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Retrospective Analysis of Spontaneous Pneumothorax Cases Associated with COVID-19

COVİD-19 ile İlişkili Spontan Pnömotoraks Vakalarının Retrospektif Olarak Analizi

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ABSTRACT

Introduction: Spontaneous pneumothorax is the presence of air in the pleural space without a history of trauma. The risk of developing spontaneous pneumothorax was 40 to 100 times higher in patients with COVID-19 compared to those without.
Objective: Within the scope of this research, we aimed to elucidate spontaneous pneumothorax cases associated with COVID-19 in a retrospective manner.
Method: Patients diagnosed with COVID-19 and spontaneous pneumothorax at our were included in this retrospective analysis. The patients' admission complaints, comorbidities, COVID-19, RT-PCR results, laboratory findings, imaging results, treatment methods applied, and hospitalization or discharge were recorded.
Results: A total of 31 patients aged between 21 and 90 were included in the analysis. Patients were divided into two subgroups: discharge (n=20) and exitus (n=11). While the average hospitalization period of the discharge group was 14.7±22/days, the average hospitalization period of the exitus group was calculated as 2.6±2.1/days ($p<0.001$). While 15 (75%) patients in the discharge group required intensive care follow-up, all in the exitus group required intensive care follow-up ($p=0.133$). A statistically significant difference was detected between the mean values of hemoglobin, INR, D-Dimer, and PLT in the laboratory examinations of the discharge group and the exitus group (p-value; 0.022, 0.004, 0.005, and 0.042, respectively). It was found that there was a strong positive relationship between the length of hospital stay of the patients and laboratory findings, PLR, and NLR (correlation coefficient: 0.818 and 0.818, respectively).
Conclusion: Although many different clinical conditions that develop during COVID-19 infection are in the literature, cases of pneumothorax and pneumomediastinum have been rarely reported. In addition, the possibility of high mortality in these clinical conditions that may be seen in the actively ongoing COVID-19 pandemic should also be taken into consideration.

Keyswords: Pneumothorax, COVID-19, Intensive Care Unit, D-dimer, Acute Respiratory Distress Syndrome.

ÖZET

Giriş: Spontan pnömotoraks, travma öyküsü olmaksızın plevral boşlukta hava bulunmasıdır. Spontan pnömotoraks gelişme riski, COVID-19 hastalarında olmayanlara göre 40 ila 100 kat daha yüksektir.
Amaç: Bu araştırma kapsamında, COVID-19'a bağlı spontan pnömotoraks vakalarının retrospektif olarak aydınlatılması amaçlandı.
Yöntem: Hastanemizde COVİD-19 tanısı alan ve spontan pnömotoraks tanısı alan hastalar bu retrospektif analize dahil edildi. Hastaların başvuru şikayetleri, yandaş hastalıkları, COVİD-19, RT-PCR sonuçları, laboratuvar bulguları, görüntüleme sonuçları, uygulanan tedavi yöntemleri, hastaneye yatış veya taburculuk durumları kaydedildi.
Bulgular: Analize yaşları 21 ile 90 arasında değişen toplam 31 hasta dahil edildi. Hastalar taburculuk (n=20) ve ölüm (n=11) olmak üzere iki alt gruba ayrıldı. Taburcu olan grubun ortalama yatış süresi 14,7±22/gün iken, ölüm grubunun ortalama yatış süresi 2,6±2,1/gün olarak hesaplandı ($p<0,001$). Taburcu olan grupta 15 (%75) hastanın yoğun bakım takibine ihtiyacı olurken, ölüm grubundaki hastaların tamamının yoğun bakım takibine ihtiyacı vardı ($p=0,133$). Taburcu edilen grup ile ölüm grubunun laboratuvar incelemelerinde ortalama hemoglobin, INR, D-Dimer ve PLT değerleri arasında istatistiksel olarak anlamlı fark saptandı (p değeri sırasıyla 0,022, 0,004, 0,005 ve 0,042). Hastaların hastanede kalış süresi ile laboratuvar bulguları, PLR ve NLR arasında güçlü pozitif ilişki olduğu belirlendi (korelasyon katsayısı: sırasıyla 0,818 ve 0,818).
Sonuç: Sonuç olarak, COVID-19 infeksiyonu sırasında gelişen birçok farklı klinik durum literatürde olmakla birlikte pnömotoraks ve pnömomediastinum olguları nadiren bildirilmiştir. Ayrıca aktif olarak devam eden COVID-19 pandemisinde görülebilecek bu klinik durumlardaki olası yüksek mortalite ihtimali de göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Pnömotoraks, COVİD-19, Yoğun Bakım Ünitesi, D-dimer, Akut Respiratuar Distres Sendromu.

