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Original Article

Internal Medicine Section

Incidence and Outcome of Spontaneous Alveolar Air Leak Events in COVID-19 Pneumonia: A Prospective Cohort Study

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ABSTRACT

Introduction: Coronavirus Disease 2019 (COVID-19) has increased the burden of hospitalised pneumonia cases and related complications. Spontaneous Pneumothorax (PT) and Pneumomediastinum (PM) have been reported in both spontaneously breathing and ventilated patients with COVID-19 pneumonia.

Aim: To determine the incidence and outcomes of spontaneous alveolar air leak events in COVID-19 pneumonia.

Materials and Methods: This prospective cohort study was carried out from June 2020 to June 2021 at a tertiary care centre in Western India. All incident cases of alveolar air leaks in COVID-19 pneumonia were included. Clinical and demographic data were collected, and statistical analysis was performed. The Chi-square test or Fisher's exact test were used to assess the differences in subgroup proportions.

Results: A total of 79 patients (63 males and 16 females) experienced spontaneous alveolar air leaks in the form of PT, PM (mediastinal emphysema), or Subcutaneous Emphysema (SE), either isolated or in combination. A total of 58 patients (73.41%) had PT, while 8 patients (10.12%) had isolated PM and 2 patients (2.53%) had isolated SE. Of the total events, 35 (44.30%) occurred in spontaneously breathing patients, among them vigorous coughing was an important precipitating factor. At the time of the incident, 1.27%, 21.52%, and 77.21% of the affected cases belonged to mild, moderate, and severe COVID-19 categories, respectively. Male patients (n-63, 79.74%) in the age group of 30-60 years were predominantly affected. A total of 38 events (48.10%) occurred within two weeks (early) of symptom onset. The PaO_2:FiO_2 ratio at the time of the alveolar leak showed a significant association with the outcome. Patients with PT had a poorer outcome compared to those with other types of alveolar leaks (p-value<0.005). Major bleeding occurred in 2 (3.33%) of the total 60 Intercostal Drainage (ICD) procedures. Prolonged alveolo-pleural fistula healed spontaneously in four out of five cases. The cumulative incidence for air leak events was 1.55%, and for barotrauma, it was 6.47%. The overall mortality in this cohort was 74.68% (n=59), while it was 29.41% (5 out of 17) in the moderate severity group. Patients with late-onset events had a better outcome (p-value<0.005).

Conclusion: In this cohort of COVID-19 pneumonia from Western India, the cumulative incidence of spontaneous alveolar air leaks was 1.55%, predominantly affecting males. The early occurrence of PT in severely hypoxic patients on mechanical ventilator was associated with higher mortality.

Keywords: Barotrauma, Mediastinal emphysema, Pneumothorax, Severe acute respiratory syndrome coronavirus 2

INTRODUCTION

The COVID-19 pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), posed multiple challenges to the healthcare system. Severe cases of COVID-19 were complicated by Acute Respiratory Distress Syndrome (ARDS), Multiorgan Dysfunction Syndrome (MODS), pulmonary embolism, myocarditis, secondary bacterial or fungal infections, and post-COVID-19 lung sequelae. Complications related to spontaneous alveolar air leaks, in the form of PT and PM, were also reported in patients with SARS-CoV-2 pneumonia [1-3]. The term spontaneous PT refers to the presence of air in the pleural space that is not caused by trauma or another obvious precipitating factor [4]. While primary spontaneous PT occurs without a clinically apparent lung condition, secondary spontaneous PT is a complication of pre-existing lung diseases, such as bronchial asthma, Chronic Obstructive Pulmonary Disease (COPD), cystic lung diseases, and some lung infections like tuberculosis or *Pneumocystis jirovecii* pneumonia [4]. PM and SE refer to the presence of air in the mediastinum and subcutaneous tissue, respectively [5].

In COVID-19 patients, spontaneous air leak events have been reported with or without Invasive Positive Pressure Ventilation (IPPV) [1-3]. There is limited Indian data on the incidence of spontaneous alveolar air leak events in COVID-19 pneumonia and the factors affecting their outcomes [6-8]. Thus, this study was conducted to estimate the incidence of PT, PM, and SE in COVID-19 pneumonia and their outcomes in a tertiary care centre in western India, which was highly affected during the COVID-19 pandemic.

MATERIALS AND METHODS

This prospective cohort study was carried out at a tertiary care hospital in Pune, Maharashtra, India, from June 2020 to June 2021, covering two major COVID-19 waves in western India. Institutional Ethical Committee (IEC) approval was obtained (IEC number-BVDUMC/IEC/23).

Inclusion criteria: All consecutive COVID-19 positive cases (as confirmed by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) or Rapid Antigen Testing (RAT)) with a clinical and/or radiological diagnosis of spontaneous PT, PM, or SE, either isolated or in combination, were included. These cases were grouped together as spontaneous alveolar air leak events in COVID-19 pneumonia.

Exclusion criteria: PT secondary to iatrogenic injuries or trauma was excluded from the study.

