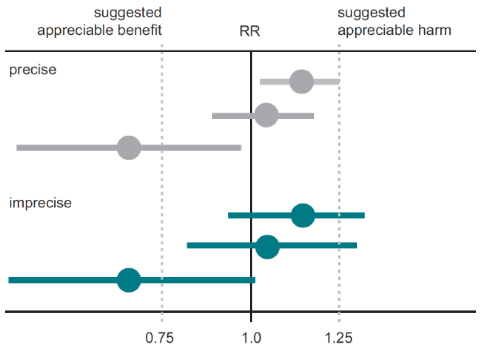
[1] Adapted from Dans Al, Dans LF and Silvestre MA. Painless Evidence – Based Medicine. 2nd edition. 2016.

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 1. 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 2. 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.

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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 for the screening and diagnosis for COVID-19. The following key questions were addressed:

Q1. Should the 14-day symptom-based test be used in screening for COVID-19 infection in apparently healthy adults and children?

Q2. Should pulse oximetry be used for at-home monitoring of COVID-19 patients?

Q3. Which clinical specimens can be used as an alternative to nasopharyngeal swab RT-PCR* for the diagnosis of COVID-19?

Q4. Among patients suspected to have COVID-19, how accurate are rapid antigen tests compared to RT-PCR for the diagnosis of COVID-19?

Q5. Among patients suspected to have COVID-19, how accurate are self-administered rapid antigen tests alone compared to RT-PCR for the diagnosis of COVID-19?

Q6. Should breath tests be used to diagnose COVID-19 infection?

Q7. Should pooled testing using RT-PCR for SARS-CoV-2, versus individual testing using RT-PCR, be used for screening and surveillance for SARS-CoV-2 in patients with suspected COVID-19 infection?

Q8. Should repeat RT-PCR testing after an initial negative RT-PCR (versus single RT-PCR testing) be done to diagnose COVID-19 in symptomatic patients?

Q9. Among COVID-19 confirmed patients, should certain RT-PCR cycle threshold values be used to determine infectivity?

Q10. Should antibody tests be used for COVID-19 seroprevalence studies and monitoring vaccine response among adults?

Q11. Among symptomatic individuals previously diagnosed with COVID-19, should antibody testing be done to diagnose presumptive COVID-19 reinfection?

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Q18. Should procalcitonin be used to guide the initiation of antibiotic therapy in patients diagnosed with COVID-19?

Q19. Should certain risk factors be used to predict the development of long COVID?

Q20. Should heparin induced thrombocytopenia (HIT) test kits be used for COVID-19 vaccine induced thrombosis with thrombocytopenia (VITT)?

Q21. Should serum tryptase be used to test individuals who had anaphylaxis after receiving COVID-19 vaccine?

Q1. Should the 14-day symptom-based test be used in screening for COVID-19 infection in apparently healthy adults and children?

As of 29 November 2021

RECOMMENDATION

We suggest to do an initial screening for ANY influenza-like illness, typical and atypical COVID-19 symptoms* within the past 14 days in apparently healthy adults and children, especially for individuals with known exposure to a laboratory-confirmed case of COVID-19. *(Very low certainty of evidence; Weak recommendation)*

**Symptoms include but not limited to: fever/chills, cough, shortness of breath/dyspnea, sore throat, runny nose, myalgia, headache, fatigue/malaise, diarrhea, nausea/vomiting, abdominal pain, anosmia, ageusia, wheezing, chest pain, altered mental status, seizures, rash, pink eye*

Consensus Issues

A weak recommendation was made based on evidence including studies that were conducted prior to the new variant of concern, Omicron, which was noted to present with symptoms not typical of previous variants. Additionally, majority of the studies were on adults while one study was on the pediatric population. The panelists emphasized that the list of symptoms is not exhaustive and that presence of any of the symptoms would warrant further investigation through a follow-up confirmatory diagnostic test.

PREVIOUS RECOMMENDATION

We suggest an initial screening for COVID-19 by checking for any influenza-like illness symptoms and typical COVID-19 symptoms* within the past 14 days in apparently healthy adults. *(Low quality of evidence; Conditional recommendation)*

Symptoms include: fever, cough, sore throat, runny nose, myalgia, headache, fatigue/malaise, diarrhea, nausea/vomiting, anosmia, ageusia, shortness of breath/dyspnea

Previous Consensus Issues

The 14-day symptom-based test is a screening strategy wherein the presence of any influenza-like illness symptoms within the past 14 days is designated as presumptive for COVID-19. It should be noted that since the recommendation is for initial screening, a follow-up confirmatory diagnostic test should be done.

WHAT'S NEW IN THIS VERSION?

- This version includes evidence on the diagnostic accuracy of 14-day symptom-based tests for both adult and pediatric populations.
- Sensitivity and specificity of individual COVID-19 symptoms, symptom combinations, and existing case definitions were also assessed in this version.

KEY FINDINGS

- Evidence on the accuracy of 14-day symptom-based testing was found from three observational studies (n=8,475). This symptom-based test had a wide range of sensitivity (2.2-100%) and specificity (29-99%) in detecting COVID-19 among adults and children. Variability in accuracy appeared to be associated with heterogeneity in the populations tested and the characteristics of the index test.

- The diagnostic accuracy of individual symptoms differed depending on the exposure history of the populations where the test was applied. For those with unclear exposure, individuals had excellent specificity (>90%) but poor sensitivity (<50%). For close contacts of confirmed COVID-19 cases, nasal congestion/rhinorrhea, headache, cough, sore throat, were the individual symptoms that had at least 70% sensitivity. For children, accuracy was highest for headache, nasal congestion or rhinorrhea, fever or chills, and sore throat.
- Combining individual symptoms can increase the specificity to as high as 99.9% but with no substantial improvements in sensitivity. The Centers for Disease Control (CDC) symptom list showed the highest sensitivity (100%) but lowest specificity (21-45%) in both adults and children population while influenza-like illness showed the highest specificity (86-96%) but lowest sensitivity (43-54%).

INTRODUCTION

Earlier local and international recommendations using symptom-based screening were based on the incubation period of COVID-19. It is hypothesized that if a 14-day symptom strategy for screening adults or children was to be implemented and the suspected individuals and their exposed contacts follow quarantine protocols, the resources needed to do serial or repeated testing will be reduced.

An earlier rapid review on this topic pooled two cohorts (n=234) and estimated the sensitivity or proportion of symptomatic SARS-CoV-2 positive cases who developed symptoms within 14 days to be at 92.8% (95% CI 89.5-96.1%).[1] The previous review also used indirect evidence from an influenza vaccine study on elderly patients and found that the development of influenza-like illness within 14 days had a specificity of 98.3% (95% CI 97.2-99.2).

This review aimed to update the evidence base on 14-day symptom-based testing for COVID-19 screening.

REVIEW METHODS

An updated systematic search was done from June 9, 2020 until October 20, 2021 through several electronic databases (MEDLINE, Cochrane CENTRAL, and HERDIN Plus), preprint servers (medRxiv and bioRxiv) and trial registries (ClinicalTrials.gov, WHO ICTRP, and ChiCTR) for studies investigating the accuracy of a 14-day symptom-based test in adults and children to screen for SARS-CoV-2 infection or COVID-19. Search terms included the following and their variations: influenza-like illness, influenza symptoms, COVID-19, SARS-CoV-2, monitoring, and surveillance and COVID-19 symptom checklist. We excluded studies that did not specify a 14-day timeframe for symptoms, those involving hospital workers and studies with small sample sizes (n<30).

RESULTS

Characteristics of included studies

Appendix 3 summarizes the characteristics of the three included studies.[2-4] In this review update, one new study [4] was added to the two studies previously included.[2,3] Two studies [3,4] involved populations with possible or confirmed exposure to a confirmed COVID-19 case, while the remaining study included patients with unclear exposure history.[2] One study [4] reported diagnostic accuracy data

specific to children. All three studies used RT-PCR with nasopharyngeal swab specimens as reference standard.[2-4] One study [3] used oropharyngeal swab (OPS) in addition to NPS while another study used anterior nares swabs.[4] All studies used symptoms found in COVID-19 and influenza-like illnesses, with varying case definitions or symptom criteria (i.e., WHO or CDC [2], CDC [3], or other [4]).

One cross-sectional study (n=8,214) in the United States evaluated the diagnostic performance of individual symptoms and various symptom combinations against a positive RT-PCR test[2].[2] Patients were 12 years or older who sought testing in statewide open-testing sites in Indiana, USA. All participants were screened for the presence of the following symptoms within the last 14 days using a standardized checklist: anosmia, ageusia, fever, chills, chest pain, vomiting, myalgia, cough, shortness of breath, sore throat, diarrhea, fatigue, headache, and runny nose. NPS specimens were collected by trained personnel using Dacron swabs during the same encounter as the symptom screening and were sent to laboratories in Indianapolis, IN. Blinding of those who interpreted the RT-PCR test was not specified. Of these, 4,772 (58%) participants were asymptomatic in the past two weeks. There were 368 (4.6%) individuals with a positive RT-PCR result and 91 (24.7%) were asymptomatic.

Another smaller cross-sectional study (n=76) investigated residents in a long-term skilled nursing facility in a Washington county where a COVID-19 outbreak occurred.[3] All consenting participants were screened for both typical (fever, cough, and shortness of breath) and atypical (malaise, nausea, sore throat, increased confusion, dizziness, diarrhea, rhinorrhea, myalgia, headache, and chills) symptoms of COVID-19 by records review and clinician interview. The study considered patients as asymptomatic if they had no symptoms and with only stable, chronic symptoms. The presence of at least one typical or atypical COVID-19 symptom was considered positive for the symptom-based test. NPS for all, and OPS for some participants were collected at the time of screening and sent for one-step real-time RT-PCR assay using the SARS-CoV-2 CDC assay protocol (Washington State Public Health Laboratory). A Ct value <40 cycles was the threshold for a positive result. Participants with positive RT-PCR test results and were asymptomatic at the time of testing were re-evaluated and assessed for any development of symptoms after one week. Those who developed new symptoms were re-categorized as pre-symptomatic. There were 53 residents (69.7%) considered as asymptomatic and 13 (24.5%) of them tested positive on RT-PCR. One week after testing, 10 of those 13 asymptomatic participants who had positive RT-PCR developed new symptoms while three remained asymptomatic. The most common symptoms that developed were fever, malaise, and cough.

A study done (n=185) in Wisconsin and Utah, United States assessed the diagnostic performance of existing case definitions of COVID-19 using symptoms reported from household contacts to a PCR-confirmed case of COVID-19.[4] Of the 185 (median age=22 yrs), 122 (66%) were adults and 63 (34%) were children. Among children, nine (14%) were less than 5 years, 19 (30%) were 5-9 years, and 35 (56%) were 10-17 years of age. Participants were assessed for the presence of COVID-19 symptoms by listing a symptom diary during the 14 days prior to enrollment and during 1-14 days after enrollment. NPS and anterior nares swabs were collected from participants on

[2] Lilly Clinical Diagnostics Lab SARS-CoV-2 test, Luminexon NxTAG CoV Extended Panel or Roche cobas SARS-CoV-2 test, unspecified Ct value

day 0 and day 14. An interim swab was also collected if any of the household contacts of participants had newly developed or had worsening symptoms of COVID-19. The study enrolled 199 household contacts of index patients with laboratory-confirmed SARS-CoV-2 infections.

Benefits and Harms of Screening

No studies that documented the effectiveness or harms of implementing a universal 14-day symptom-based screening strategy in reducing SARS-CoV2 transmission, mortality, or other patient-centered outcomes were found. These outcomes were also not evaluated in the three studies included in this review.

Diagnostic Accuracy

The sensitivity of the 14-day symptom-based test ranged from 2.2 to 100% while specificity ranged from 29 to 99.9%. Summary sensitivity and specificity estimates were not derived as studies had heterogeneous populations with variable exposure history, as well as varied index test characteristics (defining a “positive” test as either the presence of individual symptoms, symptom combinations, or fulfilment of a particular case definition/symptom criteria). These are briefly discussed in the following sections.

A. Individual symptoms

Two studies [2,4] reported the sensitivity and specificity of individual symptoms. Results differed between the two studies and may suggest that the diagnostic accuracy/performance of a 14-day symptom-based test differs when applied in populations with varying exposure history.

Nasal congestion/rhinorrhea, headache, and cough were the individual symptoms that had at least 70% sensitivity according to the study that involved adults and children with known exposure history to a COVID-19 case.[4] For children, accuracy was highest for headache (Sn 86%, Sp 80%) and nasal congestion or rhinorrhea (Sn 86%, Sp 63%), fever or chills (Sn 64%, Sp 86%), and sore throat (Sn 64%, Sp 86%).

Another study that involved patients above 12 years old with unknown exposure history reported different findings. All the individual symptoms exhibited a sensitivity of <50%, but high specificity (<90%).[2]

Table 1 shows the diagnostic accuracy of the top ten individual symptoms reported within 14 days for both adults and children.

Table 1. Diagnostic accuracy of the top ten individual symptoms reported within 14 days for both adults and children (2 studies)

Individual symptoms reported within 14 days	Dixon 2020 (> 12 y.o., unknown exposure history)		Reses 2021 (adult and children, household contacts exposed to a confirmed COVID-19 case)	
	Sn (%)	Sp (%)	Sn (%)	Sp (%)
Cough	47.60%	87.30%	74%	76%
Sore throat	24.50%	91.90%	55%	71%
Headache	39.10%	81.90%	86%	63%
Fever	35.10%	98.10%	63%	83%
Nasal congestion/rhinorrhea/runny nose	24.50%	85.30%	90%	49%
Myalgia	31.80%	92.60%	57%	85%
Shortness of breath	17.40%	94.20%	27%	92%
Anosmia	25.50%	98.90%	63%	96%
Aguesia	28.50%	98.70%		
Wheezing	-	-	10%	98%

B. Symptom combinations

Combining individual symptoms can increase the specificity to as high as 99.9%. However, it can also decrease its sensitivity.[2] The study by Kimball et al. [3] involving adults in nursing facility with possible exposure found low sensitivity but high specificity estimates with at least one typical (Sn 38.1%, Sp 81.6%) or one atypical COVID-19 symptom (Sn 13.3%, Sp 90.9%).

C. Case definitions

One study (n=185) compared the sensitivity and specificity of individual symptoms of different COVID-19 case definitions (e.g., US CDC COVID-19 like-illness, CDC symptom list, influenza-like illness, and WHO acute respiratory infection) and its combinations.[4] Existing case definitions used to classify COVID-19 showed sensitivity of 51 to 100% and specificity of 29 to 90%. The CDC symptom list showed the highest sensitivity (100%) but lowest specificity (21-45%) in both adults and children population, while influenza-like illness showed the highest specificity (86-96%) but lowest sensitivity (43-54%).

Table 2 shows the diagnostic accuracy of symptom combinations or case definitions reported within 14 days for both adults and children.

Certainty of evidence

The overall certainty of evidence for the diagnostic accuracy estimates was rated very low. Downgrading was done due to the risk of bias in two studies (patient selection, independence of index test interpretation), serious inconsistency, and serious imprecision.

Table 2. Diagnostic accuracy of symptom combinations or case definitions reported within 14 days for both adults and children (2 studies)

Symptom combinations	Kimball 2020 [3] *(adults in nursing facility, with possible exposure to confirmed COVID-19 case)*		Reses 2021 [4] *(adult and children, household contacts exposed to a confirmed COVID-19 case)*	
	Sn (%)	Sp (%)	Sn (%)	Sp (%)
At least one typical COVID-19 symptoms (fever, cough, shortness of breath)	38.1%	81.6%	-	-
At least one atypical COVID-19 symptoms (chills, malaise, sore throat, confusion, rhinorrhea, nasal congestion, myalgia, dizziness, headache, nausea, diarrhea)	13.3%	90.9%	-	-
CDC symptom list[a]	-	-	100%	29%
WHO acute respiratory infection (ARI)[b]	-	-	96%	38%
U.S. CDC COVID-19-like illness (CLI)[c]	-	-	86%	68%
Influenza-like illness (ILI)[d]	-	-	51%	90%

[a] CDC symptom list include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea. Presence of at least 1 symptom may have COVID-19. This symptom list was last updated on 13 May 2020.

[b] World Health Organization (WHO) acute respiratory infection (ARI) definition for community-based respiratory syncytial virus (RSV) surveillance. At least one of the following: shortness of breath or cough, sore throat, or coryza. Last updated 04 February 2020.

[c] U.S. Centers for Disease Control and Prevention (CDC) COVID-19-like illness definition: fever AND/OR cough or shortness of breath. This definition was used to guide early diagnostic testing strategies from 17 January 2020 to 08 March 2020.

[d] Influenza-like-illness criteria include fever AND cough and/or sore throat

EVIDENCE TO DECISION

The 14-day symptom-based test can be easily administered to anyone who needs to be screened for COVID-19 without spending any amount. No economic evaluation studies or other similar evidence were found on using a 14-day symptom testing strategy to screen for COVID-19 among adults and children.

RECOMMENDATIONS FROM OTHER GROUPS

Local societies forming the Healthcare Professionals Alliance Against COVID-19, including PSMID, PCCP, PCP, PSGIM and PCOOM, produced unified clinical decision algorithms that consider individuals without COVID-19 symptoms in the past 14 days as non-COVID-19 cases in November 2020.[5]

The WHO (2020 Dec 16) definition for suspected cases of SARS-CoV-2 infection includes the development of symptoms and meeting exposure criteria within 14 days before symptom onset.[6] The latest WHO Living Guidance (2021 Jan 25) recommends screening symptoms for all persons at the first point of contact with the health system (e.g., emergency unit, primary care clinic, community, telemedicine). A simple set of questions with symptoms including fever, cough, fatigue, anorexia, shortness of breath, and other nonspecific symptoms should be used.[7]

The US Centers for Disease Control and Prevention (CDC, 2020 Oct 21) recommends SARS-CoV-2 diagnostic (molecular or antigen) testing in patients with symptoms of COVID-19. The CDC does not routinely recommend SARS-CoV-2 testing “if you do not have COVID-19 symptoms and have not been in close contact with someone known to have SARS-CoV-2 infection (meaning being within 6 feet of an infected person for at least 15 minutes).”[8]

RESEARCH GAPS

There are no ongoing trials specifically investigating the accuracy of the 14-day symptom-based test in detecting SARS-CoV-2 infection. However, it is suggested that the performance of symptom-based tests may increase if separate tests are developed for adults and children as symptoms or clinical manifestations of COVID-19 may differ between these two groups.[4]

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Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)					Understanding symptoms of COVID-19 in pre-clinical and community-based populations may assist in clinical screening and pandemic control.
Certainty of Evidence	High	Moderate (1)	Low (3)	Very low (4)			The overall certainty of evidence was rated as very low due to risk of bias in patient selection, inconsistency, and imprecision.
Accuracy	Very Accurate	Accurate (4)	Inaccurate (3)	Very Inaccurate	Uncertain (1)		This symptom-based test had a wide range of sensitivity (2.2 to 100%) and specificity (29-99%) in detecting COVID-19 among adults and children. Variability in accuracy appeared to be associated with heterogeneity in the populations tested and the characteristics of the index test.The diagnostic accuracy of individual symptoms appear to differ depending on the exposure history of the populations where the test is applied. For those with unclear exposure, individuals had excellent specificity (> 90%) but poor sensitivity (< 50%). For close contacts of confirmed COVID-19 cases, nasal congestion/rhinorrhea, headache, cough, sore throat, were the individual symptoms that had at least 70% sensitivity. For children, accuracy was highest for headache, nasal congestion or rhinorrhea, fever or chills, and sore throat. Combining individual symptoms can increase the specificity as high as 99.9% but with no substantial improvements in sensitivity. The CDC symptom list showed the highest sensitivity (100%) but lowest specificity (21-45%) in both adults and children population while Influenza-like illness showed the highest specificity (86-96%) but lowest sensitivity (43-54%).
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			No research evidence found
Resources Required	Uncertain (3)	Large cost	Moderate Cost (1)	Negligible cost (3)	Moderate savings	Large savings (1)	No research evidence found
Certainty of evidence of required resources	No included studies (6)	Very low	Low (2)	Moderate	High		No research evidence found
Cost effectiveness	No included studies (5)	Favors 14-day test (12)	Does not favor 14-day test or the comparator (1)	Favors comparator			No research evidence found
Equity	Uncertain (5)	Reduced	Probably no impact (1)	Increased (2)			No research evidence found
Acceptability	Uncertain (4)	No	Yes (4)				No research evidence found
Feasibility	Uncertain (3)	No	Yes (5)				No research evidence found

Appendix 2. Search Yield and Results

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
MEDLINE	((influenza-like illness) OR (influenza symptoms)) AND (COVID-19) AND ((monitoring) OR (surveillance)) AND (COVID-19 symptom checklist)	10/13/21 09:05 PM	754	1
Cochrane	((COVID-19) OR (SARS-CoV-2)) AND ((influenza-like illness) OR (influenza symptoms))	09/29/21 12:13 PM	1 review 99 trials 1 editorial	0
medRxiv	((COVID-19) OR (SARS-CoV-2)) AND ((influenza-like illness) OR (influenza symptoms))	09/29/21 01:20 PM	136	0
bioRxiv	((COVID-19) OR (SARS-CoV-2)) AND ((influenza-like illness) OR (influenza symptoms))	09/29/21 01:51 PM	14	0
ClinicalTrials.gov	Condition: COVID-19 Other terms: influenza symptoms	09/29/21 01:57 PM	94	0
WHO ICTRP	((COVID-19) OR (SARS-CoV-2)) AND ((influenza-like illness) OR (influenza symptoms))	10/20/21 01:36 PM	14	0
ChiCTR	Target disease: COVID-19 Intervention: symptom	10/20/21 01:41 PM	12	0
HERDIN Plus	"COVID-19" OR "SARS-CoV-2" AND "influenza-like illness"	09/29/21 02:11 PM	18	0

Appendix 3. Characteristics of Included Studies

Table 1. Characteristics of Studies

Characteristics	Dixon 2020	Kimball 2020	Reses 2021
Sample Size (N)	8,214	76	185
Population/ Setting	≥ 12 years old, exposure to confirmed case of COVID-19 unknown	Residents in a long-term skilled nursing facility in with a possible exposure to a confirmed case of COVID-19	Household contacts (adult or child) exposed to a PCR-confirmed case of COVID-19 (adult or child)
Index Test	Any symptom within 14 days on standardized symptom checklist (WHO or CDC)	Any typical (fever, cough, SOB) or atypical (malaise, nausea, sore throat, increased confusion, dizziness, diarrhea, rhinorrhea, myalgia, headache, chills) symptom within 14 days (CDC)	Individual COVID-19 symptoms Existing COVID-19 case definitions
Reference Standard	RT-PCR (NPS)	RT-PCR (NPS for all and OPS for some)	RT-PCR (NPS and anterior nares swabs)
Outcome	Diagnosis of SARS-CoV-2 infection	Diagnosis of SARS-CoV-2 infection	Diagnosis of SARS-CoV-2 infection
Time interval between 14-day symptom based test (index test) and RT-PCR test (reference standard)	Symptom screening and RT PCR test done on same day	On day of testing and preceding 14 days For those classified as pre-symptomatic, 1 week after testing	Testing done on day 0 and day 14 of enrollment; or interim if closed contact developed new symptoms or had worsening condition
Patient sampling	*Purpose:* To identify key symptoms and symptom combinations of COVID-19 in a community-based population *Design:* cross-sectional *Participant recruitment:* random and non-random sampling *Number of patients/samples:* 8214 *Inclusion criteria:* Indiana residents age 12 years old and above *Exclusion criteria:* not mentioned	*Purpose:* To evaluate the utility of symptom screening for identification of COVID-19 *Design:* cross-sectional *Participant recruitment:* convenience sampling *Number of patients/samples:* 76 *Inclusion criteria:* skilled nursing facility residents *Exclusion criteria:* not mentioned	*Purpose:* To assess the diagnostic performance of existing case definitions using symptoms reported from contacts to a PCR-confirmed case of COVID-19 *Design:* cross-sectional *Participant recruitment:* convenience sampling *Number of patients/samples:* 185 *Inclusion criteria:* household contacts of patients with laboratory confirmed SARS-CoV2 infection *Exclusion criteria:* contacts who was not living in the home on the day of enrollment, who was hospitalized at enrollment and who did not consent to have specimens collected; contacts that had negative RT-PCR and positive serology test results
Patient characteristics and setting	*Location:* Indiana *Dates:* end of April 2020 and beginning of June 2020 *Demographics:* 55.6% Females, 44.4% Males, 80.3% Whites, 19.7% Non-whites, 7.9% Hispanics, 92.1% Non-Hispanics *Exposure history:* unknown *Onset of symptoms:* not specified	*Location:* King County, Washington *Dates:* March 2020 *Demographics:* 63% female, 37% male *Exposure history:* with a possible exposure to a confirmed case of COVID-19 *Onset of symptoms:* not specified	*Location:* Utah, United States *Dates:* March 22 to April 22, 2020 *Demographics:* includes both adult and children *Exposure history:* yes *Onset of symptoms:* 10 days
Index tests	Any symptom within 14 days on standardized symptom checklist (WHO or CDC)	Any typical (fever, cough, SOB) or atypical (malaise, nausea, sore throat, increased confusion, dizziness, diarrhea, rhinorrhea, myalgia, headache, chills) symptom within 14 days (CDC)	Individual COVID-19 symptoms and existing COVID-19 case definitions
Reference standards	RT-PCR (NPS)	RT-PCR (NPS for all and OPS for some)	RT-PCR (NPS and anterior nares swabs)
Flow and timing	Symptom screening and RT PCR test done on same day	On day of testing and preceding 14 days For those classified as pre-symptomatic, 1 week after testing	Testing done on day 0 and day 14 of enrollment

Appendix 4. Study Appraisal

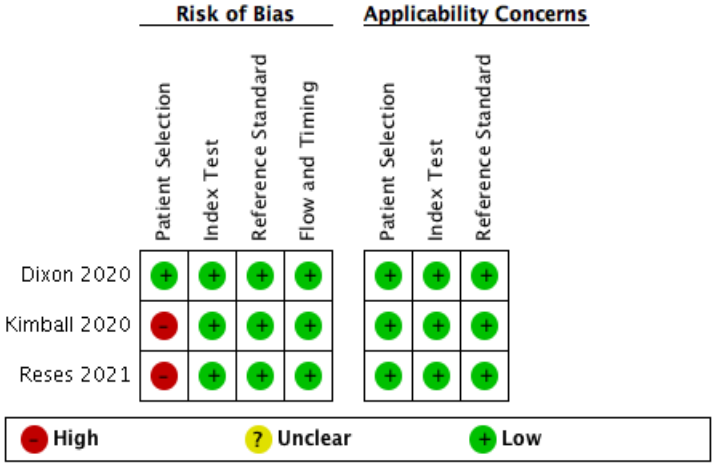

Figure 1. Summary of risk of bias and applicability concerns

Table 2. Detailed appraisal of studies

Methodological quality	Dixon 2020 [2]			Kimball 2020 [3]			Reses 2021 [4]		
Item	Authors' judgment	Risk of bias	Applicability concerns	Authors' judgment	Risk of bias	Applicability concerns	Authors' judgment	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection									
Was a consecutive or random sample of patients enrolled?	Yes			No			No		
Was a case-control design avoided?	Yes			Yes			Yes		
Did the study avoid inappropriate exclusions?	Unclear			Unclear			Yes		
Could the selection of patients have introduced bias?		Low risk			High risk			High risk	
Are there concerns that the included patient and setting do not match the review question?			Low concern			Low concern			Low concern
DOMAIN 2: Index Test									
Were the index test results interpreted without knowledge of the reference standard?	Yes			Yes			Yes		
If a threshold was used, was it pre-specified?	Unclear			Unclear			Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Low risk			Low risk			Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern			Low concern			Low concern
DOMAIN 3: Reference Standard									
Is the reference standards likely to correctly classify the target condition?	Yes			Yes			Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes			Yes			Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk			Low risk			Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern			Low concern			Low concern
DOMAIN 4: Flow and TIming									
Was there an appropriate interval between index test and reference standard?	Unclear			Unclear			Unclear		
Did all patients receive the same reference standard?	Yes			Yes			Yes		
Were all patients included in the analysis?	Yes			No			No		
Could the patient flow have introduced bias?		Low risk			Low risk			Low risk	

Appendix 5. Study Results

Tables 2 and 3. Results of Reses 2021 (adults and children) (left) and results of Dixon 2021 (adults and children) [2] (right)

	Adults & Children		Adults		Children	
SYMPTOM COMBINATIONS	**Sn (%)**	**Sp (%)**	**Sn (%)**	**Sp (%)**	**Sn (%)**	**Sp (%)**
CDC symptom list	100%	29%	100%	21%	100%	45%
WHO acute respiratory infection	96%	38%	100%	29%	86%	55%
US CDC COVID-19 like illness	86%	68%	91%	61%	71%	82%
Influenza-like illness	51%	90%	54%	86%	43%	96%
INDIVIDUAL SYMPTOMS	**Sn (%)**	**Sp (%)**	**Sn (%)**	**Sp (%)**	**Sn (%)**	**Sp (%)**
Nasal congestion or rhinorrhea	90%	49%	91%	40%	86%	63%
Headache	86%	63%	86%	54%	86%	80%
Cough	74%	76%	86%	68%	43%	90%
Taste and/or smell dysfunction	63%	96%	71%	95%	43%	96%
Fever or chills	63%	83%	63%	82%	64%	86%
Fatigue	59%	69%	63%	59%	50%	88%
Myalgia	57%	85%	63%	79%	43%	96%
Sore throat	55%	71%	51%	61%	64%	88%
Diarrhea	37%	79%	40%	82%	29%	76%
Abdominal pain	31%	88%	37%	89%	14%	88%
Chest pain	29%	90%	34%	84%	14%	100%
Shortness of breath	27%	92%	29%	89%	21%	98%
Discomfort while breathing	25%	97%	29%	95%	14%	100%
Wheezing	10%	98%	11%	97%	7%	100%

INDIVIDUAL SYMPTOMS	**Sn (%)**	**Sp (%)**
Cough	47.60%	87.30%
Headache	39.10%	81.90%
Fever	35.10%	98.10%
Fatigue	34.50%	86.00%
Myalgia	31.80%	92.60%
Ageusia	28.50%	98.70%
Anosmia	25.50%	98.90%
Sore throat	24.50%	91.90%
Runny nose	24.50%	85.30%
Chills	22.00%	97.40%
Chest pain	17.70%	96.60%
Shortness of breath	17.40%	94.20%
Diarrhea	16.00%	93.70%
Vomiting	3.30%	99.30%
SYMPTOM COMBINATIONS	**SENSITIVITY (%)**	**SPECIFICITY (%)**
Fever & Ageusia	17.10%	99.70%
Fever & Anosmia	14.40%	99.70%
Cough & Fever & Ageusia	13.30%	99.80%
Fever & Headache & Ageusia	12.80%	99.70%
Fever & Ageusia & Myalgia	12.50%	99.80%
Fever & Anosmia & Ageusia	12.20%	99.80%
Fever & Headache & Anosmia	11.40%	99.80%
Fatigue & Fever & Ageusia	11.40%	99.80%
Cough & Fever & Anosmia	11.10%	99.80%
Fever & Anosmia & Myalgia	10.10%	99.80%
Fatigue & Fever & Anosmia	9.80%	99.80%
Chills & Fever & Ageusia	9.80%	99.80%
Chills & Fever & Anosmia	7.10%	99.90%
Diarrhea & Fever & Ageusia	6.20%	99.90%
Anosmia & Vomiting	2.20%	99.90%

Appendix 6. GRADE Evidence Profile

Should 14-day symptom-based test be used to diagnose COVID-19 in apparently healthy adults and children?
Pooled sensitivity: 0.02 to 1.00
Pooled specificity: 0.29 to 1.00

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	3 studies 440 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Serious[c]	None	1 to 50	2 to 100	4 to 200	⊕◯◯◯ Very Low
False negatives (patients incorrectly classified as not having COVID-19)								0 to 49	0 to 98	0 to 196	
True negatives (patients without COVID-19)	3 studies 7839 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Serious[c]	None	275 to 949	261 to 899	232 to 799	⊕◯◯◯ Very Low
False positives (patients incorrectly classified as having COVID-19)								1 to 675	1 to 639	1 to 568	

Explanations

[a] Downgraded due to possible bias in patient selection
[b] Downgraded due to inability to determine independence of test performance
[c] Downgraded due to wide confidence interval

Q2. Should pulse oximetry be used for at-home monitoring of COVID-19 patients?

As of 22 November 2021

RECOMMENDATION

We suggest pulse oximetry with close clinical monitoring by qualified medical personnel in suspected and confirmed COVID-19 patients especially those who are at high risk for deterioration. *(Very low certainty of evidence; Weak recommendation)*

Consensus issues

A weak recommendation was made due to the limitations and risk of inaccuracy of pulse oximeters. The panel emphasized (1) ensuring the quality of the device by purchasing from reliable sources and (2) taking measures to get the best reading (e.g., following manufacturer instructions and ensuring adequate battery supply).

Considering the risk of inaccurate measurements that may result in unrecognized low oxygen saturation levels, the role of qualified medical personnel in pulse oximetry monitoring was highlighted by the panelists. Medical personnel should be available to provide instructions, to respond to caregiver and/or patient concerns, and to monitor signs and symptoms of deterioration.

KEY FINDINGS

- A total of 20 observational studies on pulse oximetry monitoring for suspected and confirmed COVID-19 patients were included in this review.
- Effect estimates could not be pooled due to serious heterogeneity across studies. Lowered percentages of admissions, readmissions, and mortalities with pulse oximetry monitoring compared to no monitoring suggest the feasibility and safety of remote monitoring using pulse oximetry but the certainty of evidence was very low.
- A single study on device accuracy showed that medical and consumer-grade pulse oximeters, particularly *Oxywatch* (Sn 92.2%, 95% CI 87.3-97.1; Sp 60%, 95% CI 49.59-70.41), *SM* (Sn 90.7%, 95% CI 85.7-95.7; Sp 67.6%, 95% CI 56.7-78.5), and *Onyx* (Sn 92.1%, 95% CI 87.3-96.8; Sp 67.6%, 95% CI 56.9-78.2), were comparable to standard emergency department (ED) monitor units.
- Another study reported that certain levels of oxygen saturation (SpO_2) have high sensitivity and specificity for risk of mortality and intensive care unit (ICU) admission. However, the overall certainty of evidence for this outcome was very low because of non-blinding, imprecision, and significant heterogeneity.

INTRODUCTION

While most patients with COVID-19 eventually recover after an initial five to seven days of viral syndrome, around 10-20% would likely deteriorate.[1] Furthermore, there have been reports of patients with no overt signs of respiratory distress but present to the hospital with lower than expected oxygen saturation levels or hypoxemia. Hypoxemia is defined as measured oxygen saturation of 94-98% or below (or below 88% for those with chronic lung disease).[2] The presence of hypoxemia is common in severe COVID-19 related pneumonia, sepsis, myocardial dysfunction, or embolic disease.[3] This phenomenon, informally called, “silent hypoxemia” or “happy

hypoxemia," describes patients with clinically significant hypoxemia (SpO_2<90%) in the absence of dyspnea and often appear clinically well. Many of these patients were reported to have radiographic findings similar to ARDS and eventually required intubation.[1]

Determining oxygen saturation, therefore, helps in triaging patients who will need hospitalization and further management, and those who can be managed and monitored at home. This method may allow early detection of signs of possible clinical deterioration, which may consequently help decongest hospitals. Healthcare systems all over the world have employed remote pulse oximetry along with other methods (e.g., monitoring vital signs, symptoms, teleconsultation) to reduce unnecessary ED visits, exposures, and PPE use.[4-7] Pulse oximetry may be a cost-effective method due to its relatively low cost, portability, non-invasiveness, and ease of use.[8-9]

This review aimed to determine whether pulse oximetry, with or without other parameters, is useful, accurate, and safe in monitoring patients with COVID-19 for the detection of clinical deterioration and, consequently, appropriate triaging of patients.

REVIEW METHODS

Systematic literature search until 04 October 2021 was performed in the following electronic databases: PMC, MEDLINE, Cochrane CENTRAL, Google Scholar, and CoAP Living Evidence on COVID-19. For the search strategy, keywords searched were MeSH terms and those in study titles. The following keywords were used: "coronavirus infections" [MeSH Terms], novel coronavirus, nCOV, covid-19, SARS COV2; Pulse Oximetry [MeSH Terms] oximeter, oximetry; monitoring; home, outpatient, pre-hospital.

Inclusion criteria for this review were as follows: (a) population - individuals with suspected or confirmed COVID-19, (b) setting - in-home monitoring and care, (c) index test/intervention - pulse oximetry monitoring (using a portable, fingertip, or commercially-available pulse oximeters) with or without other measures (e.g., monitoring symptoms, vital signs, breathlessness, perceived deterioration), (d) outcomes - diagnostic accuracy for identifying COVID-19 pneumonia (compared to RT-PCR with or without thoracic imaging as reference standard), impact on other clinical outcomes, and associated adverse effects, and (e) design - randomized controlled trials, observational studies, systematic reviews of RCTs or observational studies. References of guidelines and practice pointers obtained from the literature search were also checked and included if they reported pulse oximetry accuracy, use, feasibility, validity, benefits, or harms.

Studies were excluded if oxygen saturation levels were not monitored for all participants, if a study used smartphones or other devices to measure oxygen saturation, or if it did not report the desired outcomes. QUADAS-2 was used to assess the risk of bias. From the studies obtained during the literature search, references for focused reviews and practice pointers were checked for eligible studies. Among them was a systematic review on remote monitoring for COVID-19 (suspected and confirmed) patients.[10] Studies that employed portable pulse oximetry home monitoring for all patients in this review were included in the analysis.

RESULTS

Summary of characteristics of included studies

A total of 20 studies were included in this review, among which were one cross-sectional or cohort type accuracy, four case-control, and 15 cohort studies. One study evaluated the diagnostic accuracy of three different pulse oximeter brands (consumer-grade, medical-grade pulse as compared to standard oximeter monitor in the ED).[11] Another study reported the correlation of pulse oximetry monitoring to mortality or ICU admission.[12] Majority of the studies (n=18) described a program or model of remote patient monitoring (RPM) for patients referred from the community, seen at outpatient department (OPD), at ED, or from hospital discharge, or all sources, all of which included oxygen saturations as one of the parameters monitored. These studies reported on one or more of the following clinical outcomes: escalation/referral rates, ED attendance/ reattendance, hospitalization, length of hospital stay, ICU admission or complications, and mortality. Three studies [9,13,14] presented measures of patient satisfaction while two studies [15,16] reported the cost of monitoring.

Diagnostic accuracy of pulse oximeter

Schrading et al. [11] showed that both medical-grade (Nonin Onyx II 9550, *Onyx*) and consumer-grade pulse oximeters (Walgreen's OxyWatch C20, *OxyWatch,* and Santa Medical SM-1665, *SM*) demonstrated high sensitivity in detecting true hypoxia (SpO_2 $\leq$94% on standard ED oximetry monitoring unit) as compared to TRAM 451 pulse oximeter (wall-mounted hospital control unit). Sensitivities for each brand were 92.2% (95% CI 87.3-97.1) for *OxyWatch*, 90.7% (95% CI 85.7-95.7) for *SM,* and 92.1% (95% CI 87.3-96.8) for *Onyx*. Specificity for each brand were 60% (95% CI 49.59-70.41) for *OxyWatch*, 67.6% (95% CI 56.7-78.5) for *SM*, and 67.6% (95% CI 56.9-78.2) for *Onyx*.[11] The retrospective study employed convenience sampling, hence the risk for selection bias. Furthermore, it only reported the accuracy of the pulse oximeter device itself, making it inconsistent with the intended intervention for this current review (i.e., pulse oximetry monitoring). Therefore, this outcome was rated to have low certainty of evidence.

Accuracy of home oxygen monitoring for predicting deterioration

In terms of predicting mortality and ICU admission, a retrospective cohort study by Inada-Kim et al. [12] found that for confirmed COVID-19 patients that were brought by ambulance to the hospital from March 1 to July 30, 2021, initial oxygen saturations correlated with short-term patient mortality or ICU admission. Death and ICU admission were confirmed through hospital clinical records and linked with ambulance records. Some cutoffs for initial oxygen saturations showed moderate discriminative ability for predicting 30-day mortality with an AUROC of 0.772 (95% CI 0.712-0.833). For example, SpO2 $\leq$94% measured using an emergency medical service-issued pulse oximeter (unspecified type) among ambulance conveyances showed a sensitivity of 0.71 (95% CI 0.69 to 0.74) and specificity of 0.72 (95% CI 0.71 to 0.74). Meanwhile, SpO2 $\leq$92% of the above patients had a sensitivity of 0.62 and specificity of 0.84.[12]

The overall certainty of evidence for this outcome was rated low due to the risk of bias and indirectness. The included patients depended on subjective tagging of patients as ‘COVID’. Those that did not have a pre-hospital reading were also excluded from the analysis. Furthermore, the study only presented pre-hospital oxygen saturations and

did not employ pulse oximetry monitoring, which is different from our PICO question. The study has also not been peer-reviewed.

Clinical outcomes

A. Length of stay

Only two studies reported the length of hospital stay among those admitted after baseline oxygen saturation measurements or pulse oximetry monitoring. Lancet et al. reported that the median length of stay for survivors with baseline O_2 saturations ≤90% was five days (2-10) while for those who died was 6 days (3-12).[3] Dirikgil et al. reported length of stay in terms of bed occupancy days per 100 patients. Bed occupancy days per 100 patients was 20 days in the pulse oximetry monitoring group and 47 days in the matched control (no monitoring) group.[17]

B. Care escalation, ED attendance/re-attendance, and hospitalization

The estimated incidence of each outcome was reported. Care escalation was used as a measure of detection of hypoxia or clinical deterioration. Results showed that 21.5% of patients were referred for hypoxia or other concern as specified in the patient safety netting of remote monitoring. Among the participants, 32.2% were brought to ED for assessment or reassessment, while 25.2% were hospitalized or re-admitted. Data from Shah et al. 2020 showed that resting home SpO_2<92% was associated with an increased likelihood of hospitalization compared to SpO2≥92% (RR 7.0, 95% CI 3.4-14.5; p<0.0001).[18]

On follow up after 30 days, decreasing out-of-hospital SpO_2 in 1% increments (subdistribution hazard ratio [SHR] 0.95, 95% CI, 0.94-0.96; *P*<0.001) and increasing age in 10-year increments (SHR 0.82, 95% CI, 0.79-0.86; *P*< 0.001) were associated with a decrease in the subdistribution hazard of being discharged from the hospital on a given day, given that the patient was still in the hospital or had already died on that day. No other risk factors were identified as significant. Lancet et al. cited that these data inform triage decisions while also asserting that patients not admitted remain at risk and should be provided with close outpatient monitoring.[3]

C. ICU admission, other complications, and mortality

About 0.9% were admitted or transferred to the ICU or developed other complications. Shah et al. 2020 reported that resting home SpO_2<92% was associated with an increased risk of ICU admission (RR 9.8, 95% CI 2.2-44.6, p<0.002), ARDS (RR 8.2, 95% CI 1.7-38.7; p<0.007), and septic shock (RR 6.6, 95%CI 1.3-32.9, p=0.02). This study asserted that pulse oximetry helps detect these risks and facilitates more timely intervention. However, due to the lack of a comparator group, conclusions could not be made if the timely interventions did improve clinical outcomes.[18]

Of the total number of participants who were detected to have hypoxemia, whether or not eventually admitted, 9.2% died. Results from Lancet et al. [3] showed that increasing age in 10-year increments was also strongly associated with in-hospital mortality (OR 1.45, 95% CI, 1.33-1.58; *P*<0.001). After controlling for the competing risk of death, an out-of-hospital measured SpO_2 level ≤90% was associated with over a 50% decreased likelihood of being discharged alive (HR 0.48, 95% CI 0.43-0.54; *P*<0.001), regardless of age. Both age and out-of-hospital SpO_2 were independent predictors of in-hospital mortality and length of stay, after controlling for the competing risk of death.[3] Comparing mortalities among patient sources, Clark et al. 2020

showed that all-cause mortality was significantly higher in patients enrolled from hospital discharge (OR 8.70, 95% CI 2.53-29.89), compared to patients enrolled in primary care.[8] Inada-Kim et al. found that lower initial oxygen saturations were associated with a higher mortality rate. Oxygen saturations were the most predictive of mortality or ICU admission (AUROC 0.772, 95 % CI 0.712-0.833).[12]

Certainty of evidence
Overall certainty of the evidence for these outcomes was very low due to the serious risk of bias, inconsistency, indirectness, and imprecision. There was significant heterogeneity and no blinding or randomization. Many studies did not use a comparator and were simply descriptions of the remote monitoring or virtual hospital program implemented in their setting.

Cost
Two studies indicated the cost of remote monitoring. Gaeta et al. [15] reported cumulative home monitoring costs of $621,800 (including charges incurred due to admissions) and projected cumulative mitigated hospital charges of about $6,718,296 (IQR $4,767,344, $9,902,496), while Vindrola-Padros et al. [16] reported the mean cost per monitored patient at £400 to £553.[16]

The Department of Health (DOH) suggests that retail prices of portable or finger pulse oximeter devices as of May 6, 2021 range from Php 499.75 to Php 1,785 for pediatric and adult fingertip pulse oximeters.[19] Online shopping sites list the cost to range from Php 499 (HEALMED Pulse Oximeter, Watsons) to Php 1,580 (Inmed Pulse Oximeter Model A310, Watsons).[20-24]

OTHER CONSIDERATIONS

For home monitoring models in the UK, the mean cost per patient monitored is about £400 to £553. In the US, cumulative home monitoring costs $621,800 (including charges incurred due to hospitalization), while projected cumulative mitigated hospital charges were about US$6,718,296 (IQR $4,767,344, $9,902,496). The use of pulse oximeter devices is relatively affordable. Pulse oximeters in the country cost from Php 499 to Php1,785 and are readily available in drugstores, medical supplies, and online stores. Studies have shown that pulse oximetry monitoring received positive feedback from patient satisfaction surveys and indicated a lessening of anxiety for patients while on pulse oximetry monitoring. The pulse oximeter is easy to use, although studies emphasize ensuring training on proper use, measurement, and reporting of pulse oximetry readings. Studies have also shown its correlation with the risk of mortality and/or ICU admission or other complications.

RECOMMENDATIONS FROM OTHER GROUPS

There are currently no existing local guidelines for pulse oximetry. Table 2 lists the recommendations from other groups.

RESEARCH GAPS

There are no randomized trials comparing pulse oximetry monitoring with no pulse oximetry monitoring. Other studies would argue if such a program is ethical and feasible in a pandemic. At present, there is one randomized trial with ongoing patient inclusion that focused on pulse oximetry monitoring in addition to primary care as

opposed to primary care only. There are also no studies validating the impact of monitoring oxygen saturations on other patient outcomes

Table 2. Recommendations from other groups

Group	Recommendation
WHO COVID-19 Clinical management Living Guidance [25] (2021 Jan 25)	"A conditional recommendation for use of pulse oximetry monitoring at home as part of a package of care, including patient and provider education and appropriate follow-up, in symptomatic patients with COVID-19 and risk factors for progression to severe disease who are not hospitalized (very low certainty)." "For suggested use of pulse oximetry monitoring at home… potential benefits would outweigh the potential harms, especially if used in patients that were symptomatic and at risk for severe disease; but only as part of a larger package of care including education and follow-up."
NHS UK Guide to Pulse Oximetry [26] (2021 Jan 12)	Cohorts that will benefit most are those with a diagnosis of COVID-19 (either clinically or positive test result), and are also symptomatic and are either aged 65 years or older or under 65 years and clinically extremely vulnerable (CEV) to COVID-19.
NICE guidelines [27]	To assess the severity of illness and detect early deterioration for primary and community care settings with available pulse oximetry, use NHS England's guide to pulse oximetry in people 18 years and over with COVID-19 and for oxygen saturation levels below 91% in room air at rest in children and young people (17 years and under) with COVID-19. Caveat on difference in pulse oximeters different specifications. Under- or over-estimation can occur in borderline saturation levels; or overestimation with people with dark skin.
African CDC [28]	Instructions specified to ensure accurate readings, such as removal of nail polish or false nails, warming cold hands, measuring O2 saturations at rest, using the middle or index finger keeping the device steady on the chest at heart level, recording the highest result once reading stabilizes for five seconds. Reminders are also given to correctly distinguish the heart rate from the oxygen level readings.

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Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					Presence of hypoxemia has been observed to be a predictor for mortality and might be the only indicator of clinical deterioration in patients with no overt symptoms of respiratory distress.
Benefits	Large (4)	Moderate (2)	Small	Uncertain			Pulse oximetry monitoring may help decrease unnecessary hospitalizations, unnecessary HCW exposure, and PPE use.
Harms	Large	Moderate (4)	Small (1)	Uncertain (1)			Harms include the risk of patient not opting to go to the hospital because of normal oxygen saturations despite other signs of clinical deterioration.
Balance of Benefits and Harms	Favors pulse oximetry monitoring (2)	Probably favors pulse oximetry monitoring (4)	Does not favor pulse oximetry monitoring				Benefits include: (1) low cost, (2) ease of use, (3) allows detection of clinical deterioration associated with low oxygen saturation. Harms include: (1) interchanging readings with pulse rate may cause confusion or delay in management due to erroneous reading, and (2) opting against admission despite other clinical indications of deterioration. One study suggests not to leave the decision of presenting to the hospital to the patient alone.
Certainty of Evidence	High	Moderate (1)	Low (2)	Very low (3)			Very low overall certainty of evidence
Accuracy	Very Accurate	Accurate (6)	Inaccurate	Very Inaccurate	Uncertain		Consumer-grade (OxyWatch, SM) and medical-grade (Onyx) were comparable in detecting hypoxia as compared to ED hospital control units.
Values	Important uncertainty or variability	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			Despite ease of use, there is still a need to ensure training on proper use, measurement and reporting of pulse oximetry readings. Spot-check device prior to use by those with peripheral artery disease.
Resources Required	Uncertain	Large cost (1)	Moderate Cost (3)	Negligible cost	Moderate savings (2)	Large savings	Pulse oximeters range from Php 499 to Php1,785. Costs may be incurred if a program for remote patient monitoring (including pulse oximetry as one of the parameters monitored). Mean cost per monitored patient: £400 - £553. Cumulative costs for home monitoring: $621,800 (including charges attributed to admissions). Projected cumulative mitigated hospitalization charges: $6,718,296 (IQR: $4,767,344, $9,902,496).
Certainty of evidence of required resources	No included studies	Very low (1)	Low (3)	Moderate (2)	High		Studies that mentioned cost were from retrospective studies, and may have risk for bias in reporting values.
Cost effectiveness	No included studies (3)	Favors comparator	Does not favor either pulse oximetry monitoring or the comparator	Favors pulse oximetry monitoring (3)			No mention of cost of standard Emergency Department wall-mount pulse oximeter monitoring
Equity	Uncertain	Reduced (4)	Probably no impact	Increased (2)			Patients who cannot afford to buy a pulse oximeter will not be able to do pulse oximetry monitoring at home. Various brands may need to be checked for accuracy or validated prior to use. RPM models usually provide the pulse oximeter during the study, to be returned afterwards.
Acceptability	Uncertain	No	Yes (6)				Patients with chronic lung or heart conditions may already have an existing pulse oximeter, so monitoring will be at no cost to them.
Feasibility	Uncertain	No	Yes (6)				Success of pulse oximetry monitoring or a program of remote monitoring is attributed to 1) proper instruction of patient/caregiver on proper use and recording of readings, 2) a safety net for timely intervention in place for patients who actually have episodes of true hypoxia.

Appendix 2. Search Strategy, Yield and Results

Database (Yield)	Date of search	Search Strategy
PMC (8 studies)	Sept 23, 2021	Search (((((((("coronavirus infections"[MeSH Terms]) OR novel coronavirus[Title]) OR nCOV[Title]) OR covid-19[Title]) OR SARS COV2[Title])) AND (((PULSE OXIMETRY[MeSH Terms]) OR oximeter[Title]) OR oximetry[Title])) AND monitoring[Title]) AND (((home[Title]) OR outpatient[Title]) OR pre-hospital[Title])
Pubmed	Sept 23, 2021	("coronavirus infections"[MeSH Terms] OR "nCOV"[Title] OR "covid-19"[Title] OR "sars cov 2"[Title]) AND ("oximetry"[MeSH Terms] OR "oximeter"[Title] OR "oximetry"[Title]) AND ("monitoring"[Title] OR "screening"[Title]) AND ("home"[Title] OR "outpatient"[Title] OR "pre-hospital"[Title])
CoAP Living Evidence on COVID-19*	Sept 26, 2021	((pulse oximetry) OR (oximeter) OR (oximetry)) AND ((home) OR (outpatient) OR (pre-hospital)) AND ((monitoring) OR (screening) OR (surveillance)) Title only
Google scholar	Oct 1, 2021	allintitle: oximetry AND covid

*https://zika.ispm.unibe.ch/assets/data/pub/search_beta/
**Review of references -- 2 studies, including 1 systematic review on remote patient monitoring.
Included studies that monitored oxygen saturations. -- yield: 9 studies

Appendix 3. Table of Included Studies

Table 1. Characteristics of included studies

Study ID	Setting	Study design	P				I			C		O
			Patient population	Pt source[1]	n	Mean/ median age	Methodology/ Model	Monitoring duration	Def for hypoxia/ cutoff criterion/ criteria for escalation	RT PCR positive	Comparator / Control	Target outcomes
Gootenberg 2021 [1]	USA	Prospective observational	Presumed or confirmed COVID 19 adult pts assessed for discharge from ED but at risk for deterioration	ED	81	51.7	Patient self-monitoring (d/c & pulse ox instructions); MD follow up	7	Resting: <92%	30 (37%)	No data	Rate of ED return, hospitalization and hypoxia (assess feasibility, describe protocol)
Gal braith 2021 [29]	USA	Prospective observational	Vermont resident with positive RT PCR, who are not inmates or inpatients	C	599	No data	Daily pt pulse ox monitoring via email/ SMS/ daily calls	No data	90%	all pts	No data	None specified (described program implementation only)
Shah 2020 [18]	USA	Prospective observational	18+y/o, suspected COVID-19; discharged from ED or OPD; SpO2 > 92% on ED discharge; not pregnant; not on O2 support	ED or OPD	77	44	Thrice daily pt pulse ox monitoring via daily calls to pt	7	92%	77	Normoxemic pts (SpO2 ≥92%)	1) Hospitalization rate in resting home SpO2<92% 2) SpO2 trend, dec subsequent ED visits, hospital outcomes (LOS, TOS to ICU, Time to drop)
Kyriakides 2021 [30]	UK	Prospectiveobservational	Suspected or confirmed COVID, resting or rm air SaO2 90-94%, can use pulse ox correctly, non-admissible	C	20		Patient home SpO2 monitoring 3x daily Telephone ff-up by MD on days 2, 5, 7	7	SaO2 < 90% at rest on ≥2 occasions w/n 24hrs; Standard safety net info		NS	Rate of avoidance of hospitalization, ED reassessment, discharge from pathway
Banzi 2020 [31]	Italy	Prospective observational	Symptomatic suspected or confirmed COVID patients not for ED visit or hospitalization; no permanent motor or mental disabilities or temporary conditions	C	37	53.9	Daily visit with resting and post rapid walking test SpO2 recording	8.2	90% at rest or desaturations of ≥5% points after rapid walk test	No data	No data	Percentage of patients referred for escalation of care that were actually transferred within 24 hours of reporting; SpO2 at ED presentation
Hutchings 2020 [Preprint] [32]	Australia	Prospective observational	Patient deemed safe and able to self-isolate	C	62	median : 38	VS rec on app + standardized early warning system. 3x daily phone call & video-consult 2x daily.	8 (1-17 days)	No data	No data	No data	Care escalation rates (ED presentation and hospital admission)
Vindrola-Padros 2021	UK	Multi-site mixed	Triaged as eligible for home monitoring either in a pre-hospital model or	PC	1737	No data	App or paper diary patient recording;	14 days or until	No data	No data	no control group identified	Hospital and ICU admissions or readmissions, ED attendances,
				HD	347	No data						

[33]		methods study	from early discharge from the hospital				regular monitoring calls from PC or SC staff	symptoms resolve				mortality rates, patient satisfaction measures
O'Carroll 2020 [34]	Ireland	Prospective observational	Discharged from hospital with pulmonary infiltrates on xray & non-O2 requiring	HD	18	48	Daily SpO2 check 4x daily. Mobile app recording check & alert for breathlessness	Median 12 days	≤94%	No data	No data	Resting SpO2, rate of self-reported breathlessness in patients with COVID-19
Gaeta 2020 [15]	USA	Retro-spective	Presumptive or confirmed COVID discharged home (exertional SpO2>90% AND RR<22), with consent to early telehealth follow up	HD	488	No data	Retrospective chart review of patients enrolled in the remote patient monitoring program (monitored: s/sx, SpO2, HR, RR)	7	90% (implied)	No data	No data	ED revisit; disease course, hospital LOS, ICU requirements, respiratory support, mortality and loss to follow up
Clarke 2021 [35]	UK	Retrospective	Suspected or confirmed COVID-19 in England during Summer 2020	ALL	908	54 (med)	Analyze patient data from 4 pilot sites enrolled from primary care, ED visit or following hospital discharge. Monitoring of HR, SpO2, HR over time, symptoms and overall well-being	No data	≥95%	NS	Compare bet pt source (PC vs ED vs hosp d/c); Compare among age groups, (+/-) comorbidities, SpO2 on enrolment	rates of escalation, ED reattendances (planned or unplanned), hospitalization, death
				OPD	302	55 (med)		No data	No data	No data		
				ED	342	50		No data	No data	No data		
				HD	259	63		No data	No data	No data		
Lancet 2021 [36]	USA	Prospective observational	Alive on ED arrival, RT PCR+, documented pre-hospital SpO2 measurement on room air	Pre- ED	1673	66	Review of FDNY EMR (adult pts transported by FDNY-EMS to any NYC hospital ED March 5 - April 30, 2020)	No monitoring	<90%	No data	No data	In-hospital mortality and LOS (determine if SpO2 was an independent predictor of COVID 19 in -hospital mortality and LOS)
Grutters 2020 [37]	Netherl ands	Retrospective	COVID-19 pts discharged (with O2 support (max 3L/min) to rm air) (fr ICU	HD	33	57	Daily monitoring of SpO2, temp, COVID resp	13.4	NS	31 (94%)	No data	Reduced length of hospitalization, safety, patient satisfaction

			21%, ICU LOS 8d, on O2 on discharge 61%)				symptoms rating scale via an mobile app					
Gordon 2020 [38]	USA	Prospectiveo bservational	Discharged presumed or confirmed COVID 19, no severe symptoms	HD	225	54	MyChart Care Companion (pulse ox, thermometer, instructional packet) Portal-based RPM program	2-3wks at patient discretion median 12days		No data	Patients not referred to the program	ED or hospital readmission rate within 30 days of the initial discharge
Kodama 2020 [39]	USA	Prospectiveo bservational	Stable patients identified for discharge (>18yo, SpO2 >92% prior to and on discharge, with reliability on use of pulse oximeter and gave consent	HD	50	No data	RPM via app-based monitoring (VS at rest and 20s after exercise) by assigned nurse algorithm for monitoring and escalation	14 days	SaO2 <90% or >5% dec on exertion+ 20s HR >115 at rest, >125 exertion inc >10 b/w rest & exertion RR>22, or RR>30 exertion/ inc >8 b/w rest & exertion	No data	No data	ED visits, readmission rate
Silven 2020 [40]	Netherl ands	Prospective observational	ED pt for suspected COVID or after admission	ED/ HD	55	No data	Remote monitoring package (COVID Box); video consults, app-based monitoring, EMR	No data	Personalized thresholds or general feeling of unwellness	No data	No data	Admission rate
Francis 2020 [pre print] [41]	UK	Prospective observational study	Clinically diagnosed COVID 19 patients	ED OPD	455	48.9	Virtual hospital remote assessment (resp. MD calls on days 2-5,7,10,14 & beyond for high risk patients); pseudonymized EMR	Median 21 days	No data	31.40%	No data	Adverse outcome: Death or re-admission to inpatient hospital care over 28 days
				HD	445	61			No data	60.90%	No data	
Wilcock 2021 [pre print] [42]	UK	Prospective, observational	RT PCR positive adult pts with symptoms in the past 7 days, self-isolating at home	OPD	41	45.9	2x daily self-recording of SpO2 & symptoms (cough, loss of smell, +/- breathlessness)	14 days since COVID19 RT PCR (+)	94% and 92%	No data	No data	Proportion of people SpO2 ≤94% and ≤92%, ave. max reduction in SpO2, hospitalization rate
Dirikgil 2021 [43]	Netherl ands	Retrospective case control	all ED visits from 3/1-6/15, 2020 suspected COVID with moderate	HD	55	61	home monitoring via COVID-box (3x	28	personalized thresholds	13	Discharged patients	Total hospital admissions w/in 28 days of ff up; number of patients completing ff up

			s/sx or underlying co-morbidities				daily home monitoring; teleconsultations by a HCP				without home monitoring	without ED reassessment, bed occupancy rate
			Matched control group		110	59				7	ref	
Schra-ding 2020 [44]	USA	Prospective observational	adults presenting at ED with 1) hypoxia (SpO2 <94%), 2) an acute COPD exacerbation or 3) chest pain or dyspnea; no peripheral artery disease, anemia	ED patients convenience sample	198	median 58	measurement of oxygen saturation using (consumer-grade) Walgreen's OxyWatch C20 (OxyWatch) pulse oximeter brand	N/A	≤94%	No data	TRAM 451 pulse oximeter (wall-mounted hospital control unit)	Sensitivity and Specificity, Positive Predictive and Negative Predictive Values
					200		measurement of oxygen saturation using (consumer-grade) Santa Medical SM-1665 (SM)	N/A	≤94%	No data	TRAM 451 pulse oximeter (wall-mounted hospital control unit)	
					200		measurement of oxygen saturation using (medical-grade) Nonin Onyx II 9550 (Onyx)	N/A	≤94%	No data	TRAM 451 pulse oximeter (wall-mounted hospital control unit)	
Inada-Kim 2020 [45]	UK	Retrospective cohort	adult pts initially assessed and conveyed from ambulance service to the ED between March 1, 2020 to July 31, 2020, tagged as 'COVID-Respiratory Distress,' 'Suspected COVID,' 'COVID'	EMR from ambulance service	1080	Not Specified (only age groups reported)	Review of EMR of pts conveyed to hospital by ambulance during specified study period	N/A	Not specified	No data	None Specified	short-term (30-day) mortality or ICU admission

[1] C – Community; OPD/ PC – OutPatient Dept or Primary Care; ED – Emergency Department/ Accident & Emergency; HD – Hospital Discharge

[2] ex -sm – ex- smoker, MH – mental health

[3] Mild: SpO2≥95%; Mod: SpO2 93-94%; Severe: SpO2 ≤92%

Table 2. Outcomes of included studies

Study ID	Patient source[1]	Escalation of care (hypoxia or other concern)	ED attendance/ reattendance	Pneumonia/ abnormal CXR	Admission/ readmission	ICU Admission	Other complications	Length of hospital stay	Mortality	Cost vs savings	Patient satisfaction
Gooten berg 2021 [1]	ED	No data	23 (28%); 7 O2-requiring (15 self-presented) RT PCR+: 10	No data	Overall: 10 (12%); RT PCR pos: 5/30 (17%)	Overall: 1 (1.2%); 1 of 30 (17%)	No data	No data	0	No data	No data
Galbraith 2021 [29]	C	17	No data	No data	1	No data	No data	No data	0	No data	No data
Shah 2020 [18]	ED or OPD	19 (25%)	17	No data	16 (8 of whom came due to incidentally low SpO2) RR hospitalization (resting SpO2<92%): 7.0 (95% CI 3.4 – 14.5), p-value <0.0001	8	Resting home SpO2 < 92% associated with inc risk of ICU admission (RR=9.8, 95% CI=2.2 to 44.6, *p* <0.002) ARDS (RR = 8.2, 95%CI= 1.7 to 38.7, p<0.007); septic shock (RR=6.6, 95% CI = 1.3 to 32.9, p= 0.02)	No data	2	No data	No data
Kyriakides 2021 [30]	C	7 (35%)	35% (≥1 clinical comorbidity)	Classic CXR findings: for reassessment: 71% no reassessment: 54% || CTPA as necessary	3 (15%) (Mean age 65)	No data	No data	No data	0	No data	No data
Banzi 2020 [31]	C	1	No data	No data	1	No data	1 (abdl hemorrhage, acute toxic hepatitis & acute heart failure)	No data	0	No data	No data
Hutchings 2020 [Preprint [32]]	C	5 (3%)	4 (2.5%)	No data	3 (1.9%)	No data	No data	No data	0	No data	No data
Vindrola- Padros 2021 [33]	PC	PH: 174 (10%)	PH: 133 (76.7%)	No data	PH: 92 (52.7%)	PH: 3 (2.0%)	No data	No data	PH: 20 (1.1%)	Mean cost per monitored patient: £400 - £553	No data
	HD	EHD: 42 (12.2%)	EHD: 39 (91.8%)		EHD: 41 (74.5%)	EHD: 4 (8.5%)	No data	No data	EHD: 3 (0.9%)		No data
O'Carroll 2020 [34]	HD	5	5	3 (progressive infiltrates and worse COVID-related hypoxia)	4	0	No data	No data	0	No data	No data
Gaeta 2020 [15]	HD	90 (18.4%) virtual LOS for	90 (18.4%)	No data	43 (8.8%)	direct: 2 transfer fr ward: 5	No data	No data	Direct ICU: 2 ICU	Cumulative home monitoring	No data

		admission: 3 days							transfer fr ward: 4	costs: $621,800 (incl hosp charges) projected cumulative mitigated hosp charges: $6,718,296 (IQR: $4,767,344, $9,902,496)	
Clarke 2021 [35]	ALL	No data	52	No data	40	No data	No data	No data	All-cause: 28 (3.1), COVID: 26 With 4+ comorbids: 17 (60.1) ≥65yo: (9.3) O2s >95 (2.6) O2s 93-94 (6.1) O2s <95% (5.5)	No data	No data
	OPD	No data	ref	No data	No data	No data	No data	No data	ref	No data	No data
	ED	No data	OR 0.42 (0.02-0.89; *p* 0.024)	No data	No data	No data	No data	No data	(OR 3.40 (0.62-18.55) p0.157)	No data	No data
	HD	No data	OR 0.31 (0.15-0.68; *p* 0.003)	No data	No data	No data	No data	No data	OR 8.70 (2.53-29.89), p0.001)	No data	No data
Lancet 2021 [36]	Pre- ED	887 (53.0%)	No data	1232 (73.6%)	1514 (90.5%)	No data	No data	Median LOS, days (survivors): 5 (2-10) vs (died): 6 (3-12)	527 (31.5%)	No data	No data
Grutters 2020 [37]	HD	6 (18%)	0	COVID: CT 1, CXR: 1	3	No data	No data	Ave reduction in LOS: 5 (+3.8)	0	No data	Patient satisfaction: 97% rated home tele-monitoring as user friendly
Gordon 2020 [38]	HD	O2sats <92%: 11/315	11 (4.9%)	No data	3 (1.3%)	No data	No data	No data	No data	No data	No data

		(Patient-triggered: 34% Questionnaire-triggered: 15%)									
Kodama 2020 [39]	HD	29 (13 patients)	3 (6%)	No data	1 (2% of enrolled)	No data	1 (pulmonary embolism)	No data	No data	No data	Simplicity of sign up: 74% Ease of use: 65% Adequate handling of concerns: 74% Confidence with taking VS: 74% Satisfaction with care: 74% Likelihood of recommendation: 74%
Silven 2020 [40]	ED/ HD	No data	No data	No data	5 (9%)	No data	No data	No data	No data	No data	No data
Francis 2020 [pre print] [41]	ED OPD	76	No data	48.90%	58 (5.5%)	No data	No data	No data	18 (0.5%)	No data	No data
	HD		No data	77.50%	11.70%	No data	No data	No data	3.80%	No data	No data
Wilcock 2021 [pre print] [42]	OPD	SpO2≤94: 9 SpO2≤92% 3 (ave time to max SpO2 drop fr dx: 6.4±1.5d)	No data	No data	SpO2 93-94: 0; SpO2 <92%: 3	No data	No data	No data	0	No data	Ave Likert score anxiety reduction (1=more anxious 5=much less anxious) 4.0 Ave Likert score usefulness (1=not at all useful; 5=very useful): 4.6
Dirikgil 2021 [43]	HD	No data	No data	No data	5/ 55 (9%) RR 0.27 (95%CI 0.097-0.733; p=0.007)	No data	Completed 28 days w/o ED reassess- ment: 47 (85%)	LOS Bed occupancy days per 100 patients: 20	No data	No data	No data
	Matched control	No data	No data	No data	30/ 110 (27%)	No data	76 (69%)	LOS Bed occupancy days per 100 patients: 47	No data	No data	No data

Table 3. Accuracy outcomes of included studies

Study ID	Sub group	Sn (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)	Mc Nemar's Test (sensitivity) - *P* (Chi2-DOF)	Mortality	cost vs savings	Other Remarks
Schrading 2020 [44]	Oxy-Watch	92.17% (87.27-97.08)	60% (49.59-70.41)	75.75% (68.61-82.82)	85% (75.97-94.03)	0.001 (14.53 - 1)	NA	Almost 10-fold cost difference between medical-grade (Onyx) and consumer-grade pulse oximeters (SM, OxyWatch)	Devices selected were sensitive in detecting hypoxia using a 92% cutoff and had a strong correlation with standard ED oximetry at SpO2 cutoff of 92%, sensitivity increased--all 3 essentially 97% (99.6-94.2)
	SM	90.70% (85.69-95.71)	67.61% (56.72-78.49)	83.57% (77.43-89.71)	80% (69.88-90.12)	0.063 (3.46 - 1)	NA		
	Onyx	92.06% (87.34-96.78)	67.57% (56.90-78.23)	82.85% (73.90-92.76)	83.33% (73.90-92.75)	0.0165 (5.76 - 1)	NA		
Inada-Kim 2020 [preprint] [45]	90%	0.481 (0.445-0.516)	0.885 (0.870-0.899)				as described		Oxygen saturations were the most predictive of mortality or ICU admission (AUROC 0.772 (95 % CI: 0.712-0.833)) followed by the NEWS2 score (AUROC 0.715 (95 % CI: 0.670-0.760) patient age (AUROC 0.690 (95 % CI: 0.642-0.737)) respiration rate (AUROC 0.662 (95 % CI: 0.599-0.729))
	91%	0.553 (0.510-0.597)	0.862 (0.845-0.879)				as described		
	92%	0.624 (0.584-0.664)	0.836 (0.818-0.854)				as described		
	93%	0.664 (0.633-0.695)	0.795 (0.777-0.812)				as described		
	94%	0.713 (0.686-0.739)	0.723 (0.705-0.742)				as described		
	95%	0.760 (0.724-0.796)	0.650 (0.648-0.662)				as described		
	96%	0.841 (0.807-0.875)	0.526 (0.513-0.538)				as described		
	18-49yo	No data	No data	No data	No data	No data	0.60%		
	50-59	No data	No data	No data	No data	No data	1.30%		
	60-69	No data	No data	No data	No data	No data	6.50%		
	70-79	No data	No data	No data	No data	No data	7.00%		
	80+	No data	No data	No data	No data	No data	12.80%		

Appendix 4. Detailed Study Appraisal

	Gootenberg 2021	Galbraith 2021	Shah 2020	Kyriakides 2021	Banzi 2020	Hutchings 2020	Vindrola-Padros 2021	O'Caroll 2020	Gaeta 2020	Clarke 2021	Lancet 2021	Grutters 2020	Gordon 2020	Kodama 2020	Silven 2020	Francis 2020	Wilcock 2021	Inada-Kim 2020	Dirikgil 2021	Schrading 2020
DOMAIN 1: Patient Selection Test																				
Was a consecutive or random sample of patients enrolled?	No	Yes	No	No	Yes	No [no blinding]	No	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No	No
Was a case-control design avoided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Unsure	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes
Did the study avoid inappropriate exclusions?	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Unsure	Yes	Yes	Unsure	Yes	Yes	Yes	Yes	Yes
Could the selection of patients have introduced bias?	High Risk	No	High Risk [no blinding]	Low risk	Low risk	High RIsk	Yes	Low risk	Low risk	Low risk	Low risk	Unsure	High risk	High risk	High risk	Low risk	High Risk	High Risk	High Risk	High Risk
Are there concerns that the included patients and setting do not match the review question?	Low concern	Low concern	Low concern	Low concern	Low concern	High Risk [only patients with no comorbidities]	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	High concern	Low concern	Low concern	Low concern	Low concern	Low concern
DOMAIN 2: Index Test																				
Were the index test results interpreted without knowledge of the results of the reference standard?	Unsure	Yes	Yes	Yes	Yes	Yes	Unsure	No	No	Yes	Yes	Yes	Unsure	No	No	Unsure	No	Yes	Unsure [no mention of blinding]	Unsure
If a threshold was used, was it pre-specified?	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No	Yes	No	No	Yes	No	No	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Unclear	Unsure	High risk	High risk	Unclear	High risk	Low Risk	High risk	High Risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	High concern	Low concern	Low concern	Low concern	Low concern	Low concern	high concern	Low concern

DOMAIN 3: Reference Standard																				
Is the reference standards likely to correctly classify the target condition?	Yes	No	No	No	No	No	No	No	No	Unsure	Unsure	No	Unsure	No	No	Unsure	No	Unsure [comparison made across ages and SpO2]	No	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	No	Unsure	No	No	No	No	No	No	Unsure	Unsure	No	Unsure	No	No	Unsure	No	Unsure	Unsure	Unsure
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	unclear	unclear	High Risk	High risk	No	Unclear	High risk	High risk	Unclear	Low risk	High risk	High risk	High risk	High risk	Unclear	High risk	High Risk	High risk	High Risk
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern	High concern	High concern	High concern	High concern	High concern	High Concern	High risk	High risk	High concern	High concern	High concern	High concern	High concern	High concern	High concern	High concern	Low concern	high concern	Low concern
DOMAIN 4: Flow and Timing																				
Was there an appropriate interval between index test and reference standard?	Yes	No	No	No	No	No	No	No	No	Unsure	Unsure	No	Unsure	No	No	Unsure	No	Unsure	unsure	Yes
Did all patients receive the same reference standard?	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Unsure	No	No	no	Yes
Were all patients included in the analysis?	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Unsure	Unsure	Unsure	Yes	No	Yes	yes	No
Could the patient flow have introduced bias?	Low risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	Unclear	Unclear	High risk	High risk	High risk	High risk	High risk	High risk	High Risk	high risk	high risk

Appendix 5. GRADE Evidence Profile

Table 1. Should medical-grade Nonin Onyx II 9550 (Onyx) be used to diagnose hypoxemia in suspected and confirmed COVID patients?

Sensitivity	0.92 (95% CI: 0.87 to 0.97)		Prevalences	5%	10%	15%
Specificity	0.68 (95% CI: 0.57 to 0.78)					

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 15%	
True positives (patients with hypoxemia)	1 studies 200 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Serious[b]	Not serious	Not serious	None	46 (44 to 48)	92 (87 to 97)	138 (131 to 145)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having hypoxemia)								4 (2 to 6)	8 (3 to 13)	12 (5 to 19)	
True negatives (patients without hypoxemia)	1 studies 200 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Serious[b]	Not serious	Not serious	None	642 (541 to 743)	608 (512 to 704)	574 (484 to 665)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having hypoxemia)								308 (207 to 409)	292 (196 to 388)	276 (185 to 366)	

Table 2. Should consumer-grade OxyWatch be used to diagnose hypoxemia in suspected and confirmed COVID patients?

Sensitivity	0.92 (95% CI: 0.87 to 0.97)		Prevalences	5%	10%	15%
Specificity	0.60 (95% CI: 0.50 to 0.70)					

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 15%	
True positives (patients with hypoxemia)	1 studies 200 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Serious[b]	Not serious	Not serious	None	46 (44 to 49)	92 (87 to 97)	138 (131 to 146)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having hypoxemia)								4 (1 to 6)	8 (3 to 13)	12 (4 to 19)	
True negatives (patients without hypoxemia)	1 studies 200 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Serious[b]	Not serious	Not serious	None	570 (471 to 665)	540 (446 to 630)	510 (422 to 595)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having hypoxemia)								380 (285 to 479)	360 (270 to 454)	340 (255 to 428)	

Table 3. Should consumer-grade Santa Medical SM-1665 (SM) be used to diagnose hypoxemia in suspected and confirmed COVID patients?

Sensitivity	0.91 (95% CI: 0.86 to 0.96)		Prevalences	5%	10%	15%
Specificity	0.68 (95% CI: 0.57 to 0.78)					

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 15%	
True positives (patients with hypoxemia)	1 studies 200 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Serious[b]	Not serious	Not serious	None	45 (43 to 48)	91 (86 to 96)	136 (129 to 144)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having hypoxemia)								5 (2 to 7)	9 (4 to 14)	14 (6 to 21)	
True negatives (patients without hypoxemia)	1 studies 200 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Serious[b]	Not serious	Not serious	None	642 (539 to 746)	608 (510 to 706)	575 (482 to 667)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having hypoxemia)								308 (204 to 411)	292 (194 to 390)	275 (183 to 368)	

Table 4. Should SpO2 94% or below by Pulse Oximetry be used to diagnose risk for mortality/ ICU admission in suspected and confirmed COVID patients?

Sensitivity	0.71 (95% CI: 0.69 to 0.74)		Prevalences	5%	10%	15%
Specificity	0.72 (95% CI: 0.70 to 0.74)					

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 15%	
True positives (patients with hypoxemia)	1 studies 1080 patients	Case-control type accuracy study	Serious[a]	Serious[b]	Not serious	Not serious	None	36 (34 to 37)	71 (69 to 74)	107 (103 to 111)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having hypoxemia)								14 (13 to 16)	29 (26 to 31)	43 (39 to 47)	
True negatives (patients without hypoxemia)	1 studies 1080 patients	Case-control type accuracy study	Serious[a]	Serious[b]	Not serious	Not serious	None	687 (670 to 705)	651 (635 to 668)	615 (599 to 631)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having hypoxemia)								263 (245 to 280)	249 (232 to 265)	235 (219 to 251)	

[a]Subjective classification of symptoms consistent with COVID-19. Lack of blinding; [b]Only did a single SPO2 measurement, not pulse oximetry monitoring

Table 5. Should SpO2 92% or below by Pulse Oximetry be used to diagnose risk for mortality/ ICU admission in suspected and confirmed COVID patients?

Sensitivity	0.62 (95% CI: 0.58 to 0.66)		Prevalences	5%	10%	15%
Specificity	0.84 (95% CI: 0.82 to 0.85)					

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 15%	
True positives (patients with hypoxemia)	1 studies 1080 patients	Case-control type accuracy study	Serious[a]	Serious[b]	Not serious	Not serious	None	31 (29 to 33)	62 (58 to 66)	94 (88 to 100)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having hypoxemia)								19 (17 to 21)	38 (34 to 42)	56 (50 to 62)	
True negatives (patients without hypoxemia)	1 studies 1080 patients	Case-control type accuracy study	Serious[a]	Serious[b]	Not serious	Not serious	None	794 (777 to 811)	752 (736 to 769)	711 (695 to 726)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having hypoxemia)								156 (139 to 173)	148 (131 to 164)	139 (124 to 155)	

Explanations

[a] Subjective classification of symptoms consistent with COVID-19. Lack of blinding

[b] Only did a single SpO2 measurement, not SpO2 monitoring

Table 6. Pulse oximetry monitoring for suspected and confirmed COVID-19 patients

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulse Oximetry	Comparison	Relative (95% CI)	Absolute (95% CI)		
Care escalation (detection of hypoxia or other patient concern) (assessed with: No. of patients in whom hypoxia is detected, or referred for any concern)												
14	Observational studies	Serious [a]	Serious[b]	Serious[c]	Serious[d]	None	1378/6397 (21.5%)	No data	Not pooled	See comment	⨁◯◯◯ Very low	
Emergency Department Visits (assessed with: No. of patients who visited the ED)												
13	Observational studies	Serious [a]	Serious[b]	Serious[c]	Serious[d]	None	2130/6619 (32.2%)	No data	Not pooled	See comment	⨁◯◯◯ Very low	
Hospitalizations (assessed with: No. of patients hospitalized)												
17	Observational studies	Serious [a]	Serious[b]	Serious[c]	Serious[d]	None	1856/7351 (25.2%)	No data	Not pooled	See comment	⨁◯◯◯ Very low	
ICU admissions/ complications (assessed with: No. of ICU admissions)												
5	Observational studies	Serious [a]	Serious[b]	Serious[c]	Serious[d]	None	23/2478 (0.9%)		Not pooled	See comment	⨁◯◯◯ Very low	
Mortality (assessed with: No. of deaths)												
14	Observational studies	Serious [a]	Serious[b]	Serious[c]	Serious[d]	None	648/7021 (9.2%)		Not pooled	See comment	⨁◯◯◯ Very low	

CI: confidence interval

Explanations

[a]. Convenience sampling, no blinding done

[b]. Reported outcomes for pre-hospital O2sats only, or reported outcomes for post-inpatients only, or for outpatient only, or patients detected from the community level. Varied in monitoring models. Some are case control studies. Studies could not be pooled.

[c]. No comparator, different comparator to that of PICO question

[d]. Studies could not be pooled

Appendix 6. Table of Ongoing Studies

Title: A randomised controlled pilot trial investigating the feasibility of monitoring patients with or at risk for cardiovascular disease who have symptoms suspected of COVID-19 by pulse oximetry at home (CovidSat@Home)	
P	1) Age ≥40 years with cardiovascular risk profile or cardiovascular disease (overweight, hypertension, diabetes, smoking, coronary artery disease, previous myocardial infarction, heart failure), presumably COVID-19 (both SARS-CoV-2 positive and non-COVID-19 confirmed patients), with moderate-severe symptoms and mentally competent
I	Three times daily (and if needed any additional) measurement of oxygen saturation and pulse rate with a pulse oximeter as added to usual (primary) care
C	Usual (primary) care
O	**Primary outcome:** Feasibility defined as successful inclusion of 50 participants within 6 months **Secondary outcome:** - the feeling of safety during the first two weeks of illness as reported by the patient - disability-free survival at 45 days (% change in WHODAS-2 between baseline and day 45) - number of days alive at home during 45 days after inclusion - time to discharge from medical follow-up (defined as last contact with healh care professional according to primary care electronic health record data) - number of primary care contacts during 45 days after inclusion - number of emergency care department visits during 45 days after inclusion - proportion of hospitalised patients within 45 days after inclusion - characteristics of hospital admissions within 45 days after inclusion o clinical profile at time of hospitalisation (according to the warning signs of Dutch College of General Practitioners) o length of stay (total and stratified into ward and ICU) o proportion of patients admitted to ICU o type of treatments - 45 day mortality o overall mortality o out-of-hospital mortality o in-hospital mortality In a parallel process evaluation, we will examine how: - the intervention has been used in practice in terms of: (i) Fidelity - whether the intervention was carried out as planned; (ii) Dose - whether the intervention has been used as long and frequently as planned (iii) Adjustments - whether adjustments have been made to the intervention and why (iv) Reach - whether the intended audience has been reached and - the experiences of patients in the intervention group and their informal caregivers in terms of disease perception, fear and use of the intervention - GPs' experiences with the intervention (usability of pulse oximetry as diagnostic procedure and impact on healthcare utilization)
Status	Ongoing patient inclusion

Q3. Which clinical specimens can be used as an alternative to nasopharyngeal swab RT-PCR* for the diagnosis of COVID-19?

As of 20 February 2021

RECOMMENDATIONS

We recommend the use of the following specimens as alternative specimens to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 among symptomatic and asymptomatic patients suspected of COVID-19 in hospital and outpatient settings:

- **Oropharyngeal swab** *(Moderate certainty of evidence; Strong recommendation)*
- **Saliva drool/spit and oral saliva** *(Moderate certainty of evidence; Strong recommendation)**
- **Nasal swab/wash** *(Moderate certainty of evidence; Strong recommendation)*
- **Throat swab** *(Low certainty of evidence; Strong recommendation)*

We suggest the use of saliva swab and posterior oropharyngeal saliva specimens as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 among symptomatic and asymptomatic patients with suspected COVID-19 in hospital and community/outpatient settings. *(Low certainty of evidence; Weak recommendation)*

* Please see also separate evidence summary for saliva specimen.

We recommend against the use of sputum as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19. *(Very low certainty of evidence; Strong recommendation)*

There is no evidence to recommend the use of bronchoalveolar lavage as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19.

Consensus Issues

Currently, oropharyngeal and nasopharyngeal specimens are collected simultaneously; however, in resource-limited settings, the panel recognized the need for alternative clinical specimens to nasopharyngeal swab RT-PCR, along with the positive implication of single specimens on resource use. As a result, the use of oropharyngeal swab, oral saliva specimens, nasal swab/wash and throat swab were recommended as alternative clinical specimens to nasopharyngeal swab RT-PCR.

The differences between oropharyngeal swab and throat swab samples were clarified. Although the two specimens are collected in the same area, they were considered by the panel as dissimilar specimens due to the differences in sample collection technique. The panel made a strong recommendation for using throat swab samples due to its relatively high sensitivity.

The panel opted to strongly recommend against the use of sputum specimens as an alternative to nasopharyngeal swab samples. This was primarily due to the risk of viral transmission when obtaining sputum samples, coupled with the very low certainty of the evidence for its use.

KEY FINDINGS

- One cross-sectional study on the use of oropharyngeal swab RT-PCR as an alternative clinical specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 showed that oropharyngeal swab had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.
- A meta-analysis of 19 observational studies on the use of saliva as an alternative clinical specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 concluded that saliva had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.
- Two cross-sectional studies on the use of nasal swab/wash RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 showed that nasal swab/wash had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.
- A cross-sectional study on the use of throat swab RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 also showed that throat swab had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.
- A cross-sectional study from a meta-analysis on the use of sputum RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 showed that sputum had lower sensitivity and specificity compared to nasopharyngeal swab RT-PCR.
- All the above studies were assessed to have a low risk of bias.
- No studies compared the sensitivity and specificity of bronchoalveolar lavage RT-PCR to nasopharyngeal swab RT-PCR. Hence, no conclusion or recommendation can be made for this clinical specimen.

INTRODUCTION

Nasopharyngeal swab is the current gold standard specimen used for RT-PCR. However, obtaining such swab samples is relatively invasive, uncomfortable, and may potentially trigger coughing which may consequently increase the risk of viral transmission to health care workers who lack sufficient personal protective equipment. In addition, the need to increase capacity for SARS-CoV-2 testing in a variety of settings, along with shortages of sample collection supplies, has motivated a search for alternative specimen types with equally high sensitivities. In line with this, the diagnostic performance of other specimens such as oropharyngeal swab, saliva, endotracheal aspirate, and bronchoalveolar lavage are currently being investigated.

A similar rapid review of eight studies completed in May 2020 concluded that the pooled sensitivity of detecting SARS-CoV-2 RNA in non-respiratory tract specimens was high in saliva samples (Sn 77%, 95% CI 71-83%) and very low in stool/rectal swab (Sn 22%, 95% CI 22-37%), blood/serum (Sn 2%, 95% CI 1-3%), and urine (Sn 22%, 95% CI 18-25%) specimens.[2] This review summarizes the current evidence on the diagnostic accuracy of several types of clinical specimens.

REVIEW METHODS

A comprehensive literature search was done on January 23, 2021 in electronic databases MEDLINE, Cochrane CENTRAL, as well as www.medrxiv.org. Observational studies or systematic reviews of observational studies which compared the sensitivity of at least two respiratory specimens against nasopharyngeal swab

were included. Studies that did not have nasopharyngeal swab as the gold standard were excluded.

RESULTS

Characteristics of included studies

A total of 21 observational studies were included in this review. Of these, 12 were cohort studies, four were case controls, four were cross-sectional studies, and one is a prospective study. Nineteen of the 21 studies were previously included in one systematic review and meta-analysis [5], while two other cross-sectional studies were added.[3,4] The meta-analysis by Moreira et al. was appraised to have high methodological quality[3].

A total of 5,585 samples were evaluated across all 21 studies. Of these, 56 were nasal swab/wash [3,4], 29 were oropharyngeal swab [3], 36 were throat swab [4,5], 5,424 were saliva [5] and 40 were sputum samples.[5] All the specimens were analyzed using RT-PCR as the reference standard.[3-5] The characteristics and the results of the included studies are summarized in Appendix 1.

The overall quality of the evidence

Majority of the included studies were rated as having a low risk of bias. The included cross-sectional studies had clearly defined inclusion criteria, reliable measurement of the exposure and outcome, an objective criterion for measurement of the condition, and appropriately used statistical analysis.[3,4] However, most of the studies did not clearly state the interval between the reference and index specimen collection. The systematic review included was direct, used appropriate inclusion criteria, and performed risk bias assessment.[5]

The overall certainty of the evidence for the sensitivity and specificity of nasal swab/wash, oropharyngeal swab was downgraded to moderate because of imprecision. Additionally, the specificities of the clinical specimens had wide confidence intervals.

The overall certainty of the evidence for the sensitivity of throat swab was downgraded to moderate because of imprecision due to the small sample size. In addition, the quality of evidence of specificity of the said clinical specimen was further downgraded to low because of the small sample size and wide confidence interval.

The quality of evidence for the sensitivity of saliva was downgraded to moderate because of data inconsistency. It was rated as serious due to the different point estimates reported across the observational studies. On the other hand, the quality of evidence for the specificity was high.

The risk of bias for sputum was rated as serious because the included study used a different dilution for sputum and the gold standard thereby lowering the quality of evidence to moderate. The quality of evidence for the sensitivity of throat swab was further downgraded to low due to serious imprecision secondary to the wide confidence interval and small sample size. On the other hand, the specificity of the

[3] based on the Painless EBM criteria for appraising systematic reviews

throat swab was downgraded to very low due to very serious imprecision, owing to the very wide confidence interval and small sample size.

Diagnostic accuracy

Among the included clinical specimens, oropharyngeal swab had the highest sensitivity (Sn 100%, 95% CI 87-100%; 1 study) and specificity (Sp 100%, 95% CI 16-100%; 1 study). On the other hand, sputum had the lowest sensitivity at 63% (95% CI 45-79%; 1 study) and specificity at 40% (95% CI 5-85%; 1 study). No studies provided diagnostic accuracy measures for bronchoalveolar lavage samples. Results are summarized in Table 1.

Table 1. Sensitivities and specificities of the clinical specimens for RT-PCR.

Sample	No. of Studies	No. of samples	Quality of Evidence		Sensitivity (95%CI)	Specificity (95% CI)
			Sensitivity	Specificity		
Nasal Swab/ Wash	2	57	Moderate	Moderate	0.87 (0.74-0.95)	78% (0.40-0.97)
Oropharyngeal Swab	1	29	Moderate	Moderate	100% (0.87-1.00)	100% (0.16-1.00)
Throat Swab	1	36	Moderate	Low	93% (0.76-0.99)	89% (0.52-1.00)
Saliva	1	5424	Moderate	High	86% (0.84-0.88)	94% (0.93-0.94)
Sputum	1	40	Very Low	Very Low	63% (0.45-0.79)	40% (0.05-0.85)
Bronchoalveolar Lavage	N/A	N/A	N/A	N/A	N/A	N/A

Sources of heterogeneity

Since subgroup analysis was not done for this rapid review, the potential sources of heterogeneity cannot be ascertained. However, the succeeding statements may have influenced the computed estimates and must be considered whenever interpreting the conclusions.

Despite the generally low risk of bias across all the included studies, possible factors that may have still influenced the estimates of this study include the differences in the sample size per clinical specimen. For example, oropharyngeal swab had the highest sensitivity and specificity but there were only 29 patients included in the computation.[3] On the other hand, saliva had a lower sensitivity and specificity than oropharyngeal swab but there were 5,424 patients included in its computation.[5]

Another potential factor that may have influenced the estimate is the non-standardized timing of clinical specimen collection. Some studies collected the clinical specimen days to weeks after symptoms have resolved while other studies have collected the specimen in the pre-symptomatic period.[3-5] However, since there was no subgroup analysis done for the timing of specimen collection, it is not clear how this factor could have influenced the diagnostic accuracy of these specimens.

The definition of clinical specimens varied in some studies. Some studies have equated throat swab to oropharyngeal swab while some have considered them as two different entities. In the studies by Berenger et al. and Moreira et al., the authors classified the swabs as throat swabs and not oropharyngeal swabs.[4,5] In the study by Berenger et al., it was mentioned that the throat swabs were collected from both sides of the oropharynx and the posterior pharyngeal wall under the uvula.[4] Conversely, the study by Moreira et al did not specify the exact method of collection.[5]

For this review, the clinical specimens were analyzed according to how the authors have identified them.

Lastly, there were clinical specimen-specific factors. For sputum, the sensitivity and specificity are difficult to ascertain as not all COVID-19 patients can produce sputum for testing. Additionally, the study that was included in the analysis of the sensitivity and specificity of sputum used different dilutions for sputum and the gold standard.[5] This may explain why the computed sensitivity and specificity are low. On the other hand, the lack of data for bronchoalveolar lavage probably resulted from its relative invasiveness compared to the other clinical specimens used for the diagnosis of COVID 19.

RECOMMENDATIONS FROM OTHER GROUPS

Local interim guidelines (6 October 2020) from the Department of Health (DOH) identified nasopharyngeal swabs or lower respiratory tract specimens as the most reliable samples for RT-PCR. Combined oropharyngeal and nasopharyngeal swab samples were recommended to be collected and processed together. Nasopharyngeal swabs are preferred over oropharyngeal swabs alone because of the lower accuracy of the latter. At the time of publication of this guideline, the potential of using saliva samples was still being studied and validated by the Research Institute of Tropical Medicine.[6]

Compared to the DOH, the US Centers for Disease Control and Prevention (CDC) (as of 06 January 2021) allows more upper respiratory specimen options for RT-PCR. CDC listed the following as acceptable specimens:

1. A nasopharyngeal (NP) specimen collected by a trained healthcare provider;
2. An oropharyngeal (OP) specimen collected by a trained healthcare provider;
3. A nasal mid-turbinate specimen collected by a trained healthcare provider or by a supervised or unsupervised onsite self-collection (using a flocked tapered swab), or self-collected at home following kit collection instructions;
4. An anterior nares specimen collected by a trained healthcare provider, or by a supervised or unsupervised onsite self-collection or self-collected at home following kit collection instructions (using a flocked or spun polyester swab);
5. Nasopharyngeal wash/aspirate or nasal wash/aspirate (NW) specimen collected by a trained healthcare provider; or
6. A saliva specimen (not specified if spit or swab) collected by the person being tested, either at home or at a testing site under supervision. Collect 1-5 mL of saliva in a sterile, leak-proof screw cap container. No preservative is required.

CDC also noted that an alternative to upper respiratory tract specimens is the testing of lower respiratory tract specimens. For patients who develop a productive cough, sputum can be collected and tested when available for SARS-CoV-2. However, they have recommended against the induction of sputum. Under certain clinical circumstances (e.g., those on invasive mechanical ventilation), a lower respiratory tract aspirate or bronchoalveolar lavage specimen should be collected and tested as a lower respiratory tract specimen.[7]

RESEARCH GAPS

There are three ongoing studies listed in the NIH- U.S NLM's *ClinicalTrials.gov.* One is an RCT [8], one is a cross-sectional study [9] and one is a prospective study.[10]

One study is estimated to be completed in March 2021.[8] The other one is estimated to be completed in June 2021 [9] and the last study is estimated to be completed in March 2023.[10] The description and status of each of the aforementioned studies are summarized in Appendix 3.

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Appendix 1. Characteristics of Included Studies

First author Month-Year Country	Study Design	Sample Population	No. of Participants	Sample size / specimen	Intervention		Outcome Measured
					Reference	Index	
Calame, Adrien Aug 2020 Switzerland	Cross sectional study	≥ 18 years old and hospitalized who had a positive SARS-CoV-2 rRT-PCR in a NPS specimen in the preceding one to six days. ICU patients were excluded.	29	Nasal wash: 20 Oropharyngeal: 29 Nasopharyngeal swab:29	Nasopharyngeal swab analyzed via RT-PCR Ct is arbitrarily defined at 45	Oropharyngeal swabs, Nasal wash, which were all analyzed via RT-PCR	compared the analytical sensitivity of SARS-CoV-2 real-time RT- PCR in nasal wash (NW), oropharyngeal swab (OPS) and NPS specimens.
Berenger, Byron May 2020 Canada	Cross sectional study	COVID 19 positive individuals. (41% female, mean age 44.6 (range 18-61)	30	Nasal swab, throat swab and nasopharyngeal swab: 36	Nasopharyngeal swab analyzed via RT-PCR Ct not specified	Nasal swab and Throat Swab which were all analyzed via RT-PCR	compared the sensitivity of NP, nasal and throat swabs to detect SARS-CoV-2
Moreira, Vania January 2021 Portugal	Systematic review and meta-analysis Case control, cohort, prospective study,cross sectional	COVID 19 positive and suspected individuals	Not stated	Saliva: 4739 Deep throat swab: 685 Sputum: 20	Nasopharyngeal swab analyzed via RT-PCR Ct not specified	sputum, saliva, deep throat swab	Sensitivity and specificity of RT-PCR among the samples

Appendix 2. GRADE Evidence Profile

Question: Should Nasal Swab RT-PCR be used to diagnose COVID 19 in the general population?

Sensitivity	0.87 (95% CI: 0.74 to 0.95)
Specificity	0.78 (95% CI: 0.40 to 0.97)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	
True positives (patients with COVID 19)	2 studies 47 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	0 (0 to 0)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having COVID 19)								0 (0 to 0)	
True negatives (patients without COVID 19)	2 studies 10 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	780 (400 to 970)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having COVID 19)								220 (30 to 600)	

Question: Should Oropharyngeal RT-PCR be used to diagnose COVID 19 in the general population?

Sensitivity	1.00 (95% CI: 0.87 to 1.00)
Specificity	1.00 (95% CI: 0.16 to 1.00)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	
True positives (patients with COVID 19)	1 studies 27 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	0 (0 to 0)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having COVID 19)								0 (0 to 0)	
True negatives (patients without COVID 19)	1 studies 2 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	1000 (160 to 1000)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having COVID 19)								0 (0 to 840)	

Question: Should Should Throat Swab RT-PCR be used to diagnose COVID 19 in the general population?

Sensitivity	0.93 (95% CI: 0.76 to 0.99)
Specificity	0.89 (95% CI: 0.52 to 1.00)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	
True positives (patients with COVID 19)	1 studies 27 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	0 (0 to 0)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having COVID 19)								0 (0 to 0)	
True negatives (patients without COVID 19)	1 studies 9 patients	case-control type accuracy study	not serious	not serious	not serious	very serious	none	890 (520 to 1000)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having COVID 19)								110 (0 to 480)	

Question: Should Saliva RT-PCR be used to diagnose COVID 19 in the general population?

Sensitivity	0.86 (95% CI: 0.84 to 0.88)
Specificity	0.94 (95% CI: 0.93 to 0.94)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	
True positives (patients with COVID 19)	1 studies 1048 patients	case-control type accuracy study	not serious	not serious	serious	not serious	none	0 (0 to 0)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having COVID 19)								0 (0 to 0)	
True negatives (patients without COVID 19)	1 studies 4376 patients	case-control type accuracy study	not serious	not serious	not serious	not serious	none	940 (930 to 940)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having COVID 19)								60 (60 to 70)	

Question: Should Sputum RT-PCR be used to diagnose COVID 19 in the general population?

Sensitivity	0.63 (95% CI: 0.45 to 0.79)
Specificity	0.40 (95% CI: 0.05 to 0.85)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	
True positives (patients with COVID 19)	1 studies 35 patients	case-control type accuracy study	serious	not serious	not serious	serious	none	0 (0 to 0)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having COVID 19)								0 (0 to 0)	
True negatives (patients without COVID 19)	1 studies 5 patients	case-control type accuracy study	serious	not serious	not serious	very serious	none	400 (50 to 850)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having COVID 19)								600 (150 to 950)	

Appendix 3: Characteristics of Ongoing Studies

Study Setting	Study Type	Population	Intervention		Outcome/s	Status	Estimated Completion date
			Reference Standard	Index Test			
COVID-19: SARS-CoV-2 Detection in Saliva, Oropharyngeal and Nasopharyngeal Specimen Denmark NCT04715607	Randomized, double blind clinical trial (parallel assignment)	Symptomatic and asymptomatic individuals tested for COVID-19 in a public test center during the COVID-19 pandemic n = 22,000	Combined Saliva/OPS/NPS	Oropharyngeal swab Saliva	SARS-CoV-2 detection rates for OPS compared w/ NPS & saliva (48 hrs)	Recruiting	March 30, 2021
Saliva as Source of Detection for SARS-CoV-2 United States NCT04424446	Cross sectional	NIH staff members age 18 and older who are taking part in NIH CC SARS-CoV-2 surveillance. n = 5,000	Nasopharyngeal swab	Saliva (spit) Nasal swab	Saliva SARS-CoV-2 RT-PCR results	Recruiting	June 1, 2021
COVID-19 Biological Samples Collection (COLCOV19-BX) France NCT04332016	Prospective	Asymptomatic and symptomatic COVID-19 patients, patients who died from COVID-19, all sex, minors pregnant and breastfeeding women n = 2,000	Not stated	Whole blood samples, urine and stool samples, upper respiratory samples, post-mortem biopsies	COVID-19 disease description from blood, URT, stool, urine samples	Recruiting	March 2023

Appendix 4: Forest Plots for the Sensitivities and Specificities of Different Clinical Specimens

Nasal Swab/Wash

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berenger 2020	22	2	5	7	0.81 [0.62, 0.94]	0.78 [0.40, 0.97]
Calame 2020	19	0	1	0	0.95 [0.75, 1.00]	Not estimable

Oropharyngeal Swab

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Calame 2020	27	0	0	2	1.00 [0.87, 1.00]	1.00 [0.16, 1.00]

Throat Swab

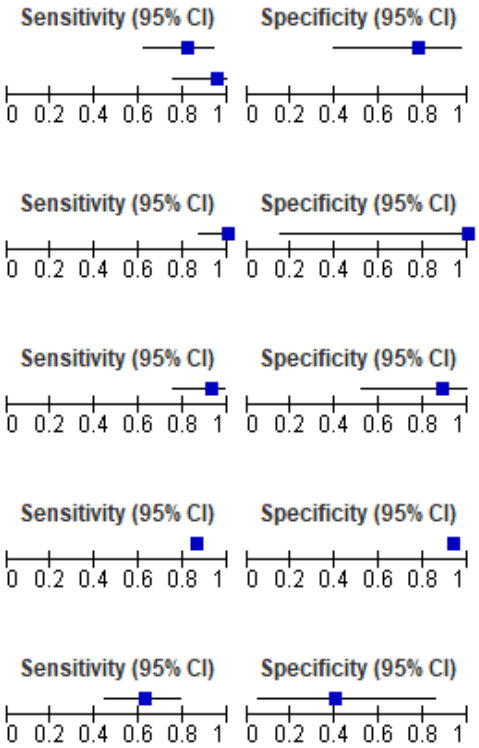
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berenger 2020	25	1	2	8	0.93 [0.76, 0.99]	0.89 [0.52, 1.00]

Saliva

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Moreira 2021	900	276	148	4100	0.86 [0.84, 0.88]	0.94 [0.93, 0.94]

Sputum

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Moreira 2021	22	3	13	2	0.63 [0.45, 0.79]	0.40 [0.05, 0.85]



Q4. Among patients suspected to have COVID-19, how accurate are rapid antigen tests compared to RT-PCR for the diagnosis of COVID-19?

As of 22 November 2021

RECOMMENDATION

We suggest the use of rapid antigen test for the diagnosis of symptomatic individuals suspected of COVID-19 as an alternative to RT-PCR if all the following conditions are met: *(Low certainty of evidence; Weak recommendation)*

a. Individuals are in the early phase of illness (less than or equal to 7 days from onset of symptoms); AND
b. Testing kits demonstrated sensitivity of more than or equal to 80% AND have very high specificity of more than or equal to 97%.

We suggest against the use of rapid antigen test for screening purposes. *(Low certainty of evidence; Weak recommendation)*

We suggest against the use of saliva as specimen for rapid antigen test in patients suspected of COVID-19 infection. *(Low certainty of evidence; Weak recommendation)*

We suggest against the use of rapid antigen tests alone in asymptomatic patients suspected of COVID-19 infection. *(Low certainty of evidence; Weak recommendation)*

We suggest the use of rapid antigen tests for the diagnosis of individuals suspected of COVID-19 during the setting of an outbreak provided that all the following conditions are met: *(Very low certainty of evidence; Weak recommendation)*

a. Individuals are in the early phase of illness (less than or equal to 7 days from onset of symptoms); AND
b. Testing kits demonstrated sensitivity of more than or equal to 80% AND have very high specificity of more than or equal to 97%.

There is insufficient evidence to recommend for or against the use of repeat antigen testing for screening or diagnosis of COVID-19. *(Very low certainty of evidence)*

A negative rapid antigen test should be confirmed with an RT-PCR in settings or situations wherein COVID-19 is highly suspected (e.g., symptomatic or asymptomatic close contacts of probable or confirmed COVID-19 individuals).

Consensus Issues

The panel was unanimous against (1) the use of rapid antigen test for screening purposes, (2) the use of saliva as specimen for rapid antigen tests, and (3) the use of rapid antigen test alone in asymptomatic patients suspected of COVID-19 infection due to the observed lower sensitivity of these tests under such conditions. A unanimous decision on the insufficiency of evidence to recommend for or against the use of repeat antigen testing was also made.

Majority of the panelists agreed that the following conditions should be met when using rapid antigen tests:

a. Individuals are in the early phase of illness, because antigen tests perform best during this period; and
b. Testing kits have a sensitivity of more than or equal to 80% and specificity of more than or equal to 97%, because the quality of the test kit should be ensured.

One of eleven panelists raised a concern on the specified sensitivity and specificity of the testing kits, as these are based on the Health Technology Assessment Council (HTAC) of the local Department of Health (DOH).

A weak recommendation on the use of rapid antigen tests for diagnosing COVID-19 suspects during outbreaks was made based on nine observational studies with unclear patient selection, conduct of reference standard, and patient flow and timing. The risk of exposure was an important consideration for the panel, citing that it is not cost-effective to test everyone during an outbreak. However, the risk stratification of participants was not specified in any of the studies.

PREVIOUS RECOMMENDATION

We recommend the use of rapid antigen test in patients suspected of COVID-19 infection meeting all the following conditions: *(Moderate quality of evidence; Strong recommendation)*

- Symptomatic AND
- Early phase ≤7 days from onset of symptoms AND
- Specific brands that demonstrated sensitivity ≥ 80% and have very high specificity (≥ 97-100%)

We recommend against the use of saliva as a specimen for rapid antigen test in patients suspected of COVID19 infection. *(Moderate quality of evidence; Strong recommendation)*

We recommend against the use of rapid antigen tests alone in asymptomatic patients suspected of COVID-19 infection*. (Moderate to high quality of evidence; Strong recommendation)*

Previous Consensus Issues

There were only two studies that used saliva as a specimen for rapid antigen test, which produced a pooled sensitivity of 17% (95% CI 13-23%) and a pooled specificity of 99% (95% CI 99-100%). Given the current evidence on the very low sensitivity for saliva, qualifying which specimen is used for a rapid antigen test is necessary.

WHAT'S NEW IN THIS VERSION?

- There are 124 new observational studies added to the initial studies evaluated in the previous evidence summary.
- New evidence on the use of antigen tests in special populations (children, healthcare workers), in the setting of an outbreak, as well as repeated/serial antigen testing were included in this review.
- Subgroup analysis was applied to the effect of cycle threshold values and additional test brands.
- Evidence on costs and resource implications of antigen testing was added.

- The certainty of evidence was downgraded due to the risk of bias and inconsistencies across evaluations resulting in a change of draft statements to *“suggest”* from *“recommend”*.

KEY FINDINGS

- A total of 164 observational studies assessed the diagnostic accuracy of rapid antigen tests (RAgTs) against reverse transcriptase-polymerase chain reaction (RT-PCR) as the reference standard. Studies included different test brands, specimen types and timing of collection, symptom status, cycle threshold (CT) values, and populations, namely impatiens, children, and healthcare workers among others.
- The overall sensitivity of RAgTs was moderate at 0.71 (95% CI 0.68-0.73) while specificity was excellent at 0.995 (95% CI 0.993-0.996). This was comparable to the data of the previous evidence summary with a pooled sensitivity of 0.72 (95% CI 0.64-0.78) and specificity of 0.99 (95% CI 0.99-1.0).
- On subgroup analysis, RAgT showed higher sensitivity when used in symptomatic individuals (Sn 0.74, 95% CI 0.71-0.78), when conducted during the early phase or first week of illness (Sn 0.79, 95% CI 0.75-0.82), in positive specimens with Ct value <25 (Sn 0.94, 95% CI 0.92-0.96), and in other Ct thresholds considered as “high” viral load (Sn 0.89, 95% CI 0.0.85-0.92). Pooled sensitivity of commonly used specimen types falls between 65% to 79%. FDA-approved RAgT brands have pooled sensitivities ranging from 0-90% with improved performance of commonly used RAgT brands when used in symptomatic individuals.
- In outbreak settings, RAgT use remained to have excellent specificity (Sp 0.966, 95% CI 0.997-0.999) with similar sensitivity (Sn 0.68, 95% CI 0.45-0.84) but with less precise estimates.
- The overall certainty of the evidence was low because of the serious risk of bias in all domains (high and unclear risk in patient selection, conduct of index test and reference standard, and flow and timing) and serious inconsistency. Despite performing pre-specified subgroup analyses, significant heterogeneity was still observed. In certain subgroup analyses such as the use of RAgT in outbreak settings and saliva specimens, the certainty of the evidence was further downgraded to very low due to imprecision attributed to wide interval estimates.

INTRODUCTION

Reverse-transcriptase polymerase chain reaction (RT-PCR) test remains to be the gold standard in the diagnosis of COVID-19. Despite excellent diagnostic accuracy, RT-PCR-based assays are not entirely practical for all testing scenarios due to their need for additional specialized equipment, specialized training of laboratory-based staff, and high cost. On the other hand, rapid antigen tests (RAgTs) detect the presence of specific viral antigens with a faster turnaround time which may be performed at the point of care, are simple to use, require shorter training, and are relatively less expensive compared to RT-PCR tests.[1] If sufficiently accurate, RAgT can facilitate timely decisions concerning the need for isolation, monitoring, treatment, and contact tracing activities.[2]

The previous review by Burog et al in March 2021 showed that the pooled sensitivity and specificity of 30 studies and 10 evaluation reports on RAgTs were 0.72 (95% CI 0.64-0.78; I^2=95.77) and 0.99 (95% CI 0.99-1.0; I^2=93.16) respectively.[3] Therefore, RAgT use was only recommended strictly for symptomatic individuals during the early

phase of illness using brands with at least moderate sensitivity (≥ 0.80) and high specificity (≥ 0.97-1.00).

With the addition of more RAgTs available for use in COVID-19 screening and diagnosis, this update investigated the diagnostic accuracy of RAgTs and compared it with that of the previous review. This can influence changes in the recommendations guiding current clinical practice.

REVIEW METHODS

MEDLINE was searched for studies published until September 30, 2021 using subject headings combined with free text terms related to COVID-19 or SARS-CoV-2 and rapid antigen tests/testing, with no language limits or method filters. Appendix 2 shows the detailed search.

Preprint studies were identified using the COVID-19 Living Evidence Database (https://zika.ispm.unibe.ch/assets/data/pub/search_beta/) with "antigen" as the search term. This database is updated daily and includes preprints from medRxiv and bioRxiv, as well as published articles from EMBASE and PubMed. The Cochrane COVID-19 Study Register (covid-19.cochrane.org/) was also searched using "antigen" as a search term. A search for related links and journals was also carried out. Bibliography sections of the included studies were reviewed for relevant articles that might be missed by database search.

To supplement the initial search yield, available data on RAgT from the FIND SARS-CoV-2 Diagnostic pipeline (https://www.finddx.org/covid-19/dx-data/) was accessed. Reported sensitivity and specificity estimates from the package inserts of RagTs approved by the Philippine FDA were also retrieved but were not included in the main analysis. Relevant clinical trials were searched on clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). Local publications such as health technology assessments on the use of RAgTs were also sought. Methodological qualities of the diagnostic studies were assessed by independent reviewers using the QUADAS-2 instrument.

Heterogeneity was determined by visual inspection of the forest plot of study evaluations and summary receiver operating characteristic (SROC) plot. Because of anticipated heterogeneity across studies, pooled sensitivity and specificity estimates were derived by stratifying studies according to test brand, CT value used, presence of symptoms, the timing of specimen collection, and special populations such as children and healthcare workers. Summary estimates for sensitivity and specificity with 95% confidence intervals were derived using a random-effects bivariate binomial model [4] fitted as a generalized linear mixed effect model using the *metandi* and *gllam* commands in Stata/MP 13.0.[5] When only fewer than four studies were available for pooling, summary estimates were computed externally through a web-based app (MetaDTA v2.01; https://crsu.shinyapps.io/dta_ma/).[6,7] Results were graphically displayed in SROC curves with the summary operating points and 95% confidence regions as well as coupled forest plots.

Sensitivity analysis was performed by removing studies with low methodologic quality or with risk of bias issues in certain QUADAS-2 domains, and subsequently assessing their impact on overall diagnostic accuracy estimates.

Out of 802 titles and abstracts screened, we retrieved 198 full-text articles relevant to the key question. Removal of duplicate copies (e.g. 40 studies included in the initial RAgT review which were already available) and articles with incomplete or no data yielded 124 new studies that were appraised and included for final analysis in this update of the evidence summary.

RESULTS

Characteristics of included studies

In addition to the 40 studies evaluated in the previous evidence review, 124 new published articles were appraised and analyzed, yielding a total of 164 included observational studies [8-171] involving 235,546 samples. Using RT-PCR as the reference standard, 25 different RAgT brands approved by the Philippine Food and Drug Administration (FDA) were evaluated. Included studies looked into screening and diagnosis of symptomatic and asymptomatic patients, employees, healthcare workers, and students in both community and hospital settings. Appendix 3 shows a summary of the characteristics of included studies.

Methodological quality of included studies

The overall methodological quality of the included studies was rated as low. In <50% of included studies, high and unclear risks of bias were seen in all domains, particularly in the patient selection and conduct of both index test and reference standard. Issues on applicability, on the other hand, were documented in < 25% of studies. The certainty of evidence was downgraded to very low when only studies on outbreak settings were pooled due to the presence of imprecision. Appendix 4 shows a detailed assessment of the risk of bias of included studies.

Diagnostic accuracy of RAgT

A. Overall diagnostic accuracy

Across 164 studies, the pooled sensitivity of RAgTs was found to be moderate at 0.71 (95% CI 0.68-0.73). Pooled specificity was excellent at 0.995 (95% CI 0.994-0.996). Visual examination of forest plots and SROC plot indicated highly heterogeneous sensitivity estimates across studies. Figure 1 shows the SROC plot.

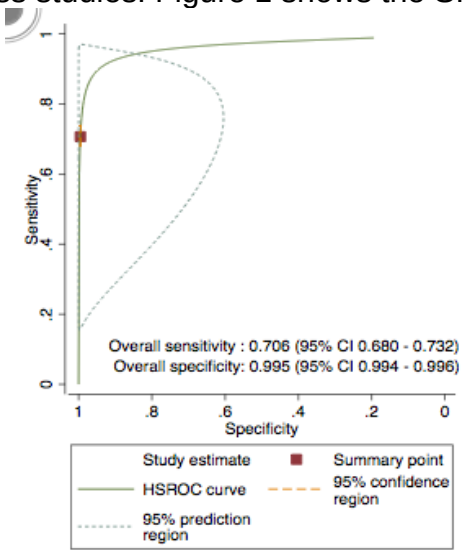


Figure 1. Summary receiver operating characteristic (SROC) plot showing the summary sensitivity and specificity point (165 studies / 272 evaluations). The 95% prediction region reflects heterogeneity in test accuracy across studies.

B. Subgroup Analysis

Table 1 shows the sensitivity of self-administered RAgTs per subgroup.

Table 1. Subgroup Analysis for Sensitivity of RAgTs

Variable	Current Review		Previous Review
	Studies/ Evaluations (Samples)	Sensitivity (95% CI)	Sensitivity (95% CI)
OVERALL	272 (235,794)	**0.71** (0.68, 0.73)	0.72 (0.64, 0.78)
Special Populations			
Children	11 (5,101)	**0.79** (0.70, 0.86)	Not evaluated
Healthcare workers	5 (1,554)	**0.82** (0.64, 0.92)	Not evaluated
Presence of symptoms			
Symptomatic	79 (45,523)	**0.74** (0.71, 0.78)	0.78 (0.69, 0.86)
Asymptomatic	55 (72,858)	**0.56** (0.51, 0.62)	0.51 (0.39, 0.63)
Timing of testing in relation to symptoms			
Early	54 (28,591)	**0.79** (0.75, 0.82)	0.71 (0.44, 0.89)
Mixed	44 (69,501)	**0.70** (0.65, 0.74)	0.81 (0.76, 0.85)
Late	23 (4,307)	**0.47** (0.39, 0.55)	0.65 (0.57, 0.71)
Test brand and presence of symptoms			
Panbio™ Ag-RDT (Abbott)	39 (29,764)	**0.72** (0.67, 0.77)	0.76 (0.61, 0.86)
● *Symptomatic*	17 (6,551)	**0.77** (0.72, 0.82)	Not evaluated
● *Asymptomatic*	11 (2,642)	**0.52** (0.45, 0.59)	Not evaluated
Standard Q COVID-19 Ag Test (SD Biosensor)	30 (24,102)	**0.72** (0.66, 0.78)	0.77 (0.58, 0.94)
● *Symptomatic*	12 (4,439)	**0.75** (0.68, 0.81)	Not evaluated
● *Asymptomatic*	7 (2,903)	**0.65** (0.59, 0.70)	Not evaluated
Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	16 (12,351)	**0.71** (0.61, 0.80)	0.66 (0.55, 0.75)
● *Symptomatic*	3 (452)	**0.83** (0.62, 0.94)	Not evaluated
● *Asymptomatic*	6 (6,070)	**0.80** (0.57, 0.93)	Not evaluated
BinaxNOW SARS-CoV-2 (Abbott)	13 (39,177)	**0.63** (0.50, 0.74)	0.90 (0.66, 0.93)
● *Symptomatic*	8 (3,425)	**0.81** (0.73, 0.87)	Not evaluated
● *Asymptomatic*	5 (6,771)	**0.61** (0.52, 0.69)	Not evaluated
Sofia SARS Antigen Fluorescent Immunoassay (Quidel)	8 (7,343)	**0.75** (0.67, 0.81)	0.70 (0.53, 0.85)
● *Symptomatic*	8 (3,798)	**0.78** (0.71, 0.84)	Not evaluated
● *Asymptomatic*	2 (2,564)	**0.58** (0.48, 0.67)	Not evaluated
Standard F Covid19 Ag FIA (SD Biosensor)	7 (4,396)	**0.72** (0.41, 0.91)	0.64 (0.40, 0.85)
● *Symptomatic*	3 (667)	**0.75** (0.43, 0.92)	Not evaluated
● *Asymptomatic*	1 (2,340)	**0.65** (0.54, 0.75)	Not evaluated
Biocredit COVID-19 Ag test (RapiGEN)	7 (827)	**0.54** (0.39, 0.69)	0.55 (0.38, 0.71)
● *Symptomatic*	2 (132)	**0.50** (0.27, 0.73)	Not evaluated
● *Asymptomatic*	1 (27)	**0.33** (0.20, 0.50)	Not evaluated
COVID-19 Rapid Antigen Test (BD Veritor)	5 (5,183)	**0.68** (0.54, 0.79)	0.76 (00.60, 0.89)
● *Symptomatic*	3 (821)	**0.83** (0.72, 0.91)	Not evaluated
● *Asymptomatic*	1 (2,317)	**0.59** (0.51, 0.66)	Not evaluated
Coronavirus Ag Rapid Test Cassette (Healgen Scientific)	3 (715)	**0.84** (0.77, 0.90)	0.77 (0.67, 0.85)
● *Symptomatic*	1 (332)	**0.79** (0.72, 0.86)	Not evaluated
VITROS Immunodiagnostic Products SARS-CoV-2 Antigen test (Ortho Clinical Diagnostics)	2 (336)	**0.78** (0.72, 0.84)	0.80 (0.74, 0.90)
NADAL COVID-19 Rapid Antigen Test (Nal Von Minden)	2 (931)	**0.74** (0.45, 0.91)	Not evaluated
AFIAS COVID-19 Ag (AFC) (Menarini)	2 (1,049)	**0.42** (0.38, 0.47)	Not evaluated
SARS-CoV-2 Antigen Rapid Test Kit (Lepu Medical)	1 (286)	**0.46** (0.36, 0.56)	Not evaluated
CareStart COVID-19 Antigen Test (Access Bio)	1 (286)	**0.46** (0.34, 0.45)	Not evaluated
Encode SARS-CoV-2 Antigen Rapid Test Device (Zhuhai Encode Medical Engineering)	1 (200)	**0.74** (0.64, 0.82)	Not evaluated
Elecsys SARS-CoV-2 Antigen assay (Roche)	1 (3,143)	**0.60** (0.55, 0.65)	Not evaluated
SIENNA COVID-19 Antigen Rapid Test Cassette	1 (150)	**0.90** (0.82, 0.95)	Not evaluated
GenBody COVAG025 Rapid Antigen Test	1 (130)	**0.90** (0.73, 0.98)	Not evaluated
Humasis COVID-Ag Test COVID-19 Antigen (Humasis)	1 (21)	**0.90** (0.70, 0.99)	Not evaluated
NowCheck COVID-19 Ag Test (Bionote)	1 (1,326)	**0.56** (0.21, 0.86)	0.89 (0.81, 0.95)
StrongStep Rapid Antigen Test (Liming)	1 (19)	**0** (0, 0.34)	Not evaluated
Huaketai SARS-CoV-2 Rapid Antigen Test (Savant)	1 (109)	**0.17** (0.09, 0.27)	0.17 (0.09, 0.27)
SARS-CoV-2 Antigen Rapid Test Kit (JOYSBIO)	1 (225)	**0.58** (0.47, 0.68)	Not evaluated
ichromaTM COVID-19 Ag (Boditech)	1 (966)	**0.41** (0.37, 0.46)	Not evaluated
CT value			
Low (<25)	40 (6,906)	**0.94** (0.92, 0.96)	Not evaluated
High (>25)	35 (5,076)	**0.39** (0.38, 0.42)	Not evaluated
Other Ct thresholds for 'higher' viral load	27 (14,398)	**0.89** (0.85, 0.92)	Not evaluated
Other Ct thresholds for 'lower' viral load	18 (1,996)	**0.29** (0.20-0.41)	Not evaluated

Specimen type			
Exhaled breath	1 (105)	**0.92** (0.64, 1.0)	Not evaluated
Nasopharyngeal and Saliva	1 (343)	**0.91** (0.76, 0.98)	Not evaluated
Nasal (anterior nares and mid-turbinate)	24 (51,399)	**0.79** (0.74, 0.83)	0.84 (0.66, 0.93)
Nasopharyngeal	99 (111,446)	**0.71** (0.68, 0.75)	0.72 (0.65, 0.78)
Nasopharyngeal and Oropharyngeal	35 (38,387)	**0.65** (0.59, 0.71)	0.65 (0.47, 0.79)
Oropharyngeal	3 (8,568)	**0.59** (0.42, 0.73)	Not evaluated
Saliva	7 (6,148)	**0.57** (0.22, 0.86)	0.17 (0.13, 0.23)
Nasal and Oropharyngeal	1 (18,457)	**0.49** (0.47, 0.51)	Not evaluated
Sputum	1 (45)	**0.11** (0.04, 0.24)	Not evaluated
In Outbreak Settings			
Overall	9 (6805)	**0.68** (0.45 - 0.84)	Not evaluated
• Symptomatic	3 (398)	**0.14 - 0.89**	Not evaluated
• Asymptomatic	3 (1142)	**0.22 - 0.92**	Not evaluated
Methodological quality			
Studies with low risk of bias	83 (73,469)	**0.75** (0.71, 0.79)	Not evaluated
Studies with high risk of bias	96 (88 252)	**0.64** (0.58, 0.69)	Not evaluated
Studies with unclear risk of bias	93 (74 073)	**0.73** (0.68. 0.77)	Not evaluated

By special population

The evidence summary update incorporated an analysis of RAgT use in special populations. The pooled sensitivity of RAgT use in children was 0.79 (95% CI 0.70-0.86; n=5,101; 11 studies) while pooled sensitivity was 0.82 (95% CI 0.64-0.92; n=1,554; 5 studies) when used among healthcare workers. Though RAgT use in both populations showed high performance, more trials may be needed to substantiate recommendations for these specific populations.

By presence of symptoms

The use of RAgT in symptomatic individuals showed higher pooled sensitivity (Sn=0.74, 95% CI 0.71-0.78; n=45,523; 79 studies) compared to that of asymptomatic individuals (Sn=0.56, 95% CI 0.51-0.62; n=72 858; 55 studies). This is consistent with previous estimates showing higher sensitivity of RAgT in symptomatic individuals (Sn 0.78, 95% CI 0.69-0.86) compared to asymptomatic individuals (Sn 0.51, 95% CI 0.39-0.63).

By time of testing in relation to symptom onset

When RAgt was used either during the early (0-7 days) or late phase (>7 days) from symptom onset, the pooled sensitivity was 0.70 (95% CI 0.65-0.74; n=69,501; 44 studies). The pooled sensitivity increased to 0.79 (95% CI 0.75-0.82; n=28,591; 54 studies) when RAgT was used in the early phase of illness and decreased to 0.47 (95% CI 0.39-0.55; n=4,307; 23 studies) when RAgT was used during the late phase of the disease.

By test brand

Moderate performance was demonstrated by the five most commonly used RAgT brands, namely Abbott Panbio (Sn 0.72, 95% CI 0.65-0.77; n=29,764; 39 studies), SD biosensor Standard Q COVID-19 Ag (Sn 0.72, 95% CI 0.66-0.78; n=24,102; 30 studies), Roche SARS-CoV-2 Rapid Antigen Test (Sn 0.71, 95% CI 0.61-0.80; n=12,351; 16 studies), Abbott BinaxNOW CoVID-19 Antigen Card (Sn 0.63, 95% CI 0.50-0.74; n=39 177; 13 studies) and Quidel Sofia SARS Antigen Fluorescent Immunoassay (Sn 0.75, 95% CI 0.67-0.81, n=7,343; 8 studies).

Subgroup analysis showed improved diagnostic performance of the above RAgT brands when used with symptomatic individuals as pooled sensitivity increased in the

range of 0.75 (95% CI 0.68-0.81; SD biosensor Standard Q COVID-19 Ag) to 0.83 (95% CI 0.62-0.94; Roche SARS-CoV-2 Rapid Antigen Test).

Though highest sensitivity was documented in the RAgT brands SIENNA COVID-19 Antigen Rapid Test (Sn 0.90, 95% CI 0.82-0.95; n=150; 1 study), GenBody COVAG025 Rapid Antigen Test (Sn 0.90, 95% CI 0.73- 0.98; n=130; 1 study) and Humasis COVID-Ag Test (Sn 0.90, 95% CI 0.70- 0.99; n=21; 1 study), their use in a limited number of samples warrant more trials to further validate their clinical utility.

By cycle threshold (Ct) value of RT-PCR

RAgTs demonstrated excellent performance in positive RT-PCR specimens having Ct value ≤25 with pooled sensitivity at 0.94 (95% CI 0.92-0.96; n=6,906; 40 studies). Studies that used Ct cutoff values other than 25 still showed better performance when samples had higher viral loads (i.e., lower Ct values) with a sensitivity of 0.89 (95% CI 0.85-0.92; n=14,398; 27 studies) versus 0.29
(95% CI 0.20-0.41; n=1,996; 18 studies) when used in those with “low” viral load.

By specimen type

RAgT using exhaled breath samples showed the highest sensitivity (Sn 0.92, 95% CI 0.64-1.00; n=105; 1 study). This was followed by samples from combined nasopharyngeal and saliva (Sn 0.91, 95% CI 0.76-0.98; n=343; 1 study). However, the use of these specimens was limited to single studies with imprecise estimates.

The more commonly used specimen types, namely nasal, nasopharyngeal, combined nasopharyngeal and oropharyngeal, have moderate sensitivities. RAgTs had a pooled sensitivity of 0.79 (95% CI 0.74-0.82; n=51,399; 24 studies) when used in nasal specimens, 0.71 (95% CI 0.67-0.74; n=111,446; 102 studies) when used in nasopharyngeal specimens, and 0.65 (95% CI 0.59-0.71; n=38,387; 35 studies) when used in combined nasopharyngeal and oropharyngeal specimens.

Sputum as a specimen type had the lowest sensitivity (Sn 0.11, 95% CI 0.04-0.24; n=45; 1 study). Seven studies using saliva as the specimen type demonstrated poor sensitivity at 0.57 (95% CI 0.22-0.86; n=6,148). This result is consistent with the findings of the previous review.

By serial/repeat testing

Two observational studies with unclear risk of bias provided data on repeat testing. In the study of Shah et al., repeat antigen testing of anterior nasal specimen using Abbott BinaxNOW CoVID-19 Antigen Card in a community setting taken within 30 minutes from the initial evaluation showed an improved sensitivity from 0.77 (95% CI 0.72-0.82) to 0.81 (95% CI 0.77-0.86). This study tested a total of 2110 patients, 1190 (56%) of which were symptomatic. [148]

Using the same specimen type and RAgT brand, McKay and colleagues employed 3 rounds of serial testing over a 13-day period (every 4-5 days) among nursing home residents and staff using RT-PCR as the reference standard. Majority of the subjects were asymptomatic (451/532 or 84.7%). Sensitivity was inconsistent across different test rounds: 1st round at 0.74 (95% CI 0.59-0.86), 2nd round at 0.63 (95% CI 0.47-0.78), and 3rd round at 0.67 (95% CI 0.41-0.88) respectively. On the other hand, specificity remained high throughout the study with a range of 0.97 to 1.0.[106]

During outbreak settings

The authors identified nine observational studies [23, 24, 27, 47, 93, 106, 112, 130, 159] that involved settings or scenarios wherein rapid antigen testing was compared to RT-PCR testing in the context of an outbreak. Six out of the nine studies consisted of a mixed population of asymptomatic and symptomatic. In studies during outbreaks and surges, rapid antigen tests had a pooled sensitivity of 0.68 (95% CI 0.45-0.84) which was similar to the overall pooled sensitivity of included studies but with less precise estimates. Pooled specificity remained excellent at 0.996 (95% CI 0.997-0.999). The certainty of evidence of the pooled studies on outbreak settings was downgraded to very low due to the presence of imprecision.

I. In Symptomatic Individuals

Three studies [23, 106, 112] provided specific data on symptomatic subjects. The three studies tested subjects within the early and late phases of illness with RT-PCR as the reference standard. A summary sensitivity estimate was not calculated due to the small number of studies and the variability in the test brands and specimens used. Sensitivity ranged from 0.14 to 0.89. When the study with the lowest sensitivity estimate and high risk of bias [112] was excluded from analysis, sensitivity ranged from 0.76 to 0.89.

In the study by Bianco et al., 231 individuals reported at least one COVID-19 symptom and were tested using LumiraDx™ SARS-CoV-2 Antigen Test with RT-PCR as the reference standard. Sensitivity and specificity were high at 0.89 (95% CI 0.0.84-0.93) and 0.88 (95% CI 0.73-0.97) respectively.

Among residents and staff of a nursing home in the study by Mckay et al., 79 paired specimens were evaluated using the BinaxNOW COVID-19 Ag Card, which showed moderate sensitivity of 0.76 (95% CI 0.58-0.89) but excellent specificity of 1.00 (95% CI 0.92-1.0)

Nagura-Ikeda reported the lowest sensitivity estimate of 0.14 (95% CI 0.07-0.27) and specificity of 1.00 (95% CI 0.8-1.0) from collected saliva specimens of 88 individuals using the Espline SARS-CoV2 (Fujirebio) Rapid Antigen Test.

II. In Asymptomatic Individuals

Three studies [23,106,112] provided data on asymptomatic subjects. A summary sensitivity estimate was not calculated due to the small number of studies and the variability in the test brands and specimens used. Sensitivity ranged from 0.22 to 0.92. When the study with the lowest sensitivity estimate [112] and high risk of bias was excluded from analysis, sensitivity ranged from 0.65 to 0.92.

The lowest sensitivity estimate of 0.22 (95% CI 0.03-0.6) was obtained from the study by Nagura-Ikeda et al. [112] which used saliva specimens and had a high risk of bias. The remaining two observational studies used nasal specimens and showed higher sensitivities but had an unclear risk of bias. In the study by Bianco et. al, 676 subjects underwent rapid antigen testing using LumiraDx™ SARS-CoV-2 Antigen Test with RT PCR as the reference standard. Sensitivity and specificity were high at 0.92 (95% CI 0.85-0.97) and 0.92 (95% CI 0.90-0.94) respectively. A total of 451 paired specimens from asymptomatic residents and staff of a nursing home were evaluated in a study

by Mckay et al. The BinaxNOW COVID-19 Ag Card was used for testing which showed poor sensitivity of 0.65 (95% CI 0.53-0.76) but excellent specificity of 0.98 (95% CI 0.96-0.99).

