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Araştırma/*Research Article*

Pneumothorax in Coronavirus Disease-19 Patients: A Retrospective Case Series

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Koronavirüs-19 Hastalarında Pnömotoraks: Retrospektif Bir Olgu Serisi

Etik Kurul Onayı: Diyarbakır Gazi Yaşargil Eğitim ve Araştırma Hastanesi Yerel Etik Kurul onayı alındı (15.01.2021-629).
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Hasta Onamı: Çalışmadaki veriler hastanenin bilgi yönetim sistemindeki kayıtlardan ve hasta dosyalarından retrospektif olarak analiz edilmiştir.

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ABSTRACT

Objective: *Pneumothorax may develop secondary to alveolar damage and barotrauma in Covid-19 patients. In this study, in the light of the literature. we aimed to present Covid-19 patients who developed pneumothorax among whom we followed up in the intensive care unit.*
Methods: *Eleven patients among 2680 patients tested positive for Covid-19 in the PCR test and developed pneumothorax in the radiologic examination were included in the study. The data were obtsined from patient follow-up forms and electronic medical records. Demographic data, blood and biochemical parameters, blood culture results, time and location of development of pneumothorax, modality, and duration of pneumothorax treatment, and mortality data were recorded.*
Results: *The frequency of development of pneumothorax was found to be 0.41%. The most common complaint was dyspnea. Comorbidiites were observed in 9 (81.8%) patients and the most common comorbidity was hypertension. It was determined that 3 (27.2%) patients did not smoke, 4 patients(36.3%) were active smokers, and 4 (36.3%) patients were ex-smokers. The mean age was 69±14.8 years, the APACHE II score were 18.8±8.7, the female/male ratio was 3/8, and the the time to pneumothorax development was 10.7±11.8 days. Pneumothorax developed in 3 (27.27%) patients on noninvasive mechanical ventilation and 8 (72.7%) patients on invasive mechanical ventilation. The mean length of stay in the intensive care unit was 21.6±26.5 days. It was found that 10 (90.9%) patients died and the mean time to mortality was 19.5±27.0 days.*
Conclusion: *In Covid-19 infection, lung protective ventilation strategies should be adopted and it should be known that the development of pneumothorax is a late complication that increases mortality and morbidity.*

Keywords: *Covid-19, intensive care, lung-protective ventilation, mortality, pneumothorax*

ÖZ

Amaç: *Covid-19 hastalarında alveolar hasar ve barotravmaya sekonder pnömotoraks gelişebilir. Bu çalışmada, yoğun bakım ünitesinde takip ettiğimiz Covid-19 hastalarından pnömotoraks gelişenlerini literatür eşliğinde sunmayı amaçladık.*
Yöntem: *Çalışmaya PCR testi pozitif olduğu saptanan 2.680 hastadan radyolojik olarak pnömotoraks geliştiği belirlenen 11 hasta dahil edildi. Veriler hasta takip formları ve elektronik tıbbi kayıtlardan alındı. Demografik veriler, tam kan ve biyokimyasalparametreleri, kan kültür sonuçları, pnömotoraks gelişim zamanı ve lokasyonu, pnömotoraks tedavi şekli, mortalite ve süresi kaydedildi.*
Bulgular: *Pnömotoraks gelişme sıklığı %0,41 bulundu. En sık başvuru yakınmasının dispne olduğu saptandı. Dokuz (%81.8)hastada comorbidite olduğu ve en sık gözlenen comorbiditenin hipertansiyon olduğu görüldü. Üç (%27,2) hastanın sigara kullanmadığı, 4(%36,3) hastanın aktif sigara içicisi olduğu ve 4 (%36.3) hastanın sigarayı bıraktığı saptandı. Hastaların yaş ortalamaları 69±14,8 yıl, APACHE II skor ortalamaları 18,8±8,7, kadın/erkek oranı 3/8 ve pnömotoraks gelişene 10,7±11,8 gün bulundu. Üç hastada (%27.27) noninvaziv mekanik ventilasyonda ve 8 hastada (%72,7) invaziv mekanik ventilasyondayken pnomotoraks geliştiği saptandı. Yoğun bakım ünitesinde ortalama kalma süresi 21,6±26,5 gündü. On (%90,9) hastanın eks olduğu ve eks olana kadar ortalama 19,5±27,0 gün geçtiği saptandı.*
Sonuç: *Covid-19 infeksiyonu sırasında hipoksemi tedavi edilirken, akciğer koruyucu ventilasyon stratejileri benimsenmeli ve pnömotoraks gelişiminin mortalite ve morbiditeyi arttıran geç dönem komplikasyon olduğu bilinmelidir.*