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INTRODUCTION

Pneumothorax is defined as free air between the visceral and parietal pleural layers. Spontaneous pneumothorax is the presence of air in the pleural space without a history of trauma. It is divided into primary and secondary spontaneous pneumothorax. While primary spontaneous pneumothorax is more common in young people, secondary spontaneous pneumothorax is mostly observed in the elderly (age>55) population (1). Although the incidence of spontaneous pneumothorax varies in various studies, it is reported as 2.2/100.000 in women and 12.3/100.000 in men. It is known that this peaks especially in young men between 16 and 25 (2). The most common presenting symptoms are sudden chest pain and shortness of breath. Contrary to popular belief, no relationship exists between physical activity and spontaneous pneumothorax (3). Although the pathophysiology of primary spontaneous pneumothorax is unclear, pulmonary bullae and the bursting of subpleural blebs are most blamed (4). The recurrence rate in a patient with pneumothorax increases after each attack. For this reason, surgery is recommended after the second pneumothorax attack (1).

The goal in pneumothorax treatment is to remove the air in the pleural space and prevent pneumothorax from occurring again. For this, tube thoracostomy is performed in the first stage. However, patients with a first attack of pneumothorax who are clinically stable can be monitored by giving O2 therapy without intervention. Publications report that simple thoracentesis and aspiration are as effective as air drainage with a traditional chest tube and have an 80% success rate in these patients. After the second pneumothorax attack, the widely accepted view is to remove the bulla and bleb structures, if any, surgically, and today, the most commonly used method for this is video-assisted thoracoscopic surgery (VATS). Whether surgery is performed or treatment is provided with simple drainage, pleurodesis is recommended (5).

The most blamed factor in the pathogenesis of pneumothorax is the bulla and bleb structures found in the parenchyma. The new coronavirus disease 2019 (COVID-19) may also disrupt the lung parenchyma structure and cause blisters and blebs. The clinical spectrum of the disease varies widely, from asymptomatic cases to severe pneumonia and severe respiratory failure. The incidence of spontaneous pneumothorax development in COVID-19 has been reported as 1%. Most of the reported cases of pneumothorax associated with COVID-19 do not have traditional risk factors or underlying predisposing lung disease (6). The risk of developing spontaneous pneumothorax was 40 to 100 times higher in patients with COVID-19 compared to those without. However, COVID-19 pneumonia, unlike other viral pneumonia, has been associated with an increased incidence of pneumothorax (7).

Pneumothorax or pneumomediastinum may occur spontaneously or due to applied mechanical ventilation in patients with acute respiratory distress syndrome (ARDS) due to COVID-19. In non-COVID-19 ARDS patients, pneumothorax and pneumomediastinum are observed at 2-15% rates, while this was 5-55% in COVID-19 patients (7, 8). A higher rate of pneumothorax and pneumomediastinum is observed in patients with COVID-19 infection who require invasive mechanical ventilation than those without COVID-19 (8). However, the mortality rate was similarly higher in patients with and without COVID-19 who develop pneumothorax and pneumomediastinum (7, 8).

Within the scope of this research, we aimed to elucidate spontaneous pneumothorax cases associated with COVID-19 in a retrospective manner.

METHOD

Patients diagnosed with COVID-19 and spontaneous pneumothorax at Sakarya Training and Research Hospital Emergency Medicine Clinic between March 2020 and March 2022 were included in this retrospective analysis. The patient data were obtained from patient files and data in the hospital automation system. The patients' admission complaints, comorbidities, COVID-19, RT-PCR results, laboratory findings, imaging results, treatment methods applied, and hospitalization or discharge were recorded.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution with protocol number E-

71522473-050.01.04-216241-28. As this was retrospective research, no informed consent was obtained from participants.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Macos 29.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the “Independent Sample T–test” was used for two groups, and the “Pearson Chi-Square Test” was used to compare categorical variables. Normality testing of variables was evaluated with the Kolmogorov Smirnov test. In comparisons between groups, "Independent Sample T-Test" was used for variables showing normal distribution for two groups, "Mann Whitney U-Test" is used for variables that do not show normal distribution, "Chi-Square or Fisher's Exact Test" is used for comparing categorical variables, and "Chi-Square or Fisher's Exact Test" is used for examining the relationship between continuous variables. “Spearman's Correlation Analysis” was utilized. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

