DOI: 10.7860/JCDR/2022/57842.17012

Original Article

Surgery Section

Assessment of Potential Risk Factors, Characteristics, and Outcome of Pneumothorax and Pneumomediastinum in Patients with COVID-19: A Retrospective Case-control Study

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ABSTRACT

Introduction: Pneumothorax (PTX) and/or Pneumomediastinum (PMD) are rare complications of Coronavirus Disease-2019 (COVID-19) and are linked to high mortality. Incidence rates vary between 0.56-2.01% in the reported literature. With clinical examination being hampered in the current pandemic setting, there is a delay in the diagnosis. There is a need to identify and establish potential predictive factors, that may aid in identifying patients with a high-risk of developing PTX and/or PMD.

Aim: To identify potential risk factors and thus, explore their association with PTX and/or PMD among patients with COVID-19.

Materials and Methods: A retrospective case-control study was conducted at MS Ramaiah Medical College and Hospital, Bangalore, Karnataka, India, over a six-month period. A total of 130 patients diagnosed with COVID-19 were recruited in a 1:3 ratio as cases and controls, respectively. The study included 31 consecutive patients with PTX and/or PMD (cases) and 99 consecutive patients serving as controls, Cases were patients, diagnosed radiologically with PTX and/or PMD, and controls were, matched individuals without PTX and/or PMD. Patient's clinical and laboratory parameters (complete blood count, renal and liver function tests, serum levels of inflammatory markers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-Dimer were tested for potential association with PTX and/or PMD. Student's t-test, Chi-square test, multivariate and univariate logistic regression analysis were performed.

Results: During the study period, there was a total of 3,251 COVID-19 admissions at the centre, with 976 patients requiring Intensive Care Unit (ICU) admission. The overall incidence of PTX and/or PMD during the study period was (31/3251) 0.95%. The previous history of COVID-19, non vaccination with COVID-19 vaccine, cough as a predominant symptom, high values of baseline CRP, total bilirubin, Aspartate Transaminase (AST), and total leukocyte counts had a positive association. In-hospital mortality (54.8% vs 33.30%) and 28-day mortality (35.7% vs 7.6%) following discharge, were higher among those with PTX and/or PMD.

Conclusion: Patients with a history of previous infection with COVID-19, non vaccination/incomplete-vaccination with COVID-19 vaccines, and patients with increasing total leukocyte counts and AST levels, high baseline total serum bilirubin were at increased risk of a detrimental clinical course and may indicate, the possibility of development of PTX and/or PMD in COVID-19 disease.

Keywords: Coronavirus disease-2019, Respiratory infections, Severe acute respiratory syndrome

INTRODUCTION

COVID-19 is an infectious respiratory disease caused by the novel coronavirus Severe Acute Respiratory Syndrome (SARS-CoV-2) that emerged in Wuhan, China at the end of 2019, resulting in a worldwide pandemic [1]. The development of PTX and/or PMD is one of the emerging respiratory complications of COVID-19 viral pneumonia. PTX is defined as the presence of air or gas in the pleural cavity (i.e., the potential space between the visceral and parietal pleura of the lung), which can impair oxygenation and/or ventilation [2], whereas, PMD also known as mediastinal emphysema is an uncommon condition characterised by the accumulation of air or gas in the mediastinum [3].

Incidence rates of PTX vary between 0.56-2.01% in reported literature so far largely comprising of case series with the majority of the cases linked to those on mechanical ventilation [4-8]. A case-control multicentre study found a higher incidence of PTX in patients with COVID-19, when compared to that in non COVID-19 infected patients despite excluding those due to invasive and non invasive ventilation [8].

The majority of secondary spontaneous PTX cases are due to Chronic Obstructive Pulmonary Disease (COPD), although most lung diseases have been reported to cause PTX including lung infections [2]. Existing studies on COVID-19 with PTX show a low representation of COPD, thus implicating the SARS-CoV-2 virus itself as the causative factor. Most viral epidemics affecting the respiratory system have demonstrated PTX as a complication and they are associated with worse patient outcomes including mortality [9,10]. Among others, *Pneumocystis jirovecii* has been frequently associated with the occurrence of PTX [11].