C. Sensitivity Analysis

RAgT showed an improved overall sensitivity when only studies with a low risk of bias (high methodological quality) were included in the analysis (pooled Sn 0.75, 95% CI 0.71-0.79; n=73,469). This estimate appears to be comparable to that of studies with an unclear risk of bias (Sn 0.73, 95% CI 0.68-0.77; n=74 073). In contrast, studies with a high risk of bias in any of the four QUADAS-2 domains (patient selection, index test, reference standard, flow interval) produced significantly lower sensitivity estimates (pooled Sn 0.64, 95% CI 0.58-0.69; n=88,252).

Ongoing Studies on RAgT

As of November 2021, there were 24 ongoing trials [172-195] on the use of RAgTs for COVID-19 registered at ClinicalTrials.gov. Most of the trials compare the accuracy of RAgTs to RT PCR. Specimen types and brands used across the trials are varied. Trials are exploring the potential of RAgTs for screening and surveillance in various settings (i.e. workplace, airports, mass gatherings, community).

OTHER CONSIDERATIONS

With the increase in RAgT use, some studies have explored the economic advantage brought by testing. A cost-benefit study by Diel and Nienhaus in Germany has shown that the implementation of the Sofia SARS Antigen FIA test saved on average about 210 euros as compared to clinical-judgment only. Furthermore, with a high prevalence rate of 15.6% in the same study population, point-of-care COVID-19 antigen testing reduced the average costs of hospitalized patients by 213 euros per tested patient.[196]

Another study has explored the economic effects of home-based RAgT in the United States of America. Despite the imperfections of home testing for COVID-19, the epidemic modeling done has shown that home-based RAgT can reduce transmission of infection and mortality at a justifiable cost.[197] No local economic evaluation study has been performed on RAgTs to date.

As there are numerous COVID-19 tests available, authorized organizations namely the Philippine Food and Drug Administration (FDA) and the Research Institute for Tropical Medicine (RITM) were tasked to evaluate commercially manufactured COVID-19 tests to ensure the quality of the tests in the local setting. [198] The Philippine FDA-approved brands are constantly being updated because of this evaluation. Among the brands included in this review, Panbio™ Ag-RDT (Abbott), Sofia SARS Antigen Fluorescent Immunoassay (Quidel), and NowCheck COVID-19 Ag Test (Bionote) have passed the performance evaluation as of August 2, 2021.[199] In an advisory dated September 13, 2021, caution was advised on the use of COVID-19 Rapid Antigen Test (BD Veritor), NADAL COVID-19 Rapid Antigen Test (Nal Von Minden), and SARS-CoV-2 Antigen Rapid Test Kit (JOYSBIO) as these brands have failed the performance evaluation.[200] Standard Q COVID-19 Ag Test (SD Biosensor) was listed under the tests being recalled for the low performance in the evaluation and for failure to explain the non-conformance of the product to the specifications declared last August 2, 2021.[201] The company distributing ichroma

COVID-19 Ag voluntarily surrendered their authorization to market the product as of June 18, 2021.[202]

The Department of Health (DOH) issued a memorandum dated September 1, 2021, which strictly placed a price cap of Php 960 for RAgT in all testing and clinical laboratories.[203] The unit cost of the different brands of RAgT kits in the market ranges from Php 250 to Php 1,600. Table 2 lists the available unit cost of RAgT kits locally. Automated RAgTs are much more costly than manually interpreted RAgT.

Table 2. Unit Price of RAgT Kits

Test Brand	Unit Cost
Sofia SARS Antigen Fluorescent Immunoassay (Quidel)	Php 1 600 (32 USD)
VITROS Immunodiagnostic Products SARS-CoV-2 Antigen test (Ortho Clinical Diagnostics)	Php 1 067 (21 USD)
COVID-19 Rapid Antigen Test (BD Veritor)	Php 907 (18 USD)
SIENNA COVID-19 Antigen Rapid Test Cassette	Php 750 (15 USD)
Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	Php 705 (14 USD)
GenBody COVAG025 Rapid Antigen Test	Php 503 (10 USD)
CareStart COVID-19 Antigen Test (Access Bio)	Php 605 (12 USD)
Standard Q COVID-19 Ag Test (SD Biosensor)	Php 550
Panbio™ Ag-RDT (Abbott) 1000-4975 tests (40-199 boxes)	Php 520 (13 USD)
NADAL COVID-19 Rapid Antigen Test (Nal Von Minden)	Php 349 (€ 6)
BinaxNOW SARS-CoV-2 (Abbott)	Php 250 (5 USD)
Coronavirus Ag Rapid Test Cassette (Healgen Scientific)	Php 680 (£ 10)

RECOMMENDATIONS FROM OTHER GROUPS

Table 3 summarizes the recommendations from different agencies, countries, and organizations regarding the use of rapid antigen tests.

Table 3. Summary of Recommendations from Other Groups

Agency	Recommendation	Date
Department of Health Health Technology Assessment Council [204]	The HTAC **does not recommend the use of rapid antigen tests** for indiscriminate use in mass screening, for return-to-work clearance and for COVID-19 diagnosis in individuals with low index of suspicion (i.e., asymptomatic and no history of exposure). Rapid antigen tests are currently recommended **by HTAC only for very specific purposes:** ● For **targeted screening and diagnosis of suspected and probable cases of COVID-19** (i.e., with a high index of suspicion), meeting the clinical and/or epidemiologic criteria in the hospital or community settings. ● For **testing of patients in the hospital setting**, where the turnaround time is critical, to guide patient cohort management to minimize transmission of COVID-19 among healthcare workers and other patients. (Hospitals are high-risk settings among healthcare workers and patients.) Otherwise, use RT-PCR in case of elective procedures; ● For **targeted screening and diagnosis of suspect and probable cases of COVID-19** (as defined above) in presumptive outbreaks where the result of the RT-PCR test of one suspect has not yet been released and in settings where RT-PCR is not immediately available or when delayed release of result or prolonged turnaround time is expected (i.e., more than 48 hours). ● For local border screening at points of entry **for individuals travelling from areas with a high daily positivity rate averaged over a seven-day period (i.e., >10%) or as reported by the DOH-Epidemiology Bureau** based on its periodic updates of prevalence rate/positivity rate; and, ● For **international border screening** at points of entry, always assume a high prevalence/positivity rate. A periodic update every month of prevalence rate/positivity rate per country is also suggested. It is recommended that the RT-PCR or RAgT test be used for screening of all incoming individuals in accordance with existing protocol and testing guidelines. Facility- or home-based quarantine shall also be implemented together with RT-PCR or Rapid Antigen testing.	Apr 30, 2021

Infectious Disease Society of America [205]	**Recommendation 1**: For symptomatic individuals suspected of having COVID-19, the IDSA panel suggests using standard NAAT (either rapid RT-PCR or laboratory-based NAAT) over rapid Ag tests (*conditional recommendation based on moderate certainty in test accuracy of rapid Ag test and very low certainty in comparative test accuracy of rapid RT-PCR* versus *rapid Ag tests*) **Recommendation 2**: For asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests using a single standard NAAT (either rapid RT-PCR or laboratory-based NAAT) over a single rapid Ag test (*conditional recommendation based on moderate certainty in test accuracy of rapid Ag tests and very low certainty in comparative test accuracy of rapid RT-PCR* versus *rapid Ag tests*) **Recommendation 3**: For asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests a single (i.e., one-time) standard NAAT (either rapid RT-PCR or laboratory-based NAAT) rather than a strategy of two consecutive rapid Ag tests (*conditional recommendation based on moderate certainty in test accuracy of molecular testing and an evidence gap to inform the test accuracy of a strategies using repeat Ag testing*) **Recommendation 4**: In asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests neither for nor against using single (i.e., one-time) rapid Ag testing over no testing (evidence gap to inform the utility of Ag testing compared to no testing) **Recommendation 5**: In asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests neither for nor against using repeat rapid Ag testing over no testing (*evidence gap to inform the utility of a strategy of Ag testing compared to no testing)*.	May 5, 2021
World Health Organization [206]	WHO recommends the use of Ag-RDTs that meet minimum performance requirements of ≥ 80% sensitivity and ≥ 97% specificity. Ag-RDTs are less sensitive than NAAT, particularly in asymptomatic populations, but careful selection of cohorts for testing can mitigate this limitation. Ag-RDTs should be prioritized for use in symptomatic individuals meeting the case definition for COVID-19, and to test asymptomatic individuals at high risk of infection, including contacts and health workers, particularly in settings where NAAT testing capacity is limited.	Oct 6, 2021
American Academy of Pediatrics [207]	Patients with symptoms consistent with COVID-19 should be tested without delay using either a NAAT (including PCR) or antigen test. The appropriate test for delayed testing of asymptomatic exposed patients is the PCR and not the rapid antigen. Testing for active SARS-CoV-2 infection using NAATs or antigen-based tests is not generally recommended for asymptomatic patients who have previously tested positive within the past 3 months.	Sep 9, 2021

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Appendix 1. Evidence to Decision

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)					
Certainty of Evidence	High	Moderate (3)	Low (6)	Very low			Overall, the studies included are of low methodological quality due to risk of bias issues and high heterogeneity among included evaluations.
Accuracy	Very Accurate	Accurate (7)	Inaccurate (2)	Very Inaccurate			Across 164 studies, the pooled sensitivity of RAgTs was found to be moderate at 0.71 (95%CI: 0.68-0.73). Pooled specificity was excellent at 0.995 (95%CI: 0.993-0.996).
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (7)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (1)	Moderate Cost (6)	Negligible cost	Moderate savings (1)	Large savings	Unit cost of the different brands of rapid antigen test kit in the market ranges from Php 250 to Php 1600.
Certainty of evidence of required resources	No included studies (1)	Very low (1)	Low (5)	Moderate (1)	High (1)		In the Philippines, the Department of Health issued a memorandum dated September 1, 2021 strictly placing a price cap of Php 960 for rapid antigen testing in all testing and clinical laboratories.
Cost effectiveness	No included studies (6)	Favors RT-PCR (1)	Does not favor either RAgT or RT-PCR	Favors RAgT (2)			No local economic evaluation studies are available as of press time on comparing rapid antigen tests and RT-PCR.
Equity	Uncertain (4)	Reduced	Probably no impact	Increased (5)			
Acceptability	Uncertain (1)	No (1)	Yes (7)				
Feasibility	Uncertain	No	Yes (9)				

Appendix 2. Search Yield and Results

Search	Query	Results	Time
#10	Search **#1 AND #8** Filters: **from 1000/1/1 - 2021/9/30** Sort by: **Most Recent**	802	04:57:47
#9	Search **#1 AND #8** Sort by: **Most Recent**	874	04:56:30
#8	Search **#7 OR #2** Sort by: **Most Recent**	18,609	04:56:20
#7	Search **#5 OR #6** Sort by: **Most Recent**	18,608	04:56:13
#6	Search: **rapid antigen test* OR "rapid antigen detection test" OR radt OR radts OR rdt OR rdts OR (antigen* n3 detect*)** Sort by: **Most Recent**	18,555	04:56:06
#5	Search **#3 and #4** Sort by: **Most Recent**	171	04:55:58
#4	Search: **(test OR tests OR detect* OR diagnos* OR kit OR kits OR assay*)** Sort by: **Most Recent**	11,628,285	04:55:41
#3	Search: **((rapid OR point-of-care OR "point of care" OR poc OR poct) n3 antigen))** Sort by: **Most Recent**	204	04:55:27
#2	Search: **"COVID-19 Ag Respi-Strip" OR "BIOCREDIT COVID-19 Ag" OR "STANDARD F COVID-19 Ag" OR "STANDARD Q COVID-19 Ag" OR "Bioeasy 2019-nCoV Ag"** Sort by: **Most Recent**	25	04:55:19
#1	Search: **("Coronavirus Infections"[Mesh] OR novel coronavirus OR NCOV OR "COVID-19"[Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2)** Sort by: **Most Recent**	205,257	04:55:11

Appendix 3. Characteristics of Included Studies

Study		Setting	RAgT Brand	Test Specimen	Population	Sample Size	Reference Standard	
							Test	Specimen
1	Okoye 2021	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	NP	Asymptomatic university students	2638	RT PCR	Nasal
2	Oh 2021	Korea	STANDARD Q COVID19 Ag (SD Biosensor)	NP	Patients admitted in the study hospital	118	RT PCR	NP
3	Lindner 202105	Germany	STANDARD Q COVID19 Ag (SD Biosensor)	MT + NP	Symptomatic patients at ambulatory testing facility	146	RT PCR	NP + OP
4	Lindner 202104	Germany	STANDARD Q COVID19 Ag (SD Biosensor)	MT	Symptomatic patients at ambulatory testing facility	287	RT PCR	NP + OP
5	Ishii 2021	Japan	ESPLINE SARS-CoV-2 (Fujirebio)	NP + Saliva	COVID and non-COVID patients admitted	271	RT PCR	NP
6	Baro 2021	Spain	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Unexposed asymptomatics during third wave in Spain	286	RT PCR	NP
7	Stokes 2021	Canada	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Symptomatic individuals	1786	RT PCR	NP
8	Torres 202101	Spain	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Asymptomatic close contacts	634	RT PCR	NP
9	Torres 202102	Spain	CLINITEST Rapid COVID-19 Antigen Test (Siemens)	NP	Symptomatic individuals and asymptomatic close contacts	270	RT PCR	NP
10	Torres 202102	Netherlands	COVID-19 Rapid Antigen Test (BD Veritor)	NP	Non-hospitalized symptomatic patients	351	RT PCR	NP
11	Yokota 2021	Japan	Lumipulse SARS-CoV-2 Antigen Kit (Fujirebio)	NP + Saliva	Inpatients and Outpatients	343	RT PCR	NP
12	Igloi 2021	Netherlands	Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	NP	Symptomatic or close contact	970	RT PCR	NP + OP
13	Courtellemont 2021	France	COVID-VIRO Antigen Rapid Test (AAZ)	NP	Asymptomatic and hospitalized	248	RT PCR	NP
14	Olearo 2021	Germany	STANDARD Q COVID19 Ag (SD Biosensor) Panbio COVID-19 Ag Rapid Test (Abbott) SARS-CoV-2 Antigen Rapid Test (MedSan GmbH) CLINITEST Rapid COVID-19 Antigen Test (Siemens)	NP + OP	Asymptomatic and hospitalized	184	RT PCR	NP + OP
15	Jaaskelainen 2021	Finland	Sofia SARS Antigen Fluorescent Immunoassay (Quidel) STANDARD Q COVID19 Ag (SD Biosensor) Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Symptomatic	188 198 190	RT-PCR	NP
16	Adnan 2021	Bangladesh	Rapid In-house ELISA (Bangladesh)	NP	No data	339	RT-PCR	NP
17	Pollock 2021a	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	Nasal	Symptomatic patients	2,482	RT-PCR	Nasal
18	Pollock 2021b	USA	CareStart COVID-19 Antigen Test (Access Bio)	Nasal	Symptomatic patients	1,603	RT-PCR	Nasal
19	Peña-Rodríguez 2021	Mexico	STANDARD Q COVID19 Ag (SD Biosensor)	NP	Symptomatic, asymptomatic, exposed contacts (3-5 days)	369	RT-PCR	NP + OP
20	Chiu 2021	USA	INDICAID COVID-19 rapid antigen test (PHASE)	Nasal	Symptomatic participants	698	RT PCR	Nasal
		HongKong			Asymptomatic participants	22994	RT PCR	Nasal + OP
21	Shaikh 2021	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	Nasal	Symptomatic children	199	RT PCR	Nasal
22	Laandas 2021	Norway	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Community and outbreak setting	4,857	RT-PCR	NP
23	Boum 2021	Cameroon	STANDARD Q COVID19 Ag (SD Biosensor)	NP	Hospitalized, asymptomatic volunteers, exposed contacts	1,195	RT-PCR	NP

24	Pickering 2021	UK	Innova Rapid SARS-CoV-2 Antigen Test (Xiamen Biotime Biotechnology) Spring Healthcare SARS-CoV-2 Antigen Rapid Test Cassette (Shanghai ZJ Bio-Tech) E25Bio Rapid Diagnostic Test (E25Bio) Encode SARS-CoV-2 Antigen Rapid Test Device (Zhuhai Encode Medical Engineering) COVID-19 Coronavirus Rapid Antigen Test Cassette (Surescreen) COVID-19 Coronavirus Rapid Antigen Test Cassette (Surescreen)	NP	Trained personnels; community settings, inpatients and outpatients	200	RT PCR	NP
25	Sood 2021	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	Nasal	Children less than 18 years	783	RT-PCR	OP
26	Matsuda 2021	Mexico	Ecotest COVID-19 Rapid Antigen Test (Verify) Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Symptomatic patients	112	RT-PCR	NP + OP
27	Bello-Chavolla 2021	Mexico	STANDARD Q COVID19 Ag (SD Biosensor)	NP	Community setting: COVID suspects	193824	RT-PCR	NP
28	Kyritsi 2021	Greece	Rapid Test Ag 2019-nCoV (PROGNOSIS, BIOTECH)	NP	Hospital setting	624	RT-PCR	NP
29	Iqbal 2021	Pakistan	Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	NP	Hospital setting: COVID suspects	170	RT-PCR	NP
30	Nikolai 2021	Germany	STANDARD Q COVID19 Ag (SD Biosensor)	Nasal + MT	Community setting: COVID suspects from ambulatory facility	228	RT-PCR	NP
31	Caruana 2021	Switzerland	Exdia COVID-19 Antigen Test (Precision-Bio) STANDARD Q COVID19 Ag (SD Biosensor) Panbio COVID-19 Ag Rapid Test (Abbott) COVID-19 Rapid Antigen Test (BD Veritor)	NP	Symptomatic and asymptomatic ER patients	532	RT-PCR	NP
32	Martin-Sanchez 2021	Spain	Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	NP	Community setting: population-based screening of asymptomatic individuals	881	RT-PCR	NP
33	Maniscalco 2021	Italy	Inflammacheck device (Exhalation technology LTD)	Exhaled breath condensate	Hospital setting: COVID suspects, convalescent patients, asymptomatic with high risk of COVID, asymptomatic with low risk of COVID	105	RT-PCR	NP
34	Merino-Amador 2021	Spain	CLINITEST Rapid COVID-19 Antigen Test (Siemens)	NP	Hospital setting: COVID suspects with exposure < 7 days or early symptoms	450	RT-PCR	NP
35	Hauser 2021	Germany	LIAISON SARS-CoV-2 Antigen Assay (DiaSorin)	NP	Hospitalized patients	196	RT-PCR	NP
36	Osterman 2021	Germany	Lumipulse SARS-CoV-2 Antigen Kit (Fujirebio) Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics) LIAISON SARS-CoV-2 Antigen Assay (DiaSorin) SARS-CoV-2 Ag ELISA (Euroimmun)	NP	Hospital setting: patients from ER or clinics	410	RT-PCR	NP
37	Andreani 2021	France	Panbio COVID-19 Ag Rapid Test (Abbott) STANDARD Q COVID19 Ag (SD Biosensor)	NP	Community settings: patients and personnels in a diagnostic facility	239	RT-PCR	NP

			Certest SARS-CoV-2 one step card test (Theradiag) Orient Gene Coronavirus Ag rapid cassette (Menarini) Espline SARS-CoV-2 (Fujirebio) Lumipulse SARS-CoV-2 Antigen Kit (Fujirebio)					
38	Salvagno 2021	Italy	Espline SARS-CoV-2 (Fujirebio)	NP	Community settings: patients with confirmed COVID	174	RT-PCR	NP
39	Lhuillier 2021	Switzerland	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Community and hospital setting: Children	822	RT-PCR	NP
40	Korenkov 2021	Germany	STANDARD Q COVID19 Ag (SD Biosensor)	NP + OP	Hospital setting: COVID suspect and Trained personnel screening	2028	RT-PCR	NP + OP
41	Bachman 2021	USA	Open-access lateral flow assay Sofia SARS Antigen Fluorescent Immunoassay (Quidel) BinaxNOW COVID-19 Antigen Card (Abbott) Meso Scale Discovery MESO Quick-Plex SQ 120 (MSD) Open-access lateral flow assay Sofia SARS Antigen Fluorescent Immunoassay (Quidel) BinaxNOW COVID-19 Antigen Card (Abbott) Meso Scale Discovery MESO Quick-Plex SQ 120 (MSD)	Anterior nares	Community settings: COVID suspects in clinics	170	RT PCR	Anterior nares + NP
42	Nomoto 2021	Japan	Lumipulse SARS-CoV-2 Antigen Kit (Fujirebio)	NP	Hospital setting: inpatients	100	RT-PCR	NP
43	Kruger 2021	Germany	LumiraDx SARS-CoV-2 Antigen (LumiraDx)	MT	Community settings: COVID suspects in Drive-in testing site and ambulatory care facility	761	RT-PCR	NP
44	Kahn 2021	Germany	Standard F Covid19 Ag FIA (SD Biosensor)	OP	Community settings; Individuals at point-of-care facilities	3110	RT-PCR	OP
45	Escriva 2021	Spain	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Community settings: nursing home residents and employees	448	RT-PCR	NP
46	Norz 2021	Germany	Elecsys SARS-CoV-2 Antigen assay (Roche)	NP + OP	Hospital settings: multicenter routine diagnostic	3139	RT-PCR	NP and OP
47	Mboma 2021	Germany	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Hospitalized patients and accompanying relatives	3,686	RT-PCR	NP
48	Stohr 2021	The Netherlands	COVID-19 Rapid Antigen Test (BD Veritor) Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	NP	Community settings	3,201	RT PCR	NP and OP
49	Allan-Blitz 2021	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	AN + OP	Community setting	15,304	RT-PCR	NP + OP + AN
50	Cassuto 2021	France	COVID-VIRO Antigen Rapid Test (AAZ)	NP	Symptomatic adult volunteers	234	RT-PCR	NP
51	Agarwal 2021	India	STANDARD Q COVID19 Ag (SD Biosensor)	NP	Hospitalized patients and asymptomatic contacts	467	RT-PCR	NP
52	Hartard 2021	France	LIAISON SARS-CoV-2 Antigen Assay (DiaSorin)	NP	Mass screening of hospitalized patients	378	RT-PCR	NP

53	Kobayashi 2021	Japan	Lumipulse SARS-CoV-2 Antigen Kit (Fujirebio)	NP + saliva	Samples from hospitals and public health centers in Japan	10,422	RT-PCR	NP
54	Wagenhauser 2021	Germany	NADAL COVID-19 Rapid Antigen Test (Nal Von Minden) Panbio COVID-19 Ag Rapid Test (Abbott) SARS-CoV-2 Antigen Rapid Test (MedSan GmbH)	OP	Mass screening of all hospitalized patients	5,056	RT-PCR	OP
55	Amer 2021	Egypt	STANDARD Q COVID19 Ag (SD Biosensor)	NP + OP	Community and hospital setting: COVID suspects Trained personnels	83	RT-PCR	NP + OP
56	Montero 2021	Spain	Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	NP + OP	Community setting: asymptomatic adults in a semi-closed community	2543	RT-PCR	NP + OP
57	Ferte 2021	France	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Community setting: symptomatic and asymptomatic students	688	RT-PCR	NP
58	Leixner 2021	Austria	AMP Rapid Test SARS-CoV-2 Ag (AMP)	NP	Hospital setting: symptomatic patients presenting at the ER	392	RT-PCR	NP + OP
59	Soleimani 2021	Belgium	BioSpeedia COVID19Speed-Antigen Test (Institut Pasteur) Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Community settings: COVID suspects or with exposure	401	RT-PCR	NP
60	Kiro 2021	India	Standard F Covid19 Ag FIA (SD Biosensor)	NP	Hospital setting: admitted patients and OPD patients from COVID screening	354	RT-PCR	NP
61	Garcia 2021	Spain	Panbio COVID-19 Ag Rapid Test (Abbott) Standard F Covid19 Ag FIA (SD Biosensor)	NP	Community settings	356	RT-PCR	NP
62	Seynaeve 2021	Belgium	COVID-19 Ag Respi-Strip (Coris Bioconcept) Coronavirus Ag Rapid Test Cassette (Healgen Scientific)	NP	Hospitalized patients	100	RT PCR	NP
63	Nsoga 2021	Nsoga	Panbio COVID-19 Ag Rapid Test (Abbott)	OP	Hospitalized patients	402	RT-PCR	NP
64	Eleftheriou 2021	Greece	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	hospitalized pediatric patients (< 16 years old) symptomatic and high risk for infection based on regional epidemiologic data	744	RT-PCR	NP
65	Fiñana 2021	UK	Innova Rapid SARS-CoV-2 Antigen Test (Xiamen Biotime Biotechnology)	NP + OP	Adults >18 years old; asymptomatic: community setting	5504	RT-PCR	NP + OP
66	Kurihara 2021	Japan	Quick Chaser Auto SARS-CoV-2 (Mizuhomedy)	NP	community: individuals that possibly contracted SARS-Cov2; referred by clinics, health centers and healthcare workers for testing	1401	RT PCR	NP
67	Ifko 2021	Slovenia	NADAL COVID-19 Rapid Antigen Test (Nal Von Minden)	NP	Long-term healthcare facility: Elderly 65 - 95 yrs old with at least one symptom of COVID	125	RT-PCR	NP
68	Karon 2021	USA	COVID-19 Rapid Antigen Test (BD Veritor)	NP	residual phosphate buffered saline samples of symptomatic and asymptomatic patients	347	RT-PCR	NP
69	Abusrewil 2021	Libya	10 brands: Fluorecare, Espline, Rapigen, Assut, Orient Gene, AMP, Acon, Abbot, Certest Biotec, Bioperfectus	NP	community setting: clinical features suggestive of COVID-19 or a history of close contact with COVID-19 positive patients	231	RT-PCR	NP

70	Orsi 2021	Italy	FREND Antigen Test (NanoEntek)	NP	Hospitalized patients	110	RT-PCR	NP
71	Brihn 2021	USA	Sofia SARS Antigen Fluorescent Immunoassay (Quidel)	Anterior Nares	Symptomatic and asymptomatic patients	2039	RT-PCR	NP
72	Osmanodja 2021	Germany	Dräger Antigen Test SARS-CoV-2 (Dräger)	Anterior Nares	Community setting	379	RT-PCR	NP + OP
73	Bornemann 2021	Germany	Sofia SARS Antigen Fluorescent Immunoassay (Quidel)	NP	Community setting	1404	RT-PCR	NP
74	Holzner 2021	Germany	STANDARD Q COVID19 Ag (SD Biosensor)	NP	Community setting	2375	RT-PCR	NP
75	Pena 2021	Chile	STANDARD Q COVID19 Ag (SD Biosensor)	NP	Community setting	842	RT-PCR	NP
76	Donapetry 2021	Spain	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Children	440	RT-PCR	NP
77	Cento 2021	Italy	LumiraDx™ SARS-CoV-2 Antigen Test	NP	Community setting	960	RT-PCR	NP
78	Klein 2021	Germany	Panbio COVID-19 Ag Rapid Test (Abbott)	NP + MT	community: symptomatic adults and high risk contact of confirmed case in SARS-Cov-2-drive in testing center:	290	RT-PCR	NP
79	Frediani 2021	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	Anterior Nares	community: community-based and hospital based testing center: age > 7 yrs old (adults and pedia) symptomatic within 7 days from onset	341	RT-PCR	NP
80	Schuit 2021	Netherlands	COVID-19 Rapid Antigen Test (BD Veritor) Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	NP + OP	Close contacts, asymptomatic individuals requesting for a COVID-19 test	2678	RT-PCR	NP + OP
81	Wachinger	Germany	STANDARD Q COVID19 Ag (SD Biosensor)	NP	Asymptomatic patients in hospitals, presenting for elective surgeries, OPD	1596	RT-PCR	Unspecified
82	Fourati 2021	France	COVID-19 Ag Respi-Strip (Coris Bioconcept) STANDARD Q COVID19 Ag (SD Biosensor) Panbio COVID-19 Ag Rapid Test (Abbott) COVID-VIRO Antigen Rapid Test (AAZ) NG-test SARS-CoV-2 Ag (NG-Biotech) BIOSYNEX COVID-19 Ag BSS-(Biosynex SA)	NP	COVID-19 patients	626	RT-PCR	NP
83	Leli 2021	Italy	LumiraDx™ SARS-CoV-2 Antigen Test	Nasal	Hospital (presenting in emergency department)	792	RT-PCR	NP
84	Sahuquillo 2021	Spain	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Hospital setting: pediatric ER; Symptomatic children aged 0-14 yrs	357	RT-PCR	NP
85	Kanauija 2021	India	COVID-19 Ag Respi-Strip (Coris Bioconcept)	NP	hospital setting (adult communicable disease ward); symptomatic adults and asymptomatic contacts	484	RT-PCR	NP
86	Dierks 2021	Germany	LumiraDx™ SARS-CoV-2 Antigen Test	NP	Hospital setting: employee of University Medical Center	444	RT-PCR	NP
87	Jung 2021	France	BIOSYNEX COVID-19 Ag BSS (Biosynex SA)	NP	hospital setting: ER & primary pediatric care center; age < 18	308	RT-PCR	NP
88	Tsai 2021	Taiwan	Vstrip COVID-19 Antigen Rapid Test (Panion & BF Biotech)	NP	Hospital setting: COVID suspects but no mention whether symptomatic or asymptomatic	61	RT-PCR	NP

89	Jegerlehner 2021	Switzerland	Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	NP	community setting: COVID testing facility; adults>18 yrs symptomatic and those suspected of exposure to infected	1462	RT-PCR	NP
90	Thakur 2021	India	Immune-chromatographic lateral flow assay PathoCatch/ACCUCARE (Lab Care Diagnostics)	NP	Community settings (Preoperative)	677	RT-PCR	NP + OP
91	Kim 2021	South Korea	GenBody COVAG025 Rapid Antigen Test	NP	Hospital setting: patients visited or admitted in the hospital	130	RT-PCR	NP
		India				200		
92	Bruzzone 2021	Italy	STANDARD Q COVID19 Ag (SD Biosensor)	NP	Hospital setting: retrospective analysis of swab samples in laboratory	321	RT-PCR	NP
			Humasis COVID-Ag Test COVID-19 Antigen (Humasis)					
			Rapid Test Prima Professional (Prima Lab)					
			BIOCREDIT COVID-19 Ag test (RapiGEN, Inc)					
			Standard F Covid19 Ag FIA (SD Biosensor)					
			LumiraDx™ SARS-CoV-2 Antigen Test					
			FREND Antigen Test (NanoEntek)					
93	Nordgren 2021	Sweden	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Community setting: Symptomatic individuals	332	RT-PCR	NP
			Coronavirus Ag Rapid Test Cassette (Healgen Scientific)					
94	Bianco 2021	Italy	LumiraDx™ SARS-CoV-2 Antigen Test	Nasal	Hospital setting: patients in adult and pedia ER and Trained personnels	907	RT-PCR	NP
95	Kolwijck 2021	Netherlands	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Hospital setting: Trained personnel at least 16 years old	433	RT-PCR	NP and OP
96	Ford 2021	USA	Sofia SARS Antigen Fluorescent Immunoassay (Quidel)	MT	Community setting: students, faculty and employee of University	1051	RT-PCR	MT
97	Kweon 2021	Korea	AFIAS COVID-19 Ag (AFC) (Menarini; Florence, Italy)	NP	Hospital setting: Mixed COVID19 and non-COVID19 patients	322	RT-PCR	NP
			ichromaTM COVID-19 Ag (Boditech)					
98	Berger 2021	Switzerland	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Hospital setting:COVID suspects at least 16 years old consulting in the hospital	535	RT-PCR	NP
			STANDARD Q COVID19 Ag (SD Biosensor)			529		
99	Van Honacker 2021	Belgium	BIOSYNEX COVID-19 Ag BSS (Biosynex SA)	NP	Hospital setting: COVID suspect and non-COVID with other respiratory isolates	100	RT-PCR	NP
			Biotical SARS-CoV-2 Ag Card (Biotical Health)			100		
			Coronavirus AG Rapid test cassette (Zhejiang Orient Gene Biotech Co., Zhejiang, China)			98		
			Panbio COVID-19 Ag Rapid Test (Abbott)			97		
			STANDARD Q COVID19 Ag (SD Biosensor)			98		
			STANDARD Q COVID19 Ag (SD Biosensor)			4207		
100	Bouassa 2021	France	SIENNA COVID-19 Antigen Rapid Test Cassette	NP	Hospital setting: retrospective study of archived NP swabs	150	RT-PCR	NP
101	Caruana 2021	Switzerland	STANDARD Q COVID19 Ag (SD Biosensor)	NP	Hospital setting: asymptomatic adults hospitalized in medical and surgical wards	116	RT-PCR	NP
102	Baccani 2021	Italy	Lumipulse SARS-CoV-2 Antigen Kit (Fujirebio)	NP	Hospital setting: inpatients in 3 Tuscan hospitals	201	RT-PCR	NP
			Standard F Covid19 Ag FIA (SD Biosensor)			93		

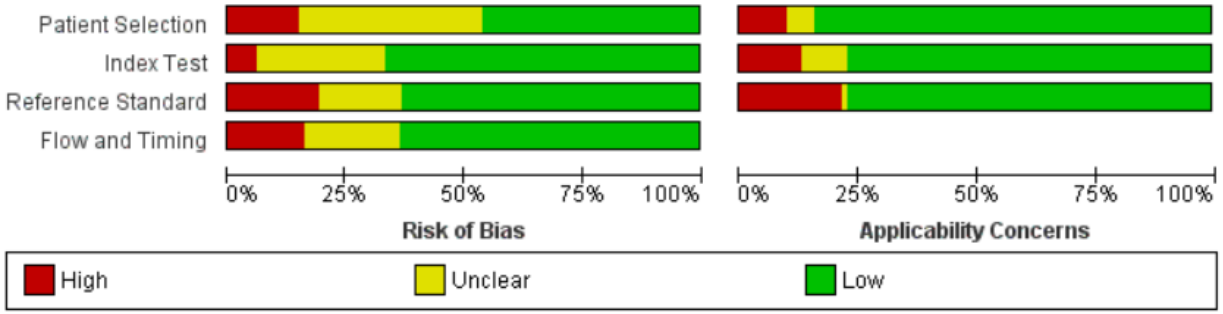
			AFIAS COVID-19 Ag (AFC) (Menarini; Florence, Italy)			81		
103	Koeleman 2021	Netherlands	Certest SARS-CoV-2 (Certest Biotec S.L., Spain)	NP and OP	Hospital setting: symptomatic ER patients, nursing home residents and Trained personnels	80	RT-PCR	NP and OP
			Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)			80		
			Romed Coronavirus Ag Rapid Test (Romed, The Netherlands)			80		
			Romed Coronavirus Ag Rapid Test (Romed, The Netherlands)			900		
104	Kruger 2021	Germany	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Community setting: patients in drive-in testing site and ambulatory testing facility	1108	RT-PCR	NP and OP
105	Denina 2021	Italy	LumiraDx™ SARS-CoV-2 Antigen Test	Nasal	Hospital setting: children admitted at the ER and hospital	191	RT-PCR	NP
107	Stokes 202109	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	Anterior nares	Hospital setting: Asymptomatic pre-surgery	997	RT-PCR	NP
107	Halfon 2021	France	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Community setting: patients screened in the laboratory	200	RT-PCR	NP
108	Paul 2021	India	VITROS Immunodiagnostic Products SARS-CoV-2 Antigen test (Ortho Clinical Diagnostics)	NP + OP	Hospital setting: symptomatic patients in OPD	148	RT-PCR	NP and OP
			Angcard® COVID-19 rapid Antigen Test kit (Angstrom® Biotech Pvt. Ltd., Alwar, Rajasthan, India)	NP				
109	Von Ahnen 2021	Germany	Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	NP	Hospital setting: screening of all employees	919	RT-PCR	NP
110	Shah 2021	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	Anterior nares	Community setting: patients recruited from community testing site	2110	RT-PCR	Anterior nares
111	McKay 2021	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	Anterior Nares	Community setting: residents and employees of nursing home	532	RT-PCR	Mixed
112	Abdelrazik 2021	Egypt	BIOCREDIT COVID-19 Ag test (RapiGEN, Inc)	NP	Patients and HCW, patient contacts	310	RT-PCR	NP
113	Albert 2020	Spain	Panbio COVID-19 Ag Rapid Test (Abbott)	NP or OP	COVID 19 test centre	497	RT-PCR	NP
114	Alemany 2020	Spain	Panbio COVID-19 Ag Rapid Test (Abbott)	NP or OP	Symptomatic patients, close contacts, preventive screening of unexposed asymptomatics	1406	RT-PCR	NP or MT
115	Asai 2021	Japan	Lumipulse SARS-CoV-2 Antigen Kit (Fujirebio)	Saliva	Suspected patients	305	RT-PCR	Saliva
116	Billaud 2020	France	Panbio COVID-19 Ag Rapid Test (Abbott)	NP or OP	Contacts	462	RT-PCR	NP or OP
117	Blairon 2020	Belgium	COVID-19 Ag Respi-Strip (Coris Bioconcept)	NP or OP	Laboratory-based	56	RT-PCR	NP
118	Bulilete 2021	Spain	Panbio COVID-19 Ag Rapid Test (Abbott)	NP	Symptomatic patients and close contacts	1369	RT-PCR	NP
119	Caputo 2021	Italy	Lumipulse SARS-CoV-2 Antigen Kit (Fujirebio)	NP	Clinical suspect, screening or contacts	4266	RT-PCR	NP
120	Cerutti 2020	Italy	STANDARD Q COVID19 Ag (SD Biosensor)	NP	Mixed	256	RT-PCR	NP
121	Chaimayo 2020	Thailand	STANDARD Q COVID19 Ag (SD Biosensor)	NP + OP	Covid-19 suspects	454	RT-PCR	NP + OP
122	Ciotti 2021	Italy	COVID-19 Ag Respi-Strip (Coris Bioconcept)	NP	Covid-19 suspects	50	RT-PCR	NP

123	Diao 2020	China	2019-nCoV Ag Fluorescence Rapid Test Kit (Bioeasy)	NP or OP	Unclear	239	RT-PCR	NP
124	Favresse 2021	Belgium	Biotical SARS-CoV-2 Ag Card (Biotical Health) Panbio COVID-19 Ag Rapid Test (Abbott) Coronavirus Ag Rapid Test Cassette (Healgen Scientific) Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics) VITROS Immunodiagnostic Products SARS-CoV-2 Antigen test (Ortho Clinical Diagnostics)	NP	Symptomatic and asymptomatic subjects	188	RT-PCR	NP
125	Fenollar 2020	France	Panbio COVID-19 Ag Rapid Test (Abbott)	NP or OP	Symptomatic patients Asymptomatic contacts	182 159	RT-PCR	NP
126	Fourati 2020	France	COVID-19 Ag Respi-Strip (Coris Bioconcept) STANDARD Q COVID19 Ag (SD Biosensor) Panbio COVID-19 Ag Rapid Test (Abbott) BIOSYNEX COVID-19 Ag BSS (Biosynex SA) COVID-VIRO Antigen Rapid Test (AAZ)	NP or OP	Laboratory-based	629 628 632 634 632	RT-PCR	NP
127	Gili 2021	Italy	Lumipulse SARS-CoV-2 Antigen Kit (Fujirebio)	NP	Screening population	1340	RT-PCR	NP
128	Gremmels 2020	Netherlands	Panbio COVID-19 Ag Rapid Test (Abbott)	NP or OP	COVID-19 test centre	1367	RT-PCR	NP
129	Gupta 2020	India	STANDARD Q COVID19 Ag (SD Biosensor)	NP or OP	COVID-19 test centre	330	RT-PCR	NP + OP
130	Herrera 2020	USA	Sofia SARS Antigen Fluorescent Immunoassay (Quidel)	NP	Symptomatic and asymptomatic healthcare workers	1172	RT-PCR	NP
131	Hirotsu 2020	Japan	Lumipulse SARS-CoV-2 Antigen Kit (Fujirebio)	NP	Hospital setting: infected and noninfected patients	313	RT-PCR	NP
132	Homza 2021	Czech Republic	SARS-CoV-2 Antigen Rapid Test Kit (JOYSBIO [Tianjin Biotechnology Co., China]) Ecotest COVID-19 Antigen Rapid Test (Assure Tech, Hangzhou, China) STANDARD Q COVID19 Ag (SD Biosensor) Immupass VivaDiag SARS-CoV-2 Ag Rapid Test (VivaChek Biotech [Hangzhou] Co., China) ND COVID-19 Ag test (NDFOS, Eumseong, Korea)	NP	COVID-19 test centre	225 179 72 268 91	RT-PCR, viral culture	NP
133	James 2021	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	NP	Symptomatic and asymptomatic patients	2339	RT-PCR	Nasal swab
134	Kruger 2020	Germany	2019-nCoV Ag Fluorescence Rapid Test Kit (Bioeasy) COVID-19 Ag Respi-Strip (Coris Bioconcept) STANDARD Q COVID19 Ag (SD Biosensor)	NP + OP	COVID-19 test centre	712 409 1216	RT-PCR	NP + OP
135	Kruttgen 2020	Germany	Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	NP	Admitted patients in the hospital	150	RT-PCR	NP
136	Lambert-Niclot 2020	France	COVID-19 Ag Respi-Strip (Coris Bioconcept)	NP or OP	Laboratory-based	138	RT-PCR	NP
137	Linares 2020	Spain	Panbio COVID-19 Ag Rapid Test (Abbott)	NP or OP	Hospital A&E	255	RT-PCR	NP
138	Liotti 2020	Italy	Standard F Covid19 Ag FIA (SD Biosensor)	NP or OP	Laboratory-based	359	RT-PCR	NP
139	Mak 2020	China	BIOCREDIT COVID-19 Ag test (RapiGEN, Inc)	Mixed respiratory samples	COVID-confirmed patients	368	RT-PCR	d respiratory sar
140	Mertens 2020	Belgium	COVID-19 Ag Respi-Strip (Coris Bioconcept)	NP or OP	Laboratory-based	328	RT-PCR	NP

141	Mockel 2021	Germany	Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)	NP + OP	COVID19 suspect adults in the emergency department	271	RT-PCR	NP
142	Muhi 2021	Australia	Panbio COVID-19 Ag Rapid Test (Abbott)	Nasal	Hospital	2602	RT-PCR + Viral culture	NP + OP
143	Nagura-Ikeda 2020	Japan	Espline SARS-CoV-2 (Fujirebio)	Saliva	Mixed	103	RT-PCR	Saliva
144	Nalumansi 2020	Uganda	STANDARD Q COVID19 Ag (SD Biosensor)	NP	COVID-19 suspects and low-risk volunteers	262	RT-PCR	NP
145	Nash 2020	USA	E25Bio Rapid Diagnostic Test (E25Bio)	NP or OP	Laboratory-based	190	RT-PCR	NP + OP
146	Osterman 022021	Germany	STANDARD Q COVID19 Ag (SD Biosensor)	NP + OP	Symptomatic patients in the ER	681	RT-PCR	NP + OP
			Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)			771		
147	Porte 2020a	Chile	2019-nCoV Ag Fluorescence Rapid Test Kit (Bioeasy)	NP + OP	Hospital A&E	127	RT-PCR	NP + OP
148	Porte 2020b	Chile	Sofia SARS Antigen Fluorescent Immunoassay (Quidel)	NP + OP	COVID-19 test centre	64	RT-PCR	NP + OP
			Standard F Covid19 Ag FIA (SD Biosensor)	NP + OP	COVID-19 test centre	64	RT-PCR	
149	Pray 2021	USA	Sofia SARS Antigen Fluorescent Immunoassay (Quidel)	Anterior Nares	students, faculty & staff of university campus	1098	RT-PCR	Anterior Nares
150	Prince-Guerra 2021	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	Anterior Nares	10 years and older receiving testing for COVID 19	4904	RT-PCR	NP
151	Ristic 2021	Serbia	STANDARD Q COVID19 Ag (SD Biosensor)	NP	triage ambulance of primary and tertiary outpatients healthcare facility; 14 - 91 yrs old	120	RT-PCR	NP
152	Rottenstreich 2021	Israel	NowCheck COVID-19 Ag Test (Bionote)	NP	Asymptomatic women admitted for delivery	1326	RT-PCR	NP
153	Schildgen 2020	Germany	BIOCREDIT COVID-19 Ag test (RapiGEN, Inc)	Mixed	Laboratory based: specimens with confirmed PCR results	73	RT-PCR	Mixed
			Panbio COVID-19 Ag Rapid Test (Abbott)					
			Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)					
154	Scohy 2020	Belgium	COVID-19 Ag Respi-Strip (Coris Bioconcept)	NP	Laboratory-based: NP specimen for COVID testing with available data on symptomatology of some specimen	148	RT-PCR	NP
155	Seitz 2021	Austria	COVID- 19 Antigen Test Cassette [hypersensitive colloidal gold] (Xiamen Zhongsheng Langjie Biotechnology Co., Ltd)	Saliva	healthy citizens of Vienna, Austria were invited to participate in a vo-luntary SARS-CoV-2 mass screening	40	RT-PCR	gargle sample
156	Shrestha 2020	Nepal	BIOCREDIT COVID-19 Ag test (RapiGEN, Inc)	NP or OP	close contacts of confirmed COVID 19	113	RT-PCR	NP
157	Takeda 2020	Japan	Espline SARS-CoV-2 (Fujirebio)	NP or OP	Laboratory-based: specimens for COVID testing	162	RT-PCR	NP
158	Turcato 2020	Italy	STANDARD Q COVID19 Ag (SD Biosensor)	NP	ER consults (COVID related and non-COVID complains) and contacts of COVID infected persons	3410	RT-PCR	NP
159	Uwamino 2021	Japan	Espline SARS-CoV-2 (Fujirebio)	NP and saliva	Adults for COVID testing	117	RT-PCR	NP and saliva

160	Veyrenche 2020	France	COVID-19 Ag Respi-Strip (Coris Bioconcept)	NP or OP	Inpatients, symptomatic adults and healthcare worker	65	RT-PCR	NP
161	Weitzel 2020	Chile	BIOCREDIT COVID-19 Ag test (RapiGEN, Inc)	NP + OP	symptomatic individuals	109	RT-PCR	NP + OP
			StrongStep Rapid Antigen Test (Liming)			19		
			Huaketai SARS-CoV-2 Rapid Antigen Test (Savant)			109		
			2019-nCoV Ag (Shenzhen Bioeasy Biotech)			111		
			COVID-19 Rapid Antigen Test (BD Veritor)			251		
162	Young 2020	USA	COVID-19 Rapid Antigen Test (BD Veritor)	NP or OP	18 years old and above with symptoms	251	RT-PCR	NP or OP
163	Pilarowski 2020	USA	BinaxNOW COVID-19 Antigen Card (Abbott)	Anterior Nares	symptomatic and asymptomatic individuals	3302	RT-PCR	Anterior Nares
164	PHE 2020	United Kingdom	Innova Rapid SARS-CoV-2 Antigen Test (Xiamen Biotime Biotechnology)	NP + OP	Hospital in-patient; contacts; patients in COVID-19 test center	3168	RT-PCR	NP + OP

Appendix 4. Risk of Bias and Applicability Concerns of Included Studies



Appendix 5. Characteristics of Ongoing Studies

NCT Number	Title	Population	Interventions	Comparator	Outcomes
NCT04878068	Study to Evaluate the Performance of the Therma COVID-19 Rapid Antigen Test for Detection of SARS-CoV-2	12 years old and above aat COVID-19 testing centre	Device: Theram COVID-19 Rapid Antigen Test; Saliva sample	RT PCR	Establish Performance of Therma COVID-19 Rapid Antigen Test, Participant Feedback, User Feedback
NCT04750629	Clinical Evaluation of a Point-of-Care (POC), COVID-19 Rapid Antigen Test (CoviDx™)	1 year old and above suspected of SARS-Cov-2	Device: POC CoviDx™ Rapid Antigen Test	SARS-Cov-2 RT-PCR	Sensitivity of SARS-CoV-2 antigen in nasal swab as compared to a high-sensitive SARS-CoV-2 RT-PCR granted Emergency Use Authorization (EUA) by the FDA
NCT05045846	Diagnostic Accuracy of Rapid Antigen Test Based on Anterior Nasal Swab Compared With RT-PCR for SARS-CoV-2 Detection.	18 years old and above who have self-booked appointment at COVID testing centre	Rapid Antigen Test Based on Anterior Nasal Swab	RT-PCR	Accuracy of anterior nasal swab in rapid antigen (Ag)-tests
NCT04733170	Clinical Performance Evaluation of KnowNow SARS-CoV-2 Test for the Detection of COVID-19 Antigen	18 years old and above suspected with COVID-19	Diagnostic Test: KnowNow SARS-CoV-2 Rapid Antigen Test	RT-PCR	Assess clinical diagnostic performance of the KnowNow SARS-CoV-2 Rapid Antigen Test, Efficacy to assess the test compared to the reference test method; Usability Questionnaire to evaluate the use of the test with 2 saliva collection methods
NCT04689399	Sensitivity and Specificity of SARS-CoV-2 Rapid Antigen Test Compared to RT-PCR Test	18 years old above with appointment at COVID-a9 testing center	Diagnostic Test: Standard Q COVID-19 Ag - test, produced by SD Biosensor INC.	RT PCR	Sensitivity and specificity of the rapid antigen test of COVID-19 Economic analyses PCR analysis on nasopharyngeal swabs
NCT04716088	Rapid Antigen Testing for SARS-CoV-2 Among Healthcare Workers to Prevent Spread of COVID-19	18 years old and above healthcare workers	Repeated Rapid antigen test for SARS CoV2	RT PCR	SARS CoV2 infection
NCT04894760	Evaluation of a COVID-19 Rapid Diagnostic Test in ER Departments in Mexico: a Multi-center Study	18 years old and above with respiratory symptoms visiting the ER	Diagnostic Test: Rapid Antigen Test (PanBio Ag test)	RT PCR	Diagnostic accuracy
NCT04403906	Somerset and South Essex Coronavirus Antigen Testing	18 years old and above with clinical indication for COVID testing	Diagnostic Test: PCL COV05 - COVID 19 Ag Rapid FIA test (Rapid Antigen Test)	RT PCR	To compare the result of SARS-COV2 PCR test to PCL rapid antigen test Number of technically failed samples due to test issues. Time taken for PCL Antigen test result
NCT04839094	Dry Versus Wet Nasopharyngeal Rapid Test for the Detection of COVID-19.	18 years old and above hospitalized with a confirmed SARS-Cov-2 infection	Diagnostic Test: rapid antigen testing; nasopharyngeal vs saliva samples	RT PCR	Diagnostic assessment Limit of detection determination.
NCT04665193	An Approach to Screening for COVID-19 at Vancouver Airport	Adults with ticket to board a flight from Vancouver International Airport	Rapid Antigen Test	none	COVID-19 status; effectiveness and feasibility of rapid antigen test in airport screening
NCT05074017	COVAG - Covid-19 Antigen Study - the Diagnostic Efficacy of SARS-CoV-2 Rapid Detection Tests	18 years old and above at testing centers in whom RT-PCR testing for SARS-CoV-2 is medically indicated or requested	2 rapid antigen tests	RT PCR	Sensitivity of the rapid antigen tests

NCT Number	Title	Population	Interventions	Comparator	Outcomes
NCT04568356	A Clinical Evaluation of COVID-19 Rapid Point of Care Antigen Tests	18 years old and above suspected with COVID	Diagnostic Test: Direct Antigen Tests for COVID-19; nasopharyngeal, nasal and saliva samples	RT PCR	Percent Positive Agreement and Negative Percent Agreement
NCT04896710	COVID-19 Rapid Testing for Self-Administration Among an Asymptomatic Sample	16 Years to 80 Years Asymptomatic	Device: SD Biosensor RAT; self-administered	professional administered SD Biosensor RAT	Concordance Ability of rapid antigen test to detect COVID-19 positive Acceptability of self-administration
NCT04977050	The Role of Frequent Point-of-care Molecular Workplace Surveillance for Miners	18 Years and above miners	Diagnostic Test: Quidel quickvue antigen test for COVID-19	RT PCR	Screening test (molecular) Diagnostic test (RT-PCR) Serologic antibody test
NCT05047900	The Impact of SARS-CoV-2 Rapid Antigen Testing Kit Screening in Bangkok Community	10 years and older in any Bangkok community	Routine Use of Rapid antigen testing kit	Did not routinely use Rapid antigen testing kit	Incidence rate of COVID19 infection Incidence rate of severe COVID19 infection Incidence of COVID19 infection in COVID19 vaccinated and unvaccinated people sensitivity and specificity of rapid antigen testing kit
NCT04808921	Performance Evaluation of SARS-COV-2 (Covid-19) Antigen Rapid Test	Child and adults clinically suspected of COVID 19	Diagnostic Test: Xiamen Wiz Biotech Co., Ltd. SARS-CoV-2 Antigen Rapid Test	RT PCR	Percent Positive Agreement and Negative Percent Agreement
NCT04348864	COVID-19 Diagnostic Self-testing Using Virtual Point-of-care	18 years old and above suspected or clinically diagnosed with COVID	Diagnostic Test: COVID-19 Antigen/Antibody Rapid Testing, mobile device image capture and telemedicine support Self-test interpretation	RT PCR; Expert Clinical Interpretation of results	Clinical accuracy of the antibody and antigen rapid tests compared to LAMP/PCR-based test result Clinical accuracy of the antibody and antigen rapid tests based on Clinical diagnosis Self-test interpretation of result vs expert clinical image interpretation of result Ease of self-testing procedure
NCT04805840	Sensitivity of Frequent SARS-CoV-2 (COVID-19) Rapid Antigen Testing Regimen	18 years old and above healthy volunteers	Frequent testing of CoV-SCAN rapid COVID-19 antigen test	RT PCR	Sensitivity of CoV-SCAN daily testing regimen Specificity of CoV-SCAN daily testing regimen Time from CoV-SCAN positive to PCR positive result
NCT04898127	Antigen Rapid Test Screening to Prevent SARS-CoV-2 Transmission (COVID-19) at Mass Gathering Events.	18 - 45 years old volunteers	Diagnostic Test: SARS-CoV-2 antigen rapid test Rapid test before access to mass gathering event (concert), provided the test result is negative.	RT PCR	SARS-CoV-2 infection Clinical COVID-19 disease Hospital admissions False positive rapid test
NCT04877002	Performance Study of SONA Saliva C-19 Rapid Test	18 years old and above presenting with COVID symptoms at the ER	Diagnostic Test: Sona Saliva C-19 Rapid Test	RT PCR	Percent Positive Agreement and Negative Percent Agreement
NCT04926779	Open Label, Single-Center Study Utilizing BIOZEK COVID-19 Antigen Rapid Test	18 years old and above with COVID-19 symptoms and close contacts	Diagnostic Test: Biozek Covid-19 Antigen Rapid Test (Saliva)	RT PCR	Sensitivity and Specificity of Biozek Covid-19 Antigen Rapid Test (Saliva) Sensitivity and Specificity of Biozek Covid-19 Antigen Rapid Test (Nasopharyngeal Swab)
NCT04805892	Open Label, Single-Center Study Utilizing BIOZEK COVID-19 Antigen Rapid Test.	18 years old and above with COVID-19 symptoms and close contacts	Diagnostic Test: BIOZEK COVID-19 Antigen Rapid Test; professional vs sel-collected	RT PCR	Sensitivity and Specificity of BIOZEK COVID-19 Antigen Rapid Test on a sample collected by healthcare professionals. Sensitivity and Specificity of BIOZEK COVID-19 Antigen Rapid Test on self-collected sample.

NCT Number	Title	Population	Interventions	Comparator	Outcomes
NCT04889365	COVID-19 Antigen Rapid Test Kit	18 years old and above with or without COVID-19 symptoms	Diagnostic Test: SG Diagnostics COVID-19 Antigen Rapid Test Kit	Diagnostic Test: Polymerase chain reaction (PCR) test	Sensitivity of SG Diagnostics COVID-19 Antigen Rapid Test Kit Specificity of SG Diagnostics COVID-19 Antigen Rapid Test Kit
NCT04872075	Study on Prevention of SARS-CoV-2 Transmission During a Large Indoor Gathering Event	18 to 45 years old healthy volunteers	Concert Attendees; Diagnostic Test: Rapid nasopharyngeal antigen test for Sars-Cov-2 Diagnostic Test: Saliva Sample	RT PCR; People staying at home	Number of participants with a positive salivary RT-PCR at day 7 after the date of the concert Number of participants in each group with a positive salivary RT-PCR the day of the concert Molecular analysis of transmission cluster

Appendix 6. GRADE Evidence Profile

A. OVERALL

Should rapid antigen test be used to diagnose COVID-19 in patients suspected to have COVID-19?
Patient or population: patients suspected to have COVID-19
Pooled sensitivity: 0.71 (95% CI: 0.68 to 0.73)
Pooled specificity: 0.99 (95% CI: 0.99 to 1.00)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	164 studies (43,943 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Not serious	None	36 (34 to 37)	71 (68 to 73)	107 (102 to 110)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having COVID-19)								14 (13 to 16)	29 (27 to 32)	43 (40 to 48)	
True negatives (patients without COVID-19)	164 studies (191,573 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Not serious	None	945 (943 to 946)	896 (894 to 896)	846 (844 to 847)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having COVID-19)								5 (4 to 7)	4 (4 to 6)	4 (3 to 6)	

CI: confidence interval

Explanations
[a] High and unclear risk on all domains (patient selection, conduct of index text and reference standard and patient flow and timing)
[b] High heterogeneity across studies (I^2 = 99% [99-100%])

B. SYMPTOMATIC

Should rapid antigen test be used to diagnose COVID-19 in symptomatic individuals suspected of COVID-19?
Patient or population: patients suspected to have COVID-19
Pooled sensitivity: 0.74 (95% CI: 0.71 to 0.78)
Pooled specificity: -

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	79 studies 45523 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[a,b]	Not serious	none	37 (36 to 39)	74 (71 to 78)	111 (107 to 117)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having COVID-19)								13 (11 to 14)	26 (22 to 29)	39 (33 to 43)	
True negatives (patients without COVID-19)	0 studies patients							0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	-
False positives (patients incorrectly classified as having COVID-19)								950 (950 to 950)	900 (900 to 900)	850 (850 to 850)	

Explanations
[a] Unclear and high risk of bias in all domains (e.g. patient selection, conduct of index test and reference stand, and patient flow)
[b] High heterogeneity (different timing of testing, test brands, specimen type)

Should rapid antigen test be used to diagnose COVID-19 in symptomatic individuals suspected of COVID-19?
Patient or population: symptomatic individuals suspected of COVID-19
Setting:
New test: Rapid antigen test |**Cut-off value**:
Pooled sensitivity:0.74 (95% CI: 0.71 to 0.78) | **Pooled specificity**: not calculated

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 5% Typically seen in	Prevalence 10% Typically seen in	Prevalence 15% Typically seen in		
True positives	**37** (36 to 39)	**74** (71 to 78)	**111** (107 to 117)	45523 (79)	⊕⊕◯◯ **Low**[a,b]
False negatives	**13** (11 to 14)	**26** (22 to 29)	**39** (33 to 43)		
True negatives					-
False positives					

CI: confidence interval
Explanations
a. Unclear and high risk of bias in all domains (e.g. patient selection, conduct of index test and reference stand, and patient flow)
b. High heterogeneity (I^2 = 99% [99-100%])

C. ASYMPTOMATIC

Should rapid antigen test be used to diagnose COVID-19 in asymptomatic individuals suspected of COVID-19?
Patient or population: patients suspected to have COVID-19
Pooled sensitivity: 0.56 (95% CI: 0.51 to 0.62)
Pooled specificity: -

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	55 studies 72858 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Not serious	None	28 (26 to 31)	56 (51 to 62)	84 (77 to 93)	⊕◯◯◯ Very Low
False negatives (patients incorrectly classified as not having COVID-19)								22 (19 to 24)	44 (38 to 49)	66 (57 to 73)	

Explanations
[a] High and unclear risk of bias in all domains (e.g. patient selection, conduct of index test and reference standard, and patient flow and timing
[b] High heterogeneity (different test brands, specimen types, timing of testing) (I^2 = 99% [99-100%])

Should rapid antigen test be used to diagnose COVID-19 in asymptomatic individuals suspected of COVID-19?
Patient or population: asymptomatic individuals suspected of COVID-19
Setting:
New test: rapid antigen test |**Cut-off value**: variable
Pooled sensitivity:0.56 (95% CI: 0.51 to 0.62) | **Pooled specificity**: not computed

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence5% Typically seen in	Prevalence10% Typically seen in	Prevalence15% Typically seen in		
True positives	**28** (26 to 31)	**56** (51 to 62)	**84** (77 to 93)	72858 (55)	⊕⊕◯◯ **Low**[a,b]
False negatives	**22** (19 to 24)	**44** (38 to 49)	**66** (57 to 73)		
True negatives					-
False positives					

CI: confidence interval

Explanations
[a] High and unclear risk of bias in all domains (e.g. patient selection, conduct of index test and reference standard, and patient flow and timing
[b] High heterogeneity (I^2 = 99% [99-100%])

D. EARLY PHASE

Should rapid antigen test be used to diagnose COVID-19 in in the early phase of illness in individuals suspected of COVID-19?
Patient or population: patients suspected to have COVID-19
Pooled sensitivity: 0.79 (95% CI: 0.75 to 0.82)
Pooled specificity: -

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	54 studies 28591 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Not serious	None	40 (38 to 41)	79 (75 to 82)	119 (112 to 123)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having COVID-19)								10 (9 to 12)	21 (18 to 25)	31 (27 to 38)	

Explanations
[a] High and unclear risk of bias in all domains (e.g. patient selection, conduct of index test and reference standard, and patient flow and timing
[b] High heterogeneity (different test brands, symptom status, specimen) (I^2 = 99% [99-100%])

Should rapid antigen test be used to diagnose COVID-19 in in the early phase of illness in individuals suspected of COVID-19??
Patient or population: in the early phase of illness in individuals suspected of COVID-19?
Setting:
New test: rapid antigen test |**Cut-off value**: variable
Pooled sensitivity:0.79 (95% CI: 0.75 to 0.82) | **Pooled specificity**: not calculated

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence5% Typically seen in	Prevalence10% Typically seen in	Prevalence15% Typically seen in		
True positives	**40** (38 to 41)	**79** (75 to 82)	**119** (112 to 123)	28591 (54)	⊕⊕◯◯ **Low**[a,b]
False negatives	**10** (9 to 12)	**21** (18 to 25)	**31** (27 to 38)		
True negatives				(0)	-
False positives					

CI: confidence interval

Explanations
[a] High and unclear risk of bias in all domains (e.g. patient selection, conduct of index test and reference standard, and patient flow and timing
[b] High heterogeneity (I^2 = 99% [99-100%])

E. SALIVA SPECIMEN

Should rapid antigen test using saliva as specimen be used to diagnose COVID-19 in individuals suspected of COVID-19?
Patient or population: patients suspected to have COVID-19
Pooled sensitivity: 0.57 (95% CI: 0.22 to 0.86)
Pooled specificity: -

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	7 studies 6148 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Serious[c]	None	28 (11 to 43)	57 (22 to 86)	85 (33 to 129)	⊕◯◯◯ Very low
False negatives (patients incorrectly classified as not having COVID-19)								22 (7 to 39)	43 (14 to 78)	65 (21 to 117)	

Explanations
[a] High and unclear risk of bias in all domains (e.g. patient selection, conduct of index test and reference standard, and patient flow and timing)
[b] High heterogeneity (I^2 = 99% [99-100%])
[c] Very wide estimates

Should rapid antigen test using saliva as specimen be used to diagnose COVID-19 in individuals suspected of COVID-19?
Patient or population: individuals suspected of COVID-19
Setting:
New test: rapid antigen test – saliva-based |**Cut-off value**: variable
Pooled sensitivity:0.57 (95% CI: 0.22 to 0.86)|**Pooled specificity**: not calculated

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence5% Typically seen in	Prevalence10% Typically seen in	Prevalence15% Typically seen in		
True positives	**28** (11 to 43)	**57** (22 to 86)	**85** (33 to 129)	6148 (7)	⊕◯◯◯ **Very low**[a,b,c]
False negatives	**22** (7 to 39)	**43** (14 to 78)	**65** (21 to 117)		
True negatives					
False positives					

CI: confidence interval
Explanations
a. High and unclear risk of bias in all domains (e.g. patient selection, conduct of index test and reference standard, and patient flow and timing)
b. High heterogeneity (I^2 = 99% [99-100%])
c. Very wide estimates

F. REPEAT TESTING

Should repeat testing using rapid antigen tests be used to diagnose COVID-19 in individuals suspected of COVID-19?
Patient or population: patients suspected to have COVID-19
Pooled sensitivity: 0.63 to 0.81
Pooled specificity: -

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	2 studies 4752 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Serious[c]	None	32 to 41	63 to 81	95 to 122	⊕◯◯◯ Very low
False negatives (patients incorrectly classified as not having COVID-19)								9 to 18	19 to 37	28 to 55	

Explanations
[a] Unclear risk of bias in patient selection and conduct of reference standard
[b] Heterogenous studies with inconsistent sensitivity values (I^2 = 99% [99-100%])
[c] Wide estimates seen especially in the study of Mckay et al.

Should repeat testing using rapid antigen tests be used to diagnose COVID-19 in individuals suspected of COVID-19?
Patient or population: individuals suspected of COVID-19
Setting:
New test: repeat antigen testing |**Cut-off value**:
Range of sensitivities:0.63 to 0.81| **Range of specificities** not calculated

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence5% Typically seen in	Prevalence10% Typically seen in	Prevalence15% Typically seen in		
True positives	32 to 41	63 to 81	95 to 122	4752 (2)	⊕◯◯◯ **Very low**[a,b,c]
False negatives	9 to 18	19 to 37	28 to 55		
True negatives	0 to 0	0 to 0	0 to 0	(0)	-
False positives	950 to 950	900 to 900	850 to 850		

CI: confidence interval

Explanations
[a] Unclear risk of bias in patient selection and conduct of reference standard
[b] Heterogenous studies with inconsistent sensitivity values
[c] Wide estimates seen especially in the study of Mckay et al.

G. CHILDREN

Should rapid antigen test be used to diagnose COVID-19 in children suspected of COVID-19?
Patient or population: patients suspected to have COVID-19
Pooled sensitivity: 0.79 (95% CI: 0.70 to 0.86)
Pooled specificity: 0.99 (95% CI: 0.96 to 1.00)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	11 studies 5101 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Not serious	None	40 (35 to 43)	79 (70 to 86)	119 (105 to 129)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having COVID-19)								10 (7 to 15)	21 (14 to 30)	31 (21 to 45)	
True negatives (patients without COVID-19)	0 studies patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Not serious	Not serious	None	945 (916 to 949)	896 (868 to 899)	846 (819 to 849)	⊕⊕⊕◯ Moderate
False positives (patients incorrectly classified as having COVID-19)								5 (1 to 34)	4 (1 to 32)	4 (1 to 31)	

Explanations
[a] High and unclear risk of bias in all domains (e.g. patient selection, conduct of index test and reference standard, and patient flow and timing)
[b] High heterogeneity (I^2 = 99% [99-100%])

Should rapid antigen test be used to diagnose COVID-19 in children suspected of COVID-19?
Patient or population: children suspected of COVID-19
Setting:
New test: rapid antigen tests |**Cut-off value**:
Pooled sensitivity:0.79 (95% CI: 0.70 to 0.86)|**Pooled specificity**:0.99 (95% CI: 0.96 to 1.00)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence5% Typically seen in	Prevalence10% Typically seen in	Prevalence15% Typically seen in		
True positives	**40** (35 to 43)	**79** (70 to 86)	**119** (105 to 129)	5101 (11)	⊕⊕◯◯ **Low**[a,b]
False negatives	**10** (7 to 15)	**21** (14 to 30)	**31** (21 to 45)		
True negatives	**945** (916 to 949)	**896** (868 to 899)	**846** (819 to 849)	5101 (11)	⊕⊕⊕◯ **Moderate**[a]
False positives	**5** (1 to 34)	**4** (1 to 32)	**4** (1 to 31)		

CI: confidence interval

Explanations
[a] High and unclear risk of bias in all domains (e.g. patient selection, conduct of index test and reference standard, and patient flow and timing)
[b] High heterogeneity

H. OUTBREAK SETTINGS

Should rapid antigen test be used to diagnose COVID-19 in individuals suspected of COVID-19 during outbreaks?
Patient or population: individuals suspected to have COVID-19 (includes both symptomatic and asymptomatic patients)
Range of sensitivity: 0.14 to 0.89
Range of specificity: 0.88 to 1.0

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	3 studies (398 patients)	Cross-sectional (cohort type accuracy study)	Very serious[a]	Not serious	Serious[b]	Serious[c]	None	7 to 45	14 to 89	21 to 134	⊕◯◯◯ Very low
False negatives (patients incorrectly classified as not having COVID-19)								5 to 43	11 to 86	16 to 129	
True negatives (patients without COVID-19)	3 studies (398)	Cross-sectional (cohort type accuracy study)	Very serious[a]	Not serious	Serious[b]	Not serious	None	836 to 950	792 to 900	748 to 850	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having COVID-19)								0 to 114	0 to 108	0 to 102	

CI: confidence interval

Explanations
[a] Majority of included studies have high risk of bias most notably in the patient selection, conduct of reference standard, and patient flow and timing
[b] High heterogeneity across studies (different timing of testing, test brands, specimen type) - I^2 = 99%
[c] Wide confidence intervals

Should rapid antigen test be used to diagnose COVID-19 in asymptomatic individuals during outbreaks?
Patient or population: asymptomatic individuals in an outbreak setting
Range sensitivity: 0.64 to 0.92
Range specificity: 0.92 to 0.98

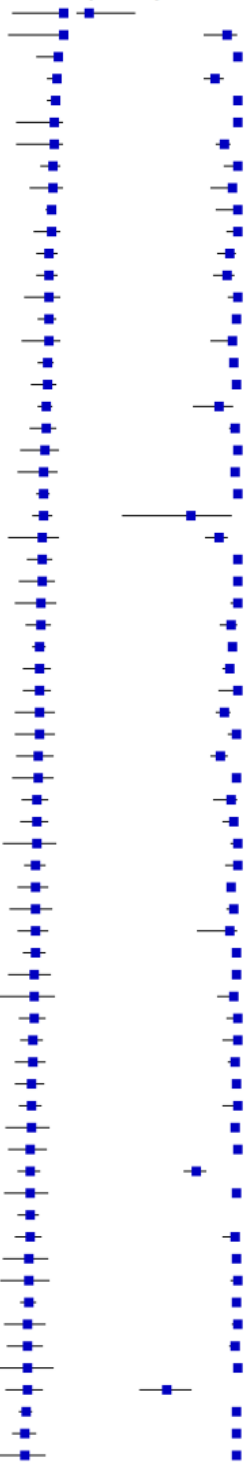
Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	2 studies (1,127 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Serious[c]	None	32 to 46	64 to 92	96 to 138	⊕◯◯◯ VeryLow
False negatives (patients incorrectly classified as not having COVID-19)								4 to 18	8 to 36	12 to 54	
True negatives (patients without COVID-19)	2 studies (1,127 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Not serious	None	874 to 931	828 to 882	782 to 833	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having COVID-19)								19 to 76	18 to 72	17 to 68	

CI: confidence interval

Explanations
[a] Unclear issues on patient selection domain
[b] High heterogeneity across studies (different test brands, different timing of testing)
[c] few studies, wide confidence interval

Appendix 7. Forest Plots

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Schildgen 2020 [C]	10	12	0	1	1.00 [0.69, 1.00]	0.08 [0.00, 0.36]
Matsuda 2021 [B]	9	2	0	31	1.00 [0.66, 1.00]	0.94 [0.80, 0.99]
Cassuto 2021	31	0	1	202	0.97 [0.84, 1.00]	1.00 [0.98, 1.00]
Courtellemont 2020	97	20	4	127	0.96 [0.90, 0.99]	0.86 [0.80, 0.91]
Pilarowski 2021 [C]	124	1	6	540	0.95 [0.90, 0.98]	1.00 [0.99, 1.00]
Van Der Moeren 202105	16	0	1	334	0.94 [0.71, 1.00]	1.00 [0.99, 1.00]
Denina 2021	16	14	1	160	0.94 [0.71, 1.00]	0.92 [0.87, 0.96]
Porte 2020a	77	0	5	45	0.94 [0.86, 0.98]	1.00 [0.92, 1.00]
Porte 2020b [A]	30	1	2	31	0.94 [0.79, 0.99]	0.97 [0.84, 1.00]
Alemany 2020	388	0	31	27	0.93 [0.90, 0.95]	1.00 [0.87, 1.00]
Orsi 2021	50	0	4	56	0.93 [0.82, 0.98]	1.00 [0.94, 1.00]
Bachman 2021 [D]	84	4	8	78	0.91 [0.84, 0.96]	0.95 [0.88, 0.99]
Bachman 2021 [C]	84	5	8	72	0.91 [0.84, 0.96]	0.94 [0.85, 0.98]
Nikolai 2021 [B]	31	0	3	62	0.91 [0.76, 0.98]	1.00 [0.94, 1.00]
Pollock 202104	116	1	12	376	0.91 [0.84, 0.95]	1.00 [0.99, 1.00]
Porte 2020b [B]	29	1	3	31	0.91 [0.75, 0.98]	0.97 [0.84, 1.00]
Turcato 2021 [A]	152	20	17	802	0.90 [0.84, 0.94]	0.98 [0.96, 0.99]
Osmanodja 2021	62	1	7	203	0.90 [0.80, 0.96]	1.00 [0.97, 1.00]
Bianco 2021	176	4	21	30	0.89 [0.84, 0.93]	0.88 [0.73, 0.97]
Klein 2021	66	3	8	189	0.89 [0.80, 0.95]	0.98 [0.96, 1.00]
Kurihara 2021	32	0	4	825	0.89 [0.74, 0.97]	1.00 [1.00, 1.00]
Jung 2021	29	4	4	271	0.88 [0.72, 0.97]	0.99 [0.96, 1.00]
Stokes 202103 [B]	268	2	37	1334	0.88 [0.84, 0.91]	1.00 [0.99, 1.00]
Stokes 202103 [A]	121	2	17	5	0.88 [0.81, 0.93]	0.71 [0.29, 0.96]
Ifko 2021	20	12	3	90	0.87 [0.66, 0.97]	0.88 [0.80, 0.94]
Kruger 2021	79	1	12	620	0.87 [0.78, 0.93]	1.00 [0.99, 1.00]
Kolwijck 2021 [A]	39	0	6	388	0.87 [0.73, 0.95]	1.00 [0.99, 1.00]
Nikolai 2021 [A]	31	0	5	96	0.86 [0.71, 0.95]	1.00 [0.96, 1.00]
Bachman 2021 [B]	79	3	13	75	0.86 [0.77, 0.92]	0.96 [0.89, 0.99]
Cento 2021	297	17	50	596	0.86 [0.81, 0.89]	0.97 [0.96, 0.98]
Chiu 2021 [A]	64	14	11	260	0.85 [0.75, 0.92]	0.95 [0.92, 0.97]
Weitzel 2020 [D]	68	0	12	31	0.85 [0.75, 0.92]	1.00 [0.89, 1.00]
Kahn 2021	34	17	6	192	0.85 [0.70, 0.94]	0.92 [0.87, 0.95]
Lindner 202105 [B]	34	1	6	105	0.85 [0.70, 0.94]	0.99 [0.95, 1.00]
Shaikh 2021	39	16	7	137	0.85 [0.71, 0.94]	0.90 [0.84, 0.94]
Schuit 2021 [A]	32	1	6	180	0.84 [0.69, 0.94]	0.99 [0.97, 1.00]
Homza 2021 [B]	72	2	14	46	0.84 [0.74, 0.91]	0.96 [0.86, 0.99]
Bachman 2021 [A]	75	2	15	77	0.83 [0.74, 0.90]	0.97 [0.91, 1.00]
James 2021 [A]	20	0	4	91	0.83 [0.63, 0.95]	1.00 [0.96, 1.00]
Jaaskelainen 2021 [C]	126	0	26	48	0.83 [0.76, 0.89]	1.00 [0.93, 1.00]
Chiu 2021 [B]	62	10	13	264	0.83 [0.72, 0.90]	0.96 [0.93, 0.98]
Lindner 202105 [A]	33	2	7	104	0.82 [0.67, 0.93]	0.98 [0.93, 1.00]
Nomoto 2021	66	1	14	19	0.82 [0.72, 0.90]	0.95 [0.75, 1.00]
Kruger 202108	113	3	24	346	0.82 [0.75, 0.88]	0.99 [0.98, 1.00]
Kruger 2020(c)	32	7	7	972	0.82 [0.66, 0.92]	0.99 [0.99, 1.00]
Matsuda 2021 [A]	18	1	4	43	0.82 [0.60, 0.95]	0.98 [0.88, 1.00]
Bachman 2021 [G]	89	0	20	60	0.82 [0.73, 0.88]	1.00 [0.94, 1.00]
Jaaskelainen 2021 [B]	128	0	30	40	0.81 [0.74, 0.87]	1.00 [0.91, 1.00]
Leli 2021	64	2	15	126	0.81 [0.71, 0.89]	0.98 [0.94, 1.00]
Bulilete 2021	70	2	17	588	0.80 [0.71, 0.88]	1.00 [0.99, 1.00]
Jaaskelainen 2021 [A]	119	0	29	40	0.80 [0.73, 0.86]	1.00 [0.91, 1.00]
Pray 2021 [A]	32	2	8	185	0.80 [0.64, 0.91]	0.99 [0.96, 1.00]
Albert 2020	43	0	11	358	0.80 [0.66, 0.89]	1.00 [0.99, 1.00]
Nordgren 2021 [B]	124	45	32	131	0.79 [0.72, 0.86]	0.74 [0.67, 0.81]
Lindner 202104 [B]	31	1	8	247	0.79 [0.64, 0.91]	1.00 [0.98, 1.00]
Fenollar 2020(a)	144	0	38	0	0.79 [0.72, 0.85]	Not estimable
Bachman 2021 [H]	87	1	23	59	0.79 [0.70, 0.86]	0.98 [0.91, 1.00]
Ford 2021	30	1	8	180	0.79 [0.63, 0.90]	0.99 [0.97, 1.00]
Ferte 2021	26	0	7	99	0.79 [0.61, 0.91]	1.00 [0.96, 1.00]
Shah 2021	221	2	60	907	0.79 [0.73, 0.83]	1.00 [0.99, 1.00]
Linares 2020	39	0	11	133	0.78 [0.64, 0.88]	1.00 [0.97, 1.00]
Asai 2021	49	4	14	238	0.78 [0.66, 0.87]	0.98 [0.96, 1.00]
Donapetry 2021	14	0	4	422	0.78 [0.52, 0.94]	1.00 [0.99, 1.00]
Homza 2021 [E]	45	18	13	23	0.78 [0.65, 0.87]	0.56 [0.40, 0.72]
Herrera 2020	352	6	107	707	0.77 [0.73, 0.80]	0.99 [0.98, 1.00]
Kanauija 2021	113	2	35	221	0.76 [0.69, 0.83]	0.99 [0.97, 1.00]
Young 2020	29	1	9	212	0.76 [0.60, 0.89]	1.00 [0.97, 1.00]



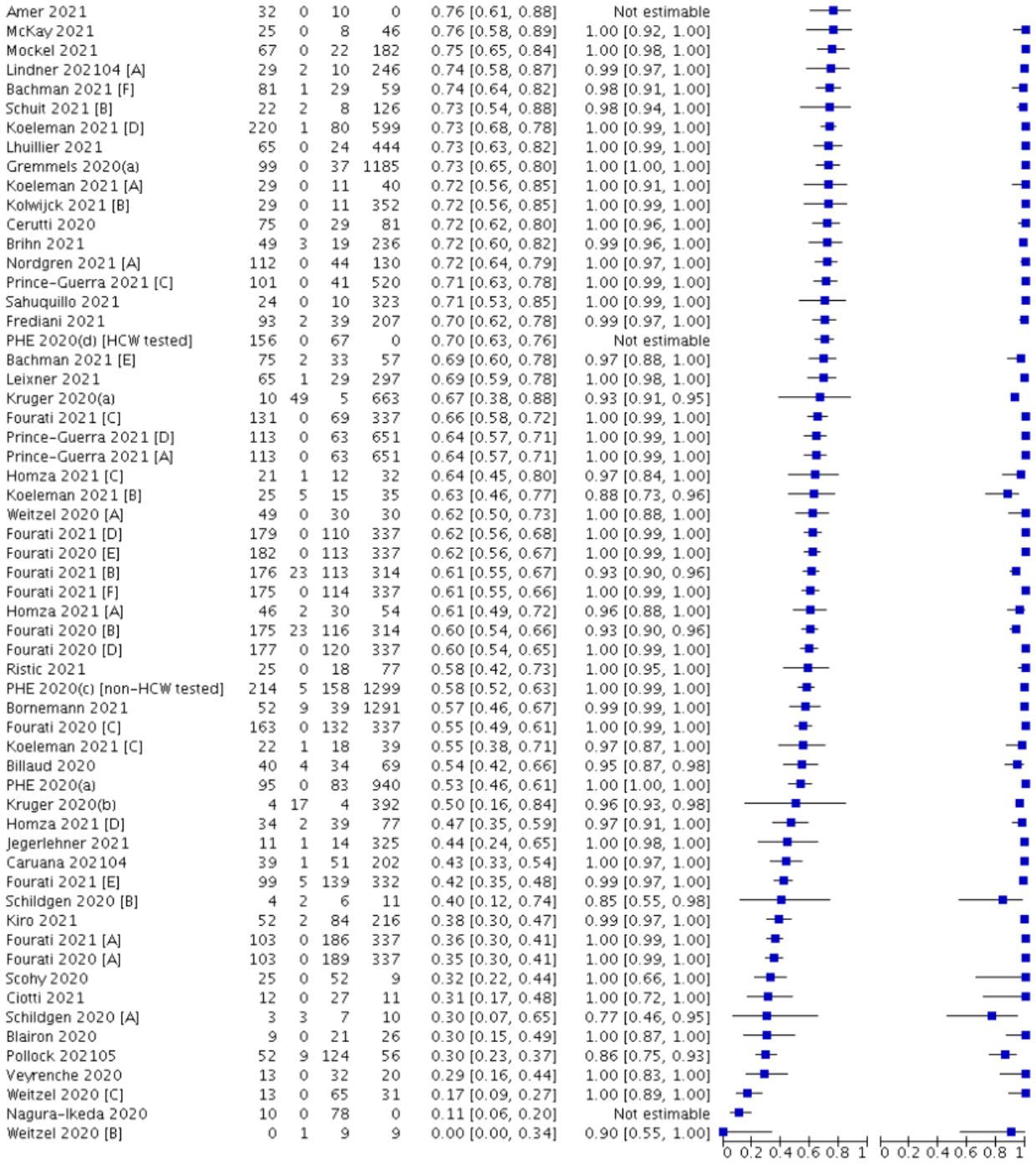


Figure 1. Sensitivity and specificity of RAgT in symptomatic individuals

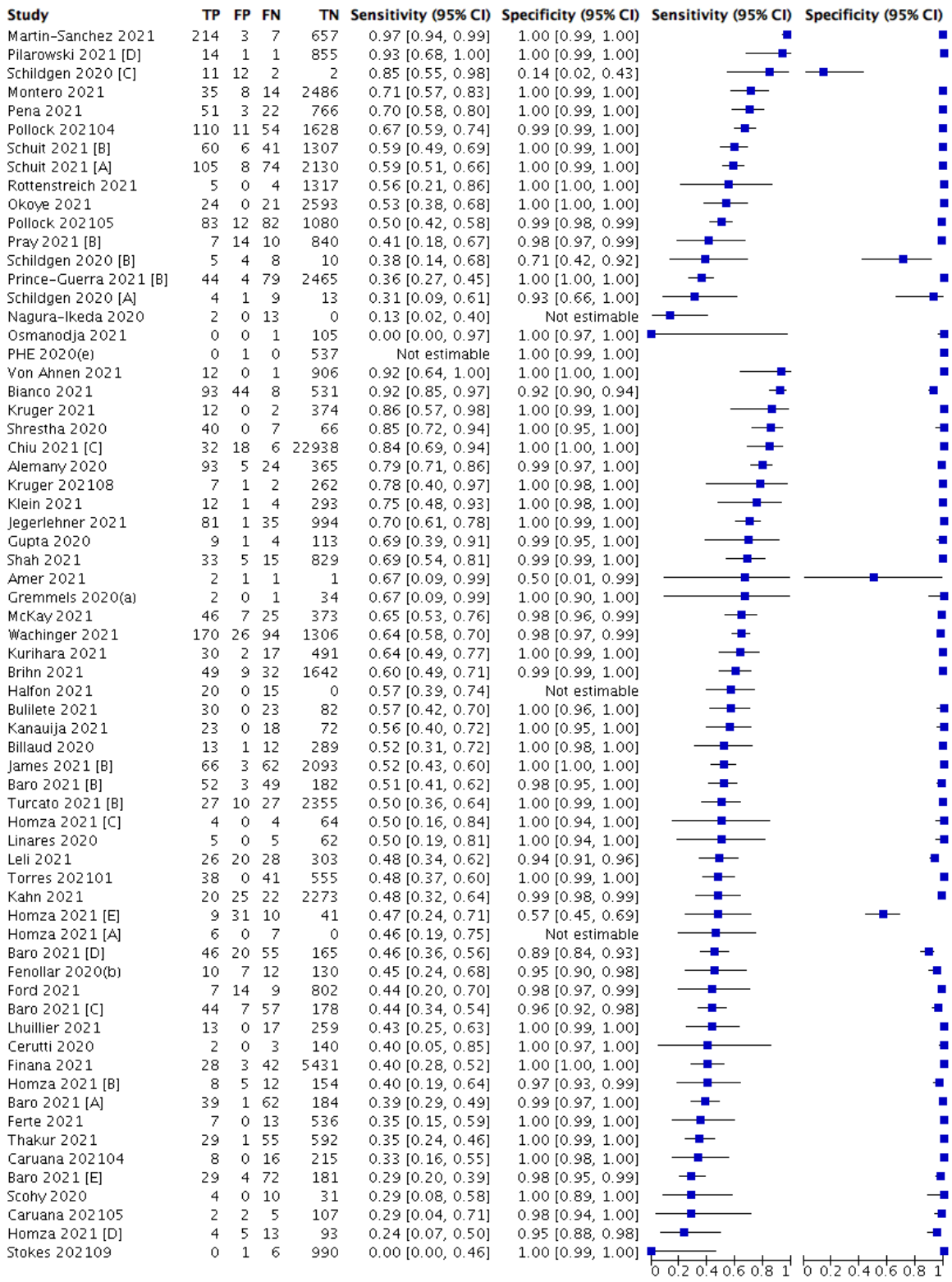
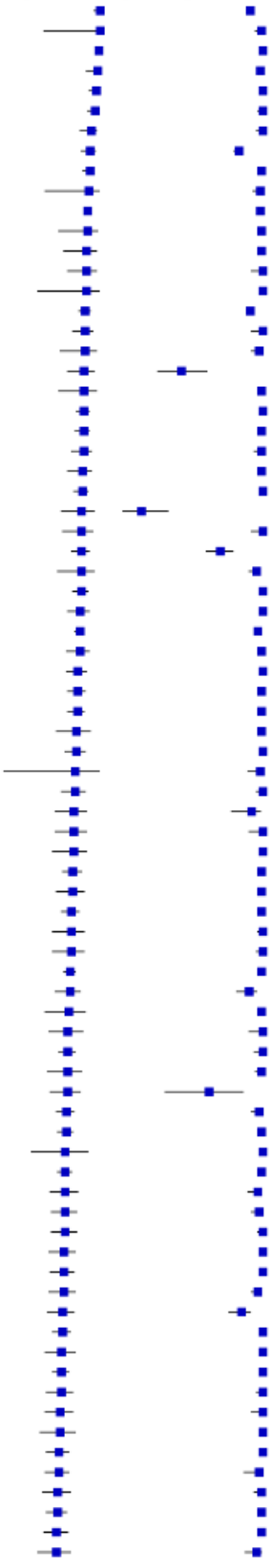


Figure 2. Sensitivity and specificity of RAgT in asymptomatic individuals

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gili 2021	90	130	0	1518	1.00 [0.96, 1.00]	0.92 [0.91, 0.93]
Ishii 2021 [D]	8	1	0	123	1.00 [0.63, 1.00]	0.99 [0.96, 1.00]
Kobayashi 2021 [A]	304	0	1	4615	1.00 [0.98, 1.00]	1.00 [1.00, 1.00]
Chaimayo 2021	59	5	1	389	0.98 [0.91, 1.00]	0.99 [0.97, 1.00]
Kobayashi 2021 [B]	111	3	3	5272	0.97 [0.93, 0.99]	1.00 [1.00, 1.00]
Courtellemont 2021	117	0	4	127	0.97 [0.92, 0.99]	1.00 [0.97, 1.00]
Kim 2021 [B]	94	0	6	100	0.94 [0.87, 0.98]	1.00 [0.96, 1.00]
Sood 2021	127	99	9	539	0.93 [0.88, 0.97]	0.84 [0.81, 0.87]
Merino-Amador 2021	179	2	13	256	0.93 [0.89, 0.96]	0.99 [0.97, 1.00]
Maniscalco 2021	12	1	1	91	0.92 [0.64, 1.00]	0.99 [0.94, 1.00]
Alemany 2020	872	5	79	450	0.92 [0.90, 0.93]	0.99 [0.97, 1.00]
Ishii 2021 [C]	22	1	2	460	0.92 [0.73, 0.99]	1.00 [0.99, 1.00]
Yokota 2021	31	2	3	307	0.91 [0.76, 0.98]	0.99 [0.98, 1.00]
Seynaeve 2021 [C]	41	0	4	50	0.91 [0.79, 0.98]	1.00 [0.93, 1.00]
Ishii 2021 [A]	10	0	1	260	0.91 [0.59, 1.00]	1.00 [0.99, 1.00]
Bianco 2021	269	48	29	561	0.90 [0.86, 0.93]	0.92 [0.90, 0.94]
Bouassa 2021	90	0	10	50	0.90 [0.82, 0.95]	1.00 [0.93, 1.00]
Kim 2021 [A]	27	2	3	98	0.90 [0.73, 0.98]	0.98 [0.93, 1.00]
Van Honacker 2021 [A]	52	21	6	18	0.90 [0.79, 0.96]	0.46 [0.30, 0.63]
Agarwal 2021	26	2	3	436	0.90 [0.73, 0.98]	1.00 [0.98, 1.00]
Pilarowski 2021 [A]	211	3	26	3062	0.89 [0.84, 0.93]	1.00 [1.00, 1.00]
Berger 2021 [B]	170	1	21	337	0.89 [0.84, 0.93]	1.00 [0.98, 1.00]
Pickering 2021 [A]	89	1	11	99	0.89 [0.81, 0.94]	0.99 [0.95, 1.00]
Osmanodja 2021	62	1	8	308	0.89 [0.79, 0.95]	1.00 [0.98, 1.00]
Karon 2021 [D]	174	0	23	150	0.88 [0.83, 0.92]	1.00 [0.98, 1.00]
Schildgen 2020 [C]	37	25	5	6	0.88 [0.74, 0.96]	0.19 [0.07, 0.37]
Seynaeve 2021 [D]	44	0	6	50	0.88 [0.76, 0.95]	1.00 [0.93, 1.00]
Andreani 2021 [F]	109	32	15	83	0.88 [0.81, 0.93]	0.72 [0.63, 0.80]
Baccani 2021 [A]	29	7	4	161	0.88 [0.72, 0.97]	0.96 [0.92, 0.98]
Karon 2021 [C]	164	0	23	150	0.88 [0.82, 0.92]	1.00 [0.98, 1.00]
Kruger 2021	92	1	14	1001	0.87 [0.79, 0.93]	1.00 [0.99, 1.00]
Caputo 2021	436	102	67	3661	0.87 [0.83, 0.90]	0.97 [0.97, 0.98]
Klein 2021	78	4	12	486	0.87 [0.78, 0.93]	0.99 [0.98, 1.00]
Berger 2021 [A]	106	0	18	411	0.85 [0.78, 0.91]	1.00 [0.99, 1.00]
Kyritsi 2021	141	1	24	458	0.85 [0.79, 0.90]	1.00 [0.99, 1.00]
Igloi 2021	158	4	28	780	0.85 [0.79, 0.90]	0.99 [0.99, 1.00]
Hartard 2021	39	2	7	330	0.85 [0.71, 0.94]	0.99 [0.98, 1.00]
Escriva 2021	99	0	18	331	0.85 [0.77, 0.91]	1.00 [0.99, 1.00]
Tsai 2021	5	1	1	54	0.83 [0.36, 1.00]	0.98 [0.90, 1.00]
Favresse 2021 [E]	80	0	16	92	0.83 [0.74, 0.90]	1.00 [0.96, 1.00]
Van Honacker 2021 [C]	48	3	10	37	0.83 [0.71, 0.91]	0.93 [0.80, 0.98]
Van Honacker 2021 [E]	48	0	10	40	0.83 [0.71, 0.91]	1.00 [0.91, 1.00]
Eleftheriou 2021	42	0	9	693	0.82 [0.69, 0.92]	1.00 [0.99, 1.00]
Kruger 202108	120	4	26	611	0.82 [0.75, 0.88]	0.99 [0.98, 1.00]
Gupta 2020	63	1	14	252	0.82 [0.71, 0.90]	1.00 [0.98, 1.00]
Nsoga 2021	136	2	32	232	0.81 [0.74, 0.87]	0.99 [0.97, 1.00]
Gremmels 2020(b)	51	0	12	145	0.81 [0.69, 0.90]	1.00 [0.97, 1.00]
Takeda 2020	50	0	12	100	0.81 [0.69, 0.90]	1.00 [0.96, 1.00]
Holzner 2021	367	8	89	1816	0.80 [0.77, 0.84]	1.00 [0.99, 1.00]
Nash 2020	80	8	20	82	0.80 [0.71, 0.87]	0.91 [0.83, 0.96]
Lindner 202104 [B]	31	1	8	247	0.79 [0.64, 0.91]	1.00 [0.98, 1.00]
Van Honacker 2021 [D]	45	0	12	40	0.79 [0.66, 0.89]	1.00 [0.91, 1.00]
Bruzzone 2021 [A]	199	0	54	68	0.79 [0.73, 0.84]	1.00 [0.95, 1.00]
Salvagno 2021	47	1	13	113	0.78 [0.66, 0.88]	0.99 [0.95, 1.00]
Amer 2021	54	5	15	9	0.78 [0.67, 0.87]	0.64 [0.35, 0.87]
Karon 2021 [B]	153	4	44	146	0.78 [0.71, 0.83]	0.97 [0.93, 0.99]
Pollock 202104	226	12	66	2004	0.77 [0.72, 0.82]	0.99 [0.99, 1.00]
Muhi 2021	17	1	5	2580	0.77 [0.55, 0.92]	1.00 [1.00, 1.00]
Shah 2021	258	7	76	1769	0.77 [0.72, 0.82]	1.00 [0.99, 1.00]
Favresse 2021 [C]	74	3	22	89	0.77 [0.67, 0.85]	0.97 [0.91, 0.99]
Pickering 2021 [B]	77	2	23	98	0.77 [0.68, 0.85]	0.98 [0.93, 1.00]
Abusrewil 2021 [A]	83	0	25	123	0.77 [0.68, 0.84]	1.00 [0.97, 1.00]
Pena-Rodriguez 2021	79	0	25	265	0.76 [0.67, 0.84]	1.00 [0.99, 1.00]
Torres 202102	88	0	28	154	0.76 [0.67, 0.83]	1.00 [0.98, 1.00]
Homza 2021 [B]	81	7	26	204	0.76 [0.66, 0.83]	0.97 [0.93, 0.99]
Pickering 2021 [C]	75	14	25	86	0.75 [0.65, 0.83]	0.86 [0.78, 0.92]
Soleimani 2021][B]	174	0	58	169	0.75 [0.69, 0.80]	1.00 [0.98, 1.00]
Kurihara 2021	62	2	21	1316	0.75 [0.64, 0.84]	1.00 [0.99, 1.00]
Landaas 2021	186	3	64	3738	0.74 [0.69, 0.80]	1.00 [1.00, 1.00]
Pickering 2021 [D]	74	0	26	100	0.74 [0.64, 0.82]	1.00 [0.96, 1.00]
Paul 2021 [A]	72	0	26	50	0.73 [0.64, 0.82]	1.00 [0.93, 1.00]
Linares 2020	44	0	16	195	0.73 [0.60, 0.84]	1.00 [0.98, 1.00]
Gremmels 2020(a)	101	0	38	1228	0.73 [0.64, 0.80]	1.00 [1.00, 1.00]
Iqbal 2021	92	1	35	42	0.72 [0.64, 0.80]	0.98 [0.88, 1.00]
Halfon 2021	72	1	28	99	0.72 [0.62, 0.81]	0.99 [0.95, 1.00]
Kanauija 2021	136	2	53	293	0.72 [0.65, 0.78]	0.99 [0.98, 1.00]
Bulilete 2021	100	2	40	670	0.71 [0.63, 0.79]	1.00 [0.99, 1.00]
Kruttgen 2020	53	3	22	72	0.71 [0.59, 0.81]	0.96 [0.89, 0.99]



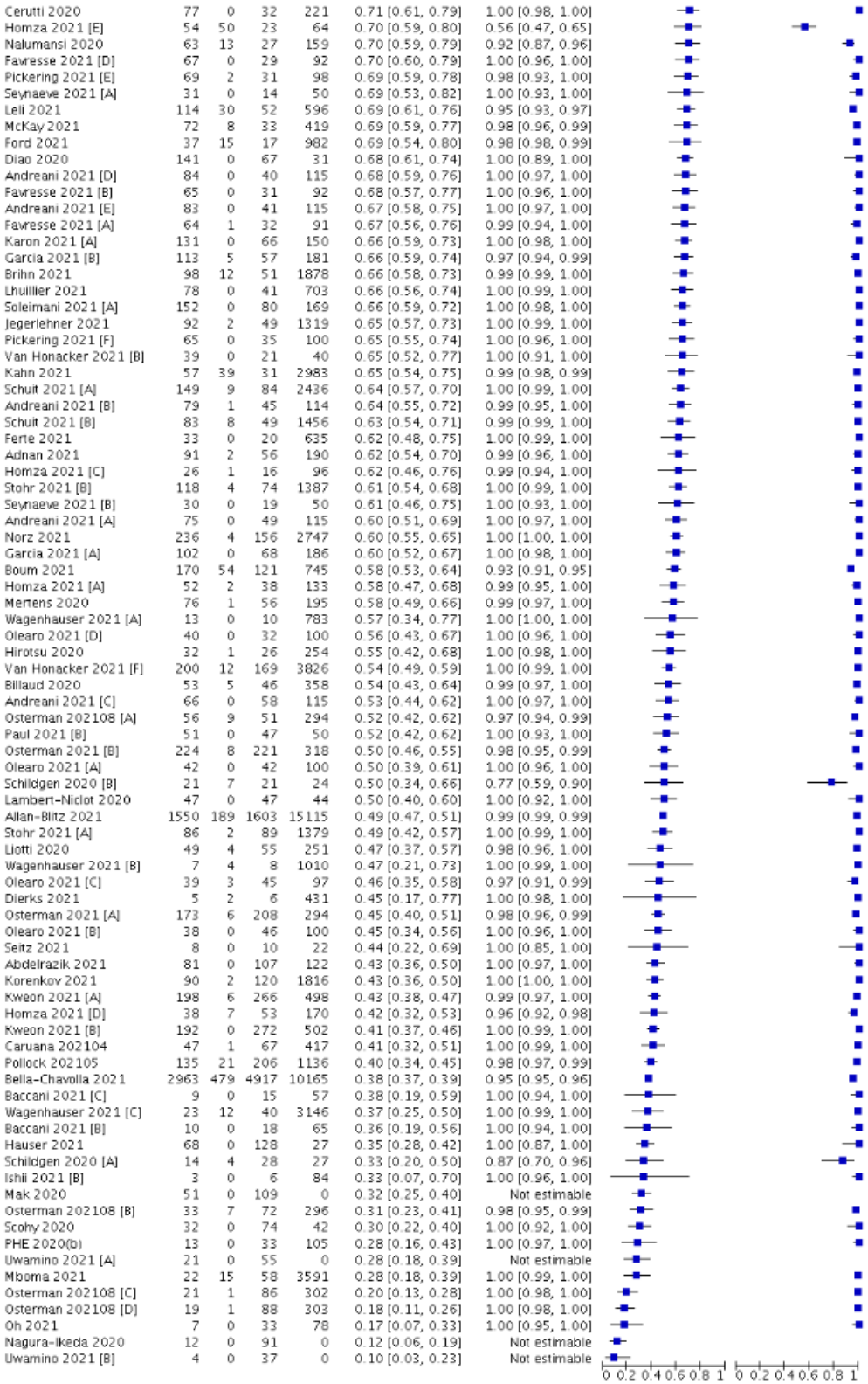
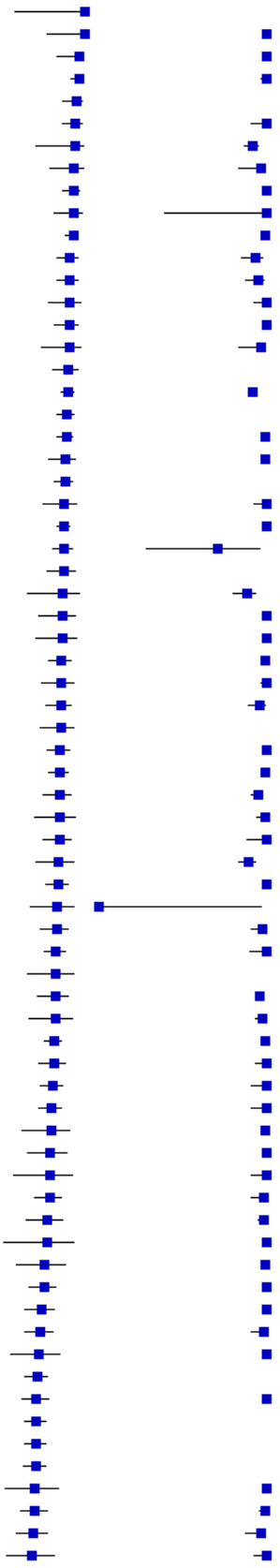


Figure 3. Sensitivity and specificity of RAgT in individuals with mixed symptoms or unreported

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kim 2021 [A]	7	0	0	0	1.00 [0.59, 1.00]	Not estimable
Muhi 2021	15	0	0	156	1.00 [0.78, 1.00]	1.00 [0.98, 1.00]
Cassuto 2021	31	0	1	202	0.97 [0.84, 1.00]	1.00 [0.98, 1.00]
Courtellemont 2021	117	0	4	127	0.97 [0.92, 0.99]	1.00 [0.97, 1.00]
Kim 2021 [B]	64	0	3	0	0.96 [0.87, 0.99]	Not estimable
Porte 2020a	72	0	4	42	0.95 [0.87, 0.99]	1.00 [0.92, 1.00]
Denina 2021	16	14	1	160	0.94 [0.71, 1.00]	0.92 [0.87, 0.96]
Porte 2020b [A]	30	1	2	31	0.94 [0.79, 0.99]	0.97 [0.84, 1.00]
Pollock 202104	104	0	7	335	0.94 [0.87, 0.97]	1.00 [0.99, 1.00]
Nomoto 2021	44	0	3	4	0.94 [0.82, 0.99]	1.00 [0.40, 1.00]
Merino-Amador 2021	179	2	13	256	0.93 [0.89, 0.96]	0.99 [0.97, 1.00]
Bachman 2021 [C]	84	5	8	72	0.91 [0.84, 0.96]	0.94 [0.85, 0.98]
Bachman 2021 [D]	84	4	8	78	0.91 [0.84, 0.96]	0.95 [0.88, 0.99]
Seynaeve 2021 [C]	41	0	4	50	0.91 [0.79, 0.98]	1.00 [0.93, 1.00]
Kruger 2021	69	1	7	533	0.91 [0.82, 0.96]	1.00 [0.99, 1.00]
Porte 2020b [B]	29	1	3	31	0.91 [0.75, 0.98]	0.97 [0.84, 1.00]
Garcia 2021 [B]	66	0	7	0	0.90 [0.81, 0.96]	Not estimable
Bianco 2021	269	48	29	561	0.90 [0.86, 0.93]	0.92 [0.90, 0.94]
Kweon 2021 [A]	135	0	16	0	0.89 [0.83, 0.94]	Not estimable
Berger 2021 [B]	170	1	21	337	0.89 [0.84, 0.93]	1.00 [0.98, 1.00]
Osmanodja 2021	62	1	8	308	0.89 [0.79, 0.95]	1.00 [0.98, 1.00]
Kweon 2021 [B]	135	0	18	0	0.88 [0.82, 0.93]	Not estimable
Seynaeve 2021 [D]	44	0	6	50	0.88 [0.76, 0.95]	1.00 [0.93, 1.00]
Stokes 202103 [B]	268	2	37	1334	0.88 [0.84, 0.91]	1.00 [0.99, 1.00]
Stokes 202103 [A]	121	2	17	5	0.88 [0.81, 0.93]	0.71 [0.29, 0.96]
Garcia 2021 [A]	64	0	9	0	0.88 [0.78, 0.94]	Not estimable
Ifko 2021	20	12	3	90	0.87 [0.66, 0.97]	0.88 [0.80, 0.94]
Kolwijck 2021 [A]	39	0	6	388	0.87 [0.73, 0.95]	1.00 [0.99, 1.00]
Linares 2020	32	0	5	846	0.86 [0.71, 0.95]	1.00 [1.00, 1.00]
Kruger 202108	102	2	16	303	0.86 [0.79, 0.92]	0.99 [0.98, 1.00]
Gupta 2020	49	0	8	134	0.86 [0.74, 0.94]	1.00 [0.97, 1.00]
Bachman 2021 [B]	79	3	13	75	0.86 [0.77, 0.92]	0.96 [0.89, 0.99]
McKay 2021	48	0	8	0	0.86 [0.74, 0.94]	Not estimable
Berger 2021 [A]	106	0	18	411	0.85 [0.78, 0.91]	1.00 [0.99, 1.00]
Kyritsi 2021	141	1	24	458	0.85 [0.79, 0.90]	1.00 [0.99, 1.00]
Chiu 2021 [A]	64	14	11	260	0.85 [0.75, 0.92]	0.95 [0.92, 0.97]
Lindner 202105 [B]	34	1	6	105	0.85 [0.70, 0.94]	0.99 [0.95, 1.00]
Weitzel 2020 [D]	68	0	12	31	0.85 [0.75, 0.92]	1.00 [0.89, 1.00]
Shaikh 2021	39	16	7	137	0.85 [0.71, 0.94]	0.90 [0.84, 0.94]
Escriva 2021	99	0	18	331	0.85 [0.77, 0.91]	1.00 [0.99, 1.00]
Amer 2021	31	1	6	0	0.84 [0.68, 0.94]	0.00 [0.00, 0.97]
Bachman 2021 [A]	75	2	15	77	0.83 [0.74, 0.90]	0.97 [0.91, 1.00]
Jaaskelainen 2021 [C]	126	0	26	38	0.83 [0.76, 0.89]	1.00 [0.91, 1.00]
Halfon 2021	29	0	6	0	0.83 [0.66, 0.93]	Not estimable
Chiu 2021 [B]	62	10	13	264	0.83 [0.72, 0.90]	0.96 [0.93, 0.98]
Lindner 202105 [A]	33	2	7	104	0.82 [0.67, 0.93]	0.98 [0.93, 1.00]
Shah 2021	199	2	44	684	0.82 [0.76, 0.87]	1.00 [0.99, 1.00]
Bachman 2021 [G]	89	0	20	60	0.82 [0.73, 0.88]	1.00 [0.94, 1.00]
Jaaskelainen 2021 [B]	128	0	30	40	0.81 [0.74, 0.87]	1.00 [0.91, 1.00]
Jaaskelainen 2021 [A]	119	0	29	40	0.80 [0.73, 0.86]	1.00 [0.91, 1.00]
Kruger 2020(c)	28	7	7	907	0.80 [0.63, 0.92]	0.99 [0.98, 1.00]
Albert 2020	43	0	11	358	0.80 [0.66, 0.89]	1.00 [0.99, 1.00]
Ristic 2021	19	0	5	39	0.79 [0.58, 0.93]	1.00 [0.91, 1.00]
Bachman 2021 [H]	87	1	23	59	0.79 [0.70, 0.86]	0.98 [0.91, 1.00]
Asai 2021	49	4	14	238	0.78 [0.66, 0.87]	0.98 [0.96, 1.00]
Donapetry 2021	14	0	4	422	0.78 [0.52, 0.94]	1.00 [0.99, 1.00]
Young 2020	29	1	9	212	0.76 [0.60, 0.89]	1.00 [0.97, 1.00]
Torres 202102	88	0	28	154	0.76 [0.67, 0.83]	1.00 [0.98, 1.00]
Gremmels 2020(a)	75	0	26	846	0.74 [0.65, 0.82]	1.00 [1.00, 1.00]
Bachman 2021 [F]	81	1	29	59	0.74 [0.64, 0.82]	0.98 [0.91, 1.00]
Kolwijck 2021 [B]	29	0	11	352	0.72 [0.56, 0.85]	1.00 [0.99, 1.00]
Fourati 2021 [B]	143	0	57	0	0.71 [0.65, 0.78]	Not estimable
Prince-Guerra 2021 [C]	101	0	41	520	0.71 [0.63, 0.78]	1.00 [0.99, 1.00]
Fourati 2020 [E]	142	0	58	0	0.71 [0.64, 0.77]	Not estimable
Fourati 2021 [D]	142	0	58	0	0.71 [0.64, 0.77]	Not estimable
Fourati 2020 [B]	141	0	58	0	0.71 [0.64, 0.77]	Not estimable
Sahuquillo 2021	24	0	10	323	0.71 [0.53, 0.85]	1.00 [0.99, 1.00]
Frediani 2021	93	2	39	207	0.70 [0.62, 0.78]	0.99 [0.97, 1.00]
Bachman 2021 [E]	75	2	33	57	0.69 [0.60, 0.78]	0.97 [0.88, 1.00]
Seynaeve 2021 [A]	31	0	14	50	0.69 [0.53, 0.82]	1.00 [0.93, 1.00]



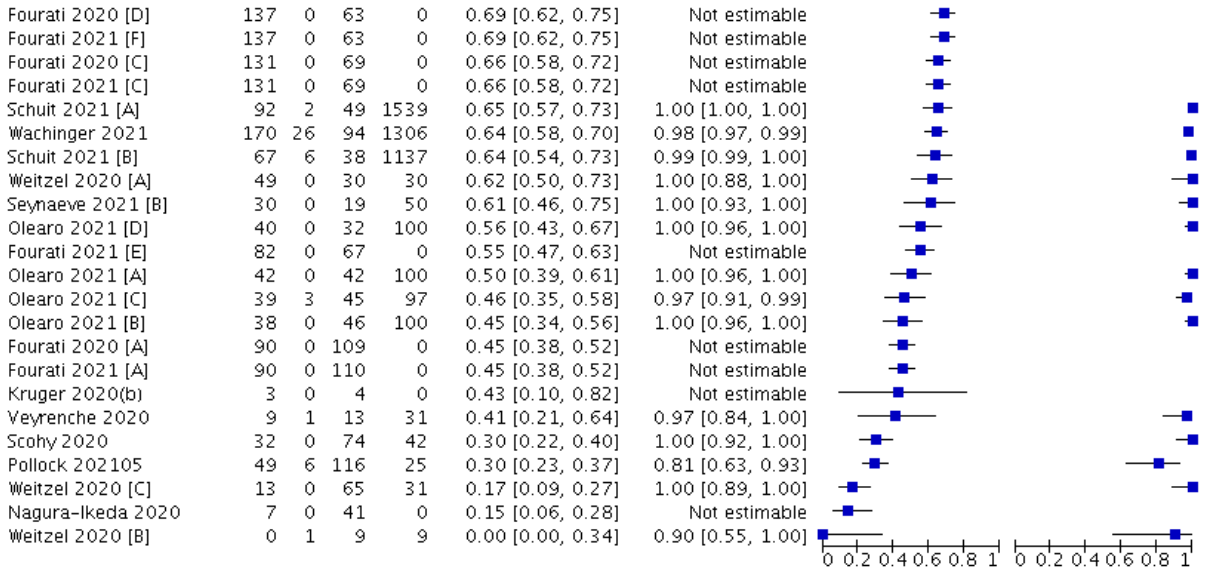


Figure 4. Sensitivity and specificity of RAgT in early testing (0-7 days after symptom onset)

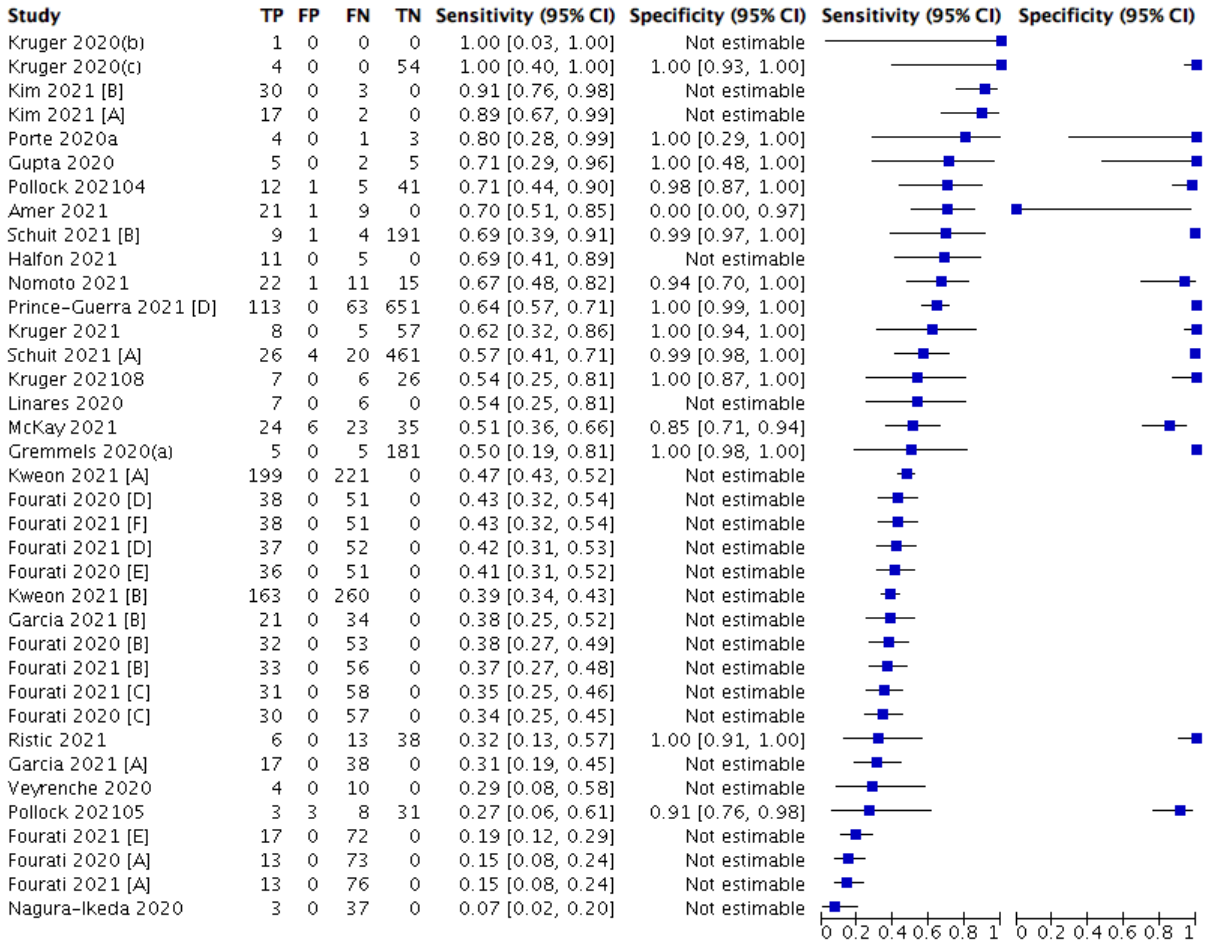


Figure 5. Sensitivity and specificity of RAgT in late testing (> 7 days)

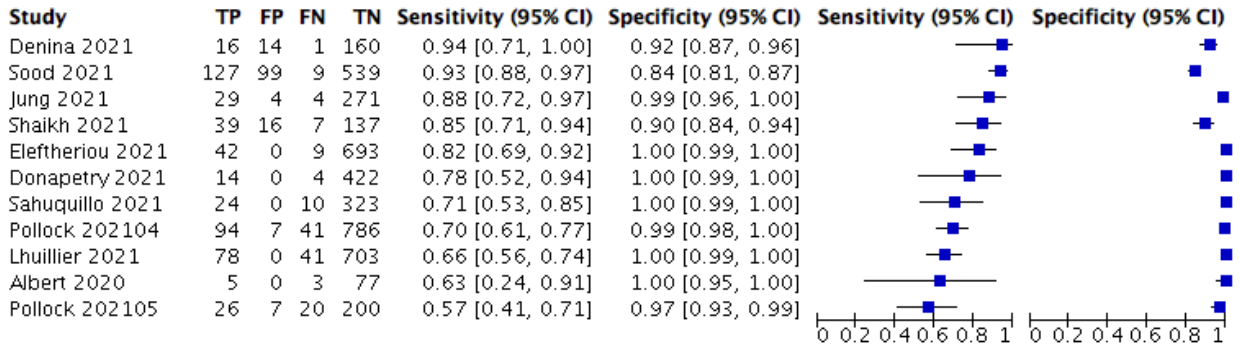


Figure 6. Sensitivity and specificity of RAgT in special population - children

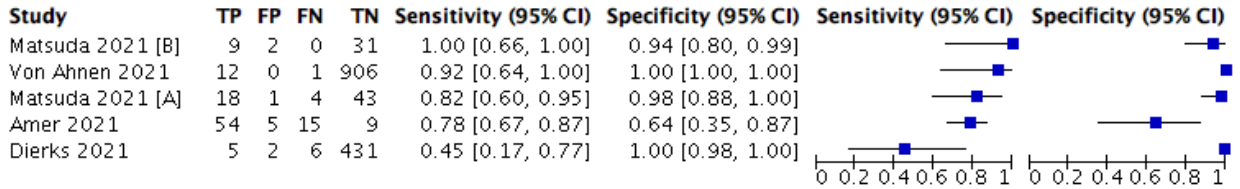


Figure 7. Sensitivity and specificity of RAgT in special population - healthcare workers

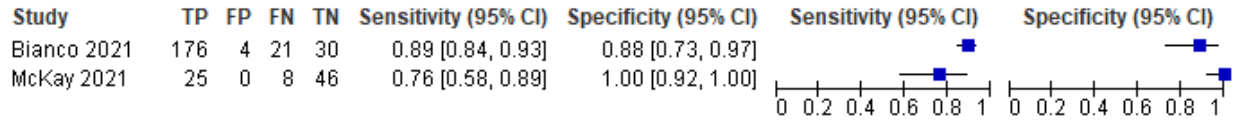


Figure 8. Sensitivity and specificity of RAgT use in symptomatic individuals in an outbreak settings

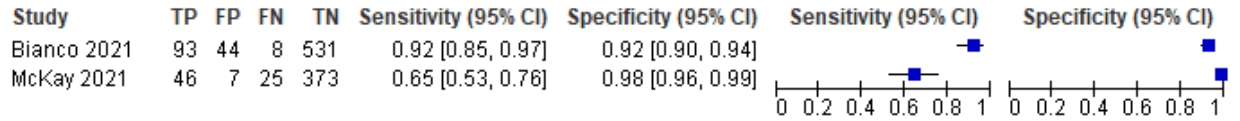


Figure 9. Sensitivity and specificity of RAgT use in asymptomatic individuals in an outbreak settings

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Matsuda 2021 [B]	9	2	0	31	1.00 [0.66, 1.00]	0.94 [0.80, 0.99]
Alemany 2020	872	5	79	450	0.92 [0.90, 0.93]	0.99 [0.97, 1.00]
Stokes 202103 [B]	268	2	37	1334	0.88 [0.84, 0.91]	1.00 [0.99, 1.00]
Stokes 202103 [A]	121	2	17	5	0.88 [0.81, 0.93]	0.71 [0.29, 0.96]
Kruger 2021	92	1	14	1001	0.87 [0.79, 0.93]	1.00 [0.99, 1.00]
Klein 2021	78	4	12	486	0.87 [0.78, 0.93]	0.99 [0.98, 1.00]
Kolwijck 2021 [A]	39	0	6	388	0.87 [0.73, 0.95]	1.00 [0.99, 1.00]
Berger 2021 [A]	106	0	18	411	0.85 [0.78, 0.91]	1.00 [0.99, 1.00]
Escriva 2021	99	0	18	331	0.85 [0.77, 0.91]	1.00 [0.99, 1.00]
Jaaskelainen 2021 [C]	126	0	26	38	0.83 [0.76, 0.89]	1.00 [0.91, 1.00]
Eleftheriou 2021	42	0	9	693	0.82 [0.69, 0.92]	1.00 [0.99, 1.00]
Gremmels 2020(b)	51	0	12	145	0.81 [0.69, 0.90]	1.00 [0.97, 1.00]
Nsoga 2021	136	2	32	232	0.81 [0.74, 0.87]	0.99 [0.97, 1.00]
Albert 2020	43	0	11	358	0.80 [0.66, 0.89]	1.00 [0.99, 1.00]
Fenollar 2020(a)	144	0	38	0	0.79 [0.72, 0.85]	Not estimable
Van Honacker 2021 [D]	45	0	12	40	0.79 [0.66, 0.89]	1.00 [0.91, 1.00]
Donapetry 2021	14	0	4	422	0.78 [0.52, 0.94]	1.00 [0.99, 1.00]
Muhi 2021	17	1	5	2580	0.77 [0.55, 0.92]	1.00 [1.00, 1.00]
Abusrewil 2021 [H]	10	0	3	10	0.77 [0.46, 0.95]	1.00 [0.69, 1.00]
Soleimani 2021][B]	174	0	58	169	0.75 [0.69, 0.80]	1.00 [0.98, 1.00]
Landaas 2021	186	3	64	3738	0.74 [0.69, 0.80]	1.00 [1.00, 1.00]
Linares 2020	44	0	16	195	0.73 [0.60, 0.84]	1.00 [0.98, 1.00]
Gremmels 2020(a)	101	0	38	1228	0.73 [0.64, 0.80]	1.00 [1.00, 1.00]
Kolwijck 2021 [B]	29	0	11	352	0.72 [0.56, 0.85]	1.00 [0.99, 1.00]
Halfon 2021	72	1	28	99	0.72 [0.62, 0.81]	0.99 [0.95, 1.00]
Nordgren 2021 [A]	112	0	44	130	0.72 [0.64, 0.79]	1.00 [0.97, 1.00]
Bulilete 2021	100	2	40	670	0.71 [0.63, 0.79]	1.00 [0.99, 1.00]
Sahuquillo 2021	24	0	10	323	0.71 [0.53, 0.85]	1.00 [0.99, 1.00]
Favresse 2021 [B]	65	0	31	92	0.68 [0.57, 0.77]	1.00 [0.96, 1.00]
Lhuillier 2021	79	0	40	703	0.66 [0.57, 0.75]	1.00 [0.99, 1.00]
Ferte 2021	33	0	20	635	0.62 [0.48, 0.75]	1.00 [0.99, 1.00]
Andreani 2021 [A]	75	0	49	115	0.60 [0.51, 0.69]	1.00 [0.97, 1.00]
Garcia 2021 [A]	102	0	68	186	0.60 [0.52, 0.67]	1.00 [0.98, 1.00]
Fourati 2021 [C]	162	0	127	337	0.56 [0.50, 0.62]	1.00 [0.99, 1.00]
Fourati 2020 [C]	163	0	132	337	0.55 [0.49, 0.61]	1.00 [0.99, 1.00]
Billaud 2020	53	5	46	358	0.54 [0.43, 0.64]	0.99 [0.97, 1.00]
Schildgen 2020 [B]	21	7	21	24	0.50 [0.34, 0.66]	0.77 [0.59, 0.90]
Torres 202101	38	0	41	555	0.48 [0.37, 0.60]	1.00 [0.99, 1.00]
Wagenhauser 2021 [B]	7	4	8	1010	0.47 [0.21, 0.73]	1.00 [0.99, 1.00]
Fenollar 2020(b)	10	7	12	130	0.45 [0.24, 0.68]	0.95 [0.90, 0.98]
Olearo 2021 [B]	38	0	46	100	0.45 [0.34, 0.56]	1.00 [0.96, 1.00]
Baro 2021 [A]	39	1	62	184	0.39 [0.29, 0.49]	0.99 [0.97, 1.00]
Mboma 2021	22	15	58	3591	0.28 [0.18, 0.39]	1.00 [0.99, 1.00]

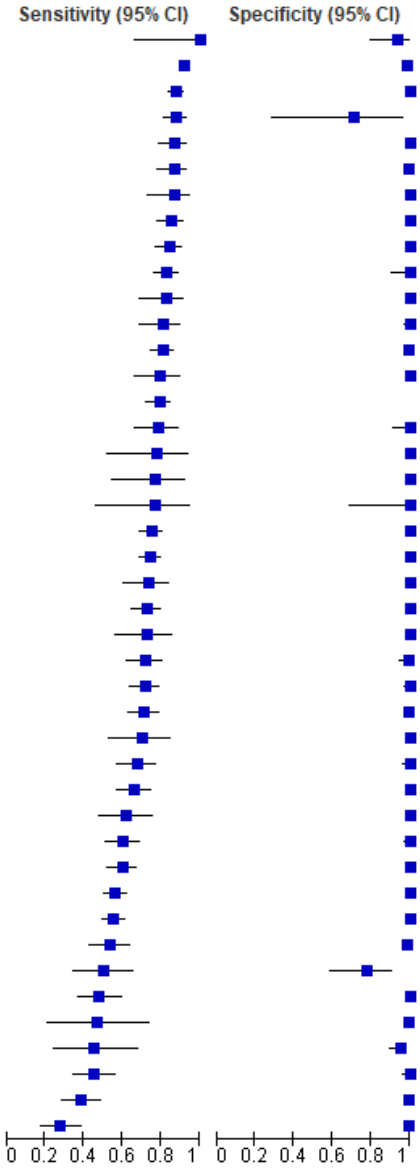


Figure 10. Sensitivity and specificity of Panbio™ Ag-RDT (Abbott)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chaimayo 2021	59	5	1	389	0.98 [0.91, 1.00]	0.99 [0.97, 1.00]
Nikolai 2021 [B]	31	0	3	62	0.91 [0.76, 0.98]	1.00 [0.94, 1.00]
Turcato 2021 [A]	152	20	17	802	0.90 [0.84, 0.94]	0.98 [0.96, 0.99]
Agarwal 2021	26	2	3	436	0.90 [0.73, 0.98]	1.00 [0.98, 1.00]
Berger 2021 [B]	170	1	21	337	0.89 [0.84, 0.93]	1.00 [0.98, 1.00]
Nikolai 2021 [A]	31	0	5	96	0.86 [0.71, 0.95]	1.00 [0.96, 1.00]
Lindner 202105 [B]	34	1	6	105	0.85 [0.70, 0.94]	0.99 [0.95, 1.00]
Van Honacker 2021 [E]	48	0	10	40	0.83 [0.71, 0.91]	1.00 [0.91, 1.00]
Lindner 202105 [A]	33	2	7	104	0.82 [0.67, 0.93]	0.98 [0.93, 1.00]
Gupta 2020	63	1	14	252	0.82 [0.71, 0.90]	1.00 [0.98, 1.00]
Jaaskelainen 2021 [B]	128	0	30	40	0.81 [0.74, 0.87]	1.00 [0.91, 1.00]
Holzner 2021	367	8	89	1816	0.80 [0.77, 0.84]	1.00 [0.99, 1.00]
Lindner 202104 [B]	31	1	8	247	0.79 [0.64, 0.91]	1.00 [0.98, 1.00]
Bruzzone 2021 [A]	199	0	54	68	0.79 [0.73, 0.84]	1.00 [0.95, 1.00]
Amer 2021	54	5	15	9	0.78 [0.67, 0.87]	0.64 [0.35, 0.87]
Kruger 2020(c)	36	9	11	1207	0.77 [0.62, 0.88]	0.99 [0.99, 1.00]
Pena-Rodriguez 2021	79	0	25	265	0.76 [0.67, 0.84]	1.00 [0.99, 1.00]
Lindner 202104 [A]	29	2	10	246	0.74 [0.58, 0.87]	0.99 [0.97, 1.00]
Cerutti 2020	77	0	32	221	0.71 [0.61, 0.79]	1.00 [0.98, 1.00]
Nalumansi 2020	63	13	27	159	0.70 [0.59, 0.79]	0.92 [0.87, 0.96]
Pena 2021	51	3	22	766	0.70 [0.58, 0.80]	1.00 [0.99, 1.00]
Wachinger 2021	170	26	94	1306	0.64 [0.58, 0.70]	0.98 [0.97, 0.99]
Andreani 2021 [B]	79	1	45	114	0.64 [0.55, 0.72]	0.99 [0.95, 1.00]
Homza 2021 [C]	26	1	16	96	0.62 [0.46, 0.76]	0.99 [0.94, 1.00]
Fourati 2021 [B]	176	23	113	314	0.61 [0.55, 0.67]	0.93 [0.90, 0.96]
Fourati 2020 [B]	175	23	116	314	0.60 [0.54, 0.66]	0.93 [0.90, 0.96]
Boum 2021	170	54	121	745	0.58 [0.53, 0.64]	0.93 [0.91, 0.95]
Ristic 2021	25	0	18	77	0.58 [0.42, 0.73]	1.00 [0.95, 1.00]
Van Honacker 2021 [F]	200	12	169	3826	0.54 [0.49, 0.59]	1.00 [0.99, 1.00]
Turcato 2021 [B]	27	10	27	2355	0.50 [0.36, 0.64]	1.00 [0.99, 1.00]
Olearo 2021 [A]	42	0	42	100	0.50 [0.39, 0.61]	1.00 [0.96, 1.00]
Osterman 2021 [A]	173	6	208	294	0.45 [0.40, 0.51]	0.98 [0.96, 0.99]
Korenkov 2021	90	2	120	1816	0.43 [0.36, 0.50]	1.00 [1.00, 1.00]
Caruana 202105	2	2	5	107	0.29 [0.04, 0.71]	0.98 [0.94, 1.00]
Oh 2021	7	0	33	78	0.17 [0.07, 0.33]	1.00 [0.95, 1.00]

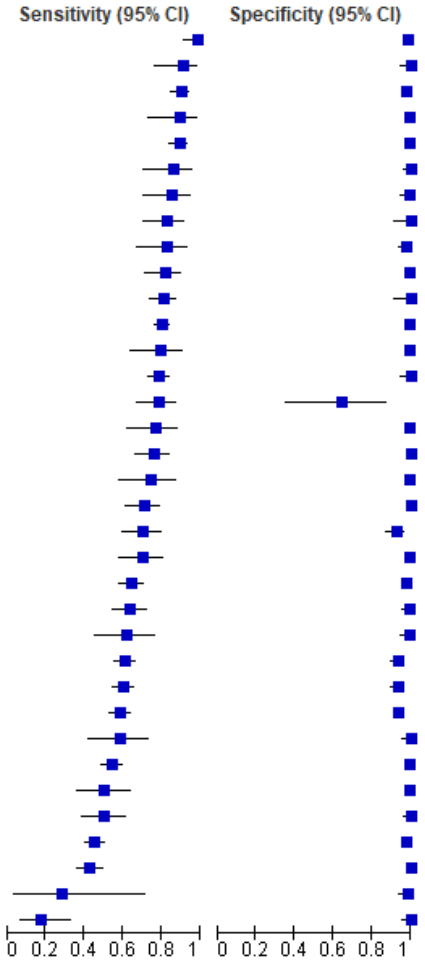


Figure 11. Sensitivity and specificity of Standard Q COVID-19 Ag Test (SD Biosensor)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Martin-Sanchez 2021	214	3	7	657	0.97 [0.94, 0.99]	1.00 [0.99, 1.00]
Von Ahnen 2021	12	0	1	906	0.92 [0.64, 1.00]	1.00 [1.00, 1.00]
Schildgen 2020 [C]	37	25	5	6	0.88 [0.74, 0.96]	0.19 [0.07, 0.37]
Igloi 2021	158	4	28	780	0.85 [0.79, 0.90]	0.99 [0.99, 1.00]
Mockel 2021	67	0	22	182	0.75 [0.65, 0.84]	1.00 [0.98, 1.00]
Iqbal 2021	92	1	35	42	0.72 [0.64, 0.80]	0.98 [0.88, 1.00]
Montero 2021	35	8	14	2486	0.71 [0.57, 0.83]	1.00 [0.99, 1.00]
Kruttgen 2020	53	3	22	72	0.71 [0.59, 0.81]	0.96 [0.89, 0.99]
Favresse 2021 [D]	67	0	29	92	0.70 [0.60, 0.79]	1.00 [0.96, 1.00]
Jegerlehner 2021	92	2	49	1319	0.65 [0.57, 0.73]	1.00 [0.99, 1.00]
Schuit 2021 [B]	83	8	49	1456	0.63 [0.54, 0.71]	0.99 [0.99, 1.00]
Koeleman 2021 [B]	25	5	15	35	0.63 [0.46, 0.77]	0.88 [0.73, 0.96]
Stohr 2021 [B]	118	4	74	1387	0.61 [0.54, 0.68]	1.00 [0.99, 1.00]
Osterman 2021 [B]	224	8	221	318	0.50 [0.46, 0.55]	0.98 [0.95, 0.99]
Baro 2021 [C]	44	7	57	178	0.44 [0.34, 0.54]	0.96 [0.92, 0.98]
Osterman 202108 [B]	33	7	72	296	0.31 [0.23, 0.41]	0.98 [0.95, 0.99]

