Original Article

Pneumothorax and pneumomediastinum in patients with COVID-19: A retrospective study from tertiary care institute in India

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SUMMARY   COVID-19 is associated with rarer extra-parenchymal manifestations, namely pneumothorax (PTX) and pneumomediastinum (PM) leading to complications and increased mortality. The study aims to describe the prevalence, risk factors for mortality, radiological characteristics and outcome of PTX/PM in patients admitted with COVID-19. This was a retrospective, single-centre, observational study in patients with confirmed COVID-19 presenting with non-iatrogenic PTX/PM from April 2020 to May 2021. Details pertaining to demographics, presentation, radiological characteristics, management and outcome were collected. Cases were classified into spontaneous and barotraumatic PTX/PM and a between-group comparison was performed using Chi-square and *t*-test. A total of 45 cases (mean age: 53.2 years, 82% males) out of 8,294 confirmed COVID-19 patients developed PTX/PM, the calculated incidence being 0.54%. 29 cases had spontaneous PTX/PM and the remaining 17 cases were attributed to barotrauma. The most common comorbidities were diabetes-mellitus (65.3%) and hypertension (42.3%). The majority of the cases had large PTX (62.1%) with tension in 8 cases (27.5%). There were predominant right-sided pneumothoraces and five were diagnosed with bronchopleural fistula. 37.7% of cases had associated subcutaneous emphysema. The median duration of PTX/PM from symptom onset was delayed at 22.5 and 17.6 days respectively. The mean CT severity score (CTSS) was 20.5 (± 4.9) with fibrosis (53.8%), bronchiectatic changes (50%) and cystic-cavitary changes (23%). There was no statistically significant difference between the spontaneous and barotrauma cohort. 71% of cases died and the majority belonged to the barotrauma cohort. It is imperative to consider the possibility of PTX/PM in patients having COVID-19, especially in those with deterioration in the disease course, both in spontaneously breathing and mechanically ventilated patients. These patients may also have a high incidence of death, reflecting the gravity of COVID-19.

Keywords   Pneumothorax, pneumomediastinum, COVID-19

1. Introduction

The COVID-19 pandemic has resulted in significant mortality and morbidity around the globe. A varied number of manifestations and complications have been reported to be associated with the disease, however, the frequency of such manifestations is difficult to quantify (*1*). SARS-CoV-2 primarily affects the lung parenchyma with features ranging from mild self-limiting upper respiratory infection to critical acute respiratory distress syndrome (ARDS). A myriad of extra-parenchymal manifestations has been documented in the backdrop of COVID-19 such as pulmonary embolism, pleural effusion, empyema, cavitation and cyst formation (*2-5*). Pneumothorax (PTX) and pneumomediastinum (PM), defined as gas in the pleural cavity and the mediastinum respectively, has also been reported in association with COVID-19, although not as frequently as lung parenchymal involvement.

PTX and PM can be either arise spontaneously or due to barotrauma. Necrotizing pneumonia or lung parenchymal involvement, due to various aetiologies,

can result in PTX/PM. The causes include commonly *Pneumocystis jirovecii* pneumonia (PCP), bacterial pneumonia caused by *Staphylococci, Mycoplasma pneumoniae, Klebsiella* and *Pseudomonas* spp., bronchiolitis obliterans organising pneumonia (BOOP) and sometimes by rarer organisms such as *Herpes simplex*, *cytomegalovirus* pneumoniae, *Aspergillus* and even influenzae virus (*6-12*). The previous Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) outbreaks have been associated with an increased incidence of PTX and PM (16.4% and 1.7-11.6%, respectively) associated with increased mortality (*13-15*). Although several studies of PTX/PM in COVID-19 exist, there is sparse data on the incidence or frequency of occurrence, especially from the Indian subcontinent. In one of the earliest studies reporting pneumothoraces by Chen *et al.*, only ~1% (1/99 patients) had radiological evidence of PTX (*16*). In another study by Yang *et al.*, out of 92 deceased COVID-19 patients, one (1.1%) had a PTX (*17*). A recent systematic review by Chong *et al.* found the incidence of PTX to be ~0.3% of hospitalised COVID-19 patients with rates increasing to 12.8-23.8% with 100% mortality in patients on invasive mechanical ventilation (*18*). The incidence of barotrauma has varied from 0-49% in traditional ARDS patients (*19*). Miro *et al.* reported a higher incidence of spontaneous PTX in patients with COVID-19 disease than among patients without COVID-19 disease (*20*). Similarly, McGuinness *et al.* reported a higher incidence of barotrauma among patients with COVID-19 acute respiratory distress syndrome in comparison to the historical controls with non-COVID-19 acute respiratory distress syndrome patients (*21*). Lemmers *et al.* found that the incidence of PTX was significantly greater in patients with COVID-19 ARDS despite the use of lung-protective ventilation, indicating that the frailty of the lung due to lung damage was contributing to the higher incidence of PTX in this patient population (*22*).

