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Original Article

The relationship between COVID-19 and pneumothorax in patients hospitalized during the pandemic

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Abstract

Objective: We aimed to determine the incidence, demographic characteristics and risk factors of "spontaneous pneumothorax (SP)" that we detected in severe COVID-19 patients with acute respiratory distress (ARDS) who were followed up in the intensive care unit (ICU) of our hospital.

Methods: This is a retrospective observational study conducted on adult COVID-19 patients admitted to our hospital between March 11, 2020, and December 31, 2021. The cases were patients who were hospitalized in the ICU with the diagnosis of COVID-19 and developed pneumothorax. Chest radiography (CXR) and computed tomography (CT) were used to diagnose pneumothorax. The medical records contained detailed demographic information, radiography images, laboratory data and information on treatment management and survival.

Results: A total of 20 patients hospitalized in the ICU with the diagnosis of COVID-19 developed pneumothorax. Of these patients, 11 (55%) were male and 9 (45%) were female. Based on our findings, 90% of the patients developed spontaneous pneumothorax during their COVID-19 disease and 10% during their post-COVID follow-up. The radiologic examination of pneumothorax patients revealed that 70% were right-sided, 15% were left-sided, and 15% were bilateral. Regarding the treatment protocol of the patients, chest drain treatment was used in 85%, while 15% were followed up with oxygen treatment. The incidence of pneumothorax was higher in males.

Conclusion: These cases suggest that pneumothorax is a complication of COVID-19. Spontaneous pneumothorax is a rare complication of COVID-19 viral pneumonia. Sudden clinical changes in patients during intensive care follow-up should be considered a preliminary diagnosis. Clinicians should be careful about the diagnosis and treatment of this complication.

Keywords: ARDS, COVID-19, pandemic, pneumothorax.

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INTRODUCTION

Pneumothorax, which is defined as the presence of air in the pleural space with or without collapse of the lung, is an emergency complication that is often life-threatening (1). Based on their etiology, pneumothoraxes can be classified as spontaneous, iatrogenic or traumatic (2). Iatrogenic pneumothorax is a side effect of a diagnostic or treatment procedure (3,4). The first instance of pneumonia with an unknown origin was reported in December 2019 in Wuhan, Hubei province, China. This pneumonia with ARDS course was found to have a novel coronavirus (SARS-CoV-2) named COVID-19 as the etiopathogenic agent (5). The World Health Organization (WHO) classified COVID-19 a pandemic on March 12, 2020, and a public health emergency on January 30, 2020. (6). Pneumothorax occurred more frequently in COVID-19-positive, mechanically ventilated patients during the COVID-19 pandemic. Pneumothorax is a documented side effect of lung ventilation, and mechanical ventilation harms the lungs (7). Due to immature lung mechanics, ventilation-related pneumothorax has been documented more frequently in the pediatric population (8-9). Pneumothorax is more likely to happen when there is a combination of parenchymal injury brought on by the infection and an inflammatory response accompanied by additional positive pressure ventilation. Although spontaneous pneumothorax has been reported in infections like COVID-19 (10,11), it is more common in those infections. 12 (5.9%) of the 202 patients in a Wuhan trial who had mechanical breathing developed pneumothorax (12). In this article, we provide our observations from a case series of 20 pneumothorax patients among 2586 COVID-19 pneumonia patients admitted to the ICU at a tertiary care facility.

MATERIALS AND METHODS

A retrospective review of the records of patients admitted with COVID-19 disease in our tertiary care hospital since March 11, 2020, was conducted. A total of 62,730 COVID-19 patients were treated during this period. The diagnosis of COVID-19 disease was made by polymerase chain reaction (PCR) testing of a nasopharyngeal swab sample. All patients underwent routine posteroanterior chest radiography (CXR) and thoracic computed tomography (CT) on admission. A study of the clinical records and chest radiography images was used to evaluate if there was a pneumothorax or not. Patients who experienced a pneumothorax at any point were thoroughly examined during clinical follow-up. Each patient's baseline laboratory test results, including WBC, lymphocyte, and neutrophil counts, platelet, urea, creatinine, and neutrophil/lymphocyte ratio, were recorded. Inflammatory markers, such as C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, D-dimer, procalcitonin, blood gas lactate, and creatine kinase, were also recorded. Respiratory support status, the fraction of inspired oxygen (FiO_2), positive end-expiratory pressure (PEEP) values, tidal volume, and duration of the mechanical ventilator (MV) stay were determined. The incidence of spontaneous pneumothorax in COVID-19 patients was calculated. The study protocol was approved by the Hitit University Faculty of Medicine Ethics Committee.