The pathogenetic basis of PTX in COVID-19 has been linked to the breakdown of alveolar membrane integrity due to direct invasion and necrosis of lung tissue including the pleura by the microorganism itself. An increase in alveolar pressure due to violent coughing can cause alveolar damage. Selective over distention of the alveoli due to mucus impaction, inflammation and consolidation can lead to alveolar rupture even in the absence of mechanical ventilation [8,12,13].

In a pandemic setting, eliciting important clinical signs that enable a diagnosis of PTX is hampered for want of safety. In addition, the threshold to perform chest imaging among physicians is highly variable leading to a missed or delayed diagnosis. In such a setting, the identification of factors that are strongly associated with the

development of PTX would play a critical role in improving patient management, yet there is scant literature on the same.

Knowledge of the potential risk factors could play an important role in the development of potential lung protective strategies in the management of COVID-19, thus present study was conducted to explore the association between risk factors for PTX and PMD among patients with COVID-19 and to determine the early outcome at 28 days discharge in patients developing PTX and/or PMD.

Potential hypotheses to be generated for the study was:

a. Patients with a high inflammatory response to SARS-CoV-2 infection are at a higher risk of developing lung damage favouring spontaneous PTX.

b. High total bilirubin is a predictor for subsequent PTX.

MATERIALS AND METHODS

This retrospective case-control study was conducted at MS Ramaiah Medical College and Hospital, Bangalore, Karnataka, India, from July 2021 to December 2021. A total of 130 patients satisfying study criteria were enrolled consecutively, for every case of PTX included, three matched controls were recruited. The present study was approved by the Institutional Medical Ethics Committee (Approval Number-MSRMC/EC/AP-05/07-2021) and informed consent was obtained from study participants or their immediate relatives, as deemed necessary.

Cases

Inclusion criteria:

- Adults diagnosed with COVID-19 infection as per Ministry of Health and Family Welfare (MOHFW) guidelines, Government of India [14].
- Radiological evidence of PTX and/or PMD on the chest radiograph or computed tomography of the thorax.
  a. PTX- The presence of hyperlucency with no lung or vascular markings in an area corresponding to the pleural space with visible visceral pleural line and partial or completely collapsed underlying lung.
  b. PMD- The presence of lucency adjacent to the mediastinal structures such as trachea, aorta, and heart.

Exclusion criteria:

- Secondary spontaneous PTX due to chronic lung disease (such as COPD, bronchial asthma, interstitial lung disease, sequelae to pulmonary tuberculosis, etc.)
- PTX due to chest trauma
- PTX due to interventions such as central venous access, pleurocentesis, etc.

Controls

Inclusion criteria:

- Adults diagnosed with COVID-19 disease as per Ministry of Health and Family Welfare (MOHFW) guidelines, Government of India [14].

Exclusion criteria:

- Evidence of PTX or PMD during and/or after hospital stay for COVID-19 management.
- Previous history of PTX and/or PMD due to any cause.

All controls were matched with cases by all of the following criteria -age, sex, disease severity and predominant method of oxygenation. They were recruited on a 3:1 basis (three controls per case).

Study Procedure

Baseline demographic data and other independent variables such as presenting complaints, co-morbidities, time from onset of symptoms to admission, disease severity (as defined in the guidelines for management of COVID-19 disease issued by the MOHFW, Government of India [14]), time to development of PTX and/or PMD from the onset of symptoms, length of hospitalisation, need for non invasive or invasive ventilation, time from intercostal tube placement to the radiological resolution of PTX, patient progress and survival, radiological features (presence/absence and persistence/resolution of PTX and/or PMD) and data on other relevant investigative tests done as per standard work-up were recorded from existing patient records. Serum levels of inflammatory markers (such as CRP, D-Dimer, and LDH at admission and their trend in serial measurements, till the time of development of PTX, were recorded from existing patient records.

Diagnosis of PTX and/or PMD was made, based on chest radiography and or computed tomography of the thorax. High Resolution Computed Tomography (HRCT) thorax for COVID-19 disease was reported using a 25-point CT severity score with a maximum score being 25. They were graded as mild, moderate, and severe based on the score. A total score of <8 was mild, 8-15 was moderate and >15 was considered severe [15].

Outcome measures for cases and controls were length of hospitalisation, in hospital-mortality and 28-day mortality.