Sample size: This was an exploratory study on COVID-19, and all incident cases over the study period were included. Informed consent was obtained from the patient or their immediate relative.

Demographic data, including age, gender, co-morbidities, and clinicoradiological characteristics, were documented. The time

of occurrence of the alveolar air leak event, clinical symptoms, ventilator parameters, requirement for Intercostal Drain (ICD), and associated complications were recorded.

Case definitions: COVID-19 positive: A nasopharyngeal swab for RT-PCR was used to establish the diagnosis of COVID-19.

Severity grading of COVID-19 disease [9]:

- Asymptomatic/Presymptomatic infection: Individuals who test positive for SARS-CoV-2 but show no symptoms consistent with COVID-19.
- Mild illness: Individuals who exhibit any signs and symptoms of COVID-19 but do not have shortness of breath or have abnormal chest imaging.
- Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and have an oxygen saturation (SpO_2) ≥94% on room air.
- Severe illness: Individuals with SpO_2 <94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.
- Critical illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Cytokine storm: The working diagnosis of cytokine storm in COVID-19 was based on supporting laboratory parameters, including C-Reactive Protein (CRP) >50 mg/L, Ferritin >700 µg/L, D-Dimer >0.5 mg/L, and Interleukin-6 >7 pg/mL [10].

Place of event: Pneumonia cases requiring less than 15 litres of oxygen on non rebreather masks with stable haemodynamics were managed in COVID wards, while critical cases were treated in the COVID-19 Intensive Care Unit (ICU).

STATISTICAL ANALYSIS

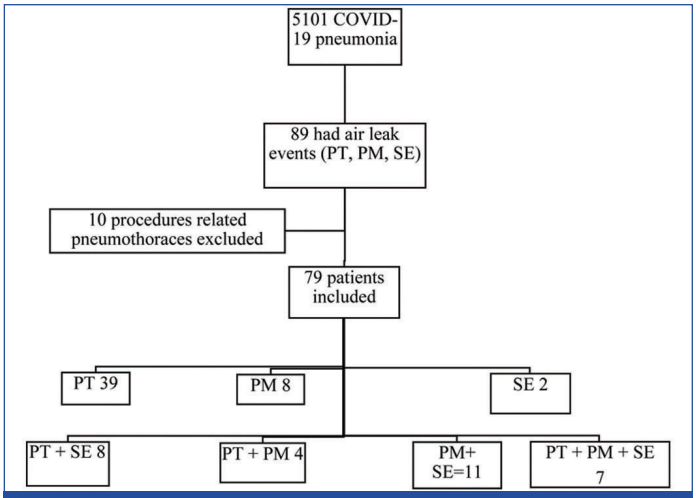
The collected data was coded and entered into a Microsoft Excel sheet. The data were analysed using Statistical Package for the Social Sciences (SPSS) version 20.0 software. The results were presented in tabular and graphical formats. For qualitative data, various rates, ratios, and percentages (%) were calculated. For quantitative data, the mean was calculated. The Chi-square test or Fisher's exact test was used to assess the differences in subgroup proportions. A p-value of <0.05 was considered statistically significant.

RESULTS

Total 5,101 SARS-CoV-2 positive patients were admitted during the study period. The study protocol for case inclusion is shown in [Table/Fig-1]. A total of 79 patients were included in the final analysis. A total of 58 (73.42%) patients suffered from spontaneous PT, with 39 (49.37%) had isolated PT, while others presented with either PM or SE.

Incidence of Alveolar Air Leak: In this study, the cumulative incidence of alveolar air leaks in COVID-19 positive cases was 1.55% (79 out of a total of 5,101). Barotrauma occurred in 6.47% (44 out of 680 patients on invasive ventilation). The incidence of PT was 1.14% (58 out of 5,101) among all hospitalised cases of COVID-19 pneumonia.

A total of 63 (79.75%) male and 16 (20.25%) female COVID-19 positive cases with alveolar air leaks were included in this cohort. Age groups from 41 to 60 years were more affected. Diabetes and hypertension were common co-morbidities in the study population. A total of 61 (77.21%) cases had severe COVID-19 pneumonia at the time of the alveolar leak [Table/Fig-2]. Total 34 (58.62%) cases had right-sided PT, while 8 (13.79%) had bilateral PT [Table/Fig-3]. Retrosternal chest pain was a predominant symptom in 14 (46.67%) of the total 30 patients with PM (mediastinal emphysema). Clinical examination revealed SE in the form of palpable crepitus and swelling of the neck and chest wall.



[Table/Fig-1]: Flow diagram of study inclusion.
PT: Pneumothorax; PM: Pneumomediastinum; SE: Subcutaneous emphysema

Characteristics of study population	n (%)
Gender	
Male	63 (79.75)
Female	16 (20.25)
Age distribution (age in years)	
21-40	21 (26.58)
41-60	33 (41.77)
61-80	25 (31.65)
Pneumonia severity	
Mild	1 (1.27)
Moderate	17 (21.52)
Severe	61 (77.21)
Co-morbidities in patients with air leak events	
Diabetes	19 (24)
Hypertension	13 (16.45)
Ischaemic heart disease	3 (3.79)
Stable chronic kidney disease	2 (2.53)
Bronchial asthma	2 (2 .53)
Chronic Obstructive Pulmonary Disease (COPD)	2 (2.53)
Morbid obesity	2 (2.53)

[Table/Fig-2]: Clinical characteristics of patients with alveolar air leak events in COVID-19.

