Bronchoscopy in Patients With Known or Suspected COVID-19

Results From the Global Pandemic SARS-CoV-2 Bronchoscopy Database (GPS-BD)

Gustavo Cumbo-Nacheli, MD, Henri Colt, MD,† Abhinav Agrawal, MD,‡ Joseph Cicenia, MD,§ Lorenzo Corbetta, MD,|| Akhil D. Goel, MD,¶ Ameena Goga, PhD,# Hans J. Lee, MD,** Septimiu Murgu, MD,†† Jasleen Pannu, MBBS,‡‡ Michal Senitko, MD,§§ Francesco Tarantini, MD,|||| Patricia Vujacich, MD,¶¶ Jonathan Williamson, MBBS, PhD,##*** Elaine Yap, MBChB, FRACP,††† and Robert J. Lentz, MD‡‡‡§§§*

Background: **Amid the Coronavirus Disease 2019 (COVID-19) pandemic, the benefits and risks of bronchoscopy remain uncertain. This study was designed to characterize bronchoscopy-related practice patterns, diagnostic yields, and adverse events involving patients with known or suspected COVID-19.**

Methods: **An online survey tool retrospectively queried bronchoscopists about their experiences with patients with known or suspected COVID-19 between March 20 and August 20, 2020. Collected data comprised the Global Pandemic SARS-CoV-2 Bronchoscopy Database (GPS-BD). All bronchoscopists and patients were anonymous with no direct investigator-to-respondent contact.**

Results: **Bronchoscopy procedures involving 289 patients from 26 countries were analyzed. One-half of patients had known COVID-19. Most (82%) had at least 1 pre-existing comorbidity, 80% had at least 1 organ failure, 51% were critically ill, and 37% were intubated at the time of the procedure. Bronchoscopy was performed with diagnostic intent in 166 (57%) patients, yielding a diagnosis in 86 (52%). and management changes in 80 (48%). Bronchoscopy was performed with therapeutic intent in 71 (25%) patients, mostly for secretion clearance (87%). Complications attributed to bronchoscopy or significant clinical decline within 12 hours of the procedure occurred in 24 (8%) cases, with 1 death.**

Conclusion: **Results from this international database provide a widely generalizable characterization of the benefits and risks of bronchoscopy in patients with known or suspected COVID-19. Bronchoscopy in this setting has reasonable clinical benefit, with diagnosis and/or management change resulting from about half of the diagnostic cases. However, it is not without risk, especially in patients with limited physiological reserve.**

Key Words: bronchoscopy, COVID-19, practices, global health, pulmonary surgical procedures, Severe Acute Respiratory Syndrome Coronavirus 2

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From the *Spectrum Health, Michigan State University School of Human Medicine, Grand Rapids, MI; †University of California, Irvine Medical Center, Irvine, CA; ‡Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New York, NY; §Cleveland Clinic, Cleveland; ‡‡Ohio State University Medical Center, Columbus, OH; **Johns Hopkins University, Baltimore, MD; ††University of Chicago, Chicago, IL; §§University of Mississippi Medical Center School of Medicine, Jackson, MS; ‡‡‡Vanderbilt University Medical Center; §§§Department of Veterans Affairs Medical Center, Nashville, TN; ||University of Florence, Florence; ||||Papa Giovanni XXIII Hospital, Bergamo, Italy; ¶All India Institute of Medical Sciences, Jodhpur, Rajasthan, India; #Steve Biko Academic Hospital, Praeteria, South Africa; ¶¶Clinicas University Hospital Buenos Aires, Buenos Aires, Argentina; ##South West Clinical School, University of New South Wales; ***MQ Health Respiratory and Sleep, Macquarie University, Sydney, Australia; and †††Middlemore Hospital, Auckland, New Zealand.
G.C.-N. and H.C. are first co-authors.
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Reprints: Gustavo Cumbo-Nacheli, MD, Spectrum Health, 4100 Lake Dr SE, Suite 200, Grand Rapids, MI 49546 (e-mail: gustavo.cumbonacheli@spectrumhealth.org).

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Bronchoscopy is a minimally invasive procedure used to clarify the cause of a respiratory illness, treat patients with a variety of lung and airway disorders, and assist in the management of critically ill patients often on mechanical ventilation. Little is known, however, regarding the risks and benefits of bronchoscopy in the setting of known or suspected Coronavirus Disease 2019 (COVID-19), the illness caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

In February 2020, the COVIDBRONCH initiative was launched (R.J.L. and H.C.) with the intent

of collecting data regarding the practice of COVID-19-related bronchoscopy.[1] Shortly after the World Health Organization (WHO) officially declared COVID-19 a pandemic in March 2020, several bronchology societies published recommendations to help ensure the safety of patients and staff, but these guidelines were based on expert opinion or extrapolated clinical experiences with outbreaks of related illnesses including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), also caused by betacoronaviruses (SARS-CoV and MERS-CoV, respectively).[2–4]

While these guidelines provided timely and much-needed guidance regarding bronchoscopy, a procedure commonly performed in severe respiratory illnesses such as those caused by SARS-CoV-2, COVID-19-specific data are necessary to better define the risks and benefits specific to this pandemic illness.[5,6] The Global Pandemic SARS-CoV-2 Bronchoscopy Database (GPS-BD) was therefore designed to gather COVID-19-related bronchoscopy experiences from bronchoscopists around the world,[1,7–14] and to characterize bronchoscopy practice patterns, diagnostic yields, and bronchoscopy-related adverse events in patients with known COVID-19 or COVID-like illness during the first 5 months of the pandemic. This study represents the first time such a tool focused on a global infectious disease is implemented in the field of bronchoscopy.