Statistical Analysis

Input of data was done using SPSS version 24. Continuous data were reported as mean and standard deviation SD whilst categorical variables were given as frequency (n) and percentage (%). These variables were found to be regularly distributed by the Shapiro-Wilk test. The chi-square test and Mann-Whitney U-test were used to compare the groups for categorical and continuous data, respectively. At p 0.05, differences were deemed statistically significant. For each patient's ventilator settings, averages of all data noted during the ICU admission were derived. For the final statistical analyses, the average for the entire ICU stay was calculated.

RESULTS

A total of 62,730 COVID-19 PCR-positive patients were admitted to our hospital between March 11, 2020, and December 31, 2021. 9,179 patients were treated as inpatients. Of these patients, 2,586 were followed up in the ICU. As a result of the retrospective cohort analysis made with the medical records of the level 3 anesthesia and reanimation intensive care, twenty patients who were admitted to the ICU due to COVID-19 pneumonia and diagnosed with pneumothorax were examined and included in the analyses. The mean age of these patients was 62.95 years (range 28-94), 55% (11) were male and 45% (9) were female. The total incidence of pneumothorax was 0.77%. The mean length of stay (LOS) in the ICU was 12 days, the mean length of ICU stay after PCR positivity was 7.2 days, the mean duration of pneumothorax development was 8.5 days, and the mean duration of ICU mechanical ventilator (MV) stay was 10.05 days. The mean of positive end-expiratory pressure (PEEP) values related to MV was 7.75, the mean of tidal volumes was 513.9 ml and the mean Fraction of inspired Oxygen (FiO_2) value was 85.5. When biochemical data were analyzed, the mean c-reactive protein (CRP) value was 117.73 mg/dl, procalcitonin value was 564.85 ng/ml, D-dimer value was 327.52 mg/dl, creatinine kinase (CK) value was 432.8

Table 1. Baseline laboratory and respiratory function data for patients with COVID-19 and pneumothorax

Variables	Mean (normal range)	Range	SD	P
Age (year)	62.95	(28-94)	20.2	.304
ICU stay (day)	12	(3-27)	7.15	.217
ICU admission time after PCR+ (day)	7.2	(1-28)	8.93	.085
Diagnosis of pneumothorax after PCR+ (day)	8.5	(1-35)	8.70	.386
MV stay time (day)	10.05	(1-30)	7.45	.234
PEEP	7.75	(5-15)	2.51	.094
Tidal volume	513.9	(400-815)	95.06	.416
FiO_2	85.5	(60-100)	18.20	**.018***
CRP (mg/dl)	117.74	(3.22-508)	142.14	.308
Procalcitonin (ng/ml)	564.85	(0.07-4,418)	1,190.68	.129
D-dimer (mg/dl)	327.52	(0.89-2,445)	587.77	.155
Lactate (U/L)	178.05	(1.94-916)	252.72	.500
LDH (U/L)	971.25	(348-5,316)	1,113.55	**.010***
Creatine Kinase (U/L)	432.8	(24-2,902)	799.68	.345
Neutrophil ($10^{\wedge 9}$/L)	19,273.65	(1,893-89,600)	18,195.72	.089
Lymphocyte ($10^{\wedge 9}$/L)	807.5	(140-3,600)	839.7	.149
Ferritin (ng/dl)	1,169.68	(185-4,601)	933.34	.382
Urea (mg/dl)	119.5	(34-281)	76.18	.111
Creatinin (mg/dl)	2.19	(0.3-6.6)	1.91	.354
Platelet ($10^{\wedge 9}$/L)	229,900	(41,000-514,000)	122,668.53	.208
WBC ($10^{\wedge 9}$/L)	16,913.3	(6,430-36,030)	7,232.37	.089
Neutrophil/Lymphocyte ratio	40.16	(0.53-119.07)	31.31	.059

**** Mann-Whitney U test (p<0.05)***

U/L and ferritin value was 1,169 ng/ml. The data of the patients are presented in **Table 1**.

