Indications, Clinical Utility, and Safety of Bronchoscopy in COVID-19

Biplab K Saha, Santu Saha, Woon H Chong, and Scott Beegle

BACKGROUND: Bronchoscopy is an aerosol-generating procedure and routine use for patients with coronavirus disease 2019 (COVID-19) has been discouraged. The purpose of this review was to discuss the indications, clinical utility, and risks associated with bronchoscopy in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia. METHODS: A literature search was performed by using appropriate key terms to identify all relevant articles from medical literature databases up to August 1, 2021. RESULTS: Twelve cohorts (9 retrospective and 3 prospective) reported the performance of 2,245 bronchoscopies in 1,345 patients with COVID-19. The majority of the subjects were male. Nearly two thirds of the bronchoscopies (62%) were performed for therapeutic indications; the rest (38%) were for diagnostic purposes. Bronchoalveolar lavage had an overall yield of 33.1% for SARS-CoV-2 in subjects with negative results of real-time polymerase chain reaction on nasopharyngeal specimens. The incidence of a secondary infection ranged from 9.3% to as high as 65%. Antibiotics were changed in a significant number of the subjects (14%–83%) based on the bronchoscopic findings. Bronchoscopy was well tolerated in most subjects except those who required noninvasive ventilation, in whom the intubation rate after the procedure was 60%. The rate of transmission of SARS-CoV-2 among health-care workers was minimum. CONCLUSIONS: Bronchoscopy in patients with COVID-19 results in a significant change in patient management. Transmission of SARS-CoV-2 seems to be low with consistent use of appropriate personal protective equipment by health-care workers. Therefore, bronchoscopic evaluation should be considered for all diagnostic and therapeutic indications in this patient population. *Key words: SARS-CoV-2; COVID-19; bronchoscopy; indications; complications.* [Respir Care 2022;67(2):241–251. © 2022 Daedalus Enterprises]

Introduction

Bronchoscopy is a commonly performed procedure for evaluation of respiratory diseases. It is a safe, minimally invasive technique that has an important diagnostic and therapeutic role.[1] Bronchoscopy is often performed as an outpatient or, when necessary, as an urgent or emergent procedure in the in-patient setting, such as in the ICU. Bronchoscopy is generally well tolerated by patients with minimal risk of serious complications.[2] Bronchoscopy is an aerosol-generating procedure and, therefore, has the potential for airborne transmission of diseases that affect the respiratory tract, for example, tuberculosis.[3] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative organism for coronavirus disease 2019 (COVID-19) and is responsible for the ongoing pandemic.[4,5] SARS-CoV-2 typically spreads by respiratory droplets and aerosols; therefore, performing bronchoscopy in this patient population has the potential to further increase the risk of exposure to health-care workers.[6] As a result, professional societies recommended universal use of personal protective equipment (PPE) for health-care workers, testing patients for COVID-19 infection before bronchoscopy, and performing the procedure in a timely and safe manner for patients with COVID-19.[7-10]

Dr BK Saha is affiliated with the Division of Pulmonary and Critical Care Medicine, Ozarks Medical Center, West Plains, Missouri. Dr S Saha is affiliated with the Division of Internal Medicine, Bangladesh Medical College, Dhaka, Bangladesh. Drs Chong and Beegle are affiliated with the Division of Pulmonary and Critical Care Medicine, Albany Medical Center College, Albany, New York.

The authors have disclosed no conflicts of interest.

Supplementary material related to this paper is available at http://rc.rcjournal.com.

Correspondence: Biplab K Saha MD, Division of Pulmonary and Critical Care Medicine, Ozarks Medical Center, West Plains, 1100 N Kentucky Avenue, MO 65775. E-mail: spanophiliac@yahoo.com.

DOI: 10.4187/respcare.09405

However, the overall number of bronchoscopies performed in patients with or without COVID-19 during this pandemic had been significantly low.[11-13] Avoidance of bronchoscopy in patients with COVID-19 carries the risk of misdiagnosis of their disease, the possibility of missing potentially curable cancers, and suboptimal treatment of secondary infections. There are several reports of bronchoscopic evaluation of patients with COVID-19 for different indications. Thus far, no reviews have systematically evaluated the role of bronchoscopy in this patient population. This article critically reviewed the medical literature and informs the reader with regard to the indications, bronchoscopic findings, clinical utility, and complications of bronchoscopy in patients with COVID-19.

Methods

This systematic review was performed and reported by following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines.[14]

Study Objectives

The primary objectives of the study were to determine the indications, utility, and complications of bronchoscopy in patients with COVID-19 pneumonia. The secondary objectives were to assess the patient demographics, bronchoscopic findings, benefits of PPE, and the risk of transmission of COVID-19 among health-care workers. In this study, the utility of bronchoscopy is defined as the new diagnosis of a secondary bacterial, viral, and fungal infection; changes in antimicrobials, systemic corticosteroids, and anticoagulation management.

Search Criteria

The MEDLINE, PubMed, and World Health Organization COVID-19 databases were searched by using the following formula: "(severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 or coronavirus disease 2019 or COVID-19) and bronchoscopy." The bibliography of the identified literature was then scrutinized to determine additional articles that met the inclusion criteria for our study.

Inclusion Criteria

Articles that fulfilled the following criteria were included in our study: (1) case control or cohort studies that reported the performance of bronchoscopy in subjects with COVID-19 either confirmed by real-time polymerase chain reaction or suspected based on the clinical or radiologic progression; (2) studies that reported bronchoscopy, bronchial wash, and bronchoalveolar lavage (BAL) performed both in the ICU and non-ICU settings; and (3) articles published in peer-reviewed journals or a preprint server between January 1, 2020, and August 1, 2021.

