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***Original Article*** / *Özgün Makale*

# Prognostic factors and their effects on mortality in patients with COVID-19 with pneumothorax

*Pnömotoraks gelişen COVID-19 hastalarında prognostik faktörler ve mortaliteye etkileri*

**Osman Yakşi, Ali Kılıçgün**

Department of Thoracic Surgery, Bolu Abant Izzet Baysal University Faculty of Medicine, Bolu, Turkey

***ABSTRACT***

***Background:*** The aim of this study was to investigate the factors affecting pneumothorax development, lung expansion difficulty, and the impact on mortality in novel coronavirus 2019 (COVID-19) patients.

***Methods:*** Between March 2020 and January 2021, a total of 6,108 COVID-19 patients (3,050 males, 3,058 females; mean age: 49±17.6 years, range, 12 to 89 years) who presented to our hospital were retrospectively analyzed. The patients were divided into two groups. Group 1 (the COVID-19-pneumothorax group) consisted of patients developing pneumothorax while under treatment for COVID-19. Group 2 (COVID-19-without pneumothorax group) consisted of consecutive patients with pulmonary involvement during the same period, requiring intensive care, but not developing pneumothorax. Biochemical test results were examined for the day of hospitalization, day of transfer to intensive care unit, and Day 5 of intensive care unit stay. Lung parenchyma involvement rates on thoracic computed tomography, duration of drainage, duration of intensive care unit stay, and morbidity/mortality data were investigated.

***Results:*** Of all patients with COVID-19, 2,342 were admitted to our clinic and 460 needed intensive care. Pneumothorax developed in 21 patients (0.34% of all patients and 0.9% of hospitalized patients). Significant involvement diffusion on computed tomography, ferritin and D-dimer elevation, and low lymphocyte (%) values were observed in the COVID-19 patients with pneumothorax. Pneumothorax development, and ferritin and D-dimer elevation were most correlated with mortality at regression analysis. There was a significant difference in difficulty in lung expansion between COVID-19 patients who developed pneumothorax and who did not.

***Conclusion:*** Pneumothorax may develop in COVID-19 patients whose biochemical parameters worsen, and expansion difficulty may be experienced, which is likely to be associated with mortality.

***Keywords:*** COVID-19, pneumothorax, SARS-CoV-2.

***ÖZ***

***Amaç:*** Bu çalışmada yeni koronavirüs 2019 (COVID-19) hastalarında pnömotoraks gelişimini etkileyen faktörler, akciğer ekspansiyon güçlüğü ve mortalite üzerine etkisi incelendi.

***Çalışma planı:*** Mart 2020 - Ocak 2021 tarihleri arasında hastanemize başvuran toplam 6108 COVID-19 hastası (3050 erkek, 3058 kadın; ort. yaş: 49±17.6 yıl; dağılım, 12-89 yıl) retrospektif olarak incelendi. Hastalar iki gruba ayrıldı. Grup 1 (COVID-19-pnömotoraks grubu), COVID-19 tedavisi altındayken pnömotoraks gelişen hastalardan oluşuyordu. Grup 2 (COVID-19-pnömotorakssız grup), aynı dönemde yoğun bakım gerektiren ancak pnömotoraks gelişmeyen akciğer tutulumlu ardışık hastalardan oluşuyordu. Hastaneye yatış gününde, yoğun bakım ünitesine sevk gününde ve yoğun bakım ünitesinde yatışın beşinci gününde biyokimya test sonuçları değerlendirildi. Göğüs bilgisayarlı tomografide akciğer parankim tutulum oranları, drenaj süresi, yoğun bakım ünitesinde yatış süresi ve morbidite/mortalite verileri incelendi.

***Bulgular:*** COVID-19'lu hastaların 2342'si kliniğimize kabul edilirken, 460'ı yoğun bakıma gereksinim duydu. Yirmi bir hastada pnömotoraks gelişti (tüm hastaların %0.34'ü ve hastanede yatan hastaların %0.9'u). Pnömotorakslı COVID-19'lu hastalarda bilgisayarlı tomografide anlamlı tutulum yaygınlığı, ferritin ve D-dimer artışı ve düşük lenfosit (%) değerleri gözlendi. Pnömotoraks gelişimi ve ferritin ve D-dimer yüksekliği, regresyon analizinde mortalite ile en fazla ilişkiliydi. Pnömotoraks gelişen ve gelişmeyen COVID-19'lu hastalar arasında akciğer ekspansiyon güçlüğü açısından anlamlı bir fark vardı.