Clinical presentation of alveolar air leaks in spontaneously breathing patients	
• Prolonged coughing bouts • Acute worsening of breathlessness • Retrosternal chest pain • Palpable crepitus on chest wall and neck Subcutaneous Emphysema (SE)	
Timing of event from symptom onset (n-79)	
Early (1-2 weeks)	38 (48.10)
Late (2 weeks)	
2-4 weeks	36 (45.57)
> 4 weeks	5 (6.33)
PaO_2:FiO_2 ratio at the time of event (n-79)	
<100	41 (51.90)
<200-100	31 (39.24)
<300-200	7 (8.86)
Side of Pneumothorax (PT) (n-58)	
Right	34 (58.62)
Left	16 (27.59)
Bilateral	8 (13.79)
Complications of Intercostal Drainage (ICD) (n-60)	
Bleeding	6 (10)

Empyema	6 (10)
Other complications (n-79) in this cohort	
Cytokine storm	38 (48.10)
Acute Kidney injury	5 (6.33)
Sepsis	19 (24.05)
Bacterial pneumonia	17 (21.52)
Invasive aspergillosis	2 (2.53)

[Table/Fig-3]: Characteristics of alveolar leaks and complications of Intercostal Drainage (ICD).

[Table/Fig-4] gives distribution of cases according to the place of event and the pattern of alveolar leaks. Five patients had PT or PM at the time of hospitalisation. The other cases are divided (inpatient ward/ICU) as per COVID-19 severity. Out of a total of 79 patients, 35 (44.30%) were spontaneously breathing at the time of the air leak event, while 44 (55.70%) had barotrauma. All patients with severe pneumonia who were on a mechanical ventilator (IPPV) died, with the exception of two -one with PM and the other with PM+SE.

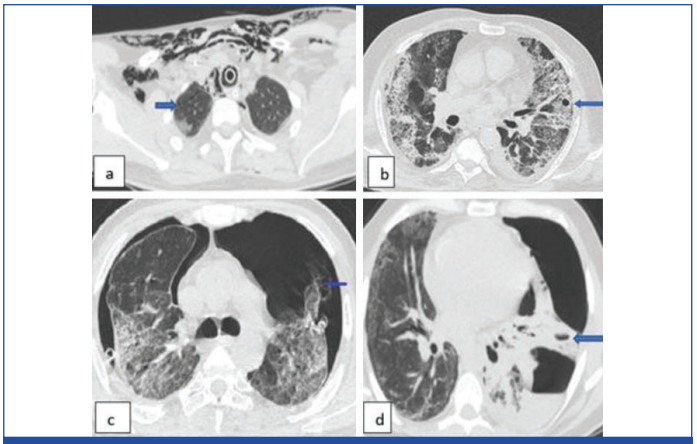
Place of event (COVID severity and O_2 support at the time of event)		Out of hospital event (Mild 1, Mod 4)	O_2 ward (Mod)	Critical care (Severe)			Total
				HFNC	NIV	IPPV	
Total cases		5	13	13	4	44	79
Pneumothorax (PT)		3	3	5	2	26	39
Pneumomediastinum		1	2	3	0	2	8
Subcutaneous Emphysema		0	0	0	1	1	2
PT+SE		0	0	3	0	5	8
PT+PM		0	3	1	0	0	4
PM+SE		0	4	1	1	5	11
PT+PM+SE		1	1	0	0	5	7
ICD (Bilateral)*		4	6	5 (+2)*	2	35(+6)*	52 (+8)*
Prolonged BPF (>4wks)		1	1	1	2	0	5
Outcome	Death	1	4	10	2	42	59 (74.68%)
	Survived	4	9	3	2	2	20 (25.32%)

[Table/Fig-4]: Alveolar air leak events and outcome related to COVID-19 severity. *Bilateral ICD in total 8 (2+6) patients (Abbreviations: PT: pneumothorax; PM: Pneumomediastinum; SE: Subcutaneous emphysema; NIV: Non-invasive ventilation; HFNC: High flow nasal cannula; IPPV: Invasive positive pressure ventilation; BPF: Broncho-pleural fistula; ICD: Intercostal drain; O2: Oxygen)