Exclusion Criteria

The exclusion criteria were as follows: (1) articles that reported subjects age < 18 years; (2) articles in the form of "case reports," and (3) literature not in the English language.

Data Collection Process

Two researchers (BKS, SS) independently performed eligibility assessment of the data in a standardized manner to identify articles that reported the performance of bronchoscopy in patients with COVID-19 or with suspected COVID-19. The reviewers (BKS, SS) were blinded to each other's assessment. Any disagreement between them was resolved by discussion and input from the third researcher (WHC). After the citations were identified, duplicate records were removed. The abstract of each citation was then screened for relevance to our study. Unrelated citations were excluded. The full texts of the remaining articles were then reviewed, along with the careful examination of the bibliography of the published articles.

Data Abstraction

Included studies were coded, and the extracted data from the studies were then tabulated in a standardized Excel sheet (Microsoft, Redmond, Washington). The following data were gathered from full-text articles: patient demographics, study design, date of participant enrollment, year of publication, number of patients in the study, indication for bronchoscopy, secondary infections identified, bronchoscopic findings, changes in management after bronchoscopy, number of bronchoscopists, total number of bronchoscopies, ventilator management during bronchoscopy, use of PPE, and rates of SARS-CoV-2 transmission or rates of infections among health-care workers. The characteristics and outcomes of all included studies were analyzed.

Study Risk and Bias Assessment

BKS and SS independently performed quality assessments by using the Newcastle-Ottawa Scale[15]; they were blinded to each other's assessments. The Newcastle-Ottawa Scale contains 9 items for cohort and case-control studies. In the Newcastle-Ottawa Scale, the total score ranges from 0 to 9 and is categorized into 3 groups: low quality, 0–3; moderate quality, 4–6; and high quality, 7–9.

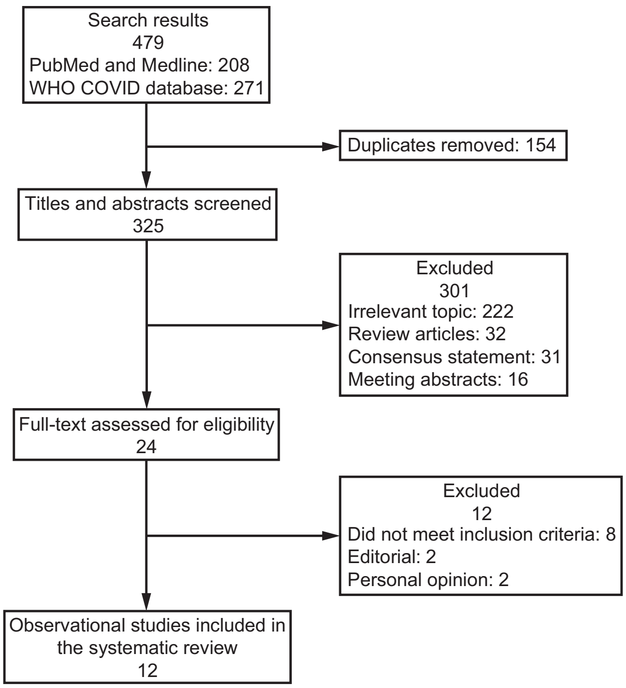

Fig. 1. Flow chart.

Any disagreements between the researchers were resolved by discussion among investigators.

Results

Study Selection

A total of 479 citations were identified in the initial search. After the removal of duplicates (no. = 154) and those that did not meet the inclusion criteria (by title, abstract, and full text review: no. = 313), 12 studies were eligible and included for this systematic review (Fig. 1).

Study Characteristics

The study characteristics are reported in Table 1. Nine retrospective[11,18,19,20,21,22,23,24,26] and 3 prospective cohort studies[16,17,25] were included. Eight studies[16,17,18,19,20,23,24,26] were from a single center, whereas 4 studies were conducted as multi-center studies.[11,21,22,25] Overall, the relevant data were collected by researchers between March 2020 and December 2020. A total of 11 articles[11,17,18-26] were peer reviewed at the time of this review. Eight studies were[11,16,17,19,20,24,25,26] published in 2021 and four in 2020.[17,20,21-22] One manuscript was published on a preprint server (medRxiv) in 2021.[16] Three studies were reported from Italy and Spain; 2 studies from the United States; and 1 study each from France, Belgium, Germany, and India. All included studies were of moderate quality (Table 2).

Patient Demographics and Diagnosis of COVID-19

All the subjects included in this systematic review were diagnosed with COVID-19 either by real-time polymerase chain reaction of the nasopharyngeal swab or suspected to have the disease from their clinical and radiologic presentation and progression. Eight studies[11,17,21,22,23,25,26,27] specified the sex distribution among patients who underwent bronchoscopy, and most of the patients were male (70.9%–83.6%). The median and mean age ranged from 60 to 64.6 y and 59 to 62.1 y, respectively. The age of the patient population was not specified in 3 studies.[17-19] Complete demographic data were not available for all studies (Supplementary Table 1, see related supplemental material at http://rc.rcjournal.com).

All subjects underwent bronchoscopy in the hospital after being admitted as in-patients. A total of 1,345 subjects underwent 2,245 bronchoscopies. The severity of illness among the subjects (patients on room air, oxygen supplementation, noninvasive ventilation [NIV], or intubated) while undergoing bronchoscopy was specified by 11 of the 12 studies (92%).[11,16,17,18,19,20,21,23,24,25,26] The majority of the bronchoscopies were performed in the patients who were intubated, 1,879 of 2,245 (83.7%). Six of the 12 studies[16,18,19,20,24,26] (50%) only included subjects who were intubated and mechanically ventilated in the ICU; 73 of 1,345 subjects (5.4%) were receiving extracorporeal membrane oxygenation and 10 of 1,345 (0.7%) required NIV support; 107 of 1,345 of the subjects (7.9%) received varying quantities of oxygen during the bronchoscopy. Only 13 of 1,345 (0.9%) subjects were specified to be on room air.