A total of 31 patients aged between 21 and 90 were included in the analysis. Patients were divided into two subgroups: discharge (n=20) and exitus (n=11). There was no statistically significant difference between the discharge and exitus groups regarding additional diseases (malignancy, diabetes mellitus, hypertension, chronic pulmonary obstructive disease, palsy, and chronic kidney disease). While the average hospitalization period of the discharge group was 14.7±22/days, the average hospitalization period of the exitus group was calculated as 2.6±2.1/days, and a statistically significant difference was found between them (p<0.001). While 15 (75%) patients in the discharge group required intensive care follow-up, all in the exitus group required intensive care follow-up (p =0.133). The distribution of demographic and clinical findings of the patients according to their final status is denoted in Table 1. When the table is examined, no statistically significant difference was seen in all demographic and clinical findings, except the length of stay, according to the final status of the patients.

Table 1. Distribution of Demographic and Clinical Characteristics of Patients

Variables	Total (n=31)	Discharged (n=20)	Deceased (n=11)	p-value
Spontaneous PNX	27 (87,1)	16 (80)	11 (100)	0,269
Age (year)				0,241
Mean±SD	50,9±22,6	47,4±22	57,5±23,3	
Median (Min-Max)	50 (21-90)	48,5 (21-86)	57 (21-90)	
Duration of Hospitalization				**<0,001**
Mean±SD	10,4±18,5	**14,7±22**	**2,6±2,1**	
Median (Min-Max)	5 (1-99)	**9 (1-99)**	**2 (1-6)**	
Comorbid Diseases				
Malignity	4 (12,9)	2 (10)	2 (18,2)	0,601
DM	16 (51,6)	8 (40)	8 (72,7)	0,171
Hypertension	12 (38,7)	7 (35)	5 (45,5)	0,705
COPD	12 (38,7)	6 (30)	6 (54,5)	0,255
Palsy	3 (9,7)	1 (5)	2 (18,2)	0,281
CKD	7 (22,6)	3 (15)	4 (36,4)	0,210
CORADS				0,088
CORADS-2	3 (9,7)	2 (10)	1 (9,1)	
CORADS-3	8 (25,8)	6 (30)	2 (18,2)	
CORADS-4	9 (29)	8 (40)	1 (9,1)	
CORADS-5	11 (35,5)	4 (20)	7 (63,6)	
PNX				0,707
Left	14 (45,2)	10 (50)	4 (36,4)	
Right	17 (54,8)	10 (50)	7 (63,6)	
Pneumomediastinum	1 (3,2)	0 (0)	1 (9,1)	0,355
Intensive Care Unit	26 (83,9)	15 (75)	11 (100)	0,133
Thoracic Tube	30 (96,8)	19 (95)	11 (100)	1,000
Thoracotomy	1 (3,2)	1 (5)	0 (0)	1,000

PNX: Pneumothorax; SD: Standard Deviation; DM: Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease.

The distribution of laboratory measurements according to the final status of the patients is elaborated in Table 2. When the table was examined, it was observed that there was a statistically significant difference in hemoglobin, international normalized ratio (INR), D-Dimer, and platelet (PLT) measurements between the two groups. A statistically significant difference was detected between the mean values of hemoglobin, INR, D-Dimer, and PLT in the laboratory examinations of the discharge group and the exitus group (p-value; 0.022, 0.004, 0.005, and 0.042, respectively). It was found that there was a strong positive relationship between the length of hospital stay of the patients and laboratory findings, platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) (correlation coefficient: 0.818 and 0.818, respectively).

