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Research article

"Pneumomediastinum: A marker of severity in Covid-19 disease"

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ABSTRACT

Objective: The goal of this study was to look at the incidence, risk factors, clinical characteristics, and radiological aspects of COVID-19 patients who developed pneumomediastinum and compare these features between those who died and those who survived.

Materials and methods: This retrospective observational study included COVID-19 patients having pneumomediastinum on CT from May 2020 to May 2021 in a COVID-19 care hospital. 1st wave patients were considered between the period of May 2020 to January 2021 and those in the second wave between February 2021 to May 2021. The clinical details were analyzed by a consultant intensivist and CT scans were read by a team of 6 resident radiologists and 5 experienced radiologists. Demographic data, co-morbidities, clinical parameters, hemodynamic markers, radiological involvement and associated complications were analyzed.

Results: During the study period, 10,605 COVID-19 patients were admitted to our hospital of which 5689 underwent CT scan. 66 patients were detected to have pneumomediastinum on CT; 26 of them in the first wave and 40 in the second wave. Out of 66, 28 patients were admitted to ICU, 9 during the first wave and 18 during the second wave. The overall incidence of developing pneumomediastinum was 1.16%. Incidence in the 1st wave was 1.0% and in the 2nd wave was 1.29%. The overall mortality rate in admitted COVID-19 patients was 12.83% while it was 43.9% in COVID-19 patients who developed pneumomediastinum. Incidence of pneumomediastinum and pneumothorax was high in patients with extensive parenchymal involvement. 59/66 (89%) cases of pneumomediastinum had severe CT score on imaging.

Conclusion: We conclude that pneumomediastinum is a marker of poor prognosis. Timely diagnosis of interstitial emphysema or pneumomediastinum will aid in planning early protective ventilation strategies and timely intervention of complications.

1. Introduction

As the world ascends through one of the largest pandemics in recent centuries, our understanding of the natural history of the disease keeps growing each passing day. The disease has resulted in severe morbidity and mortality. The spectrum of post COVID-19 complications is increasing day by day and posing challenges to the healthcare workers. However, there are many aspects of this deadly disease yet to be understood.

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During the initial months of the COVID-19 pandemic, spontaneous pneumomediastinum (PM) was considered as a rare complication of the disease. However, during the second wave, we observed an increasing number of patients developing PM. Limited information is available about this entity; the majority of them being case reports or case series containing a small number of patients [1].

Pneumomediastinum, also known as mediastinal emphysema, is the accumulation of air in the mediastinum, first described by Laennec in 1819 [2]. Kouritas et al. divided it into two categories: primary/spontaneous and secondary PM. Iatrogenic, nontraumatic and traumatic PM are the three types of secondary PM. The presence of air within the mediastinum without a known reason is known as spontaneous PM [3,4].

Macklin et al., in 1944 described the pathophysiology of spontaneous PM as an increasing pressure gradient across the alveoli and interstitium leading to alveolar rupture. The collected air infiltrates the mediastinum through the venous sheaths [5,6]. The identification of interstitial lung emphysema due to alveolar rupture (Macklin-effect) can be done on CT scans [2] (Fig. 1A–D).

Increased intra-alveolar pressure or decreased pressure in the peri-alveolar interstitial space generates the pressure gradient. The first is seen during the Valsalva maneuver and situations that trigger it, such as coughing, defecation, vomiting, or childbirth. Excessive respiratory attempts, diabetic ketoacidosis, and other conditions are examples of the second [5].

In the general population, spontaneous PM is more commonly seen in young males with a predisposition in those having asthma and chronic obstructive pulmonary disease [7].

PM is considered as a benign entity and is treated conservatively as mediastinal soft tissues eventually cause resorption of the air within the cavity [3].

In patients suffering from COVID-19 infection, barotrauma was considered to be the most common cause of secondary PM (1). Many studies done previously show that PM, pneumothorax, subcutaneous emphysema in COVID-19 patients have been observed without mechanical ventilation associated barotrauma. It is postulated that the alveolar wall could become more susceptible due to inflammation and spontaneous PM is triggered by persistent cough or any other process leading to increased alveolar pressure [8].

The objectives of our study were to determine the incidence of pneumomediastinum in COVID-19 patients of a tertiary care center in India and determine their mortality rate, study the probable risk factors, clinical characteristics, radiological features and outcome of the disease. Considering the high mortality in these patients, we also compared the clinical and radiological parameters between the patients who died and those who survived.

2. Material and methods

2.1. Study design

This is a retrospective observational study done in a tertiary care hospital in Pune, India with 550 beds (483 in wards, 62 in Intensive Care Unit and 5 in emergency room) designated specifically for the management of COVID-19 patients. All patients were