Indication, Utility, and Bronchoscopic Findings

Bronchoscopies were performed for both diagnostic and therapeutic indications. The indications for bronchoscopy were specified in all but 1 study (Supplementary Table 1, see related supplemental material at http://rc.rcjournal.com).[20] A total of 724 of 1,906 bronchoscopies (38%) were diagnostic, whereas the rest, 1,182 of 1,906 (62%) (10 studies), were performed for therapeutic reasons. Among all the diagnostic bronchoscopies, 179 of 724 (24.7%) were done to evaluate for SARS-CoV-2 infection. The remainder of the diagnostic bronchoscopies were undertaken for the suspicion of secondary infection or concerns for a non-COVID-19 diagnosis. Primary indications for therapeutic bronchoscopy were airway occlusion by mucus plug as manifested by atelectasis or segmental collapse on chest radiology,[16-18,21,24] increased airway resistance,[17] and overall increased airway mucus with or without definitive airway occlusion.[16,18,24] The utility refers to the microbiologic diagnostic yield, change in therapeutic interventions as a direct result of bronchoscopic evaluation, and a positive change in the patient's clinical status. The indication,

Table 1. Characteristics of Included Observational Studies

Study	Y	Country	Type of Study	Study Period	subject Population	No. Centers	Type of subjects	Study Objectives
Guarino et al[17]	2021	Italy	Prospective study	Mar 1, 2020 to Jun 1, 2020	Subjects with proven or suspected COVID-19	Single	Intubated (88.5%), NIV (8.5%), sedated (3.5%)	Description of indications, bronchoscopic findings, and procedural safety
Mondoni et al[21]	2020	Italy	Retrospective study	Mar 1, 2020 to Apr 15, 2020	Subjects with proven COVID-19 by real-time polymerase chain reaction, and suspected subjects	Multi-center; 6 centers	subjects on room air (11.9%), supplemental oxygen (75.3%), NIV (2.7%), intubated (8.2%), and ECMO (1.8%)	Diagnostic yield of bronchoscopy in subjects with negative NP swab result; indication of bronchoscopy; assessment of the safety for health-care workers
Patrucco et al[22]	2020	Italy	Retrospective study	Mar 15, 2020 to May 17, 2020	Subjects with diagnosed and suspected COVID-19	Multi-center; 3 centers	Most subjects were hospitalized in the internal medicine ward (63.3%)	Evaluation of BAL in the detection of SARS-CoV-2; radiologic, clinical and bronchoscopic findings in subjects with COVID-19
Chang et al[20]	2021	United States	Retrospective study	Mar 13, 2020 to Apr 2fourth 2020	Subjects with confirmed COVID-19	Single	Intubated s	Safety of bronchoscopy in subjects with COVID-19 and risks of transmission among health-care workers; evaluation of secondary bacterial and fungal pneumonia
Torrego et al[18]	2020	Spain	Retrospective study	Mar 13, 2020 to Apr 4, 2020	Subjects with COVID-19	Single	Intubated	Description of indications, bronchoscopic findings, and incidence of secondary infection
Bruyneel et al[23]	2020	Belgium	Retrospective study	Mar 6, 2020 to Apr 2first 2020	Subjects with confirmed COVID-19 and 2 with suspected COVID-19 on radiology	Single	Intubated (90.6%)	Assessment of indication, procedures, complications, and impact of bronchoscopy on clinical course
Mehta et al[16]	2021	India	Prospective study	Aug 2sixth 2020 to Dec 3, 2020	Subjects with confirmed COVID-19	Single	Intubated	Description of indications, bronchoscopic findings, utility, and safety among health-care workers
Baron et al[19]	2021	France	Retrospective study	Mar 3first 2020 to Jun 3, 2020	Subjects with confirmed COVID-19 and 2 suspected cases	Single	Intubated	Evaluation of secondary infection
Loor et al[24]	2021	Spain	Retrospective study	NS	Subjects with confirmed COVID-19	Single	Intubated	Determination indications, impact on clinical management, safety, and complications of bronchoscopy
Mahmood et al[11]	2021	United States	Retrospective study	Mar 1, 2020 to Jul 3first 2020	Subjects with suspected and confirmed COVID-19	Multi-center; 4 academic centers	Intubated (86.8%); rest in medical wards; ECMO 5 (9.4%)	Assessment of clinical utilization of bronchoscopy and diagnostic yield of bronchoscopy in subjects with negative NP swab results
Arenas-De Larriva et al[25]	2021	Spain	Prospective study	Feb 20, 2020 to Jun 30, 2020	Subjects with suspected and confirmed COVID-19	Multi-center; 17 secondary and tertiary hospitals	subjects who were intubated (93.2%); ECMO 66 (6.6%)	Impact of bronchoscopic findings on the outcome of subjects; diagnostic yield of bronchoscopy with negative NP swab results
Cornelissen et al[26]	2021	Germany	Retrospective study	Feb 2third 2020 to Nov 3, 2020	Subjects with confirmed COVID-19	Single	Intubated	Assessment of bronchoalveolar lavage fluid characteristics; evaluation for secondary infection

COVID-19 = coronavirus disease 2019
NIV = noninvasive ventilation
ECMO = extracorporeal membrane oxygenation
NP = nasopharyngeal
NS = not specified
BAL = bronchoalveolar lavage

