Spontaneous pneumothorax in COVID-19: a single center experience

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Abstract. – OBJECTIVE: The effect of pulmonary complications of COVID-19, such as pneumothorax, pneumomediastinum, and subcutaneous emphysema, is still unclear. This study aimed at investigating the relationship between COVID-19 and spontaneous pneumothorax.

PATIENTS AND METHODS: This study was conducted as a single-center retrospective study. Groups were assigned as study and control groups. The study group (n=120) included patients who were followed up in ICU and developed pneumothorax during their follow-up. The control group (n=120) included patients who did not develop a pneumothorax in ICU and who had been randomly selected using hospital records. Demographic findings, laboratory parameters, radiological findings, clinical management, patients' follow-up patterns, and survival status of the patients were recorded.

RESULTS: There was a significant relationship between gender, outcome, last hospitalization, general condition, first follow-up, intubation, uptake tomography, uptake rate, CO-RADS, and involvement variables between groups ($p<0.05$). In the survival analysis performed in the control and study groups, a significant difference was obtained between the averages of the two groups (LogRank=3.944, $p<0.05$). Intubation and mortality rates of the patients who developed pneumothorax during the patient follow-ups were significantly higher than the control group.

CONCLUSIONS: We found that patients diagnosed with COVID-19 who developed pneumothorax during intensive care follow-up had a higher hospital stay and intubation rate. The pneumothorax rate was also higher in follow-up methods such as noninvasive/HFO providing PEEP to the patients. The data in our study may help reducing mortality by shedding light on the early prevention and recognition of pneumothorax in critically ill patients diagnosed with COVID-19.

Key Words:
  Pneumothorax, COVID-19.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which started to appear in December 2019, is spreading rapidly around the world and constitutes a serious public health problem for humanity[1]. Complications affecting many organs or systems can be observed in the course of the disease or after treatment of COVID-19. The most affected organ with complications is the lung[2]. In COVID-19, as in other respiratory viral infections, nonspecific symptoms such as fever, dry cough, shortness of breath, myalgia, fatigue and diarrhea may be observed[3]. The incidence of these complications is not known yet, but pneumothorax and pneumomediastinum are among them. The term pneumothorax is defined as the presence of air in the pleural space.

In contrast, pneumomediastinum is the escape of air from the esophagus or airways into the mediastinum, the central chest cavity. Spontaneous pneumothorax is the development of pneumothorax even though there is no trauma or iatrogenic cause. While primary spontaneous pneumothorax occurs without any lung disease, secondary spontaneous pneumothorax occurs as a complication of pre-existing lung disease[4]. Pneumonia, pneumothorax, and pneumomediastinum are rare complications of COVID-19. It has been reported that the mortality rate of patients who develop pneumothorax is high[5,6].

The mechanism of spontaneous pneumothorax and pneumomediastinum in COVID-19 infection is unknown. However, this situation is thought to occur in the server of cystic and fibrotic changes in the lung parenchyma, especially in patients requiring intensive care admission. In particular, studies[7-10] have shown that high peak inspiratory pressure (PIP) (greater than 40-50 cm H_2O), high

positive end-expiratory pressure (PEEP), and increased intrathoracic pressure resulting from invasive and noninvasive mechanical ventilation applied to high tidal volumes increase the incidence of pneumothorax and pneumomediastinum.

Although pneumothorax, pneumomediastinum, and subcutaneous emphysema are rare complications independent from follow-up in COVID-19 patients, they have a high mortality rate, especially in patients requiring intensive care hospitalization. In our study, we investigated the cause of existing complications in patients who were followed up in the second and third-level intensive care units and who developed pneumothorax, pneumomediastinum, and subcutaneous emphysema because of radiological examinations during their follow-up. We tried to determine the relationship between these complications with follow-up methods and laboratory parameters. We also examined the effect on mortality rate and duration.

Patients and Methods

The study was a single-center retrospective study with COVID-19 RT-PCR-positive patients who applied to the COVID-19 clinics in Erzurum City Hospital, in accordance with the Declaration of Helsinki. Patients or their legal representatives were informed about the study verbally and in writing. Erzurum City Hospital Local Clinical Research Ethics Committee (Ministry of Health) approved the study.