***Sonuç:*** Biyokimya parametreleri kötüleşen COVID-19'lu hastalarda mortalite ile ilişkili olabilen pnömotoraks gelişebilir ve ekspansiyon güçlüğü yaşanabilir.

***Anahtar sözcükler:*** COVID-19, pnömotoraks, SARS-CoV-2.

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**Correspondence:** Osman Yakşi, MD. Bolu Abant İzzet Baysal Üniversitesi Tıp Fakültesi, Göğüs Cerrahisi Anabilim Dalı, 14030 Bolu, Türkiye.
Tel: +90 505 - 309 88 61 e-mail: oyaksi@hotmail.com

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Novel coronavirus 2019 (COVID-19) disease caused by the agent severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was first reported in the Wuhan city of China in December 2019. The World Health Organization (WHO) declared this viral pneumonia a pandemic in March 2020.[1] The COVID-19 outbreak subsequently spread rapidly across the world, exhibiting a broad spectrum of severity.

The most common respiratory symptoms among hospitalized patients are cough, respiratory difficulty, and fever.[2] Pneumothorax is a life-threatening medical emergency characterized by air accumulation in the pleural space and collapse of the lung.[3] The incidence of pneumothorax has increased during the COVID-19 pandemic, particularly among mechanically ventilated individuals with COVID-19 infection.[4] Mechanical ventilation results in harmful effects on the lung, and pneumothorax is a well-described complication of lung ventilation.[5] While cases of spontaneous pneumothorax have been reported in the context of infections, including COVID-19, the likelihood of pneumothorax increases due to a combination of parenchymal injury resulting from underlying infection and the inflammatory response, together with positive pressure ventilation.[6,7] Pneumothorax may be a poor prognostic factor in COVID-19 patients, and one that can be missed, particularly in individuals under mechanical ventilation.[8]

In the present study, we aimed to investigate the incidence of pneumothorax in COVID-19 patients, the radiological factors, its effect on the course of the disease, differences with other pneumothorax patients, and the impact on mortality.

## PATIENTS AND METHODS

This single center, retrospective study was conducted at Bolu Abant Izzet Baysal University Faculty of Medicine, Department of Thoracic Surgery between March 2020 and January 2021. A total of 6,108 COVID-19 patients (3,050 males, 3,058 females; mean age: 49±17.6 years, range, 12 to 89 years) who presented to our hospital were included. Of the patients, 2,342 were admitted to the ward and 460 to the intensive care unit (ICU). A written informed consent was obtained from each patient. The study protocol was approved by the Ministry of Health of Republic of Turkey and Bolu Abant Izzet Baysal University Clinical Ethics Committee (date, no: 02.02.2021, 2021/31). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients were divided into two groups. Group 1 (the COVID-19-pneumothorax group) consisted of patients developing pneumothorax while under treatment for COVID-19 in our hospital. All patients developing pneumothorax during COVID-19 treatment were included in this group. Group 2 (COVID-19-without pneumothorax group) consisted of consecutive patients with pulmonary involvement during the same period, requiring intensive care, but not developing pneumothorax. The patients in Groups 1 and 2 were examined retrospectively in terms of age, sex, polymerase chain reaction (PCR) results, presence of additional disease, days of intensive care, duration of hospitalization/mortality, and intubation status. Ferritin, D-dimer, white blood count (WBC), fibrinogen, lymphocyte, and C-reactive protein (CRP) data were retrieved. Data were recorded for day of hospitalization (admission), day of transfer to intensive care (intensive care 1), and day five of intensive care (intensive care 5). Pulmonary involvement was classified as percentages of findings at thoracic computed tomography (CT) 0 to 20% Grade 1, 20 to 40% Grade 2, 40 to 60% Grade 3, 60 to 80% Grade 4, and above 80% Grade 5.

Group 1 and Group 2 were compared in terms of age, sex, biochemical values, degree of thoracic CT pulmonary involvement, and mortality.

### Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. Data of COVID-19-pneumothorax and COVID-19 without pneumothorax including sociodemographic characteristics, laboratory results, and CT lesions level were analyzed. The Student t-test was used for normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. The chi-square test was used to analyze categorical variables. Linear regression analysis was used for mortality in COVID-19 patients. A $p$ value of $<0.05$ was considered statistically significant.

## RESULTS

Of all patients, 219 died during the study period with a mortality rate of 3.58%. Pneumothorax developed in 0.35% of all patients, and in 0.9% of hospitalized patients. In the majority of patients, COVID-19 was diagnosed based on the PCR testing of nasopharyngeal swabs. The PCR tests were positive in 19 of the 21 patients in Group 1 and in all 20 patients in Group 2.

**Table 1. Sociodemographic and clinical characteristics of COVID-19 patients with and without pneumothorax**

| | COVID with pneumothorax | | COVID without pneumothorax | | | |
|---|---|---|---|---|---|---|
| | n | Mean±SD | n | Mean±SD | F/X² | *p* |
| Age (year) | | 67.5±13.0 | | 71.8±11.3 | 0.384 | 0.269 |
| Sex | | | | | | |
| Male | 14 | | 10 | | | |
| Female | 7 | | 10 | | | |
| Mortality | 18 | | 2 | | 28.003 | 0.001 |
| Computed tomography (%) | | 3.4±1.2 | | 2.7±0.8 | 120.00 | 0.043 |
| WBC presentation | | 10.9±5.1 | | 10.2±7.0 | 175.00 | 0.361 |
| WBC intensive care 1 | | 14.3±7.0 | | 8.8±3.5 | 7.84 | 0.03 |
| WBC intensive care 5 | | 15.5±8.5 | | 12.2±7.9 | 0.286 | 0.296 |
| Lymphocyte percentage presentation | | 10.6±6.6 | | 14.4±6.7 | 0.08 | 0.077 |
| Lymphocyte percentage intensive care 1 | | 8.0±7.5 | | 12.2±8.0 | 130.00 | 0.037 |
| Lymphocyte percentage intensive care 5 | | 6.5±6.2 | | 9.1±6.2 | 0.02 | 0.191 |
| Ferritin presentation | | 662.4±574.3 | | 554.1±539.1 | 197.50 | 0.744 |
| Ferritin intensive care 1 | | 1,110.1±692.3 | | 733.9±582.9 | 141.00 | 0.071 |
| Ferritin intensive care 5 | | 1,124.3±652.0 | | 569.9±473.7 | 104.0 | 0.006 |
| D-dimer presentation | | 5.1±7.4 | | 2.5±2.2 | 186.50 | 0.539 |
| D-dimer intensive care 1 | | 6.1±9.4 | | 2.9±2.9 | 933 | 0.334 |
| D-dimer intensive care 5 | | 3.5±5.3 | | 4.2±4.8 | 0.09 | 0.764 |
| Fibrinogen presentation | | 470.7±172.5 | | 726.0±0.0 | 4.00 | 0.064 |
| Fibrinogen intensive care 1 | | 592.9±145.1 | | 594.0±43.8 | 2.99 | 0.992 |
| Fibrinogen intensive care 5 | | 573.0±136.5 | | 491.0±254.4 | 0.275 | 0.600 |
| CRP presentation | | 96.7±67.2 | | 136.2±74.4 | 0.155 | 0.082 |
| CRP intensive care 1 | | 145.7±125.6 | | 57.4±45.9 | 79.00 | 0.01 |
| CRP intensive care 5 | | 102.6±72.4 | | 46.0±57.6 | 1.83 | 00.09 |
| Intensive care days | | | | | 132.50 | 0.043 |

PX: Pneumothorax; SD: Standard deviation; CT: Computed tomography; WBC: White blood cell; CRP: C-reactive protein; Student t-test for normally distributed data, and the Mann-Whitney U-test for non-normally distributed data.

