SYSTEMATIC REVIEW

Diagnostic value of bronchoscopy in Sars-Cov-2 infection: A systematic review

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Abstract

Objective: To investigate the diagnostic performance of bronchoscopy in patients with coronavirus disease 2019 infection.

Method: The systematic review was conducted in April 2021 and comprised search of published articles and preprint servers for original articles assessing diagnostic performance of bronchoscopy in patients with suspected coronavirus disease 2019 infection. The primary outcome of interest was diagnostic sensitivity of bronchoalveolar lavage in the patients. The quality of each study was assessed using the Quality Assessment, Data Abstraction and Synthesis-2 tool.

Results: Of the 29 full-text articles assessed for eligibility, 4(13.8%) were included collectively comprising 209 patients who had undergone bronchoalveolar lavage. Mean sensitivity of bronchoalveolar lavage was 83.5% ± 10.63 (range: 68.2-940%). Overall, the 4 studies had an unclear or low risk of bias.

Conclusion: Limited data suggested that bronchoscopy with bronchoalveolar lavage did not have reliably higher diagnostic sensitivity than that reported for either nasopharyngeal or oropharyngeal swabs.

Keywords: Bronchoscopy and interventional techniques, COVID-19, Diagnostic techniques.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 and has since caused a global pandemic with well over 156 million confirmed cases of coronavirus disease 2019 (COVID-19) and over 3 million attributable deaths.[1] As the name implies, the virus belongs to the coronavirus family along with other viruses, such as Middle East Respiratory Syndrome (MERS-CoV) and severe acute respiratory syndrome CoV-1 (SARS-CoV-1). Both SARS-CoV-1 and SARS-CoV-2 bind to the angiotensin-converting enzyme 2 (ACE-2) receptor, which is preferentially expressed in the lower respiratory tract (LRT) as opposed to the upper respiratory tract (URT), with a notable exception being the oral cavity where ACE-2 is abundantly expressed.[2] A study showed that LRT samples, like sputum, endotracheal tube aspirate and bronchoalveolar lavage [BAL], had greater diagnostic sensitivity for SARS-CoV-1 compared to URT samples.[3]

Laboratory diagnosis of SAR-CoV-2 is usually obtained through reverse transcription polymerase chain reaction (RT-PCR) testing of URT samples, typically either with a nasopharyngeal swab (NPS) or an oropharyngeal swab (OPS). However, published data show widely varying detection rates of SARS-CoV-2 among such samples.[4,5] This raises concerns about the ability of these diagnostic procedures to reliably confirm or exclude a SARS-CoV-2 infection. False negatives (FNs) may be attributed to poor sample collection technique and an early course of infection with a low viral load. Additionally, it may also be attributed to the pathogenesis of the disease itself due to the spatial location of the ACE-2 receptors.

A number of publications report instances where suspected COVID-19 patients who tested negative after OPS and NPS were found to be positive for SARS-CoV-2 on PCR involving samples obtained via bronchoscopy.[2,5,6] However, the diagnostic sensitivity of bronchoscopy in COVID-19 is unclear. Given its higher risk of procedural complications and greater occupational hazard due to aerosolization, societal guidelines recommend against it unless necessary.[7] On the other hand, knowledge of the sensitivity of bronchoscopy and its ability to capture false negative results from less invasive testing could help clinicians obtain accurate diagnosis where it could make an impact on management decisions (e.g., to enable antiviral drug administration as per institutional policy, to enable enrollment in a clinical trial as per study protocol,

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or to avoid discontinuation of pathogen-specific isolation precautions following FN diagnostic tests). The current systematic review of studies was planned to investigate the diagnostic performance of bronchoscopy in patients with COVID-19 infection.