In the management of pneumothorax, 17 (85%) patients required the placement of a chest tube and closed underwater drainage technique. 70% (14/20) of the patients had right-sided pneumothorax, 15% (3/20) had left-sided pneumothorax and 15% (3/20) had bilateral pneumothorax. In the COVID-19 active period, pneumothorax was detected in 90% (18/20) of the patients, while in the post-COVID follow-up period, it was detected in 10% (2/20). Based on medical treatment protocols, 100% (20/20) of patients received steroids as an immunosuppressant, 55% (11/20) received anakinra, and 5% (1/20) received tocilizumab in addition to steroids. The most common comorbidity was hypertension, which affected 40% of patients (8/20). The demographic characteristics and treatments of the patients are presented in **Table 2**.

DISCUSSION

Pneumothorax is a potentially fatal consequence and a medical emergency that is described as the presence of air in the pleural space with or without lung collapse (1). Spontaneous pneumothorax refers to the leakage of air into the mediastinum that occurs without traumatic or iatrogenic origin. The development of pneumothorax

Table 2. Demographic data of the patients

Variables		**Frequency (n)**	
Gender	*Male*	*11*	55%
Time	*COVID*	*18*	90%
Area	*Right-sided pneumothorax*	*14*	70%
	Left-sided pneumothorax	*3*	15%
	Bilaterally		
Pneumothorax treatment	Chest drain	*17*	85%
Immunomodulatory therapy	*Steroid*	*20*	100%
	Anakinra	*11*	55%
Comorbidities	Cardiovascular diseases (HT, CHF, Arrhythmia)	8/20	40%
	Endocrine diseases (DM)	2/20	10%
	Chest diseases (COPD, Asthma, PTE, etc.)	3/20	15%
	Cerebrovascular diseases (CVD)	3/20	15%
	Renal diseases (CF, transplanted, BPH)	4/20	20%
	Malignancy (Ca etc.)	1/20	5%
	Hematological diseases (MM, CML)	2/20	10%
	Rheumatologic diseases	1/20	5%
Prognosis	Ex	17/20	85%

has been reported in both viral pneumonia cases and bacterial pneumonia cases (13,14). Studies of spontaneous pneumothorax in COVID-19 patients imply that, in addition to the stress brought on by the ventilator in patients receiving mechanical ventilation, the COVID-19 infection itself may bring on pneumothorax. In critically ill patients with COVID-19 pneumonia, limited data are available regarding patient-related factors that may contribute to pneumothorax (16). It is noteworthy that ARDS is the main cause of mortality in COVID-19 infection; however, there is an increase in publications reporting serious pulmonary complications such as pneumothorax (17,18), pneumomediastinum (19,20), and pulmonary embolism (21). The incidence and mean number of days for the development of pneumothorax during mechanical ventilation for the treatment of ARDS in COVID-19 patients is unclear. In our study, the incidence was 0.77% compared with 0.66% in the study of Zantah et al. (22). Our findings are supported by the findings of Aujayeb who reported an incidence of >1% (23). In the study of Shaikh et al., the mean duration of MV was 25.37 (24). In the study by Aujayeb, the mean duration of pneumothorax after respiratory symptoms was 13 days (23). In our study, the mean duration of MV stay was around 10.05 days and pneumothorax occurrence was 8.5 days after PCR positivity. The results are close to each other but vary. We think that the current results vary due to the triage criteria of the countries and human factors.

With the implementation of a protective lung ventilation strategy, the incidence of pneumothorax decreases as COVID-19 patient experience increases. Studies on lung protective ventilation performed on COVID-19 patients

found that the risk of pneumothorax decreased over time, with the majority of cases occurring in the first few weeks of mechanical breathing. (16, 25). Mechanical ventilation used for ARDS treatment of COVID-19 patients is closely associated with the severity and duration of injury, barotrauma, and volutrauma. It occurs especially in cases of high positive end-expiratory pressure (PEEP), high tidal volumes, high peak inspiratory pressures (PIP) (>40 to 50 cmH2O), and minute ventilation. In a retrospective study by McGuinness et al., it was reported that barotrauma-related complications occurred in 24% of cases. This study also reported that barotrauma was an independent risk factor for mortality in COVID-19 infection (16, 26-30). In our study, the mean PEEP values were found to be 7.75 cm H2O, the mean tidal volume was 513.9 ml, and the mean FiO2 value was 85.5, which was found to be highly consistent with the follow-up of severe ARDS patients. Even at moderate and low positive end-expiratory pressure (PEEP) levels (8–10 cmH2O), it appears to cause high stress in COVID-19 patients followed up with severe ARDS. There is a need for further studies that involve increasing the number of patients and monitoring more respiratory parameters to validate this hypothesis.

