Original Article

Pneumothorax as a Poor Prognostic Indicator in COVID-19 in Turkey: A Propensity Score Matching Analysis

M Özgel, İ Gülçek[1], M Ağar[2], H Ulutaş[3]

Department of Thoracic Surgery, Malatya Training Research Hospital, Malatya Turgut Ozal University Medical Faculty, Malatya, [1]Department of Thoracic Surgery, Gaziantep City Hospital, Gaziantep, [2]Department of Thoracic Surgery, Elazıg Fethi Sekin City Hospital, Elazıg, [3]Department of Thoracic Surgery, Medical Point Hospital, İzmir Economy University, İzmir, Turkey

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Abstract

Background: Spontaneous pneumothorax in COVID-19 occurs infrequently but in up to 15% of patients dependent on mechanical ventilation (MV). Pneumothorax-related deaths account for 1% of all COVID-19-related deaths. **Aim:** To determine factors associated with pneumothorax in COVID-19 patients and the effect of pneumothorax on early survival. **Methods:** This was a retrospective study of 4799 COVID-19–positive hospitalized patients. The groups were homogenized using propensity score matching (PSM) in two groups comprising 67 COVID-19 patients each. The prevalence of pneumothorax was determined. Multiple logistic regression was used to determine factors associated with pneumothorax. *P* value < 0.05 was taken as significant. **Results:** The prevalence of pneumothorax in COVID-19 patients was 1.6%. Lung disease, comorbidities, and oxygen support, which were significantly different between the two groups before PSM, were homogenized after PSM. In a univariate analysis, symptom duration ($P < 0.001$), neutrophilia ($P < 0.001$), lymphopenia ($P < 0.001$), neutrophil–lymphocyte ratio ($P = 0.003$), ferritin levels ($P = 0.012$), D-dimer levels ($P = 0.011$), MV support ($P < 0.001$), antibiotherapy ($P < 0.001$), length of hospital stay ($P = 0.009$), and death ($P = 0.002$) differed significantly between the groups. Pneumothorax had a significant negative effect on survival (32.8% vs. 59.7%, $P = 0.01$). In a multivariate regression model, factors associated with pneumothorax were duration of symptoms (Adjusted Odds ratio (AOR) 1.68; 95% Confidence Interval (CI): 1.26-2.25; $P = 0.001$), mechanical ventilation (AOR 23.92; 95% CI: 4.12-138.72; $P = <0.001$), dual antibiotics (AOR 8.28; 95% CI: 1.56-43.86; $P = 0.013$), neutrophilia (AOR: 1.08; 95% CI: 1.02-1.14; $P = 0.011$), and lymphopenia (AOR: 0.92; 95% CI: 0.86-0.90; $P = 0.022$). **Conclusion:** The presence of pneumothorax was associated with poor survival in COVID-19 patients. Patients with a prolonged time from symptom onset to treatment and those dependent on mechanical ventilation in intensive care were in the high risk group for the development of pneumothorax.

Keywords: *COVID-19, pneumothorax, prognostic factors, survival*

Introduction

Coronavirus disease 2019 (COVID-19) may cause spontaneous pneumothorax due to many progressive pathological changes in the lungs, such as pneumonia, cystic changes, and enlargement of the blebs.[1,2] Sometimes, in clinically observed severe COVID-19 cases, pneumothorax may develop without clinical or radiological parenchymal changes in the lung.[3,4]

Of patients requiring hospitalization due to COVID-19, spontaneous pneumothorax was reported in 1%, pneumonia in 3%, and mechanical ventilation (MV) in 6%.[5-7] COVID-19 is a cause of secondary spontaneous

Address for correspondence: Dr. İ Gülçek, Department of Thoracic Surgery, Gaziantep City Hospital, 27010, Şahinbey, Gaziantep, Turkey.
E-mail: ilhamgulcek@gmail.com

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pneumothorax.[8] Pneumothorax-related deaths constitute 1% of all COVID-19-related deaths.[9]

Ground-glass infiltrates (peripheral, posteriorly located, and with or without consolidation predominantly affecting the lower lobes) have been seen on chest computed tomography images of COVID-19 patients. In addition, cavitation, halo sign, pleural effusion, and mediastinal lymph adenopathies are seen more rarely.[10] These radiological appearances have been reported to be due to focal edema, organizing pneumonia, and diffuse alveolar damage.[11]

Many studies have reported occurrences of pneumothorax/pneumomediastinum in patients with COVID-19 during the pandemic. Most of these studies were limited by selection bias, as the patients and groups were not homogeneously distributed.[2,3,9] We aimed to obtain more consistent results by homogenizing groups using propensity score matching (PSM) to add to the literature on this subject.