Table 2. Newcastle-Ottawa Scale Score of the Included Studies

Study	Type of Study	Selection*				Comparability		Outcome/Exposure†			Total Score
		1	2	3	4			a	b	c	
Guarino et al[17]	Prospective cohort	×	NA	×	×	NA	NA	×	×	×	6
Mondoni et al[21]	Retrospective cohort	×	NA	×	×	NA	NA	×	×	×	6
Patrucco et al[22]	Retrospective cohort	×	NA	×	×	NA	NA	×	×	NA	5
Chang et al[20]	Retrospective cohort	×	NA	×	×	NA	NA	×	×	×	6
Torrego et al[18]	Retrospective cohort	×	NA	×	×	NA	NA	×	NA	×	5
Bruyneel et al[23]	Retrospective cohort	×	NA	×	×	NA	NA	×	NA	×	5
Mehta et al[16]	Prospective cohort	×	NA	×	×	NA	NA	×	×	×	6
Baron et al[19]	Retrospective cohort	×	NA	×	×	NA	NA	×	NA	×	5
Loor et al[24]	Retrospective cohort	×	NA	×	×	NA	NA	×	NA	×	5
Mahmood et al[11]	Retrospective cohort	×	NA	×	×	NA	NA	×	×	×	6
Arenas-De Larriva et al[25]	Prospective cohort	×	NA	×	×	NA	NA	×	×	×	6
Cornelissen et al[26]	Retrospective cohort	×	NA	×	×	NA	NA	×	×	NA	5

*Selection: 1, representativeness of the exposed cohort; 2, selection of the non-exposed cohort; 3, ascertainment of exposure; 4, demonstration that outcome of interest was not present at the start of the study.
†Outcome/Exposure: a, assessment of outcome; b, was follow-up long enough for outcomes to occur; c, adequacy of follow-up of cohorts.
NA = not applicable

utility, and bronchoscopic findings in the reported studies are summarized in Supplementary Table 1, (see related supplemental material at http://rc.rcjournal.com).

Peri-Procedural Risk

Based on our review, bronchoscopy and BAL were well tolerated in most patients, including those who were critically ill and in ICU. No severe adverse events related to bronchoscopy were reported in any subject (Supplementary Table 1, see related supplemental material at http://rc.rcjournal.com). No patient had a cardiopulmonary arrest, pneumothorax, or cardiac arrhythmia. When specified, transient hypoxemia ($S_{pO_2} < 90\%$) was described in 10 of 331 of procedures (3%) ($n = 2$).[21,24] Six of 10 subjects (60%) who were on NIV required intubation after bronchoscopic evaluation.[17,23]

Bronchoscopy Technique and Use of PPE

All bronchoscopies were performed in accordance with the guidelines[7,9,10] provided by the World Health Organization, Centers for Disease Control and Prevention, and other professional societies. Eleven[11,16,17,18,19,20,21,22,23,24,26] of 12 studies (92%) specified the use of PPE. All the health-care workers used full PPE, including gown, face shield, eye protector, shoe cover, double gloves, filtering face pieces (FFP2/FFP3), N95 mask, and, sometimes, a powered air-purifying respirator (Table 3). The use of negative pressure rooms for bronchoscopy was not universal. Four of 7 studies[11,17,19,20] (57%) reported the use of negative pressure rooms for all their procedures. Bronchoscopies in the other 3 studies[18,24,25] were performed without negative pressure rooms. One study reported that > 90% of the bronchoscopies were performed without negative pressure rooms.[25] Flexible bronchoscopy was performed in all but 1 patient.[21] Disposable bronchoscope was used for all the patients in 6 of 9 reports (67%).[17,18,20,21,23,24] Two studies used both disposable and non-disposable bronchoscopes,[11,25] whereas, in 1 study, only a non-disposable bronchoscope was used.[26] Bruyneel et al[23] reused a disposable bronchoscope in 15 ICU subjects who required repeated procedures. The bronchoscopes were processed in the typical way after the initial bronchoscopy.[23]

The number of bronchoscopists and other health-care workers who participated in bronchoscopy procedures varied significantly among the studies. Six of nine studies (67%) reported 1 bronchoscopist being present in the room during the procedure.[16,17,19-21,23] Of these 6 studies, a bedside nurse was available to assist the operator in four.[17,19,21,23] Chang et al[20] specified the presence of the bedside nurse immediately outside the room, whereas Mehta et al[16] had a nurse, a technician, and a respiratory therapist assist with the bronchoscopy (Table 3). Torrego et al[18] reported using a second bronchoscopist for assistance with the ventilator during bronchoscopy. The other health-care workers were available outside the room in this study. Two studies reported a specific practice before entering the room, including preparation of all necessary supplies to reduce the stay inside the room.[17,18]

Transmission Risk of SARS-CoV-2 Among Health-Care Workers

Nine of the included studies[16,17,18,19,20,21,23,24,26] reported SARS-CoV-2 transmission risks among health-care workers (Table 3). Among the studies that specified the