240 patients included in the study were divided into study and control groups. In the study group (n=120), patients who were followed up in the second and third-level intensive care units and who developed pneumothorax, pneumomediastinum, and subcutaneous emphysema, as a result of radiological examinations during their follow-up, were included. The control group (n=120) was hospitalized in the second and third-level intensive care units, meeting the inclusion criteria; patients who did not develop a pneumothorax, pneumomediastinum, or subcutaneous emphysema were randomly selected using Microsoft Excel. Patients with a negative PCR test, younger than 18 years of age, incomplete data, and a history of chest, heart, and esophageal surgery and pneumothorax were excluded from the study.

Data were obtained from patients' follow-up forms and electronic medical records by an experienced anesthesiologist in the intensive care unit.

In the patients' follow-up forms, demographic information, laboratory parameters (including complete blood count, C-reactive protein, ferritin, fibrinogen, and D-dimer), and radiological findings (chest radiography) were available. Computed tomography (CT) results were added to the follow-up forms by including the CO-RADS scoring in patients with clinical necessity. In addition, the patient's clinical management, patient follow-up patterns (nasal cannula, mask with reservoir, CPAP/HFO, MV), and survival status were also recorded.

Sample Size

The study's primary aim was to compare the effects of pneumothorax, pneumomediastinum, and subcutaneous emphysema on mortality and morbidity in the control group and COVID-19 patients. A preliminary study was performed on 30 patients from each group in our clinic. The mean hospital stay was 19.43±8.1 days in the control group and 25.10±10.80 days in the study group.

Statistical Analysis

The sample size was calculated using the G*Power 3.1.9.7 analysis program (Heinrich-Heine-Universitat Düsseldorf, Germany) at 95% power and 5% significance level, and the effect size was found to be 0.59. Approximately 65 patients per group were required to obtain significant statistical value. SPSS 25 program was used in the analysis of the data (IBM Corp., Armonk, NY, USA). The Chi-square test, which examines the relationship between two categorical variables, was used in the relationship between demographic variables and groups. The Student's *t*-test or Mann-Whitney U were analyzed to compare the measurements between groups according to normality. The effects of various variables on patients' survival were analyzed using logistic regression and survival status according to the number of days of hospitalization using the Kaplan-Meier method. In statistical analysis, the $p<0.05$ significance level was checked.

Results

In this study, 240 patients were evaluated, and 67 patients were excluded for various reasons. The study, in which 173 patients participated, comprised 108 patients in the control group and 65 patients in the study group. According to

the CONSORT guidelines, the flowchart of the study is given in Figure 1[11]. The Chi-square test analyzed the relationship between patient groups and demographic variables (Table I). There was a significant relationship between gender, outcome, last hospitalization, general condition, first follow-up, intubation, uptake tomography, uptake rate, CO-RADS, and involvement variables between groups ($p<0.05$). According to gender, the proportion of women in the control group is higher than that of men in the study group. While the rate of discharge and death was higher in the control group than in inpatients, the mortality rate was the highest in the study group ($p<0.05$). While the rate of patients whose last hospitalization was in the service and the 3rd step emergency service was higher in the control group than in the 2nd step emergency service, the rate of the 3rd step emergency service patients was the highest in the study group ($p<0.05$). The rate of those with poor general conditions was higher in both control and study groups ($p<0.05$). While the rate of those with a reservoir mask at the first follow-up was highest in the control group, the rate of those with CBAP/HFO was the highest in the study group ($p<0.05$). The intubation rate was higher in both the control and study groups, and the intubation rate was higher in the study group ($p<0.05$). The study group observed that those with access tomography involvement were more common ($p<0.05$). Finally, the rate of bilateral involvement was higher in both groups than in a single group ($p<0.05$).