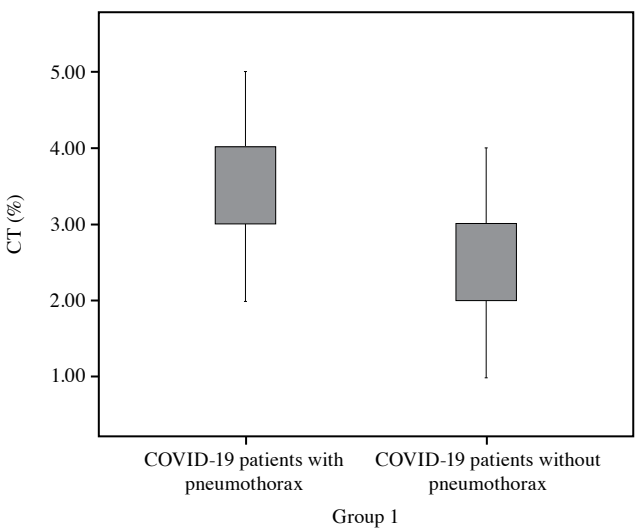


**Figure 1.** Percentage of pneumonia on thoracic CT of COVID-19 patients with and without pneumothorax.
CT: Computed tomography.

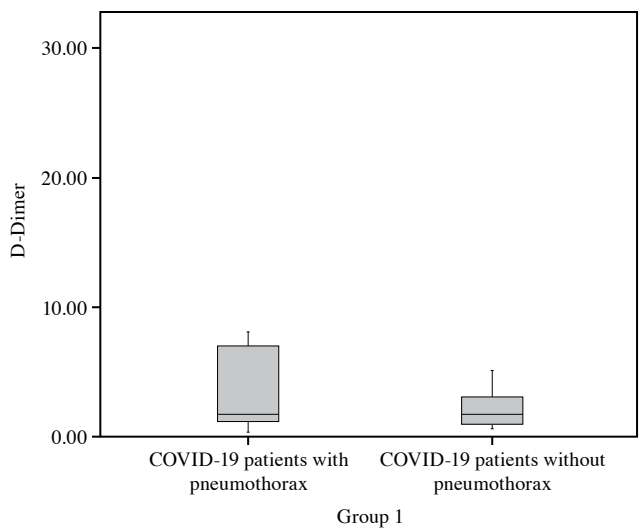


**Figure 2.** D-dimer level of COVID-19 patients with and without pneumothorax.

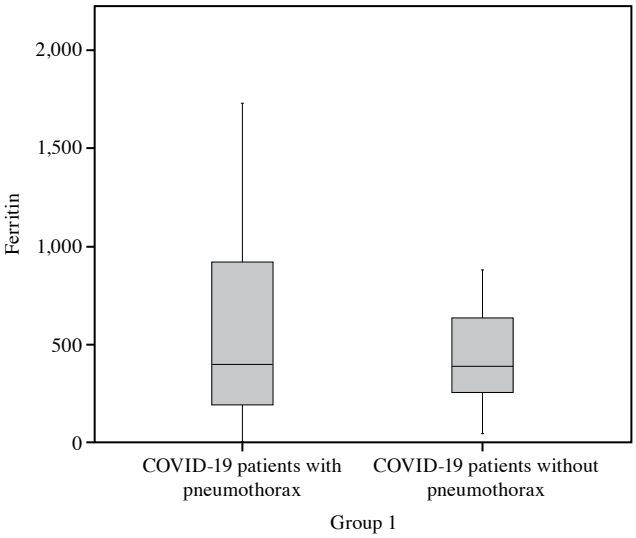


**Figure 3.** Ferritin level of COVID-19 patients with and without pneumothorax.

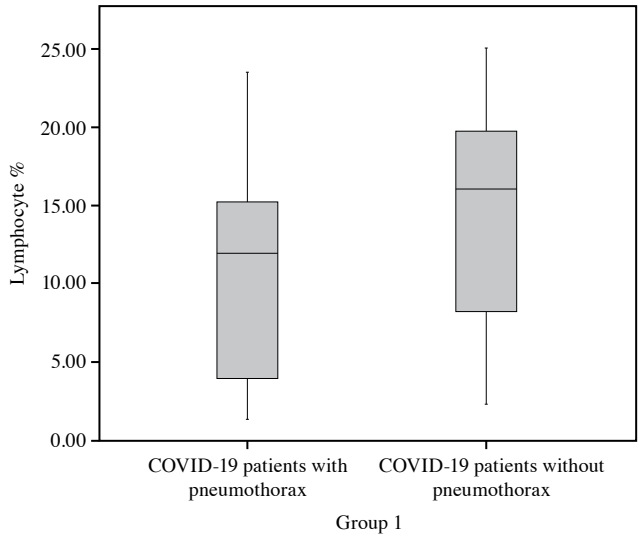


**Figure 4.** Lymphocyte percentages of COVID-19 patients with and without pneumothorax.

Comparison between Groups 1 and 2 revealed significantly higher ferritin and D-dimer levels, low lymphocyte (percentage) values, and increased spread of involvement on CT in the pneumothorax group ($p<0.005$) (Table 1) (Figures 1-4).