Table 3. Bronchoscopy Technique and Use of PPE

Study	Preoxygenation for Apneic Bronchoscopy	Neuromuscular Blockade	PPE	Negative Pressure Rooms	Bronchoscope	No. Bronchoscopist per Procedure	No. Other Health-Care Workers	Duration, min	Transmission of SARS-CoV-2
Guarino et al[17]	Yes; 100% oxygen for 5–10 min	No	Preplanned dressing and undressing procedure; PPE included protective full body suit, FFP2/ FFP3 masks, head gear, shoe covers, double gloves	Yes; for all bronchoscopies	Disposable scope for all procedures	1	1 bedside nurse	3–8	None of the 115 health-care workers involved
Mondoni et al[21]	NS	NS	Yes; WHO[45] recommendation on air-borne precaution and aerosol generating procedures were strictly followed	NS	Disposable scope for all cases	1	1 bedside nurse	NS	None; followed up for >15 d after bronchoscopy
Patrucco et al[22]	NR	NS; conscious sedation (116); general anesthesia (15)	Yes; not specifically mentioned	NS	NR	NR	NR	8 (7–9)	NR
Chang et al[20]	Yes; for 2 min with 100% oxygen	Used before the procedure	Yes; gown, N95 mask, hair cover, face shield and gloves	Yes; for all bronchoscopies	Disposable scope for all cases	1	Bedside nurse immediately available outside	NS	None of the 10 bronchoscopists were infected with a > 2 wk post procedure follow-up
Torrego et al[18]	Yes; F_{IO_2} was increased to attain S_{pO_2} 95%–98%	No	Yes; all necessary equipment were prepared before entering the room; level 3 PPE; plastic gown with head and neck cover, N95/FFP3, eye protection, double gloves	Not always used	Disposable scope for all cases	1 bronchoscopist; occasional assistance from the intensivist	Ancillary staff was not in the room	<10	1/3 bronchoscopist was infected
Bruyneel et al[23]	NS	NS	PAPR (reused after disinfection), FFP2, double layered, protective uniform, double gloves	NS	Disposable scope for all cases; 15 scopes were used more than once in the same patient	1 bronchoscopist	1 bedside nurse	NS	None got infected in 3-month follow-up
Mehta et al[16]	Yes; for 20 min with 100% oxygen	Yes	Yes; body gown, P 100 respirator, face shield, double gloves	Yes; for all procedures	NS	1 bronchoscopist	1 ICU nurse, 1 RT, and 1 technician	NS	None got infected during the duration of the study
Baron et al[19]	NS (standard guideline was followed)	NS	NS	NS	NS	1 bronchoscopist	1 bedside nurse (of 3 dedicated nurses)		2 bronchoscopists and 3 nurses: none got infected by serologic testing

(Continued)

Table 3. Continued

Study	Preoxygenation for Apneic Bronchoscopy	Neuromuscular Blockade	PPE	Negative Pressure Rooms	Bronchoscope	No. Bronchoscopist per Procedure	No. Other Health-Care Workers	Duration, min	Transmission of SARS-CoV-2
Loor et al[24]	NS	NS	Yes; FF3, body gown, eye protection, double gloves, hair cover, shoe cover	Most bronchoscopies were performed in non-negative pressure room	Disposable scope for all cases	NS	NS	NS	None of the bronchoscopists were infected
Mahmood et al[11]	NS	NS; general/deep sedation (51); moderate (1); awake (1)	Yes; PAPR or N95, face shields	Yes; for all procedures	Disposable (36); non-disposable (17)	NR	NR	NR	NS
Arenas-De Larriva et al[25]	NS	NS	The recommendations could not be universally followed	90.7% of bronchoscopies were performed in non-negative pressure room	Disposable (94.5%); non-disposable (5.5%)	1–5 health-care workers per procedure		NR	NR
Cornelissen et al[26]	NS	NS	Yes; NS	NS	Non-disposable for all cases	A total of 5 bronchoscopists performed all procedures	NR	NR	All tested negative by serologic testing

PPE = personal protective equipment
SARS-CoV-2 = severe acute respiratory syndrome coronavirus disease 2019
FFP = filtering face piece
NS = not specified
WHO = World Health Organization
NR = not reported
PAPR = powered air-purifying respirator
RT = respiratory therapist

incidence of transmission, 646 patients underwent a total of 1,034 bronchoscopies in our review. Only 1 study reported 1 bronchoscopist who developed COVID-19 during the third week of study and needed to be replaced by another bronchoscopist.[18]

Discussion

Since the beginning of the pandemic, the transmission of SARS-CoV-2 among health-care workers has been reported in multiple studies. The rate of transmission varied between 4.1% and 18%.[27-29] Because bronchoscopy is an aerosol-generating procedure, it has been hypothesized to carry a high risk for SARS-CoV-2 transmission.[3] Predominantly small cohorts of patients with COVID-19 who have undergone bronchoscopy have been reported in the literature. Bronchoscopic evaluation resulted in superior diagnostic yield on microbiologic studies and changed treatment plans for many patients.

The rate of a positive SARS-CoV-2 results by real-time polymerase chain reaction from a lower respiratory tract sample has varied in the literature. Wang et al[30] reported a 92% positivity (14/15) on the BAL specimen. In our study, a significant number of subjects with a false-negative result were eventually correctly diagnosed by bronchoscopy. The rate varied between 2.3% and 55.1%, with an overall yield of 92 of 278 (33.1%). These differences could be due to better characterization of radiologic abnormalities caused by SARS-CoV-2 pneumonia and the performance of bronchoscopy on patients without such patterns to exclude rather than make a diagnosis of COVID-19. Most of the included subjects had double-negative nasopharyngeal real-time polymerase chain reaction results, which likely also reduced the likelihood of a positive test result. The yield of the bronchial wash and BAL were similar.[22] This finding was crucial because large-volume BAL may be avoided by performing a bronchial wash with a small volume of normal saline solution. Wang et al[30] reported a diagnostic yield of 63% from endobronchial brush biopsy specimens.