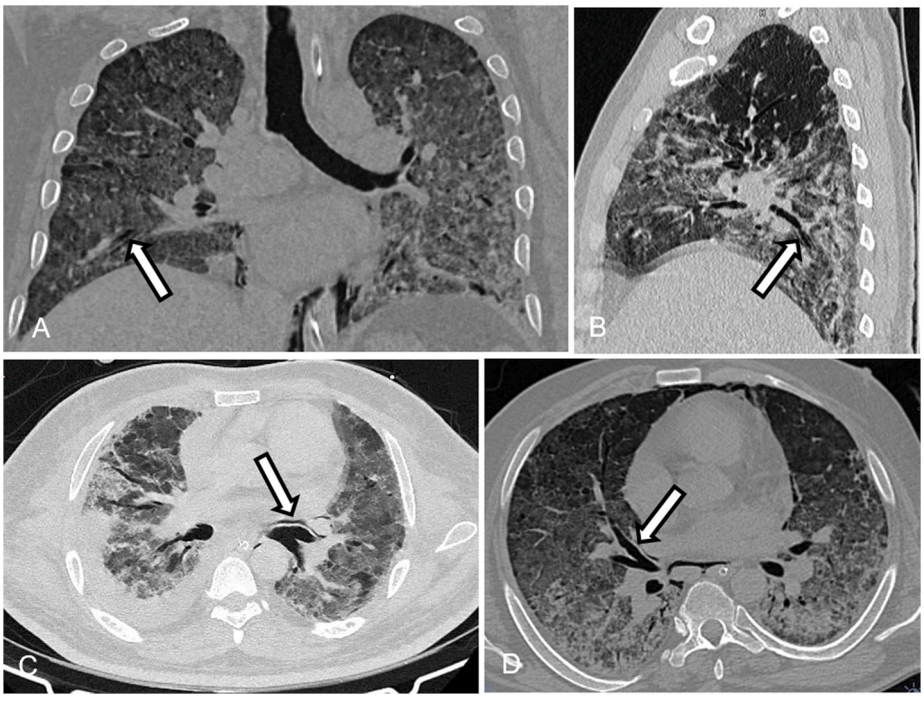

Fig. 1. Coronal reformatted (A), Sagittal reformatted (B) and axial (C and D) CT images in lung window showing the presence of Macklin effect i. e air dissection along the peribronchovascular sheaths (marked by white arrow).

diagnosed to be COVID-19 positive based on Reverse Transcriptase Polymerase Chain Reaction (RTPCR)/COVID-19 antigen test/CT results as per the government policy.

2.2. Inclusion and exclusion criteria

All the COVID-19 patients, who were diagnosed to have mediastinal and/or subcutaneous emphysema on CT during the period of May 2020 to May 2021 were included in the study.

Patients with a history of invasive procedures who were diagnosed to have a tracheal or esophageal injury during the CT scan which led to PM were excluded from the study. Also COVID-19 patients having direct chest trauma and non COVID-19 patients developing spontaneous PM were excluded.

3. Methods

The study was approved by the Ethical committee of the hospital (approval number: IHR-2021-Jul-No-421). Waiver of consent was given as the study involved retrospective observational analysis of the data.

Our institutional database was checked to retrieve demographic details, comorbidities, clinical parameters, hemodynamic markers, the requirement of oxygen therapy and mode of administration, day of illness when PM/PT was detected, associated clinical complications, prognosis in these patients and day of illness at the time of death (wherever applicable). The clinical details were analyzed by a consultant intensivist with 15 years of experience. The patients seen in 1st wave and 2nd wave of the pandemic were segregated to compare the incidence and mortality rate of PM developing in COVID-19 patients. 1st wave patients were considered between the period of May 2020 to January 2021 and those in the second wave between February 2021 to May 2021.

Mortality was collected post 3 months of admission or at the end of hospital stay whichever was longer.

Radiological analysis;

Chest CT scans were performed on either 64 slice or 128 slice CT scanners. The studies were performed in supine position with maximum inspiration and with or without intravenous contrast administration. Intravenous iodinated contrast was given in patients who underwent CT pulmonary angiography studies to rule out pulmonary embolism, pulmonary arterial hypertension or pulmonary artery aneurysm. The acquisition parameters for the 64 slice scanner were 130 kVp, 70 mAs, 1.3 mm/rotation pitch, 5 mm slice thickness for acquisition. Images were reconstructed with 1 mm thickness 0.7 increment. The acquisition parameters for 128 slice scanner were 120 kVp, 10 mAs (variable), 0.9 mm/rotation pitch, 5 mm slice thickness for acquisition. Images were reconstructed with a thickness of 0.625 mm.

CT scans were read by a team of 6 resident radiologists and finalized by 5 experienced radiologists with more than 10 years of experience. CT images were assessed in 'lung window settings' and categorized according to the extent of PM (body segments involved), lung parenchymal involvement and severity of the disease, presence of associated features like lung cysts, emphysema, etc [2]. A meticulous search was done to identify the interstitial lung emphysema due to alveolar rupture (suggesting Macklin effect) on CT scans. The extension of emphysema (mediastinal and subcutaneous) was categorized based on 5 body segments involved, namely mediastinum (i.e. PM), head and neck, chest wall, abdomen and upper limbs [2].

Statistical analysis;

The data on categorical variables are shown as n (% of cases) and data on continuous variables are presented as mean and standard deviation (SD) or Median (Min – Max). The inter-group statistical comparison of the distribution of categorical variables is tested using the Chi-Square test or Fisher's exact probability test if more than 20% of cells have an expected frequency of less than 5. The inter-group statistical comparison of means of continuous variables is done using an independent sample *t*-test for normally distributed variables. The inter-group statistical comparison of medians of continuous variables is done using the Mann-Whitney *U* test for non-normally distributed variables. The underlying normality assumption was tested before subjecting the study variables to a *t*-test. All results are shown in tabular as well as graphical format to visualize the statistically significant difference more clearly.

In the entire study, p-values less than 0.05 are considered as statistically significant. The entire data is statistically analyzed using Statistical Package for Social Sciences (SPSS ver 21.0, IBM Corporation, USA) for MS Windows.