Mortality occurred in 18 of the 21 patients in Group 1 (85.7%) and in two of 20 patients in Group 2 (10%). Pulmonary expansion deficit developed in 17 of 21 patients in Group 1 and air leakage persisted. Empyema developed in one of these patients, pulmonary abscess

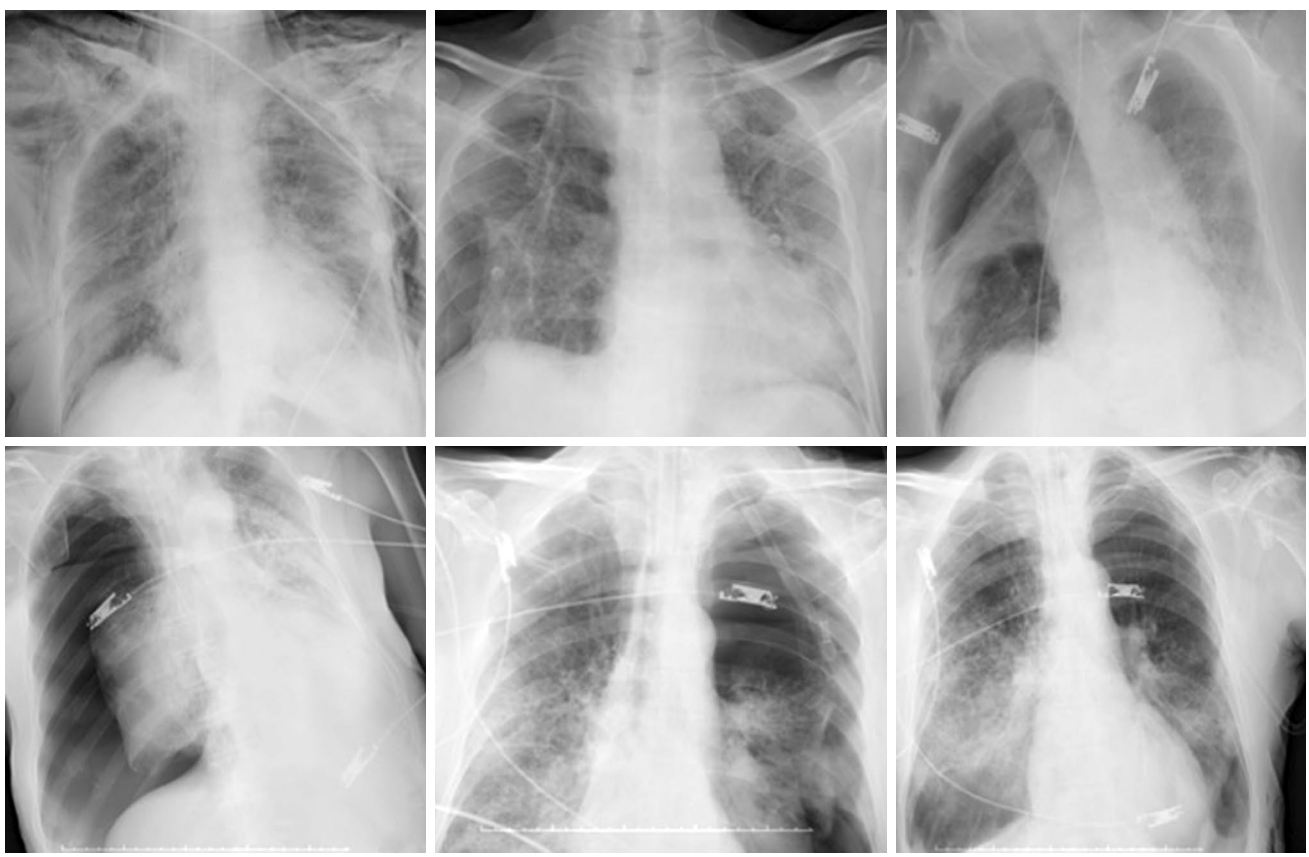

**Figure 5.** Thoracic computed tomography images of COVID-19 patients with pneumomediastinum and pneumothorax.