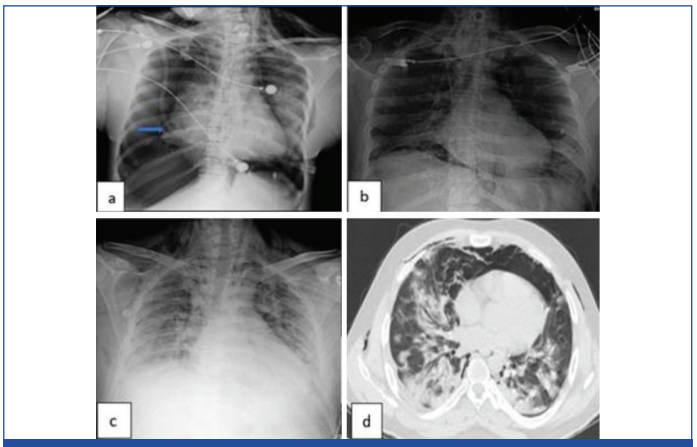
Early versus late events: In 38 (48.10%) cases, alveolar air leaks occurred within two weeks of symptom onset. Radiologically, these patients had severe disease with bilateral patchy Ground-Glass Opacities (GGO) and extensive consolidation. Interstitial emphysema was noted on HRCT in 2 (2.53%) cases [Table/Fig-5a]. Patients with late-onset alveolar air leak events had subpleural blebs, parenchymal cysts, or cavitations contributing to the risk of alveolar rupture [Table/Fig-5b-d].

Radiological findings: All patients had features of COVID-19 pneumonia with varying degrees of bilateral GGO and consolidation, as shown in [Table/Fig-5,6]. Chest X-rays (CXR) showed lung cysts in 4 cases (5.06%) [Table/Fig-6a] and cavities in 2 cases (2.53%). Thirty-eight patients (48.10%) who experienced air leak events underwent High-Resolution Computed Tomography (HRCT) scans during hospitalisation. On HRCT, 19 cases (24.09%) presented with discrete lung cysts [Table/Fig-5b], and subpleural multiple bullae were observed in two cases (2.53%) [Table/Fig-5c]. Additionally, one case (1.26%) demonstrated a cavity with hydro-pneumothorax [Table/Fig-5d]. No cysts were detected in the other cases.

Outcome: [Table/Fig-4,7,8] summarises the outcomes in this cohort of COVID-19 pneumonia patients. A total of 20 patients (25.32%)



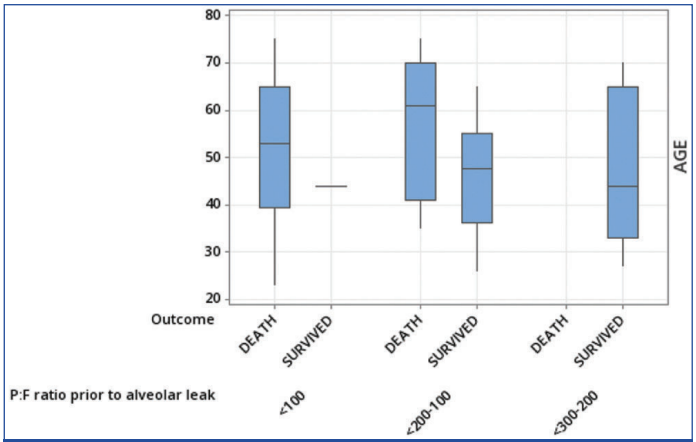
[Table/Fig-5]: HRCT: a) Interstitial emphysema right upper lobe in the first week from symptom onset; b) Bilateral cyst formation in 3rd week from symptom onset; c) Bilateral pneumothoraces with cystic and fibrotic lung changes, subpleural bullae; d) Left hydropneumothorax with cavitating pneumonia.



[Table/Fig-6]: Chest X-ray: (a) Lung cysts and blebs with bilateral Pneumothorax (PT) and subcutaneous emphysema; (b) Pneumomediastinum (PM) on day 24 of symptom onset; (c) Subcutaneous emphysema on day 12 of symptom onset; (d) HRCT: Small right Pneumothorax (PT), Pneumomediastinum (PM) and subcutaneous emphysema in the first week from symptom onset.

Parameters	Death n (%)	Survived n (%)	Chi-square	p-value
Severity of COVID-19 pneumonia (n-78)†				
Moderate	5 (29.41)	12 (70.59)	25.21	<0.001
Severe	54 (88.52)	7 (11.47)		
Time of occurrence				
Early	36 (94.7)	2 (5.3)	15.57	<0.001
Late	23 (56.1)	18 (43.9)		
Pneumothorax (PT)				
Yes	47 (81.0)	11 (19)	4.65	0.034
No	12 (57.1)	9 (42.9)		
Acidosis on Arterial Blood Gas (ABG) analysis				
Yes	35 (94.6)	2 (5.4)	14.59	<0.001
No	24 (57.1)	18 (42.9)		
Breathing at the time of event				
Spontaneous	17 (48.6)	18 (51.4)	22.66	<0.001
Invasive ventilation	42 (95.5)	2 (4.5)		
Gender				
Male	46 (73.0)	17 (27.0)		0.749 Fisher's exact test
Female	13 (81.3)	3 (18.8)		
Secondary infection				
Yes	15 (88.2)	2 (11.8)		0.212 Fisher's exact test
No	44 (71.0)	18 (29.0)		