The bronchoscopic findings were nonspecific and are summarized in Supplementary Table 1, see related supplemental material at http://rc.rcjournal.com. Although some investigators reported normal mucosa in a minority of subjects, most subjects demonstrated hyperemic and inflamed airways.[18,24] Development of airway polyps was also reported.[31] As with previous studies, thick airway secretions were also observed in the current review.[32,33] Mucus plugs that resulted in airway occlusion that caused hypoxia were likely the cause of an unusually high number of the required bronchoscopies observed in some studies.[20,23,24] Guarino et al[17] reported performing bronchoscopies in 33% of the subjects, Loor et al[24] performed 222 procedures in their series of 75 subjects. A recent study also reported the presence of thick mucus during 60% of bronchoscopies.[25]

The most common sites for a mucus plug were bilateral lower lobes, but involvement of more proximal airways, including the trachea, was also seen.[25] Clearance of mucus was associated with improved oxygenation.[24] The presence of hemorrhagic secretion in the distal airways was found to be an independent predictor of increased mortality.[25] Guarino et al[17] reported a group of 30 subjects who were intubated and who underwent bronchoscopic evaluation for a rapid increase in pulmonary resistance. None of these subjects had any evidence of airway occlusion on bronchoscopy, but 23 of 30 (76.7%) were eventually found to have pulmonary thromboembolism.[17] Acute pulmonary embolism is a known cause of bronchoconstriction and should be considered in the differential diagnoses, especially if the bronchoscopy reveals no airway obstruction.[34]

Bronchoscopy brought on a number of modifications in the management of these patients. These changes can be categorized as (1) identification of secondary infection, (2) adjustment of antimicrobials, (3) alteration in systemic corticosteroid therapy, and (4) changes in anticoagulation therapy. Secondary bacterial and fungal infection is associated with increased morbidity and mortality in patients with COVID-19.[35] The incidence of secondary infection varied widely. Bacterial and fungal isolates were identified in a significant number of subjects in our study and resulted in the optimization of antibiotic, antiviral, and antifungal therapy (Supplementary Table 1, see related supplemental material at http://rc.rcjournal.com). These isolated bacteria showed a similar distribution as seen in subjects without COVID-19 and with ARDS.[18,36-38] Whether SARS-CoV-2 represents a specific risk factor for invasive *Aspergillus* infection is currently unknown.

However, a large number of patients with COVID-19 have been reported to have had invasive pulmonary aspergillosis.[39] The rate of *Aspergillus* infection was as high as 25% in 1 study.[19] Therefore, as with influenza, a low threshold of suspicion is necessary to identify *Aspergillus* infection early in patients with COVID-19.[40] Several studies specified changes in the existing antibiotic regimen based on bronchoscopy results.[16,18,19,23,24] The rate of antibiotic change varied from 14% to 83% among the included studies. Similarly, antifungal treatment modification and initiation of antiviral treatment for non-COVID-19 viral infection were also reported.[19]

Corticosteroid and systemic anticoagulation are commonly used in patients who are critically ill and with COVID-19. Low-dose dexamethasone has been shown to improve mortality in patients who are critically ill with COVID-19, and is recommended by all major guidelines.[41] However, systemic corticosteroids can predispose patients to secondary bacterial and fungal infections, and, therefore, identification of secondary infection may necessitate reduction or discontinuation of systemic steroid therapy.[42] Mehta et al[16] reported discontinuation of systemic corticosteroids in 6% of their subjects, Baron et al[19] were able to initiate such therapy in 21% of their subjects after bronchoscopy.

Development of alveolar hemorrhage can be a life-threatening complication of therapeutic anticoagulation. Systemic anticoagulation increases the risk of alveolar bleeding, which can be easily diagnosed on bronchoscopy and BAL. Mehta et al[16] and Loor et al[24] reported modification of anticoagulant therapy for a number of subjects after bronchoscopy. Bronchoscopy helped to diagnose other non-COVID-19, noninfectious diseases such as organizing pneumonia and vasculitis. Pulmonary malignancy was identified in 8 of 86 subjects in the report by Patrucco et al.[22] In addition, bronchoscopy provided the diagnosis of non-COVID-19 lower respiratory tract infection by other pathogens. Bronchoscopy and BAL seemed to be associated with a low risk of complications. No major adverse events including cardiac arrhythmia or cardiac arrest were reported in any patient. Mild hypoxemia and fever were reported in a minority of patients. Importantly, when bronchoscopy was performed in patients who required NIV, the procedures were associated with severe hypoxia (S_{pO_2} < 60%), and the majority of patients subsequently were intubated (6 / 10). Therefore, bronchoscopy in patients who required NIV may be associated with further worsening of hypoxemia and precipitation of respiratory failure that requires ventilatory support.

The major concern with regard to SARS-CoV-2 transmission among health-care workers was minimum in our study. Only 1 health-care worker was infected among all the studies included in this review. In addition, in a retrospective observational study that included 280 subjects who underwent > 450 bronchoscopic procedures in the ICU by 35 bronchoscopists, only 1 operator serologically tested positive for COVID-19 without any reported acute illness.[29] As with other respiratory pathogens, SARS-CoV-2 can be transmitted by respiratory droplets and aerosols, and respiratory particles that measure in between these.[6] Use of negative pressure rooms and frequent air exchanges (at least 12 times an hour) reduces the quantity of infectious particles in the room and likely provides beneficial protective effects.[42] Similarly, neuromuscular blockade, apneic bronchoscopy, clamping of the endotracheal tube, and disconnection from the ventilator during the insertion and withdrawal of the bronchoscope may reduce the risk further. In addition, the preparation of salinesolution-filled BAL syringes outside the patients' rooms is likely to shorten the procedure time.[17] Minimizing the number of healthcare workers in the room during the actual procedure reduces exposure and may have contributed to the observed low transmission rate.

