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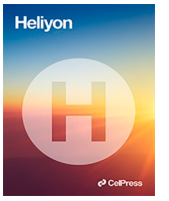

Research article

Pneumomediastinum and pneumothorax in coronavirus disease-2019: Description of a case series and a matched cohort study

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ABSTRACT

Objective: To describe the characteristics of COVID-19 patients with pneumothorax and pneumomediastinum (PTX/PM) and their association with patient outcomes.
Patients and methods: Adults admitted to five Mayo Clinic hospitals with COVID-19 between 03/2020–01/2022 were evaluated. PTX/PM was defined by imaging. Descriptive analyses and a matched (age, sex, admission month, COVID-19 severity) cohort comparison was performed. Hospital mortality, length of stay (LOS), and predisposing factors were assessed.
Results: Among 6663 patients, 197 had PTX/PM (3 %) (75 PM, 40 PTX, 82 both). The median age was 59, with 71 % males. Exposure to invasive and non-invasive mechanical ventilation and high-flow nasal cannula before PTX/PM were 42 %, 17 %, and 20 %, respectively. Among isolated PTX

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; CI, confidence interval; COVID-19, Coronavirus disease 2019; HFNC, high flow nasal cannula; IMV, invasive mechanical ventilation; IQR, interquartile range; LOS, length of stay; NIV, Noninvasive mechanical ventilation; OR, odds ratio; PEEP, positive end-expiratory pressure; PTX, Pneumothorax; PM, pneumomediastinum; SARS-CoV, severe acute respiratory syndrome coronavirus; WHO scale, World Health Organization Ordinal Scale for Clinical Improvement.

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and PM/PTX patients 70 % and 53.7 % underwent an intervention, respectively, while 96 % of the PM-only group was followed conservatively.
A total of 171 patients with PTX/PM were compared to 171 matched controls. PTX/PM patients had more underlying lung disease (40.9 *vs.* 23.4 %, $p < 0.001$) and lower median body mass index (BMI) (29.5 *vs.* 31.3 kg/m^2, $p = .007$) than controls. Among patients with available data, PTX/PM patients had higher median positive end-expiratory and plateau pressures than controls; however, differences were not significant (10 *vs.* 8 cmH_2O; p = 0.38 and 28 *vs.* 22 cmH_2O; $p =$ 0.11, respectively). PTX/PM patients had a higher odds of mortality (adjusted odds ratio [95%CI]: 3.37 [1.61–7.07]) and longer mean LOS (percent change [95%CI]: 39 [9–77]) than controls.
Conclusion: In COVID-19 patients with similar severity, PTX/PM patients had more underlying lung disease and lower BMI. They had significantly increased mortality and LOS.

1. Introduction

Pneumothorax (PTX) and/or pneumomediastinum (PM) are one of the many complications that critically ill patients with acute respiratory distress syndrome (ARDS) may develop. These complications are usually associated with barotrauma [1] and the incidence is reported to range from 8-10 %–42 % in patients with ARDS [2]. As severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection spread worldwide as virus-induced ARDS, clinicians noticed a spike in PTX/PM incidence, leading to case reports and case series [3–9]. Spontaneous PTX/PM and isolated PM have been described as complications of COVID-19 [9], with a wide range of incidence from 10 % in patients with COVID-19-related ARDS, increasing to 24 % in patients receiving mechanical ventilation, and 56 % in patients requiring invasive mechanical ventilation (IMV) [10]. However, there are some aspects of these complications which still need to be explored.

Infectious pathogens, especially those that cause pulmonary necrosis, can cause PTX, such as *Pneumocystis jirovecii* and *Mycobacterium tuberculosis* [11–13]. Other mechanisms of PTX in infections were also reported, including alveolar rupture, barotrauma, inflammatory-induced parenchymal injury, pathogen-induced damage, and fibrosis [14–19]. It was also reported in other viral pneumonias such as influenza-related pneumonias and earlier coronavirus pandemics [20–23]. However, existing literature suggests some differences in timing and predisposing conditions of PTX/PM in COVID-19 setting [24,25]. Additionally, the incidence of PTX/PM varied considerably, reported as 1.7 % and 7.1 % in SARS-CoV-1 infection and Middle Eastern Respiratory Syndrome Coronavirus infections, respectively [22,23]. The incidence of PTX/PM in COVID-19 has been reported to be as high as 15 %, suggesting distinct pattern [26]. Even though the mechanism of PTX/PM is not fully elucidated in COVID-19 settings, it is believed to be multifactorial, including the Macklin effect, caused by air dissecting along bronchoalveolar sheaths following alveolar rupture [15,27], diffuse alveolar damage due to the aggressive pathophysiology of COVID-19 [18,28], and a potential specific vulnerability of lung parenchyma to SARS-CoV-2 infection. Barotrauma has also been cited as a potential mechanism [29], alongside a potential impact of severe cough [30].

Based on some existing literature, PTX during a non-COVID-19 coronavirus infection is a grave prognostic marker [22,31]. With respect to COVID-19, a large retrospective study conducted in the United Kingdom concluded that PTX did not affect prognosis [32]. A recent systematic review, however, reported a mortality rate of 46 % in COVID-19 patients, which was considerably higher than non-COVID-19 [33]. These conflicting reports emphasize the need for further studies on PTX/PM in COVID-19 patients and their predisposing risk factors. It remains unclear whether these complications are associated with unfavorable COVID-19 outcomes.