The groups found a statistically significant difference between CRP, D-dimer, ferritin, fibrinogen, lymphocyte, lymphocyte percentage, and PRC and WBC measurements ($p<0.05$). Accordingly, while the average of CRP, D-dimer, ferritin, fibrinogen, and PRC measurements was higher in the study group, the average of WBC, lymphocyte, and lymphocyte percentage measurements was higher in the normal group. There
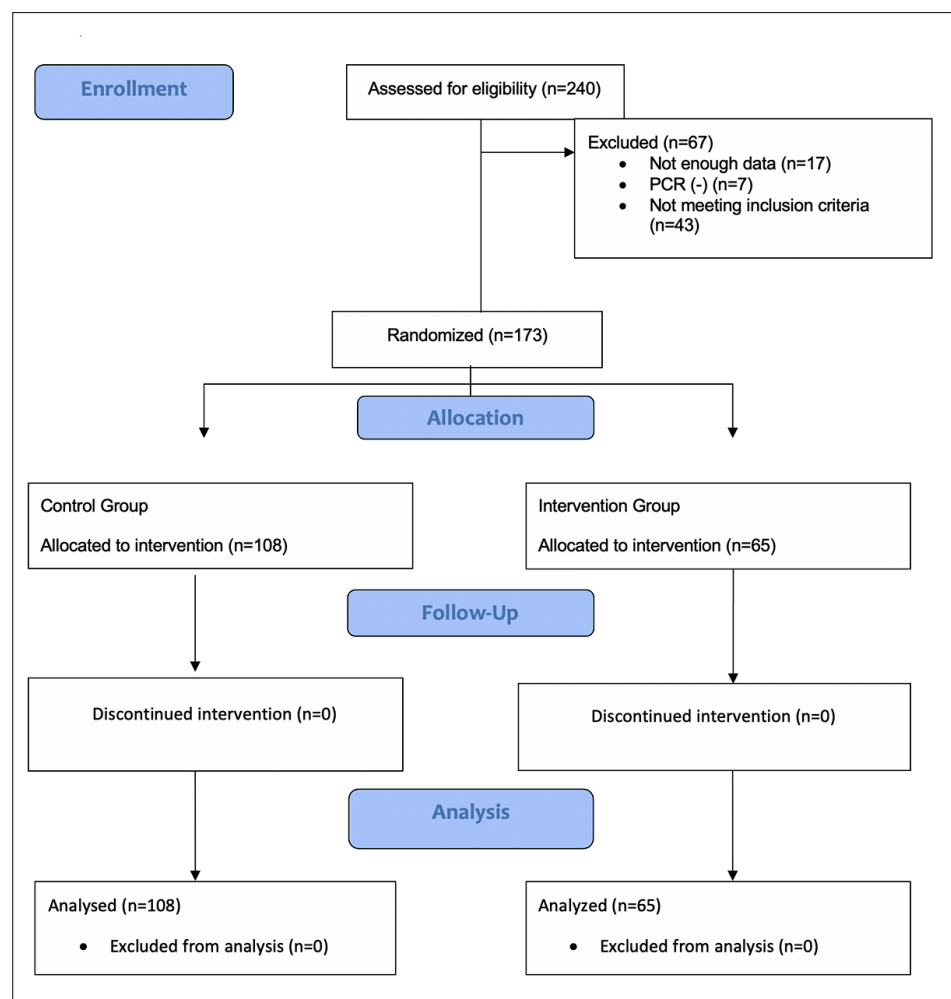

Figure 1. Consort diagram of the study among patients.

Table I. Demographic comparison of the groups.

	Group	Control group n (%)	Study group	*p*
Gender	Female	65 (60.2)	22 (33.8)	0.001*
	Male	43 (39.8)	43 (66.2)	
Survival	Discharge	46 (42.6)	13 (20)	0.000*
	Hospitalization	21 (19.4)	0 (0)	
	Death	41 (38)	52 (80)	
First Hospitalization	Ward	55 (50.9)	41 (63.1)	0.245
	Level 2 ICU	35 (32.4)	14 (21.5)	
	Level 3 ICU	18 (16.7)	10 (15.4)	
Last Hospitalization	Ward	43 (39.8)	1 (1.5)	0.000*
	Level 2 ICU	19 (17.6)	5 (7.7)	
	Level 3 ICU	46 (42.6)	59 (90.8)	
General Condition	Moderate	38 (35.2)	1 (1.5)	0.000*
	Bad	70 (64.8)	64 (98.5)	
First Follow-up	Nasal Cannula	11 (10.2)	0 (0)	0.000*
	Reservoir Mask	41 (38)	12 (18.5)	
	Noninvasive MV/HFO	26 (24.1)	28 (43.1)	
	MV	30 (27.8)	25 (38.5)	
Intibation	No	48 (44.4)	8 (12.3)	0.000*
	Yes	60 (55.6)	57 (87.7)	
CT involvement at first admission	No	2 (1.9)	0 (0)	0.030*
	Yes	83 (76.9)	60 (92.3)	
	Suspicious	23 (21.3)	5 (7.7)	
Lung involvement rate	Mild	31 (28.7)	0 (0)	0.000*
	Moderate	45 (41.7)	29 (44.6)	
	Severe	32 (29.6)	24 (36.9)	
	Very Severe	0 (0)	12 (18.5)	
CO-RADS	3	28 (25.9)	5 (7.7)	0.000*
	4	31 (28.7)	40 (61.5)	
	5	49 (45.4)	20 (30.8)	
Lung involvement	One sided	40 (37)	11 (16.9)	0.005*
	Bilateral	68 (63)	54 (83.1)	