The use of PPE is crucial to minimize the risk of disease transmission during bronchoscopy. All involved health-care workers were reported to have used appropriate PPE, except in 1 study.[25] The rate of SARS-CoV-2 transmission among health-care workers was not specified in this study. A complete set of PPE includes a fitted high-filtration mask (or powered air-purifying respirator), eye protection (goggles or face shield), hair cover, body gown, shoe cover, and double gloves. A systematic approach in donning and doffing of PPE is essential.[44] The bronchoscopies were performed in various settings, including the ICU, bronchoscopy suite, medical wards, and the operating room. However, the vast majority of bronchoscopies (84%) were performed in subjects who were intubated and on mechanical ventilation, with or without paralytics. It is unclear if the safety data from a patient who was intubated, on mechanical ventilation, paralyzed, and undergoing apneic bronchoscopy can be generalized to other patient populations, such as a patient undergoing bronchoscopy under moderate sedation in the endoscopy suite. Whether every protective measure that was undertaken is necessary is also unknown. Well-designed prospective studies in the future may provide valuable data to answer these concerns. Both disposable and non-disposable bronchoscopes were used without any heightened risk of disease transmission in our study. When processed in the usual manner, disposable bronchoscopes could potentially be used for repeated bronchoscopy in the same patient, if necessary.

Limitations of the Study

Our study had several limitations. First, most studies included in this systematic review are composed of small cohorts of subjects and the results may not be generalizable. Second, there is a risk of publication bias because bronchoscopies in these subjects that have been complicated by adverse effects, non-utility, or disease transmission may not have been reported. Third, the majority of the reports were retrospective chart reviews. As a result, the reported data were not complete for many studies. Similarly, there was significant heterogeneity among reports. Fourth, the majority of the studies were single-center based, which may have affected the outcomes of the study. Fifth, the overall quality of the studies was medium because no control group was available.

Conclusions

Bronchoscopic evaluation of these subjects with COVID-19 seemed to be safe and potentially added small additional risks to health-care workers when appropriate precautions were taken. Bronchoscopy helps with the diagnosis of SARS-CoV-2 pneumonia and with the identification of secondary infections, thereby assisting in the institution of appropriate antimicrobial therapy and adjustment of systemic corticosteroid treatment. Alveolar hemorrhage can be a life-threatening complication of therapeutic anticoagulation and can be easily identified on bronchoscopy as well. In addition, clearance of thick airway secretion and mucus plugs may improve oxygenation. Bronchoscopy in patients who require NIV may be complicated by severe hypoxemia and precipitation of ventilator-dependent respiratory failure, and should be performed with caution. With proper use of PPE, bronchoscopic intervention likely poses minimal risk to healthcare workers while possibly providing significant benefit to the patient.