METHODS

An online survey tool named the GPS-BD was designed to query bronchoscopists during a 5-month period between March 20, 2020 and August 20, 2020. All data collected were anonymous with no direct investigator-to-respondent contact. All data were entered by the participating bronchoscopist retrospectively for bronchoscopies that met inclusion criteria. No data that might permit identification of an individual bronchoscopist or patient were recorded. The survey was conducted in REDCap[15,16] and was predominantly distributed electronically through large, international, nonpublic medical social media groups devoted the discussion of bronchoscopy, critical care, and COVID-19.

Bronchoscopies for any indication in a patient with known or suspected COVID-19 were eligible for inclusion in the database. Known COVID-19 was defined as patients with detectable SARS-CoV-2 by rRT-PCR of any mucus membrane or body fluid obtained in the course of illness before bronchoscopy. Suspected COVID-19 (or "COVID-like illness") was defined as (1) at least 1 SARS-CoV-2 test had been sent because of suspicion for COVID-19, or (2) patient symptoms triggered precautionary COVID-related isolation per local protocol, or (3) the bronchoscopist harbored at least moderate pretest probability of COVID-19 regardless of prior SARS-CoV-2 RT-PCR results. The study protocol was approved as exempt research at Vanderbilt University Medical Center (IRB# #20046).

Three primary outcomes of interest were predefined: (1) in patients with known or suspected COVID-19, how often does bronchoscopy establish a new diagnosis; (2) in patients with known or suspected COVID-19 illness or COVID-19-like disease, how often do bronchoscopy results alter clinical management; and (3) in patients with known COVID-19 or COVID-like illness who undergo bronchoscopy, what is the incidence of a composite of (a) bronchoscopy-related adverse events plus (b) clinical deterioration within 12 hours of the procedure.

Descriptive statistics included means and SD for continuous variables and percentages and frequencies for categorical variables. Between-group comparisons were conducted with t tests for continuous variables and χ^2 test for categorical variables. Analysis was performed using JASP 0.14 (University of Amsterdam, Amsterdam, The Netherlands).

RESULTS

Between March 20, 2020 and August 20, 2020, experiences from 313 bronchoscopies were entered into the GPS-BD, of which 289 from 26 countries met inclusion criteria and were analyzed (Fig. 1). Half were from Europe and about one-third were from the United States (including 18 states). The majority (250/289, 85%) were performed in major academic or public/government institutions (Fig. 2).

SARS-CoV-2 rt-PCR was positive before bronchoscopy in 142 cases (49%). Most patients (237, 82%) had at least 1 pre-existing comorbidity, and 114 (39%) were current or former smokers. Mean age was 55 ± 17.4 years. Most patients were male (207, 72%). The majority of patients were inpatients, including 148 (51%) critically ill ICU patients, 108 of whom (37%) required mechanical ventilation at the time of bronchoscopy (Table 1). On average, bronchoscopy was performed on hospital day 13 in the setting of at least 1 organ failure in 80% of cases, most frequently respiratory failure (78%), with mean SaO_2 to FiO_2 ratio of 247 for the entire cohort. The most frequent radiologic findings