In this retrospective, multicenter, matched cohort study, our primary aims were to describe the characteristics and presentation of PTX/PM and explore the effects of PTX/PM on mortality and outcomes in adult patients hospitalized with COVID-19. Our secondary aim was to determine predisposing risk factors for developing PTX/PM in COVID-19 patients.

2. Materials and methods

This study protocol was evaluated by the institutional review board at Mayo Clinic and approved as exempt (IRB: 21-010686, IRB for the main study: 20-002610, approval date: 3/23/2020). Mayo Clinic Institutional SARS-CoV-2/COVID-19 Research Task Force approval was also obtained. Per the study protocol approved in our institution, informed consent was waived under Common Rule 45 CFR 46.116. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [34].

2.1. Design, setting, and participants

This study had a matched cohort design. All adult patients hospitalized with SARS-CoV-2 infection with PTX/PM on at least two consecutive pulmonary imaging studies were included. This analysis excluded patients who developed the PTX/PM after a sternotomy or as a complication of an intervention (i.e., catheter placement), or patients who did not provide research authorization.

After ascertaining the eligible patients, each PTX/PM was 1:1 matched to a patient who did not develop these complications during the admission of interest. The matching was performed according to age (within five years), sex, hospital admission timing (within three months), World Health Organization Ordinal Scale for Clinical Improvement (WHO scale) [35] (on admission day, and on the day before PTX/PM occurrence or the corresponding day (within three days, to enhance the likelihood of finding suitable matching

patients). The corresponding day for patients who did not develop PTX/PM was determined based on the hospital length of stay (LOS). For instance, if a patient developed PTX/PM on the 9th day after admission, a matching control patient was identified as an individual who had similar disease severity (determined by the WHO scale) between the 7th and 11th days of hospitalization and did not develop PTX/PM during their COVID-19 course, which was determined via chart reviews.

2.2. Data acquisition

We complemented the data already obtained by the Mayo Clinic-Society of Critical Care Medicine Viral Infection and Respiratory Illness Universal Study (VIRUS) COVID-19 registry for granularity [36,37]. The PTX/PM patients were determined by free-text searches using the Advanced Text Explorer [38]. The radiology notes of eligible patients between March 2020 and January 2022 were screened and confirmed via chart reviews by researchers (AT, SQ, MS, SW, JPD, SK, JT).

Due to the structure of VIRUS Registry data in daily treatment with extracorporeal membrane oxygenation and renal replacement therapy, the WHO scale was calculated as follows: a score of $\leq$4 indicated that the patient was either on room air or receiving oxygen support via nasal prongs or a mask, a score of 5 indicated non-invasive mechanical ventilation (NIV) or high-flow nasal cannula (HFNC), and a score of $\geq$6 indicated the patient was on IMV. PTX/PM patients on extracorporeal membrane oxygenation were included in descriptive calculations but excluded from the comparative analysis to avoid its impact on respiratory parameters. A matching patient was randomly selected from the VIRUS Registry database of enrolled patients from the five participating Mayo Clinic campuses (Rochester, Arizona, Florida, Mankato, and Eau Claire). The comparative analyses excluded PTX/PM patients without matches (Fig. 1).

The VIRUS Registry provided baseline variables and admission-related specifics such as timing or medication administrations. Additional data variables were collected by retrospective chart reviews (AT, SQ, AD, DVM, FT, SW, and NS). Vitals, laboratory data, and respiratory support details were collected for the day before PTX/PM development and the matching admission day for the controls. If the patient had PTX and PM asynchronously, the date of the first incident was noted. The highest values of positive end-expiratory pressure (PEEP), tidal volume, the fraction of inspired oxygen, plateau, and peak pressures (i.e., the day before the incident and the matching day for controls) were included in the analysis. These parameters were compared between those for whom the data were available and their matched controls (i.e., PEEP, tidal volume, plateau pressure, and peak pressure were only available for those who were on IMV on the day of interest).

Data regarding PTX/PM presentation, extent, and treatment interventions were also collected. The presence and severity of PTX/