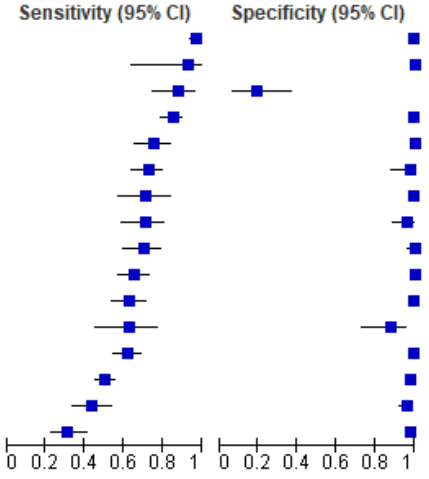


Figure 12. Sensitivity and specificity of Roche SARS-CoV-2 Rapid Antigen Test (Roche Diagnostics)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sood 2021	127	99	9	539	0.93 [0.88, 0.97]	0.84 [0.81, 0.87]
Bachman 2021 [C]	84	5	8	72	0.91 [0.84, 0.96]	0.94 [0.85, 0.98]
Pilarowski 2021 [A]	211	3	26	3062	0.89 [0.84, 0.93]	1.00 [1.00, 1.00]
Shaikh 2021	39	16	7	137	0.85 [0.71, 0.94]	0.90 [0.84, 0.94]
James 2021 [A]	20	0	4	91	0.83 [0.63, 0.95]	1.00 [0.96, 1.00]
Bachman 2021 [G]	89	0	20	60	0.82 [0.73, 0.88]	1.00 [0.94, 1.00]
Pollock 202104	226	12	66	2004	0.77 [0.72, 0.82]	0.99 [0.99, 1.00]
Shah 2021	258	7	76	1769	0.77 [0.72, 0.82]	1.00 [0.99, 1.00]
Prince-Guerra 2021 [C]	101	0	41	520	0.71 [0.63, 0.78]	1.00 [0.99, 1.00]
Frediani 2021	93	2	39	207	0.70 [0.62, 0.78]	0.99 [0.97, 1.00]
McKay 2021	72	8	33	419	0.69 [0.59, 0.77]	0.98 [0.96, 0.99]
Prince-Guerra 2021 [A]	113	0	63	651	0.64 [0.57, 0.71]	1.00 [0.99, 1.00]
Prince-Guerra 2021 [D]	113	0	63	651	0.64 [0.57, 0.71]	1.00 [0.99, 1.00]
Okoye 2021	24	0	21	2593	0.53 [0.38, 0.68]	1.00 [1.00, 1.00]
Allan-Blitz 2021	1550	189	1603	15115	0.49 [0.47, 0.51]	0.99 [0.99, 0.99]
Prince-Guerra 2021 [B]	44	4	79	2465	0.36 [0.27, 0.45]	1.00 [1.00, 1.00]
James 2021 [B]	3	62	2093	0	0.00 [0.00, 0.00]	0.00 [0.00, 0.06]
Stokes 202109	0	1	6	990	0.00 [0.00, 0.46]	1.00 [0.99, 1.00]

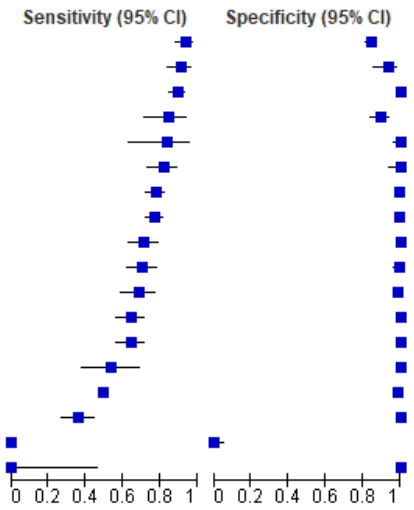


Figure 13. Sensitivity and specificity of Binax NOW SARS-CoV-2 (Abbott)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Porte 2020b [A]	30	1	2	31	0.94 [0.79, 0.99]	0.97 [0.84, 1.00]
Bachman 2021 [B]	79	3	13	75	0.86 [0.77, 0.92]	0.96 [0.89, 0.99]
Jaaskelainen 2021 [A]	119	0	29	40	0.80 [0.73, 0.86]	1.00 [0.91, 1.00]
Pray 2021 [A]	32	2	8	185	0.80 [0.64, 0.91]	0.99 [0.96, 1.00]
Herrera 2020	352	6	107	707	0.77 [0.73, 0.80]	0.99 [0.98, 1.00]
Bachman 2021 [F]	81	1	29	59	0.74 [0.64, 0.82]	0.98 [0.91, 1.00]
Ford 2021	37	15	17	982	0.69 [0.54, 0.80]	0.98 [0.98, 0.99]
Brihn 2021	98	12	51	1878	0.66 [0.58, 0.73]	0.99 [0.99, 1.00]
Bornemann 2021	52	9	39	1291	0.57 [0.46, 0.67]	0.99 [0.99, 1.00]
Pray 2021 [B]	7	14	10	840	0.41 [0.18, 0.67]	0.98 [0.97, 0.99]

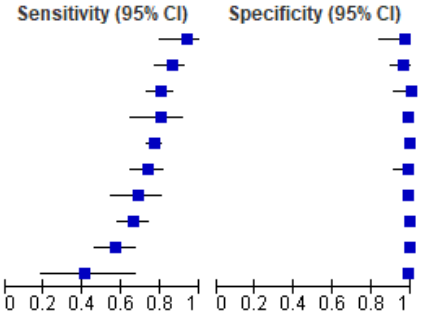


Figure 14. Sensitivity and specificity of Sofia SARS Antigen Fluorescent Immunoassay (Quidel)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bruzzone 2021 [E]	60	0	0	0	1.00 [0.94, 1.00]	Not estimable
Porte 2020b [B]	29	1	3	31	0.91 [0.75, 0.98]	0.97 [0.84, 1.00]
Garcia 2021 [B]	113	5	57	181	0.66 [0.59, 0.74]	0.97 [0.94, 0.99]
Kahn 2021	57	39	31	2983	0.65 [0.54, 0.75]	0.99 [0.98, 0.99]
Liotti 2020	49	4	55	251	0.47 [0.37, 0.57]	0.98 [0.96, 1.00]
Kiro 2021	52	2	84	216	0.38 [0.30, 0.47]	0.99 [0.97, 1.00]
Baccani 2021 [B]	10	0	18	65	0.36 [0.19, 0.56]	1.00 [0.94, 1.00]

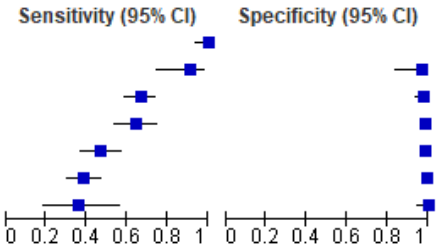


Figure 15. Sensitivity and specificity of Standard F Covid19 Ag FIA (SD Biosensor)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Shrestha 2020	40	0	7	66	0.85 [0.72, 0.94]	1.00 [0.95, 1.00]
Bruzzone 2021 [D]	15	0	8	0	0.65 [0.43, 0.84]	Not estimable
Abusrewil 2021 [C]	10	0	6	23	0.63 [0.35, 0.85]	1.00 [0.85, 1.00]
Weitzel 2020 [A]	49	0	30	30	0.62 [0.50, 0.73]	1.00 [0.88, 1.00]
Abdelrazik 2021	81	0	107	122	0.43 [0.36, 0.50]	1.00 [0.97, 1.00]
Schildgen 2020 [A]	14	4	28	27	0.33 [0.20, 0.50]	0.87 [0.70, 0.96]
Mak 2020	51	0	109	0	0.32 [0.25, 0.40]	Not estimable

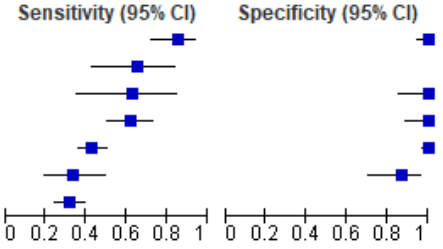


Figure 16. Sensitivity and specificity of Biocredit COVID-19 Ag test (RapiGEN)

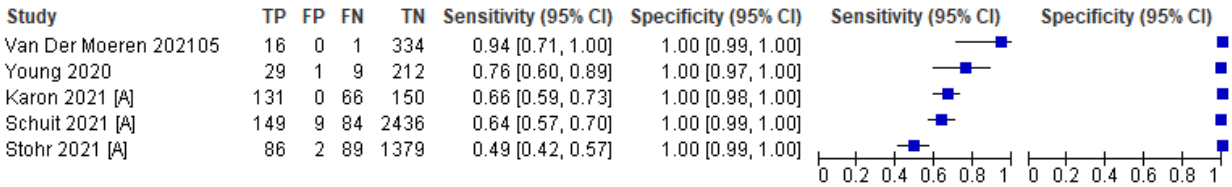


Figure 17. Sensitivity and specificity of COVID-19 Rapid Antigen Test (BD Veritor)

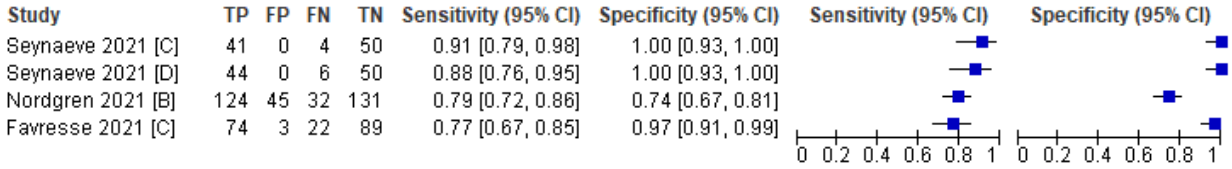


Figure 18. Sensitivity and specificity of Coronavirus Ag Rapid Test Cassette (Healgen Scientific)

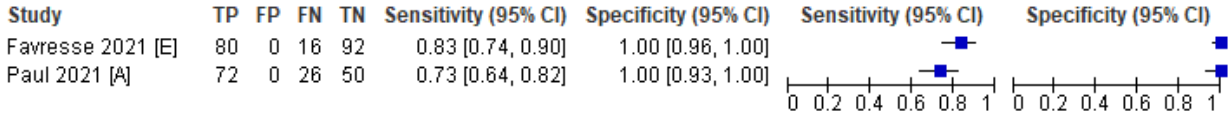


Figure 19. Sensitivity and specificity of VITROS Immunodiagnostic Products SARS-CoV-2 Antigen test (Ortho Clinical Diagnostics)

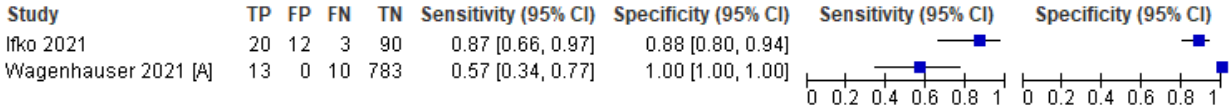


Figure 20. Sensitivity and specificity of NADAL COVID-19 Rapid Antigen Test (Nal Von Minden)

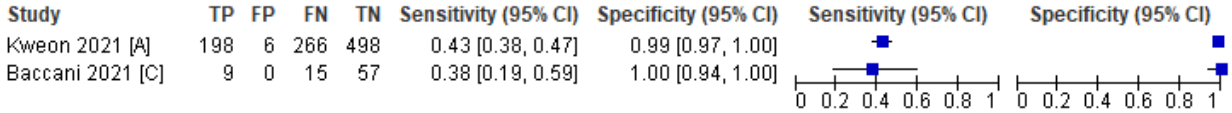


Figure 21. Sensitivity and specificity of AFIAS COVID-19 Ag (AFC) (Menarini)

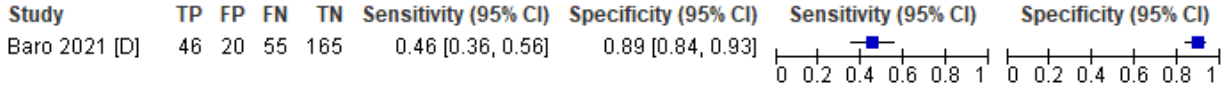


Figure 22. Sensitivity and specificity of SARS-CoV-2 Antigen Rapid Test Kit (Lepu Medical)

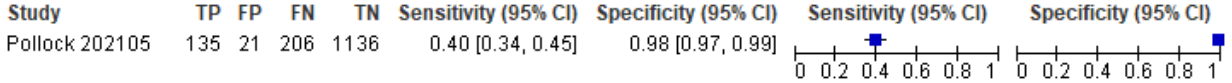


Figure 23. Sensitivity and specificity of CareStart COVID-19 Antigen Test (Access Bio)

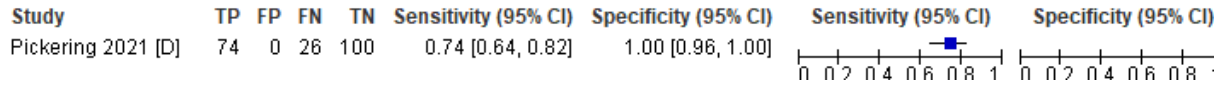


Figure 24. Sensitivity and specificity of Encode SARS-CoV-2 Antigen Rapid Test Device (Zhuhai Encode Medical Engineering)

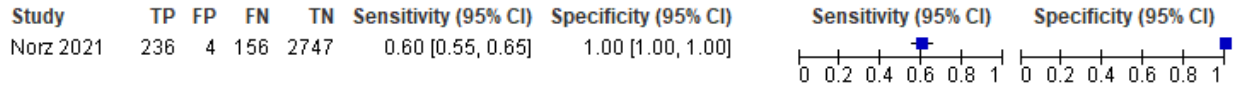


Figure 25. Sensitivity and specificity of Elecsys SARS-CoV-2 Antigen assay (Roche)

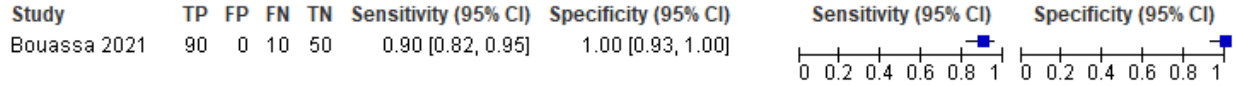


Figure 26. Sensitivity and specificity of SIENNA COVID-19 Antigen Rapid Test Cassette

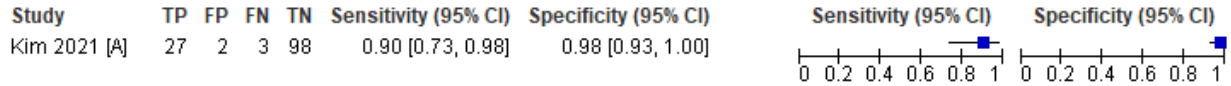


Figure 27. Sensitivity and specificity of GenBody COVAG025 Rapid Antigen Test

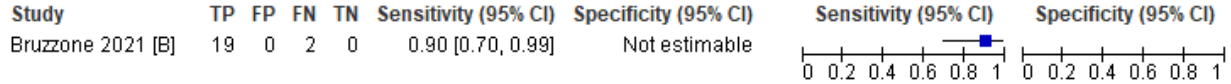


Figure 28. Sensitivity and specificity of Humasis COVID-Ag Test COVID-19 Antigen (Humasis)

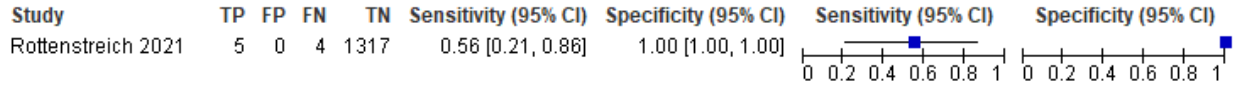


Figure 29. Sensitivity and specificity of NowCheck COVID-19 Ag Test (Bionote)

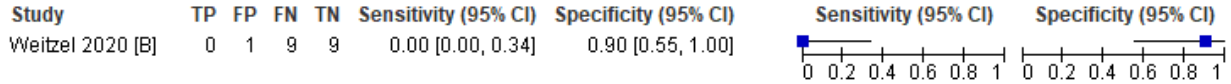


Figure 30. Sensitivity and specificity of StrongStep Rapid Antigen Test (Liming)

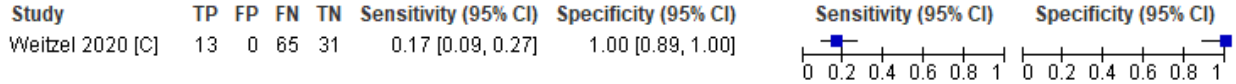


Figure 31. Sensitivity and specificity of Huaketai SARS-CoV-2 Rapid Antigen Test (Savant)

Figure 32. Sensitivity and specificity of SARS-CoV-2 Antigen Rapid Test Kit (JOYSBIO)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kweon 2021 [B]	192	0	272	502	0.41 [0.37, 0.46]	1.00 [0.99, 1.00]

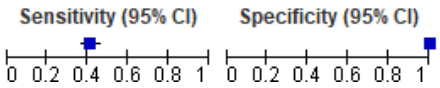


Figure 33. Sensitivity and specificity of ichromaTM COVID-19 Ag (Boditech)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Van Honacker 2021 [C]	32	0	0	0	1.00 [0.89, 1.00]	Not estimable
Van Honacker 2021 [A]	32	0	0	0	1.00 [0.89, 1.00]	Not estimable
Van Honacker 2021 [E]	32	0	0	0	1.00 [0.89, 1.00]	Not estimable
Porte 2020b [B]	27	0	0	0	1.00 [0.87, 1.00]	Not estimable
Porte 2020b [A]	27	0	0	0	1.00 [0.87, 1.00]	Not estimable
Porte 2020a	52	0	0	0	1.00 [0.93, 1.00]	Not estimable
Takeda 2020	32	0	0	0	1.00 [0.89, 1.00]	Not estimable
Scohy 2020	10	0	0	0	1.00 [0.69, 1.00]	Not estimable
PHE 2020(b)	8	0	0	0	1.00 [0.63, 1.00]	Not estimable
Leixner 2021	33	0	0	0	1.00 [0.89, 1.00]	Not estimable
Jung 2021	23	0	0	0	1.00 [0.85, 1.00]	Not estimable
Kim 2021 [A]	15	0	0	0	1.00 [0.78, 1.00]	Not estimable
Kruger 2020(c)	18	0	0	0	1.00 [0.81, 1.00]	Not estimable
Fenollar 2020(b)	1	0	0	0	1.00 [0.03, 1.00]	Not estimable
Baccani 2021 [C]	5	0	0	0	1.00 [0.48, 1.00]	Not estimable
Baccani 2021 [B]	5	0	0	0	1.00 [0.48, 1.00]	Not estimable
Baccani 2021 [A]	5	0	0	0	1.00 [0.48, 1.00]	Not estimable
Weitzel 2020 [D]	54	0	0	0	1.00 [0.93, 1.00]	Not estimable
Jaaskelainen 2021 [B]	96	0	1	0	0.99 [0.94, 1.00]	Not estimable
Alemany 2020	557	0	6	0	0.99 [0.98, 1.00]	Not estimable
Jaaskelainen 2021 [A]	88	0	1	0	0.99 [0.94, 1.00]	Not estimable
PHE 2020(a)	58	0	1	0	0.98 [0.91, 1.00]	Not estimable
Kweon 2021 [B]	107	0	2	0	0.98 [0.94, 1.00]	Not estimable
Jaaskelainen 2021 [C]	90	0	2	0	0.98 [0.92, 1.00]	Not estimable
Kurihara 2021	44	0	1	0	0.98 [0.88, 1.00]	Not estimable
Garcia 2021 [B]	82	0	2	0	0.98 [0.92, 1.00]	Not estimable
Soleimani 2021][B]	151	0	5	0	0.97 [0.93, 0.99]	Not estimable
Van Honacker 2021 [D]	30	0	1	0	0.97 [0.83, 1.00]	Not estimable
Garcia 2021 [A]	81	0	3	0	0.96 [0.90, 0.99]	Not estimable
Fenollar 2020(a)	106	0	4	0	0.96 [0.91, 0.99]	Not estimable
Kweon 2021 [A]	105	0	4	0	0.96 [0.91, 0.99]	Not estimable
Halfon 2021	52	0	2	0	0.96 [0.87, 1.00]	Not estimable
Fourati 2020 [E]	125	0	5	0	0.96 [0.91, 0.99]	Not estimable
Fourati 2021 [D]	125	0	5	0	0.96 [0.91, 0.99]	Not estimable
Kruger 2021	69	0	3	0	0.96 [0.88, 0.99]	Not estimable
Van Honacker 2021 [F]	161	0	8	0	0.95 [0.91, 0.98]	Not estimable
Liotti 2020	20	0	1	0	0.95 [0.76, 1.00]	Not estimable
Hartard 2021	39	0	2	0	0.95 [0.83, 0.99]	Not estimable
Paul 2021 [A]	66	0	4	0	0.94 [0.86, 0.98]	Not estimable
Eleftheriou 2021	33	0	2	0	0.94 [0.81, 0.99]	Not estimable
Fourati 2021 [F]	122	0	8	0	0.94 [0.88, 0.97]	Not estimable
Fourati 2020 [D]	122	0	8	0	0.94 [0.88, 0.97]	Not estimable
Nordgren 2021 [B]	106	0	7	0	0.94 [0.88, 0.97]	Not estimable
Van Honacker 2021 [B]	30	0	2	0	0.94 [0.79, 0.99]	Not estimable
Montero 2021	30	0	2	0	0.94 [0.79, 0.99]	Not estimable
Fourati 2021 [B]	121	0	9	0	0.93 [0.87, 0.97]	Not estimable
Fourati 2020 [B]	118	0	9	0	0.93 [0.87, 0.97]	Not estimable
Hauser 2021	52	0	5	0	0.91 [0.81, 0.97]	Not estimable
Kim 2021 [B]	49	0	5	0	0.91 [0.80, 0.97]	Not estimable
Nash 2020	48	0	5	0	0.91 [0.79, 0.97]	Not estimable
Soleimani 2021 [A]	141	0	15	0	0.90 [0.85, 0.95]	Not estimable
Kruger 2020(a)	8	0	1	0	0.89 [0.52, 1.00]	Not estimable
Nordgren 2021 [A]	100	0	13	0	0.88 [0.81, 0.94]	Not estimable
Fourati 2020 [C]	113	0	17	0	0.87 [0.80, 0.92]	Not estimable
PHE 2020(c) [non-HCW tested]	92	0	14	0	0.87 [0.79, 0.93]	Not estimable
Veyrenche 2020	13	0	2	0	0.87 [0.60, 0.98]	Not estimable
Bulilete 2021	38	0	6	0	0.86 [0.73, 0.95]	Not estimable
Ford 2021	23	0	4	0	0.85 [0.66, 0.96]	Not estimable
Weitzel 2020 [A]	45	0	8	0	0.85 [0.72, 0.93]	Not estimable
Lambert-Niclot 2020	37	0	8	0	0.82 [0.68, 0.92]	Not estimable
Mertens 2020	65	0	23	0	0.74 [0.63, 0.83]	Not estimable
Fourati 2021 [A]	93	0	37	0	0.72 [0.63, 0.79]	Not estimable
Fourati 2020 [A]	91	0	37	0	0.71 [0.62, 0.79]	Not estimable
Finana 2021	25	0	11	0	0.69 [0.52, 0.84]	Not estimable
Fourati 2021 [C]	113	0	55	0	0.67 [0.60, 0.74]	Not estimable
Kruger 2020(b)	2	0	1	0	0.67 [0.09, 0.99]	Not estimable
Wachinger 2021	170	26	94	1306	0.64 [0.58, 0.70]	0.98 [0.97, 0.99]
Paul 2021 [B]	51	0	29	0	0.64 [0.52, 0.74]	Not estimable
Fourati 2021 [E]	81	0	49	0	0.62 [0.53, 0.71]	Not estimable
Thakur 2021	27	0	33	0	0.45 [0.32, 0.58]	Not estimable
Oh 2021	7	0	10	101	0.41 [0.18, 0.67]	1.00 [0.96, 1.00]
Weitzel 2020 [C]	11	0	41	0	0.21 [0.11, 0.35]	Not estimable

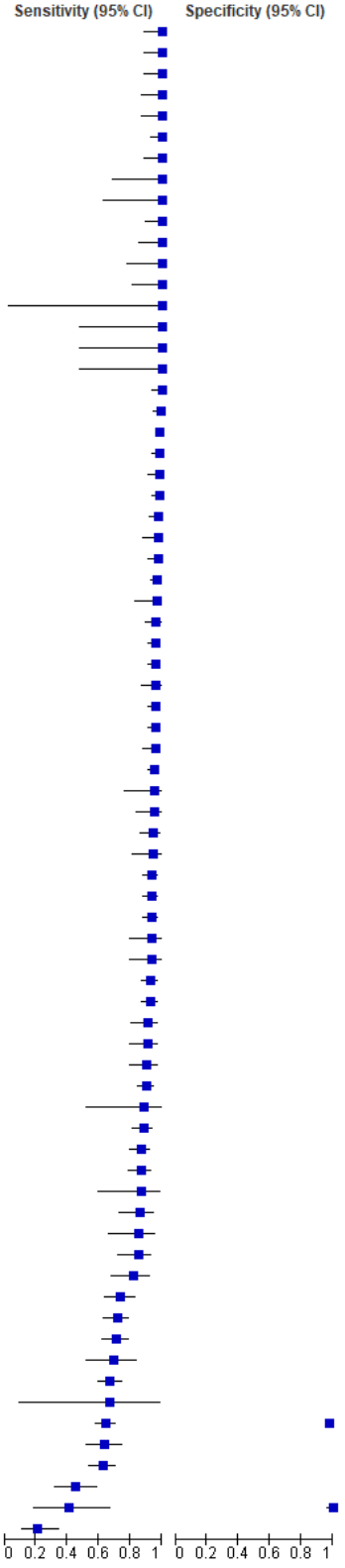


Figure 34. Sensitivity and specificity of RAgT if Ct value < 25

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baccani 2021 [A]	9	0	0	0	1.00 [0.66, 1.00]	Not estimable
Kim 2021 [B]	45	0	1	0	0.98 [0.88, 1.00]	Not estimable
Van Honacker 2021 [A]	30	0	6	0	0.83 [0.67, 0.94]	Not estimable
Jaaskelainen 2021 [A]	28	0	6	0	0.82 [0.65, 0.93]	Not estimable
Alemany 2020	315	0	73	0	0.81 [0.77, 0.85]	Not estimable
Kim 2021 [A]	11	0	3	0	0.79 [0.49, 0.95]	Not estimable
Jaaskelainen 2021 [C]	26	0	8	0	0.76 [0.59, 0.89]	Not estimable
Porte 2020a	13	0	5	0	0.72 [0.47, 0.90]	Not estimable
Van Honacker 2021 [C]	26	0	10	0	0.72 [0.55, 0.86]	Not estimable
Jaaskelainen 2021 [B]	24	0	11	0	0.69 [0.51, 0.83]	Not estimable
Nash 2020	32	0	15	0	0.68 [0.53, 0.81]	Not estimable
Kruger 2021	22	0	11	0	0.67 [0.48, 0.82]	Not estimable
Kruger 2020(c)	18	0	11	0	0.62 [0.42, 0.79]	Not estimable
Van Honacker 2021 [E]	16	0	10	0	0.62 [0.41, 0.80]	Not estimable
Porte 2020b [A]	3	0	2	0	0.60 [0.15, 0.95]	Not estimable
Takeda 2020	18	0	12	0	0.60 [0.41, 0.77]	Not estimable
Jung 2021	6	0	4	0	0.60 [0.26, 0.88]	Not estimable
Van Honacker 2021 [D]	15	0	11	0	0.58 [0.37, 0.77]	Not estimable
Eleftheriou 2021	9	0	7	0	0.56 [0.30, 0.80]	Not estimable
Ford 2021	15	0	12	0	0.56 [0.35, 0.75]	Not estimable
Baccani 2021 [C]	5	0	4	0	0.56 [0.21, 0.86]	Not estimable
Weitzel 2020 [D]	14	0	12	0	0.54 [0.33, 0.73]	Not estimable
Fenollar 2020(a)	38	0	34	0	0.53 [0.41, 0.65]	Not estimable
Kurihara 2021	18	0	20	0	0.47 [0.31, 0.64]	Not estimable
PHE 2020(c) [non-HCW tested]	122	0	144	0	0.46 [0.40, 0.52]	Not estimable
Baccani 2021 [B]	4	0	5	0	0.44 [0.14, 0.79]	Not estimable
Halfon 2021	20	0	26	0	0.43 [0.29, 0.59]	Not estimable
Fenollar 2020(b)	9	0	12	0	0.43 [0.22, 0.66]	Not estimable
Nordgren 2021 [B]	18	0	25	0	0.42 [0.27, 0.58]	Not estimable
Porte 2020b [B]	2	0	3	0	0.40 [0.05, 0.85]	Not estimable
Kruger 2020(b)	2	0	3	0	0.40 [0.05, 0.85]	Not estimable
Garcia 2021 [B]	31	0	55	0	0.36 [0.26, 0.47]	Not estimable
Fourati 2020 [B]	57	0	103	0	0.36 [0.28, 0.44]	Not estimable
Fourati 2021 [B]	58	0	105	0	0.36 [0.28, 0.43]	Not estimable
Bulilete 2021	7	0	13	0	0.35 [0.15, 0.59]	Not estimable
Liotti 2020	29	0	54	0	0.35 [0.25, 0.46]	Not estimable
Fourati 2020 [E]	56	0	105	0	0.35 [0.27, 0.43]	Not estimable
Van Honacker 2021 [B]	9	0	17	0	0.35 [0.17, 0.56]	Not estimable
Fourati 2021 [D]	56	0	107	0	0.34 [0.27, 0.42]	Not estimable
Fourati 2020 [D]	55	0	108	0	0.34 [0.27, 0.42]	Not estimable
Fourati 2021 [F]	55	0	108	0	0.34 [0.27, 0.42]	Not estimable
PHE 2020(a)	37	0	82	0	0.31 [0.23, 0.40]	Not estimable
Fourati 2020 [C]	49	0	112	0	0.30 [0.23, 0.38]	Not estimable
Fourati 2021 [C]	49	0	114	0	0.30 [0.23, 0.38]	Not estimable
Montero 2021	5	0	12	0	0.29 [0.10, 0.56]	Not estimable
Nordgren 2021 [A]	12	0	31	0	0.28 [0.15, 0.44]	Not estimable
Van Honacker 2021 [F]	39	0	109	0	0.26 [0.19, 0.34]	Not estimable
Kweon 2021 [A]	93	0	262	0	0.26 [0.22, 0.31]	Not estimable
Kruger 2020(a)	2	0	6	0	0.25 [0.03, 0.65]	Not estimable
Mertens 2020	11	0	33	0	0.25 [0.13, 0.40]	Not estimable
Garcia 2021 [A]	21	0	65	0	0.24 [0.16, 0.35]	Not estimable
Kweon 2021 [B]	85	0	270	0	0.24 [0.20, 0.29]	Not estimable
Scohy 2020	22	0	74	0	0.23 [0.15, 0.33]	Not estimable
Lambert-Niclot 2020	10	0	39	0	0.20 [0.10, 0.34]	Not estimable
Weitzel 2020 [A]	4	0	22	0	0.15 [0.04, 0.35]	Not estimable
Hauser 2021	16	0	96	0	0.14 [0.08, 0.22]	Not estimable
PHE 2020(b)	5	0	33	0	0.13 [0.04, 0.28]	Not estimable
Fourati 2021 [E]	15	0	148	0	0.09 [0.05, 0.15]	Not estimable
Finana 2021	3	0	31	0	0.09 [0.02, 0.24]	Not estimable
Thakur 2021	4	0	44	0	0.08 [0.02, 0.20]	Not estimable
Weitzel 2020 [C]	2	0	24	0	0.08 [0.01, 0.25]	Not estimable
Fourati 2020 [A]	12	0	148	0	0.07 [0.04, 0.13]	Not estimable
Fourati 2021 [A]	12	0	151	0	0.07 [0.04, 0.13]	Not estimable
Veyrenche 2020	0	0	30	0	0.00 [0.00, 0.12]	Not estimable
Hartard 2021	0	0	5	0	0.00 [0.00, 0.52]	Not estimable

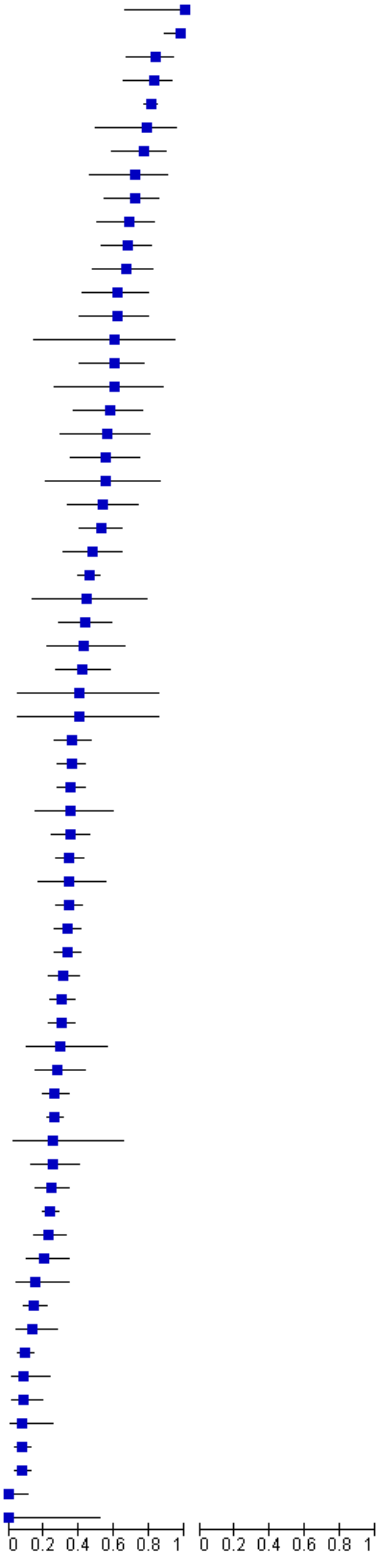


Figure 35. Sensitivity and specificity of RAgT if Ct value > 25

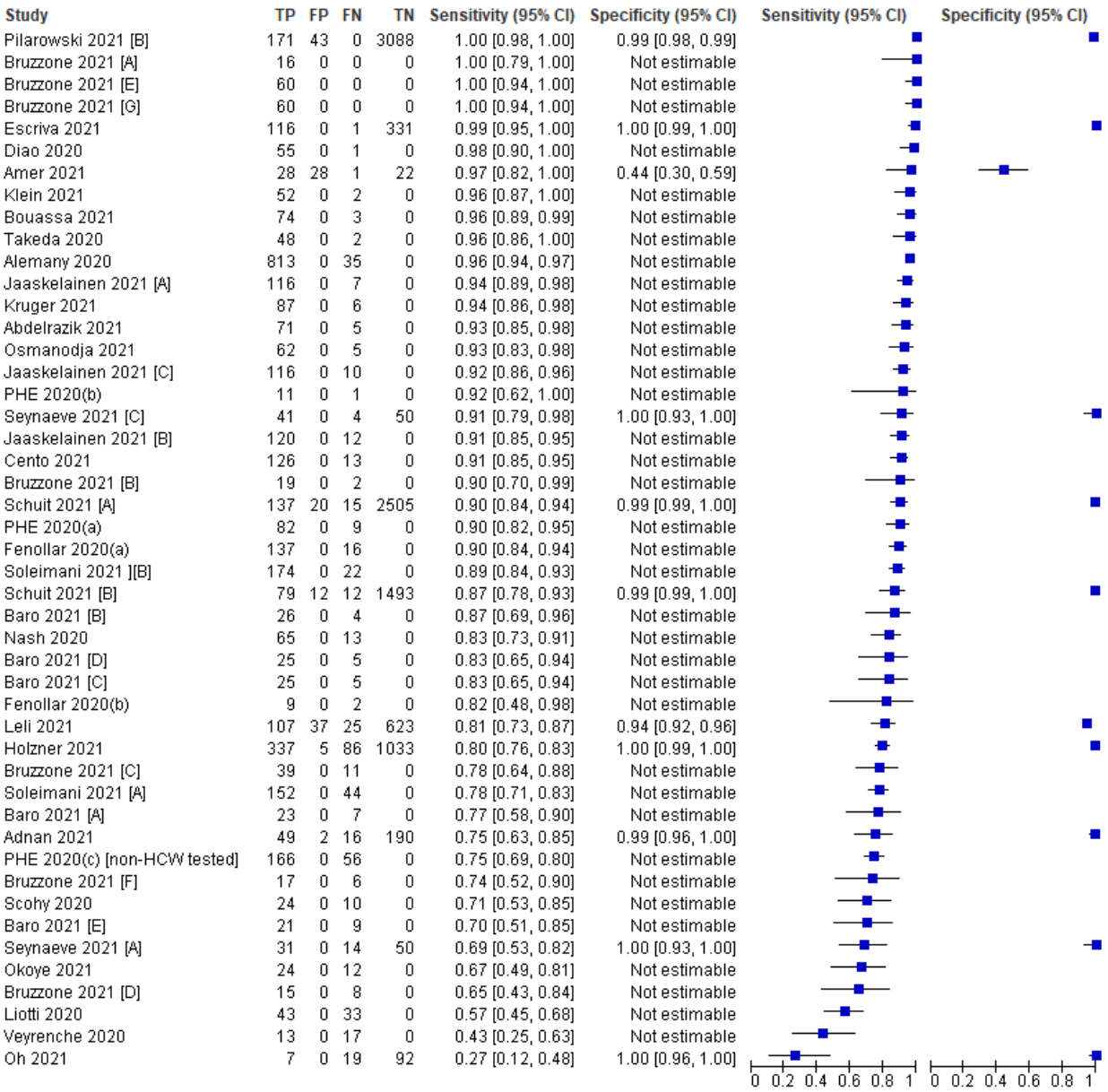


Figure 36. Sensitivity and specificity of RAgT if other Ct thresholds for 'higher' viral load

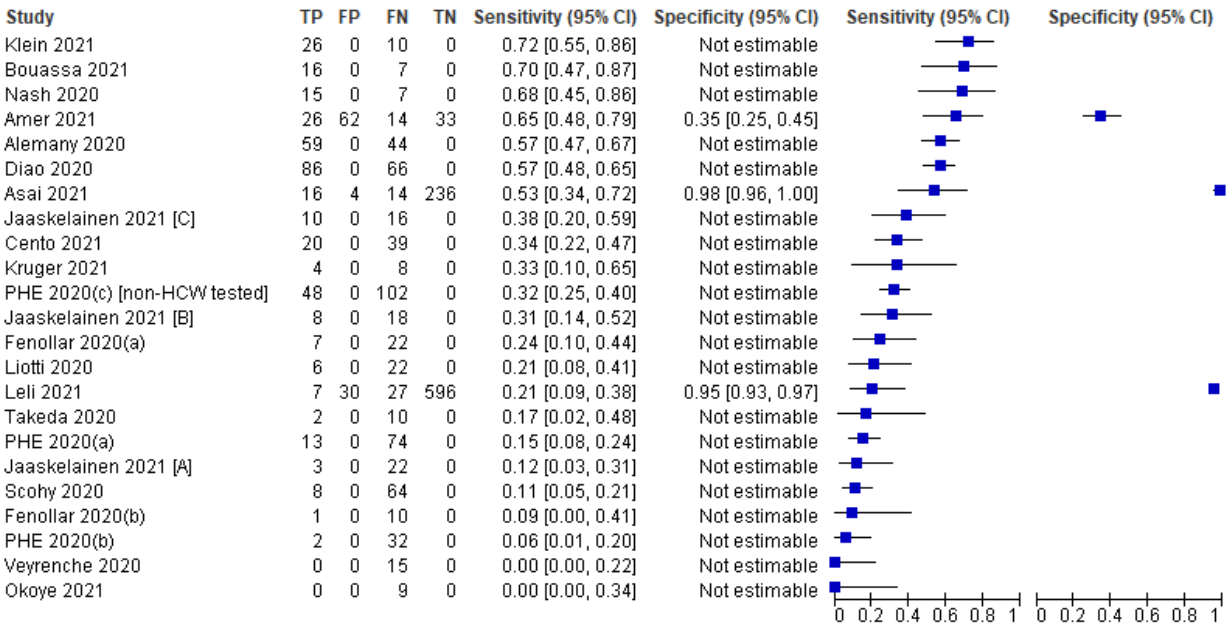


Figure 37. Sensitivity and specificity of RAgT if other Ct thresholds for ‘lower' viral load

Saliva

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ishii 2021 [D]	8	1	0	123	1.00 [0.63, 1.00]	0.99 [0.96, 1.00]
Kobayashi 2021 [B]	111	3	3	5272	0.97 [0.93, 0.99]	1.00 [1.00, 1.00]
Asai 2021	49	4	14	238	0.78 [0.66, 0.87]	0.98 [0.96, 1.00]
Seitz 2021	8	0	10	22	0.44 [0.22, 0.69]	1.00 [0.85, 1.00]
Mak 2020	18	0	27	0	0.40 [0.26, 0.56]	Not estimable
Ishii 2021 [B]	3	0	6	84	0.33 [0.07, 0.70]	1.00 [0.96, 1.00]
Nagura-Ikeda 2020	12	0	91	0	0.12 [0.06, 0.19]	Not estimable
Uwamino 2021 [B]	4	0	37	0	0.10 [0.03, 0.23]	Not estimable

Sputum

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Mak 2020	5	0	40	0	0.11 [0.04, 0.24]	Not estimable

NP + saliva

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Yokota 2021	31	2	3	307	0.91 [0.76, 0.98]	0.99 [0.98, 1.00]

Exhaled breath

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Maniscalco 2021	12	1	1	91	0.92 [0.64, 1.00]	0.99 [0.94, 1.00]

OP

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nsoga 2021	136	2	32	232	0.81 [0.74, 0.87]	0.99 [0.97, 1.00]
Kahn 2021	57	39	31	2983	0.65 [0.54, 0.75]	0.99 [0.98, 0.99]
Wagenhauser 2021 [A]	13	0	10	783	0.57 [0.34, 0.77]	1.00 [1.00, 1.00]
Wagenhauser 2021 [B]	7	4	8	1010	0.47 [0.21, 0.73]	1.00 [0.99, 1.00]
Wagenhauser 2021 [C]	23	12	40	3146	0.37 [0.25, 0.50]	1.00 [0.99, 1.00]

Nasal + OP

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Allan-Blitz 2021	1550	189	1603	15115	0.49 [0.47, 0.51]	0.99 [0.99, 0.99]

Nasal (anterior nares + mid turbinate)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Denina 2021	16	14	1	160	0.94 [0.71, 1.00]	0.92 [0.87, 0.96]
Sood 2021	127	99	9	539	0.93 [0.88, 0.97]	0.84 [0.81, 0.87]
Bachman 2021 [C]	84	5	8	72	0.91 [0.84, 0.96]	0.94 [0.85, 0.98]
Bachman 2021 [D]	84	4	8	78	0.91 [0.84, 0.96]	0.95 [0.88, 0.99]
Nikolai 2021 [B]	31	0	3	62	0.91 [0.76, 0.98]	1.00 [0.94, 1.00]
Bianco 2021	269	48	29	561	0.90 [0.86, 0.93]	0.92 [0.90, 0.94]
Pilarowski 2021 [A]	211	3	26	3062	0.89 [0.84, 0.93]	1.00 [1.00, 1.00]
Osmanodja 2021	62	1	8	308	0.89 [0.79, 0.95]	1.00 [0.98, 1.00]
Nikolai 2021 [A]	31	0	5	96	0.86 [0.71, 0.95]	1.00 [0.96, 1.00]
Bachman 2021 [B]	79	3	13	75	0.86 [0.77, 0.92]	0.96 [0.89, 0.99]
Chiu 2021 [A]	64	14	11	260	0.85 [0.75, 0.92]	0.95 [0.92, 0.97]
Shaikh 2021	39	16	7	137	0.85 [0.71, 0.94]	0.90 [0.84, 0.94]
Klein 2021	38	2	7	243	0.84 [0.71, 0.94]	0.99 [0.97, 1.00]
Chiu 2021 [C]	32	18	6	22938	0.84 [0.69, 0.94]	1.00 [1.00, 1.00]
Bachman 2021 [A]	75	2	15	77	0.83 [0.74, 0.90]	0.97 [0.91, 1.00]
Chiu 2021 [B]	62	10	13	264	0.83 [0.72, 0.90]	0.96 [0.93, 0.98]
Lindner 202105 [A]	33	2	7	104	0.82 [0.67, 0.93]	0.98 [0.93, 1.00]
Kruger 202108	120	4	26	611	0.82 [0.75, 0.88]	0.99 [0.98, 1.00]
Bachman 2021 [G]	89	0	20	60	0.82 [0.73, 0.88]	1.00 [0.94, 1.00]
Pray 2021 [A]	32	2	8	185	0.80 [0.64, 0.91]	0.99 [0.96, 1.00]
Bachman 2021 [H]	87	1	23	59	0.79 [0.70, 0.86]	0.98 [0.91, 1.00]
Pollock 202104	226	12	66	2004	0.77 [0.72, 0.82]	0.99 [0.99, 1.00]
Muhi 2021	17	1	5	2580	0.77 [0.55, 0.92]	1.00 [1.00, 1.00]
Shah 2021	258	7	76	1769	0.77 [0.72, 0.82]	1.00 [0.99, 1.00]
Lindner 202104 [A]	29	2	10	246	0.74 [0.58, 0.87]	0.99 [0.97, 1.00]
Bachman 2021 [F]	81	1	29	59	0.74 [0.64, 0.82]	0.98 [0.91, 1.00]
Prince-Guerra 2021 [C]	101	0	41	520	0.71 [0.63, 0.78]	1.00 [0.99, 1.00]
Frediani 2021	93	2	39	207	0.70 [0.62, 0.78]	0.99 [0.97, 1.00]
Bachman 2021 [E]	75	2	33	57	0.69 [0.60, 0.78]	0.97 [0.88, 1.00]
Leli 2021	114	30	52	596	0.69 [0.61, 0.76]	0.95 [0.93, 0.97]
Ford 2021	37	15	17	982	0.69 [0.54, 0.80]	0.98 [0.98, 0.99]
McKay 2021	2	0	1	134	0.67 [0.09, 0.99]	1.00 [0.97, 1.00]
Brihn 2021	98	12	51	1878	0.66 [0.58, 0.73]	0.99 [0.99, 1.00]
Prince-Guerra 2021 [A]	113	0	63	651	0.64 [0.57, 0.71]	1.00 [0.99, 1.00]
Prince-Guerra 2021 [D]	113	0	63	651	0.64 [0.57, 0.71]	1.00 [0.99, 1.00]
Pray 2021 [B]	7	14	10	840	0.41 [0.18, 0.67]	0.98 [0.97, 0.99]
Pollock 202105	135	21	206	1136	0.40 [0.34, 0.45]	0.98 [0.97, 0.99]
Prince-Guerra 2021 [B]	44	4	79	2465	0.36 [0.27, 0.45]	1.00 [1.00, 1.00]

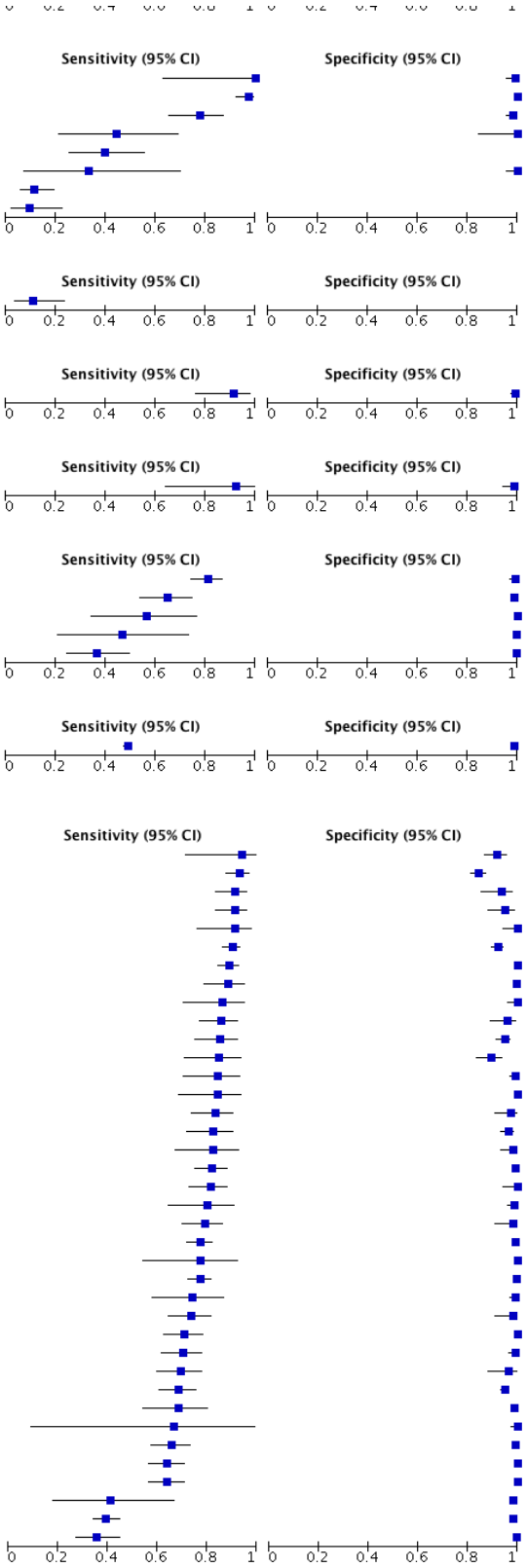


Figure 38. Sensitivity and specificity of RAgT per specimen

Q5. Among patients suspected to have COVID-19, how accurate are self-administered rapid antigen tests alone compared to RT-PCR for the diagnosis of COVID-19?

As of 11 November 2021

RECOMMENDATIONS

We suggest the use of self-administered rapid antigen test for the diagnosis of COVID-19 in symptomatic individuals, provided that ALL OF THE FOLLOWING conditions are met: *(Low certainty of evidence; Weak recommendation)*

1. Ease of collecting samples is ensured;
2. Ease of interpretation is ensured;
3. Test kits have passed flex studies; AND
4. Individuals present with symptoms for less than 7 days.

We suggest against the use of self-administered rapid antigen test for routine screening of COVID-19. *(Low certainty of evidence; Weak recommendation)*

Consensus Issues

The Panel unanimously agreed that all of the following four conditions should be met when using self-administered antigen tests for the diagnosis of COVID-19:

1. Ease of sample collection, because incorrect performance of self-administered tests largely affects diagnostic accuracy;
2. Ease of interpretation, because proper interpretation is important for the accurate clinical management of patients;
3. The test kits should have passed the flex studies, because the quality of the self-administered test kit should be ensured; and
4. Individuals present with symptoms for less than 7 days, because antigen tests perform best during this period; and beyond this, the use of the test is not cost-effective, thereby incurring costs without added benefit.

The panel decided on a weak recommendation based on evidence including seven observational studies where the performance of self-testing by participants was supervised by trained personnel either onsite or via telehealth. None were conducted in a home setting. Additionally, the studies did not specify if the participants were close contacts of COVID-19 patients or if they have a high- or low-risk of contracting COVID-19.

Other issues raised include (1) the lack of locally FDA-approved self-administered antigen test kits, (2) differentiating antigen tests manufactured for self-administration versus those that are not (i.e., for trained personnel), (3) the method of reporting the test results, and (4) the subsequent management and/or protocols after a positive test result (e.g., contact tracing).

KEY FINDINGS

- Seven observational studies assessed the diagnostic accuracy of self-administered rapid antigen tests against RT-PCR as the reference standard. The studies included varied test brands (n=6), specimen types, and symptom status.

- The pooled sensitivity of self-administered rapid antigen test was moderate at 0.77 (95% CI 0.62-0.87) while the pooled specificity was high at 0.996 (95% CI 0.99-1.00). Pooled sensitivity estimates must be interpreted with caution due to the substantial heterogeneity (I^2=94%) across studies.
- On subgroup analysis, self-administered rapid antigen test showed higher sensitivity when used in the following conditions:
  - Symptomatic individuals (Sn 0.81, 95% CI 0.69-0.89);
  - Specimens taken from exhaled breath (Sn 0.92, 95% CI 0.64-1.0) or nasal mid-turbinate (Sn 0.81, 95% CI 0.73-0.87);
  - Specimens with high viral loads at RT-PCR cycle threshold <25 (Sn 0.87, 95% CI 0.68-0.88);
  - Specific brands of rapid antigen test, namely Inflammacheck device (Sn 0.92, 95% CI 0.64-1.0), Drager antigen test (Sn 0.89, 95% CI 0.79-0.95), and Abbott Panbio (Sn 0.84, 95% CI 0.71-0.94); and
  - Studies with high methodological quality or low risk of bias (Sn 0.79, 95% CI 0.68-0.86).
- The overall certainty of the evidence for test sensitivity was low because of serious inconsistency (high heterogeneity) and risk of bias issues (patient selection, conduct of index test, and reference standard).

INTRODUCTION

Reverse-transcriptase polymerase chain reaction (RT-PCR) tests are considered the gold standard and the most sensitive option in the clinical diagnostic detection of SARS-CoV-2. However, RT-PCR-based assay is not entirely practical for all testing scenarios due to its need for additional specialized equipment, trained laboratory-based staff, and high cost. Recently, immunoassays such as rapid antigen tests (RAgTs) can detect the presence of specific viral antigens with a faster turnaround time, which may be performed at the point of care, and are relatively less expensive compared to RT-PCR tests.[1]

The review by Burog et al. in March 2021 showed that the pooled sensitivity and specificity of 30 studies and 10 evaluation reports on RAgTs were 72% (95% CI 64-78%, I^2=95.77) and 99% (95% CI 99-100%, I^2=93.16) respectively.[2] The pooled sensitivity of RAgTs was based on studies where testing was conducted by trained healthcare personnel. Only recently have studies evaluated the potential applicability of RAgTs among untrained users by way of self-administration.

Due to the ease of use of RAgTs, the use of self-administered RAgT or self-testing is being considered. As per World Health Organization (WHO) definition, self-testing involves either self-sampling, self-performance of testing, self-reading of test results, or all three. Self-administered RAgTs may potentially cut costs on personnel and equipment, with an added option of being done in the home setting.[1] Additionally, conventional nasopharyngeal swabs frequently induce pain and are perceived as uncomfortable and traumatizing.[3] However, the accuracy of self-testing or self-administration may be affected by the incorrect performance of the user or patient. Hence, in this review, the existing evidence on the diagnostic accuracy of self-administered RAgTs in detecting SARS-CoV-2 will be evaluated.

REVIEW METHODS

A literature search was done using MEDLINE. Medical subject headings (MESH) combined with free text terms related to COVID-19 or SARS-CoV-2 and rapid antigen tests/testing were used, with no language limits or method filters.

Preprint studies were identified using the COVID-19 Living Evidence Database (https://zika.ispm.unibe.ch/assets/data/pub/search_beta/) with "antigen" as the search term. This database is updated daily and includes preprints from medRxiv and bioRxiv, as well as published articles from EMBASE and PubMed. The Cochrane COVID-19 Study Register (covid-19.cochrane.org/) was also searched using "antigen" as a search term. A search for related links and journals was also carried out. Bibliography sections of the included studies were reviewed for relevant articles that might be missed by database search. The final search was done on September 14, 2021.

To supplement the initial search yield, available data on RAgT from the FIND SARS-CoV-2 Diagnostic pipeline (https://www.finddx.org/covid-19/dx-data/) was retrieved. Relevant clinical trials were searched on clinicaltrials.gov. Local publications such as health technology assessments on the use of RAgTs were also sought. Methodological qualities of the diagnostic studies were assessed by independent reviewers using the QUADAS-2 instrument.

Heterogeneity was determined by visual inspection of the forest plots. Because of anticipated heterogeneity across studies, pooled sensitivity and specificity estimates were derived by stratifying studies according to test brand, type of specimen used, cycle threshold value used, and participant characteristics. Summary estimates were computed externally through a web-based app (MetaDTA v2.01; https://crsu.shinyapps.io/dta_ma/). Sensitivity analysis was performed by removing studies with low methodologic quality or with risk of bias issues in certain QUADAS-2 domains, and subsequently assessing their impact on overall diagnostic accuracy estimates.

A total of 475 titles and abstracts were screened, among which 192 full-text articles with correspondence to the key question were retrieved. A review of the retrieved articles yielded seven studies that specifically tackled the diagnostic accuracy of self-administered RAgTs.

RESULTS

Characteristics of included studies

Seven observational studies including a total sample of 6,755 were found on self-administered antigen testing. Six different RAgT brands were evaluated using RT-PCR as the reference standard. All studies were done in a community setting. The studies used varied RAgT specimens: three used nasal mid-turbinate specimens [4-6], two used anterior nares specimens [7,8], one used combined nasal and oropharyngeal swabs [9], and one used exhaled breath condensates.[10] Three studies included only symptomatic patients [5,6,8], one included only asymptomatic patients [9], and three included both symptomatic and asymptomatic patients.[4,7,10] Only one study included children as participants, but the study did not provide sufficient data to allow subgroup analysis for this clinical population.[9] None of the studies were done in a home setting. All studies involved personnel who supervised

the participant at the study site. Appendix 3 shows a summary of the characteristics of included studies.

Methodological quality of included studies

The overall methodological quality of the included studies was rated as moderate. Two were rated as high quality [5,6] while five were of moderate quality [4,7-10] due to issues of unclear patient selection, index test, and reference standard. Appendix 4 shows a detailed assessment of the risk of bias in included studies.

Diagnostic accuracy of self-administered RAgT

A. Overall diagnostic accuracy

Pooled analysis of the seven studies showed that self-administered RAgT had a moderate sensitivity at 0.77 (95% CI 0.62-0.87) with high heterogeneity (I^2=94%), and excellent specificity at 0.996 (95% CI 0.99-1.00). Figure 1 shows the forest plots of the pooled sensitivity and a pooled specificity of self-administered RAgTs.

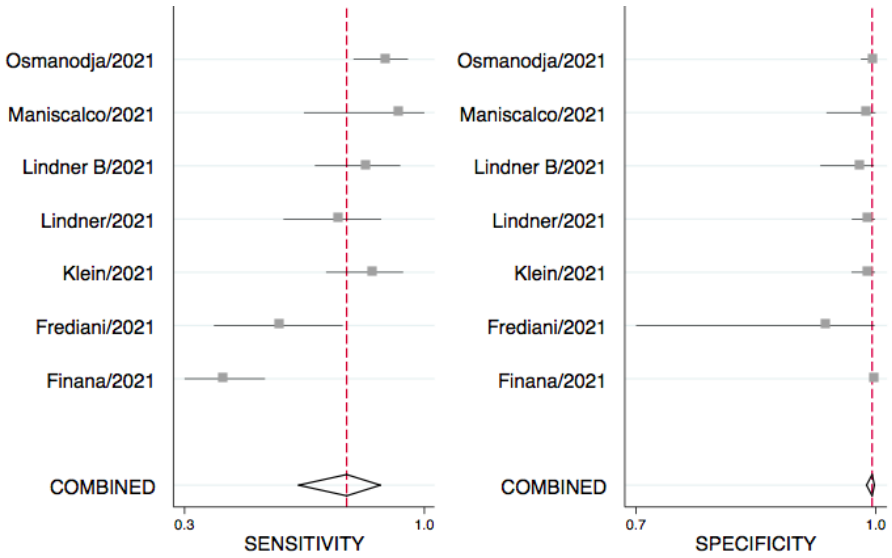


Figure 1. Forest plots of pooled sensitivity and specificity of self-administered RAgTs

B. Subgroup Analysis

Table 1 shows the sensitivity of self-administered RAgTs per subgroup.

Table 1. Subgroup Analysis for Sensitivity of Self-administered RAgTs

Variable	References	No. of Studies (no. of participants)	Sensitivity	95% CI
Presence of symptoms				
Mixed	[10]	1 (105)	0.92	(0.64, 1.00)
Symptomatic	[4-7,9]	5 (883)	0.81	(0.69, 0.89)
Asymptomatic	[4,7,8]	3 (5,765)	0.41	(0.31, 0.53)
Timing of testing in relation to symptoms				
Mixed	[4,5]	2 (577)	0.80	(0.70, 0.87)
Early	[5,7,9]	3 (569)	0.79	(0.62, 0.90)
Asymptomatic	[8]	1 (5,504)	0.40	(0.28, 0.52)
Test brand				
Inflammacheck® device (Exhalation technology LTD, Cambridge, UK)	[10]	1 (105)	0.92	(0.64, 1.00)

Dräger Antigen Test SARS-CoV-2 (Dräger Safety AG and Co. KGaA, Lübeck, Germany)	[7]	1 (379)	0.89	(0.79, 0.95)
Panbio™ Ag-RDT (Abbott)	[4]	1 (290)	0.84	(0.71, 0.94)
STANDARD Q COVID-19 Ag Test (SD Biosensor, Korea)	[5.6]	2 (433)	0.79	(0.68, 0.86)
BinaxNOW SARS-CoV-2 (Abbott)	[9]	1 (44)	0.57	(0.37, 0.76)
Innova LFT (Innova Medical Group Inc)	[8]	1 (5,504)	0.40	(0.28, 0.52)
Specimen type				
Exhaled breath condensate	[10]	1 (105)	0.92	(0.64, 1.00)
Nasal mid-turbinate	[4-6]	3 (723)	0.81	(0.73, 0.87)
Anterior nares	[7,9]	2 (423)	0.77	(0.49, 0.92)
Nasal + oropharyngeal	[8]	1 (5,504)	0.40	(0.28, 0.52)
Cycle threshold (Ct) value				
Low (<25)[a]	[4,8]	2 (63)	0.87	(0.86, 0.87)
Mixed[b]	[5-7,9,10]	5 (961)	0.80	(0.68, 0.88)
High (>25)[c]	[4,8]	2 (52)	0.30	(0.05, 0.79)
Methodological quality				
Studies with no serious risk of bias	[5,6]	2 (433)	0.79	(0.68, 0.86)
Studies with serious risk of bias				
related to patient selection	[4,7,10]	3 (774)	0.88	(0.80, 0.93)
related to index test administration	[7-9]	3 (5,927)	0.63	(0.55, 0.70)
related to reference standard administration	[4,9]	2 (334)	0.74	(0.62, 0.84)

[a] One study [8] used Ct values of 18.3-24.4, while another study [4] used 12.7-23.1.
[b] One study [6] used Ct values of 17.3-35.5, while four studies [5,7,9,10] did not report any Ct value.
[c] One study [8] used Ct values of 24.4-35.5, while another study [4] used 23.1-34.5.

By presence of symptoms

The pooled sensitivity of self-administered RAgTs was higher in symptomatic (Sn 0.81, 95% CI 0.69-0.89; n=883; 5 studies) than in asymptomatic individuals (Sn 0.41, 95% CI 0.31-0.53; n=3; 3 studies).

By time of testing in relation to symptom onset

When used during the early phase of the disease (0 to 7 days), the pooled sensitivity of self-administered RAgTs was 0.79 (95% CI 0.62-0.90; n=569; 3 studies). Studies that used self-administered RAgTs in both the early (0 to 7 days) and late phase (>7 days) of the disease had a pooled sensitivity of 0.80 (95% CI 0.70-0.87; n=577; 2 studies). None of the studies used self-administered RAgTs exclusively during the late phase.

By test brand

Among the brands of RAgTs, ***Inflammacheck® device*** had the highest pooled sensitivity (Sn 0.92, 95% CI 0.64-1.0; n=105). This specific RAgT uses exhaled breath condensate as a test specimen. Two other brands showed a sensitivity of more than 0.80, which include ***Dräger Antigen Test SARS-CoV-2*** (Sn 0.89, 95% CI 0.79-0.95; n=379) and ***Abbott Panbio*** (Sn 0.84, 95% CI 0.71-0.94, n=290). Two studies that used ***STANDARD Q COVID-19 Ag Test*** had a pooled sensitivity of 0.79 (95% CI 0.68-0.86; n=433). Poor sensitivities were demonstrated by two RAgT brands, namely ***Innova LFT*** (Sn 0.40, 95% CI 0.28-0.52; n=5504) and ***BinaxNOW SARS-CoV-2*** (Sn 0.57, 95% CI 0.37-0.76; n=44).

By type of specimen used for the index test
The specimen types with the highest pooled sensitivities were those taken from exhaled breath (Sn 0.92, 95% CI 0.64-1.0; n=105), followed by those taken from the nasal mid-turbinate (Sn 0.81, 95% CI 0.73-0.87; n=723). Anterior nares specimen showed a pooled sensitivity of 0.77 (95% CI 0.49-0.92; n=423). The specimen type with the lowest sensitivity was the combined nasal and oropharyngeal specimens (Sn 0.40, 95% CI 0.28-0.52; n=5,504)**.** This is probably due to the difficulty of taking specimens from the combined nasal and oropharyngeal compared to a nasal swab alone.

By cycle threshold (Ct) value used for the RT-PCR
RAgTs performed better when tested against RT-PCR assays that used lower Ct values of <25 (Sn 0.87, 95% CI 0.86-0.87) compared to those that used higher Ct values of >25 (Sn 0.30, 95% CI 0.05-0.79) as the criterion for classifying positive COVID-19 cases. This may indicate that RAgT is most sensitive when applied to samples with high viral loads.

C. Sensitivity analysis
Self-administered tests showed slightly higher sensitivity when only studies with high methodological quality were included in the analysis (Sn 0.79, 95% CI 0.68-0.86; n=433; 2 studies). Studies with potential risk of bias issues related to the conduct of the RAgT or reference standard reduced the test sensitivity of RAgTs. Studies with potential selection bias tended to inflate the sensitivity estimate (Sn 0.88, 95% CI 0.80-0.93; n=774).

Ongoing Studies on Self-Administered Rapid Antigen Tests
As of October 2021, there were four ongoing studies on self-administered RAgTs evaluating different brands (Biozek, SG Diagnostics, Lucira, and Theram) registered in clinicaltrials.gov.[11-14] All studies evaluate these RAgTs against RT-PCR using conventional sampling methods (trained personnel). Appendix 5 shows the details of the registered studies.

OTHER CONSIDERATIONS

In the United States of America, a study done by Paltiel et al. showed the clinical and economic effects of widespread home-based antigen testing. A simple compartmental epidemic modeling was used. Compared to no testing at all, the use of home-based antigen testing yielded the following incremental cost-effectiveness ratio: $7,890 per infection averted and $1.43 million per death averted.[15] There is no local data on the economic evaluation of self-administered RAgT.

Results of flex or robustness studies are one of the considerations of WHO for the Emergency Use Listings (WHO EUL) of in vitro diagnostics (IVDs) for detecting SARS-Cov-2.[16] The US Food and Drug Administration (US FDA) also takes into account flex studies prior to giving Emergency Use Authorization for molecular and antigen diagnostic COVID-10 tests for home use.[17] Flex studies are expected to challenge the kit or system under various conditions of stress. This is to identify potential device deficiencies and determine the robustness (i.e., ability of the test to be unaffected by slight variations) of the kit.[16] The test should still function properly under various conditions of improper use.[18] Examples of conditions that flex studies of RAgTs should consider are the following: multiple skill levels of users (includes reader and

reagent problems), specimen and/or reagent volume, operating temperature, visual reading, specimen type, device orientation, and disturbances during analysis.[16,17]

Among the test kits included in this review, Standard Q Covid-19 Ag test (SD Biosensor), Innova LFT (Innova Medical Group), Panbio Ag-RDT (Abbott), and BinaxNow SARS-CoV-2 (Abbott) have approval from foreign agencies.[19-21] However, at the time of the conduct of the included studies in this review, the approval of these brands was for use by trained professionals. Recently, self-test versions of the aforementioned RAgT brands were released.[20-23] However, these were not yet the specific kits used in the included studies.

The Philippine Food and Drug Administration (FDA) and the Research Institute of Tropical Medicine (RITM) are currently evaluating the commercially manufactured COVID-19 rapid antigen test kits.[24] However, there is no FDA-approved self-administered rapid antigen test kit. There is no available cost-effective analysis study specific for self-administered RAgT.

In the Philippines, the Department of Health (DOH) issued a memorandum dated September 1, 2021 strictly placing a price cap of Php 960 for RAgTs in all testing and clinical laboratories.[25] Table 2 lists the unit cost of the self-administered RAgT kits used by the studies included in this review.

Table 2. Unit Price of Self-Administered RAgT Kits

Brand	Unit Price per Test
Dräger Antigen Test SARS-CoV-2	Not available
Panbio™ Ag-RDT[a]	Php 520 or USD 13
STANDARD Q COVID-19 Ag Test	Php 550
BinaxNOW SARS-CoV-2 (Abbott)	Php 250 or USD 5
Innova LFT (Innova Medical Group Inc)	Not available
Inflammacheck® device	Not available

[a] 1,000-4975 tests (40-199 boxes)

RECOMMENDATIONS FROM OTHER GROUPS

Table 3 summarizes the recommendations from different agencies, countries, and organizations regarding the use of self-administered RAgTs.

Table 3. Summary of Recommendations from Other Groups

Agency	Recommendation	Date
DOH HTAC [18]	No specific clause on self-administered testing was indicated. However, guidance was provided on providing a minimum of 4-hour long training of healthcare professionals in performing antigen testing to optimize performance.	April 29, 2021
WHO [19]	At present, there is insufficient evidence to make recommendations. Research into potential benefits and harm are still under review.	June 25, 2021
UK NHS [20]	Regular rapid lateral flow tests (twice a week, every 3 to 4 days) are recommended, using the NHS Test and Trace COVID-19 Self-Test kit that can be done by individuals without symptoms of COVID-19.	October 14, 2021
Government of the Netherlands [21]	Rapid antigen self-testing can be done for individuals with no symptoms of COVID-19, specifically for the following situations: 1. Recent travel to the Netherlands from a country with a 'yellow' or 'green' travel advisory 2. Returning to work 3. Returning to school either as a pupil or a staff member 4. Attending classes in secondary vocational education or higher	August 17, 2021

	education 5. Childcare worker or a childminder	
NSW, Australia [22]	Rapid antigen tests are required to be used under the supervision of a health practitioner who has been trained in the correct use of the device and interpretation of results. Trained staff needs to be available onsite to perform or supervise the collection of the sample (if self-collected) and to perform the test during the consultation with the health practitioner.	August 2021
Canada [23]	Specimen collection for antigen point-of-care testing may be done with the supervision of a trained individual or done by the person being tested ('self-swabbing'). Self-swabbing with point-of-care antigen test is not currently approved by Health Canada.	August 25, 2021
US CDC [24]	Self-tests may be performed by a person at home or anywhere, provided that all instructions for performing the test must be followed. Self-tests can be used by anyone who is symptomatic regardless of their vaccination status. Unvaccinated persons with no COVID-19 symptoms can also use self-tests, especially if they were potentially exposed to someone with COVID-19.	October 4, 2021

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Appendix 1. Evidence to Decision

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					
Certainty of Evidence	High	Moderate (4)	Low (5)	Very low			Overall, the studies included are of moderate methodological quality. Two studies are of high quality. Five studies are of moderate quality due to unclear issues on patient selection, index test and reference standard.
Accuracy	Very Accurate	Accurate (8)	Inaccurate (1)	Very Inaccurate			Across 7 studies, the pooled sensitivity of self-administered RAgTs was found to be moderate at 0.77 (95%CI: 0.62-0.87), with high heterogeneity (I^2 = 94%). Pooled specificity was excellent at 0.996 (95%CI: 0.99-1.00).
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Cost (6)	Negligible cost	Moderate savings	Large savings (3)	The cost per unit of each rapid antigen test ranges from Php 250 to Php 500.
Certainty of evidence of required resources	No included studies (2)	Very low	Low (5)	Moderate (2)	High		In the Philippines, the Department of Health issued a memorandum dated September 1, 2021 strictly placing a price cap of Php 960 for rapid antigen testing in all testing and clinical laboratories.
Cost effectiveness	No included studies (5)	Favors RT-PCR (2)	Does not favor either RAgT or RT-PCR	Favors RAgT (2)			No local cost-effectiveness studies are available as of press time on comparing self-administered rapid antigen tests and RT-PCR.
Equity	Uncertain (6)	Reduced	Probably no impact	Increased (3)			
Acceptability	Uncertain (4)	No (2)	Yes (3)				
Feasibility	Uncertain (3)	No	Yes (6)				

Appendix 2. Search Yield and Results

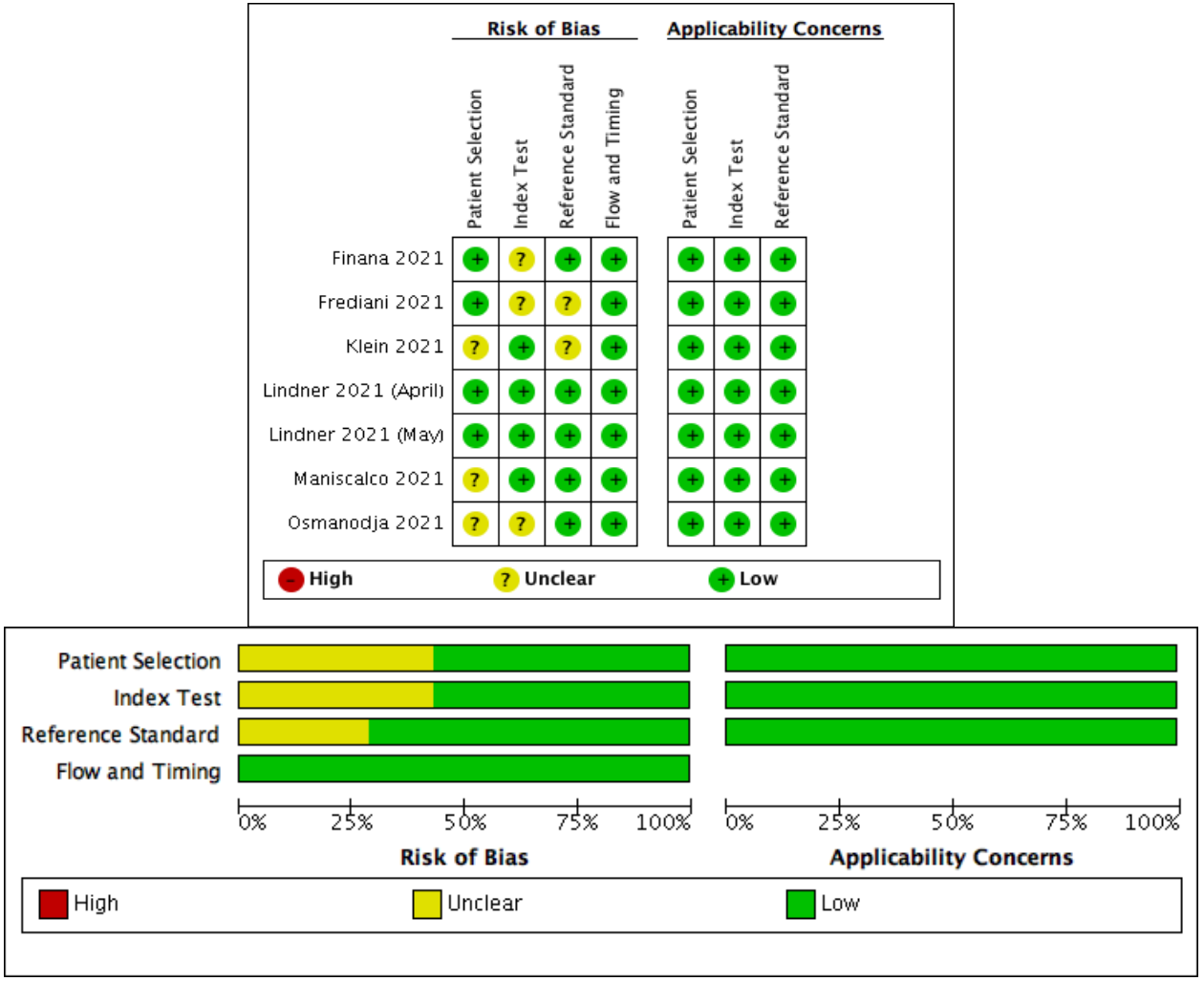
Search	Query	Results	Time
#9	Search **#1 and #8** Filters: **from 2021/3 - 2021/9/14** Sort by: **Most Recent**	475	02:52:17
#8	Search **#7 OR #2** Filters: **from 2021/3 - 2021/9/14** Sort by: **Most Recent**	1,017	02:51:40
#7	Search **#5 OR #6** Filters: **from 2021/3 - 2021/9/14** Sort by: **Most Recent**	1,016	02:51:26
#6	Search: **rapid antigen test* OR "rapid antigen detection test" OR radt OR radts OR rdt OR rdts OR (antigen* n3 detect*)** Filters: **from 2021/3 - 2021/9/14** Sort by: **Most Recent**	1,016	02:51:17
#5	Search **#3 and #4** Filters: **from 2021/3 - 2021/9/14** Sort by: **Most Recent**	9	02:51:05
#4	Search: **(test OR tests OR detect* OR diagnos* OR kit OR kits OR assay*)** Filters: **from 2021/3 - 2021/9/14** Sort by: **Most Recent**	413,770	02:50:56
#3	Search: **((rapid OR point-of-care OR "point of care" OR poc OR poct) n3 antigen))** Filters: **from 2021/3 - 2021/9/14** Sort by: **Most Recent**	9	02:50:45
#2	Search: **"COVID-19 Ag Respi-Strip" OR "BIOCREDIT COVID-19 Ag" OR "STANDARD F COVID-19 Ag" OR "STANDARD Q COVID-19 Ag" OR "Bioeasy 2019-nCoV Ag"** Filters: **from 2021/3 - 2021/9/14** Sort by: **Most Recent**	13	02:50:29
#1	Search: **("Coronavirus Infections"[Mesh] OR novel coronavirus OR NCOV OR "COVID-19"[Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2)** Filters: **from 2021/3 - 2021/9/14** Sort by: **Most Recent**	77,879	02:50:18

Appendix 3. Characteristics of Included Studies

Study ID	Setting	Index Test	Index Test Specimen	Population	Sample Size	Reference Standard	
						Test	Specimen
Lindner 2021 [5]	Germany	STANDARD Q COVID-19 Ag Test (SD Biosensor, Korea)	NMT for self-administered, NP for staff-collected	Symptomatic patients at ambulatory testing facility (community setting)	146	RT-PCR (not specified)	NP/OP
Lindner 2021 [6]	Germany	STANDARD Q COVID-19 Ag Test (SD Biosensor, Korea)	NMT for self-administered, NP for staff-collected	Symptomatic patients at ambulatory testing facility (community setting)	287	Roche Cobas and Tib Molbiol®	NP/OP
Maniscalco 2021 [10]	Italy	Inflammacheck® device (Exhalation technology LTD, Cambridge, UK)	Exhaled breath condensate	≥ 18 y/o with or without symptoms in a community setting	105	NeumoDx	NP
Osmanodja 2021 [7]	Germany	Dräger Antigen Test SARS-CoV-2 by Dräger Safety AG and Co. KGaA (Lübeck, Germany)	Anterior Nares	≥ 18 y/o with or without symptoms in a community setting	379	Roche Cobas SARS-CoV-2 assay (Pleasanton, CA, USA)	NP and OP
Fiñana 2021 [8]	UK	Innova LFT	Combined throat and nose	> 18 y/o with or without symptoms in a community setting	5504	TaqPath; ThermoFisher Scientific	Combined throat and nose (also collected by participant)
Klein 2021 [4]	Germany	Panbio™ Ag-RDT	NMT for self-administered, NP for staff-collected	Symptomatic adults and high-risk contacts of confirmed SARS-Cov-2 in an in-drive in testing center (community setting)	290	Tib Molbiol®	NP
Frediani 2021 [9]	USA	BinaxNOW SARS-CoV-2 (Abbott)	Anterior nares	> 7 y/o (adults and pedia) symptomatic within 7 days from onset in community-based and hospital-based testing center (community setting)	44 self-collected; 297 staff-collected	Cobas 6800 (Roche Diagnostics), Abbott Alinity (Abbott Labs), Panther Fusion (Hologic)	NP

NMT: Nasal midturbinate; **NP**: Nasopharyngeal; **OP**: Oropharyngeal.

Appendix 4. Risk of Bias and Applicability Concerns of Included Studies



Appendix 5. Characteristics of Ongoing Studies

Title / Study Design / NCT	Population	Intervention	Comparator	Outcomes	Status
Open Label, Single-Center Study Utilizing BIOZEK COVID-19 Antigen Rapid Test [11] • Open-label, single-center study • Quality Research and Invention LLC, Southampton, New York, USA • NCT04926779	**Inclusion Criteria** ∉ ≥18 y/o and have had an RT-PCR test performed prior to enrollment. ∉ Able to understand and willingly sign a written informed consent ∉ Needs to meet at least 1 of the following: ○ Currently experiencing symptoms of COVID-19 ○ Clinically diagnosed or suspected to have COVID-19 ○ Recent past (3 weeks) exhibited symptoms of COVID-19 ○ Capable of performing a self-collection of a nasopharyngeal sample with use of nasal swab kit ○ Capable of performing a self-collection of an oral fluid sample with use of oral fluid collection kit ○ Interacted with a COVID-19 positive individual **Exclusion Criteria** ∉ Cannot perform self-collection of a nasopharyngeal sample with use of nasal swab kit ∉ Cannot perform self-collection of an oral fluid sample with use of oral fluid collection kit ∉ Have a deviated nasal septum ∉ Cognitively impaired individuals resulting in the inability to provide informed consent	Biozek COVID-19 Antigen Rapid Test Results Performed on Self-collected Samples	COVID-19 RT-PCR as a Standard of Care	**Primary** • Sensitivity and Specificity of Biozek Covid-19 Antigen Rapid Test (Saliva) • Sensitivity and Specificity of Biozek Covid-19 Antigen Rapid Test (Nasopharyngeal Swab)	**Recruiting** **Study start**: May 24, 2021 **Primary completion**: September 20, 2021 **Study completion**: September 20, 2021
COVID-19 Antigen Rapid Test Kit (SETCOV) [12] • Prospective cohort study (Observational) • Polish Society of Disaster Medicine • NCT04889365	Volunteers with or without COVID-19 symptoms **Inclusion Criteria** ● Adult (aged ≥ 18 years) volunteers **Exclusion Criteria** ∉ Children (aged < 18years)	SG Diagnostics COVID-19 Antigen Rapid Test Kit (self-use)	Polymerase chain reaction (PCR) test	**Primary** ● Sensitivity of SG Diagnostics COVID-19 Antigen Rapid Test Kit ● Specificity of SG Diagnostics COVID-19 Antigen Rapid Test Kit	**Active, not recruiting** **Study start**: May 11, 2021 **Primary completion**: June 30, 2021 **Study completion**: July 10, 2022

Title / Study Design / NCT	Population	Intervention	Comparator	Outcomes	Status
A Study to Evaluate the Performance of the Lucira Health All-in-One COVID-19 Test Kit vs Hologic Panther Fusion [13] • Open label, single group assignment • Lucira Health Inc. • NCT04720794	**Inclusion Criteria** • Ages 18-75 • Must be able to read and write in English or Spanish • Must be willing to try rapid COVID-19 test and self-collect a nasal swab sample in both nostrils • Must be one of the following: ○ Currently experiencing a fever of 100· Fahrenheit and above or self-reports having fever within the past 48 hours and experiencing at least one (1) additional associated CDC COVID-19 symptoms. ○ Previously tested positive for COVID-19 in past 14 days, and experiencing at least one (1) additional associated CDC COVID-19 symptom ○ Currently experiencing at least three (3) additional associated CDC COVID-19 symptoms so long as at least at least one (1) symptom is either: cough, shortness of breath, and/or new loss of taste or smell. **Exclusion Criteria** • Currently suffering from nasal trauma such as a nosebleed • Received a nasal rinse/wash/aspirate for standard of care testing	Lucira COVID-19 All-In-One test kit (self-collected)	Hologic Panther Fusion RT-PCR assay	**Primary** • COVID-19 Prevalence Rate/Expected Values counts • COVID-19 Prevalence Rate/Expected Values percentages **Secondary** • Collection Performance/Incidence Rate counts • Collection Performance/Incidence Rate percentages • Sensitivity and specificity **Other measures** • Invalid rates	**Completed** **Study start**: September 25, 2020 **Primary completion**: October 20, 2020 **Study completion**: October 20, 2020
Study to Evaluate the Performance of the Therma COVID-19 Rapid Antigen Test for Detection of SARS-CoV-2 [14] • Retrospective Cohort, observational • Cannabis Research Associates • NCT04878068	Potential participants attending a COVID-19 testing centre for a PCR test will be approached to determine eligibility and obtain consent after they have had their PCR test completed. Three hundred participants will be recruited into the study.	Theram COVID-19 Rapid Antigen Test (self-collected)	COVID-19 RT-PCR Test	**Primary** • Establish Performance of Therma COVID-19 Rapid Antigen Test **Secondary** • Participant Feedback • User Feedback	**Not yet recruiting** **Study start**: May 15, 2021 **Estimated Primary completion**: June 30, 2021 **Estimated Study completion**: June 30, 2021

Appendix 6. GRADE Evidence Profile

Should self-administered rapid antigen test be used to diagnose COVID-19 in symptomatic individuals?
Patient or population: symptomatic individuals
Setting: Community
New test: Self-administered rapid antigen tests
Cut-off value: Not applicable
Pooled sensitivity: 0.81 (95% CI: 0.69 to 0.89)
Pooled specificity: -- (95% CI: -- to --)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	5 studies (750 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Not serious	None	41 (34 to 45)	81 (69 to 89)	162 (138 to 178)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having COVID-19)								9 (5 to 16)	19 (11 to 31)	38 (22 to 62)	
True negatives (patients without COVID-19)	5 studies (750 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Not serious	Not serious	None	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having COVID-19)								950 (950 to 950)	900 (900 to 900)	800 (800 to 800)	

CI: confidence interval

Explanations
[a] Unclear issues in patient selection and conduct of index test and reference standard
[b] Significant heterogeneity among included studies

Should self-administered rapid antigen test be used to diagnose COVID-19 in asymptomatic individuals?
Patient or population: asymptomatic individuals
Setting: Community
New test: Self-administered rapid antigen tests
Cut-off value: Not applicable
Pooled sensitivity: 0.41 (95% CI: 0.31 to 0.53)
Pooled specificity: -- (95% CI: -- to --)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	3 studies (5,765 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Serious[b]	Not serious	None	21 (16 to 27)	41 (31 to 53)	82 (62 to 106)	⨁⨁◯◯ Low[a,b]
False negatives (patients incorrectly classified as not having COVID-19)								29 (23 to 34)	59 (47 to 69)	118 (94 to 138)	
True negatives (patients without COVID-19)	5 studies (5,765 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Not serious	Not serious	None	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	⨁⨁◯◯ Low[a,b]
False positives (patients incorrectly classified as having COVID-19)								950 (950 to 950)	900 (900 to 900)	800 (800 to 800)	

CI: confidence interval

Explanations
[a] Unclear issues in patient selection and conduct of index test and reference standard
[b] Significant heterogeneity among included studies

Q6. Should breath tests be used to diagnose COVID-19 infection?

As of 29 November 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of breath test in detecting COVID-19 infection. *(Low certainty of evidence)*

Consensus Issues

Despite the addition of five new studies since the previous recommendation, insufficient evidence remains to recommend for or against breath tests. The diagnostic accuracy of breath tests cannot be ascertained due to the heterogeneity across studies. The panel also raised concerns on the availability and accessibility of the test, its cost, and ease of use.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of breath test in detecting COVID-19 infection. *(Low quality of evidence)*

Previous Consensus Issues

No recommendation was made as there was only one study found that used a technology that is not accessible at the moment.

WHAT'S NEW IN THIS VERSION?

- Five new studies were included, featuring three cross-sectional studies and two prospective studies.
- Breath test analysis utilizing spectrometry and rapid antigen were included in addition to olfactory technology.

KEY FINDINGS

This review included three cross-sectional and three prospective studies on the use of breath tests in the diagnosis of COVID-19 infection. The overall accuracy of breath tests was high, with a sensitivity of 97% (95% CI 0.90-0.99) and specificity of 85% (95% CI 0.72-0.92). However, the overall certainty of evidence was low due to significant heterogeneity. This heterogeneity may be attributed to the different mechanisms of the devices despite using the same idea of breath testing.

INTRODUCTION

Reverse transcription-polymerase chain reaction (RT-PCR) remains to be the gold standard for SARS-COV2 testing. Collection of specimens for RT-PCR requires time-consuming invasive procedures which also entail biohazard exposure to health personnel acquiring the sample.[1,2] Breath testing, a novel method, addresses these concerns as samples are obtained via non-invasive sampling and results are usually rapidly acquired with a turnover time of 60 seconds to 10 minutes.[3] Testing usually requires the individual to blow or breathe into a disposable mouthpiece that is connected to a breath sampler. The information is fed into an analyzer, which then produces the result.

Breath testing analyzes the composition of either volatile organic compounds (VOCs) or antigen present in exhaled breath [3,4] to confirm the presence of an infection. Metabolic changes from respiratory viral infection lead to changes in breath profiles, suggesting that infection-associated VOCs may be used to develop non-invasive diagnostic modalities through breath analyzers using sensor arrays or electronic noses. At present, the US, Finland, Singapore, India, and Israel are testing whether this technology can be used as a mass screening tool for COVID-19.[5,6] This study updates the previous evidence reviewed by Manalo et al. 2021 on the diagnostic accuracy of breath tests.[7]

REVIEW METHODS

A literature search was done for articles that investigated the utility of breath tests in diagnosing COVID-19 among COVID-19 suspects. A systematic literature search until 4 October 2021 was performed in online databases (MEDLINE and Cochrane CENTRAL Database), trial registries (ClinicalTrials.gov and WHO International Clinical Trials Registry Platform), and pre-print servers (MedRxiv, BioRxiv, and chinaRxiv).

The search terms “COVID-19”, “SARS-COV2”, “Breath Test”, “Volatile Organic Compounds”, “Sensitivity”, and “Specificity” were used. No language restrictions were applied. Narratives, commentaries, case reports and case series articles, and case-control studies were excluded from the analysis. Summary estimates for sensitivity and specificity were derived using a bivariate mixed-effects binary regression modeling through the *midas* command in Stata 14.0. Subgroup analysis was performed according to the mechanism of breath testing (VOCs using spectrometry, VOCs using olfactory technology, and rapid-antigen using Inflammacheck® technology).

RESULTS

Characteristics of included studies

Five additional studies were added to the previous version of this review, bringing the total to six studies. Three were prospective studies [8,9,10] and three were cross-sectional studies.[3,4,11] The population included in the studies were all suspects for SARS-CoV-2 infection ranging from asymptomatic, symptomatic, to severely ill individuals. Most of the studies included a mix of these range of symptoms. Diagnosis was confirmed using RT-PCR as the reference standard. All of the studies utilized a breath test as the index test. However, the device and the composition of breath (VOCs or antigen) used for analysis differed across the included studies. VOCs were analyzed more commonly across the studies.

Methodological quality

The overall methodological quality of the studies was moderate to high. Two studies [4,10] presented with low risk of bias. Most of the studies rated as moderate methodological quality were unclear on how the index test and/or reference standard avoid influencing the other.

Diagnostic accuracy of breath tests

A. Overall diagnostic accuracy

Breath testing showed an overall pooled sensitivity of 97% (95% CI 0.90-0.99) and specificity of 85% (95% CI 0.72-0.92) based on 6 studies. Although diagnostic

accuracy appeared moderate to high, substantial heterogeneity was noted for both the summary sensitivity (I^2=88.32) and specificity (I^2=94.18) estimates. The composition used for analysis (VOCs or antigen) and the device used were identified as possible sources of heterogeneity.

Table 1. Subgroup analysis for sensitivity and specificity of breath testing

Variable	SENSITIVITY			SPECIFICITY		
	Current Review		Previous Review	Current Review		Previous Review
	Studies (number of samples)	Sensitivity (95%CI)	Sensitivity (95%CI)	Studies (Samples)	Specificity (95%CI)	Specificity (95%CI)
OVERALL	**6 (493)**	**0.97 (0.90-0.99)**	**0.99 (0.97-1.00)**	**6 (4,553)**	**0.85 (0.72, 0.92)**	**0.79 (0.78, 0.81)**
Method of Breath Testing						
VOCs using Spectrometry	3 (75)	0.90 (0.77-0.96)	-	3 (137)	0.88 (0.74-0.95)	-
VOCs using Olfactory Technology	2 (405)	0.99 (0.93-1.00)	-	2 (4,524)	0.74 (0.64-0.82)	-
Rapid-antigen using exhaled breath condensate	1 (13)	0.92 (0.64-1.00)	-	1 (92)	0.99 (0.94-1.00)	-
Symptomatology						
Symptomatic	4 (396)	0.95 (0.86-0.98)	1.00 (0.98-1.00)	4 (2,663)	0.73 (0.63-0.82)	0.80 (0.78-0.82)
Mixed	2 (29)	0.92 (0.64-1.00) to 1.00 (0.79-1.00)	-	2 (150)	0.97 (0.88-1.00) to 0.99 (0.94-1.00)	-
Asymptomatic	1 (68)	1.00 (0.95-1.00)	0.98 (0.90-0.99)	1 (1,740)	0.78 (0.76-0.80)	0.78 (0.75-0.81)

B. Subgroup analysis

By method of breath testing

Subgroup analysis by the method of breath testing showed that VOCs using olfactory technology had the highest sensitivity (Sn 0.99, 95% CI 0.93-1.00), followed by rapid antigen using Inflammacheck® technology (Sn 0.92, 95% CI 0.64-1.00), and VOCs using spectrometry (Sn 0.90, 95% CI 0.77-0.96). The highest specificity was demonstrated by rapid antigen using Inflammacheck® technology (Sp 0.99, 95% CI 0.94-1.00), followed by VOCs using spectrometry (Sp 0.88, 95% CI 0.74-0.95), and VOCs using olfactory technology (Sp 0.74, 95% CI 0.64-0.82).

While breath tests that analyze VOCs through spectrometry demonstrate high sensitivity, its diagnostic accuracy for SARS-COV2 cannot be ascertained completely because of inconsistencies in the specificities across included studies in this subgroup. Additionally, the pooled number of patients became significantly low from the subgrouping, thereby affecting the test sensitivity and specificity.

Likewise, the diagnostic accuracy of breath tests that analyze VOCs through olfactory technology cannot be ascertained. Current evidence shows serious heterogeneity of both sensitivity and specificity which may be attributed to the differences in the devices used across the studies despite using the same mechanism of breath testing.

Rapid antigen testing using Inflammacheck® on exhaled breath condensate included only one study. As such, the subgroup was assessed to have serious imprecision from

the low sample size. Furthermore, publication bias is a concern as there is only one study in this subgroup.

B. By symptomatology

When used for testing symptomatic individuals, four studies showed that breath tests had high sensitivity at 0.95 (95% CI 0.86-0.98) and moderate specificity at 0.73 (95% CI 0.63-0.82). One study provided evidence that breath tests had comparable sensitivity and specificity estimates for asymptomatics (Sn = 1.00 [95% CI 0.95-1.00], Sp = 0.78 [95% CI 0.76-0.80]). Two studies that evaluated breath tests on mixed populations showed excellent sensitivity and specificity estimates.

RECOMMENDATIONS FROM OTHER GROUPS

Currently, there are no published recommendations on the use of breath tests in the diagnosis of COVID-19 infection from the World Health Organization, US National Institutes of Health, and the Centers for Disease Control. The Malaysian Health Technology Assessment Section (MaHTAS) [7] of the Ministry of Health Malaysia recognized the good sensitivity and specificity of breath test analysis to discriminate and screen for COVID-19 infection among COVID-19 confirmed patients and healthy controls. However, further evaluation and validation studies with a larger sample size are required to ascertain its effectiveness and safety.

RESEARCH GAPS

Information about the cost of breath testing, its resource requirements, and its cost-effectiveness in local and international settings is limited. In May 2021, it was announced that breathalyzer tests were done in a deployment trial in Singapore involving incoming travelers from Malaysia. Individuals who tested positive for the breath test underwent a confirmatory PCR swab. No results were published. The prices of the breath tests were listed as S$5 (Php 190) to S$20 (Php 735).

One non-randomized clinical trial on breath test in Israel (n=4,000) was estimated to be done by July 2021 but is still actively recruiting status. Three observational studies (n=500) from the US and Canada are currently investigating the diagnostic accuracy of breath tests in COVID-19 infection among asymptomatic and symptomatic individuals. The estimated completion is at the end of 2021 for the study from the US, and March to September 2022 for the remaining two studies.

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Appendix 1. Evidence to Decision (n=11)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (11)					RT-PCR currently being used as gold standard requires time-consuming and invasive specimen collection which is also hazardous to health personnel acquiring the sample.
Benefits	Large (5)	Moderate (6)	Small	Uncertain			Breath testing will decrease the need for significant health personnel contact during specimen collection and time needed for analysis will be greatly reduced. Breath testing does not require invasive nasopharyngeal and/oropharyngeal collection.
Harms	Large	Moderate	Small (5)	Uncertain (6)			
Balance of Benefits and Harms	Favors the use of breath test (1)	Probably favors the use of breath test (6)	Does not favor the use of breath test (4)				
Certainty of Evidence	High	Moderate (2)	Low (8)	Very low (1)			Pooled results showed sensitivity of 0.97 (0.90-0.99) and specificity of 0.85 (0.72-0.92). However, significant heterogeneity is apparent with I2 = 88.32 and I2 = 94.18 respectively. Subgroup analysis was done to the identified of heterogeneity, but the heterogeneity was not addressed in all subgroups. As the sample size became smaller and the studies were distributed to different subgroups in the process, concern regarding imprecision and publication bias became apparent.
Accuracy	Very Accurate	Accurate (3)	Inaccurate (1)	Very Inaccurate (1)	Uncertain (6)		
Values	Important uncertainty or variability (4)	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			No evidence found.
Resources Required	Uncertain	Large cost	Moderate Cost (5)	Negligible cost (1)	Moderate savings (2)	Large savings (3)	Breath testing requires minimal personnel and requires less time. A COVID-19 Breath Testing device from Singapore, BreFence Go COVID-19 Breath Test, costs around 5 to 20 USD.
Certainty of evidence of required resources	No included studies (4)	Very low (1)	Low (4)	Moderate (2)	High		No evidence found.
Cost effectiveness	No included studies (9)	Favors comparator (1)	Does not favor either breath tests or the comparator (1)	Favors breath tests			No evidence found.
Equity	Uncertain (6)	Reduced (1)	Probably no impact (1)	Increased (3)			No evidence found.
Acceptability	Uncertain (5)	No (1)	Yes (5)				No evidence found.
Feasibility	Uncertain (5)	No	Yes (6)				No evidence found.

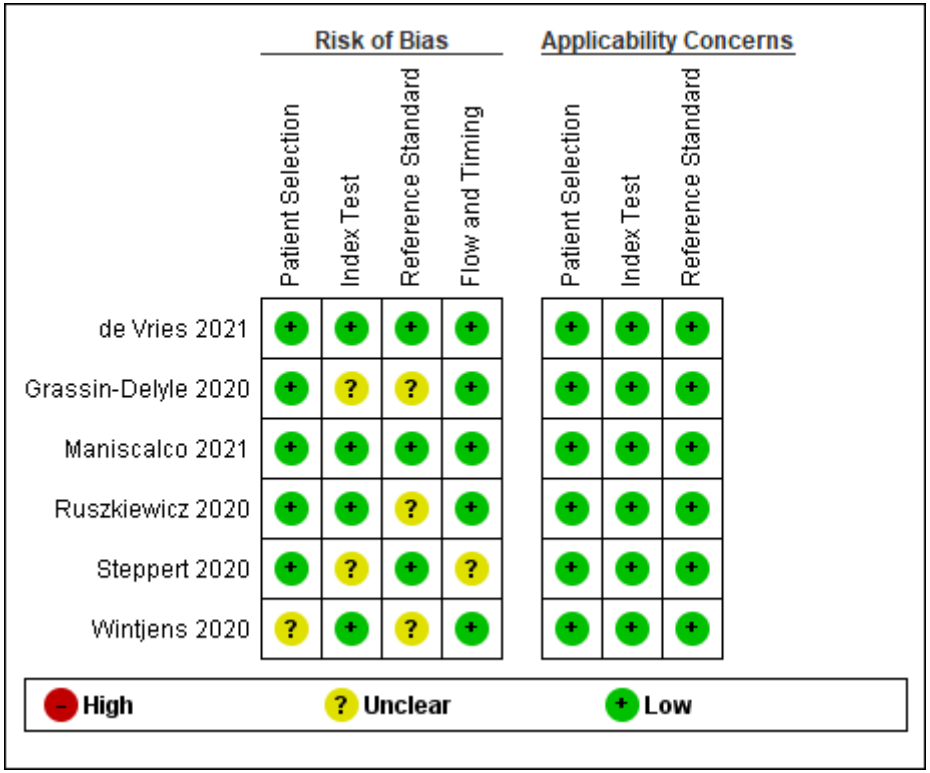
Appendix 2. Search Yield and Results

Database	Search Strategy	Results	Eligible Studies
PubMed	((“Sensitivity”) OR (“Specificity”)) AND ((COVID-19) OR (SARS-COV-2)) AND ((Breath Test) OR (Volatile Organic Compounds))	36	6
Cochrane	((“Sensitivity”) OR (“Specificity”)) AND ((COVID-19) OR (SARS-COV-2)) AND ((Breath Test) OR (Volatile Organic Compounds))	64	1 review, 63 trials
medRxiv	((“Sensitivity”) OR (“Specificity”)) AND ((COVID-19) OR (SARS-COV-2)) AND ((Breath Test) OR (Volatile Organic Compounds))	947	2
bioRxiv	((“Sensitivity”) OR (“Specificity”)) AND ((COVID-19) OR (SARS-COV-2)) AND ((Breath Test) OR (Volatile Organic Compounds))	258	0
chinaRxiv	All Fields:(Breath Test) AND All Fields:(Covid-19)	5	0
Clinicaltrials.gov	Condition or Disease: COVID-19 | Other Terms: Breath Test	44	4 ongoing research of interest
WHO ICTRP	** Updated 28 September 2021*	11791 registered trials	0
ChiCTR	Target Disease: COVID-19 | Intervention: Breath Test	0	0
HERDIN Plus	All Fields: COVID-19 AND All Fields: Breath Test	1	0

Appendix 3. Table of Included Studies

Study (Sample)	Study Design	Population	Index Test	Gold Standard	Outcome
De Vries 2021 [10] (n=4,510)	Prospective real-world study	Individuals 18 and above with symptoms suggestive of COVID-19 and/or who had been in contact to a known case	Breath testing for VOCs (eNose)	RT-PCR	*Validation Set:* (n=1,808) Sn: 1.00(0.95, 1.00) Sp: 0.78(0.76, 0.80) *Replication Set:* (n=1,948) Sn: 1.00(0.98, 1.00) Sp: 0.80(0.78, 0.82) *Asymptomatic Set:* (n=754) Sn: 0.98(0.89, 1.00) Sp: 0.78(0.75, 0.81)
Grassin-Delyle 2020 [9] (n=40)	Prospective Observational Study	Adult patients above 18 years old in the intensive care unit requiring mechanical ventilation	Breath testing for VOC2 (mass spectrometry [Ionicon Analytic GmBH])	RT-PCR	Sn: 0.89(0.72, 0.98) Sp: 0.92(0.62, 1.00)
Maniscalco 2021 [4] (n=105)	Cross-sectional multicenter study	Adult patients above 18 years old with clinical suspicion of COVID-19	Breath testing utilizing rapid-antigen on exhaled breath condensate (Inflammacheck®)	RT-PCR	Sn: 0.92(0.64, 1.00) Sp: 0.99(0.94, 1.00)
Ruszkiewicz 2020 [3] (n=98)	Independent observational prevalence study	Patients presenting with respiratory at the emergency room	Breath testing for VOCs (gas chromatography-ion mobility spectrometry [BreathSpec])	RT-PCR	*Edinburgh Set:* (n=33) Sn: 0.81(0.58, 0.95) Sp: 0.75(0.43, 0.95) *Dortmund Set:* (n=65) Sn: 0.90(0.55, 1.00) Sp: 0.80(0.67, 0.90)
Steppert 2020 [11] (n=74)	Proof of concept study	Adults with suspected COVID-19	Breath testing for VOCs (multi-capillary-coupled ion mobility spectrometry [STEP IMS NOO])	RT-PCR	Sn: 1.00(0.79, 1.00) Sp: 0.97(0.88, 1.00)
Wintjens 2020 [8] (n=219)	Prospective proof of principle study	Employees with COVID-19 symptoms	Breath testing for VOCs (Aenose)	RT-PCR	Sn: 0.86(0.74, 0.94) Sp: 0.54(0.46, 0.62)

Appendix 4. Detailed Study Appraisal



Appendix 5. GRADE Evidence Profile

Should breath test be used to diagnose COVID-19 in clinically suspected individuals?

Pooled sensitivity: 0.97 (95% CI: 0.90 to 0.99)

Pooled specificity: 0.85 (95% CI: 0.72 to 0.92)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 9.4%	
True positives (patients with COVID-19)	6 studies (493 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Very serious[a]	Not serious	None	91 (85 to 93)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having COVID-19)								3 (1 to 9)	
True negatives (patients without COVID-19)	6 studies (4,553 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Very serious[b]	Not serious	None	770 (652 to 834)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having COVID-19)								136 (72 to 254)	

Should breath test for VOCs by spectrometry be used to diagnose COVID-19 in clinically suspected individuals?
Pooled sensitivity: 0.90 (95% CI: 0.77 to 0.96)
Pooled specificity: 0.88 (95% CI: 0.74 to 0.95)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 32%	
True positives (patients with COVID-19)	3 studies (75 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Serious[a]	None	288 (246 to 307)	⊕⊕⊕◯ Moderate
False negatives (patients incorrectly classified as not having COVID-19)								32 (13 to 74)	
True negatives (patients without COVID-19)	3 studies (137 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Serious[b]	Serious[a]	None	598 (503 to 646)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having COVID-19)								82 (34 to 177)	

Should breath test for VOCs by olfactory technology be used to diagnose COVID-19 in clinically suspected individuals?
Pooled sensitivity: 0.99 (95% CI: 0.93 to 1.00)
Pooled specificity: 0.74 (95% CI: 0.64 to 0.82)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 8.4%	
True positives (patients with COVID-19)	2 studies (405 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Very serious[a]	Not serious	None	83 (78 to 84)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having COVID-19)								1 (0 to 6)	
True negatives (patients without COVID-19)	2 studies (4,324 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Very serious[b]	Not serious	None	678 (586 to 751)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having COVID-19)								238 (165 to 330)	

Should breath test utilizing rapid-antigen on exhaled breath condensate be used to diagnose COVID-19 in clinically suspected individuals?
Pooled sensitivity: 0.92 (95% CI: 0.64 to 1.00)
Pooled specificity: 0.99 (95% CI: 0.94 to 1.00)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 11.4%	
True positives (patients with COVID-19)	1 study (13 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Very serious[a]	Publication bias strongly suspected[b]	105 (73 to 114)	⊕◯◯◯ Very low
False negatives (patients incorrectly classified as not having COVID-19)								9 (0 to 41)	
True negatives (patients without COVID-19)	1 study (92 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Very serious[a]	Publication bias strongly suspected[b]	887 (833 to 886)	⊕◯◯◯ Very low
False positives (patients incorrectly classified as having COVID-19)								9 (0 to 53)	

Should breath test be used to diagnose COVID-19 in clinically suspected symptomatic individuals?
Pooled sensitivity: 0.95 (95% CI: 0.86 to 0.98)
Pooled specificity: 0.73 (95% CI: 0.63 to 0.82)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 12.36%	
True positives (patients with COVID-19)	4 studies (396 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Very serious[a]	Not serious	None	117 (106 to 121)	⊕◯◯◯ Very low
False negatives (patients incorrectly classified as not having COVID-19)								7 (3 to 18)	
True negatives (patients without COVID-19)	4 studies (2,663 patients)	Cross-sectional (cohort type accuracy study)	N ot serious	Not serious	Very serious[b]	Not serious	None	640 (552 to 719)	⊕◯◯◯ Very low
False positives (patients incorrectly classified as having COVID-19)								236 (157 to 324)	

Should breath test be used to diagnose COVID-19 in clinically suspected individuals regardless of symptomatology?
Pooled sensitivity: 0.92 (95% CI: 0.92 to 1.00)
Pooled specificity: 0.77 (95% CI: 0.97 to 0.99)

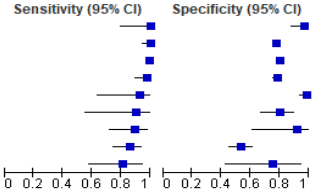
Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 8.9%	
True positives (patients with COVID-19)	2 studies (29 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Very serious[a]	None	82 to 89	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having COVID-19)								0 to 7	
True negatives (patients without COVID-19)	2 studies (150 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Serious[b]	None	884 to 902	⊕⊕⊕◯ Moderate
False positives (patients incorrectly classified as having COVID-19)								9 to 27	

Should breath test be used to diagnose COVID-19 in clinically suspected asymptomatic individuals?
Pooled sensitivity: 1.00 (95% CI: 0.95 to 1.00)
Pooled specificity: 0.78 (95% CI: 0.76 to 0.80)

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 8.9%	
True positives (patients with COVID-19)	1 study (68 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Very serious[a]	Publication bias strongly suspected[b]	38 (36 to 38)	⊕◯◯◯ Very Low
False negatives (patients incorrectly classified as not having COVID-19)								0 (0 to 2)	
True negatives (patients without COVID-19)	1 study (1,740 patients)	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Very serious[a]	Publication bias strongly suspected[b]	750 (731 to 770)	⊕⊕⊕◯ Moderate
False positives (patients incorrectly classified as having COVID-19)								212 (192 to 231)	

Appendix 6. Forest plots

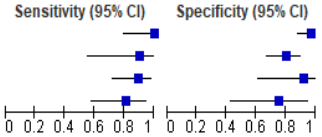
Study	TP	FP	FN	TN	Breath Test Diagnosis Method	Breath Test Device	Sensitivity (95% CI)	Specificity (95% CI)
Steppert 2020	16	2	0	56	Volatile Organic Compounds	Multicapillary Column Coupled - Ion Mobility Spectrometry (STEP IMS NOO)	1.00 [0.79, 1.00]	0.97 [0.88, 1.00]
de Vries 2021 (VS)	68	383	0	1357	Volatile Organic Compounds	eNose (SpiroNose - Breathomix)	1.00 [0.95, 1.00]	0.78 [0.76, 0.80]
de Vries 2021 (RS)	229	347	1	1371	Volatile Organic Compounds	eNose (SpiroNose - Breathomix)	1.00 [0.98, 1.00]	0.80 [0.78, 0.82]
de Vries 2021 (AS)	49	152	1	552	Volatile Organic Compounds	eNose (SpiroNose - Breathomix)	0.98 [0.89, 1.00]	0.78 [0.75, 0.81]
Maniscalco 2021	12	1	1	91	Rapid-Antigen	Inflammacheck (Exhalation Technology LTD)	0.92 [0.64, 1.00]	0.99 [0.94, 1.00]
Ruszkiewicz 2020 (D)	9	11	1	44	Volatile Organic Compounds	Gas Chromatography-Ion Mobility Spectrometry (BreathSpec)	0.90 [0.55, 1.00]	0.80 [0.67, 0.90]
Grassin-Delyle 2020	25	1	3	11	Volatile Organic Compounds	Mass Spectrometry (Ionicon Analytic GmbH)	0.89 [0.72, 0.98]	0.92 [0.62, 1.00]
Wintjens 2020	49	75	8	87	Volatile Organic Compounds	Aenose (The Aeonose Company)	0.86 [0.74, 0.94]	0.54 [0.46, 0.62]
Ruszkiewicz 2020 (E)	17	3	4	9	Volatile Organic Compounds	Gas Chromatography-Ion Mobility Spectrometry (BreathSpec)	0.81 [0.58, 0.95]	0.75 [0.43, 0.95]



Pooled Sn: 0.97 (0.90, 1.00) with I^2=88.32; Pooled Sp: 0.85(0.72, 0.92); I^2=94.18

Figure 1. Overall sensitivity and specificity of breath test

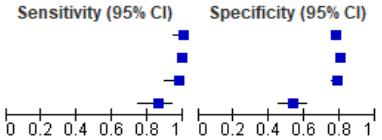
Study	TP	FP	FN	TN	Breath Test Diagnosis Method	Breath Test Device	Sensitivity (95% CI)	Specificity (95% CI)
Steppert 2020	16	2	0	56	Volatile Organic Compounds	Multicapillary Column Coupled - Ion Mobility Spectrometry (STEP IMS NOO)	1.00 [0.79, 1.00]	0.97 [0.88, 1.00]
Ruszkiewicz 2020 (D)	9	11	1	44	Volatile Organic Compounds	Gas Chromatography-Ion Mobility Spectrometry (BreathSpec)	0.90 [0.55, 1.00]	0.80 [0.67, 0.90]
Grassin-Delyle 2020	25	1	3	11	Volatile Organic Compounds	Mass Spectrometry (Ionicon Analytic GmbH)	0.89 [0.72, 0.98]	0.92 [0.62, 1.00]
Ruszkiewicz 2020 (E)	17	3	4	9	Volatile Organic Compounds	Gas Chromatography-Ion Mobility Spectrometry (BreathSpec)	0.81 [0.58, 0.95]	0.75 [0.43, 0.95]



Pooled Sn: 0.90(0.77, 0.96) with I^2=27.69; Pooled Sp: 0.88(0.74, 0.95) with I^2=67.55

Figure 2. Sensitivity and specificity of breath test for VOCs using spectrometry

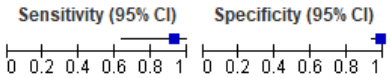
Study	TP	FP	FN	TN	Breath Test Diagnosis Method	Breath Test Device	Sensitivity (95% CI)	Specificity (95% CI)
de Vries 2021 (VS)	68	383	0	1357	Volatile Organic Compounds	eNose (SpiroNose - Breathomix)	1.00 [0.95, 1.00]	0.78 [0.76, 0.80]
de Vries 2021 (RS)	229	347	1	1371	Volatile Organic Compounds	eNose (SpiroNose - Breathomix)	1.00 [0.98, 1.00]	0.80 [0.78, 0.82]
de Vries 2021 (AS)	49	152	1	552	Volatile Organic Compounds	eNose (SpiroNose - Breathomix)	0.98 [0.89, 1.00]	0.78 [0.75, 0.81]
Wintjens 2020	49	75	8	87	Volatile Organic Compounds	Aenose (The Aeonose Company)	0.86 [0.74, 0.94]	0.54 [0.46, 0.62]



Pooled Sn: 0.99(0.93, 1.00) with I^2=91.63; Pooled Sp: 0.74(0.64-0.82) with I^2=96.90

Figure 3. Sensitivity and specificity of breath test for VOCs using olfactory technology

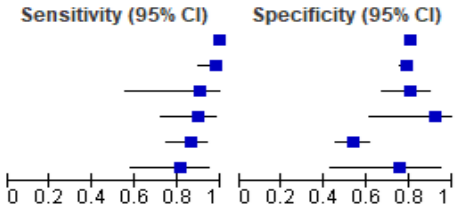
Study	TP	FP	FN	TN	Breath Test Diagnosis Method	Breath Test Device	Sensitivity (95% CI)	Specificity (95% CI)
Maniscalco 2021	12	1	1	91	Rapid-Antigen	Inflammacheck (Exhalation Technology LTD)	0.92 [0.64, 1.00]	0.99 [0.94, 1.00]



Sn: 0.92 (0.64, 1.00); Sp: 0.99 (0.94, 1.00)

Figure 4. Sensitivity and specificity of breath test for rapid-antigen on exhaled breath condensate

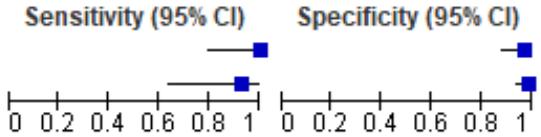
Study	TP	FP	FN	TN	Symptomatology	Sensitivity (95% CI)	Specificity (95% CI)
de Vries 2021 (RS)	229	347	1	1371	Symptomatic	1.00 [0.98, 1.00]	0.80 [0.78, 0.82]
de Vries 2021 (AS)	49	152	1	552	Symptomatic	0.98 [0.89, 1.00]	0.78 [0.75, 0.81]
Ruszkiewicz 2020 (D)	9	11	1	44	Symptomatic	0.90 [0.55, 1.00]	0.80 [0.67, 0.90]
Grassin-Delyle 2020	25	1	3	11	Symptomatic	0.89 [0.72, 0.98]	0.92 [0.62, 1.00]
Wintjens 2020	49	75	8	87	Symptomatic	0.86 [0.74, 0.94]	0.54 [0.46, 0.62]
Ruszkiewicz 2020 (E)	17	3	4	9	Symptomatic	0.81 [0.58, 0.95]	0.75 [0.43, 0.95]



Pooled Sn: 0.95 (0.86, 0.98) with I^2=84.88; Pooled Sp: 0.73 (0.63, 0.82) with I^2=94.58

Figure 5. Sensitivity and specificity of breath test in symptomatic individuals

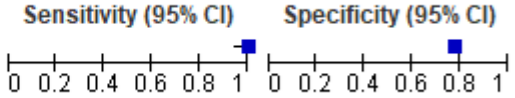
Study	TP	FP	FN	TN	Symptomatology	Sensitivity (95% CI)	Specificity (95% CI)
Steppert 2020	16	2	0	56	Mixed	1.00 [0.79, 1.00]	0.97 [0.88, 1.00]
Maniscalco 2021	12	1	1	91	Mixed	0.92 [0.64, 1.00]	0.99 [0.94, 1.00]



Pooled Sn: 0.96 (0.74, 1.00) with I^2=4.24; Pooled Sp: 0.98 (0.94, 0.99) with I^2=66.89

Figure 6. Sensitivity and specificity of breath test in symptomatic and asymptomatic individuals

Study	TP	FP	FN	TN	Symptomatology	Sensitivity (95% CI)	Specificity (95% CI)
de Vries 2021 (VS)	68	383	0	1357	Asymptomatic	1.00 [0.95, 1.00]	0.78 [0.76, 0.80]



Sn: 1.00 (0.95, 1.00); Sp: 0.78 (0.76, 0.80)

Figure 7. Sensitivity and specificity of breath test in asymptomatic individuals

Appendix 7. Table of Ongoing Studies

Study ID Design	Design	Sample Size	Population / Setting	Intervention/s	Gold Standard
NCT04602949 (Israel)	Non-randomized open-label clinical trial	4000	COVID-19	Breath Test Analysis	RT-PCR
NCT04867213 (Canada)	Prospective Cohort (Observational)	200	COVID-19	Breath Test Analysis	RT-PCR
NCT04341012 (United States of America)	Prospective Cohort (Observational)	200	COVID-19 & Liver Disease	Breath Test Analysis	RT-PCR
NCT04760639 (United States of America)	Feasibility study (Observational)	100	COVID-19	Breath Test Analysis	RT-PCR

Q7. Should pooled testing using RT-PCR for SARS-CoV-2, versus individual testing using RT-PCR, be used for screening and surveillance for SARS-CoV-2 in patients with suspected COVID-19 infection?

As of 6 March 2021

RECOMMENDATION

We suggest the use of pooled RT-PCR testing in targeted* low-risk and low-prevalence populations using a pool size of 5 in individuals suspected of COVID-19 infection. *(Moderate certainty of evidence; Weak recommendation)*

**For targeted populations refer to the list of Philippine Society of Pathologists and Department of Health*

Consensus Issues

The set recommendation included positivity rate and pool size; however, there were no studies that investigated the specificity and sensitivity of pooled testing for different pool sizes across different prevalence settings. Since the data presented did not clearly define the risk or the prevalence settings, pooled testing was suggested to be used only at a specific target population despite the moderate quality of evidence.

KEY FINDINGS

- Twenty-one cross-sectional studies (N=220,253) were found that used pooled RT-PCR testing for SARS-CoV2. Six were diagnostic accuracy studies that compared pooled testing with individual testing, and 15 were pragmatic clinical validation studies of pooled testing that did individual testing of positive pools. Studies had varying study populations, use case, index test kits, and pool sizes (5 to 16).
- Among the six diagnostic accuracy studies with a total of 5,987 participants, there was moderately high pooled sensitivity (Sn 81%, 95% CI 72-88%; I^2=73.6%; moderate certainty of evidence) and high pooled specificity (Sp 99%, 95% CI 98-100%; I^2=1.84%; high certainty of evidence), given the positivity rate of 2.7 to 15% within the study populations.
- The positive predictive value based on 21 studies ranged from 67 to 100%.
- Resource savings in the number of test kits used ranged from 49 to 89%.
- Identified harms of pooled testing were delayed turnaround time for positive samples and laboratory errors.
- The overall risk of bias was low in seven studies, among which were six diagnostic accuracy studies that contributed to pooled sensitivity and specificity, and low in 14 studies, mainly due to the lack of independent assessment between the index and reference tests.

INTRODUCTION

Pooled testing is the process of combining equal parts of samples from a certain number of individuals and processing them in a single batch. Two approaches are used: (1) sample/media pooling which combines aliquots of transport media containing individual samples, and (2) swab pooling which involves mixing multiple samples in a single transport media. When a pooled sample tests negative, all individual samples

are presumed to be negative. On the other hand, pooled samples that test positive will require retesting of individual samples to identify the positive specimen. This type of sampling is the Dorfman staged pooling, which is the simplest and most commonly used type of pooling.

Pooling is generally an efficient method to increase throughput while saving resources. However, due to diluted samples, fewer viral particles become available for detection, consequently increasing the likelihood of false-negative results and the turnaround time for processing specimens. As such, its implementation has been limited to screening and surveillance in populations with a low prevalence of COVID-19.[1-4] The diagnostic accuracy of this testing method and its recommended use need to be determined.

REVIEW METHODS

Living CPGs, HTAs, or living reviews were searched from the following sources on February 10, 2021: Australian National COVID-19 Clinical Evidence (https://covid19evidence.net.au/), UK Oxford COVID-19 Evidence Service (https://www.cebm.net/oxford-covid-19-evidence-service), and DOH Health Technology Assessment website (https://hta.doh.gov.ph/).

To obtain additional cross-sectional studies or systematic reviews of cross-sectional studies that were not yet included in the existing reviews, a comprehensive search of MEDLINE and Cochrane CENTRAL (31 Dec 2020) was performed using search strategies that included the concepts of pooled testing and COVID-19 for studies. The following inclusion criteria were applied.

Population	Patients suspected of COVID-19, any age, any sex, any comorbidity, with or without symptoms, any onset/timing of symptoms
Intervention/ Index Test	Pooled testing using RT-PCR from different individuals, any brand of test kit, any specimen (nasopharyngeal, oropharyngeal, saliva, etc.), any pool size or method, whether samples pooled prior to or after RNA extraction
Comparator/ Reference Standard	Individual testing using RT-PCR of deconvoluted samples from the pools, any brand of test kit, any specimen (nasopharyngeal, oropharyngeal, saliva, etc.)
Outcomes	Any measure of diagnostic performance (sensitivity, specificity, PPV or NPV, or any data that can be used to compute these outcomes), resources saved, turnaround time, harms

Retrospective case-control study designs that involved laboratory validation studies using previously known positive or negative samples, as well as modeling or simulation studies on pooling that did not include actual patient samples, were excluded.

Individual and pooled diagnostic performance measures, namely, sensitivity, specificity, positive and negative predictive values, and likelihood ratios, were derived using pools as the unit of analysis in 6/21 studies.[5-9,13] The same computations were then performed using individuals as the unit of analysis in 5 of the 6 aforementioned studies (all except Wang et al). The remaining 15 studies only had data for the calculation of the positive predictive value, positivity rate, and the number of tests or resources saved.

Subgroup analysis was performed based on variables that were hypothesized to affect the sensitivity of pooled sampling, particularly those leading to higher levels of true positive and fewer levels of false-negative results. These included the following:

- Test use case (i.e., screening, surveillance, or both)
- Symptom status (i.e., asymptomatic, symptomatic, unknown)
- Pool size (e.g., 5, 10, other)
- Specimen used (e.g., nasopharyngeal, nasal swab, etc.)
- Brand of PCR test kit
- Cycle threshold (Ct) values for RT-PCR positivity

Post-hoc subgroup analyses for positivity rate, method of pooling (random versus non-random), amount of aliquot per sample, and timing of processing, were also performed.

RESULTS

Characteristics of included studies

A total of 21 cross-sectional studies that recruited persons suspected to have COVID-19 (N=220,253) were found. Two studies [10, 11] were previously included in a local rapid review on the PSMID website (12 studies, 21 July 2020) [12] and a scoping review (9 studies, 23 Nov 2020) [2], while five studies [6,8,13-15] were previously included in the Philippine DOH HTA rapid review.[16-17] Fourteen additional studies were found since the last search date of the DOH HTA review (3 October 2020). Only six studies had complete 2x2 tables and were eligible for meta-analysis. The characteristics of included studies are detailed in Appendix 1.

The studies were performed in 13 countries: USA (n=5), India (n=4), Spain (n=3), and one study each from Australia, Brazil, China, Germany, Iran, Israel, Italy, Latvia, Philippines, and Thailand. The most common settings were hospitals (n=6), communities (n=4), and outpatient clinics (n=2). One study each was done among residents and workers at care homes; among employees from a supermarket; among arriving travelers from high-risk areas (Wuhan) at an airport; at a textile factory with an ongoing outbreak; and at a research institute. The community prevalence, as reported in seven studies, ranged from 0.5 to 10%. Only six studies reported the presence or absence of symptoms among participants. The participants in five of the studies were asymptomatic. Among these were healthcare workers in the US (Das 2020), volunteer employees in a supermarket in the Philippines [13], subjects at a research institute [18], subjects at an unspecified healthcare facility [19], and low-risk admitted patients in a hospital who did not have any history, physical exam, laboratory and imaging findings of COVID-19.[14] Both symptomatic and asymptomatic participants were included in two studies.[9,20] The first study was done among patients in screening clinics and tertiary care hospitals, including suspect cases admitted in the COVID wards, while the second study included follow-up samples from known COVID-19 patients enrolled in clinical trials.

The sample size in these studies ranged from 60 to 117,576 (median n=3,509). The number of individual samples per pool ranged from 4 to 16. Majority (18/21, 85.7%) of the studies pooled nasopharyngeal, nasal/mid-turbinate, oropharyngeal swabs, or a combination of these specimens. Two studies pooled saliva [15,21], while one study pooled mostly throat washes.[7] Majority (17/21) pooled samples and media. Only two

pooled swabs [5,14], one study [22] pooled both samples and RNA, and one study [15] pooled RNA.

All the studies included in this review used pooled testing using RT-PCR versus individual testing of samples from deconvoluted pools as their reference standard. Validated RT-PCR tests were also used as the index test using the pooled human samples. In this review, the index test is defined as an “RT-PCR used to diagnose SARS-CoV-2 virus in pooled human samples of saliva and/or oropharynx, nasopharynx.” While the brands of RT-PCR test kits used in the studies were generally reported (COBAS, Taq Path kit, CDC, Viasure, TaqMMan, AllPlex, LabGun, Xpert Xpress, Real Star, Gene Xpert, Sansure, Real Time Fluorescent, RealTime Multiplex Kit, Panther Fusion, Panther Aptima and Panther Aptima 450), a few were not specified, including one which was merely described as a laboratory-developed test (LDT). All except two studies [11,23] did preliminary laboratory validation of their planned pool size using known positive and n-1 negative samples.

Most studies [20, 21] did a two-stage Dorfman pooling, wherein positive pools were subjected to individual testing of the samples contained in those pools. In six studies [5-9,13], samples in negative pools were also tested individually. One study [13] also used three-stage (10-5-1) and four-stage (20-10-5-1) pooling. These methods entailed an initial testing of the biggest pool, and the subsequent formation and testing of smaller sub-pools following a positive result from the former until individual samples were tested. One study [18] did two replicates of each primary pool of three samples so that each mixed group (comprising six samples) contained two different primary pools.

Overall quality of evidence

The overall risk of bias in the included studies was rated high in 14/21 (67%) studies. Only the seven studies that did individual testing of both positive and negative pools [5-9,13] and the studies that stated blinded independent assessments [8,22] had a low risk of bias. A summary of the risk of bias ratings is shown in Appendix 5.

Fifteen studies that did deconvolution (i.e., individual testing for the pools that tested positive for the index test) were not likely to have an independent interpretation of the individual samples since testing from a positive pool was known. Ideally, all pooled samples should have been tested individually by blinded laboratory technicians, regardless of the result of pooled sampling test (index test). Only six studies [5-9,13] deconvoluted the negative pools, allowing them to measure the true and false-negative rates in their studies. In the study by Wang et al., the authors only indicated the number of pools that tested positive. The number of positive individual samples upon deconvolution was not specified, disallowing the measure of prevalence.[9] In the study by Lo, the authors only indicated the number of individuals that tested positive or negative for both index and reference tests but not the number of positive pools, which would have had at least one positive individual sample. However, subsequent communication from the author provided the data for the derivation of the 2x2 table.[13]

Outcomes

Diagnostic Accuracy

For the six studies that provided complete data for diagnostic accuracy using pools as the unit of analysis, the pool size ranged from 5 to 16. Pooled sensitivity, using pools as the unit of analysis, was 81% (95% CI 72-88%). However, the initial sensitivities taken from the individual studies were highly variable: 28.6 [7], 75% [8], 74 to 85% [9], 93.4% [6], and 100%.[5] Specificity was high at 98 to 100%. Similarly, a high positive predictive value (PPV) was noted in five studies at 92.3 to 100%. The negative predictive value (NPV) was high for three studies with NPVs of 97.2% [6], 95.8% [8], and 100% [5] and moderate for two studies with NPVs of 80.8% [7] and 84 to 90%.[9]

Pooled analysis of 5 studies (except Wang study) using individuals as the unit of analysis showed that sensitivity (Sn 83%, 95% CI 55-95%; I^2=92.8%) and specificity (Sp 100%, 95% CI 99-100%) did not change markedly. However, the heterogeneity for specificity increased to I^2=87.6%.

Only PPV could be computed for the 15 other studies. Across all 21 studies, the PPV ranged from 66.7 to 100% with only two studies recording a value below 90%. Prevalence in all included studies was from 0.02% [24] to 15%.[5]

Among the studies that used pools as a unit of analysis, the sensitivity reported by the Lusebrink study appeared to be an outlier, reporting a particularly low sensitivity of 29% (2/7 pools). According to their report, they used a pool size of 10 for hospital staff screening in Germany and collected mostly throat wash specimens (88%) using saline solution gargle. Moreover, they used a bigger aliquot (300 microliters per individual sample) than the recommended 200 microliters by the Korean Society of Laboratory Medicine.[25] Out of 28 pools, there were five false-negative pools, one of which turned out to have two positive individual samples. In addition, one of the two positive pools contained an invalid specimen. Upon retesting the 17 pools with invalid specimens and false-negative pools using a lower pool size of five, the sensitivity increased to 76.5% (13/17 pools). The authors concluded that the presence of PCR inhibitors in one invalid sample may have had a crucial effect on the pooled sample, and recommended against a Ct cut-off of 30 or above.

Of particular interest among the studies that used individuals as the unit of analysis was the local study by Lo et al. [13], which showed that sensitivity increased from 50% to 83% as they reduced the number of stages in the pooling strategy from 4-stage (Dorfman 20-10-5-1) to 2-stage (Dorfman 5-1). Specificity remained high at 100% in all three pooling strategies as shown in Table 1.

Table 1. Summary of results of Lo study (individuals as the unit of analysis)

Pooling method	Sn (%)	95% CI	Sp (%)	95% CI
Dorfman 5-1	83.33	51.59 to 97.91	100.00	99.14 to 100.00
Dorfman 10-5-1	58.33	27.67 to 84.83	100.00	99.14 to 100.00
Dorfman 20-10-5-1	50.00	21.09 to 78.91	100.00	99.14 to 100.00

Data source: Lo et al. An Evaluation of Pooling Strategies for qRT-PCR Testing for SARS-CoV-2 Infection by the PSP. Phil J Pathol.2020:5(2)

Subgroup analysis for sensitivity

Similar to the HTAC review, subgroup analysis suggested that higher sensitivity was obtained with a use case of screening and diagnosis, use of saliva and

nasopharyngeal specimens, pool size of 5, and Ct value of less than 40 (see Appendix 6, Subgroup analyses). However, the effects of these explanatory variables may need further confirmation due to the small number of studies, the lack of at least two pooled studies in most subgroups, and the overlapping confidence intervals for sensitivity between subgroups.