4. Results

During the study period, 10,605 COVID-19 patients were admitted to our hospital, of which 7579 patients were admitted during the 1st wave (from May 1, 2020 to Jan 31, 2021) and 3026 patients were admitted during the 2nd wave (from Feb 1, 2021 to April 30, 2021). Total COVID deaths in both waves were 1361, out of which 778 were in the 1st wave and 583 were in the 2nd wave.

Chest CT is an important tool in the assessment of COVID-19 patients. It helped to triage the patients presenting in our hospital according to the CT severity score as well as other radiological findings. CT scan was performed in total 5689 patients, out of which 2600 were performed during first wave and 3089 during second wave. 4456 scans were performed on 64 slice CT scanner and 1233 were performed on 18 slice CT scanner.

66 patients were detected to have pneumomediastinum on CT scan; 26 of them in the first wave and 40 in the second wave (Fig. 2). Out of these 66, 28 patients were admitted to in Intensive Care Unit (ICU) and 38 patients were managed in general and Non Invasive Ventilation (NIV) wards. 51 patients out of these 66 patients were detected to have raised d Dimer and subjected on contrast study. Pulmonary embolism was detected in 7 patients.

The affected age group ranged from 24 to 75 years, mean 52 years. PM was more commonly found in males (83%), however

mortality was significantly more in females (72%). Table 1.

Various associated co-morbidities were hypertension (HTN) (16), diabetes mellitus (DM) (8), ischemic heart disease (4), chronic kidney disease (3), chronic liver disease (1), chronic obstructive pulmonary disease (2) and known malignancies (3). The most common were HTN (24%) and DM (12%). 4 patients had both DM and HTN. 32 patients (48.5%) did not have any co-morbidity. One of the 3 patients with known malignancies was a case of carcinoma lung (Fig. 3).

One patient was a known case of autosomal dominant polycystic kidney disease (ADPKD) who had developed lung cysts and PM (Fig. 4C and D). Very few such cases of ADPKD developing lung cysts are reported in the literature (Fig. 4C- marked by white arrow).

As per the WHO guidelines, disease severity was assessed based on SpO2 levels on admission to the hospital [9]. Accordingly, 16 patients were categorized under mild grade (24.2%), 22 under moderate grade (33.3%) and 28 under severe grade (42.4%) (Table 1).

Oxygenation and Lab parameters (Table 2):

The infective markers were raised in most of the study subjects [10]. The median CRP level for the entire study population was 102.0 mg/l (range 6.7–3896.0), 121 mg/l in the group with mortality and 78.1 mg/l in the group with recovery. The median D dimer level for the entire study population was 1345 ng/ml (263.0–22407.0), 1600 ng/ml in the group with mortality and 1294 ng/ml in the group with recovery.

The median IL-6 for the entire study population was 33.4 pg/ml (6.2–288), ferritin level was 738.32 ng/ml (214.0–6903.1) and LDH was 667 (352.0–1319.0).

56 patients (84.8%) who developed PM, had no prior history of iatrogenic intervention. However, high pressure oxygen therapy in the form of High Flow Nasal Oxygen (HFNO) and Non Invasive Ventilation (NIV) was given to 13 (19.7%) and 30 (45.5%) patients respectively. 45.5% of patients developing PM were on NIV with 55% mortality amongst them (Table 1).

Radiological parameters assessment (Table 3):

Based on the 25 point CT severity score given by Chang et al. [11], 3 patients (4.5%) were classified as a mild grade, 4 (6%) as moderate and 59 (89%) as a severe grade.

Bilateral PM was seen in 53 (80.3%) patients, 23 (35%) patients had associated PT and 48 (73%) patients had subcutaneous emphysema. 1 patient had epidural pneumorrhachis. 3 patients had associated pneumopericardium and all three of them succumbed to the illness.

Regarding the extension of emphysema (mediastinal and subcutaneous) in 5 body segments, 51 patients (77%) had less than 3 segments involved, out of which 23 (45%) died. 8 patients (12%) had more than 3 segments involved, out of which 3 (37%) died (Table 4) (Fig. 5A–D).

The interstitial lung emphysema due to alveolar rupture (Macklin-effect) was seen in 42 (63.6%) patients.

At the time of diagnosis of PM on CT, 23 were in the acute phase (35%), 36 in subacute (54%) and 7 in chronic phase (11%) [12]. Changes of fibrosis and bronchiectasis, either isolated or together were seen in 40 patients (60.6%). Lung cysts were seen in 13 (19.7%) patients (Fig. 4 A).

Other associated CT features seen were pleural effusion, pericardial effusion, emphysematous changes, secondary/superadded infective pathologies. Pulmonary embolism, a known complication of COVID-19 disease was seen in 7 patients (10%).

29/66 patients succumbed to the illness (43.9%). Various causes of death were septic shock, acute respiratory distress syndrome (ARDS), acute coronary syndrome, most common being septic shock (41.4%) and ARDS (37.9%) (Table 1).