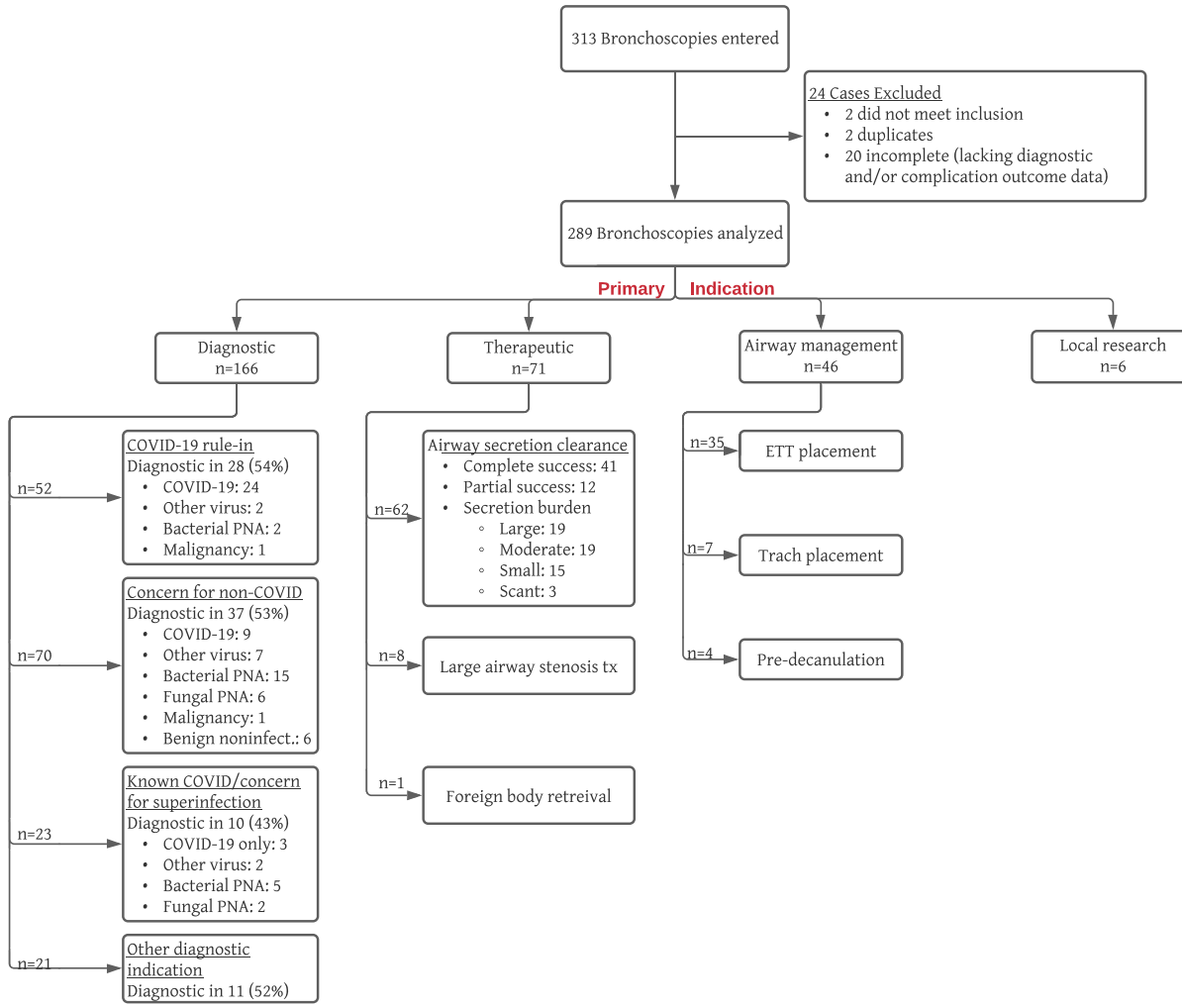

FIGURE 1. Study flow and outcomes according to bronchoscopy indications. COVID-19 indicates Coronavirus Disease 2019; ETT, endotracheal tube; PNA, pneumonia.

were bilateral interstitial infiltrates. See Table 2 for additional day of bronchoscopy clinical data.

Most bronchoscopies (166, 57%) were performed for diagnostic purposes, with specific indications including attempt to rule-in COVID-19, known COVID-19 with concern for co-infection, and concern for non-COVID lung disease detailed in Figure 1. Bronchoalveolar lavage (BAL) and bronchial washings were performed in 87 (52%) and 37 (22%) cases, respectively. A specific diagnosis was established by bronchoscopy in 86 cases (52%), with BAL representing the highest-yield procedure, contributing to 80 diagnoses, with minor contributions from other modalities (Table 3, Fig. 3). BAL SARS-CoV-2 RT-PCR was positive in 39 of 87 BALs (44%), including 24 of 52 (46%) performed specifically in an attempt to rule-in COVID-19 and in 10 of 46 cases (22%) with known COVID-19. SARS-CoV-2 was detected in 3 of 31 non-BAL specimens tested, all large airway washes. A mean of 2.0 ± 0.7 noninvasive SARS-CoV-2 rt-PCR assays were sent before bronchoscopies with rule-in COVID-19 as the primary indication. Results from diagnostic bronchoscopies prompted management changes in 80 of 166 cases (48%) including initiation of medical treatment (27%), change in hospital ward (15%), removal of existing treatment (7%), and changes in goals of care (5%; Table 3).

Procedures were performed with therapeutic intent in 71 cases (25%), including secretion clearance and urgent airway interventions despite concern for COVID-19, with most remaining bronchoscopies performed to assist with airway management (46, 16%) (Fig. 1). Of those performed to clear airway secretions, obstructive mucous plugs were found in 51 of 62 procedures (82%) and secretion burden was subjectively judged as large or moderate in more than half (38/55) (Table 4).

Region		Country		Hospital type	
Europe	147 (50.9%)	Italy	91 (31.5%)	Major academic	140 (48.4%)
North America	91 (31.5%)	USA	90 (31.1%)	Major public/government	105 (36.3%)
South America	39 (13.5%)	Spain	30 (10.4%)	Major private	30 (10.4%)
Asia	10 (3.5%)	Argentina	25 (8.7%)	Other	14 (4.8%)
Australia/Oceania	2 (0.7%)	Other	53 (18.3%)		