In terms of test brand, the 7500 Fast QuantStudio 6 Pro was found to have the highest sensitivity at 100% (95% CI 83.2-100%) based on a small-scale study (n=280, with 28 pools of 10 samples) that recruited both asymptomatic and pre-symptomatic patients in Brazil.[5] This test brand was not included in the HTAC review.[17] The local study by Lo et al. that used the Sansure 2019-nCoV Diagnostic Extraction Kit on a MA6000 PCR machine (China) had a sensitivity ranging from 83% (if using a pool size of 5) to 50% (is using a pool size of 20). Evidence is insufficient at this time to conclude which test brand is superior.

Subgroup analysis according to disease prevalence could not be performed as only one study provided data on the prevalence (4.8%).[8] It should be noted, however, that the value of pooled testing comes from its cost-saving feature, which is much needed in low-income countries. While performing pooled testing in populations with a high prevalence of the disease would yield higher true positives and lower false-negative results, the cost of running RT-PCR in the individual samples that yield positive tests in pooled sampling would increase rather than decrease the cost of diagnosis of the disease in high prevalence areas. Thus, to ensure cost-effectiveness while obtaining acceptable sensitivity and optimal pool size, pooled testing should be conducted in targeted populations where the risk of disease and the community prevalence are low. Based on subgroup analysis, pooled testing is recommended for screening of SARS-CoV-2 using a pool size of five. Further studies on the impact of other variables such as community prevalence, cut-off values for positivity, presence, and timing of symptoms, method of pooling (random vs non-random), amount of aliquot per sample, and timing of processing, are needed.

Resource savings and turnaround time

Resource savings reported from 21 studies ranged from 48% (pool size of 5 to 16; 15% positivity rate) [5] to 90% (pool size of 10; 0.07% positivity rate).[11] In the local study by Lo et al., the percent savings increased at a constant positivity rate of 2.7% with more stages of pooling, from 69% (2-stage Dorfman 5-1) to 79% (3-stage Dorfman 10-5-1) to 83% (4-stage Dorfman 20-10-5-1). Unfortunately, a decreasing sensitivity from 83.3% to 50% and an increasing delay in turnaround time from two to four batch runs for positive pools were also observed. For negative samples, the average turnaround time was from 1.09 to 1.44 batch runs, indicating that most of the negative samples tested using Dorfman 5-1 would still be released on the same batch run (Table 2).

Table 2. Turnaround times (Lo et al.)

Method	Turnaround time (TAT) (no. of batch runs)	
	Positive pools	Negative pools
Dorfman 5-1	2	1.09
Dorfman 10-5-1	3	1.21
Dorfman 20-10-5-1	4	1.44

Laboratory errors

One study [24] reported two significant human errors that occurred during the first period of high throughput testing using the pooling strategy, namely inaccurate manipulation of a sample and incorrect orientation of a 96-well sample block. These errors were attributed to the extremely high test throughput and the relative novelty of the pooling protocol. These errors were then mitigated by postponing the reporting of negative pooled samples until the individual testing and analysis of positive pools were complete.

RECOMMENDATIONS FROM OTHER GROUPS

The use of pooled testing for either screening, diagnosis, or surveillance has been recommended by several local and international health agencies.

The CDC (23 Oct 2020) published interim guidance that authorizes certified laboratories to use specimen pooling to expand SARS-CoV-2 nucleic acid diagnostic or screening testing capacity.[2]

The US FDA (25 Aug 2020) encourages developers to consider validating their tests first by screening asymptomatic individuals and by testing pooled samples in settings with low prevalence, wherein more negative results are expected.[26]

The European CDC (28 May 2020) recommended [27] and provided methodology [28] for a binary splitting pooling method or a single-stage non-adaptive group-testing approach for up to 1.3% positivity without the need to subsequently test individual samples.

The College of American Pathologists (CAP) (n.d.) stated that although pooled testing may conserve RT-PCR test kits in low-prevalence settings, the challenges for proper implementation include lack of infrastructure such as automated equipment, reduced sensitivity due to dilution of specimens, and increased turnaround time for positive tests due to multistage process.[29]

The Philippine Society of Pathologists Inc. (PSP) (29 May 2020) recommended in its position paper the implementation of pooled RT-PCR COVID testing to expand testing capacity, reduce the turnaround time, and conserve reagents and human resources.[30] It recommended screening asymptomatic persons in targeted populations, including low-prevalence communities (10% or less) (Table 3), and a pool size of 5 until an accurate prevalence of cases with SARS-CoV-2 is identified in the population.[13]

The Philippine Department of Health (DOH) Health Technology Assessment Council (HTAC) (11 Dec 2020) noted that pooled testing works well in low-prevalence (<5%) areas and small pool sizes. They recommended a pool size of 5 and the use of RT-PCR test kits that are validated by the Research Institute of Tropical Medicine and approved by the Food and Drug Administration or other authorized institutions for pooled testing use. They recommended a minimum sensitivity of 90% and specified a Ct cut-off that must be extended 3 Ct beyond the recommended value of the manufacturer.[31]

The Philippine DOH (23 Nov 2020) has issued interim guidelines through Department Memorandum 2020-0539 [29] specifying eligible populations for pooled testing based on the pooling protocols set by the Philippine Society of Pathologists, Inc., RITM, and DOH [28] (Table 4).

Table 3. Targeted populations for pooled testing based on the Philippine Society of Pathologists (Appendix C in Lo et al. 2020)

A. Low prevalence communities (10% or less) for epidemiologic surveillance and aggressive contact tracing;
B. Targeted community testing in areas that are under lockdown to identify additional infected individuals and to guide in decisions for lifting the lockdown;
C. Surveillance of healthcare workers and all workers in the healthcare facility
D. Workplace testing to include factory workers, market vendors, call center agents, transportation workers, and others;
E. Border testing at airports and seaports for inbound foreign travelers and returning residents;
F. Overseas deployment of OFWs;
G. Returning OFWs;
H. Frontline government workers (police, military, quarantine, immigration officers to name a few);
I. Locally Stranded Individuals (LSI)
J. Any other vulnerable populations to be determined in the future

Table 4. Eligible populations for pooled testing based on DOH Memorandum 2020-5039[11]

1. Screening of population groups
a. Inbound international travelers, including returning Filipinos, Overseas Filipino Workers, and foreigners; and
b. Interzonal domestic travelers, including returning residents.
2. Surveillance of population groups
a. Health care workers in health facilities;
b. Frontline government workers (police, military, quarantine, immigration officers, to name a few);
c. Factory workers, market vendors, call center agents, transportation workers, and others in workplace settings;
d. Other populations to be determined in the future.
3. Surveillance of communities that fulfill any of the two (2) criteria
a. COVID-free Municipalities: No cases reported yet since the start of the pandemic and/or for 2 weeks by the date of the report
b. Attack Rate: Municipalities/cities with an attack rate less than 100 per 100,000 population based on the data for the last two weeks.
c. Should results of pooled testing manifest an Attack Rate of more than 100 per 1,000 population or a Prevalence Rate of more than 10%, pooled testing shall be discontinued.

RESEARCH GAPS

Pooled testing methods in included studies differed in pool size, the number of pooling stages, brand of the test kit, and Ct cut-off for positivity, with positivity rates ranging from <1% to as high as 15%. Since each laboratory has its workflow and validation methods, the optimal pooling strategy would depend on their initial validation findings and the current community prevalence.

There are two ongoing studies: a validation study on RT-PCR, pooled RT-PCR, LAMP, and pooled LAMP in the diagnosis of COVID-19 (NCT04581083; recruiting; estimated study completion: 30 Nov 2020) [12] and a multi-center validation of SARS CoV-2 RT-PCR testing using combinatorial tapestry pooling (CTRI/2020/06/026005; registered 21 Jun 2020; not yet recruiting).

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Appendix 1. Characteristics of Included Studies

	Study ID	Use Case	N	Symptom Status	Specimen Used	Brand of RT-PCR test kit	Ct value for positivity	Pool size	Prevalence / Rate of Positivity	Pooling method[b]
1	Abdalhamid (USA)	Screening	60	At risk for COVID-19 (determined by the public health dept)	NP	CDC (2019-nCoV) Real-Time RT-PCR Diagnostic Panel kit (CDC, Atlanta, GA)	<40	5	3.33	2-stage/ pooled sample/media
2	Alcoba-Florez (Spain)	Not stated	4475	Persons tested at University Hospital Nuestra Señora de Candelaria in August 2020	NP	Real Accurate Quadruplex corona-plus PCR Kit (PathoFinder, The Netherlands) TaqPath COVID-19 CE-IVD RT-PCR Kit (Thermo Fisher Scientific, Waltham, MA, USA)	< 40	5	N/A	2-stage/ pooled sample/media
3	Alizad-Rahvar (Iran)	Screening	263	Not stated	Throat swabs	(2019-nCoV) Real-Time Multiplex kit (Liferiver)	<45	6	7.6	2-stage w/ groupMix method/pooled sample/media
4	Barak(1) (Israel)	Not stated	117576	Symptomatic but also asymptomatic carriers	NP	TaqPath qPCR Master Mix on the QuantStudio 5 Real-Time PCR Instrument	Not stated	8	1.7	2-stage/ pooled sample/media
	Barak(2)		16240					5	5.76	
5	Cesselli (Italy)	Screening	3592	Asymptomatic subjects	NP	DiaSorin Molecular SimplexaTM COVID-19 direct assay system	< 37	8	0.64	2-stage/ pooled sample/media
6	Chhikara (India)	Screening	500	Suspected COVID-19 patients	Throat swabs and NP	Taq Man probe–based commercial kit (Taq Path kit) in Applied Biosystem 7500 real-time machine (ABI, USA).	< 37	5	4.2	2-stage/ pooled samples & RNA
7	Chong(1) (Australia)	Not stated	10,312	Samples from lower acuity settings	Variety of swabs, including dry swabs	SARS-CoV-2 rRT-PCR Pooled sample: RdRp gene Individual sample: E or N gene	45	8	0.63	2-stage/ pooled samples/media
	Chong(2)	Not stated		Samples from lower acuity settings	Variety of swabs, including dry swabs	SARS-CoV-2 rRT-PCR Pooled sample: RdRp gene Individual sample: E or N gene	45	4		
	Chong(3)	Not stated	19,388	Samples from lower acuity settings	Variety of swabs, including dry swabs	SARS-CoV-2 rRT-PCR Pooled sample: RdRp gene Individual sample: E or N gene	45	4	0.02	
8	Christoff (Brazil)	Screening	613	Asymptomatic and presymptomatic patients	NP	7500 Fast,QuantStudio 6 Pro Real Time PCR (Applied Biosystems,	< 40	5 to 16; ave 13.67	15.33	2-stage/pooled swabs

					‘swab from nostril into 5 ml of saline”	USA), or in a CFX 384 (BioRad, USA); genes E and RdRp				
9	Das (USA)	Screening	7000	Asymptomatic HCWs	MidTurbinate[	CDC (2019-nCoV) Real-Time RT-PCR Diagnostic Panel kit (CDC, Atlanta, GA) & Panther Fusion SARS-COV-s LDT	< 36	10	0.11	2-stage/ pooled
10	De Salazar (Spain, 9 sites)	Screening and diagnosis	3509	Patients or health professionals (at least 24 were for clearance after testing positive for SARS-CoV2)	NP Random pooling according to availability at each site; Processed within 24 h; Aliquot amount not stated	Viasure SARS-CoV-2 Real Time PCR (CerTest) TaqMan2019-nCoV Assay Kit v1 (Thermo Fisher Scientific) Allplex 2019-nCoV Assay (Seegene) Light Mix E gene (Roche)	<35	9,10	6.87	2-stage/pooled samples/media
11	Garg 2020a (1) (India)	Screening	4620	Samples referred for testing to COVID laboratory, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow.	NP and OP	LabGun COVID-19 RT-PCR Kit (Lab Genomics)	Not stated	10	1.56	2-staged/ pooled samples/media
	Garg 2020a(2)		14950					5	1.38	
12	Gavars (Latvia)	Screening	3660	workers in a textile factory with an outbreak; 68% asymptomatic	Saliva	laboratory-developed and validated test method which detects S and N genes of the SARS-CoV-2 virus (LoD=1 cp/rxn)	Not stated	5	1.17	2-stage/ pooled
13	Hogan (USA)	Screening	3660	Samples for routine respiratory virus testing Stanford Health Care Clinical Virology Laboratory	NP and OP	Not stated (Germany kit)	Not stated	10	0.07	2-stage
14	Li 2020 (China)	Screening	944	High risk exposure	NP	Xpert Xpress SARS-CoV-2 assay (Sunnyvale, CA); cartridge-based	Not stated	9 or 10	0.21	2-stage/ pooled samples/media
15	Lo 2020 (Philippines)	Screening	440	volunteer employees from a supermarket chain excluded those with fever, cough, colds, or shortness of breath at the time of interview, those with previous RT-PCR testing, pregnant women, less than 18 years of age	NP and OP 50 µL	Sansure Novel Coronavirus (2019-NCoV) Nucleic Acid Acid Diagnostic kit; RT-PCR performed on MA6000 PCR machine (China)	For pooled testing, any target gene amplification (ORF1 and N genes) regardless of Ct value, degree of amplification of curve properties	5 10-5-1 20-10-5-1	2.73	2-, 3-, 4-stage pooling/ pooled samples/media

							(sigmoid or non-sigmoid) will be considered positive Individual testing will undergo the same interpretation as manufacturer's specifications			
16	Lusebrink (Germany)	Screening	280	Healthcare staff	Throat washes (n=327), swabs (n=32), bronchoalveolar lavages[ABC5] (n=1) 30 µL	RealStar SARS-CoV-2 RT-PCR Kit (Altona Diagnostics, Hamburg, Germany)	<30	10	2.86	2-stage/ pooled samples
17	Mastrianni (USA)	Screening patients for admission into either COVID or non-COVID units	530	Patients at low risk for SARS-CoV-2 admitted to a community hospital; without complaints8suggestive of COVID-19, may have had negative inflammatory markers, no significant lymphopenia and negative imaging	NP	Gene Xpert, cartridge-based	Not stated	2 to 3	0.75	2-stage/ pooled swabs
18	Mohanty (India)	Screening	7228	symptomatic and asymptomatic individuals with either travel history or active contacts of a laboratory-confirmed case.	Nasal, NP, and throat swabs	Taqman primer probe designed by NIV, Pune, India and Invitrogen SuperScriptTM III Platinum One-Step Quantitative RT-PCR Kit/AgPath-ID TM One-Step RT-PCR Kit on a AriaMx Real-time PCR Instrument (Agilent, California, USA).	≤ 35	4	2.07	2-stage/ pooled samples/media
19	Pasomsub(1) (Thailand)	Screening	200	Patients under investigation for COVID-19 during the outbreak in Bangkok, Thailand	Saliva	SARS-CoV-2 Nucleic Acid Diagnostic Kit (Sansure, Changsha, China)	≤ 45.1	5	8.5	2-stage/ pooled RNA

	Pasomsub(2)							10		
20	Singh (India)	Screening	545	Suspected COVID-19 patients	NP and OP 200 µL	Real-Time Fluorescent RT-PCR Kit for Detecting SARS-CoV-2 (BGI, Hong Kong)	≤ 35	5	4.58	2-stage/ pooled sample/media
21	Wang(1) (USA)	Screening and diagnosis	880	Samples from tertiary-care academic hospitals and affiliated outpatient facilities in the San Francisco Bay Area of California.	NP and OP 500 µL/8 = 62.5 µL	Laboratory-developed test (LDT) targeting the envelope gene with the Rotor-Gene Q Instrument (QIA-GEN) *As per manufacturer's recommendation & ROC curve analysis of pooled relative light unit (RLU) values, with individual test as reference standard, to determine optimal RLU discriminated threshold	40-45 (for indeterminate) <35 (positive)	8	6.6	2-stage/ pooled samples/media
	Wang(2)					Panther Fusion SARS-CoV-2 assay (Hologic)				
	Wang(3)					Panther Aptima SARS-CoV-2 assay (Hologic)				
	Wang(4)					Panther Aptima-450 SARS-CoV-2 assay (Hologic)				

Appendix 2. GRADE Evidence Profile

Question: Should pooled testing using RT-PCR for SARS-CoV-2 be used to screen for COVID-19 in suspected patients with COVID-10?

Sensitivity	0.81 (95% CI: 0.72 to 0.88)			Prevalences	1%	5%	10%				
Specificity	0.99 (95% CI: 0.98 to 1.00)										
Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 15%	
True positives (patients with COVID-19)	6 studies 5987 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Serious [a]	Not serious [b]	None	8 (7 to 9)	41 (36 to 44)	81 (72 to 88)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having COVID-19)								2 (1 to 3)	9 (6 to 14)	19 (12 to 28)	
True negatives (patients without COVID-19)	6 studies 5987 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious [c]	Not serious	None	980 (970 to 990)	941 (931 to 950)	891 (882 to 900)	⊕⊕⊕⊕ HIGH
False positives (patients incorrectly classified as having COVID-19)								10 (0 to 20)	9 (0 to 19)	9 (0 to 18)	

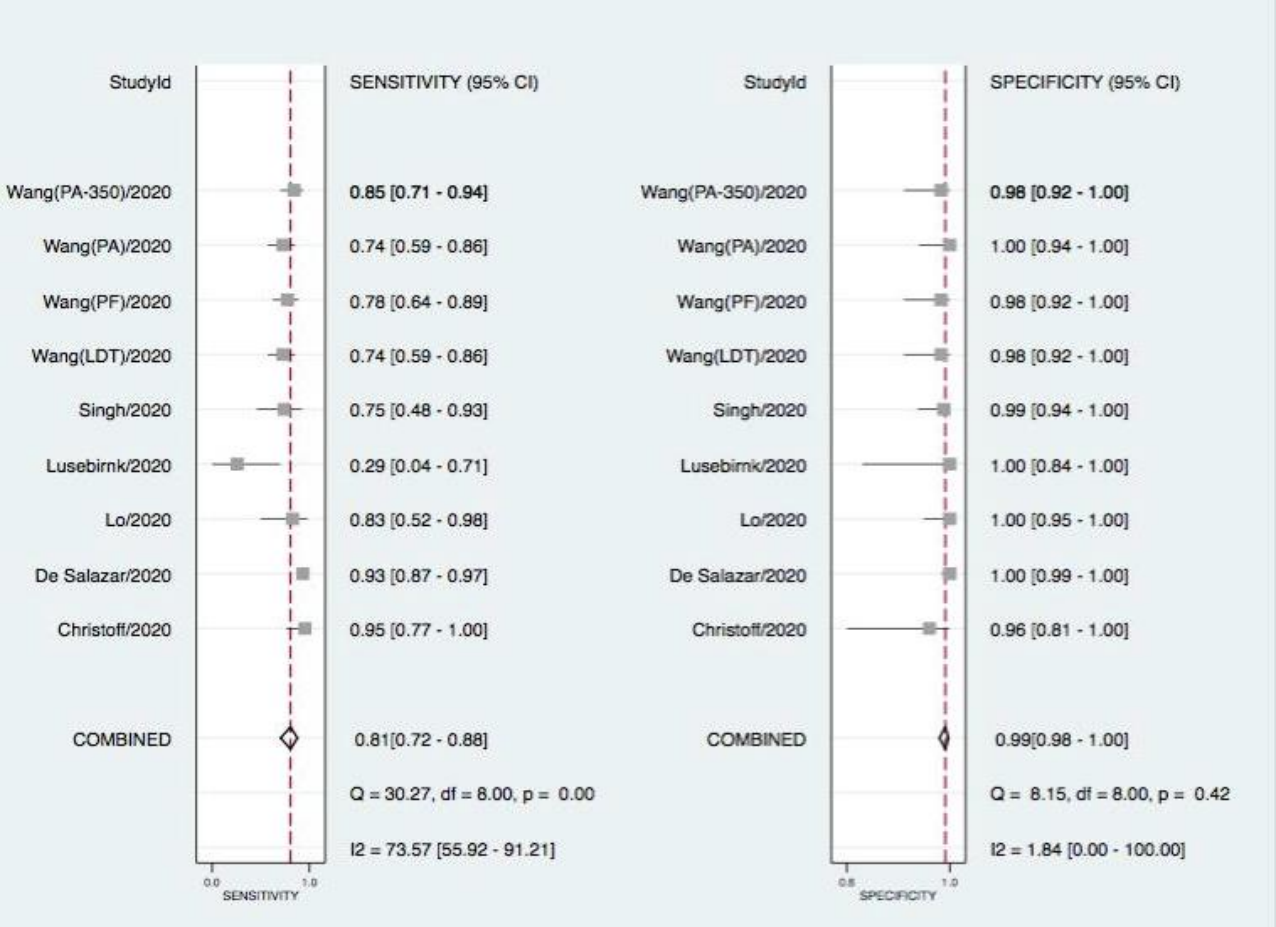
Explanations

[a] I2=77.7%

[b] wide CIs that crosses line of significance

[c] different study population, pool size, brand of test kit

Appendix 3. Forest plot for sensitivity and specificity for pools as unit of analysis (N=6 studies)



Appendix 4. Characteristics of Ongoing Studies

No	Clinical Trial ID / Title	Study design, sample size	Country	Population	Intervention Group	Comparison Group	Clinical Outcomes
1	**Validation of SARS CoV-2 RT-PCR testing using combinatorial tapestry pooling of samples: a multi-centre study (CTRI/2020/06/026005)**	Retrospective observational; N=321 Not yet recruiting Registered on: 21/06/2020	India	Age 1 day to 99 years, both genders, NP swabs submitted for COVID-19 testing	Combinatorial tapestry pooling	Individual testing	Primary outcome: Sn and Sp of combinatorial tapestry pooled testing vs individual testing Secondary outcome: Sn and Sp of simple pooled testing vs individual testing
2	**Validation of Laboratory Techniques, Strategies, and Types of Samples for Epidemiological Control in the Covid-19 Pandemic** (NCT04581083) Recruiting Estimated study completion date: November 30, 2020	Cross-sectional; N=30 Completed: October 30, 2020	Bolivia	Age 21-64 Symptomatic: Subjects with signs and symptoms of respiratory infection less than or equal to 3 days, preferably with clinical and molecular diagnosis compatible with Covid-19. Asymptomatics: Subjects who have had direct contact with people infected and who have not shown any symptoms related to Covid-19. Negative: Individuals with negative RT-PCR testing for SARS-CoV-2 (reference test) who have not manifested any symptoms seven days prior to sampling.	Pooled RT-PCR	individual RT-PCR	Validation

Appendix 5. Appraisal of Included Studies

Clinical Question: **Among patients with suspected COVID-19, how accurate is pooling of samples as compared to individual testing using RT-PCR?**

Directness

	Clinical Question	Research Question
Population	Patients suspected of having COVID-19	Patients suspected of having COVID-19
Exposure	Pooled sampling compared to individual sampling using RT-PCR	Study of unknown samples: For all 19 studies, pools with positive results were compared with individual testing using RT-PCR detection of SARS-CoV-2 For 5 studies, pools with negative results were also compared with individual testing using RT-PCR detection of SARS-CoV-2
Outcome	Presence or Absence of SARS-CoV-2 RNA	Presence or Absence of SARS-CoV-2

Validity

	Study ID	APPRAISAL #1: Was the reference standard an acceptable one?	APPRAISAL#2: Was "definition" of the index test and the ref standard independent?	APPRAISAL#3: Was "performance" of the index test and the ref standard independent?	APPRAISAL#4: Was the ref standard interpreted independently of the index test?	Overall risk of bias 1-2 high risk; 3-4 low risk
1	Abdalhamid	YES	YES	NO	No information	HIGH
2	Alcoba-Florez	YES	YES	NO	No information	HIGH
3	Alizad-Rahvar	YES	YES	NO	No information	HIGH
4	Barak	YES	YES	NO	No information	HIGH
5	Cesselli	YES	YES	NO	No information	HIGH
6	Chhikara	YES	YES	NO	YES	LOW
7	Chong	YES	YES	NO	No information	HIGH
8	Christoff	YES	YES	YES	No information	LOW
9	Das	YES	YES	NO	No information	HIGH
10	De Salazar	YES	YES	YES	No information	LOW
11	Garg 2020a	YES	YES	NO	No information	HIGH
12	Gavars	YES	YES	NO	No information	HIGH
13	Hogan	YES	YES	NO	No information	HIGH
14	Li	YES	YES	NO	No information	HIGH
15	Lo	YES	YES	YES	No information	LOW
16	Lusebrink	YES	YES	YES	No information	LOW
17	Mastrianni	YES	YES	NO	No information	HIGH
18	Mohanty	YES	YES	NO	No information	HIGH
19	Pasomsub	YES	YES	NO	no information	HIGH
20	Singh	YES	YES	YES	YES	LOW
21	Wang	YES	YES	YES	No information	LOW

Appendix 6. Subgroup Analyses

Covariate	Studies		Number of Pools	Sensitivity	
Pool Size	**N**	**Study ID**	**n**	**Sn (%)**	**95% CI**
5	2	Lo, Singh	197	0.73	0.51-0.95
6-10	3	De Salazar, Lusebrink , Wang(1), Wang(2), Wang(3), Wang(4)	820	0.52	0.08-0.97
5-16	1	Christoff	45	1.00	0.83-1.00
Positivity rate (%)	**n**	**Study ID**	**N**	**Sn (%)**	**95% CI**
0-5	3	Lo, Lusebrink, Singh	225	0.52	0.08-0.95
>5-10	2	De Salazar, Wang	792	0.78	0.60-0.97
>10-15	1	Christoff	45	1.00	0.83-1.00
Ct value for positivity	**n**	**Study ID**	**N**	**Sn (%)**	**95% CI**
Any amplification	1	Lo	44	0.83	0.56 – 0.98
<40	2	Christoff, Wang	484	0.84	0.68-1.00
<35	1	Singh	109	0.75	0.48-0.93
<30	1	Lusebrink	28	0.29	0.04-0.71
Not stated	1	De Salazar	352	0.93	0.87-0.97
RT-PCR Brand	**n**	**Study ID**	**N**	**Sn (%)**	**95% CI**
Sansure	1	Lo	44	0.83	0.56 – 0.98
7500 Fast QuantStudio 6 Pro	1	Christoff	45	1.00	0.83-1.00
Viasure+TaqMan+Allplex	1	De Salazar	352	0.93	0.87-0.97
RealStar SARS-CoV-2	1	Lusebrink	28	0.29	0.04-0.71
Real-Time Fluoroscent RT-PCR	1	Singh	109	0.75	0.48-0.93
Laboratory-developed test	1	Wang(1)	110	0.75	0.48-0.93
Panther Fusion	1	Wang(2)	110	0.74	0.59-0.86
Panther Aptima 450	1	Wang(3)	110	0.78	0.64-0.89
Panther Aptima	1	Wang(4)	110	0.74	0.59-0.86
Symptom presence	**n**	**Study ID**	**N**	**Sn (%)**	**95% CI**
Asymptomatic	1	Lo	44	0.83	0.56 – 0.98
Mixed	2	Christoff, Wang	485	0.84	0.68-1.00
Unspecified	3	de Salazar, Lusebrink, Singh	489	0.52	0.08-0.97
Use Case	**n**	**Study ID**	**N**	**Sn (%)**	**95% CI**
Surveillance	0	-	-	-	-
Screening	4	Christoff, Lo, Lusebrink, Singh	270	0.82	0.40-0.97
Screening and diagnosis	2	De Salazar, Wang(1), Wang(2), Wang(3), Wang(4)	1144	0.78	0.60-0.97
Specimen Used	**n**	**Study ID**	**N**	**Sn (%)**	**95% CI**
Nasopharyngeal (NP)	2	Christoff, de Salazar	397	0.92	0.84-1.00
NP + Oropharyngeal (OP)	3	Lo, Singh, Wang	636	0.73	0.51-0.95
Throat washes	1	Lusebrink	28	0.29	**0.04-0.71**
Timing of processing	**n**	**Study ID**	**N**	**Sn (%)**	**95% CI**
Within 24 hours	2	De Salazar, Singh	461	0.74	0.51-0.97
Within 48 hours	1	Christoff	45	1.00	0.83-1.00
Not stated	3	Lo, Lusebrink, Wang	556	0.50	0.08-0.95

Method of pooling	n	Study ID	N	Sn (%)	95% CI
Random	1	De Salazar	352	0.93	0.87-0.97
Non-random (e.g. consecutive)	1	Singh	109	0.75	0.48-0.93
Both random and non-random	**1**	Wang(1), Wang(2), Wang(3), Wang(4)	440	0.76	0.60-0.92
Not stated	**2**	Christoff, Lusebrink	73	0.54	0.08-1.00
Amount of aliquot per individual sample in pool (µL)	**n**	**Study ID**	**N**	**Sn (%)**	**95% CI**
50	1	Lo	44	0.83	0.56 – 0.98
200	**1**	Singh	109	0.75	0.48-0.93
300	**1**	Lusebrink	28	0.29	0.04-0.71
500	**1**	Wang	440	0.76	0.60-0.92
“swab from nostril into 5 ml of saline”	**1**	Christoff	45	1.00	0.83-1.00
Not stated	**1**	De Salazar	352	0.93	0.87-0.97

Appendix 7. Summary of diagnostic accuracy results (by pools as unit of analysis)

	STUDY ID	TP	FN	FP	TN	Sn %	95% CI	Sp %	95% CI	PPV %	95% CI	NPV %	95% CI	Accuracy%	95% CI	Positivity rate %	95% CI	% Savings in Tests Used
1	Abdalhamid	2	NA	0	NA	NA	NA	NA	NA	100%	–	NA	NA	NA	NA	3.33	0.41 to 11.53	63.33
2	Alcoba-Florez	162	NA	0	NA	NA	NA	NA	NA	100	–	NA	NA	NA	NA	NA	NA	61.90
3	Alizad-Rahvar	3	NA	0	NA	NA	NA	NA	NA	100	29.2 to 100	NA	NA	NA	NA	7.6	0.09 to 2.72	62.74
4	Barak (1) (P8)	1313	NA	54	NA	NA	NA	NA	NA	96.05	94.88 to 97.02	NA	NA	NA	NA	1.7	1.62 to 1.77	78.20
	Barak (1) (P5)	679	NA	38	NA	NA	NA	NA	NA	94.70	92.6 to 96.22	NA	NA	NA	NA	5.76	5.41 to 6.13%	80.00
5	Cesselli	20	NA	0	NA	NA	NA	NA	NA	100	83.16 to 100	NA	NA	NA	NA	0.64	.41 to 0.96	83.05
6	Chhikara	11	NA	0	NA	NA	NA	NA	NA	100%	–	NA	NA	NA	NA	4.2	2.62 to 6.35	69.00
7	Chong(1)	8	NA	0	NA	NA	NA	NA	NA	100%	–	NA	NA	NA	NA	0.08	0.03 to 0.15	74.90
	Chong(2)	49	NA	0	NA	NA	NA	NA	NA	100%	–	NA	NA	NA	NA			
	Chong (3)	3	NA	0	NA	NA	NA	NA	NA	100	–	NA	NA	NA	NA	0.29	0.22 to 0.38	74.94
8	**Christoff**	**20**	**0**	**0**	**25**	**100**	**83.16 to 100**	**100**	**86.28 to 100**	**100**	**–**	**100**	**–**	**100**	**92.13 to 100**	**15.33**	**12.57 to 18.43**	**48.06**
9	Das	8	NA	0	NA	NA	NA	NA	NA	100%	–	NA	NA	NA	NA	0.11	0.05 to 0.23	88.86
10	**De Salazar**	**99**	**7**	**0**	**246**	**93.40**	**86.87 to 97.30**	**100**	**98.51 to 100**	**100%**	**–**	**97.23%**	**94.50% to 98.63%**	**98.01%**	**95.95% to 99.20%**	**6.87**	**6.05 to 7.76**	**61.76**
11	Garg 2020a	61	NA	0	NA	NA	NA	NA	NA	100	–	NA	NA	NA	NA	1.56	1.22 to 1.96%	76.80
		194	NA	0	NA	NA	NA	NA	NA	100	–	NA	NA	NA	NA	1.38	1.2o to 1.58%	73.51
12	Gavars	43	NA	0	NA	NA	NA	NA	NA	100	–	NA	NA	NA	NA	1.20	0.87 to 1.61	78.25
13	Hogan	2	NA	1	NA	**100**		NA		66.7	20.6 to 93.9	NA	NA	NA	NA	0.07	0.01 to 0.25	88.90
14	Li	NA	0	NA	NA	NA	NA	NA	NA	100	–	NA	NA	NA	NA	0.21	0.03 to 0.76	87.92
15	**Lo(1) (5-1)**	**10**	**2**	**0**	**76**	**83.33**	**51.59 to 97.91**	**100**	**99.14 to 100**	**100**	**–**	**99.53**	**98.37 to 99.87**	**–**	**–**	**2.73**	**1.42 to 4.72**	**69.00**
16	**Lusebrink**	**2**	**5**	**0**	**21**	**28.57**	**3.67 to 70.9**	**100**	**83.89 to 100**	**100**	**–**	**80.77**	**72.44 to 87.03**	**82.14**	**63.11 to 93.94**	**2.86**	**1.24 to 5.55**	**65.00**
17	Mastrianni	4	NA	0	NA	NA	NA	NA	NA	100		NA	NA	NA	NA	0.75	0.21 to 1.92	64.34

18	Mohanty	150	NA	49	NA	NA	NA	NA	NA	75%	68.8 to 81.2	NA	NA	NA	NA	19	16 to 23	63.99
19	Pasomsub(1)	13	NA	0	NA	NA	NA	NA	NA	100		NA	NA	NA	NA	8.5	5.0 to 13.3	47.50
	Pasomsub(2)	13	NA	0	NA	NA	NA	NA	NA	100		NA	NA	NA	NA			40.00
20	**Singh**	**12**	**4**	**1**	**92**	**75.00 %**	**47.62% to 92.73%**	**98.92 %**	**94.15 % to 99.97 %**	**92.31 %**	**62.60% to 98.85%**	**95.83%**	**90.78% to 98.17%**	**95.41%**	**89.62% to 98.49%**	**4.58**	**2.99 to 6.70**	68.07
21	**Wang(1)LDT]**	**34**	**12**	**1**	**63**	**73.91 %**	**58.87% to 85.73%**	**98.44 %**	**91.60 % to 99.96 %**	**97.14 %**	**82.84% to 99.58%**	**84.00%**	**76.33% to 89.53%**	**88.18%**	**80.64% to 93.55%**	**6.59**	**5.04 to 8.44**	55.68
	Wang(1)PF	**36**	**10**	**1**	**63**	**78.26 %**	**63.64% to 89.05%**	**98.44 %**	**91.60 % to 99.96 %**	**97.30 %**	**83.66% to 99.61%**	**86.30%**	**78.44% to 91.60%**	**90.00%**	**82.81% to 94.90%**			53.86
	Wang(1)PA	**34**	**12**	**0**	**64**	**73.91 %**	**58.87% to 85.73%**	**100.00 %**	**94.40 % to 100.00 %**	**100**	**–**	**84.21%**	**76.63% to 89.66%**	**89.09%**	**81.72% to 94.23%**			56.59
	Wang(1)PA-350	**39**	**7**	**1**	**63**	**84.78 %**	**71.13% to 93.66%**	**98.44 %**	**91.60 % to 99.96 %**	**97.50 %**	**84.75% to 99.64%**	**90.00%**	**81.97% to 94.69%**	**92.73%**	**86.17% to 96.81%**			51.14

Note: In bold font are 6 studies with complete data for 2x2 table for unit of analysis as pools; In italics are data of Lo for 10-5-1 and 20-10-5-1 pooling methods for unit of analysis as individuals, while rest of studies provided data for unit of analysis as pools

Appendix 8. Summary of diagnostic accuracy (by individuals)

STUDY ID	TP	FN	FP	TN	Sn %	95% CI	Sp %	95% CI	PPV %	95% CI	NPV %	95% CI	Accuracy	95% CI
Christoff	94	0	0	519	100.00%	96.15% to 100.00%	100.00%	99.29% to 100.00%	100%		100%		100.00%	99.40% to 100.00%
De Salazar	234	7	0	3268	97.10%	94.11% to 98.82%	100.00%	99.89% to 100.00%	100%		99.79%	99.56% to 99.90%	99.80%	99.59% to 99.92%
Lo(1)	10	2	0	428	83.33%	51.59% to 97.91%	100.00%	99.14% to 100.00%	100%	–	99.53%	98.37% to 99.87%	99.55%	98.37% to 99.94%
Lo(2)	7	5	0	428	58.33%	27.67% to 84.83%	100.00%	99.14% to 100.00%	100%	–	98.85%	97.77% to 99.41%	98.86%	97.37% to 99.63%
Lo(3)	6	6	0	428	50.00%	21.09% to 78.91%	100.00%	99.14% to 100.00%	100%	–	98.62%	97.59% to 99.21%	98.64%	97.06% to 99.50%
Lusebrink	2	6	0	272	25.00%	3.19% to 65.09%	100.00%	98.65% to 100.00%	100%		97.84%	96.81% to 98.54%	97.86%	95.39% to 99.21%
Singh	21	4	5	460	84.00%	63.92% to 95.46%	98.92%	97.51% to 99.65%	80.77%	63.34% to 91.08%	99.14%	97.91% to 99.65%	98.16%	96.54% to 99.16%

Q8. Should repeat RT-PCR testing after an initial negative RT-PCR (versus single RT-PCR testing) be done to diagnose COVID-19 in symptomatic patients?

As of 6 March 2021

RECOMMENDATION

We suggest repeating RT-PCR testing when the initial RT-PCR test is negative in symptomatic patients with high index of suspicion for COVID-19 infection. *(Low certainty of evidence; Weak recommendation)*

Consensus Issues

The recommendation applies only to symptomatic patients with high index of suspicion for COVID-19. Since the disease severity and the level of suspicion were not clearly defined in the studies, the level of suspicion may vary. Moreover, no specific recommendation was made regarding the specific time interval between the initial and the repeat test as well as the frequency of repeat PCR tests.

KEY FINDINGS

- Two cohort studies involving 368 patients were found on the accuracy of repeat RT-PCR testing after an initial negative test to diagnose COVID-19 in symptomatic patients with a high index of suspicion. The evidence was assigned a low-quality rating due to the serious risk of bias and serious imprecision.
- The sensitivity of repeat RT-PCR testing ranged from 0.83 (95% CI 0.75-0.90) to 0.85 (95% CI 0.62-0.97), approximately 15% higher compared to the sensitivity of a single RT-PCR test, which ranged from 0.68 (95% CI 0.58-0.76) to 0.70 (95% CI 0.46-0.88).
- The specificity of repeat testing was consistently very high (Sp 1.00, 95% CI 0.89-1.00).

INTRODUCTION

False-negative rates for single RT-PCR have been reported to occur in 7% (5 in 70) [1] to 19% [2-4] of suspected COVID-19 patients. These were higher than the acceptable false-negative rate of <2%.[5] RT-PCR sensitivity is affected by the duration of illness (i.e., the time between symptom onset to testing), specimen location (URT vs LRT) [6-8], and cycle threshold for positivity.[9] Repeat testing is usually done 24 hours to four days after a negative initial RT-PCR among hospitalized adults suspected to have COVID-19.

A high index of suspicion for COVID-19 infection is considered in symptomatic patients presenting with, but not limited to the following:

a. Clinical deterioration in the presence of an established disease etiology (i.e., have severe or progressive disease even with adequate treatment), with possible coinfection with COVID-19.
b. No other etiology for the patient's signs and symptoms has been identified despite work-up.
c. Clinical specimen(s) initially sent was/were deemed to be unsatisfactory or insufficient (delay in transport and processing, only NPS or OPS was sent).[10]

REVIEW METHODS

The search was conducted in databases such as MEDLINE and Cochrane. Preprints were also searched in MedRxiv, ChinaXiv, and BioRxiv databases. The search was conducted using the following search terms: COVID-19, SARS-CoV-2, NAAT, RT-PCR, PCR, repeat testing, repeat test, cumulative test, and serial test. Reference lists of selected articles were reviewed for inclusion. Two reviewers independently screened titles and abstracts initially, then the eligible full-text studies.

Cohort, cross-sectional and case-control studies that evaluated diagnostic test accuracy and provided complete data to estimate both the sensitivity and specificity of the index test were included. Studies that used a combination of tests and clinical criteria as their reference standard were excluded. Studies with inconclusive results for patients were excluded from the analysis. We also excluded studies that reported on the number of specimens, rather than the number of patients.

RESULTS

Characteristics of included studies

Two pre-print cohort studies were identified, which involved 366 hospitalized adult patients and two children with suspected COVID-19 of varying severity, all of whom had initial RT-PCR testing.[11,12] One study involved 53 patients who underwent a second RT-PCR test after three days, which was compared against metagenomic sequencing as the reference standard.[12] The other study enrolled 315 patients and employed repeat/cumulative RT-PCR testing every 24 hours for at most five tests.[11]

Methodological quality

Overall quality of evidence was rated low due to the serious risk of bias and serious imprecision. Differences in the type of specimen used (throat swab versus nasopharyngeal swab) and timing of specimen collection from symptom onset were the sources of bias, along with the lack of independence in the interpretation of the reference test from the index test. Imprecision was attributed to the small sample size in the studies.

Diagnostic accuracy

The sensitivity of repeat RT-PCR testing ranged from 0.83 (95% CI 0.75-0.90) to 0.85 (95% CI 0.62-0.97), approximately 15% higher compared to the sensitivity of a single RT-PCR test, which ranged from 0.68 (95% CI 0.58-0.76) to 0.70 (95% CI 0.46-0.88). The specificity of repeat testing was consistently very high at 1.00 (95% CI 0.89-1.00).

Benefits and harms

Both studies did not specifically report on patient outcomes or harm. Based on the resulting diagnostic performance measures, it can be derived that repeat RT-PCR testing reduced the false-negative rate of single RT-PCR by approximately 15%, that is from 30% to 15% in one study and from 32% to 17% in another. This is still a high false-negative rate compared to the acceptable false-negative rate of 2% determined by IDSA.[5]

RECOMMENDATIONS FROM OTHER GROUPS

CDC (07 January 2021) recommends repeat testing of symptomatic individuals in certain healthcare settings (e.g., patients at risk for severe illness, critical nature of

healthcare personnel, challenges with social distancing, assisted living facilities, intermediate care facilities for individuals with intellectual disabilities, institutions for mental disease, and psychiatric residential treatment facilities).[13]

IDSA (23 December 2020) and PSMID (29 July 2020) recommend repeat testing for symptomatic patients with an initial negative COVID-19 test result if there is an intermediate [5] to high index of suspicion for COVID-19 infection.[10] Such conditions include, but are not limited, to the following:

a. Clinical deterioration in the presence of an established disease etiology despite adequate treatment, in which case coinfection with COVID-19 should be considered. A single negative test result, particularly if it was from an upper respiratory tract specimen, does not exclude infection. Repeat sampling and testing, preferably of a lower respiratory specimen, is strongly recommended in severe or progressive disease.
b. No other etiology for the patient's signs and symptoms has been identified despite work-up.
c. Clinical specimen(s) initially sent was/were deemed to be unsatisfactory or insufficient (delay in transport and processing, only NPS or OPS was sent).
d. Repeat testing is recommended 24-48 hours after an initial negative test.[5]

RESEARCH GAPS

No ongoing or planned studies related to this topic were found.

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Appendix 1. Characteristic of Included Studies

Author	Study Design	Sample Size	Population	Index Test/s	Reference Test	Outcome
Ai J (Apr 2020)[10]	Cohort	315	315 adults hospitalized, suspected COVID-19	Two to five repeat RT-PCR done at 24 hours' interval	Positive in any 1 to at most 5 repeat/ cumulative RT-PCR testing	Sensitivity Specificity
Ai JW (Feb 2020)[11]	Multi-center Cohort	53	53 Suspected COVID-19	Repeat RT-PCR three days after initial RT-PCR test	metagenomic sequencing	Sensitivity Specificity

Appendix 2. GRADE Evidence Profile

Question: Should [Repeat RT-PCR] after an initial negative test vs. [Single RT-PCR] be used to diagnose [COVID-19] in [suspected COVID-19 patients]?

	Repeat RT-PCR after an initial negative test	Single RT-PCR				
Sensitivity	0.83 to 0.85	0.68 to 0.70	Prevalences	10%	40%	0%
Specificity	0.89 to 1.00	0.89 to 1.00				

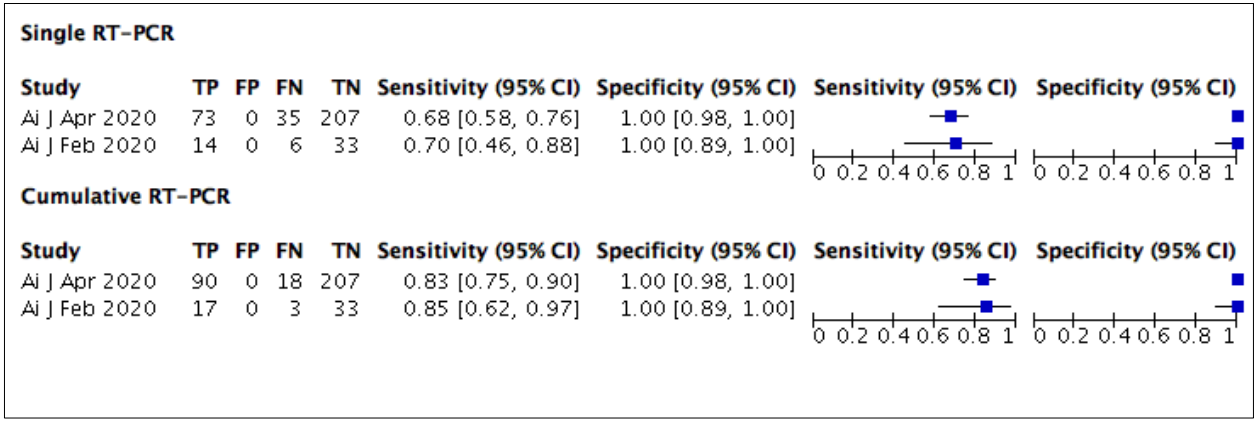
Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 10%		Pre-test probability of 40%		Pre-test probability of 0%		
True positives (patients with COVID-19)	2 studies 128 patients	Cross-sectional (cohort type accuracy study)	Serious [1,a]	Not serious	Not serious	Serious [2,b]	None	83 to 85	68 to 70	332 to 340	272 to 280	0 to 0	0 to 0	⊕⊕◯◯ Low
								15 more to 15 more TP in [Repeat RT-PCR] after an initial negative test		**60 more to 60 more TP in [Repeat RT-PCR] after an initial negative test**		**0 fewer to 0 fewer TP in [Repeat RT-PCR] after an initial negative test**		
False negatives (patients incorrectly classified as not having COVID-19)								15 to 17	30 to 32	60 to 68	120 to 128	0 to 0	0 to 0	
								15 fewer to 15 fewer FN in [Repeat RT-PCR] after an initial negative test		**60 fewer to 60 fewer FN in [Repeat RT-PCR] after an initial negative test**		**0 fewer to 0 fewer FN in [Repeat RT-PCR] after an initial negative test**		
True negatives (patients without COVID-19)	2 studies 240 patients	Cross-sectional (cohort type accuracy study)						801 to 900	801 to 900	534 to 600	534 to 600	890 to 1000	890 to 1000	⊕⊕◯◯ Low
								0 fewer to 0 fewer TN in [Repeat RT-PCR] after an initial negative test		**0 fewer to 0 fewer TN in [Repeat RT-PCR] after an initial negative test**		**0 fewer to 0 fewer TN in [Repeat RT-PCR] after an initial negative test**		
False positives (patients incorrectly classified as having COVID-19)								0 to 99	0 to 99	0 to 66	0 to 66	0 to 110	0 to 110	
								0 fewer to 0 fewer FP in [Repeat RT-PCR] after an initial negative test		**0 fewer to 0 fewer FP in [Repeat RT-PCR] after an initial negative test**		**0 fewer to 0 fewer FP in [Repeat RT-PCR] after an initial negative test**		

Explanations

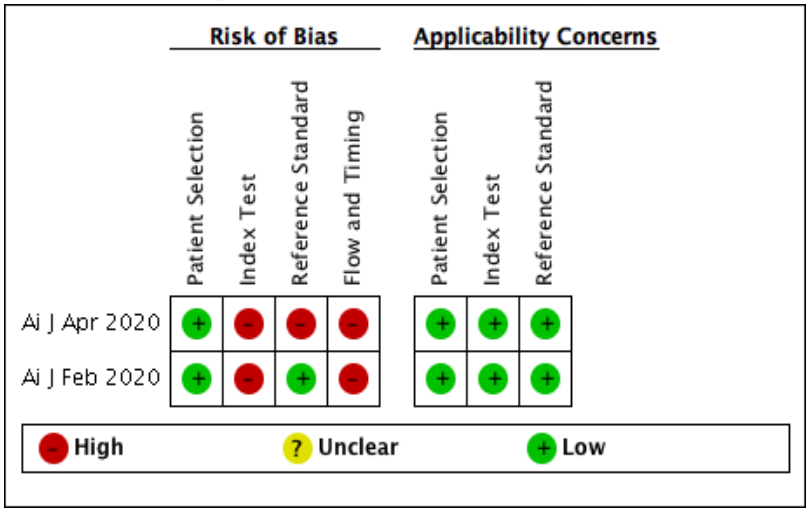
[a] There was no independent interpretation of the reference test from the index test.

[b] The sample size was small.

Appendix 3. Forest plot showing sensitivity and specificity of single and repeat RT-PCR testing



Appendix 4. Risk of bias and applicability concerns summary



Q9. Among COVID-19 confirmed patients, should certain RT-PCR cycle threshold values be used to determine infectivity?

As of 15 December 2021

RECOMMENDATION

There is insufficient evidence to recommend an RT-PCR cycle threshold cut-off value to determine infectivity among COVID-19 confirmed patients. Interpretation of RT-PCR cycle threshold values may vary and is dependent on the PCR assay used, gene target, sample type, and timing of sample collection. *(Very low certainty of evidence)*

Consensus Issues

RT-PCR cycle threshold values may have utility specifically for patients with previously documented COVID-19 infection. However, evidence remains insufficient on the cut-off cycle threshold value that differentiates infectious virus from viral remnants.

KEY FINDINGS

- Twelve observational studies were included in this review on the use of cycle threshold (Ct) as a surrogate marker of infectivity as evidenced by viral isolation in culture. One systematic review and meta-analysis was included on the association of Ct value with patient clinical outcomes.
- Very low certainty evidence showed that among COVID-19 cases, Ct values of 24 to 35.6 were associated with isolation of SARS-CoV-2 virus in culture. Lower Ct values (Ct <25-30) were associated with increased disease severity and mortality.
- Among convalescent and clinically recovered patients with persistent positive RT-PCR tests, Ct values ranged from 30 to 41.7. Samples from these cases had a low yield of virus isolation in culture and had degraded viral fragments on genome sequencing.
- Interpretation of Ct values must be done with caution due to variations in PCR assay methods, target gene, sample type, and timing of sample collection.

INTRODUCTION

Cycle threshold (Ct) value is defined as the number of cycles of amplification required for the fluorescence of a PCR product to exceed the background signal and be detected to cross a threshold of positivity. Ct values are inversely related to viral load and can provide an indirect method of quantifying the copy number of viral RNA in a sample. Because of its correlation with viral load, some studies have suggested that lower Ct values may be associated with worse outcomes and may carry some prognostic value.[1] However, Ct values cannot be directly compared across assays and must be interpreted with caution as these are influenced by sample type, the timing of sample collection, assay design, and pre-analytic issues. It is currently unclear whether certain Ct values could be used as a marker of infectivity and as a guide to patient management decisions.[2-4]

REVIEW METHODS

A comprehensive literature search in MEDLINE, Cochrane Library, and Scopus was done last September 23, 2021 using search terms related to SARS-CoV-2, COVID, cycle threshold, viral load, and viral culture. Studies were included if these (a) involved

patients with suspected or confirmed COVID-19 tested using RT-PCR, (b) used upper or lower respiratory tract samples (e.g., oropharyngeal, nasopharyngeal, sputum, endotracheal aspirate) for RT-PCR, and (c) confirmed infectivity of these samples through viral isolation in culture. Study designs were limited to observational, cross-sectional studies, or systematic reviews of observational studies. The detailed search strategy is found in Appendix 2.

The methodological quality of the included observational studies was appraised using the Newcastle Ottawa Scale for cross-sectional studies.[5,6] When possible, subgroup analysis was performed to explore the influence of covariates (e.g., severity, symptom status, target gene) on the Ct values. The methodological quality of the systematic review and meta-analysis was appraised using the Painless Evidence Based Medicine critical appraisal of systematic reviews and meta-analyses.[7]

RESULTS

Summary of characteristics of included studies

The aforementioned search strategy yielded a total of 829 studies, which included four systematic reviews.[1,7-9] After screening for eligibility, removal of duplicates, and cross-referencing, 12 studies [10-21] and one systematic review and meta-analysis [22] were included in this review. Nine cross-sectional, one longitudinal, one cohort study, and one brief report were done in various locations in Europe (United Kingdom, France, Austria, Italy, Spain), North America (Canada, United States of America), Australia, and Asia (Taiwan, Singapore). The studies were all peer-reviewed except for two studies, among which one was a pre-proof and the other a brief report.[11,15]

The 12 observational studies had a total of 1,728 respiratory tract samples (oropharyngeal, nasal, and nasopharyngeal swabs, sputum, and bronchial aspirates) from COVID-19 confirmed subjects (active and recovered cases, symptomatic and asymptomatic cases, varying disease severities, healthcare workers, inpatients and outpatients, and nursing home residents and staff) that were analyzed. The duration of data collection ranged from one to five months where the earliest sampling was done in January 2020 and the latest sampling last August 2020. The timing of sample collection relative to symptom onset ranged from 0 to 51 days. Ct values from various target genes (E, N, M, nsp12, S, nsp 2, RdRp, ORF1ab) corresponding to samples with viral isolation in culture were identified. Specific PCR assays used varied across studies and were not identified in some studies.

With regard to the association between Ct values and other clinical outcomes (e.g., hospitalization, disease severity, and mortality), data were obtained from a systematic review [22] that included 7 studies (n=3,291).

The characteristics of the included studies are detailed in Appendix 3.

Summary of results of included studies

A. Ct value and clinical outcomes

Seven studies from the systematic review and meta-analysis by Shah et al. [22] revealed no difference in the mean Ct values for those who were hospitalized when compared to those who were not hospitalized (MD 0.062, 95% CI -1.933 to 2.056). There was a statistically significant increase in disease severity (OR 2.31 95% CI 1.7-

3.13) and increase in mortality (OR 2.95, 95% CI 2.19-3.96) of lower Ct values (<25 or 25-30) when compared with higher Ct values (>30).

B. Ct value and viral isolation in culture (infectivity)

Eleven out of 12 studies yielded isolation of the virus in culture. Ct value corresponding to viral isolation in culture ranged from 24 to 35.6. Singanayagam et al. [9] estimated that the odds ratio of recovering infectious virus decreased by 0.67 for each unit increase in Ct value (95% CI 0.57-0.77), while Bullard et al. [16] demonstrated an odds ratio for a positive viral culture of 0.64 (95% CI 0.49-0.84) for every 1 unit increase in Ct. However, these studies had varied populations studied, PCR assay used, target gene investigated, and culture methods and techniques employed.

Table 1. Cycle threshold cut off value associated with viral isolation in culture

Study	Specimen	Target gene	Cut off Ct value associated with viral isolation
Bullard 2020 [16]	NP, ETT	E	24
Brown 2020 [15]	Nasal, throat swab	RdRp, E, N, ORF1lab	26.2
Young 2020 [20]	NP	Not stated	30
Basile 2020 [18]	Mixed URT + LRT	E, RdRp, N, M, ORF1 lab	32
Gniazdowsky 2020 [17]	NP	S, Nsp2	32.1
La Scola 2020 [10]	NP, sputum	E	33
Folguiera 2021 [14]	NP, bronchial aspirates	E	35
Ladhani 2020 [13]	Nasal swab	ORF1lab	35
Singanayagam 2020 [9]	Mixed URT	RdRp	35
Huang 2020 [19]	NP, OP, sputum	E, N, nsp12	35.2
Piralla 2020 [12]	Nasal	E, N	35.6

ETT: endotracheal tube aspirate, LRT: lower respiratory tract, NP: nasopharyngeal, OP: oropharyngeal, URT: upper respiratory tract.

C. Subgroup Analysis

Symptomatic vs asymptomatic

One study revealed no statistically significant difference in the Ct value and live virus recovery of symptomatic and asymptomatic cases.[10] In this study by Singanayagam et al., the reported median Ct was 31.23 (IQR 28.21-32.97) in asymptomatic cases, 30.94 (IQR 27.08-34.57) in mild to moderate cases, and 32.55 (IQR 28.39-33.66) in severe.[10] Culture positivity rates were also comparable in symptomatic and asymptomatic cases, with an estimated OR of 0.66 (95% CI 0.34-1.310).[10]

Clinically recovered or convalescent cases

Two studies included patients who were clinically recovered or labeled as ‘convalescent’ with either persistently positive SARS-CoV-2 RT-PCR or had a positive result after a negative result. The timing of sample collection had a median of 23 days (range 5-51 days) from the day of RT-PCR positivity or a median of 37 days (range 19-58 days) from symptom onset [11] or during their time of discharge or continuation of the isolation period.[12] Laferl et al. [12] recorded a mean Ct value of 37.4, a median of 37.3, and a range of 30.8 to 41.7. No virus was isolated in all the samples collected. Piralla et al. [12] reported the viral load in clinically recovered patients at the time of discharge with a median Ct value of 36.8 (range 30-39.4). Furthermore, only 2.3% of these samples yielded viral isolation in culture and subsequent genome sequencing of these samples revealed non-functional viral genomes. Table 2 lists the studies on clinically recovered and convalescent cases.

Table 2. Characteristics of studies on clinically recovered and convalescent cases

Study	Population	PCR Assay	Timing of sample collection	Target Gene	Sample Type	Ct value	Culture Positivity	Genome Sequencing
Laferl et al. [12]	Conva-lescent HCW	Thermo Fisher Scientific USA	23 days (range 5-51 days) from day of RT PCR positivity or median of 37 days (range 19-58 days) from symptom onset	E	OPS, NPS	**Mean**: 37.4 **Median**: 37.3 **Range**: 30.8 -41.7	**0%**	Not done
Piralla et al. [13]	Clinically recovered COVID-19 patients	Seegene Allplex 2019 nCOV assay	During the time of discharge or during isolation	E, N	Nasal swab	**Median**: 36.8 **Range**: 30-39.4	**2.3%** **Median Ct value (culture positive):** 35.6 **Median Ct value (culture negative):** 36.9 P = 0.37	Samples from positive culture did not have the whole viral genome ~ non functional residual RNA

Target gene

Huang et al. [20] compared the Ct values of culture-positive and culture-negative from three target genes: N, E, and nsp12. For the 3 genes, Ct values from culture-positive samples were lower than from culture-negative samples. N as the target gene showed higher Ct values compared to nsp12 and E as target genes for the same sample.

Table 3. Ct values of culture-positive and culture-negative samples per target gene

Genes	Culture Positive		Culture Negative	
	Mean Ct value (SEM)	Range	Mean Ct value (SEM)	Range
Nsp 12	23.9 (0.78)	17.75-31.47	29.26(0.69)	22.32-36.52
E	22.39 (0.75)	16.85-31.46	28.92 (0.65)	20.89-38.33
N	27.29 (0.77)	22.14-35.2	27.29(0.77)	22.14-35.2

Type of sample

Basile et al. revealed a statistically significant difference in the Ct values of upper respiratory tract samples and lower respiratory tract samples of active inpatient and outpatient cases.[19] Higher Ct values were recorded from samples of the upper respiratory tract (mean Ct 26.76) as compared to the lower respiratory tract (mean Ct 34.41).

Whole Genome Sequencing

Two studies performed whole-genome sequencing in samples that yielded virus isolation in culture.[13,20] In the samples coming from 50 active cases [20], culturable specimens had a higher correlation between structural and non-structural genes. Non-culturable specimens were characterized by higher or lower nsp12 RNA levels, suggesting existing degraded intermediates. In samples of clinically-recovered cases who persistently tested positive for RT-PCR [13], genome sequencing revealed non-functional and residual RNA.

Ongoing Studies
No ongoing studies were found in the search strategy done.

CERTAINTY OF EVIDENCE

For the association of Ct values with viral isolation in culture, the overall certainty of evidence was rated very low due to the serious risk of bias and inconsistency. All studies were assessed to have unclear to high risk for selection bias due to either unclear sampling method or use of convenience sampling. Majority of the included studies lack statistical methods for justifying sample size and controlling confounders. The serious inconsistency noted was related to the heterogeneity in RT-PCR characteristics and Ct values reported.

For the association of Ct values with clinical outcomes, the overall certainty of the evidence was rated very low due to the moderate to high risk of bias and heterogeneity brought about by the difference in assay characteristics.

The table of risk of bias scoring is shown in Appendix 4.

OTHER CONSIDERATIONS

Table 4 lists other considerations on the utility of Ct values.

Table 4. Other considerations on the utility of Ct values.

Equity	Any patient subjected to RT-PCR testing can retrieve its Ct value with no additional cost.
Cost	RT-PCR (DOH Price Cap): ● Minimum P3,800.00 ● Maximum P4,500.00
Acceptability	Any patient subjected to RT PCR testing can retrieve its cycle threshold value with no additional processing and analysis required.
Feasibility	Any patient subjected to RT PCR testing can retrieve its cycle threshold value with no additional processing and analysis required. Ct value determination is part of the routine processing of RT-PCR but is not routinely reported in the official results. Cut-off values are machine-dependent.

RECOMMENDATIONS FROM OTHER GROUPS

The **United States Center for Disease Control** (CDC) released information on the utility of Ct values in their Frequently Asked Questions [3] last August 25, 2021. The response stated that Ct values from different RT-PCR tests cannot be compared due to differences in nucleic acid target, platform, etc. Ct values should not be used to determine an individual's viral load, level of infectiousness, or eligibility to be released from isolation or quarantine. From a public health perspective, however, CDC maintains that median Ct values from a population or group may be valuable for public health to evaluate viral load and transmissibility for a particular SARS-CoV-2 variant or to compare the viral load between two groups (e.g., vaccinated versus unvaccinated individuals).

Public Health England [2] released a guide for health protection teams that stated that Ct values are not directly comparable between assays and may not be reported by some RT-PCR platforms in use. Interpreting single positive Ct values for staging infectious course, prognosis, infectivity, or as an indicator of recovery must be done with context about the clinical history.

On the other hand, **Public Health Ontario** [23] stated that SARS-CoV-2 Ct values may be of use when interpreting positive laboratory results derived from patients with low pretest probability, in particular, asymptomatic persons with no epidemiologic link to a confirmed COVID-19 case.

RESEARCH GAPS

Additional studies are required to investigate the utility of Ct values and cell culture results in making clinical decisions and developing diagnostic strategies that can differentiate shedding versus active replication and will be very valuable for infection control.[12] Larger studies are needed to establish Ct criteria that reliably correlate with loss of infectivity and that utilize additional gene targets.

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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)					Surrogate marker for infectiousness is important in patient management decisions since the gold standard, viral culture, is costly and would need more resources and time.
Benefits	Large (1)	Moderate (3)	Small (3)	Uncertain			Cycle threshold may have the potential to be a surrogate marker of infectiousness. However, no effect estimates can be generated from the evidences reviewed on the benefit of cycle threshold determination.
Harms	Large (1)	Moderate	Small (3)	Uncertain (3)			No evidence on the harm of cycle threshold determination.
Balance of Benefits and Harms	Favors the use of RT-PCR Ct values (1)	Probably favors the use of RT-PCR Ct values (3)	Does not favor the use of RT-PCR Ct values (3)				No evidence on the effect estimates generated on the benefit or harm of cycle threshold determination.
Certainty of Evidence	High (1)	Moderate	Low (1)	Very low (5)			The overall certainty of evidence was very low due to fair risk of overall bias attributed to selection bias and lack of statistical methods for sample size justification and control of confounders in some studies.
Accuracy	Very Accurate	Accurate (1)	Inaccurate (1)	Very Inaccurate	Uncertain (5)		No evidence on the diagnostic accuracy.
Values	Important uncertainty or variability	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability (1)			No evidence found.
Resources Required	Uncertain (1)	Large cost	Moderate Cost	Negligible cost (5)	Moderate savings	Large savings (1)	There is no added cost when cycle threshold is requested in addition to RT-PCR. RT-PCR minimum cost is P3,800.00, maximum cost or price cap at P4,500.00 (DOH).
Certainty of evidence of required resources	No included studies (3)	Very low (1)	Low (2)	Moderate (1)	High		Cost of RT-PCR may vary depending on the hospital or laboratory.
Cost effectiveness	No included studies (4)	Favors comparator	Does not favor either RT-PCR Ct values or the comparator (2)	Favors the use of RT-PCR Ct values (1)			No cost effectiveness study is available
Equity	Uncertain (3)	Reduced (2)	Probably no impact (1)	Increased (1)			RT-PCR is the standard test to confirm COVID-19 disease which has been made available to the public with reduced cost and can be subsidized by PhilHealth.
Acceptability	Uncertain (2)	No	Yes (5)				RT-PCR is the standard test to confirm COVID-19 disease which can provide Ct values. No additional procedure to be done to determine Ct on the part of the patient, doctor, and laboratory personnel apart from the usual OPS/NPS and laboratory processing of RT-PCR.
Feasibility	Uncertain	No	Yes (7)				Ct value determination is part of the RT-PCR process.

Appendix 2. Search Yield and Results

Data Base	Search Strategy	Yield
Medline	(Corona virus disease OR COVID-19 OR SARS CoV 2) AND (cycle threshold OR cycle threshold value OR Ct value) AND (Viral load) Filters: Free full text, Meta-analysis, Review, Systematic Review	328
Cochrane	(COVID 19 OR SARS CoV 2) AND (cycle threshold OR Viral load OR viral culture)	467
Scopus	(COVID 19 OR SARS CoV 2) AND (cycle threshold OR Viral load OR viral culture)	34

Appendix 3. Characteristics of Included Studies

Table 1. Included studies on the association of Ct values with viral isolation in culture

Study [Reference Number]	Country	Design	Peer reviewed	Number of samples (patients)	Population	Sample type	RT-PCR Target	Timing of RT-PCR testing	Outcome
Singanayagam 2020 [10]	United Kingdom	Cross-sectional, retrospective, single center (NRL)	Yes	324 (253)	Samples from COVID-19 patients from range of clinical scenarios (community, HCW surveillance, outbreak, asymptomatic close contacts) 92% - asymptomatic/mild-to-moderate cases	Mixed URT (some self sampled)	RdRp gene	Not reported	Median Ct values for asymptomatic, mild-to-moderate, severe cases Odds ratio (of recovering infectious virus for each unit increase in Ct value)
La Scola 2020 [11]	France	Cross Sectional, retrospective, single center	(Only Brief Report/ Preliminary Clinical Study)	183 (155)	Samples of COVID-19 patients received at the sole diagnostic center in Marseille	NPS 95% Sputum 5%	E gene	Not reported	RT-PCR Ct value and viral isolation in culture
Laferl 2020 [12]	Austria	Longitudinal, prospective, single center	Yes	58 (15) 24/58 RT-PCR positive	Convalescent healthy HCW with COVID-19 in isolation (13/15, symptomatic), Ct $\leq$ 42	OPS 50% NPS 50%	E gene	median 23 days (range 5-51 days RT-PCR positivity); median 37 days (range 19 – 58 days) from symptom onset	RT-PCR Ct value and viral isolation in culture IgM, IgG
Piralla 2020 [13]	Italy	Cross-sectional, multi-center, prospective	Yes	387 (number of patients not specified)	COVID-19 patients, clinically recovered with low viral load Ct > 30 (persistently positive) 'convalescent patients' HCW, hospitalized, part of epidemic response	nasal	E and N genes	Time of discharge or quarantine period	% positivity RT-PCR Ct value (positive vs negative culture) Genone Sequencing
Ladhani 2020 [14]	London	Single Population Cohort, prospective, multicenter	Yes	158 cases (105 residents, 53 staff)	COVID-19 lab confirmed residents and healthcare workers of nursing homes (Ct < 35)	Nasal swabs	ORF1ab gene	Not stated (status taken at Day 0, Day 14)	%positivity RT-PCR CT values Whole genone sequencing
Folgueira 2020 [15]	Spain	Cross-sectional, retrospective, single center	No	106 (105)	COVID-19 lab confirmed outpatient (Mild, HCWs) and hospitalized (severe) patients	102 nasopharyngeal exudates and 4 bronchial aspirates (ICU cases)	E gene	Mild cases median 3 days Severe median 6 days	% positivity RT-PCR CT value (mild vs severe forms)

Brown 2020 [16]	England	Cross Sectional, prospective, Multicenter	Yes	23 HCW	Healthcare workers	Nasal and throat swab	ORF1ab; RdRp, E, and N	Various presentation (asymptomatic, presymptomatic, symptomatic) 17 previous symptomatic median day of symptom 27 days (range 3-43 days)	% positivity RT-PCR CT values
Bullard 2020 [17]	Canada	Cross-sectional, retrospective	Yes	90 samples	Samples of COVID suspects	NP and ETT	E gene	Not stated	RT-PCR Ct value and viral isolation in culture STT
Gniazdowski 2020 [18]	USA	Cross-sectional, single center, retrospective	Yes	131 samples	COVID-19 patients hospitalized in JHH	NPS	S gene, Nsp2 gene	Not stated	Ct value and viral isolation in culture Prolonged positive Positive after negative WGS ddPCR
Basile 2020 [19]	Australia	Cross-sectional, retrospective	Yes	56 samples	COVID-19 patients with varying severity (91%-outpatient, 6.1%-inpatients, 2.6%-critical) 1. Routine lab as part of outbreak 2. ICU cases Persistent positive	Mixed URT and LRT	E, RdRp,N,M, ORF1ab (Ct at N gene)	0-29 days	Ct values at N gene and virus isolation in culture
Huang 2020 [20]	Taiwan	Cross-sectional, retrospective	Yes	60 (50)	COVID-19 lab confirmed cases in virology lab	OP, NP, sputum	nsp12, E, and N genes	Not stated	%positivity RT-PCR Ct value (positive vs negative culture) Genome copy numbers
Young 2020 [21]	Singapore	Single Population Cohort, prospective, multi center	Yes	152 (74)	COVID-19 lab confirmed	Nasopharyngeal	Not stated	Various severities	%positivity RT-PCR CT values Disease severity Seroconversion

Table 2. Included studies on the association of Ct values with clinical outcomes

Study [Reference Number]	Country	Design	Peer Review	Number of Subjects	Population	Sample Type	Outcome
Shah et al [22]	Minnesota, USA	Systematic Review and Meta-analysis	Yes	13885 (18 studies) 3291 (7 studies for meta-analysis)	COVID-19 confirmed cases	NP or NP/OPS	Hospitalization Disease severity Mortality

Appendix 4. Study Appraisal

Table 1. Newcastle-Ottawa Scale for appraisal of cross-sectional studies

	Singanayagam [10]	La Scola [11]	Laferl [12]	Piralla [13]	Ladhani [14]	Folgueira [15]	Brown [16]	Bullard [17]	Gniazdowsky [18]	Basile [19]	Huang [20]	Young [21]
SELECTION												
Representativeness of the sample	0 Sampling design not stated	0 Sampling design not stated	0 Unclear, subjects by invitation	0 Sampling design not stated	0 Sampling design not stated	0 Sampling design not stated	0 Convenience sampling	0 Sampling design not stated	0 Sampling design not stated (hospitalized with comorbidities)	0 Sampling design not stated	0 Sampling design not stated	0 Sampling design not stated
Sample Size	0 Not stated	0 Not stated	0 Not stated	0 Not stated	0 Not stated	0 Not stated	1	0 Not stated	0 Not stated	0 Not stated	0 Not stated	0 Not stated
Non Respondents	0 Not stated	0 Not stated	0 Not stated	0 Not stated	0 Not stated	0 Not stated	0 Not stated	0 Not stated	0 Not stated	0 Not stated	0 Not stated	0 Not stated
Ascertainment of exposure	1	1	1	1	1	1	1	1	1	1	1	1
COMPARABILITY												
Comparable subjects in different outcome groups, based on study design or analysis, confounders controlled	1 Subgroup analysis done	0 Not stated	0 Not stated	1 Subgroup analysis done	1	0 Not stated	1 MVA done	1	0 Not stated	0 Not stated	1 Subgroup analysis done	0 Not stated
OUTCOME												
Assessment of outcome	1	1	1	1	1	1	1	1	1	1	1	1
Statistical test	1	1	Not stated	1	1	1	1	1	1	1	1	1
TOTAL	4	3	2	4	4	3	5	4	3	3	4	3

Table 2. Critical Appraisal of systematic review and meta-analysis (Shah et al.)

Criteria	Appraisal
1. Appraising directness	Direct P – COVID -19 cases E – Ct values O – Infectivity for guidance of patient management decisions*
2. Appraising validity (inclusion criteria, search strategy, validity assessed, reproducible)	Valid Inclusion criteria stated Comprehensive literature search done January 28, 2021 Moderate to high risk of bias 2 reviewers
3. Appraising the results (overall results, precision, heterogeneity)	Odds Ratio and MD reported Imprecision noted (wide CI), Significant heterogeneity (I2 > 50%)
4. Applicability	For CPG development
5. Individualizing results	For CPG development

** In this systematic review, Ct value was used as a surrogate marker of viral load for prognostication which may guide patient management decisions*

Q10. Should antibody tests be used for COVID-19 seroprevalence studies and monitoring vaccine response among adults?

As of 22 November 2021

RECOMMENDATIONS

We suggest using antibody tests that accurately measure IgG or total antibodies to determine COVID-19 seroprevalence among adults when needed for public health purposes. *(Very low certainty of evidence; Weak recommendation)*

We suggest against using antibody tests detecting IgM to determine COVID-19 seroprevalence among adults when needed for public health purposes. *(Very low certainty of evidence; Weak recommendation)*

We suggest against using lateral flow immunoassay (LFIA) tests to determine COVID-19 seroprevalence among adults when needed for public health purposes. *(Very low certainty of evidence; Weak recommendation)*

We recommend against routine measurement of SARS-CoV-2 antibody titers after vaccination. *(No evidence; Strong recommendation)*

Consensus Issues

Recommendations on antibody testing were made in the context of public health purposes (i.e., to identify the percentage of people in a population who may have been previously infected). The panel was unanimous against the use of antibody tests detecting IgM and LFIA tests while the majority voted for the use of antibody tests detecting IgG or total antibodies with a weak recommendation. Concern was raised about the cross-reactivity of the tests with other coronaviruses. Thus, emphasis was made on ensuring the accuracy of the antibody test kits used.

The panel was initially divided about antibody testing post-vaccination. Six of eleven panelists voted that there is insufficient evidence to recommend for or against it, citing that the public should be given the choice given the lack of evidence. On the other hand, five panelists voted against routine antibody testing post-vaccination despite the lack of evidence due to: (1) the unavailability of a real neutralizing antibody test in the market and (2) the unclear cutoff of antibody level that is predictive of COVID-19 protection. The panelists eventually reached a consensus in the second round of voting, with the majority choosing a strong recommendation because antibody tests post-vaccination lack clinical utility at this point.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of zinc as adjunct treatment for patients
We suggest using antibody tests with high sensitivity and specificity (e.g., total antibody or IgG assays, ELISA, ECLIA) to determine COVID-19 seroprevalence among adults. *(Very low quality of evidence; Conditional recommendation)*

We recommend against using antibody tests detecting IgM to determine COVID-19 seroprevalence among adults. *(Very low quality of evidence; Strong recommendation)*

We recommend against using rapid antibody tests (e.g., LFIA) to determine COVID-19 seroprevalence among adults. *(Very low quality of evidence; Strong recommendation)*

Previous Consensus Issues
The different recommendations were made considering the different laboratory techniques and antibodies detected when using antibody testing to detect COVID-19.

Majority voted for a strong recommendation against the use of antibody tests detecting IgM to determine COVID-19 seroprevalence among adults despite the very low quality of evidence because IgM may only suggest relatively recent infection. Others voted for a conditional found for antibody tests detecting IgM. One panelist opined that there may still be settings in which IgM antibody tests can be useful because of its good correlation with IgG tests based on local experience in a hospital setting. Meanwhile, the use of rapid antibody tests was not recommended due to the very low quality of evidence resulting from the significant heterogeneity detected across studies.

WHAT'S NEW IN THIS VERSION?

- Six new seroprevalence studies, including one preprint article, were added in this review to determine the diagnostic accuracy of COVID-19 antibody tests.
- An additional search for the accuracy of antibody tests in detecting breakthrough infection among vaccinated individuals was conducted but did not yield any relevant articles.

KEY FINDINGS

- This review included 19 observational studies (n=28,566 samples) that evaluated the diagnostic accuracy of antibody tests compared with reverse transcription-polymerase chain reaction (RT-PCR) in seroprevalence studies.
- The studies were of moderate to high methodologic quality. The overall certainty of the evidence was rated very low due to the serious risk of bias (recall bias) and inconsistency.
- Heterogeneity across studies was substantial (I^2>90%). The sensitivity of antibody tests ranged from 14.4 to 100% while specificity ranged from 54.9 to 99.6%.
- No studies evaluating the accuracy of antibody tests in determining vaccine response compared to RT-PCR-diagnosed breakthrough infections were found.

INTRODUCTION

In SARS-CoV-2, the structural nucleocapsid and spike proteins were found to be dominant antigens for host immune response, and have become the basis for detecting antibodies to immunoglobulins (Ig) that bind to these proteins.[1] Generally, antibodies are classified as neutralizing antibodies (i.e. cause virus particles to lose infectivity) and binding antibodies.[2] The latter are detected by lateral flow point-of-care fingerstick tests.[3] The binding antibodies IgM and IgA appear within five days from symptom onset while IgG rises shortly afterwards.[1]

While SARS-CoV-2 serology can be useful in clinical, occupational health, and public health settings, it is not a replacement for virologic testing.[3] Validating antibody tests is important because certain assays may cross-react with other coronaviruses among other concerns. To be clinically useful, antibody tests should have high sensitivity and specificity. Specificity is particularly important in large serosurveillance studies in areas with a low expected prevalence of prior SARS-CoV-2 infection.[2]

As of October 26, 2021, the Philippine Food and Drug Administration (FDA) has approved six rapid antibody tests after performance validation by the Research Institute for Tropical Medicine (RITM).[4]

This review sought to answer the following clinical questions:

(1) Among adults in seroprevalence studies, how accurate are antibody tests in detecting COVID-19 compared to nucleic acid amplification tests (NAAT) such as RT-PCR?
(2) Among adults vaccinated against COVID-19, how accurate are antibody tests in determining vaccine response compared to RT-PCR-diagnosed breakthrough infection?

REVIEW METHODS

To identify new studies for this review update, electronic searches were performed on several databases (MEDLINE through PubMed, Cochrane CENTRAL, medRxiv, bioRxiv, ClinicalTrials.gov) from March 25, 2021 to October 15, 2021 using the following terms: seroprevalence, serosurveillance, antibody test, serology, accuracy, sensitivity, specificity, predictive value, COVID-19, and SARS-CoV-2. No language restrictions were applied. To address the question on vaccine response, an additional search was conducted on October 22, 2021 using free-text terms (vaccinated, infection, breakthrough), an age filter (19+ years), and the PubMed diagnosis filter for COVID-19.

Studies that used SARS-CoV-2 antibody tests to determine COVID-19 seroprevalence among adults were included. A positive NAAT such as RT-PCR was used as an acceptable reference standard following several previous reviews.[5-7]

Studies on non-human populations and pediatric age groups, assay validation studies, the use of pre-pandemic samples (i.e. for specificity), and specimens other than serum, plasma, or whole blood (e.g. saliva) were excluded. Articles with published data insufficient to construct a 2x2 table for diagnostic accuracy and those that reported less than 100 samples (similar to an earlier rapid review [5]) were also excluded.

The methodological quality of the included studies was assessed using QUADAS-2. The 'meta' package in R (R Foundation for Statistical Computing 2019) was used to determine sensitivity, specificity, and measures of heterogeneity, as well as to generate forest plots. Random effects models were used in conducting univariate meta-analyses. Planned subgroup analyses according to the type of population tested, serology technique used, and antibody detected were performed. To further investigate heterogeneity, exploratory analyses were conducted according to publication status and whether the RT-PCR result was self-reported.

RESULTS

Seroprevalence Studies

A. Included Studies

Nineteen studies meeting the inclusion criteria were included in this review. Seven articles were available as preprints.[8-14] There were a total of 23 comparisons of

antibody tests with RT-PCR (n=28,566 samples). Seropositivity was as low as 0.80% [15] to as high as 44.58%.[16]
The most common technique used was enzyme-linked immunosorbent assay (ELISA; 6 studies) [8,10,14,17-19] followed by Chemiluminescent immunoassay (CLIA; 3 studies) [12,15,20,21] and electrochemiluminescence immunoassay (ECLIA; 3 studies).[20-22] Other serology tests used were chemiluminescent microparticle immunoassay (CMIA), enzyme-linked fluorescence assay (ELFA), and microneutralization assay.

IgG was the most frequent anti-SARS-Cov-2 antibody detected (10 studies) [8,11,12,15,16,19-21,23,24]. Total antibody detection was used by five studies [9,10,17,20,22]. Only one study each used IgM alone [11] or neutralizing antibody.[25] Two studies used IgM and IgG in combination [13,18], while another study used either IgA or IgG to indicate a positive test.[14] One study used a variety of antibody tests and could not be classified in the prior categories.[26]

B. Methodological Quality
Eight studies were at risk of recall bias because of self-reporting and were therefore deemed as moderate quality.[8-10,14,16,19,24,26] Another study was considered moderate quality because participants without PCR testing were lumped together with those who had negative RT-PCR results.[20] The rest of the studies had a low risk of bias and were deemed to have high methodological quality.

C. Diagnostic Accuracy
The measures of diagnostic test accuracy varied across included studies (n=28,566). The sensitivity of antibody tests ranged from 14.4% (95% CI 9.4-20.6%) to 100% (95% CI 83.2-100%). Meanwhile, specificity of the index test ranged from 54.9% (95% CI 49.5-60.3%) to 99.6% (95% CI 97.8-100%).

Heterogeneity was considerable (I^2=96.3% for sensitivity and I^2=99.1% for specificity) and was not reduced in almost all subgroup analyses. The type of antibody detected may account for some heterogeneity, yet this remained moderate to substantial.

Sensitivity was highest in a small study that used a variety of antibody tests, including for IgM and IgG as well as IgG alone (Sn 91.2%, 95% CI 76.0-97.1%; n=152).[26] This was followed by total antibody (Sn 41.0-98.2%; I^2=97.7%) and IgG tests (Sn 15.6-100%; I^2=96.4%). Meanwhile, specificity was highest in one study that used either IgA or IgG (Sp 97.7%, 95% CI 95.5-98%; n=356).[14]

Among the individual serology techniques used, the point estimates for sensitivity were highest in ELISA (Sn 42.9-98.2%; I^2=91%) and CMIA (Sn 79.5-88.8%; I^2=84%). On the other hand, LFIA had the highest specificity among the subgroups (Sp 92.0-98.6%; I^2=78%).

In seroprevalence studies among general adult populations, the sensitivity of antibody tests ranged from 15.0 to 100%, while specificity ranged from 54.9 to 97.7%. Among healthcare and other frontline workers (i.e. police and fire personnel), sensitivity varied from 39.8 to 98.2% and specificity from 59.4 to 97.8%. Antibody tests among patient populations had sensitivity ranging from 14.4 to 91.2% and specificity from 92.9 to 99.6%.

D. Ongoing Studies

We found no ongoing studies evaluating the accuracy of antibody tests against NAATs in seroprevalence studies.

Vaccine Response

No available studies evaluated the diagnostic accuracy of antibody tests compared with RT-PCR in determining vaccine response among adults who received COVID-19 vaccination.

EVIDENCE TO DECISION

Rapid antibody tests for COVID-19 may cost around Php 400 to 700.[27] Neutralization tests however may be as much as Php 2,300.[28] There is no available evidence on the cost-effectiveness and acceptability of antibody tests in the Philippine setting.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1 summarizes the recommendations from various regulatory agencies.

RESEARCH GAPS

The seroprevalence studies have considerable variability in the estimates of diagnostic accuracy probably due to methodological differences. Many of these studies rely on self-reporting of RT-PCR results.

Direct evidence on whether the detection of antibodies after COVID-19 vaccination is protective against breakthrough infection is still wanting.

Table 1. Summary of Recommendations from Other Groups

Guideline / Agency	Recommendation	Strength of Recommen-dation	Certainty of Evidence
Philippine Food and Drug Administration	"There are **no currently available** FDA approved COVID-19 test kits in the Philippines that differentiate the antibody protection gained from natural COVID-19 infection and the immunity from vaccination."	-	-
Health Technology Assessment Council (Philippines) 01 August 2020	HTAC does **not recommend** the use of rapid antibody tests "in seroprevalence surveys, return-to-work decisions, or entry-to-country/ province policies due to the lack of evidence regarding the link of the presence of antibodies and the immunity to subsequent infection AND on the persistence of protection from COVID-19."	-	-
U.S. Centers for Disease Control and Prevention 21 September 2021	"Antibody tests **can be used** in seroprevalence studies to estimate the cumulative incidence of infection (or vaccination) in a community."	-	-
Infectious Disease Society of America 18 August 2020	"The IDSA panel makes **no recommendation** either for or against using IgM antibodies to detect evidence of past SARS-CoV-2 infection"	Conditional	Very Low
	"The IDSA panel suggests **against using IgA** antibodies to detect evidence of past SARS-CoV-2 infection"	Conditional	Very Low
	"The IDSA panel suggests **against using IgM or IgG** antibody combination tests to detect evidence of past SARS-CoV-2 infection"	Conditional	Very Low
	Benefits and Harms: "IgA tests or LF devices with both IgM and IgG targets… all suffer from lower specificity compared to tests involving IgG or total antibody targets, leading to increased false-positive rates. These tests would falsely increase	-	-

	seroprevalence and potentially mislead public health officials, policymakers, and the general public.”		

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Appendix 1. Evidence to Decision

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (3)	Yes (7)					
Certainty of Evidence	High	Moderate	Low (2)	Very low (8)			The overall certainty of evidence is very low after downgrading for serious risk of bias (recall bias) and very serious inconsistency (I^2 > 90%).
Accuracy	Very Accurate	Accurate	Inaccurate (6)	Very Inaccurate (1)	Uncertain (3)		In seroprevalence studies among adults, point estimates of the sensitivity of antibody tests ranged from 14.4 to 100%. Their specificity ranged from 54.9 to 99.6%. There was substantial heterogeneity across studies.
Values	Important uncertainty or variability (4)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain (1)	Large cost (3)	Moderate Cost (6)	Negligible cost	Moderate savings	Large savings	Rapid antibody tests for COVID-19 may cost around Php 400 to 700. Neutralization tests however may be as much as Php 2,300.
Certainty of evidence of required resources	No included studies (7)	Very low (1)	Low (2)	Moderate	High		
Cost effectiveness	No included studies (6)	Favors the comparison (1)	Does not favor either antibody testing or the comparator (3)	Favors antibody testing			No local cost-effectiveness studies found.
Equity	Uncertain (5)	Reduced	Probably no impact (5)	Increased			
Acceptability	Uncertain (6)	No (3)	Yes (1)				
Feasibility	Uncertain (4)	No (3)	Yes (3)				

Appendix 2. Search Yield and Results

Database	Search Terms	Date and Time	Yield
PubMed	((sensitivity) OR (specificity) OR (accuracy) OR (predictive value)) AND ((((antibody test) OR (serology)) AND ((seroprevalence) OR (serosurveillance))) AND ((((("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [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]))) Filter: From 03/25/2021 Species: Humans	15 October 2021 21:34	103
PubMed	(((antibody test) OR (serology)) AND (vaccinated)) AND (infection OR breakthrough) AND (LitCDIAGNOSIS[filter]) Filter: Adult: 19+ years	22 October 2021 10:17	219
The Cochrane Library	((COVID-19) OR (SARS-CoV-2)) AND ((serology) OR (antibody test)) Filter: From 03/25/2021 Filter: From 2021 (trials)	15 October 2021 20:46	5 reviews 6 protocols 94 trials 2 special collections
MedRxiv & BioRxiv	(COVID-19 OR SARS-CoV-2) AND (serology) AND (seroprevalence OR serosurveillance) Filter: From 03/25/2021	15 October 2021 20:50	390
ClinicalTrials.gov	seroprevalence AND (antibody test) | COVID-19	26 October 23:13	72

Appendix 3. Characteristics of Included Studies

Study ID, Study Design, and Country	Sample Size	Population	Index Test	Reference Standard	Outcome
Caillard 2021* Cross-sectional France	152	Kidney transplant recipients with functioning grafts from a single center **Age**: Not specified **Symptoms**: 81% of seropositive patients	**Various antibody tests**: Various tests including (1) Architect Abbott Elecsys: SARS-CoV-2 IgG (Abbott Laboratories, Abbott Park, USA); (2) Euroimmun (HUS); (3) Euroimmun (Lübeck, Germany); (4) Elecsys anti SARS Cov2 Roche Cobas (Roche Diagnostic GmbH, Mannheim, Germany); (5) Orient Gene Biotech COVID-19 IgG/IgM Rapid Test Cassette (Orient Gene Biotech, Zhejiang, China); (6) Biosynex COVID-19 BSS (Biosynex, Fribourg, Switzerland); (7) VIDAS Anti-SARS CoV-2 IgG and IgM (BioMérieux, Marcy-l'Etoile, France); (8) CLIA Maglumi ; MAGLUMI 2019 nCov IgM and IgG (SNIBE - Shenzhen New Industries Biomedical Engineering, Shenzhen, China); (9) Platelia SARS-CoV-2 Total Ab method (Bio-Rad, HERCULES,USA) **Antibody detected**: Varied **Target antigen**: Varied **Timing**: Not specified	Self-reported RT-PCR using a nasopharyngeal swab	Diagnostic accuracy
Carrat 2021* Prospective cohort France	242	General adult population from three regions **Age**: 56% were < 60 years **Symptoms**: 47% of seropositive patients with median 56 days (IQR 40-61) from specimen collection	**ELISA**: EuroimmunVR (Lübeck, Germany) **Antibody detected**: IgG (optical density ratio ≥ 1.1) **Target antigen**: Spike protein **Timing**: Not specified	Self-reported RT-PCR result	Diagnostic accuracy
Khan 2021* Cross-sectional India	1,088	General adult population **Age**: 42.9% were 30-49 years **Symptoms**: 7.6% with COVID-19-like symptoms within 3 months prior	**CMIA**: Abbott SARS-COV-2 IgG assay **Antibody detected**: IgG (cut-off index ≥ 1.4) **Target antigen**: Nucleocapsid **Timing**: Not specified	Self-reported RT-PCR result	Diagnostic accuracy
Lorent 2021* Cross-sectional Poland *Preprint*	356	Adult volunteers in the Poznan metropolitan area **Age**: Mean 38.7 years +/- 12.7 **Symptoms**: Asymptomatic	**ELISA**: EuroImmun anti-SARS-CoV-2 assay **Antibody detected**: IgA or IgG **Target antigen**: Spike **Timing**: Not specified	Self-reported previous RT-PCR result	Diagnostic accuracy

Study ID, Study Design, and Country	Sample Size	Population	Index Test	Reference Standard	Outcome
Nasrallah 2021* Cross-sectional Qatar	393	Volunteers **Age**: Not specified **Symptoms**: Not specified	(1) **ELFA**: BioMérieux VidasIII assay **Antibody detected**: IgG (>= 1.0) **Target antigen**: Spike (2) **CLIA**: Mindray CL-900i anti-ARS-CoV-2 IgG **Antibody detected**: IgG (>= 10.0) **Target antigen**: Nucleocapsid and sike (3) **ECLIA:** Roche Elecsys Anti-SARS-CoV-2 (index >= 1.0) **Antibody detected**: IgG **Target antigen**: Nucleocapsid **Timing**: At time of enrollment	RT-PCR using nasopharyngeal and oropharyngeal swabs	Diagnostic accuracy
Papasavas 2021* Prospective cohort USA	1,317	Healthcare workers and allied professionals **Age**: Median 43 years (range 18-81) **Symptoms**: 75.2% among seropositive	**CMIA**: Abbott Archiect i2000 (Abbott Park, IL) **Antibody detected: IgG (index ≥ 1.4)** **Target antigen**: Nucleocapsid **Timing**: Not specified	Self-reported previous RT-PCR result	Diagnostic accuracy
Afzal 2020 Cross-sectional Pakistan	426	Patients in outpatient and emergency departments **Age**: Mean 42.43 years +/- 16.67 **Symptoms**: 43.6% among included participants	**ECLIA***:* Roche Cobas e601 immunoassay analyzer **Antibody detected**: Total antibody (reactive if cut-off > 1.000) **Target antigen**: Nucleocapsid **Timing**: 15-21 days after RT PCR result	RT-PCR result within 15-21 days presented by patient	Diagnostic accuracy
Flannery 2020 Cross-sectional USA	1,109	Pregnant women presenting for delivery **Age**: Median 31 (IQR 27-35) **Symptoms**: Not specified	In-house **ELISA** modified from protocol by Amanat et al. 2020 **Antibody detected**: IgM or IgG (seropositive if either IgG or IgM > 0.48 arbitrary units) **Target antigen**: Spike **Timing**: 67% taken within 6 days after RT PCR result	RT-PCR using nasopharyngeal specimen (device not specified)	Diagnostic accuracy
Fong 2020 Cross-sectional Italy	250	Cancer patients consecutively enrolled **Age**: Median 69 years (oncology) and 71 years (hematology) **Symptoms**: Not specified	**CLIA**: Abbott Architect SARS-CoV-2 IgG assay **Antibody detected**: IgG **Target antigen**: Nucleocapsid **Timing**: Not specified	RT-PCR using nasopharyngeal swabs (device not specified)	Diagnostic accuracy

Study ID, Study Design, and Country	Sample Size	Population	Index Test	Reference Standard	Outcome
Gonzalez 2020 Cross-sectional Colombia *Preprint*	237	University staff **Age**: Mean 36.14 years +/- 9.66 **Symptoms**: 10/32 seropositive individuals were symptomatic	**CLIA**: Abbott IgG Architect SARS-CoV-2 Assay (Abbott, Abbott Park IL, USA) **Antibody detected**: IgG (seropositive if > 1.40) **Target antigen**: Nucleocapsid **Timing**: 91 days after RT PCR (average)	RT-PCR using nasopharyngeal swabs: U-TOP COVID-19 detection Kit (SeaSun Biomaterial Inc., Daejeon, South Korea); Ct threshold not specified	Diagnostic accuracy
Ige 2020 Cross-sectional Nigeria *Preprint*	521	Patients in community isolation centers **Age**: Mean age 35.2 years +/- 15 **Symptoms**: Not specified	**LFIA**: Innovita® (Biological 116 Technology CO., LTD, China) **Antibody detected**: IgM & IgG **Target antigen**: Spike and nucleocapsid **Timing**: At time of enrollment	PCR using oral and nasopharyngeal swabs: Liferiver extraction kits (Shanghai, China) and primers from Genefinders Company LTD (South Korea); Ct threshold not specified	Diagnostic accuracy
Jespersen 2020 Cross-sectional Denmark	4,797	Healthcare and administrative personnel at hospitals, prehospital services, and specialist practitioners **Age**: Not specified **Symptoms**: Not specified	**ELISA**: Wantai Biological Pharmacy Enterprise Co, Ltd (Beijing, China) **Antibody detected**: Total antibody (seropositive if A/CO ≥ 1.1) **Target antigen**: Spike **Timing**: Not specified	RT-PCR using oropharyngeal swab, nasopharyngeal swab or tracheal aspirate: Cobas® SARS-CoV-2 test (Cobas® 6800 System) or in-house PCR analysis; Ct threshold not specified	Diagnostic accuracy
Morgat 2020 Prospective cohort study Belgium *Preprint*	699	Healthcare workers (48% worked in a COVID-19 ward) **Age**: median 39.5 (IQR 32-49) **Symptoms**: 51/241 (21.2%) had at least one symptom	**ELISA**: Euroimmun (anti-SARS-CoV-2 IgG ELISA, reference EI 2606-9601 G, Medizinische Labordiagnostika AG) **Antibody detected**: IgG (seropositive if S/N ratio ≥ 1.1) **Target antigen**: Spike **Timing**: Not specified	Self-reported previous PCR result	Diagnostic accuracy
Mulchandani 2020 Cross-sectional UK *Preprint*	2,847	Frontline workers, i.e. police and fire, healthcare **Age**: Median 43 years (range 19-73) **Symptoms**: None in the last 7 days; 33% previously with symptoms compatible with COVID-19	[1] **ECLIA**: Roche Elecsys ® Anti-SARS-CoV-2 **Antibody detected**: Total antibody, predominantly IgG (positive if COI ≥ 1.0) **Target antigen**: Nucleocapsid [2] **ELISA**: EUROIMMUN Anti-SARS-CoV-2 ELISA (IgG) assays **Antibody detected**: IgG (positive if ratio > 0.8) **Target antigen**: Spike *Considered seropositive if positive on either assay (N.B. listed under IgG subgroup)* **Timing**: Median 75 days (IQR 63-92 days) from symptom onset among symptomatic	Self-reported previous PCR result via nasal and/or throat swab	Diagnostic accuracy

Study ID, Study Design, and Country	Sample Size	Population	Index Test	Reference Standard	Outcome
Percivalle 2020 Cross-sectional Italy	390	Asymptomatic blood donors **Age**: Median 46 years, range 19-70 **Symptoms**: None during enrollment	In-house SARS-CoV-2 **microneutralization assay** **Antibody detected**: Neutralizing antibodies (positive titer >= 1:10) **Target antigen**: - **Timing**: At time of enrollment (paired with nasal swab)	RT-PCR using nasal swabs: QIAGEN (Qiagen, Hilden, Germany); Ct threshold not specified	Diagnostic accuracy
Robinson 2021 UK	10,640	Hospital staff: (1) Western Sussex Hospitals NHS Foundation Trust (WSHT) (2) Brighton and Sussex University Hospitals (BSUH) **Age**: Not specified **Symptoms**: 28.7% among recruited	[1] **CLIA**: Abbott ARCHITECT i2000 (Abbott, California) **Antibody detected**: IgG (seropositive if COI > 1.4) **Target antigen**: Nucleocapsid **Timing**: 97 days after symptom onset in patients with positive RT PCR (median, WSHT cohort) [2] **ECLIA**: Cobas e411 analyser (Roche Anti-SARS-Diagnostics, Mannheim Germany) and Roche Elecsys® CoV-2 sandwich immunoassay **Antibody detected**: IgM & IgG (seropositive if COI > 1.0; N.B. listed under Total Antibody subgroup) **Target antigen**: Nucleocapsid **Timing**: 53 days after PCR, 61 days after symptom onset (median, WSHT cohort)	RT-PCR using nasopharyngeal swabs (device not specified)	Diagnostic accuracy
Santarelli 2021 Cross-sectional USA	108	General adult population ≥ 18 years, convenience sample **Age**: Mean 49.4 years **Symptoms**: None during enrollment; 33% of seropositive participants had symptoms within the past two months	**LFIA**: VITROS Anti-SARS-CoV-2 IgG test (Ortho-Clinical Diagnostics Inc.) **Antibody detected**: IgG Target antigen: Spike **Timing**: Not specified	RT-PCR result from review of medical records	Diagnostic accuracy
Shields 2020 Cross-sectional UK *Preprint*	216	Healthcare workers who were not hospitalized for COVID-19 but previously self-isolated due to symptoms experienced by themselves or household contacts **Age**: Median 41.0 (IQR 31-50) **Symptoms**: 87.7% among recruited with at least one SARS-CoV-2 symptom	**ELISA**: IgGAM ELISA that measures the total antibody response (Product code: MK654, The Binding Site (TBS), Birmingham) **Antibody detected**: IgG, IgA & IgM (positive if ratio > 1; N.B. listed under Total Antibody subgroup) **Target antigen**: Spike **Timing**: Not specified	Self-reported previous PCR result	Diagnostic accuracy
Silva 2020 Cross-sectional Brazil *Preprint*	321	Staff at the Adolfo Lutz Institute (analytical laboratory) and Ministry of Health **Age**: Median 50 years (IQR 40-57) **Symptoms**: 48% among recruited with at least one symptom	**LFIA**: SARS-CoV-2 Wondfo (Guangzhou Wondfo Biotech Co., Ltd., China) **Antibody detected**: IgG or IgM **Target antigen**: Spike **Timing**: At time of enrollment	RT-PCR using NP swab, OP swab or throat wash (Allplex 2019-nCoV Assay (Seegene, Korea); Ct up to 37	Diagnostic accuracy

* New study added in this update

Appendix 4. Study Appraisal

Table 1. Risk of bias assessment of newly included studies using QUADAS-2

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Caillard 2021	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Carrat 2021	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Khan 2021	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Lorent 2021	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Nasrallah 2021	Low risk	Low risk	Low risk ☺	Low risk	Low risk	Low risk	Low risk
Papasavas 2021	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk

Table 2. Risk of bias assessment of previously included studies using validity criteria from DOH Manual / Painless Evidence-Based Medicine (2nd edition)

Study	Acceptable reference standard	Definitions of index test and reference standard independent	Performance of index test and reference standard independent	Interpretation of index test and reference standard independent
Afzal 2020 [22]	Low	Low	Low	Low
Flannery 2020 [18]	Low	Low	Low	Low
Fong 2020 [15]	Low	Low	Low	Low
Gonzalez 2020 [12]	Low	Low	Low	Low
Ige 2020 [11]	Low	Low	Low	Low
Jespersen 2020 [17]	Low	Low	Low	Low
Mortgat 2020 [8]	Unclear	Low	Low	Low
Mulchandani 2020 [9]	Unclear	Low	Low	Low
Percivalle 2020 [25]	Low	Low	Low	Low
Robinson 2021 [20]	Unclear	Low	Low	Low
Santarelli 2021 [23]	Low	Low	Low	Low
Shields 2020 [10]	Unclear	Low	Low	Low
Silva 2020 [13]	Low	Low	Low	Low

Appendix 5. GRADE Evidence Profile

Should antibody tests be used to screen for COVID-19 in seroprevalence studies?
Sensitivity: 0.14 to 1.00
Specificity: 0.55 to 1.00
Prevalences: 1%, 10%, 40%

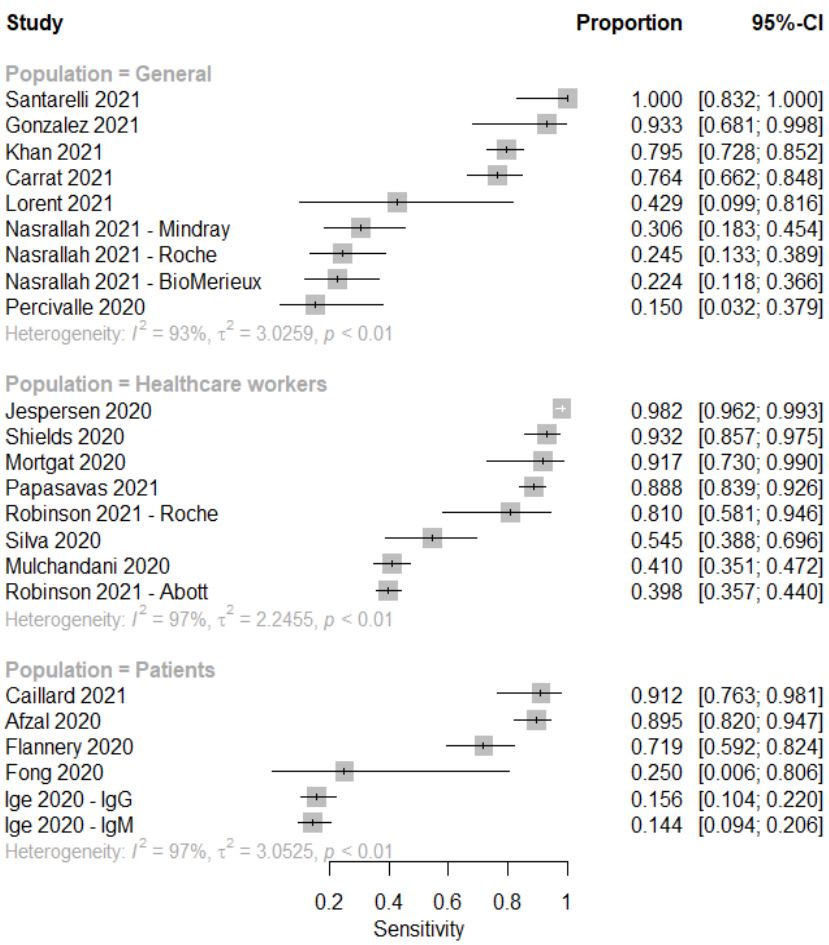
Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 1%	Pre-test probability of 10%	Pre-test probability of 40%	
True positives (patients with hypoxemia)	19 studies (2581 patients)	Cohort & case-control type studies	Serious[a]	Not serious	Very serious[b]	Serious	None	**1 to 10**	**14 to 100**	**58 to 400**	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having hypoxemia)								**0 to 9**	**0 to 86**	**0 to 342**	
True negatives (patients without hypoxemia)	19 studies (25985 patients)	Cohort & case-control type studies	Serious[a]	Not serious	Very serious[b]	Not serious	None	**544 to 986**	**494 to 896**	**329 to 598**	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having hypoxemia)								**4 to 446**	**4 to 406**	**2 to 271**	

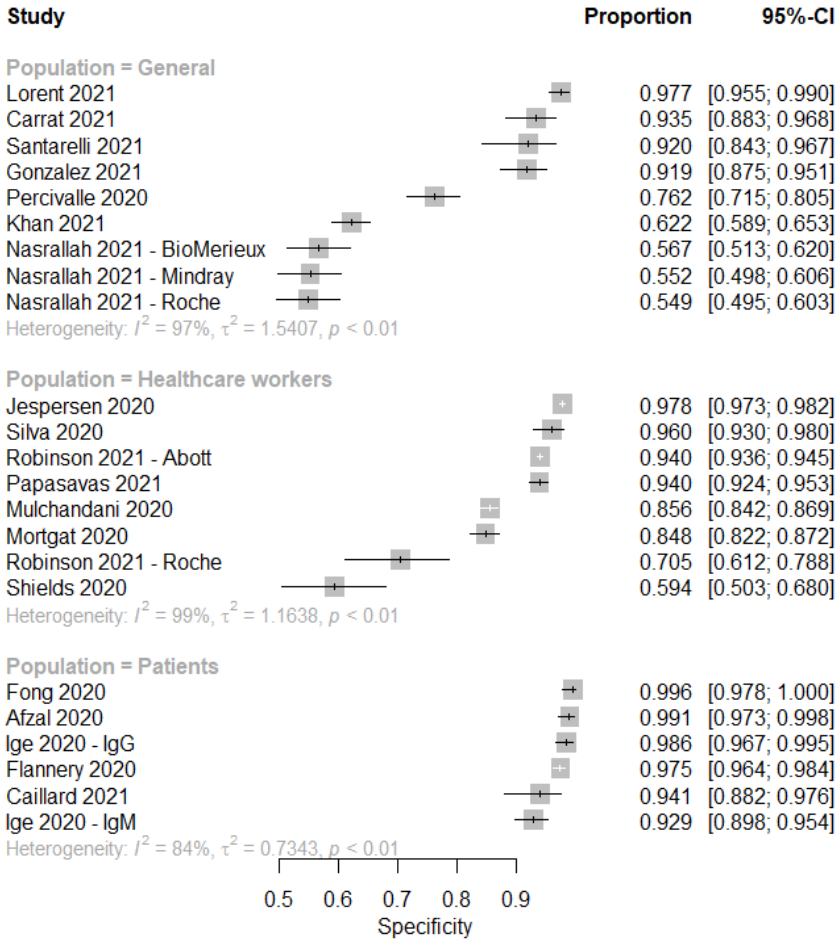
Explanations

[a] Several studies vulnerable to recall bias (self-reported RT PCR), and one study assumed those not tested with RT PCR as being negative for the reference standard

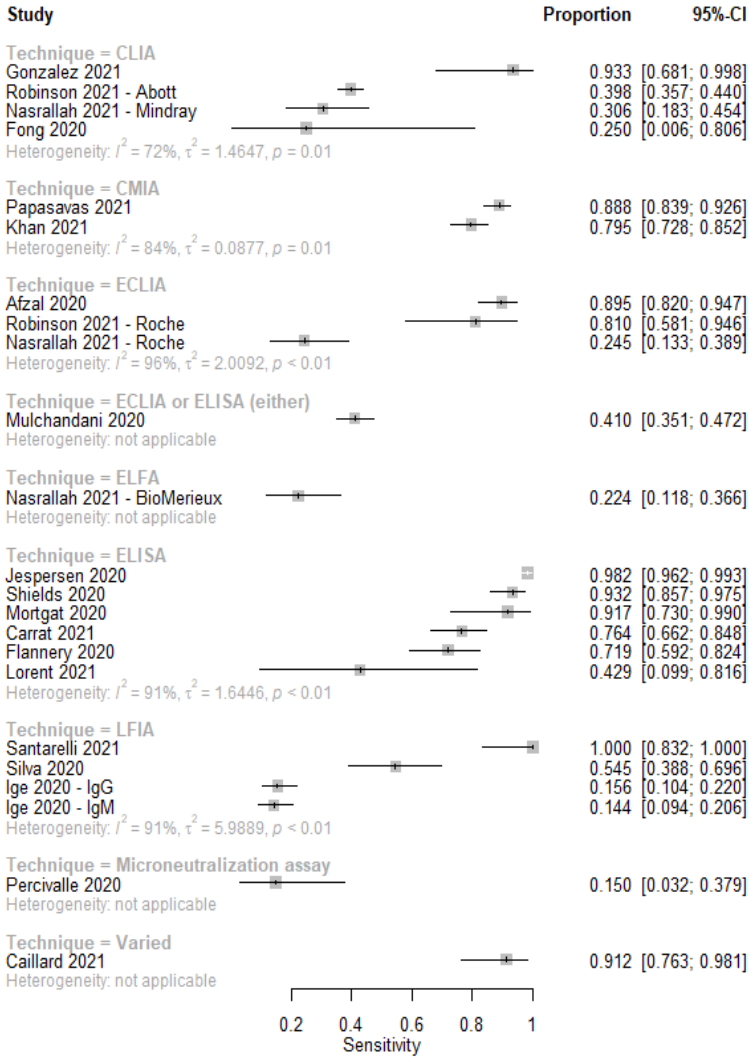
[b] Substantial heterogeneity across studies (I^2>90%)

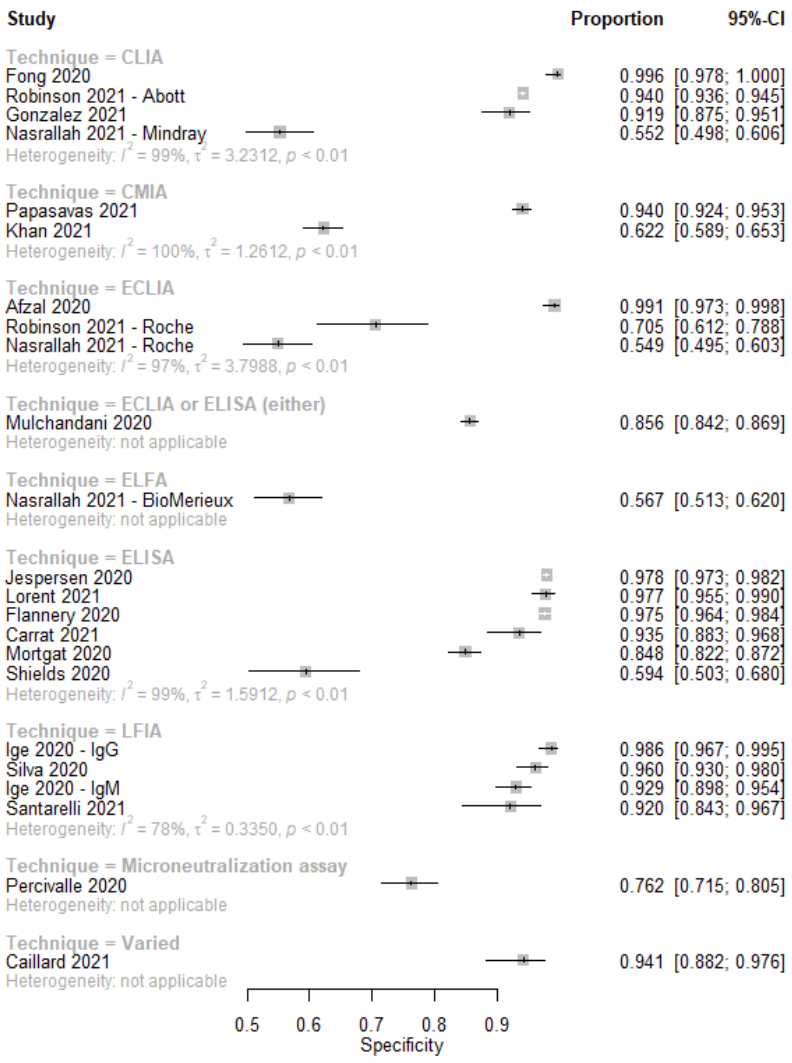
Appendix 6. Forest Plots



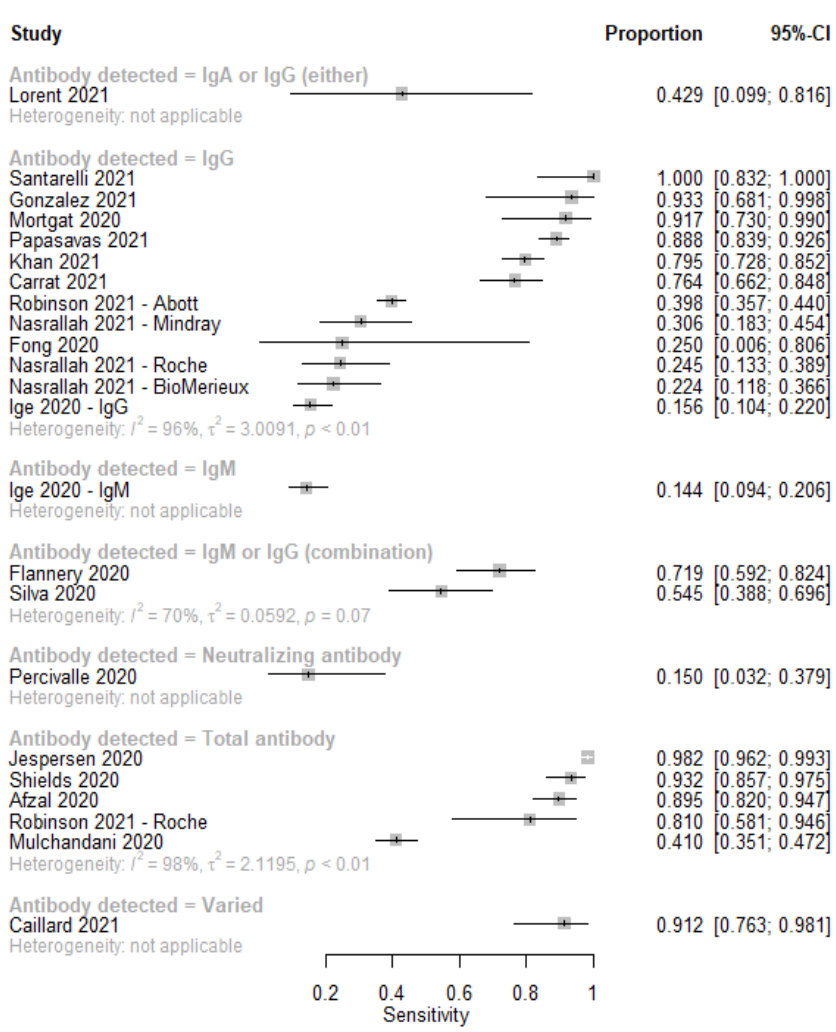


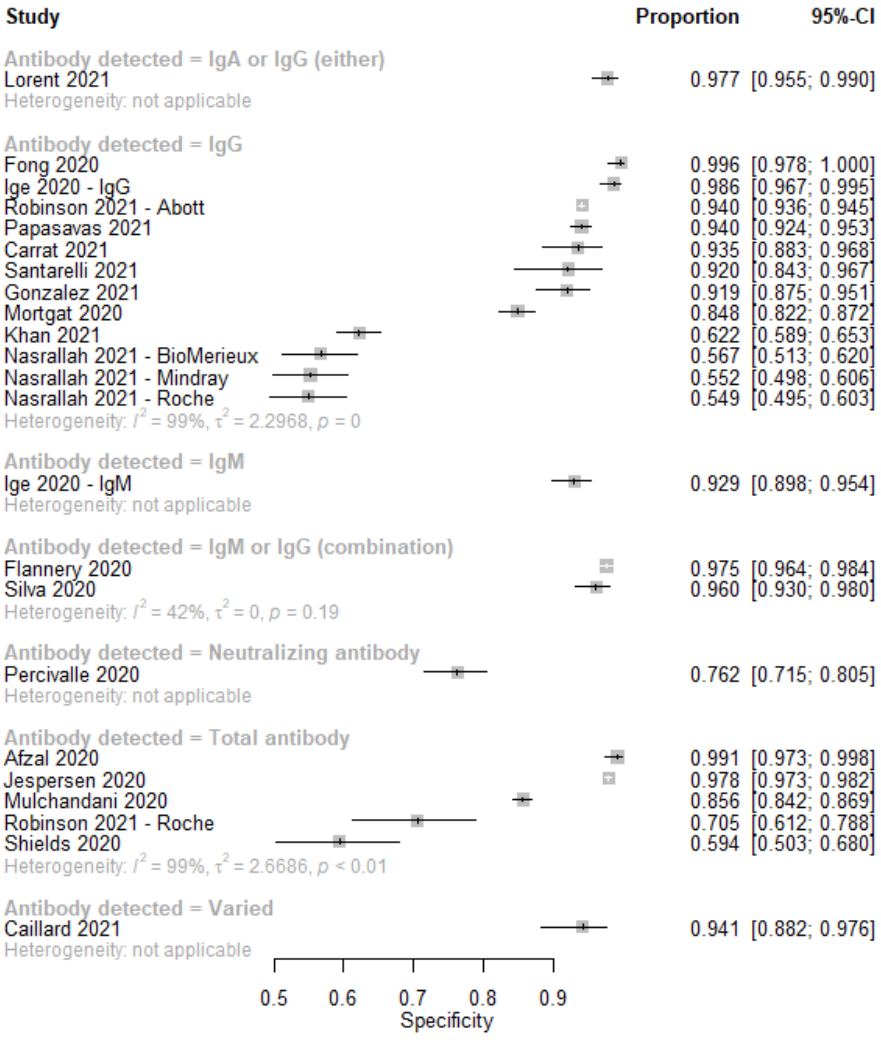
Figures 1 and 2. Sensitivity (left) and specificity (right) of antibody tests in COVID-19 seroprevalence studies according to population





Figures 3 and 4. Sensitivity (left) and specificity (right) of antibody tests in COVID-19 seroprevalence studies according to serology technique used





Figures 5 and 6. Sensitivity (left) and specificity (right) of antibody tests in COVID-19 seroprevalence studies according to type of antibody detected

Appendix 7. Subgroup Analyses

Subgroup	No. of comparisons	Sensitivity (95% CI)	I^2	Specificity (95% CI)	I^2
Population					
Healthcare workers	8	0.817 (0.603 – 0.929)	97.3%	0.897 (0.803 – 0.949)	98.9%
General	9	0.590 (0.300 – 0.828)	92.9%	0.817 (0.662 – 0.911)	96.9%
Patients	6	0.541 (0.215 – 0.835)	97.3%	0.978 (0.954 – 0.990)	84.5%
Serology Technique					
CLIA	4	0.501 (0.209 – 0.792)	72.0%	0.934 (0.697 – 0.989)	99.4%
CMIA	2	0.847 (0.772 – 0.901)	84.2%	0.835 (0.514 – 0.960)	99.6%
ECLIA	3	0.697 (0.302 – 0.925)	96.2%	0.869 (0.413 – 0.984)	96.8%
ECLIA or ELISA (either)	1	0.410 (0.353 – 0.470)	-	0.856 (0.842 – 0.869)	-
ELFA	1	0.224 (0.129 – 0.362)	-	0.567 (0.514 – 0.618)	-
ELISA	6	0.870 (0.690 – 0.953)	91.1%	0.935 (0.838 – 0.976)	98.8%
LFIA	4	0.545 (0.084 – 0.940)	90.6%	0.957 (0.921 – 0.978)	77.8%
Microneutralization assay	1	0.150 (0.049 – 0.376)	-	0.762 (0.716 – 0.803)	-
Varied	1	0.912 (0.760 – 0.971)	-	0.941 (0.881 – 0.971)	-
Antibody Detected					
IgA or IgG (either)	1	0.429 (0.144 – 0.770)	-	0.977 (0.955 – 0.98)	-
IgG	12	0.637 (0.383 – 0.832)	96.4%	0.890 (0.771 – 0.951)	99.3%
IgM	1	0.144 (0.098 – 0.205)	-	0.929 (0.898 – 0.952)	-
IgM or IgG (combination)	2	0.643 (0.516 – 0.753)	70.4%	0.972 (0.962 – 0.980)	42.5%
Neutralizing antibody	1	0.150 (0.049 – 0.376)	-	0.762 (0.716 – 0.803)	-
Total antibody	5	0.881 (0.663 – 0.965)	97.7%	0.907 (0.696 – 0.977)	99.1%
Varied	1	0.912 (0.760 – 0.971)	-	0.941 (0.881 – 0.971)	-
Self-Reported RT PCR (post hoc)					
No	15	0.584 (0.334 – 0.797)	95.6%	0.924 (0.843 – 0.965)	99.2%
Yes	8	0.808 (0.662 – 0.901)	95.8%	0.883 (0.778 – 0.942)	98.4%
Preprint (post hoc)					
No	15	0.708 (0.490 – 0.860)	96.3%	0.904 (0.807 – 0.955)	99.4%
Yes	8	0.603 (0.303 – 0.841)	95.3%	0.924 (0.844 – 0.964)	95.7%

Q11. Among symptomatic individuals previously diagnosed with COVID-19, should antibody testing be done to diagnose presumptive COVID-19 reinfection?

As of 09 April 2021

RECOMMENDATION

We recommend against the use of SARS-CoV-2 Antibody testing to diagnose presumptive COVID-19 reinfection among symptomatic patients previously diagnosed with COVID-19* *(Very low certainty of evidence; Strong recommendation)*

**NAAT (RT-PCR) and Genomic sequencing are the recommended diagnostic tests to confirm COVID-19 reinfection.*

Consensus issues

The studies reviewed did not perform subgroup analysis according to 4-fold titer rise at a given interval. Due to the very low quality of evidence, the use of SARS-CoV-2 Ab testing to diagnose presumptive COVID-19 reinfection was not recommended.

KEY FINDINGS

- No studies directly assessed the accuracy of SARS-CoV-2 antibody testing in diagnosing presumptive COVID-19 reinfection compared to RT-PCR as the reference standard. Only three retrospective observational studies reported on the accuracy of SARS-CoV-2 IgG/IgM antibody in diagnosing COVID-19. There is very low certainty regarding these estimates due to the very serious risk of bias concerns, imprecision, indirectness, and inconsistency.
- SARS-CoV-2 IgG/IgM has a sensitivity that ranged from 0.19 (95% CI 0.4-0.46) to 0.89 (95% CI 0.71- 0.98) and a specificity that ranged from of 0.50 (95% CI 0.01-0.99) to 1.00 (95% CI 0.89-1.00).
- Subgroup analysis suggested that the sensitivity of antibody testing was low under the following conditions: (a) use of antibody test within 0-15 days from symptom onset, (b) use of antibody tests that assess IgM, (c) use of lateral flow qualitative immunoassay technique (LFIA) technique.
- Specificity was consistently high (>89%) regardless of the type of antibody detected or if either LFIA or chemiluminescence immunoassay (CLIA) techniques were done. However, specificity was high only if the test was performed more than 16 days from symptom onset.

INTRODUCTION

Several cases of reinfection with SARS-CoV-2 have been reported [1,2] with a median interval from initial COVID-19 infection of 71 days (range 19-250).[3-5] Presumptive COVID-19 reinfection is considered in symptomatic individuals previously diagnosed with COVID-19 when other alternative diagnoses are ruled out and a positive NAAT result is found.[6] COVID-19 reinfection is subsequently confirmed through genomic sequencing.

Studies suggest that >90% of recovered COVID-19 patients develop anti-SARS-CoV-2 antibodies.[7-11] In some reports, the duration of IgG/IgM positivity ranged from one to four months after the acute infection.[1,8,12,] Correlates of immunity to COVID-19

have not been established, although a positive serologic test may indicate resolving or previous infection.[6] CDC has released the “Investigative Criteria for Suspected Cases of SARS-CoV-2 Reinfection.” These include the presence of symptoms compatible with COVID-19, prior COVID-19 diagnosis, no obvious alternative etiology for COVID-19-like symptoms, and close contact with a laboratory-confirmed COVID-19 and detection of SARS-CoV-2 RNA.[6]

Antibody testing may play a role in the diagnosis of COVID-19 in patients who present beyond the first week from symptom onset, particularly when molecular testing has failed to detect SARS-CoV-2. Confirming COVID-19 diagnosis using serologic tests requires detection of SARS-CoV-2 IgM and IgG in serum or a four-fold or greater increase in titer observed during convalescence compared with the acute phase. FDA approval is given to antibody tests with at least 90% sensitivity and 95% specificity.

REVIEW METHODS

A comprehensive literature search across several electronic databases was done on February 17, 2021. Studies considered eligible for this review included cross-sectional studies that evaluated the diagnostic performance of SARS-CoV-2 antibody in symptomatic patients suspected to have COVID-19 reinfection. The reference standard was RT-PCR. Studies on sensitivity or specificity alone, those that used other reference standards with RT-PCR, and those that included healthy individuals as controls were excluded.

RESULTS

Characteristics of included studies

No studies directly assessed the accuracy of SARs-CoV-2 antibody in diagnosing presumptive COVID-19 reinfection compared to RT-PCR as the reference standard.

Indirect evidence came from three observational cross-sectional studies on the diagnostic performance of SARS-CoV-2 antibody testing on COVID-19 infection involving a total 429 symptomatic, hospitalized and non-hospitalized patients.[13-15] Previous COVID-19 infection among the patients was not specified in any of the studies. Two studies were pre-prints.[14,15] One study assessed combined IgG/IgM using LFIA technique [15], another assessed IgM or IgG separately using chemiluminescence immunoassay [13], while the remaining study assessed combined IgG/IgM but with an unspecified, rapid analytic technique.[14] The reference standard used for all three studies was RT-PCR. The time interval between the conduct of the antibody testing and the RT-PCR varied among the studies: simultaneous [15], 15 days [13], or an unspecified interval.[14] antibody testing was done up to 30 days from symptom onset.[13,14]

Methodological quality

The overall quality of evidence was rated very low. Downgrading occurred due to indirectness, very serious risk of bias, inconsistency, and imprecision due to small sample sizes.[14] It was unclear whether antibody testing was interpreted without knowledge of the RT-PCR results in two studies.[13,14] Moreover, the time interval between the conduct of the index test and the reference standard was unreported. Incomplete data was noted in 17/267 (6%) of patients in two studies.[13,15] Inconsistency was observed in the choices of specimen sites (URT in two studies and

URT or LRT in one study), the timing of testing of the index and reference tests (simultaneous versus 15-day interval vs unclear), and the type of antibody test.

Outcomes

Diagnostic accuracy

SARS-CoV2 IgG/IgM, IgG or IgM antibody had a sensitivity ranging from 0.29 (95% CI 0.18- 0.41) to 0.89 (95% CI 0.71- 0.98) and specificity of 0.50 (95% CI 0.01-0.99) to 1.00 (95% CI 0.89-1.00). We did not calculate for pooled sensitivity and specificity estimates due to the limited number of studies as well as significant heterogeneity noted upon visual inspection of the forest plots.

Subgroup analysis according to time of testing from symptom onset showed that the sensitivity of antibody testing was lowest when performed on day 0 to day 7 (Sn 19%, 95% CI 4-46%), highest on day 8 to 15 (Sn 100%, 95% CI 54-100%). Performing the test beyond day 16 showed moderate-to-high sensitivity values ranging from 48 to 100%. In terms of the type of technique used, LFIA showed poor sensitivity (Sn 29%, 95% CI 18-41%). antibody tests that used IgM also showed poorer sensitivities (<70%) compared to IgG (>70%).

Specificity was consistently high (>89%) regardless of the type of antibody detected or if either LFIA or CLIA technique was done. However, lower and less precise specificity estimates were seen in studies that used antibody testing within the first 15 days from symptom onset. Specificity was high when antibody testing was used more than 16 days from symptom onset (Sp 90%, 95% CI 82-95%).

Table 1. Accuracy of COVID-19 antibody tests for seroprevalence stratified by potential sources of heterogeneity

		IgG		IgM		Combined IgG/IgM	
Subgroup	No. of studies (Sample size)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Symptom onset							
0-7 days	1 (25)	-	**-**	**-**	-	**19%** (4-46)	78% (40-97)
8-15 days	1 (8)	**-**	**-**	**-**	-	**100%** (54-100)	50% (0.01-0.99)
> 16 days	2 (142)	**89%** (71-98)	**91% (76-98)**	**48%** (29-68**)**	**100%** (89-100)	**86%** (79-91)	90% (82-95)
Laboratory technique							
LFIA	1 (190)					**29%** (18-41)	**89%** (82-94)
CLIA	1(60)	89% (71-98)	**91% (76-98)**	**48% (29-68)**	**100% (89-100)**		
Unspecified	1 (179)					86% (77-92)	91% (83-96)

RECOMMENDATIONS FROM OTHER GROUPS

CDC (Oct 27, 2020) does not recommend antibody testing to diagnose current COVID-19.

PSMID (July 20, 2020) does not recommend antibody tests as stand-alone tests for the diagnosis of COVID-19.[16]

COVID-Low and Middle Income Countries (LMIC) Task Force (22 Jan 2021) suggests against using SARSCoV-2 antibody testing for the detection of active or past SARS-CoV-2 infection until there is better evidence for its usefulness.[17]

CDC proposes investigative criteria for identifying cases suspected of COVID-19 reinfection. These include the presence of symptoms compatible with COVID-19, prior COVID-19 diagnosis, no obvious alternative etiology for COVID-19-like symptoms, and close contact with a laboratory-confirmed COVID-19 and detection of SARS-CoV-2 RNA.[6]

RESEARCH GAPS

There are no ongoing studies on the accuracy of antibody testing in diagnosing COVID-19 presumptive reinfection.