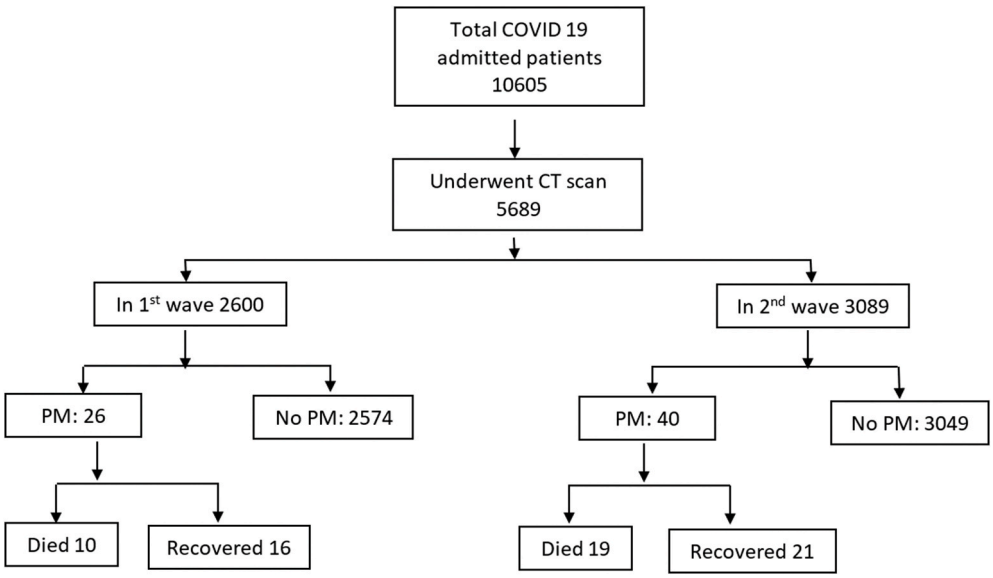

Fig. 2. Flowchart showing distribution of admitted COVID- 19 patients in both the waves.

Table 1
Distribution of clinical parameters in COVID-19 patients with pneumomediastinum.

Parameters		Total (n = 66)	Mortality (n = 29)	Recovered (n = 37)	*P*-value
Sex	Male	55 (83.3)	21 (72.4)	34 (91.9)	0.048*
	Female	11 (16.7)	8 (27.6)	3 (8.1)	
Age (years)	Mean ± SD	52.0 ± 13.2	54.6 ± 13.1	50.0 ± 13.1	0.165
Co-morbidity	Nil	32 (48.5)	11 (37.9)	21 (56.8)	0.388
	Diabetes mellitus (DM)	8 (12.1)	4 (13.8)	4 (10.8)	
	Hypertension (HTN)	16 (24.2)	7 (24.1)	9 (24.3)	
	DM + HTN	4 (6.0)	3 (10.3)	1 (2.7)	
	Other	6 (9.0)	4 (13.8)	2 (5.4)	
SpO2 (%)	Mild	16 (24.2)	9 (31.0)	7 (18.9)	0.306
	Moderate	22 (33.3)	7 (24.1)	15 (40.5)	
	Severe	28 (42.4)	13 (44.8)	15 (40.5)	
Iatrogenic procedure done before scan	Yes	10 (15.1)	7 (24.1)	3 (8.1)	0.092
	No	56 (84.8)	22 (75.9)	34 (91.9)	
Type of ventilation/oxygenation	O2	13 (19.7)	1 (3.4)	12 (32.4)	0.004*
	HFNO	13 (19.7)	6 (20.7)	7 (18.9)	0.858
	NIV	30 (45.5)	16 (55.2)	14 (37.8)	0.160
	Mechanical ventilation	8 (12.1)	6 (20.7)	2 (5.4)	0.125
	Intervention for Pneumothorax	14 (21.2)	7 (24.1)	7 (18.9)	0.607
Duration between Positive to PM	Median (Min – Max)	16 (1–41)	17 (2–41)	16 (1–34)	0.948
Duration between PM to death	Median (Min – Max)	6 (1–31)	6 (1–31)	–	–
Duration between Positive to death	Median (Min – Max)	24 (4–54)	24 (4–54)	–	–
Cause of death	Septic shock	12 (41.4)	12 (41.4)	–	–
	ARDS	11 (37.9)	8 (27.6)		
	Acute coronary syndrome	3 (10.3)	3 (10.3)		
	Other	3 (10.3)	3 (10.3)		

Values are n (% of cases) unless otherwise stated. *P-value<0.05.

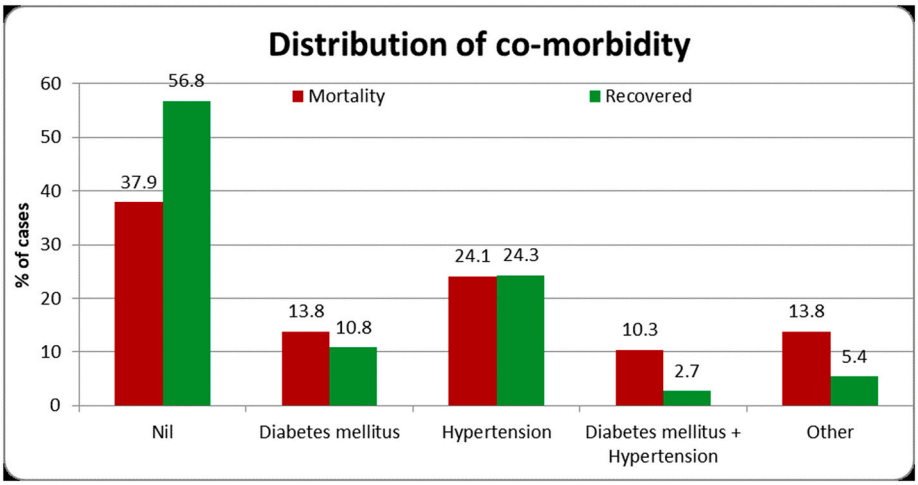

Fig. 3. Distribution of co-morbidity.