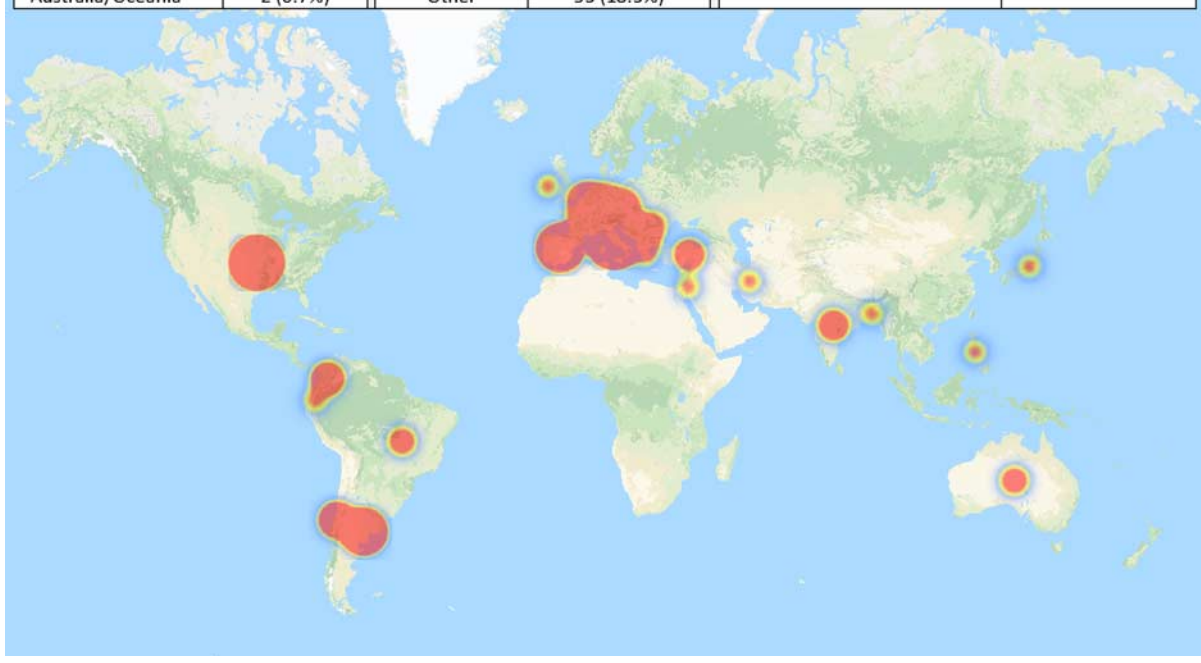

FIGURE 2. Study participation heatmap.

An adverse event deemed related to the bronchoscopy occurred in 14 procedures (5%) and a significant clinical decline of any etiology occurred within 12 hours of 18 procedures (6%), with a composite outcome of either event occurring in 24 of 289 cases (8%) (Table 5). New or worsening hypoxemia was the most frequent adverse event with endotracheal intubation and mechanical ventilation required in 7 (2.4%) cases. One bronchoscopy-related death was reported in a patient with known COVID-19. The pre-procedure mean SaO_2 to FiO_2 ratio was lower in patients who suffered a complication or significant clinical decline following bronchoscopy than in those who did not (mean S/F 205 vs. 250, mean difference 45.4, 95% confidence interval: 8.3-99, $P = 0.1$). There were no significant differences between groups regarding age, sex, presence of pre-existing comorbidities or current organ failure, known versus suspected COVID-19, bronchoscopy indication, or performance of BAL versus not.

DISCUSSION

This international database of bronchoscopies performed in patients with known or suspected COVID-19 provides the most thorough, pragmatic, and generalizable characterization of the diagnostic and therapeutic performance and risks of bronchoscopy in this clinical setting to date. We found most bronchoscopies were performed at referral centers for diagnostic purposes in patients with one or more organ failures. At least one specific diagnosis was established by 52% of diagnostic bronchoscopies and 48% altered clinical management. Therapeutic bronchoscopy was also commonly reported, including secretion clearance in intubated patients and use in airway management. Bronchoscopy-related adverse events and/or significant clinical decline within 12 hours were not infrequent, occurring in 8% of cases.

Early in the COVID-19 pandemic, several bronchology societies discouraged bronchoscopy in patients with known or suspected COVID-19. They cited concerns for bronchoscopy staff safety during this aerosol-generating procedure, particularly amid uncertain diagnostic yield and possible risk to patients with COVID-19.[17] Since this time, some data have become available regarding the utility and risks of bronchoscopy in this clinical setting. All existing studies are retrospective and many are

TABLE 1. Patient Demographics, COVID-19 Status, and Comorbidities

	Overall (n = 289), n (%)
Age	55.5 (± 17.4)
Male	207 (71.6)
COVID-19 status	
Lab confirmed SARS-CoV-2 infection	142 (49.1)
Suspected COVID-19	147 (50.9)
Comorbidity present before bronchoscopy	237 (82)
Chronic respiratory disease	62 (21.5)
Chronic cardiovascular disease	141 (48.8)
DM	62 (21.5)
Obesity	46 (15.9)
Active malignancy	50 (17.3)
Chronic liver disease	8 (2.8)
CKD	14 (4.8)
Rheumatic disease	8 (2.8)
Solid organ transplant recipient	21 (7.3)
Tobacco use status	
Current smoker	31 (10.7)
Former smoker	83 (28.7)
Never smoked	118 (40.8)
Unknown/missing	57 (19.7)
Admission status	
Outpatient	14 (4.8)
Emergency department	8 (2.8)
Regular floor/ward	91 (31.5)
Stepdown/intermediate care ward	28 (9.7)
Intensive care unit	148 (51.2)
Mechanically ventilated	108 (37.4)
Not ventilated	24 (8.3)
ECMO support	16 (5.5)
Bronchoscopy setting	
ICU at bedside	141 (48.8)
Bronchoscopy suite or operating room	98 (33.9)
Non-ICU room at bedside	48 (16.6)
Emergency room	2 (0.7)

CKD indicates chronic kidney disease; COVID-19, Coronavirus Disease 2019; ECMO, extra corporeal membrane oxygenation; DM, diabetes mellitus; ICU, intensive care unit.