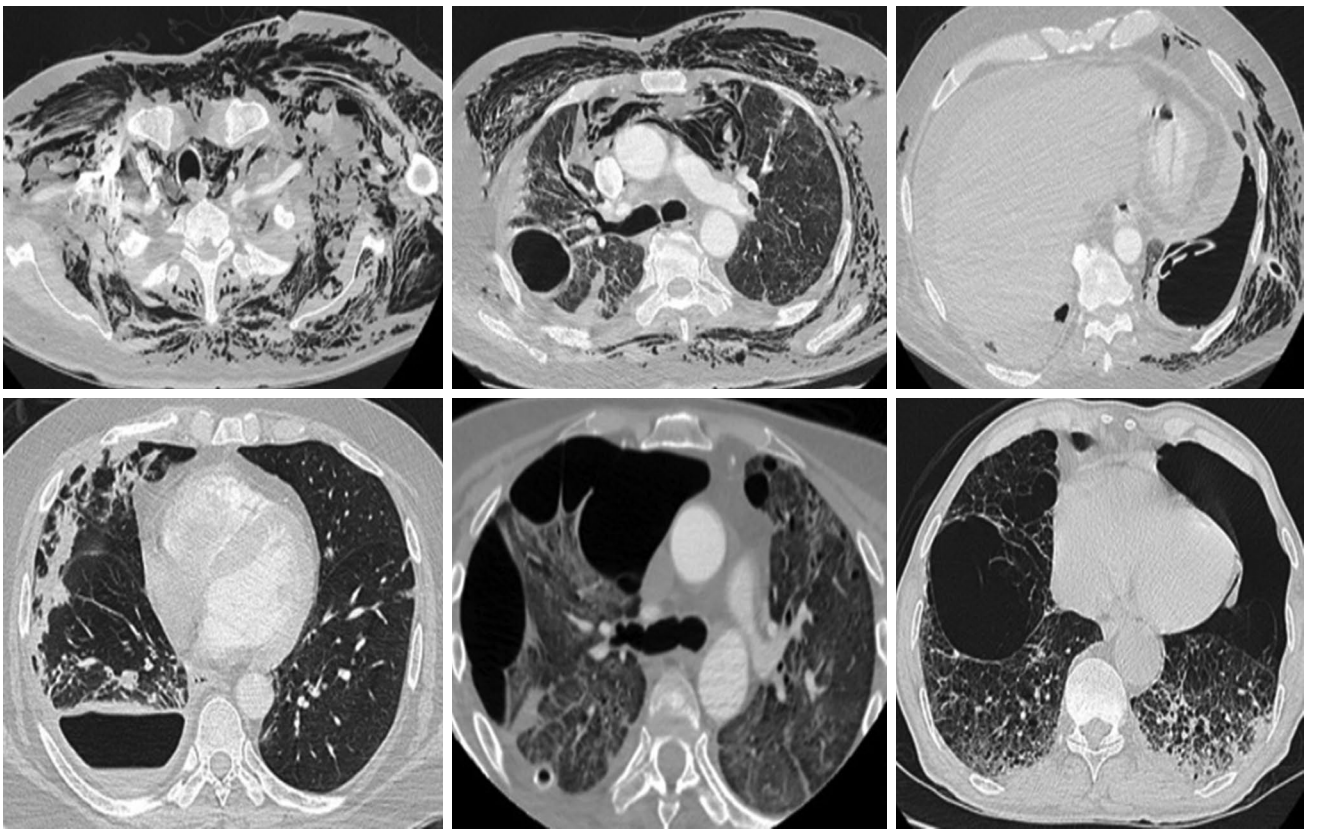

**Figure 6.** Chest X-ray images of COVID-19 patients with pneumomediastinum and pneumothorax.

in one, and subcutaneous emphysema in one, and pneumomediastinum in two. Air leakage persisted in the majority of Group 1 patients (80.9%, 17/21), while pulmonary expansion did not occur, and the chest drains were not removed (Figures 5 and 6).