Values were expressed as number and frequency (%). *Chi-square test. ICU: Intensive Care Unit; MV: Mechanical Ventilation; HFO: High Frequency Oscillations.

was a significant difference between the number of hospitalization days and hospitalization SpO_2 measurements according to the patient groups ($p<0.05$) (Table II).

The logistic regression model of age, gender, hospitalization SpO_2, involvement rate, CO-RADS[12,] and amount of attitude variables was significant [$\chi^2_{(6)}=54.295$, $p<0.001$]. The Cox-Snall

Table II. Comparison of laboratory and other measurements between groups.

	Control group	Study group	*p*
CRP	61.8 ± 65.1	80.3 ± 74.6	0.000*
D-dimer	3,863.1 ± 7,524.7	4,683.9 ± 8,115.6	0.000*
Ferritin	664.3 ± 687.3	1,185.8 ± 1,236.2	0.000*
Fibrinogen	388.1 ± 157.1	425.7 ± 185.4	0.000*
Lymphocyte	2 ± 6.9	0.8 ± 0.7	0.000*
Lymphocyte (%)	13.2 ± 13.9	9.4 ± 8.7	0.000*
PRC	287.9 ± 1,065.2	382.7 ± 2,956.1	0.000*
WBC	12.6 ± 20	11.1 ± 6.8	0.005*
Age	68.9 ± 16.1	66.3 ± 16.2	0.303**
Hospitalization days	24 ± 15.1	29.5 ± 14.2	0.019**
Hospitalization SpO_2	83.4 ± 6.2	80 ± 8.5	0.003**

Values were expressed as mean ± standard deviation. *Mann-Whitney U test; **Student's *t*-test. CRP: C-Reactive Protein; PRC: Procalcitonin; WBC: White Blood Cells; SPO_2: Oxygen Saturation.

Table III. Logistic regression.

	B	S.E.	Wald	p	OR	95% CI for OR	
Age	-0.029	0.012	5.457	**0.019**	0.972	0.949	0.995
Gender (Male)	-0.618	0.364	2.88	0.09	0.539	0.264	1.1
Hospitalization SpO_2	0.077	0.029	6.863	**0.009**	1.08	1.02	1.144
Involvement rate			7.871	**0.049**			
Involvement rate (Middle)	-0.074	0.894	0.007	0.934	0.928	0.161	5.358
Involvement rate (Heavy)	-0.832	0.999	0.693	0.405	0.435	0.061	3.086
Involvement rate (Very Heavy)	-3.103	1.444	4.619	**0.032**	0.045	0.003	0.761
CO-RADS			6.208	**0.045**			
CO-RADS (4)	-0.772	0.902	0.732	0.392	0.462	0.079	2.707
CO-RADS (5)	0.386	0.996	0.15	0.698	1.471	0.209	10.356
Lung involvement (Bilateral)	-1.149	0.548	4.401	**0.036**	0.317	0.108	0.927
Constant	-2.807	2.686	1.092	0.296	0.060		
$R^2 = 0.269$ (Cox-Snell)	$\chi^2_{(6)} = 54.295$						
$R^2 = 0.36$ (Nagelkare)	$p = .000$						

CI: Confidence Interval; OR: Odds Ratio; SE: Standard Error.