Materials and Methods

The systematic review was conducted in April 2021 and comprised search of published articles and preprint servers for original articles assessing diagnostic performance of bronchoscopy in patients with suspected VOVID-19 infection. The study was done in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) checklist.[8]

Literature search was conducted on MEDLINE (Ovid), Embase (Elsevier), Web of Science Core Collection (Clarivate) and the Cochrane COVID-19 Study Register.[9]

Appendix: Complete Databases Search Strategies.

MEDLINE (Ovid)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 09, 2021

April 09, 2021

555 Records

1. (betacoronavirus/ OR middle east respiratory syndrome coronavirus/ OR sars virus/ OR coronavirus infections/ OR severe acute respiratory syndrome/)
2. (nCoV* or 2019nCoV or 2019 nCoV or 19nCoV or COVID19* or COVID2019 or COVID or SARS-COV-2 or SARSCOV-2 or SARSCOV2 or SARS-CoV2 or hCoV2 or 2019ncov or "2019 ncov" OR Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,nm,ox,rx,px.
3. ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf.
4. ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf.
5. (SARSCOV* or severe acute respiratory syndrome* or sudden acute respiratory syndrome* or SARS or MERS or MERSCoV* or middle east respiratory or camel flu or EMC 2012).ti,ab,kf.
6. or/1-5
7. exp bronchoscopy/ OR exp bronchoscopes/ OR exp bronchoalveolar lavage/ OR exp bronchoalveolar lavage fluid/
8. (bronchoscop* OR laryngotracheobronchoscopy* OR tracheobronchoscopy* OR bal OR balf).ab,ti,kf.
9. ((bronchial OR bronchoalveolar OR bronchopulmonary OR tracheal OR intratracheal) adj3 (lavage OR aspirate* OR fluid OR wash* OR brush*)).ab,ti,kf.
10. or/7-9
11. 6 and 10

Embase (Elsevier)

April 09, 2021

1171 Records

1. 'betacoronavirus'/de OR 'Middle East respiratory syndrome coronavirus'/exp OR 'SARS-related coronavirus'/exp OR 'Coronavirus infection'/de OR 'coronavirus disease 2019'/exp OR 'Middle East respiratory syndrome'/exp OR 'severe acute respiratory syndrome'/exp
2. (nCoV* or 2019nCoV or '2019 nCoV' or 19nCoV or COVID19* or COVID2019 or COVID or 'SARS-COV-2' or 'SARSCOV-2' or SARSCOV2 or 'SARS-CoV2' or hCoV2 or 2019ncov or '2019 ncov'):ab,kw,ti
3. ((new or novel or '19' or '2019' or Wuhan or Hubei or China or Chinese) NEAR/3 (coronavirus* or 'corona virus*' or betacoronavirus* or CoV or HCoV)):ab,kw,ti
4. ((Wuhan or Hubei) NEAR/5 pneumonia):ab,kw,ti
5. (SARSCOV* or 'severe acute respiratory syndrome*' or 'sudden acute respiratory syndrome*' or SARS or MERS or MERSCoV* or 'middle east respiratory' or 'camel flu' or 'EMC 2012'):ab,kw,ti
6. #1 OR #2 OR #3 OR #4 OR #5
7. 'bronchoscopy'/exp OR 'bronchoscope'/exp OR 'lung lavage'/exp OR 'bronchoalveolar lavage fluid'/exp
8. (bronchoscop* OR laryngotracheobronchoscopy* OR tracheobronchoscopy* OR bal OR balf):ab,kw,ti
9. ((bronchial OR bronchoalveolar OR bronchopulmonary OR tracheal OR intratracheal) NEAR/3 (lavage OR aspirate* OR fluid OR wash* OR brush*)):ab,kw,ti
10. #7 OR #8 OR #9
11. #6 AND #10