We present here a large cohort of PTX/PM from India, developing in admitted COVID-19 patients, and describe the demographic details, clinical features, management, risk factor for mortality and outcome of COVID-19 patients presenting with these entities.

2. Materials and Methods

This retrospective observational study was approved by the institutional ethics committee of the All India Institute of Medical Sciences (Institute Reference number IECPG/373/6/2021) and the need for patient consent was waived given the retrospective nature of the study. The authors used the electronic medical record (EMR) to attain clinical variables and admission details. All the relevant imaging studies were obtained by using the Picture Archiving and Communication System (PACS) and were reviewed by a pulmonologist

and a radiologist independently (each with experience in the respective field of more than 10 years each). Only the cases where there was an agreement on diagnosis were included in this study.

2.1. Subject population

Case files of all patients aged > 18 years with COVID-19 confirmed by RT-PCR or SARS-CoV-2 Antigen-RDT assay between 1st April 2020 to 31st May 2021 at our tertiary care facility were reviewed. Only those cases meeting the World Health Organisation (WHO) case definition of confirmed SARS-CoV-2 infection were included (*23*). Medical records reporting PTX and/or PM were reviewed. Cases with a history of iatrogenic PTX as a result of central venous catheter insertion or tracheal injury post-intubation were excluded.

2.2. Clinical data collection

To describe the characteristics of the cohort, demographic, clinical course and management details were obtained for each case and recorded in a predesigned proforma. Demographic parameters included age, sex, smoking status and underlying comorbidities. Details pertaining to COVID-19 included the initial COVID-19 severity classification at the time of presentation to our facility, and the severity at the time of developing PTX/PM, initial symptomatology of COVID-19 chiefly fever, cough, expectoration, shortness of breath, fatigue, myalgia, sore-throat, anosmia, ageusia and diarrhoea. Details about PTX/PM include the size of PTX, site of PTX (unilateral *vs.* bilateral and right *vs.* left-sided), associated PM and subcutaneous emphysema, day of onset of PTX/PM from COVID-19 symptom onset and the mode of oxygenation at the time of diagnosis of PTX/PM. Patients were subsequently divided into two groups for comparison – spontaneous and barotraumatic PTX/PM. Any patient who developed PTX/PM at room air, facemask, nasal prong or high-frequency nasal cannula (HFNC) were considered to have secondary spontaneous PTX/PM, while patients on positive pressure ventilation viz. non-invasive ventilation mask (NIV) and invasive mechanical ventilation (IMV) resulting in PTX/PM were considered to have barotraumatic PTX/PM. Size of PTX was based on the 2003 British Thoracic Society (BTS) guideline (*24*) for classification of PTX based on the radiographic film. Small PTX: distance < 2 cm between the lung margin and the chest wall at the level of the hilum. Large PTX: distance ≥ 2 cm between the lung margin and the chest wall at the level of the hilum. Tension PTX: Presence of mid-line shift or presence of hemodynamic compromise due to the PTX. In cases of broncho-pleural fistula, Cerfolio's classification was used for grading (*25*). Details about the diagnosis, management were collected including modality of

imaging used for diagnosis of PTX/PM, conservative versus pigtail insertion/water seal intercostal tube drainage for management of PTX/PM and final outcome of the patient, *i.e.*, death or discharge.

2.3. Imaging characteristics

Chest radiograph imaging feature of all patients was analysed and was scored based on the 18-point Brixia scoring developed by Borghesi *et al.* (26) exclusively for COVID-19 patients. This was done to quantify the degree of lung involvement and its correlation to developing PTX/PM. HRCT chest was also evaluated whenever available and the findings were recorded into the following categories: CTSS, ground-glass opacification, consolidation, bronchiectasis, interlobular septal thickening, fibrosis, cysts and others.