[Table/Fig-7]: Association of various parameters with the final outcome (p<0.05) is considered as significant.
†For the purpose of analysis, 2x2 contingency table, total 78 cases from moderate and severe COVID-19 were included, one case of mild disease which survived was excluded



[Table/Fig-8]: Boxplot of outcome in relation to age in years and PaO_2:FiO_2 ratio. The horizontal line in the middle of the box is the median value for age. The lower and upper boundaries indicate the 25th and 75th percentile respectively. The highest and lowest value is indicated by lines (whiskers) drawn from the box. The median age of patients survived was lower (44, 47.5) compared to those who died (53, 61). Severe hypoxia (PaO_2:FiO_2 ratio<100) prior to alveolar leak event was associated with higher mortality.

survived, 18 of them had late-onset alveolar air leak events. Overall mortality in this group was 74.68% (n=59). Mortality among females was 81.3%, while it was 73% among males. The gender difference in mortality was not statistically significant (p-value=0.749). In this study, mortality in patients with moderate COVID-19 was 29.41%, primarily due to progressive worsening of hypoxia or sepsis, whereas it was 88.52% in ICU patients with severe COVID-19. In subgroup analysis, invasively ventilated patients with early occurrences of air leak, a PaO_2:FiO_2 ratio of less than 100 at the time of air leak, and acidosis on arterial blood gas analysis had higher mortality (p-value <0.001). Patients with pneumothorax had poorer outcomes compared to those with isolated subcutaneous emphysema or pneumomediastinum [Table/Fig-7]. In the subgroup analysis, PaO_2:FiO_2 ratio of less than 100 at the time of air leak had higher mortality. The median age of those who died was higher than that of those who survived, as illustrated in the boxplot [Table/Fig-8].

Eight patients (28.57%) out of a total of 28 with severe SE required decompressing incisions. There were 60 Intercostal Drainage (ICD) procedures performed on 52 patients, 8 (15.38%) of whom had bilateral pneumothorax. Non trocar ICD tubes, ranging in size from 20 to 24, were used in the majority of cases, while a pigtail catheter was inserted in two cases. There was a persistent air leak due to Bronchopleural Fistula (BPF) beyond 4-6 weeks in 5 (9.61%) patients. One case with pyopneumothorax and BPF required lobectomy, while the others were managed conservatively. Histopathological examination of the resected lung segments showed micro-abscesses with vasculitis.

Complications related to ICD [Table/Fig-3]:

Bleeding: Out of the 60 ICD procedures, self-limiting bleeding occurred after emergency ICD in 6 (10%) cases of tension PT. These patients had severe COVID-19 pneumonia and were on therapeutic anticoagulation. Major bleeding complicated two cases (3.33%), around 400 mL-600 mL lost within 4-6 hours post-ICD insertion. One patient on Non Invasive Ventilation (NIV) survived with spontaneous cessation of bleeding but later developed segmental pulmonary artery embolism. The other case, complicated by sepsis and coagulopathy, died due to simultaneous multisite bleeding, shock, and severe hypoxia.

Empyema: Post-ICD empyema secondary to nosocomial pathogens developed after the second week of ICD in 6 (10%) cases. All recovered with antibiotics and ICD drainage.

DISCUSSION

Alveolar air leak events PT, PM in COVID-19 pneumonia have been reported in both spontaneously breathing and ventilated patients. Secondary spontaneous PT has also been reported in cases of H1N1, SARS, and Middle East Respiratory Syndrome (MERS) viral pneumonia-associated Acute Respiratory Distress Syndrome (ARDS) [11-13].

The present study provides a large single-institution data from western India on spontaneous alveolar air leak events in COVID-19 pneumonia. The proportion of alveolar air leaks occurring in spontaneously breathing patients was higher (44.30%) in this study group compared to other studies (20-33%) [6,14]. The male population was affected more than the female population (4:1), which was consistent with other studies [1,14]. In a study by Martinelli AW et al., 90% of the patients were aged between 30 and 70 years, similar to present study cohort [1]. Co-morbid conditions such as diabetes and hypertension were associated with increased severity of SARS-CoV-2 pneumonia [15]. Asthma and COPD are known risk factors for secondary spontaneous pneumothorax [4]. However, this study cohort had a very low prevalence of underlying respiratory conditions that predispose individuals to spontaneous PT. Right-sided PT was more common than left-sided (58.62% vs. 27.59%). In a study by Geraci TC et al., 50% of cases had right-sided PT [14]. The average median age of those who died was 57 years. In a multicentric study from Mumbai, the mean population age was 60 years, with a mortality rate of 74% [6]. The severity of COVID-19 pneumonia was associated with an increased risk of spontaneous air leak events (p-value<0.001), which may be related to severity of alveolar damage. Cases of pneumothorax related to SARS were also associated with severe diffuse alveolar damage [16].

