

# Bronchoscopy Characteristics and Outcome in Severe COVID-19 Patients: A Single Centre Study from North India

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## Abstract

**Background:** Bronchoscopy may be required in patients with severe COVID-19 to manage complications such as atelectasis or haemoptysis. Bronchoscopy in COVID-19, on the other hand, is not without risks and there are various guidelines to reduce clinical practise variability, but the supporting scientific evidence is scarce so, the present study was conducted with an aim to describe the bronchoscopy findings including BAL results and its association with patient outcome. **Subjects and Methods:** The present cross-sectional observational study was conducted among 120 critically ill patients requiring invasive mechanical ventilation for severe COVID-19 pneumonia admitted at tertiary care hospital during April 2020 to SEP 2021. Bronchoscopy procedure were performed under usual intravenous sedation and with pressure-controlled ventilation mode. After taking informed consent from relatives a pretested proforma was used to record the relevant details. The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20. Level of significance was set at  $P \leq 0.05$ . **Results:** The mean age of the subjects in the present study was  $51.3 \pm 17.1$  years. Around two third of subjects were males (65.8%). In this study, 27.0 % of BAL samples were positive for bacterial cultures or CB-NAAT, whereas 12.2 % of BAL samples revealed fungi on culture or spores on KOH mount. Thick mucus secretion was observed more frequently ( $p < 0.05$ ) among dead patients (64.5%) as compared to discharged patients (38.2%). **Conclusion :** In conclusion, haematic secretions and thick mucus secretion in the respiratory tract, as well as an absence of diffuse mucosal hyperaemia, are poor prognostic factors.

**Keywords:** Bronchoscopy, COVID-19, BAL, Pneumonia, Comorbidity.

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Received: 27 January 2022

Revised: 16 March 2022

Accepted: 25 March 2022

Published: 15 April 2022

## Introduction

The first cases of coronavirus disease 2019 (COVID-19) were reported in Wuhan, China, in December 2019, and the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has rapidly expanded to pandemic proportions since then. As of August 2021, almost 200 million individuals had been infected, with over 4 million people dying as a result of the disease.<sup>[1]</sup> Asymptomatic virus shedding is one of the most difficult aspects of efficiently managing the virus's spread. Indeed, previous studies have shown that nearly 80% of recorded cases had very mild symptoms, or even no clinical signs at all, despite the fact that they are still spreading the virus.<sup>[2,3]</sup>

SARS-CoV-2 enters human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on mucosal surfaces, which is extensively expressed on alveolar epithelial type II cells and to a lesser extent in upper airway epithelial

cells (oral, nasal, and the pharynx).<sup>[4-6]</sup> As a result, reverse transcriptase polymerase chain reaction (RT-PCR) with samples obtained from the upper respiratory tract is the gold standard diagnostic test for detecting current SARS-CoV-2 infections (nasopharyngeal nasal or oropharyngeal swabs). The active viral replication of the virus can be targeted and recognised in the upper airways during the prodromal phase, when contagiousness is higher.<sup>[7]</sup>

Bronchoscopy's significance in COVID-19 is a point of contention. Bronchoscopy could give enhanced sensitivity by acquiring samples from the lower respiratory tract in patients with clinical suspicion of COVID-19 and negative nasopharyngeal swab specimen results by real-time PCR with reverse transcription (RT-PCR).<sup>[7]</sup> Bronchoscopy may be required in patients with severe COVID-19 who are primarily admitted to the intensive care unit (ICU) to manage complications such as atelectasis or haemoptysis, to resolve mechanical ventilation difficulties, and to rule

out superinfection. Bronchoscopy in COVID-19, on the other hand, is not without risks, including disease spread to healthcare personnel. Although various scientific associations have released guidelines to reduce clinical practise variability, the supporting scientific evidence is scarce and mostly consists of short series.<sup>[8-10]</sup>

So, the present study was conducted with an aim to describe the bronchoscopy findings including BAL results and to find the association of baseline characteristics, clinical features, laboratory parameter and bronchoscopy findings with the outcome among patients (discharged or death).

## Subjects and Methods

### Study setting and subject

The present cross-sectional observational study was conducted among critically ill patients requiring invasive mechanical ventilation for severe COVID-19 pneumonia (aged 18 years and above), admitted at Central Medical Centre, HISAR during April 2020 to SEP 2021. The inclusion criteria were patients with SARS-CoV-2 pneumonia confirmed by RT-PCR of nasopharyngeal swab specimens, together with signs, symptoms and radiological findings suggestive of COVID-19 pneumonia who required a bronchoscopy. The patients where bronchoscopy was performed after virological resolution (confirmed by two consecutive RT-PCR negative tests); and interval between COVID-19 confirmation and endoscopic examination longer than 30 days were not included in the study.