Web of Science (Clarivate)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

April 09, 2021

364 Records

1. TS=("nCoV*" OR "2019nCoV" OR "2019 nCoV" OR "19nCoV" OR "COVID19*" OR "COVID2019" OR "COVID" OR "SARS-COV-2" OR "SARSCOV-2" OR "SARSCOV2" OR "SARS-CoV2" OR "hCoV2" OR "2019ncov" OR "2019 ncov")
2. TS=(("new" OR "novel" OR "19" OR "2019" OR "Wuhan" OR "Hubei" OR "China" OR "Chinese") NEAR/3 ("coronavirus*" OR "corona virus*" OR "betacoronavirus*" OR "CoV" OR "HCoV"))
3. TS=(("Wuhan" OR "Hubei") NEAR/5 "pneumonia")
4. TS=("SARSCOV*" OR "severe acute respiratory syndrome*" OR "sudden acute respiratory syndrome*" OR "SARS" OR "MERS" OR "MERSCoV*" OR "middle east respiratory" OR "camel flu" OR "EMC 2012")
5. #1 OR #2 OR #3 OR #4
6. TS=("bronchoscop*" OR "laryngotracheobronchoscopy*" OR "tracheobronchoscopy*" OR "bal" OR "balf")
7. TS=(("bronchial" OR "bronchoalveolar" OR "bronchopulmonary" OR "tracheal" OR "intratracheal") NEAR/3 ("lavage" OR "aspirate*" OR "fluid" OR "wash*" OR "brush*"))
8. #6 OR #7
9. #5 AND #8

Cochrane COVID-19 Study Register

https://covid-19.cochrane.org

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249 Studies

bronchoscop* OR laryngotracheobronchoscopy* OR tracheobronchoscopy* OR bal OR balf OR "bronchial lavage" OR "bronchial fluid" OR "bronchial aspirate" OR "bronchial wash" OR "tracheal lavage" OR "tracheal wash" OR "tracheal brush" OR "intratracheal lavage" OR "intratracheal wash"

Preprints: bioRxiv, medRxiv, preprints.org via Google Scholar

April 09, 2021

54 Studies

site:medrxiv.org

site:biorxiv.org

site:preprints.org

(covid|covid19|sars|mers|severe acute respiratory|sudden acute respiratory|middle east respiratory)(bronchoscope|bronchoscopic|bronchoscopy|bronchial lavage|bronchial fluid|bronchial aspirate|bronchial wash|tracheal lavage|tracheal wash)

Controlled vocabulary terms were used when available and appropriate, and no language limits were applied. Bibliographies of the shortlisted articles were also reviewed (Appendix). Given the rapidly expanding literature on COVID-19, preprints available through medRxiv.org, bioRxiv.org, and preprints.org were also examined through Google Scholar.[10]

The search was done following the population, intervention, comparison, outcome, study type (PICOS) framework.[11]

The included studies were either observational or experimental those with adult patients aged 18 years and above infected with SARS-CoV-2 using bronchoscopy with BAL, with or without additional sampling, such as bronchial brushing (BB) or bronchial washing (BW), and where the primary outcome was diagnostic sensitivity for SARS-CoV-2 infection.

Those excluded were case reports or series with <5 subjects, conference abstracts, articles published in language other than English, studies with overlapping datasets, and review papers.

Study selection was a two-staged process with titles and/or abstracts of studies screened first, following retrieval using the search strategy. The full texts of shortlisted studies were assessed for eligibility by two reviewers. Any disagreement was resolved through discussion with a third reviewer.

To systematically assess study quality, the Quality Assessment, Data Abstraction and Synthesis-2 (QUADAS-2) tool[12] was used. Studies were independently scored by two researchers across four domains, namely index test, reference standard, patient selection and flow and timing. The risk of bias for each publication was labelled as low, high or unclear for each domain. Inter-rater agreement was determined using Cohen's kappa statistics.

The primary outcome of interest was the diagnostic sensitivity of BAL in patients with confirmed COVID-19 infection. Sensitivity was defined as the proportion of SARS-CoV-2-infected patients, as confirmed by any PCR-based laboratory test, who were BAL PCR-positive. The diagnostic performance of other bronchoscopic sampling methods, such as BB and BW, were also examined and so were endotracheal aspirates, if possible. Data on safety of bronchoscopy in these patients was also reviewed.