STATISTICAL ANALYSIS

Descriptive statistics comprising mean±SD for continuous variables and percentage (proportions) for discontinuous variables was used to describe the data. The results were analysed using Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA). Student's t-test, Chi-square test, multivariate and univariate logistic regression analysis were performed. Receiver Operating Characteristic (ROC) curve was plotted to identify the optimum sensitivity and specificity. Statistical significance was considered at p <0.05 (95% confidence interval was taken).

RESULTS

During the study period, there was a total of 3,251 COVID-19 admissions at our centre with 976 patients requiring ICU admission. Present study included 31 consecutive patients with PTX and/or PMD (cases) and 99 consecutive patients serving as controls, all of whom satisfied the study criteria.

Age

The difference in distribution between the two groups was not statistically different [Table/Fig-1]. The mean age of patients among cases was 51.10±18.55 years, with the majority being above the age of 60 years (35.5%, n=11/31). Among controls, the mean age was 53.91±15.55 years with the majority being above the age of 60 years (37.4%, n=37/99) [Table/Fig-2].

Variables	Cases (N=31)	Controls (N=99)	p-value
Age category (years)			
18-29	4 (12.9)	4 (4)	p=0.28
30-45	9 (29)	26 (26.3)	
45-59	7 (22.6)	32 (32.3)	
≥60	11 (35.5)	37 (37.4)	
Gender			
Male	22 (71)	50 (50.5)	p=0.06
Female	9 (29)	49 (49.5)	

[Table/Fig-1]: Distribution of cases by age category and gender (frequency expressed as n, %).
Chi-square test, Fisher's-Exact test

Gender

Males formed the majority in both groups, accounting for 71% (n=22/31) among cases and 50.5% (n=50/99) among controls, their distribution was not statistically significant (p=0.06), [Table/Fig-1].

Characteristic	Cases (n=31)	Controls (n=99)	p-value
Age (Mean±SD in years)	51.10±18.55	53.91±15.55	0.553
Symptoms			
Cough	22 (71)	27 (27.3)	<0.001
Breathlessness	14 (45.2)	39 (39.4)	0.569
Fever	16 (51.6)	45 (45.5)	0.549
Easy fatiguability	8 (25.8)	42 (42.4)	0.097
Diarrhoea	7 (22.6)	23 (23.2)	0.94
Other symptoms	5 (16.1)	11 (11.1)	0.458
Co-morbidities			
Diabetes mellitus	12 (38.7)	30 (30.3)	0.382
Hypertension	6 (19.4)	31 (31.3)	0.198
Hypothyroidism	3 (9.7)	2 (2)	0.053
Respiratory co-morbidities	0	0	
Others	1 (3.2)	2 (2)	0.696
Number of co-morbidities			
0	17 (54.8)	40 (40.40)	0.005
1	8 (40.4)	53 (53.5)	
2	4 (12.9)	6 (6.1)	
3	2 (6.5)	00	
Presence of smoking history	13(41.9)	44 (44.4)	0.806
Previous history of COVID-19 infection	9 (29)	11 (11.1)	0.016
Vaccinated with COVID-19 vaccine	17 (71)	86 (86.9)	0.039
CT Severity score by HRCT Thorax (Mean±SD)	15.55±4.40	14.80±3.64	0.81
Oxygenation technique			
Non Rebreathing Mask (NRBM)	5 (16.1)	17 (17.2)	0.893
High Flow Nasal Oxygenation (HFNO)	7 (22.6)	24 (24.2)	0.85
Non Invasive Ventilation (NIV)	19 (61.3)	58 (58.6)	0.789
Ventilator at admission	11 (35.5)	35(35.4)	0.989
Length of hospitalisation			
<14 days	4 (12.9)	44 (44.4)	0.001
≥14 days	27 (87.1)	55 (55.6)	
Length of ICU stay			
<7 days	1(3.2)	29 (29.3)	0.003
≥7 days	30 (96.8)	70 (70.7)	
In-hospital mortality	17 (54.8)	33 (33.30)	0.032
28-day mortality	5/14 (35.7)	5/66 (7.6)	0.004

[Table/Fig-2]: Baseline characteristics (frequency expressed as n, %). Chi-square test, Fisher's-Exact test