### Sample size

The sample size was calculated as 96 using formula the sample size for the cross-sectional study ( $N = z^2 p(1-p)/d^2$ ) considering the prevalence of in-hospital mortality in patients showing an endoscopic feature indicating poor prognosis as 40% (p), where N= sample size, p=prevalence, q=(1-prevalance), d= allowable error or precision or variability=10.<sup>[11]</sup> All consecutive patients who met the inclusion criteria were assessed for eligibility and recruited until the desired sample size was achieved.

### Data collection

After taking informed consent from relatives a pretested proforma was used to record the relevant baseline details (including Age, Gender, Comorbidities, Days from the onset of symptoms to admission, Days from the COVID-19 diagnosis to BALF performing, In-hospital mortality and Length of hospital stay); clinical characteristics (Clinical features of COVID-19, Laboratory parameters, Chest radiograph abnormalities); Bronchoscopic findings (including Microscopic agents in BAL) and; Treatment given based on bronchoscopy findings At the time of admission 10 mL of blood sample was collected from each patient for laboratory investigations such as

complete blood counts (CBC); serum electrolytes; renal and liver function tests; D-dimer, CRP and IL6. All tests were performed in an appropriate autoanalyzer after complying internal quality control.

### Bronchoscopy procedure

Before the procedure, all the necessary equipment and materials were prepared outside the patient room, including saline, syringes, mucoactive drugs, microbiological recipients, connections, and bronchoscopy system (scope and screen. As recommended, level III of personal protective equipment was used, including N95 or FFP3 mask, goggles, double gloves, and a plastic protective gown including head and neck cover. Procedures were performed in either supine or prone position, under usual intravenous sedation and with pressure-controlled ventilation mode. Disposable scopes were used in all cases (Ambu a Scope 4 Broncho, Large 5.8/2.8. Ambu A/S), and minimal staff attended the procedure bedside (one expert bronchoscopist occasionally accompanied by a staff intensivist). Bronchoscopic examination included orotracheal tube positioning check, direct inspection of tracheal and bronchial mucosa, suctioning of secretions, and a mini-BAL with 60-ml saline aliquots at room temperature was performed just before the end of procedure for microbiological sampling. The bronchial segment to perform the BAL was chosen according to the radiological information. The duration of the procedures was never more than 10 minutes. Before the procedure, FIO<sub>2</sub> was increased so as to reach a peripheral oxygen saturation of 95%–98%.

### Statistical analysis

The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics included computation of percentages, means and standard deviations. The unpaired t test (for quantitative data to compare two independent two groups) was used for quantitative data comparison of all clinical indicators. Chi-square test and fisher exact test were used for qualitative data whenever two or more than two groups were used to compare. Level of significance was set at  $P \leq 0.05$ .

## Results

The mean age of the subjects in the present study was  $51.3 \pm 17.1$  years. Around two third of subjects were males (65.8%). The most common associated comorbidity among the subjects was type 2 diabetes mellitus (45.8%). In present study the mean period from the onset of symptoms to admission was  $9.1 \pm 1.7$  days, and the mean period from the COVID-19 diagnosis to Bronchoscopy was  $4.1 \pm 1.2$  days. Present study showed that in-hospital mortality rate among subjects

**Table 1: Baseline characteristics of patients with COVID-19.**

Variables	Number/Mean	Percentage/SD
Age (in years)	51.3	17.1
Gender		
Female	41	34.2
Male	79	65.8
Comorbidities*		
DM T2	55	45.8
PTB	7	5.8
HTN	11	9.2
Birth deformity	7	5.8
BPH	5	4.2
CVS	6	5.0
No comorbidity	42	35.0
Days from the onset of symptoms to admission	9.1	1.7
Days from the COVID-19 diagnosis to Bronchoscopy	4.1	1.2
In-hospital mortality	31	25.8
Length of hospital stay (in days) <sup>#</sup>	28.2	5.6

\*Multiple Responses

#Discharged patients

was 25.8% and the average length of hospital stay among discharged patient was  $28.2 \pm 5.6$  [Table 1].