In a separate post-hoc analysis, the researchers reviewed published studies on adult patients with suspected SARS-CoV-2 infection and negative initial testing by OPS and/or NPS who subsequently underwent bronchoscopy with BAL. Such analysis sought to assess the real-world clinical utility of BAL among suspected COVID-19 patients with one or more negative tests performed through less invasive means.

Results

Of the 2447 search results, 2393(97.7%) were located through electronic database searching and 54(2.2%) from preprint and bibliography searching. After removing duplicate records, 1501(61.3%) records were screened for

Table-1: Study Characteristics of COVID-19 positive patients undergoing bronchoscopy.

First author (year)	Country	Study Type	LRT sampling method	Population undergoing LRT sampling			Positive Diagnosis of Covid-19	PCR Kit Used
				n	Male	Mean or median Age		
1. Wang et al (2020)[5]	China	Prospective observational	BAL BB	15 13	68%*	44*	Symptoms and radiology and confirmed by SARS-CoV-2 detection	NA
2. Yang et al (2020)[26]	China	Prospective observational	BAL	66	47.1%†	47.5†	Guangdong CDC confirmed 2019-nCoV infected patients	qRT-PCR: GeneoDX Co., Ltd, Shanghai, China
3. Zhou et al (2020)[27]	China	Case Series	BAL	5	71.4%‡	47.3‡	Viral RNA detection with PCR from Oral Swabs	HiScript II One Step qRT–PCR SYBR Green Kit (Vazyme Biotech)
4. Gao et al (2021)[24]	United States	Retrospective observational	BAL	123	84%	63	Viral RNA detection with PCR from Nasopharyngeal Swabs	Multiple (See online supplement Table S3)

COVID-19: Coronavirus disease 2019, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, BAL: Bronchoalveolar lavage, BB: Bronchial brushing, qRT-PCR: Quantitative reverse transcription polymerase chain reaction, RNA: Ribonucleic acid,

* among overall population of 205 patients

† among overall population of 410 patients

‡ among overall population of 7 patients.

Table-2: Complete details for PCR kits used in the studies.

First author (year)	Country	Study Type	PCR Kit Used
1. Wang et al (2020)[5]	China	Prospective observational	Not Available
2. Yang et al (2020)[26]	China	Prospective observational	qRT-PCR: GeneoDX Co., Ltd, Shanghai, China
3. Zhou et al (2020)[27]	China	Case Series	HiScript II One Step qRT–PCR SYBR Green Kit (Vazyme Biotech)
4. Gao et al (2021)[24]	United States	Retrospective observational	The NP tests were run on the following platforms: 52 Abbott ID NOW, 5 Becton-Dickinson, 28 Cepheid, 33 in-house, and 5 not listed. The BAL tests were run on the following platforms: 0 Abbott ID NOW, 10 Becton-Dickinson, 84 Cepheid, and 29 in-house Of the 14 discordant NP and BAL cases, the NP tests were performed on 6 Abbott ID NOW, 2 BectonDickinson, 4 Cepheid, and 2 in-house–developed PCR platforms, whereas the BAL tests were performed on 2 Becton-Dickinson, 11 Cepheid, and 2 in-house platforms

COVID-19: Coronavirus disease 2019, qRT-PCR: Quantitative reverse transcription polymerase chain reaction, BAL: Bronchoalveolar lavage, NP: Nasopharyngeal.

Table-3: Sensitivity of PCR-based testing using bronchoscopic samples in diagnosing COVID-19.

