

Incidence and Prognosis of Pneumothorax and Pneumomediastinum in Hospitalized Patients With COVID-19 Pneumonia

Ahad Azeem, MD; Dua Noor Butt, MD; Margaret Carrig, BS; Bryan Krajcicek, MD; Christopher Destache, Pharm D; Manasa Velagapudi, MBBS

ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) can cause multisystem complications, with pulmonary involvement associated with the highest mortality. Pneumothorax (PT) and pneumomediastinum (PM) are uncommon complications of COVID-19 that have been reported to occur in the absence of trauma or mechanical ventilation. This study seeks to determine the incidence of these complications in patients with COVID-19 and evaluate clinical characteristics and outcomes.

Methods: We identified 3375 patients admitted to our health system during March 2020 through November 2020 who tested positive for SARS-CoV-2 with a polymerase chain reaction test. Patients were screened for PT or PM and were matched to COVID-19–positive patients without PT and/or PM. Data compared demographics, clinical characteristics, and laboratory values.

Results: Out of a total of 3375 COVID-19 admissions, 33 patients with PT/PM (1%) were compared to 32 matched controls without PT and/or PM. The patients with PT and/or PM demonstrated a significantly higher incidence of concomitant cancer diagnosis than those without PT and/or PM (18% vs 3%, respectively; $P=0.05$). Those with PT and/or PM required significantly more invasive mechanical ventilation than those without PT and/or PM (79% vs 47%; $P<0.01$). Mortality was significantly higher among those patients with PT and/or PM than those without PT/PM (55% vs 25%; $P<0.05$).

Discussion: A significant number of COVID-19 patients with PT and/or PM had a concomitant cancer diagnosis, required supplemental oxygen on admission, and invasive mechanical ventilation during hospitalization. Additionally, the COVID patients with PT and/or PM had significantly higher mortality compared to those without PT and/or PM. However, with all retrospective studies, there are limitations.

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Author Affiliations: Division of Infectious Disease, Creighton University School of Medicine, Omaha, Nebraska (Azeem, Velagapudi); Department of Internal Medicine, Creighton University School of Medicine, Omaha, Neb (Noor, Carrig); Division of Pulmonary, Critical Care and Sleep Medicine, Creighton University School of Medicine, Omaha, Neb (Krajcicek); Creighton University School of Pharmacy and Health Professions, Omaha, Neb (Destache).

Corresponding Author: Dua Noor Butt, MD, 7500 Mercy Rd, Omaha, NE 68124; phone 402.978.0938; email dbu02503@creighton.edu.

INTRODUCTION

In December 2019, several cases of pneumonia were identified in Wuhan, Hubei Province, China.^{1,2} All of these patients were linked to a local seafood market, where live animals were being sold. On January 7, the pathogen for these cases was identified by the Chinese Center of Disease Control and Prevention as a novel coronavirus that belongs to the *Orthocoronavirinae* family and was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The disease caused by this virus was named coronavirus disease-19 or COVID-19. Novel coronavirus primarily affects the respiratory system but also has demonstrated multisystem dysfunction affecting the heart, kidneys, circulatory system, liver, gastrointestinal tract, and blood cells precipitating hemolysis.³ Respiratory complications of COVID-19 occur with a wide spectrum ranging from self-limiting mild upper respiratory infection

to significant hypoxia secondary to acute respiratory distress syndrome (ARDS).⁴

Barotrauma, which includes pneumothorax (PT) and pneumomediastinum (PM), recently has been observed as an emerging complication in COVID-19 patients. Traumatic pneumothorax results from an injury to the pleura, including iatrogenic cases during medical procedures, whereas primary spontaneous pneumothorax is defined as PT that presents in an otherwise healthy lung without any precipitating external events. Secondary spontaneous pneumothorax is defined as PT that occurs as a complication of underlying lung disease. In prior studies, the reported incidence of PT and/or PM in COVID-19 patients was 1%.⁵

However, in a recent case-control study assessing 601 critically ill intensive care unit (ICU) patients with COVID-19 requiring invasive mechanical ventilation, the reported incidence was up to 12.8%.⁶

There are several proposed mechanisms for the development of PT and PM in patients with COVID-19. Formation of pneumatocele or cysts in the affected lung tissue in the absence of positive pressure ventilation suggests direct parenchymal injury induced by the virus itself and the body's immune system.^{7,8} We performed a retrospective cohort study to determine the incidence, risk factors, and outcomes of PT and/or PM in hospitalized patients with COVID-19 over the course of 9 months.