Four patients under mechanical ventilation among 17 patients in Group 1 developed pneumothorax during follow-up in the ward. All patients developing pneumothorax required ICU stay. Seven patients in Group 2 required mechanical ventilation, while the other patients in that group receiving non-invasive therapies (high-flow oxygen and non-invasive mechanical ventilation) without requiring intubation in the ICU.

**Table 2. Predictors of mortality in COVID-19 patients with linear regression models**

| Variable | B | SEB | β |
|---|---|---|---|
| Pneumothorax | -0.930 | 0.092 | 0.930* |
| Ferritin | 0.000 | 0.000 | 0.0.165* |
| D-dimer | -0.30 | 0.008 | 0.0.088* |

B: Beta; SEB: Standart error of beta.

The most common additional disease in both Groups 1 and 2 was hypertension (5/21 and 4/20, respectively).

Regression analysis identified pneumothorax development, and D-dimer and ferritin elevation as being most closely associated with mortality (Table 2).

## DISCUSSION

The first publications were also from Wuhan, China. In a case series of 1,099 patients, invasive mechanical ventilation was applied in 2.3% of cases, with a mortality rate of 1.4%.[9] Lymphopenia developed in 83.2% of patients, and CRP elevation was observed in most. In the present study, 6,108 COVID-19 patients presented to our hospital during the study period. Of the patients, 2,342 were admitted to the ward, while 460 patients were sent to the ICU. Two hundred nineteen patients died during this period with a mortality rate of 3.58%.

Pneumothorax development in COVID-19 patients is uncommon. However, it is more common than non-COVID-19 spontaneous pneumothorax. The SARS-CoV-2 infection may play a direct role in this

increased incidence. In a multi-center study from Spain, pneumothorax developed in 40 of 71,904 patients presenting to emergency departments.[10] The incidence of spontaneous pneumothorax in COVID-19 was higher (34.2 *vs*. 8.2/100,000 per year). Dyspnea, chest pain, low saturation, tachypnea, and leukocyte count elevation were more common in COVID-19 patients who developed spontaneous pneumothorax.

Pneumothorax development in COVID-19 patients has also been linked to poor prognosis.[10] In a study of 3,000 patients, pneumothorax developed in 0.66% of cases.[11] Pneumothorax development in four patients was associated with mechanical ventilation, while pneumothorax was spontaneous in two patients. The mortality rate was 66.6%. In the present study, pneumothorax developed in 0.34% of COVID-19 patients presenting to hospital and in 0.9% of hospitalized COVID-19 patients.

The most common comorbid diseases in a study of 5,700 hospitalized patients were hypertension, obesity, and diabetes.[12] Intensive care was required in 14.2% of cases, and invasive mechanical ventilation in 12.2%. Mortality occurred in 21%. A low lymphocyte count was found to be prognostic. The decrease in lymphocyte values was greater in patients aged over 65 years, and was also prognostic in terms of repeat admissions after discharge. The most common comorbid disease in the present series, at similar rates, in both Group 1 and Group 2 was hypertension (5/21 and 4/20, respectively).

Pneumothorax development is a complication seen in patients undergoing mechanical ventilation. It has been described as a fatal complication in COVID-19 patients. Pneumothorax development was reported in five of 150 ICU patients in a study.[4] Pneumothorax was bilateral in four (80%) of these, and mortality occurred in three (60%). A study from Wuhan in China reported pneumothorax development in 12 (5.9%) of 202 patients under mechanical ventilation.[13] In the present study, pneumothorax developed in 21 of 460 patients in the ICU setting. This yields a rate of 4.5%, consistent with previous studies in the literature.

Düz et al.[14] reported important findings in their meta-analysis concerning D-dimer levels in COVID-19 patients. They suggested that D-dimer elevation was capable of predicting the severity of the disease, and pulmonary complications and thromboembolic events before they occurred. The pooled results of all the studies included revealed significantly higher D-dimer concentrations in more severe COVID-19 patients (SMD: 2.32 μg/mL; 95% confidence interval [CI], 0.72-3.92 μg/mL, p<0.001). D-dimer was found to be significantly higher in patients with severe disease than in all COVID-19 patients (SMD: 2.01 μg/mL; 95% CI, 0.25-3.77 μg/mL, p=0.08). The mechanism involved in the increase in D-dimer in patients with severe disease is still unknown, although the authors suggested that these findings might be useful in the early detection of severe disease and in early treatment. One of the most important findings of the present study is the effect of D-dimer elevation on mortality. D-dimer and ferritin values in both Group 1 and Group 2 were compared on admission to hospital, on the first day of ICU, and on the fifth. Pneumothorax development, and D-dimer and ferritin elevations, were identified as the factors with the greatest effects on mortality at regression analysis.