Table 2. Distribution of Patients' Laboratory Findings

Laboratory	Total(n=31)	Discharged(n=20)	Deceased(n=11)	p-value
Hemoglobin				**0,022**
Mean±SD	13,1±2,2	**13,8±1,8**	**11,8±2,4**	
Median (Min-Max)	13,7 (8,7-16,6)	**14,2 (9,1-16,6)**	**11,2 (8,7-15,7)**	
WBC				0,353
Mean±SD	14,7±7,8	13,4±5	16,9±11,3	
Median (Min-Max)	13,3 (2-37,5)	12,6 (5,9-23,6)	13,8 (2-37,5)	
Lymphocyte				0,934
Mean±SD	2,8±3,4	2,3±1,8	3,6±5,3	
Median (Min-Max)	1,8 (0,2-18,9)	1,8 (0,4-6,7)	1,8 (0,2-18,9)	
CRP				0,510
Mean±SD	77,5±86,1	73,2±83,3	84,2±94,1	
Median (Min-Max)	35 (1,6-331,7)	31 (3,7-256)	60 (1,6-331,7)	
PLR				0,173
Mean±SD	187±189,4	207,6±181,8	149,7±206,1	
Median (Min-Max)	125,7 (10,9-750)	138,6 (32,4-652,3)	72,5 (10,9-750)	
Troponin				0,087
Mean±SD	66,1±181,5	25,7±67,8	139,5±284,4	
Median (Min-Max)	8 (0,1-872)	6,7 (0,1-309)	11,3 (4,6-872)	
Ferritin				0,591
Mean±SD	453,5±551,6	306±338,2	721,5±756,9	
Median (Min-Max)	185 (13-1941)	186,5 (35-1461)	167 (13-1941)	
INR				**0,004**
Mean±SD	1,3±0,2	**1,2±0,1**	**1,4±0,2**	
Median (Min-Max)	1,3 (1,1-1,7)	**1,2 (1,1-1,6)**	**1,4 (1,2-1,7)**	
NLR				0,804
Mean±SD	8,3±8,9	8,2±8,8	8,4±9,4	
Median (Min-Max)	4,3 (0,3-33)	4,6 (0,3-28,4)	4,3 (0,3-33)	
GFR				0,087
Ortalama±SS	100,7±44,5	106,8±23	89,6±68,7	
Medyan (Min-Max)	106 (12,6-259)	111,4 (63-132,1)	96,3 (12,6-259)	
D-Dimer				**0,005**
Mean±SD	2358,3±3353,2	**1535,5±2170,5**	**3854,3±4578,6**	
Median (Min-Max)	895 (103-14400)	**664,5 (103-8360)**	**1647 (884-14400)**	
Lactate				0,066
Mean±SD	2,9±2,5	2,1±0,8	4,5±3,6	
Median (Min-Max)	2 (1,1-10,6)	1,8 (1,1-3,7)	2,7 (1,1-10,6)	
Neutrophil				0,478
Mean±SD	10,6±6,3	9,9±4,6	12±8,8	
Median (Min-Max)	9,3 (1,2-31,9)	9,5 (3,2-20,5)	7,7 (1,2-31,9)	
PLT				**0,042**
Mean±SD	243,1±106	**271,5±103,3**	**191,4±94,2**	
Median (Min-Max)	226 (25-545)	**246,5 (146-545)**	**182 (25-377)**	

SD: Standard Deviation; WBC: White Blood Cell; CRP:C-reactive Protein; PLR: Platelet-to-lymphocyte Ratio; INR: International Normalized Ratio; NLR: Neutrophil-to-lymphocyte Ratio; GFR: Glomerular Filtration Rate; PLT: Platelet.

The correlation analysis evaluated the relationship between the length of stay and laboratory measurements of the patients (Table 3). As a result of the significant relationship between the variables, a positive correlation coefficient indicates a positive linear relationship between the variables, and a negative correlation indicates a reverse linear relationship. The value ranges of the correlation coefficient are expressed as follows;

Correlation coefficient;

- If it is between 0.00-0.29, the relationship is weak,
- If it is between 0.30-0.49, the relationship between two variables is low,
- If it is between 0.50-0.69, the relationship between two variables is medium,
- If it is between 0.70-0.89, the relationship between the two variables is strong and
- The fact that it is between 0.90 and 1.00 indicates that the relationship between the two variables is very strong.

Table 3. Investigation of the Relationship between Length of Stay and Laboratory Findings

		Duration of Hospitalization	PLR	NLR	D-Dimer	Ferritin
Duration of Hospitalization	Correlation Coefficient	1,000	0,062	-0,114	**-0,438**	-0,054
	p-value		0,742	0,541	**0,014**	0,772
PLR	Correlation Coefficient	0,062	1,000	**0,818**	-0,317	-0,069
	p-value	0,742		**<0,001**	0,082	0,711
NLR	Correlation Coefficient	-0,114	**0,818**	1,000	0,000	-0,090
	p-value	0,541	**<0,001**		0,998	0,631
D-Dimer	Correlation Coefficient	**-0,438**	-0,317	0,000	1,000	**0,359**
	p-value	**0,014**	0,082	0,998		**0,047**
Ferritin	Correlation Coefficient	-0,054	-0,069	-0,090	**0,359**	1,000
	p-value	0,772	0,711	0,631	**0,047**	

PLR: Platelet-to-lymphocyte Ratio; NLR: Neutrophil-to-lymphocyte Ratio.

When the table was examined, it was determined that there was a low inverse relationship between the length of stay and D-dimer, a strong linear relationship between PLR and NLR, and a low linear relationship between D-dimer and ferritin.