METHODS

Study Design and Population

This was an Institutional Review Board-approved retrospective chart review of patients in the CHI Health Nebraska health system that includes 6 health care facilities serving patients in Nebraska and Iowa. Adult patients age 19 and older admitted during March 2020 through November 2020 who tested positive for COVID-19 via a polymerase chain reaction (PCR) test and who developed spontaneous PT or PM during their inpatient hospital stay were included. This period involved multiple surges of the COVID-19 pandemic prior to vaccine availability. COVID-19–positive patients without spontaneous PT or PM during their inpatient ICU hospitalization served as control patients. Those who had COVID-19–like symptoms but negative COVID-19 PCR testing were excluded, as were patients with PT or PM secondary to trauma without a positive COVID-19 PCR test result.

Data Collection

Electronic medical records (Epic Systems Corp, Verona, Wisconsin) were reviewed retrospectively for demographic, clinical, and laboratory values for all patients who met the inclusion criteria of COVID-19 with PT/PM. These patients were matched by age (± 1 year), gender, and recent ICU admission to the admission date with a positive COVID-19 test to a group of patients without PT/PM. If there was more than 1 possible match, the match was chosen at random. One patient could not be age-matched to a COVID-19–positive patient without PT. Admission data included the need for supplemental oxygen and the following commonly performed labs: lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, and procalcitonin. The electronic medical records were further reviewed to assess for comorbidities related to COVID-19 risk and respiratory disease, including body mass index (BMI), hypertension, diabetes, cancer, chronic obstructive pulmonary disease (COPD), asthma, interstitial lung disease, and other underlying lung diseases. The course of the disease from symptom onset to PT/PM was measured. Data on vasopressor requirements in the PT/PM cohort

were compared with controls. Information on whether a chest tube was placed, initiation of new renal replacement therapy, and initiation of extracorporeal membrane oxygenation (ECMO) during the hospital stay were collected.

The number of days of invasive and noninvasive mechanical ventilation, if applicable, after the PT/PM was recorded. Records were reviewed to determine whether palliative care was consulted during the hospital course. The primary outcomes of this study were mortality and length of hospital stay. Secondary outcomes were vasopressor requirement, laboratory inflammatory markers, need for the palliative care team, and need for invasive mechanical ventilation. All of these variables were compared statistically.

Statistical Analysis

Data were reviewed and entered in SPSS Statistics version 27 (IBM Corp) for statistical analysis. Discrete variables were analyzed by chi-square, and continuous variables were analyzed by *t* test or Mann-Whitney U test. Statistical significance was determined based on a *P* value ≤ 0.05 .

RESULTS

Cohort Demographics

A total of 33 patients with COVID-19 had PT and/or PM out of 3375 COVID-19 admissions, with a calculated incidence of 1%. PT alone was more prevalent than PM alone (61% vs 21%, respectively) and both PT and PM concomitantly (18%). The median age in the study group was 67 years (range 39–98 years) (Table 1). Males were predominantly affected with PT/PM (70%), consistent with the overall COVID-19 pandemic. Twenty-two patients (667%) were White, 5 (15%) were African American, 4 (12%) were Hispanic, 2 (6%) were Asian. Twenty-four patients (73%) had a BMI greater than 25, and 6 patients (18%) had a BMI greater than 35. Among both groups, no statistically significant difference was noted in the comorbidities (BMI, hypertension, diabetes, COPD, asthma, interstitial lung disease, and other underlying lung diseases). PT/PM was more common in patients with a history of cancer (COVID-19 with PT/PM: 18% vs COVID-19 without PT/PM: 3%; *P* = 0.05).

Patient Outcomes

Patients with PT and/or PM required significantly more oxygen support (nasal cannula, high-flow noninvasive ventilation, and invasive mechanical ventilation) on hospital admission compared to patients without PT and/or PM (85% vs 59%, respectively; *P* = 0.03). Similarly, the need for invasive mechanical ventilation was significantly higher among COVID-19 patients with PT/PM than those without PT/PM (79% vs 47%; *P* < 0.01). Among the patients with PT/PM (*n* = 26), only 10 patients were mechanically ventilated at the time of PT/PM. These patients (*n* = 10) averaged 3.2 (± 4.6) days of mechanical ventilation before PM/PT. No difference (*P* > 0.05) was noted in the laboratory