The average duration between diagnosis of COVID-19 and development of PM was 16 days (ranging from 1 to 41 days) and the average duration between detection of PM and death was 6 days (ranging from 1 day to 31 days). Severe cases of pneumomediastinum were followed up with alternate day portable chest Xray. The average time to death from diagnosis of COVID-19 was 24 days (4–54) in the patients who developed PM (Table 1) (Fig. 6).

The overall incidence of developing PM amongst the patients subjected to CT scan was 1.16%. Incidence in the 1st wave was 1.0% and that in the 2nd wave was 1.29%.

The overall mortality rate in admitted COVID-19 patients was 12.83% while that in PM developing COVID-19 patients was 43.9%, which was significantly high (Fig. 7A and B).

5. Discussion

This retrospective observational study is the first of its kind done in India to the best of our knowledge, which has assessed the clinical and radiological parameters of COVID-19 patients developing PM and compared the two groups, those with fatal outcomes and

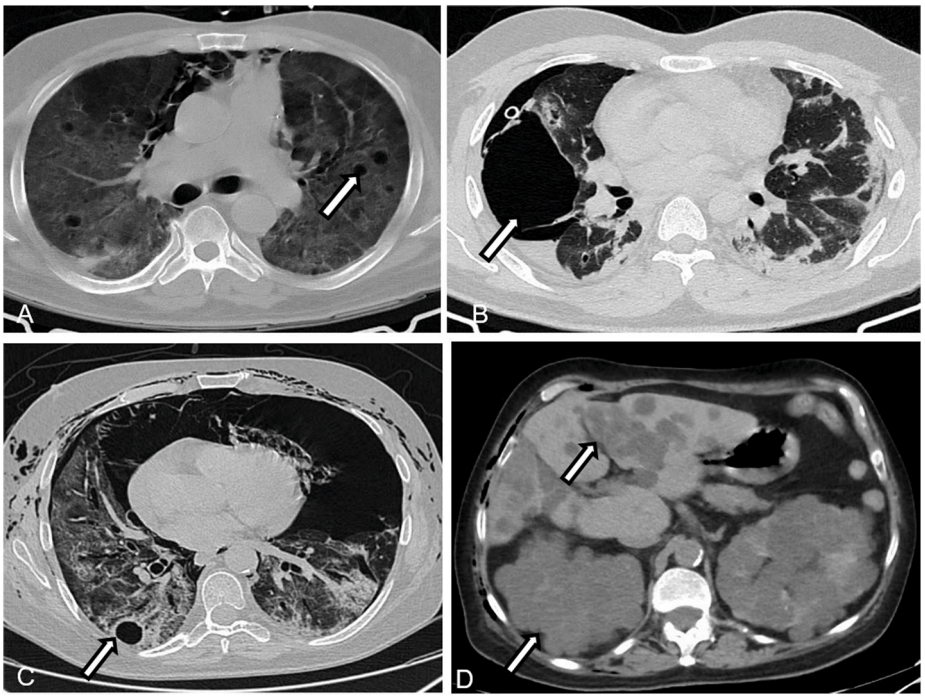

Fig. 4. Cystic lung pathologies in COVID-19 patients predisposing to pneumomediastinum. A: Axial CT image in lung window showing the presence of multiple small lung parenchymal cysts (marked by white arrow). B: Axial CT image in lung window showing the presence of an emphysematous bulla in the right lower lobe (marked by white arrow). C, D: Case of Autosomal dominant polycystic kidney disease showing C: Presence of lung cysts in axial CT image in lung window (marked by white arrow). D: Multiple hepatic and renal cysts in axial CT image in soft tissue window (marked by white arrow).

Table 2
Analysis of laboratory parameters in COVID-19 patients with Pneumomediastinum.

Parameters		Total (n = 66)	Mortality (n = 29)	Recovered (n = 37)	*P*-value
CRP (mg/l)	Median (Min – Max)	102.0 (6.7–3896.0)	121.0 (6.7–3896.0)	78.1 (19.6–285.6)	0.200
d Dimer (ng/ml)	Median (Min – Max)	1345 (263.0–2407.0)	1600.0 (263.0–16616.0)	1294.4 (288.0–22407.0)	0.371
IL6 (pg/ml)	Median (Min – Max)	33.4 (6.2–288)	32.0 (16.6–288.0)	33.4 (6.2–200.0)	0.967
LDH	Median (Min – Max)	667 (352.0–1319.0)	667.0 (352.0–1319.0)	923.0 (574.0–1272.0)	0.770
Ferritin (ng/ml)	Median (Min – Max)	738.32 (214.0–6903.1)	734.5 (214.0–1997.0)	738.3 (301.5–6903.1)	0.791

Values are n (% of cases) unless otherwise stated.

those who recovered. We have also compared the incidence and mortality rates between the 1st and 2nd waves of the pandemic.

Since the evolution of the COVID-19 pandemic, PM was considered as a rare complication of this disease and having a benign course. Few scientific papers have been published in the medical literature on this topic however limited data is available about the risk factors and prognosis of these patients. The sample size of prior studies was small.

The study done by Brito et al., analyzed the relation of Macklin effect with PM and outcome in these patients [2]. Another multicenter study done in Spain by Oscar Miro et al., compared the COVID-19 and non COVID-19 patients developing PM with respect to clinical characteristics and their outcome. They found an increased incidence of PM in COVID-19 patients compared to non-COVID-19 patients admitted to ICU [13].