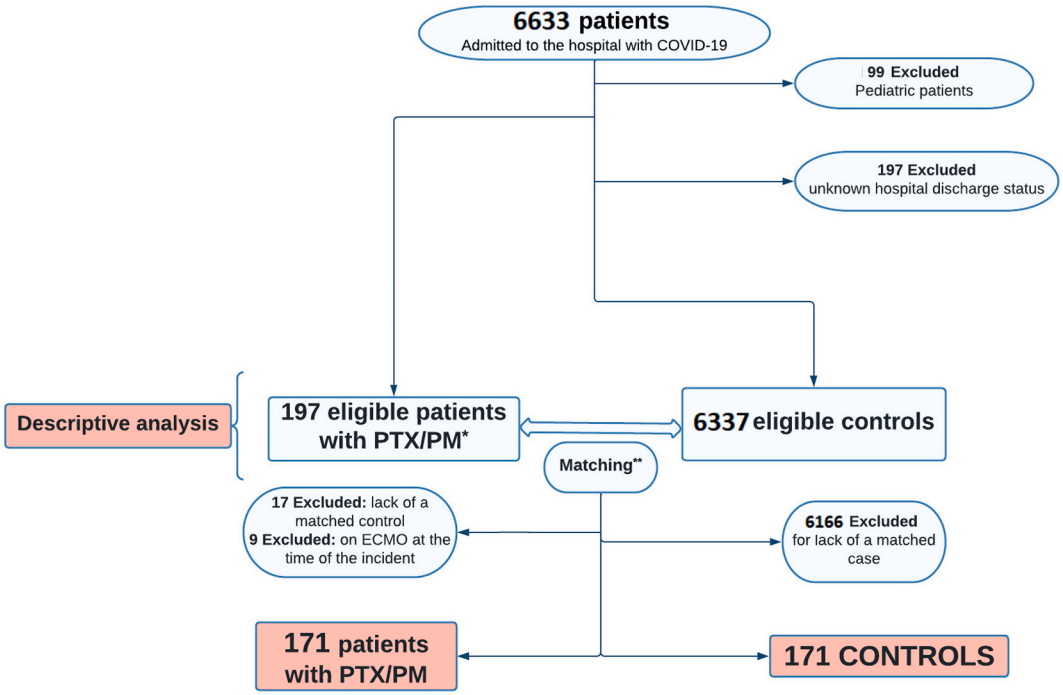

Fig. 1. Flowchart for the identification of cases and controls.
COVID-19: Coronavirus Disease 2019.
* Cases were patients whose COVID-19 disease course were complicated by pneumothorax and/or pneumomediastinum during their related admission process.
** Case and control matching was performed by age, sex, the time of admission (month), World Health Organization ordinal scale at the time of admission, and the day before pneumothorax for cases and the matching admission day for controls.

PM was noted solely according to the radiology reports, regardless of imaging modality or clinical characteristics [39].

In order to assess how various SARS-CoV-2 variants might influence the occurrence of PTX/PM, we analyzed the distribution of cases across different time periods. Patient admission dates were categorized into three phases: the initial phase (from the beginning of the study until the end of February 2021), the Delta variant phase (encompassing the period from March 2021 to the end of November 2021) [40], and the Omicron variant phase (covering from December 2021 until the study's conclusion) [41].

2.3. Outcomes

Hospital mortality and LOS were the study's primary outcomes. We also evaluated predisposing factors for PTX/PM development. To eliminate the impact of in-hospital mortality, the hospital LOS comparison only included patients who were discharged alive [42]. Another outcome of interest was the discharge disposition, which was collected for patients who were discharged alive and classified as either home or others (e.g., skilled nursing facility, hospice, long-term healthcare facility). We also examined the frequency distribution of PTX/PM patients among all admissions over the course of the months.

2.4. Statistical analyses

Descriptive summary statistics were performed for patients with isolated PTX, isolated PM, and both PTX/PM. Continuous variables were summarized by the median and interquartile range (IQR), while categorical variables were expressed as numbers and percents. Univariate analyses in the un-matched dataset (i.e., patients with PTX/PM only) were performed using chi-square test.

To determine risk factors associated with PTX/PM, a case-control analysis was performed within the 1:1 matched patient group. For this analysis a conditional logistic regression model was employed where PTX/PM was the outcome. A matched cohort design was utilized to evaluate the impact of PTX/PM on hospital mortality, LOS, and discharge disposition. As our dataset for the comparative analyses was matched, i.e., the observations were not independent, we used conditional logistic regression for binary outcomes, and a linear mixed model test for the LOS. Both of these methods operate under the assumption of independence within the matched sets, meaning that the outcome of one case or control does not influence another, a condition which was met in our study. They also assume a sufficient number of matched sets, a criterion which was satisfied for the outcomes of our matched cohort analyses. Linear mixed models also assume a normal distribution. However, since the distribution of the LOS was skewed in our dataset, a log transformation on LOS variable was employed. Multivariable analyses were performed, adjusting for patient factors that were identified in the

Table 1
Baseline characteristics.

Variables	Total ($n = 197$)
Age, median (IQR)	59 [47–69]
Sex, no. (%)	
Male	140 (71.1 %)
Race, no. (%)	
White	150 (76.1 %)
American Indian or Alaska Native	11 (5.6 %)
Asian	6 (3 %)
Others	30 (15.2 %)
Ethnicity, no. (%)	
Non-Hispanic	162 (82.2 %)
Hispanic	25 (12.7 %)
Comorbidities, no. (%)	
Obesity (BMI≥30 kg/m^2)	90 (45.7 %)
Hypertension	89 (45.2 %)
Chronic pulmonary diseases	79 (40.1 %)
– Asthma	22 (11.2 %)
– Chronic obstructive pulmonary disease	9 (4.6 %)
Diabetes	62 (31.5 %)
Chronic cardiovascular disease	41 (20.8 %)
Chronic kidney disease	39 (19.8 %)
Malignancy	28 (14.2 %)
Transplant	24 (12.2 %)
Prehospital systemic steroid use, no. (%)	19 (9.6 %)
Smoking history, no. (%)	
Never smoker	148 (75.1 %)
Former smoker	25 (12.7 %)
Current smoker	24 (12.2 %)
COVID-19 vaccination history, $n = 152$, no. (%)	21 (13.8 %)
WHO scale at the time of admission	
≤4	84 (42.6 %)
5	58 (29.4 %)
≥6	55 (27.9 %)

BMI: Body mass index, IQR: interquartile range.

univariate analyses and were prevalent in >15 % of the cohort (i.e., body mass index [BMI] [in lieu of obesity] and chronic pulmonary diseases). Missing data were considered missing without further actions. No multiple test corrections were done. Results were reported in terms of *p*-values, odds ratios (OR), coefficients, and 95 % confidence intervals (95 % CI). A two-sided *p*-value of <.05 was considered significant. SPSS version 27.0 (Statistical Package for Social Sciences, IBM, USA) software package was used for matching and the descriptive calculations. In contrast, comparative tests were conducted using R statistical software (R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/, version 3.4). There were no software-specific settings employed related to algorithms or output formatting.