Table 1. Demographics and Outcomes

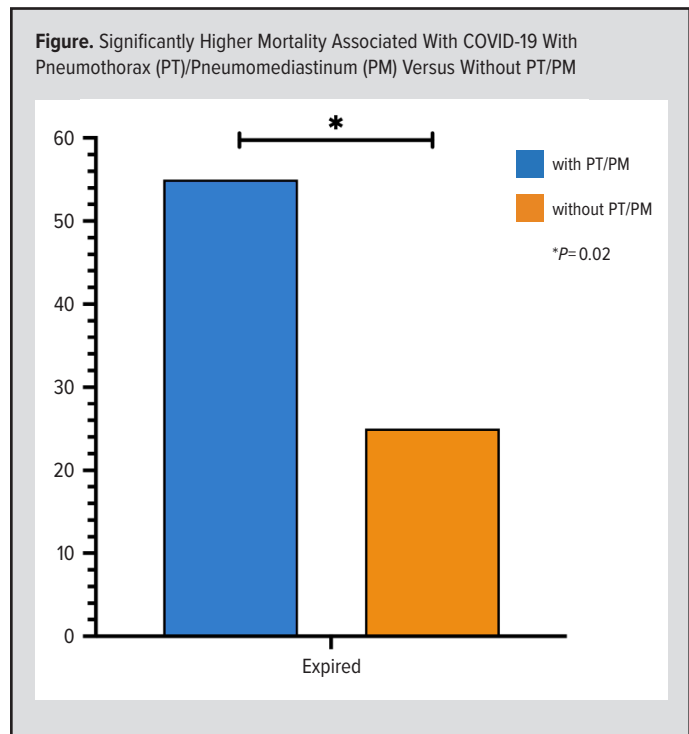
Variable	COVID-19 w/ PT/PM (n=33)	COVID-19 w/out PT/PM (n=32)	P value
Race			0.09
Asian	1	0	
Hispanic	4	11	
African American	5	7	
White	22	12	
Sex			0.63
Male	23	24	
Female	10	8	
Oxygen requirement (at admission)			0.033
Room air	5	13	
Nasal cannula	13	9	
High-flow nasal cannula	7	1	
NIPPV	3	1	
Mechanical ventilation	5	8	
Comorbidities			
Hypertension	26	25	0.94
Diabetes mellitus	15	18	0.38
Cancer	6	1	0.05
COPD	9	5	0.25
Asthma	4	3	0.72
Interstitial lung disease	1	0	0.32
Other underlying lung disease	5	6	0.69
Hospital course			
Mechanical ventilation	26	15	0.008
Initiation of RRT	4	2	0.41
ECMO	2	1	0.57
Outcome			0.02
Discharge to home	14	24	
Death	18	8	
Palliative care consults	20	8	0.004
Length of hospital stay, days	18.7	15.8	0.75

Abbreviations: PT, pneumothorax; PM, pneumomediastinum; NIPPV, noninvasive mechanical ventilation; COPD, chronic obstructive pulmonary disease; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

Table 2. Laboratory Tests and Other Parameters

Variable	COVID-19 w/ PT/PM Mean (±SD)	COVID-19 w/out PT/PM Mean (±SD)	P value
Admission lab tests			
LDH (U/L)	447.8±13.0	415.6±453.4	> 0.05
CRP (mg/L)	144.5±95.3	112.7±91.3	> 0.05
Ferritin (ug/L)	1037.6±799.0	1298.3±1868.5	> 0.05
Procalcitonin (ng/mL)	1.4±3.2	2.7±8.5	> 0.05
Days of symptom onset to PT/PM	11.5±10.3		
Days of vasopressor support	5.9±5.1	3.26±5.8	> 0.05

Abbreviations: PT, pneumothorax; PM, pneumomediastinum; LDH, lactate dehydrogenase; CRP, C-reactive protein.



tests from admission (LDH, CRP, ferritin, and procalcitonin) between both groups. Mean (±SD) number of days from symptom onset to the development of PT/PM was 11.5 (±10.3). Days of vasopressor requirement averaged approximately 2 days longer for COVID-19 patients with PT/PM (5.9±5.1 days) compared to the group without PT/PM (3.26±5.8 days), which did not reach statistical difference (Table 2). COVID-19–positive patients with PT and/or PM were noted to have significantly higher mortality compared to the control group (55% vs 25%; $P < 0.05$). (Figure 1) The palliative care team was consulted more often in PT/PM group than the group PT/PM (61% vs 25%; $P < 0.05$). Finally, the length of hospitalization averaged 3 days longer for patients with PT and/or PM (18.7±18.4 days) than the control group (15.9±10.3 days).