TABLE 2. Clinical Status on the Day of Bronchoscopy (n = 289)

Hospital LOS, days (n = 265)	13.1 (SD: 13.5)
ICU LOS, days (n = 148)	10.7 (SD: 8.8)
Days of MV (n = 122)	10.6 (SD: 9)
Days of ECMO support (n = 16)	9.5 (SD: 6.2)
Organ system failure at time of bronchoscopy, n (%)	
None	58 (20.1)
Respiratory	225 (77.9)
Cardiovascular	72 (24.9)
CNS	21 (7.3)
Hepatic	8 (2.8)
Renal	45 (15.6)
Other	19 (6.6)
Prebronch P/F ratio (n = 84)	163 (SD: 102)
Prebronch S/F ratio (n = 286)	247 (SD: 126)
Requiring vasoactive mediations, n (%)	56 (19.4)
Preprocedure findings on chest radiograph, n (%)	
Interstitial infiltrates	120 (41.5)
Consolidation(s)	55 (19)
Unilateral distribution	45 (15.6)
Bilateral distribution	187 (64.7)
Diffuse abnormality	57 (19.7)
Focal abnormality	12 (4.2)
Multifocal abnormalities	58 (20.1)
Normal parenchyma	12 (4.2)
Pleural effusion	27 (9.3)
Bilateral	15 (59.3)
Right only	8 (29.6)
Left only	4 (14.8)

CNS indicates central nervous system; ECMO, extra corporeal membrane oxygenation; ICU, intensive care unit; LOS, length of hospital stay; MV, mechanical ventilation.

limited to ICU patients with known COVID-19 or report results from only patients in whom BAL was performed.[5,8–13]

Two multicenter reports from Italy provide the most general characterization of the diagnostic performance of bronchoscopy in patients with known or suspected COVID-19. One, by Mondoni and colleagues, included 109 bronchoscopies performed in 6 hospitals in a cohort in which 10% were critically ill. Analysis of BAL fluid detected SARS-CoV-2 in 43 of 78 cases (55%) with negative noninvasive assays, while another 15 (19%) revealed bacterial or fungal pneumonia.[5] The other, from Patrucco and colleagues, reports on 131 bronchoscopies from three hospitals including 9% critically ill patients in which a BAL was sent for SARS-CoV-2 rt-PCR, the majority of which were performed to rule-in COVID-19 (65%), with suspected alternative diagnosis or suspected superinfection in 33%.[12] The detection rate of BAL for SARS-CoV-2 was 33%. At least 1 pathogen was recovered in 46 cases (35%) with 15 noninfectious diagnoses established for an overall per-case diagnostic yield of 47%. An additional series of exclusively intubated patients with known or suspected COVID-19 who underwent BAL showed a diagnostic yield for SARS-CoV-2 of 63% (78 of 123), including 8 with negative concomitant nasopharyngeal assays, with growth in bacterial culture in 42 cases (34%), predominantly in patients without COVID-19 (25 of 45, 56%).[10]

Bronchoscopy established any specific diagnosis in 52% of cases in this larger, more broadly multicenter database. Diagnostic rate was consistent across specific diagnostic indications, including attempt to rule-in COVID-19 (diagnostic in 54%, with COVID-19 diagnosed in 46% of this subgroup), concern for a non-COVID

TABLE 3. Diagnostic Techniques, Yields, and Management Changes for Diagnostic Bronchoscopies

	Performed (n = 166), n (%)	Contributed to Diagnosis, n (%)
Diagnostic techniques		
Bronchoalveolar lavage	87 (52.4)	80 (92)
Bronchial wash	37 (22.3)	15 (40.5)
Transbronchial forceps biopsy	10 (6)	6 (60)
Peripheral transbronchial needle aspiration	1 (0.5)	1 (100)
Central transbronchial needle aspiration	6 (3.6)	5 (83.3)
Endobronchial biopsy	6 (3.6)	3 (50)
Cytology brush	4 (2.5)	1 (25)
Diagnoses established by bronchoscopy	86 (51.8)	
SARS-CoV-2 detected	37 (22)	
Other respiratory virus*	11 (6.6)	
Bacterial PNA†	24 (14.5)	
Fungal PNA‡	9 (5.4)	
Noninfectious benign diagnosis§	11 (6.6)	
Malignancy	6 (3.6)	
Bronchoscopy changed management	80 (48.2)	
New treatment initiated	45 (27.1)	
Antibiotic	25	
Antiviral mediation	10	
Corticosteroid	7	
Antifungal	5	
Other COVID-specific therapy‖	8	
Change in hospital/ward location	25 (15.1)	
Removal of existing treatment	12 (7.2)	
Antibiotic	5	
Antiviral mediation	1	
Corticosteroid	2	
Antifungal	1	
Hydroxychloroquine	5	
Change in goals of care	8 (4.8)	

*Influenza (2), HSV (1), EBV (1), CMV (4), Rhinovirus (2), not specified (1).

†*Enterococcus* spp. (3), *Klebsiella pneumoniae* (2), *Streptococcus* spp. (1), *Staphylococcus aureus* (7), *Mycoplasma pneumoniae* (2), *Pseudomonas* (5), *Stenotrophomonas* spp. (2), *Enterobacter* spp. (1), *Acinetobacter* (1), *Hemophilus influenzae* (1), *Serratia* spp. (1).

‡*Aspergillus fumigatus* (4), *Candida albicans* (1), PJP (2), not specified (2).

§Granulomatous process (3), organizing PNA (1), ILD (1), other not specified (6).

‖HCQ (5), tocilizumab (2), IVIg (1).