Presenting Symptoms

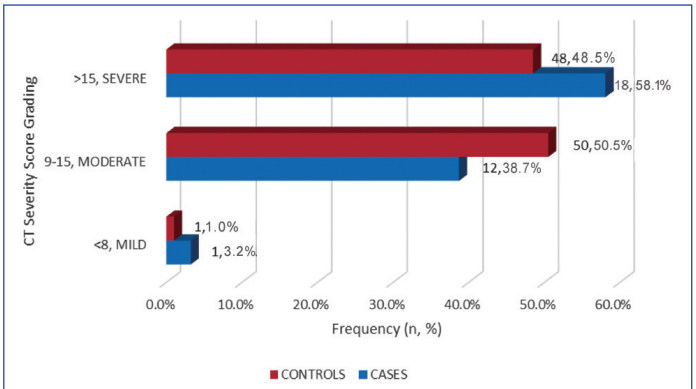
Patients were managed as per standard practice, outlined by the MoHFW, Government of India [14], for the clinical management of COVID-19. The mean time period from onset of symptoms to admission was 6.32±2.66 days among cases, whereas, it was 5.46±2.26 days among controls, the difference was not statistically significant, p=0.227. Cough was the predominant symptom among cases, whereas fever was the predominant symptom among controls [Table/Fig-2].

Co-morbidities

Atleast 17 (54.8%) among cases and 40 (40.4%) among controls had no co-morbidities. Diabetes mellitus was the predominant co-morbidity in the two groups [Table/Fig-2]. Among those with co-morbidities, the majority in both groups had a single co-morbid disease, this difference was statistically significant (p=0.005) [Table/Fig-2]. The mean duration between the two episodes of COVID-19 disease as documented in case records was 110.66±45.96 days among cases and 124.09±46.19 days among controls.

Radiology

All patients with moderate to severe COVID-19 disease were subjected to HRCT of the thorax. The mean CT severity score reported was 15.55±4.40 among cases and 14.80±3.64 among controls, this difference was not statistically significant p=0.81 [Table/Fig-1]. The distribution of subjects by CT severity score is depicted in [Table/Fig-3]. The mean time for the occurrence of PTX from the day of admission was 10.26 ±14.86 days with a median of five days. The right lung was affected in 18 (58.1%) cases, the left lung in 10 (32.2%), and both lungs in the remaining 3 (9.7%) cases. Among these cases, 16.1% (n=5/31) had evidence of PMD and 25.8% (n=8/31) had evidence of subcutaneous emphysema.



[Table/Fig-3]: Distribution by CT severity score.

Tube thoracostomy was performed in all cases, 80.6 % (n=25/31) experienced resolution of PTX followed by removal of the intercostal tube; among them, the mean time for resolution of PTX was 10.72±5.08 days.

Overall, 35.5% (n=11/31) of cases received ventilator support in the form of non invasive ventilation from the day of admission and 74.2% (n=23/31) were on ventilator support at the time of detection of pneumothorax/pneumomediastinum.

Method of Oxygenation

The patients of both groups were distributed by their predominant method of oxygenation during the hospital stay, the differences were not statistically significant [Table/Fig-2].

Haematological Parameters

The baseline panel of investigations performed in both groups were recorded, and the differences in their means were computed and are outlined in [Table/Fig-4]. The multiple regression model revealed, total leukocyte count (OR=1; 95% CI=1,1; p=0.038), AST (OR=1.013; 95% CI=1,1.026; p=0.045), D-dimer (OR=0.79; 95% CI=0.633, 0.995; p=0.046), CRP (OR=0.97; 95% CI=0.95; p=0.005), Serum albumin (OR=0.243, 95, 0.992% CI=0.085, 0.697; p=0.009) as having significant association to the development of PTX and/or PMD, [Table/Fig-5].

Blood investigations	Group	N	Mean±Std. Deviation	p-value
C-Reactive Protein (mg/dL)	Cases	31	50.06±62.44	0.032*
	Controls	99	24.57±19.70	
Lactate dehydrogenase (mg/dL)	Cases	31	666.77±498.23	0.06
	Controls	99	485.10±267.58	
D-DIMER (µ/mL)	Cases	31	2.83±3.79	0.039*
	Controls	99	1.34±1.37	
Haemoglobin (g/L)	Cases	31	13.00±2.20	0.849
	Controls	99	12.91±1.84	
Packed cell volume (%)	Cases	31	39.67±6.44	0.418
	Controls	99	38.63±5.25	
Total leukocyte count (cells/mm^3)	Cases	31	11788.06±5365.59	0.022*
	Controls	99	9310.10±4020.31	