Anahtar kelimeler: *akciğer koruyucu ventilasyon, Covid-19, mortalite, pnömotoraks, yoğun*

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INTRODUCTION

Covid-19 (SARS-CoV-2), a zoonotic virus that first appeared in Wuhan City , the capital of Hubei Province in China in December 2019, shows rapid transmission from person to person and causes severe pneumonia. [1,2] As a result of its rapid transmission, after it was seen in other countries of the world, it was declared as a Covid-19 pandemic by the World Health Organization on 11 March 2020. [3] As of now, the disease has infected 115,864,376, and killed 2,573,576 people. [4]

Despite vaccine and antiviral drug studies in the world, transmission has not yet been fully prevented and effective treatment has not been provided yet. Although Covid-19 infection generally shows a good prognosis in most patients, it progresses rapidly in some patients, leading to acute respiratory distress syndrome (ARDS). Hypoxemic respiratory failure, which is the most common complication of COVID-19, is tried to be treated with invasive and noninvasive mechanical ventilation support. However, during this supportive treatment, undesirable conditions such as pneumothorax, pneumomediastinum, subcutaneous emphysema or even pneumopericardium may develop in patients. [7-9]

During the treatment and follow-up of cases with Covid 19, it is necessary to kept in mind and state the importance of rapid diagnosis and treatment options of conditions such as pneumothorax, tension pneumothorax that may cause hypoxemia or mortality by deepening existing hypoxemia. Therefore, in our study, in the light of the literature we aimed to present the patients who were followed up in our level 3 intensive care unit due to Covid-19 and developed pneumothorax during treatment, since March 11, 2020, when the first Covid-19 case was seen in Turkey, until today.

MATERIAL and METHOD

The study was conducted as a single-center retrospective study. Approval of the hospital ethics committee was obtained (15/01/2021-629). In the study, out of 2680 patients who were followed up in our level 3 intensive care unit and tested positive for Covid-19 with the polymerase chain reaction (PCR) test by taking nasopharyngeal and oropharyngeal swap samples, 11 patients who were found to have developed pneumothorax during radiological examination were included in the study. The study was conducted in accordance with the Helsinki Declaration 2008 criteria.

The patients who were <18 years of age, whose final treatment had not been concluded at the time of the study, cases with incomplete data, and had a history of thoracic surgery and pneumothorax were excluded from the study.

The data were obtained from patient follow-up forms and electronic medical records by an experienced anesthesiologist in the intensive care unit. Demographic data, comorbidit(ies, blood group antigens, APACHE II scores, blood biochemistry parameters, neutrophil / lymphocyte ratios, platelet values, smoking history were recorded. Complaints of the patients during admission, blood culture results, need for noninvasive mechanical ventilation,and intubation, mechanical ventilation mode applied to the patients, PEEP values, and length of stay in the intensive care unit were recorded. The radiological images of the patients were examined and the duration of pneumothorax development and the location of the pneumothorax were determined. The pneumothorax treatment approach applied to the patients was recorded. Exited patients were identified and the time of mortality was recorded.

Statistical analysis

SPSS 22.0 for Windows program (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Numerical data were expressed as mean and standard deviation, while categorical data were expressed as frequency and percentage.

RESULTS

The study included 11 patients who were found to have developed pneumothorax as detected during radiological examination from 2680 patients who were followed up in the intensive care unit due to Covid-19. The prevalence of pneumothorax development in patients followed up in the intensive care unit was 0.41%. The demographic and clinical characteristics of the patients are shown in **Table I**.

The mean age of the patients was 69 ± 14.8 years. Three patients were female and 8 were male. Nine (81.8%) patients had comorbidities and hypertension was the most common comorbidity. It was determined that 3 (27.2%) patients did not smoke, 4 (36.3%) patients were active smokers, and 4 (36.3%) patients were ex-smokers.