CMV indicates cytomegalovirus; COVID, Coronavirus Disease; EBV, Epstein Barr virus; HCQ, hydroxychloroquine; HSV, herpes simplex virus; ILD; interstitial lung disease; IVIg, intravenous immunoglobulin; PJP, pneumocystis jiroveci pneumonia; PNA, pneumonia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

etiology (diagnostic in 53%), and concern for superinfection in a patient with known COVID-19 (diagnostic in 43%), as detailed in Figure 1. Our detection rate of SARS-CoV-2 in BAL fluid of 44% is also similar to prior reports, which range from 37% to 63%.[10–14] Multiple factors probably contribute to variable BAL detection rates of SARS-CoV-2 across available studies, including different assays used, variation in BAL techniques, and duration of illness before bronchoscopy. Most patients in our cohort underwent bronchoscopy relatively late in the course of their disease, on hospital day 13 (and mechanical ventilation day 11, for those intubated). Because the quantity of PCR-detectable genetic material declines over time,[7] we suspect this reduced its overall diagnostic yield in our patients. Bronchoscopy late in the hospital course may also partially explain the relatively common finding of superinfection, as could selection bias (bronchoscopy being performed in a subset of patients in which superinfection is felt to be especially likely). It is also noteworthy that BAL was only performed in 87 of 166 diagnostic bronchoscopies (52%), despite its long history as being superior to a large airway wash for diagnosing respiratory infections (as demonstrated here with only 3/31 washes positive for SARS-CoV-2). Figure 3 provides a visual representation of the large discrepancy between diagnoses established by the 3 most common sampling techniques (BAL, bronchial wash, and transbronchial biopsy) and the degree of diagnostic overlap between these techniques.

Management changes attributed to bronchoscopy in the setting of the COVID-19 pandemic have been seldom reported. Ora et al,[11] in a series of 28 cases of suspected COVID-19 despite negative nasopharyngeal assays, did not detect SARS-CoV-2 in any BAL specimens, but did identify bacterial or fungal pathogens in 39% of cases. This led to management changes in 13 patients (46%). In other series of critically ill COVID-19 patients, investigators report management changes in 15% to 28% of cases following bronchoscopy.[8,13] We report management changes in 48% and provide more granular data about these changes than published in prior reports: the predominant change being the initiation of new therapies (antibiotics, antiviral, COVID-specific therapies; Table 3). It is noteworthy that non-COVID infectious lung disease, often with specific treatments available, was detected in one-quarter of our cases and in 19% to 64% in other series to date, including one in which bronchoscopic cultures were positive in 35% of cases when tracheal aspirates were negative. This highlights the potential importance of bronchoscopy when there is concern for bacterial superinfection.[5,8–13]

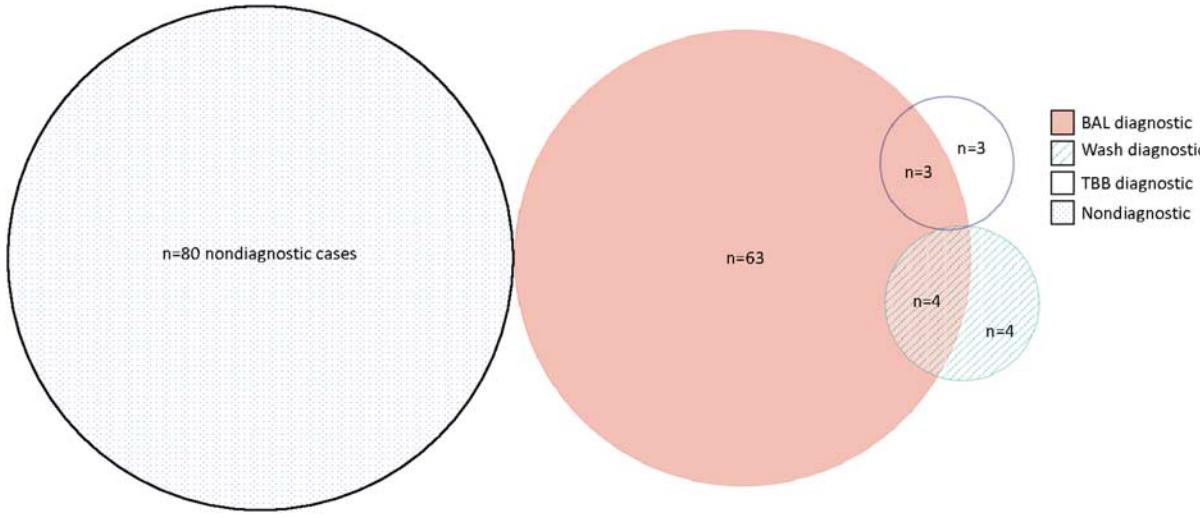

FIGURE 3. Contributions and diagnostic overlap of common techniques represented by area-proportionate Euler diagram. This figure excludes nine diagnoses by uncommon technique without overlap with another technique (EBUS-TBNA ×2, endobronchial brush ×1, endobronchial forceps biopsy ×2, airway survey without biopsy ×4). BAL indicates bronchoalveolar lavage; EBUS-TBNA, endobronchial ultrasound guided-transbronchial needle aspiration; TBB, transbronchial biopsies.

We found that 71 of 289 (25%) reported bronchoscopies were performed with a primary therapeutic intent. Most (62) were performed to clear suspected airway secretions, with a moderate to large secretion burden identified in the majority of these cases. Frequency of therapeutic bronchoscopy, particularly for secretion clearance, are highly variable in the existing literature, as are reports of airway secretion burden.[6,18–20] Torrego et al[13] report an incidence of tenacious airway secretions in 95% of critically ill COVID-19 patients, and Bruyneel et al[8] performed bronchoscopy in 70 of 90 instances in 32 critically ill COVID-19 patients because of concern for obstructive airway secretions. Several other series make no mention of excessive secretion burden.[8,11,14] Torrego et al[13] hypothesized that variations in suctioning systems and heat and moisture exchangers might account for variability in secretion burden between centers. Our international data make it clear that secretion burden is an issue in a substantial proportion of COVID-19 patients, for which bronchoscopy (with suction or suction plus saline lavage) leads to complete or partial clearance in more than 85% of patients undergoing said procedure.