2.4. Statistical analysis

STATA version 12.1 (StataCorp) was used for the statistical analyses in this study. Categorical variables were represented as frequency and percentages while continuous variables were represented as mean (± standard deviation). Chi-square test and *t*-test/ Wilcoxon rank-sum test were applied to calculate statistical differences between categorical variables and continuous variables respectively. Survival data were used to generate Kaplan-Meier curves with STATA version 12.1 (StataCorp). Survival was compared using the log-rank test. A *p*-value of < 0.05 was considered to assume statistical significance.

3. Results

From 1st April 2020 to 31st May 2021, a total of 45 patients were identified to have PTX/PM after reviewing the electronic database. During this study period, a total of 8,294 patients diagnosed with COVID-19 were admitted to our tertiary care centre which is dedicated to COVID-19 services. The calculated frequency was 0.54% (95% CI: 0.4-0.73%). A total of 16 patients had isolated PTX, 16 patients had isolated PM and 13 patients developed concurrent PTX with PM as shown in Table 1. The mean (± SD) age of the cohort was 53.2 ± 14.9 years and the male to female ratio was 4.6:1.

Pre-existing comorbidities were present in 57.7% (*n* = 26) of the population with 12 cases (46%) having more than one comorbidity. The most common comorbidity was diabetes mellitus (65.3%) followed by hypertension (42.3%), coronary artery disease and malignancy (19.2% each), hypothyroidism and chronic kidney disease (7.6% each) and hypertriglyceridemia (3.8%). Three cases had a prior history of pulmonary tuberculosis. A total of 9 cases (31%) were current or ex-smokers in this cohort. There was no significant statistical difference between the spontaneous and barotrauma group concerning comorbidities and smoking status.

Table 1. Baseline characteristics of COVID-19 patients with PTX and/or PM and comparison between patients developing spontaneous versus barotraumatic PTX/PM

Variables	Total, *n* (%)	Spontaneous *n* (%)	Barotrauma *n* (%)	*p*-value
Age in years[a]	53.28 ± 14.9	51.8 ± 13.9	55.5 ± 16.5	
Sex				0.98
Male	37 (82.2%)	23 (62.1%)	14 (37.8%)	
Female	8 (17.7%)	5 (62.5%)	3 (37.5%)	
Comorbidities (*n* = 26)				
Diabetes Mellitus	17 (65.3%)	11 (64.7%)	6 (35.2%)	0.77
Hypertension	11 (42.3%)	8 (72.7%)	3 (27.2%)	0.49
Coronary artery disease	5 (19.2%)	3 (60%)	2 (40%)	1.00
Hypothyroidism	2 (7.6%)	0 (0%)	2 (100%)	0.13
Malignancy	5 (19.2%)	5 (100%)	0 (0%)	0.14
Chronic kidney disease	2 (7.6%)	2 (100%)	0 (0%)	0.51
Hypertriglyceridemia	1 (3.8%)	1 (100%)	0 (0%)	0.37
COPD/Asthma	1 (3.8%)	0 (0%)	1 (100%)	0.37
Smoking status (*n* = 29)				
Smoker	9 (31%)	7 (77.7%)	2 (22.2%)	0.43
Symptoms (*n* = 45)				
Fever	32 (71.1%)	20 (62.5%)	12 (37.5%)	0.95
Dry cough	21 (46.6%)	14 (66.6%)	7 (33.3%)	0.56
Expectoration	4 (8.8%)	1 (25%)	3 (75%)	0.14
Shortness of breath	40 (88.8%)	26 (65%)	14 (35%)	0.35
Fatigue	3 (6.6%)	3 (100%)	0 (0%)	0.27
Myalgia	3 (6.6)	2 (66.6%)	1 (33.3%)	1.00
Sore-throat	7 (15.5%)	6 (85.7%)	1 (14.2%)	0.22
Diarrhoea	2 (4.4%)	1 (50%)	1 (50%)	1.00
Nausea	1 (2.2%)	1 (100%)	0 (0%)	1.00
Anosmia/Ageusia	2 (4.4%)	1 (50%)	1 (50%)	1.00

a: Mean ± Standard Deviation.