In present study [Table 2] the commonly presented clinical features among subjects were fever (75.0%), cough (40.0%), dyspnoea (35.0%) and chest pain (30.0%). Bilateral interstitial (31.7%) and bilateral consolidation (38.3%) was observed abnormalities on the chest radiograph of more than two third of study subjects. The COVID-19 specific therapy included drugs such as solumedrol (34.2%), remdesivir (29.2%) and hydroxychloroquine (29.2%).

The bronchoscopy procedure [Table 3] done among subjects showed thick mucus secretion among 35.1% of subjects, followed by fluid mucus secretion among 17.5% subjects, each mucus plug & hematic secretions among 13.6% subjects and diffuse mucosal hyperaemia among around one tenth of subjects ( 9.1%). BAL was performed among 74 subjects and BAL results, showed that 27.0% (20/74) of BAL samples were positive for bacterial cultures or CB-NAAT [Mycobacteria (n=4), Pseudomonas aeruginosa (n=3), Staphylococcus aureus (n=3), Klebsiella aerogenes (n=2), Acinetobacter baumannii (n=4), Enterococcus faecalis (n=2), Escherichia coli (n=1), or Prevotella melaninogenica (n=1)] and 12.2% (9/74) of BAL samples yielded fungi on culture or spores on KOH mount [Aspergillus niger (n=5), Aspergillus fumigatus (n=3), or Candida albicans (n=1)]. BAL galactomannan was determined in 6 subjects.

As a result of BAL [Table 4], a new antibiotic was prescribed in 16.7% of subjects (20/120). Also, antifungal medication (single or combined) was initiated in 7.5% of subjects (9/120).

The mean age was  $47.2 \pm 12.4$  years among discharged patients whereas it was  $55.6 \pm 8.9$  years among dead patients which reflects that the mortality increased with the increase of age ( $P=0.0007$ ). In present study, the mean period from the onset of symptoms to admission was  $10.1 \pm 1.6$  days in discharged patients and  $8.4 \pm 1.9$  days in dead patients, which shows that among patients where the condition degraded intensely, got admitted to hospital earlier and had poor prognosis [Table 5]. There was statistically significant difference in the laboratory parameters of discharged and dead patients for PaO<sub>2</sub>/FiO<sub>2</sub> Ratio (discharged:  $177.2 \pm 26.3$  vs dead:  $160.5 \pm 21.4$ ,  $P=0.001$ ); D-dimer (discharged:  $1396.2 \pm 366.7$   $\mu\text{g/L}$  vs dead:  $1720.3 \pm 260.9$   $\mu\text{g/L}$ ,  $P<0.0001$ ); and IL6 (discharged:  $67.1 \pm 32.1$  ng/L vs dead:  $247.9 \pm 213.3$  ng/L,  $P<0.0001$ ). The bronchoscopy findings such as thick mucus secretion was observed more frequently among dead patients (64.5%) as compared to discharged patients (38.2%), and this difference was statistically significant ( $P=0.011$ ). Similarly haematic secretion was observed more frequently among dead patients (29.0%) as compared to discharged patients (13.5%), and this difference was statistically significant ( $P=0.049$ ).

Table 2: Clinical and laboratory characteristics of patients with COVID-19.

Variables	Number/Mean	Percentage/SD
<b>Clinical features of COVID-19*</b>		
Fever	90	75.0
Cough	48	40.0
Blood mixed sputum	6	5.0
Haemoptysis	18	15.0
Pedal edema	6	5.0
Wheezing	8	6.7
Expectoration	11	9.2
Nausea	7	5.8
Pain abdomen	12	10.0
Slurred speech	6	5.0
Dyspnea	42	35.0
Loss of appetite	16	13.3
Chest pain	36	30.0
<b>Laboratory parameters</b>		
PaO <sub>2</sub> /FiO <sub>2</sub> Ratio	157.9	21.6
D-dimer ( $\mu\text{g/L}$ )	1412.3	277.3
IL6 (ng/L)	96.1	61.2
CRP (mg/dL)	85.8	24.5
<b>Chest radiograph abnormalities</b>		
Normal	4	3.3
Unilateral interstitial	7	5.8
Bilateral interstitial	38	31.7
Unilateral consolidation	13	10.8
Bilateral consolidation	46	38.3
Pleural effusion/ others	12	10.0
<b>COVID-19-specific therapy*</b>		
Solumedrol	41	34.2
Adalimumab	12	10.0
Bevacizumab	19	15.8
Remdesivir	35	29.2
LMWM	8	6.7
Plasma	7	5.8
Azithromycin	11	9.2
Hydroxychloroquine	35	29.2
Maxotaz	15	12.5