REFERENCES

1. Jolliet P, Chevrolet JC. Bronchoscopy in the intensive care unit. Intensive Care Med 1992;18(3):160-169.
2. Jin F, Mu D, Chu D, Fu E, Xie Y, Liu T. Severe complications of bronchoscopy. Respiration 2008;76(4):429-433.
3. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS One 2012;7(4): e35797.
4. Saha BK, Bonnier A, Chong W. Antimalarials as antivirals for COVID-19: believe it or not! Am J Med Sci 2020;360(6):618-630.
5. Saha BK, Chong WH, Austin A, Kathuria R, Datar P, Shkolnik B, et al. Pleural abnormalities in COVID-19: a narrative review. J Thorac Dis 2021;13(7):4484-4499.
6. Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. BMJ 2020;371:m3862.
7. Wahidi MM, Lamb C, Murgu S, Musani A, Shojaee S, Sachdeva A, et al. American Association for Bronchology and Interventional Pulmonology (AABIP) Statement on the Use of Bronchoscopy and Respiratory Specimen Collection in Patients With Suspected or Confirmed COVID-19 Infection. J Bronchology Interv Pulmonol 2020;27(4):e52-e54.
8. Wahidi MM, Shojaee S, Lamb CR, Ost D, Maldonado F, Eapen G, et al. The use of bronchoscopy during the coronavirus disease 2019 pandemic. Chest 2020;158(3):1268-1281.
9. Luo F, Darwiche K, Singh S, Torrego A, Steinfort DP, Gasparini S, et al. Performing bronchoscopy in times of the COVID-19 pandemic: practice statement from an international expert panel. Respiration 2020;99(5):417-422.
10. Guedes F, Boléo-Tomé JP, Rodrigues LV, Bastos HN, Campainha S, de Santis M, et al. Recommendations for interventional pulmonology during COVID-19 outbreak: a consensus statement from the Portuguese Pulmonology Society. Pulmonology 2020;26(6):386-397.
11. Mahmood K, Abbott M, Van Nostrand K, Bechara R, Gonzalez AV, Brucker A, et al. Low utilisation of bronchoscopy to assess COVID-19 respiratory infection: a multicenter experience. BMJ Open Resp Res 2021;8(1):e000962.
12. Goto T. Effect of the coronavirus disease pandemic on bronchoscopic diagnosis of lung cancer in a provincial city in Japan. J Cardiothorac Surg 2021;16(1):115.
13. Hilzenrat RA, Deen SA, Yee J, Grant KA, Ashrafi AS, Coughlin S, et al. Thoracic surgeon impressions of the impact of the COVID-19 pandemic on lung cancer care–lessons from the first wave in Canada. Curr Oncol 2021;28(1):940-949.
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021 Mar 29;10(1):89.
15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603-615.
16. Mehta R, Bansal S, Kumar A, Thorbole A, Chakravarthi L, Kalpakam H. Bronchoscopy in COVID19 ARDS patients on mechanical ventilation – a prospective study. medRxiv. 2021.02.02.21250362 2021.
17. Guarino C, Cesaro C, Fiorentino G, Rossi F, Polverino BM, Fragranza F, et al. Bronchoscopy in COVID-19 patients: when, how and why. Experience in clinical practice. Monaldi Arch Chest Dis 2021;91(2).
18. Torrego A, Pajares V, Fernández-Arias C, Vera P, Mancebo J. Bronchoscopy in patients with COVID-19 with invasive mechanical ventilation: a single-center experience. Am J Respir Crit Care Med 2020;202(2):284-287.
19. Baron A, Hachem M, Tran Van Nhieu J, Botterel F, Fourati S, Carteaux G, et al. Bronchoalveolar lavage in patients with COVID-19 with invasive mechanical ventilation for acute respiratory distress syndrome. Ann Am Thorac Soc 2021;18(4):723-726.
20. Chang SH, Jiang J, Kon ZN, Williams DM, Geraci TC, Smith DE, et al. Safety and efficacy of bronchoscopy in critically ill patients with coronavirus disease 2019. Chest 2021;159(2):870-872.
21. Mondoni M, Sferrazza Papa GF, Rinaldo R, Faverio P, Marruchella A, D'Arcangelo F, et al. Utility and safety of bronchoscopy during the SARS-CoV-2 outbreak in Italy: a retrospective, multicentre study. Eur Respir J 2020;56(4):2002767.
22. Patrucco F, Albera C, Bellocchia M, Foci V, Gavelli F, Castello LM, et al. SARS-CoV-2 detection on bronchoalveolar lavage: an Italian multicenter experience. Respiration 2020;99(11):970-978.
23. Bruyneel M, Gabrovska M, Rummens P, Roman A, Claus M, Stevens E, et al. Bronchoscopy in COVID-19 intensive care unit patients. Respirology 2020;25(12):1313-1315.
24. Loor K, Álvarez A, Felipe Montiel A, Ferrer R, Roca O, García-de-Acilu M, et al. Safety, diagnostic, and therapeutic value of flexible bronchoscopy in critically ill COVID-19 patients. Can J Anaesth 2020;68(3)434-435.
25. Arenas-De Larriva M, Martín-DeLeon R, Urrutia Royo B, Fernández-Navamuel I, Gimenez Velando A, Nuñez García L, et al. The role of bronchoscopy in patients with SARS-CoV-2 pneumonia. ERJ Open Res 2021;7(3):00165-2021.
26. Cornelissen CG, Bergs I, Müller AG, Daher A, Kersten A, Balfanz P, et al. Broncho-alveolar lavage in patients with acute respiratory distress syndrome due to COVID-19. Intern Med J 2021;51(6):965-967.
27. Çelebi G, Pişkin N, Çelik Bekleviç A, Altunay Y, Salcı Keleş A, Tüz MA, et al. Specific risk factors for SARS-CoV-2 transmission among health care workers in a university hospital. Am J Infect Control 2020;48(10):1225-1230.
28. Keeley AJ, Evans C, Colton H, Ankcorn M, Cope A, State A, et al. Roll-out of SARS-CoV-2 testing for healthcare workers at a large NHS Foundation Trust in the United Kingdom. Euro Surveill 2020;25 (14):2000433.
29. Gao CA, Bailey JI, Walter JM, Coleman JM, Malsin ES, Argento AC, et al. Bronchoscopy on intubated patients with COVID-19 is associated with low infectious risk to operators. Ann Am Thorac Soc 2021;18(7):1243-1246.
30. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020;323(18):1843-1844.
31. Sanivarapu R, Kang J, Anjum F. Rare endobronchial polyps due to SARS-CoV-2 infection. J Bronchology Interv Pulmonol 2021;28(2): e31-e33.
32. Wang C, Xie J, Zhao L, Fei X, Zhang H, Tan Y, et al. Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients. EBioMedicine 2020;57:102833.
33. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deigendesch N, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated

findings in lungs and other organs suggesting vascular dysfunction. Histopathology 2020;77(2):198-209.

34. Vidal Melo MF, Harris RS, Layfield D, Musch G, Venegas JG. Changes in regional ventilation after autologous blood clot pulmonary embolism. Anesthesiology 2002;97(3):671-681.
35. Chong WH, Saha BK, Ramani A, Chopra A. State-of-the-art review of secondary pulmonary infections in patients with COVID-19 pneumonia. Infection 2021;49(4):591-605.
36. Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al.; COVID-19 Researchers Group. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect 2021;27(1):83-88.
37. Fu Y, Yang Q, Xu M, Kong H, Chen H, Fu Y, et al. Secondary bacterial infections in critical ill patients with coronavirus disease 2019. Open Forum Infect Dis 2020;7(6):ofaa220.
38. Karmen-Tuohy S, Carlucci PM, Zervou FN, Zacharioudakis IM, Rebick G, Klein E, et al. Outcomes among HIV-positive patients hospitalized with COVID-19. J Acquir Immune Defic Syndr 2020;85(1):6-10.
39. Chong WH, Neu KP. Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. J Hosp Infect 2021;113:115-129.
40. Saha BK, Chong W. A 61-year-old man with influenza pneumonia and new onset hemoptysis. Chest 2021;160(2):e181-e184.
41. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384(8):693-704.
42. Khilnani GC, Hadda V. Corticosteroids and ARDS: a review of treatment and prevention evidence. Lung India 2011;28(2):114-119.
43. Al-Benna S. Negative pressure rooms and COVID-19. J Perioper Pract 2021;31(1-2):18-23.
44. Eber E, Goussard P. Bronchoscopy precautions and recommendations in the COVID-19 pandemic. Paediatr Respir Rev 2021;37:68-73.
45. World Health Organization (WHO). Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. Available at: WHO/2019-nCoV/IPC/2020.3. *Accessed March 18, 2020.*