Pneumothorax is an important prognostic factor that determines hospitalization of COVID-19 patients. The variability of biochemical parameters at the pathological level changes the clinical course and increases the complication rate.[12] This study investigated the effect of pneumothorax in COVID-19 patients on their prognosis.

Methods

This was a retrospective study conducted in two centers, namely, Malatya Turgut Ozal University Training and Research Hospital and Inonu University Turgut Ozal Medicine Center, Turkey. Data from patients hospitalized and treated for COVID-19 between March 2020 and January 2022 were analyzed. Both centers use the Ministry of Health COVID-19 Outbreak Management and Operation Guide for the diagnosis and treatment of patients. Patients with a positive COVID-19 test who were hospitalized (in the service unit or intensive care unit) were included in the study. Patients with iatrogenic pneumothorax and outpatients were excluded from the study. Antibiotics were administered to patients with a hospital stay of more than 48 hours and bacterial growth in body fluids (e.g., sputum, blood, or urine). Patients with drug resistance on an antibiogram were switched to dual antibiotics.

The sample size after propensity scoring matching was 67 patients for each group, and in a power analysis, the power of the study with an effect size of 0.5 was determined to be 90%.[13] The study group consisted of patients who had COVID-19 and developed pneumothorax, while the control group consisted of patients who had COVID-19 and no pneumothorax. We evaluated patients' age, gender, smoking habits, status of other diseases, duration of symptoms, presence of pneumothorax, tube thoracostomy duration, length of hospital stay, medical support treatment, need for respiratory support, laboratory test results, and discharge information.

Ethical consideration

The study design met the criteria of the Declaration of Helsinki and was approved by the Ethics Committee of Institutional Review Board of Malatya Turgut Ozal University on the 6th of February 2022 (No. 2022-20). All patients signed an informed consent form.

Statistical analysis

In our study, PSM analysis was performed to reduce potential bias and ensure homogeneity between groups. After calculating the propensity scores for age, gender, smoking, comorbid lung disease, other comorbidities, oxygen support, and oxygen saturation variables, 1:1 groups were matched using a caliper distance of 0.2. A nearest neighbor procedure was used for the matching. Standardized differences were examined to compare patient characteristics before and after matching. Statistical analyses were performed using the SPSS software package (version 22 for Windows) and the program R (version 2.15.2 for Windows). In combining these programs and performing the PSM analysis, we used developer-based software, which was provided via a custom dialog in the SPSS menu.

A Shapiro–Wilk test, histograms, and skewness and kurtosis parameters were used to assess normality. Descriptive statistics such as mean ± standard deviation were used for normally distributed variables, median and range for variables with non-normal distributions, and the number and percentage of patients for nominal variables. Chi-square and Fisher's exact tests were used to analyze the relationships between categorical variables. To evaluate the relationship between continuous variables, a Mann–Whitney *U* test was used if the variables were non-normally distributed, and a Student's *t*-test was used if they were normally distributed. Factors that produced significant results in univariate analyses were included in a multivariate logistic regression model.

The longest hospital stay was considered to be the follow-up period, and early survival was analyzed accordingly. A Kaplan–Meier test was used for survival analysis, and a Cox regression was used to model survival. A *P* value less than 0.05 was considered statistically significant.

Results

We analyzed data from a total of 4799 COVID-19–positive patients. Of these patients, 3.542 (73.8%) were followed up and treated in the service unit and 1257 (26.2%) in the intensive care unit. Pneumothorax

Table 1: Distribution of parameters used in PSM between the two groups before and after matching