Platelet count (lakhs/mm^3)	Cases	31	2.67±1.07	0.811
	Controls	99	2.62±1.24	
Serum creatinine (mg/dL)	Cases	31	1.03±0.99	0.327
	Controls	99	1.23±1.06	
Serum blood urea nitrogen (mg/dL)	Cases	31	17.61±9.30	0.127
	Controls	99	20.82±12.33	
Serum uric acid (mg/dL)	Cases	31	4.59±1.42	0.067
	Controls	99	6.06±7.49	
Total bilirubin (mg/dL)	Cases	31	0.82±0.36	0.004*
	Controls	99	1.11±0.71	
Direct bilirubin (mg/dL)	Cases	31	0.37±0.25	0.005*
	Controls	99	0.57±0.52	
Aspartate transaminase (IU/L)	Cases	31	49.32±28.32	0.035*
	Controls	99	65.06±52.67	
Alanine transaminase (IU/L)	Cases	31	63.03±47.38	0.832
	Controls	99	65.11±47.18	
Total protein (g/dL)	Cases	31	6.17±0.96	0.017*
	Controls	99	5.68±0.89	
Serum albumin (g/dL)	Cases	31	3.60±0.47	0.016*
	Controls	99	3.35±0.52	
Serum globulin (g/dL)	Cases	31	2.37±0.65	0.985
	Controls	99	2.37±0.58	

[Table/Fig-4]: Comparison of mean values of baseline haematological parameters between cases and controls.
Student's t-test

Variables	Stnd. Error	p-value	Odds ratio	95% CI for odds ratio	
				Lower	Upper
D-dimer (µ/mL)	0.115	0.046*	0.794	0.633	0.995
C-Reactive protein (mg/dL)	0.01	0.005*	0.973	0.954	0.992
Total leukocyte count (TLC)	0	0.038*	1	1	1
Total bilirubin (mg/dL)	1.007	0.312	2.768	0.384	19.933
Direct bilirubin (mg/dL)	1.49	0.789	0.671	0.036	12.445
Aspartate transaminase (IU/L)	0.006	0.045*	1.013	1	1.026
Total protein (g/dL)	0.304	0.055	0.558	0.308	1.012
Serum albumin (g/dL)	0.538	0.009*	0.243	0.085	0.697
Constant	2.954	0.001*	45342.11		

[Table/Fig-5]: Results of multivariate logistic regression analysis of significant parameters multivariate logistic regression.

Cut-off Value of Total Bilirubin

Authors hypothesised the role of total bilirubin as a potential predictor, univariate Logistic regression model was employed to test the hypothesis, thus, 0.64 mg/dL of total bilirubin can be taken as a cut-off value predictive of PTX and/or PMD based on ROC curve with an area of 0.38, the sensitivity of 71%, and specificity of 25.3% with 95% CI=0.277-0.482 [Table/Fig-6].

Outcome Assessment

The difference in immediate outcomes with respect to the change in haematological parameters at baseline and at the occurrence of disease was analysed, and a fall in platelet count during the course of illness among cases, was found to have a statistically significant association with worse immediate outcome (p=0.001) [Table/Fig-7].

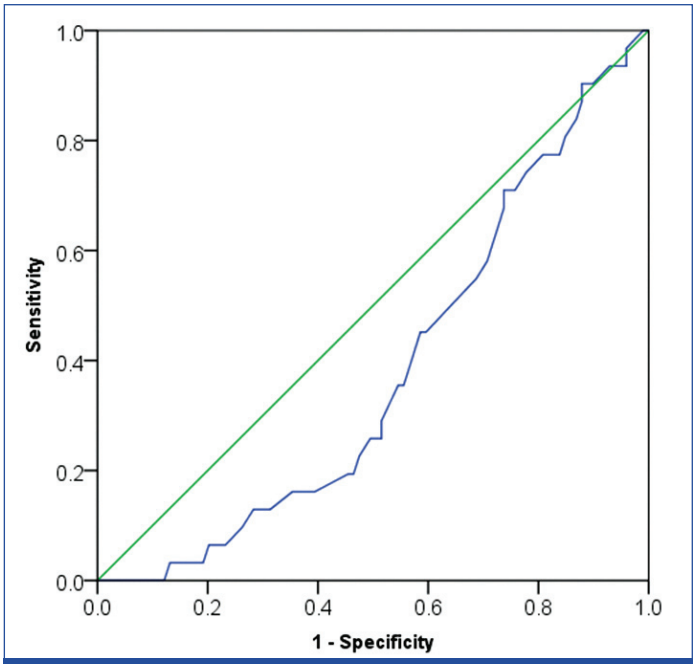
DISCUSSION

The second wave of the COVID-19 pandemic in India witnessed high rates of mortality and morbidity, mostly linked to the delta variant of the virus [16].