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Appendix 1. Characteristics of Included Studies

Study ID and Country	Study Design	Population	Index Test/s	Reference Standard	Testing Interval (days)
Jin 2020 China	Retrospective Cross-sectional	n = 76 Median age 47 yo (IQR range 35-59) Hospitalized patients	SARS-CoV-2 IgG SARS-CoV-2 IgM CLIA on day 18 from symptom onset (IQR 11-23 days)	RT-PCR from oral swab or sputum on day 3 of symptom onset (IQR 2-7 days)	15 days
Liu Ying 2020	Retrospective observational	n=179 inpatient and outpatient cases mild to critical 23-80 years old	SARS-CoV-2 IgG/IgM (unspecified analytic technique) 30 days from symptom onset (+/- 17 days) in PCR -positive patients 8 days (+/- 14 days) in PCR- negative patients	RT- PCR from nasal and pharyngeal swabs	Unreported time interval
Paradiso 2020	Observational	n=191 14 (8.7%) asymptomatic median age 58.5 years symptomatic patients seen in the emergency room	SARS-CoV-2 IgG/IgM (lateral flow qualitative immunoassay)	RT-PCR from nasopharyngeal/ oropharyngeal swab	Simultaneous

Appendix 2. GRADE Evidence Profile

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	
True positives (patients with [Presumptive COVID-19 Reinfection])	3 studies 187 patients	Cross-sectional (cohort type accuracy study)	Very serious [a,b,c,d]	Serious [e]	Serious [f]	Serious [g]	None	0 (0 to 0)	⊕◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having [Presumptive COVID-19 Reinfection])								0 (0 to 0)	
True negatives (patients without [Presumptive COVID-19 Reinfection])	3 studies 187 patients	Cross-sectional (cohort type accuracy study)	Very serious [a,b,c,d]	Serious [e]	Serious [f]	Not serious	None	0 (0 to 0)	⊕◯◯◯ VERY LOW
False positives (patients incorrectly classified as having [Presumptive COVID-19 Reinfection])								1000 (1000 to 1000)	

Explanations

[a]. It was unclear if consecutive patients or random sample of patients were enrolled.
[b]. It was unclear if the reference and index tests were interpreted independently from each other.
[c]. Different specimens were used, either nasopharyngeal or oropharyngeal, or sputum.
[d]. Interval between timing of tests was not reported in 2 studies.
[e]. Did not state if patients were previously diagnosed with COVID-19.
[f]. Heterogeneity can be attributed to different Ab testing technique, timing of testing and type of Ab (IgG/IgM or IgG only or IgM only.
[g]. Small sample size in 2 studies

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Appendix 3. Forest Plots

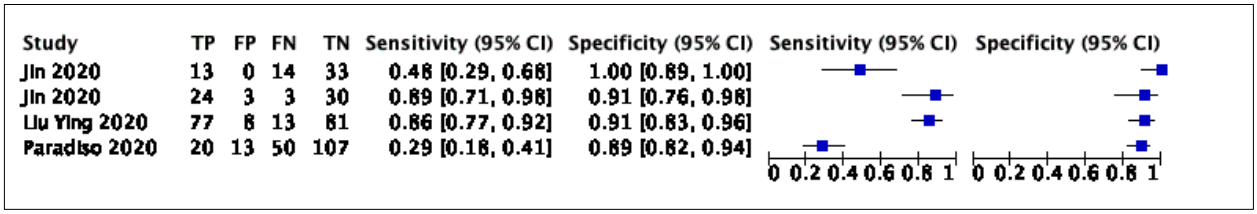


Figure 1. Forest Plot of the Overall Sensitivity and Specificity of SARS-CoV-2 Ab

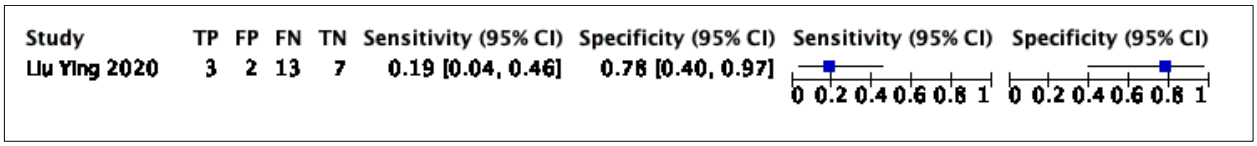


Figure 2. Forest Plot of 4 SARS-CoV-2 IgG IgM Day 0-7

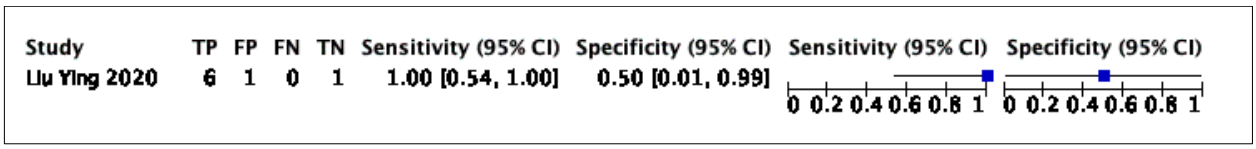


Figure 3. Forest Plot of 5 SARS-CoV-2 IgG IgM Day 8-15

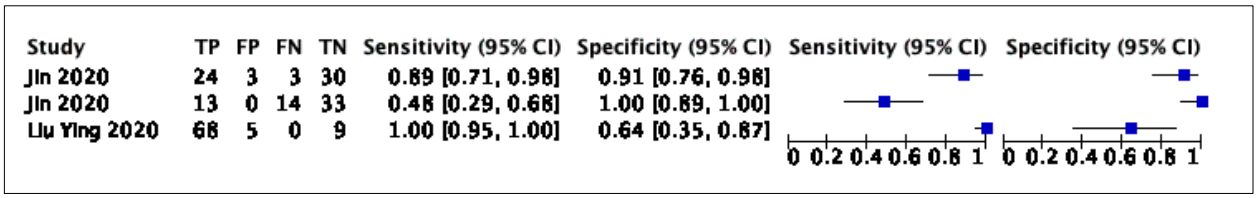


Figure 4. Forest Plot of 6 SARS-CoV-2 IgG IgM (>/=) Day 16

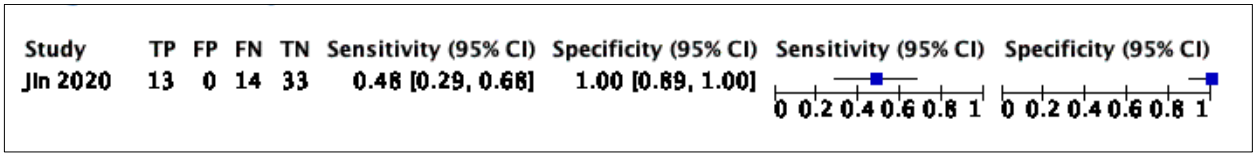


Figure 5. Forest Plot of 2 SARS-CoV-2 IgM Ab

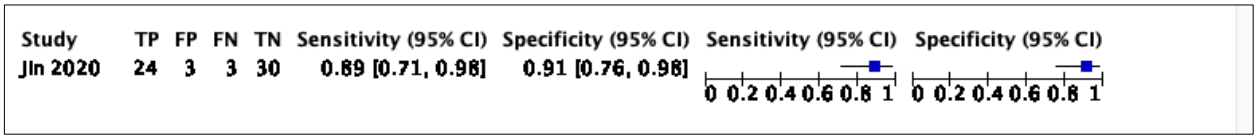


Figure 6. Forest Plot of 1 SARS-CoV-2 IgG Ab

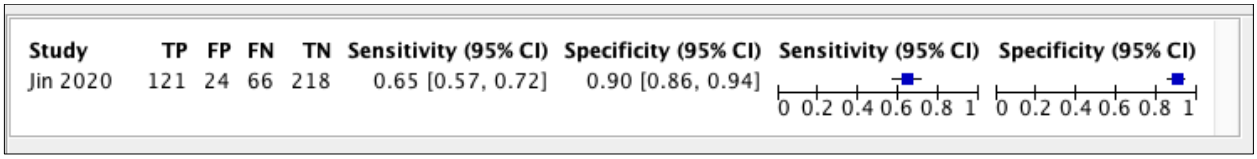
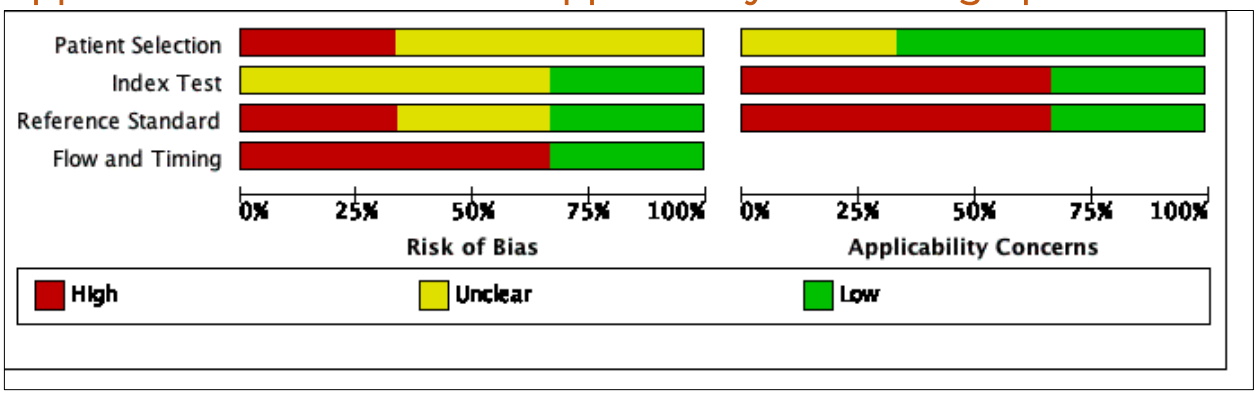
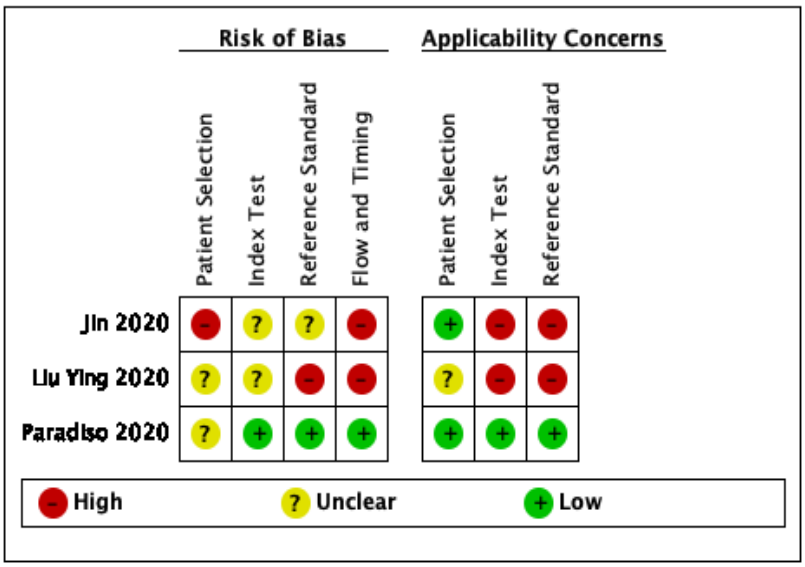


Figure 7. Forest Plot of the Sensitivity and Specificity of SARS-CoV-2 IgG Ab

Appendix 4. Risk of bias and applicability concerns graph



Appendix 5. Risk of bias and applicability concerns summary



Q12. Among asymptomatic individuals scheduled for non-urgent, non-emergency surgery, should RT-PCR and clinical risk assessment vs clinical risk assessment alone be done to screen for COVID-19?

As of 09 April 2021

RECOMMENDATION

We recommend using both clinical risk assessment and RT-PCR* to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery. *(Very low certainty of evidence; Strong recommendation)*

We recommend using both clinical risk assessment and Antigen-Rapid Diagnostic Test (Ag-RDT) to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery when RT-PCR testing is not available or when prolonged turnaround time is a concern.** *(Very low certainty of evidence; Strong recommendation)*

**Always use high-risk PPE regardless of RT-PCR or Ag-RDT test results in areas with prevalence of 1% or higher*
***Ag-RDT should have a Sn of 80% and Sp of 97%*

Consensus Issues
Despite the very low quality of evidence, the majority voted to strongly recommend the use of both RT-PCR testing and clinical risk assessment to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery primarily due to the potential impact of a false negative result on the safety of the patient and health care staff involved as well as on the infection control processes of hospitals. RT-PCR was also recommended as it is now readily available in most hospitals. However, a panelist suggested that RT-PCR and PPE should only be conditionally recommended in areas with prevalence rates of 1% or higher.

The specification of the sensitivity and specificity for the Ag-RDT was the reason for the strong recommendation on the use of clinical risk assessment and Ag-RDT to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery when RT-PCR testing is not available. However, other panelists were concerned about the availability of antigen tests that would meet the set specification in terms of sensitivity and specificity.

KEY FINDINGS

- Based on one cohort study with very low quality, the diagnostic accuracy of clinical risk assessment alone in detecting COVID-19 compared to RT-PCR was found to be poor, with a sensitivity of 0.42 (95% CI 0.15-0.72) and a specificity of 0.85 (95% CI 0.76-0.92). Clinical risk assessment also resulted in more false-negative and false-positive results.
- Very low certainty evidence from one economic modeling study suggested that universal pre-endoscopy virus testing using Ag-RDT, standard RT-PCR, or rapid PCR combined with high-risk PPE use in all patients irrespective of test results was more cost-effective compared to no pre-endoscopy testing and no high-risk

PPE use, at an assumed prevalence rate of 1% or higher among asymptomatic individuals.

- Patients for elective surgery who tested positive on any pre-operative COVID-19 tests or clinical assessment were at least three times more at risk of experiencing pulmonary complications or death compared to those who tested negative based on one cohort study with very low quality. Delaying surgery to at least seven weeks from a COVID-19 diagnosis also showed benefit. Given this data on the risks and benefits associated with a COVID-19 diagnosis as well as the high false-negative rates of clinical risk assessment alone, a clinical risk assessment would appear to cause more harm compared to more objective tests.

INTRODUCTION

The COVID-19 pandemic has led to deferral and postponement of surgeries, especially non-essential or elective ones, in institutions across the globe. Asymptomatic COVID-19 patients undergoing surgery are at a higher risk of postoperative mortality and ICU admission compared to those without COVID-19.[1-3] The proportion of asymptomatic COVID-19 cases was reported to be 17.9%.[4] Hence, ascertaining the COVID-19 status of asymptomatic surgical candidates informs decisions to prevent viral transmission and reduce postoperative complications.

Recommendations for routine RT-PCR testing have been made for elective surgical candidates suspected of COVID-19 based on the availability of the test, turnaround time, availability of PPE, and disease prevalence.[5] Its results also depend on sampling technique, specimen handling, and timing of specimen collection from symptom onset.[6,7] False-negative rates for RT-PCR were estimated to reach as high as 16%.[8]

Clinical risk assessment includes determining a history of close contact with a confirmed COVID-19 case (i.e., within 6 feet for a total of 15 minutes or more) and evaluating symptoms. Risk is also considered high if a person has taken part in activities where physical distancing is difficult to maintain, such as travel, attending large social or mass gatherings, or being in crowded indoor settings.[9] Its diagnostic performance for screening asymptomatic surgical candidates remains to be determined.

REVIEW METHODS

A comprehensive search on PubMed and Cochrane CENTRAL was done with the following search terms using our PICO: COVID-19, SARS-CoV-2, surgery, operation, preoperative, postoperative, testing, RT-PCR. We also searched for preprints on ChinaXiv, MedRxiv, and Biorxiv and the reference lists of identified articles. The last search was done on March 10, 2021 without language restrictions. The following inclusion criteria were used for this review:

- Study design: randomized controlled trials, controlled clinical trials, observational studies
- Population: asymptomatic individuals scheduled for non-urgent, non-emergency surgery
- Exposure: clinical risk assessment or other pre-operative COVID-19 testing methods
- Outcome: diagnostic accuracy, post-operative outcomes, cost-effectiveness

For the outcome of diagnostic accuracy, studies that did not report sufficient data to calculate the sensitivity and specificity estimates were excluded.

There were no studies that provided direct evidence on the effects of clinical risk assessment and pre-operative RT-PCR testing vs clinical risk assessment alone on management decisions and postoperative outcomes in asymptomatic patients scheduled for non-emergency surgery.

RESULTS

Characteristics of included studies

Three eligible studies informed this review.[10-12]

One retrospective cohort study assessed the accuracy of clinical risk assessment for screening COVID-19, using RT-PCR as the reference standard. In this study, 99 asymptomatic adult patients (mean age 64.1 ± 30 years, scheduled for inpatient orthopedic surgery) underwent both clinical assessment (i.e., temperature testing and Centers for Disease Control and Prevention-based symptom screening questionnaires for COVID-19) and nasopharyngeal swab RT-PCR testing.[10]

One multi-center, international, prospective cohort study [11] provided indirect evidence on the impact of pre-operative COVID-19 testing on postoperative outcomes (complications, mortality on day 30). The study involved a total of 140,231 consecutive patients who underwent elective or emergency surgery for any indication. Of these, 3,127 (2.2.%) were confirmed COVID-19 cases (1,384 or 44.3% were asymptomatic; 1,726 or 55.2% were symptomatic; and 17 or 0.5% had unknown symptom status). In this study, COVID-19 diagnosis was made based on either clinical or other objective tests: (a) RT-PCR swab in 79.5% (2486/3127), (b) rapid antigen test in 2.8% (87/3127), (c) CT scan in 3.8% (118/3127), (d) antibody test in 9.0% (280/3127), and (e) a clinical diagnosis in 5.0% (156/3127). However, the study did not report data to allow comparisons between these different types of pre-operative tests on both patients with or without symptoms.

The cost-effectiveness of pre-endoscopy SARS-CoV-2 testing and the use of high-risk PPE was assessed in one economic evaluation study.[12] The costs, effects, and incremental cost-effectiveness ratios (ICERs) were calculated for eight different combinations of infection prevention and testing strategies. These testing strategies included clinical signs screening, decentralized point-of-care antigen test, centralized rapid PCR, and standard PCR test. A Monte Carlo simulation for 4 different prevalence rates (0.01%, 0.1%, 1%, and 5%) was done based on a model of 10,000 asymptomatic patients, 20 full-time HCWs wearing two N95 masks per day, and 250 working days.

Methodological quality

Overall quality of the body of evidence was downgraded to very low due to the serious risk of bias, indirectness, and serious imprecision (Appendix 2). The GRADE rating for the retrospective cohort study was low; downgraded due to a serious risk of bias and serious imprecision. The GRADE rating for the prospective cohort study was low; downgraded due to indirectness.

Outcomes

Diagnostic accuracy

Clinical risk assessment had a sensitivity of 0.42 (95% CI 0.15-0.72) and specificity of 0.85 (95% CI 0.76-0.92) based on 1 retrospective cohort study with very low quality.[10] This translates to a false negative rate of 0.58 and a false positive rate of 0.15.

Harms associated with a false negative

Indirect evidence showing the possible harms resulting from a false negative diagnosis was derived from the prospective cohort study which reported on the postoperative outcomes for patients tested for COVID-19. However, it was not possible to calculate risk ratios specifically for asymptomatic patients or for specific test methods (clinical risk assessment, antigen, RT-PCR). The certainty of this evidence was rated very low due to serious indirectness (combined data from asymptomatic and symptomatic, no subgroup analysis according to the testing method).

Among patients who had elective surgery within 0-7 weeks after getting a positive result from any pre-operative COVID-19 test result (not specific to clinical or other testing methods), the risk of 30-day postoperative mortality and pulmonary complications were both at least 3 times higher (RR 3.96, 95% CI 3.41-4.59) and (RR 3.41, 95% CI 3.04-3.83) compared to those who tested negative.[11]

Surgeries that were delayed after ascertainment of COVID-19 status showed better post-surgical outcomes; however, this effect was only significant for surgeries done at least seven weeks from COVID-19 diagnosis. In particular, postoperative mortality and complications were comparable to patients without COVID-19, with an RR of 1.46 (95% CI 0.73-2.92) and 1.37 (95% CI 0.91-2.08), respectively.[11]

Cost-effectiveness

Very low certainty evidence suggests that universal pre-endoscopy virus testing using Ag-RDT, standard RT-PCR, or rapid PCR combined with high-risk PPE use in all patients irrespective of test results was found to be more cost-effective compared to no pre-endoscopy testing and no high-risk PPE use, at an assumed prevalence rate of 1% or higher among asymptomatic individuals. Among the different tests, Ag-RDT with high-risk PPE was found to be the most cost-effective strategy (ICER = -26,286 €) followed by rapid PCR with high-risk PPE use (ICER = -13,703 €) then standard RT-PCR (ICE= -11,128€). The high cost of standard PCR (273.35€) and rapid PCR (167.85€) compared with rapid Ag test (17.30€) as well as their turnaround times (standard PCR=2 days, Rapid PCR=1 day, Ag-RDT<1 day) seemed to favor Ag-RDT in terms of cost-effectiveness.[13] The quality of this evidence was very low due to the very serious risk of bias (use of assumptions/simulations versus observational data, incomplete costing data) and serious indirectness (different country, healthcare system).

RECOMMENDATIONS FROM OTHER GROUPS

Both CDC (07 December 2020) and IDSA (23 December 2020) suggest RT-PCR testing of asymptomatic individuals without known exposure when the results will impact isolation/quarantine/personal protective equipment (PPE) usage decisions, dictate eligibility for surgery.[9,13]

Similarly, IDSA suggests RT-PCR testing for asymptomatic individuals without known exposure to COVID-19 who are undergoing major time-sensitive surgeries (i.e., medically necessary surgeries that need to be done within three months). To limit potential poor outcomes, deferring non-emergent surgeries should be considered for patients testing positive for SARS-CoV-2. Decisions about PPE use for the aerosol-generating portions of these procedures may be dependent on test results when PPE supplies are limited. However, due to the risk of false negatives, caution should be exercised by healthcare workers who will be in close contact with/exposed to the upper respiratory tract (e.g., anesthesia personnel, ENT procedures).

The Philippine Society for Microbiological and Infectious Diseases (PSMID) and Philippine Hospital Infection Control Society (PHICS) (26 May 2020) recommend COVID-19 clinical risk assessment for patients about to undergo surgery, and if available, RT-PCR. Accessibility, turnaround time, and cost-effectiveness (cost of RT-PCR vs. cost of PPE) are important considerations when RT-PCR is to be requested.[5]

On the other hand, PSMID, and PHICS recommend RT-PCR, particularly for individuals who will undergo high-risk surgical procedures, even if they are asymptomatic.[5] Other national and international groups recommend preoperative RT-PCR testing, regardless of symptoms or exposure.[14-18]

RESEARCH GAPS

Currently, there are no ongoing studies on this topic.

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Appendix 1. Characteristics of Included Studies

Author	Study Design	Patient Selection	Outcome
Gruskay 2020	Retrospective cohort	n=99 Symptomatic and asymptomatic patients who had preoperative RT-PCR testing prior to orthopedic surgery	Sensitivity Specificity
COVIDSrug Collaborative 2021	International, prospective cohort	n=96,018 Symptomatic and asymptomatic RT-PCR-confirmed COVID-19 Patients without COVID-19 diagnosis	Post-operative complications and 30-day post-operative mortality within 0-2 weeks after COVID-19 diagnosis Post-operative complications 30-day post-operative mortality if elective surgery was delayed from at least 7 weeks after COVID-19 diagnosis
Ebigbo 2020 Germany	Model- based assumption	10 000 asymptomatic patients scheduled for endoscopy	Incremental Cost-effectiveness Ratio

Appendix 2. GRADE Evidence Profile

Sensitivity	0.42 (95% CI: 0.19 to 0.68)
Specificity	0.85 (95% CI: 0.76 to 0.91)

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 24%	Pre-test probability of 32%	
True positives (patients with hypoxemia)	1 studies 12 patients	Cross-sectional (cohort type accuracy study)	Serious [1,a,b]	Not serious	Not serious	Serious [1,c]	None	21 (10 to 34)	101 (46 to 163)	134 (61 to 218)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having hypoxemia)								29 (16 to 40)	139 (77 to 194)	186 (102 to 259)	
True negatives (patients without hypoxemia)	1 studies 87 patients	Cross-sectional (cohort type accuracy study)	Serious [1,a,b]	Not serious	Not serious	Not serious [1,c]	None	808 (722 to 864)	646 (578 to 692)	578 (517 to 619)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having hypoxemia)								142 (86 to 228)	114 (68 to 182)	102 (61 to 163)	

Explanations

[a] The interval between clinical risk assessment and RT-PCR testing was not reported.

[b] The study excluded 42 patients (30% of the recruited participants) who had clinical risk assessment but no RT-PCR testing.

[c] The sample size was small (n=99).

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CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	COVID-19 patients	Non-COVID-19 patients	Relative (95% CI)	Absolute (95% CI)	CERTAINTY	IMPORTANCE
Postoperative 30-day mortality												
1	Observational studies	Not serious	Not serious	Very serious [1,a,b]	Not serious	None	17/338 (5.0%)	588/95680 (0.6%)	**RR 8.18** (5.11 to 13.10)	**44 more per 1,000** (from 25 more to 74 more)	⊕◯◯◯ VERY LOW	
Pulmonary complications												
1	Observational studies	Not serious	Not serious	Very serious [1,a,b]	Not serious	None	21/338 (6.2%)	1720/95680 (1.8%)	**RR 3.46** (2.28 to 5.24)	**44 more per 1,000** (from 23 more to 76 more)	⊕◯◯◯ VERY LOW	
Post-operative mortality (Surgery delayed for at least 7 weeks after COVID-19 diagnosis)												
1	Observational studies	Not serious	Not serious	Very serious [1,a,b]	Not serious	None	8/892 (0.9%)	588/95680 (0.6%)	**RR 1.46** (0.73 to 2.92)	**3 more per 1,000** (from 2 fewer to 12 more)	⊕◯◯◯ VERY LOW	
Post-operative complications (Surgery delayed for at least 7 weeks after COVID-19 diagnosis)												
1	Observational studies	Not serious	Not serious	Very serious [1,a,b]	Not serious	None	22/892 (2.5%)	1720/95680 (1.8%)	**RR 1.37** (0.91 to 2.08)	**7 more per 1,000** (from 2 fewer to 19 more)	⊕◯◯◯ VERY LOW	

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

Explanations

[a]. The study compared the outcomes of surgery between those with COVID-19 or no COVID-19 based on PCR testing, rather than outcomes of surgery based on clinical risk assessment alone vs clinical risk assessment and PCR testing

[b]. There was indirectness that was attributed to combined symptomatic (55.2%) and asymptomatic (44.8%) COVID-19 patients.

References

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Appendix 3. Forest Plot

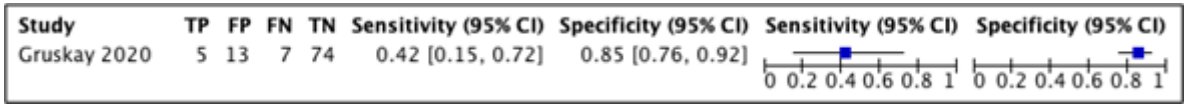

Figure 1. Forest plot of the sensitivity and specificity of clinical risk assessment in diagnosing COVID-19.

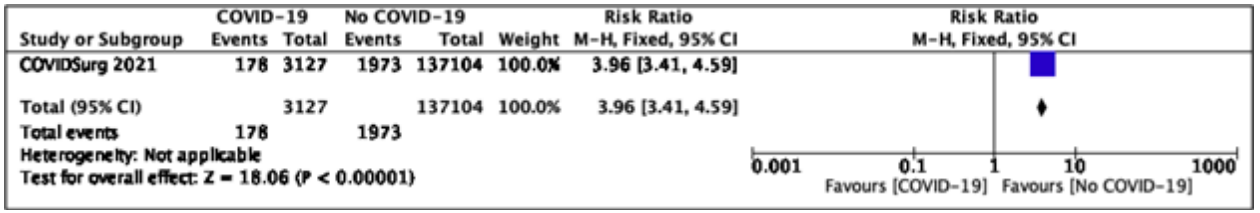

Figure 2. Forest Plot of Post-operative mortality

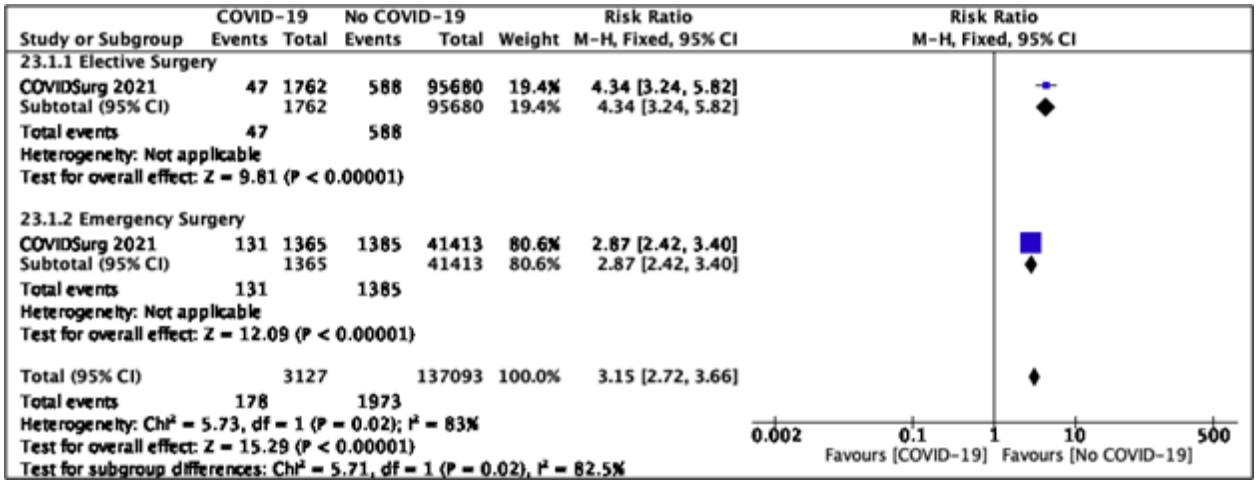

Figure 3. Forest Plot of Post-operative mortality (urgency of surgery)

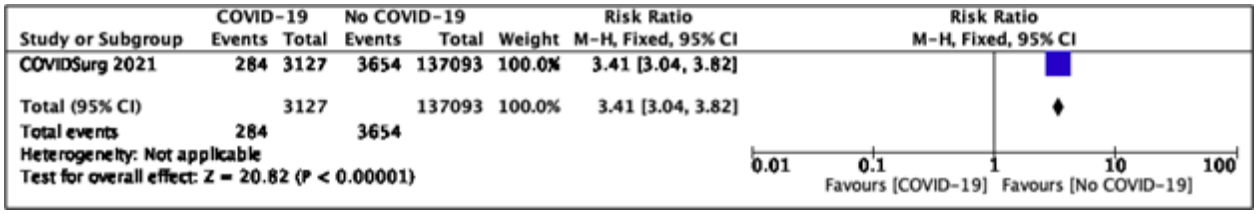

Figure 4. Forest Plot of Pulmonary Complications

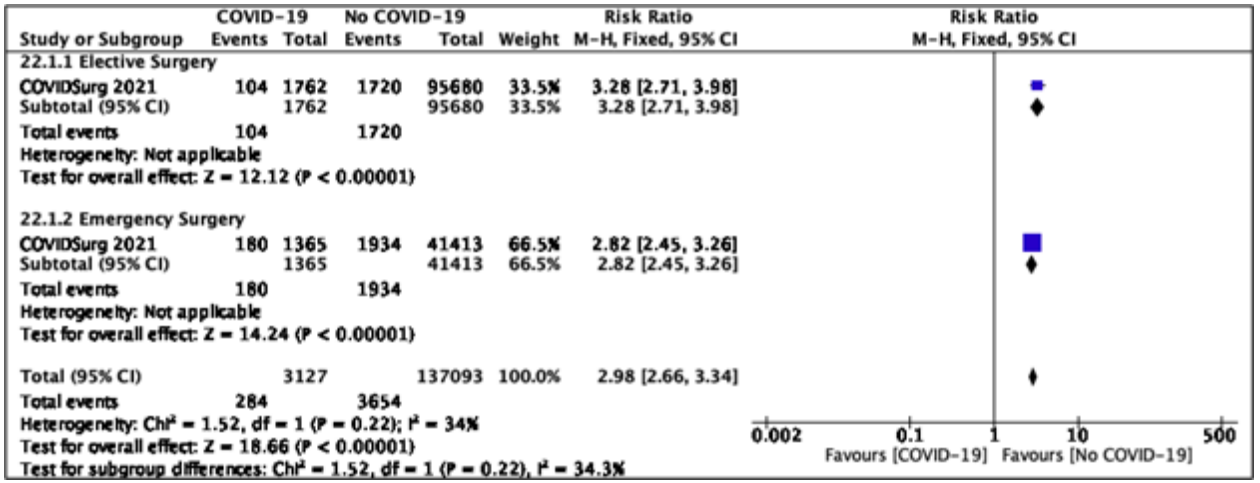

Figure 5. Forest Plot of Post-operative pulmonary complications (urgency of surgery)

Appendix 4. Cost-Effectiveness of Pre-endoscopy testing and use of high-risk PPE (Emigmo, 2020)

Strategy		ICER value		
		Prevalence		
Control Strategy: No diagnostic test No high risk PPE		0.01% (0.005-0.02)	1% (0.5-2%)	5% (2.5-10%)
Ag test	no high risk PPE	11,774	-13,035	-15,240
	high risk PPE	17,451	-22,716	-26,286
Rapid PCR	no high risk PPE	145,570	345	-12, 564
	high risk PPE	155, 150	659	-13,073
Standard PCR	no high risk PPE	249,022	10,690	-10,495
	high risk PPE	258,557	10,887	-11, 128

Appendix 5. Sensitivity and specificity of the tests (Emigmo, 2020)

	Standard PCR Cobas Assay	Rapid PCR Xpert Cepheid	Rapid Antigen test
Sensitivity (95% CI)	0.97 (0.92-0.97)	0.95 (0.92-0.98)	0.57 (0.48-0.6)
Specificity (95% CI)	1.00 (0.96- 0.99)	1.00 (0.96-0.99)	1.00 (0.98-0.99)

Appendix 6. Cost and turn-around time of SARS-CoV2 virus tests (Emigmo, 2020)

	Standard PCR test	Rapid PCR test	Rapid Ag test
Cost (€)	273.35	167.85	17.30
Turnaround time (hours)	48	24	-------

Q13. What criteria should be used for allowing workers who were previously infected with COVID-19 to return to work?

As of 17 December 2021

RECOMMENDATION

For asymptomatic, not severely immunocompromised fully vaccinated adults, we suggest the use of the following symptom-based criteria for return to work clearance: *(Very low certainty of evidence; Weak recommendation)*

a. At least 8 days have passed since the first positive COVID-19 RT-PCR test; AND
b. No symptoms have developed during this period.

For asymptomatic, not severely immunocompromised not fully vaccinated adults, we suggest the use of the following symptom-based criteria for return to work clearance: *(Very low certainty of evidence; Weak recommendation)*

a. At least 10 days have passed since the first positive COVID-19 RT-PCR test; AND
b. No symptoms have developed during this period.

For symptomatic, not severely immunocompromised adults with mild-to-moderate COVID-19 diagnosis and any vaccination status, we suggest the use of the following symptom-based criteria for return to work clearance:
(Very low certainty of evidence; Weak recommendation)

a. At least 10 days have passed since the onset of symptoms; AND
b. No fever during the previous 24 hours; AND
c. There has been substantial improvement in respiratory symptoms of the acute illness.

For symptomatic, not severely immunocompromised adults with severe-to-critical COVID-19 diagnosis and any vaccination status, we suggest the use of the following symptom-based criteria for return to work clearance:
(Very low certainty of evidence; Weak recommendation)

a. At least 21 days have passed since the onset of symptoms; AND
b. No fever during the previous 24 hours; AND
c. There has been substantial improvement in respiratory symptoms of the acute illness.

For symptomatic, severely immunocompromised adults with any vaccination status, we suggest the use of the following for return to work clearance:
(Very low certainty of evidence; Weak recommendation)

a. At least 22 days have passed since the onset of symptoms; AND
b. No fever during the previous 24 hours; AND
c. There has been substantial improvement in respiratory symptoms of the acute illness; AND
d. PCR test results are negative on at least 1 respiratory specimen.

Note:
Severely immunocompromised individuals include the following:

- Individuals receiving active chemotherapy for cancer

- Being within one year out from receiving a hematopoietic stem cell or solid organ transplant
- Untreated HIV infection with CD4 <200
- Primary immunodeficiency
- Taking immunosuppressive medications (e.g., drugs to suppress rejection of transplanted organs or to treat rheumatologic conditions such as mycophenolate and rituximab)
- Taking more than 20mg a day of prednisone for more than 14 days

Consensus Issues
The evidence base included studies that investigated the clearance of COVID-19 infection in relation to vaccination status, symptom presentation (i.e., asymptomatic versus symptomatic), and immunocompromised state (i.e., non-, moderately, or severely immunocompromised). These factors were taken into consideration in recommending the criteria for allowing workers who were previously infected with COVID-19 to return to work.

Despite studies including non, moderately, and severely immunocompromised individuals, the panelists decided to make recommendations that only distinguished severely versus non-severely immunocompromised individuals due to insufficiency of evidence among moderately immunocompromised individuals.

Among asymptomatic, not severely immunocompromised individuals, separate recommendations were made depending on vaccination status. Evidence base including one study showed faster viral clearance and shorter infection duration by two days among fully vaccinated compared to not fully vaccinated individuals. The panelists unanimously voted for a weak recommendation due to indirectness of the evidence, wherein the reference standard used was time to RT-PCR clearance instead of viral culture positivity.

Among severely immunocompromised individuals, the evidence on prolonged viral shedding was an important consideration for the panelists. However, data remains lacking on the duration of infectivity of the virus among this subgroup. The evidence base included only one study on this subgroup and the reference standard for infectivity was RT-PCR instead of viral culture. For this reason, a panelist opined that a test-based criteria for clearance to work would be a more prudent strategy compared to a symptom-based criteria. However, concern on the impracticality of a test-based approach was raised as this may lead to prolonged isolation of patients who continue to shed detectable SARS-CoV-2 RNA on RT-PCR but are no longer infectious. A weak recommendation was made mainly due to the very low certainty of evidence..

PREVIOUS RECOMMENDATION

Symptom-based strategy:

We recommend the use of symptom-based strategy for the discontinuation of isolation and return to work clearance of the following:

a. Asymptomatic adults who are not severely immunocompromised if they fulfill the following: *(Very low certainty of evidence; Strong recommendation)*
   - remained asymptomatic throughout their infection
   - 10 days have passed from the first positive viral diagnostic test (RT-PCR or rapid antigen)

b. Adults who had mild to moderate COVID-19 who are not severely immunocompromised if they fulfill the following: *(Very low certainty of evidence; Strong recommendation)*
   - afebrile for at least 24 hours without use of antipyretic medications
   - respiratory symptoms have improved (cough, shortness of breath)
   - 10 days have passed from symptom onset

c. Adults who had severe to critical COVID-19 who are not severely immunocompromised if they fulfill the following: *(Very low certainty of evidence; Strong recommendation)*
   - afebrile for at least 24 hours without use of antipyretic medications
   - respiratory symptoms have improved (cough, shortness of breath)
   - 21 days have passed from symptom onset

A repeat negative RT-PCR test is no longer needed for discharge of immunocompetent patients with probable or confirmed COVID-19 regardless of severity, because, in most cases, it results in prolonged isolation of patients who continue to shed detectable SARS-CoV-2 RNA but are no longer infectious.

Test-based strategy

We suggest the use of test-based strategy using RT-PCR for the discontinuation of isolation and return to work clearance of the following: *(Very low quality of evidence; Conditional recommendation)*

a. Severely immunocompromised adults
b. Health care workers

if they fulfill the following:

- Afebrile for at least 24 hours without use of antipyretic medications
- Respiratory symptoms have improved (cough, shortness of breath)
- With at least 1 negative RT-PCR test of a respiratory specimen

<u>Severely immunocompromised:</u> Ongoing chemotherapy for cancer, or within one year from receiving a hematopoietic stem cell or solid organ transplant; untreated HIV infection with CD4 count < 200, combined primary immunodeficiency disorder, and receipt of prednisone >20mg/day for more than 14 days, may cause a higher degree of immunocompromised and require actions such as lengthening the duration of work restrictions. Other less immunocompromising conditions include advanced old age, DM, CKD. The degree of immunocompromise is determined by the health care provider, and preventive actions are adapted to each individual and situation.

WHAT'S NEW IN THIS VERSION?

- An updated search was performed to include studies evaluating the relationship of vaccination status on various outcomes related to infectivity or transmissibility.

KEY FINDINGS

- This review included six observational studies that explored the relationship between vaccination status on various outcomes related to infectivity. From this data, the review provides additional recommendations related to the duration of isolation for return-to-work clearance.
- One study found no significant difference (p=0.16) in the proportion of culture-positive results between fully vaccinated and not fully vaccinated individuals (OR 0.67, 95% CI 0.38-1.18). The duration of viral culture positivity between the two groups was comparable (median of 5 days for both) and suggested no significant difference in terms of duration of infectivity (mean difference=0 days). Another study concluded that vaccinated individuals had faster viral clearance by 2 days (5.5 days, 95% credible intervals [CrI] 4.6-6.5) versus 7.5 days for unvaccinated (95% CrI 6.8-8.2 days) and shorter infection duration by 2.3 days (8.7 days, 95% CrI 7.6-9.9) versus 11.0 days (95% CrI 10.3-11.8) for unvaccinated).
- Based on three observational studies, the secondary attack rate was lower by 8.43% (95% CI -18.03%, 1.17%) for fully vaccinated compared to not fully vaccinated individuals, but this difference was not statistically significant (P=0.09).
- Compared to immunocompetent individuals, time to PCR clearance was not significantly different for severely (adjusted hazards ratios [aHR] 0.98, 95% CI 0.84-1.15) and moderately immunocompromised patients (aHR 0.86; 95% CI 0.71-1.05). Delayed time to PCR clearance was seen for specific subgroups of patients: solid organ transplant (aHR 0.64, 95% CI 0.42-0.97), diabetes (aHR 0.82, 95% CI 0.73-0.93), obesity (aHR 0.90, 95% CI 0.83-0.98), rheumatologic disease (aHR 0.90, 95% CI 0.83-0.98), ≥3 comorbidities (aHR 0.73, 95% CI0.60-0.88), older age (aHR 0.996, 95% CI 0.993-0.999).
- The overall certainty of the evidence for each of the outcomes was rated very low. Downgrading occurred due to the risk of bias issues across the included studies, imprecision related to wide confidence intervals and small sample sizes, and inconsistency.

INTRODUCTION

Patients recovering from COVID-19 may remain infectious for a certain period. Thus, it is paramount that they are allowed to return to work only after they have ceased being contagious. The symptom-based strategy has been suggested as a potentially more cost-effective alternative than test-based strategies (e.g., RT-PCR or viral culture) for identifying COVID-19 patients who are no longer infectious and can be allowed to discontinue isolation and return to work.[1]

With the advent of vaccination and the emergence of new and more transmissible variants (e.g., delta variant), recommendations on return-to-work criteria need to be updated. The Department of Health (DOH) of the Philippines has already recommended mass vaccination, especially among the vulnerable and working population as the safety and efficacy of COVID vaccines in reducing the risk of severe illness became more established. As of December 9, 2021, at least 39.5 million Filipinos have been fully vaccinated, with 2.8 million healthcare workers and 17.9

million front liners in essential sectors.[2,3]

Fully vaccinated individuals may still contract breakthrough infections and transmit the disease at the same level as unvaccinated individuals.[4] Whether vaccinated individuals spread the virus for a shorter duration compared to unvaccinated individuals remains uncertain. This review aimed to update recommendations on return-to-work clearance in relation to symptom- versus test-based strategies and duration of isolation, with particular focus on an individuals' vaccination status, COVID-19 symptom presentation, and immunocompromised state.

REVIEW METHODS

A comprehensive search for published articles was conducted on November 25, 2021 in MEDLINE, Cochrane Library, UpToDate, medrxiv.org, WHO trial registry, and ClinicalTrial.gov databases. Free text and keywords related to "COVID-19", "COVID Vaccination", "Delta Variant", and "Transmission" were used. There were no restrictions on the type of vaccine received, number of doses given, age, sex, race, language, and co-morbidities.

The following studies were included: (a) observational studies, non-randomized or randomized clinical trials that investigated the effect of COVID vaccination status on return-to-work guidance for workers previously infected with COVID-19; and (b) observational studies that assessed the difference in disease transmission between vaccinated and unvaccinated individuals, as these would provide evidence that the probability of recovering replication-competent viruses declines faster among vaccinated individuals. These studies would justify shortening the isolation days required before clearing a recovered COVID-19 patient to return to work.

RESULTS

Characteristics of included studies

Evidence from the initial version of this review was obtained from three cohort studies [5-7], two cross-sectional studies [8,9], and two case series.[10,11] In this update, six prospective cohort studies [12-17] were added to the existing evidence base. Of these, one preprint study and one published study from the USA evaluated the difference in viral transmission dynamics between vaccinated and vaccinated individuals. Both were conducted during the delta variant outbreak (up to August 2021). Three studies provided data on secondary attack rates. One study assessed the time to PCR clearance among severely immunocompromised adults.

Six cohort studies were conducted among the general population. All studies involved vaccinated and unvaccinated patients who tested positive for COVID-19 via RT-PCR. The characteristics of these studies are summarized in Appendix 3. The following outcomes were evaluated among vaccinated and unvaccinated individuals: (1) infectivity assessed by viral culture positivity, (2) duration of infectivity (assessed by culture or positive PCR), (3) duration of viral clearance assessed by PCR, (4) difference in cycle threshold levels and viral load, (5) viral load (via cycle threshold values), and (6) secondary attack rates.

Overall summary of methodological quality

The overall certainty of the evidence for each of the outcomes was rated very low. Downgrading occurred due to the risk of bias issues across the included studies,

imprecision related to wide confidence intervals and small sample sizes, and inconsistency.

Summary of results of included studies

A. Duration of infectivity (according to COVID-19 severity)

The likelihood of recovering a viable virus generally declined after the onset of symptoms. A prospective cohort study with 100 COVID-19 patients with different severities by Young et al. estimated the mean duration of viral shedding via RT-PCR at 16.7 days (95% CI 15.2, 18.3). For patients with mild to moderate COVID-19, replication-competent virus has not been recovered after 10 days following symptom onset.[2] The cross-sectional study by van Kampen et al. found that patients that had severe or critical COVID-19 had detectable and viable virus eight days or more since the onset of symptoms, with one patient remaining infectious up to 20 days after symptom onset.[4]

The quality of evidence for the outcome of the duration of infectivity was further degraded to very low due to imprecision from small sample sizes as well as very serious risk of bias concerns secondary to the inclusion of case series designs and variable methods for measuring infectivity.[5,6]

B. Duration of infectivity (according to vaccination status)

The study by Salvatore et al. included 95 eligible incarcerated persons with PCR-confirmed COVID-19 infection, among which 78 (82%) were fully vaccinated and 17 (18%) were partially vaccinated or unvaccinated. Majority of the vaccinated received the Pfizer vaccine (73%), followed by Moderna (18%), and Janssen (9%) vaccines. Viral culture results were available for 842/978 (86.6%) specimens collected.

In the study by Kissler et al. 2021 involving 173 people (90% male) affiliated with the National Basketball Association (NBA), 37 (21.4%) had breakthrough infections or positive PCR results at least two weeks from the receipt of the final dose. Of these 37 breakthrough infections, 25 or 67.6% occurred in delta variant cases and 4 or 10.8% in alpha variant cases. Most breakthrough infections were seen in recipients of the Pfizer vaccine (23-62%), followed by the Janssen vaccine (8-22%). The study assessed viral clearance duration (i.e., time from peak viral concentration to clearance of acute infection) and duration of acute infection (i.e., time from detection to clearance of acute infection).

Viral culture positivity as outcome measure

The study by Salvatore et al. found no significant difference (p=0.16) in the proportion of culture-positive results between fully vaccinated (57/690 or 8%) and not fully vaccinated (18/152 or 12%) individuals (OR 0.67, 95% CI 0.38-1.18). Likewise, the two groups had comparable viral culture positivity (median [MD] 5 days for both) and shortened duration of infection (MD 0 days).

Shorter culture positivity was seen for fully vaccinated participants who received Moderna than those who received Pfizer (p=0.048) or Janssen vaccines (p=0.003). No significant difference was seen between Pfizer and Janssen vaccines (p=0.12).

In contrast, the Kissler 2021 study concluded that vaccinated individuals had faster viral clearance by 2 days (5.5 days, 95% Crl 4.6-6.5) compared to those unvaccinated

(7.5 days, 95% CrI 6.8-8.2 days). Vaccinated individuals also had a shorter infection duration by 2.3 days (8.7 days, 95% CrI 7.6, 9.9] compared to the unvaccinated (11.0 days, 95% CrI 10.3-11.8). Viral clearance was measured with longitudinal quantitative RT-PCR tests using anterior nares or oropharyngeal samples. The certainty of the effect estimates for this study was affected by several factors including imprecision (a small sample size preventing sufficient subgroup analysis according to variant or vaccination status) and risk of bias (most participants were healthy young men athletes, no systematic tracking of symptoms, and no testing for the presence of infectious virus).

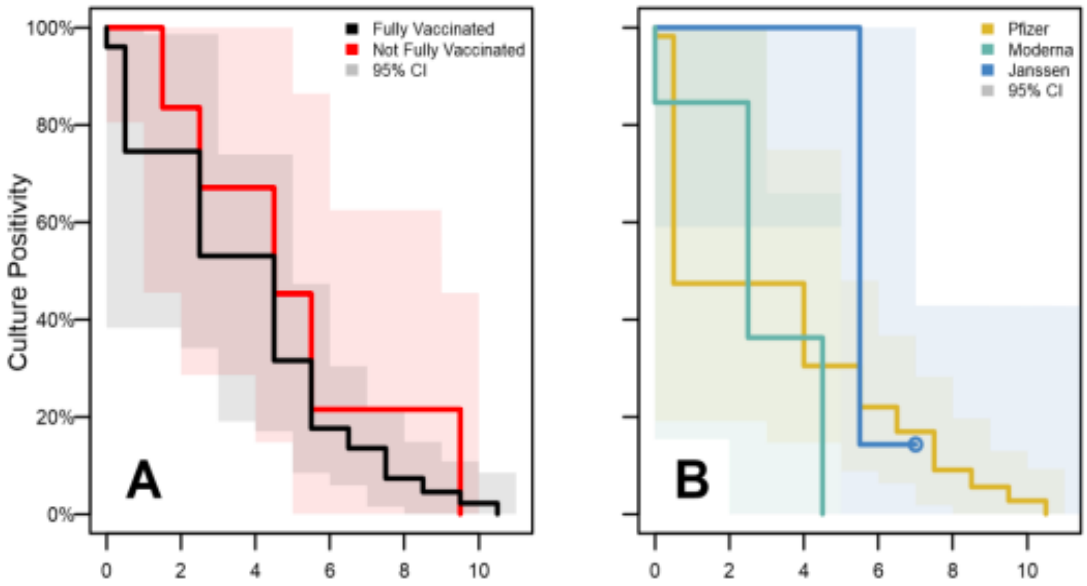

Figure 1. SARS-CoV-2 viral culture test positivity survival curves according to (A) vaccination status and (B) vaccine type received (Salvatore et al., 2021)

C. Secondary attack rate for vaccinated and unvaccinated individuals

Secondary attack rate refers to the probability that an infection occurs among susceptible people within a specific group (i.e., household or close contacts). This metric reflects how likely it is for vaccinated and unvaccinated COVID-19 patients to transmit the disease to their household contacts.[18]

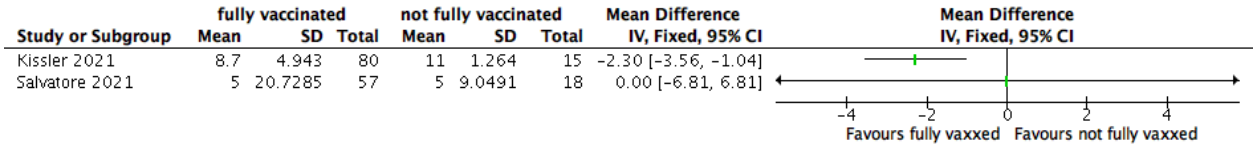

Figure 2. Duration of infectivity between vaccinated and unvaccinated individuals

Three observational studies (n=249,036) showed lower secondary attack rates for vaccinated individuals (MD -8.43%, 95% CI -18.03%, 1.17%). However, interval estimates for all three studies were imprecise and crossed the unity line. Likewise, the pooled effect estimate was also imprecise, suggesting that this difference is not statistically significant between the two groups.[12,13,16]

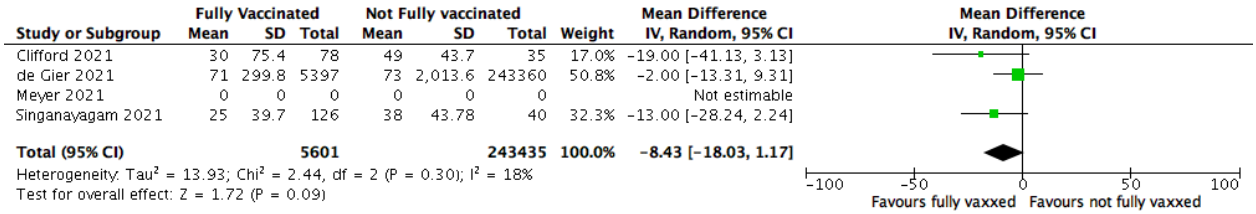

Figure. 3 Secondary attack rate between vaccinated and unvaccinated individuals

D. Duration of infectivity: immunocompromised individuals

A March 2021 prospective cohort study in the USA by Epstein et al. provided data related to the time to achieve SARS-CoV-2 PCR clearance among 3,758 severely immunocompromised adults. On average, patients were tested at least three times with PCR. The certainty of evidence for this outcome was low as the study had sampling issues and did not use viral culture studies to assess infectivity.

The median time to PCR clearance (interquartile range) was 22 days (4–34) for the severely immunocompromised, 20 days (8–33) for the moderately immunocompromised, and 16 days (6–29) for the non-immunocompromised. Adjust hazards ratios (aHR) showed a delayed time to PCR clearance for the following subset of patients: solid organ transplant (aHR 0.64, 95% CI 0.42-0.97), diabetes (aHR 0.82, 95% CI 0.73-0.93), obesity (aHR 0.90, 95% CI 0.83-0.98), rheumatologic disease (aHR 0.90, 95% CI 0.83-0.98), ≥3 comorbidities (aHR 0.73, 95% CI 0.60-0.88), and older age (aHR 0.996, 95% CI 0.993-0.999). Compared to immunocompetent individuals, time to PCR clearance was similar for severely (aHR 0.98, 95% CI 0.84-1.15) and moderately immunocompromised patients (aHR 0.86, 95% CI 0.71-1.05).

E. Impact of a test-based strategy on costs and acute care length of stay

Low-quality evidence from a cohort study [6] involving 11 hospitalized veterans concluded that testing-based isolation practices generated a cumulative 123 excess bed days of care and $454,669 (~Php 22,069,633) in additional cost under a test-based rather than symptom-based isolation strategy. The median excess acute-care length of stay was eight days (range 0–27 days). Among ten patients with Allocation Resource Center (ARC) financial data, median excess cost was $39,067 (range $0–$111,505 or Php 0-5,412,452) and cost per additional inpatient day was $3,645 (range $2,998–$5,335 or Php 145,523-258,961). In total, 275 bed days and $952,983 (Php 46,257,794) were spent in acute care, of which >40% could have been avoided using new symptom-based recommendations.[6] The certainty of this estimate was rated very low due to the indirectness from using data only on severe, elderly patients.

F. Impact of symptom-based strategy on days of work lost

Low-quality evidence from one cohort study [7] by Shenoy et al. estimated that time plus symptom-based criteria would have resulted in 4,097 fewer lost workdays, or an average of 7.2 fewer days of work lost per employee.[7] In this study, healthcare workers (n=425) diagnosed and treated for COVID-19 had prolonged recovery of viral RNA. The average interval between the first positive to first negative RT-PCR tests was 17 days, while the average interval between the first positive to second negative RT-PCR test was 19.5 (SD 6.1) days. The median time to work clearance was 29 days (95% CI 28-31). Using a test-based strategy resulted in a median time to return to work of 19 days. The quality of evidence for this outcome was downgraded due to indirectness.

RECOMMENDATIONS FROM OTHER GROUPS

Department of Health of the Philippines

As of October 7, 2021, DOH has released an IATF Resolution No. 142 s.2021 outlining return to work guidelines for employees infected with COVID-19.[19] A ***symptom-based strategy is currently used***, with different duration of isolation days prescribed for individuals with varying vaccination status (e.g., 7 days for fully vaccinated close contacts, 14 days for unknown vaccine status).

US Centers for Disease Control and Prevention (CDC)

As of September 10, 2021, the US CDC has updated their Interim Guidance for Managing Healthcare Personnel (HCP) with SARS-CoV-2 Infection or Exposure to SARS-CoV-2.[20] A ***symptom-based strategy is still preferred in most clinical situations*** for determining when HCP with SARS-CoV-2 infection could return to work. No guidelines specific for vaccinated individuals are currently made.

As of December 23, 2021, this guidance by CDC was updated due to the SARS-CoV-2 Omicron variant. In this update, asymptomatic HCP with higher-risk exposures will be allowed to return to work if they have received all COVID-19 vaccine doses including booster dose, and remain asymptomatic or test negative for SARS-CoV-2. For HCP who test positive for SARS-CoV-2, they are required to quarantine for 10 days regardless of vaccination status. Quarantine duration may be reduced to 7 days if HCPs have a negative test (taken within 48 hours before return to work), if asymptomatic or mildly symptomatic (with improving symptoms).

UK Health Department

As of November 30, 2021, the United Kingdom Health Department has released a guideline for the management of staff and exposed patients/residents in health and social care settings. [21] Return to work criteria are based on a ***combination of both test-based and symptom-based strategies***. No distinction was made based on vaccination status.

Australian Health Department

As of November 2021, Health Direct, a government-funded service of the Australian Health Department, has published the following recommendation.[22] A ***symptom-based strategy is generally used***, with a provision for shortening the required isolation days for PCR-confirmed asymptomatic cases (10 to 7 days for fully vaccinated, 14 to 10 days for other vaccine status) and symptomatic cases (14 to 10 days for fully vaccinated, 20 to 14 days for other vaccine status). A test-based strategy with ***two repeat PCR tests is recommended for significantly immunocompromised individuals*** regardless of vaccination status.

RESEARCH GAPS

Currently, there are no ongoing studies about the effect of vaccination on outbreak infection and how it may affect the strategy on the criteria for allowing workers to return to work listed in the NIH-U.S. NLM's *ClinicalTrials.gov* and Cochrane Library. However, some studies can indirectly support earlier return to work through a decrease in transmission. These studies are listed in Appendix 6.

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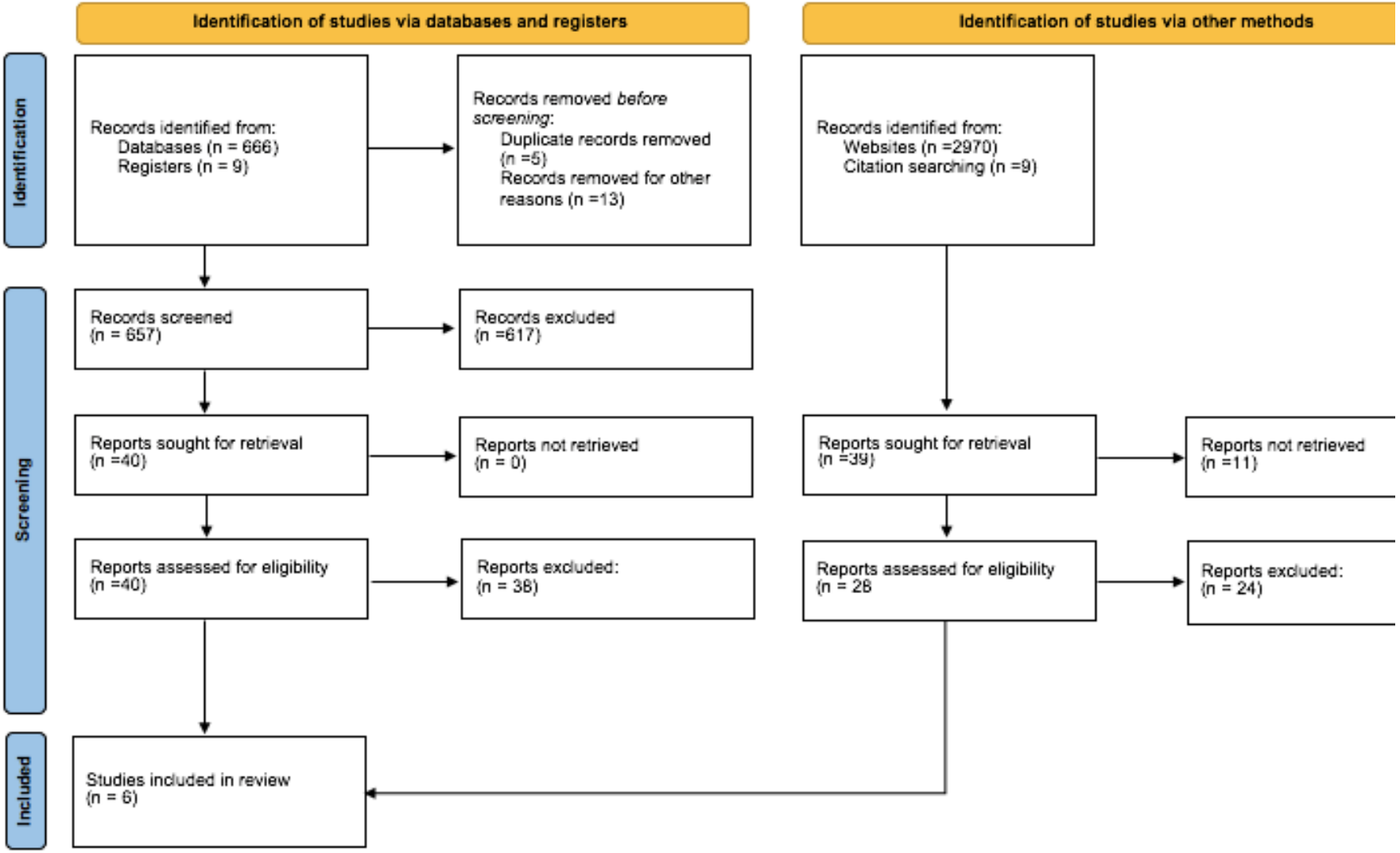
Appendix 1. Evidence to Decision

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (3)					In the advent of vaccination and emergence of new and more transmissible variants (e.g., delta variant), recommendations on return-to-work criteria need to be updated.
Benefits	Large (1)	Moderate (1)	Small	Uncertain (1)			Fully vaccinated individuals showed shorter duration of infection (2.26 days) using RT-PCR positivity as the outcome measure. No difference in duration of culture positivity was noted between fully vaccinated and unvaccinated /partially vaccinated groups.No significant differences were also noted in terms of average Ct values [MD 1.98, 95% CI -1.27, 5.23]), viral load, secondary attack rate (MD 8.4, 95% CI -18.0, 1.17).
Harms	Large	Moderate (1)	Small	Uncertain			Very low certainty of evidence suggests that a test-based strategy is associated with higher false negative rates after 9 days from symptom onset, higher excess costs and length of stay for hospitalized patients, and greater lost workdays.
Balance of Benefits and Harms	Favors the use of criteria (1)	Probably favors the use of criteria (1)	Does not favor the use of criteria (1)				
Certainty of Evidence	High	Moderate (1)	Low	Very low (3)			For CT level, the overall certainty of evidence is very low because of its indirectness as it is just a surrogate marker for viral load. For days of infectivity, the overall certainty is very low due to insufficient follow up. For secondary attack rate, the overall certainty is very low due to imprecision. Very low certainty of evidence suggests that a test-based strategy is associated with higher false negative rates after 9 days from symptom onset, higher excess costs and length of stay for hospitalized patients, and greater lost workdays.
Accuracy	Very Accurate	Accurate (1)	Inaccurate (1)	Very Inaccurate	Uncertain (1)		
Values	Important uncertainty or variability	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability	No important uncertainty or variability (1)			No research evidence found.
Resources Required	Uncertain (1)	Large cost	Moderate Cost	Negligible cost or savings	Moderate savings (1)	Large savings(1)	RT-PCR costs Php 3800-4500. Days in isolation: 275 bed days and $952,983 (Php 46,257,794) were spent in acute care, of which >40% could have been avoided using new symptom-based recommendations.
Certainty of evidence of required resources	No included studies (2)	Very low	Low (1)	Moderate	High		
Cost effectiveness	No included studies (2)	Favors using comparator	Does not favor either using the criteria or the comparator	Favors the criteria (1)			No local data on economic evaluation of RT PCR. No data as well on the cost of isolation facility and days of income lost.
Equity	Uncertain (2)	Reduced	Probably no impact	Increased (1)			
Acceptability	Uncertain (2)	No	Yes (1)				
Feasibility	Uncertain (1)	No	Yes (2)				

Appendix 2. Search Yield and Results



Appendix 3. Characteristics of Included Studies

Table 1. Characteristics of included studies in updated review

First Author- Year- Setting	Type of Study	Population Characteristics	Sample Size	Control	Intervention	Outcome
Clifford, Samuel 2021 United Kingdom	Prospective Cohort	213 index samples and 312 contacts	525	Unvaccinated	Vaccinated	Vaccine effectiveness, Vaccine effectiveness to infection, vaccine effectiveness to transmission, Secondary attack rate
De Gier, Brechje 2021 Netherlands	Retrospective Cohort	7,771 contacts of 4,921 index cases. Of the index cases 1,740 were fully vaccinated (35.4%) and 2,641 (53.7%) were unvaccinated. Of the contacts 4,189 (53.9%) were fully vaccinated and 2,941 were unvaccinated (37.8%)	12,692	Unvaccinated	Vaccinated	Vaccine effectiveness against transmission Vaccine effectiveness against infection
Kissler, Stephen 2021 Boston, USA	Retrospective Cohort	173 with acute SARS COV 2 from National Basketball Association	173	Unvaccinated	Vaccinated	Mean viral trajectories among alpha and delta infection Viral dynamics between vaccinated and unvaccinated
Salvatore, Phillip 2021 USA	Prospective cohort	95 participants from Texas Federal prison, 78 fully vaccinated, 17 partially vaccinated	95	Partially vaccinated	Vaccinated	RT PCR positivity, Viral culture positivity
Singana-yagam, Anika 2021 United Kingdom	Prospective cohort	471 index case, 602 community contact	1,073	Unvaccinated	Vaccinated	Secondary attack rate, Vaccine effectiveness
Epstein, Rachel 2021 Boston, USA	Prospective cohort	433 immunocompromised 3322 immunocompetent	3,758	Unvaccinated	Vaccinated	PCR clearance

Table 2. Characteristics of included studies from previous review

First Author- Year- Setting	Type of Study	Population Characteristics	Sample Size	Intervention		Outcome
				Reference	Index	
Young, Barnaby 2020 Singapore	Prospective Cohort	COVID-19 patients, mean age was 46 years (95% confidence interval [CI] 43-49), males comprised 56 (56%) and 38 (38%) had comorbidities. Median time from symptom onset to hospital admission was 5.3 days (interquartile range (IQR) 1.3-8).	100	Viral Culture	RT-PCR	Cumulative frequency of PCR Cycle threshold (Ct) value and viral culture, Kaplan Meier plot of time to cessation of viral shedding by duration of illness stratified by disease severity, IgG and IgM readings stratified by disease severity and time to first positive antibody level.
Bullard, Jared 2020 Canada	Retrospective cross sectional study	90 COVID-19 RT-PCR positive samples	90 samples	Viral Culture	RT-PCR	Infectivity, CT values and symptom to test, comparison of symptom onset to test to the probability of successful cultivation on Vero cells
Van Kampen, Jeroen 2021 Netherlands	Cross sectional study	129 hospitalized individuals with COVID-19, for whom at least one virus culture from a respiratory tract sample was available. Of these, 89 patients (69.0%) had been admitted to intensive care and the remaining 40 patients (31.0%) were admitted to the medium care. Thirty patients were immunosuppressed (23%) of whom 19 (14.7%) were non- severely immunocompromised and 11 (8.5%) were severely immunocompromised	129	Viral Culture	RT-PCR, Antibody titers	Duration of symptoms for infectious virus shedding, key determinants for infectious virus shedding and the probability of isolating a virus based on the levels of antibody titer
Aydillo, Teresa 2020 New York	Case Series	20 immunocompromised patients with COVID-19. Of the 20 patients, 15 were receiving active treatment or chemotherapy. Eleven had severe Covid-19.	20	Viral Culture	RT-PCR	Viability of virus, variant identification
Tarhini, Hassan 2021 United States	Case Series	3 deeply immunocompromised patients with COVID-19	3	Viral Culture	RT-PCR	Viability and duration of viral shedding
Wu, Chenwei 2020 Washington	Cohort	70 veterans diagnosed with COVID-19 with 29 (41.4%) requiring hospitalization. All were male, with a median age of 74 years (range, 68–100). In addition, 9 (81.8%) had severe illness and 1 (9.1%) was immunocompromised due to solid-organ transplantation	11	Test based strategy	Symptom based strategy	Estimated excess acute-care length of stay and extra cost **Note:** Excess acute-care length of stay was defined as the difference between the true discharge date and the discharge eligibility date. Excess cost of care was determined by multiplying the “excess” fraction of a patient’s stay by the total acute-care cost reported by the Veterans Health Administration (VHA) Allocation Resource Center (ARC). ARC costs are based on the managerial cost accounting system used widely in VHA cost-effectiveness research, adjusted for administrative overhead and special fees. Emergency department and intensive care costs were excluded.
Shenoy, Erica 2020 Massachusetts	Cohort	1049 COVID-19 positive health care workers	1049	Test based strategy	Symptom based + time based strategy	mean and median number of days from first positive to first negative test, Kaplan-Meier estimate of median time to clearance, test-based clearance, additional days of work lost per employee

						than would have been accrued using the time plus symptom-based clearance method. **Note:** Lost work days were calculated comparing a time plus symptom–based clearance to the test-based protocol. For the former, it was assumed that the day the employee was tested under test-based clearance indicated the resolution of symptoms.
Duan, Ping 2020 China	Cross sectional study	4729 asymptomatic subjects were included in the study. The male-to-female ratio in the total population is about 1:2, with a centralised age distribution between 18.0 and 60.0 years, with a median age of 33.0 (IQR: 28.0–47.0) years. Medical staff (62.93%) accounted for the largest proportion, followed by rear-service personnel (30.73%) and administrative staff (6.34%).	4729	RT-PCR	Symptom based CT Scan Antibody levels	% abnormal initial physical examination, false negative rate

Appendix 4. GRADE Evidence Profile

Vaccination compared to none in decreasing the duration of isolation among COVID-confirmed

Table 1. Decreasing Days of Infectiousness

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	
							Without vaccination	With vaccination		Risk without vaccination	Risk difference with vaccination
Secondary Attack Rate											
249,036 (3 observational studies)	Not serious	Not serious	Not serious	Serious [a]	None	⊕◯◯◯ Very low	243,435	5,601	-	The mean secondary attack rate was 0	MD **8.43 lower** (18.03 lower to 1.17 higher)
Days of Infectivity											
170 (2 observational studies)	Serious[b]	Serious[c]	Not serious	Serious[d]	None	⊕◯◯◯ Very low	Kissler 2021 study concluded that vaccinated individuals had faster viral clearance by 2 days (5.5 days, 95% CrI 4.6, 6.5) compared to those unvaccinated (7.5 days, 95% CrI 6.8, 8.2 days). Vaccinated individuals also had shorter infection duration by 2.3 days (8.7 days, 95% CrI 7.6, 9.9] compared to the unvaccinated (11.0 days, 95% CrI 10.3, 11.8). Salvatore et al. found no significant difference (p=0.16) in the proportion of culture-positive results between fully vaccinated (57/690 or 8%) and not fully vaccinated (18/152 or 12%) individuals (OR 0.67, 95% CI 0.38, 1.18). Likewise, the two groups had comparable viral culture positivity (median [MD] 5 days for both) and shortened duration of infection (MD 0 days).				

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

Explanations

[a]. the confidence interval crosses the line of unity

[b]. the study of Salvatorre was graded with fair quality based on New Castle Ottawa due to short follow up duration, in the study of Kissler the population is also not comparable to the general population for it consist of healthy young men.

[c]. the two studies have different outcomes, Salvatore has same duration of infectivity while on Kissler it favored vaccination with less than 2.3 days

[d]. the studies were imprecise, CI crosses line of unity

Table 2. Duration of Infectivity among Immunocompromised and Immunocompetent

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	
							Immunocompetent	Immunocompromised		Risk if immunocompetent	Risk if immunocompromised
Time to PCR clearance											
3,758 (1 observational study)	not serious	not serious	not serious	Not serious	none	⨁⨁◯◯ low	3,222	436	-	The mean time to PCR clearance was 0	MD **0.98 higher** (0.84 higher to 1.15 higher)

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

Table 3. Symptom- versus test-based criteria

OUTCOME	CERTAINTY ASSESSMENT							Effect estimate	Test accuracy CoE
	No of studies	Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias		
Duration of infectivity	5 studies (342 patients)	Cross-sectional (cohort type accuracy study), case series	Very serious[a,b]	Serious	Not serious	Not serious	None	**Mild-moderate: virus cannot be cultured day 10 Severe: virus can be cultured at day 10-20 Immunocompromised: prolonged viral shedding up to 4 months**	⨁◯◯◯ VERY LOW
Exces costs	1 study (11 patients)	Cross-sectional (cohort type accuracy study),	Very serious[b,c]	Serious	Not serious	Not serious	None	**$454,669 (~Php 22,069,633) Excess cost under a testing-based rather than symptom-based isolation strategy**	⨁◯◯◯ VERY LOW
Excess acute care length of stay	1 study (11 patients)	Cross-sectional (cohort type accuracy study),	Very serious[b,c]	Serious	Not serious	Not serious	None	**Median: 8 days (range 0-27)**	⨁◯◯◯ VERY LOW
Days of work lost	1 study (1,049 patients)	Cross-sectional (cohort type accuracy study),	Very serious[c,d,e]	Serious	Not serious	Not serious	None	**Average of 7.2 fewer days of work lost per employee**	⨁◯◯◯ VERY LOW
False negative RT-PCR	1 study (4,729 patients)	Cross-sectional (cohort type accuracy study),	Very serious[d,f]	Serious	Not serious	Not serious	None	**170/72 (98.8%)**	⨁◯◯◯ VERY LOW

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

Explanations

[a]. Study design
[b]. Small sample size
[c]. Theoretical assumptions
[d]. Selection bias
[e]. Unclear index test
[f]. Problem with interpretation of index test

Appendix 5. Detailed Study Appraisal

Table 1. New Castle Ottawa Scale

Study	Selection					Comparability		Outcomes		Total quality score
	Representativeness of exposed Cohort	Selection of non-exposed cohort	Ascertainment of Exposure	Demonstration that outcome of interest was not present at the start of study	Adjust for the most important risk factors	Adjust for other risk factors	Ascertainment of outcome	Follow up length	Loss to follow up rate	
Clifford 2021	1	1	1	1	1	1	1	1	1	9
De Gier 2021	1	1	1	1	1	1	1	1	1	9
Kissler 2021	1	1	0	1	1	1	1	1	1	8
Salvatore 2021	1	1	1	1	1	1	1	0	1	8
Singanayagam 2021	1	1	1	1	1	1	1	1	1	9
Epstein 2021	1	1	1	1	1	1	1	1	1	9

Appendix 6. Characteristic of Ongoing Studies

Question: Can vaccination decrease the duration of infectivity of COVID 19 hence allowing earlier return to work?

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
A Study of SARS CoV-2 Infection and Potential Transmission in Individuals Immunized With Moderna Vaccine NCT04811664 Match 23, 2021	Experimental: Immediate Vaccination Participants will receive Moderna COVID-19 Vaccine in 100 mcg dose given as 0.5 ml IM into the deltoid muscle on Day 1 and Day 29. Experimental: Immediate Vaccination Participants will receive Moderna COVID-19 Vaccine in 100 mcg dose given as 0.5 ml IM into the deltoid muscle on Day 113 and Day 141.	Control: Vaccine Declined Participants who prefer not to be vaccinated, If requested, participant will be offered vaccine if they have not received vaccine outside of the study	- 12,000 participants randomized 1:1 >Immediate Vaccination -Group 1 (at Months 0 and 1) or Standard of Care -Group 2, with vaccination given at Months 4 and 5 if not received off-study previously. -Up to an additional 6,000 participants will be enrolled into the Vaccine Declined *RECRUITING*	Primary Outcome Measures: - Efficacy of Moderna COVID-19 Vaccine against SARS-CoV-2 infection -Effect of Moderna COVID-19 Vaccine on peak nasal viral load Secondary Outcome Measures: -Impact on secondary transmission -Prevent serologically confirmed infection -Prevent disease confirmed PCR test and symptoms -Magnitude of viral load over time -Efficacy regardless of baseline serostatus -Immunogenicity -Immune response correlating with acquisition, viral load, secondary infection -Efficacy against asymptomatic infection -Efficacy on Viral load -Efficacy on Secondary transmission
Long-Term Experience and Health Effects of COVID-19 NCT04477902 July 2020	None *Observational		1. 18 years of age or older 2. Any gender specification 3. Has consented to proceed with survey 4. Is able to complete the survey via email on a regular basis 5. COMPLETED	Primary Outcome Measures Longitudinal -To gain on-going COVID-19 feedback/data to drive timely action locally and nationally in order to mitigate transmission -looking on Risk reduction and Quality of life
COVID 19 Infection in After Vaccination NCT05033834 September 5, 2021	Fully vaccinated	Partially vaccinated	Patients 18 years old and above of both genders. -Received at least one dose of COVID-19 registered vaccines. -Diagnosed COVID-19 positive after vaccination by real time PCR (confirmed case) or combined clinical and radiological diagnosis (possible case). NOT YET RECRUITING	Primary Outcome - assess the prevalence of COVID-19 infection after vaccination Secondary Outcome -evaluate the severity of infection after vaccination -Predict possible risk factors of post vaccination infection (adherence to protective measures)
National Cohort Study of Effectiveness and Safety of SARS-CoV-2 Vaccines (ENFORCE) NCT04760132 February 18, 2021	Cominarty Vaccine Moderna Astra-Zeneca	None	-Male or female eligible for SARS-CoV-2 immunization (as defined by SST in the national vaccination plan) -willing and able to comply with trial protocol (re-visits and biological samples) RECRUITING	Primary Outcome -Assessment of the effectiveness of citizens being vaccinated with one of the SARS-CoV-2 vaccine -minimal protective neutralising antibody titre Secondary Outcome

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
				-Number of beakthrough infections in the 24 months period will be used to compare the effectiveness between the vaccines -Assessment of the safety of the vaccines -Assessment of any Adverse Event

Appendix 7. Guidelines from Other Groups

Table 1. DOH Return to Work Criteria (IATF Resolution No. 142; October 7, 2021)

Population	Criteria for Return to Work	
Unknown Vaccine status with Close contacts	Fourteen (14)-day quarantine has been completed regardless of negative test result	
Fully vaccinated individuals with Close Contact	Seven (7) day- quarantine period, provided that the individual remains asymptomatic for the duration of the seven-day period with the first day being the date immediately after the last exposure	
Suspect, probable or confirmed cases, regardless of vaccine status	Asymptomatic	Ten (10)-day isolation have passed from the first viral diagnostic test and remained asymptomatic throughout their infection
	Mild to Moderate COVID-19 confirmed	Ten (10)-day isolation have passed from onset of the first symptom, respiratory symptoms have improved (cough, shortness of breath), AND have been afebrile for at least 24 hours without use of antipyretic medications
	Severe and Critical COVID-19 confirmed	Twenty-one (21)-day isolation has passed from onset of the first symptom, respiratory symptoms have improved (cough, shortness of breath) AND have been afebrile for at least 24 hours without the use of antipyretic medications

Table 2. Interim Guidance for Managing Healthcare Personnel with SARS-CoV-2 Infection or Exposure to SARS-CoV-2 (CDC; Sep 10, 2021)

Population	Criteria
Symptom-based strategy	
Asymptomatic (NOT moderately to severely immunocompromised)	• At least 10 days have passed since the date of their 1st positive viral diagnostic test
Mild to moderate (NOT moderately to severely immunocompromised)	• At least 10 days have passed *since symptoms first appeared* **and** • At least 24 hours have passed *since last fever* without the use of fever-reducing medications **and** • Symptoms (e.g., cough, shortness of breath) have improved
Severe to critical (Moderately to severely immunocompromised)	• At least 10 days and up to 20 days* have passed *since symptoms first appeared* **and** • At least 24 hours have passed *since last fever* without the use of fever-reducing medications **and** • Symptoms (e.g., cough, shortness of breath) have improved • Consider consultation with infection control experts
Test-based strategy	
Symptomatic	• Resolution of fever without the use of fever-reducing medications **and** • Improvement in symptoms (e.g., cough, shortness of breath), **and** • Results are negative from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens) tested using an FDA-authorized laboratory-based nucleic acid amplification test (NAAT) to detect SARS-CoV-2 RNA
Asymptomatic	• Results are negative from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens) tested using an FDA-authorized laboratory-based nucleic acid amplification test (NAAT) to detect SARS-CoV-2 RNA

NOTES:
1. HCP who are moderately to severely immunocompromised may produce replication-competent virus beyond 20 days after symptom onset or, for those who were asymptomatic throughout their infection, the date of their first positive viral test.
2. After returning to work, HCP should self-monitor for symptoms and seek re-evaluation from occupational health if symptoms recur or worsen.

Work Restrictions for HCP With SARS-CoV-2 Infection and Exposures

HCP are considered "boosted" if they have received all COVID-19 vaccine doses, including a booster dose, as recommended by CDC. HCP are considered "vaccinated" or "unvaccinated" if they have NOT received all COVID-19 vaccine doses, including a booster dose, as recommended by CDC.

For more details, including recommendations for healthcare personnel who are immunocompromised, refer to Interim Guidance for Managing Healthcare Personnel with SARS-CoV-2 Infection or Exposure to SARS-CoV-2 (conventional standards) and Strategies to Mitigate Healthcare Personnel Staffing Shortages (contingency and crisis standards).

Work Restrictions for HCP With SARS-CoV-2 Infection

Vaccination Status	Conventional	Contingency	Crisis
Boosted, Vaccinated, or Unvaccinated	10 days OR 7 days with negative test†, if asymptomatic or mildly symptomatic (with improving symptoms)	5 days with/without negative test, if asymptomatic or mildly symptomatic (with improving symptoms)	No work restriction, with prioritization considerations (e.g., asymptomatic or mildly symptomatic)

Work Restrictions for Asymptomatic HCP with Exposures

Vaccination Status	Conventional	Contingency	Crisis
Boosted	No work restrictions, with negative test on days 2‡ and 5–7	No work restrictions	No work restrictions
Vaccinated or Unvaccinated, even if within 90 days of prior infection	10 days OR 7 days with negative test	No work restriction with negative tests on days 1‡, 2, 3, & 5–7	No work restrictions (test if possible)

†Negative test result within 48 hours before returning to work

‡For calculating day of test: 1) for those with infection consider day of symptom onset (or first positive test if asymptomatic) as day 0; 2) for those with exposure consider day of exposure as day 0

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Table 3. Guideline for Management of Staff and Exposed Patients/Residents in Health and Social Care Settings (UKHD; Nov 30, 2021)

Population	Test Result	Return to Work Criteria
Symptomatic	Negative	• Medically fit to return • Subject to discussion with their line manager or employer and a local risk assessment
	Positive	• Medically fit to return • 10-day isolation period has ended • Afebrile for 48 hours without the use of medication to control fever
	Inconclusive	• Continue to self-isolate • Do another PCR test • Can return to work after isolation period has ended OR if repeat PCR is negative
Asymptomatic	Positive PCR or LFD self-antigen test followed by PCR	• 10-day isolation period has ended • Remain asymptomatic • If symptoms develop during the 10-day isolation period, self-isolate for 10 days form day of symptom onset

Table 4. Australian Health Department

Population	Test Result	Return to Work Criteria
Symptomatic	Fully vaccinated	• 14 days have passed since symptoms began **and** • No fever for past 72 hours **and** • Substantial improvement in respiratory symptoms of acute illness **and** • Patient is not significantly immunocompromised OR • At least 10 days have passed since symptoms began • Two consecutive negative PCR tests taken at least 24 hours apart from day 7 from symptom onset
	Unvaccinated, partially vaccinated, or unknown vaccine status	• 20 days have passed since symptoms began **and** • No fever for past 72 hours **and** • Substantial improvement in respiratory symptoms of acute illness **and** • Patient is not significantly immunocompromised OR • At least 14 days have passed since symptoms began • Two consecutive negative PCR tests taken at least 24 hours apart from day 10 from symptom onset
Asymptomatic	Fully vaccinated	• Completed 10 days of isolation since 1st positive PCR test • No symptoms have developed during the isolation period • Earlier release may be supported by some jurisdictions if PCR test is negative on the 7th day and no symptoms have developed throughout the 7-day isolation period
	Unvaccinated, partially vaccinated, or unknown vaccine status	• Completed 14 days of isolation since 1st positive PCR test • No symptoms have developed during the isolation period • Earlier release may be supported by some jurisdictions if PCR test is negative on the 10th day and no symptoms have developed throughout the 10-day isolation period
Significantly immune-compromised	Any vaccination status	• PCR tests are negative on at least 2 consecutive respiratory specimens collected at least 24 hours apart after day 7 from onset of symptoms

Q14. Among individuals suspected of COVID-19, how accurate are thoracic imaging modalities compared to RT-PCR alone in diagnosing COVID-19?

As of 13 December 2021

RECOMMENDATIONS

Chest X-Ray

We suggest against the use of chest x-ray to diagnose COVID-19 infection among asymptomatic individuals. *(Very low certainty of evidence; Weak recommendation)*

We suggest chest x-ray to facilitate rapid triage, infection control, and clinical management among any of the following: *(Very low certainty of evidence; Weak recommendation)*

- Patients with mild features of COVID-19 at risk for progression
- Patients with moderate to severe features of COVID 19
- Patients with symptoms of at least 5 days duration

Lung Ultrasound

We suggest against the use of lung ultrasound alone in diagnosing patients with suspected COVID-19 infection. *(Very low certainty of evidence; Weak recommendation)*

Chest CT Scan

We suggest against the routine use of CT scan for diagnosing COVID-19 among suspected patients with COVID-19 presenting at the emergency department if RT-PCR testing is readily available with timely results. *(Very low certainty of evidence; Weak recommendation)*

If RT-PCR is not available, we suggest using non-contrast chest CT scan for symptomatic patients suspected of having COVID-19 to guide early triage and management under the following conditions: *(Very low certainty of evidence; Weak recommendation)*

- Mild COVID-19 patients who are at risk for progression
- Moderate to severe COVID-19 patients

Consensus Issues

The panel was unanimous against the use of chest x-ray and lung ultrasound in diagnosing COVID-19 due to the widespread availability of alternatives, such as antigen testing, even in the absence of RT-PCR. Additionally, the evidence base showed that detecting COVID-19 through these imaging modalities are dependent on the experience of the reader. However, a weak recommendation was decided since the evidence did not compare these imaging modalities with rapid antigen tests. The panel was also unanimous in recommending chest x-ray to facilitate triage, infection control, and clinical management, especially in the absence of RT-PCR and rapid antigen tests, due to the widespread availability and rapid results of chest x-ray. A weak recommendation was made, however, since the accuracy of this modality varies depending on the experience of the reader.

Similarly, the panel was for the use of non-contrast chest CT scan in guiding early triage and clinical management if RT-PCR is not available. A weak recommendation for this was made due to concerns on its risk of radiation and cost, and the evidence base including studies conducted abroad.

PREVIOUS RECOMMENDATION

Chest X-Ray

We suggest against the use of chest x-ray to diagnose COVID-19 infection among asymptomatic individuals *(Very low quality of evidence; Conditional recommendation).*

We suggest chest x-ray to facilitate rapid triage, infection control and clinical management among any of the following *(Very low quality of evidence; Conditional recommendation)*:

- Patients with mild features of COVID 19 at risk for progression
- Patients with moderate to severe features of COVID 19
- Patients with symptoms of at least 5 days duration

Consensus Issues

The use of chest X-ray to diagnose COVID-19 infection among asymptomatic individuals was not suggested due to the very low quality of evidence related to its diagnostic accuracy. High heterogeneity across studies was also observed and the studies reviewed did not perform subgroup analysis according to severity of COVID-19. However, chest x-ray is still suggested for specific instances as there would be a high yield in detecting significant pulmonary abnormalities in these settings.

Lung Ultrasound

We suggest against the use of lung ultrasound alone in diagnosing patients with suspected COVID-19 infection. *(Low quality of evidence, Conditional recommendation)*

Consensus Issues

Majority of the panelists voted for a conditional recommendation against lung ultrasound alone due to the low quality of evidence related to its diagnostic accuracy. Some panelists argued that a strong recommendation against the use of lung ultrasound alone in diagnosing suspected COVID-19 patients should be made since it has not been found to be as accurate as the current gold standard, which is RT-PCR. Despite its limitations, lung ultrasound is still considered a valuable prognostic tool to assess clinical deterioration as it can predict the presence of abnormalities in the lung findings of COVID-19 patients.

Chest CT Scan

We suggest against the routine use of CT scan for diagnosing COVID-19 among suspected patients with COVID-19 presenting at the emergency department if RT-PCR testing is readily available with timely results. *(Very low quality of evidence; Conditional recommendation).*

If RT-PCR test is not available, we suggest using non-contrast chest CT scan for symptomatic patients suspected of having COVID-19 to guide early triage and management under the following conditions *(Very low quality of evidence; Conditional recommendation)*:

- Mild COVID-19 patients who are at risk for progression
- Moderate to severe COVID-19 patients

WHAT'S NEW IN THIS VERSION?

- This review update combined evidence from three previous reviews on chest x-ray, lung ultrasound, and chest CT-scan.
- There are seven new observational studies for chest x-ray, three new observational studies for the lung ultrasound and 20 new observational studies for chest CT scan.
- Additional subgroup analyses were done, particularly on the presence of symptoms, timing of testing, reader experience and on the category of index test positivity.
- Previous recommendations were retained except for the downgrading of the certainty of evidence for lung ultrasound from "Low" to "Very Low".

KEY FINDINGS

- A total of 81 observational studies were assessed for the diagnostic accuracy of chest x-ray, lung ultrasound, and chest CT scan against reverse transcriptase-polymerase chain reaction (RT-PCR) on individuals suspected of COVID-19.
- **Chest x-ray:** Overall sensitivity was 72% (62-81%) and overall specificity was 76% (67-86%). Results were comparable to the findings of the previous review that showed a sensitivity of 74% and specificity of 76%. Considerable heterogeneity is still seen (I^2=95%). Sensitivity was higher for studies that involved experienced readers, used standardized chest x-ray scoring systems, and when testing was done late in the disease course. Studies with high risk of bias tended to produce similar but less precise estimates. Overall certainty of evidence remained very low due to very serious risk of bias and inconsistency, and serious imprecision.
- **Lung ultrasound:** Overall sensitivity was 93% (86-97%) and specificity was 52% (33-71%). The previous review showed a lower sensitivity of 88% but a higher specificity of 63%. Sensitivity appeared higher when the test is used for symptomatic patients and when reader impression is used instead of a scoring system. The highest accuracy estimates were produced when only high quality studies were included in the analysis (Sn 97%, 95% CI 89-100%; Sp 73%, 95% CI 45-92%). Overall certainty of evidence was downgraded from low to very low due to very serious inconsistency, and seriousness on risk of bias and imprecision.
- **Chest CT scan:** Overall sensitivity was 85% (81-88%) and overall specificity was 78% (71-84%). Heterogeneity was very high at I^2=100%. Findings were almost similar to the estimates (Sn 88% and Sp 80%) of the previous review. Accuracy estimates were higher under the following situations: (1) test is used among symptomatic patients, (2) contrast-enhanced CT scan machines, (3) results are interpreted by experienced readers, (4) standardized scoring systems are used, (5) when only high-quality studies were considered. Overall certainty of evidence remained very low due to the seriousness of risk of bias and impression, and the very serious issues on inconsistency.

INTRODUCTION

Timely and appropriate assessment is necessary for patients who are suspected to have COVID-19. The current reference standard for the diagnosis of COVID-19 is the reverse transcriptase polymerase chain reaction (RT-PCR). This requires sophisticated equipment and trained specialists, and may take at least 24 hours to produce results.[1] In settings where RT-PCR is not available, chest imaging plays an

important role in the diagnostic work-up of suspected symptomatic COVID-19 individuals.[2]

Present literature on COVID-19 is dominated by chest computed tomography (CT) scan as a primary imaging modality.[3,4] Some hospitals have set up CT scan machines dedicated solely for suspected COVID-19 patients. However, this may not be accessible, affordable, and feasible in primary care settings. In contrast, chest x-ray is more ubiquitous, readily available, and produces less radiation compared to CT scan.[5] Lung ultrasound is likewise accessible and can be used at the bedside but is limited by its inability to provide a comprehensive view of deep portions of lung parenchyma.[6,7] The accuracy of these diagnostic modalities may vary depending on the level of experience of the radiologist or reader.[8]

This review update collated previous evidence summaries related to the diagnostic accuracy of these thoracic imaging modalities compared to RT-PCR alone in diagnosing COVID-19 among individuals suspected of COVID-19.

REVIEW METHODS

Search Strategy

A literature search for studies published from January 2020 to November 20, 2021 on the following electronic databases was conducted: MEDLINE, COVID-19 Living Evidence Database (https://zika.ispm.unibe.ch/assets/data/pub/search_beta/) and Cochrane COVID-19 Study Register (covid-19.cochrane.org/) using subject headings combined with text words related to “chest xray,” “chest radiograph,” “chest ultrasound,” “lung ultrasound,” “chest computed tomography scan,” “polymerase chain reaction, reverse transcriptase,” “COVID-19,” “SARS-Cov-2” with no language limits or method filters. To supplement the initial yield, the references sections of the included studies were reviewed for relevant articles.

Eligibility Criteria

This review included observational studies, randomized controlled trials (RCTs), and systematic reviews of observational studies that evaluated the diagnostic accuracy of the three imaging modalities for diagnosing COVID-19 among individuals suspected of COVID-19. Index tests included chest radiograph, lung ultrasound, and chest CT scan. Reference standard was a positive RT-PCR test for SARS-CoV-2 infection. Articles that had no available full text reports or did not have sufficient data to produce estimates of test accuracy or provide data for a 2x2 contingency table were excluded. Case reports and case series were also excluded. Studies that involved only PCR-positive samples were excluded as well. Appendix 3 lists the included studies.

Data Analysis

The studies were appraised using the QUADAS-2 tool. Measures of diagnostic accuracy, such as sensitivity and specificity values, were pooled using STATA version 14 and MetaDTA v2.01 (https://crsu.shinyapps.io/dta_ma/). Heterogeneity was determined by calculating I^2 using STATA version 14 and visual inspection of the forest plot. Subgroup analysis on symptomatology, timing of testing in relation to onset of symptoms, and category of index test positivity were performed depending on data availability. Sensitivity analyses were performed to determine the impact of risk of bias on sensitivity or specificity estimates.

RESULTS

The initial search yielded a total of 1,032 titles and abstracts. With the application of the criteria and the removal of articles with duplicates and articles with incomplete data, a total 81 observational studies (11 on chest x-ray alone, four on lung ultrasound alone, 56 on chest CT alone, three on both chest x-ray and chest CT scan, four on both lung ultrasound and chest x-ray, and three on both lung ultrasound and chest CT scan) were included in this evidence summary.

Chest X-Ray

A. Characteristics of Included Studies

The diagnostic accuracy of chest x-ray was reported in 18 observational studies (ten retrospective cohort, six prospective cohort, and two case-control studies) involving various countries with a mix of adult and pediatric patient populations (n=9,616).[9-26] Seven new studies were added from the previous review. COVID-19 was confirmed using RT-PCR in these populations. Of these 18 studies, 13 (72%) involved symptomatic patients, one (6%) involved asymptomatic patients, and four (22%) recruited patients with mixed symptom profiles. There were no studies with specific data on the severity of COVID-19 on presentation, the vaccination status of patients, or the predominant COVID-19 variant that was prevalent during the time of the study.

Eleven studies (61%) did not specify the type of machine used, while seven of 18 (39%) studies used portable or bedside x-rays. Experienced radiologists or readers were involved in eleven studies (61%), while two studies (11%) involved inexperienced readers. The rest of the studies did not specify the reader experience. In the included studies, inexperienced readers were non-radiologist readers or radiologists with less than five years of experience.

Definitions of positive chest x-ray results varied considerably across studies but most studies used common findings seen in radiographs of patients with COVID-19 pneumonia (e.g., presence of ground-glass/peripheral/interstitial/alveolar opacities, consolidations, reticulations, pleural effusion, atelectasis, among others). Most studies used the overall impression of readers as the basis for a positive result, eight studies used previously established scoring systems (i.e. The British Society of Thoracic Imaging or BTSI reporting criteria; Radiographic Assessment of Lung Edema or RALE criteria), and three studies used unvalidated classification systems involving Likert scales.

The detailed characteristics of included studies are described in Appendix 3.

B. Overall certainty of evidence

The overall certainty of evidence for the diagnostic accuracy of chest x-ray was very low. Very serious risk of bias was noted in the studies (10 studies with high risk of bias and eight with unclear risk of bias). There were very serious issues on inconsistency due to considerable heterogeneity, and serious issues of imprecision due to wide confidence interval values (See Appendix 4 for the Risk of Bias Ratings and Appendix 6 for the GRADE Evidence Profile).

C. Outcomes

Diagnostic performance of chest x-ray

Chest x-ray showed a pooled sensitivity of 72% (95% CI 0.62-0.81) and specificity of 78% (95% CI 0.67-0.86) in diagnosing COVID-19 . Significant heterogeneity was observed across studies (I^2=95%) possibly due to several factors: presence of symptoms, experience of chest x-ray readers, timing of chest x-ray in relation to symptom onset, definition of index test positivity. The previous review showed a sensitivity of 74% (95% CI 0.59-0.85) and specificity of 76% (95% CI 0.67-0.83).[5] (See Appendix 5 for the Forest Plot)

Results of the subgroup analyses are summarized in Table 1. Subgroup analysis based on population characteristics (age and severity of disease) was not possible due to the lack of available aggregated data.

Table 1. Subgroup analyses of the diagnostic accuracy of chest x-ray for detecting COVID-19 infection

Subgroups	No. of Studies	n	Sensitivity	95% CI	Specificity	95% CI
Presence of Symptoms						
Symptomatic	13	4,164	0.74	0.64, 0.83	0.76	0.67, 0.83
Asymptomatic	1	85	0.75	0.19, 0.99	0.74	0.63, 0.83
Mixed	4	1,899	0.79	0.66, 0.87	0.58	0.47, 0.68
Reader Experience						
Experienced	11	4,531	0.64	0.50, 0.76	0.87	0.74, 0.94
Inexperienced	2	572	0.24	0.12, 0.43	0.99	0.80, 0.99
Timing of Testing in Relation to Symptom Onset						
Early	3	810	0.37-0.55	-	0.65-0.83	-
Late	3	572	0.75-0.79	-	0.49-0.79	-
Mixed	7	2,195	0.72	0.58, 0.82	0.74	0.63, 0.82
Category of Index Test Positivity						
Reader impression	10	6,586	0.65	0.49, 0.77	0.82	0.67, 0.91
Scoring system	8	3,041	0.81	0.69, 0.88	0.71	0.59, 0.81
Sensitivity Analysis						
High risk of bias	10	5,944	0.69	0.52, 0.83	0.81	0.64, 0.91

1. Presence of Symptoms

Although the pooled sensitivity and specificity of chest x-ray appeared comparable between symptomatic (Sn 0.74; Sp 0.76) and asymptomatic patients (Sn 0.75; Sp 0.74), data on asymptomatic patients were reported in only one study, and with imprecise results.[15]

2. Reader Experience

Studies involving experienced radiologists reported significantly higher sensitivity (Sn 0.64) than less or inexperienced readers (Sn 0.24). The level of experience did not appear to significantly influence the test specificity (Sp 0.87 in experienced vs. Sp 0.99 in less or inexperienced readers).

3. Timing of Testing in Relation to Symptom Onset

Only three studies had specific data on the timing of chest x-ray in relation to symptom onset.[15,17,24] These studies had varying cut-offs for early and late timing of testing. In one study, early testing was defined as three days or less from the symptom onset.[15] The other study used five days as the cut-off.[17] The third study was able to compute the diagnostic accuracy of chest x-ray performed within two days from symptom onset and within 11 days after symptom onset.[24] Pooling of the estimates was not done due to the varying definitions. Range Sensitivity of chest x-ray increased

over time (Early Sn 0.37-0.55 vs. Late Sn 0.75-0.79) while the specificity of chest x-ray decreased (Early Sp 0.65-0.83 vs. Late Sp 0.49-0.70) over time.

4. Index Test Positivity
Using a scoring system in evaluating chest x-ray offers an advantage (Sn 0.81, 95% CI 0.69, 0.88) compared to a reader's impression (Sn 0.65, 95% CI 0.49-0.77).

5. Sensitivity Analysis
Studies with high risk of bias showed a negative effect on the sensitivity of chest x-ray (Sn 0.69, 95% CI 0.52, 0.83). Studies with unclear risk of bias showed comparable sensitivity (Sn 0.74, 95% CI 0.64, 0.82) and specificity (Sp 0.72, 95% CI 0.56-0.84) with the overall estimates.

Common findings and distribution on initial chest x-ray
Among the included studies, six had data on the common chest x-ray findings.[17-19,22,24,26] Table 2 summarizes the abnormalities found on chest x-rays in individuals with COVID-19. The most common findings included the presence of opacities (four studies, 1.4-86.1%) specifically ground glass opacities (two studies, 26.1-30.5%), followed by reticular opacities (one study, 29.7%), and alveolar opacities (one study, 25.9%). The presence of consolidations (three studies, 1.4%-66.8%) and pleural effusion (four studies, 2.6-6.4%) were likewise reported. In chest x-ray findings, lesions were most likely to present with alveolar pattern (one study, 86.1%), with bilateral lung involvement (five studies, 23.9-85%), multiple lung lobe involvement (two studies, 4.5-25.3%), and lower lobe involvement (one study, 83.7%).

One study noted that alveolar and reticular opacities were common findings seen in chest x-rays performed within five days from symptom onset.[17] Same features were found in chest x-rays performed after five days from symptom onset. More samples with bilateral and multilobular involvement were found in chest x-rays performed after five days from symptom onset compared to those done earlier.

Table 2. Common findings on chest x-ray

Chest x-ray findings	No. of studies	Prevalence in studies	No. of reported cases	Total no. of patients	Percentage of patients
FEATURES					
Presence of opacities	**4**	**1.4-86.1%**	**1,524**	**6,644**	**22.9%**
Ground glass opacities	2	26.1-30.5%	55	193	28.5%
Peripheral opacities	1	10.4%	52	500	10.4%
Interstitial and airspace opacities	1	25.4%	127	500	25.4%
Diffuse airspace opacities	1	3.0%	15	500	3.0%
Alveolar opacities	1	25.9%	134	518	25.9%
Reticular opacities	1	29.7%	154	518	29,7%
Consolidation	**3**	**1.4-66.8%**	**407**	**1,138**	**35.8%**
Pleural effusion	**4**	**2.6-6.4%**	**64**	**1,656**	**3.9%**

Chest x-ray findings	No. of studies	Prevalence in studies	No. of reported cases	Total no. of patients	Percentage of patients
DISTRIBUTION OF LESIONS					
Pattern of lesion					
Interstitial	1	42.0%	37	88	42.0%
Alveolar	1	86.1%	459	533	86.1%
Laterality of lesion					
Bilateral	5	23.9-85%	702	1,373	51.1%
Unilateral	2	4.7-7.6%	14	234	6.0%
Lobar involvement					
Unilobular	1	8.0%	7	88	8.0%
Multilobular	2	4.5-25.3%	135	606	22.3%
Lobar location					
Upper lobe	1	0.2%	1	533	0.2%
Lower lobe	1	83.7%	446	533	83.7%
Upper and lower lobe	1	3.2%	17	533	3.2%
FEATURES FOUND IN CHEST X-RAY DONE WITHIN 5 DAYS FROM SYMPTOM ONSET					
Lesions					
Alveolar opacities	1	17.2%	46	372	12.4%
Reticular opacities	1	17.2%	64	372	17.2%
Pleural effusion	1	4.8%	18	372	4.8%
DISTRIBUTION OF LESIONS IN CHEST X-RAY DONE WITHIN 5 DAYS FROM SYMPTOM ONSET					
Laterality of lesion					
Bilateral	1	11.8%	44	372	11.8%
Lobar involvement					
Multilobular	1	12.9%	48	372	12.9%
FEATURES FOUND IN CHEST X-RAY DONE AFTER 5 DAYS FROM SYMPTOM ONSET					
Lesions					
Alveolar opacities	1	60.3%	88	146	60.3%
Reticular opacities	1	61.6%	90	146	61.6%
Pleural effusion	1	8.2%	12	146	8.2%
DISTRIBUTION OF LESIONS IN CHEST X-RAY DONE AFTER 5 DAYS FROM SYMPTOM ONSET					
Laterality of lesion					
Bilateral	1	84.9%	124	146	84.9%
Lobar involvement					
Multilobular	1	83.6%	122	146	83.6%

Lung Ultrasound

A. Characteristics of Included Studies

The diagnostic accuracy of lung ultrasound was reported in 11 observational studies (nine prospective cohort studies and two retrospective cohort studies) involving exclusively adult population from multiple countries (n=1,076).[13,21,22,26-33] Three new studies were added from the previous review. All studies used POCUS (Point-of-Care Ultrasound). Nine out of 11 studies were done in the emergency room setting. Ten studies involved symptomatic patients and only one study involved asymptomatic patients. There were no studies with specific data on the vaccination status of patients or the predominant COVID-19 variant that was prevalent during the time of the study. All studies used RT-PCR as the reference standard for the diagnosis of COVID-19.

Experienced readers were involved in most (8/11 or 72%) of the studies, while one study involved inexperienced readers. While most studies relied on reader impression on the ascertainment of a positive diagnosis, two studies used formal scoring systems like the POCUS (Point-of-Care Ultrasound) for pulmonary manifestations of COVID-19. Positive characteristics in lung ultrasound include the presence of B-lines or the presence of vertical hyperechoic artifacts departing from the pleura and directing in-depth, representing thickened peripheral interlobular septa. There were variations in the brand of ultrasound machine, type of probe used (curvilinear, curved, Butterfly IQ), and scanning protocols applied (e.g., BLUE protocol, 12-zone, 8-zone).

B. Overall certainty of evidence

The overall certainty of evidence for the diagnostic accuracy of lung ultrasound was very low. Serious risk of bias was noted in some studies (five with high risk of bias and five with unclear risk of bias). In all four domains of QUADAS-2, unclear risk of bias was mostly seen. Very serious issues on inconsistency was due to considerable heterogeneity. There was seriousness on imprecision due to wide confidence interval values (See Appendix 4 for the Risk of Bias Ratings and Appendix 6 for the GRADE Evidence Profile).

C. Outcomes

Diagnostic performance of lung ultrasound

Lung ultrasound demonstrated a pooled sensitivity of 93% (95% CI 0.86-0.97) and specificity of 52% (95% CI 0.33-0.71) in diagnosing COVID-19. Similar to chest x-ray, significant heterogeneity was observed across studies (I^2=98%), possibly because of a number of factors, including the number of patients sampled per study, definition of index test positivity, and experience of readers. The previous review showed a sensitivity of 88% (95% CI 0.79-0.93) and a specificity of 63% (95% CI 0.47-0.77).[34]

Table 3 shows the subgroup analyses based on presence of symptoms, reader experience, and index test of positivity. Subgroup analyses based on population characteristics (age, severity of disease) and timing of testing were not done due to insufficient aggregated data.

Table 3. Subgroup analyses of the diagnostic accuracy of lung ultrasound for detecting COVID-19 infection

Subgroups	No. of Studies	n	Sensitivity	95% CI	Specificity	95% CI
Presence of Symptoms						
Symptomatic	10	918	0.93	0.85, 0.97	0.50	0.29, 0.72
Asymptomatic	1	58	0.70	0.51, 0.84	0.68	0.46, 0.85
Reader Experience						
Experienced	8	738	0.95	0.88, 0.98	0.43	0.23, 0.67
Inexperienced	1	101	0.97	0.89, 1.0	0.14	0.05, 0.29
Category of Index Test Positivity						
Reader impression	9	833	0.95	0.86, 0.98	0.52	0.28, 0.75
Scoring system	2	243	0.86	0.64, 0.96	0.58	0.49, 0.67
Sensitivity Analysis						
High risk of bias	5	512	0.97	0.89, 0.99	0.37	0.14, 0.67
Unclear risk of bias	5	487	0.83	0.69, 0.92	0.64	0.39, 0.83
Low risk of bias	1	77	0.97	0.89, 1.0	0.73	0.45, 0.92

1. Presence of Symptoms

Ten studies had specific data on the use of lung ultrasound on symptomatic suspected COVID-19 patients. This yielded a sensitivity of 93% (95% CI 0.85-0.97). One study showed a lower sensitivity (Sn 0.70, 95% CI 0.51-0.84) for asymptomatic patients. This study was done in a setting of a nursing home. These asymptomatic patients were contacts of positive COVID-19 patients in the nursing home.[29]

2. Reader Experience

Inexperienced readers had comparable sensitivity with the experienced reader (Sn 97% vs. Sn 95%). Specificity was much lower (Sn 0.14, 95% CI 0.05-0.29) with inexperienced readers. However, data on inexperienced readers was limited to a single study and the estimates were less precise. Inexperienced readers in that study were first to third year emergency medicine residents with credentials for point-of-care

ultrasound that reviewed a two-minute video on lung ultrasound findings for viral pneumonia prior to the start of study.[13] They have less experience compared to the other readers in the included studies.

3. Index Test Positivity

In determining a positive lung ultrasound result, a reader's impression showed a higher sensitivity (Sn 0.95, 95% CI 0.86-0.98) compared to using a scoring system (Sn 0.86, 95% CI 0.64-0.96). Specificity between the two were comparable (Sp 0.52 vs. Sp 0.58). Data on the use of a scoring system in determining a positive ultrasound were limited to two studies.[29,31]

4. Sensitivity Analysis

In the sensitivity analysis, studies with high risk of bias showed a higher sensitivity (Sn 0.97, 95% CI 0.89-0.99) compared to the overall estimates (Sn 0.93, 95% CI 86-97). Most of these studies had patient selection bias. Studies with unclear risk of bias showed a lower sensitivity (Sn 0.83, 95% CI 0.69-0.92). Most of these studies had observer bias.

Common findings on ultrasound

Among the included studies, four have data on the common lung ultrasound findings [21,22,26,30]. Table 4 summarizes the abnormalities found on lung ultrasound imaging in individuals with COVID-19. The most common findings in lung ultrasound were the presence of B-lines, with little difference between confluent (42.7%) and isolated (38.2%) B-lines. Presence of consolidations were noted in two studies (23.3-31.7%). Other findings were pleural effusion (2 studies, 12.4-12.7%), irregular pleural lines (42.7%), pleural thickening (48.8%) and air bronchograms (27.0%) predominantly involving multiple lung lobes (54%).

Table 4. Common Findings on Lung Ultrasound

Lung ultrasound findings	No. of studies	Prevalence in studies	No. of reported cases	Total no. of patients	Percentage of patients
FEATURES					
Presence of B-lines	**4**	**38.2-69.8%**	**176**	**331**	**53.2%**
Confluent B-lines	1	42.7%	38	89	42.7%
Isolated B-lines	1	38.2%	34	89	38.2%
Presence of consolidations	**3**	**23.3-31.7%**	**55**	**195**	**28.2%**
Pleural effusion	**2**	**12.4-12.7%**	**19**	**152**	**12.5%**
Irregular pleural lines	**1**	**42.7%**	**38**	**89**	**42.7%**
Pleural thickening	**1**	**48.8%**	**21**	**43**	**48.8%**
Air bronchogram	**1**	**27.0%**	**17**	**63**	**27.0%**
DISTRIBUTION OF LESIONS					
Laterality of lesion					
Bilateral	3	28.1-76.6%	204	466	43.8%
Lobar involvement					
Multilobular	1	54.0%	34	63	54.0%
Lobar predominance					
Upper lobe	1	11.1%	7	63	11.1%
Middle lobe	1	9.5%	6	63	9.5%
Lower lobe	1	49.2%	31	63	49.2%

Chest Tomography Scan (CT Scan)

A. Characteristics of Included Studies

The diagnostic accuracy of CT scan was reported in 62 observational studies (two cross-sectional studies, seven prospective cohort studies, 52 retrospective cohort

studies, and one case-control study) involving multiple countries with a total sample of 39,929.[9,18,24,30,32-33,35-90]. Twenty new studies were added in this review. Forty-five studies exclusively involved adult patients, three studies exclusively involved the pediatric population, while the rest of the studies have unspecified or mixed population characteristics. Majority of the studies involved symptomatic patients (40/62 studies, 65%). Thirty studies (48%) specified the use of chest CT scan in the emergency room setting. There were no studies with specific data on the vaccination status of patients or the predominant COVID-19 variant that was prevalent during the time of the study. All studies used RT-PCR as the reference standard for the diagnosis of COVID-19.

Experienced radiologists or readers were involved in the majority (39/62 or 63%) of the studies, while three studies involved inexperienced readers. The studies utilized varied standards to qualify for reader experience. For this review, experienced readers included consultants or experts in CT imaging evaluation, and readers with more than five years of experience. Readers with less than five years of experience, radiologists-in-training, and non-radiologist readers (i.e. radiographers) were tagged as inexperienced readers.

Majority of the studies were not able to describe the type of CT used, but some reported using non-contrast enhanced or plain (19 studies), contrast-enhanced (1 study), low-dose (8 studies), and high-resolution CT scans (5 studies). Twenty-seven studies relied on reader impression as an index of test positivity, while 35 studies used different scoring systems to ascertain the diagnosis of COVID-19. Scoring systems include COVID-19 Reporting and Data System (CO-RADS), CT Involvement Scores (CTIS), British Society of Thoracic Imaging (BTSI), chest CT scan severity score (CTSS), French Society of Radiology Criteria, and Radiology Society of North America (RSNA). A few used an unvalidated scoring system.

B. Overall certainty of evidence

The overall certainty of evidence for the diagnostic accuracy of CT scan was very low. Serious risk of bias was noted due to unclear risk on all four appraisal domains (32 studies with unclear risk of bias and 28 studies with high risk of bias). The considerable heterogeneity led to a very serious inconsistency. Serious imprecision due to wide confidence interval values were also noted (See Appendix 4 for the Risk of Bias Ratings and Appendix 6 for the GRADE Evidence Profile).

C. Outcomes

Diagnostic performance of CT scan

The pooled sensitivity and specificity of CT scan in diagnosing COVID-19 was 85% (95% CI 0.81-0.88) and 78% (95% CI 0.71-0.84) respectively. Very high heterogeneity was observed across studies (I^2=100%) possibly because of a number of factors including number of patients sampled per study, definition of index test positivity, and experience of readers. The previous review showed a sensitivity of 88% (95% CI 0.84-0.90) and specificity of 80% (95% CI 0.74-0.84).[91]

Results of the subgroup analyses are summarized in Table 5. Subgroup analysis based on population characteristics (i.e. severity of disease) was not possible due to lack of aggregated data. Table 5 describes the subgroup analyses based on presence

of symptoms, timing of testing in relation to symptom onset, reader experience, category of index test positivity, types of CT scan used, and pediatric population.

Table 5. Subgroup analyses of the diagnostic accuracy of chest CT scan for detecting COVID-19 infection

Subgroups	No. of Studies	n	Sensitivity	95% CI	Specificity	95% CI
Overall	**62**	**39,929**	**0.85**	**0.81, 0.88**	**0.78**	**0.71, 0.84**
Presence of Symptoms						
Symptomatic	40	28,722	0.88	0.85, 0.91	0.78	0.71, 0.84
Mixed	14	9,162	0.75	0.65, 0.83	0.82	0.66, 0.91
Reader Experience						
Experienced	39	28,112	0.84	0.79, 0.87	0.79	0.68, 0.87
Inexperienced	3	5,785	0.74	0.57, 0.86	0.82	0.79, 0.85
Timing of Testing in Relation to Symptom Onset						
Late	1	3,141	0.88	0.87, 0.89	0.65	0.59, 0.71
Mixed	15	13,638	0.88	0.84, 0.92	0.80	0.69, 0.87
Category of Index Test Positivity						
Reader impression	27	17,184	0.87	0.80, 0.91	0.70	0.55, 0.82
Scoring system	35	22,745	0.84	0.79, 0.87	0.83	0.77, 0.87
Type of CT scan Used						
Non-contrast enhanced	19	10,420	0.84	0.78, 0.88	0.83	0.67, 0.92
Contrast-enhanced	1	694	0.90	0.86, 0.93	0.88	0.84, 0.91
High resolution (HRCT)	5	11,891	0.88	0.76, 0.94	0.70	0.42, 0.88
Low-dose	8	1,438	0.89	0.78, 0.94	0.78	0.69, 0.85
Others (special groups)						
Pediatric population	4	371	0.53	0.34, 0.71	0.60	0.23, 0.88
Sensitivity Analysis						
High risk of bias	28	12,849	0.87	0.84, 0.90	0.82	0.77, 0.87
Unclear risk of bias	32	26,749	0.82	0.76, 0.88	0.75	0.61, 0.85
Low risk of bias	2	331	0.90	0.55, 0.98	0.52	0.39, 0.64

1. Presence of Symptoms

No specific data were available on the use of chest CT scan for asymptomatic individuals. However, studies with both symptomatic and asymptomatic individuals showed a lower sensitivity of chest CT scan (Sn 0.75, 95% CI 0.65-0.83) compared to symptomatic individuals alone (Sn 0.88, 95% CI 0.85-0.91).

2. Reader Experience

Sensitivity was higher in experienced readers (Sn 0.84, 95%CI 0.79-0.87) than inexperienced readers (Sn 0.74, 95% CI 0.57-0.86). Specificity was higher in inexperienced readers (Sp 0.82, 95% CI 0.79-0.85). However, data on inexperienced readers are limited.

3. Timing of Testing in Relation to Symptom Onset

Only one study described the diagnostic accuracy of chest CT scan based on the timing of testing in relation to symptom onset.[80] This study showed that sensitivity was 0.88 (95% CI 0.87-0.89) when chest CT scan was done five days after symptom onset. This is similar to the sensitivity found in studies that performed the chest CT scan at both early and late timing (up to 14 days) in relation to symptom onset (Sn 0.88, 95% CI 0.84-0.92; 15 studies). However, data remains limited.

4. Index Test Positivity

Using a scoring system to determine a positive CT scan showed comparable sensitivity with a reader's impression (Sn 0.84 vs. Sn 0.87). Specificity was higher (Sp 0.83, 95% CI 0.77-0.87) with the use of a scoring system.

5. Type of CT scan used

Studies that used contrast-enhanced CT scan (Sn 0.90, 95% 0.86-0.93; 1 study), high resolution CT scan (Sn 0.88, 95% CI 0.76-0.94; 5 studies), and low-dose CT scan (Sn 0.89, 95% CI 0.78-0.94; 8 studies) demonstrated higher sensitivity than studies that used plain/non-contrast enhanced CT scan (Sn 0.84, 95% CI 0.78-0.88; 19 studies). However, there were only a few studies on this.

6. Pediatric Population

Four studies were conducted among the pediatric population.[37,60,77,84] Sensitivity of CT scan in children was 0.53 (95% CI 0.34-0.71) while specificity was 0.6 (95% CI 0.23-0.88).

7. Sensitivity Analysis

Studies with low risk of bias showed increased sensitivity (Sn 0.90, 95% CI 0.55-0.98) compared to the overall sensitivity (Sn 0.85, 95%CI 0.81-0.88). However, this was limited to two studies only. A higher sensitivity was also seen in studies with high risk of bias (Sn 0.87, 95% CI 0.84-0.90). These studies have patient selection bias and observer bias. Studies with unclear risk of bias lead to a lower sensitivity (Sn 0.82, 95% CI 0.76-0.88).

Common findings on CT scan

Among the included studies, 20 have data on the common findings of COVID-19 on chest CT scan.[18,24,30,35-37,43,45,52,53,60,65-68,79,72,75,81] Two studies on the pediatric population described the common chest CT findings in children. Overall, the most common CT scan finding was ground glass opacities (20 studies, 9.5-90.4%) with 2,097 total reported cases among COVID-19 patients. This finding is consistent among the pediatric population (2 studies, 9.5-31.5%). Other common findings were consolidation pneumonia (16 studies, 1.4-70.4%) and a description of crazy paving patterns (8 studies, 6.7-71.1%). Distribution of lesions were found to be located more on the periphery (11 studies, 16.2-79.5%) than in central/perihilar regions (7 studies, 1.7-60.2%), involved both lungs (12 studies, 6.1-73.4%), and involved multiple lobes (7 studies, 8.8-66.7%). These and other findings are summarized in Table 6.

Table 6. Abnormalities found on CT scan among Individuals with COVID-19

CT scan findings	No. of studies	Prevalence in studies	No. of reported cases	Total no. of patients	Percentage of patients
FEATURES					
Ground glass opacities	20	9.5-90.4%	2,097	4,749	44.2%
Ground glass opacities with consolidation	8	1.5-38.4%	191	954	20.0%
Consolidation	16	1.4-70.4%	1,356	4,198	32.3%
Crazy paving pattern	8	6.7-71.1%	469	2,234	21.0%
Air bronchogram	6	0.2-39.6%	152	1,380	11.0%
Vascular enlargement	8	5.4-43.5%	272	1,646	16.5%
Interlobular septal wall thickening	5	0.8-54.0%	96	1,497	6.4%
Halo sign	7	0.4-10.8%	40	1,311	3.1%
Nodules	7	1.4-17.8%	118	2,139	5.5%
Lymphadenopathy	9	0.7-21.5%	169	2,147	7.9%
Pleural effusion	12	0.7-15.9%	143	2,447	5.8%

CT scan findings	No. of studies	Prevalence in studies	No. of reported cases	Total no. of patients	Percentage of patients
DISTRIBUTION OF LESIONS					
Predominant distribution					
Central/perihilar	7	1.7-60.2%	183	1,278	14.3%
Peripheral	11	16.2-79.5%	964	1,971	48.9%
Laterality of lesion					
Bilateral	12	6.1-73.4%	1,258	2,605	48.3%
Unilateral	4	0.9-7.9%	41	977	4.2%
Lobar involvement					
Unilobular	4	0.5-46.6%	54	910	5.9%
Multilobular	7	8.8-66.7%	497	1,219	40.8%
FEATURES (PEDIATRIC PATIENTS)					
Ground glass opacities	2	9.5-31.5%	42	237	17.7%
Ground glass opacities with consolidation	1	4.1%	6	148	4.1%
Consolidation	2	2.0-9.0%	11	237	4.6%
Vascular enlargement	2	5.4-10.1%	17	237	7.2%
Halo sign	2	2.2-5.4%	10	237	4.2%
Nodules	1	1.4%	2	148	1.4%
Lymphadenopathy	1	0.7%	1	148	0.7%
Pleural effusion	1	0.7%	1	148	0.7%
DISTRIBUTION OF LESIONS (PEDIATRIC PATIENTS)					
Predominant distribution					
Central/perihilar	1	5.6%	5	89	5.6%
Peripheral	1	33.7%	30	89	33.7%
Laterality of lesion					
Bilateral	1	6.1%	9	148	6.1%
Unilateral	1	9.5%	14	148	9.5%
Lobar involvement					
Unilobular	1	6.6%	10	148	6.8%
Multilobular	1	8.8%	13	148	8.8%

OTHER CONSIDERATIONS

The usual cost of the three imaging modalities are listed in Table 7. Chest x-ray ranges from Php 250 to Php 1,450. Lung ultrasound ranges from Php 360 to 2,500. Chest CT scan ranges from Php 2,600 to 12,700. These prices do not include the additional costs for physical protective equipment and will vary per institution.

Table 7. Prices of Chest Imaging Modalities in the Philippines

	Chest X-Ray	Lung Ultrasound	CT scan
Government	Adult: Php 250-530 Child: Php 260-550	Php 360-640	High Resolution: Php 4,000-5,500 Plain: Php 2,650-Php 3,000 Contrast-enhanced: Php 7,340
Private	PA: Php 350 PA/L: Php 690-1459.20 Child: Php 480	Php 1,000-2,582	Plain: Php 3,550-12,702.45

In Canada, a cost-benefit analysis study on the use of portable chest radiography through glass during the COVID-19 pandemic was done. The results showed a net benefit of 9.87 USD per patient imaged and a projected net cost saving of 51, 451.84 USD per year.[92] In the Philippines, there is no local data on the economic evaluation on the use of chest x-ray, lung ultrasound, and chest CT scan for the diagnosis of COVID-19.

RECOMMENDATIONS FROM OTHER GROUPS

World Health Organization (June 11, 2020) [93]

The World Health Organization (WHO) suggests against the use of chest imaging (including chest x-ray, lung ultrasound, and CT scan) in COVID-19 for symptomatic patients when RT-PCR testing is available with timely results. RT-PCR should be done to confirm the diagnosis of COVID-19 (Low certainty of evidence; conditional recommendation). However, WHO suggests using chest imaging (with no preference to one specific imaging modality) for the diagnostic workup of COVID-19 when: (1) RT-PCR testing is not available; (2) RT-PCR testing is available, but results are delayed; and (3) initial RT-PCR testing is negative, but with high clinical suspicion of COVID-19 (Low certainty of evidence, conditional recommendation). Chest imaging should be used in conjunction with clinical and laboratory data.

Philippine Pediatric Society & Pediatric Infectious Disease Society of the Philippines (February 6, 2021) [94]

According to the Philippine Pediatric Society, ancillary laboratory tests may aid in (1) screening and triaging of children presenting with symptoms, and (2) assessing the severity of symptoms and need for further management. If either exposure evaluation, clinical evaluation, or ancillary laboratory tests (particularly imaging procedures) is positive, the diagnosis of COVID-19 should be considered.

Chest x-ray is the recommended first line imaging modality in children suspected to have COVID-19 presenting with respiratory symptoms. However, this modality has limited sensitivity and specificity. Hence, a negative chest x-ray does not exclude pulmonary involvement in patients with laboratory-confirmed COVID-19, nor does it indicate absence of infection in cases of suspected COVID-19 not yet confirmed by RT-PCR.

Chest CT scan is not recommended as the initial diagnostic test in pediatric patients suspected to have COVID-19**.** Chest CT scan findings of COVID-19 in the pediatric population are not pathognomonic but may be suggestive of the diagnosis in the appropriate clinical setting. It may be considered in patients with a worsening clinical course who are not responding appropriately to therapy, or to further investigate a specific pulmonary condition.

Chest ultrasound has been used as an alternative to chest x-ray and chest CT scan in the diagnosis of pneumonia in COVID-19 patients due to its ease of use at point-of-care, absence of radiation exposure, and lower cost than CT scan. No specific recommendation is given for chest ultrasound.

US Centers for Disease Control (CDC) (February 16, 2021) [95]

The Centers for Disease Control (CDC) does not recommend CXR or CT to diagnose COVID-19. Viral testing remains the only specific method of diagnosis. Confirmation with the viral test is required, even if radiologic findings are suggestive of COVID-19 on CXR or CT.

American College of Radiology (ACR) (March 22, 2020) [96]

The American College of Radiology recommends against the use of CT scan as a first-line test to diagnose COVID-19. CT should be used sparingly and reserved for hospitalized, symptomatic patients with specific clinical indications for CT.

ONGOING STUDIES

There are eight ongoing studies (four on chest CT scan, one chest x-ray and two lung ultrasound) registered at clinicaltrials.gov.[97-104] These studies are on the use of thoracic imaging in the diagnosis of COVID-19 in suspected individuals with RT PCR as the reference standard. (See Appendix 7 for details on Ongoing Studies).