As contemplated by a few previous studies, the cause of developing PM in COVID-19 pneumonia is thought to be the damage to the alveoli caused by inflammation and parenchymal ischemia which is exacerbated by a persistent cough and high intra-alveolar pressure in long standing disease [14]. As 77.3% (45.5% on NIV) of our patients were on positive pressure ventilation at the time of detection of PM, barotrauma could also be one of the causative factors for developing PM as postulated by previous studies [14]. End expiratory pressure given by NIV causes an increase in the pressure gradient across alveoli and interstitium which might overdistend inflamed alveoli leading to their rupture.

Interstitial lung emphysema (due to Macklin effect) was identified in almost 63% of patients which supports the theory behind its pathophysiology i.e. alveolar damage and air leaking through bronchovascular sheath. It could be identified even in those patients with minimal PM.

The parenchymal findings seen on CT in COVID-19 included groundglass densities, superimposed reticular thickening leading to

Table 3
Assessment of radiological parameters in COVID-19 patients with pneumomediastinum.

Parameters		Total (n = 66)	Mortality (n = 29)	Recovered (n = 37)	*P*-value
Initial CT score	Mild	3 (4.5)	1 (3.4)	2 (5.4)	0.671
	Moderate	4 (6.0)	1 (3.4)	3 (8.1)	
	Severe	59 (89.4)	27 (93.1)	32 (86.5)	
Pneumothorax	Nil	43 (65.1)	19 (65.5)	24 (64.9)	0.958
	UL	19 (28.8)	8 (27.6)	11 (29.7)	
	BL	4 (6.0)	2 (6.9)	2 (5.4)	
Pneumomediastinum	Nil	7 (10.6)	3 (10.3)	4 (10.8)	0.952
	UL	6 (9)	3 (10.3)	3 (8.1)	
	BL	53 (80.3)	23 (79.3)	30 (81.1)	
Subcutaneous emphysema		48 (72.7)	20 (69.0)	28 (75.7)	0.544
Pneumopericardium	Yes	3 (4.5)	3 (10.3)	0	0.080
	No	63 (95.5)	26 (89.7)	37 (100.0)	
Epidural pneumorrhachis	Yes	1 (1.5)	0	1 (2.7)	0.999
	No	65 (98.5)	29 (100.0)	36 (97.3)	
Macklin effect	Yes	42 (63.6)	15 (51.7)	27 (73.0)	0.075
	No	24 (36.4)	14 (48.3)	10 (27.0)	
Staging	Acute	23 (34.8)	15 (51.7)	8 (21.6)	0.022*
	Subacute	36 (54.5)	13 (44.8)	23 (62.2)	
	Chronic	7 (10.6)	1 (3.4)	6 (16.2)	
Bronchiectasis/Fibrosis	Nil	26 (39.4)	16 (55.2)	10 (27.0)	0.144
	Both	12 (18.2)	4 (13.8)	8 (21.6)	
	Bronchiectasis	16 (24.2)	5 (17.2)	11 (29.7)	
	Fibrosis	12 (18.2)	4 (13.8)	8 (21.6)	
Lung cysts	Yes	13 (19.7)	7 (24.1)	6 (16.2)	0.422
	No	53 (80.3)	22 (75.9)	31 (83.8)	
Pulmonary embolism	Yes	7 (10.6)	2 (6.9)	5 (13.5)	0.453
	No	59 (89.4)	27 (93.1)	32 (86.5)	

Values are n (% of cases) unless otherwise stated. *P-value<0.05.

Table 4
Distribution of body segments involved in mediastinal and subcutaneous emphysema.

Parameters		Total (n = 66)	Mortality (n = 29)	Recovered (n = 37)	*P*-value
Segment involved	M	59 (89.4)	26 (89.7)	33 (89.2)	0.999
	N	44 (66.7)	19 (65.5)	25 (67.6)	0.999
	C	17 (25.8)	4 (13.8)	13 (35.1)	0.087
	A	4 (6.1)	3 (10.3)	1 (2.7)	0.312
	UL	9 (13.6)	3 (10.3)	6 (16.2)	0.720
No. of segments involved	Nil	7 (10.6)	3 (10.3)	4 (10.8)	0.920
	≤3	51 (77.3)	23 (79.3)	28 (75.7)	
	>3	8 (12.1)	3 (10.3)	5 (13.5)	

Values are n (% of cases) unless otherwise stated.
A-Subcutaneous emphysema in abdominal wall, C-Subcutaneous emphysema in chest wall, *M*-Pneumomediastinum, *N*-Subcutaneous emphysema in neck region, UL-Subcutaneous emphysema in upper limbs.

crazy paving pattern and also areas of consolidation. Most of the patients showed bilateral and peripheral distribution of the groundglass opacities. Bronchiectasis and changes of fibrosis were also seen.

As the extent of parenchymal involvement increases, the chances of alveolar injury increase. This signifies that chances of PM are much more in extensive parenchymal involvement i.e. in severe grade patients. We observed most of our study subjects (59/66) had severe grade of involvement on CT and were in the subacute stage of the pathology. This shows that peribronchial fibrosis in conjunction with coughing bouts or high pressure gradient might increase the traction on small airways leading to disruption of bronchoalveolar junction.

Pulmonary cyst or bullae formation is seen in association with COVID-19 pneumonia and is also considered to be one of the underlying causes for pneumothorax or PM if they rupture [14,15] (Fig. 4 B). Associated pneumothorax was seen in 35% of patients and surgical emphysema in 74% of patients which is consistent with other case series [2,14]. According to previous studies, pneumothorax and PM in COVID-19 patients were considered a marker of poor prognosis [8,14]. The extent of subcutaneous emphysema had no significant impact on the prognosis of the patient.