Studies conducted across the globe, have established a higher incidence of PTX with the COVID-19 compared to that observed in the general population, indicating a direct link to the occurrence of PTX, secondary to COVID-19 disease [8,13]. During the study period, the incidence of PTX and/or PMD was found to be 0.95% overall and 31/976 (3.17%) among those requiring ICU care, this was within the range of overall incidence found in similar studies [8,13,17-19].

Whilst studies, propose numerous causal mechanisms to the occurrence of PTX and/or PMD, none have been established with certainty, as autopsies are performed sparingly in COVID-19 patients, thereby, limiting the possibility of direct macroscopic and microscopic examination of the lungs [8,13,17].

In the present study, age, gender and severity matched study population, we found that subjects who had a history of previous



[Table/Fig-6]: Determination of the cut-off value of baseline serum total bilirubin levels for predicting PTX and/or PMD by ROC curve.
The area under the curve (AUC) of Receiver Operating Characteristic (ROC) analysis for predicting PTX and/or PMD was 0.38, with sensitivity 71% and specificity 25.3%, and the cut-off value of baseline serum total bilirubin levels was 0.64 mg/dL

Haematological parameters	Immediate outcome		p-value
	Expired n=17	Alive n=14	
	Mean±SD	Mean±SD	
C-Reactive protein (mg/dL)	-13.2171±79.2328	11.46071±66.26471	0.353
Lactate dehydrogenase (mg/dL)	18.41176±599.1117	-104.571±715.0143	0.613
D-dimer (µ/mL)	1.584118±3.483567	-1.78429±6.673541	0.104
Haemoglobin (g/L)	-0.57059±3.292561	-0.14286±3.362855	0.725
Packed cell volume (%)	2.147059±9.309345	-0.31571±7.894677	0.432
Total leukocyte count (TLC)	3209.41±10528.31	2461.43±6345.021	0.809
Platelet Count (PC)	1.891176±1.573971	-1.20714±1.134606	0.001*
Serum creatinine (mg/dL)	-0.24118±1.3493	0.375714±0.980265	0.152
Serum blood urea nitrogen (mg/dL)	5.185294±9.688621	7.456429±19.2017	0.692
Serum uric acid (mg/dL)	-0.75882±2.640326	-0.41429±2.17887	0.694
Total bilirubin (mg/dL)	0.829412±1.197651	0.298571±0.672251	0.132
Direct bilirubin (mg/dL)	0.585882±0.956459	0.201429±0.381452	0.144
Aspartate transaminase (IU/L)	47.47±92.451	35.29±58.676	0.66
Alanine transaminase (IU/L)	14.82±95.532	41.36±68.781	0.377
Total protein (g/dL)	-0.62824±0.993254	-0.75±1.731496	0.818
Serum albumin (g/dL)	-0.60588±0.690535	-0.16429±0.675514	0.084
Serum globulin (g/dL)	-0.02353±0.808957	0.204286±0.841032	0.452

[Table/Fig-7]: Difference in immediate outcomes with respect to the change in hematological between baseline and at the occurrence of disease.
Student's t-test

COVID-19 disease had a higher likelihood of developing PTX/PMD (p=0.016). This opens up the possibility of another causal mechanism of PTX, occurring in a lung already suffering from the residual damage of a previous COVID-19 infection. However, as the present study was a retrospective study, the authors were limited in their ability to analyse in depth various aspects of this association, a systematic review of case reports of COVID-19 reinfection by Wang J et al., found that 18.8% (3/16) had more severe disease during the second episode, however, there is no literature to date, depicting its association with PTX [20].

Achieving immunity either through natural infection or vaccination is important in negating adverse outcomes associated with COVID-19 disease, the unvaccinated experienced worse outcomes than the vaccinated in this study (p=0.039), higher incidence of severe COVID-19 disease in the unvaccinated has been established by a study [21], hence, the association with PTX is likely due to the predilection for severe disease, in this subgroup.