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Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (1)	Yes (8)					In settings where RT-PCR is not available, thoracic imaging plays an important role in the diagnostic work-up of suspected symptomaticCOVID-19 individuals.
Benefits	Large (2)	Moderate (3)	Small (2)	Uncertain (2)			
Harms	Large	Moderate (2)	Small (5)	Uncertain (2)			For chest x-ray, using the pooled sensitivity of 72%, the false negative rate is at 28%.For lung ultrasound, using the pooled sensitivity of 93%, the false negative rate is at 7%.For chest CT scan, using the pooled sensitivity of 85%, the false negative rate is at 15%.
Balance of Benefits and Harms	Favors the use of thoracic imaging (5)	Probably favors the use of thoracic imaging (2)	Does not favor the use of thoracic imaging (2)				
Certainty of Evidence	High (1)	Moderate	Low (2)	Very low (6)			For chest x-ray, certainty of evidence is Very low due to the very serious risk of bias, very high heterogeneity and imprecision. For lung ultrasound and chest CT scan, certainty of evidence is Very Low due to serious risk of bias, imprecision, and very high heterogeneity. For chest x-ray, Sn 72% (62-81%) and Sp 76% (67-86%). Sensitivity was higher for studies that involved experienced readers, used standardized CXR scoring systems, and when testing was done late in the disease course. For lung ultrasound, Sn 93% (86-97%) and Sp 52% (33-71%). Sensitivity appeared higher when the test was used for symptomatic patients and when reader impression was used instead of a scoring system. For chest CT scan, Sn 85% (81-88%) and Sp 78% (71-84%). Accuracy estimates were higher under the following situations: (1) test is used among symptomatic patients, (2) contrast-enhanced CT scan machines, (3) results are interpreted by experienced readers, (4) standardized scoring systems are used.
Accuracy	Very Accurate	Accurate (6)	Inaccurate (1)	Very Inaccurate	Uncertain		
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (3)	Moderate Cost (5)	Negligible cost or savings	Moderate savings (1)	Large savings	Chest x-ray cost range: Php 250 - Php 1450. Lung Ultrasound cost range: Php 360 - 2,500. Chest CT scan cost range: Php 2,600 - 12,700.
Certainty of evidence of required resources	No included studies (6)	Very low (2)	Low (1)	Moderate	High		

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Cost effectiveness	No included studies (4)	Favors using thoracic imaging (2)	Does not favor either using thoracic imaging or the comparator (2)	Favors comparison (1)		No local data on economic evaluation of chest x-ray, lung ultrasound and chest CT scan specifically for COVID-19.
Equity	Uncertain (2)	Reduced (4)	Probably no impact	Increased (3)		
Acceptability	Uncertain (1)	No (1)	Yes (7)			
Feasibility	Uncertain (2)	No	Yes (7)			

Appendix 2. Search Yield and Results

Search	Query	Results
#9	Search: **(((((((covid-19) OR (novel coronavirus)) OR (SARS-Cov-2)) OR (NCOV)) OR (covid-19[MeSH Terms])) OR (SARS-CoV-2[MeSH Terms])) OR (novel coronavirus[MeSH Terms])) OR (coronavirus infections[MeSH Terms])) AND (((((((RT PCR) OR (RT-PCR)) OR (reverse transcriptase polymerase chain reaction)) OR (RT-PCR[MeSH Terms])) OR (polymerase chain reaction, reverse transcriptase[MeSH Terms])) OR (pcr, reverse transcriptase[MeSH Terms])) AND (((((((chest computed tomography) OR (chest CT scan)) OR (chest CAT scan)) OR (chest computed tomography scan[MeSH Terms])) OR (chest CT scan[MeSH Terms])) OR (chest CAT scan[MeSH Terms])) OR (((((((chest ultrasound) OR (lung ultrasound)) OR (thoracic ultrasound)) OR (chest ultrasonography)) OR (lung ultrasonography)) OR (thoracic ultrasonography)) OR (chest ultrasound[MeSH Terms])) OR (lung ultrasound[MeSH Terms])) OR (thoracic ultrasound[MeSH Terms]))) OR ((((((chest x-ray) OR (chest radiograph)) OR (chest xray)) OR (chest xray[MeSH Terms])) OR (chest x-ray[MeSH Terms])) OR (chest radiograph[MeSH Terms])))))** Filters: **from 2020/1/1 - 2021/11/20** Sort by: **Most Recent**	973
#8	Search: **(((((((covid-19) OR (novel coronavirus)) OR (SARS-Cov-2)) OR (NCOV)) OR (covid-19[MeSH Terms])) OR (SARS-CoV-2[MeSH Terms])) OR (novel coronavirus[MeSH Terms])) OR (coronavirus infections[MeSH Terms])) AND (((((((RT PCR) OR (RT-PCR)) OR (reverse transcriptase polymerase chain reaction)) OR (RT-PCR[MeSH Terms])) OR (polymerase chain reaction, reverse transcriptase[MeSH Terms])) OR (pcr, reverse transcriptase[MeSH Terms])) AND (((((((chest computed tomography) OR (chest CT scan)) OR (chest CAT scan)) OR (chest computed tomography scan[MeSH Terms])) OR (chest CT scan[MeSH Terms])) OR (chest CAT scan[MeSH Terms])) OR (((((((chest ultrasound) OR (lung ultrasound)) OR (thoracic ultrasound)) OR (chest ultrasonography)) OR (lung ultrasonography)) OR (thoracic ultrasonography)) OR (chest ultrasound[MeSH Terms])) OR (lung ultrasound[MeSH Terms])) OR (thoracic ultrasound[MeSH Terms]))) OR ((((((chest x-ray) OR (chest radiograph)) OR (chest xray)) OR (chest xray[MeSH Terms])) OR (chest x-ray[MeSH Terms])) OR (chest radiograph[MeSH Terms])))))** Sort by: **Most Recent**	1,006
#7	Search: **((((((RT PCR) OR (RT-PCR)) OR (reverse transcriptase polymerase chain reaction)) OR (RT-PCR[MeSH Terms])) OR (polymerase chain reaction, reverse transcriptase[MeSH Terms])) OR (pcr, reverse transcriptase[MeSH Terms])) AND (((((((chest computed tomography) OR (chest CT scan)) OR (chest CAT scan)) OR (chest computed tomography scan[MeSH Terms])) OR (chest CT scan[MeSH Terms])) OR (chest CAT scan[MeSH Terms])) OR (((((((chest ultrasound) OR (lung ultrasound)) OR (thoracic ultrasound)) OR (chest ultrasonography)) OR (lung ultrasonography)) OR (thoracic ultrasonography)) OR (chest ultrasound[MeSH Terms])) OR (lung ultrasound[MeSH Terms])) OR (thoracic ultrasound[MeSH Terms]))) OR ((((((chest x-ray) OR (chest radiograph)) OR (chest xray)) OR (chest xray[MeSH Terms])) OR (chest x-ray[MeSH Terms])) OR (chest radiograph[MeSH Terms])))** Sort by: **Most Recent**	1,353
#6	Search: **(((((RT PCR) OR (RT-PCR)) OR (reverse transcriptase polymerase chain reaction)) OR (RT-PCR[MeSH Terms])) OR (polymerase chain reaction, reverse transcriptase[MeSH Terms])) OR (pcr, reverse transcriptase[MeSH Terms])** Sort by: **Most Recent**	276,677
#5	Search: **(((((((chest computed tomography) OR (chest CT scan)) OR (chest CAT scan)) OR (chest computed tomography scan[MeSH Terms])) OR (chest CT scan[MeSH Terms])) OR (chest CAT scan[MeSH Terms])) OR (((((((((chest ultrasound) OR (lung ultrasound)) OR (thoracic ultrasound)) OR (chest ultrasonography)) OR (lung ultrasonography)) OR (thoracic ultrasonography)) OR (chest ultrasound[MeSH Terms])) OR (lung ultrasound[MeSH Terms])) OR (thoracic ultrasound[MeSH Terms]))) OR ((((((chest x-ray) OR (chest radiograph)) OR (chest xray)) OR (chest xray[MeSH Terms])) OR (chest x-ray[MeSH Terms])) OR (chest radiograph[MeSH Terms]))** Sort by: **Most Recent**	255,939
#4	Search: **(((((chest computed tomography) OR (chest CT scan)) OR (chest CAT scan)) OR (chest computed tomography scan[MeSH Terms])) OR (chest CT scan[MeSH Terms])) OR (chest CAT scan[MeSH Terms])** Sort by: **Most Recent**	56,031
#3	Search: **(((((((chest ultrasound) OR (lung ultrasound)) OR (thoracic ultrasound)) OR (chest ultrasonography)) OR (lung ultrasonography)) OR (thoracic ultrasonography)) OR (chest ultrasound[MeSH Terms])) OR (lung ultrasound[MeSH Terms])) OR (thoracic ultrasound[MeSH Terms])** Sort by: **Most Recent**	210,782
#2	Search: **(((((chest x-ray) OR (chest radiograph)) OR (chest xray)) OR (chest xray[MeSH Terms])) OR (chest x-ray[MeSH Terms])) OR (chest radiograph[MeSH Terms])** Sort by: **Most Recent**	107,091
#1	Search: **(((((((covid-19) OR (novel coronavirus)) OR (SARS-Cov-2)) OR (NCOV)) OR (covid-19[MeSH Terms])) OR (SARS-CoV-2[MeSH Terms])) OR (novel coronavirus[MeSH Terms])) OR (coronavirus infections[MeSH Terms])** Sort by: **Most Recent**	210,386

Appendix 3. Characteristics of Included Studies

Study ID	Type of Study	Country	Population Description/Setting	Sample Size	Index Test	Index Test Criteria for Positivity	Reader Experience Description	Reference Standard	Number in Reference Section
Ai 2020	observational, retrospective, single center	China	adult suspected COVID-19 patients (unclear symptomatology)	1014	CT: not specified	Chest CT scan positive: GGO, consolidation, reticulation and/or thickened interlobular septa (nodules) and lesion distribution	Two radiologists with 12 and 3 years	RT PCR	[35]
Aslan 2020	observational, retrospective, single center	Turkey	adult suspected COVID-19 patients (all symptomatic) in emergency department	306	CT: low-dose CT	Radiological evidence of COVID-19 pneumonia, including presence of GGO, mixed GGO (GGO and consolidation), consolidation, distribution and number of lobes and segment affected by GGO and/or consolidation, etc	two experienced radiologist	RT PCR	[36]
Bagci 2021	observational, retrospective, single center	Turkey	electronic archive records of children aged 0-18 yrs old suspected of COVID-19 (symptomatics and possibly asymptomatic) who underwent CT scan	89	CT: not specified	presence of pulmonary lesions (GGO, consolidation, halo sign, nodules, vascular fullness, fibrosis), lesion type, pulmonary involvement areas, and maximum lobe involvement percentage	single experienced pediatric radiologist	RT PCR	[37]
Bar 2020	observational, prospective, single center	France	adults (unclear symptomatology) admitted to the emergency room whose lungs were imaged with ultrasound for suspected COVID-19 infection and who had a SARS-CoV-2 RT-PCR test	100	LUS: point-of-care US, BLUE protocol, curved probe	unclear	LUS done by emergency physician but experience not reported	RT PCR	[27]
Barbosa 2020	observational, retrospective, single center	Brazil	adult suspected COVID-19 patients (all symptomatic)	91	CT: not specified	Radiology Society of North America (RSNA)	two experienced radiologist	RT PCR	[38]
Bellini 2020	observational, retrospective, single center	Italy	suspected of COVID-19 (all symptomatic) presenting at the ER	572	CT: non-contrast enhanced CT	COVID-19 Reporting and Data System (CO-RADS)	radiologists and radiographers	RT PCR	[39]
Berkel 2021	observational, retrospective, single center	Belgium	CT scan records of suspected COVID-19 (unclear symptomatology) who underwent CT scan and RT PCR in a hospital	200	CT: mixed types	mixed: CO-RADS + CTIS	a senior thoracic radiologist with 21-year experience and a resident radiologist with one-year experience with discrepant cases were evaluated by a senior thoracic	RT PCR	[40]

							radiologist with 10-year experience		
Besutti 2020	observational, cross-sectional, single center	Italy	suspected of COVID-19 (all symptomatic) presenting at the ER	696	CT: non-contrast enhanced CT	a structured report about probability of COVID19 pneumonia (radiologist impression – highly suggestive, suggestive, not suggestive)	radiologist, no details on experience	RT PCR	[41]
Bitar 2021	observational, prospective, single center	Kuwait	adults with suspected COVID-19 infection (symptomatic only) who were transferred to ICU	77	LUS: point-of-care US, 12-zone scan, curvilinear	4 LUS findings of COVID pneumonia: Bilateral B-lines in separate forms and bilateral patchy shining white lung areas in multiform clusters, where all these signs are represented and sharply alternated to “spared areas”; Bilateral diffuse irregularities of the pleural line; Absence of significant pleural effusion; Presence of multiple subpleural consolidations of various sizes	Level 4 operator in critical care clinical ultrasound (entrusted to act unsupervised)	RT PCR	[28]
Borakati 2020	observational, retrospective, single center	UK	electronic records of suspected of COVID-19 (symptomatic or asymptomatic) presenting at the ER who had RT PCR, CXR and Ct scan done	CXR: 860 CT: 302	CXR: Not specified CT: different types	CXR: British Society of Thoracic Imaging (BSTI) reporting criteria CT: British Society of Thoracic Imaging (BSTI) reporting criteria	consultant radiologist	RT PCR	[9]
Cartocci 2020	observational, retrospective, single center	Italy	adults suspected of COVID-19 (all symptomatic) presenting at the ER	314	CT: not specified	classification system based another study (typical CT pattern, possible CT pattern, inconsistent CT pattern, negative for pneumonia)	radiologist with 8 and 16 yrs of experience	RT PCR	[42]
Caruso 2020	observational, prospective, single center	Italy	adults suspected of COVID-19 (all symptomatic) presenting at the ER	158	CT: non-contrast enhanced CT	pneumonia (GGO, multlobar, bilateral distribution, oosterior involvement)	radiologist with 5 and 25 years of thoracic imaging experience	RT PCR	[43]
Choudhury 2020	observational, prospective, single center	India	suspected of COVID-19 (all symptomatic) presenting in a respiratory unit	97	CXR: Not specified	previously unvalidated Likert score (scores 1 to 5) based on radiographic features thought to be related to COVID-19	radiologist: experience not specified	RT PCR	[10]
Cozzi 2020	observational, retrospective, single center	Italy	all patients presenting to the emergency department for suspected SARS-CoV-2 infection (symptomatic or asymptomatic) who underwent both a nasopharyngeal swab for RT-PCR and an anteroposterior bedside CXR within 12 h from admission.	535	CXR: portable/bed side	The presence of interstitial infiltrates with predominantly bilateral and basal distribution	2 groups of radiologist (1 group with 10 or more years of experience & another group with less than 10 years of experience)	RT PCR	[11]
De Smet 2020	observational, prospective, single center	Belgium	admitted to the hospital with clinical suspicion of COVID-19 pneumonia (symptomatic	859	CT: non-contrast	COVID-19 Reporting and Data System (CO-RADS)	cardiothoracic radiologist with 9	RT PCR	[44]

			individuals) and individuals without COVID-19 symptoms but admitted for other medical emergencies, scheduled surgery, or medical procedures and psychiatric or geriatric care (“asymptomatic")		enhanced CT		and 24 yrs of experience		
Debray 2020	observational, retrospective, single center	France	adults suspected of COVID-19 (unclear symptomatology)	241	CT: non-contrast enhanced CT	French Society of Radiology criteria	radiologists and emergency physicians	RT PCR	[45]
Deng 2020	observational, retrospective, single center	China	suspected of COVID-19 (all symptomatic)	587	CT: high-resolution CT	Any of the following: GGO; Thickened blood vessels; Thickened bronchial shadows passing through; With or without localized lobular septal grid thickening; Single or multiple real shadows	radiologist with 5 and 20 yrs of experience	RT PCR	[46]
Dini 2020	observational, prospective, multi center	Italy	more than 70 yrs old suspected of COVID-19 in nursing homes (symptomatic and asymptomatic who are contacts of previously positive COVID)	150	LUS: point-of-care US, not specified scan protocol, curvilinear probe	4-level scoring system	Reader not specified	RT PCR	[29]
Dofferhoff 2020	observational, prospective, single center	Netherlands	suspected of COVID-19 (all symptomatic) presenting at the ER	312	CT: low-dose CT	COVID-19 Reporting and Data System (CO-RADS)	radiologist, no details on experience	RT PCR	[47]
Du 2021	observational, retrospective, multi center	Hong Kong	more than 16 years old with clinical suspicion of COVID-19 infection (all symptomatic) presenting to the accident and emergency department in different hospitals in Hong Kong	605	CXR: Not specified	pre-defined set of CXR findings were used based on local experience and emerging literature to define “typical” radiographic features of COVID-19	four board certified radiologist with subspeciality training in thoracic radiology (experience: 2 to 15 years)	RT PCR	[12]
Ducray 2020	observational, retrospective, multi center	France	adults suspected of COVID-19 (symptomatic or asymptomatic) presenting at the ER	694	CT: contrast-enhanced CT	classification system: surely COVID+, possible COVID+, COVID-	senior radiologist, no details on experience	RT PCR	[48]
Falasachi 2020	observational, retrospective, single center	Italy	adults suspected of COVID-19 (all symptomatic) presenting at the ER during peak of Italian pandemic	773	CT: non-contrast enhanced CT	Radiology Society of North America (RSNA)	Two radiologists with more than 10 years of thoracic imaging experience	RT PCR	[49]
Fonsi 2020	observational, prospective, single center	Italy	adults suspected (all symptomatic) of COVID-19 at ER	63	LUS: point-of-care US, 12-zone	LUS: unclear CT features: GGOs; consolidation; a mixed GGO and consolidation	LUS: 2 examiners who were	RT PCR	[30]

					scan, curvilinear CT: non-contrast enhanced CT	pattern; single or multiple solid nodules surrounded by GGOs; a focal or multifocal distribution; GGO and consolidation location; multilobe involvement; a bilater- al distribution; interlobular septal thickening; an air bronchogram; the presence of cavitation; bronchial wall thickening; bronchiec- tasis; mediastinal lymph node enlargement; pleural effusion; and pericardial effusion	experienced in echography CT: 2 radiologists, who were experienced in chest imaging, studied all chest CT images.		
Fujioka 2020	observational, retrospective, single center	Japan	adults suspected of COVID-19 (all symptomatic)	154	CT: not specified	COVID-19 Reporting and Data System (CO-RADS)	radiologist resident and board-certified radiologist	RT PCR	[50]
Gezer 2020	observational, retrospective, single center	Turkey	adults suspected of COVID-19 (all symptomatic)	222	CT: non-contrast enhanced CT	unclear definition	radiologist with 14 yrs of experience	RT PCR	[51]
Giannitto 2020	observational, retrospective, single center	Italy	adults suspected of COVID-19 (all symptomatic) presenting at the ER	68	CT: non-contrast enhanced CT	classification system: surely COVID+, possible COVID+, COVID-	Two radiologists with five and fifteen years of experience	RT PCR	[52]
Gibbons 2021	observational, prospective, single center	USA	more than 18 years old presenting at the ER with signs and symptoms of COVID-19	101	CXR: portable/bed side LUS: point-of-care US, 8-zone scan, Butterfly iQ	CXR: presence of infiltrate or pneumona LUS findings consistent with viral/atypical pneumonia: irregular pleural line, B-lines, consolidation, and pleural effusion; he presence of three or more B-lines was considered positive; the presence of a single confluent B-line encompassing a third or more of the visualized distal intercostal space was considered positive; presence of one of the aforementioned sonographic findings defined a positive zone; presence of two or more positive zones was defined as diagnostic	CXR: Not specified LUS: Experienced-ultrasound-fellowship-trained emergency medical doctors; Inexperienced - postgraduate year (PGY)1–3 emergency medicine resident or emergency medicine attending with American College of Emergency Physician (ACEP) credentials for	RT PCR	[13]

							point-of-care ultrasound, the reviewed a 2 min video on LUS for viral pneumonia prior to start of study		
Gichoya 2021	observational, retrospective, single center, case-control	USA	retrieved and reviewed the chest radiographs taken at the time of ER presentation of known COVID PCR positive and COVID PCR negative patients	1638	CXR: different types	instructed to label images with the single best label from the following six choices: Normal, COVID-19, Other Infectious, Other Noninfectious, Nondiagnostic Image, or Endotracheal Tube Present.	radiologist with varying specialties and experiences	RT PCR	[14]
Gietema 2020	observational, prospective, single center	Netherlands	adults suspected of COVID-19 (all symptomatic) presenting at the ER	193	CT: non-contrast enhanced CT	standardized imaging reporting system (typical for COVID-19, equivocal, non COVID-19)	initial reading by resident but final reading done by experienced chest radiologist with 12 years of experience	RT PCR	[53]
Grando 2020	observational, cross-sectional, single center	Brazil	Patients with suspected COVID-19 pneumonia (all symptomatics) submitted to RT-PCR test and chest computed tomography	159	CT: high-resolution	Radiology Society of North America (RSNA)	2 radiologist (1 and 10 yrs of experience) but discordant reports evaluated by another radiologist with 12 yrs experience	RT PCR	[54]
Guillo 2020	observational, retrospective, single center	France	adults suspected of COVID-19 (all symptomatic) presenting at the ER	214	CT: non-contrast enhanced CT	structured report about probability of COVID-19 pneumonia based on the presence of GGOs, with or without crazy paving pattern, isolated or admixed with perilobular or linear consolidation, their peripheral or central distribution	initial reading by radiology resident then approved by a senior radiologist. Secondarily independently reviewed by an experienced chest radiologist with 20 years of experience (blinded to 1st review0	RT PCR	[55]
Haak 2020	observational, prospective, single center	Netherlands	more than 16 years old suspected of COVID (all symptomatic) presenting to the ED	93	LUS: point-of-care US,	POCUS of the lungs scoring system for pulmonary manifestation of COVID-19	Emergency Medicine resident with 2.5	RT PCR	[31]

					12-zone scan, curved		years of POCUS experience did the ultrasound but the reading was done by an emergency physician and expert sonographer		
He 2020	observational, retrospective, single center	China	suspected COVID-19 patients (unclear symptomatology)	82	CT: non-contrast enhanced CT	GGO with or without consolidation, crazy paving pattern, peripheral and diffuse distribution and bilateral/multilobular involvement	Two experienced general radiologists with 17 and 14 years of experience	RT PCR	[56]
Herman s 2020	observational, prospective, single center	Netherlan ds	adults suspected COVID-19 patients (symptomatic and asymptomatic) presenting at the ER	319	CT: not specified	COVID-19 Reporting and Data System (CO-RADS)	Twenty board-certified radiologists	RT PCR	[57]
Hernigo u 2020	observational, retrospective, single center	Belgium	adults suspected COVID-19 patients (symptomatic and asymptomatic) presenting at the ER with diagnosis of trauma that underwent chest CT	47	CT: low-dose CT	unclear definition	read by two radiologist (one with 30 years of experience)	RT PCR	[58]
Herpe 2020	observational, prospective, single center	France	suspected COVID-19 patients (all symptomatic)	4824	CT: not specified	bilateral GGO with peripheral distribution, bilateral paving appearance with intralobular thickening, reverse halo sign, or other signs compatible with organizing pneumonia	experienced radiologist with at least 5 yrs of experience	RT PCR	[59]
Hwang 2020	observational, retrospective, single center	Korea	People who visited a tertiary hospital with suspected COVID-19 (symptomatic or asymptomatic) who underwent chest x-ray	332	CXR: portable/bed side	abnormality suggesting pneumonia	thoracic radiologist with 9 years of experience	RT PCR	[15]
Hwang 2021	observational, retrospective, multi center	Korea	Patients with and without COVID-19 confirmed with RT-PCR that underwent CXR and chest CT in four different institutions	172	CXR: Not specified	Five point scale score: a) score 1, definitely absent; b) score 2, probably absent; c) score 3, equivocal; d) score 4, probably present; and e) score 5, definitely present.	5 thoracic radiologists with range of 5 - 29 yerars of experience & non-radiologist physicians	RT PCR	[16]
Ippolito 2020	observational, retrospective, single center	Italy	patients suspected of COVID-19 (all symptomatic) presenting at the ER who underwent CXR & PCR	518	CXR: portable/bed side	presence of reticulations, alveolar opacities or both	single radiologist with more than 15 years of experience	RT PCR	[17]
Kalin 2021	observational, retrospective, single center	Turkey	pediatric patients (0–18 age) who were referred to the radiology department with suspicion of	148	CT: low-dose CT	CT findings consistent of pneumonia; details not specified	pediatric radiologist with	RT PCR	[60]

			COVID-19 (unclear symptomatology) pneumonia and underwent low-dose chest CT scan				15 yrs of experience		
Kavak 2021	observational, retrospective, single center	Turkey	patients with history of contact or symptoms of COVID-19 presenting at the ER that underwent chest CT examination	903	CT: non-contrast enhanced CT	Radiology Society of North America (RSNA) & British Society of Thoracic Imaging (BSTI) reporting criteria	two radiologists with a 14 and 15 years of experience	RT PCR	[61]
Khan 2021	observational, prospective, single center	Pakistan	confirmed and suspected COVID-19 (all symptomatics) patients admitted in the ward and ICU that was referred for chest X-rays and computed tomography (CT) scans	CXR: 533; CT: 97	CXR: portable/bed side CT: mixed types	CXR: Radiographic Assessment of Lung Edema (RALE) criteria CT: chest CT scan severity score (CTSS)	2 junior radiologist and 2 senior radiologist with 10 years of experience	RT PCR	[18]
Kiziloglu 2021	observational, retrospective, single center	Turkey	more than 18 years old suspected of COVID-19 (all symptomatic) presenting at the ER	173	CT: not specified	thorax CT images were classified as normal, non- COVID lung findings, compatible with low probability COVID- 19, intermediate probability COVID- 19 and high probability-definite COVID- 19 as defined in other studies	Two radiologists experienced in the field of thorax CT	RT PCR	[62]
Korevaar 2020	observational, retrospective, single center	Netherlands	adults suspected of COVID-19 (all symptomatic) presenting at the ER	239	CT: low-dose CT	COVID-19 Reporting and Data System (CO-RADS)	radiologist, no details on experience	RT PCR	[63]
Krdzalic 2020	observational, retrospective, single center	Netherlands	adults suspected of COVID-19 (all symptomatic)	56	CT: non-contrast enhanced CT	COVID-19 Reporting and Data System (CO-RADS)	chest radiologist with 5 years of experience in chest CT interpretation	RT PCR	[64]
Kuzan 2020	observational, retrospective, single center	Turkey	adults suspected of COVID-19 (all symptomatic) presenting at the ER	120	CT: non-contrast enhanced CT	British Society of Thoracic Imaging (BSTI) reporting criteria	radiologist, no details on experience	RT PCR	[65]
Li 2020	observational, retrospective, mulit center	China	adults suspected of COVID-19 (all symptomatic)	92	CT: not specified	specific scoring criteria based on literature findings	two radiologists with 3 and 10 years of experience in chest imaging	RT PCR	[66]
Lieveld 2020	observational, prospective, multi center	Netherlands	patients 18 years and older who were referred to the ED for internal medicine with suspected COVID-19 (all symptomatic)	186	LUS: point-of-care US, 12-zone scan, probe not specified CT: not specified	LUS: three or more B-lines and/or consolidation in two or more zones unilaterally or in one or more zones bilaterally CT: COVID-19 Reporting and Data System (CO-RADS)	LUS: performed or supervised by internists (mostly registrars) who were certified in point-of-care ultrasound and had performed at least 20 supervised LUS	RT PCR	[32]

							CT: not specified		
Luo L 2020	observational, retrospective, single center	China	adults suspected of COVID-19 (all symptomatic)	73	CT: not specified	scoring system was developed (with scores from -4 to +7)	two cardiothoracic radiologist with 15 and 25 years of experience	RT PCR	[67]
Luo N 2020	observational, retrospective, single center	China	adults suspected of COVID-19 (unclear symptomatology)	140	CT: not specified	unclear definition	cardiothoracic radiologist, no details on experience	RT PCR	[68]
Majeed 2021	observational, prospective, single center	Pakistan	12 to 90 years old with symptoms of COVID that underwent CXR	105	CXR: portable/bed side	British Society of Thoracic Imaging (BSTI) reporting criteria	2 radiologist with 5 and 20 years of experience	RT PCR	[19]
Mei 2020	observational, retrospective, multi center	USA	suspected COVID-19 patients (symptomatic and asymptomatic)	905	CT: not specified	unclear definition	thoracic radiologist with 10 years of experience	RT PCR	[69]
Mirahmadizadeh 2021	observational, cross-sectional, single center	Iran	adult suspected COVID-19 patients (unclear symptomatology)	54	CT: not specified	presence of GGO & consolidation	not specified reader	RT PCR	[70]
MM Santos 2020	observational, retrospective, single center	Brazil	adults suspected of COVID-19 (all symptomatic) presenting at the ER	75	CT: not specified	Radiology Society of North America (RSNA)	two radiologists with 4 and 11 years of experience in chest imaging	RT PCR	[71]
Murphy 2020	observational, retrospective, single center	Netherlands	suspected of COVID-19 (all symptomatic)	454	CXR: Not specified	Classification system: normal, no finding (category 0); abnormal but no lung opacity consistent with pneumonia (category 1); lung opacity consistent with pneumonia (unlikely COVID-19) (category 2); lung opacity consistent with pneumonia (consistent with COVID-19) (category 3).	6 radiologist with 5 to 30 years of experience	RT PCR	[20]
Nair 2021	observational, retrospective, single center	Qatar	records of patients with clinical suspicion of COVID-19 (all symptomatic) in whom a CT chest examination was done	984	CT: not specified	COVID-19 Reporting and Data System (CO-RADS)	Fellowship trained chest radiologists with experience of reporting more than 200 COVID-19 CT chests; general radiologists without any sub-speciality fellowships with reporting	RT PCR	[72]

							experience of 100 to 150 COVID-19 CT chest cases; and radiologist in training in PGY-5 with reporting experience of less than 100 COVID-19 CT chests		
Narinx 2020	observational, retrospective, single center	Belgium	suspected of COVID-19 (all symptomatic) presenting at the ER	90	LUS: point-of-care US, BLUE protocol, curved probe CT: low-dose CT	LUS: positive if one or more BLUE points showed a positive B-line parameter CT: suggestive for or inconsistent with COVID-19 infection based on the presence of clinical manifestations as presented by another study	LUS: emergency medical doctor all certified for lung ultrasound (US) and each having more than 5 years of US experience CT: two cardiothoracic radiologists (with 8 and 7 years of cardiothoracic imaging experience)	RT PCR	[33]
Ohana 2020	observational, retrospective, single center	France	adult patients with a clinical suspicion of Covid-19 (all symptomatic) admitted to the Emergency Department during first wave in France	2194	CT: non-contrast enhanced CT	typical Covid-19 lesions: bilateral and predominantly peripheral and sub-pleural ground glass opacities and/or alveolar consolidations	Ten consultant radiologists (4 specialized in chest imaging) with 5–30 years of experience were	RT PCR	[73]
Ozer 2021	observational, retrospective, single center	Turkey	more than 18 yrs old suspected of COVID-19 (symptomatic or asymptomatic) admitted at the ER or outpatient clinics who underwent chest CT and RT PCR	1186	CT: non-contrast enhanced CT	Radiology Society of North America (RSNA)	radiologist with 5 yrs of experience, resident radiologist but overall decision is done with a thoracic radiologist with 8 yrs of experience	RT PCR	[74]
Ozkaraf akili 2021	observational, retrospective, single center	Turkey	more than 18 years old with symptoms of COVID-19 admitted	569	CT: non-contrast	CT findings consistent of pneumonia; details not specified	2 experienced radiologists	RT PCR	[75]

			at the ER who underwent chest CT and RT PCR		enhanced CT				
Pare 2020	observational, retrospective, single center	USA	suspected of COVID-19 (all symptomatic) presenting at the ER who underwent PCR, LUS & CXR	43	CXR: Not specified LUS: point-of-care US, 12 zone scan, mixed probes	CXR: report included infection in the differential, as defined by words such as opacity, consolidation, or airspace disease; negative if no abnormality was noted, an abnormality was noted but attributed to a non-infectious etiology, or was inconclusive for infectious process; LUS: presence of B-lines	CXR: Not specified; only mentioned that official xray report was used: LUS: expert emergency physicians with clinical ultrasound fellowship training	RT PCR	[21]
Patel 2020	observational, retrospective, single center	USA	suspected COVID-19 patients (all symptomatic) presenting in the ER	317	CT: high-resolution CT	Scoring system: consistent with multifocal pneumonia (category 1); indeterminate for multifocal pneumonia (category 2); not consistent with multifocal pneumonia (category 3)	3 radiologist with more than 20 years of experience	RT PCR	[76]
Peng 2020	observational, retrospective, single center	China	pediatric patients suspected of COVID-19 (symptomatic and asymptomatic)	72	CT: not specified	presence of GGO, consolidations, with surrounding halo sign, nodules, residual fibre strip, lymphadenopathy	Two experienced pediatric radiologist	RT PCR	[77]
Peyrony 2020	observational, prospective, single center	France	adult patients with suspected COVID-19 (all symptomatic) who were tested for SARS-CoV-2 in the emergency department	CXR: 129; LUS: 84	CXR: Not specified LUS: point-of-care US, scan protocol & probe not specified	CXR: linclear; LUS: presence of B-lines	CXR: Not specified; LUS: emergency physician but experience not reported	RT PCR	[22]
Prokop 2020	observational, retrospective, single center	Netherlands	suspected COVID-19 patients (all symptomatic) presenting in the ER	105	CT: not specified	COVID-19 Reporting and Data System (CO-RADS)	radiologists with varying years of experience	RT PCR	[78]
Ravikanth 2021	observational, cross-sectional, single center	India	adults with clinical suspicion of COVID-19 (all symptomatic) referred to a tertiary care hospital	348	CT: non-contrast enhanced CT	assessed as suspicious or not suspicious of COVID; details not specified	initial judgment by senior resident but final reading by experienced chest radiologist	RT PCR	[79]
Revel 2021	observational, retrospective, multi center	France	CT scans of individuals more than 18 years old suspected of COVID-19 (all symptomatic) presenting at the ER of 20 hospitals during first wave of SARS-CoV-2 inFrance	10735	CT: high-resolution CT	French Society of Radiology criteria	junior radiologist (0.6 to 3 yrs of experience) and senior radiologist (5 to	RT PCR	[80]

							34 years of experience)		
Saeed 2021	observational, retrospective, single center	UAE	suspected to have COVID-19 infection (symptomatics and asymptomatics) presenting at the ER	93	CT: high-resolution CT	Radiology Society of North America (RSNA)	Two radiologists with more than 8 years of experience	RT PCR	[81]
Schiaffino 2020	observational, retrospective, single center	Italy	suspected of COVID-19 (unclear symptomatology) presenting at the ER	535	CXR: portable/bed side	positive or negative according to original radiologic reports	radiologist experience not specified	RT PCR	[23]
Schulze-Hagen 2020	observational, prospective, single center	Germany	adults suspected of COVID-19 (all symptomatic) presenting at the ER	191	CT: low-dose CT	COVID-19 Reporting and Data System (CO-RADS)	radiologist, no details on experience	RT PCR	[82]
Shirota 2021	observational, retrospective, multi center	Japan	suspected to have COVIDD-19 infection (symptomatics and asymptomatic close contact) who underwent chest CT and RT PCR in the hospital and outpatient setting	66	CT: not specified	Radiology Society of North America (RSNA)	two board-certified diagnostic radiologists with 6 and 11 years of experience with chest CT	RT PCR	[83]
Simsek Yurt 2021	observational, retrospective, single center	Turkey	patients admitted to the Emergency Department with the prediagnosis of COVID- 19 (symptomatic and asymptomatic)	3334	CT: not specified	occurrences of peripheral, bilateral, ground glass opacity, multifocal round ground glass opacity (they can be accompanied by other findings of organised pneumonia such as paving stone appearance, consolidation, reverse- halo)	not specified reader	RT PCR	[84]
Song 2020	observational, retrospective, single center	China	adults suspected of COVID-19 (all symptomatic)	211	CT: not specified	diagnosis of viral pneumonia accdg to: multiple bilateral, ill-defined GGOs or mixed consolidation with diffuse peripheral distribution or bilateral pulmonary consolidation	2 radiologists with 8 and 4 years of experience	RT PCR	[85]
Stephanie 2020	observational, retrospective, multi center, case-control	USA	adults who had undergone both at least one nucleic acid amplification–based COVID-19 detection test and at least one chest radiography or CT examination that was performed within a week of testing	CXR: 500; CT: 169	CXR: Not specified CT: Not specified	CXR: assign a severity score for the chest radiography findings: normal, mild, moderate, or severe based on predominant pattern on chest radiographs electing from interstitial opacities, interstitial and airspace (IA) opacities, atelectasis, diffuse airspace (DA) opacities, lobar consolidation, or peripheral opacities; also assigned COVID-19 likelihood score between 1 and 5 (1 being “very unlikely,” 3 being “intermediate likelihood,” and 5 being “highly likely”) CT: CTSS + COVID-19 Likelihood score	varying reader experience in different institutions (4 to 29 years of experience)	RT PCR	[24]

Stevens 2020	observational, retrospective, single center	UK	adults suspected of COVID-19 (all symptomatic) attending the Emergency Department	320	CXR: Not specified	British Society of Thoracic Imaging (BSTI) reporting criteria	consultant practitioner radiologist and advanced practitioner radiologist	RT PCR	[25]
Stuewe 2020	observational, retrospective, single center	Germany	adults suspected of COVID-19 (all symptomatic)	105	CT: low-dose CT	unclear definition	radiologist	RT PCR	[86]
Thomas 2021	observational, retrospective, multi center	France	patients suspected of COVID-19 pneumonia who underwent RT-PCR and chest CT	487	CT: not specified	positive for COVID-19: in cases of typical imaging patterns, including bilateral, subpleural and peripheral ground-glass opacities (GGOs), crazy paving appearance (GGOs and inter-/intra-lobular septal thickening), and bronchovascular thickening.	experimented radiologist senior (mean 10 years of experience ± 5) and one resident (mean 3 years of experience ± 2) using standardized CT reports	RT PCR	[87]
Tung-Chen 2021	observational, prospective, multi center	Spain	more than 18 years old presenting at the ER with clinical suspicion of COVID-19 (all symptomatic) requiring CXR	88	CXR: Not specified LUS: point-of-care US, 12 zone scan, mixed probes	CXR: GGO, interstitial pattern LUS: bilateral pattern of B-lines, isolated or confluent, irregular pleural lines, and/or sub- pleural consolidations	CXR: Two radiologist trainees with 2–4 years of experience under the supervision of a senior radiologist with more than 10 years of experience LUS: UTZ fellowship trained emergency physicians	RT PCR	[26]
Vicini 2021	observational, retrospective, single center	Italy	CT images of patients who underwent RT-PCR and chest CT due to COVID-19 suspicion (all symptomatic)	714	CT: not specified	COVID-19 Reporting and Data System (CO-RADS)	2 radiologist with more than 5 years experience; 2 highly experienced radiographers ; 2 less experienced radiographers	RT PCR	[88]

Wang 2020	observational, retrospective, single center	China	suspected of COVID-10 (symptomatic and asymptomatic)	190	CT: not specified	Standardized imaging reporting system: infectious disease, viral pneumonia is highly likely (class 1), infectious lesions, viral pneumonia (class 2), infectious lesions, pathogens to be investigated (class 3), infectious lesions (class 4)	not specified	RT PCR	[89]
Xiong 2020	observational, prospective, single center	China	suspected of COVID-10 (unclear symptomatology)	47	CT: not specified	subpleural GGO without pleural effusion, bronchial changes or lymphadenopathy	radiologist, no details on experience	RT PCR	[90]

Appendix 4. Detailed Study Appraisal

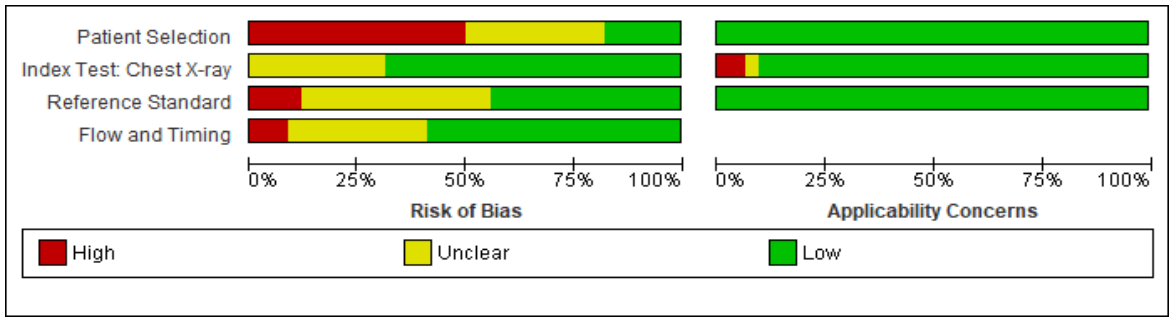


Figure 1. Risk of Bias Ratings of CXR studies

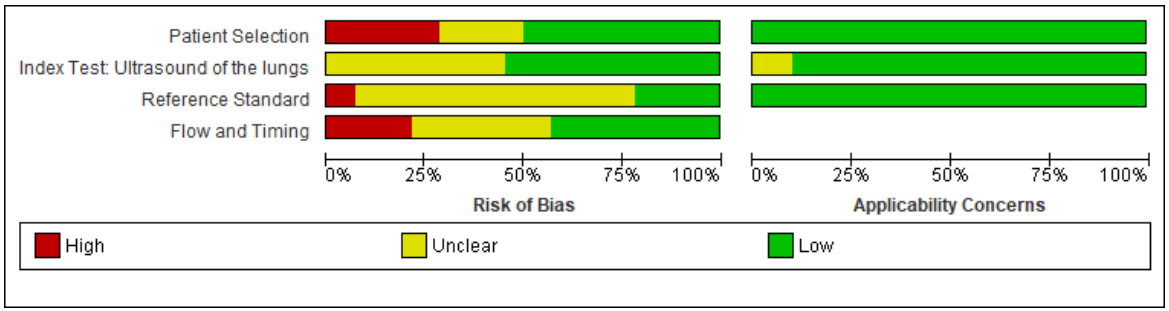


Figure 2. Risk of Bias Ratings of Lung Ultrasound studies

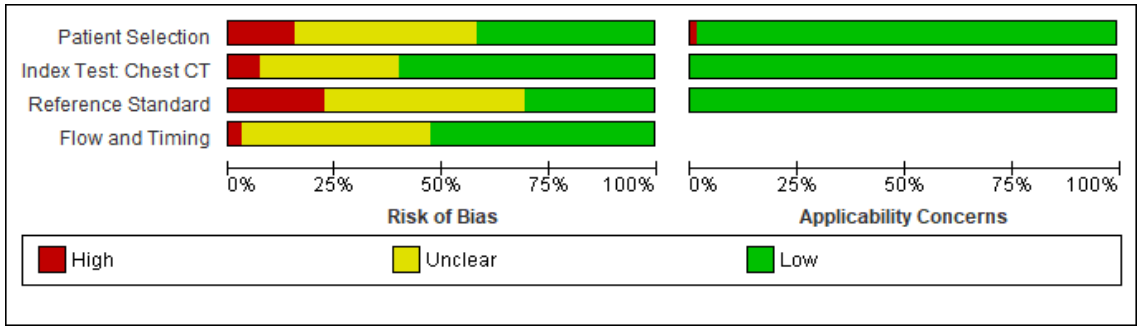


Figure 3. Risk of Bias Ratings of CT scan studies

Appendix 5. Forest Plots

A. Chest X-ray

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Stevens 2020	234	8	14	64	0.94 [0.91, 0.97]	0.89 [0.79, 0.95]
Choudhury 2020	27	25	2	43	0.93 [0.77, 0.99]	0.63 [0.51, 0.75]
Schiaffino 2020	363	50	45	77	0.89 [0.86, 0.92]	0.61 [0.52, 0.69]
Cozzi 2020	363	50	45	77	0.89 [0.86, 0.92]	0.61 [0.52, 0.69]
Khan 2021	471	1	59	2	0.89 [0.86, 0.91]	0.67 [0.09, 0.99]
Tung-Chen 2021	47	24	6	53	0.89 [0.77, 0.96]	0.69 [0.57, 0.79]
Majeed 2021	63	10	12	20	0.84 [0.74, 0.91]	0.67 [0.47, 0.83]
Borakati 2020	441	186	107	126	0.80 [0.77, 0.84]	0.40 [0.35, 0.46]
Peyrony 2020	61	20	19	29	0.76 [0.65, 0.85]	0.59 [0.44, 0.73]
Hwang 2020 [A]	11	105	5	211	0.69 [0.41, 0.89]	0.67 [0.61, 0.72]
Murphy 2020	146	45	77	186	0.65 [0.59, 0.72]	0.81 [0.75, 0.85]
Hwang 2021 [A]	52	22	28	59	0.65 [0.54, 0.75]	0.73 [0.62, 0.82]
Ippolito 2020	116	35	88	279	0.57 [0.50, 0.64]	0.89 [0.85, 0.92]
Gibbons 2021	36	21	28	16	0.56 [0.43, 0.69]	0.43 [0.27, 0.61]
Du 2021[B]	15	17	12	338	0.56 [0.35, 0.75]	0.95 [0.92, 0.97]
Du 2021 [A]	22	144	18	421	0.55 [0.38, 0.71]	0.75 [0.71, 0.78]
Stephanie 2020	136	43	113	208	0.55 [0.48, 0.61]	0.83 [0.78, 0.87]
Pare 2020	14	4	13	12	0.52 [0.32, 0.71]	0.75 [0.48, 0.93]
Gichoya 2021 [B]	274	44	414	906	0.40 [0.36, 0.44]	0.95 [0.94, 0.97]
Gichoya 2021 [A]	110	6	578	944	0.16 [0.13, 0.19]	0.99 [0.99, 1.00]

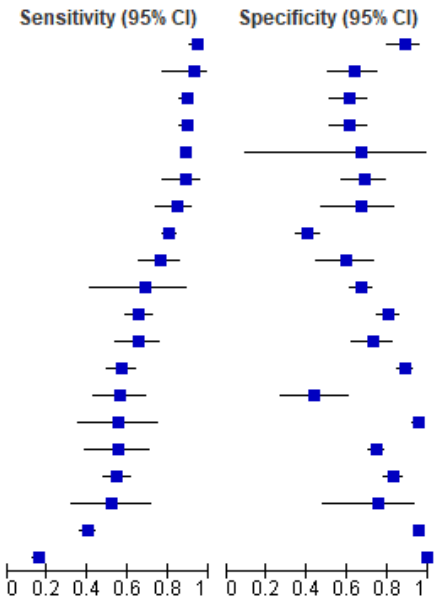


Figure 1. Forest Plot of CXR studies (Overall)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Stevens 2020	234	8	14	64	0.94 [0.91, 0.97]	0.89 [0.79, 0.95]
Choudhury 2020	27	25	2	43	0.93 [0.77, 0.99]	0.63 [0.51, 0.75]
Khan 2021	471	1	59	2	0.89 [0.86, 0.91]	0.67 [0.09, 0.99]
Tung-Chen 2021	47	24	6	53	0.89 [0.77, 0.96]	0.69 [0.57, 0.79]
Majeed 2021	63	10	12	20	0.84 [0.74, 0.91]	0.67 [0.47, 0.83]
Peyrony 2020	61	20	19	29	0.76 [0.65, 0.85]	0.59 [0.44, 0.73]
Hwang 2020 [A]	8	84	4	151	0.67 [0.35, 0.90]	0.64 [0.58, 0.70]
Murphy 2020	146	45	77	186	0.65 [0.59, 0.72]	0.81 [0.75, 0.85]
Ippolito 2020	116	35	88	279	0.57 [0.50, 0.64]	0.89 [0.85, 0.92]
Gibbons 2021	36	21	28	16	0.56 [0.43, 0.69]	0.43 [0.27, 0.61]
Du 2021[B]	15	17	12	338	0.56 [0.35, 0.75]	0.95 [0.92, 0.97]
Du 2021 [A]	22	144	18	421	0.55 [0.38, 0.71]	0.75 [0.71, 0.78]
Stephanie 2020	136	43	113	208	0.55 [0.48, 0.61]	0.83 [0.78, 0.87]
Pare 2020	14	4	13	12	0.52 [0.32, 0.71]	0.75 [0.48, 0.93]

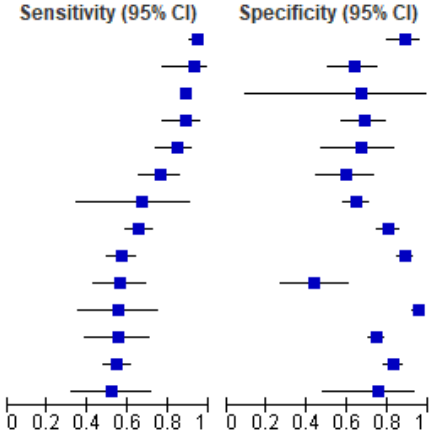


Figure 2. Forest Plot of CXR studies (Subgroup analysis: symptomatic patients)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hwang 2020 [A]	3	21	1	60	0.75 [0.19, 0.99]	0.74 [0.63, 0.83]

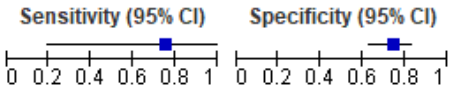


Figure 3. Forest plot of CXR studies (Subgroup analysis: asymptomatic patients)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cozzi 2020	363	50	45	77	0.89 [0.86, 0.92]	0.61 [0.52, 0.69]
Borakati 2020	441	186	107	126	0.80 [0.77, 0.84]	0.40 [0.35, 0.46]
Hwang 2020 [A]	11	105	5	211	0.69 [0.41, 0.89]	0.67 [0.61, 0.72]
Hwang 2021 [A]	52	33	28	59	0.65 [0.54, 0.75]	0.64 [0.53, 0.74]

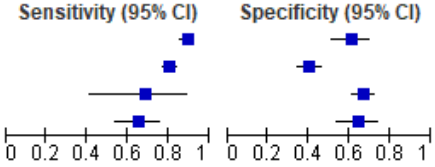


Figure 4. Forest plot of CXR studies (Subgroup analysis: mixed)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Stevens 2020	234	8	14	64	0.94 [0.91, 0.97]	0.89 [0.79, 0.95]
Cozzi 2020	298	66	34	37	0.90 [0.86, 0.93]	0.36 [0.27, 0.46]
Tung-Chen 2021	47	24	6	53	0.89 [0.77, 0.96]	0.69 [0.57, 0.79]
Majeed 2021	63	10	12	20	0.84 [0.74, 0.91]	0.67 [0.47, 0.83]
Borakati 2020	441	186	107	126	0.80 [0.77, 0.84]	0.40 [0.35, 0.46]
Hwang 2020 [A]	11	105	5	211	0.69 [0.41, 0.89]	0.67 [0.61, 0.72]
Murphy 2020	146	45	77	186	0.65 [0.59, 0.72]	0.81 [0.75, 0.85]
Hwang 2021 [A]	52	33	28	59	0.65 [0.54, 0.75]	0.64 [0.53, 0.74]
Ippolito 2020	116	35	88	279	0.57 [0.50, 0.64]	0.89 [0.85, 0.92]
Du 2021 [A]	22	144	18	421	0.55 [0.38, 0.71]	0.75 [0.71, 0.78]
Gichoya 2021 [K]	27	4	23	46	0.54 [0.39, 0.68]	0.92 [0.81, 0.98]
Gichoya 2021 [I]	21	1	29	49	0.42 [0.28, 0.57]	0.98 [0.89, 1.00]
Gichoya 2021 [H]	19	1	31	49	0.38 [0.25, 0.53]	0.98 [0.89, 1.00]
Gichoya 2021 [F]	17	1	33	49	0.34 [0.21, 0.49]	0.98 [0.89, 1.00]
Gichoya 2021 [C]	14	1	36	49	0.28 [0.16, 0.42]	0.98 [0.89, 1.00]
Gichoya 2021 [D]	12	0	38	50	0.24 [0.13, 0.38]	1.00 [0.93, 1.00]

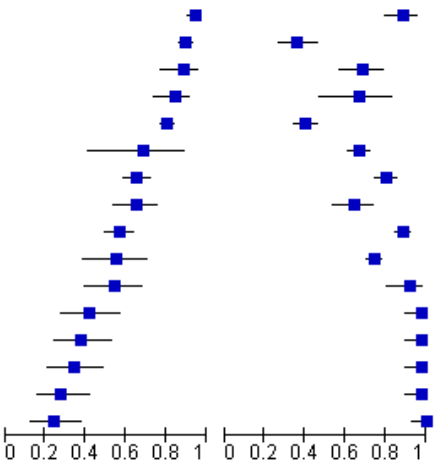


Figure 5. Forest plot of CXR studies (Subgroup analysis: experienced reader)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hwang 2021 [A]	43	38	37	54	0.54 [0.42, 0.65]	0.59 [0.48, 0.69]
Gichoya 2021 [G]	19	1	31	49	0.38 [0.25, 0.53]	0.98 [0.89, 1.00]
Gichoya 2021 [J]	13	1	37	49	0.26 [0.15, 0.40]	0.98 [0.89, 1.00]
Gichoya 2021 [L]	6	0	44	50	0.12 [0.05, 0.24]	1.00 [0.93, 1.00]
Gichoya 2021 [E]	4	0	46	50	0.08 [0.02, 0.19]	1.00 [0.93, 1.00]

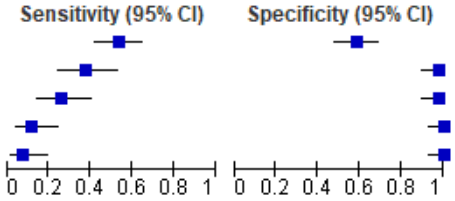


Figure 6. Forest plot of CXR studies (Subgroup analysis: inexperienced reader)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Schiaffino 2020	363	50	45	77	0.89 [0.86, 0.92]	0.61 [0.52, 0.69]
Cozzi 2020	363	50	45	77	0.89 [0.86, 0.92]	0.61 [0.52, 0.69]
Tung-Chen 2021	47	24	6	53	0.89 [0.77, 0.96]	0.69 [0.57, 0.79]
Peyrony 2020	61	20	19	29	0.76 [0.65, 0.85]	0.59 [0.44, 0.73]
Hwang 2020 [A]	11	105	5	211	0.69 [0.41, 0.89]	0.67 [0.61, 0.72]
Ippolito 2020	116	35	88	279	0.57 [0.50, 0.64]	0.89 [0.85, 0.92]
Gibbons 2021	36	21	28	16	0.56 [0.43, 0.69]	0.43 [0.27, 0.61]
Du 2021 [B]	15	17	12	338	0.56 [0.35, 0.75]	0.95 [0.92, 0.97]
Du 2021 [A]	22	144	18	421	0.55 [0.38, 0.71]	0.75 [0.71, 0.78]
Pare 2020	14	4	13	12	0.52 [0.32, 0.71]	0.75 [0.48, 0.93]
Gichoya 2021 [B]	274	44	414	906	0.40 [0.36, 0.44]	0.95 [0.94, 0.97]
Gichoya 2021 [A]	110	6	578	944	0.16 [0.13, 0.19]	0.99 [0.99, 1.00]

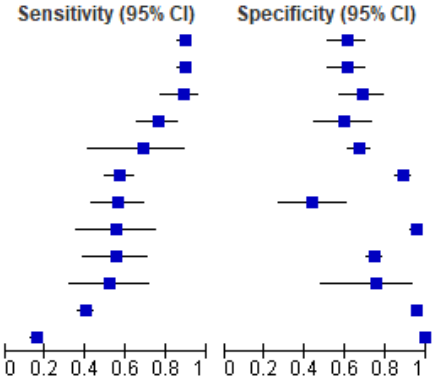


Figure 7. Forest plot of CXR studies (Subgroup analysis: Reader Impression)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Stevens 2020	234	8	14	64	0.94 [0.91, 0.97]	0.89 [0.79, 0.95]
Choudhury 2020	27	25	2	43	0.93 [0.77, 0.99]	0.63 [0.51, 0.75]
Khan 2021	471	1	59	2	0.89 [0.86, 0.91]	0.67 [0.09, 0.99]
Majeed 2021	63	10	12	20	0.84 [0.74, 0.91]	0.67 [0.47, 0.83]
Borakati 2020	441	186	107	126	0.80 [0.77, 0.84]	0.40 [0.35, 0.46]
Murphy 2020	146	45	77	186	0.65 [0.59, 0.72]	0.81 [0.75, 0.85]
Hwang 2020 [A]	52	33	28	59	0.65 [0.54, 0.75]	0.64 [0.53, 0.74]
Stephanie 2020	136	43	113	208	0.55 [0.48, 0.61]	0.83 [0.78, 0.87]

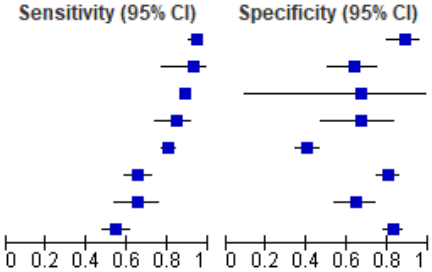


Figure 8. Forest plot of CXR studies (Subgroup analysis: Scoring System)

B. Lung Ultrasound

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gibbons 2021	64	32	0	5	1.00 [0.94, 1.00]	0.14 [0.05, 0.29]
Tung-Chen 2021	53	33	1	2	0.98 [0.90, 1.00]	0.06 [0.01, 0.19]
Bitar 2021	60	4	2	11	0.97 [0.89, 1.00]	0.73 [0.45, 0.92]
Bar 2020	30	26	1	43	0.97 [0.83, 1.00]	0.62 [0.50, 0.74]
Haak 2020	23	28	1	41	0.96 [0.79, 1.00]	0.59 [0.47, 0.71]
Narinx 2020	14	59	1	16	0.93 [0.68, 1.00]	0.21 [0.13, 0.32]
Lieveld 2020	79	29	7	71	0.92 [0.84, 0.97]	0.71 [0.61, 0.80]
Pare 2020	24	7	3	9	0.89 [0.71, 0.98]	0.56 [0.30, 0.80]
Dini 2020	74	24	20	32	0.79 [0.69, 0.86]	0.57 [0.43, 0.70]
Peyrony 2020	36	4	11	33	0.77 [0.62, 0.88]	0.89 [0.75, 0.97]
Fonsi 2020	30	4	14	15	0.68 [0.52, 0.81]	0.79 [0.54, 0.94]

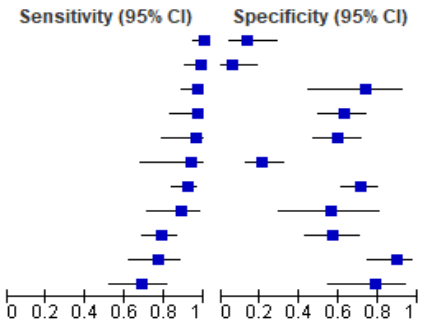


Figure 9. Forest Plot of LUS studies (Overall)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gibbons 2021	64	32	0	5	1.00 [0.94, 1.00]	0.14 [0.05, 0.29]
Tung-Chen 2021	53	33	1	2	0.98 [0.90, 1.00]	0.06 [0.01, 0.19]
Bitar 2021	60	4	2	11	0.97 [0.89, 1.00]	0.73 [0.45, 0.92]
Haak 2020	23	28	1	41	0.96 [0.79, 1.00]	0.59 [0.47, 0.71]
Narinx 2020	14	59	1	16	0.93 [0.68, 1.00]	0.21 [0.13, 0.32]
Lieveld 2020	79	29	7	71	0.92 [0.84, 0.97]	0.71 [0.61, 0.80]
Pare 2020	24	7	3	9	0.89 [0.71, 0.98]	0.56 [0.30, 0.80]
Dini 2020	51	16	10	15	0.84 [0.72, 0.92]	0.48 [0.30, 0.67]
Peyrony 2020	36	4	11	33	0.77 [0.62, 0.88]	0.89 [0.75, 0.97]
Fonsi 2020	30	4	14	15	0.68 [0.52, 0.81]	0.79 [0.54, 0.94]

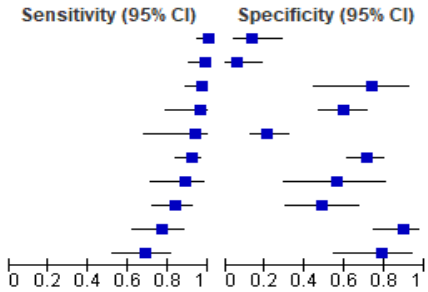


Figure 10. Forest Plot of LUS studies (Subgroup analysis: Symptomatic patients)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dini 2020	23	8	10	17	0.70 [0.51, 0.84]	0.68 [0.46, 0.85]

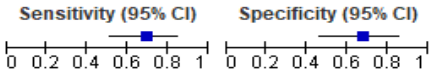


Figure 11. Forest Plot of LUS studies (Subgroup analysis: Asymptomatic patients)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gibbons 2021	64	32	0	5	1.00 [0.94, 1.00]	0.14 [0.05, 0.29]
Tung-Chen 2021	53	33	1	2	0.98 [0.90, 1.00]	0.06 [0.01, 0.19]
Bitar 2021	60	4	2	11	0.97 [0.89, 1.00]	0.73 [0.45, 0.92]
Haak 2020	23	28	1	41	0.96 [0.79, 1.00]	0.59 [0.47, 0.71]
Narinx 2020	14	59	1	16	0.93 [0.68, 1.00]	0.21 [0.13, 0.32]
Lieveld 2020	79	29	7	71	0.92 [0.84, 0.97]	0.71 [0.61, 0.80]
Pare 2020	24	7	3	9	0.89 [0.71, 0.98]	0.56 [0.30, 0.80]
Fonsi 2020	30	4	14	11	0.68 [0.52, 0.81]	0.73 [0.45, 0.92]

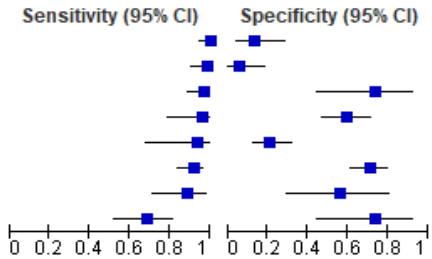


Figure 12. Forest Plot of LUS studies (Subgroup analysis: Experienced reader)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gibbons 2021	62	32	2	5	0.97 [0.89, 1.00]	0.14 [0.05, 0.29]

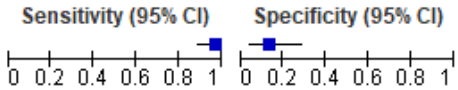


Figure 13. Forest Plot of LUS studies (Subgroup analysis: Inexperienced reader)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gibbons 2021	64	32	0	5	1.00 [0.94, 1.00]	0.14 [0.05, 0.29]
Tung-Chen 2021	53	33	1	2	0.98 [0.90, 1.00]	0.06 [0.01, 0.19]
Bitar 2021	60	4	2	11	0.97 [0.89, 1.00]	0.73 [0.45, 0.92]
Bar 2020	30	26	1	43	0.97 [0.83, 1.00]	0.62 [0.50, 0.74]
Narinx 2020	14	59	1	16	0.93 [0.68, 1.00]	0.21 [0.13, 0.32]
Lieveld 2020	79	29	7	71	0.92 [0.84, 0.97]	0.71 [0.61, 0.80]
Pare 2020	24	7	3	9	0.89 [0.71, 0.98]	0.56 [0.30, 0.80]
Peyrony 2020	36	4	11	33	0.77 [0.62, 0.88]	0.89 [0.75, 0.97]
Fonsi 2020	30	4	14	15	0.68 [0.52, 0.81]	0.79 [0.54, 0.94]

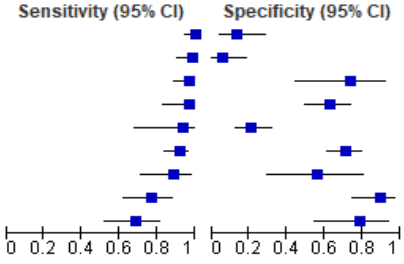


Figure 14. Forest Plot of LUS studies (Subgroup analysis: Reader Impression)

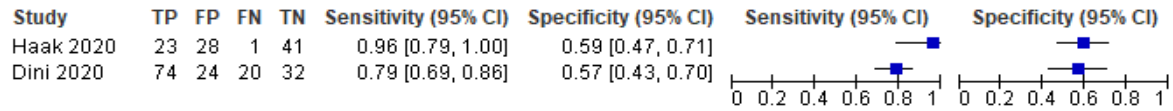


Figure 15. Forest Plot of LUS studies (Subgroup analysis: Scoring System)

C. Chest CT scan

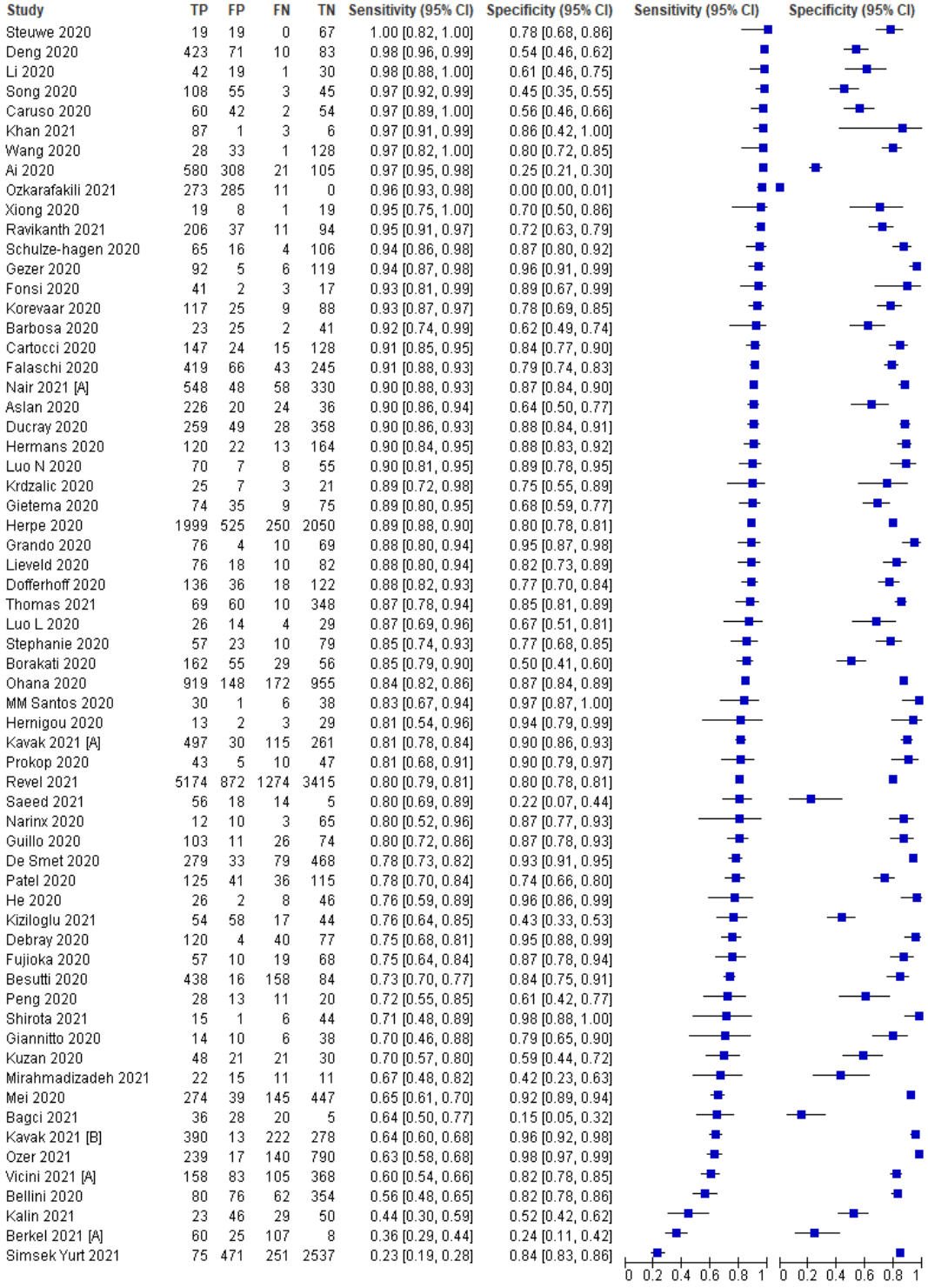


Figure 16. Forest Plot of CT scan studies (Overall)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Steuwe 2020	19	19	0	67	1.00 [0.82, 1.00]	0.78 [0.68, 0.86]
Deng 2020	423	71	10	83	0.98 [0.96, 0.99]	0.54 [0.46, 0.62]
Li 2020	42	19	1	30	0.98 [0.88, 1.00]	0.61 [0.46, 0.75]
Song 2020	108	55	3	45	0.97 [0.92, 0.99]	0.45 [0.35, 0.55]
Caruso 2020	60	42	2	54	0.97 [0.89, 1.00]	0.56 [0.46, 0.66]
Khan 2021	87	1	3	6	0.97 [0.91, 0.99]	0.86 [0.42, 1.00]
Ozkarafakili 2021	273	285	11	0	0.96 [0.93, 0.98]	0.00 [0.00, 0.01]
Ravikanth 2021	206	37	11	94	0.95 [0.91, 0.97]	0.72 [0.63, 0.79]
Schulze-hagen 2020	65	16	4	106	0.94 [0.86, 0.98]	0.87 [0.80, 0.92]
Gezer 2020	92	5	6	119	0.94 [0.87, 0.98]	0.96 [0.91, 0.99]
Fonsi 2020	41	2	3	17	0.93 [0.81, 0.99]	0.89 [0.67, 0.99]
Korevaar 2020	117	25	9	88	0.93 [0.87, 0.97]	0.78 [0.69, 0.85]
Barbosa 2020	23	25	2	41	0.92 [0.74, 0.99]	0.62 [0.49, 0.74]
Cartocci 2020	147	24	15	128	0.91 [0.85, 0.95]	0.84 [0.77, 0.90]
Falaschi 2020	419	66	43	245	0.91 [0.88, 0.93]	0.79 [0.74, 0.83]
Nair 2021 [A]	548	48	58	330	0.90 [0.88, 0.93]	0.87 [0.84, 0.90]
Aslan 2020	226	20	24	36	0.90 [0.86, 0.94]	0.64 [0.50, 0.77]
Krdzalic 2020	25	7	3	21	0.89 [0.72, 0.98]	0.75 [0.55, 0.89]
Gietema 2020	74	35	9	75	0.89 [0.80, 0.95]	0.68 [0.59, 0.77]
Herpe 2020	1999	525	250	2050	0.89 [0.88, 0.90]	0.80 [0.78, 0.81]
Lieveld 2020	76	18	10	82	0.88 [0.80, 0.94]	0.82 [0.73, 0.89]
Grando 2020	76	4	10	69	0.88 [0.80, 0.94]	0.95 [0.87, 0.98]
Dofferhoff 2020	136	36	18	122	0.88 [0.82, 0.93]	0.77 [0.70, 0.84]
Thomas 2021	69	60	10	348	0.87 [0.78, 0.94]	0.85 [0.81, 0.89]
Luo L 2020	26	14	4	29	0.87 [0.69, 0.96]	0.67 [0.51, 0.81]
Stephanie 2020	57	23	10	79	0.85 [0.74, 0.93]	0.77 [0.68, 0.85]
Ohana 2020	919	148	172	955	0.84 [0.82, 0.86]	0.87 [0.84, 0.89]
MM Santos 2020	30	1	6	38	0.83 [0.67, 0.94]	0.97 [0.87, 1.00]
Prokop 2020	43	5	10	47	0.81 [0.68, 0.91]	0.90 [0.79, 0.97]
Revel 2021	5174	872	1274	3415	0.80 [0.79, 0.81]	0.80 [0.78, 0.81]
Narinx 2020	12	10	3	65	0.80 [0.52, 0.96]	0.87 [0.77, 0.93]
Guillo 2020	103	11	26	74	0.80 [0.72, 0.86]	0.87 [0.78, 0.93]
De Smet 2020	279	33	79	468	0.78 [0.73, 0.82]	0.93 [0.91, 0.95]
Patel 2020	125	41	36	115	0.78 [0.70, 0.84]	0.74 [0.66, 0.80]
Fujioka 2020	57	10	19	68	0.75 [0.64, 0.84]	0.87 [0.78, 0.94]
Besutti 2020	438	16	158	84	0.73 [0.70, 0.77]	0.84 [0.75, 0.91]
Giannitto 2020	14	10	6	38	0.70 [0.46, 0.88]	0.79 [0.65, 0.90]
Kuzan 2020	48	21	21	30	0.70 [0.57, 0.80]	0.59 [0.44, 0.72]
Vicini 2021 [A]	158	83	105	368	0.60 [0.54, 0.66]	0.82 [0.78, 0.85]
Bellini 2020	80	76	62	354	0.56 [0.48, 0.65]	0.82 [0.78, 0.86]

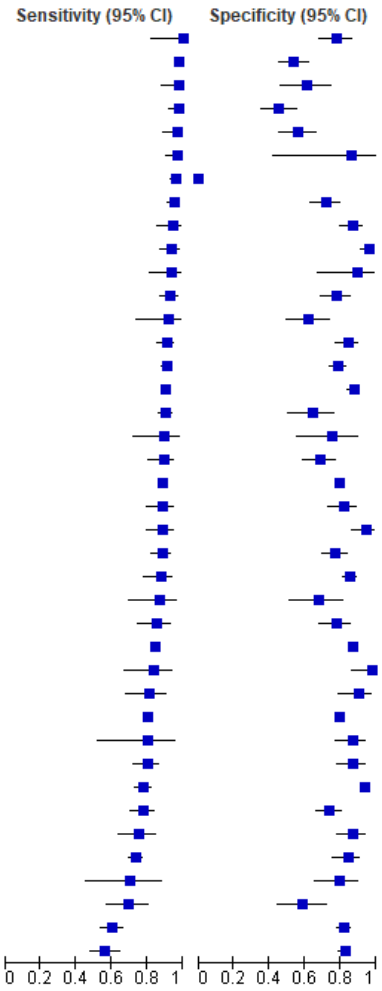
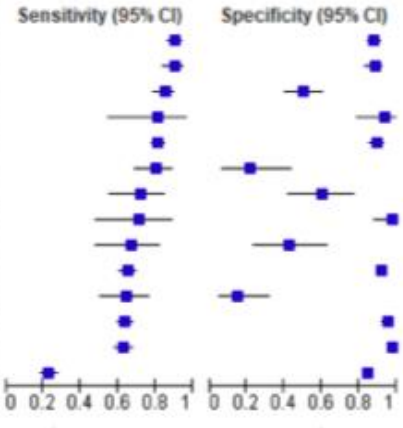


Figure 17. Forest Plot of CT scan studies (Subgroup analysis: symptomatic patients)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ducray 2020	259	49	28	358	0.90 [0.86, 0.93]	0.88 [0.84, 0.91]
Hermans 2020	120	22	13	164	0.90 [0.84, 0.95]	0.88 [0.83, 0.92]
Borakati 2020	162	55	29	56	0.85 [0.79, 0.90]	0.50 [0.41, 0.60]
Hernigou 2020	13	2	3	29	0.81 [0.54, 0.96]	0.94 [0.79, 0.99]
Kavak 2021 [A]	497	30	115	261	0.81 [0.78, 0.84]	0.90 [0.86, 0.93]
Saeed 2021	56	18	14	5	0.80 [0.69, 0.89]	0.22 [0.07, 0.44]
Peng 2020	28	13	11	20	0.72 [0.55, 0.85]	0.61 [0.42, 0.77]
Shirota 2021	15	1	6	44	0.71 [0.48, 0.89]	0.98 [0.88, 1.00]
Mirahmadizadeh 2021	22	15	11	11	0.67 [0.48, 0.82]	0.42 [0.23, 0.63]
Mei 2020	274	39	145	447	0.65 [0.61, 0.70]	0.92 [0.89, 0.94]
Bagci 2021	36	28	20	5	0.64 [0.50, 0.77]	0.15 [0.05, 0.32]
Kavak 2021 [B]	390	13	222	278	0.64 [0.60, 0.68]	0.96 [0.92, 0.98]
Ozer 2021	239	17	140	790	0.63 [0.58, 0.68]	0.98 [0.97, 0.99]
Simsek Yurt 2021	75	471	251	2537	0.23 [0.19, 0.28]	0.84 [0.83, 0.86]



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Wang 2020	28	33	1	128	0.97 [0.82, 1.00]	0.80 [0.72, 0.85]
Ducray 2020	259	49	28	358	0.90 [0.86, 0.93]	0.88 [0.84, 0.91]
Hermans 2020	120	22	13	164	0.90 [0.84, 0.95]	0.88 [0.83, 0.92]
Borakati 2020	162	55	29	56	0.85 [0.79, 0.90]	0.50 [0.41, 0.60]
Hernigou 2020	13	2	3	29	0.81 [0.54, 0.96]	0.94 [0.79, 0.99]
Kavak 2021 [A]	497	30	115	261	0.81 [0.78, 0.84]	0.90 [0.86, 0.93]
Saeed 2021	56	18	14	5	0.80 [0.69, 0.89]	0.22 [0.07, 0.44]
Peng 2020	28	13	11	20	0.72 [0.55, 0.85]	0.61 [0.42, 0.77]
Shirota 2021	15	1	6	44	0.71 [0.48, 0.89]	0.98 [0.88, 1.00]
Mirahmadizadeh 2021	22	15	11	11	0.67 [0.48, 0.82]	0.42 [0.23, 0.63]
Mei 2020	274	39	145	447	0.65 [0.61, 0.70]	0.92 [0.89, 0.94]
Bagci 2021	36	28	20	5	0.64 [0.50, 0.77]	0.15 [0.05, 0.32]
Kavak 2021 [B]	390	13	222	278	0.64 [0.60, 0.68]	0.96 [0.92, 0.98]
Ozer 2021	239	17	140	790	0.63 [0.58, 0.68]	0.98 [0.97, 0.99]
Simsek Yurt 2021	75	471	251	2537	0.23 [0.19, 0.28]	0.84 [0.83, 0.86]

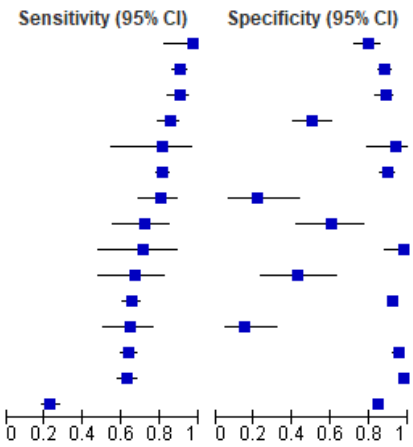


Figure 18. Forest Plot of CT scan studies (Subgroup analysis: both symptomatic& asymptomatic patients)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Deng 2020	423	71	10	83	0.98 [0.96, 0.99]	0.54 [0.46, 0.62]
Caruso 2020	60	42	2	54	0.97 [0.89, 1.00]	0.56 [0.46, 0.66]
Ozkarafakili 2021	273	285	11	0	0.96 [0.93, 0.98]	0.00 [0.00, 0.01]
Ravikanth 2021	206	37	11	94	0.95 [0.91, 0.97]	0.72 [0.63, 0.79]
Gezer 2020	92	5	6	119	0.94 [0.87, 0.98]	0.96 [0.91, 0.99]
Fonsi 2020	41	2	3	17	0.93 [0.81, 0.99]	0.89 [0.67, 0.99]
Barbosa 2020	23	25	2	41	0.92 [0.74, 0.99]	0.62 [0.49, 0.74]
Nair 2021 [C]	551	11	55	367	0.91 [0.88, 0.93]	0.97 [0.95, 0.99]
Cartocci 2020	147	24	15	128	0.91 [0.85, 0.95]	0.84 [0.77, 0.90]
Falaschi 2020	419	66	43	245	0.91 [0.88, 0.93]	0.79 [0.74, 0.83]
Aslan 2020	226	20	24	36	0.90 [0.86, 0.94]	0.64 [0.50, 0.77]
Hermans 2020	120	22	13	164	0.90 [0.84, 0.95]	0.88 [0.83, 0.92]
Nair 2021 [B]	545	68	61	310	0.90 [0.87, 0.92]	0.82 [0.78, 0.86]
Krdzalic 2020	25	7	3	21	0.89 [0.72, 0.98]	0.75 [0.55, 0.89]
Gietema 2020	74	35	9	75	0.89 [0.80, 0.95]	0.68 [0.59, 0.77]
Herpe 2020	1999	525	250	2050	0.89 [0.88, 0.90]	0.80 [0.78, 0.81]
Grando 2020	76	4	10	69	0.88 [0.80, 0.94]	0.95 [0.87, 0.98]
Luo L 2020	26	14	4	29	0.87 [0.69, 0.96]	0.67 [0.51, 0.81]
Borakati 2020	162	55	29	56	0.85 [0.79, 0.90]	0.50 [0.41, 0.60]
Ohana 2020	919	148	172	955	0.84 [0.82, 0.86]	0.87 [0.84, 0.89]
MM Santos 2020	30	1	6	38	0.83 [0.67, 0.94]	0.97 [0.87, 1.00]
Hernigou 2020	13	2	3	29	0.81 [0.54, 0.96]	0.94 [0.79, 0.99]
Kavak 2021 [A]	497	30	115	261	0.81 [0.78, 0.84]	0.90 [0.86, 0.93]
Revel 2021	3536	611	853	2362	0.81 [0.79, 0.82]	0.79 [0.78, 0.81]
Saeed 2021	56	18	14	5	0.80 [0.69, 0.89]	0.22 [0.07, 0.44]
Narinx 2020	12	10	3	65	0.80 [0.52, 0.96]	0.87 [0.77, 0.93]
De Smet 2020	279	33	79	468	0.78 [0.73, 0.82]	0.93 [0.91, 0.95]
Patel 2020	125	41	36	115	0.78 [0.70, 0.84]	0.74 [0.66, 0.80]
He 2020	26	2	8	46	0.76 [0.59, 0.89]	0.96 [0.86, 0.99]
Kiziloglu 2021	54	58	17	44	0.76 [0.64, 0.85]	0.43 [0.33, 0.53]
Debray 2020	120	4	40	77	0.75 [0.68, 0.81]	0.95 [0.88, 0.99]
Peng 2020	28	13	11	20	0.72 [0.55, 0.85]	0.61 [0.42, 0.77]
Shirota 2021	15	1	6	44	0.71 [0.48, 0.89]	0.98 [0.88, 1.00]
Giannitto 2020	14	10	6	38	0.70 [0.46, 0.88]	0.79 [0.65, 0.90]
Mei 2020	274	39	145	447	0.65 [0.61, 0.70]	0.92 [0.89, 0.94]
Bagci 2021	36	28	20	5	0.64 [0.50, 0.77]	0.15 [0.05, 0.32]
Kavak 2021 [B]	390	13	222	278	0.64 [0.60, 0.68]	0.96 [0.92, 0.98]
Ozer 2021	239	17	140	790	0.63 [0.58, 0.68]	0.98 [0.97, 0.99]
Vicini 2021 [A]	158	83	105	368	0.60 [0.54, 0.66]	0.82 [0.78, 0.85]
Kalin 2021	23	46	29	50	0.44 [0.30, 0.59]	0.52 [0.42, 0.62]
Berkel 2021 [A]	60	25	107	8	0.36 [0.29, 0.44]	0.24 [0.11, 0.42]

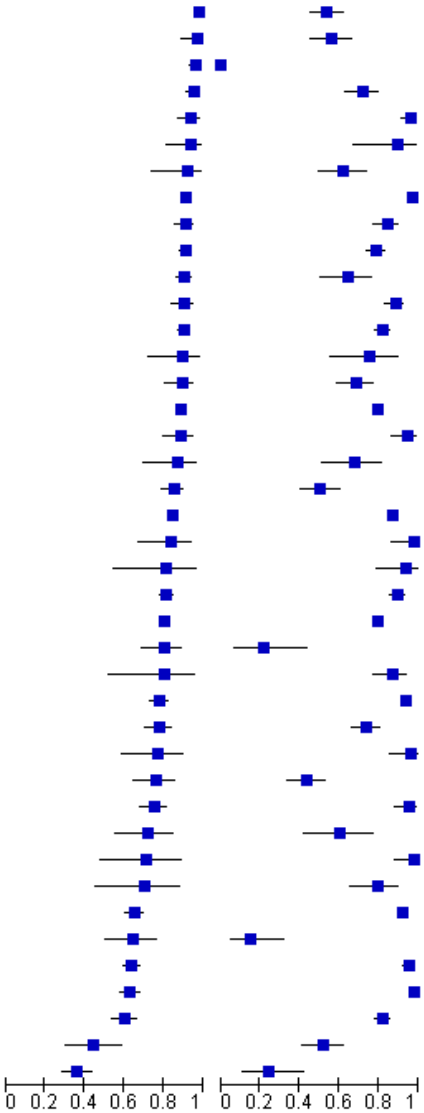


Figure 19. Forest Plot of CT scan studies (Subgroup analysis: experienced readers)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nair 2021 [D]	545	49	61	329	0.90 [0.87, 0.92]	0.87 [0.83, 0.90]
Revel 2021	1638	261	421	1053	0.80 [0.78, 0.81]	0.80 [0.78, 0.82]
Vicini 2021 [B]	154	82	109	369	0.59 [0.52, 0.65]	0.82 [0.78, 0.85]
Vicini 2021 [C]	148	83	115	368	0.56 [0.50, 0.62]	0.82 [0.78, 0.85]

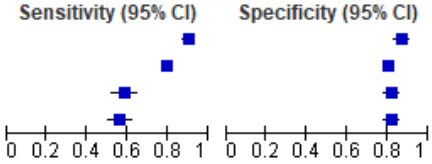


Figure 20. Forest Plot of CT scan studies (Subgroup analysis: inexperienced readers)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Revel 2021	2550	87	342	162	0.88 [0.87, 0.89]	0.65 [0.59, 0.71]

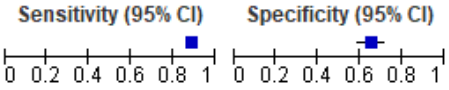


Figure 21. Forest Plot of CT scan studies (Subgroup analysis: Timing of Testing in Relation to Symptom Onset - Late)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Song 2020	108	55	3	45	0.97 [0.92, 0.99]	0.45 [0.35, 0.55]
Khan 2021	87	1	3	6	0.97 [0.91, 0.99]	0.86 [0.42, 1.00]
Schulze-hagen 2020	65	16	4	106	0.94 [0.86, 0.98]	0.87 [0.80, 0.92]
Korevaar 2020	117	25	9	88	0.93 [0.87, 0.97]	0.78 [0.69, 0.85]
Barbosa 2020	23	25	2	41	0.92 [0.74, 0.99]	0.62 [0.49, 0.74]
Nair 2021 [A]	548	48	58	330	0.90 [0.88, 0.93]	0.87 [0.84, 0.90]
Hermans 2020	120	22	13	164	0.90 [0.84, 0.95]	0.88 [0.83, 0.92]
Krdzalic 2020	25	7	3	21	0.89 [0.72, 0.98]	0.75 [0.55, 0.89]
Stephanie 2020	57	23	10	79	0.85 [0.74, 0.93]	0.77 [0.68, 0.85]
Prokop 2020	43	5	10	47	0.81 [0.68, 0.91]	0.90 [0.79, 0.97]
Revel 2021	5174	872	1274	3415	0.80 [0.79, 0.81]	0.80 [0.78, 0.81]
Saeed 2021	56	18	14	5	0.80 [0.69, 0.89]	0.22 [0.07, 0.44]
Guillo 2020	103	11	26	74	0.80 [0.72, 0.86]	0.87 [0.78, 0.93]
Shirota 2021	15	1	6	44	0.71 [0.48, 0.89]	0.98 [0.88, 1.00]
Giannitto 2020	14	10	6	38	0.70 [0.46, 0.88]	0.79 [0.65, 0.90]

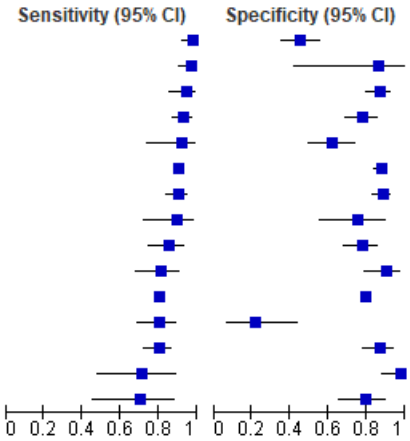


Figure 22. Forest Plot of CT scan studies (Subgroup analysis: Timing of Testing in Relation to Symptom Onset - Mixed: Early & Late)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Steuwe 2020	19	19	0	67	1.00 [0.82, 1.00]	0.78 [0.68, 0.86]
Deng 2020	423	71	10	83	0.98 [0.96, 0.99]	0.54 [0.46, 0.62]
Song 2020	108	55	3	45	0.97 [0.92, 0.99]	0.45 [0.35, 0.55]
Caruso 2020	60	42	2	54	0.97 [0.89, 1.00]	0.56 [0.46, 0.66]
Ai 2020	580	308	21	105	0.97 [0.95, 0.98]	0.25 [0.21, 0.30]
Ozkarafakili 2021	273	285	11	0	0.96 [0.93, 0.98]	0.00 [0.00, 0.01]
Xiong 2020	19	8	1	19	0.95 [0.75, 1.00]	0.70 [0.50, 0.86]
Ravikanth 2021	206	37	11	94	0.95 [0.91, 0.97]	0.72 [0.63, 0.79]
Gezer 2020	92	5	6	119	0.94 [0.87, 0.98]	0.96 [0.91, 0.99]
Fonsi 2020	41	2	3	17	0.93 [0.81, 0.99]	0.89 [0.67, 0.99]
Aslan 2020	226	20	24	36	0.90 [0.86, 0.94]	0.64 [0.50, 0.77]
Luo N 2020	70	7	8	55	0.90 [0.81, 0.95]	0.89 [0.78, 0.95]
Herpe 2020	1999	525	250	2050	0.89 [0.88, 0.90]	0.80 [0.78, 0.81]
Thomas 2021	69	60	10	348	0.87 [0.78, 0.94]	0.85 [0.81, 0.89]
Ohana 2020	919	148	172	955	0.84 [0.82, 0.86]	0.87 [0.84, 0.89]
Hernigou 2020	13	2	3	29	0.81 [0.54, 0.96]	0.94 [0.79, 0.99]
Narinx 2020	12	10	3	65	0.80 [0.52, 0.96]	0.87 [0.77, 0.93]
Guillo 2020	103	11	26	74	0.80 [0.72, 0.86]	0.87 [0.78, 0.93]
He 2020	26	2	8	46	0.76 [0.59, 0.89]	0.96 [0.86, 0.99]
Kiziloglu 2021	54	58	17	44	0.76 [0.64, 0.85]	0.43 [0.33, 0.53]
Besutti 2020	438	16	158	84	0.73 [0.70, 0.77]	0.84 [0.75, 0.91]
Peng 2020	28	13	11	20	0.72 [0.55, 0.85]	0.61 [0.42, 0.77]
Mirahmadizadeh 2021	22	15	11	11	0.67 [0.48, 0.82]	0.42 [0.23, 0.63]
Mei 2020	274	39	145	447	0.65 [0.61, 0.70]	0.92 [0.89, 0.94]
Bagci 2021	36	28	20	5	0.64 [0.50, 0.77]	0.15 [0.05, 0.32]
Kalin 2021	23	46	29	50	0.44 [0.30, 0.59]	0.52 [0.42, 0.62]
Simsek Yurt 2021	75	471	251	2537	0.23 [0.19, 0.28]	0.84 [0.83, 0.86]

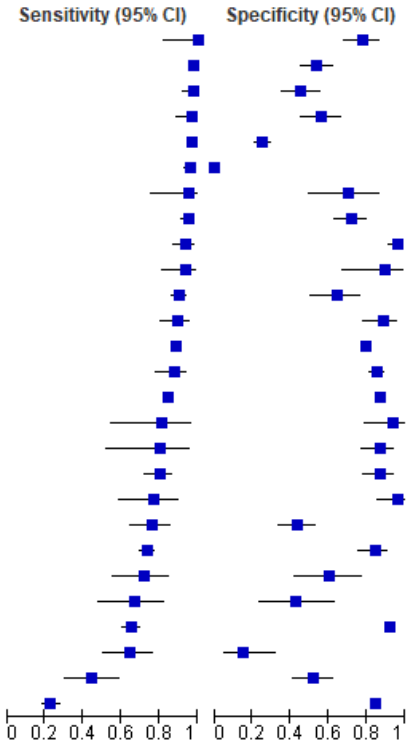


Figure 23. Forest Plot of CT scan studies (Subgroup analysis: Index Test of Positivity - Reader Impression)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Li 2020	42	19	1	30	0.98 [0.88, 1.00]	0.61 [0.46, 0.75]
Khan 2021	87	1	3	6	0.97 [0.91, 0.99]	0.86 [0.42, 1.00]
Wang 2020	28	33	1	128	0.97 [0.82, 1.00]	0.80 [0.72, 0.85]
Schulze-hagen 2020	65	16	4	106	0.94 [0.86, 0.98]	0.87 [0.80, 0.92]
Korevaar 2020	117	25	9	88	0.93 [0.87, 0.97]	0.78 [0.69, 0.85]
Barbosa 2020	23	25	2	41	0.92 [0.74, 0.99]	0.62 [0.49, 0.74]
Cartocci 2020	147	24	15	128	0.91 [0.85, 0.95]	0.84 [0.77, 0.90]
Falaschi 2020	419	66	43	245	0.91 [0.88, 0.93]	0.79 [0.74, 0.83]
Nair 2021 [A]	548	48	58	330	0.90 [0.88, 0.93]	0.87 [0.84, 0.90]
Ducray 2020	259	49	28	358	0.90 [0.86, 0.93]	0.88 [0.84, 0.91]
Hermans 2020	120	22	13	164	0.90 [0.84, 0.95]	0.88 [0.83, 0.92]
Krdzalic 2020	25	7	3	21	0.89 [0.72, 0.98]	0.75 [0.55, 0.89]
Gietema 2020	74	35	9	75	0.89 [0.80, 0.95]	0.68 [0.59, 0.77]
Grando 2020	76	4	10	69	0.88 [0.80, 0.94]	0.95 [0.87, 0.98]
Lieveld 2020	76	18	10	82	0.88 [0.80, 0.94]	0.82 [0.73, 0.89]
Dofferhoff 2020	136	36	18	122	0.88 [0.82, 0.93]	0.77 [0.70, 0.84]
Luo L 2020	26	14	4	29	0.87 [0.69, 0.96]	0.67 [0.51, 0.81]
Stephanie 2020	57	23	10	79	0.85 [0.74, 0.93]	0.77 [0.68, 0.85]
Borakati 2020	162	55	29	56	0.85 [0.79, 0.90]	0.50 [0.41, 0.60]
MM Santos 2020	30	1	6	38	0.83 [0.67, 0.94]	0.97 [0.87, 1.00]
Kavak 2021 [A]	497	30	115	261	0.81 [0.78, 0.84]	0.90 [0.86, 0.93]
Prokop 2020	43	5	10	47	0.81 [0.68, 0.91]	0.90 [0.79, 0.97]
Revel 2021	5174	872	1274	3415	0.80 [0.79, 0.81]	0.80 [0.78, 0.81]
Saeed 2021	56	18	14	5	0.80 [0.69, 0.89]	0.22 [0.07, 0.44]
De Smet 2020	279	33	79	468	0.78 [0.73, 0.82]	0.93 [0.91, 0.95]
Patel 2020	125	41	36	115	0.78 [0.70, 0.84]	0.74 [0.66, 0.80]
Fujioka 2020	57	10	19	68	0.75 [0.64, 0.84]	0.87 [0.78, 0.94]
Debray 2020	120	4	40	77	0.75 [0.68, 0.81]	0.95 [0.88, 0.99]
Shirota 2021	15	1	6	44	0.71 [0.48, 0.89]	0.98 [0.88, 1.00]
Giannitto 2020	14	10	6	38	0.70 [0.46, 0.88]	0.79 [0.65, 0.90]
Kuzan 2020	48	21	21	30	0.70 [0.57, 0.80]	0.59 [0.44, 0.72]
Kavak 2021 [B]	390	13	222	278	0.64 [0.60, 0.68]	0.96 [0.92, 0.98]
Ozer 2021	239	17	140	790	0.63 [0.58, 0.68]	0.98 [0.97, 0.99]
Vicini 2021 [A]	158	83	105	368	0.60 [0.54, 0.66]	0.82 [0.78, 0.85]
Bellini 2020	80	76	62	354	0.56 [0.48, 0.65]	0.82 [0.78, 0.86]
Berkel 2021 [A]	60	25	107	8	0.36 [0.29, 0.44]	0.24 [0.11, 0.42]

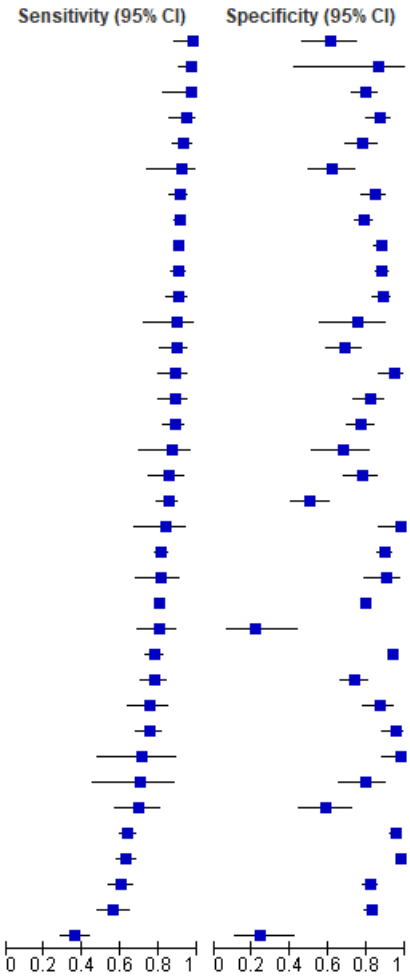


Figure 24. Forest Plot of CT scan studies (Subgroup analysis: Index Test of Positivity -Scoring System)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Caruso 2020	60	42	2	54	0.97 [0.89, 1.00]	0.56 [0.46, 0.66]
Ozkarafakili 2021	273	285	11	0	0.96 [0.93, 0.98]	0.00 [0.00, 0.01]
Ravikanth 2021	206	37	11	94	0.95 [0.91, 0.97]	0.72 [0.63, 0.79]
Gezer 2020	92	5	6	119	0.94 [0.87, 0.98]	0.96 [0.91, 0.99]
Fonsi 2020	41	2	3	17	0.93 [0.81, 0.99]	0.89 [0.67, 0.99]
Falaschi 2020	419	66	43	245	0.91 [0.88, 0.93]	0.79 [0.74, 0.83]
Krdzalic 2020	25	7	3	21	0.89 [0.72, 0.98]	0.75 [0.55, 0.89]
Gietema 2020	74	35	9	75	0.89 [0.80, 0.95]	0.68 [0.59, 0.77]
Ohana 2020	919	148	172	955	0.84 [0.82, 0.86]	0.87 [0.84, 0.89]
Kavak 2021 [A]	497	30	115	261	0.81 [0.78, 0.84]	0.90 [0.86, 0.93]
Guillo 2020	103	11	26	74	0.80 [0.72, 0.86]	0.87 [0.78, 0.93]
De Smet 2020	279	33	79	468	0.78 [0.73, 0.82]	0.93 [0.91, 0.95]
He 2020	26	2	8	46	0.76 [0.59, 0.89]	0.96 [0.86, 0.99]
Debray 2020	120	4	40	77	0.75 [0.68, 0.81]	0.95 [0.88, 0.99]
Besutti 2020	438	16	158	84	0.73 [0.70, 0.77]	0.84 [0.75, 0.91]
Giannitto 2020	14	10	6	38	0.70 [0.46, 0.88]	0.79 [0.65, 0.90]
Kuzan 2020	48	21	21	30	0.70 [0.57, 0.80]	0.59 [0.44, 0.72]
Kavak 2021 [B]	390	13	222	278	0.64 [0.60, 0.68]	0.96 [0.92, 0.98]
Ozer 2021	239	17	140	790	0.63 [0.58, 0.68]	0.98 [0.97, 0.99]
Bellini 2020	80	76	62	354	0.56 [0.48, 0.65]	0.82 [0.78, 0.86]

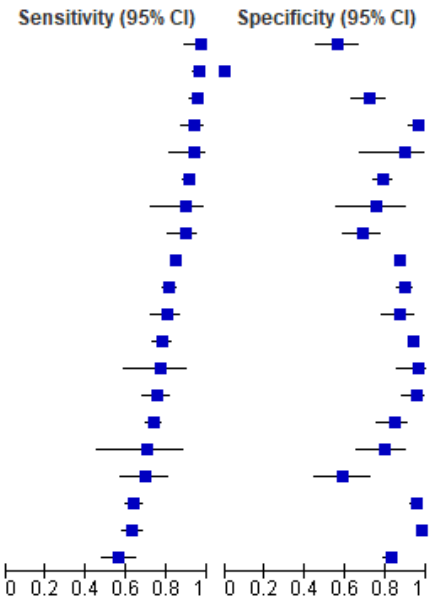


Figure 25.Forest Plot of CT scan studies (Subgroup analysis: Type - Non-contrast enhanced/plain CT scan)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ducray 2020	259	49	28	358	0.90 [0.86, 0.93]	0.88 [0.84, 0.91]		

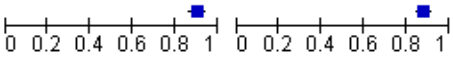


Figure 26. Forest Plot of CT scan studies (Subgroup analysis: Type - Contrast enhanced CT scan)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Deng 2020	423	71	10	83	0.98 [0.96, 0.99]	0.54 [0.46, 0.62]		
Grando 2020	76	4	10	69	0.88 [0.80, 0.94]	0.95 [0.87, 0.98]		
Revel 2021	5174	872	1274	3415	0.80 [0.79, 0.81]	0.80 [0.78, 0.81]		
Saeed 2021	56	18	14	5	0.80 [0.69, 0.89]	0.22 [0.07, 0.44]		
Patel 2020	125	41	36	115	0.78 [0.70, 0.84]	0.74 [0.66, 0.80]		

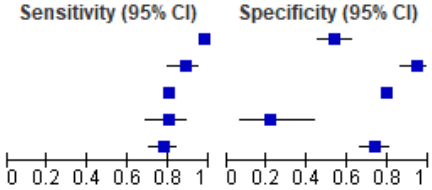


Figure 27. Forest Plot of CT scan studies (Subgroup analysis: Type - High-resolution CT scan)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Steuwe 2020	19	19	0	67	1.00 [0.82, 1.00]	0.78 [0.68, 0.86]		
Schulze-hagen 2020	65	16	4	106	0.94 [0.86, 0.98]	0.87 [0.80, 0.92]		
Korevaar 2020	117	25	9	88	0.93 [0.87, 0.97]	0.78 [0.69, 0.85]		
Aslan 2020	226	20	24	36	0.90 [0.86, 0.94]	0.64 [0.50, 0.77]		
Dofferhoff 2020	136	36	18	122	0.88 [0.82, 0.93]	0.77 [0.70, 0.84]		
Hernigou 2020	13	2	3	29	0.81 [0.54, 0.96]	0.94 [0.79, 0.99]		
Narinx 2020	12	10	3	65	0.80 [0.52, 0.96]	0.87 [0.77, 0.93]		
Khan 2021	23	46	29	50	0.44 [0.30, 0.59]	0.52 [0.42, 0.62]		

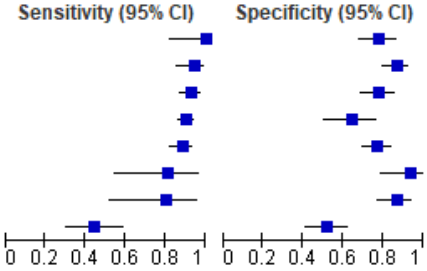


Figure 28. Forest Plot of CT scan studies (Subgroup analysis: Type - Low-dose CT scan)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Peng 2020	28	13	11	20	0.72 [0.55, 0.85]	0.61 [0.42, 0.77]		
Bagci 2021	36	28	20	5	0.64 [0.50, 0.77]	0.15 [0.05, 0.32]		
Kalin 2021	23	46	29	50	0.44 [0.30, 0.59]	0.52 [0.42, 0.62]		
Simsek Yurt 2021	1	3	4	54	0.20 [0.01, 0.72]	0.95 [0.85, 0.99]		

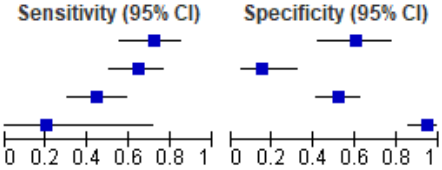


Figure 29. Forest Plot of CT scan studies (Subgroup analysis: Type - Pediatric Population)

Appendix 6. GRADE Evidence

Should Chest X-ray be used to diagnose COVID-19 in suspected individuals?
Pooled sensitivity: 0.72 (95% CI: 0.61 to 0.81)
Pooled specificity: 0.78 (95% CI: 0.67 to 0.86)

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	18 studies (9,616 patients)	Cohort & case-control type studies	Very serious[a]	Not serious	Very serious[b]	Serious[c]	None	36 (31 to 41)	72 (61 to 81)	108 (92 to 122)	⊕◯◯◯ Very Low
False negatives (patients incorrectly classified as not having COVID-19)								14 (9 to 19)	28 (19 to 39)	42 (28 to 58)	
True negatives (patients without COVID-19)	18 studies (9,616 patients)	Cohort & case-control type studies	Very serious[a]	Not serious	Very serious[b]	Very serious[d]	None	741 (637 to 817)	702 (603 to 774)	663 (570 to 731)	⊕◯◯◯ Very Low
False positives (patients incorrectly classified as having COVID-19)								209 (133 to 313)	198 (126 to 297)	187 (119 to 280)	

CI: confidence interval

Explanations
[a] high risk on patient selection, conduct of reference standard, and patient flow and timing plus unclear risk on all four domains
[b] considerable heterogeneity (I2 = 95%)
[c] wide confidence intervals
[d] very wide values in confidence interval

Should lung ultrasound be used to diagnose COVID-19 in suspected individuals?
Pooled sensitivity: 0.93 (95% CI: 0.86 to 0.97)
Pooled specificity: 0.52 (95% CI: 0.33 to 0.71)

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	11 studies (1,076 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Very serious[b]	Serious[c]	None	47 (43 to 49)	93 (86 to 97)	140 (129 to 146)	⊕◯◯◯ Very Low
False negatives (patients incorrectly classified as not having COVID-19)								3 (1 to 7)	7 (3 to 14)	10 (4 to 21)	
True negatives (patients without COVID-19)	11 studies (1,076 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Very serious[b]	Very serious[d]	None	494 (314 to 675)	468 (297 to 639)	442 (281 to 603)	⊕◯◯◯ Very Low
False positives (patients incorrectly classified as having COVID-19)								456 (275 to 636)	432 (261 to 603)	408 (247 to 569)	

CI: confidence interval

Explanations
[a] mostly unclear risk on all four domains
[b] considerable heterogeneity (I2 = 98%)
[c] wide confidence intervals
[d] very wide values in the confidence intervals

Should chest CT scan be used to diagnose COVID-19 in suspected individuals?
Pooled sensitivity: 0.85 (95% CI: 0.81 to 0.87)
Pooled specificity: 0.78 (95% CI: 0.71 to 0.83)

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	62 studies (39,929 patients)	Cohort & case-control type studies	Serious[a]	Not serious	Very serious[b]	Serious[c]	None	43 (41 to 44)	85 (81 to 87)	128 (122 to 131)	⨁◯◯◯ Very Low
False negatives (patients incorrectly classified as not having COVID-19)								7 (6 to 9)	15 (13 to 19)	22 (19 to 28)	
True negatives (patients without COVID-19)	62 studies (39,929 patients)	Cohort & case-control type studies	Serious[a]	Not serious	Very serious[b]	Very serious[d]	None	741 (675 to 789)	702 (639 to 747)	663 (603 to 705)	⨁◯◯◯ Very Low
False positives (patients incorrectly classified as having COVID-19)								209 (161 to 275)	198 (153 to 261)	187 (145 to 247)	

CI: confidence interval

Explanations
[a] mostly unclear risk on all four domains
[b] considerable heterogeneity (I2=100%)
[c] wide confidence intervals
[d] very wide values in confidence intervals

Appendix 7. Characteristics of Ongoing Studies

NCT Number	Title	Population	Interventions	Comparator	Outcomes
NCT04479319 [97]	Decision Support System Algorithm for COVID-19 Diagnosis	Adult patients with a differential diagnosis of COVID-19 and tested for it with Thorax CT and RT-PCR in Turkey.	Thorax CT	RT-PCR for SARS-CoV-2.	Diagnosing COVID-19 (Determination of sensitivity and specificity in predicting COVID-19 diagnosis of hybrid decision support system)
NCT04377685 [98]	Prediction of Clinical Course in COVID19 Patients (COVID-CTPRED)	patient admitted to the emergency room of COVID-19 confirmed by RT-PCR	Chest CT scan on admission to the hospital	RT-PCR for SARS-CoV-2.	diagnostic of COVID disease composite
NCT04339686 [99]	Multicentric Retrospective Observational Study of Thoracic Scanner Performance in COVID Screening.	All patients suspected of COVID 19 consulting for diagnostic	Thoracic CT Scan	RT-PCR for SARS-CoV-2.	Diagnostic performance of chest CT in screening for pulmonary lesions in clinical suspicions of COVID; Compare the diagnostic performance of chest CT and RT-PCR in COVID 19 at the initial consultation (screening)
NCT04357938 [100]	Risk Stratification With Chest CT to Rule-out Suspected SARS-CoV-2 Infections (SCout)	Patients with unspecific symptoms of SARS-CoV-2 infection who are to be admitted to hospital for any disease and who provide written informed consent to undergo rt-PCR, chest CT, and antibody test.	Chest CT imaging	RT-PCR for SARS-CoV-2.	Sensitivity and specificity of chest CT in detecting pneumonia in unspecific symptomatic patients who are to be admitted to hospital and who are rt-PCR negative for SARS-CoV-2;
NCT04370275 [101]	Accuracy of Lung Ultrasound in the Diagnosis of covid19 Pneumonia: a Multicenter Study in the Italian Outbreak	People entering the Emergency Room during the SARS-CoV-2 epidemic	Lung Ultrasound	RT-PCR	Negative Predictive Value, Positive Predictive Value, Sensitivity and Specificity Lung Ultrasound in the diagnosis of COVID-19
NCT04353141 [102]	International Lung UltraSound Analysis (ILUSA) Study (ILUSA)	All consecutive pregnant patients who are admitted to the hospital for delivery, cesarean section or admission for at least one night.	standardized Lung Ultrasound (LUS) examination	RT-PCR	Diagnostic performance of LUS to predict poor outcome
NCT04327674 [103]	The Use of Focused Lung Ultrasound in Patients Suspected of COVID-19	All patients who have symptoms on COVID-19 and is seen at a hospital.	Focuses Lung Ultrasound	RT-PCR & chest x-ray	FLUS findings and respiratory failure; FLUS findings and SAR-CoV-2 PCR-test result; FLUS findings and admission to intensive care; FLUS findings and chest x-ray
NCT04561024 [104]	Evaluation of a COVID-19 Pneumonia CXR AI Detection Algorithm	There will be three subsets of study population in this study; patients who were: (1) RT-PCR confirmed COVID-19 positive; (2) RT-PCR confirmed COVID-19 negative; (3) either had a diagnosis of pneumonia before the 1st January 2020.	Deep Learning CNN model in chest x-ray	RT-PCR	Diagnostic Performance of AI model

Q15. Among adult patients diagnosed with COVID-19, should prognostic models be used to predict the likelihood of severe disease and mortality?

As of 17 December 2021

RECOMMENDATIONS

<u>To guide the decision to admit adult patients with COVID-19 to the hospital:</u>
We suggest the use of age, BUN, number of comorbidities, CRP, SpO2/FiO2 ratio, platelet count, Heart rate (ABC2-SPH) risk score, Confusion Urea Respiration Blood Pressure (CURB-65) severity score, Risk Stratification in the Emergency Department in Acutely Ill Older Patients (RISE-UP) score, and Rapid Emergency Medicine Score (REMS). *(Low certainty of evidence; Weak recommendation)*

There is insufficient evidence to recommend the use of 4C Mortality Score, COVID Outcome Prediction in the Emergency Department (COPE) model, and Quick Sepsis-related Organ Failure Assessment (qSOFA) score. *(Very low certainty of evidence)*

<u>To guide in the expectant monitoring of hospitalized adult patients:</u>
We suggest the use of the 4C Deterioration model. *(Low certainty of evidence; Weak recommendation)*

There is insufficient evidence to recommend the use of Modified Early Warning Score (MEWS) and National Early Warning Score 2 (NEWS2), Clinical Frailty Scale (CFS), and the COVID-GRAM model. *(Very low certainty of evidence)*

Consensus Issues
The recommendations on prognostic models are limited to adult patients since the evidence base included studies only on the adult population. No studies were conducted among pediatric patients. The panelists were unanimous in all recommendations on prognostic models..

PREVIOUS RECOMMENDATIONS

<u>To guide the decision to admit patients with COVID-19 to the hospital:</u>
We suggest the use of Age, BUN, number of Comorbidities, CRP, SpO2/FiO2 ratio, Platelet count, Heart rate (ABC2-SPH) risk score, Confusion Urea Respiration Blood Pressure (CURB-65) severity score, Risk Stratification in the Emergency Department in Acutely Ill Older Patients (RISE-UP) score, and Rapid Emergency Medicine Score (REMS). *(Low quality of evidence; Conditional recommendation)*

There is insufficient evidence to recommend the use of 4C Mortality Score, COVID Outcome Prediction in the Emergency Department (COPE) model, and Quick Sepsis-related Organ Failure Assessment (qSOFA) score. *(Very low quality of evidence)*

<u>To guide in the expectant monitoring of hospitalized patients:</u>
We suggest the use of the 4C Deterioration model. *(Low quality of evidence; Conditional recommendation)*

There is insufficient evidence to recommend the use of Modified Early Warning Score (MEWS) and National Early Warning Score 2 (NEWS2). *(Very low quality of evidence)*

Consensus Issues
There was a high certainty of evidence that the QCOVID model can predict mortality from COVID-19. However, there was an issue on applicability as some of the components of this model (i.e., geographic region and Townsend deprivation quintile) is specific for the general population of England. Hence, its use warrants reconsideration of the component prognostic factors and validation in the Philippine setting before any recommendations can be made.

It was noted that the qSOFA model was already being used by some hospitals and centers in the Philippines. Clinicians should be guided on its use as it was found to have a very low quality of evidence for prediction of mortality of inpatients. There are other prognostic models such as the CURB-65, RISE-UP and REMS which are pre-existing models designed for specific patient populations and the ABC2-SPH model which has a good discrimination performance. All of these were found to have better quality of evidence compared with qSOFA. The 4C Mortality score and COPE model were also found to have a very low quality of evidence to predict mortality. Further, it was observed that there was a decrease in the discriminatory ability of the COPE model when externally validated. In terms of clinical deterioration, the 4C deterioration score was found to have a better predictive ability and quality of evidence compared to MEWS and NEWS2 model. Like the QCOVID model, these prognostic models also need to be locally validated but the components of these models can be easily obtained especially in the hospital setting, making the validation process easier.

WHAT'S NEW IN THIS VERSION?

- New validation studies for COVID-GRAM and Clinical Frailty Scale were added.
- Two other studies on 4C Mortality Score were added.

KEY FINDINGS

- In this version, two new prognostic models were reviewed and 13 new studies were added. One study is a binational prospective cohort that validated the 4C mortality score and COVID-GRAM on a larger population in South America and Europe. Three more studies validated COVID-GRAM but have an overall unclear risk of bias and low quality of evidence. Nine studies validated the use of the Clinical Frailty Scale in prognosticating elderly COVID-19 patients, but the overall assessment for risk of bias was rated high and the level of evidence was rated very low.
- In total, 46 cohort studies on prognostic models for clinical deterioration and mortality of individuals with COVID-19 were found. Most of the studies (n=36) were assessed to have a high risk of bias due to issues in participant selection and analysis. There were eight studies with unclear, and two with low risk of bias.
- For predicting mortality, the following models demonstrated fair-to-good predictive ability: 4C mortality score, ABC2-SPH, CURB-65, REMS, RISE UP, and COVID-GRAM models. Poor to fair prediction was noted for the qSOFA model, with one new study yielding lower AUC estimates compared to the previously included studies. Only one model, the QCOVID model for mortality validated for the UK setting, demonstrated high predictive ability.
- For predicting clinical deterioration, available prognostic models showed varied performance. The 4C deterioration which has been investigated in only one study

with a low risk of bias showed fair predictive ability. The MEWS model has a poor prediction of clinical deterioration while NEWS2 has inconsistent prediction (poor to good). The Clinical Frailty Scale (CFS), increases the risk of mortality among elderly COVID-19 patients.

- None of these models has been validated in the Philippine population. Thus, validation studies are needed before these models can be used to inform practice.

INTRODUCTION

As of December 06, 2021, there have been a total of 265,194,191 confirmed cases of COVID-19 reported to WHO. In the Philippines, deaths have numbered to 49,591 out of the 2,835,345 cases as of December 7, 2021, 0.1% of which are tagged as severe and critical. To reduce the risk of severe disease and mortality, numerous studies have assessed the usefulness of prognostic models that aim to identify patients at high risk of adverse outcomes from COVID-19. These models include early warning scores that were originally developed to identify and monitor inpatients at risk of deterioration (to facilitate transfer to intensive care units) or new models that were developed to predict the likelihood of severity or mortality among COVID-19 patients (referred to in this report as “pre-existing models” and “COVID-19-specific models”, respectively).

REVIEW METHODS

In this version, we extended the literature search to cover studies published between March 8, 2021 and November 27, 2021 in the following electronic databases: MEDLINE, Cochrane Central, McMaster Evidence-Based Alerts, Cornell Open Access Publication (COAP), and Living Overview of the Evidence (L•OVE). Included articles were also hand-searched for their references to supplement yield. Search terms “death” or “mortality”, “severe”, and “predict” were used. The search yielded both published articles and preprints.

The criteria for inclusion of studies were as follows: (1) population: adults diagnosed with COVID-19 infection, (2) intervention: prognostic models with external validation, (3) outcome: worsening severity or clinical deterioration or poor outcomes and/or mortality; and (4) cross-sectional, case-control, or cohort studies. Studies were excluded if they met any of the following criteria: (1) development of prediction models through machine-learning algorithms or artificial intelligence without an available online tool; (2) number of outcome events (severe disease or mortality) <100. There were 45 articles that met our inclusion criteria.

We used the CHecklist for Critical Appraisal and data extraction for Systematic Reviews of prediction Modelling Studies (CHARMS) to plan the review.[5] The Prediction model Risk Of Bias ASsessment Tool (PROBAST) was used as a guide to appraise the risk of bias and concern for applicability for each article as low, high, or unclear.[6] We extracted the following details of the studies: participants, setting, study design, the predictive performance of each model, and methods of calibration and discrimination. Discrepancies in appraisal and data extraction were resolved through discussion and eventual agreement between the two authors.

RESULTS

Characteristics of included studies

As of November 27, 2021, we found 46 studies that met the inclusion criteria.[7-52] Thirteen (13) new studies were added to the 33 studies included in the previous review version. The characteristics of these studies are summarized in Appendix 2.

Setting, Study Design

Most of the studies were done in Europe, specifically in the United Kingdom (16 studies), Spain (6), Netherlands (3), Italy (3), Switzerland (2), Denmark (1), France (1), Belgium (1), Germany (1). The rest were done in the US (6), Mexico (1), Brazil (3), China (4), and Turkey (2). All selected studies were cohorts – eight prospective and 38 retrospective. Most studies were done during the early part of the pandemic (first half of 2020) but ten studies collected data extending to or exclusively during the second half of 2020 up to January 2021. These latter studies may reflect the possible effects of the changing incidence and prevalence of infection on model performance.[1,53]

Population

Most studies obtained data from electronic medical databases of secondary or tertiary medical centers, wherein the prognostic model was applied during the emergency department visit or hospital admission. In seven articles, the data were obtained from cohorts of patients (both ambulatory and hospitalized) whose primary care physicians' electronic health records were linked with hospital data and enrolled in regional, national, or international databases, most of them established even prior to the pandemic. Seven articles involved the elderly population, most of which were admitted to ICUs of different hospitals. Most of the studies included confirmed PCR-positive adults with community-acquired COVID. Eight studies included suspected or clinically diagnosed COVID (typical symptoms, chest CT infiltrates, and the absence of an alternative diagnosis). Three studies specified the inclusion of nosocomial COVID in their population.

Outcomes

The prediction outcome of interest is death in 34 studies, admission to the intensive care unit in seven, or a composite of death or clinical deterioration in twelve studies. Some studies determined multiple outcomes. Another study looked at the survival status of patients after 90 days. Death was determined either during the in-hospital stay or over a specified period (14, 28, or 30-day). Clinical deterioration or progression of COVID-19 severity was usually defined as admission to an intensive care setting, need for oxygen supplementation (non-invasive or mechanical ventilation), or death. One study looked at thromboembolism as an outcome. Among the studies done on the general population, the mortality rate was 0.020 to 0.077% in the England population and 8.2% in the Denmark population. The mortality rate among hospitalized patients was 5.5 to 45.63%.

Exposure

Twenty-two studies validated 14 different pre-existing prediction models (pre-COVID-19 pandemic). Twenty-three articles focused on the development and/or validation of 44 new models for the prediction of outcomes in COVID-19 patients. One study included both pre-existing and COVID-specific models. seven studies validated the use of the clinical frailty scale in the prognosis of elderly COVID-19 patients. The

components of the models were of varying complexity – from a few patient characteristics to combinations of demographic features, comorbidity, clinical features, and laboratory tests and scales.

Overall summary of methodological quality
The assessments of the 45 articles are presented in Appendix 3.

The overall risk of bias was assessed to be high in 36 (78%) studies, low in two studies, and unclear in eight studies. Contributory to this assessment is the high risk of bias for the participant domain in 11 studies, predictor domain in two studies, outcome domain in six studies, and the analysis domain in 23 studies. Particularly for the participant domain, a high risk of bias was due to the inclusion of severely ill patients that was a result of the studies being done in tertiary centers and specialized COVID-designated hospitals. Some studies excluded patients with incomplete data.

For the analysis domain, causes for high risk of bias include the following: a small number of participants with the outcome relative to the number of predictors; mishandling of continuous predictors; exclusion of patients lost to follow up and those with missing data from the analysis; lack of imputation for missing data; selection of predictors based on univariable analysis (leading to loss of information and consequent reduction of the model's predictive ability); lack of accounting for censoring and competing risks, as well as for model overfitting or optimism; and lack of information on model performance measures (usually on calibration).

Among the issues in the predictor and outcome domains are lack of blinding for outcome during data abstraction; lack of clear information on the timing of determination of predictors; and the insufficient time interval between assessment of predictor and outcome.

Overall concern for applicability was unclear for all studies due to the inclusion of laboratory and/or imaging predictors, which may not be available in many local health facilities. Moreover, a delay in test results due to prolonged laboratory and imaging turnaround time may limit the application of prognostic models that are intended for immediate use to aid patient diagnosis or on admission to the emergency department. Models that include comorbidities as predictors with reliance on ICD-10 may be difficult to apply in our setting because most hospitals lack a readily-available database of comorbidities, leading to potential recall bias.

The GRADEpro Guidance Development Tool (GDT) was used to assess the certainty of the evidence for eight models that had multiple validation studies and six models with only one published validation study but had very low to low certainty of evidence (See Appendix 4 for GRADE Evidence Profiles).

Summary of results of included studies
Models with more than one external validation study were focused on in this review to obtain information both about the accuracy of the model in predicting the outcome of interest and the consistency of prediction (See Table 1). Studies on prognostic models with only one external validation but were assessed to have an unclear or low risk of bias are briefly mentioned. In all studies, the ability of a prediction model to

discriminate among individuals who will develop an event or outcome (e.g., mortality or severity) from those who will not is measured by the area under the curve (AUC).

Models for prediction of mortality in the general population (ambulatory and hospitalized)

QCOVID model

The QCOVID model developed by Clift et al., [7] and further validated by Nafilyan et al. [8] used data from a large network of primary care datasets with linkage to hospitalization data. It shows excellent discrimination of mortality risk but its use is quite specific to England by the nature of its components (geography, accommodation, Townsend deprivation index) and scoring system. It has the potential to help patients and doctors reach a shared understanding of the mortality risk of COVID-19 diagnosed in the community even before the availability of laboratory tests. It was designed to be applied across the adult population for risk stratification for public health purposes during the pandemic, to support shared management of risk and occupational exposure, and in early targeting of vaccines to people most at risk.[7]

The studies of Clift [7] and Nafilyan [8] were assessed to have a low risk of bias and high certainty of evidence. However, for the QCOVID model to be used in the Philippines, it has to be modified and validated.

COPE model

The COPE model was also developed from the general population (around 2 million Dutch recruited at the point of RT-PCR testing). Its base model (age, sex, BMI) has an excellent prediction of death at the point of diagnosis (AUC 0.902) which falls to fair prediction at hospital admission (AUC 0.785). When validated in a UK cohort, the prediction of death on diagnosis is much lower (AUC 0.742). This study has an unclear risk of bias and the certainty of the evidence is low.[9]

Models for prediction of poor outcomes among hospitalized patients

Mortality

CURB-65, REMS, RISE-UP

Pre-existing models such as CURB-65, REMS, and RISE-UP are established scoring systems that were designed for specific patient populations. CURB-65 is a tool that has been validated for use among patients with community-acquired pneumonia for the prediction of 30-day mortality. REMS was intended to predict in-hospital mortality for patients presenting at the emergency department regardless of disease, while RISE-UP was designed for mortality prediction specifically for elderly patients in the emergency room. Several studies [10-19] have validated these models for use in COVID-19 as most of the affected patients, especially in the early part of the pandemic, were older than 65 years and presented with pneumonia. Their relative simplicity and popular use among clinicians have made them attractive models for risk stratification in COVID-19. These three models were found to have fair to good discriminative performance for mortality when validated in COVID-19 patients, with estimated AUCs ranging from 0.70 to 0.84. However, most validation studies were found to have a high risk of bias, with low certainty of evidence, except the one by Gupta et al. [18] which has an unclear risk of bias.

4C Mortality Score

Two studies on prognostic models for mortality among hospitalized patients at low risk of bias deserve some mention. The 4C Mortality Score was developed and validated from the International Severe Acute Respiratory and Emerging Infections Consortium Coronavirus Clinical Characterisation Consortium (ISARIC4C) study, which involved 260 hospitals in the United Kingdom.[16] The model's components (age, sex, number of comorbidities, vital signs, and BUN and CRP) are available in most hospitals. The model, which exhibited fair discriminative ability, was developed using a cohort of seriously-ill patients and may not be generalizable to patients in the community with lower mortality risk.

Two new validation studies on the 4C Mortality score were reviewed. One is a bi-national study involving the Latin American and Spanish population, however, has fair discrimination (AUC 0.78).[15] The other study involved the Turkish population but also showed fair discrimination (AUC 0.784).[16] Both studies also have low certainty of evidence.

ABC_2-SPH

The ABC-SPH model was developed and validated in Brazil using variables commonly available in most emergency departments around the globe (age, number of comorbidities, heart rate, SpO2/FiO2 ratio, BUN, CRP, and platelet count).[21] It has an AUC above 0.8, indicating good discrimination. On external validation on a Spanish cohort with patients from the early part of the pandemic, the model was found to potentially underestimate mortality in patients who are at higher risk of death. The certainty of evidence from this study is low.

Other prognostic models

The rest of the models for the prediction of mortality among hospitalized patients were at high risk of bias and with very low certainty of evidence.

Clinical Deterioration

4C Mortality Score

A study of 66,136 adults with confirmed COVID-19 belonging to the ISARIC 4C cohort in the UK done by Gupta et al. found that most in-hospital deterioration occurred around 4 days (1-9 days) from admission and declined with increasing time thereafter.[22] In-hospital clinical deterioration was defined as a need for non-invasive or invasive oxygen supplementation, admission to an intensive care unit, or death.

Early warning scores (NEWS2, MEWS)

Early warning scores like NEWS2 and MEWS which use easy-to-obtain physical examination findings as predictors for in-hospital deterioration are desired during this early phase of hospitalization. They can easily be used in all clinical settings without the need for additional training of medical staff and pose no socio-economic issues like cost and availability of tests. However, validation studies of these two prognostic models for clinical deterioration showed poor to fair and poor discrimination indices of NEWS2 and MEWS, respectively.

The study by Gupta [22] mentioned above was found to be of low risk of bias and will be mentioned here briefly. It developed and validated the 4C model for clinical deterioration, for use on admission for community-acquired COVID-19 cases, or at the

initial assessment of suspected nosocomial COVID-19. It showed fair discrimination (AUC 0.77; 0.76-0.78). The certainty of evidence from this study is low.

COVID-GRAM

Four studies [15-17,25] provided data on the ability of COVID-GRAM to predict critical illness, 30-day mortality, or ICU requirement among inpatients with COVID-19. The model includes the following as predictors: X-ray abnormality, age, hemoptysis, dyspnea, sensorium, number of comorbidities, cancer history, neutrophil-lymphocyte ratio (NLR), lactate dehydrogenase, and direct bilirubin.

COVID-GRAM showed fair predictive ability for mortality with an AUC of 0.88 [17] and 0.77.[11] In studies that reported poor outcome as a composite score, COVID-GRAM was reported to have good predictive ability with an AUC of 0.88 (0.85-0.91) [25] and 0.77.[17] However, the majority of the studies did not account for patients with missing data, hence a very serious risk of bias and low certainty of evidence. Moreover, COVID-GRAM has not been validated locally.

Clinical Frailty Scale

The Clinical Frailty Scale is a well-validated scale used to quantify the degree of disability from frailty. Several studies have tried validating its use in the prognosis of elderly COVID-19 patients, however, only nine studies [26-34] met the inclusion criteria for this review. The COVIP study assessed the overall survival at 30 days and correlated it with the level of frailty on admission and found out that only 41% of frail COVID patients survived ($p<0.001$). However, this study had a high risk of bias and the overall quality of evidence for the rest of the studies is very low. No AUC values were reported across the studies.

Other prognostic models

The rest of the studies on prognostic models for clinical deterioration of hospitalized patients with COVID-19 were at high risk of bias and with very low certainty of evidence.

RECOMMENDATIONS FROM OTHER GROUPS

The Australian guidelines for the clinical care of people with COVID-19 [54] recommend monitoring markers of clinical progression, such as rapidly progressive respiratory failure and sepsis, especially on days five to ten after the onset of symptoms. This was not developed with an evidence-based framework but formed through a consensus process.

The WHO COVID-19 Clinical management Living guidance (23 November 2021) [55] recommends the use of clinical judgment, including consideration of patients' values and preferences and local and national policy if available, to guide management decisions including admission to hospital and the ICU rather than currently available prediction models for prognosis when caring for patients with COVID-19 of any severity assessed in a clinic or hospital (conditional recommendation, very low certainty).

RESEARCH GAPS

There is at least one ongoing study registered on clinicaltrials.gov for prediction models for COVID-19 in various countries – one retrospective (case-only) study in

China. the CODED study in Italy has already been completed but not yet published.[56-59] These models look at combinations of demographic, clinical, biological, and/or imaging parameters with or without the use of machine-based learning.

Despite the large number of studies being produced, the majority of prediction models for adverse COVID-19 outcomes continue to suffer from selection bias, overfitting, and/or the lack of external validation. Article appraisals and the conduct of systematic reviews have paved the way for improved quality of studies.

Validation of these prognostic models in the Filipino population is needed, and the use of these models must not replace clinical judgment with due consideration of patients' values and preferences. As the predictive performance of a model may differ depending on the setting and population to which it is applied, the importance of conducting external validation studies in settings where the model is intended to be used cannot be overemphasized. Pooling of multicenter data across heterogeneous settings and populations may help increase the robustness of model performance evaluation, especially when substantiated by meta-analyses. Moreover, the studies that met our criteria did not include validation of prognostic models in the pediatric population. With the rising trend in pediatric COVID cases, it is prudent to look at these validation studies as well.

Table 1. Models with more than one external validation study in this review. Prognostic models that have additional studies in this update are highlighted in yellow and in bold.