	Unmatched comparisons				Matched comparisons			
	COVID-19 + Pneumothorax (*n*=75)	COVID-19 + Non-Pneumothorax (*n*=125)	*P*	Std diff.	COVID-19 + Pneumothorax (*n*=67)	COVID-19 + Non-Pneumothorax (*n*=67)	*P*	Std diff.
Age (years), mean±SD	64.30±15.9	63.04±16.4	0.593	0.080	63.38±15.85	64.37±16.51	0.725	-0.062
Sex, male, *n* (%)	44 (58.7)	70 (56.0)	0.712	-0.054	39 (58.2)	41 (61.2)	0.725	0.060
Smoking, *n* (%)	23 (30.7)	54 (43.2)	0.078	0.270	21 (31.3)	20 (29.9)	0.851	-0.032
Lung Disease, *n* (%)	19 (25.3)	50 (40)	0.035	-0.335	19 (28.4)	15 (22.4)	0.427	0.136
Chronic Disease, *n* (%)	41 (54.7)	95 (76.0)	0.002	-0.426	40 (59.7)	43 (64.2)	0.594	-0.089
Oxygen Support (lt/min)	5.06±1.95	6.19±2.33	0.005	-0.495	5.39±1.62	5.38±2.15	0.980	0.005
SpO_2, %, mean±SD	84.50±12.67	85.65±8.60	0.449	-0.090	85.71±11.49	86.19±9.76	0.797	-0.038