\*Multiple Responses

## Discussion

Older age, men, more comorbidities, lymphopenia, elevated D dimer and serum ferritin, and the degree of pneumonia in the chest CT are all well-established clinical, analytical,

and radiological indicators of poor outcomes in COVID-19 patients.<sup>[12,13]</sup> This is the first study in a developing country with just enough participants to examine the effect of bronchoscopic findings on outcomes in COVID-19 patients

**Table 3: Bronchoscopy and BAL findings of patients with COVID-19.**

Variables	Number	Percentage
<b>Bronchoscopic findings*</b>		
Normal/Nil/Non-significant	10	6.5
Diffuse mucosal hyperaemia	14	9.1
Thick mucus secretion	54	35.1
Fluid mucus secretion	27	17.5
Mucus plugs	21	13.6
Haematic secretions	21	13.6
Intrabronchial clots	7	4.5
<b>Microscopic agents in BAL (n=74)</b>		
Bacteria	20	27.0
Fungi	9	12.2
Nil/Normal/Non-significant	45	60.8

\*Multiple Responses

**Table 4: Treatment given based on bronchoscopy and BAL findings among patients with COVID-19.**

Treatment	Number	Percentage
Amphotericin B	6	5.0
Antibiotics/ATT	20	16.7
Posaconazole	8	6.7
Tecocin	5	4.2
Itraconazole	7	5.8

who were hospitalised.

Because widespread mucosal hyperaemia is likely a characteristic of an initial stage of COVID-19, showing acute inflammation, it was linked to lower in-hospital death rates.<sup>[14]</sup> With or without anti-inflammatory medicines like corticosteroids, this state may still be reversed.<sup>[14,15]</sup> The absence of this endoscopic finding in the presence of prolonged respiratory insufficiency, on the other hand, may suggest a poor prognosis.

Thick mucus secretion in the distal bronchial tube was found to be an independent predictor of higher in-hospital mortality. Thick mucus secretion, in contrast to diffuse mucosal hyperaemia, could result in irreversible damage to the capillaries and interstitial/alveolar space, as seen in the most advanced and severe cases of COVID-19.<sup>[16-18]</sup> Another explanation of inadequate ventilation due to full bronchial obstruction is haematic secretions from the lower respiratory tract, which may exacerbate the most advanced and severe cases of COVID-19 with a higher mortality rate.<sup>[18]</sup>

Indeed, the presence of haematic secretions and thick mucus secretions were found as subgroups of very sick patients (13.6 percent and 35.1 percent, respectively) with greater in-hospital mortality (29.0 percent and 64.5 percent respectively). More research into this subpopulation is needed to identify more

aggressive and life-saving interventions.

In this study, 27.0 percent of BAL samples were positive for bacterial cultures or CB-NAAT (Mycobacteria, *P. aeruginosa*, *S. aureus*, *K. aerogenes*, *A. baumannii*, *E. faecalis*, *E. coli*, or *P. melaninogenica*), whereas 12.2 percent of BAL samples revealed fungi on culture or spores on KOH mount (*Aspergillus niger*, *Aspergillus fumigatus*, or *Candida albicans*). These findings are consistent with the microbiological flora reported in ventilator-associated pneumonia.<sup>[19]</sup>

Patients with COVID-19 who are mechanically ventilated are at risk of developing ventilator-associated pneumonia (VAP), which may go unnoticed due to its clinical and radiographic similarities to COVID-19. In these patients, the incidence of VAP ranges from 29 to 80 percent, with a hazard ratio of 2.1 as compared to non-COVID-19 patients.<sup>[20-22]</sup> This high incidence could be attributed to a number of variables, including treatment-related immunological compromise and protracted mechanical support or sedation. Bronchoscopy may aid in the formulation of the accurate diagnosis in these circumstances.

In COVID-19 patients admitted in the ICU, fungal co-infection has been shown to occur up to 34% of the time, and COVID-19 associated pulmonary aspergillosis (CAPA) has a mortality



Table 5: Predictors of mortality among patients with COVID-19.