Model First Author Country	Population	Outcome	Predictors	Risk-based on cut-off scores	Discrimination Performance (AUC, 95% CI if provided)*	Online risk calculator
QCOVID Clift [7] Nafilyan [8] (England)	General population	Mortality	Age Sex Geographic region Ethnicity Townsend deprivation quintile Accommodation Body mass index Chronic kidney disease (CKD) Learning disability Chemotherapy Cancer/immunosuppression other comorbidities	Online calculator gives absolute risk	Clift Period 1 (Jan-Apr 2020) • Men 0.93 (0.92, 0.93) • Women 0.93 (0.92, 0.94) Period 2 (May-Jun 2020) • Men 0.93 (0.92, 0.95) • Women 0.95 (0.94, 0.96) Nafilyan Period 1 • Men 0.935 (0.933, 0.937) • Women 0.945 (0.943, 0.947) Period 2 • Men 0.944 (0.942, 0.946) • Women 0.956 (0.954, 0.958)	https://qcovid.org
4C Mortality Score Knight [20] (UK) Van Dam [14] (Netherlands) **Neto [15] (Brazil, Spain)** **Doganay [16] (Turkey)**	Inpatients	Mortality (30-day) in-hospital mortality In-hospital mortality ICU requirement	Age Sex Number of comorbidities Respiratory rat Peripheral oxygen saturation Glasgow coma scale (GCS) Blood urea nitrogen (BUN) C-reactive protein (CRP)	Mortality risk (Score range: 0-21) Low: 0-3 Intermediate:4-8 High: 9-14 Very high:≥15	Knight 0.767 (0.76, 0.77) Van Dam 0.84 (0.79, 0.88) **Neto 0.78 (0.75, 0.81)** **Doganay** • **In-hospital mortality 0.784 (0.774, 0.820)** • **ICU requirement 0.797 (0.758, 0.32)**	https://isaric4c.net/risk
Confusion Urea Respiration Blood Pressure (CURB-65) Artero [10] (Spain) Bradley [11] (UK) Liu FY [12] (China) Nava [13] (US) van Dam [14] (Netherlands) **Neto (Brazil, Spain) [15]** **Doganay [16] (Turkey)** **Armiñanzas [17] (Spain)**	Inpatients	Mortality (30-day) Overall mortality	Age Confusion Respiratory rate (RR) Blood pressure BUN		Artero 0.82 (0.82,0.84) Bradley 0.75 Liu FY 0.77 (0.72, 0.81) Nava 0.78 van Dam 0.75 (0.70, 0.80) **Neto 0.74 (0.72,0.77)** **Doganay 0.846 (0.810,0.877)** **Armiñanzas 0.727**	https://www.mdcalc.com/curb-65-score-pneumonia-severity

Rapid Emergency Medicine Score (REMS) Gupta [18] (UK) Liu FY [12] (China) van Dam [14] (Netherlands	Patients at Emergency Department (ED)	Mortality (in-hospital)	Age Pulse rate (PR Mean arterial pressure (MAP) RR GCS Oxygen saturation (SpO2)		Gupta 0.76 (0.71, 0.81) Liu FY 0.84 (0.8, 0.88) van Dam 0.73 (0.68, 0.78)	https://www.mdcalc.com/rapid-emergency-medicine-score-rems
Risk Stratification in the Emergency Department in Acutely Ill Older Patients (RISE UP) Van Dam [14] Van Dam [19] (Netherlands)	Patients at ED, Inpatients	30-day mortality	Age HR MAP RR SpO2 GCS BUN Bilirubin Albumin Lactate dehydrogenase (LDH)	<10%- very low risk of mortality >30%- high risk of mortality	van Dam 0.77 (0.73, 0.81) van Dam 0.83 (0.79, 0.88)	P(30-day mortality)=1/(1+exp (-(−2.083+0.795 * (0.050*Age +1.115*≥2 Abnormal Vital Signs (yes=1, no=0)– 0.112*Albumin (in g/L) +0.284* (BUN (in mmol/ L)/5) +0.120* (LDH (in U/L)/100)+0.875* Bilirubin>20 µmol/L (yes=1, no=0))))
Quick Sepsis-related Organ Failure Assessment (qSOFA) Artero [13] (Spain) Bradley [14] (UK) Gupta [18] (UK) Liu FY [15] (China) **Neto [11] (Spain, Brazil)**	Inpatients	Mortality (in-hospital)	Mental status (GCS) RR Systolic blood pressure (SBP)		Artero 0.73 (0.71, 0.74) Bradley 0.62 Gupta 0.6 (0.54, 0.65) Liu FY 0.69 (0.64, 0.75) **Neto 0.63 (0.6,0.66)**	https://www.mdcalc.com › qsofa-quick-sofa-score-sepsis
National Early Warning Score 2 (NEWS2) Baker [20] (UK) Bradley [11] (UK) Carr [24] (UK) Gupta [18] (UK) Gupta [22] (UK)	Inpatients on admission	Risk of clinical deterioration (CD)	RR PR Hypercapneic respiratory failure Room air or with supplemental O2 Temp SBP Consciousness		Baker 0.7 (0.65, 0.77) Gupta 0.69 (0.68, 0.70) Carr • CD in 3 days 0.72,0.77 • CD in 14 days 0.70, 0.74 Gupta • CD in 1-day 0.78 (0.73, 0.83)	https://www.mdcalc.com/national-early-warning-score-news-2
Modified Early Warning Score (MEWS) Gupta [18] (UK) Gupta [22] (UK)	Inpatients	Risk of clinical deterioration	SBP Heart rate (HR) RR Temperature Alert Voice Response Pain Response Unresponsive (AVPU) score		Gupta 0.6 (0.56, 0.65) Gupta 0.63 (0.62, 0.64)	https://www.mdcalc.com/modified-early-warning-score-mews-clinical-deterioration

COVID-GRAM **Armiñanzas [17] (Spain)** **Liang [25] (China)** **Doganay [16] (Turkey)** **Neto [15] (Brazil)**	Inpatients	Critical illness 30-day mortality ICU requirement	X-ray abnormality Age Hemoptysis Dyspnea Unconsciousness Number of comorbidities Cancer history Neutrophil/Lymphocytes (NLR) Lactate Dehydrogenase (LDH) Direct Bilirubin	<1.7% - Low 1.7% to <40.4% - Medium >/= 40.4% - High	**Armiñanzas** • **critical illness 0.779** • **30-day mortality 0.88** **Liang** • **DC 0.88 (0.85-0.91)** **Liang** • **VC 0.88 (0.84-0.93)** **Doganay** • **mortality, 0.701 (0.658, 0.742)** • **ICU requirement 0.684 (0.640-0.725)** **Neto** • **0.77 (0.75-0.8)**	https://www.mdcalc.com/covid-gram-critical-illness-risk-score
Clinical Frailty Scale **Apea [26] (UK)** **Cobos-Siles [27] (Spain)** **Dres [28] (France)** **Miles [29] (UK)** **Aw [30] (UK)** **Jung [31] (Germany)** **Aliberti [32] (Brazil)** **Hewitt [33] (UK) (Italy)** **Thompson [34] (UK)**	Inpatients	30-day mortality Day 90 mortality Survival at 30 days Death within 30 days and 6 months of hospital admission	Clinical Frailty Scale		**Apea** • **RCFS Asian 1.98 (1.37, 2.86)** **Black** • **1.67 (1.14, 2.45)** **Cobos-Siles** • **8.73 (1.37-55.46)** **Dres** • **CFS 4 Univariate HR 2.14 (1.71, 2.68) Multivariate HR 2.24 (1.63, 3.09)** • **CFS 5 Univariate 2.81 (2.17, 3.64) Multivariate 2.83 (1.96, 4.08)** **Miles** • **CFS Univariate HR 1.12 (1.02, 1.23) Multivariate HR 1.88 (1.37, 2.59)** • **CFS x COVID-19 Multivariate HR 0.51 (0.27, 0.71)** **Aw** • **CFS 4 HR 1.23 (0.73, 2.07)** • **CFS 5 HR 1.18 (0.70, 1.99)** • **CFS 6 2.20 (1.41, 3.43) CFS 7-9 2.20 (1.41, 3.43)** **Jung** • **3.20 (2.56, 4.13)** • **2.41 (1.77, 3.27)** • **1.86 (1.36, 2.52)** **Aliberti** **30-day mortality** • **CFS 4 1.4 (1.1, 1.7)** • **CFS 5 1.5 (1.1, 1.9)** • **CFS 6 1.8 (1.4, 2.3)** • **CFS 7-9 2.1 (1.6, 2.7)** **6-month mortality** • **CFS 4 1.4 (1.1, 1.7)** • **CFS 5 1.5 (1.1, 1.8)** • **CFS 6 1.9 (1.5, 2.4)**	https://www.mdcalc.com/csha-clinical-frailty-scale-cfs

					• **CFS 7-9 2.3 (1.8, 2.9)** **Hewitt** • **CFS 3-4 1.55 (1.00, 2.41)** • **CFS 5-6 (1.83 (1.15, 2.91)** • **CFS 7-9 2.39 (1.5, 3.81)** **Thompson** • **Median CFS OR 1.72 (1.52, 1.94)**	

**Discrimination performance: ability of the model to discriminate between those who will and will not develop the outcome of interest. An area under the curve (AUC) of 0.90-1.0 indicates excellent discriminatory capacity of the model; 0.80-0.90 good; 0.70-0.80 fair; 0.60-0.70 poor; <0.60 failure to discriminate.*
**Hazard ratio: a hazard ratio greater than 1 suggests an increased risk, below 1 suggests a smaller risk*

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 4)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (1)	Yes (3)					In order to reduce the risk of severe disease and mortality, numerous studies have assessed the usefulness of prognostic models that aim to identify patients at high risk of adverse outcomes from COVID-19.
Certainty of Evidence	High	Moderate	Low (2)	Very low (2)			- Thirty-three (36) cohort studies on prognostic models for clinical deterioration and mortality of individuals with COVID-19 were found. Most of the studies (n = 31) were assessed to have high risk of bias due to issues in participant selection and analysis. - For predicting mortality, the following models demonstrated fair-to-good predictive ability: 4C mortality score, ABC2-SPH, CURB-65, REMS, RISE UP and COVID-GRAM models. Poor to fair prediction was noted for the qSOFA model. Only one model, the QCOVID model for mortality validated for the UK setting, demonstrated high predictive ability but this model has been validated in the UK setting. - For predicting clinical deterioration, available prognostic models showed varied performance. The 4C deterioration which has been investigated in only one study with low risk of bias, showed fair predictive ability. The MEWS model has poor prediction of clinical deterioration while NEWS2 has inconsistent prediction (poor to good). The Clinical Frailty Scale (CFS), increases the risk of mortality among elderly COVID-19 patients.
Accuracy	Very Accurate	Accurate	Inaccurate (4)	Very Inaccurate	Uncertain		
Values	Important uncertainty or variability	Possibly important uncertainty or variability (1)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			No research evidence found.
Resources Required	Uncertain (2)	Large cost (1)	Moderate Cost	Negligible cost or savings (1)	Moderate savings	Large savings	
Certainty of evidence of required resources	No included studies (2)	Very low (1)	Low (1)	Moderate	High		
Cost effectiveness	No included studies (3)	Favors using comparator	Does not favor either using prognostic models or the comparator (1)	Favors the prognostic models			
Equity	Uncertain (2)	Reduced	Probably no impact (1)	Increased (1)			
Acceptability	Uncertain (2)	No	Yes (2)				
Feasibility	Uncertain (2)	No	Yes (2)				

Appendix 2. Characteristics of Included Studies

Author and year Model	Study design and Setting	Specific Outcome	Time point of model application	Population and sample size	Candidate predictors	Determination of candidate predictors	Final predictors	Performance AUC (95% CI)
Adderley 2021 [35]	Retrospective cohort UK Jan 1-Sep 12, 2020 Last admission on Aug 16, 2020	28-day outcomes Mortality Training cohort (TC) n=288 (7.48%) Validation cohort (VC) n=1668 (27.35%) Admission to intensive care unit (ICU) TC, n= 183 (4.75%) VC, n= 722 (12.66%)	Admission or up to 72h from admission	TC Inpatients RT-PCR positive (RT-PCR+) n = 3849 VC RT-PCR+ or antibody test-positive n=6099	Demographic features Clinical features Laboratory features Imaging Frailty score Glasgow Coma Score (GCS) Comorbidity 63 candidate predictors for model development 27 candidate predictors in external validation population	Literature review Discussion with experts Available collected variables Time series analysis	Mortality model: Age, breathlessness, sputum, systolic blood pressure (SBP),Temperature (temp), Respiratory rate (RR), Oxygen saturation (O2sat) , FiO2, alkaline phosphatase (ALP), C-reactive protein (CRP), Calcium, Eosinophils, Glucose, pH, Urea, WBC count, platelets, and frailty score ICU admission model: age, gender, fever, new onset diarrhoea or vomiting, heart rate (HR),RR, FiO2, temp Albumin, CRP, eGFR, pH, monocytes, WBC, frailty score, and GCS Reduced model: Age, SBP, temp, RR, O2 sat, FiO2, frailty score, pH,urea, CRP	TC Mortality 0.778 (0.741, 0.815) ICU admission 0.892 (0.865, 0.920) Reduced model Mortality TC 0.791 (0.761, 0.822); VC 0.767 (0.754, 0.780) ICU admission TC 0.906 (0.883, 0.929) VC 0.811 (0.795, 0.828)
Ageno 2020 [36] Italy	Retrospective cohort Five centers Feb 17 - May 8, 2020	Severe outcome defined as non-invasive ventilation (NIV), intubation, or death n= 275 (45.08%)	Admission	Inpatients RT-PCR+ n = 610	Demographic features Comorbidity Laboratory tests	No explanation for selection Multivariate logistic regression with backward selection, LASSO, Random Forest	Age Coronary heart disease PCR, AST, D-dimer, NLR 6 variables 13 points	0.80 Cut-off 7 points in VCt Sensitivity0.93 Specificity 0.34 PPV 0.59 NPV 0.82.
Aliberti 2021 [32] CFS Brazil	Retrospective cohort Hospital das Clinicas, Brazil	Time to death within 30 days and 6 months of hospital admission	Admission	Inpatients age 50 or more, RT PCR+ and serologic N = 1830	n/a	n/a	CFS	30-day mortality CFS 1-3 reference 4 crude HR 1.5 (1.2-1.9) adjusted HR 1.4 (1.1-1.7)

	March 30 to July 7, 2020							5 crude HR 1.9 (1.5-2.4) adjusted HR 1.5 (1.1-1.9) 6 crude HR 2.3 (1.8-2.9) adjusted HR 1.8 (1.4-2.3) 7-9 crude HR 2.6 (2.1-3.4) adjusted HR 2.1 (1.6-2.7) 6-month mortality CFS 1-3 reference 4 crude HR 1.5 (1.2-1.8) adjusted HR 1.4 (1.1-1.7) 5 crude HR 1.9 (1.6-2.4) adjusted HR 1.5 (1.1-1.8) 6 crude HR 2.3 (1.8-2.9) adjusted HR 1.9 (1.5-2.4) 7-9 crude HR 2.6 (2.1-3.4) adjusted HR 2.1 (1.8-2.9)
Apea et al. 2020 [26] CFS UK	Prospective 5 acute hospitals May 20 2020	30-day mortality	Admission	Inpatients RT PCR + n = 1996	n/a	n/a	CFS	RCFS Asian 1.98 (1.37-2.86) Black 1.67 (1.14-2.45)
Armiñanzas 2021 [17] COVID GRAM CURB-65 Spain	Retrospective Hospital Universitario Marques de Valdecilla February to May 2020	Critical illness as a composite endpoint of ICU admission and 30-day mortality N=110 (21.0%)	Admission	Adult inpatients RT PCR+ N=523	n/a	n/a	COVID-GRAM CURB-65	CURB-65 0.727 COVID-GRAM 0.88
Artero et al., 2020 [10] Spain	Retrospective cohort Multi-center March- May 2020	Mortality, all-cause n= 2135 (20.9%) ICU/mechanical ventilation n=907 (8.9%)	Admission	Inpatients RT-PCR+/ antibody+ n =10,238	N/A	N/A	Pneumonia Severity Index CURB-65 qSOFA (altered mental status, RR, SBP)	*Mortality* PSI 0.835 (0.826, 0.845) CURB-65 0.825 (0.815, 0.835) MuLBSTA 0.715 (0.703, 0.727) qSOFA: 0.728 (0.715, 0.741)

							MuLBSTA: Age, smoking, bacteria infection, HPN Lymphocytes Imaging- multilobar infiltrates	*ICU admission* PSI 0.539 (0.521, 0.557) CURB-65 0.562 (0.544, 0.580) MuLBSTA 0.658 (0.640, 0.677) qSOFA 0.616 (0.598, 0.635) *Mechanical ventilation* PSI 0.560 (0.540, 0.579) CURB-65 0.572 (0.553, 0.592) MuLBSTA 0.678 (0.657, 0.698) qSOFA 0.624 (0.603, 0.644)
Aw et al. 2020 [30] CFS UK	Retrospective March 1 2020 to April 30 2020	all-cause mortality	Admission	Inpatients diagnosed with COVID-19 n=677	n/a	n/a	CFS	Aw CFS 4 HR 1.23 (0.73-2.07) CFS 5 HR 1.18 (0.70-1.99) CFS 6 2.20 (1.41-3.43) CFS 7-9 2.20 (1.41-3.43)
Baker 2021 [23] UK	Retrospective cohort Single-center Jan- Apr, 2020	Clinical deterioration defined as initiation of NIV or mechanical ventilation (MV), ICU admission, end of care, or in-hospital death *Data censored at 28 days for patients still admitted n= 133 (44.9%)	Admission	Inpatients RT-PCR+ n = 296 131 with severe covid on admission	N/A	N/A	NEWS2:HR, BP, temp, RR, O2 sat, level of consciousness	0.70 (0.65–0.77)
Bartoletti 2020 [37] Italy	Retrospective cohort study Multi- centre Feb- April, 2020	Severe respiratory failure- SpO2 <93% with 100% FiO2, RR>30/ min or respiratory distress n=367 (32.97%)	Admission	Inpatients RT-PCR+ n = 1113	Demographic,Comorbidities Symptoms on admission Laboratory tests	No explanation	PREDI-CO score: Age Obesity, RR Fever at hospitalization Lymphocytes Creatinine, CRP, LDH	0.85 (0.81-0.88)

Berenguer 2021 [38] Spain	Retrospective cohort Feb- April, 2020	30-day mortality n= 341 (5.5%)	Admission	Inpatients RT-PCR+ n = 6161	Demographic ComorbiditiesSigns and symptoms Laboratory tests	17 baseline variables found to be independently associated with death in the COVID-19 Spain cohort	COVID-19 SEIMC score Age, sex Dyspnea, age-adjusted SaO2 NLR, eGFR by CKD-EPI	0.831 (0.806–0.856)
Bradley 2020 [11] UK	Prospective Seven respiratory hospitals in NW England April 1-14, 2020	30-day mortality n=300 (36.14%) ICU admission n=142 (17.10%)	Admission	Consecutive adults admitted meeting the Public Health England inpatient case definition for COVID-19 and PCR+ n=800			CURB-65 NEWS2 qSOFA	30-day mortality CURB-65- 0.75 NEWS2- 0.67 qSOFA- 0.62 72-h mortality CURB-65- 0.76 NEWS2- 0.78 qSOFA 0.65 ICU admission CURB-65 0.63 NEWS2 0.65 qSOFA 0.55
Carr 2021 [24] UK	Retrospective cohort study Multi- center Feb-Aug, 2020	Severe covid-19 outcomes (transfer to ICU or death at 3 and 14 days from admission or symptom onset for nosocomial COVID TC 3-day n = 389 (30.48%) 14-day n= 163 VC 3-day n= 27-289 14-day n=39-391	Admission (up to 48h after admission)	Inpatients RT-PCR+ n = 7513 TC, n = 1276 (1 hospital of NHS Hospitals Trust) C,n = 6237 (5 centers of NHS Hospitals Trust, 1 hospital in Norway, 2 hospitals in Wuhan, China)	Age, sex, ethnicity, select comorbidity, physiologic measures (NEWS2), biomarkers (alb, CRP, GFR, lymphocyte ct, neutrophil ct, platelet ct, NLR, lym-CRP ratio, urea)	routinely obtained parameters available in a wide range of settings Regularised logistic regression with least absolute shrinkage & selection operator (LASSO) estimator	Model 1: NEWS2 only Model 2: NEWS2 + age Model 3: Supplemented NEWS2 score Age Supplemental O2 flow rate, O2 sat, eGFR Urea, CRP, Neutrophil count NLR	NEWS2 3-day: 0.717-0.772 14-day: 0.697-0.743 NEWS+age 3-day: 0.717-0.772 14-day severe outcome: 0.686-0.815 All features 3-day: 0.716-0.831 14-day: 0.762-0.864 *All models showed evidence of increasing miscalibration as new predictors are added to the model
Castro 2021 [39] USA	Retrospective cohort study Multi- center- 2 academic centers and 4 commu-nity hospitals June 7, 2020- Jan 22, 2021	1) Severe illness (composite of ICU admission, mechanical ventilation, or mortality) n=241 (8.3%) 2) mortality n=167 (5.8%)	Admission	Inpatients RT-PCR+ within 5 days of admission (n = 2,892) 2 academic medical centers, 4 community hospitals Mass General Brigham Data Registry Enterprise Data Warehouse	Age, SpO2 Comorbidity (CCI)	N/A Logistic regression Survival analysis Right-censoring	Severe illness model: Age, SpO2, BUN, CRP, crea, low eGFR, eosinophils, ,glucose, LDH, lymphocytes, low ALC,monocytes, neutrophil, high ANC,plt, Trop T Charlson comorbidity index (CCI), prior respiratory infections Mortality model: Same as severe illness model plus low MCH ,high ANC, high absolute nucleated RBC , low plt PCT, RDW,Trop T, high WBC CCI, COPD or	severe illness: 0.79 (95% CI:0.75-0.81) mortality: 0.83 (95% CI:0.80-0.87)

				(Temporal validation)			bronchiectasis, dementia or delirium external causes of injury lung CA respiratory failure or insufficiency	
Chua 2020 [40] UK	Prospective Multi- center March 1-May 16, 2020	In-hospital mortality TC, n=294 (29.9%) (university hospital NHS Hospitals Trust) VC1 ISARIC n=4319 (30.35%) VC2 n= 94 (32.41%) (university hospital NHS Hospitals)	Presentation to ED	Adults ≥18 years old PCR+ at Emergency Department (ED) TC n=983 VC 1 n=14231 VC 2 n=290 n=5 confined at cut-off day	NEWS Demographic Routine laboratory tests	Usual data collected at the ED	SOARS11 SpO2, obesity, age, RR, stroke, smoking, dementia, CKD with stage, Wbc count, lymphocytes CXR (≥4 zones affected) SOARS5: SpO2, Obesity, Age, RR Stroke history	SOARS11 TC 0.82 VC1 0.80 VC2 0.74
Clift 2020 [7] UK	Retrospective	Time to death from COVID-19 TC n=4384 deaths (0.07%)[#] VC1: Jan 24- Apr 30, 2020 n=1722 (0.07%)[#] VC 2: May1- Jun 30,2020 n =621 (0.02%)[#] [#]% deaths in whole population (includes those with and without COVID-19	Not specified	Adults 19-100 years old QResearch database (1205 general practices in England linked to death and hospital registries TC n=6.08 million VC n= 2.17 million	Demographic data Comorbidity	Data available in the database	QCOVID Age Ethnicity Deprivation index BMI Comorbidity	Period 1 Women 0.93 (0.92, 0.94) Men0.93 (0.92, 0.93) Period 2 Women 0.95 (0.94, 0.96) Men0.93 (0.92, 0.95)
Cobos-Siles et al. 2020 [27] CFS Spain	Retrospective	Mortality	Not specified	Inpatients RT PCR+ n=128	n/a	n/a	CFS	HR 8.73 (1.37-55.46)
Codon 2021 [41] CHADS CHA2DS2-VASc Spain	Retrospective Mar1- Apr 20, 2020	Thromboembolism n= 115 (3.78%) Mortality n=626 (20.58%)	Not stated i Presumed to be on admission	Inpatients confirmed COVID completed 1-month follow-up or died, Mar 1-Apr 20,2020	CHADS and CHA2DS2-VASc	–	CHADS CHF or LV ejection fraction ≤40, HPN, Age Stroke, transient ischaemic attack (TIA), systemic embolism CHA2DS2-VASc score: age, sex, history of stroke, TIA, CHF, HPN, thromboembolism, diabetes mellitus	Thromboembolism CHADS 0.497 (0.452,0.542) CHA2DS2-VASc 0.490 (0.440,0.541) Mortality CHADS 0.788 (0.770–0.807) CHA2DS2-VASc 0.794 (0.775,0.812)
Doganay 2021 [16]	Retrospective	Mortality n=120 (24.94%)	Admission	COVID-19 patients 18 and	n/a	n/a	Multiple models	Mortality

CURB65 ISARIC-4C COVID-GRAM Turkey	Kartal Dr. Lufti Kirdar City September 1 to December 2020	ICU requirement n = 85 (17.67%)		above RT PCR + n=481				CURB 65 0.846 (0.810-0.877) ISARIC 4C 0.784 (0.744-0.820) COVID GRAM 0.701 (0.658-0.742) ICU requirement CURB 65 0.898 (0.867-0.923) ISARIC 4C 0.797 (0.758-0.832) COVID-GRAM 0.684 (0.640-0.725)
Dres et al. 2021 [28] CFS France Switzerland Belgium	Retrospective	Day-90 mortality n=549	Admission	Inpatients ICU RT PCR+ n=1199	n/a	n/a	CFS	Dres CFS 4 Univariate HR 2.14 (1.71-2.68) Multivariate HR 2.24 (1.63-3.09) CFS 5 Univariate 2.81 (2.17-3.64) Multivariate 2.83 (1.96-4.08)
El-Solh 2020 [42] US	Retrospective cohort Jan-May, 2020	In-hospital mortality n=475 (29.07%)	Admission	Inpatients RT-PCR+ n = 1634	–	–	Chen: Age, CHD, CVD, dyspnea, PCT, AST Shang: Age, CHD, % lymphocytes, PCT, D-dimer Wang Clinical model: age, HPN, CHD Laboratory model: Age, hsCRP, peripheral capillary O2 sat, neutrophil and lymphocyte count, D-dimer, AST, GFR Yu: age, male sex, history of diabetes, lymphopenia, increased PCT	Chen 14-day mortality: 0.67 (0.64–0.70) 21-day mortality: 0.68 (0.65–0.71) 28-day mortality: 0.69 (0.66–0.72) Shang.: 0.72 (0.69–0.74) Yu: 0.63 (0.60, 0.66) Wang: 0.69 (0.66, 0.72)
Goodacre 2021 [60] PRIEST UK	Retrospective March 26-May 29, 2022	Adverse outcome Derivation cohort n=11773 Validation cohort n=9118	Hospital admission	Adult COVID in patients DC 11773 VC 9118	Age, sex, RR, SBP, oxygen saturation, inspired oxygen, temperature, HR, NEWS2	LASSO regression	RR, O2 saturation, HR, SBP, Temp, Alertness, Inspired oxygen, Sex, Age, Performance status	DC 0.80 (0.79-.81) VC 0.83 (0.82-0.84)
Gupta 2020 [18] Multiple models 2(UK)	Retrospective Feb-Apr 2020	Mortality N=115 (28%) Clinical deterioration (ventilatory support	On hospital admission	Consecutive adults admitted to University College Hospital London, PCR+	n/a	n/a	22 models	Mortality Lu: 12-day 0.72 (0.67, 0.76) 30-day CURB-65: 0.74 (0.69, 0.79)

		or death) N=180 (43.8%		or clinically diagnosed COVID-19 (diagnosis of ID Specialist - clinical features, laboratory, radiologic results without alternative diagnosis. n=411				BelloChavolla 0.66 (0.6, 0.72) In-hospital REMS: 0.76 (0.71, 0.81) qSOFA: 0.6 (0.54, 0.65) Xie: 0.76 (0.69, 0.82) Hu 0.74 (0.68, 0.79) Caramelo: 0.71 (0.66, 0.76) Zhang: 0.7 (0.65, 0.76) Yan: 0.58 (0.49, 0.67) Deterioration NEWS1 day 0.78 (0.73, 0.83) Ji: 10 days 0.56 (0.5, 0.62) Carr: 14 days 0.78 (0.74, 0.82) Guo: 0.67 (0.61, 0.73) Zhang: 0.74 (0.69, 0.79) Galloway: 0.72 (0.68, 0.77) TACTIC: 0.7 (0.65, 0.75) Colombi: 0.69 (0.63, 0.74) Huang: 0.67 (0.61, 0.73) Shi: 0.61 (0.56, 0.66) MEWS: 0.6 (0.56, 0.65)
Gupta , 2020 [22] UK	Prospective cohort Feb-Aug 2020	in-hospital clinical deterioration- initiation of ventilatory support (NIV, MV, ECMO); admission to ICU or death n = 31 924 (43.17%)	Admission or first clinical suspicion of covid	Inpatients Suspected/ Confirmed RT-PCR+ n = 73 948	Demographic, clinical, laboratory features, comorbidities	Review of iterature, availability in >60% of the study population	4C Deterioration Score: Age, sex + comorbidity + nosocomial infection + radiographic infiltrates + periph O2 sat + room air or o2, GCS, Urea, CRP, lymphocyte	0.77 (95% CI 0.76, 0.78)
Hewitt 2020 [33] CFS UK Italy	Retrospective cohort Feb 27-April 28, 2020	In-hospital mortality	Admission	Inpatients RT PCR+ N=1564 Italy n=154 UK n=1410	n/a	n/a	CFS	CFS 1-2 HR 1 3-4 HR 1.55 (1.00-2.41) 5-6 HR 1.83 (1.15-2.91) 7-9 2.39 (1.5-3.81)
Jung et al. [31] CFS Germany	Prospective multicenter cohort March 19 to May 26 2020	survival status at 30 days after ICU admission (97%)	Admission	70 years and older with proven COVID-19 n=1346	n/a	n/a	CFS	Jung 3.20 (2.56-4.13) 2.41 (1.77-3.27) 1.86 (1.36-2.52)
King , 2021 [43] VACO	Retrospective Feb-July 2020	30-day mortality TC n=480 (13%) VC1 n=253 (12%)	Admission	Inpatients RT-PCR+ inpatients testing + within	DemographicComorbidity	Multivariable logistic regression	Age Sex Comorbidity MI or PVD	Hospital cohort: 0.80 (0.77, 0.83)

USA		VC2 n=403 (5%)		14 days before or in the hospital (D1/ later)				Medicare cohort: 0.67 (0.67, 0.68) 0.68 (0.68 – 0.68)
Knight 2020 [20] 4C Mortality Score UK	Prospective cohort Feb-Jun 2020	Mortality TC n=11426 (32.22%) Feb 6-May 20, 2020 VC n=6729 (30.09%) May 21-June 29, 2020 No recorded outcome considered alive.	Hospital admission	Inpatients ≥ 18 years RT-PCR+ TC n= 35463 VC n= 22,361 (Temporal validation)	Patient and clinical variables Clinical biomarkers for COVID-19	41 candidate predictors selected a priori based on influence on outcome of pneumonia & flu-like illness, COVID-19, available for 2/3 of patients in TC 3-step model development	Age, sex, number of comorbidities RR, O2 sat, GCS, Urea,CRP	TC 0.786 (0.781,0.79) VC 0.767 (0.76, 0.773)
Li 2020 [44] PLANS China	Retrospective Jan-Mar 2020	In-hospital mortality TC n=211 (20.93%) VC n=162 (15.71%)	On admission	Inpatients Adults RT-PCR+ TC (2 hospitals) Jan 1-Feb 10, 2020 n=1008 VC (1 hospital) Jan 14-Mar 8, 2020), n=1031	Patient characteristicLaboratory tests	Clinical knowledge, literature, data availability Multivariable Fine-Gray model	Platelet count, lymphocyte count, Age Neutrophil count Sex	TC 0.85 (0.83, 0.87) VC 0.87 (0.85, 0.89)
Liang 2020 [25] COVID-GRAM China	Retropsective 575 hospitals in China January 2020	Critical illness defined as a composite measure of admission to the ICU, invasive ventilation, or death	admission	Inpatients Adults RT PCR + DC n=1590 VC n=710	72 variables including clinical signs and symptoms, imaging results, laboratory findings, demographic variables, and medical history	LASSO regression	X-ray abnormality, age, hemoptysis, dyspnea, unconsciousness, no. of comorbidities, cancer history, neutrophil to lymphocyte ratio, Lactate dehydrogenase U/L, direct bilirubin umol/L	DC 0.88 (0.84-0.93) VC 0.88 (0.84-0.93)
Liu FY 2020 [12] NEWS NEWS2REMS CURB- 65 qSOFA China	Retrospective Single- COVID center Jan 30-Mar 14, 2020	In-hospital death N=121 (17.98%)	On admission	Inpatients Adults RT-PCR+	n/a	n/a	NEWS NEWS2 REMS CURB-65 qSOFA	0.882 (0.847–0.916) 0.880 (0.845–0.914) 0.839 (0.800–0.879) 0.766 (0.718–0.814) 0.694 (0.641–0.746)
Liu H 2021 [45] PAWNN China	Retrospective Jan-Apr 2020	In-hospital death TC n =773 (7.88%)	Admission and throughout hospitalization	Inpatients RT-PCR+ or clinically diagnosed	38 candidate predictors Demographic Clinical findings	Generalized linear mixed modelling, Cox regression model	Platelet count Age WBC count Neutrophil count Neutrophil:lymphocyte ratio	TC 0.92-93 (0.91, 0.94) VC Chinese 0.97

		VC: China 211 (7.7%) Italian 77 (33.92%)		Excluded leukemia inpatients at study end TC n=9810 VC1 n=2739 VC2 n=227	Laboratory tests-CBC			(0.96–0.98) Italian 0.80 (0.74, 0.86)
Mancilla-Galindo, 2021 [46] Mexico	Retrospective	Mortality TC n=9228 (11.01%) VC n=5278 (5.28%)	Not mentioned	Inpatients Ambulatory RT-PCR+ TC n=83779 VC n=100,000	Demographic, Clinical Comorbidity	Demographic Patient history predictors for low-resource settings Univariate and multivariate regression	Age Sex Diabetes COPD Immunosuppression Hypertension Obesity CKD	0.8 (0.796, 0.804)
Marcolino 2021 [21] ABC_2-SPH Brazil	Retrospective Mar-Jul 2020. Aug-Sep 2020	In-hospital deaths TC n=806 (20.26%) VC1 Brazil n=208 (19.73%) VC2 Spain 82 (17.29%)	Admission	Inpatients PCR+ TC n=3978 VC1 n=1054 VC2 n=474	20 predictors chosen a priori Demographic Comorbidity Vital signs Laboratory tests	Least absolute shrinkage and selection operator (LASSO) logistic regression	Age, blood urea nitrogen, number of comorbidities, HR, CRP, SpO2/FiO2 ratio, platelet count	TC 0.844 (0.829,0.859) VC1 0.859 (0.833, 0.885) VC2 0.899 (0.864,0.934)
Miles et al. [29] CFS UK	prospective May 2020	all-cause mortality n=217	Admission	Inpatients RT-PCR+ n=217 COVID-19 cases	n/a	n/a	CFS	Miles CFS Univariate HR 1.12 (1..02-1.23) Multivariate HR 1.88 (1.37-2.59) CFS x COVID-19 Multivariate HR 0.51 (0.27-0.71)
Nafilyan 2021 [8] QCOVID England	Retrospective Jan-July 2020	Suspected/ confirmed COVID-related death (ICD code) n=26,985 (0.077%)[#] deaths in Period 1 (Jan 24-Apr 30, 2020) n=13,177 (0.037%)[#] in Period 2 (May1-Jul 28, 2020) [#]% deaths in whole population (includes those with and without COVID-19	No particular time	Adults n=34.897M (ONS PH Health Linked Data Asset linked to primary care and hospital databases) Patients entered the COVID cohort on Jan 24 & follow-up till Jul 28,2020	Demographic data Comorbidity	n/a	QCOVID Age, Sex Region Ethnicity Townsend deprivation scale Accommodation BMI Comorbidity (CKD, Cancer, Chemotherapy, Immunosuppression, Learning Disability Others)	C statistic Period 1 Men 0.935 (0.933, 0.937) Women 0.945 (0.943, 0.947) Period 2 Men 0.944 (0.942, 0.946) Women 0.956 (0.954, 0.958)

Nava 2020 [13] US	Retrospective Teaching community hospital Mar-May 2020	In-hospital mortality n=101 (32.26%) ICU admission n=98 (31.3%)		Inpatients adults COVID-19 pneumonia n=313			CURB-65 Quick COVID-19 Severity Index (qCSI) Brescia-COVID Respiratory Severity Scale (BCRSS)	CURB-65 0.781 qCSI score 0.711 BCRSS prediction rule 0.663
Nicholson 2021 [47] VICE DICE US	Retrospective Metropolitan hospital network until May 19, 2020	Death TC n=111 (19.2%) VC n=99 (21.33%) Mechanical Ventilation TC n=243 (42.04%) VC n=161 (34.69%	On admission Laboratory tests within 24 hours of admission (Research Patient Data Repository)	Inpatients Adults RT-PCR+ Observed until discharge TC n=1042 VC1= 578 (1 hospital) VC2 n= 464 (4 hospitals)	Demographic, clinical, and admission laboratory data	Multivariate logistic regression analysis with backwards selection stepwise method	DICE: Age, male sex, CAD, DM, chronic statin use, SpO2:FiO2 ratio,BMI, NLR, platelet count, procalcitonin VICE: DM SpO2:FiO2 ratio, CRP, LDH	DICE TC 0.91 (0.87,0.94) VC 0.79 (0.74,0.84) VICE TC 0.84 (0.80,0.87) VC 0.86 (0.82,0.90)
Neto 2021 [15] CURB CURB 65 QSOFA PSI SMART COP IDSA/ATS Minor REA-ICU SCAP COVID GRAM CALL 4C Brazil Spain	Binational retrospective cohort Hospital das Clinicas in Sao Paulo, Brazil Hospital Clinic Barcelona	In hospital mortality 30 days n=320 (23.48%), Brazil n=228 (24.65), Spain n=92 (21%) ICU admission n=646 (47.4%), Brazil n=487 (52.65%), Spain n=159 (36.3%)	On the first medical assessment in the emergency department and laboratory tests were taken from the first available result up to 48 h after admission	Adult in-patients (Barcelona – RT PCR + only, Sao Paulo, RT PCR + and clinical-epidemiologically diagnosed) All N=1363 Brazil n=925, Spain n=438	n/a	n/a	Multiple models	30-day in-hospital mortality CURB 0.71 (0.68-0.74) CURB65 0.74 (0.72-0.77) QSOFA 0.63 (0.6-0.66) PSI 0.79 (0.77-0.82) SMART COP (0.71 (0.68-0.74) IDSA/ATS Minor 0.73 (0.7-0.76) REA-ICU 0.69 (0.65-0.72) SCAP 0.74 (0.71-0.77) COVID GRAM 0.77 (0.75-0.8) CALL 0.71 (0.68-0.74) 4C 0.78 (0.75-0.81) 7-day ICU admission CURB 0.59 (0.55-0.62) CURB65 0.54 (0.51-0.58) QSOFA 0.59 (0.56-0.62) PSI 0.52 (0.49-0.56) SMART COP (0.64 (0.61-0.67) IDSA/ATS Minor 0.6 (0.57-0.64) REA-ICU 0.6 (0.67-0.63) SCAP 0.6 (0.57-0.63) COVID GRAM 0.52 (0.48-0.55)

								CALL 0.52 (0.49-0.56) 4C 0.55 (0.52-0.59)
Paranjape 2021 [48] Calculator for ICU transfer US	Retrospective Large metropolitan health system Mar-Jul 2020	Transfer to ICU service TC n=804 (39.92%) VC n= 192 (28,61%)	On admission	Inpatients Adults RT-PCR+, TC Mar-Jul n=2014 VC: July n=671	Demographic (age, sex, race, BMI), temp, SpO2 on room air CRP, LDH, ferritin, D dimer, absolute lymphocyte count Comorbidities- HTN, DM CKD,Asthma, COPD, CAD	Multivariate Logistic Regression analysis with backwards selection stepwise method	DM, CAD, CKD, CRP, LDH	TC 0.752 VC 0.769
Richardson 2021 [49] NEWS2/NEWS UK	Retrospective	Death 24 hrs-9 48 hrs-15 72 hrs-33 In-hospital- 199 (32.09%)	Within 24 hours of admission	Adults non-elective admission (COVID or not) discharged Mar11-Jun 13, 2020 COVID as ICD-coded in EMR	n/a	n/a	NEWS: RR, HR, temp, O2Sat, O2 supplement, AVPU, SBP NEWS2 NEWS and alertness includes confusion	NEWS 0.64 NEWS2 0.64 72hours NEWS: 0.75 NEWS2: 0.71 48 hours NEWS: 0.78 NEWS2: 0.76 24hours NEWS: 0.84 NEWS2: 0.86
Schoning 2021 [50] COSA Switzerland	Retrospective Prospective validation Feb-Nov 2020	Severe TC n=63 (31.82%) VC n=105 (22.87%)	On admission Lab values 3 days before or up to 1 day after PCR+	In- and outpatients 198 PCR+ TC n=198 Feb-Aug VC n=459 Sep-Nov	Medical history, demographicsTop 20 laboratory tests routinely assessed on admission	Logistic regression Repeated cross-validation	COSA score Sex CRP Sodium Hemoglobin eGFR Glucose Leukocyte count	TC 0.94 (0.87, 0.95) VC 0.85
Solem 2021 [9] COPE Denmark	Prospective cohort 2 regions Denmark Mar 1 to June 16, 2020	TC Hospital admission n=1359 (34.5%) ICU n=181 (4.6%) Death n=324 (8.2% of COVID-19 patients or 0.01% of whole population tested) VC Hospitalized n=753 (45.63%) ICU n=131 (17.4%) Deaths n=305 (18.48%)	Different time points: Diagnosis First 12 h of hospital admission 12 hours prior to ICU admission -12 hours after ICU admission	Adults at PCR test (Regional EMR with in-hospital data) 394 4 RT-PCR+ out of 2.6M tested TC Denmark VC: UK Biobank n=1650	Demographic data Comorbidity Temporal features In-hospital laboratory tests	Available information in the EMR Random forests Cross-validation	Base model- Age, sex, BMI Model 2: Base +comorbidity Model 3: Model 2+temporal features Model 4: Model 3+in-hospital laboratory tests	TC: Risk of death 0.906 at diagnosis, 0.818, at admission 0.721 at ICU admission ICU admission On diagnosis, Model 2,3 &4 with improved prediction On admission Model 4 significantly improves prediction VC On Diagnosis Mortality 0.742 ICU admission 0.529 Hospital admission 0.661

Tanboga 2021 [51] CORONATION TURKEY	Retrospective National database Mar-Jun 2020	Total deaths n=2682 (4.4%) ICU n=7688 (13%) Mechanical ventilation n=4867 (8%) 30-day death TC n=2343 (6%) VC n=339 (2%) ICU TC n=6160 (15%) VC n=1528 (8%) Mechanical ventilation TC n=4158 (10%) VC n=709 (4%)	Admission	Inpatient RT-PCR+ n=60,980 TC n=41,300 VC n=19,6809	Demographic data ComorbiditiesLung CT Laboratory tests	Data from public health management system for COVID-19 specific data during index hospitalization (symptoms, biomarkers, medication, comorbidity, clinical outcomes)	Age, findings from lung CT, LDH, CRP, comorbidities, NLR, and D-dimer	Temporal validation TC 0.933 (0.929–0.937) VC 0.956 (0.948–0.964) Geographic validation Istanbul TC Istanbul 0.958 (0.939 –0.972) VC: Anatolia region 0.896 (0.890–0.902)
Van Dam 2020 [14] Netherlands	Retrospective study ED of a single secondary/ tertiary hospital Mar-May 2020	30-day mortality N=95/403 (23.57%)	On admission	Adults on ED consult RT-PCR+ or clinical diagnosis (symptom, CT findings with consent) n=403 307were admitted	n/a	n/a	RISE-UP CURB-65 MEWS REMS abbMEDS SOFA APACHE II	30-day mortality 0.83 (0.79-0.88) 0.75 (0.70-0.80) 0.64 (0.58-0.70) 0.73(0.68-0.78) 0.75(0.70-0.81) 0.72(0.67-0.78) 0.71(0.65-0.78)
Van Dam 2021[19] RISE UP Netherlands	Retrospective 2 EDs Mar-May 2020	30-day mortality n=167 (26%) Composite of 30-day mortality,ICU ICU n=102 (15.9%)	During Emergency Department Visit	Adults on ED visits RT-PCR+ or clinically diagnosed (symptom, CT finding)			RISE-UP score Age, abnormal vital signs (any of HR, MAP, RR, O2Sat, temp, GCS) serum albumin BUN, LDH, bilirubin with or without O2 supplement	Mortality 0.77 (0.73, 0.81) Composite 0.72 (0.68,0.76)
Van Klaveren 2021 [52] COPE Netherlands	Retrospective 4 hospitals Mar-Aug 2020	326 deaths (10.02%)	Admission to hospital	Admitted from ED suspected COVID 19 n=3252 Temporal validation	Patient characteristics (sex, age, BMI) Vital statistics Laboratory tests	Literature review Available at ED setting Logistic regression with post-hoc uniform shrinkage	Age, RR, CRP, LDH, alb, urea	AUC in 4 hospitals: 0.82 [0.78; 0.86] 0.82[0.74; 0.90] 0.79 [0.70;0.88] 0.83 [0.79; 0.86]

***AUC** = Area Under the Curve; **VC**=Validation cohort; **TC**=Training cohort*

Appendix 3. Clinical appraisal of included studies using the PROBAST tool

Study	ROB				Applicability			Overall judgment	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
Adderley et al.	L	L	L	H	U	U	L	**H**	**U**
Ageno et al.	L	L	L	H	U	U	L	**H**	**U**
Artero et al.	H	U	L	H	U	U	L	**H**	**U**
Baker et al.	H	L	H	H	U	L	L	**H**	**U**
Bartoletti et al.	H	L	H	H	U	U	L	**H**	**U**
Berenguer et al.	L	L	L	H	U	U	L	**H**	**U**
Bradley et al.	H	L	H	U	U	U	L	**H**	**U**
Carr et al.	L	L	L	H	L	U	U	**H**	**U**
Castro et al.	L	L	L	H	U	U	L	**H**	**U**
Chua	H	H	U	U	U	U	L	**H**	**U**
Clift et al.	L	L	L	L	U	U	L	**L**	**U**
Codon	H	U	U	H	U	U	L	**H**	**U**
El Sohl et a.	H	L	L	H	U	U	L	**H**	**U**
Gupta 2020	H	L	L	U	U	U	L	**H**	**U**
Gupta 2021 4C	L	U	L	L	U	U	L	**U**	**U**
King et al.	L	L	L	H	L	U	L	**H**	**U**
Knight	L	L	L	U	U	U	L	**U**	**U**
Li J	H	U	H	L	U	U	L	**H**	**U**
Liu FY	H	L	L	H	U	U	L	**H**	**U**
Liu H	L	L	U	H	U	U	L	**H**	**U**
Mancilla-Galindo	H	L	L	H	L	U	L	**H**	**U**
Marcolino	L	L	L	U	U	U	L	**U**	**U**
Nafilyan	L	L	L	L	U	U	L	**L**	**U**
Nava	U	U	H	H	U	U	L	**H**	**U**
Nicholson	L	U	L	H	U	U	L	**H**	**U**
Paranjape	L	U	U	H	U	U	L	**H**	**U**
Richadson	L	L	L	H	U	U	L	**H**	**U**
Schoning	U	U	L	H	U	U	L	**H**	**U**
Solem	L	L	L	U	U	U	L	**U**	**U**
Tanboga	U	U	H	H	U	U	L	**H**	**U**
van Dam RISE UP	L	U	L	H	U	U	L	**H**	**U**
van Dam	L	L	L	H	U	U	L	**H**	**U**
van Klaveren	U	H	U	H	U	U	L	**H**	**U**
Liang 2020	U	U	L	H	L	L	U	**H**	**U**
Armiñanzas 2021	L	U	L	H	L	L	U	**H**	**U**
Neto 2021	L	U	L	L	L	L	L	**U**	**L**
Doganay 2021	L	U	L	H	L	L	L	**H**	**L**
Aliberti 2021	L	U	L	H	L	L	L	**H**	**L**
Apea 2020	U	U	L	H	L	L	L	**H**	**L**
Aw 2020	L	U	L	U	L	L	L	**U**	**L**
Cobos-Siles 2020	U	L	L	U	L	L	L	**U**	**L**
Dres 2021	U	U	L	U	L	L	L	**U**	**L**
Hewitt 2020	L	U	L	H	L	L	L	**H**	**L**
Jung 2021	H	H	L	U	U	L	L	**H**	**U**
Miles 2020	L	U	L	H	L	L	L	**H**	**L**
Thompson 2021	U	U	L	U	L	L	L	**U**	**L**

Appendix 4. GRADE Evidence Profile

Author(s): Patricia Pauline Remalante-Rayco, Evelyn Salido
Question: Prognostic models compared to no prognostic models for prediction of worsening severity/clinical deterioration/poor outcomes and mortality in adults with COVID-19
Setting:
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
QCOVID									
2	observational studies	not serious	not serious	not serious	not serious	very strong association		⨁⨁⨁⨁ HIGH	
4C Deterioration Score									
1	observational studies	not serious	not serious	not serious	not serious	none		⨁⨁◯◯ LOW	
COPE									
1	observational studies	serious [a]	not serious	not serious	not serious	none		⨁◯◯◯ VERY LOW	
ABC2-SPH									
1	observational studies	serious [b]	not serious	not serious	not serious	strong association		⨁⨁◯◯ LOW	
4C Mortality Score									
2	observational studies	serious [b]	not serious	not serious	not serious	none		⨁◯◯◯ VERY LOW	
CURB-65									
5	observational studies	serious [c,d,e]	not serious	not serious	not serious	strong association		⨁⨁◯◯ LOW	
REMS									
3	observational studies	serious [c,e]	not serious	not serious	not serious	strong association		⨁⨁◯◯ LOW	
RISE-UP									
2	observational studies	serious [c,d,e]	not serious	not serious	not serious	strong association		⨁⨁◯◯ LOW	
qSOFA									
4	observational studies	serious [c,e]	not serious	not serious	not serious	none		⨁◯◯◯ VERY LOW	
MEWS									
2	observational studies	serious [e]	not serious	not serious	not serious	none		⨁◯◯◯ VERY LOW	
NEWS2									
5	observational studies	serious [c,d,e,f]	serious [g]	not serious	not serious	none		⨁◯◯◯ VERY LOW	

CI: Confidence interval

Explanations

a. Did not account for censoring
b. Continuous predictors were dichotomized
c. Exclusion of participants with missing data
d. Calibration not done
e. Complexities in data not addressed
f. Small number of events relative to number of predictors
g. Outlier study (1 study with higher AUC)

Appendix 5. Characteristics of Ongoing Studies

Study name	Methods	Participants	Interventions	Outcomes	Starting date	Notes
NCT04366024 A Novel Nomogram to Predict Severity of COVID-19	Retrospective observational study (case-only)	COVID-19 disease patients confirmed by virus nucleic acid RT-PCR and CT	Clinical diagnosis	Consistency of predicted severe rate and observed severe rate of COVID-19 patients (Time frame: up to 3 months) Duration of severe illness (Time frame: up to 3 months)	January 17, 2020	Recruiting
NCT04629183 Risk Stratification of COVID-19 Patients Discharged From the Emergency Department (CODED)	Prospective cohort study	Adult patients (>18 years) subjected to a first ED visit for physician-confirmed COVID-19, discharged from the ED based on attending physician's or patient's decision (independent from study participation)	Integrated clinical evaluation	Primary: Composite outcome of death (any cause), hospital admission (any cause) (Time Frame: up to 30 days) Secondary: Death from COVID-19; death from other disease; hospital admission for COVID-19; hospital admission for other disease (Time Frame for all secondary outcomes: 30 days)	November 1, 2020	Recruiting

Q16. Should LDH, CRP, and Ferritin be used to guide immunotherapy in patients with COVID-19?

As of 13 December 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of specific cut-off values of CRP, LDH and Ferritin to guide the initiation of immunotherapy in patients with COVID-19 *(Very low certainty of evidence)*

Consensus Issues

The evidence base included studies that investigated the levels of LDH, CRP, and ferritin that are correlated with progression to severe disease, poor outcomes, or mortality, rather than improved survival with immunotherapy. Thus, the panel unanimously decided that insufficient evidence remains to use specific cut-off values of these markers to guide immunotherapy. Additionally, the panel cited the availability of other parameters that may be used to guide initiation of immunotherapy besides these markers.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of specific cut-off values of CRP, LDH, and ferritin to guide the initiation of immunotherapy in patients with COVID-19. *(Very low quality of evidence)*

Previous Consensus Issues

It was noted that varying cut-off values of LDH, CRP, and ferritin were used across the studies to predict mortality and severity of disease. Thus, no specific levels could be recommended to guide initiation of immunotherapy for COVID-19 patients.

KEY FINDINGS

- Moderate quality of evidence showed significant correlation of CRP >10 mg/L with mortality (four studies) and poor outcome (ten studies).
- High quality of evidence from seven studies showed significant correlation between elevated LDH and progression to severe disease.
- Moderate quality of evidence from 18 studies showed significant correlation between LDH >250 U/L and poor outcome.
- Low quality of evidence from four studies did not find significant correlation between elevated LDH and mortality.
- Very low quality of evidence showed significant correlation between elevated CRP and progression to severe disease (one study) and ICU admission (one study) in pediatric patients.

INTRODUCTION

Severe COVID-19 disease is characterized by an immunologic and hyperinflammatory response known as the cytokine release syndrome (CRS), whereby elevated pro-inflammatory cytokines, such as IL-2, IL-6, IL-10, and TNF-α cause multiple organ dysfunction, and possibly death. This uncontrolled immune response serves as the basis of immunotherapy in severe to critical COVID-19.[1]

Determining the onset of CRS is largely a clinical dilemma, as testing for the cytokines that herald it are not readily available in most institutions, and when they are, come at a high cost. Meanwhile, other markers of inflammation, such as lactate dehydrogenase (LDH), C-reactive protein (CRP), and ferritin have also been observed to be elevated in COVID-19 and, in some earlier cohort studies, were found to be associated with disease severity, progression, and mortality.[2] These are more readily available and less costly compared to testing for cytokines.

Current international society recommendations have utilized these inflammatory markers as guides for initiation of immunotherapy. For instance, the recommendation for initiation of tocilizumab is a CRP level of ≥75mg/L [3–6] and/or a ferritin level of ≥1,000 ng/ml.[7] Serial monitoring of LDH, ferritin, and CRP are also recommended for patients undergoing immunotherapy.[7,8] However, these cut-off levels were based on earlier cohort studies on patients with COVID-19 from Wuhan, China.[9] Subsequent systematic reviews and meta-analyses [10–13] have consistently revealed the value of CRP and LDH in predicting severe outcomes in COVID-19. However, the cut-off points vary between studies, making it difficult to generalize.

A previous review for the COVID-19 Living Clinical Practice Guidelines by Ibañez et al. [14] reported varying CRP, LDH, and ferritin cut-off values for disease severity, progression, and mortality in early observational studies and did not recommend specific biomarker levels for the initiation of immunotherapy. This review sought to build on previous evidence to determine the cut-off values of CRP, LDH, and ferritin associated with COVID-19 severity, progression, and mortality in pediatric and adult patients based on pooled data in systematic reviews and meta-analyses.

REVIEW METHODS

A literature search was done for published studies from 14 May 2021 up to 19 November in MEDLINE, the Cochrane COVID-19 Living Study Register, and the COAP COVID-19 Living Evidence Database. The MEDLINE search was done using the following terms: “CRP” OR “C-reactive protein” OR “hsCRP” OR “ferritin” OR “ferritin” [Mesh] OR “lactate dehydrogenase” OR “LDH” AND “Mortality” OR “Mortality” [Mesh] OR “Severity” OR “Severity” [Mesh] AND COVID-19. The Cochrane and Living Evidence databases were searched with combinations and derivations of the terms “CRP,” “LDH,” “ferritin,” “COVID-19,” “mortality,” and “severity.”

Included in this review were systematic reviews and meta-analyses that recruited adult and pediatric hospitalized patients diagnosed with COVID-19 and reported baseline CRP, ferritin, and LDH values, and the following outcomes: mortality, disease severity upon admission, and progression to more severe stages (e.g., need for mechanical ventilation or ICU admission). Excluded from this review were studies that did not report an effect estimate (e.g., odds ratio, hazards ratio) for the biomarkers of interest, studies not written in English, conference abstracts, and preprint studies. The respective corresponding authors were contacted via e-mail for studies with inaccessible full-text articles, supplementary materials, or presented data.

Methodological quality of the included systematic reviews was assessed using the appraisal criteria by Dans et al.[15] Certainty of evidence for outcomes with cut-off values was determined using GRADE approach.

RESULTS

Characteristics of Included Studies

A total of 4,076 titles and abstracts were retrieved from the database search, among which were ten meta-analyses that satisfied the inclusion and exclusion criteria. Eight reviews [16-23] were of adult patients or had no specific age criteria, while two [24-25] were of pediatric patients. Eight reviews [17,19-25] measured baseline CRP levels, six reviews [17,20-23,25] measured LDH levels, and four reviews [16,18,19,21] measured ferritin levels. Regarding outcomes, seven reviews [17-19, 21-24] used mortality, eight reviews [16-19,21-22,24-25] used severe disease or manifestations thereof such as intensive care unit (ICU) admission or mechanical ventilation, two reviews [23-24] used progression to severe disease, and two reviews [20,22] used a composite of poor outcomes. All the included meta-analyses reviewed observational studies; notably, one review was entirely of case series.[23] Regarding effect measures, two reviews [20,24] used odds ratio (OR) with biomarker cut-off values, two reviews [23,25] used OR with no specific cutoff-value, one review [17] used difference of medians, and the remaining six used standardized mean difference (SMD) or weighted mean difference (WMD).

Appendix 3 shows a summary of the characteristics of included studies.

Risk of Bias Assessment

Based on the Painless Evidence-Based Medicine approach, all the included meta-analyses closely approximated the research question posed in this review. The determination of biomarker levels either was coincident with or preceded the stated outcome in all included reviews. Unbiased criteria were used to determine biomarker levels and outcome in all reviews. One review [24] did not report patient group comparisons for its included studies, while the remaining reviews reported discrepancies between groups. There was no mention of follow-up rate for any review.

Biological applicability issues were noted. Three reviews [19,21,23] had body of literature that mainly comprised of Chinese studies thereby affecting generalizability. Another review [18] had between-study heterogeneity for severe/critical disease attributed to differences in age and comorbidities, and heterogeneity for mortality attributed to differences in age and proportion of patients with male sex. On the other hand, the reviews on pediatric patients included one study [24] where males had higher prevalence of underlying childhood diseases than females, which may distort the correlation between biomarkers and outcomes. No socio-economic applicability issues were mentioned in any of the studies.

Appendix 4 shows the detailed risk of bias assessment of the included studies.

Summary of Results of Included Studies

A. Outcome: Mortality

CRP

Six reviews [17,19,21-24] discussed CRP and mortality. One meta-analysis [23] with five studies and 1,565 patients used OR to report a significant correlation between increased CRP and mortality (OR 2.48, 95% CI 1.37, 4.50). The upper limit of the locally defined reference range per study was used as the cut-off point. Four reviews [17,19,21,22] reported that CRP levels were significantly higher in non-survivors than

in survivors. One review on children and adolescents [24] with two studies and 72 patients showed that CRP levels were not significantly different between survivors and non-survivors (WMD -8.89, 95% CI -59.98, 42.20).

Ferritin
Three reviews [18,19,21] discussed ferritin and mortality. All three reported significantly higher levels of ferritin in non-survivors compared to survivors.

LDH
Four reviews [19,21-23] discussed LDH and mortality. One review [23] of four studies with 1,791 patients did not find a significant correlation between increased LDH and mortality (OR 5.23, 95% CI 0.91, 30.06). The three remaining reviews reported significantly higher levels of LDH in non-survivors compared to survivors.

Table 1 of Appendix 5 shows a summary of the association of CRP, ferritin, and LDH with mortality.

B. Outcome: COVID-19 severe disease
CRP
Four reviews [18-19,22,25] discussed CRP and severe disease. One review on pediatric patients [25] did not find a significant correlation between CRP levels and severe disease (OR 2.17, 95% CI 0.51, 3.84) with no stated cut-off value. The other three reviews reported significantly higher levels of CRP between patients with severe and non-severe disease

Three reviews [17,22,24] discussed CRP and ICU admission. One review on pediatric patients [24] reported a significant correlation between CRP >10 mg/L and ICU admission (OR 8.00, 95% CI 1.60, 39.97) based on one study (54 patients) with very low-quality evidence. This review also reported significantly increased CRP for pediatric patients admitted to the ICU, which is also reflected in the remaining two reviews.

One review [18] reported a significant increase in CRP levels in patients with acute respiratory distress syndrome (ARDS). One review on pediatric patients [24] reported a significant increase in CRP levels in patients requiring respiratory support.

Table 2 of Appendix 4 shows the effect estimates on the association of CRP, ferritin, and LDH with COVID-19 severe disease.

Ferritin
Four reviews [16,18,19,21] discussed ferritin and severe disease on admission. All four reported significantly higher levels of ferritin in non-survivors compared to survivors.

One study [18] reported significantly increased ferritin levels for patients who underwent ICU admission and mechanical ventilation compared to those who did not.

Table 3 of Appendix 5 shows the effect estimates on the association of ferritin with severe disease on admission.

LDH

Three reviews [21-22,25] discussed LDH and severe disease. One review [25] on pediatric patients with 52 studies and 203 patients did not find a significant correlation between increased LDH and severe disease (OR 1.60, 95% CI 0.92, 4.51). The other two reviews reported significantly higher levels of CRP between patients with severe and non-severe disease. Table 2 of Appendix 5 shows the effect estimates on the association of LDH with severe disease on admission.

Two reviews [17,22] reported significantly higher levels of LDH in patients requiring ICU admission. Table 3 of Appendix 5 shows the effect estimates on the association of LDH with ICU admission.

C. Outcome: Disease progression

CRP

Two reviews [23,24] discussed CRP and progression to severe disease. One review [24] with five studies and 1,565 patients reported a significant correlation between increased CRP and progression to severe disease (OR 5.57, 95% CI 4.41, 7.04) based on locally defined reference ranges. One review on pediatric patients [23] reported a significant correlation between CRP ≥80 mg/L and progression to severe disease (OR 11.0, 95% CI 4.37, 31.37) based on one study (250 patients) with very low-quality evidence. The latter also reported significantly higher CRP levels in patients who progressed to severe disease compared to those who did not (WMD 33.29, 95% CI 11.12, 55.33).

Ferritin

No review discussed ferritin and progression to severe disease.

LDH

One review [23] with seven studies and 1,337 patients reported a significant correlation between increased LDH levels and progression to severe disease (OR 4.12, 95% CI 2.88, 5.90) with no stated cut-off value.

Table 4 of Appendix 5 shows the effect estimates on the association of CRP and LDH with progression to severe disease.

D. Outcome: Composite poor prognosis

CRP

Two reviews [20,22] discussed CRP and composite poor outcome. One review of 20 studies with 3,313 patients [20] reported a significant correlation between CRP >10 mg/L and composite poor outcome (OR 3.97, 95% CI 2.89, 5.45). Another review [22] reported a significant increase in CRP in patients with poor outcomes.

Ferritin

No review discussed ferritin and composite poor outcome.

LDH

Two reviews [20,22] discussed LDH and composite poor outcome. One review of 18 studies with 3,641 patients [20] reported a significant correlation between LDH >250 U/L and composite poor outcome (OR 5.48, 95% CI 3.89, 7.71). Another review [22] reported a significant increase in LDH in patients with poor outcomes.

Table 5 of Appendix 5 shows the effect estimates on the association of CRP and LDH with composite poor prognosis.

Certainty of Evidence Assessment
The evidence for the correlation of CRP >10 mg/L with poor outcome (20 studies) and with mortality (4 studies) were assessed to have moderate certainty of evidence based on serious limitations in inconsistency. The evidence for the correlation of CRP >10 mg/dL with pediatric ICU admission (1 study), and CRP ≥80 mg/L with progression to severe disease in pediatric patients (1 study) had very low certainty of evidence based on serious limitations in risk of bias, inconsistency, and imprecision.

The evidence on the correlation of LDH with the progression to severe disease (7 studies) was rated to have high certainty of evidence. The correlation of LDH >250 U/L with poor outcome (18 studies) had moderate certainty of evidence based on serious limitations in inconsistency, while the correlation of LDH with mortality (4 studies) had low certainty of evidence based on serious limitations in inconsistency and imprecision.

RECOMMENDATIONS FROM OTHER GROUPS

The latest recommendations from the **United States National Institutes of Health** [4] and the **Infectious Disease Society of America** [5] for the use of tocilizumab (April 2021) are heavily based on the results of the RECOVERY trial [3], which reports significant benefit for tocilizumab for patients with systemic inflammation, defined as **CRP ≥75 mg/L**.

The **National Institute for Health and Care Excellence (NICE)** in the United Kingdom (March 2021) recommends the use of tocilizumab as well as sarilumab, a novel IL-6 inhibitor, for adult patients requiring supplemental oxygen and **CRP ≥75 mg/L**.[6]

The **National Institute for Infectious Diseases in Italy** (February 2020) recommended the use of **ferritin, CRP and LDH for serial monitoring** during infusion of immunotherapy (such as Tocilizumab) and failure to reduce levels by 50% from baseline levels warrant a second dose of therapy.[8]

The **Kuwaiti Ministry of Health** issued a guideline in April 2020 recommending the use of tocilizumab for adults with severe or critical COVID-19 suspected to have cytokine release syndrome, as shown by **high CRP (≥100 mg/L)** or **ferritin (≥1,000 ng/ml)** levels, in addition to **high LDH (≥200 U/L)** levels, elevated **D-dimer (>250 ng/ml)**, and the need for ICU supportive care with mechanical ventilation for ≤48 hours.[26]

Local guidelines from the Philippines last July 2020 stated the use of **ferritin >1,000 ng/ml** as one of the indications for initiating Tocilizumab. Furthermore, they stated serial monitoring of ferritin, CRP, and LDH during therapy.[7]

RESEARCH GAPS

As of December 2021, there were two ongoing clinical trials on inflammatory phenotypes in COVID-19. Studies on the outcomes of immunotherapy initiated at specific levels of LDH, CRP, and ferritin, as well as the trends in the level of these

biomarkers on subsequent monitoring would provide more direct evidence as to the role of these biomarkers in optimal COVID-19 management. Additionally, analyses on the levels of LDH, CRP, and ferritin at which a second dose of immunotherapy (e.g., tocilizumab) would lead to optimal outcomes should be undertaken.

Appendix 7 lists the characteristics of the ongoing trials.

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Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					Severe COVID-19 disease is characterized by an immunologic and hyperinflammatory response known as the cytokine release syndrome (CRS), whereby elevated pro-inflammatory cytokines,such as IL-2, IL-6, IL-10, and TNF-α cause multiple organ dysfunction, and possibly death. This uncontrolled immune response serves as the basis of immunotherapy in severe to critical COVID-19.
Certainty of Evidence	High	Moderate (6)	Low (3)	Very low			Moderate quality of evidence showed significant correlation between CRP>10 mg/L and mortality (4 studies) and poor outcome (10 studies). High quality of evidence from seven studies showed significant correlation between elevated LDH and progression to severe disease. Moderate quality of evidence from 18 studies showed significant correlation between LDH >250 U/L and poor outcome. Low-quality evidence from 4 studies does not find significant correlation between elevated LDH and mortality. Very low quality of evidence showed significant correlation between elevated CRP and progression to severe disease (1 study) and ICU admission (1 study) in pediatric patients.
Accuracy	Very Accurate	Accurate (6)	Inaccurate (2)	Very Inaccurate	Uncertain (1)		
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability	No important uncertainty or variability			No evidence found.
Resources Required	Uncertain	Large cost (2)	Moderate Cost (5)	Negligible cost or savings (2)	Moderate savings	Large savings	Immunohistochemical CRP costs Php 600.
Certainty of evidence of required resources	No included studies (4)	Very low	Low (2)	Moderate (2)	High (1)		
Cost effectiveness	No included studies (5)	Favors using the markers (3)	Does not favor either using the markers or the comparator (1)	Favors comparison			
Equity	Uncertain (4)	Reduced (2)	Probably no impact (1)	Increased (1)			
Acceptability	Uncertain (5)	No	Yes (4)				
Feasibility	Uncertain (2)	No	Yes (7)				

Appendix 2. Search Yield and Results

Database	Search terms	Number of entries
MEDLINE	("CRP" OR "C-reactive protein" OR "hsCRP" OR "ferritin" OR "ferritin" [Mesh] OR "lactate dehydrogenase" OR "LDH") AND ("Mortality" OR "Mortality" [Mesh] OR "Severity" OR "Severity" [Mesh]) AND COVID-19	871
Cochrane COVID-19 Study Register	("CRP" OR "C-reactive protein" OR "hsCRP" OR "high-sensitivity C-reactive protein" OR "high sensitivity C-reactive protein" OR "ferritin" OR "serum ferritin" OR "lactate dehydrogenase" OR "LDH") and ("Mortality" OR severity OR severe OR ICU OR "intensive care unit" OR complication OR complications) and ("COVID-19" or COVID or coronavirus OR "coronavirus disease-19" OR "coronavirus disease 19")	1971
COVID-19 Living Evidence Database	((CRP) OR (C-reactive protein) OR (hsCRP) OR (ferritin) OR (lactate dehydrogenase) OR (LDH)) AND ((Mortality) OR (Severity)) AND (COVID-19)	1234

Appendix 3. Characteristics of Included Studies

Study ID	Patient population	Study types	Studies (sample size)	Biomarker (cut-off if stated)	Outcome	Effect estimate[b]
Hossein Kazemi 2021	Patients with COVID-19	Retrospective, prospective, descriptive observational studies	18 (2459)	Ferritin	Severity	MD
Katzenschlager 2021	Patients with COVID-19	Retrospective, prospective cohort	88 (69762)	CRP, LDH	Severity, mortality	DoM
Kaushal 2021	Adult patients with COVID-19	Retrospective, prospective, ambispective studies	163 (n/a)	Ferritin	Severity, mortality	SMD
Mahat 2021	Patients with COVID-19	Cohort, case control, cross-sectional studies; case series	83 (17299)	CRP, Ferritin	Severity, mortality	SMD
Malik 2021	Hospitalized patients with COVID-19	Retrospective, prospective studies	32 (10491)	CRP, LDH	Composite[a]	OR
Melo 2021	Adult patients with COVID-19	Retrospective, prospective studies	40 (9833)	CRP	Severity, mortality	MD
Shi 2021	Pediatric patients with COVID-19	Cohort studies, case-control studies; case series	56 (79104)	CRP	Severity, progression, mortality	OR, WMD
Wang 2021	Adult patients with COVID-19	Retrospective studies, cohort studies, case-control studies	32 (7739)	CRP, LDH	Severity, mortality, composite[a]	SMD
Zhang 2021	Patients with COVID-19	Retrospective studies	34 (344431)	CRP, LDH	Progression, mortality	OR
Zhou 2021	Pediatric patients with COVID-19	Case series	52 (203)	CRP, LDH	Severity	OR

Legend: **DoM**, difference of medians; **MD**, mean difference; **OR**, odds ratio; **SMD**, standardized mean difference; **WMD**, weighted mean difference.

[a] Composite outcome (severe disease, ICU admission, mechanical ventilation, mortality)

[b] As reported by study authors

Appendix 4. Risk of Bias Assessment

	Hossein Kazemi 2021	Katzenschlager 2021	Kaushal 2021	Mahat 2021	Malik 2021	Melo 2021	Shi 2021	Wang 2021	Zhang 2021	Zhou 2021
I. APPRAISING DIRECTNESS										
Did the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (E) and outcome (O)?	P - Patients with COVID-19 E - HLH score parameters (hemoglobin, WBC, neutrophils, lymphocytes, platelets, AST, ferritin, fibrinogen, fever) O - Severe COVID-19	P - Patients with COVID-19 E - COVID-19 symptoms, comorbidities, treatment regimens, laboratory values (WBC, neutrophils, lymphocytes, D-dimer, CRP, LDH, troponin I) O - Hospitalization, intubation, ICU admission, mortality	P - Adult patients with COVID-19 E - Serum ferritin level O - RT-PCR positive COVID-19, severe/critical disease, mortality, ICU admission, mechanical ventilation, liver/heart/kidney involvement, thrombotic complications	P - Patients with laboratory-confirmed COVID-19 E - Inflammatory biomarkers O - Severe disease, mortality	P - Hospitalized patients with COVID-19 E - Inflammatory biomarkers O - Composite of poor outcomes (ICU admission, O2St <90%, mechanical ventilation, severe disease, mortality)	P - Adult patients with COVID-19 E - Inflammatory biomarkers O - Severe disease, mortality	P - Pediatric patients with COVID-19 E - Age, sex, comorbidities, symptoms, laboratory findings O - Mortality, ICU admission, respiratory support, progression to severe/critical disease	P - Adult patients with COVID-19 E - CRP, LDH, serum amyloid A O - Poor outcome (severe disease, mortality, need for ICU care, ARDS)	P - Patients with COVID-19 E - CRP O - Progression to severe disease, mortality	P - Pediatric patients with COVID-19 E - Age, sex, comorbidities, symptoms, chest radiography features, laboratory biomarkers O - Severe disease
II. APPRAISING VALIDITY										
Did exposure precede outcome in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the patient groups being compared sufficiently similar with respect to baseline characteristics? If not, were statistical adjustments made?	No; Meta-regression using random effects model	No; Meta-regression with random-effects model (Quantile Estimation approach)	No; Univariate meta-regression for categories with >10 studies or with high heterogeneity	No; Random/fixed-effects meta-regression	No; Meta-regression using random effects model	No; Meta-regression using random-effects model	Not stated; Random/fixed-effects meta-regression	No; Random/fixed-effects meta-regression	No; Random/fixed-effects meta-regression	No; Logistic regression analysis
Were unbiased criteria used to determine exposure in all patients?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were unbiased criteria used to detect outcome in all patients?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was follow-up rate adequate?	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
III. APPRAISING RESULTS										

	Hossein Kazemi 2021	Katzenschlager 2021	Kaushal 2021	Mahat 2021	Malik 2021	Melo 2021	Shi 2021	Wang 2021	Zhang 2021	Zhou 2021
1. How strong is the association between exposure and outcome?	Ferritin (ng/mL): MD 437.25 (100.37, 774.13)	ICU admission: CRP - DoM 56.41 (39.8, 73.02) LDH - DoM 140.4 (81.04, 199.6) Mortality: CRP - 69.1 (50.43, 87.77) LDH - 189.49 (155, 223.98)	Severe/critical disease: SMD 0.882 (0.738, 1.026) Mortality: SMD 0.734 (0.530, 0.938) ICU admission: SMD 0.674 (0.515, 0.833) Mechanical ventilation: SMD 0.430 (0.258, 0.602)	Severe disease: CRP - SMD 1.14 (0.97, 1.32) Ferritin - SMD 0.71 (0.60, 0.81) Mortality: CRP - SMD 1.18 (0.80, 1.55) Ferritin - SMD 0.95 (0.74, 1.17)	CRP >10 mg/L: OR 3.97 (2.89, 5.45) LDH >250 U/L: OR 5.48 (3.89, 7.71)	Severe disease: CRP - MD 53.54 (39.79, 67.29) LDH - MD 153.58 (87.09, 220.08) Ferritin - MD 654.4 (383.48, 925.33) Mortality: CRP - MD 58.48 (43.45, 73.61) LDH - MD 230.99 (192.29, 269.70) Ferritin - MD 853.43 (601.20, 1105.67)	Mortality: CRP: WMD -8.89 (-59.98, 42.20) ICU admission: CRP >10 mg/dL: OR 8.00 (1.60, 39.97) CRP: WMD 60.04 (23.83, 96.26) Respiratory support: CRP: WMD 18.20 (7.31, 29.09) Progression to severe/critical disease: CRP ≥ 80 mg/L: OR 11.0 (4.37, 31.37) CRP: WMD 33.29 (11.25, 55.33)	CRP: Composite poor outcome: SMD 0.98 (0.85, 1.11) Severe disease: SMD 0.94 (0.78, 1.11) Mortality: SMD 0.84 (0.64, 1.05) Need for ICU care: SMD 1.50 (1.30, 1.69) ARDS: SMD 0.78 (0.20, 1.36) LDH: Composite poor outcome: SMD 1.18 (1.00, 1.36) Severe disease: SMD 1.05 (0.81, 1.29) Mortality: SMD 1.22 (0.94, 1.51) Need for ICU care: SMD 1.56 (1.02, 2.10)	CRP progression: OR 5.57 (4.41, 7.04) CRP mortality: OR 2.48 (1.37, 4.50) LDH progression: OR 4.12 (2.88, 5.90) LDH mortality: OR 5.23 (0.91, 30.06) *cut-off values = upper limit of locally defined reference range	CRP: OR 2.17 (0.51-3.84) LDH: OR 1.60 (0.92-4.51)
2. How precise is the estimate of the risk?										
IV. ASSESSING APPLICABILITY										
Are there biologic issues that may affect applicability of treatment?	Not stated *Comorbidities may affect increase/decrease of acute-phase reactants and/or risk of progression to severe disease	Not stated	High heterogeneity for studies involving severe/critical disease attriuted to differences in age and comorbidities; High heterogeneity for studies involving mortality attriuted to differences in age and male sex	Majority of studies from China, affecting generalizability	No data on changing levels of biomarkers during disease course, which may predict clinical course	Most studies involve Asian patients, which may affect generalizability	Males have higher prevalence of underlying childhood diseases than girls	Not stated	All included studies involving CRP and LDH were done on Chinese patients	Not stated

	Hossein Kazemi 2021	Katzenschlager 2021	Kaushal 2021	Mahat 2021	Malik 2021	Melo 2021	Shi 2021	Wang 2021	Zhang 2021	Zhou 2021
Are there socio-economic issues affecting applicability of treatment?	Not stated *Socioeconomic status may affect progression to severe disease	Not stated	None stated	None stated	None stated	None stated	None stated	Not stated	None stated	Not stated

Appendix 5. Summary of Findings

Table 1. Association of CRP, ferritin, and LDH with mortality

Biomarker	Meta-analysis Number of studies (sample size)	Population age group	Biomarker cut-off (mg/L)	Effect Estimate[a]	95% CI	Heterogeneity (I^2, %)	Interpretation (Significant? Yes/No)
CRP and mortality	**Katzenschlager 2021** 34 studies	Not stated	None	DoM 56.41 (39.8, 73.02)		95.99%	Yes
	Mahat 2021 19 studies (n=4318)	Not stated	None	SMD 1.18 (0.80, 1.55)		94%	Yes
	Melo 2021 15 studies (n=3755)	Adults	None	MD 17.93 (11.89, 23.98)		99%	Yes
	Shi 2021 2 studies (n=72)	Pediatric patients	None	WMD -8.89 (-59.98, 42.20)		0%	No
	Wang 2021 10 studies (n=3035)	Adults	None	SMD 0.84 (0.64, 1.05)		Not stated	Yes
	Zhang 2021 4 studies (n=1855)	Not stated	Upper limit of locally-defined reference range	OR 2.48 (1.37, 4.50)		73%	Yes
FERRITIN and mortality	**Kaushal 2021** 57 studies	Adults	None	SMD 0.734 (0.530, 0.938)		97.29%	Yes
	Mahat 2021 11 studies (n=2554)	Not stated	None	SMD 0.95 (0.74-1.17)		76%	Yes
	Melo 2021 9 studies (n=2088)	Not stated	None	MD 853.43 (601.20, 1105.67)		94%	Yes
LDH and mortality	**Katzenschlager 2021** 23 studies	Not stated	None	DoM 189.49 (155, 223.98)		75.03%	Yes
	Melo 2021 10 studies (n=2622)	Adults	None	MD 230.99 (192.29, 269.70)		96%	Yes
	Wang 2021 12 studies (n=4000)	Adults	None	SMD 1.22 (0.94, 1.51)		Not stated	Yes
	Zhang 2021 4 studies (n=1791)	Not stated	Upper limit of locally-defined reference range	OR 5.23 (0.91, 30.06)		85%	No

[a] Effect estimates as reported by study authors

Table 2. Association of CRP, ferritin, and LDH with severe disease

Biomarker	Meta-analysis Number of studies (sample size)	Population age group	Biomarker cut-off (mg/L)	Effect Estimate[a]	95% CI	Heterogeneity (I^2, %)	Interpretation (Significant? Yes/No)
CRP and severe disease	**Mahat 2021** 44 studies (n=7898)	Not stated	None	SMD 1.14 (0.97, 1.32)		90%	Yes
	Melo 2021 14 studies (n=4138)	Adults	None	MD 53.54 (39.79, 67.29)		97%	Yes
	Wang 2021 11 studies (n=1909)	Adults	None	SMD 0.94 (0.78, 1.11)		Not stated	Yes
	Zhou 2021 52 studies (n=203)	Pediatric patients	Not stated	OR 2.17 (0.51, 3.84)		Not stated	No
FERRITIN and severe disease	**Hossein Kazemi 2021** 5 studies (n=264)	Not stated	None	MD 437.25 (100.37, 774.13)		68.20%	Yes
	Kaushal 2021 39 studies	Adults	None	SMD 0.882 (0.738, 1.626)		85.6%	Yes
	Mahat 2021 9 studies (n=1609)	Not stated	None	SMD 0.71 (0.60, 0.81)		5%	Yes
	Melo 2021 6 studies (n=3470)	Adults	None	MD 654.4 (353.48, 925.33)		96%	Yes
LDH and severe disease	**Melo 2021** 10 studies (n=2622)	Adults	None	MD 230.99 (192.29, 269.70)		96%	Yes
	Wang 2021 12 studies (n=4000)	Adults	None	SMD 1.22 (0.94, 1.51)		Not stated	Yes
	Zhou 2021 52 studies (n=203)	Pediatric patients	Not stated	OR 1.60 (0.92, 4.51)		Not stated	No

[a] Effect estimates as reported by study authors

Table 3. Association of CRP, ferritin, and LDH with ICU admission, mechanical ventilation, and ARDS

Biomarker	Meta-analysis Number of studies (sample size)	Population age group	Biomarker cut-off (mg/L)	Effect Estimate[a]	95% CI	Heterogeneity (I^2, %)	Interpretation (Significant? Yes/No)
CRP and ICU admission	**Katzenschlager 2021** 10 studies	Not stated	None	DoM 56.41 (39.8, 73.02)		76.56%	Yes
	Shi 2021	Pediatric patients	CRP >10 mg/dL 1 study (n=54)	OR 8.00 (1.60, 39.97)		100%	Yes
			None 6 studies (n=365)	WMD 60.04 (23.82, 96.26)		38.6^	Yes
	Wang 2021 4 studies (n=802)	Adults	None	SMD 1.50 (1.30, 1.69)		Not stated	Yes
CRP and need for respiratory support	**Shi 2021** 1 study (n=37)	Pediatric patients	None	WMD 18.20 (7.31, 29.09)		100%	Yes
CRP and ARDS	**Wang 2021** 2 studies (n=121)	Adults	None	SMD 0.78 (0.20, 1.36)		Not stated	Yes
FERRITIN and ICU admission	**Kaushal 2021** 21 studies	Adults	None	SMD 0.674 (0.515, 0.833)		80.32%	Yes
FERRITIN and mechani-cal ventilation	**Kaushal 2021** 8 studies	Adults	None	SMD 0.430 (0.258, 0.602)		32.79%	Yes
LDH and ICU admission	**Katzenschlager 2021** 23 studies	Not stated	None	DoM 189.49 (155, 223.98)		75.03%	Yes
	Wang 2021 3 studies (n=762)	Adults	None	SMD 1.56 (1.02, 2.10)		Not stated	Yes

Table 4. Association of CRP, ferritin, and LDH with progression to severe disease

Biomarker	Meta-analysis Number of studies (sample size)	Population age group	Biomarker cut-off (mg/L)	Effect Estimate[a]	95% CI	Heterogeneity (I^2)	Interpretation (Significant? Yes/No)
CRP and progression	**Shi 2021**	Pediatric patients	CRP ≥ 80 mg/dL 1 study (n=250)	OR 11.0 (4.37, 31.37)		100%	Yes
			None 5 studies (n=347)	WMD 33.29 (11.25, 55.33)		94.3%	Yes
	Zhang 2021 5 studies (n=1565)	Not stated	Upper limit of locally-defined reference range	OR 5.57 (4.41, 7.04)		35%	Yes
LDH and progression	**Zhang 2021** 7 studies (n=1337)	Not stated	Upper limit of locally-defined reference range	OR 4.12 (2.88, 5.90)		49%	Yes

Table 5. Association of CRP, ferritin, and LDH with composite poor outcome

Biomarker	Meta-analysis Number of studies (sample size)	Population age group	Biomarker cut-off (mg/L)	Effect Estimate[a]	95% CI	Heterogeneity (I^2)	Interpretation (Significant? Yes/No)
CRP and composite poor outcome	**Malik 2021** 20 studies (n=3313)	Not stated	CRP > 10 mg/L	OR 3.97 (2.89, 5.45)		52%	Yes
	Wang 2021 24 studies	Adults	None	SMD 0.98 (0.85, 1.11)		86.6%	Yes
LDH and composite poor outcome	**Malik 2021** 20 studies (n=3313)	Not stated	LDH >250 U/L	OR 5.48 (3.89, 7.71)		67%	Yes
	Wang 2021 25 studies	Adults	None	SMD 1.18 (1.00, 1.36)		85.4%	Yes

Appendix 6. GRADE Certainty of Evidence Profile

Number of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
CRP >10 mg/L and poor outcome									
20	Observational studies	Not serious	Serious	Not serious	Not serious	None	All included studies were graded as having low (65%) and moderate (35%) risk of bias using the Newcastle-Ottawa Scale. Heterogeneity was 52%, marked by the authors as significant. Cut-off values were determined based on four component studies with thresholds of 3, 5, 8, and 15 mg/L.	⊕⊕⊕◯ MODERATE	IMPORTANT
CRP >10 mg/dL and ICU admission in pediatric patients									
1	Observational studies	Serious	Serious	Not serious	Serious	None	Review authors cited the included study as limited in study design. Heterogeneity was 100%. The included study had a less than optimal information sample size (n=42).	⊕◯◯◯ VERY LOW	IMPORTANT
CRP and mortality									
4	Observational studies	Not serious	Serious	Not serious	Not serious	None	Included studies were all rated 8/9 on the Newcastle-Ottawa Scale, indicating low risk of bias. Heterogeneity of 73% was considered significant. Sample size (n=1855) met optimal sample size requirement. Only one of the included studies reported a CRP cut-off (>10 mg/L). None of the studies reported effects in multivariate analysis.	⊕⊕⊕◯ MODERATE	IMPORTANT
CRP ≥ 80 mg/L and progression to severe disease in pediatric patients									
1	Observational studies	Serious	Serious	Not serious	Serious	None	Review authors cited the included study as limited in study design. Heterogeneity was 100%. The included study had a less than optimal information sample size (n=250).	⊕◯◯◯ VERY LOW	IMPORTANT
LDH >250 U/L and poor outcome									
18	Observational studies	Not serious	Serious	Not serious	Not serious	None	All included studies were graded as having low (67%) and moderate (33%) risk of bias using the Newcastle-Ottawa Scale. Heterogeneity was 67%, marked by the authors as significant. Cut-off values were determined based on three component studies with thresholds of 225, 440, and 550 U/L.	⊕⊕⊕◯ MODERATE	IMPORTANT
LDH and mortality									
4	Observational studies	Not serious	Serious	Not serious	Serious	None	Risk of bias score of the studies was 8 via NOS, indicating low risk of bias. Heterogeneity was significant at 85%. The CIs crossed the clinical decision threshold (OR 5.23, 95% CI 0.91-30.06). Two of the studies enumerated LDH thresholds at 245 and 250 U/L respectively. None of the studies reported effects in multivariate analysis.	⊕⊕◯◯ LOW	IMPORTANT
LDH and progression to severe disease									
7	Observational studies	Not serious	Not serious	Not serious	Not serious	None	Risk of bias scores of the studies were 7-8 via NOS, indicating low risk of bias. Heterogeneity was not significant at 49%. Two studies reported LDH threshold of 245 U/L, two studies reported 250 U/L, and one reported 445 U/L. Two of the studies used multivariate analysis.	⊕⊕⊕⊕ HIGH	IMPORTANT

Appendix 7. Characteristics of Ongoing Clinical Trials

Clinical Trial Identifier (Location)	Official Title	Methodology	Outcome Measures	Population	Estimated Date of Completion
NCT04818866 United States	International Study of Inflammation in COVID-19 (ISIC)	Diagnostic Test: SuPAR, C-reactive protein, Ferritin, D-Dimer, Procalcitonin, Interleukin-6, Lactate Dehydrogenase	Primary: In-hospital incidence of death, need for mechanical ventilation and need for renal replacement therapy Secondary: length of hospitalization, acute kidney injury, cardiovascular events, mortality, need for renal replacement therapy, need for mechanical ventilation within 6 months	n=2500 18 years and older	December 30, 2022
NCT04867161 Czech Republic	Superinfection and Hyperinflammatory Phenotype in COVID-19 (Coronavirus Disease 2019) Pneumonia Patients (SUPER-HI)	Observational prospective cohort study Laboratory sampling, bronchoalveolar lavage	Primary: To investigate the role of inflammatory markers (CRP, PCP, PSP, IL-6) as diagnostic tools for superinfection in COVID-19 pneumonia patients. Secondary: To assess the association between hyperinflammatory phenotype and course of illness and mortality rates in COVID-19 pneumonia patients.	n=300 18 to 99 years	December 31, 2022

Q17. Should D-dimer be used to guide anticoagulation among adult patients with COVID-19?

As of 26 May 2021

RECOMMENDATION

We suggest the use of D-dimer to guide anticoagulation of adult patients with COVID-19, because of its significant association with mortality, thromboembolism, and worsening of disease. *(Low certainty of evidence; Weak recommendation)*

Consensus Issues

Due to the varied cut-off values used in the included studies for this review, the recommendation did not include a specific cut-off value of D-dimer to predict mortality, thromboembolism and worsening severity of disease. Further, the laboratories in the Philippines also make use of varying cut-offs due to the different assays and machines used, hence, it is difficult to define a specific cut-off value.

KEY FINDINGS

- We found a total of 25 observational studies on the association between D-dimer and the outcomes of mortality, worsening severity, or thromboembolism. In general, the included studies showed increased odds of in-hospital mortality (OR 5.57, 95% CI 2.74-11.31), worsening severity (critical illness OR 1.91-2.58); disease progression (HR 2.84, 95% CI 2.10-3.85), or need for mechanical ventilation (HR 3.28, 95% CI 1.071-0.10), and thromboembolism (OR 5.61, 95% CI 3.97-7.94), with higher D-dimer levels across different COVID-19 severities.
- Most studies yielded imprecise effect measures, due to the small number of event outcomes. Most of the studies were found to have serious risk of bias, with issues on data censoring, incomplete laboratory data, and unclear adequacy of follow-up rates. Differences in D-dimer cut-offs, definitions of critical illness and disease progression, and severities of COVID-19 in the study population contributed to the heterogeneity across studies.
- While the predictive ability of D-dimer for mortality appeared to be fair to good, prediction of worsening severity or progression of disease is inconsistent.

INTRODUCTION

Thromboembolic manifestations are reported in COVID-19 patients, resulting in increased morbidity and mortality. Mechanisms of coagulopathy in COVID-19 include endothelial dysfunction resulting in excessive thrombin formation and decreased fibrinolysis, hypoxemia, and hyperinflammatory state leading to increased blood viscosity and unstable hemostasis.

SARS-CoV-2 infection has been associated with an increase in coagulation markers such as fibrin, fibrin degradation products, fibrinogen, and D-dimer. Several studies have shown the association of D-dimer with thromboembolic events, severity of COVID-19, and mortality.[1-3] In a recent meta-analysis, a D-dimer level higher than 500 or 1,000 ng/mL was associated with a higher risk of mortality (OR 4.81, 3.15-7.34) and severe COVID-19 (OR 3.27, 2.46-4.36).[4] However, this systematic review did not apply restrictions in the selection of studies and included even those without multivariate analysis.

REVIEW METHODS

The MEDLINE, Cochrane Library, Cornell Open Access Publication (COAP), MedRxIV, and BioRxIV databases were searched for published articles and preprints using the search strategy for COVID-19, as well as the terms “D-dimer” or “D dimer”. An electronic search of the article references was also done. Inclusion criteria were as follows: (1) population: hospitalized adults with SARS-CoV-2 infection, (2) intervention: D-dimer level, (3) outcome: mortality, worsening severity (defined as progression from the current COVID-19 category to a more severe one), ICU admission, or need for mechanical ventilation), or thromboembolism; and (4) cohort studies, randomized controlled trials (RCT), and/or systematic reviews with or without meta-analyses of RCTs or observational studies. Studies without multivariate analysis and D-dimer cut-offs, as well as case reports, case series, and observational studies without control groups were excluded.

RESULTS

A total of 25 observational studies [1-3,5-26] were found on the utility of D-dimer for three outcomes, namely mortality, worsening severity, and thromboembolism. Seven studies specified the assay method used for D-dimer measurement. Among these methods are immunoturbidimetric assay [11], high-sensitivity latex dimer assay using 3.2% citrated plasma [21,24], latex-enhanced photometric immunoassay [2], and a quantitative D-dimer assay with a threshold of 500 ng/mL.[7,8,14]

Mortality

We included ten studies: nine cohort studies [2,5-10,21,24] and one case-control study [11] reporting on the outcome of mortality (Table 1). Five were done in China, three in the USA, and two in Spain.

Nine studies looked at inpatients with COVID-19 in general [2,6-11,21,24]. One study included patients with severe or critical COVID-19 who were admitted to the intensive care unit.[5]

Pooled results from five studies that reported on in-hospital mortality among COVID-19 patients regardless of severity showed increased odds of in-hospital mortality with D-dimer levels above 500 ng/mL (OR 5.33, 95% CI 2.85-9.97) (Figure 1).[6,7,9-11] The study by Alabyad et al. [24] that found no significant association between D-dimer and mortality could not be included in the forest plot due to the unavailability of both the actual OR and raw data for OR computation.[24]

Three retrospective cohort studies reporting hazard ratios showed an increased risk of in-hospital mortality, 30-day all-cause mortality, and in-ICU mortality with admission D-dimer levels ranging from 1112 to 2000 ng/mL among patients with COVID-19, regardless of disease severity.[2,5,8] Two of these studies found that admission D-dimer levels above 1,500 ng/mL already conferred an almost fourfold increase in in-ICU death 14 days from admission (HR 3.600, 95% CI 1.46-8.91) and that patients with levels above 2000 ng/mL had 22% higher risk of in-hospital death (HR 22.4, 95% CI 2.86-175.7).[5,21] In the study of Peiro et al. [8], a slightly lower D-dimer cut-off of 1,112 ng/mL had almost the same effect on 30-day in-hospital mortality (HR 3.35, 95% CI 1.58-7.13). Creel-Bulos and colleagues [21], who used peak D-dimer levels (the maximum level of D-dimer throughout hospitalization), also found that patients with

values peaking at higher than 3000 ng/mL had almost five times greater risk of in-hospital death (OR 4.847, 95% CI 0.933-25.167).

Table 1. Characteristics of included studies (n=10) with mortality outcomes.

Characteristic	Number of Studies	Studies
Study Design		
Prospective cohort	1	[10]
Retrospective cohort	8	[2,5-9,21,24]
Case-control study	1	[11]
Country		
China	5	[2,5,6,9,11]
USA	3	[7,21,24]
Spain	2	[8,10]
Number of Centers		
1	5	[2,5,8,11,21]
2	2	[6,9]
>2	3	[7,10,24]
Study Population		
All admitted patients	9	[2,6-11,21,24]
Severe and/or critical patients only	1	[5]
D-dimer cutoffs for analysis (ng/mL)		
500	2	[6,10]
1000	3	[7,9,11]
1112	1	[2]
1500	1	[8]
2000	2	[5,24]
3000	2	[21,24]
Timing of D-dimer		
Admission	6	[2,6,8-9,11,24]
Initial clinical evaluation	1	[7]
Baseline	1	[10]
ICU admission	1	[5]
Peak	1	[21]
Outcome measure		
Adjusted OR	6	[6-7,9,10-11,24]
Adjusted HR	3	[2,5,8]
AUC	3	[2,8,11]

For the prediction of in-hospital mortality, a D-dimer cut-off level of 2000 ng/mL was shown to have good sensitivity (88.2%-92.3%) and specificity (71.3%-82.2%), with areas under the curve ranging from 0.85 to 0.89 indicating good discriminatory ability.[2,11] However, this cut-off has not been externally validated.

Worsening severity

All six studies on the association between baseline or admission levels of D-dimer and worsening severity were retrospective cohort studies [3,7,12-13,24,26] (Table 2). Four studies investigated patients with COVID-19 in general [7,13,24,26], while the other two studies included patients with mild COVID-19 [12] and non-severe COVID-19 (defined as stable patients without dyspnea or desaturation, or those whose status improved).[3] These studies used different outcome definitions and D-dimer cut-offs that ranged from 140 ng/mL [3] to ≥3000 ng/mL.[24]

Disease progression

Regarding disease progression, which referred to the development of a more severe stage of COVID-19, Cen and co-authors found that patients with mild COVID-19 had a threefold higher risk of progression to severe illness, critical illness, or death if their D-dimer levels were at least 500 ng/mL (HR 2.85, 95% CI 2.10-3.85).[12]

Critical illness

Two studies had varying definitions of "critical illness" that included different combinations of respiratory distress or failure, need for mechanical ventilation, and ICU admission [7,13]. The odds of critical illness were two to three times higher among patients with D-dimer levels above 660 ng/mL (OR 1.911, 95% CI 1.050-3.478) [13] or 1,000 ng/mL (OR 2.58, 95% CI 1.57-4.24).[7]

Need for mechanical ventilation

One study showed that adults with COVID-19 and D-dimer levels of more than 1,500 ng/mL had a three-fold higher risk of needing mechanical ventilation (HR 3.28, 95% CI 1.07-10.10).[26] The study by Alabyad et al. stated that D-dimer was not found to be associated with either ICU admission or intubation, but also did not report the ORs or the raw numbers.[24]

Table 2. Characteristics of included studies (n=6) with disease progression outcomes.

Characteristic	Number of Studies	Studies
Study Design		
Retrospective cohort	6	[3,7,12-13,24,26]
Number of Centers		
1	1	[13]
2	1	[3]
>2	4	[7,12,24,26]
Country		
China	4	[3,12-13,26]
USA	2	[7,24]
Study Population		
All admitted patients	4	[7,13,24,26]
Mild/nonsevere only	2	[3,12]
D-dimer cutoffs for analysis (ng/ml)		
140	1	[13]
500	1	[12]
660	1	[3]
1000	1	[7]
1500	1	[26]
2000	1	[24]
3000	1	[24]
Timing of D-dimer		
Admission	4	[3,13,24,26]
Baseline	1	[12]
Initial clinical evaluation	1	[7]
Outcome measure		
Adjusted OR	4	[7,13,24,26]
Adjusted HR	2	[12,27]
AUC	2	[3,13]

The discriminative ability of D-dimer to predict worsening severity was determined in two studies, but the results appear inconsistent.[3,13] In terms of progression from non-severe to severe COVID-19, a D-dimer cut-off of 140 ng/mL was shown to have poor discriminative ability (AUC 0.64, 95% CI 0.57-0.70), with good sensitivity (88%) but poor specificity (39%).[3] For the development of critical illness (defined as a composite of acute respiratory distress syndrome, ICU admission, or death), a higher D-dimer cut-off of 660 ng/mL showed a good ability to discriminate patients who will develop the outcome from those who will not (AUC 0.873, 95% CI 0.806-0.923, $p<0.0001$), with a good balance of sensitivity (82.35%) and specificity (81.75%).[13]

Thromboembolism

We included 14 observational studies on the relationship between D-dimer and thrombosis in COVID-19 (Table 3). Most of the studies were single-center retrospective cohorts from Europe and the USA and included COVID-19 patients of varying severity. The subjects in all studies were given prophylactic and/or therapeutic

anticoagulation even prior to diagnosis of thrombosis. Most studies had repeated determinations of D-dimer but the admission value was the basis of analysis in six of these studies.[1,7,20,22-24]

Table 3. Characteristics of included studies (n=14) with thromboembolic outcomes.

Characteristic	Number of Studies	Studies
Study Design		
Prospective cohort	3	[1,14,18]
Retrospective cohort	10	[7,15-16,17,19-22,24-25]
Cross-sectional study	1	[23]
Country		
China	1	[23]
USA	6	[7,17, 21-22,24,25]
Europe	7	[1,14-16,18,19-20]
Number of Centers		
1	11	[1,14-18,20-22,23,25]
>2	3	[7,19,24]
Study Population		
All admitted	11	[1,7,14-17,20,21,23,25]
Non-ICU only	1	[18]
Critically ill or mechanically ventilated only	1	[19]
Nonmechanically ventilated and non-expired	1	[22]
D-dimer cutoffs for analysis (ng/ml)		
500	1	[23]
956	1	[14]
1000	4	[1,19,22,23]
1500	1	[25]
2000	3	[21,22,24]
2500	1	[7]
2590	1	[16]
3000	2	[21,24]
5000	2	[19,22]
6000	2	[1,15]
10,000	1	[19]
15,000	1	[19]
Timing of D-dimer		
Admission	6	[1,7,14,16,22,24]
Mixed (Admission and during hospitalization)	1	[20]
Not mentioned	6	[15,18,19,21,23,25]
Within 24-48hr of DVT imaging/nearest to the time DVT UTZ	1	[17]
Performance of Imaging Procedure		
With suspicion of thrombosis (at risk, symptomatic)	11	[1,7,15-17,19-22,24-25]
Routine/screening	3	[14,18,23]
Outcome		
Pulmonary thromboembolism	4	[1,14-16]
Deep vein thrombosis	3	[18,23,24]
Venous thromboembolism (pulmonary & deep vein)	5	[17,19-22,25]
Arterial and venous thrombosis	2	[7,24]
Outcome measure		
Adjusted OR	12	[1,7,15-18,20-25]
Adjusted HR	1	[14]

The presence of thrombosis was determined through imaging in 13 studies. Al-Samkari included patients with clinically diagnosed thrombotic events (as imaging was not possible) after adjudication by two independent reviewers.[7] Three studies [14,18,23] conducted screening imaging, while the rest proceeded with imaging because of clinical suspicion of thrombosis. Two studies reported arterial, venous, and clinically significant non-vessel thromboses; the rest only venous thromboembolism (VTE).

Incidence of Thromboembolism

The incidence of pulmonary thromboembolism ranged from 18.5 to 51%, DVT from 14.7 to 46%, and pulmonary and/or DVT from 9.3-41.7% among those who underwent

an imaging procedure (n=13 studies). Two studies reported an overall incidence of pulmonary embolism in the hospitalized population of 2.6% (95% CI 1.7-3.5) and 6.4% [1,15], and one study on VTE of 3.5%.[25] A study of arterial, venous, and clinically significant non-vessel thrombosis had an overall VTE incidence of 4.8% (95% CI 2.9-7.3) and an overall thrombosis rate of 9.5% (95% CI 6.8-12.8).[6]

Association between D-dimer level and thromboembolism
All studies performed multivariate analysis and showed an association between elevated D-dimer and thrombosis at a cut-off of 1,000 ng/mL (OR 5.6, 95% CI 3.97-7.94]) (Figure 2).

Overall summary of methodological quality
Across the three outcomes, the risk of bias was judged to be serious due to the lack of accounting for censoring and other possible prognostic variables (e.g., the exclusion of certain variables without available data, such as IL-6 in some studies. Many studies had small outcome events relative to the number of candidate predictors, resulting in very wide confidence intervals. In addition, not all of the included patients had complete laboratory measurements because of the retrospective nature of the studies; this may contribute to residual confounding effects.

For studies on thromboembolism, most studies had imprecision due to low event rates and a few studies had a serious risk of bias due to incomplete prognostic factors or inadequate follow-up.

RECOMMENDATIONS FROM OTHER GROUPS

The US NIH COVID-19 Treatment Guidelines state that for hospitalized patients, data is insufficient to recommend either for or against the use of D-dimer in guiding management decisions.[27]

Several US hospitals have included D-dimer measurement as a guide for monitoring and anticoagulant therapy. According to the guidance made by Massachusetts General Hospital for its medical professionals, D-dimer should be measured daily (or whenever labs are being drawn, if less frequent than this) if the baseline D-dimer obtained was above 1,000 ng/mL and if subsequent levels remain above this value.[28] Meanwhile, the University Health System in Texas uses D-dimer levels as a dosing guide, with patients being escalated to therapeutic anticoagulation doses (enoxaparin 1 mg/kg subcutaneously twice a day) when D-dimer levels are above 5,000 ng/mL and being given high-dose prophylactic doses (enoxaparin 0.5 mg/kg subcutaneously twice a day) either when baseline D-dimer at least 2000 to 3000 ng/mL, or when D-dimer has decreased to ≤2,000 ng/mL.[29]

The PSMID and other medical specialty societies in its interim guidance for adults with COVID-19 recommended D-dimer as one of the ancillary tests when COVID-19 is suspected, to prognosticate and guide management. Anticoagulation therapy in the form of heparin or low-molecular weight heparin is recommended for patients with a D-dimer level of >1,000 ng/ml.[30]

RESEARCH GAPS

Prospective studies on the utility of D-dimer as a biomarker predictive of COVID-19 outcomes may help reduce the limitations inherent to retrospective studies, such as

information bias (missing data due to reliance on existing records) and selection bias (due to inclusion of individuals after the outcome has occurred). Matching by age and/or sex in future studies is recommended. Efforts to set up standardized collection times, methods, and reference values for D-dimer are desired.

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Appendix 1. Characteristics of Included Studies

Mortality (n=10 studies)

Author (Year) Study design	Population and number of outcome events	Outcome	D-dimer timing	D-dimer association with outcome	Prediction of outcome
Zhou (2020) [6] China Retro cohort Multicenter	Hospitalized adults with confirmed COVID-19 (191) Deaths (54) D-dimer ≤500 ng/mL (55) D-dimer >500 ng/mL (117)	In-hospital death	Admission	Reference for multivariate analysis: ≤0.5 D-dimer >1000 ng/mL: OR 18.42 (2.64, 128.55, p=0.0033) >500 ng/mL: OR 2.14 (0.21, 21.39, p=0.52)	None
Yao (2020) [11] China Case control Single-center	Hospitalized adults with confirmed COVID-19 (248) Deaths (17)	Mortality	Admission	D-dimer measured using Sysmex, CS5100 Reference for multivariate analysis: <1000 ng/mL 1000-2000 ng/mL: OR 2.21 (0.12, 38.61) p=0.612 >2000 ng/L: OR 10.17 (1.10, 94.38) p = 0.041	For prediction of in-hospital mortality: D-dimer > 2140 ng/mL Sn 88.2% Sp 71.3% (AUC 0.85; 95% CI = 0.77–0.92)
Zhang L (2020) [2] China Retrospective cohort single-center	Hospitalized adults with confirmed COVID-19 (248) Deaths (13)	In-hospital mortality	Admission (within 24h)	D-dimer measured using CS5100 automatic coagulation analyzer (Sysmex, Japan) Kaplan-Meier cut-off: D-dimer ≥2000 ng/mL as predictor of in-hosp mortality Adjusted HR 22.4 (2.86, 175.7) on Cox proportional hazard analysis p=0.003 after adjusting for sex, age, underlying disease	For prediction of in-hospital mortality: D-dimer ≥2000 ng/mL Sn 92.3% Sp 83.3% (AUC 0.89; No CI reported)
Al-Samkari (2020) [7] USA Retrospective cohort Multicenter	Adults with confirmed covid from the Research Patient Data Registry at Partners Healthcare (400) - mortality models included only patients reaching completion of hospitalization (discharge or death) Deaths (29) Critically ill (144) D-dimer ≤1000 (148) 1001-2500 (78) >2500 (26)	In-hospital mortality	Initial clinical evaluation	D-dimer measured in FEU using Vidas (bioMerieux) in 2 laboratories, Sta-Liatest (Stago) in 2 laboratories, and HS 500 (Instrumentation Laboratory) in 1 laboratory Reference for multivariate analysis: D-dimer ≤1000 ng/mL D-dimer 1001-2500 ng/mL: Adjusted OR 6.26 (1.53, 25.58) >2500 ng/mL: Adjusted OR 15.14 (2.19, 104.53)	None
Gil-Rodrigo (2020) [10] Spain	Hospitalized adults with covid, either RT-PCR-confirmed or clinically diagnosed (1000) Deaths (119) ICU (62)	In-hospital mortality Composite of in-hosp	Baseline	Reference for multivariate analysis: D-dimer >500 ng/mL In-hospital mortality: Adjusted OR 2.96 (1.58, 5.54)	None

Prospective nested cohort study Multicenter March 1- Apr 30, 2020	Invasive mechanical ventilation (IMV) (46) Patients with D-dimer measurement (759; 443 of them have D-dimer >500 mg/mL)	mortality/ICU admission/ need for IMV		Composite of in-hosp mortality/ICU admission/need for MV: Adjusted OR 2.42 (1.44, 4.06)	
Peiro (2021) [8] Spain Retrospective cohort study Single-center Mar 16-May 15, 2020	Hospitalized adults with covid, either RT-PCR-confirmed or clinically diagnosed, with biomarker information (196) Deaths (37; 10 in low d-dimer; 27 in high d-dimer) D-dimer <1112 ng/mL (119) D-dimer ≥1112 ng/mL (77)	30-day all-cause mortality	Admission	D-dimer measured using ACL TOP 500 CTSVR using HemosIL D-Dimer HS- 500 (HemosIL, Instrumentation Laboratory, Bedford, MA) Reference for multivariate analysis: D-dimer ≥1112 ng/mL Adjusted HR 3.35; 95% CI 1.58–7.13; p<0.002	None
Yang (2020) [9] China Retrospective cohort study Multicenter (2 hospitals) Jan 10-Feb 29, 2020; pts followed from admission to Mar 20, 2020/ discharge/death	Hospitalized adults with covid, either RT-PCR-confirmed or clinically diagnosed, with biomarker information (196) Deaths (58)	In-hospital mortality	dmission	Reference for multivariate analysis: D-dimer >1000 ng/mL In-hospital mortality: OR 9.51 (3.61, 25) p<0.001 Other findings (serial biomarker measurements of each patient for dynamic change analysis): D-dimer raised rapidly from day 12 in non-survivors and its level was significantly higher than in survivors	None
Zhang W (2021) [5] China Retrospective cohort study Single-center Admitted bet Jan 20-Feb 26, 2020; outcome monitored until Mar 4, 2020	Hospitalized adults with confirmed covid (203) Deaths (58; 51.7% severe, 43.1% critical) Hospitalized adults with confirmed severe or critical COVID-19 and admitted to ICU (158) Deaths (77) Patients into 4 groups based on their D-dimer level at the time of ICU admission: D0 (normal DD): DD <1.5 ug/mL (57) D1-D3 (abnormal DD): D1:1.5≤DD<10 ug/mL (38) D2: 10≤DD<40 ug/mL (31) D3: ≥40 ug/mL (32)	In-ICU death	ICU admission	Reference for multivariate analysis: D-dimer <1500 ng/mL for in-ICU-death: D-dimer 1500-10,000 ng/mL: HR 3.600 (1.455, 8.911) p=0.006 10000-40000 ng/mL: HR 4.160 (1.727, 10.022) p=0.001 >40000 ng/mL: HR 2.732 (1.077, 6.927) p=0.034 7-day mortality: no significant diff among D1, D2, and D3 groups 14-day mortality rate: significantly lower in D0 vs D1-D3 (all p<0.01); also significantly lower in D1	None

				vs D2-D3 (p<0.05); but no diff between D2 and D3	
Creel-Bulos (2020) [21] USA Retrospective cohort study Single-center Mar 12-Apr 6, 2020, Reviewed from admission through discharge or until the censor date of April 30, 2020	Hospitalized adults with confirmed COVID-19 with D-dimer measurements (115) Deaths (21) Peak D-dimer >2000 ng/mL (83) Peak D-dimer >3000 ng/mL (74) (Patients with overlapping D-dimer values not reported)	In-hospital mortality	Peak (maximum) D-dimer throughout hospitalization	high sensitivity latex dimer assay (Instrumentation Laboratories, Bedford, MA) *Most patients had a single D-dimer level on a given day Mean value was used if >1 d-dimer measurement was made in one day Peak d-dimer of >3000 ng/mL: OR 4.847 (0.933, 25.167) p=0.060 on multivariate analysis Peak d-dimer of >2000 ng/mL was not found to be predictive of mortality even on univariate analysis	Death was not predicted by pre-VTE ceiling D-dimer, change (absolute increase) in D-dimer, rate of D-dimer rise, or peak D-dimer (maximum level from hospital days 1-7) >2500 ng/mL
Alabyad (2020) [24] USA Retrospective cohort study multi-center April 3-July 31, 2020 Reviewed from admission through discharge or until the censor date of September 14, 2020	Hospitalized adults with confirmed COVID-19 who had markers of coagulation and hemostatic activation (MOCHA) measurements that included D-dimer (276) Deaths (31) Admission D-dimer >2000 ng/mL (51) Admission D-dimer >3000 ng/mL (40) (Patients with overlapping D-dimer values not reported)	In-hospital mortality	Admission	ORs and raw numbers for mortality not reported	Not reported

Worsening severity (n=6 studies)

Author (Year) Study design	Population	Outcome	D-dimer timing	D-dimer association with outcome	Prediction of outcome
Yue (2020) [13] China Retrospective cohort study Single-center Jan 18-Feb 16, 2020	Hospitalized adults with confirmed covid (180) Divided into critical and noncritical according to presence of absence of end-point events: Critical (20; no deaths) Noncritical (160; 14 deaths)	Critical illness (defined as composite endpoint of ICU admission, ARDS, or death)	Admission	Reference for multivariate analysis: D-dimer >660 ng/mL Critical illness OR 1.911 (1.050, 3.478) p=0.034	AUC 0.873 (0.806, 0.923) p <0.0001 Sn 82.35% Sp 81.75 AUC improved if DD is combined with CRP and CT scan score to 0.921 (0.863, 0.960) p <0.0001 Sn 82.35% Sp 89.43%
Cen (2020) [12] China Retrospective cohort Single-center	Hospitalized adults with confirmed MILD COVID-19 (1007) 1007 broken down into stable (720) and progression (severe = 222, critical = 22, deceased =43)	Disease progression (patients who recovered OR became symptomatically stable, vs those who developed severe* disease, critical illness**, or died) *Severe defined as either: (a) respiratory rate >30 breaths/min, or (b) oxygen saturation ≤93%, (c) PF ratio ≤300 mmHg **Critical defined as any of the following: (a) shock, (b) respiratory failure requiring mechanical ventilation, or (c) organ failure requiring ICU admission	"Baseline" (unknown if on admission, but probably)	Reference for multivariate analysis: D-dimer ≥500 ng/mL Disease progression HR 2.846 (2.103, 3.851)	None
Duan (2020) [3] China Retrospective cohort study Multicenter (2 hospitals) Data collection from Jan 1 to Feb 29, 2020	Hospitalized adults with confirmed nonsevere* COVID-19 (348) Stable/improved (328); progression to severe (20)	Progression to severe* case *Severe defined as those meeting ANY the ff: 1) dyspnea, RR >30 breaths/min; 2) O2 sat <93% in ambient air; 3) PFratio <300	Admission	Reference value and machine for D-dimer unspecified	DD cutoff >140 ng/mL by Youden index AUC* 0.64 (0.57, 0.70) Sn 88% Sp 39%
Al-Samkari (2020) [7] USA Retrospective cohort Multicenter	Adults with confirmed covid from the Research Patient Data Registry at Partners Healthcare (400) - mortality models included only patients reaching completion of hospitalization (discharge or death) Deaths (29) Critically ill (144)	Critical illness (defined as requirement for endotracheal intubation and mechanical ventila- tion, including patients for whom intubation was clinically indicated but who chose to forego it)	Initial clinical evaluation	D-dimer measured in FEU using Vidas (bioMerieux) in 2 laboratories, Sta-Liatest (Stago) in 2 laboratories, and HS 500 (Instrumentation Laboratory) in 1 laboratory Reference for multivariate analysis: D-dimer ≤1000 ng/mL	None

				D-dimer 1001-2500 ng/mL: Adjusted OR 2.58 (1.57, 4.24) >2500 ng/mL: Adjusted OR 2.05 (1.03, 4.07)	
Wang (2020) [26] China Retrospective cohort study Multicenter Until January 31, 2020 (unknown study start date)	Hospitalized adults with confirmed COVID-19 and were mechanically ventilated (141) Non-invasive ventilation (91); invasive mechanical ventilation (50)	Need for invasive mechanical ventilation	Admission	Reference for multivariate analysis: D-dimer >1500 ng/mL HR 3.05 (1.07, 8.69) *p* = 0.037 OR 3.28 (1.07, 10.10) p = 0.039	None
Alabyad (2020) [24] USA Retrospective cohort study multi-center April 3-July 31, 2020 Reviewed from admission through discharge or until the censor date of September 14, 2020	Hospitalized adults with confirmed COVID-19 who had markers of coagulation and hemostatic activation (MOCHA) measurements that included D-dimer (276) ICU admission (159) Intubation (90) Admission D-dimer >2000 ng/mL (51) Admission D-dimer >3000 ng/mL (40) (Patients with overlapping D-dimer values not reported)	ICU admission Intubation	Admission	ORs and raw numbers for ICU admission and intubation not reported	Not reported

Thromboembolism (n=14 studies)

Study	Population	Site of Thrombosis and Proportion details	D-dimer (ng/ml) median (IQR) (unless specified)	Association of D-dimer with thrombosis (effect size (95% CI))	Prediction of thrombosis
Al-Samkari (2020) [7] USA Retrospective cohort Multicenter	Adults with confirmed covid from the Research Patient Data Registry at Partners Healthcare (400) - mortality models included only patients reaching completion of hospitalization (discharge or death) Deaths (29) Critically ill (144) D-dimer ≤1000 (148) 1001-2500 (78) >2500 (26)	Thrombotic complications	Initial clinical evaluation	D-dimer measured in FEU using Vidas (bioMerieux) in 2 laboratories, Sta-Liatest (Stago) in 2 laboratories, and HS 500 (Instrumentation Laboratory) in 1 laboratory Reference for multivariate analysis: D-dimer ≤1000 ng/mL D-dimer 1001-2500 ng/mL: Adjusted OR 3.04 (1.26-7.31) >2500 ng/mL: Adjusted OR 6.79 (2.39-19.30) Combined OR (1001-2500 and >2500): OR 3.530 (1.6677-7.4930)	None
Benito 2020 [1] Prospective Spain Mar-Apr 2020	Hospitalized, n=1,275 Suspected thrombosis with CTPA, n=76 March- standard prophylactic anticoagulation April- standard therapeutic anticoagulation	Pulmonary: 32/76 (42.1%) Cumulative incidence 2.6% (95 CI 1.7–3.5%) None: 44/76 (57.9%)	Admission 5,274.5 (16,419) Peak 22,791 (42,552) Admission 1,045.5 (6,287.8) Peak 6039.5 (15,982.3)	Admission 1,000 ng/mL OR 4.5 (1.2–17.2) Peak 6,000 ng/mL OR 5.6 (1.3–24.5)	No data
Garcia-Ortega 2021 [14] Prospective Spain Mar 8-Apr 25, 2020	Hospitalized 119 randomly selected from 272 admitted patients Routine CTPA Prophylactic anticoagulation	Pulmonary: 26/73 (35.6%) None: 47/73 (64.4%)	Admission, mean (SD) 6270 (13,814) 2384 (6134)	Admission HR 1.02 (1.01–1.04)	No data
Mestre-Gomez 2020 [15] Retrospective Spain Mar 30-Apr 12, 2020	Hospitalized Not critically ill Prophylactic anticoagulation	Pulmonary: 29/91 (31.9%) Cumulative incidence 29/452 (6.4%) None: 62/91 (68.1%)	Peak median (Q1-Q3) 7230 ng/mL (2105–16,415) 14,480 ng/mL (5540–33,170)	With dyslipidemia, OR 3.77; CI 95% (1.18–12.16) Without dyslipidemia, (OR 9.06; CI 95% (1.88, 43.60).	Peak D-dimer cut-off of > 5000 ng/mLl and history of Dyslipidemia AUC-ROC 0.755

Mouhat 2020 [16] Retrospective France April-May 2020	349 hospitalized Severe COVID-19 Suspected PE in 162 Prophylactic or therapeutic anticoagulation at discretion of AP	Pulmonary: 44/162 (27.2%) None: 118/162 (72.8%)	5364 ng/mL (2928–12 275) 1310 ng/mL (800–2335)	D-dimer on day of CTPA OR 4.0 (95% CI 2.4–6.7) per quartile increase in D-dimer on day of CTPA For D-dimer >2590 ng/mL: OR 16.9 (95% CI 6.3-45)	Cut-off value of 2590 ng/mL AUC 0.88
Cho 2021 [17] Retrospective Mar1-May 13, 2020, USA	Hospitalized 1170 screened Imaging at AP discretion N=158 included 90% on prophylactic anticoagulation	DVT 52/158 (32.9%) None 106/158	Highest level prior to US median, 13,602 ng/mL [IQR, 6616-36,543 ng/mL] 2880 ng/mL [IQR, 1030-9126 ng/mL]	D-dimer >6494 ng/mL: OR 6.12; (95% CI 2.79-13.39)	6494 ng/mL for DVT SN 80.8% SP 68.9% NPV 88.0% The C statistic (AUC) was 0.802
Demelo-Rodriguez 2020 [18] Prospective Spain April 1-15, 2020	Non-ICU All screened for asymptomatic DVT if with D-dimer>1000 ng/ml and hospitalized for ≥48 hours, all on prophylactic anticoagulation	DVT: 23/156 (14.7%) None: 133/156	4527 ng/mL (IQR 1925–9144) ng/mL 2050 ng/mL (IQR 1428–3235 ng/mL)	Adjusted OR 9.8; CI 95% 2.9–33.7	To rule out asymptomatic DVT, D-dimer cutoff 1570 ng/mL SN 95.7%, SP 29.3%, PPV 19% NPV 97.5%
Zhang 2020 [23] Cross-sectional survey China Jan 29-Feb 29, 2020; followed up until Mar 24, 2020	Hospitalized ≥3 days adult pts with COVID-19, critical; all with DVT screening (N = 159 screened, 143 with imaging) 37% on prophylactic anticoagulation	DVT: 66/143 (46.15) None: 77/143	6600 ng/mL (2500, 8000) 0.9 (0.4, 3.5)	Admission D-dimer >1000 ng/mL (OR 5.818 (1.422–23.809] odds of DVT OR 13.506 [95% CI, 1.334– 136.741] odds of PROXIMAL DVT OR, 3.564 [95% CI, 1.122–11.323] odds of DISTAL DVT	AUC 0.708 (0.622, 0.784) Sn 88.52% Sp 52.86%
Dujardin 2020 [19] Retrospective Amsterdam Mar13-Apr9, 2020	ICU patients Observation (data extracted) till death/discharge Weekly screening US, suspected PE had CTPA, D-dimer done 2x a week All with prophylactic anticoagulation	VTE: 53/127 (41.7%) None: 64/127 (58.3)		Multivariate analysis D-dimer not associated with VTE. Only CRP was associated with VTE.	D-dimer cut-off >2000 ng/mL SN 80 (61–92) SP 29 (15–49) PPV 53 (46–61) NPV 60 (38–79) D-dimer AUC 0.64

Kampouri 2020 [20[Retrospective Switzerland Feb 28-Apr 30, 2020, follow-up till May 5.	All documented COVID-19 with consent for data review, n=443 Documented VTE (imaging) on admission or during hospitalization Crea-clearance adjusted thromboprophylaxis for all in the ICU.	VTE: 41/443 (9.3%) 14/41 On admission 27/41 during hospital stay None: 402/443	D-dimer (ng/ml) (among 363 patients) 3610.0 (1934.0-7093.8) 1039.0 (549.0-2020.0)	VTE on admission >3120 ng/ml- OR 15.8, 95% CI 4.7-52.9 VTE during hospitalization > 5611 ng/ml OR 6.3, 95% CI 2.4-16.2	To predict VTE on admission D-dimer value ≥ 3000 ng/ml SN 71.4 SP 87.9 PPV 99. NPV 87.4 Diagnostic Accuracy 0.797 Wells score for PE ≥ 2 points or D-dimer value ≥1000 ng/ml SN 92.9 SP 46.9 PPV 5.4 NPV 99.5 DA 0.483
Creel-Bulos 2020 [21] Retrospective USA Mar 12-Apr 6, 2020, Reviewed from admission through discharge or until the censor date of April 30, 2020	All severity of COVID Criteria for imaging not mentioned Therapeutic anticoagulation in 59 patients (51%)	VTE: 27/115 (23%) None: 88/115 (76.6)	Median D-dimer within the first 7 days of hospitalization 6450 ng/mL 1596 ng/mL	2000 ng/mL: OR 9.592 (95% CI 1.110-82.866) 3000 ng/mL: OR 15.595 (95% CI 1.902-127.848) Combined OR (2000 and 3000): OR 14.1404 (1.83-109.26)	Prediction of future VTE Within first 7 HD peak level >2500 ng/mL, AUC 0.72 Only change (absolute increase) in D-dimer level (AUC=0.72 P=.004) and rate of D-dimer rise (AUC=0.75 P=.001) were also predictive of VTE Diagnosis of VTE- rise of >150ng/mL/d or >2000ng/mL within any 24 hour period

					through HD10 Sensitivity 75% Specificity 74%
Nauka 2020 [22] Retrospective USA Mar11-May2, 2020	Hospitalized & discharged, not critical, had imaging during hospitalization or within 14 days post-discharge (performed at provider's discretion) D-dimer within 48h of admission 3855 screened, 306 had imaging 193 had prophylactic or therapeutic anticoagulation	VTE: 67/306 (21.9%) 67/2630 (2.5%) estimated population prevalence None: 239/306	5200 ng/mL [1900–20000] 1700 ng/mL [900–3500]	≥2000 ng/mL OR 3.9 (1.1,14.6) ≥5000 ng/mL OR 10.8 (3, 39.2)	None
Rali 2020 [25] Retrospective USA Apr1-27, 2020	147/703 (20.9% of admissions to COVID unit) had imaging for high clinical suspicion of VTE, CTPA and/or extremity venous duplex US (proximal DVT only) VTE prophylaxis at admission or sequential compression devices	VTE:25/147 None: 122/147		admission D-dimer level 1500 ng/mL: adjusted OR 3.55; 1.29-9.78	None
Alabyad 2020 [24] Retrospective cohort USA Multicenter Apr 3-Jul 31, 2021 (censored till Sep 14, 2020)	Hospitalized On prophylactic anticoagulation Outcomes of DVT, pulmonary embolus, MI, ischemic stroke, dialysis or central line clots (with imaging & adjudication), plasma D-dimer within 72 hours of admission (reference value <574 ng/mL) N=276, 58% in ICU (159)	45 patients (16%) with thrombosis DVT 24 (8.7%) PE in 8 (2.9%), MI in 4 (1.5%), ischemic stroke in 5 (1.8%) central or dialysis line thrombosis in 7 (2.5%), 6 (2.2%) RRT thrombosis 1 (0.4%) patient ECMO circuit thrombosis		D-dimer ≥2000 ng/mL (OR 3.1, 95% CI 1.5–6.6; p = .003) D-dimer ≥ 3000 ng/mL (OR 3.6, 95% CI 1.6–7.9; p = .002) Associated with thrombosis within 14 days of admission D-dimer ≥2000 ng/mL (OR 2.5, 95% CI 1.1–5.9	Cut-off ≥ 2000 Total thrombotic endpoints Sensitivity 33% Specificity 84% PPV 29% NPV 87% Thrombotic endpoints within 14 days from admission Sensitivity 31% Specificity 83% PPV 20% NPV 90% Total VTE Sensitivity 39% Specificity 84% PPV 24% NPV 92% VTE <14 days from admission Sensitivity 44% Specificity 84% PPV 20% NPV 94%

Appendix 2. GRADE Evidence Profile

Question: D-dimer levels for mortality, worsening severity, and thromboembolism among COVID-19 patients?
Setting: COVID-19 patients
Author(s): Patricia Pauline M. Remalante-Rayco, Evelyn O. Salido, Joey A. Tabula

Nº of studies	Certainty assessment						Certainty
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Mortality							
5	Observational studies	Serious [a,b,c,d]	Not serious	Not serious	Serious [e]	Strong association dose response gradient	⊕⊕⊕⊕ HIGH
Worsening Severity							
6	Observational studies	Serious [a,b,d]	Serious [f,g]	Not serious	Not serious	None	⊕⊕◯◯ LOW
Thromboembolism							
12	Observational studies	Serious [c,e]	Not serious	Not serious	Not serious	Strong association dose response gradient	⊕⊕⊕⊕ HIGH

Explanations
[a] Did not account for censoring
[b] Patients with incomplete laboratory data were included
[c] Not all prognostic variables were considered
[d] Small number of events relative to number of predictors
[e] Small number of outcome events
[f] Different d-dimer cut-off values were used
[g] Different effect measures used for the outcome

Appendix 3. Forest Plots

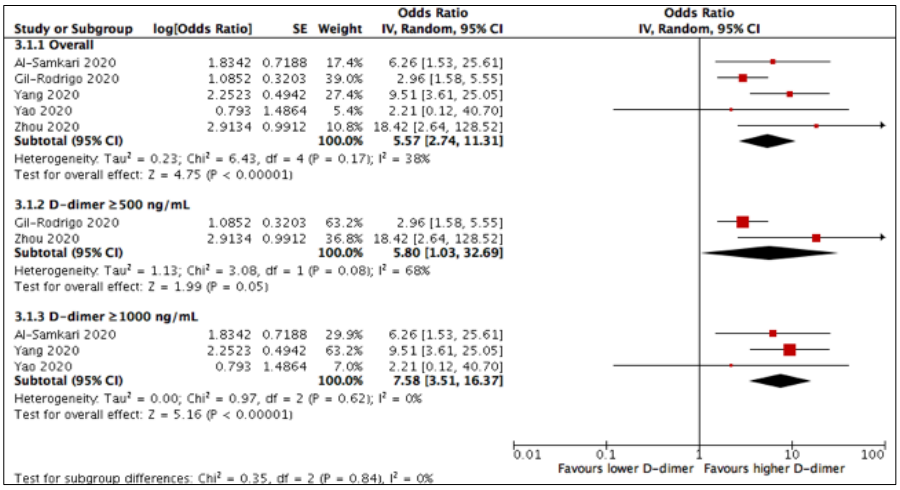

Figure 1. Comparison of mortality between patients with low D-dimer <500 ng/mL versus D-dimer ≥500 ng/mL among adults with confirmed COVID-19, with subgroup analyses at cut-off values of 500 ng/mL and 1000 ng/mL

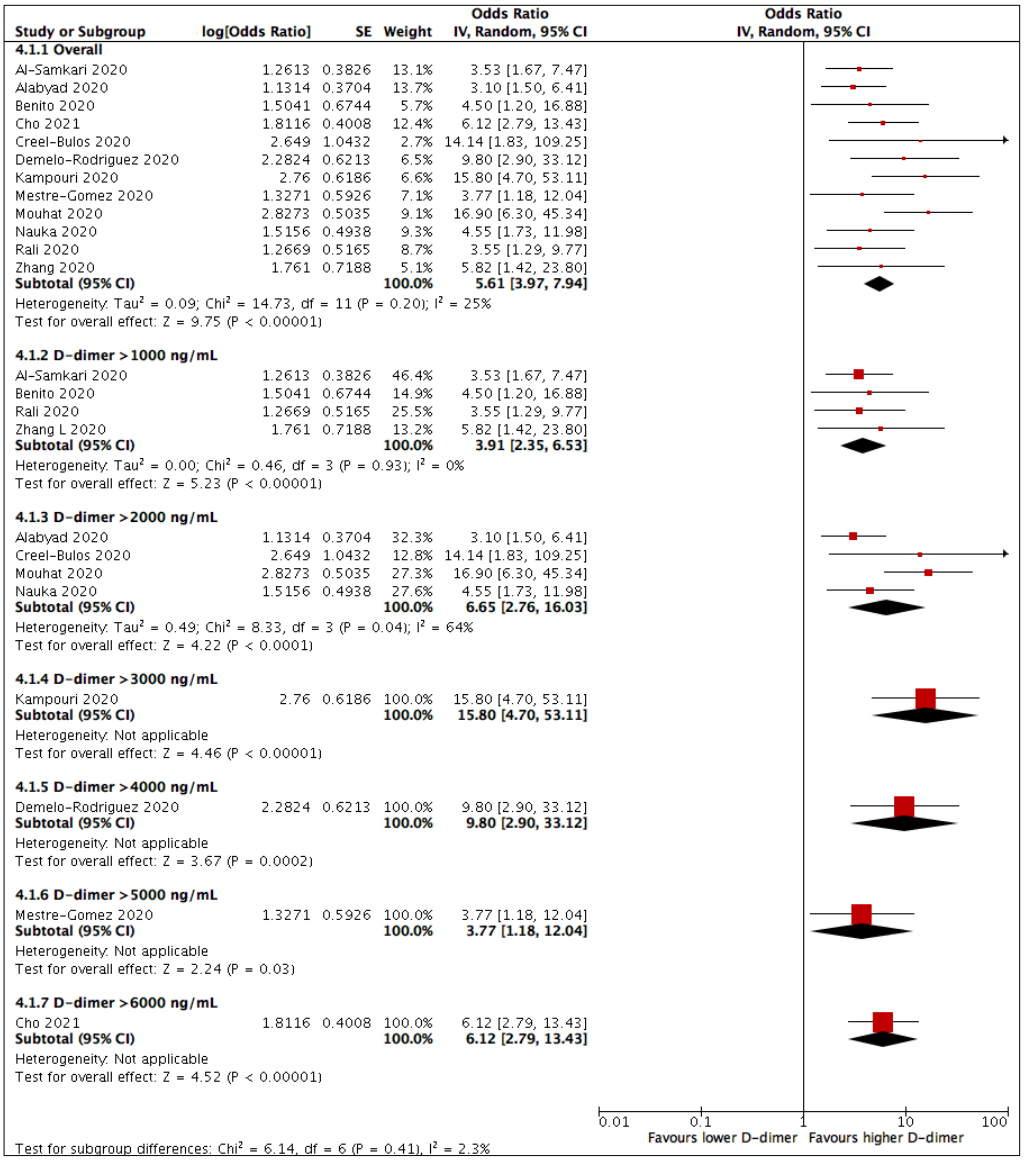

Figure 2. Comparison of thromboembolism between patients with low D-dimer <1000 ng/mL versus D-dimer ≥1000 ng/mL among adults with confirmed COVID-19, with subgroup analyses at cut-off values of 1000, 2000, 3000, 4000, 5000, and 6000 ng/mL

Appendix 4. Detailed Study Appraisal

Table 1. Articles on Mortality

Author and Year	Direct?	Included all important factors?*	Unbiased criteria for outcome?**	Adequate follow-up rate?***	Separate validation study for prediction rule done?	Risk of Bias
Zhou (2020)	Yes (35 % severe, 28% critical)	Yes (Nonsurvivor group was older, had more comorbidities, more tachypneic/tachycardic, higher risk scores)	Yes	Yes	n/a	Very Serious limitation Selection bias: patients still admitted are excluded and may underestimate mortality
Yao (2020)	Yes	Yes Pts with high d-dimer were older, more had HPN, more had severe and critical covid, higher severity scores, higher mortality	Yes	Yes	n/a	Serious limitation Imprecision: Wide CI due to low number of events (n=17)
Zhang L (2020)	Yes (severe 44%, critical 20%)	Yes Pts with D-dimer ≥2.0 ug/mL were older, more comorbids, more deaths	Yes	Yes	n/a	Serious limitation Imprecision: Wide CI due to low number of events (n=13)
Al-Samkari (2020)	Yes (critical 36%)	Yes Pts who are critically ill have more diabetes, CKD on dialysis and less chronic lung disease	Yes	Yes	n/a	Serious limitation Imprecision: Wide CI due to low number of events (n=29)
Gil-Rodrigo (2020)	Yes	Yes Nonsurvivors and patients with composite events were older and had higher prevalence of obesity	Yes	Yes	n/a	Serious limitation: Imprecision from the small number of events per predictor Impact on effect size from incomplete laboratory data leading to exclusion of potentially important prognostic variables and the obviation of collinearity
Peiro (2021)	Yes	No Limited number of variables in Cox regression analyses More nonsurvivors were older, smokers, had hypertension, had myocardial infarction, chronic kidney disease, and chronic pulmonary disease	Yes	Yes	n/a	Serious limitation: impact on effect size Number of variables included was limited (to avoid overfitting); hence multivariable Cox regression analyses were adjusted only by age, hypertension,

						history of chronic pulmonary disease, renal impairment at admission, and d-dimer level
Yang (2020)	Yes	Yes More nonsurvivors were older, had COPD, had hypertension, had severe or critical COVID-19, and had higher levels of cardiac biomarkers, inflammatory indicators and coagulation function	Yes	Yes	n/a	Serious limitation: Impact on effect size/estimation of OR -data censoring -exclusion of variables like SaO2 and IL-6 from the final logistic model due to absence of events (possibly overestimating the effect of d-dimer)
Zhang W (2021)	No Only ICU patients were included	Yes	Yes	Unclear (not mentioned if all patients had known outcomes)	n/a	Serious limitation: Imprecision Small number of events per predictor (3.66 events per candidate predictor)
Creel-Bulos (2020)	Yes	Yes	Yes	Yes	n/a	Serious limitation: Impact on effect size/estimation of OR due to: -lack of imputation for missing data -Inconsistency in daily D-dimer testing in all patients due to lack of a universal policy for D-dimer testing -Data censoring
Alabyad (2020)	Yes	Yes	Yes	Yes	n/a	No ORs reported

Table 2. Articles on Worsening Severity

Author and Year	Direct?	Included all important factors?*	Unbiased criteria for outcome?**	Adequate follow-up rate?***	Separate validation study for prediction rule done?	Limitations
Yue (2020)	Yes	Yes	Yes	Yes	n/a	Serious limitation: Impact on effect size from incomplete laboratory data leading to exclusion of potentially important prognostic variables and the obviation of collinearity
Cen (2020)	No (mild COVID-19 only)	Yes Patients in the progressive group were older, mostly males, had more comorbidities	Yes	Yes	n/a	Serious limitation: Impact on effect size from incomplete laboratory data leading to exclusion of potentially important prognostic variables and the obviation of collinearity -data censoring (28-day follow-up only)
Duan (2020)	No (nonsevere COVID-19 only)	Yes Patients in the progressive group were older, with higher body temperature, heart rate, and laboratory parameters	Yes	Yes	n/a	Serious limitation: Impact on effect size from incomplete laboratory data leading to exclusion of potentially important prognostic variables and the obviation of collinearity -data censoring (28-day follow-up only)
Al-Samkari (2020)	Yes (critical 36%)	Yes Pts who are critically ill have more diabetes, CKD on dialysis and less chronic lung disease	Yes	Yes	n/a	Serious limitation: Impact on effect size from incomplete laboratory data leading to exclusion of potentially important prognostic variables and the obviation of collinearity
Wang (2020)	Yes	Yes	Yes	Yes	n/a	Serious limitation: Impact on effect size from data censoring
Alabyad (2020)	Yes	Yes	Yes	Yes	n/a	No ORs reported

Table 3. Articles on Thromboembolism

Author (Year)	Included all important factors?*	Unbiased criteria for outcome?**	Adequate follow-up rate?***	Separate validation study for prediction rule done?	Overall Risk of Bias (Not serious, Serious, Very Serious)	Any imprecision?
Al-Samkari (2020)	Yes	Yes	Yes	n/a	Serious	Likely yes
Benito (2020)	Yes	Yes	Probably yes	n/a	Not serious	Likely yes
Garcia-Ortega (2021)	Yes	Yes	Probably yes	n/a	Not serious	Likely yes
Mestre-Gomez (2020)	Yes	Yes	Yes	n/a	Not serious	Likely yes
Mouhat (2020)	Yes	Yes	Yes	n/a	Not serious	Likely yes
Cho (2021)	Yes	Yes	Unclear	n/a	Serious	Likely yes
Demelo-Rodriguez (2020)	Yes	Probably yes	Probably yes	n/a	Not serious	Likely yes
Dujardin (2020)	Maybe not	Yes	Yes	n/a	Serious	Likely yes
Kampouri (2020)	Yes	Yes	Probably yes	n/a	Not serious	Likely yes
Creel-Bulos (2020)	Yes	Yes	Unclear	n/a	Serious	Likely yes
Nauka (2020)	Maybe not	Yes	Yes	n/a	Serious	Likely yes
Zhang (2020)	Yes	Yes	Yes	n/a	Not serious	Likely yes
Alabyad (2020)	Yes	Yes	Yes	n/a	Not serious	Likely yes
Rali (2020)	Yes	Probably not	Yes	n/a	Serious	Likely yes

*All prognostic factors are said to be considered if either of the following is done:
1. Homogeneous subgroup of individuals with specific combination of prognostic factors
2. Clinical prediction rule used
**Outcomes are said to be unbiased if hard outcomes are used (e.g, mortality). For soft outcomes, bases or criteria need to be defined
***Follow-up is said to be adequate if the conclusions are similar between best-case and worst-case scenarios; worst outcomes are assumed for drop-outs

Q18. Should procalcitonin be used to guide the initiation of antibiotic therapy in patients diagnosed with COVID-19?