Likewise, the presence of cough as a predominant symptom expressed a significant statistical difference between the two groups. Miró Ò et al., found a complaint of dyspnoea as a strong association with the development of PTX (p=0.02) [8]. Interestingly, the presence of respiratory co-morbidities was low in present study population, just as in studies by Martinelli AW et al., [13], Miró Ò et al., [8], and Udwadia ZF et al., [18]. One likely explanation that needs validation, is a behavioural adaptation to stronger preventive practices for COVID-19 disease, likely due to the fear of suffering severe disease, on account of the chronic lung disease.

While the majority of patients in present study, received ventilator support in the form of non invasive ventilation, 38.7% of cases with PTX received no ventilator support. The ventilator settings were not included for analysis, due to missing data in records among the majority. Present study found that in-hospital mortality was worse among controls, who received ventilator support (p=0.056), although it did not achieve statistical significance, on the other hand, there was no difference among the cases (p=0.564). Zhou C et al., [22] in their study found, that mechanically ventilated patients had a higher incidence of PTX, the incidence was higher in those with ARDS, the occurrence ranging between 14-87%, similar results were also elucidated by Gattinoni L et al., [23].

When haematological parameters were compared, CRP, D-dimer, TLC, total and direct bilirubin, and AST were significantly higher among cases than in controls, the differences express significance both statistically and clinically. Zantah M, et al., found that the presence of lymphopenia and elevated inflammatory markers including CRP, ferritin, D-dimer, and IL-6, had significant associations with spontaneous PTX [4].

Gong J et al., [24] and Wang XH et al., [7] found high total bilirubin among patients with severe COVID-19 disease, present study established a positive association of high total bilirubin with the occurrence of PTX compared to controls. Liu Z et al., [25] found elevated total bilirubin and elevated transaminases in their study, only high levels of AST established a positive association in present study. Present study found that high total bilirubin at a cut-off 0.64 mg/dL was associated with PTX, however, this value being in the normal range (0.2-1 mg/dL), holds low significance for clinical application. The high bilirubin in COVID-19 disease represents direct hepatocyte injury by the virus, due to the expression of Angiotensin Converting Enzyme-2 (ACE-2) receptors in the duct epithelial cells and hepatocytes, although at a much high concentration, than the former [26].

Immediate and late mortality was high among patients with PTX, [Table/Fig-2]. Miró Ò et al., in their case control multicentre study [8] and Udwadia ZF et al., [18] in their retrospective study (overall mortality 74%), found similar outcomes, on the other hand, Martinelli AW et al., [13] in their multicentre retrospective case series, found that the presence of PTX did not significantly increase the rate of mortality, where survival of 63.1% was noted among such patient, however the latter being a case series with no control group for comparison is limited in its ability to make an assertion as such, yet as iterated by Martinelli AW et al., [13], PTX attributable to COVID-19 disease must not be viewed as a lost cause while prognosticating a patient.

The present study raises important questions on potential risk factors for the development of air leak syndromes in COVID-19 disease, additionally, the role of haematological parameters in prognostication and its ability to identify patients with a higher risk of developing PTX remains circumspect, inspite of the statistically significant results, authors have demonstrated as the clinical application of these parameters, is limited by numerous confounders. The presence of air leak is a marker for adverse outcomes, tube thoracostomy remains the treatment of choice in clinically significant PTX.

Limitation(s)

The limitations of present study include its retrospective nature and its relatively low sample size. A study with larger sample size and prospective design can validate the findings of present study.

CONCLUSION(S)

Elucidating a history of previous COVID-19 disease and nil or incomplete vaccination with COVID-19 vaccines among patients with current COVID-19 infection may provide a clue towards anticipating a detrimental clinical course. In addition, high baseline serum total bilirubin levels, progressively increasing total leukocyte counts, and serum aspartate transaminase levels may be viewed with high suspicion to the possibility of developing PTX and/ or pneumomediastinum.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 21, 2022
- Manual Googling: Aug 23, 2022
- iThenticate Software: Aug 26, 2022 (10%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **May 17, 2022**
Date of Peer Review: **Jun 22, 2022**
Date of Acceptance: **Aug 27, 2022**
Date of Publishing: **Nov 01, 2022**