TABLE 4. Airway Secretion Burden and Clearance Techniques

Airway secretion clearance	n = 62
Obstructive mucus plugs present, n (%)	51 (82.3)
Within endotracheal/tracheostomy tube	6
Trachea	11
Mainstem bronchus or bronchus intermedius	29
Lobar bronchus	20
Segmental bronchus	13
Subsegmental bronchi	3
Therapeutic techniques for airway secretion clearance, n (%)	n = 62
Scope suction plus saline lavage	45 (72.6)
Scope suction only	21 (33.9)
Mucolytic instillation	4 (6.5)
Cryoextraction using flexible cryoprobe	1 (1.6)

Bronchoscopy-related adverse events were associated with 14 of 289 cases (5%). Clinical decline within 12 hours of bronchoscopy occurred in 18 of 289 cases (6%), with a composite of adverse event and/or clinical decline occurring in 24 (8%) cases and one death in a patient with known COVID-19. Pre-COVID-19 literature suggests bronchoscopy is associated with significant complications in 4% to 15% of ICU patients.[21,22] Bruyneel et al[8] reported no significant differences in mortality between patients requiring bronchoscopy (28%) and those not requiring bronchoscopy (19%) in a series of COVID-19 ICU patients but did not comment on specific complications. Chang et al,[9] reporting on 241 bronchoscopies in intubated COVID-19 patients, found three dislodged endotracheal tubes (1%). Mondoni et al[5] reported a complication rate of 5% (5 of 109), including worsened hypoxemia but no deaths, in a cohort containing only 10% critically ill patients. We provide a more robust characterization of periprocedural complications than these COVID-specific studies, with most complications in our report relating to worsened hypoxemia or need for intubation (Table 5).

TABLE 5. Bronchoscopy-related Adverse Events According to Procedure Indication

	Overall (n = 289), n (%)	Procedure Indication, n (%)			
		Diagnostic (n = 152)	Therapeutic (n = 65)	Airway (n = 42)	Research (n = 6)
Bronchoscopy-related adverse event	14 (4.9)	8 (4.8)	5 (7)	1 (2.2)	0
Clinical decline within 12 h	18 (6.2)	12 (7.3)	2 (2.9)	4 (8.7)	0
Composite AE+clinical decline in 12 h	24 (8.3)	14 (8.4)	6 (8.5)	4 (8.7)	0
Specific complications					
New/worsened oxygen requirement	17 (5.9)	11 (6.6)	3 (4.2)	3 (6.5)	0
Intubation	7 (2.4)	5 (3)	0	2 (4.3)	0
New salvage maneuver for hypoxemia*	2 (0.7)	1 (0.6)	0	1 (2.2)	0
New/worsening shock	2 (0.7)	0	1 (1.4)	1 (2.2)	0
Pneumothorax requiring chest tube	1 (0.3)	0	1 (1.4)	0	0
Hemoptysis	1 (0.3)	1 (0.6)	0	0	0
Cerebrovascular accident	1 (0.3)	1 (0.6)	0	0	0
Death	1 (0.3)	0	0	1 (2.2)	0

*Prone, paralysis, inhaled vasodilator, salvage ventilation mode, extra corporeal membrane oxygenation.

The slightly higher rate of complication and/or peribronchoscopy clinical decline noted in our study than prior COVID-specific series is likely multifactorial. First, our cohort with approximately half critically ill patients provides a more balanced estimate of bronchoscopic risk than existing studies, which include either predominantly general ward patients or exclusively intubated patients. Prolonged median length of stay and critical illness, high rates of organ failures, and mean SaO_2:FiO_2 ratio of 247 (correcting to a PaO_2: FiO_2 ratio of 218) suggest an overall cohort without much physiological reserve in which complications are more likely to occur.[18,20] We found that adverse events did not cluster within diagnostic, therapeutic, or airway management indications, but were uniformly distributed across indications (Table 5). Across patient and procedure factors, only lower S/F ratio was associated with complication or periprocedural clinical decline; this finding of more risk in patients with more advanced respiratory failure is not unexpected. Performance of a BAL was not associated with significant complications. Unbiased recognition and/or attribution of adverse events is particularly challenging in retrospective studies, where there may be an impetus to not attribute complications to a procedure.[5] In our study, we controlled for this bias by including significant clinical decline in the composite primary safety outcome. Finally, there has significant debate in the critical care literature regarding the use of noninvasive positive pressure ventilation and high flow nasal cannula in COVID-19 patients, and bronchoscopy in these patients might be approached more cautiously. Of those patients who underwent bronchoscopy through NIPPV mask (n = 17) or through nose/mouth while requiring high flow nasal cannula (n = 44), 1 patient required intubation within 12 hours (1 of 61, 1.6%) and 5 experienced significantly worsened hypoxemia (5 of 61, 8.2%), rates similar to that seen in the overall studied cohort. Our study, which includes worldwide data, is the largest series to date characterizing bronchoscopy in known or suspected COVID-19. The results from this collective initiative provide better understanding of practice patterns between centers and shed light on COVID-19-specific bronchoscopy risks and benefits during the first months of the pandemic. The enthusiastic participation by numerous bronchoscopists from 26 countries is encouraging and exemplifies how an international group of airway specialists can be queried using a clearly constructed database to answer specific clinical questions.