As of 13 December 2021

RECOMMENDATIONS

For initiating antibiotic therapy

We suggest against the use of procalcitonin alone as a basis for initiating antibiotic therapy among COVID-19 confirmed patients. *(Very low certainty of evidence; Weak recommendation)*

For discontinuing antibiotic therapy

If available, we recommend using a procalcitonin level of less than or equal to 0.25 ng/mL for discontinuing antibiotic therapy among COVID-19 confirmed patients. *(Very low certainty of evidence; Strong recommendation)*

Consensus Issues

Antibiotic misuse and abuse among COVID-19 patients is a common practice that needs to be addressed. Thus, the panel recognized that procalcitonin may have utility in guiding antibiotic use among COVID-19 patients. However, the panel was against the use of procalcitonin alone in initiating antibiotic therapy, citing that clinical evaluation and other laboratory parameters should be considered as well since procalcitonin levels can be elevated in certain conditions even in the absence of bacterial infection. Additionally, the evidence base included studies that investigated absolute cut-offs of procalcitonin rather than the comparative decrease or increase in its levels.

In contrast, the panel was unanimous in recommending the use of procalcitonin levels to discontinue antibiotic therapy among COVID-19 patients. This was to provide guidance to practitioners due to the common practice of continuing antibiotics indefinitely among critically ill patients.

Cited reasons for a weak recommendation on the use of procalcitonin for discontinuing antibiotic therapy include:

1) Concerns on the cost and availability of procalcitonin;
2) Very low certainty of evidence; and
3) Use of indirect evidence to identify the cut-off level for discontinuation (i.e., the evidence base aimed to identify procalcitonin levels that differentiate the presence or absence of co-infection rather than the continuation or discontinuation of antibiotic therapy).

Cited reasons for a strong recommendation on the use of procalcitonin for discontinuing antibiotic therapy include:

1) The need to prevent antibiotic resistance, considering that multidrug resistance is a common cause of death among critically ill or severe COVID-19 patients; and
2) To prevent the higher costs associated with unnecessary antibiotic use (i.e., While procalcitonin is expensive, even an extra day of unnecessary antibiotic therapy would equate to higher costs for the patient).

KEY FINDINGS

- Four retrospective cohort studies were included in this review. Three provided data for calculation of diagnostic accuracy estimates, while one reported on the benefits and safety of using an antimicrobial therapy discontinuation protocol based on procalcitonin measurements. Studies used varying cut-off levels for procalcitonin and used it for guiding discontinuation of antibiotics.
- Sensitivity ranged from 0.40 to 0.87, while specificity ranged from 0.43 to 0.88. Across the three studies, a total of 42/816 (5.1%) had positive results on microbiological testing. No stratification as to whether patients with higher procalcitonin levels were associated with more severe or less severe COVID-19 cases.
- Using procalcitonin-based algorithms was found to be associated with lower antimicrobial exposure (mean 5.4 vs. 4.4 days) and consumption (mean DDD 8.4 vs. 6.8). This translates to a 30% lower risk for both mean duration of antibiotic therapy (adjusted ratios of means [ROM] 0.70; 95% CI 0.6-0.9) as well as mean DDD (ROM 0.70, 95% CI 0.6-0.8). A trend towards lower 30-day mortality rates was noted for participants with procalcitonin measurements (adjusted prevalence ratio [PR] 0.6, 95% CI 0.4-1.1). Mean patient antimicrobial consumption also showed a decreasing trend over time in the procalcitonin group (βslope −0.07, 95% CI −0.11, −0.03) compared to those without procalcitonin measurements.
- Overall certainty of evidence was rated very low due to serious risk of bias, imprecision, and inconsistency.

INTRODUCTION

Procalcitonin is a protein prohormone of calcitonin produced by the C-cells of the thyroid gland. Its serum levels increase in systemic bacterial infection due to activation by cytokines and bacterial endotoxins.[1] Viral infections do not induce procalcitonin synthesis, thus the diagnostic marker can be used to distinguish between viral and bacterial infections.[2] In 2010, the PRORATA clinical trial designated a procalcitonin level of <0.25 ng/mL as a cut-off value to not initiate antibiotic use in the intensive care unit setting.[3] A diagnostic accuracy study by Self et al. in 2017 showed an association between increased probability of bacterial infection with high serum procalcitonin levels on admission; however, no threshold perfectly discriminated bacterial versus viral detection.[2]

COVID-19 patients generally have low procalcitonin levels but as disease severity becomes worse and systemic inflammation occurs, procalcitonin levels may rise.[4] Early stage COVID-19 and community-acquired pneumonia typically have similar initial presentation and the hyperinflammatory phase of COVID-19 makes it difficult to distinguish from secondary bacterial infection. Thus, starting an empiric antibiotic among COVID-19 patients is a common practice among clinicians.[5]

A review of evidence by Rawson et al. in 2020 showed low rates of bacterial/fungal co-infection among patients with COVID-19 in contrast to the high rates of antimicrobial prescribing among them.[6] Their study concluded that there should be evidence-based antimicrobial prescribing and stewardship strategies for COVID-19 patients to prevent the consequences of unintended antimicrobial use.

This evidence summary reviewed the utility of procalcitonin levels among COVID-19 confirmed patients in differentiating the presence or absence of community-acquired and nosocomial bacterial co-infections.

REVIEW METHODS

The PubMed for MEDLINE database, US NIH ClinicalTrials.gov, and WHO International Clinical Trials Registry were searched on 6 November 2021 using the search terms “SARSCoV2" or “COVID-19" and "procalcitonin" and "bacterial pneumonia" or "bacterial infections" or "sepsis". Observational studies or clinical trials that provided data to allow calculation of diagnostic accuracy measures were included. Eligible studies should use procalcitonin regardless of cut-off value for positivity, and microbiological testing as reference standard for detecting bacterial infection. Literature reviews, editorials, case reports, and case series were excluded.

RESULTS

Characteristics of Included Studies

Diagnostic accuracy, relationship of procalcitonin with clinical outcomes

Three retrospective cohort studies among hospitalized COVID-19 confirmed patients (N=816) investigated the prevalence of bacterial co-infection and secondary bacterial infections through culture of blood, sputum, bronchoalveolar lavage washing, and urine specimens. Microbiologic testing results were then compared with serum procalcitonin levels. Based on culture results, patients were divided into two groups: (1) those with at least one additional pathogen isolated in any of the cultures and (2) those with no additional pathogen isolated. Different cut-off values were used for procalcitonin: 0.25 ng/mL, 0.25 pg/mL, and 0.1 ng/mL

For each group in Hughes et al. and Chen et al., the patients were further divided into two subgroups depending on whether procalcitonin levels were less than 0.25 ng/mL or more than or equal to 0.25 ng/mL. Cheng et al., described the prevalence of culture-positive bacterial infection among patients suspected with superimposed nosocomial bacterial infection at a designated cut-off of more than 0.1 ng/mL. Diagnostic accuracy for bacterial co-infection of procalcitonin for the three studies above was measured.

Of those with bacterial growth in culture specimens, one study (Chen et al.) further classified the patients into having co-infection (community-acquired infection) or superimposed bacterial infection (nosocomial infection). Of the 52 cases with growth, 25 (48%) had community-acquired infections, 25 (48%) had hospital-acquired infections, and 2 (4%) patients had both community and hospital-acquired infections.[7] In the other study by Hughes et al., all five cases with bacterial growth were community acquired.[8]

Benefits and safety of procalcitonin-guided protocols

One retrospective, cohort study in the UK (Calderon et al., 2021) assessed the effectiveness and safety of a procalcitonin-guided protocol on the use of empirical antimicrobials among suspected and confirmed COVID-19 pneumonia (n=259). Of the 117 patients with procalcitonin measurements, 73 (62.4%) had levels ≤0.25 ng/mL. No diagnostic accuracy measures were reported in this study, although there were ten patients (8.5%) with positive blood culture and four (3.4%) with positive sputum cultures seen in the procalcitonin group.

A cut off level of ≤0.25 ng/mL was used to indicate stopping antimicrobial treatment, while higher levels either support or encourage continuing antimicrobials (0.25-0.4 ng/mL - supported; 0.5-1.9 ng/mL - encouraged; >2.0 - strongly encouraged). Procalcitonin results were interpreted along with other parameters (e.g., clinical suspicion of sepsis, CXR changes, infection other than respiratory illness). Outcomes included the following: (1) duration of antimicrobial exposure, (2) per-patient antimicrobial consumption (WHO Defined Daily Dose method), (3) safety (composite of death, admission to ICU >72 hours after starting antimicrobials, or readmission to hospital within 30 days).

Overall certainty of evidence

The overall certainty of evidence was rated very low for diagnostic accuracy. Studies had serious risk of bias issues related to timing of microbiologic testing in relation to procalcitonin measurements and representativeness of the sample population. Downgrading was also done due to imprecision in the estimates as well as inconsistent findings reported across the studies.

Summary of results of included studies

Diagnostic accuracy of procalcitonin

Varying diagnostic accuracy estimates were derived from three cohort studies. Sensitivity ranged from 0.40 to 0.87, while specificity ranged from 0.43 to 0.88. Across the three studies, a total of 42/816 (5.1%) had positive results on microbiological testing.

Using a cut-off value of **>0.1 ng/mL**, data from 212 COVID-19 patients with nosocomial infection in one study from China (Cheng et al. 2020) showed that the sensitivity of procalcitonin to detect culture-positive bacterial infection was 0.87 (95% CI 0.70-0.96) while the specificity was at 0.43 (95% CI 0.35-0.50). Of the 212 patients, 31 had positive culture isolates indicating a prevalence of 14.6%.

Using a cut-off value of **≥0.25 ng/mL**, another study from China (Chen et al., 2020) estimated a sensitivity of 0.50 (95% CI 0.12-0.88) and specificity of 0.88 (95% CI 0.84-0.91). A relatively similar sensitivity estimate of 0.40 (95% CI 0.05-0.85) but significantly lower specificity estimate of 0.65 (95% CI 0.58-0.72) was reported by a study in the UK. This study used a lower cut off level at **≥0.25 pg/mL**. Both studies documented very low prevalence (<3%) of bacterial growth in culture of specimens collected from COVID-19 confirmed patients.

Study	TP	FP	FN	TN	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Hughes 2021	2	67	3	124	0.25 pg/mL	0.40 [0.05, 0.85]	0.65 [0.58, 0.72]		
Chen 2020	3	49	3	353	0.25 ng/mL	0.50 [0.12, 0.88]	0.88 [0.84, 0.91]		
Cheng 2020	27	104	4	77	0.1 ng/mL	0.87 [0.70, 0.96]	0.43 [0.35, 0.50]		

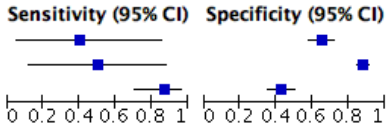

Figure 1. Accuracy of procalcitonin for detecting culture-positive bacterial infections in patients with COVID-19

Relationship of procalcitonin with disease severity

All studies did not specify whether the patients were admitted in the ward or intensive care unit (ICU). No stratification as to whether patients with higher procalcitonin levels were associated with a more severe or less severe COVID-19 case was done by both studies. However, Chen et al. showed that most culture-positive patients were those

with mild to moderate COVID-19 (30 patients or 57.7%) severity, while seven (13.5%) had severe COVID, and 15 (28.8%) had critical COVID-19 infection. However, this may be compounded by the baseline numbers showing a higher pool of patients with mild to moderate and less patients with severe or critical COVID.

Relationship of bacterial co-infection with mortality rate

Chen et al. demonstrated that COVID-19 patients with bacterial growth on culture specimens had a higher mortality rate (5.8%) versus COVID-19 patients without growth (0%), necessitating clinicians to ensure early identification of bacterial co-infection to initiate timely antibiotic treatment.[8] However, signs and symptoms of bacterial infection present similarly to COVID-19 infection. Hence, ancillary tests that allow clinicians to differentiate COVID-19 with or without bacterial infection are helpful to decrease hospital costs and improve adherence of clinicians to antimicrobial stewardship. Although bacterial culture is definitive in identifying the presence of bacterial pathogens, the turnaround time for its results are not as readily available as serum procalcitonin levels, leaving clinicians to rely on clinical data in decision-making.

Benefits and harms of procalcitonin-guided protocols

Based on the Calderon et al. 2021 study, patients with procalcitonin measurements had lower antimicrobial exposure (mean 5.4 vs. 4.4 days) and consumption (mean DDD 8.4 vs. 6.8). This translates to a 30% lower risk for both mean duration of antibiotic therapy (adjusted ratios of means [ROM] 0.70, 95% CI 0.6-0.9) as well as mean DDD (ROM 0.70, 95% CI 0.6-0.8).

In terms of safety, no significant differences were found between the groups. A trend towards lower 30-day mortality rates was noted for participants with procalcitonin measurements (adjusted prevalence ratio [PR] 0.6, 95% CI 0.4-1.1), although this was not statistically significant after adjusting for confounding variables such as age. Mean patient antimicrobial consumption also showed a decreasing trend over time in the procalcitonin group (βslope −0.07, 95% CI −0.11, −0.03), in contrast with the non-procalcitonin group (βslope −0.01, 95% CI −0.05, 0.02).

OTHER CONSIDERATIONS

Availability

Procalcitonin assay can be readily performed using available blood sample at the emergency department. This makes procalcitonin a potential test for aiding therapeutic dilemma of whether to start antibiotic therapy among COVID-19 patients. This, however, should be interpreted in conjunction with clinical examination and other laboratory parameters available as procalcitonin can be elevated in certain conditions such as chronic kidney disease and during a later severe course of COVID-19.[9]

Cost-Effectiveness

There is limited data on the cost-effectiveness of procalcitonin. Collins et al. reported decreased hospital costs with procalcitonin-guided antibiotic treatment in the ICU setting.[10] There are no studies on the availability of procalcitonin among hospitals in the Philippines as well as studies on equity, acceptability, and feasibility.

The standard price of procalcitonin at the Philippine General Hospital is Php 2,935. No published economic evaluation has been found investigating the cost-effectiveness of procalcitonin assays for this purpose.

RECOMMENDATIONS FROM OTHER GROUPS

The Philippine **Clinical Practice Guidelines for Sepsis and Septic Shock in Adults 2020** [11] recommended that when there is uncertainty, procalcitonin may be used as an adjunct to support the diagnosis of sepsis in adults (weak recommendation, low quality of evidence).

The **2021 Surviving Sepsis Campaign** [12] suggested using procalcitonin along with clinical evaluation to decide when to discontinue antimicrobials in adults with an initial diagnosis of sepsis or septic shock, if the optimal duration of therapy is unclear and if procalcitonin is available.

There are currently no recommendations on the use of procalcitonin to determine bacterial infection among COVID-19-confirmed patients from the WHO Living Clinical Practice Guidelines, [13] the NIH COVID-19 Treatment Guidelines, [14] and the Infectious Disease Society of America COVID-19 Guidelines.[15]

RESEARCH GAPS

Currently, there are no ongoing clinical trials on the use of procalcitonin levels to detect bacterial infection among COVID-19 confirmed patients. While culture of blood, respiratory tract specimens, urine, and other bodily fluids is the gold standard, bacterial culture has a relatively low yield and is affected by multiple factors such as adequate sampling, transport, specimen processing, and interpretation. Investigating the benefits of procalcitonin among clinically diagnosed bacterial pneumonia or sepsis in COVID-19 patients is also recommended for future research. In addition, the included studies did not specifically aim to determine the diagnostic accuracy of procalcitonin. Lastly, while a cut-off of more than or equal to 0.25 ng/mL was used in the two studies as recommended by the PRORATA trial [16] among non-COVID patients, no specific cut-off level has yet been proposed among COVID-19 patients.

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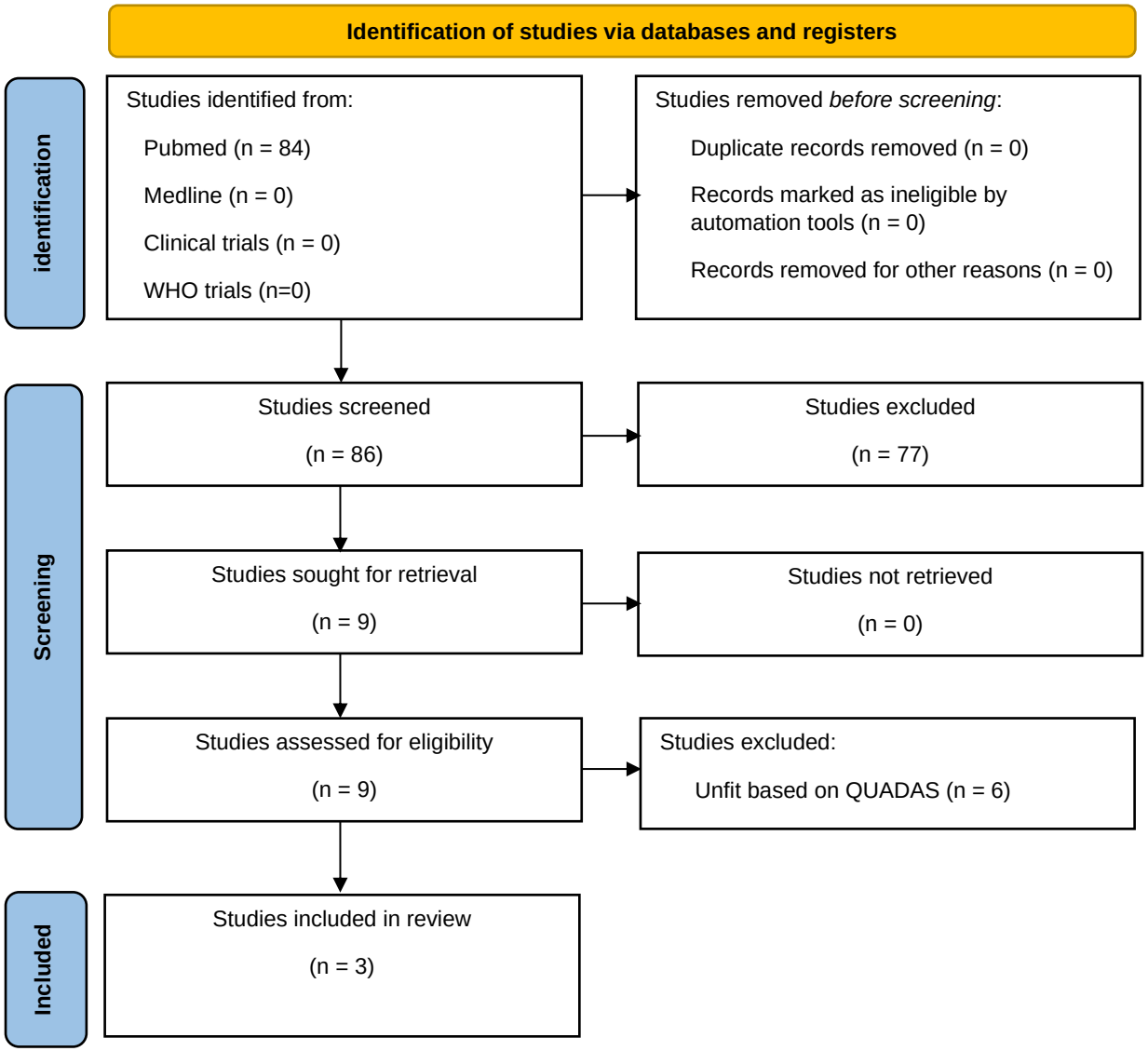
Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)					Diagnostic modalities that help determine the likelihood of bacterial infection on top of COVID-19 infection can help direct whether to initiate and/or continue antibiotic treatment.
Benefits	Large (1)	Moderate (6)	Small (1)	Uncertain			Using procalcitonin-based algorithms was found to be associated with lower antimicrobial exposure (mean 5.4 vs. 4.4 days) and consumption (mean DDD 8.4 vs 6.8). This translates to a 30% lower risk for both mean duration of antibiotic therapy (adjusted ratios of means [ROM] 0.70, 95% CI 0.6, 0.9) as well as mean DDD (ROM 0.70; 95% CI 0.6, 0.8). Potential to prevent unnecessary exposure and adverse reactions to antibiotics, prevent antibiotic resistance, prevent unnecessary prolonged hospital stay for IV antibiotic completion, and decrease overall hospital cost.
Harms	Large	Moderate (2)	Small (6)	Uncertain (1)			Based on available retrospective studies, there is no to minimal harm on performing serum procalcitonin determination among COVID-19 confirmed patients. A trend towards lower 30-day mortality rates was noted for participants with procalcitonin measurements (adjusted prevalence ratio [PR] = 0.6, 95% CI 0.4, 1.1). Mean patient antimicrobial consumption also showed a decreasing trend over time in the procalcitonin group (βslope −0.07, 95% CI: −0.11, −0.03) compared to those without procalcitonin measurements.
Balance of Benefits and Harms	Favors the use of procalcitonin (2)	Probably favors the use of procalcitonin (6)	Does not favor the use of procalcitonin				
Certainty of Evidence	High	Moderate (1)	Low (1)	Very low (6)			Overall certainty of evidence was rated very low due to serious risk of bias, imprecision, and inconsistency.
Accuracy	Very Accurate	Accurate (1)	Inaccurate (6)	Very Inaccurate	Uncertain (1)		Sensitivity ranged from 0.40 to 0.87, while specificity ranged from 0.43 to 0.88. Across the 3 studies, a total of 42/816 (5.1%) had positive results on microbiological testing.
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability	No important uncertainty or variability			No evidence
Resources Required	Uncertain	Large cost (4)	Moderate Cost (4)	Negligible cost or savings	Moderate savings	Large savings	While limited data is available in cost-effectiveness, Collins et al. reported decreased hospital costs with procalcitonin-guided antibiotic treatment in the ICU setting. The availability of the test (serum procalcitonin) may vary from institution to institution depending on available laboratory facilities. The standard price of Procalcitonin at the Philippine General Hospital is Php 2,935.
Certainty of evidence of required resources	No included studies (2)	Very low (3)	Low (2)	Moderate	High (1)		
Cost effectiveness	No included studies	Favors using procalcitonin (7)	Does not favor either using the procalcitonin or the comparator	Favors comparison (1)			No evidence

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Equity	Uncertain (3)	Reduced (3)	Probably no impact (2)	Increased (1)		Based on available retrospective studies, there is no to minimal harm on performing serum procalcitonin determination among COVID-19 confirmed patients. Decreased hospital cost will also be favorable to patients and health facilities. Prevention of antibiotic-resistant organisms will also benefit the larger society.
Acceptability	Uncertain (3)	No	Yes (5)			Procalcitonin determination is already part of the routine tests done for COVID-19 confirmed patients, but cut-off values may vary from institution to institution.
Feasibility	Uncertain (1)	No	Yes (7)			

Appendix 2. Search Yield and Results



Appendix 3. Characteristics of Included Studies

Study ID Title Author	Study Design	Setting/ Country	N	Population	Intervention	Comparator/ Control	Outcomes
Clinical and etiological analysis of co-infections and secondary infections in COVID-19 patients: An observational study Chen et al 2021	Retrospective Cohort	Shenzhen Third People's Hospital, Shenzen, China	408	Hospitalized adult patients -COVID-19 confirmed via SARS-COV2 RT-PCR -mild, moderate and severe COVID-19 infections - with at least one microbiological test besides SARS-COV2 RT-PCR Exclusion: Patients with no microbiologic testing	Serum procalcitonin level	Blood samples and nasopharyngeal swabs and lower respiratory samples sent to the laboratory for molecular assay and/or conventional culture.	Clinical and etiological characteristics associated with co-infections and secondary infections of COVID-19 patients Identification of bacterial pathogens In-hospital Mortality rate Median hospital Stay
Hughes et al 2021 Procalcitonin to guide antibacterial prescribing in patients hospitalized with COVID-19 United Kingdom	Retrospective observational analysis	To analyze the correlation of PCT with antibacterial prescribing, confirmed bacterial infections, and determine if PCT aids with 48-72 hr review of antimicrobial therapy	624	> 18 years old Positive for COVID-19 RT PCR Exclusion: - COVID-19 suspect only 196 of which had serum procalcitonin determination 106 (54%) with antibiotics initiated on admission 85 (66%) continued antibiotics for > 72 hr	Procalcitonin serum assays (Alinity i B·R·A·H·M·S, Abbott, VA, USA); values of 0.25 pg/mL at 6–24 h post-COVID diagnosis Cutoff for positivity >= 0.25 pg/mL	Positive microbiological isolates (within 5 days of admission) that warranted targeted antibacterial treatment by the on-duty microbiology team	Clinical and etiological characteristics associated with co-infections and secondary infections of COVID-19 patients Idenfitication of bacterial pathogens In-hospital Mortality at 30 days Median Hospital Stay Prevalence of carbapenem and systemic antifungal treatment during admission
Cheng et al 2020 Analysis of the risk factors for nosocomial bacterial infection in patients with COVID-19 in a tertiary hospital Huangshi, China	Retrospective cohort	To explore exposure of risk factors and its impact on incidence of nosocomial bacterial infection in patients with suspected and confirmed COVID-19	212	> 16 years old Positive for COVID-19 RT PCR 108 (50.9%) males 31 (14.6%) confirmed bacterial isolation (12 LRTI, 10 UTI, 7 blood, 1 URTI, 1 GIT) Exclusion: COVID-19 suspect only Community-acquired bacterial infection	Procalcitonin serum assays (cutoff for positivity > 0.1 ng/mL)	Positive microbiological isolates from urine, blood, lower respiratory tract specimens	Risk factors for the nosocomial bacterial infection of patients with COVID-19 Nosocomial bacterial infection rate among patients on mechanical ventilator, with indwelling urinary catheter, and arteriovenous catheterization
Calderon et al 2021 Evaluation of procalcitonin-guided antimicrobial	Retrospective cohort	To evaluate the effectiveness and safety of a	259	Lab-confirmed or clinically-suspected COVID-19 Exclusion criteria: < 18 years old	Procalcitonin (Cobas Elecsys BRAHMS; 22 serum for this assay was collected)		Duration of antimicrobial exposure (time from first to last dose plus dosing interval)

Study ID Title Author	Study Design	Setting/ Country	N	Population	Intervention	Comparator/ Control	Outcomes
stewardship in patients admitted to hospital with COVID-19 pneumonia United Kingdom		procalcitonin-guided antimicrobial decision-aid in noncritically ill patients with COVID-19 pneumonia		Admission to HDU or ICU within 72 hrs of admission Not receiving antimicrobials during their admission Indication for antimicrobial treatment other than respiratory tract infection Antimicrobials being stopped as part of treatment rationalization in end-of-life care	cut off: 0.25 ng/mL		Per-patient antimicrobial consumption (WHO Defined Daily Dose method) Safety (composite of death, admission to ICU > 72 hr after starting antimicrobials, or readmission to hospital within 30 days)

Appendix 4. GRADE Evidence Profile

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 11.2%	Pre-test probability of 14%	Pre-test probability of 19%	
True positives	3 studies (42 patients)	Case-control type accuracy study	Serious	Not serious	Serious	Very serious[a]	All plausible residual confounding would reduce the demonstrated effect	60 (13 to 106)	21 (5 to 38)	102 (23 to 81)	⊕◯◯◯ Very Low
False negatives								52 (6 to 99)	19 (2 to 35)	88 (9 to 167)	
True negatives	3 studies (744 patients)	Case-control type accuracy study	Serious	Not serious	Serious	Very serious[a]	All plausible residual confounding would reduce the demonstrated effect	662 (515 to 808)	715 (557 to 874)	603 (407 to 737)	⊕◯◯◯ Very Low
False positives								226 (80 to 373)	245 (86 to 403)	207 (73 to 340)	
Antimicrobial exposure	1 study	Cohort	Serious[b]	Serious[c]	Not serious	Not serious	None	Patients with procalcitonin measurements had lower antimicrobial exposure (mean 5.4 vs. 4.4 days) and consumption (mean DDD 8.4 vs 6.8). This translates to a 30% lower risk for both mean duration of antibiotic therapy (adjusted ratios of means [ROM] = 0.70; 95% CI 0.6-0.9) as well as mean DDD (ROM = 0.70; 95% CI 0.6-0.8)			⊕⊕◯◯ Low
Safety (30-day mortality rate, antimicrobial consumption)	1 study	Cohort	Serious[b]	Serious[c]	Not serious	Serious[d]	None	A trend towards lower 30-day mortality rates was noted for participants with procalcitonin measurements (adjusted prevalence ratio [PR] = 0.6; 95% CI 0.4-1.1), although this was not statistically significant after adjusting for confounding variables such as age. Mean patient antimicrobial consumption also showed a decreasing trend over time in the procalcitonin group (βslope=−0.07, 95% CI: −0.11 to −0.03), in contrast with the non-procalcitonin group (βslope=−0.01, 95% CI: −0.05 to 0.02).			⊕◯◯◯ Very Low

CI: confidence interval

Explanations

[a] There is no proven cut-off or threshold for serum procalcitonin levels among COVID

[b] majority of the patient cohort were admitted prior to the routine use of dexamethasone (22 June 2020) and remdesivir (5 June 2020) for patients with COVID-19 in the UK, potentially impacting the extrapolation of the mortality and safety outcomes. Clinicians may have limited their use of the procalcitonin assay in patients in whom the presence of bacterial infection seemed less likely, such as those without clear clinical signs and symptoms suggestive of bacterial pneumonia

[c] Discontinuation of antimicrobial therapy, not initiation d. Confidence intervals crossed 1.0

Appendix 5. Detailed Study Appraisal

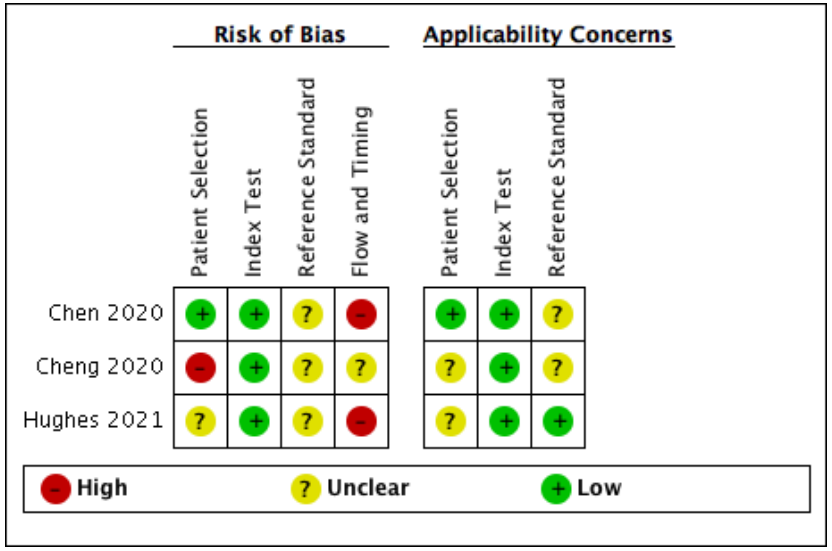


Figure 1. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

Q19. Should certain risk factors be used to predict the development of long COVID?

As of 29 November 2021

RECOMMENDATION

There is insufficient evidence in using symptoms*, biologic factors or severity of acute COVID-19 in predicting the development of long covid symptoms. *(Very low certainty of evidence)*

**The most common symptoms of long COVID identified were fatigue, dyspnea, sleep disturbance, anxiety or depression, and memory impairment.*

Consensus Issues

Predicting the development of long COVID-19 using risk factors can help identify which patients should be followed up more closely. However, there is insufficient evidence on the predictive risk factors, precluding any recommendation to be made.

KEY FINDINGS

- Evidence for this review was obtained from 37 observational studies included in two systematic reviews as well as three additional observational studies describing possible risk factors for the development of long COVID.
- Majority of hospitalized patients diagnosed as having long COVID presented with the following symptoms: weakness, fatigue, dyspnea, cognitive/memory impairment, sleep disorder, and anxiety/psychosocial symptoms.
- For patients in the community setting, dyspnea, reduced quality of life, weakness, chest pain, palpitations, arthralgia, and myalgia were highly common. Older age, females, presence of comorbidities, and more severe status during the initial infection were likely to be associated with the development of long COVID during follow-up, although studies showed inconsistent results.
- Very low certainty evidence showed that some of these risk factors were associated with individual symptoms characteristic of long COVID. Our analysis was limited by the significant heterogeneity among the studies included, the different time frames of follow-up, and the studies' inclusion criteria.

INTRODUCTION

The current understanding of COVID-19 has gone past the acute phase of infection as recent literature recognizes the chronic effects of illness. Long COVID, post-COVID syndrome, or post-acute sequelae of COVID-19 (PASC) refers to the persistence or new-onset COVID-19-related symptoms among patients with probable or confirmed COVID-19 after the acute phase of illness and could not be explained by other conditions.[1] This condition, however, has a different temporal cut-off, prompting the World Health Organization (WHO) to come up with a clinical definition citing three months after the acute phase as the time to consider symptoms as part of long COVID and these symptoms usually may extend for 2 months.[1] Uncertain information about this condition remains as affected people present differently and with varying durations of symptoms. A better understanding of this condition especially with the identification of the people who could develop it can lead to better appropriation of resources for long-term patient support and services both at an individual and societal level.[2,3]

REVIEW METHODS

A systematic literature search was performed for studies that investigated the presentation, biologic factors, and laboratory or imaging tests of patients with suspected or confirmed COVID-19 who developed long COVID symptoms (population). A comprehensive literature search was done in PubMed, MedRxiv, Google scholar, and Cochrane Library on October 23, 2021 using a combination of free text and MeSH terms related to “long COVID,” “post-COVID-19 syndrome,” “post-acute COVID,” “long haul COVID,” “risk factors,” and “predictors”. Systematic reviews were considered for inclusion in this review due to the expected wide range of results and volume of observational studies on the topic. The methodological quality of each included systematic review was assessed using the AMSTAR-2 tool. To supplement the yield, further search for observational or clinical studies was done following the date of the last search of the systematic review with the highest quality. Studies describing only symptoms of long COVID or follow-up studies with no or insufficient data regarding initial presentation were excluded.

RESULTS

Characteristics of Included Studies

Three relevant systematic reviews that described the potential risk factors associated with long COVID symptoms were identified.[4-6] Two of these were rated as high-quality reviews, while one was rated low (see Appendix). The latter only included five studies describing possible risk factors for long COVID descriptively (no statistical analysis), were also included in the two hence only results from the studies included in the two high-quality reviews (64 studies encompassing 16,391 patients) were added in the analysis.[5,6] Three additional studies [7-9] were found after the last search date of Michelen review on March 17, 2021. Two of these additional studies included pulmonary imaging reports [7,8] and one on neurologic sequelae of COVID-19 [9]. One study reported chest CT imaging findings after one, three, and six months of hospital discharge and described what factors led to persistent pulmonary findings. Another study used chest radiograph [8] as the imaging modality to determine the resolution or persistence of abnormal findings after 12 weeks of follow-up.

Due to the wide scope of long COVID, all the reviews employed a wide search strategy. Preprints or non-peer-reviewed articles were excluded in both systematic reviews. In the two systematic reviews, 41 studies investigated potential risk factors, of which four were duplicates thereby yielding a total of 37 unique studies. The remaining studies reported the symptoms of patients on follow-up and were used to identify the common symptoms of long COVID.

The definition of long COVID varied between the systematic reviews. Martimbianco et al. [5] defined it as symptoms for more than three weeks after the initial infection, hence excluding studies with symptoms presenting less than this period. Michelen et al. [6] included studies with a follow-up period of more than 12 weeks, following the definition of the National Institutes of Health. The latter review also excluded studies with less than 100 participants to avoid a small-study effect.

Methodological quality of included studies

Overall, the studies included in this review ranged from low quality/high risk of bias to high-quality cohort studies. Concerns for bias arise from the incomplete or unclear recruitment process, unclear assessment of response for the outcomes, several studies employing different data collection methods, and questionable generalizability of results to the wider population with COVID-19. The systematic review by Martimbianco et al. [5] used the National Institute of Health Quality Assessment Tool for case series studies for all included studies. Of the 25 included studies, five were deemed as moderate quality studies while the rest were of high quality. The systematic review by Michelen et al. [6] used a validated tool by Hoy et al. made for prevalence studies. Of the included studies, the risk of bias was rated as high in 12 (31%) studies, moderate in 22 (56%) studies, and low in 5 (13%) studies. For the three additional observational studies, the risk of bias was rated low based on the Cochrane risk of bias tool for cohorts. The last study set a six-month follow-up period and described the psychiatric and neurological symptoms at follow-up and their associated factors. This study was assessed to have a low risk of bias.[9] Appendix 3 shows the methodological assessment employed by the included systematic reviews.

Most commonly reported / most prevalent[4] symptoms of long COVID

Due to the significant heterogeneity of the studies, pooling of the risk factors was not done. The most common symptoms of long COVID are shown in Table 1. Michelen et al. [6] provided point prevalence and corresponding interval estimates while Martimbianco et al. [5] only presented ranges.

Table 1. Most commonly reported symptoms of patients with long COVID

Michelen et al. [6]			Martimbianco et al. [5]			
Symptoms	Studies	Prevalence (95% CI)	Symptoms	Studies	Maximum %	Minimum %
HOSPITALIZED						
Weakness	1	54.48 (46-62.7)	**Fatigue/ asthenia**	18	64	6.6
Reduced quality of life	1	47.96 (43.77-52.18)	**Dyspnea**	16	61	5.5
Weight loss	1	37.31 (29.55-45.79)	**Cough/ sputum production**	13	59	1.8
Fatigue	11	37.10 (26.45-49.06)	**Cognitive/ memory/ concentration impairment**	9	57.1	18
Memory impairment	3	34.78 (23.64-47.88)	**Post-traumatic stress/ psychological symptoms/ mood changes**	5	57.1	5.8
Other respiratory symptoms	2	32.43 (2.22-91.02)	**Sleep disorder/ insomnia**	5	53	21.7
Dyspnea	14	28.68 (18.48-41.64)	**Physical dysfunction**	4	28.3	4
Anxiety	4	25.58 (6.36-63.49)				
COMMUNITY SETTING (MIXED POPULATIONS)						
Dyspnea	3	32.57 (14.26-58.38)	**Chest pain**	7	89	0.4
Reduced quality of life	2	30.34 (7.43-70.27)	**Pain and discomfort**	3	66	19

[4] Occurring in at least 25% of the population in the studies

Weakness	1	29.82 (25.42-34.61)	**Palpitations**	4	62	9
			Arthralgia	9	54.7	5.9
			Myalgia	10	50.6	2

Majority of hospitalized patients deemed to have long COVID had the following most commonly reported symptoms: weakness, fatigue, dyspnea, cognitive/memory impairment, sleep disorder, and anxiety/psychosocial symptoms. For patients in the community setting, dyspnea, reduced quality of life and weakness, chest pain, palpitations, arthralgia, and myalgia were highly common. Anosmia was reported to persist among non-hospitalized COVID-19 patients.

Data from two additional observational studies also reflected the same findings from the reviews. The study by Wallis noted that 65% of previously hospitalized COVID patients presented with persistent symptoms, the most common of which were fatigue (41%) and dyspnea/breathlessness (38%). On the other hand, the study by Pilloto found the following symptoms to persistent at 6-month follow-up: fatigue (34%), memory complaints (32%), sleep disorder (32%), myalgia (30%), and depression (27%).

Risk factors associated with the development of individual symptoms in long COVID

The reported risk factors varied across studies, with inconsistent or contradicting results as summarized in Table 2. However, more studies have reported that advanced age, females, and more severe status during the initial infection were likely to be associated with the development of long COVID during follow-up.

Evidence was limited regarding certain risk factors and their association with individual symptoms that are typically seen in patients with long COVID. Fatigue was associated with older age, but studies show inconsistent results regarding its relationship with females, and initial COVID severity. Sleep disturbance and psychosocial symptoms were both associated with severe COVID and female sex. Functional impairment was associated with severe COVID, presence of comorbidities, and older age.

Appendix 4 provides the risk factors with reported significant associations to date based on the living systematic review by Michelen et al. Of the included studies, only 13 were able to perform multivariate analysis (Appendix 5).

Table 2. Risk factors associated with the most common individual symptoms of long COVID from studies that have multivariate analysis (no pooling of studies done)

Symptom	Risk factor	Description
Fatigue	Severity	• More severe presentation OR 2.69 (95% CI 1.46-4.96)
	Sex	• Females at risk p=0.02 from one study • Females show more symptoms of fatigue or muscle weakness OR 2.69 (1.46-4.96)
Dyspnea	Severity	• More severe disease as evidenced by DLCO < 80% OR 592 (95% CI 2.28-15.37)
	Sex	• Females showed a higher risk of lung diffusion impairment OR 4.6 (95% CI, 1.85-11.48)
Functional impairment	Severity	• ICU admission OR 3.1 (95% CI, 1.3-7.9) • ICU admission or use of mechanical ventilation OR 1.049 (1.009-1.090)
	Old age	• OR 2.6 (95% CI, 1.192-5.671) based on one study • Based on walking ability, P< 0.02 according to one study
	Comorbid	• An increasing number of comorbidities increases the risk for limitation in walk test p<0.01

Anxiety/depression or any psychiatric symptoms	Severity	• History of prior psychiatric condition and presence of psychopathology after one-month p =.006 and p = <0.0001
	Sex	• Females at risk for persistence of depressive symptoms according to one study p =0.003 • Increase risk for anxiety or depression, OR 1.77 (95% CI 1.05-2.97)

EVIDENCE TO DECISION

Due to varying and incomplete data on long covid, no studies were found on the cost-effectiveness of the approach of predicting its development. An individualized approach and follow-up plan would still be beneficial in addressing symptoms after the acute phase of the disease.

RECOMMENDATIONS FROM OTHER GROUPS

The National Institute for Health and Care Excellence (NICE) defines post-COVID as the persistence of COVID-19 symptoms for more than 12 weeks with no other proven diagnosis. They recommend that patients diagnosed or suspected of having COVID-19 should be advised about the unique course of recovery of individuals (i.e., patients may have persistent symptoms or may develop new symptoms differently which can occur at different times) and that these are not dependent on the severity of their acute COVID-19 illness. An initial consultation is advised if symptoms persist for more than four weeks and a screening questionnaire should be used to capture all possible symptoms. Due to the wide symptomatology of COVID-19 and its post-acute phase, shared decision-making between the patients and healthcare workers should guide the course of monitoring and management.[10] The CDC likewise emphasized this shared decision-making framework in managing patients after their acute COVID-19 infection due to the incomplete understanding of post-COVID-19 symptoms.[11]

RESEARCH GAPS

Current knowledge on the natural course of COVID-19 including the duration of symptoms after the acute phase of the disease is still growing. Evidence is inconsistent because of the significant heterogeneity of the population base and multiple factors that have to be considered. There are currently 51 listed observational studies on Clinicaltrials.gov that aim to investigate the symptoms and laboratory findings of the post-acute phase of COVID-19. No study aimed to specifically investigate the risk factors or predictors of its development.

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Appendix 1. Evidence to Decision

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (7)					There is still a lot of uncertain information about long COVID as affected people present differently and with varied durations of symptoms.
Benefits	Large (2)	Moderate (1)	Small (2)	Uncertain (2)			A better understanding of long covid especially with the identification of the people who could possibly develop it can lead to better appropriation of resources for long-term patient support and services both at an individual and societal level
Harms	Large (1)	Moderate (1)	Small (4)	Uncertain (1)			
Balance of Benefits and Harms	Favors the use of using risk factors (1)	Probably favors the use of using risk factors (4)	Does not favor the use of risk factors (2)				
Certainty of Evidence	High (1)	Moderate	Low (3)	Very low (3)			Very low (from observational studies with varying results and significant heterogeneity)
Accuracy	Very Accurate (1)	Accurate (1)	Inaccurate (2)	Very Inaccurate (1)	Uncertain (3)		
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			
Resources Required	Uncertain (2)	Large cost	Moderate Cost (1)	Negligible cost or savings (4)	Moderate savings	Large savings	
Certainty of evidence of required resources	No included studies (2)	Very low (3)	Low (2)	Moderate	High (1)		
Cost effectiveness	No included studies (4)	Favors using risk factors (2)	Does not favor either using the risk factors or the comparator	Favors comparison (1)			
Equity	Uncertain (2)	Reduced (2)	Probably no impact	Increased (3)			
Acceptability	Uncertain (2)	No	Yes (5)				
Feasibility	Uncertain (3)	No	Yes (4)				

Appendix 2. Characteristics of Included Studies

Table 1. Characteristics of the included systematic reviews

Review Year Journal	Review aim	Search strategy	PICO	Data Analysis
Martimbianco et al 2021 Sao Paolo, Brazil *Int J Clin Pract.* [5]	To identify, systematically evaluate and summarise the best available evidence on the frequency of long COVID-19, the characteristics of its clinical manifestations, and the adopted criteria for its diagnosis, and potential risk factors	**Databases:** CINAHL, CENTRAL, EMBASE, Health Systems Evidence, LILACS, Caribbean Health Sciences Literature, MEDLINE, McMaster Daily News COVDI-19, Oxfird COVID-19 evidence service, WHO, opengrey database **Language restrictions:** none **Strategy:** (Pubmed) MeSH terms for COVID-19 OR SARS-CoV 2 AND long-COVID OR post-acute viral syndrome Extensive search strategy for each database available **Last date of search:** February 1, 2021 **Exclusion criteria:** single case reports, pre-print or no peer-review process	**Population:** patients with symptoms after COVID-19 disease or those considered to have long covid symptoms **Intervention:** follow-up assessment **Outcome:** primary outcomes: frequency of long COVID-19 or persistence of clinical manifestations after the acute phase as defined by the authors of the primary studies, frequency of signs and symptoms after the acute phase of COVID-19 Secondary outcomes: frequency of the criteria used to define long COVID-19, mean duration of long COVID-19, risk factors associated with the occurrence of long COVID-19 **Study design:** experimental, observational longitudinal comparative, cross-sectional, controlled or uncontrolled before-and-after studies, **Preprints:** not included **Definitions:** temporal criteria to define long-COVID varies from 3 to 24 weeks after acute phase or hospital discharge	**Risk of bias:** Cochrane Risk of bias tool for RCTs, ROBINS-1 for cohorts, case-control, before-after study, and non-randomised trials. Joanna Briggs Institute checklist for analytical cross-sectional studies, NIH quality assessment tool for case series and single arm cohorts. **Publication bias:** not assessed **Subgroup analysis:** none **Sensitivity analysis:** no meta-analysis **Statistical analysis** Random-effects meta-analyses using RevMan 5.4 Qualitative synthesis
Michelen *et al* 2021 *BMJ Globl Health* [6]	To synthesize and continually update the evidence on the character and prevalence of long COVID	**Databases:** Medline, CINAHL, Global health (Ovid), WHO Global research Database on COVID-19, Litcovid, google scholar **Language restrictions:** none **Strategy:** wide search strategy employed. Main strings of keywords and phrases associated with "long covid" "hospitalization" and "quarantine", "symptoms" and "complications". Full search strategy available **Last date of search:** March 17, 2021 **Exclusion criteria** <100 subjects, reviews and opinion pieces, unclear follow-up period or follow-up less than 12 weeks post onset	**Population:** laboratory confirmed and/or clinically diagnosed COVID-19 with symptoms or outcomes assessed at 12 or more weeks post COVID-19 onset **Intervention:** Follow-up assessment at 12 or more weeks after onset of COVID-19 **Outcome:** Signs and symptoms Imaging and diagnostics Risk factors **Study design:** All study design except for reviews and opinion pieces **Preprints:** excluded	**Risk of bias:** using validated tool for prevalence studies by Hoy et al. **Publication bias:** Funnel plot **Subgroup analysis:** Hospitalised, Non-hospitalised or mixed Physiologic clustering of symptoms Settings Continents Follow-up timing **Sensitivity analysis** Meta-regression analysis on percentage of females and ICU patients Freeman-Tukey double arcsine transformation using inverse variance to examine impact of high risk of bias **Statistical analysis:** Proportion of symptoms estimated using exact method. Random intercept logistic regression model with Hartung-Knapp modification I2 to assess heterogeneity Metaprop and ggplot2 in R (v.4.0.5) via RStudio (V.1.3.1093)

Table 2. Characteristics of the additional studies identified

Review Year Journal	PICO	Data Analysis	Key Findings
Liu, et al, 2021 Quant Imaging Med Surg [7]	**Population**: COVID-19 survivors discharged from Chonqing University Three Gorges Hospital from Feb 10,2020 to March 15, 2020 China **Intervention**: Chest CT imaging (non contrast enhanced) using one of two standard machines. Imaging taken at the supine position Cardiopulmonary exercise texting on a treadmill **Control**: CT at admission, at discharge, at 1, 3 and 6 months after discharge **Outcome**: Total opacity score, lung volume, volume of opacity, percentage of opacity *Pulmonary function* **Method**: prospective cohort study (single center) **Exclusions**: -did not undergo CT scan at admission or discharge -had mild type COVID-19 -had history of lung cancer, tuberculosis or interstitial lung disease	**Risk of bias:** Cochrane RoB tool for cohorts (low) **Statistical analysis** Kolmogorov-Smirnov analysis to test variance in homogeneity Continuous variables compared using 2 independent samples t-test (homogeneity of variance) or Mann-Whitney U test (heterogeneity of variance) Categorical variables compared by the X^2 test or Fisher's exact test between groups	N=52 (26 male, 26 female) 32 moderate20 severe Median age 50.5 (IQR 41.3-57) 39/52 with complete resolution (28 in moderate group, 11 in severe group, p< 0.001) **Risk factors of incomplete resolution at 6 months (using chi square test):** Age > 50 years old (p<0.004) Severe COVID-19 (p<0.008) Hospital stay > 18 days (p<0.006) Mechanical ventilation (p<0.002) Steroid therapy (p<0.002) immunoglobulin therapy (p<0.004) Opacity score >4 at discharge (p<0.001) Volume of opacity at discharge > 235 ml (p<0.001) Males and females no difference (p<0.749
Wallis et al, 2021 Respir Res [8]	**Population**: Hospitalized COVID-19 patients in University Hospital Southampton NHS Foundation Trust seen for virtual check-up after 12weeks, UK **Intervention**: On follow-up 12 weeks after discharge, chest radiograph and blood tests obtained **Control**: Baseline and 12-week follow-up chest radiograph severity score **Outcome**: chest radiograph severity score resolution vs persistence **M**: prospective cohort study (single center) **Exclusions**: Discharged to a nursing home, had severe dementia, had metastatic malignancy with less than 1 yr predicted survival rate	**Risk of bias:** Cochrane RoB tool for cohorts (low) **Statistical analysis** Between group comparisons for continuous variables using Mann-Whitney U test Correlation between continuous variables using Spearman's correlation coefficients Difference in distribution of categorical variables between independent groups using chi square test or Fisher's exact test Time to event analysis using cox regression analysis	N=101 (53.5% male) Median age 53.0 (IQR, 45-63) Clinical outcomes: 65% had one or more persistent symptoms Fatigue (41%) Breathlessness (38%) 32/101 (31.6%) had persistent chest radiograph changes **Risk factors** Longer length of stay (20.5 vs 8 days, p< 0.01) HR 1.060 (1.032-1.090) Current or previous smokers (56% vs 23%, p <0.02) HR 3.286 (1.352-7.982) Obesity HR 2.717 (1.114406.454) Not significant Admission to level 2 or 3 facility (45% vs 19%, p 0.01)□ not statistically significant after Age Oxygen support Ethnicity Asthma diabetes Hypertension Sex

Review Year Journal	PICO	Data Analysis	Key Findings
Pilotto et al, 2021 Neurological Sciences [9]	**Population**: COVID-19 survivors discharged between February and April 2020 from a COVID-19 unit of the ASST Spedali Civili Brescia Hospital, Italy **Intervention**: Follow-up study at 6 months (standard evaluation od med history, self-reported neurological symptoms and complete neurologic exam) **Outcome:** Presence of neurological signs and symptoms, Risk factors **Method**: longitudinal study **Exclusions**: premorbid neurologic conditions	**Risk of bias:** Cochrane RoB tool for cohorts (low) **Statistical analysis** Dichotomous variables Fisher's exact test Continuous variables using ANOVA with Bonferroni correction Univariable and multivariable logistic regression models to assess risk factors	N=165 Symptoms at follow-up Fatigue (34%) Memory complaints (31.5%) Sleep disorders (31.5%) Myalgia (30.3%) Depressive symptom/anxiety (26.7%) **Risk factors** Moderate/severe group increased risk for: Memory complaints OR 2.6, 95% 1.18-5.8) Decrease in independency in ADL OR 2.6 (95% CI, 1.12-6.2) Confusion OR 2.9 (95%CI, 1.12-7.8) Fatigue OR2.1 (95% CI, 0.95-4.6) Visual disturbance OR 3.5, 95% CI (1.5-8.4) Predictors for symptoms development: Premorbid comorbidities (p=0.006, beta 0.26) Age at admission (p=0.04, beta 0.17) Severity (p=0.04, beta 0.22) Predictors for neurologic abnormalities: Duration of hospitalization (p=0.02) Premorbid comorbidities (p=0.03)

Appendix 3. Detailed Study Appraisal

Table 1. Assessment of included studies using AMSTAR

AMSTAR Items	Iqbal[4] (2021)	Martimbianco[5] (2021)	Michelen[6] (2021)
Date of last search	March 2021	February 1,2021	March 17,2021
Rating of overall confidence in the results of the review[§]	**LOW**	**HIGH**	**HIGH**
1. Research questions, inclusion criteria include PICO components	YES	YES	YES
2.* Protocol registered before commencement of the review	YES	YES	YES
3. Selection of study designs to be included were explained	YES	YES	YES
4.* Adequacy of literature search	YES	YES	YES
5. Study selection done by at least 2 reviewers	YES	YES	YES
6. Data extraction done by at least 2 reviewers	YES	YES	YES
7.* Justification for excluding individual studies	YES	YES	YES
8. Described included studies in adequate detail	YES	YES	YES
9.* ROB from individual studies being included in the review	YES	YES	YES
10. Reported sources of funding for studies included	NO	YES	YES
11.* Appropriateness of meta-analytical methods	YES	YES	YES
12. Potential impact of ROB in individual studies	YES	YES	YES
13.* Consideration of ROB when interpreting review results	YES	YES	YES
14. Sufficient explanation of heterogeneity	YES	YES	YES
15.* Assessment of presence and likely impact of publication bias	NO	NO	YES
16. Reported potential COI sources, funding they received	YES	YES	YES

NOTES:

[§] AMSTAR-2 rating for overall confidence.

*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.

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

Table 2. Risk of bias assessment using Cochrane risk of bias tool for observational studies

Study	Selection	Exposure	Outcome at start	Adjustment	Prognostic factors	Assessment of outcome	Follow-up	Co-interventions	Risk of Bias
Liu	Y	Y	N/A	Y	Y	Y	Y	Y	Low
Wallis	Y	Y	N/A	Y	Y	Y	Y	Y	Low
Pilloto	Y	Y	Y	Y	Y	Y	Y	Y	low

Table 3. Methodological quality of included studies in Martimbianco et al., using the NIH Quality Assessment Tool for Case Series Studies

Criteria/Judgment		1	2	3	4	5	6	7	8	9	Score	%	Quality*
1	Bellan 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
2	Carfi 2020	No	Yes	Yes	Yes	NA	Yes	NA	No	Yes	5/7	71.4	Moderate
3	Carvalho-Schneider 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
4	El Sayed 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
5	Garrigues 2020	No	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
6	Guedj 2020	No	Yes	Yes	Yes	NA	No	NA	Yes	Yes	6/7	85.7	High
7	Halpin 2020	No	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
8	Huang 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
9	Jacobs 2020	No	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	6/7	85.7	High
10	Liang 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
11	Lu 2020	Yes	Yes	Yes	Yes	NA	No	NA	Yes	Yes	6/7	85.7	High
12	Moreno-Perez 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
13	Nehme 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	No	No	5/7	71.4	Moderate
14	Otte 2020a /Otte 2020b	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	No	6/7	85.7	High
15	Petersen 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
16	Puchner 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
17	Ramani 2021	No	Yes	Yes	Yes	NA	Yes	NA	No	No	4/7	57.1	Moderate
18	Rosales-Castillo 2021	No	Yes	Yes	Yes	NA	Yes	NA	NA	Yes	5/6	83.3	High
19	Roth 2021	No	Yes	Yes	Yes	NA	Yes	NA	NA	Yes	5/6	83.3	High
20	Simani 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
21	Suarez-Robles 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	NA	Yes	6/6	100	High
22	Tarazona-Fernandez 2020	No	Yes	Yes	Yes	NA	Yes	NA	NA	No	4/6	66.7	Moderate
23	Van den Borst 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
24	Xiong 2021	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7/7	100	High
25	Zhao 2020	No	Yes	Yes	Yes	NA	No	NA	Yes	No	4/7	57.1	Moderate

NA: not applied; NR: nor reported.

NIH Quality Assessment Tool for Case Series Studies

*(1) Was the study question or objective clearly stated? (2) Was the study population clearly and fully described, including a case definition? (3) Were the cases consecutive? (4) Were the subjects comparable? (5) Was the intervention clearly described? (6) Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? (7) Was the length of follow-up adequate? (8) Were the statistical methods well-described? (9) Were the results well-described? * Considering the frequency of compliance with the relevant items, at the discretion of the review authors, the studies were categorized as presenting: high quality (80% or more of accomplished items), moderate quality (=>50% to <80%) or low quality (< 50%).*

Table 4. Risk of Bias assessment for studies included in the SR by Michelen et al.

Study	Representation of national population (e.g. age, sex, occupation)	Sampling frame true or close representation of target population	Random selection used to select sample, OR, census undertaken	Likelihood of non-response bias minimal	Data collected directly from subjects (opposed to proxy)	Acceptable case definition used	Instrument to measure parameter of interest has reliability and validity (if necessary)	Same mode of data collection used for all subjects	Length of shortest prevalence period for parameter of interest appropriate	Numerator(s)/ denominator(s) for parameter of interest appropriate	Overall risk of bias
Alharthy et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Anastasio et al.	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Arnold et al.	High risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Baricich et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High risk	High risk
Bellan et al.	High risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Blanco et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Doyle et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Einvik et al.	High risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Garrigues et al.	High risk	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High risk
Gherlone et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High risk	High risk
Han et al.	High risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Hopkins et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	High risk
Huang et al.	Low Risk	Low Risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Jacobson et al.	High risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Klein et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	High risk
Lerum et al.	High risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High risk	Low Risk	Moderate risk
Logue et al.	High risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Mazza et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Mendez et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High risk	Low Risk	High risk
Nguyen et al.	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Moderate risk
Nugent et al.	High risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Parente-Arias et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Petersen et al.	Low Risk	Low Risk	High risk	High risk	Low Risk	Low Risk	High risk	Low Risk	High risk	Low Risk	High risk
Qin et al.	High risk	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High risk
Qu et al.	Low Risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Rass et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Sibila et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High risk	High risk
Simani et al.	Low Risk	Low Risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Sonnweber et al.	High risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Stavem et al.	Low Risk	High risk	High risk	Low Risk	Low Risk	Low Risk	High risk	Low Risk	High risk	Low Risk	High risk
Suarez-Robles et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Sykes et al.	High risk	Low Risk	Low Risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Taboada et al.	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Venturelli et al.	Low Risk	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Weng et al.	High risk	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High risk	High risk
Xiong et al.	Low Risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Xu et al.	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate risk
Zhang et al. (a)	High risk	High risk	High risk	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High risk	High risk
Zhang et al. (b)	High risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Low Risk | Moderate risk | High risk

Appendix 4. Results of Included Studies

Table 1. Long COVID symptoms reported in the included studies

Study	Symptoms by system								
	Cardio-Pulmonary	Gastro-intestinal	Musculo-skeletal	Neuro-cognitive	Neurologic and neuro-muscular	Psychological and social	Systemic	Upper respiratory	Others
IQBAL ACUTE POST COVID Symptom proportion (# of studies) (95% CI) Total (T) Subgroup analysis based on Community (C) Previously hospitalized (H) Mixed (M)	Cough T (5): 0.07 (0.03-0.11) C (1) 0.14 (0.07-0.24) H (3): 0.07 (0.05-0.10) M (1): 0.03 (0.01-0.05) Dyspnea T (6): 0.35 (0.16-0.56) H (5): 0.41 (0.32-0.51) M (1): 0.05 (0.04-0.08)				Ageusia T (7): 0.20 (0.07-0.36) C (3): 0.41 (0.21-0.62) H (3): 0.06 (0.01-0.14) M (1): 0.14 (0.08-0.21) Anosmia T (9) 0.21 (0.11-0.33) C (5) 0.51 (0.42-0.61) H (3): 0.06 (0.02-0.13) M (1): 0.07 (0.04-0.13)	Depression T (3): 0.20 (0.09-0.33) H (2): 0.14 (0.08-0.21) M (1) 0.31 (0.27-0.36)	Fatigue: T (9): 0.37 (0.20-0.56) C (3): 0.15 (0.11-0.19) H (4): 0.62 (0.54-0.71) M (2): 0.26 (0-0.69)		
CHRONIC POST COVID	Cough T (5): 0.11 (0.07-0.17) H (3): 0.16 (0.12-0.20) M (2):0.07 (0.05-0.09) Chest pain/tightness T (6): 0.17 (0.05-0.35) H (2): 0.10 (0.06-0.14) M (4): 0.21 (0.05-0.44) Dyspnea T (7): 0.39 (0.16-0.64) H (4): 0.43 (0.35-0.52) M (3): 0.32 (0.01-0.80)				Ageusia T (6): 0.18 (0.10-0.28) C (2): 0.21 (0.11-0.33) H (1): 0.11 (0.06-0.17) M (3): 0.18 (0.05-0.37) Anosmia T (8): 0.17 (0.10-0.25) C (2): 0.34 (0.15-0.55) H (3): 0.16 (0.12-0.20_ M (3):0.09 (0.03-0.19) Headache T/M (3): 0.12 (0-0.44)		Fatigue: T (9): 0.48 (0.23-0.73) C (3): 0.61 (0.09-0.99) H (2): 0.47 (0.32-0.63) M (4): 0.38 (0.04-0.82)		Sleep disturbance T (4): 0.44 (0.08-0.85) C (1): 0.88 (0.86-0.89) H: 0.28 (0.23-0.33)

Study	Symptoms by system								
	Cardio-Pulmonary	Gastro-intestinal	Musculo-skeletal	Neuro-cognitive	Neurologic and neuro-muscular	Psychological and social	Systemic	Upper respiratory	Others
Martimbianco	Any CV symptom N=1 13% Chest pain N= 7 studies 0.4-89% Cough/sputum production N= 13 studies 1.8-59% Dyspnea N= 16 studies 5.5-61% Palpitations N= 4 studies 9-62%	Diarrhea and GI symptoms N= 9 studies 1.3-33% Fecal incontinence N= 1 study 3% Lack of appetite N= 2 studies 6.2-8%	Arthralgia N= 9 studies 5.9-54.7% Limb numbness N= 1 study 6.6% Limb edema N=1 study 2.6% Myalgia N= 10 studies 2-50.6% Mobility dysfunction N= 2 studies 6.6-7%	Cognitive/memory/ concentration impairment N= 9 studies 18-57.1%	Ageusia/dysgeusia (N=15 studies) 1-21.6% Anosmia (N=19 studies) 0-26.2% Headache N= 10 studies 2-39% Hearing loss N=1 study 1.6% Sensitivity d/o 1 study 7.5% Tremor 1 study 1.6% Vision changes 1 study 1.6%	Communication difficulty N=1 6% Depression and anxiety N= 5 studies 3-25% PTS/mood changes/ psychological symptoms N= 5 studies 5.8-57.1% Functional impairment N= 2 studies 5.7-50% Physical dysfunction N= 4 studies 4-28.3% Sleep disturbance N= 5 studies 21.7-53%	Chills N= 1 study 4.6% Fatigue/asthenia N= 17 studies 6.6-64% Fever N= 6 studies 0-20% Pain and discomfort N= 3 studies 19-66% Vertigo/dizziness N= 3 studies 2.6-6%	Rhinitis 1 study 16.7% Red eyes 1 study 13.9% Sore throat/throat pain N= 5 studies 3.2-11%	Cutaneous signs N=4 studies 1.5-20% Hair loss N= 3 studies 20-28.6% Laryngeal sensitivity N= 1 study 17% Swallow problem 1 study 8% Sweating 1 study 23.6% Urinary incontinence 1 study 10% Voice change 1study 20%
Michelen Subgroup analysis Hospitalised (H) Non-hospitalised (c) Mixed (M) (N studies), proportion (95% CI)	Breathlessness/ dyspnea H (14): 28.68 (18.48-41.64) M (3): 32.57 (14.26-58.38) C (4) 13.72 (8.51-21.37) Chest pain H (11): 5.92 (2.45-13.63)	Diarrhea H (7): 2.93 (0.9-9.12) M (1): 8.89 (5.12-15) C (3) 4.16 (0.72-20.65) Nausea or vomiting H (2) 5.84 (0-100)	Impaired mobility H (5): 17.33 (4.75- 46.83) M (1): 5.19 (2.49-10.48) Joint pain/ arthralgia H (8): 9.36 (5.25-16.14) C (1): 9.31 (6.95-12.36)	Confusion M (4): 10.86 (3.45-29.36) C (1): 9.31 (6.95-12.36) Memory impairment H (3): 34.78 (23.64-47.88 M (2): 8.06 (0-99.97)	Decreased sensation or sensibility H (1) 7.46 (4.06-13.31) M (1): 14.81 (9.76-21.85) Headache H (5): 2.98 (0.47-16.53) M (3): 3.30 (0.12-50.2)	Anxiety H(4): 25.58 (6.36-63.49) M (3): 11.60 (6.03-21.15) Care dependency H (1) 1.55 (1.05-2.29) M (2): 12 (0.39-82.45) Depression	Dizziness H (2) 4.21 (0.08-83.74 M (2): 3.78 (0.03-83.74) C (1): 6.68 (4.68-9.45) Fatigue H (11): 37.10 (26.45-49.06) M (3) 21.04 (10.48-37.75)	Nasal congestion H (1): 4.55 (0.64-26.15) C (3): 4.99 (2.72-8.99) Other respi symptoms H (2): 32.43 (2.22-91.02) C (1): 2.88 (1.68-4.9)	Hair loss H(4): 23.54 (17.68-30.61) M (1): 3.17 (1.81-5.49) C (1): 10.42 (5.70-18.29) Skin rash H (3): 3.53 (0.75-15.11) C (1): 1.55 (0.74-3.22)

Study	Symptoms by system								
	Cardio-Pulmonary	Gastro-intestinal	Musculo-skeletal	Neuro-cognitive	Neurologic and neuro-muscular	Psychological and social	Systemic	Upper respiratory	Others
	M (2): 6.18 (0.01-97.66) C (1) 14.58 (8.83-23.13) Cough H (11): 10.52 (5.93-17.98) M (3): 4.91 (0.25-51.82) C (3) 5.95 (1.53-20.5) Excessive sputum/ expectoration H (5): 6.02 (3.2-11.03) C (1): 3.55 (2.18-5.71) Other CVS symptoms H (2): 4.2 (0-99.97) M (1): 0.13 (0.02-0.92) Palpitations H (6): 12.43 (7.78-19.29_ M (2): 4.67 (0.60-28.47) C (1): 7.29 (3.52-14.51)	M (1): 8.89 (5.12-15) C (2): 3.66 (0-98.24) Stomach/abd pain H (2): 4.63 (0.03-89.2) M (1): 0.65 (0.27-1.56) C (1): 3.33 (2.01-5.44) Weight loss H (1): 37.31 (29.55-45.79) C (1): 10.83 (8.23-14.12)	Muscle pain/myalgia H (7): 12.46 (4.3-31.09) M (4): 10.86 (3.45-29.36) C (2): 10.76 (0.24-85.64)	C (1): 15.62 (9.64-24.32) Other cognitive impairment H (1): 9.7 (5.72-15.99) M (2): 23.55 (0-100)	C (4): 8.82 (4.41-16.85) Smell disturbance H (9): 12.16 (7.98-18.1) M (6): 14.63 (5.46-33.72) C (5): 22.19 (11.69-38.04) Taste disturbance H (8): 11.07 (6.9-17.28) M (5): 14.5 (3.4-44.98) C (5): 16.83 (7.91-32.26) Tingling/paresthesia H (1): 3.28 (1.24-8.41) M (1): 21.48 (15.36-29.21) Tremors H (1): 4.65 (3.16-6.79) M (1): 9.63 (5.67-15.88) C (1) 0.89 (0.33-2.34) Visual disturbance M (1): 6.67 (3.5-12.32) C (1) 4.21 (2.7-6.51) Walking/gait abnormality H (2) 4.01 (0.34-33.61) M (1) 5.19 (2.49-10.48)	H (2) 10.38 (0-9.83) M (4) 6.8 (3.99 11.37) Low mood/ dysphoria H (2): 9.49 (0-100) M (1): 0 (0-100) PTSD H (3) 10.52 (3.06-30.44) M (3) 8.73 (0.46-66.23) C (1) 7.03 (5.02-9.78) Reduced QoL H (1) 47.96 (43.77-52.18) M (2) 30.34 (7.43-70/27) Sleep disorder H (5): 25.81 (18.85-34.26) M (4): 10.66 (1.76-44.22)	C (4): 24.6 (20.11-29.72) Fever H (4) 0.85 (0.02-24.2) M (1) 21.04 (10.48-37.75) C (3): 1.41 (0.06-24.82) Sweat or night sweats H (1) 23.61 (20.21-27.38) M (1) 24.14 (17.87-31.76) Weakness H (1): 54.48 (46-62.7) M (1) 29.82 (25.42-34.61)	Sore throat H (4) 4.81 (1.6-13.6) M (2) 4.39 (0.32-39.44)	

Table 2. Symptoms associated with the development of long COVID as reported by the included studies

Studies	Factors (Studies)	Long COVID symptoms associated with (if specified)
Martim-bianco [5] (14 studies)	**Severity** (9 studies)	● 1 study: **hospital admission** during the acute phase **led to persistent symptoms** ● 2 studies: **hospital admission had no effect** to development of persistent symptoms ● 1 study: **ICU admission led to functional impairment** on follow-up ● 3 studies: **ICU admission has no association** with any long covid symptoms ● 1 study: mild to moderate symptoms had higher risk for dyspnea compared to those with severe disease during the acute phase ● 1 study: those with severe disease requiring HFNC, NIV or MV were at risk to develop dyspnea, fatigue or muscle weakness, mobility problems, pain or discomfort, anxiety or depression and a DLCO of < 80%
	Specific symptoms (2 studies)	● 2 studies: **no specific symptoms** were found to be predictive of long covid based
	Age (10 studies)	● 4 studies: **no association for age** and prolonged symptoms of COVID-19 ● 6 studies: **older age led to symptoms of long covid**, including functional impairment, dyspnea, fatigue or muscle weakness, and persistence of symptoms during the acute phase
	Sex (8 studies)	● 3 studies: **female sex** was associated with fatigue or muscle weakness, anxiety or depression and persistent symptoms ● 1 study: **male sex** was associated with fatigue or muscle weakness ● 4 studies: **no association** with any long covid symptoms
	Comorbid condition (5 studies)	● 1 study: **COPD was linked** to functional impairment ● 4 studies: **comorbid conditions are not predictive** of long covid symptoms
	Others	● Other investigated factors that were **not seen to be associated** with long covid were smoking status (1 study), educational level (1 study), treatment received during the acute phase (2 studies) and inflammatory markers (1 study)
Michelen [6] (39 studies)	**Severity** (22 studies)	**Dyspnea/shortness of breath during acute phase** ● 3 studies: RF for persistent symptoms in general, physical decline, fatigue, polypnea and increased resting heart rate ● 1 study: not associated **Prolonged hospital stay** ● 2 studies: RF for lung pathology and limitation of functional status **Admission to ICU/requiring mechanical ventilation** ● 7 studies: RF for limitation of functional status/physical impairment, persistence of symptoms, DLCO < 80%, persistent CT abnormalities, new neurologic symptoms, anxiety, dyspnea and fatigue ● 2 studies: not RF **Pneumonia/lung pathology during acute phase** ● 2 studies: RF for dyspnea and increase pulmonary CT imaging findings ● 5 studies: severity not associated with any symptoms
	Age (6 studies)	● 6 studies: older age is a risk factor for the development of functional impairment, persistence of initial symptoms, mobility problems, sleep or neurologic disturbance, and poor quality of life scores
	Sex (10 studies)	● 8 studies: female gender is reported to be associated with a risk for functional impairment, persistence of initial symptoms, fatigue or muscle weakness, pain or discomfort, anxiety or depression, DLCO < 80%, sleep disturbance and poor quality of life scores ● 2 studies: male gender thought to be a risk for mobility problem and spirometric abnormality on follow-up
	Comorbid condition (7 studies)	● 7 studies: presence of comorbid conditions is associated with increased risk for functional impairment, persistence of initial symptoms, mobility problems, anxiety or depression and spirometric abnormality
Additional studies identified		
Liu	● Age more than 50 years old, severe COVID-19 status during the acute phase, hospital stay >18 days, mechanical ventilation, steroid or immunoglobulin therapy were associated with incomplete resolution of pulmonary pathologies imaged via a chest CT scan. ● Having an imaging opacity score of >4 and volume of opacity >235 mL at discharge were predictive of persistence of pulmonary findings after 6 months of the initial infection. ● Sex was not associated with persistence of pulmonary pathology.	

Studies	Factors (Studies)	Long COVID symptoms associated with (if specified)
Wallis		● Among admitted patients with COVID-19, those who had a longer hospital stay (20 days or more), were current or previous smoker and who are obese were more prone to have persistence of pulmonary abnormalities on chest radiographs after 12 weeks of discharge. ● Severity of condition, age, oxygen support, sex, ethnicity, and comorbid conditions such as asthma, diabetes or hypertension were not associated with persistence of chest x-ray findings
Pilloto		● Those with moderate to severe conditions during the acute phase of infection had an increased risk for memory problems, functional impairment, confusion, fatigue and visual disturbance ● An older age, presence of comorbidities, and more severe condition had more symptoms at follow-up ● Longer duration of hospitalization and presence of comorbidities were associated with neurologic abnormalities on follow-up

Table 3. Risk factors associated with individual symptoms of long COVID

Symptom	Risk factor	Description
Fatigue	Severity	● One study stated that those who required HFNC, NIV or MV during the acute phase were at increased risk to develop fatigue (OR 2.69, 95%CI 1.46-4.96) ● One study reported that patients that had fatigue had more severe disease during the acute phase (p <0.02) ● One study reported that those with moderate to severe condition had increased risk to develop fatigue on follow-up (OR 2.1, 95% CI 0.95-4.6)
	Older age	● Older population was at risk for fatigue in one study (OR 1.17, 95%CI 1.07-1.27) ● Another study stated that the age group of 41-60 years old (47%) and 61-80yrs old (42%) had less incidence of fatigue compared to 20-40yrs old (11%)
	Sex	● Female sex was associated with fatigue in one study (OR 1.33, 95%CI, 1.05-1.67). ● Another study reported that 66% of those with fatigue were females. ● One study found that male sex was more predisposed to fatigue (OR 2.65, 95%CI 1.07-6.9)
Dyspnea	Severity	● One study said that dyspnea on follow-up was worse in mild cases compared to moderate to critical patients (p<0.001) ● This was countered by one study that said those requiring HFNC, NIV or MV were prone to develop dyspnea (OR 2.15, 95%CI 1.28-3.59) ● Two studies also said that severity of initial symptoms were predictive of dyspnea (p=0.001, p <0.05)
Sleep disturbance	Severity	● Severity of initial symptoms are predictive according to one study (p=0.001)
	Sex	● Female were at risk according to one study (p=0.009)
Functional impairment	Severity	● ICU admission is a risk factor for functional impairment according to one study (OR 2.59, 95% CI 1.06-6.36) ● The severity ofa initial symptoms are also predictive of functional impairment (OR 3.1, 95%CI 1.3-7.9)
	Old age	● Old age was predictive according to three studies ○ OR 0.96 (95% CI 0.93-0.99) ○ p=0.028 ○ OR 2.6 (95%CI 1.19-5.67)
	Comorbids	● Presence of comorbidity is RF according to one study (p=0.031) while another study specified COPD as a predictive factor COPD (OR 12.7, 95% CI 1.41-1114.85)
	Sex	● Females are at risk for functional impairment according to one study (p= 0.003).
Anxiety/depression or any psychiatric symptoms	Severity	● Those requiring HFNC, NIV, MV during the acute phase were prone to develop these symptoms (OR 1.77, 95% CI 1.05-2.97) ● Severity of initial symptoms specifically neuropsychiatric symptoms (p=<0.001) and GI symptoms (p=0.016)
	Sex	● Female sex was more associated with anxiety/depression or any psychiatric symptoms with an OR of 1.8 (95%CI 1.39-2.34) in one study. This is supported by two other studies with p=0.003 and p=0.001. ● One study found no difference between males and females

Appendix 5. Significant risk factors for long COVID

Source: Michelen, et al. BMJ Global Health 2021; 6:e005427. doi: 10.1136/bmjgh-2021-005427

Supplement 14: Risk factors

Study	Category	Risk factor	Associated with	Method	P Value/ CI
Nguyen et al.	Sex	Female sex	Persistent symptoms	Chi-squared or the Fisher exact test	p = 0.02
Mazza et al.	Sex	Female sex	Persistence of depressive symptomatology	Multivariate GLM analysis	(Wilks' λ = 0.92; F = 5.76; p = 0.003)
	Comorbidities	Previous psychiatric diagnosis			(Wilks' λ = 0.93; F = 5.29; p = 0.006)
	Severity	Presence of psychopathology at one-month			(Wilks' λ = 0.82; F = 15.16; p < 0.001)
Parentes-Arias et al.	Age	<60 years	Olfactory dysfunction	Multivariable-adjusted ORs	p = 0.028
	Sex	Female sex			p = 0.003
	Comorbidities	1 comorbidity			p = 0.031
Xiong et al.	Sex	Female sex	Covid-19 sequelae	Multivariable logistic regression model	Physical decline/fatigue (p < 0.01) Postactivity polypnoea (p= 0.04) Alopecia (p < 0.01)
	Severity	Dyspnea during hospitalisation	Physical decline/fatigue, postactivity polypnoea and resting heart rate increases	Univariate analysis	Physical decline/fatigue (p=.02) Postactivity polypnoea (p=.01) Resting heart rate increases (p=.01)
Sykes et al.	Sex	Female sex	Persistent symptoms	Chi-Square and Mann–Whitney U testing	Anxiety (p=0.001),low mood (p=0.031), myalgia (p=0.022), fatigue (p=0.004), sleep disturbance (p=0.009), and memory impairment (p=0.001)
Taboada et al.	Age	Age	Limitations in the functional status (grade II-IV of PCSF)	Multivariate logistic regression model	(OR = 2.600, 95% CI: 1.192–5.671)
	Severity	Length of hospital stay			(OR = 1.049, 95% CI: 1.009–1.090)
	Severity	Admission to ICU / mechanical ventilation			P < 0.001
Qu et al.	Sex	Female sex	Poor QoL scores	Logistic regression	(OR: 1.79, 95% CI: 1.04–3.06)
	Age	Older age (≥60 years)			(OR: 2.44, 95% CI: 1.33–4.47)
	Severity	Physical symptom after discharge			(OR: 40.15, 95% CI: 9.68–166.49)
Einvik et al.	Sex	Female sex	Symptoms of post-traumatic stress	Multivariable linear regression	NR
	Ethnicity	Born outside Norway			

	Severity	Dyspnoea during COVID-19			
Gherlone et al.	Comorbidities	COPD	Dry mouth	Multivariable analysis	(OR= 9.10, 95% CI: 1.8 -68.49)
Stavem et al.	Severity	Number of symptoms (10–23)	Symptoms at follow-up	Multivariable negative binomial regression analysis	(OR= 4.16, 95% CI:2.57 to 6.72, p<0.001)
	Comorbidities	≥2			(OR=2.52, 95%CI: 1.58 to 4.02, p<0.001)
Baricich et al.	Severity	ICU admission	Physical impairment	Multivariable logistic regression model	(OR: 3.1, 95%CI: 1.3-7.9, p=0.01)
	Age	Age	walking ability (SPPB)		p <0.02
	Comorbidities	Number or comorbidities	walking ability (SPPB) 2MWT		p <0.01 p <0.04
	Sex	Male gender	SPPB total score		p <0.01
Jacobson et al.	Ethnicity	Latin ethnicity	lower expected 6-MWT	Multivariate analysis	(-7.40 [-11.55-{-3.25}], p=0.001
	Comorbidities	BMI			(-0.52 [-0.81-{-0.22}], p=0.001)
	Severity	Persistence of symptoms at follow up	Shortness of breath		P=0.004
Petersen et al.	Age	Individuals in age group 50-66 compared with the youngest groups: 0-17 years 18-34 years	Persistent symptoms	Age-stratified analysis	p=0.003 p=0.001
Alharthy et al.	Severity	Increased incidence of dyspnoea and fever prior to hospital admission, decreased ICU admission PaO2/FiO2 ratio < 100, longer duration of mechanical ventilation, increased inflammatory biomarkers such as lactate dehydrogenase, ferritin, and D-dimers on ICU admission, and significant lung abnormalities detected by LUS	Persistent symptoms	Continuous variables using the Wilcoxon rank sum or the student's t-test. Categorical variables were examined using the Fisher's exact test or the Chi square test	p < 0.05

Anastasio et al.	Severity	Pneumonia and ARDS	Shortness of breath	Pearson's correlation coefficient and Cox regression were used	Patients who developed ARDS showed higher SBP (p=0.05) and DBP (p=0.02) and lower SpO2 during 6 MWT (p=0.004), FVC (p=0.004) and TLC (p<0.001). Patients without ARDS showed higher SR (p<0.001), RV (p<0.001), TLC (p<0.001) and RV/TLC (p=0.05).
Han et al.	Severity	Higher baseline CT lung involvement score (>=18 out of a possible score of 25)	Fibrotic-like changes in the lung at 6 months	Multivariate analysis	(OR: 4.2, 95%CI: 1.2-14)
Blanco et al.	Severity	Severity of the disease	DLCO <80% and a lower serum lactate dehydrogenase level	Multivariate analysis	DLCO<80% (OR 5.92; 95%CI 2.28–15.37; p < 0.0001) Serum lactate dehydrogenase (OR 0.98; 95%CI 0.97–0.99)
Lerum et al.	Severity	ICU admission	Persistent CT abnormalities and problems in usual activities	Mann–Whitney U-tests or Chi-squared tests	p=.031
Bellan et al.	Severity	Higher DLCO	Decreased risk of physical impairment	Univariate analysis and logistic regression models	(OR, 0.96 [95% CI, 0.94-0.98]; P < .001)
	Comorbidities	COPD	Increase risk of physical impairment		(OR, 12.70 [95% CI, 1.41-114.85]; P = .02)
Sonnweber et al.	Severity	Age, gender, and pre-existing diseases such as cardiovascular diseases, pulmonary diseases, diabetes mellitus type 2, and malignancy	Persistence of symptoms, patient performance status, and CT findings at follow-up	Friedman's or Wilcoxon signed-rank test	p=0.042 to p<0.001
Mendez et al.	Sex	Female sex	Impaired DLCO	Linear regression analysis	0.002
	Severity	ICU patients	Pulmonary embolism		p<0.001
		D-dimer levels	Impaired DLCO		p= 0.011
Blanco et al.	Severity	Lower serum LDH levels	Impaired DLCO	Multivariate analysis	OR 0.98; 95% CI 0.97-0.99; p 0.002
Qin et al.	Severity	Higher TSS of the chest and ARDS lymphocyte count, MPA diameter on admission and ARDS	Impaired DLCO	Univariable analysis	TSS>10.5 (OR: 10.5; 95%CI: 2.5-44.1; P=0.001) ARDS (OR: 4.6; 95%CI: 1.4-15.5; P=0.014)
		Long hospital stay	Lung sequelae		
Rass et al.	Severity	ICU patients	New neurological diseases	Chi-square or Kruskal-Wallis test	P=0.001
	Age	Elderly	Neurological signs	NR	NR
Weng et al.	Severity	Less severe (Lower frequency of supplemental oxygen therapy (79% vs 94%; p=0·016), and lower frequency of ICU admission	Gastrointestinal sequelae	Univariable and multivariable logistic regressions	p=0·016
		Treated more often with proton pump inhibitors (PPIs) and corticosteroids and were less frequently treated with enteral nutrition			PPI (p=0.000) Corticosteroids (p=0.024) Enteral nutrition (p=0.007)
Arnold et al.	Severity	Severe cases	Lower physical score	Mann Whitney-U and Kruskal Wallis tests for continuous data and Fisher's exact test or Chi-squared testing for categorical data.	NR
Sibila et al.	Sex	Male gender	Spirometric abnormalities 3 months after discharge,=	NR	Reduced FEV1: (76.9% vs 51.2%, p = 0.005) Reduced FVC: (76.3% vs 51.6%, p = 0.008)
	Comorbidities	Cardiovascular disease and diabetes			Reduced FEV1: Cardiovascular disease (34.2% vs 9.4%, p = 0.001) Diabetes (28.9% vs 12%, p = 0.02) Reduced FVC: Cardiovascular disease (29.7% vs 11.0%, p = 0.009)
Huang et al.	Severity	Participants with severity scale 5–6	Higher risk of lung diffusion impairment, anxiety or depression, and fatigue or muscle weakness	Multivariable analysis	OR 4·60 (95% CI 1·85–11·48) for diffusion impairment, OR 1·77 (1·05–2·97) for anxiety or depression, and OR 2·69 (1·46–4·96) for fatigue or muscle weakness
	Sex	Female sex			

ARDS: Acute respiratory distress syndrome; BMI: Body mass index; CT: Computerised Topography; DCLO: diffusing capacity for carbon monoxide; ICU: Intensive care unit; LDH: Lactate dehydrogenase; LUS: lung ultrasound; MWT: minute walking test; NR: Not reported; OR: Odds Ratio; PCSF: post covid functional status; QoL: Quality of life; SPPB: Short Physical Performance Battery test; TSS: Toxic shock syndrome

Q20. Should heparin induced thrombocytopenia (HIT) test kits be used for COVID-19 vaccine induced thrombosis with thrombocytopenia (VITT)?

As of 29 November 2021

RECOMMENDATION

We suggest against the use of PF4 antibody ELISA Heparin Induced Thrombocytopenia (HIT) test kits and non-ELISA rapid HIT test kits for COVID-19 Vaccine Induced Thrombosis and Thrombocytopenia (VITT). *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues

The panel unanimously decided against the use of HIT test kits for COVID-19 VITT, citing that the test has a slow turnaround time and immediate clinical management remains the same regardless of the test result. Concerns were also raised on its cost-effectiveness as well as availability in the local setting. Test kits employing ELISA demonstrate relatively high sensitivity and specificity but have limited availability locally.

KEY FINDINGS

- One cross-sectional observational study [1] was included on the use of anti-platelet factor 4 (anti-PF4) assay test kits for the diagnosis of COVID-19 vaccine-induced thrombosis and thrombocytopenia (VITT).
- The overall certainty of evidence was very low because of serious concerns of the risk of bias, inconsistency, and imprecision.
- The study analyzed samples from 43 patients with suspected VITT using six brands of anti-PF4 ELISA test kits and four brands of anti-PF4 non-ELISA test kits. Sensitivity ranged from 0.71-0.97 and specificity ranged from 0.56-1.00 for the ELISA test kits, while sensitivity ranged from 0.00-0.45 and specificity ranged from 0.67-1.00 for the non-ELISA test kits.

INTRODUCTION

Rare cases presenting with signs and symptoms of thrombosis and thrombocytopenia have been reported following vaccination with viral vector-based COVID-19 vaccines, defined as COVID-19 vaccine-induced thrombosis and thrombocytopenia (VITT). Clinical presentation of COVID-19 VITT closely resembles heparin-induced thrombocytopenia (HIT), which involves platelet factor 4 (PF4) antibodies complexed with heparin.[2] Interactions between COVID-19 vaccines and platelets or PF4 may play a role in the pathophysiology of VITT, hence prompting the use of PF4 antibody test kits typically applied in the diagnostic workup of HIT to be investigated for COVID-19 VITT.

REVIEW METHODS

The review searched for studies that enrolled patients with suspected VITT after administration of COVID-19 vaccines who were tested with anti-PF4 assay HIT test kits, using sensitivity and specificity as the outcomes of interest.

A search was done through PubMed and Google Scholar from inception to 03 Oct 2021 using the following search terms: “(SARS-CoV 2 vaccine OR COVID-19 vaccine

OR COVID vaccine) AND (vaccine induced immune thrombotic thrombocytopenic OR Vaccine-induced immune thrombosis with thrombocytopenia OR vaccine associated immune thrombotic thrombocytopenic OR VITT OR VATT) AND (PF4 OR ELISA OR anti-PF4 assay OR heparin induced thrombocytopenia assay)." References and citations were cross-referenced for relevant articles. Initially intended inclusion criteria were randomized controlled trials, observational studies, or systematic reviews that enrolled patients with suspected VITT after administration of COVID-19 vaccines tested with anti-PF4 assay HIT test kits. Exclusion criteria were studies that tested anti-PF4 test kits in non-COVID vaccine related settings, and study designs that were limited to only case studies, case series, or consensus reports.

RESULTS

Characteristics of Included Studies

The initial search yielded 55 studies, majority of which were case reports, case series, consensus reports, or proposed guidelines. No randomized controlled trials (RCT) or case-control studies were found. The search yielded three systematic reviews [2-4] that summarized findings from only case reports and case series regarding COVID-19 VITT. The search also yielded two cross-sectional studies [1,5] that compared sensitivities of different brands and methods of anti-PF4 antibody assays among patients with clinical signs and symptoms of suspected VITT. One [5] of the two cross-sectional studies was excluded because it only analyzed samples from one patient across different brands of the assay.

One cross-sectional observational study was ultimately included in the analysis. Platton et al. [1] evaluated 50 samples from 43 patients that were referred to the UK Expert Haematology Panel multidisciplinary team for suspected VITT five to 28 days after the administration of ChAdOx1 nCoV-19 vaccines.

Samples were tested using the index test of PF4 antibody test kits traditionally used for HIT. Six brands of anti-PF4 ELISA test kits (four IgG-specific and two polyspecific) and four brands of anti-PF4 non-ELISA test kits were included. The reference standard was clinical presentation suggestive of VITT as evaluated by the UK Expert Haematology Panel. Based on signs and symptoms of thrombosis, thrombocytopenia, and elevated D-dimer, patients with suspected VITT were classified into possible VITT, probable VITT, or unlikely VITT. Samples were taken before treatment initiation and were measured for optical density according to manufacturer specifications to determine the positivity or negativity of the test result. The computed sensitivity and specificity are summarized in Table 1.

Diagnostic Accuracy

The accuracy of HIT tests varied across test kit types and brands as shown in Table 1 and the paired forest plots and SROC curves in Appendix 6.

A. ELISA test kits

ELISA test kits showed moderate to high sensitivity across test brands ranging from 0.71 to 0.97. Specificity ranged from 0.56 to 1.00, with IgG-specific test kits appearing to have higher specificities (Range 0.78-1.00) compared to polyspecific test kits (Range 0.56-0.67). Among the six different ELISA test kit brands, **Asserachrom HPIA IgG ELISA** showed the highest accuracy with a sensitivity of 0.91 (95% CI 0.76-0.98) and specificity of 1.00 (95% CI 0.660-1.00).

B. Non-ELISA test kits

Compared to ELISA test kits, non-ELISA test kits demonstrated poorer sensitivity ranging from 0 to 0.45, but with high specificity from 0.67 to 1.00. Of the four non-ELISA test kits evaluated in the study, Diamed PaGIA gel rapid test showed the highest sensitivity at 0.45 (95% CI 0.28-0.64) but also the poorest specificity at 0.67 (95% CI 0.30-0.93).

Table 1. Sensitivity and specificity of brands of anti-PF4 assays

Test	Sensitivity (95% CI)	Specificity (95% CI)
ELISA test kits, IgG-specific		
AESKULISA HiT II IgG ELISA	0.71 (0.53-0.85)	0.89 (0.52-1.00)
Asserachrom HPIA IgG ELISA	0.91 (0.76-0.98)	1.00 (0.66-1.00)
Lifecodes PF4 IgG ELISA	0.94 (0.80-0.99)	0.78 (0.40-0.97)
Zymutest HIA IgG ELISA	0.94 (0.80-0.99)	0.78 (0.40-0.97)
ELISA test kits, polyspecific		
Asserachrom HPIA polyspecific ELISA	0.97 (0.85-1.00)	0.67 (0.30-0.93)
Lifecodes PF4 Enhanced polyspecific ELISA	0.97 (0.85-1.00)	0.56 (0.21-0.86)
Non-ELISA test kits		
Diamed PaGIA gel rapid test	0.45 (0.28-0.64)	0.67 (0.30-0.93)
HemosIL AcuStar HIT-IgG rapid test	0.06 (0.01-0.20)	1.00 (0.66-1.00)
HemosIL HIT-Ab rapid test	0.00 (0.00-0.19)	1.00 (0.63-1.00)
STic Expert rapid test	0.04 (0.00-0.21)	1.00 (0.16-1.00)

Certainty of evidence

The overall certainty of evidence was rated very low because of the serious risk of bias and imprecision from a small sample size. Using the QUADAS-2 tool [6], the study was assessed to be at risk of bias due to unclear concerns with patient selection (consecutive enrolment and unnecessary exclusions), blinded interpretation of index tests, flow, and timing of conduct of index tests, and reference standard, and applicability concerns due to unreported baseline patient characteristics. A summarized tabular representation of QUADAS-2 results is in Appendix 4. Concerns with imprecision were attributed to evidence coming from a single observational study, of which the sample size was small.

OTHER FACTORS IN EVIDENCE TO DECISION

Immunoassay tests like anti-PF4 ELISA are observed to have relatively high sensitivity and efficiency due to compatibility with testing in large batches. However, these are also time-consuming with a slow turnaround time especially compared to rapid tests and can be expensive in commercial use. Meanwhile, non-ELISA tests for anti-PF4 such as particle gel immunoassay, lateral flow assay, and automated latex-based assays have a much faster turnaround time suited to urgent testing, but have more variations in sensitivity, specificity, and expense, and have interobserver variability.[7]

Despite its high sensitivity, the literature notes that there is still a likelihood of false-negative results with ELISA anti-PF4 test kits. The likelihood of false negatives is even greater in non-ELISA test kits.[8] Thus, the interpretation of anti-PF4 test kits must be done alongside the complete clinical picture of patients with suspected VITT, including platelet count, D-dimer, and imaging as pertinent.

Estimated costs for various anti-PF4 HIT test assays were $52 (P2,623) for ELISA, $84 (P4,274) for AcuStar IgG rapid test, and $120 (P6,042) for Diamed PaGIA.[9] Anti-PF4 HIT test kits have very limited availability in the Philippines, found only as non-

ELISA tests in two hospitals in Metro Manila with estimated costs ranging from P9,363 to PHP13,800.

For applicability and appropriateness in the local context, as of May 2021 the Department of Health (DOH) acknowledged reports of COVID-19 VITT following the administration of viral vector-based vaccines such as the ChAdOx1 nCoV-19 vaccine, which is among the COVID-19 vaccines distributed in the country. After a temporary suspension in administration, the DOH resumed vaccination with ChAdOx1 nCoV-19 and reported no local cases of VITT in the Philippines.[10]

Additionally, anti-PF4 testing may have prolonged turnaround times and VITT is an urgent medical condition. Requesting physicians should not wait for anti-PF4 results and are advised to immediately treat patients with a high index of suspicion of VITT.[8,11] It is also important to note that patients with COVID-19 disease itself can also present with positive results in anti-PF4 antibody testing, likely in association with the prothrombotic state in COVID-19 disease.[12] It is recommended that monitoring and surveillance of COVID-19 vaccine-related adverse events continue to be strengthened, including the expansion of novel avenues for active reporting of adverse events.[13]

RECOMMENDATIONS FROM OTHER GROUPS

Several international organizations have made recommendations in support for anti-PF4 testing in COVID-19 VITT.[8,11,13-15] These groups have also specified that anti-PF4 ELISA test kits be used. These recommendations are summarized in Table 2. No local guidelines on testing for suspected VITT were found.

Table 2. Recommendations from other groups for testing in COVID-19 VITT

Organization	Date	Recommendation
National Institute for Health and Care Excellence (NICE)	July 29, 2021	• For probable VITT, use ELISA for anti-PF4 antibodies to confirm the diagnosis.
US CDC Advisory Committee on Immunization Practices (ACIP)	May 12, 2021	• For Tier 1 TTS (thrombosis in unusual location), positive hepatin-PF4 ELISA is supportive but not required • For Tier 2 TTS (thrombosis in common location only), positive PF4 ELISA is required
American Society of Hematology (ASH)	August 12, 2021	• PF4-ELISA as part of initial work-up of suspected TTS; draw blood prior to any therapy
Expert Haematology Panel / British Society of Haematology	August 30, 2021	• PF4 antibodies are detected by ELISA • Not by other HIT assay methods – negative results and cannot be relied upon
International Society of Thrombosis and Hematology (ISTH)	April 20, 2021	• Not all HIT assays can detect PF4 antibodies – ELISA is the most reliable • If a reliable PF4 assay is negative: VITT is excluded • If a reliable PF4 assay is positive: VITT is likely • If PF4 assay unavailable: >4x elevated D-dimer is highly suggestive of VITT

RESEARCH GAPS

More studies with a higher certainty of evidence are needed to improve guidance on testing for VITT. One observational study was included in this review. To date, the majority of published studies on anti-PF4 HIT testing for VITT are case series, case reports, and consensus statements.

A search for ongoing studies in *ClinicalTrials.gov* found an observational study based in the US titled the National Vaccine Adverse Event Reporting Survey and Etiology

(NVAERS) which aims to enroll 100,000 participants for reporting any adverse events, including thrombosis, within 60 days after receipt of any vaccine dose, including but not limited to vaccines for COVID, hepatitis, measles, seasonal influenza, and other diseases. No other ongoing COVID-19 studies related to HIT test kits or VITT were found.

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Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (4)	Yes (5)					No local VITT events reported.
Benefits	Large (1)	Moderate (5)	Small (2)	Uncertain (1)			The study by Platton et all suggests moderate to high sensitivity and moderate to high specificity for ELISA test kits. In combination with clinical diagnosis, it may contribute to the diagnosis of VITT.
Harms	Large (1)	Moderate (6)	Small (1)	Uncertain (1)			The results from Platton's study show there is some risk of misdiagnosis, particularly with false negative test results with non-ELISA tests. This may lead to harmful consequences if VITT is missed or undiagnosed.
Balance of Benefits and Harms	Favors the use of HIT test	Probably favors the use of HIT test (7)	Does not favor the use of HIT test (2)				The moderate to high sensitivity and specificity shown in Platton 2021 suggests its contribution to the workup of COVID-19 VITT, but more studies with improved certainty are needed.
Certainty of Evidence	High	Moderate	Low (5)	Very low (4)			Only one observational study [1] was included in the analysis. It had uncertain risk of bias and uncertain concerns of applicability, hence low certainty of evidence.
Accuracy	Very Accurate	Accurate (2)	Inaccurate (4)	Very Inaccurate	Uncertain (3)		The sensitivity across brands of ELISA anti-PF4 test kits ranged from 0.71-0.97, while specificity ranged from 0.56-1.00, suggesting its accuracy. However, sensitivity ranged from 0.00-0.45 and specificity ranged from 0.56-1.00 in non-ELISA kits.
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability	No important uncertainty or variability			The risk of underdiagnosis of VITT due to false negatives may be an important point of uncertainty, as the prothrombotic condition necessitates hospitalization and anticoagulant therapy. However, other means of diagnosis of VITT are also important, such as clinical presentation, platelet count, D-dimer, and imaging.
Resources Required	Uncertain (2)	Large cost (3)	Moderate Cost (4)	Negligible cost or savings	Moderate savings	Large savings	Immunoassays are expensive, including the ELISA test kits included in the study. However, missing the diagnosis of VITT is potentially more expensive given hospitalization and anticoagulation treatment are part of the management of VITT.
Certainty of evidence of required resources	No included studies (5)	Very low (2)	Low	Moderate (2)	High		No evidence found.
Cost effectiveness	No included studies (2)	Favors HIT tests	Does not favor either HIT tests or the comparator (1)	Favors comparison (6)			The reference standard of clinical diagnosis is more cost-effective than immunoassay testing.
Equity	Uncertain (2)	Reduced (4)	Probably no impact (3)	Increased			Anti-PF4 immunoassay testing is expensive and not readily accessible.
Acceptability	Uncertain (8)	No (1)	Yes				While COVID-19 VITT is of clinical concern, applicability to the local setting is uncertain because despite availability of viral vector COVID vaccines, the DOH has not reported any cases of VITT in the Philippines to date. Information about accessibility and cost of anti-PF4 testing in the local setting is not readily available.
Feasibility	Uncertain (5)	No (3)	Yes (1)				

Appendix 2. Search Yield and Results

Database	Search Terms	Yield
PubMed and Google Scholar	"*(SARS-CoV 2 vaccine OR COVID-19 vaccine OR COVID vaccine) AND (vaccine induced immune thrombotic thrombocytopenic OR Vaccine-induced immune thrombosis with thrombocytopenia OR vaccine associated immune thrombotic thrombocytopenic OR VITT OR VATT) AND (PF4 OR ELISA OR anti-PF4 assay OR heparin induced thrombocytopenia assay)*	55 studies

Appendix 3. Characteristics of Included Studies

Title/ Author	Study design	Country	Number of patients	Population	Index Test / Exposure	Reference Standard / Control	Outcomes
Platton 2021	Cross-sectional, observational study	UK	50 samples from 43 patients	Patients with suspected VITT (based on clinical presentation, platelet count, D-dimer level)	IgG specific anti-PF4 ELISA (Asserachrom, Lifecodes, Hyphen Biomed, Zymutest, AESKULISA) Polyspecific anti-PF4 ELISA (IgG, IgA, IgM) (Asserachrom, Lifecodes) Rapid anti-PF4 non-ELISA assays (Diamed, STic Expert, HemosIL Acustar HIT-IgG, HemosIL HIT-Ab)	Clinical diagnosis of VITT (VITT unlikely, VITT possible, VITT probable)	Optical density; Anti-PF4 assay result (positive or negative); Sensitivity; Specificity

Appendix 4. Detailed Study Appraisal

Table 1. QUADAS-2 summarized results for Platton 2021

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Platton 2021	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk

Table 2. QUADAS-2 signaling questions for Platton 2021

PATIENT SELECTION	
A. Risk of Bias	
Patient sampling	50 samples from 43 patients with suspected VITT that were referred to the UK Expert Haematology Panel multi-disciplinary team. All samples were analyzed before therapeutic treatment of VITT.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk
B. Concerns Regarding Applicability	
Patient characteristics and setting	Patient baseline characteristics were not reported. Study was conducted in the UK.
Are there concerns that the included patients and setting do not match the review question?	Unclear concern
INDEX TEST	
Index tests	Anti-platelet 4 (anti-PF4) serologic assays measure the presence of anti-platelet 4-heparin antibodies. They can be ELISA-based or non-ELISA based, such as particle gel, lateral flow, chemoluminescence, and latex-agglutination. Anti-PF4 assays are traditionally used for screening for HIT. The results are positive or negative, based on optical density (OD) predetermined cutoffs set by laboratories. Both ELISA-based and non-ELISA methods, as well as different brands among these, were assessed.
A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk
B. Concerns Regarding Applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
REFERENCE STANDARD	
A. Risk of Bias	
Target condition and reference standard	VITT is described as signs and symptoms of thrombosis and thrombocytopenia following immunization with COVID-19 vaccines. Aside from clinical signs of thrombosis at unusual sites and thrombocytopenia, it is also associated with elevated D-dimer and anti-PF4 antibodies. It is similar in presentation to heparin-induced thrombocytopenia (HIT) but unlike HIT, patients with VITT have no known exposure to heparin and instead occurs following inoculation with COVID-19 vaccines.For the study, patients were assessed as suspected VITT and then divided into probable VITT, possible VITT, and unlikely VITT.
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns Regarding Applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
FLOW AND TIMING	
A. Risk of Bias	
Flow and timing	All patients in whom the anti-PF4 assays were tested were assessed for suspected VITT. The time interval between clinical assessment of VITT and testing with the index test was not explicitly reported.
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Appendix 5. GRADE Evidence Profile

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 0.00142%	
True positives (patients with VITT)	1 study (43 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Not serious	Serious[b]	None	0 to 0	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having VITT)								0 to 0	
True negatives (patients without VITT)	1 study (43 patients)	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious	Not serious	Serious[b]	None	560 to 1,000	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having VITT)								0 to 440	

*Pretest probability is based on incidence estimates by NICE of 14.2 cases of VITT per million doses [9].

Appendix 6. Forest Plots

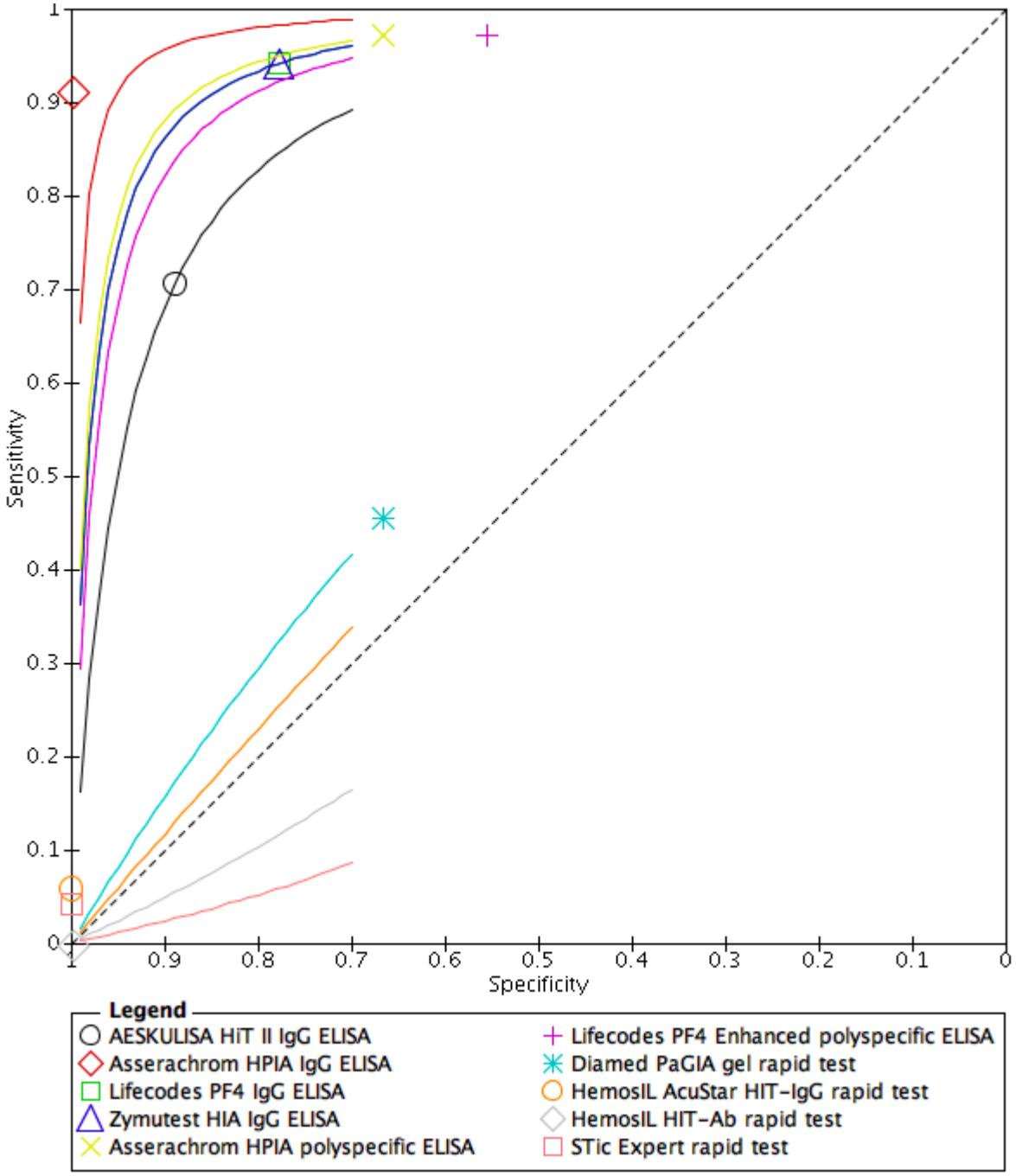

Figure 1. Summary receiver operating characteristic curves (SROC) for different HIT test kits.

AESKULISA HiT II IgG ELISA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Platton 2021	24	1	10	8	0.71 [0.53, 0.85]	0.89 [0.52, 1.00]		

Asserachrom HPIA IgG ELISA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Platton 2021	31	0	3	9	0.91 [0.76, 0.98]	1.00 [0.66, 1.00]		

Lifecodes PF4 IgG ELISA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Platton 2021	32	2	2	7	0.94 [0.80, 0.99]	0.78 [0.40, 0.97]		

Zymutest HIA IgG ELISA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Platton 2021	32	2	2	7	0.94 [0.80, 0.99]	0.78 [0.40, 0.97]		

Figure 2. ELISA test kits, IgG-specific

Asserachrom HPIA polyspecific ELISA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Platton 2021	33	3	1	6	0.97 [0.85, 1.00]	0.67 [0.30, 0.93]		

Lifecodes PF4 Enhanced polyspecific ELISA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Platton 2021	33	4	1	5	0.97 [0.85, 1.00]	0.56 [0.21, 0.86]		

Figure 3. ELISA test kits, polyspecific

Diamed PaGIA gel rapid test

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Platton 2021	15	3	18	6	0.45 [0.28, 0.64]	0.67 [0.30, 0.93]		

HemosIL AcuStar HIT-IgG rapid test

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Platton 2021	2	0	32	9	0.06 [0.01, 0.20]	1.00 [0.66, 1.00]		

HemosIL HIT-Ab rapid test

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Platton 2021	0	0	18	8	0.00 [0.00, 0.19]	1.00 [0.63, 1.00]		

STic Expert rapid test

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Platton 2021	1	0	23	2	0.04 [0.00, 0.21]	1.00 [0.16, 1.00]		

Figure 4. Non-ELISA test kits

Q21. Should serum tryptase be used to test individuals who had anaphylaxis after receiving COVID-19 vaccine?

As of 29 November 2021

RECOMMENDATION

We suggest against using serum tryptase for patients who had anaphylaxis after receiving COVID-19 vaccine. *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues

The panel unanimously decided against the use of serum tryptase to diagnose COVID-19 vaccine-induced anaphylaxis, citing that the test is not cost-effective, and anaphylaxis remains to be a clinical diagnosis. While serum tryptase may have a role in patients with atypical presentation, it would still be prudent to treat the patient especially if there is high clinical suspicion regardless of the test result. Additionally, the use of tryptase test in settings of mass vaccination poses feasibility issues because (1) the sample should be taken within 30 minutes up to 2 hours after the patient presents with a reaction, and (2) there is a paucity of laboratories offering the test. However, a weak recommendation was made since the test may still benefit a small subset of the population and may have more utility in the emergency department setting.

KEY FINDINGS

- Eleven observational studies (five case reports, two case series, three retrospective chart reviews, and one prospective survey) with 33 total patients showed conflicting results and uncertainty concerning the use of serum tryptase in the diagnosis of COVID-19 vaccine-induced anaphylaxis.
- Nine patients presented with a history of allergy but none of them showed elevated tryptase levels.
- Four patients presented with elevated serum tryptase levels but have no allergic history elicited/provided.
- There is uncertainty with regards to the accuracy of serum tryptase in the diagnosis of COVID-19 vaccine-induced anaphylaxis due to the lack of study samples.
- The overall certainty of the evidence was very low because of heterogeneity in the duration of tryptase determination, the definition of elevated values, variable clinical classification criteria, and the lack of an objective reference standard for the diagnosis of anaphylaxis.

INTRODUCTION

COVID-19 vaccines have been given emergency authorization by the US-Food and Drug Administration (FDA) since December 2020. Since then, there has been worldwide adoption and acceptance of these vaccines. Current vaccines worldwide employed the use of mRNA, inactivated, and recombinant adenovirus vaccines with efficacy rates as high as 95% in preventing COVID-19 illness.[1] However, multiple studies have documented a range of side effects associated with COVID-19 vaccines, particularly the mRNA vaccines. These typically include localized pain and skin reactions.[2,3] Recent literature showed that excipients were the culprit substances

implicated in anaphylactic reactions, particularly Polyethylene glycol (PEG) and Polysorbate, which were commonly overlooked as an allergenic substance.[4]

A recent systematic review and meta-analysis of 26 studies published in October 2021 showed an estimated pooled prevalence of anaphylaxis at 5.58 cases per 1 million doses administered.[4] Risk factors seen for anaphylactic reactions were female sex and history of atopy.[4] Episodes of severe allergic reactions and anaphylaxis were also recorded in the Vaccine Adverse Effect Reporting System (VAERS) under the Centers for Disease Control (CDC) and the US FDA. During December 14-23, 2020, VAERS has recorded 21 cases of anaphylaxis out of 1,893,360 doses of the Pfizer-BioNTech COVID-19 vaccine.[5] The most common clinical manifestations of anaphylaxis recorded were urticaria, angioedema, rash, sense, and globus sensation. Signs and symptoms of anaphylaxis were evident among patients who had a previous history of allergic reactions, particularly in people with previous anaphylactic reactions.[3,5,6]

Due to the recorded anaphylactic reactions, serum tryptase measurement has been suggested by the World Allergy Organization (WAO) as a means of diagnosing anaphylaxis. Serum tryptase levels become elevated during episodes of anaphylaxis with peak levels within 1-2 hours after its onset. Baseline total tryptase levels range from 1 to 11.4 ng/mL with an average of 3 to 5 ng/mL, although some studies show that acute elevations from the baseline within the normal range may also be clinically relevant. Commercial assays measure serum tryptase release after mast cell activation, which is representative of mast cell burden instead of anaphylaxis per se. Although elevated serum tryptase levels support the diagnosis of anaphylaxis, normal serum levels do not exclude it. Regardless, it has been recommended as part of the management of COVID-19 vaccine anaphylaxis for accurate diagnosis, especially for patients with unclear predisposition and symptomatology.[7,8]

REVIEW METHODS

A systematic search was conducted in several electronic databases (MEDLINE through PubMed, Cochrane CENTRAL, medRxiv, bioRxiv, ClinicalTrials.gov, WHO registry, and Living Evidence on COVID-19) until October 25, 2021. Eligibility criteria for this review were as follows: population- COVID-19 vaccinated patients with anaphylaxis, index test - serum tryptase, reference standard -clinical, study designs - observational studies. Due to the expected low incidence rate of COVID-19 vaccine-related anaphylactic reactions, published case reports and case series were also included. Articles not written in English as well as studies involving pediatric patients were excluded.

Data related to the following were extracted: dose of the vaccine (first vs second), type of vaccine, gender, and allergic history. When possible, an exploratory analysis was done to establish the possible influence of certain variables (e.g., allergy history, type of SARS-CoV-2 vaccine used) on the diagnostic accuracy of serum tryptase. Methodological quality assessment for bias was done using the QUADAS-2 assessment scale. Appendix 4 shows the assessment of bias.

RESULTS

Characteristics of included studies

Eleven studies were considered eligible for inclusion in this review: five case reports [9-13], two case series [14,15], three retrospective reviews [16-18] and one prospective survey (n=1,365).[19] In total, data from 33 patients were analyzed. The study population consisted of patients who were diagnosed with anaphylaxis after receiving a COVID-19 vaccine. The index test used was serum tryptase with notable variations in the time of sample extraction, fluoroimmunoassay assay techniques, and the definition of elevated tryptase. Case series and case reports reported serum tryptase values as elevated if they are above a certain cut-off value. The prospective and retrospective reviews (except Kohli-Pamnani) defined elevated tryptase levels if they are above a predetermined set-point (>[2+1.2x baseline tryptase level]). Clinical parameters were used as the reference standard for the diagnosis of anaphylaxis. There was noted heterogeneity concerning the definition of anaphylaxis in the studies. Some studies strictly used clinical criteria [9-13,19] while other studies used less subjective criteria such as Brighton anaphylaxis criteria.[14-18]

Five of eleven studies included patients (n=15) who had previous allergic reactions.[9-10,14-16] Of the 33 total patients, 19 (57%) patients were given mRNA vaccines (Pfizer-BioNTech and Moderna vaccine), 6 (18%) received inactivated vaccines (CoronaVac). The vaccines given to the remaining 8 patients (24%) were not disclosed.

Relationship between serum tryptase levels and anaphylactic reactions

Eight studies (n=29) showed no elevation in serum tryptase levels [8-11,14-17], however four studies (n=4) showed elevation in serum tryptase levels above 2ng/ml-14ng/ml.[11-13,19] Nine of the 33 patients presented with a history of allergy but none of them showed elevated tryptase levels. Among these patients, three had a history of anaphylaxis while seven had a history of allergic rhinitis.[9-10,14-16] Two of the four patients with a reported elevation (8.25ng/ml-12.5ng/ml) of serum tryptase had no history of previous allergic reactions, while no data was available for the other two patients.[13,17-19]

EVIDENCE TO DECISION

Table 1 lists other considerations for the use of serum tryptase test.

Table 1. Other considerations on the use of serum tryptase test

Benefit	The use of serum tryptase does not greatly influence the clinical management of patients with anaphylaxis given that the condition is primarily a clinical diagnosis. It may be offered to patients with ambiguous clinical manifestations of anaphylaxis
Harm	No evidence of harm was found in the included studies.
Equity	-
Cost	UP-PGH Medical Research laboratory: P5,000 Makati Medical Center Laboratory: P9,770-P11,730
Acceptability	No evidence was found. Very few laboratories currently offer this test, which makes the processing of samples difficult and introduces logistical issues. Serum tryptase levels also have short peak levels.
Feasibility	The paucity of laboratories offering this test makes the processing of samples difficult and poses logistical problems. Serum tryptase levels have short peak levels.

RECOMMENDATIONS FROM OTHER GROUPS

The WAO Anaphylaxis Committee recommends that tryptase is important in the accurate diagnosis of anaphylaxis, particularly for adults with ambiguous history and symptomatology. The sample should be taken within 30 minutes up to two hours after a reaction, with baseline samples at least 24 hours after resolution of symptoms.[8]

No specific immunoassay kit was mentioned in this recommendation.

RESEARCH GAPS

In light of the small sample sizes in the current evidence, more comparative validation studies are needed to clarify the utility of serum tryptase in detecting post-COVID 19 vaccine-related anaphylaxis. Further studies are needed to determine the incidence of anaphylaxis with vaccine types other than mRNA vaccines.

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Appendix 1. Evidence to Decision

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (3)	Yes (5)					Serum tryptase test can be used to augment diagnosis of anaphylaxis in patients with unclear history of symptomatology.
Benefits	Large	Moderate (2)	Small (5)	Uncertain (1)			Being primarily a clinical diagnosis, an elevated tryptase does not drastically change the management of anaphylaxis.
Harms	Large	Moderate (1)	Small (5)	Uncertain (2)			No research evidence found.
Balance of Benefits and Harms	Favors the use of serum tryptase	Probably favors the use of serum tryptase (2)	Does not favor the use of serum tryptase (6)				Being primarily a clinical diagnosis, an elevated tryptase does not drastically change the management of anaphylaxis.
Certainty of Evidence	High	Moderate	Low (4)	Very low (4)			Eight studies (n=29) showed no elevation in serum tryptase levels, while four studies (n=4) showed elevation in serum tryptase levels.
Accuracy	Very Accurate	Accurate	Inaccurate (4)	Very Inaccurate (1)	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 (2)			No research evidence found.
Resources Required	Uncertain	Large cost (6)	Moderate Cost (2)	Negligible cost or savings	Moderate savings	Large savings	UP-PGH Medical Research laboratory: P5,000; and Makati Medical Center Laboratory: P9,770-P11,730.
Certainty of evidence of required resources	No included studies (5)	Very low	Low (1)	Moderate (1)	High (1)		No research evidence found.
Cost effectiveness	No included studies (3)	Favors serum tryptase	Does not favor either serum tryptase or the comparator (3)	Favors comparison (2)			No research evidence found/
Equity	Uncertain (4)	Reduced (1)	Probably no impact (3)	Increased			Serum tryptase test does not change the clinical management of patients since anaphylaxis is primarily managed on a clinical and emergent basis.
Acceptability	Uncertain (3)	No (5)	Yes				The test is expensive and is not readily available in all laboratories inthe country
Feasibility	Uncertain (1)	No (6)	Yes (1)				

Appendix 2. Search Yield and Results

Research Question:

Should serum tryptase be used to test individuals who had anaphylaxis or severe allergic reactions after receiving COVID vaccine?

P- COVID-19 vaccinated patients

E- Serum Tryptase

O- Anaphylaxis

Table 1. Summary of search terms and yields per database

Database	Search Terms	Results	Included Studies
Medline	**COVID-19 vaccine (#1)** Keywords: “SARS-CoV 2 vaccine”[tiab] OR “COVID-19 vaccine”[tiab] OR "COVID-19 Vaccines"[Mesh] Mesh: "COVID-19 Vaccines"[Mesh] **Anaphylaxis/ allergy (#2)** Keywords: Anaphyla*[tiab] OR Hypersensitivity[tiab] OR Hypersens*[tiab] OR Anaphylaxis[tiab] OR "Hypersensitivity"[Mesh] OR "Anaphylaxis"[Mesh] Mesh: "Hypersensitivity"[Mesh] OR "Anaphylaxis"[Mesh] **Serum tryptase (#3)** Keywords: Tryptas*[tiab] OR "Tryptases"[Mesh] Mesh: "Tryptases"[Mesh] #1 AND #2 AND #3: 3 results #1 AND #2: 194 results #1 AND #2 (Meta,RCT,Systematic review filter): 3 results (0 included in systematic review) ("COVID-19 vaccine"[tiab]) AND (tryptase[tiab]): 2 results (no yield) “COVID-19 vaccine” AND tryptase	57	11
Cochrane	COVID-19 vaccine AND Anaphylaxis	6	0
Medrxiv and bioRxiv	COVID-19 vaccine AND anaphylaxis: 62 results (0 included in systematic review) COVID-19 vaccine AND tryptase: 3 results (0 included in systematic review)	11	0
clinicaltrials.gov	COVID-19 vaccine AND anaphylaxis	6 (studies currently recruiting, none completed yet)	0
WHO registry[a]	Anaphylaxis (restrict to COVID-19)	0	0
Living Evidence on COVID-19[b]	((COVID-19 vaccine) AND (Tryptase))	1	1 (duplicate)

[a] https://www.who.int/clinical-trials-registry-platform

[b] https://zika.ispm.unibe.ch/assets/data/pub/search_beta/

Table 2. Mesh terms used

Mesh terms under the MEDLINE databasePopulation	COVID-19 vaccine, SARS-Cov 2 vaccine, mRNA-1273 vaccine, ChAdOx1vaccine, BNT162 vaccine, Gam-COVID-Vac vaccine, HIPRA SARS-CoV-2 vaccine, Ad5-nCoV vaccine, SCTV01C vaccine, EpiVacCorona vaccine, versamune-CoV-2FC vaccine, ARCT-154 vaccine, MVC-COV1901 vaccine, Ad26.COV.S vaccine, lentiviral minigene vaccine
Exposure	Serum Tryptase
Outcome	Anaphylaxis

Appendix 3. Characteristics of Included Studies

Study	Study Design	Population	Allergy History	Index Test	Reference Standard
Sellatur ay et al. 2021 [9]	Case report	**52-year old female**; throat constriction, cough and then loss of consciousness immediately after receiving the **Pfizer/BioNTech** vaccine **(first dose)**	Drug anaphylaxis: Azithromycin Urticaria: Polyethylene glycol	Tryptase taken 1.5 hours later was **3.9 ng/ml (normal range 2–14 ng/ml)**	Clinical
Pitlick et al. 2021 [17]	Case report	**42 year old female**; facial angioedema, pruritic rash 10 minutes post-vaccination of **Pfizer/BioNTech vaccine (first dose)** 30 hours post-vaccination;tongue swelling (noted by husband), sensation of throat closing, eye puffiness, diaphoresis, and lightheadedness	No previous anaphylactic nor atopic history	A tryptase drawn 90 minutes (1.5 hours) after symptom onset was **elevated** at **12.5 ng/mL (<11.5 ng/mL)**	Clinical
Lim et al. 2021 [10]	Case series	**Patient 1:** **42 year old male;** flushing, periorbital edema, globus sensation, and wheezing 30 min after the **second** dose of the **Pfizer BNT162b2** vaccine **Patient 2:** **32 year old female;** flushing, periorbital edema, globus sensation, and wheezing 30 min after the **second** dose of the **Pfizer BNT162b2** vaccine. Symptoms recurred at 8 and 27 h post-vaccination **Patient 3:** **40 year old female**;generalised urticaria, periorbital edema, globus sensation, and breathlessness 20 min after receiving the **second** dose of the **Pfizer BNT162b2**	**Patient 1:** Poorly-controlled asthma, urticaria to Etoricoxib **Patient 2:** Mild, intermittent allergic rhinitis **Patient 3:** Mild, intermittent chronic rhinosinusitis	**Patient 1:** 2 hours after vaccination: 3.2ng/ml (cut-off <11.4ng/ml) **Patient 2:** 6 hours after vaccination: 2.2ng/ml (cut-off <11.4ng/ml) 41 hours after vaccination: 3ng/ml (cut-off value <11.4ng/ml) **Patient 3:** 6 hours after vaccination: 2.3ng/ml (cut-off value <11.4ng/ml) 22 hours after vaccination: 1.9ng/ml (cut-off value <11.4ng/ml)	Brighton Collaboration case definition criteria
Restivo et al. 2021 [11]	Case report	**30 year old female**;erythematous spots on the face and neck, and a feeling of a slurred mouth and hoarseness 5 hours after receiving **Pfizer-BioNTech** vaccine **(first dose)**	Urticaria-angioedema episode in 2009 and multiple other immediate cutaneous reaction elicited by chocolate, honey, some cosmetics, and detergents	2.03mcg/L (cut-off value 10mcg/L)* 1 month after vaccination: 3.55mcg/L (cut-off value 10mcg/L) ** No time mentioned*	Clinical

Laisuan et al. [12]	Retrospective review	6 patients with anaphylaxis and serum tryptase **CoronaVac** First dose: Patient 2,5, and 6 Second dose: Patient 10 and 11	Patient 2: Allergic rhinitis Patient 5: Allergic rhinitis Patient 6: - Patient 9: Allergic rhinitis Patient 10: Allergic rhinitis Patient 11: Allergic rhinitis	Peak serum tryptase value exceeding 1.2 multiplied by the baseline serum tryptase plus 2, **all** available paired samples were interpreted as **negative** Peak: 30-90 minutes after reaction Baseline: >24 hours after complete resolution of all clinical symptoms Patient 2: Peak: 1.57mcg/L Baseline: 1.47mcg/L Patient 5: Peak: 3.54mcg/L Baseline: N/A Patient 6: Peak: 2.3mcg/L Baseline: 1.45mcg/L Patient 9: Peak: 2.93mcg/L Baseline: 4.01mcg/L Patient 10: Peak: 3.11mcg/L Baseline: 2.93mcg/L Patient 11: Peak: 2.29mcg/L Baseline: 2.23mcg/L	Brighton Collaboration case definition criteria Ring and Messmer Anaphylaxis severity
Jiang et al. 2021 [13]	Case report	**56-year-old woman** received her **first dose** of the **Pfizer-BioNTech** messenger RNA (mRNA) vaccine (BNT162b2) Dizziness, lightheaded, dyspneic, throat tightening, and abdominal pain	None	Tryptase level was collected approximately 90 minutes after the index event, which was **6 ng/mL (reference range < 11.5 ng/mL)**	Clinical
Rasmussen et al. 2021 [14]	Retrospective review	9 anaphylaxis patients given **mRNA vaccines**	None for patient N60 No data for 8 other patients	Baseline level of s-tryptase >12 µg/L was considered elevated, and a s-tryptase level, measured following the acute allergic reaction, was considered elevated from baseline, when exceeding baseline s-tryptase x 1.2 + 2 **N60 (Pfizer-BioNTech)**	Brighton level of diagnostic certainty

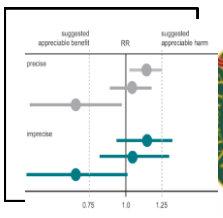
				Upper airway swelling, urticaria, and fell unconscious Serum Tryptase **8.25 µg/L (basal level 3.01 µg/L)** **Eight (unknown vaccine)** patients met the Brighton criteria level 2 or 3 after the first COVID-19 vaccination; **No increase** in serum Tryptase	
Blument al et al. 2021 [18]	Prospective (survey)	1 patient with recorded tryptase (given **Moderna vaccine**)	No data	Elevated tryptase level was defined as either above the upper limit of normal or >(2+1.2x baseline tryptase level). Baseline tryptase: 4.3ng/ml Acute tryptase level: 7.7ng/ml **(elevated)**	Clinical
Warren et al. 2021 [15]	Case series	7 patients with anaphylaxis and serum tryptase determination (**mRNA vaccine**) 50-59F Abdominal pain, dyspnea,hypotension, erythema,lightheadedness 40-49F Cough,cyanosis,generalized pruritus,localized urticaria, tachypnea 50-59F Dizziness, shortness of breath,stridor 30-39F Throat swelling, throat itching, localized angioedema with worsening 30-39F No Diaphoresis, generalized urticaria, lightheadedness, nausea 30-39F Generalized pruritus, cough 40-49F Shortness of breath, fhushing,rash, difficulty of breathing	50-59F No allergy/anaphylaxis history 40-49F (+)Drug,food, and latex allergy (+) Drug and food anaphylaxis 50-59F (+) Drug allergy and anaphylaxis 30-39F (+) Drug allergy 30-39F No allergy/anaphylaxis history 30-39F (+) Drug allergy 40-49F (+) Food allergy	Tryptase was taken within 2 hours after the allergic reaction 50-59F Baseline: 6ng/ml After reaction: 25ng/ml 40-49F Baseline: 4ng/ml After reaction: 16ng/ml 50-59F Baseline: 3ng/ml After reaction: 20ng/ml 30-39F Baseline: 6ng/ml After reaction: 19ng/ml 30-39F Baseline: 2ng/ml After reaction: 16ng/ml 30-39F Baseline: 5ng/ml After reaction: 21ng/ml 40-49F Baseline: 3ng/ml After reaction: 14ng/ml	Brighton anaphylaxis criteria

Park et al. 2021 [16]	Case report	34/F 3 min of **Pfizer-BioNTech** Covid-19 vaccine administration, she developed flushing, urticaria on her extremities and face, generalized pruritus, tongue swelling, nausea, light-headedness, racing pulse, and shortness of breath with absence of wheezing	None	Serum tryptase (7 and 26 days) 4.7mcg/L and 5.4mcg/ml **(within reference range)**	Clinical
Kohli-Pamnani et al. 2021 [19]	Retrospective review	1 patient experienced nausea and pruritus during skin testing (**Moderna**) that necessitated intramuscular epinephrine	No data	Elevated serum tryptase level (11.6 µg/L) was obtained with 24-hour delay (basal and post unavailable)	Clinical

Appendix 4. Study Appraisal using QUADAS-2

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Sellaturay	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Pitlick	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Lim	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Restivo	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Laisuan	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Jiang	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Rasmussen	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Blumenthal	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Warren	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Park	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Kohli-Pamnani	🟢	⚫	🟢	🟢	🟢	⚫	🟢

🟢 Low Risk 🔴 High Risk ⚫ Unclear Risk


suggested appreciable benefit
RR
suggested appreciable harm
precise
imprecise
0.75
1.0
1.25