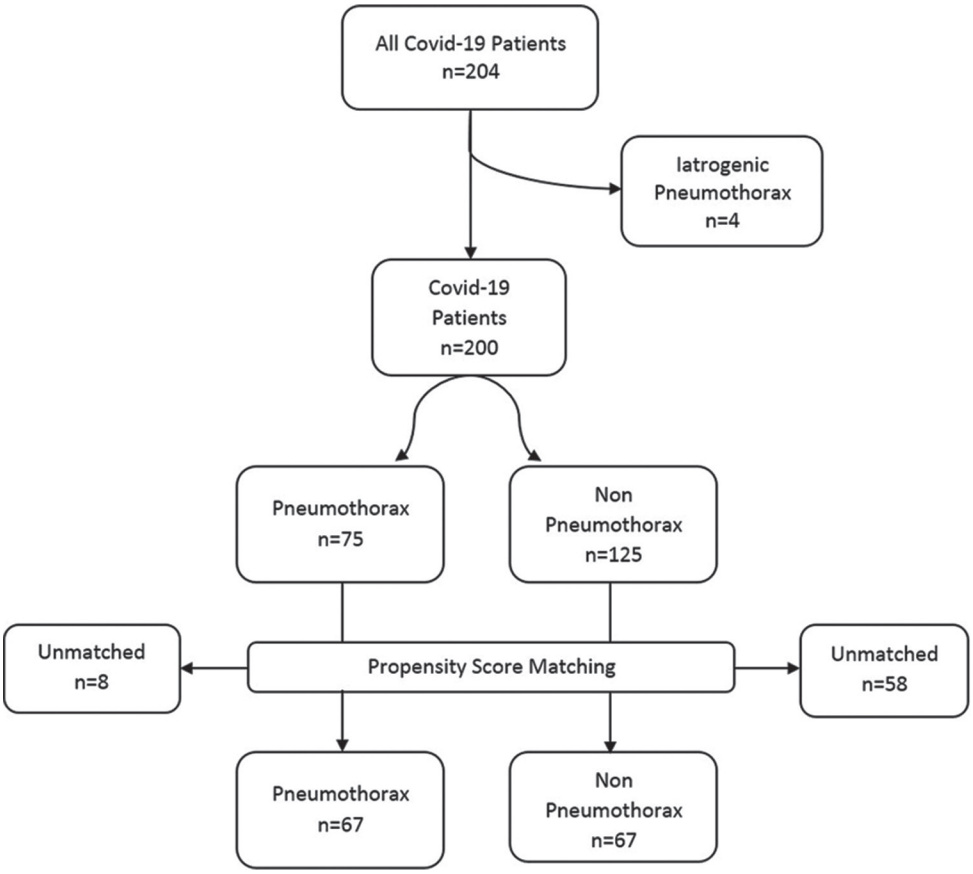

Figure 1: Flow chart

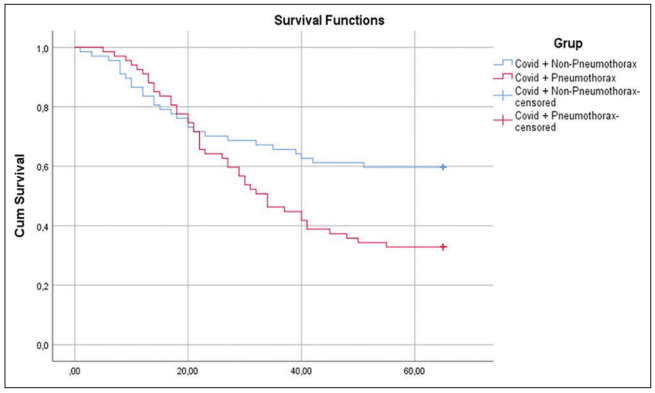

Figure 2: Survival Curves

was detected in 75 (37.5%) of these patients. In general, the prevalence of spontaneous pneumothorax in COVID-19 patients was 1.6%. Four patients with iatrogenic pneumothorax were excluded from the study. After the groups were homogenized using PSM, eight patients from the pneumothorax group and 58 patients from the control group were excluded from the match. The distribution was made so that the number of patients in each of the groups was 67 [Figure 1].

A comparison before PSM showed that lung disease, comorbid diseases, and oxygen support significantly differed between the two groups (P = 0.035,

Table 2: Intergroup comparison of clinical data

	Total (*n*=134)	COVID-19 + Pneumothorax (*n*=67)	COVID-19 + Non-Pneumothorax (*n*=67)	*P*
Duration of Symptoms, (days), mean±SD	4.58±3.18	5.85±3.78	3.33±1.71	<0.001
Radiological findings				
Pleural Effusion, *n* (%)	9 (6.7)	7 (10.4)	2 (3.0)	0.165
Pneumomediastinum, *n* (%)	13 (9.7)	13 (19.4)	0 (0)	<0.001
Ventilation support				
MV, *n* (%)	46 (34.3)	40 (59.7)	6 (9)	<0.001
NIMV, *n* (%)	19 (14.2)	12 (17.9)	7 (10.4)	0.216
Antibiotherapy				<0.001
None	29 (21.6)	5 (7.5)	24 (35.8)	
Mono	47 (35.1)	19 (28.4)	28 (41.8)	
Dual	58 (43.3)	43 (64.2)	15 (22.4)	
Length of stay, (days), mean±SD	18.54±13.35	21.53±14.09	15.55±11.94	0.009
Death, *n*, (%)	72 (53.7)	45 (67.2)	27 (40.3)	0.002

Table 3: Comparison of laboratory findings at admission between groups

	COVID-19 + Pneumothorax (*n*=67)	COVID-19 + Non-Pneumothorax (*n*=67)	*P*
Laboratory findings, (mean±SD)			
Neutrophils, count	11.96±7.13	9.43±6.84	0.038
Neutrophils, %	87.61±9.94	79.76±16.25	0.001
Lymphocytes, count	0.83±1.08	1.31±2.44	0.149
Lymphocytes, %	7.15±6.76	13.12±13.06	0.001
Neutrophils- Lymphocytes Ratio	26.46±26.20	14.78±17.51	0.003
CRP	11.08±8.76	8.82±8.12	0.125
Ferritin	1063.81±680.65	771.70±635.79	0.012
LDH	716.36±1213.48	562.36±540.78	0.345
D-Dimer	4.76±6.02	2.58±3.27	0.011
Troponin	70.88±104.33	631.25±5090.03	0.373
Procalcitonin	23.77±113.44	6.86±39.50	0.252
IL-6	763.19±1711.44	340.33±957.75	0.450

Table 4: Logistic regression analysis of significant variables on pneumothorax

	B	*P*	AOR	95% CI for EXP(*B*)	
				Lower	Upper
Duration of Symptoms	0.518	0.001	1.678	1.249	2.254
Antibiotherapy, Mono	-0.677	0.520	0.508	0.065	3.997
Antibiotherapy, Dual	2.114	0.013	8.282	1.564	43.857
Mechanic Ventilation	3.175	<0.001	23.916	4.123	138.715
Neutrophils, %	0.073	0.011	1.075	1.017	1.137
Neutrophils, count	-0.112	0.069	0.894	0.792	1.009
Lymphocytes, %	-0.079	0.022	0.924	0.864	0.989
NLR	0.001	0.947	1.001	0.964	1.041
Ferritin	<0.001	0.564	1.000	0.999	1.001
D-Dimer	0.034	0.648	1.034	0.895	1.194

P = 0.002, P = 0.005, respectively). After PSM, the differences in these parameters between the two groups disappeared (P = 0.427, P = 0.549, P = 0.980, respectively). There was a more homogeneous distribution after PSM [Table 1].