3. Results

3.1. Descriptive analysis of the cases

We identified 197 patients with PTX/PM (3 %) among 6663 COVID-19 patients admitted to five Mayo Clinic Hospitals. Demographics and baseline characteristics of the patients are outlined in Table 1. Among the included cases, 44 PTX/PM were identified on the day of admission. During their admission for COVID-19, 156 of the patients developed ARDS, 120 being severe, while 29 had moderate, and 6 had mild ARDS.

The distribution of patients to the categories of PTX, PM, and both groups and details regarding their management were provided in Table 2. Whether or not patients underwent intervention did not affect hospital mortality. This was true of the whole PTX/PM group ($p = 0.30$), the subgroups with isolated PTX, and both PTX/PM ($p = .51$ and $p = .67$, respectively). Since 96 % of the patients with isolated PM were followed up without an intervention, a comparative test was not calculated in this group.

As we examined the distribution of patients over time, the percentage of patients with PTX/PM among all admissions significantly increased over time: 1.4 % during the initial phase, 4.8 % during the Delta variant period, and 9.8 % during the Omicron variant era ($p < 0.001$).

Table 2
Clinical information related to pneumothorax and/or pneumomediastinum and the COVID-19-related admission period.

Variables	Total ($n = 197$)	Isolated PM ($n = 75$)	Isolated PTX ($n = 40$)	Both ($n = 82$)
Positive pressure respiratory support received before developing pneumothorax or pneumomediastinum, no. (%)[a]				
Invasive mechanically ventilated	82 (41.6 %)	27 (36 %)	17 (42.5 %)	38 (46.3 %)
Received noninvasive mechanical ventilation	34 (17.3 %)	13 (17.3 %)	5 (12.5 %)	16 (19.5 %)
Received oxygen via high flow nasal cannula	39 (19.8 %)	19 (25.3 %)	4 (10 %)	16 (19.5 %)
No high pressure respiratory support exposure	33 (16.8 %)	13 (17.3 %)	10 (25 %)	10 (12.2 %)
Missing or unknown	9 (4.6 %)	3 (4 %)	4 (10 %)	2 (2.4 %)
Duration of exposure to positive pressure respiratory support before PTX/PM (if not before transfer), days, $n = 172$, median (IQR)	8 (2.25–11.75)	8 (2–11)	12 (0–28)	7 (3–10)
The extent of the disease, no. (%)[b]				
Extensive-large	58 (29.4 %)	14 (18.7 %)	9 (22.5 %)	35 (42.7 %)
Moderate	42 (21.3 %)	16 (21.3 %)	8 (22 %)	18 (22 %)
Small or simple	66 (33.5 %)	27 (36 %)	14 (35 %)	25 (30.5 %)
Not reported	31 (15.7 %)	18 (24 %)	9 (22.5 %)	4 (4.9 %)
Duration between hospital admission and development of pneumothorax/ pneumomediastinum, days, median (IQR)	7 (1–11)	8.5 (0–17)	6 (0–11)	7.5 (2–11)
SOFA score at the day of admission, median (IQR)	3 (2–6)	3 (2–6)	4 (2.25–8)	3 (2–6)
Diagnostic setting, no. (%)				
Clinical deterioration/lack of clinical improvement	136 (69 %)	44 (58.7 %)	20 (50 %)	72 (87.8 %)
Present during the evaluation at the time of admission	31 (15.7 %)	16 (21.3 %)	9 (22.5 %)	6 (7.3 %)
Incidentally	30 (15.2 %)	15 (20 %)	11 (20 %)	4 (4.%)
Treatment, no. (%)				
Conservative	120 (60.9 %)	72 (96 %)	12 (30 %)	36 (43.9 %)
Surgical chest tube placement	36 (18.3 %)	1 (1.3 %)	15 (37.5 %)	20 (24.4 %)
Pigtail catheter	37 (18.8 %)	–	13 (32.5 %)	24 (29.3 %)
Missing or unknown	4 (2 %)	2 (2.7 %)	–	2 (2.4 %)
ICU admission, no. (%)	146 (75.6 %)	51 (68 %)	27 (67.5 %)	68 (82.9 %)
In-hospital mortality, $n = 194$[c], no. (%)	80 (41.2 %)	27 (36.5 %)	13 (32.5 %)	40 (50 %)
Hospital length of stay for those discharged alive, $n = 114$	20.2 (11.9–37.5)	18 (11.6–39.9)	20.5 [7–42]	23.2 (13.2–46)

ARDS: Acute respiratory distress syndrome, COVID-19: Coronavirus disease 2019, ICU: intensive care unit, PM: Pneumomediastinum, PTX: Pneumothorax, SOFA: Sequential organ failure assessment.

[a] If more than one modality were present, the data was provided by the highest intensity, i.e., invasive mechanical ventilation, non-invasive mechanical ventilation, high flow nasal cannula.

[b] Based on radiology-grading criteria (Zylak et al., 2000).