After diagnosing PM or interstitial emphysema, clinicians need to lower the oxygen pressure to prevent further damage to the alveoli. The aim is to achieve adequate oxygenation while maintaining lower peak and mean airway pressures. This will minimize the air leak through the defects. In cases of localized distribution of air in PM, lateral decubitus positioning can be tried by keeping the affected lung in the dependent position which might plug the defect. Hence precise localization of interstitial air needs to be conveyed by the radiologists in localized PM.

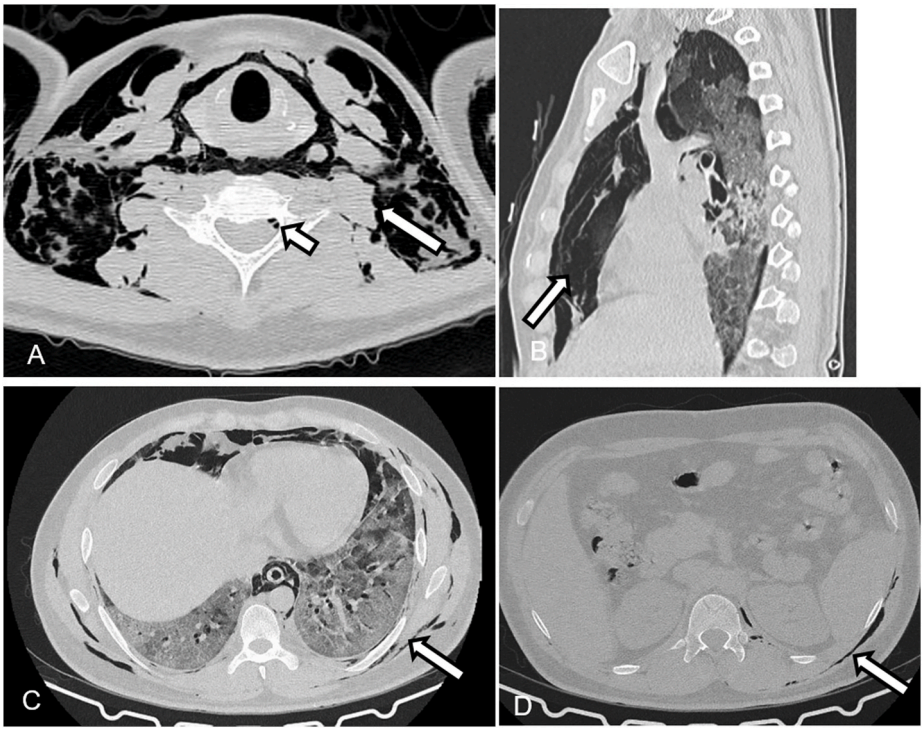

Fig. 5. Segmental distribution of subcutaneous and mediastinal emphysema. Axial (A, C, D) and Sagittal reformatted (B) CT images in lung window showing A: Subcutaneous emphysema in the neck region (long arrow) and epidural pneumorrhachis (short arrow), B: Tension pneumomediastinum (marked by white arrow)., C: Subcutaneous emphysema in the chest wall (marked by white arrow), D: Subcutaneous emphysema in the abdominal wall (marked by white arrow).

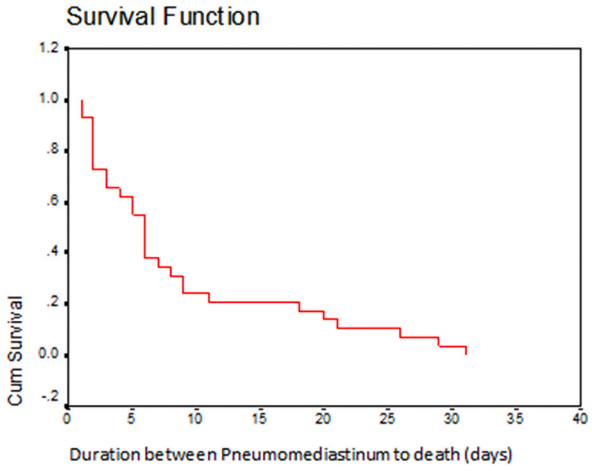

Fig. 6. KM curve showing cumulative survival against the duration between PM to the death.

If the air leak from the alveoli continues, PM may progress to malignant or tension PM over time resulting in a significant mass effect on the mediastinal vasculature, trachea and heart simulating cardiac tamponade. This may lead to fatal outcome. Very few cases of tension PM are reported in the literature. We had seen one patient of tension PM who eventually recovered on conservative management.

Another late complication of PM is pneumopericardium [1]. Pneumopericardium has a grave prognosis due to the risk of significant hemodynamic compromise. In our study, all 3 patients having pneumopericardium had fatal outcome.