Management of patients with acute respiratory distress syndrome (ARDS) involves g-protective mechanical ventilation in which tidal volumes are limited to 6 mL/kg, and plateau pressures to 30 $cmH_2O$, as recommended in the current guidelines. Barotrauma is frequently described as a complication in critical ARDS patients resulting from various etiologies. The reported incidence is approximately 10%. Barotrauma is also usually linked to higher airway pressures.[15] It is also a significant cause of pneumothorax in intubated patients and those under mechanical ventilation. In another study of 161 patients in the ICU, mechanical ventilation was performed in 96, nine of whom developed pneumothorax.[16] Eight of these patients died, and one was discharged. The mean age of the patients was 66.6 years. However, mortality was not attributed to pneumothorax, but rather to sepsis secondary to bacterial infection. Acute respiratory distress syndrome and sepsis develop frequently in the intensive care patient group and are factors capable of leading to mortality.

In another case series, cases of pneumomediastinum developed during pneumothorax and COVID-19 pneumonia.[17] Seventy-one cases from 16 centers were investigated retrospectively. The noteworthy finding from that study was that pneumothorax developed during spontaneous respiration in 30% of patients. However, all patients were intubated due to ARDS. Pneumothorax developed during the first week of admission to the ICU. Mortality was higher after the age of 70 years. They also suggested that pneumomediastinum might not be a poor prognostic factor. Pneumomediastinum developed in two patients in the present study, subcutaneous emphysema in one, empyema in one, and lung abscess in one. However,

these data are not sufficient to determine the effect of these complications.

In their study, Ceylan et al.[18] recommended an extra drainage bottle and filter in terms of safe chest tube application. Drains were installed in 13 patients for various reasons (six with pneumothorax), and the mortality rate in this group was 46.1%. Precautions against contamination are taken during all medical procedures in our hospital for the protection of health workers and other patients.

The COVID-19 was usually based on PCR testing of nasopharyngeal samples. The PCR tests were positive in 19 of 21 patients in Group 1 and in all 20 patients in Group 2. Two patients in Group 1 were diagnosed with on the basis of the following reported criteria: typical and frequently reported signs of COVID-19 including bilateral, multifocal, lower lobe and posterior-predominant ground-glass opacities, accompanied by a crazy-paving appearance and consolidations. Atypical chest CT findings in COVID-19 pneumonia include central and peribronchovascular involvement, isolated upper lobe involvement, solitary involvement, lobar consolidation, nodule formation, subpleural sparing, and pleural and pericardial effusion. An awareness of such atypical findings capable of confusion with other diseases is essential, if misdiagnosis is to be avoided.[19]

One series evaluating five patients developing pneumothorax and administered mechanical ventilation showed that pneumothorax was associated with the increased mortality.[4] The authors concluded that further large-series studies were needed to establish whether or not pneumothorax is an independent risk factor. The development of pneumothorax in the present study was found to be predictive of mortality, together with D-dimer and ferritin. The same study also reported that refractory air leak developed after chest tube insertion. Air leak persisted in a large proportion of our cases, and difficulty was experienced in terms of pulmonary expansion.

One of the limitations of our study is that the control group, which was consisted of ICU patients, did not cover all COVID-19 patients hospitalized in the same period. During the pandemic, the treatment protocol varied with the newly discoverd evidences. Therefore, all COVID-19 patients in our study may not have received a single treatment regimen.

In conclusion, the parameters used in our study were mostly associated with mortality (development of pneumothorax, high D-dimer, and low ferritin) in COVID-19 patients. However, surgical decision making is difficult in COVID-19 patients with infected pneumothorax whose general clinical is unstable. We believe that chest surgeons are exposed to this difficulty during the COVID-19 pandemic. Further studies with larger series are needed to draw more reliable conclusions on this subject.

**Declaration of conflicting interests**

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