[c] Patients who are still in the hospital were excluded ($n = 3$).

3.2. PTX/PM and positive pressure ventilation

155 of 188 PTX/PM cases (82.4 %) with available oxygen support data before the PTX/PM developed these complications after receiving positive pressure ventilation at some point during admission (IMV, NIV, and HFNC for 82, 34, and 39 cases, respectively). A total of 118 patients required IMV support. Other specifics related to the disease courses are shown in Table 2. Among 153 cases with available vital and respiratory support data on the day before PM/PTX, 35.6 % received IMV while 17.8 % received NIV. At the time of admission, patients had increased C-reactive protein (median [IQR] = 113 [57, 187] mg/dL), ferritin (median [IQR] = 903 [521, 1926] microgram/L), lactate dehydrogenase (median [IQR] = 447 [237, 447] mmol/L), and D-dimer levels (median [IQR] = 1446 [805, 4125] ng/mL). During the period between the admission and the occurrence of PTX/PM, the median CRP and ferritin levels decreased (Δ CRP median [iQR] = −51 [−125, 0] and Δ Ferritin median [iQR] = −63 [−142, 51]) while the median D-dimer levels increased (median [iQR] = 202 [−501, 1130]). Supplementary Table 1 lists respiratory support and laboratory values.

3.3. Matched cohort analysis results

The matching process was depicted in Fig. 1, and the baseline characteristics are outlined in Table 3.

Underlying pulmonary comorbidities and malignancy were more common in patients with PTX/PM (41 % *vs.* 23 %; $p < .001$, OR [95 % CI] = 2.25 [1.39–3.64)], and 16 % *vs.* 4 %; $p < .001$, OR [95 % CI] = 4.5 [1.86–10.9], for cases and controls respectively). The median BMI was higher for controls than for cases (31.3 kg/m^2 vs. 29.5 kg/m^2, $p = .007$). When we evaluated the impact of underlying pulmonary comorbidities and BMI collectively in a multivariable logistic regression model, both variables were significantly predictive of PTX/PM. The adjusted OR for pulmonary comorbidities [95 % C.I.] = 2.55 [1.53, 4.25], adjusted estimate for BMI [95 % C.I.] = 0.65 [0.49, 0.85]. When we investigated the laboratory variables, among 111 pairs for whom D-dimer levels on the day before PTX/PM (and the matching day for control patients) were available, it was significantly higher for patients with PTX/PM compared to controls (median [iQR] = 1596 [886, 3734] *vs.* median [iQR] = 933 [628, 1735] for PTX/PM patients and controls, respectively, $p = .0040$). Among 109 pairs for whom CRP levels on the day before PTX/PM were available, there was no significant difference between those with PTX/PM compared to controls (median [iQR] = 36.5 [10.2, 128.9] vs. median [iQR] = 74.4 [48.3, 125.6] for PTX/PM patients and controls, respectively, $p = .153$).

The mechanical ventilation parameters were compared among patients who were on IMV on the day before PTX/PM (and the matching day for controls) and had available data. Thus, a small portion of patients were included in the analyses for PEEP, plateau, and driving pressure (14, 12, and 12 pairs of matched patients, respectively). Results of these comparative analyses were shown in Table 4.

Univariable and multivariable analyses results for hospital mortality, hospital LOS, and discharge disposition were shown in Table 5). The odds of in-hospital mortality were higher in patients with PTX/PM compared to controls both in univariate and adjusted analyses (OR [95 % CI] = 3.36 [1.85–6.10] and coefficient [95 % CI] = 3.37 (1.61–7.07), respectively).

Table 3
Baseline characteristics of patients included in the analyses.

Variables	Patients w.PTX and/or PM (n = 171)	Matched[a] controls (n = 171)	Odds ratio (95 % CI)	P value
Race, no. (%)			1.64 (1.00–2.70)	0.05
White, non-Hispanic	122 (71.3 %)	138 (80.7 %)		
Others	49 (28.7 %)	33 (19.3 %)		
Comorbidities, no. (%)				
Obesity (BMI≥30 kg/m^2)	76 (44.4 %)	95 (55.9 %)	**0.60 (0.37–0.95)**	**0.03**
BMI, kg/m^2, median (IQR)[b], n = 170 pairs	29.5 (25.8–34.8)	31.3 (26.8–38.4)	**0.96 (0.93, 0.99)**	**0.007**
Hypertension	81 (47.4 %)	93 (54.4 %)	0.75 (0.49–1.16)	0.192
Chronic pulmonary diseases	70 (40.9 %)	40 (23.4 %)	**2.25 (1.39–3.64)**	**<0.001**
Diabetes	57 (33.3 %)	47 (27.5 %)	1.35 (0.83–2.18)	0.227
Chronic cardiovascular disease	38 (22.2 %)	25 (14.6 %)	1.68 (0.96–2.97)	0.072
Chronic kidney disease	35 (20.5 %)	45 (26.3 %)	0.74 (0.45–1.20)	0.22
Malignancy	28 (16.4 %)	7 (4.1 %)	**4.5 (1.86–10.9)**	**<0.001**
Transplant	22 (12.9 %)	9 (5.3 %)	**2.86 (1.21–6.76)**	**0.017**
Prehospital systemic steroid use, no. (%), n = 143 pairs	13 (9 %)	10 (7 %)	1.3 (0.57–2.97)	0.533

95 % CI: 95 % confidence interval, PM: Pneumomediastinum, PTX: Pneumothorax.