First author (year)	LRT sampling method	Total patients undergoing LRT sampling method with Positive diagnosis*	Number of positive tests by LRT sampling method (TP)	Number of negative tests by LRT sampling method (FN)	Calculated Sensitivity for LRT sampling method (TP/TP+FN)
1. Wang et al (2020)[5]	BAL	15	14	1	14/15 (93.3%)
	BB	13	6	7	6/13 (46.1%)
2. Yang et al (2020)[26]	BAL	66	45	21	45/66 (68.2%)
3. Zhou et al (2020)[27]	BAL	5	4	1	4/5 (80.0%)
4. Gao et al (2021)[24]	BAL	84	79	5	79/84 (94.0%)

*Positive diagnosis was made by any test with laboratory confirmation using PCR
COVID-19: Coronavirus disease 2019, PCR: Polymerase chain reaction, LRT: Lower respiratory tract, BAL: Bronchoalveolar lavage, BB: Bronchial brushing,
TP: True positive, FN: False negative.

Table-4: Reviewer 1 quality assessment scores for the included studies using Quality Assessment, Data Abstraction and Synthesis-2 (QUADAS-2) tool.

Study	Risk of Bias				Applicability		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Wang et al (2020)[5]	L	L	L	U	L	L	L
Yang et al (2020)[26]	L	H	U	U	L	L	U
Zhou et al (2020)[27]	L	L	L	L	L	L	L
Gao et al (2021)[24]	L	L	L	L	L	L	L

H: High. L: Low. U: Unclear.

relevance. Finally, of the 29(1.9%) full-text documents assessed for eligibility, 4(13.8%) studies were included (Figure).

Altogether, 209 BAL samples and 13 BB samples were obtained (Table-1). PCR kits used in the studies were noted in detail (Table-2). The mean sensitivity values of PCR-based testing using bronchoscopic samples showed mean values of 83.5%±10.6 (range: 68.2-94.0%) (Table-3).

None of the studies reported any adverse patient event, like respiratory failure, hemodynamic compromise, or deaths resulting from bronchoscopy. No data were reported on occupational exposures to SARS-CoV-2 stemming from bronchoscopy.

The risk of bias varied widely but was felt to be either

Table-5: Reviewer 2 quality assessment scores for the included studies using Quality Assessment, Data Abstraction and Synthesis-2 (QUADAS-2) tool.

Study	Risk of Bias				Applicability		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Wang et al (2020)[5]	L	L	L	U	L	L	L
Yang et al (2020)[26]	L	H	U	U	L	L	U
Zhou et al (2020)[27]	L	U	L	L	L	L	L
Gao et al (2021)[24]	L	U	L	L	L	L	L

H: High. L: Low. U: Unclear.

Table-6: Diagnostic yield of bronchoscopic testing among suspected COVID-19 cases with negative upper respiratory tract samples.