This study highlights the outcomes of cases in relation to the timing of the occurrence of alveolar air leaks. Early occurrence of air leaks within two weeks of symptom onset was associated with poor outcomes (p-value<0.001). Multiple mechanisms play a role in spontaneous alveolar air leaks in COVID-19 pneumonia. One such mechanism is extensive alveolar injury caused by the SARS-CoV-2 virus, leading to alveolar rupture secondary to damage of type-1 and type-2 alveolar epithelial cells [17]. This can explain the early events occurring during the acute phase within two weeks of illness. Another mechanism could involve the formation of cystic spaces in the lungs, which are prone to rupture [18,19]. The cause may be ischaemic injury leading to decreased lung compliance and cyst formation or could be secondary to resolving consolidation [20]. This mechanism will be responsible for late events that occur after two weeks of illness.

In the present study, 51.90% of air leaks occurred after two weeks (late events) of symptom onset. In a large multicentric case series, pneumothorax events were reported after a median of 14 days of hospitalisation [11]. The present study can relate these early and late radiological findings, ranging from bilateral subpleural patchy GGO with extensive consolidation and interstitial emphysema in early cases to cyst or bullae formation with interstitial thickening in late events. Another added risk factor was cavitating pneumonia and Pyo-pneumothorax secondary to *Klebsiella pneumoniae*. There is a higher risk of these infections in critically ill COVID-19 patients [21]. Secondary bacterial infections were lower in those who survived, but the difference was not statistically significant.

In the present study, two patients had interstitial emphysema and PM [Table/Fig-5a] without PT on HRCT. Most of the awake patients had severe bouts of dry cough as a predominant symptom. This leads to an increase in alveolar pressure and contributes to alveolar rupture in already damaged parenchyma [22,23]. Sudden alveolar rupture resulting in interstitial emphysema and PM can be explained by the Macklin effect [23].

Invasive Positive Pressure Ventilation (IPPV) may also contribute to barotrauma in addition to the mechanisms mentioned above. According to an update by Diaz R and Heller D every mechanically ventilated patient is at risk for barotrauma [24]. This risk significantly

increases with ventilator settings such as large tidal volumes or high Positive End-Expiratory Pressure (PEEP), which manifest as high plateau pressures [25]. The COVID-ARDS ventilation in the study population was in accordance to the ARDSnet protocol of low tidal volume, i.e., 4-6 ml/kg of ideal body weight, along with prone positioning [25]. Four patients had plateau pressures between 30 and 40 cm H_2O just before the event. Plateau pressures more than 35 cm H_2O are associated with an increased risk of barotrauma [26].

In the present study, the incidence of PT was 1.14% among hospitalised cases of COVID-19 pneumonia, which was in accordance with recent studies [1,6]. Retrospective studies have shown that PT in COVID-19 might occur in 1% of the total hospitalised patients and in 2% of ICU admissions, contributing to 1% of deaths from COVID-19 infection [27-29].

In a similar study by Tetaj N et al., the incidence of barotrauma was 5.8% in COVID-19 patients on invasive ventilation, compared to 6.47% in this cohort [30]. This incidence of barotrauma in COVID-19 was quite low compared to MERS-CoV infected patients (30%) and SARS infected patients (12-34%) [11,12,31].

In the present study, patients with a late occurrence of alveolar air leak had better survival outcomes, even though prolonged ICD was required in few of them. This point towards the primary disease processes, such as ARDS or the cytokine storm, may contribute to increased mortality in the early phase. Other studies in COVID-19 support these findings [15,29].

In severe COVID-19 cases requiring mechanical ventilation, reported mortality rates range from 57% to 94% [6,15,32,33]. In the present study, among a cohort of COVID-19 patients with air leak events, the mortality rate in those with moderate COVID-19 pneumonia (admitted to the ward) was 29.41% (5/17). The overall mortality rate in moderate to severe COVID-19 cases with alveolar air leaks was 74.68%, which was similar to the findings of a multicentric study from western India, where the mortality rate was 74% [6]. In a study by Geraci TC et al., the in-hospital mortality rate was 58% for COVID-19 patients who developed PT, with most events occurred beyond the second week of hospitalisation [14]. This aligns with the findings of the present study, where the mortality rate for late-onset air leak events was 56%. Mortality among the female subgroup was slightly higher than that of males, as most of the cases belonged to age group of 61-70 year age group. Patients with acidosis (pH < 7.35) had significantly increased mortality. Similar findings were noted by Martinelli AW et al., [1].

In the study by Martinelli AW et al., the 28-day mortality rate did not significantly differ between those who developed PT and those with isolated PM [1]. In the present study, there was a statistically significant difference in mortality between the PT group and other cases of alveolar air leaks without PT. These findings correlate with the systematic review by Zhong Z et al., [34].

In the present study, the incidence of major bleeding complications from the insertion of an ICD was very low at 3.33%, similar to the study by Geraci TC et al., [14]. Bleeding complications are known to occur in pleural procedures [4]. Severe cases of COVID-19 pneumonia were on therapeutic anticoagulation, and spontaneous cessation of bleeding occurred after anticoagulation was withheld [8]. In non life-threatening situations, adherence to the protocol for periprocedural management of anticoagulation is necessary. Surgical intervention was required in only one case of persistent Bronchopleural Fistula (BPF). In the study by Geraci TC et al., 5% of cases underwent surgical intervention [14]. [Table/Fig-9] highlights the salient review of relevant studies on COVID-19-related PT/ barotrauma [1,6,14,30].