The most common presenting symptom at admission was shortness of breath (88%) followed by fever (71.1%), cough without expectoration (46.6%), sore throat (15.5%), cough with expectoration (8.8%), fatigue and myalgia (both 6.6%), diarrhoea and anosmia/ageusia (4.4%) and nausea (2.2%). There was no significant statistical difference between the two groups (spontaneous and barotrauma induced) with regards to cough. Of the 29 cases with pneumothoraces, based on the BTS 2003 classification of size of PTX, 37.9% (n = 11) had a small PTX and 62.1% (n = 18) had large pneumothoraces of which 27.5% (n = 8) had tension pneumothoraces. Five cases were diagnosed with bronchopleural fistula with three cases having grade 3 air leak based on Cerfolio classification. Majority of the cases had unilateral PTX (86.2%, n = 25), however 68% (n = 16) had right-sided involvement. Associated subcutaneous emphysema was present in 37.7% (n = 17) cases with similar distribution between the two groups. The mean (± SD) duration from symptom onset to developing PTX/PM was 22.5 (± 11.5) days and 17.6 (± 8.8) days respectively. The most common mode of oxygenation at the time of developing PTX/PM in the spontaneous group was nasal prong/face-mask (57%, n = 16) followed by HFNC (28.5%, n = 8) and room air (14.2%, n = 4). In the barotrauma patients, NIV (58.8%, n = 7) was the most common modality of respiratory support while the rest (41%, n = 7) were on invasive mechanical ventilation. The mean PEEP given in the barotrauma cohort was 8.9 (± 1.4) cm of H_2O. The radiological modality of PTX/PM diagnosis was chest radiograph in 75.5 (n = 34) and the rest were diagnosed based on chest computed tomography.

Immediate intercostal tube drainage or pigtail insertion was done in 57.7% (n = 26) cases while the rest were managed conservatively. A conservative approach was taken in all of the cases of isolated PM (with or without subcutaneous emphysema) and three cases of small PTX without much symptomatology. In our cohort, 71% (n = 32) of the cases died. The proportion of patients discharged was higher in the spontaneous group although it was not statistically significant (p value 0.08). The median duration of hospitalisation was 17.5 (± 12.9) days. The details are enumerated in Table 2. Kaplan-Meier curve was plotted to determine the probability of survival between the PM cohort and the PTX with/without PM cohort. Even though the overall survival duration was not significant between the two groups concerning days from the event (PM and/or PTX) to death, there was a trend towards significance (p value = 0.07) showing an increased survival in patients with PM *vs.* PTX as shown in Figure 1A. On the other hand, overall survival was non-significant with regards to the time of COVID-19 symptom onset to developing PTX/PM (p value = 0.27) as shown in Figure 1B.

Table 3 demonstrates the radiological characterization of the cohort. The most common chest CT feature was ground-glass opacification (82%) characteristic of COVID-19 pneumonia. Other principal findings were consolidation (50%), fibrosis (53.8%) with interlobular septal thickening (42.3%) and bronchiectatic changes (50%). A significant number of cases had cystic changes (23%) and lung cavitation, which is an unusual feature of COVID-19 infection and was present in 3 cases (11.5%). The mean CT severity score was 20.5 (± 4.9) which indicated that the majority of cases had severe

Table 2. Characteristics, management and outcome of PTX/PM in COVID-19 and comparison between patients developing spontaneous versus barotraumatic PTX/PM

Parameters	Total, n (%)	Spontaneous, n (%)	Barotrauma, n (%)	P-value
Isolated pneumothorax	16 (35.5%)	11 (68.7%)	5 (31.2%)	-
Isolated pneumomediastinum	16 (35.5%)	10 (62.5%)	6 (37.5%)	
Pneumothorax and pneumomediastinum	13 (28.9%)	7 (53.8%)	6 (46.1%)	
Pneumothorax size (n = 29)				0.51
Small	11 (37.9)	6 (54.5)	5 (45.4)	
Large/Tension	18 (62.1)	12 (66.6)	6 (33.3)	
Site of pneumothorax (n = 29)				0.13
Unilateral	25 (86.2)	17 (68)	8 (32)	
Right side	17	12	5	
Bilateral	4 (13.7)	1 (25)	3 (75)	
Associated Subcutaneous emphysema (n = 45)	17 (37.7)	9 (52.9)	8 (47.0)	0.31
Mode of oxygenation (n = 45)	45			
Room air		4 (14.2)	0	
Nasal prong/face mask		16 (57.1)	0	
HFNC		8 (28.5)	0	
NIV		0	10 (58.8)	
Invasive mechanical ventilation		0	7 (41.1)	
Management				0.91
Intercostal tube drain/pigtail	26 (57.7)	16 (61.5)	10 (38.4)	
Conservative	19 (42.2)	12 (63.1)	7 (36.8)	
Outcome				0.08
Death	32 (71)	17 (53.1)	15 (46.8)	
Discharge	13 (28.9)	11 (84.6)	2 (15.3)	

COVID-19. For the evaluation of the chest radiograph, the Brixia scoring developed by Borghesi *et al.* (26) was utilised. The mean (± SD) Brixia score for the patients was 3.275 (± 2.59) and there was no statistical difference between patients who survived and patients who died.