Nonetheless, this study has several weaknesses. Its retrospective nature introduces the possibility of recall bias. Referral bias (it is likely not all COVID-19-related bronchoscopies performed by participating proceduralists were ultimately submitted to the database) and convenience sampling could have biased some results as well. As a descriptive study, we were not testing a specific intervention with respect to optimizing clinical outcomes. In addition, voluntary participation mainly by physicians in large institutions may not be generalizable to bronchoscopies performed at hospitals in a different setting. While interpreting diagnostic data divided by primary procedure indication provides a sense of an operator's pretest probability, respondents retrospectively chose the primary indication for bronchoscopy, and may have selected an indication that matched procedure findings. In addition, we did not

collect long-term data regarding patient outcomes or bronchoscopists' COVID-19 health status. This is because data collected were appropriately limited by privacy and confidentiality concerns. Finally, treatments provided to COVID-19 patients have changed constantly since the study period, such that estimations of the rate of management changes might not reflect current circumstances.

CONCLUSIONS

In this large international retrospective series of bronchoscopy in the setting of known or suspected COVID-19, most procedures were performed for a diagnostic indication. A specific diagnosis was identified in 52% of cases, leading to a management change in 48%. Therapeutic bronchoscopy, principally to manage obstructive airway secretions, was the indication for 25% of cases and was almost always successful. The rate of complications or significant clinical decline following bronchoscopy was 8%. Similar to other infectious lung disease settings, bronchoscopy in known or suspected COVID-19 has reasonable clinical benefits, but these must be weighed against the risk for clinical decline, particularly in patients with more limited physiological reserve.

REFERENCES

1. Mulrennan S, Colt H. Medical information and social media in the time of COVID-19. *Respirology*. 2020;25:578–579.
2. Lentz RJ, Colt H. Summarizing societal guidelines regarding bronchoscopy during the COVID-19 pandemic. *Respirology*. 2020;25:574–577.
3. Pritchett MA, Oberg CL, Belanger A, et al. Society for Advanced Bronchoscopy Consensus Statement and Guidelines for bronchoscopy and airway management amid the COVID-19 pandemic. *J Thorac Dis*. 2020;12:1781–1798.
4. Wahidi MM, Lamb C, Murgu S, 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 Bronchol Interv Pulmonol*. 2020;27:e52–e54.
5. Mondoni M, Papa GFS, Rinaldo R, et al. Utility and safety of bronchoscopy during the SARS-CoV-2 outbreak in Italy: a retrospective, multicentre study. *Eur Respir J*. 2020;56:1–4.
6. Schnabel RM, van der Velden K, Osinski A, et al. Clinical course and complications following diagnostic bronchoalveolar lavage in critically ill mechanically ventilated patients. *BMC Pulm Med*. 2015;15:107.
7. Abid MB, Chhabra S, Buchan B, et al. Bronchoalveolar lavage-based COVID-19 testing in patients with cancer. *Hematol Oncol Stem Cell Ther*. 2020;14:65–70.
8. Bruyneel M, Gabrovska M, Rummens P, et al. Bronchoscopy in COVID-19 intensive care unit patients. *Respirology*. 2020;25:1313–1315.
9. Chang SH, Jiang J, Kon ZN, et al. Safety and efficacy of bronchoscopy in critically ill patients with coronavirus disease 2019. *Chest*. 2020;159:870–872.
10. Gao CA, Cuttica MJ, Malsin ES, et al. Comparing nasopharyngeal and bronchoalveolar lavage SARS-CoV-2 assays in respiratory failure. *Am J Respir Crit Care Med*. 2020;203:127–129.
11. Ora K, Puxeddu E, Cavalli F, et al. Does bronchoscopy help the diagnosis in COVID-19 infection? *Eur Respir J*. 2020;56:2.
12. Patrucco F, Albera C, Bellocchia M, et al. SARS-CoV-2 detection on bronchoalveolar lavage: an Italian multicenter experience. *Respiration*. 2020;99:970–978.
13. Torrego A, Pajares V, Fernández-Arias C, et al. Bronchoscopy in patients with COVID-19 with invasive mechanical ventilation: a single-center experience. *Am J Respir Crit Care Med*. 2020;202:284–287.
14. Vergnon JM, Trosini-Desert V, Fournier C, et al. Bronchoscopy use in the COVID-19 era. *Respir Med Res*. 2020;78:100760.
15. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
16. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381.
17. Brown J, Gregson FKA, Shrimpton A, et al. A quantitative evaluation of aerosol generation during tracheal intubation and extubation. *Anaesthesia*. 2021;76:174–181.
18. Jelic S, Cunningham JA. Clinical review: airway hygiene in the intensive care unit. *Crit Care*. 2008;12:209.
19. Marini JJ, Pierson DJ, Hudson LD. Acute lobar atelectasis: a prospective comparison of fiberoptic bronchoscopy and respiratory therapy. *Am Rev Respir Dis*. 1979;119:971–978.
20. Rice TW, Wheeler AP, Bernard GR, et al. Comparison of the SpO_2/FIO_2 ratio and the PaO_2/FIO_2 ratio in patients with acute lung injury or ARDS. *Chest*. 2007;132:410–417.
21. Cracco C, Fartoukh M, Prodanovic H, et al. Safety of performing fiberoptic bronchoscopy in critically ill hypoxemic patients with acute respiratory failure. *Intensive Care Med*. 2013;39:45–52.
22. Jolliet P, Chevrolet JC. Bronchoscopy in the intensive care unit. *Intensive Care Med*. 1992;18:160–169.