There have been multiple case reports of spontaneous pneumothorax in COVID-19 infected patients (11, 31-34). Recent case reports and reviews reveal that the progression of COVID-19 infection naturally predisposes to pneumothorax formation (16, 35, 36). Several theories have been detailed, despite the fact that the mechanism of pneumothorax development is not entirely understood.

As in other respiratory tract infections, damage to the alveolar wall that occurs in COVID-19 infections causes cystic formations in the alveoli. Moreover, ischemic parenchymal damage due to ARDS caused by COVID-19 infection, damage caused by inflammatory mediators, and fibroblast activation all combine to form exudates that cause the formation of alveolar cystic lesions (35-37). In their study, Martinelli et al. reported a significant correlation between blood gases with high mortality in patients with severely damaged lung tissue. The study supports that lung tissue damage may be an existing cause. All of the patients in our study were intubated with severe ARDS and followed up in MV and FiO2 and LDH values were significantly correlated with mortality ($p<0.05$). In our study, although the mean values of CRP, Ferritin, D-Dimer, and Procalcitonin, which are inflammation markers, were higher than normal, the difference was not significant. Zantah et al. reported that higher-than-normal values of biomarkers were statistically significant. These markers support the expected values in severe ARDS cases (37-39). Sihoe et al. noted in their study that the mean neutrophil count of patients with COVID-19 pneumothorax tended to be higher than previously reported cohorts of similar SARS patients with ARDS (40). In our study, the mean neutrophil count of the patients was significantly higher than normal levels and supported the study. We think that this result indicates the severity of inflammation.

Pneumothorax has a wide range of clinical manifestations. It can be asymptomatic or can range from life-threatening. Therefore, treatment strategies are also variable. Small to limited pneumothorax confirmed by imaging techniques and clinically stable patients can be treated with clinical follow-up. In symptomatic patients, treatment and follow-up are continued with the interventional procedure in patients with larger pneumothorax with hemodynamic and respiratory instability (41,42). Martinelli et al. reported that 69.3% of patients were treated with chest drain, 29.03% with clinical follow-up, and 1.67% with surgical intervention after chest drain (43). Meanwhile, in our study, we found that 85% of patients were followed up with chest drain and 15% with clinical follow-up and the results were similar and supported the studies.

Nistor et al. reported a survival rate of 18.75% after the occurrence of these complications in their study. In another study, Shaikh et al. reported a survival rate of 48.8% (24). In the study by Zantah et al., the survival rate was 33.4% (44). In our study, the survival rate was found to be 15%. We think that the varying results may be attributed to the different population sizes of the studies, as well as differences in the criteria for admitting patients to intensive care units.

It was observed that drainage of the pleural space in patients with pneumothorax developing in COVID-19 pneumonia did not change the prognosis in existing ARDS lung tissue (45). We think that the probable cause was prolonged ventilation and existing comorbidities leading to death in most of these cases.

Limitations:

The limitations of the present study are that it is retrospective and the exact incidence cannot be calculated due to the small sample size. In the study, the sample size can be expanded to evaluate the differences in mortality and overall survival in COVID-19 patients with or without pneumothorax. As our study is a retrospective observational case study, it cannot conclusively prove the causality of pneumothorax due to COVID-19 infection.

CONCLUSION

Spontaneous pneumothorax is an extremely rare complication in COVID-19 patients. Pneumothorax can be a consequence of alveolar damage caused by COVID-19 pneumonia, or it can be a serious life-threatening complication of the ventilator therapy required to manage pneumonia. Although the actual incidence of pneumothorax in patients on mechanical ventilator support with ICU follow-up for COVID-19 pneumonia is unknown, our case series suggests that this is a significant number. It has been observed that if there is a pneumothorax with COVID-19, it has a more mortal course. This study can be used to evaluate the prognostic significance of pneumothorax, particularly in critically ill patients with COVID-19 infection, whether it is an independent predictor of mortality, and to collect more data for future studies.

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Ethical approval and consent to participate: The study was conducted with the the conditions recommended by the Helsinki Declaration. The study was carried out with the permission of Hitit University Medicine of Faculty Hospital after the approval of the local ethics committee (Application No: 2021-98, Decision No: 2021-69)
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Authorship Contributions: All of the authors declare that they have all participated in the design of the study, supervision, data collection &/or processing, performed data analysis, literature search, written, critical review.

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