4. Discussion

In our cohort of 8,294 hospitalized COVID-19 patients, the prevalence of PTX and/or PM was 0.54% (95% CI: 0.4-0.73%), with prevalence of PTX and PM being both 0.2% (95% CI: 0.1-0.3%) and that of combined PTX/PM being 0.16% (95% CI: 0.08-0.3%). This study

pegs the prevalence of PTX and/or PM in COVID-19 patients reflecting on the frequency of occurrence of this serious complication against the backdrop of lung involvement by SARS-CoV-2. A systematic review, which did not include any Indian studies, had found the prevalence of PTX of 0.3% and 12.8-23.8% in hospitalized COVID-19 patients and those requiring invasive mechanical ventilation respectively (*18*). The incidence of spontaneous PTX/PM was 0.48% in our cohort, which was similar to the incidence of spontaneous PTX (0.66%) reported from over 3,000 patients by Zantah *et al.* in their single centre study from the USA (*27*). However smaller studies had reported higher percentages (≥ 1%) (*17,28*). The incidence of PTX associated with ARDS or mechanical ventilation in COVID-19 patients seems to be higher ranging from 10-56% (*18,29*). This study also provides a prevalence estimate of 0.2% of PM with or without PTX in COVID-19 patients, which is lower than that observed by Tacconi *et al.* (2.3%) in a select group of patients (*29*). Spontaneous and barotrauma-related PTX and/or PM constituted 62% and 38% of the total 45 cases in our cohort. There were no significant differences between the spontaneous and barotrauma-related groups in terms of clinical parameters, radiological features or outcome.

Figure 1. (A) Kaplan-Meier survival curve from the time of the event (PTX/PM) to time of death in days between PM (blue) and PTX (red). Log-rank test, *p* = 0.07. **(B)** Kaplan-Meier survival curve from the time of the COVID-19 symptom onset to time of the event (PTX/PM) in days between PM (blue) and PTX (red). Log-rank test, *p* = 0.27.

The postulated mechanism for the development of PTX/PM is linked to the development of diffuse alveolar damage, cystic lesions due to fibro-inflammatory changes and fibrosis. Alveolar rupture, with or without the contribution of increased intrathoracic pressure during coughing or positive pressure ventilation, typically results in PTX or PM. PM and resulting subcutaneous emphysema, without concomitant significant PTX, can ensue due to the phenomenon of the Macklin effect (*30*). The pathologic features in the lungs of patients with COVID-19 pneumonia closely resemble those of SARS and MERS outbreaks. Histologic examinations have reported diffuse alveolar damage with fibromyxoid inflammatory exudates along with cystic lesions (*31*). In our cohort where CT imaging was available (26 cases), 53.8% of cases had evidence of fibrosis while 23% had cystic-cavitation changes, both of which are known contributing factors for the development of PTX/PM. The mean CTSS score for the cases was 20.5, indicating
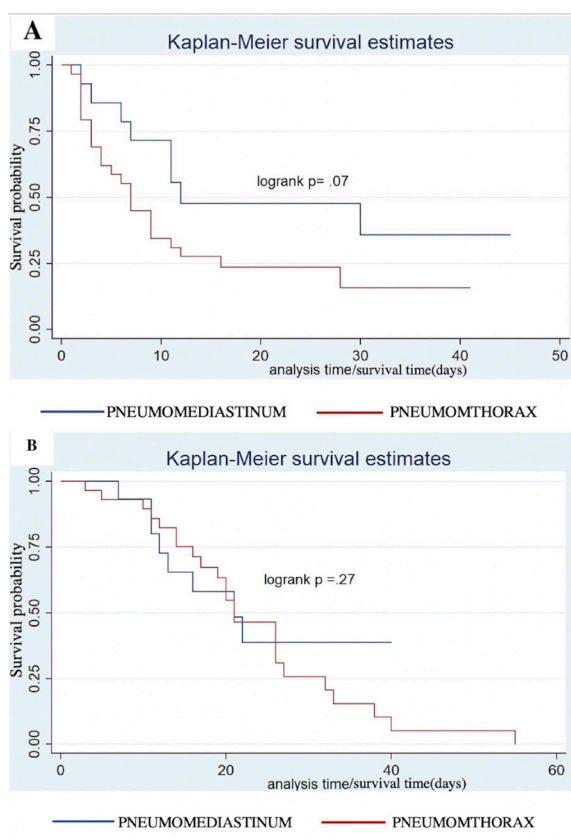
Table 3. Radiological characteristics in COVID-19 patients with PTX/PM