Study [ref]	Year	Country	No. of patients	Objectives	Incidence rate: Overall, Barotrauma	Mortality/ survival	Conclusion
Martinelli AW et al., [1]	2020	United Kingdom	71	Multicentric retrospective analysis to describe clinical characteristics and outcome	1%	Survival 63.1±6.5%	Acidosis (pH<7.35) was associated with poor prognosis. Survival at 28 days was not significantly different following PT or isolated PM.
Tetaj N et al., [30]	2021	Italy	40	Incidence of PT/ PM in hospitalised cases also focusing on the three waves	1.6%, 7.2%	Mortality 47.2%	Incidence of barotrauma did not differ significantly between the three waves. The occurrence of barotrauma is associated with a high probability of ICU admission.
Udwadia ZF et al., [6]	2021	India	42	Multicentric retrospective review of incidence, clinical and radiological characteristics, outcome	3.2% in severe disease	Mortality 74%	Air leaks contributed to increased mortality in severe COVID-19 pneumonia. 33.3% developed this complication breathing spontaneously.
Geraci TC et al., [14]	2022	New York	118	Retrospective analysis of clinical outcomes, tube complications and mortality	7.4%	58%	Incidence is higher on invasive ventilation and associated with increased mortality. A 67.8% were barotrauma cases.
Present study	2024	India	79	Single centre prospective, observational cohort to assess clinical characteristics, risk factors and outcome	1.55%, 6.47%	Overall, 74.68%	44.30% events occurred in spontaneously breathing patients. Occurrence of PT was associated with higher mortality compared to other alveolar leaks. Early event in severely hypoxic patients contributed to higher mortality (p-value<0.05).

[Table/Fig-9]: Comparison of various studies of alveolar air leaks in COVID-19 [1,6,14,30].

Limitation(s)

As this was a single-centre study, the results cannot be generalised. Many asymptomatic patients with subtle PT, PM, and SE may have been missed, as serial HRCT scans were not performed in all hospitalised patients. This study does not comment on the incidence of PT in the male and female populations separately, the incidence in COVID-19 patients on non invasive ventilation (NIV) or high-flow nasal cannula (HFNC), or the comparative outcomes of patients without air leak events.

CONCLUSION(S)

In this cohort of COVID-19 cases from western India, the cumulative incidence of spontaneous alveolar air leak was 1.55%. The occurrence of PT within the first two weeks of illness in a severely hypoxemic patients on invasive mechanical ventilator carries poor prognosis. There is a need for multicentric prospective case-control studies to determine the incidence of spontaneous secondary PT and the factors affecting its outcome.

REFERENCES

[1] Martinelli AW, Ingle T, Newman J, Nadeem I, Jackson K, Lane ND, et al. COVID-19 and pneumothorax: A multicentre retrospective case series. Eur Respir J. 2020;56(5):2002697.Availablefrom:https://doi.org/10.1183/13993003.02697-2020.
[2] Zhou C, Gao C, Xie Y, Xu M. COVID-19 with spontaneous pneumomediastinum. Lancet Infect Dis. 2020;20(4):510.
[3] Wali A, Rizzo V, Bille A, Routledge T, Chambers A. Pneumomediastinum following intubation in COVID-19 patients: A case series. Anaesthesia. 2020;75(8):1076-81.
[4] Noppen M. Spontaneous pneumothorax: Epidemiology, pathophysiology and cause. Eur Respir Rev. 2010;19:217-19.