** Patients were 1:1 matched for these criteria. Thus, comparative calculations were not performed for these variables.

[a] Matching was performed by age, sex, the time of admission (month), World Health Organization ordinal scale at the time of admission, and the day before pneumothorax for cases and the matching admission day for controls. Those patients who could not be matched (n = 17) and who were on extracorporeal membrane oxygenation treatment at the time of incident (n = 9) are excluded from this analysis and the calculations were conducted on171 cases and 171 matched controls.

[b] The odds ratio and 95 % CI for the BMI value was reported according to one standard deviation change in the value rather than one unit change.

Table 4
Ventilator related parameters and blood gas analysis of PTX/PM and control patients.

Variables	Number of available pairs	Patients w.PTX and/or PM (n = 171[b])	Matched[a] controls (n = 171[b])	Odds ratio (95 % CI)	P value
For patients who were on IMV, n = 114:					
Tidal volume set[b], median (IQR), mL/kg	25	385 (353–450)	405 (330–450)	1.00 (1.00, 0.99)	0.464
PEEP[b], median (IQR), mmHg	14	10 (10–12)	8 (8–10)	1.12 (0.87, 1.44)	0.379
Plateau pressure[b], median (IQR), cmH_2O	12	28 (25–30)	22 (17–25)	1.14 (0.97, 1.34)	0.111
Driving pressure [b]	12	15 (13–19)	12 (8–14)	1.10 (0.95, 1.27)	0.195
FiO_2	77	75 (55–100)	65 (45–100)	1.01 (1.00, 1.03)	0.089
PaO_2	30	68 (59–80)	72 (62–91)	0.99 (1.00, 0.97)	0.516
PaO_2/FiO_2	27	95 (72–131)	94 (69–187)	0.84 (0.34, 2.10)	0.714
SpO_2	84	87.5 (84–90)	88 (84–90)	**1.09 (1.02, 1.17)**	**0.013**

IQR: interquartile range, IMV: invasive mechanical ventilation, kg: kilograms, mL: milliliters, mm: millimeters, PEEP: Positive end-expiratory pressure.

[a] Case and control matching was performed by age, sex, the time of admission (month), World Health Organization ordinal scale at the time of admission, and the day before pneumothorax for cases and the matching admission day for controls.

[b] Matched case and control patients who were on IMV on the day of interest.

Table 5
COVID-19 outcome comparisons of the matched cohort.

				Univariate analysis		Adjusted[b] analysis	
Variables	Number of available pairs	Patients w.PTX and/or PM (n = 171)	Matched[a] controls (n = 171)	Odds ratio (95 % CI)	P value	Odds ratio (95 % CI)	P value
In-hospital mortality no. (%)	171	**69 (40.3 %)**	**36 (21.1 %)**	**3.36 (1.85–6.10)**	**<0.001**	**3.37 (1.61–7.07)**	**<0.001**
Discharge disposition, no. (%)[c]	91			0.5 (0.24–1.03)	0.061	0.68 (0.30–1.57)	0.372
Home		62 (68 %)	73 (80 %)				
Other		29 (32 %)	18 (20 %)				
				Percent change (95 % CI)	P value	Percent change (95 % CI)	P value
Hospital length of stay, median (IQR)[c]	88	**19 (9–30)**	**10 (5–15)**	**39 (10–76)**	**<0.001**	**39 (9–77)**	**<0.001**

[a] Case and control matching was performed by age, sex, the time of admission (month), World Health Organization ordinal scale at the time of admission, and the day before pneumothorax for cases and the matching admission day for controls.

[b] The analysis is adjusted for body mass index (standard deviation) and chronic pulmonary diseases.

[c] Among patients who were discharged alive; for being discharged to somewhere other than home.

4. Discussion

This matched cohort analysis compared hospitalized COVID-19 patients who developed PTX/PM to similar-severity patients who did not. In-hospital mortality was higher in patients whose COVID-19 course was complicated with PTX/PM. Those discharged alive had longer hospital LOS if they developed PTX/PM. Patients with PTX/PM had a higher prevalence of pulmonary comorbidities, and a lower median BMI than those without.

The incidence of PTX/PM in our study was 3 %, lower than most reports in COVID-19 [43,44]. However, the reported frequency of PTX has risen over the course of the pandemic, due to different virus variants [44]. Though the span of our study period was extensive, the VIRUS registry's patient enrollment decreased over the time due to decreased enrollment efforts [45]. Our low incidence rates might be explained by relatively higher frequency of patients enrolled earlier in the pandemic, in concordance with reports from that period [46,47]. The median age for PTX/PM was 59 years, with 71.1 % males. Previous studies have also reported males in their 5th to 6th decades are more commonly affected by this complication [48]. Interestingly, previous studies have not shown an association between baseline characteristics such as underlying pulmonary diseases or smoking history with PTX development [32,48]. In our research, patients with underlying pulmonary comorbidities were 2.25 (95 % CI: 1.39–3.64) times more prevalent in PTX/PM group than controls ($p < 001$).

Almost all PTX/PM patients had increased C-reactive protein, ferritin, and D-dimer levels. This suggests a hyperactive, dysregulated immune response and cytokine storm causing hyperinflammatory ARDS, leading to critical illness and increased mortality [49–51]. Though not statistically significant, patients with PTX/PM had a higher median fraction of inspired oxygen and lower PaO_2 before the development of these complications than controls. Furthermore, their lowest SpO_2 levels recorded on the day before PTX/PM was significantly lower. These findings were in concordance with the literature reporting worse respiratory parameters in critically ill COVID-19 patients who developed PTX [52].