The overall incidence of PM in our study was found to be higher compared to previous studies [13,16,17]. The mortality rate of COVID-19 patients developing PM is not given in the literature for such a large group. Our study showed 43.93% of mortality rate in PM patients, which is quite high. Since our hospital is a tertiary care referral center and many critical patients were referred for further

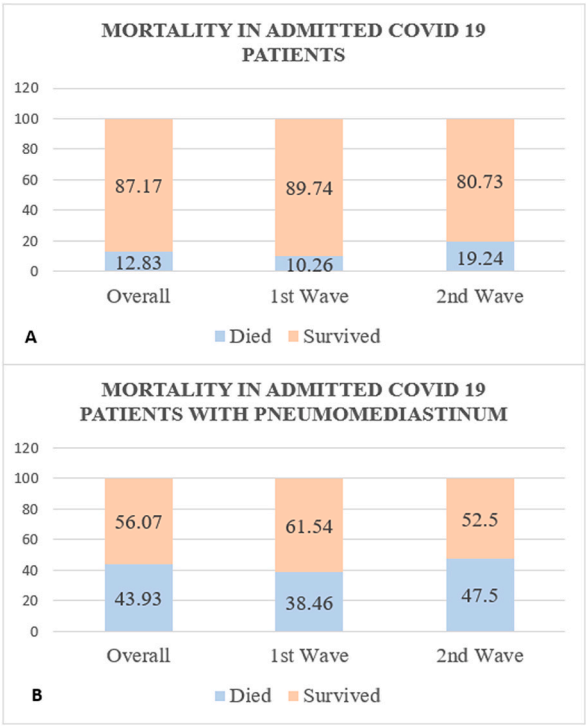

Fig. 7. Overview of "Mortality rates". A) In admitted COVID-19 patients B) In those admitted COVID-19 patients who developed pneumomediastinum.

management, this could be one of the reasons for high incidence and mortality rates.

Considering the high mortality in PM patients, we tried to find its association with clinical and radiological parameters. For that, we compared all the collected data between the two groups, i.e. patients who died and those who recovered.

Mortality was high in females (8 out of 11) as compared to males and it was found to be statistically significant. Significant increase in the risk of disease severity as well as in-hospital death is seen in COVID 19 patients with DM. The risk increases further if the patient has other associated co morbidities [18]. Patients having both DM and HTN showed high chances of mortality (3 out of 4) as compared to individual co-morbidities.

Median CRP values and d Dimer values were moderately high in those patients who died as compared to those who recovered, though not statistically significant.

8 patients were on mechanical ventilation prior to the diagnosis of PM. However, no statistically significant association was found between the mechanical ventilation and PM. Amongst the radiological parameters, most of the patients in the acute phase had fatal outcomes (15 out of 23) and it was statistically significant. No significant association was found in the rest of the clinical, laboratory and radiological parameters between the two groups.

Our study had few limitations. RTPCR was not done in all cases included in this study. Cases suspected clinically to have COVID 19 infection during the pandemic and those with positive rapid antigen test were included. Since we belong to a resource limited healthcare system, only those patients having respiratory symptoms are referred for CT scan by the emergency physicians. We might have missed clinically stable COVID-19 patients having PM and those referred from outside hospitals with already diagnosed PM.

We did not compare the clinical, radiological parameters and prognostication between those COVID-19 patients developing PM and those without PM. A larger study or meta-analysis may be needed to address this query.

Spontaneous PM can be concluded to be an uncommon complication of COVID-19 disease. Patients with known viral illnesses like SARS had also shown PM which was presumed to be due to widespread alveolar damage. PM with severe parenchymal pneumonia, makes the management of a patient extremely challenging.

Clinicians should be mindful of the likelihood of PM in patients with a long hospital stay, substantial parenchymal involvement, and severe hypoxia requiring high-pressure oxygenation. As a consequence of COVID-19 pneumonia, subcutaneous emphysema in the supraclavicular fossa may be the initial sign of pneumomediastinum. A thorough examination of this area on a chest radiograph is recommended.

Though PM has a benign course, it is associated with a bad prognosis when it occurs in the context of severe pulmonary injury, although it may resolve if the lungs are less severely affected by the COVID-19 infection.

When a follow up CT scan is done in worsening patients to look for progression of the disease, pulmonary thromboembolism or other complications, emphasis must also be given to early identification of interstitial emphysema (Macklin effect) on CT [19] as it can progress to PM and malignant/tension PM. However, there is no significant association of interstitial emphysema with the mortality in

our study.

6. Conclusion

We conclude that PM is a marker of poor prognosis though not the sole cause. We strongly discourage the thought of giving diagnostic and therapeutic nihilism to PM in COVID-19 patients as it has an impact on the morbidity of the patients and hospital stay. Hence meticulous search to diagnose interstitial emphysema (due to Macklin effect) or PM is needed which will aid in planning early protective ventilation strategies and timely intervention of any lethal complications.

Author contribution statement

NIVEDITA SHAILESH KHAIRE, MBBS., DMRD., DNB; DR SONALI DESHMUKH, MBBS MD; DR. ESHA ANIL AGARWAL, MBBS: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

DR SANJAY KHALADKAR, MBBS MD; DR NILESH MAHALE, MBBS MD: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

DR SANJAY DESAI, MBBS MD DNB FRCR; DR ASHWINI KULKARNI, MBBS MD: Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

PM	Pneumomediastinum
COVID-19	Coronavirus Disease
CT	Computed Tomography
RTPCR	Reverse Transcriptase Polymerase Chain Reaction
PT	Pneumothorax
kVp	Kilovolt Peak
mAs	Milli Ampere Second
SD	Standard Deviation
ICU	Intensive Care Unit
NIV	Non Invasive Ventilation
HTN	Hypertension
DM	Diabetes Mellitus
ADPKD	Autosomal Dominant Polycystic Kidney Disease
CRP	C-Reactive Protein
IL-6	Interleukin - 6
LDH	Lactate Dehydrogenase
HFNO	High Flow Nasal Oxygen
ARDS	Acute Respiratory Distress Syndrome
SARS	Severe Acute Respiratory Syndrome

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