R squared, and Nagelkerke R squared values indicated how much of the variability in the dependent variable was explained by the independent variables. At least 26.9% and at most 36% of the variability regarding the status of patients in the dead or right group was explained by the variables in the logistic regression model. The correct classification rate of the patients was 72.8% (Table III).

Age (B=-0.029, Wald=5.457, $p<0.05$), hospitalization SpO_2 (B=0.077, Wald=6.863, $p<0.05$), involvement rate (Wald=7.871, $p<0.05$), CO-RADS (Wald the effects of the variables=6.208, $p<0.05$) and the amount of involvement (B=-1.149, Wald=4.401, $p<0.05$) on the survival probability of the patients are significant. The B coefficient for age was negative, and the probability of being alive decreased as the patient's age increased. As the age increases, the probability of being alive [(1-0.972)*100] was 2.8% lower. The B coefficient for hospitalization SpO_2 was obtained as positive, and the increase in the hospitalization SpO_2 values of the patients increases the probability of being alive. An increase in the hospitalization SpO_2 values meant that the probability of survival of the patients [(1.08-1)*100] was 8% higher. Patients with very severe involvement showed a 95.5% lower probability of survival than patients with mild involvement. The probability of survival of moderate and severe patients compared to mild patients was similar and had no effect. The effect of CO-RADS patients on being alive or in the death group was statistically significant, but the probability of being in the right group of patients with

CO-RADS values of 4 and 5 was not significant compared to those with a CO-RADS value of 3. Finally, patients with bilateral involvement were 68.3% less likely to survive compared to those with a single involvement (Table III).

The survival analysis regarding the number of hospitalization days was analyzed by Kaplan Meier analysis (Figure 2). In the survival analysis performed in the control and study groups,
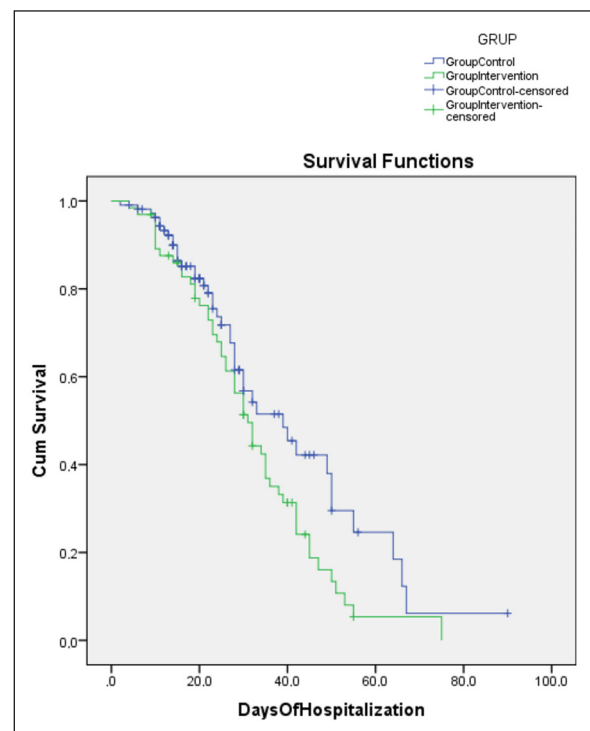

Figure 2. Graph of survival by days of hospitalization.

a significant difference was obtained between the averages of the two groups (LogRank=3.944, $p<0.05$). The mean number of days of hospitalization was 41.12 ± 3.31 for the patients in the control group and 32.77 ± 2.21 for the study group, and the survival rate was higher in the normal group (Table IV).

Discussion

COVID-19, which started in China in December 2019, affected the whole world in a short time and caused a large number of deaths, which has been rapidly increasing all over the world[13]. Although the lung is the most affected organ in COVID-19, the virus can affect many organs, including kidney and liver, causing multi-organ dysfunctions. Refractory hypoxemia and ARDS may occur secondary to lung involvement. ARDS is one of the leading causes of death for critically ill patients with COVID-19[14].

One of the common complications of ARDS is pneumothorax. Although the incidence of pneumothorax varies between 1% and 80% in patients who develop ARDS, it remains significantly mortal[15,16].

Although the incidence is low in patients with a diagnosis of COVID-19, pneumothorax may develop[17]. It usually occurs after fibrotic changes in the lung parenchyma in severe patients who will require intensive care admission. In addition, studies[7,10] have shown that invasive or noninvasive mechanical ventilation increases the incidence of pneumothorax and pneumomediastinum due to high PEEP and PIP.