First author (year)	Country	Study Type	Negative Diagnosis of Covid-19	PCR Kit Used	Initial Test	LRT sampling method	# of positive test by LRT method/# of Covid-19 negative patients	# of negative test by LRT method/# of Covid-19 negative patients
1. Ora et al (2020)[19]	Italy	Prospective observational	Viral RNA detection with PCR from NPS/OPS	NA	NPS/OPS*	BAL	BAL (0/28)	BAL (28/28)
1.5 Chang et al (2020)[21]	United States	Prospective observational	Viral RNA detection with PCR from NPS	Cepheid Xpert Xpress SARS-CoV-2	NPS	BAL	BAL (0/177)	BAL (177/177)
2. Stadlmann et al (2020)[28]	Switzerland	Case Report	Viral RNA detection with PCR from NPS	NA	NPS	BAL	BAL (1/1)	BAL (0/1)
3. Hauge et al (2020)[29]	Norway	Case Report	Viral RNA detection with PCR from NPS	NA	NPS	BAL	BAL (1/1)	BAL (0/1)
4.Gualano et al (2020)[6]	Rome	Case Report	Viral RNA detection with PCR from OPS	NA	OPS	BAL	BAL (1/1)	BAL (0/1)
5. Valan et al (2020)[30]	Norway	Case Report	Viral RNA detection with PCR from NPS	NA	NPS	BAL	BAL (1/1)	BAL (0/1)
6. Winichakoon et al (2020)[2]	Thailand	Case Report	Viral RNA detection with PCR from NPS/OPS	NA	NPS/OPS	BAL	BAL (1/1)	BAL (0/1)
7. Zhang et al (2020)[31]	China	Case Report	COVID-19 ribonucleic acid test from NPS	NA	NPS	BAL	BAL (1/1)	BAL (0/1)
8. Joob et al (2020)[32]	Thailand	Case Report	Viral RNA detection with PCR from NPS	NA	NPS	BAL	BAL (1/1)	BAL (0/1)
9. Wu et al (2020)[33]	China	Case Report	Viral RNA detection with PCR from NPS	NA	NPS	BAL	BAL (1/1)	BAL (0/1)
10.Furong et al (2020)[34]	China	Case Series	Viral RNA detection with PCR from Throat Swabs	NA	TS	BAL	BAL (2/2)	BAL (0/2)
12. Ng et al (2021)[35]	China	Case Report	Viral RNA detection with PCR from NPS/TS/DTS	NA	NPS/ TS/ DTS	BAL	BAL (1/4)	BAL (0/4)
13. Verleden et al (2020)[36]	Belgium	Case Series	Viral RNA detection with PCR from NPS	NA	NPS	BAL	BAL (2/2)	BAL (0/2)
14. Ramos et al (2020)[37]	United States	Case Report	Viral RNA detection with PCR from NPS	NA	NPS	BAL	BAL (3/3)	BAL (0/3)
15. Seo et al (2021)[38]	Korea	Case Report	Viral RNA detection with PCR from NPS	NA	NPS	BAL	BAL (1/1)	BAL (0/1)

*All patients underwent three consecutive upper respiratory tract samples (NPS, OPS, or a combination thereof)

COVID-19: Coronavirus disease 2019, PCR: Polymerase chain reaction, LRT: Lower respiratory tract, RNA: Ribonucleic acid, BAL: Bronchoalveolar lavage, NA: Not Available, NPS: Nasopharyngeal swab, OPS: Oropharyngeal swab, TS: Throat swab, DTS: Deep-throat swab.