Variables	Number (%) / Mean±SD		P value
	Discharged (n=89)	Death (n=31)	
Age (in years)	47.2±12.4	55.6±8.9	P=0.0007
<b>Gender</b>			
Female (n=41)	30 (33.7)	11 (35.4)	P=0.857
Male (n=79)	59 (66.3)	20 (64.6)	
<b>Comorbidities</b>			
Yes (n=78)	62 (69.7)	16 (51.6)	P=0.695
No (n=42)	27 (30.3)	15 (48.4)	
Days from the onset of symptoms to admission	10.1±1.6	8.4±1.9	P<0.0001
Days from the COVID-19 diagnosis to Bronchoscopy	4.2±1.2	4.1±1.3	P=0.696
<b>Multiple Clinical features of COVID-19</b>			
Yes (n=82)	59 (66.3)	23 (74.2)	P=0.415
No (n=38)	30 (33.7)	8 (25.8)	
<b>Laboratory parameters</b>			
PaO <sub>2</sub> /FiO <sub>2</sub> Ratio	177.2±26.3	160.5±21.4	P=0.001
D-dimer (μg/L)	1396.2±366.7	1720.3±260.9	P<0.0001
IL6 (ng/L)	67.1±32.1	247.9±213.3	P<0.0001
CRP (mg/dL)	86.6±21.9	84.5±34.3	P=0.695
<b>Chest radiograph abnormalities</b>			
Unilateral/ Bilateral interstitial (n=45)	34 (38.2)	11 (35.5)	P=0.787
Unilateral consolidation (n=13)	9 (10.1)	4 (12.9)	P=0.666
Bilateral consolidation (n=46)	36 (40.4)	10 (32.2)	P=0.419
Pleural effusion/ others (n=12)	7 (7.9)	5 (16.1)	P=0.186
Normal (n=4)	3 (3.4)	1 (3.2)	P=0.969
<b>Bronchoscopic findings*</b>			
Normal/Nil/Non-significant (n=10)	7 (7.9)	3 (9.7)	P=0.753
Diffuse mucosal hyperaemia (n=14)	11 (12.3)	3 (9.7)	P=0.688
Thick mucus secretion (n=54)	34 (38.2)	20 (64.5)	P=0.011
Fluid mucus secretion (n=27)	21 (23.6)	6 (19.4)	P=0.626
Mucus plugs (n=21)	14 (15.7)	7 (22.6)	P=0.387
Haematic secretions (n=21)	12 (13.5)	9 (29.0)	P=0.049
Intrabronchial clots (n=7)	5 (5.6)	2 (6.5)	P=0.236

\*Multiple Responses

rate of 36%.<sup>[23]</sup> Lung aspergillosis, like COVID-19, can cause fever, dyspnea, respiratory failure, and pulmonary infiltrates. As a result, microbiological criteria are used to diagnose CAPA, and BAL analysis is a key tool in this process.<sup>[23]</sup>

Endoscopic bronchoscopy can also indicate the existence of lesions (such as epithelial plaques, pseudomembranes, or ulceration of the bronchial mucosa) that aren't apparent on radiography. These observations were seen in six COVID-

19 patients. Only a bronchial biopsy allowed an accurate diagnosis of CAPA because the lesions appeared as lung cancer involvement.

### Limitation

However, it is impossible to assess the benefits of bronchoscopy against the potential risks to the patient and the

bronchoscopist in this observational study. To investigate the impact on patient-centered outcomes, a new study design would have been required.

## Conclusion

In conclusion, thick hypersecretion in the airway is the most prevalent complication seen in critically ill, mechanically ventilated COVID-19 patients, and these patients can benefit from specific bronchoscopy intervention. When a clinical suspicion of superinfection exists, BAL can be used to confirm it. Bronchoscopy allows for the removal of mucus plugs and intrabronchial clots, as well as the resolution of atelectasis, in severely ill COVID-19 patients, resulting in improved mechanical ventilation. Finally, haematic secretions and thick mucus secretion in the respiratory tract, as well as an absence of diffuse mucosal hyperaemia, are poor prognostic factors.

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[journal.pone.0238825](https://doi.org/10.1371/journal.pone.0238825).

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**How to cite this article:** Kumar D, Popli S. Bronchoscopy Characteristics and Outcome in Severe COVID-19 Patients: A Single Centre Study from North India. *Asian J. Med. Res.* 2022; 11(2):37-44.

DOI: [dx.doi.org/10.47009/ajmr.2022.11.2.7](https://doi.org/10.47009/ajmr.2022.11.2.7)

**Source of Support:** Nil, **Conflict of Interest:** None declared.