The mean duration of symptoms before hospital admission was 5.85 days in the pneumothorax group and 3.33 days in the control group. This duration was significantly shorter in the control group ($p < 0.001$). Radiological findings differed between the groups. Pneumomediastinum was observed in 13 (19.4%) patients in the pneumothorax group and none in the control group ($p < 0.001$).

Due to respiratory failure, while 46 (34.3%) patients needed mechanical ventilation (MV), 19 (14.2%) patients were given non-invasive mechanical ventilation (NIMV) support. MV support was given to 40 (59.7%) patients in the pneumothorax group and six (9%) patients in the control group. A statistically significant difference was found between the groups in the need for MV ($p < 0.001$).

In the pneumothorax group, single antibiotic treatment was administered to 19 (28.4%) patients, dual antibiotic treatment was provided to 43 (64.2%) patients, and antibiotic treatment was not required for five (7.5%)

Table 5: Univariate survival analysis and multivariate Cox regression analysis of the presence of pneumothorax in COVID-19 patients

	Mean Survival	%	Univariate Analysis, *P*	Multivariate Analysis (Cox Regression)	
				HR (95% CI)	*P*
COVID-19 + Pneumothorax	38.44	32.8	0.01	1.853 (1.143–2.993)	0.012
COVID-19 + Non-Pneumothorax	46.49	59.7			
Total	42.47	46.3			

patients. In the control group, single antibiotic treatment was given to 28 (41.8%) patients, and dual antibiotic treatment was given to 15 (22.4%) patients. Antibiotic therapy was not required for 24 (35.8%) patients. A statistically significant difference was found between the two groups in antibiotic therapy regimen ($p < 0.001$).

The mean hospital stay was 18.54 days across all patients. While this period was 21.53 days in the pneumothorax group, it was 15.55 days in the control group; this difference was statistically significant ($P = 0.009$).

Early hospital mortality was 53.7%. Mortality was observed in 45 (67.2%) patients in the pneumothorax group and in 27 (40.3%) patients in the control group; this difference was statistically significant ($P = 0.002$). A comparison of the clinical data of patients by group is shown in Table 2.

We compared laboratory findings between the two groups. The neutrophil count was significantly higher in the pneumothorax group than in the control group (11.96 vs. 9.43; $P = 0.038$), and the neutrophil percentage was also significantly higher in the pneumothorax group. The lymphocyte percentage was significantly lower in the pneumothorax group (7.15% vs. 13.12%; $P = 0.001$). While the neutrophil–lymphocyte ratio (NLR) was 26.46 in the pneumothorax group, it was 14.78 in the control group, which was significantly lower ($P = 0.003$). The ferritin and D-dimer levels were also significantly higher in the pneumothorax group (1063 vs 771; $P = 0.012$ and 4.76 vs 2.58; $P = 0.011$, respectively). There were no significant differences between the groups in terms of troponin, procalcitonin, C-reactive protein (CRP), lactate dehydrogenase (LDH), or IL-6 levels. A comparison of the laboratory values of both groups is shown in Table 3.

In a multivariate regression model, factors associated with pneumothorax were duration of symptoms (Adjusted Odds ratio (AOR) 1.68; Confidence Interval (CI): 1.26-2.25; $P = 0.001$), MV (AOR 23.92; CI: 4.12-138.72; $P \leq 0.001$), dual antibiotics (AOR 8.28; CI: 1.56-43.86; $P = 0.013$) neutrophilia (AOR: 1.08; CI: 1.02-1.14; $P = 0.011$), lymphopenia (AOR: 0.92; CI: 0.86-0.90; $P = 0.022$), high neutrophil percentage (AOR: 1.08; 95% CI: 1.02-1.14; $P = 0.011$), and low lymphocyte percentage (AOR 0.92; 95% CI: 0.86-0.99; $P = 0.022$) [Table 4].

The early-term survival analysis was performed based on the longest hospital stay as the follow-up period. Accordingly, the total survival time of the patients was 42.47 days, and the survival rate was 46.3%. When the effect of pneumothorax development on the early survival of COVID-19 patients was examined, the survival time was 46.49 days and the survival rate was 59.7% in the control group, whereas the survival time was 38.44 days and the survival rate was 32.8% in COVID-19 patients with pneumothorax [Table 5]. These differences were statistically significant. The development of pneumothorax was a prognostic factor for poor early survival in COVID-19 patients ($P = 0.01$) [Figure 2].