DISCUSSION

PT and PM are rare complications of COVID-19, but they are associated with significant morbidity and mortality. To explain this, there are many case series in the literature, but this is one of the few case-control studies that describe the incidence and outcomes of PT and PM in COVID-19 patients with or without use of invasive mechanical ventilation. During the viral replication phase, SARS-CoV-2 causes damage to epithelial cells in the lungs, which produces a surge of cytokines leading to damage of circulatory system and failure of multiple vital organs simultaneously.⁹ Damage to this circulation barrier leads to acute respiratory distress syndrome (ARDS) in the lungs that, in turn, alters the static compliance of lungs. The increased pressure gradient across the inflamed alveolar wall can be a cause of increased incidence of spontaneous PT/PM in such a patient population.^{10,11}

In addition to SARS-CoV-2, barotrauma is a well-known complication secondary to *pneumocystis jirovecii*, severe acute respiratory syndrome (SARS), and Middle Eastern respiratory syndrome (MERS).⁵

Our results demonstrated that COVID-19–positive patients with PT/PM had higher morbidity and mortality than those who did not develop this complication. Previously published literature demonstrated varying incidence from 1% to as high as 13%.^{6,12,13} After analyzing the retrospective charts, we found an incidence of 1% among 3375 COVID-19 admissions. Male sex was predominantly affected, and PT was seen more frequently than PM alone or combined.

Our retrospective review demonstrated more severe hypoxia and increased oxygen demand at the time of admission in COVID-19 patients with PT/PM compared to controls, even before the development of PT/PM. It is plausible that the degree of hypoxia and severity of the disease is associated with the development of barotrauma later. All of the patients were assessed for comorbidities, and among diabetes, hypertension, COPD, reactive airway disease, and interstitial lung disease, only history of cancer was statistically important for the development of PT/PM. Unlike previously published literature, no correlation was found with a history of diabetes or asthma.^{4,14}

In our cohort of patients with barotrauma, 21% (7 out of 33) did not require invasive mechanical ventilation during the hospital stay. Nineteen patients (58%) who developed PT/PM required chest tube placement. Percutaneous intervention was used in all except one, who required a surgical thoracostomy tube. Gazivoda et al did not notice changes in mortality with the placement of thoracostomy tube.⁴ Similarly, patients with PT/PM required more invasive mechanical ventilation compared to controls, but no difference was seen with initiation of renal replacement therapy or ECMO between both groups. Patients with PT/PM requiring mechanical ventilation (n = 26) were analyzed further, and it was determined that mechanical ventilation preceded development of PT/PM in only 10 patients (38.5%), leaving most of the patient population (61.5%) with no exposure to barotrauma prior to PT/PM development. This supports the idea of direct viral damage to lung tissue causing decreased lung compliance, as described in recent studies.^{10,11} The number of days on mechanical ventilation prior to incidence of PT/PM averaged 3.2 (± 4.6) days.

Patients with isolated PM secondary to COVID-19 can be managed conservatively with serial imaging and avoiding high positive end-expiratory pressure (PEEP) during invasive mechanical ventilation.^{15,16} In contrast to our results, a large case series from the United Kingdom demonstrated significantly higher mortality in the COVID-19–positive patients with PT/PM compared to COVID-19–positive patients without PT/PM (55% vs 25%).¹⁷ Lung protective mechanisms during invasive ventilation are needed to lower the risk of barotrauma in patients with ARDS.¹⁸

In the study group of COVID-19 patients with PT/PM, the palliative care team was consulted more often than for the control group, which can reflect the severe overall morbidity secondary to barotrauma in COVID-19–positive patients. No statistical significance was seen in the length of hospital stay and days with vasopressor requirement between the groups, but patients with PT/PM averaged 3 days longer hospitalization and 2 days longer vasopressors, which could be clinically significant.

Limitations

There are limitations to our study. This is a retrospective review of a patient population from the US Midwest. Our institution followed guidelines from the Infectious Disease Society of America for treatment of critically ill COVID-19 patients, but treatment options for COVID-19 were not considered in this study to calculate the incidence and mortality in COVID-19–positive patients with PT and/or PM. Previously published literature demonstrated some benefits with the use of remdesivir and corticosteroids.⁴ We did not include patients with isolated subcutaneous emphysema. Excessive positive pressure ventilation in ARDS can be associated with increased occurrence of PT and/or PM, but we did not evaluate the tidal volumes and PEEP for this study.⁵ The matching criteria used for this study was retrospective and could suffer from selection bias. We conducted our study prior to the availability of vaccination against COVID-19, which can alter the disease severity in the future and potentially outcomes in patients with barotrauma.

CONCLUSIONS

COVID-19 patients with PT and/or PM required significantly more oxygen on admission, had a higher prevalence of cancer diagnosis, and required more invasive mechanical ventilation support. There was a significantly higher mortality in the patients with PT and/or PM than those without PT and/or PM. Palliative care consultation should be sought sooner when needed.

Funding/Support: None declared.

Financial Disclosures: None declared.

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