	Total, *n* (%)	Spontaneous, *n* (%)	Barotrauma, *n* (%)	*P*-value
Radiological features (*n* = 26)				
Ground glass opacities	22 (84.0)	17 (77.2)	5 (22.7)	0.28
Consolidation	13 (50.0)	7 (53.8)	6 (46.1)	0.07
Bronchiectasis	14 (53.8)	10 (71.4)	4 (28.5)	1.00
Fibrosis	13 (50)	9 (69.2)	4 (30.7)	1.00
Interlobular septal thickening	11 (42.3)	8 (72.7)	3 (27.2)	1.00
Cysts	6 (23.0)	5 (83.3)	1 (16.6)	1.00
Cavitation	3 (11.5)	1 (33.3)	2 (60.6)	0.16

that the development of PTX/PM was related to the severity of lung involvement by COVID-19. The mean age of the cases was 53 years and the complication was more common in the male gender. Incidentally, men, as compared to women, are more likely to be afflicted by severe form of the COVID-19 infection as shown by a recent meta-analysis by Peckham *et al.* (32). Only one patient had underlying respiratory comorbidity (3.8%) while significant smoking history was present in 31% indicating that COVID-19 was responsible for PTX/PM in the vast majority. Brixia Scoring for the cases showed a mean value of 3.275 and it did not predict mortality.

An interesting observation made in our study was that right-sided PTX was more common than the left side (Right: left = 2:1). A similar observation was found by Miro *et al.* who reported that COVID-19-related PTX was 3.85-fold more likely to occur on the right side and at higher frequency (81.1% versus 52.7%; $p < 0.001$) as compared to non-COVID-19 patients (*20*). The likely explanation for such observation may be a heightened degree of involvement of the right lung vis-à-vis the left lung, as reported by previous research (*33-35*). There could be several reasons for this, including the larger size and number of segments of the right lung, as well as the larger diameter of the right main bronchus leading to greater delivery of viral particles to the right lung - causing relatively more damage (*34*).

Another interesting finding in this study was the median duration of PTX/PM from symptom onset which was 22.5 and 17.6 days respectively. Similarly, delayed onset of PTX/PM has been seen in most of the previous larger studies. The late onset of this complication suggests a sustained period of lung inflammation with extensive parenchymal injury followed by fibrosis and cyst formation in the late phase of COVID-19 pneumonia. The late finding is also supported by the typical radiologic findings in COVID-19 patients (*36*) comprising of inflammation of the lung parenchyma that predominantly affects the peripheries progressing to consolidation and eventually involves the overlying pleura leading to various pleural manifestations such as PTX and pleural effusion. The majority of the cases in our study died (71%) and most of the cases who survived belonged to the spontaneous group as opposed to the barotrauma group even though there was no statistical significance. Such high mortality is comparable to a recent systematic review by Chong *et al.* reporting an overall mortality rate of 74.2% (*18*). The mortality rate of severe COVID-19 is known to be very high and our study demonstrates that severe COVID-19 patients with PTX/PM have a very prognosis. With regards to isolated PM, the mortality rate was 0.56% which was considerable drawing to the conclusion that not only PTX but also PM is a significant predictor of poor outcome in patients with COVID-19. Kaplan-Meier survival curve depicted in Figures 1A and 1B

shows that the PM cohort of cases had better chances of survival as compared to cases with PTX. The possible explanation lies in the fact that PTX results in decreased lung volume leading to further compromise of lung function in the already poor compliant lung parenchyma culminating in a poor outcome. On the other hand, pneumomeiastinum doesn't result in compromise of lung function unless the size is massive with all the cases undergoing conservative management possibly explaining the improved survival.

This study involves the largest cohort of patients from the Indian subcontinent concerning the prevalence, clinico-radiological characteristics and outcome of PTX and/or PM in COVID-19 patients. However, this study is not without limitations. The most significant one was that it was a retrospective study from a single tertiary centre, with potential risks of information and selection biases.

5. Conclusion

It is thus imperative to consider the possibility of PTX and/or PM in patients having COVID-19, especially in those with deterioration in the disease course, both in spontaneously breathing as well as mechanically ventilated patients. These patients may also have a high incidence of death, apparently reflecting the gravity of COVID-19 disease.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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