Discussion

COVID-19 causes serious damage to the respiratory system. As a result of this damage, air can pass into the intrapleural space, and pneumothorax can develop. Treatment of COVID-19 patients who develop pneumothorax is more complicated, and the condition adversely affects the prognosis of the disease. In a study by Geraci *et al*.,[14] the incidence of pneumothorax in COVID-19 patients was reported as 7.4%. In our study, this rate was 1.6%. This difference may be because only patients with spontaneous pneumothorax were included in our study. In the same study, the need for tube thoracostomy was 78% in patients with pneumothorax, while this rate was 88% in our study. Among the heterogeneous groups, the mortality rate of COVID-19 patients with pneumothorax was 58%, which was statistically significantly higher than in COVID-19 patients without pneumothorax.[14] In our study, the groups were homogenized using PSM, and the mortality of COVID-19 patients with pneumothorax was 67.2%, which was statistically significantly higher than in COVID-19 patients without pneumothorax.

In our study, the duration of symptoms before admission into the hospital was significantly longer in the pneumothorax group. No information on this pattern was found in the literature. However, many studies have reported that pneumothorax and pneumomediastinum were observed together during the COVID-19 pandemic. Although the occurrence

of pneumothorax and pneumomediastinum due to COVID-19 is rare, it is an aggravating factor. In studies in which pneumothorax and pneumomediastinum were evaluated jointly, their co-occurrence was reported as 5.1%, while isolated pneumothoraces without pneumomediastinum were reported in some studies.[5,14-18] In our study, the pneumomediastinum rate in the COVID-19 pneumothorax group was 19.4%, and pneumomediastinum was statistically significantly more common in the pneumothorax group according to radiological findings. We suggest that this difference arose because these groups were not homogenized in other studies in the literature.

In patients with pneumothorax due to COVID-19, an increased need for NIMV and MV occurred due to the development of respiratory failure, which adversely affected the prognosis. This rate ranged between 38.4 and 80.5% in other studies and was associated with an increase in mortality rate and a worse prognosis.[12,14,15] In our study, the need for MV was 34.3% in the pneumothorax group, while the need for NIMV was 14.2%; this difference was statistically significant.

In this study, both groups were given single or multiple antibiotics for prolonged hospitalization and nosocomial infections in addition to their antiviral treatments. This was especially common in the pneumothorax group. A statistically significant difference was found between the two groups in the use of single or multiple antibiotics.

Pneumothorax has led to prolonged hospitalization durations for COVID-19 infection. The hospitalization durations reported in the literature for patients that developed pneumothorax due to COVID-19 are longer than for control groups.[14,15,19] Therefore, pneumothorax is a prognostic factor that determines hospitalization length. In our study, the hospitalization duration was significantly longer for patients that developed pneumothorax due to COVID-19, which is consistent with results reported in the literature.[14,15,19]

Neutrophilia and lymphopenia contribute to the development of pneumothorax by causing acute lung injury.[16] Pathological changes arising from these inflammatory markers both trigger the development of pneumothorax in patients with COVID-19 and delay the healing of lung damage during the pneumothorax follow-up and treatment process. Delayed treatment of pneumothorax leads to longer hospitalizations and nosocomial infections, thereby increasing the risk of mortality due to sepsis and acute respiratory distress syndrome. Inflammatory markers, such as levels of neutrophils, lymphocytes, ferritin, and D-dimer and the NLR, differed significantly between the two groups in our study. No significant differences were observed in other laboratory parameters.

The length of symptom duration before admission, use of dual antibiotics, use of MV, and presence of neutrophilia and lymphopenia were factors found to be associated with the development of pneumothorax in this study on multivariate analysis. Similar results were obtained in another study of COVID-19 patients who developed pneumothorax.[18]

Conclusion

The development of pneumothorax in COVID-19 patients, an indicator of poor early-term survival. Serum inflammatory markers of symptomatic patients with delayed access to treatment or mechanically ventilated patients should be closely monitored. Healthcare providers should be aware that the risk of pneumothorax is high in these patient groups.

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Conflicts of interest

There are no conflicts of interest.

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