An obvious risk factor for PTX/PM is barotrauma in patients receiving positive pressure ventilation. Invasively ventilated patients admitted to the intensive care unit had a notable incidence (6.1–15 %)[54–59]. However, lower incidences were reported (0.97–2%) in all hospitalized COVID-19 patients [32,53,54]. Our data revealed that a significant portion of patients who developed PTX/PM received IMV, with 36 % of PM, 43 % of PTX, and 46.3 % of PTX and PM. Ten percent of PTX/PM were present upon hospital admission, disproving that barotrauma is the only underlying cause, consistent with what other reports [48]. It is currently poorly understood, but prolonged coughing was suggested as a potential contributor [23], causing an abrupt rise in distal airway pressure, and resulting in alveolar rupture. The Macklin effect has also been hypothesized as an explanation. This effect refers to the development of PM without a PTX resulting from the evacuation of alveolar air under conditions of elevated intrathoracic pressure along the bronchovascular bundle [55]. Additionally, the virus's predisposition to peripheral bronchoalveolar locations combined with hyperinflammation has been suggested as another possible mechanism [56]. A considerable number of patients also developed PTX/PM on NIV and HFNC. In these patients, alongside the other potential mechanisms leading to these complications in patients neither on IMV nor HFNC/NIV, patient self-inflicted lung injury might play a role, particularly in the context of prolonged respiratory failure and delayed intubation, leading to increased transpulmonary pressures and lung stress [57], however, we did not test it in our study.

Few studies have examined ventilatory parameters and barotrauma risk in mechanically ventilated patients. In those studies, patients with higher peak inspiratory pressure, plateau pressure, or tidal volume did not have a higher risk of developing a PTX [10, 24]. In our study, we compared PEEP, plateau, and driving pressures on the day before PTX/PM for those who were on IMV on the day before the incident, to matched controls. Our analysis did not reveal any statistically significant association. However, concluding that there is no association would be inaccurate, as our study lacked the power to adequately assess such a relationship.

One major risk factor for PTX/PM in our study was underlying pulmonary comorbidities. Additionally, patients with PTX/PM had a lower median BMI. Though certain pulmonary comorbidities such as asthma and chronic obstructive pulmonary disease are known risk factors in PTX/PM, studies in COVID-19 patients show conflicting results [58–62]. Though the lack of specification of underlying pulmonary diseases in our study precludes us from discussing the mechanism, keeping in mind the higher tendency of PTX/PM in COVID-19 patients with pulmonary comorbidities is an important conclusion. Lower BMI was linked to PTX and iatrogenic PM recurrence in non-COVID-19 patients [63,64]. Another study on patients with interstitial lung disease showed an inverse relationship between PM occurrence and BMI levels [65]. The association between PTX/PM and lower BMI appears to be complex and multifactorial. To explain this relationship, several hypotheses have been proposed. One theory suggests that individuals with taller stature and longer, narrower airways are more likely to develop subpleural blebs, potentially leading to PTX/PM [16]. The "obesity paradox" is another potential explanation [66]. Lastly, it is proposed that nutritional deficiencies associated with a lower BMI could impair lung tissue remodeling, elevating the risk of PTX/PM [64]. Our study also indicates that lower BMI might be a risk factor for PTX/PM in COVID-19.

There was a significantly higher in-hospital mortality in COVID-19 patients with PTX/PM, 40.3 % *vs.* those without, 21.1 %, (adjusted OR 3.37, $p < 0.001$). This contrasts with existing published literature by Martinelli et al. and McGuinness et al., both of whom state that mortality rates of individuals with and without a PTX or PM were not significantly different [26,32]. In addition, McGuinness et al. found no difference in mortality between mechanically ventilated patients who experienced barotrauma and those who did not [26].

Patients who developed a PTX/PM had a longer hospital stay than controls, with a median LOS of 19 days *vs.* 10 days for controls (the percent change in adjusted analysis is 34 %, $p < 0.001$), respectively. Similarly, Matteo et al. have found congruent findings of increased hospital LOS [67]. All patients who developed PTX/PM were hospitalized for an average of 7 days (1–11 days) before the development of PTX/PM.

Prior studies showed that around 30 % of patients with PTX were managed successfully without invasive procedures [47, 57, 68]. This was in conformance with our results for patients with isolated PTX. However, most patients with isolated PM or accompanying PM were followed up without an intervention. Although some studies showed a survival benefit for interventions in patients with PTX in COVID-19 patients, a study comparing COVID-19 patients with PTX and pleural effusion to non-COVID-19 patients showed that the benefit of tube thoracostomy was more limited in the former [68–70]. There is no consensus regarding the treatment of PTX/PM in COVID-19 patients yet. Our analysis did not show a benefit of interventions on in-hospital mortality.

The advantage of the VIRUS registry is that it tracks the occurrence of cases since the start of the pandemic. From this data, we were able to detect a surge of cases with PTX/PM between spring to fall 2021, suggesting that the delta variant may have further predisposed patients to this complication. The delta variant caused more severe disease, which is congruent with this finding [71]. This may also confound our findings when comparing outcomes with other similar studies (including the incidence, mortality, and LOS). Interestingly, the incidence of PTX/PM was found to be even higher in December 2021 and January 2022. However, due to the limited number of cases admitted during this period, we are unable to make definitive conclusions.