In a study by Wang et al[18], patients who developed pneumothorax with a diagnosis of COVID-19 were retrospectively screened, and the causes of pneumothorax were investigated. The incidence of pneumothorax in ARDS patients was 10%, 24% in mechanical ventilation patients, and 56% in patients requiring invasive mechanical ventilation. The mortality rate was recorded as 80%. Although such data are compatible with

our study, the follow-up methods were examined in more detail, and the pneumothorax rate in patients followed up with HFO/noninvasive MV was found to be statistically higher than in other forms of follow-up. In addition, our study's mortality rate was higher, in line with the study performed in the group developing pneumothorax. The data in our study and the literature suggest that this fatal picture is associated with follow-up patterns. Considering the current literature, it can be concluded that lung-protective mechanical ventilation can reduce pneumothorax and mortality rates.

In a case series in the literature[19], patients with pneumothorax and pneumomediastinum diagnosed with COVID-19 were examined, and it was determined that the majority of the patients were male, and some accompanying pulmonary comorbidities were found. In addition, the process resulted in mortality in more than half of the patients. Consistent with our study, it can be concluded from this case series that pneumothorax and pneumomediastinum might be possible complications of COVID-19 pneumonia and worsen the prognosis of patients with underlying lung diseases.

In the study conducted by Guven et al[20] comparing the pneumothorax that developed due to mechanical ventilation and developed independently of mechanical ventilation in COVID-19, it was concluded that barotrauma due to mechanical ventilation increased the incidence of pneumothorax, in line with our study. In addition, they also found that in ARDS due to COVID-19, alveolar injury caused by infection, with the contribution of mechanical ventilation, can cause more frequent barotrauma than classical ARDS, and this situation significantly extends the duration of stay in mechanical ventilation and intensive care unit, in line with our study. In order to reduce mortality and morbidity in these patients, mechanical ventilation should be considered within the framework of lung protection strategies, and complications should be diagnosed and treated early.

Table IV. Kaplan-Meier survival analysis.

	Mean estimate ± S.E.	LogRank	*p*
Group Control	41.129 ± 3.311	3.944	0.047
Group Study	32.774 ± 2.216		

S.E.: Standard Error.

In our study, we found that the rate of pneumothorax was higher in patients who followed up with HFO. When we look at other studies[21], there were patients diagnosed with COVID-19 who developed pneumothorax and pneumomediastinum during follow-up with HFO, an open system that provides very low PEEP. However, the literature is controversial in this regard. In some studies[22], inconsistent with ours, it was argued that HFO provides safe and effective respiratory support for critical COVID-19 and has a positive role in related complications, such as pneumomediastinum and pneumothorax. HFO may be associated with a higher incidence of barotrauma compared to standard, low-flow treatments. Because it causes PEEP, it can also contribute to alveolar damage by tearing the alveolar walls in the presence of diffuse neutrophilic infiltrates in the alveoli. On the other hand, it is safer than mechanical ventilation because the PEEP created using HFO is not as high as in closed-system devices. If oxygenation deteriorates rapidly in a patient supplemented with HFO, pneumothorax should be suspected. However, HFNC is a relatively safe and often preferred ventilation method for many patients with respiratory failure due to COVID-19[23].

Our study, which investigated the causes and consequences of pneumothorax, pneumomediastinum, and subcutaneous emphysema in COVID-19, is retrospective, and larger studies can be conducted by increasing the number of patients and the follow-up period after hospitalization.

Conclusions

Our study found that the hospitalization period and intubation rate were higher in patients diagnosed with COVID-19 who developed pneumothorax during intensive care follow-up. In addition, the mortality rate was significantly higher in this patient group. The pneumothorax rate was also higher in follow-up methods such as noninvasive/HFO providing PEEP to the patients. In our study, we summarized the follow-up methods, clinical and laboratory characteristics, and length of stay of COVID-19 patients who developed pneumothorax. The data in our study may help reduce mortality by shedding light on the early prevention and diagnosis of pneumothorax in critically ill patients diagnosed with COVID-19.

Informed Consent
Not applicable.

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