DISCUSSION

The mortality rate in COVID-19 patients who developed pneumothorax and pneumomediastinum was approximately 10% higher than in COVID-19 patients who did not develop these complications (60% vs. 53%) (9). This situation appears to be similar in patients without COVID-19 (7,8). The median hospital stay of patients who developed pneumothorax and pneumomediastinum was found to be 39.5 days, and their mortality was high at 75%. COVID-19-related pneumothorax appears to be associated with an increased likelihood of long-term hospitalization and death (10). Pneumothorax associated with COVID-19 tends to be right-sided (11). Miro et al. stated that COVID-19-related pneumothorax was 3.8 times more likely to occur in the right hemithorax among COVID-19 patients (12).

Cases of pneumothorax, pneumomediastinum, and subcutaneous emphysema developing based on COVID-19 pneumonia are rarely reported in the literature and generally in the form of case reports. The largest series in the literature is a study that was obtained by collecting data from 16 separate centers in England and included 71 patients (60 with pneumothorax and 11 with pneumomediastinum) (13). In this study, pneumothorax and pneumomediastinum developing in patients under 70 did not affect mortality due to COVID-19. However, it has been reported that significantly lower survival occurs in patients over the age of 70 who develop pneumothorax and pneumomediastinum.

Alveolar destruction and spontaneous alveolar rupture caused by destructive damage to the lung parenchyma, as well as alveolar damage and rupture caused by positive pressure air given by respiratory support devices, be effective in the mechanism of pneumothorax, pneumomediastinum and subcutaneous emphysema that develop based on COVID-19 (14, 15). Some studies in the literature have reported that complications in COVID-19 patients without comorbidities may occur as a result of widespread parenchymal involvement with progressively developing severe pneumonia (14, 16, 17). In support of these data, our study examined cases of pneumothorax, pneumomediastinum, and subcutaneous emphysema that developed due to the effect of barotrauma during ICU treatment and included cases of COVID-19 complications that were thought to be the result of spontaneous alveolar rupture during home treatment.

In the study conducted by Martinelli et al. (16), it was reported that pneumothorax development based on COVID-19 increased the mortality level in patients with comorbidities such as diabetes mellitus, hypertension, and heart failure, but there was no statistically significant difference. In the case report of Quincho-Lopez et al. (18), 2 patients were evaluated, and the condition of a 55-year-old female patient became critical after the development of pneumothorax due to COVID-19 infection and mortality. The other patient was discharged without any problems. Despite the limitations of a single case report, the observation of mortality in this 55-year-old patient with no comorbidities is noteworthy.

In the case report of Elhakim et al. (19), a COVID-19 patient who developed pneumothorax, pneumomediastinum, and subcutaneous emphysema, which was not related to smoking, comorbidities, and barotrauma with high flow oxygen or mechanical ventilation, was presented. It was reported that this patient was discharged home due to treatment. In our study, it was determined that 8 out of 15 patients who developed pneumothorax, pneumomediastinum, and subcutaneous emphysema during home treatment developed only complications arising from COVID-19 pneumonia, without any additional risk factors for the development of pneumothorax and pneumomediastinum. In the other 7 patients in this group, There were additional risk factors such as asthma, smoking, bullous lung disease, and obesity.

In the study of Vega et al. (20) showing the mortality of pneumothorax, pneumomediastinum, and subcutaneous emphysema due to COVID-19 pneumonia, it was reported that the follow-up of 3 patients with the findings resulted in mortality. What makes this study different from other studies is that it is possible to make a diagnosis directly with thorax CT in case of sudden changes in the general condition of patients during hospital treatment. Transport of seriously ill COVID-19 patients followed in the ICU to thorax CT was not deemed appropriate due to the life-threatening situation it could cause. These cases could be diagnosed with portable chest radiographs taken at the bedside.

In our study, a statistically significant difference was achieved in the mean values of hemoglobin, INR, D-Dimer, and PLT in the laboratory examinations of the discharge group and the exitus group. It was found that there was a strong positive relationship between the length of hospital stay of the patients and laboratory findings, PLR, and NLR. As a result of the significant relationship between the variables, a positive correlation coefficient indicates a positive linear relationship between the variables, and a negative correlation indicates a reverse linear relationship. A low inverse relationship was observed between the length of stay and D-dimer, a strong linear relationship between PLR and NLR, and a low linear relationship between D-dimer and ferritin.

CONCLUSION

As a result, although many different clinical conditions that develop during COVID-19 infection are in the literature, cases of pneumothorax and pneumomediastinum have been rarely reported. In addition, the possibility of high mortality in these clinical conditions that may be seen in the actively ongoing COVID-19 pandemic should also be considered.

DESCRIPTIONS

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