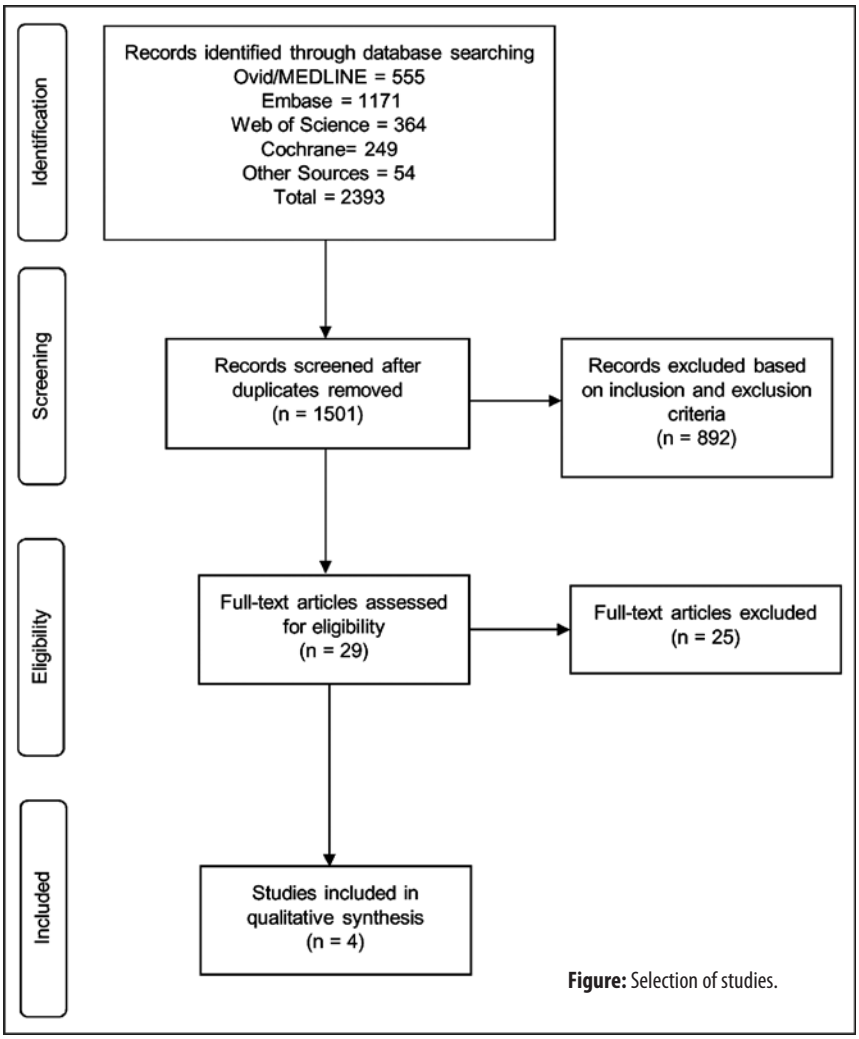

Figure: Selection of studies.

unclear or low in most cases, while the Cohen kappa statistic for interrater agreement was 0.87 (Tables-4, 5).

During the post-hoc analysis, 2 case series and 11 case reports described patients who were successfully diagnosed with COVID-19 using BAL PCR following negative URT sampling, while 2 sizeable prospective observational studies showed that BAL PCR returned negative in all of the initially negative URT samples among 205 adults with suspected COVID-19 infection (Table-6).

Discussion

The systematic review of limited observational data found that bronchoscopy with BAL had a reasonably high but variable sensitivity for the diagnosis of active SARS-CoV-2 infection, with reported values ranging from 68.2% to 94%. The yield of bronchoscopy was likely to be low in patients who may have undergone more than one URT sampling.

The reported diagnostic sensitivity of bronchoscopy with BAL compared favourably with that for NPS, which is variably reported to be anywhere from 54% to 98.3% but mostly around 70%.[13-15] On the other hand, OPS have been reported to have a sensitivity significantly lower than NPS with sensitivity reported as low as 21.1%.[14] Throughout the pandemic, NPS and OPS have by and large remained the diagnostic modality of choice in diagnosing COVID-19. A combination of relatively easy sampling and accessibility as well as favourable economics has made these tests widespread in use. Yet variable sensitivities and diagnostics yields, likely due to variations in sampling techniques and viral loads, have also meant that several COVID-19 cases remain undetected, leading to a delay in appropriate isolation and institution of specific therapies.

How does bronchoscopic sampling compare to less invasive means of obtaining LRT samples, such as obtaining expectorated or induced sputum, or obtaining tracheal aspirates in patients with an existing endotracheal or tracheostomy tube? According to one systematic review, RT-PCR testing of sputum samples had a reported sensitivity of 97.2% (90.3-99.7%).[16] Another systematic review found that the sample positivity was higher in sputum specimens compared to NPS and OPS.[13] There is paucity of data on the ability of tracheal aspirates to diagnose SARS-CoV-2 infection. Ling et al. reported that in 2 patients, viral loads from tracheal aspirates were consistently higher than NPS samples.[17] Previous studies with regard to SARS-CoV-1 and MERS-CoV have reported that tracheal aspirates had a greater diagnostic yield for SARS-CoV-1 than URT samples.[3]