[5] Maunder RJ, Pierson DJ, Hudson LD. Subcutaneous and mediastinal emphysema: Pathophysiology, diagnosis and management. Arch Intern Med. 1984;144:1447-53.
[6] Udwadia ZF, Toraskar KK, Pinto L, Mullerpatan J, Wagh HD, Mascarenhas JM, et al. Increased frequency of pneumothorax and pneumomediastinum in COVID-19 patients admitted in the ICU: A multicentre study from Mumbai, India. Clin Med (Lond). 2021;21(6):e615-e619.
[7] Paul SS, Mohan Lal B, Ray A, Meena VP, Garg RK, Tiwari P, et al. Pneumothorax and pneumomediastinum in patients with COVID-19: A retrospective study from tertiary care institute in India. Drug Discov Ther. 2021;15(6):310-16. Doi: 10.5582/ddt.2021.01105. PMID: 35034924.
[8] Kedia Y, Awad NT, Nair J, Patil D, Amin P, Vijayan S, et al. Spontaneous pneumothorax in patients of COVID-19 pneumonia. J Assoc Physicians India. 2022;70(2):11-12. PMID: 35436820.
[9] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. [Internet]. [cited 2021 May 10]. Available at https://www.covid19treatmentguidelines.nih.gov/.
[10] Jialal I, Devaraj S. Defining the cytokine storm syndrome of COVID-19: Role of the clinical laboratory. Ann Clin Lab Sci. 2020;50(5):703-05.
[11] Shim SS, Kim Y, Ryu YJ. Novel influenza A (H1N1) infection: Chest CT findings from 21 cases in Seoul, Korea. Clin Radiol. 2011;66(2):118-24.
[12] Das KM, Lee EY, Al Jawder SE, Enani MA, Singh R, Skakni L, et al. Acute middle east respiratory syndrome coronavirus: Temporal lung changes observed on the chest radiographs of 55 patients. AJR Am J Roentgenol. 2015;205(3):W267-74. Doi: 10.2214/AJR.15.14445. Epub 2015 Jun 23. PMID: 26102309.
[13] Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: A prospective study. Lancet. 2003;361(9371):1767-72. Doi: 10.1016/s0140-6736(03)13412-5. PMID: 12781535; PMCID: PMC7112410.
[14] Geraci TC, Williams D, Chen S, Grossi E, Chang S, Cerfolio RJ, et al. Incidence, management, and outcomes of patients with COVID-19 and pneumothorax. Ann Thorac Surg. 2022;114(2):401-07.
[15] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81. Doi: 10.1016/S2213-2600(20)30079-5.
[16] Hosseiny M, Kooraki S, Gholamrezanezhad A, Reddy S, Myers L. Radiology perspective of coronavirus disease 2019 (COVID-19): Lessons from severe acute respiratory syndrome and Middle East respiratory syndrome. Am J Roentgenology. 2020;214(5):1078-82.
[17] Gralinski LE, Baric RS. Molecular pathology of emerging coronavirus infections. J Pathol. 2015;235:185-95.
[18] Rodrigues RS, Barreto MM, Werberich GM, Marchiori E. Cystic airspaces associated with COVID-19 pneumonia. Lung India. 2020;37:551-53.
[19] Sun R, Liu H, Wang X. Mediastinal emphysema, giant bulla, and pneumothorax developed during the course of COVID-19 pneumonia. Korean J Radiol. 2020;21(5):541.
[20] Aguilar PM, De Lucas EZ, Walther RÁ. Lung cysts in a patient with SARS-CoV-2. Medicina Clinica (English Ed.). 2020;155(7):325.
[21] Anokar A, Jedge P, Shah J, Chougale S. The utility of a modified technique for lower respiratory tract sampling in COVID-19 ICU and review of diagnostic approaches in suspected ventilator associated pneumonia. Critical Care Innovations. 2021;4(3):01-14.
[22] Park SJ, Park JY, Jung J, Park SY. Clinical manifestations of spontaneous pneumomediastinum. The Korean Journal of Thoracic and Cardiovascular Surgery. 2016;49(4):287.
[23] Macklin MT, Macklin CC. Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: An interpretation of the clinical literature in the light of laboratory experiment. Medicine. 1944;23:281-358.
[24] Diaz R, Heller D. Barotrauma and Mechanical Ventilation. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; [Internet]. [cited 2021 Aug 09]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545226/.
[25] Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Eng J Med. 2000;342(18):1301-08.
[26] Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, et al. Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: A 28-day international study. JAMA. 2002;287(3):345-55. Doi: 10.1001/jama.287.3.345.
[27] Attaway AH, Scheraga RG, Bhimraj A, Biehl M, Hatipoğlu U. Severe COVID-19 pneumonia: Pathogenesis and clinical management. BMJ. 2021;372:n436.
[28] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;395(10223):507-13. Doi: 10.1016/S0140-6736(20)30211-7.
[29] Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Analysis of 92 deceased patients with COVID-19. J Med Virol. 2020;92(11):2511-15. Doi: 10.1002/jmv.25891. Epub 2020 Aug 21. PMID: 32293741; PMCID: PMC7262332.
[30] Tetaj N, Garotto G, Albarello F, Mastrobattista A, Maritti M, Stazi GV, et al. Incidence of pneumothorax and pneumomediastinum in 497 COVID-19 patients with moderate-severe ARDS over a year of the pandemic: An observational study in an Italian third level COVID-19 hospital. J Clin Med. 2021;10(23):5608. Doi: 10.3390/jcm10235608.
[31] Fowler RA, Lapinsky SE, Hallett D, Detsky AS, Sibbald WJ, Slutsky AS, et al. Critically ill patients with severe acute respiratory syndrome. JAMA. 2003;290(3):367-73. Doi: 10.1001/jama.290.3.367.
[32] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-62. Doi: 10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11.
[33] Umeh C, Tuscher L, Ranchithan S, Watanabe K, Gupta R. Predictors of COVID-19 mortality in critically ill ICU patients: A multicenter retrospective observational study. Cureus. 2022;14(1):e20952.
[34] Zhong Z, Guo J, Li X, Han Y. Effects of pulmonary air leak on patients with coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. BMC Pulm Med. 2023;23(1):398. Doi: 10 .1186/s12890-023-02710-2.

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