4.1. Strengths and limitations

Our study has several strengths. Our multicenter cohort originating from different geographic settings spanning three states and incorporating academic and community health facilities and encompassing a diverse patient population with a considerable proportion of minority patients, helps to increase its generalizability. Furthermore, matching the PTX/PM patients to those who did not develop PTX/PM and who were admitted around the same time of the pandemic, helped reduce any confounding impact of the progress being made around COVID-19 therapeutics and prevention (i.e., availability of vaccination, recommendations of systemic steroids or remdesivir). Additionally, matching two comparison groups according to the WHO ordinal scales at the time of admission

and the day of interest ensured the similarity COVID-19 severity of the patient groups.

The study's results should be considered in the context of its limitations. Free-text screening may have biased our sampling method. Nevertheless, confirming the diagnoses by manual chart reviews has likely mitigated the impact of this bias. The PTX/PM diagnoses depended solely on the radiology reports and charts, without confirming by radiological images for the purposes of this study. Additionally, certain important variables, such as ventilation parameters were unavailable for some of the patients, further limiting our sample size and power of analysis to detect differences. Furthermore, while we matched the patients based on disease severity and the timing of infection, certain baseline characteristics were left out of the matching process as one of the study aims was to determine predisposing risk factors for developing PTX/PM in COVID-19 patients. To account for their impact on hospitalization outcomes, the analyses were adjusted for their impact on hospitalization outcomes; however, this was not ideal. Lastly, we acknowledge the limitations that are inherent to a retrospective study, relying upon retrospective chart reviews in both the VIRUS Registry and this specific analysis. The challenging pandemic circumstances and the vast amount of data required for the VIRUS Registry led issues with missing data variables and declining enrollment rates during the latter phases of the study. To mitigate this challenge, we supplemented the dataset using internal resources and chart reviews. Nevertheless, there were still variables that remained unmeasured or uncollected, potentially impacting the results of the study.

4.2. Implications for practice and further research

When treating COVID-19 patients, clinicians should consider previous lung disease and lower BMI as potential risk factors for PTX/PM. Other risk factors hypothesized to contribute, such as cough, are less easily quantified but may become relevant with future studies. Additionally, the large proportion of patients managed conservatively in our study may indicate the safety of conservative management and appropriate monitoring strategies for patients with PTX/PM, however, treatment approaches should be further studied in future research endeavors.

5. Conclusion

In a large cohort of hospitalized adult patients with COVID-19, we investigated the risk factors for PTX/PM and found an association of underlying pulmonary comorbidities and lower BMI with increased odds of PTX/PM. When we looked into the impact of PTX/PM development on hospitalization outcomes, we discovered that patients who develop PTX/PM had higher hospital mortality rates and longer hospital stays than patients with similar COVID-19 severity but without PTX/PM.

Ethics statement

This study protocol was reviewed and approved by the institutional review board at Mayo Clinic with the approval number 21–010686 (IRB for the main study: 20–002610, approval date: 3/23/2020). Mayo Clinic Institutional SARS-CoV-2/COVID-19 Research Task Force approval was also obtained. Per the study protocol approved in our institution, informed consent was waived under Common Rule 45 CFR 46.116.

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Data availability statement

Our research data has not been deposited into a publicly available repository. However, it will be made available to researchers who provide a methodologically sound proposal from the corresponding author at any time.

CRediT authorship contribution statement

Aysun Tekin: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Anusha Devarajan:** Writing – original draft, Methodology, Investigation. **Kenneth K. Sakata:** Writing – review & editing, Data curation, Conceptualization. **Shahraz Qamar:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Mayank Sharma:** Investigation, Data curation, Conceptualization. **Diana J. Valencia Morales:** Writing – review & editing, Formal analysis, Data curation. **Michael Malinchoc:** Methodology, Investigation, Formal analysis. **Fahimeh Talaei:** Writing – review & editing, Investigation, Data curation. **Stephanie Welle:** Writing – review & editing, Data curation, Conceptualization. **Jamil Taji:** Writing – review & editing, Data curation,

Conceptualization. **Sandeep Khosa:** Writing – review & editing, Data curation, Conceptualization. **Nikhil Sharma:** Writing – review & editing, Investigation, Data curation. **Meghan Brown:** Writing – review & editing, Investigation, Data curation. **Amos Lal:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Vikas Bansal:** Resources, Project administration, Data curation. **Syed Anjum Khan:** Writing – review & editing, Investigation, Conceptualization. **Abigail T. La Nou:** Writing – review & editing, Investigation, Data curation. **Devang Sanghavi:** Writing – review & editing, Investigation, Data curation. **Rodrigo Cartin-Ceba:** Writing – review & editing, Investigation, Data curation. **Rahul Kashyap:** Writing – review & editing, Project administration, Funding acquisition, Data curation. **Ognjen Gajic:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Juan P. Domecq:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Natalya Azadeh:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

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Dr. Aysun Tekin and Dr. Anusha Devarajan contributed equally to the design of the study, data collection, and preparation of the manuscript. Mr. Michael Malinchoc has conducted the comparative statistical analyses. Dr. Aysun Tekin is the guarantor of the content of the manuscript including the data and analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33679.

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