So, where should bronchoscopy be placed in the diagnostic algorithm for suspected SARS-CoV-2 infection? Should we move to the potentially most sensitive test upfront or reserve it for cases where an NPS, for example, comes back negative? There are various layers to this question. First, the laws of probability dictate that repeating any test, such as NPS, would add to pooled sensitivity and, therefore, decrease the number of FN

cases. Thus, if repeating a less invasive test is safer or cost-effective, it may be preferable to choosing a more invasive option for repeat testing. Secondly, there is little reported data on the safety or cost of bronchoscopy in these patients. Finally, it is not clear to if bronchoscopy has a distinctly higher sensitivity for SAR-CoV-2 infection than the less invasive alternatives.[18] Ora et al. found that bronchoscopy did not identify a single case of previously missed COVID-19 infection in a series of 28 consecutive patients with clinically suspected infection in correlation with three negative NPS and/or OPS smears on consecutive days.[19] Similarly, Geri et al. reported that among 79 consecutive patients undergoing BAL due to negative or indeterminate URT samples and continued clinical suspicion of COVID-19 infection, only 2 were positive for CVOID-19 PCR.[20] A more recent study of asymptomatic adults undergoing scheduled bronchoscopy for various reasons found a 100% concordance between negative pre-procedure NPS testing and BAL testing.[21] As such, in the presence of consistently negative URT samples as well as normal computed tomography (CT) scans, the utility of diagnostic bronchoscopy may be limited. One potential exception may be any situation in which it would be desirable to sample higher viral loads (as perhaps may be suitable in certain research studies). Hamid et al. found that "deeper" samples (i.e., BAL samples coupled with endotracheal aspirates) had a significantly higher viral load than less invasive samples, such as NPS.[22] This may vary with disease timeline and disease severity, however, with some data suggesting that BAL viral load may decrease with disease progression and may in fact be lower than NPS viral load among more severely sick, critically ill patients.[23,24]

Furthermore, institutional clinical protocols for cases of suspected or confirmed SARS-CoV-2 infection should be borne in mind when weighing the pros and cons of opting for a diagnostic bronchoscopy. If "suspected" and "confirmed" SARS-CoV-2 infected patients are managed in an identical manner in terms of isolation protocols, provision of critical care where needed, administration of anti-inflammatory and anticoagulant pharmacotherapy, etc., the value added by a diagnostic bronchoscopy in the setting of one or more negative less invasive tests may be diminished. This becomes all the more relevant considering the presumable additional occupational hazards associated with performance of a bronchoscopy. It is also worth investigating, though outside the immediate scope of the current review, whether the viral load associated with a negative FN NPS or OPS can be expected to be low enough to make transmission significantly less likely even in the presence of active COVID-19 illness. However, a confirmed diagnosis of COVID-19 via a bronchoscopy may well lead to a distinct change in management in certain cases.[25] Experts have published guidelines to suggest that diagnostic bronchoscopy should only be considered as a last resort for COVID-19 testing.[7]

The current systematic review has several limitations. The studies included generally had modest sample sizes. Due to regional differences, a non-uniformity of PCR-based assays and differences in test characteristics within the laboratories were also noted. Furthermore, a uniform gold standard test was not used in all the studies reviewed. Robust prospective data is required to directly compare BAL with other LRT samples, including sputum testing and, where applicable, tracheal aspirate testing. This would enable accurate assessment of concordance rates and quantify the value added by bronchoscopy in the setting of negative LRT samples from other sources.

Conclusion

Though limited, data suggested that bronchoscopy with BAL did not reliably have higher diagnostic sensitivity than that reported for either NPS or OPS. Larger studies are needed for a head-to-head comparison of each test's diagnostic performance. The real-world clinical utility of BAL in suspected COVID-19 patients with one or more negative diagnostic tests merits further investigation. While it may be an option for suspected COVID-19 cases with previous negative tests, physicians should tread with caution while assessing the risks and benefits on a case-by-case basis keeping in mind the actual clinical utility of achieving a confirmatory diagnosis using a procedure that carries higher costs and potentially higher risks to the patient as well as to the medical personnel.

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