Table I: Demographic and clinical characteristics of patients

Characteristics	n=11
Age (year)	69±14.8
>65 age	7
Gender (Male/Female)	8/3
Apache II score	18.8±8.7
Comorbidity (Yes/No)	9/2
Diabetes mellitus type 2	2
Coronary artery disease	3
Chronic obstructive pulmonary disease	1
Hypertension	6
Chronic renal disease	2
Smoking	
No smoking	3
Current smoking	4
Ex-smoker	3
ICU days	21.6±26.5
Mortality (Yes/No)	10/1
Time to exitus (day)	19.5±27.0

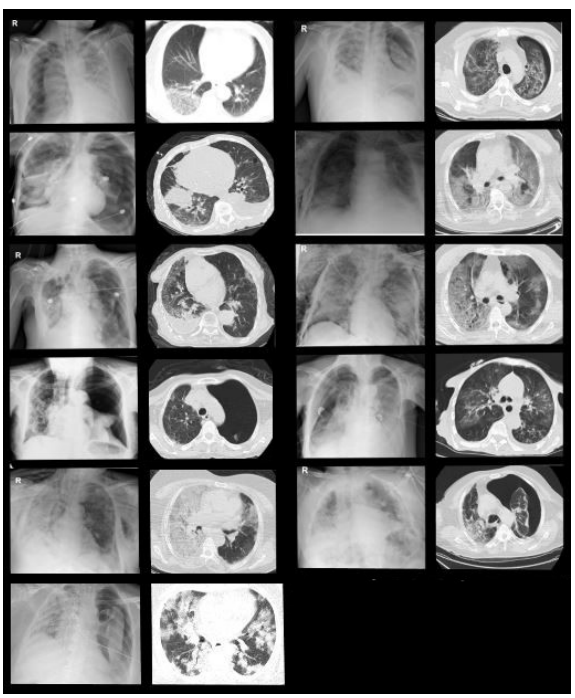
Abbreviation: ICU; Intensive care unit

The average length of stay in the intensive care unit was 21.6 ± 26.5 days. The mean APACHE II score was calculated as 18.8 ± 8.7. It was determined that 10 (90.9%) patients died and the mean time to mortality was 19.5 ± 27.0 days (Table I).The clinical characteristics of the patients are shown in **Table II.** When the complaints of the patients at hospital admission were examined, it was observed that dyspnea was the most common complaint. The time to develop pneumothorax after admission to the intensive care unit was 10.7 ± 11.8 days. It was found that pneumothorax developed during non-invasive mechanical ventilation in 3 patients (27.27%) and during invasive mechanical ventilation in 8 patients (72.7%). It was found that pneumothorax developed in the right lung in 6, and in the left lung in 5 patients (**Figure 1**). The most

Table II: Clinical features of patients with pneumothorax

	n=11
Symptoms at Presentation	
Fever	1
Cough	4
General status disorder	3
Dyspnoea	10
Time to development of pneumothroax (After ICU admission)	10.7±11.8
Location of Pneumothorax (Left/Right)	5/6
Mechanical ventilation (Yes/No)	8/3
Ventilation modes	
P-SIMV	6
PRVC	2
HFOV	2
CPAP	1
PEEP	7.7±4.2
Blood culture results	
Acinetobacter baumannii	6
Klebsiella pneumoniae	2
Sterile	3
Treatment	
Chest drain	10
Conservative	1

Abbreviations: CPAP; Continuous positive airway pressure ventilation, HFOV; High-frequency oscillatory ventilation, ICU; Intensive care unit, PEEP; Positive end expiratory pressure, PRVC; Pressure regulated volume control ventilation, P-SIMV; Pressure synchronized intermittent mandatory ventilation



commonly used mode of mechanical ventilation in intubated patients was P-SIMV (75%). The mean PEEP value of the patients was 7.7 ± 4.2. While chest tube was applied in 10 (90.9%)patients, conservative approach was preferred in 1 patient. When the bacterial growths in blood cultures were examined, Growth of *Acinetobacter Baumannii* was observed in 6 (54.5%) and *Klebsiella Pneumoniae* in 2 (18.1%) patients. No growth was detected in the blood culture of 3 (27.2%) patients. The laboratory parameters of the patients are shown in **Table III.**

Table III: Baseline laboratory data of patients (Mean ± (SD)

	n=11
White blood cells (x10^3/uL)	13.6±7.7
Neutrophil (x10^3/uL)	12.4±7.7
Lymphocytes (x10^3/uL)	0.77±0.45
Neutrophil/Lymphocyte ratio	24.7±25.2
Platelets (x10^3/uL)	221.8±70.0
Hematocrit (g/L)	43.2±4.6
Alanine aminotransferase (U/L)	45.7±41.4
Aspartate aminotransferas (U/L)	49.4±50.0
Lactate dehydrogenase (U/L)	547.5±309.6
Sodium (mEq/L)	135.4±2.9
Potassium (mEq/L)	4.4±0.8
Chlorine (mEq/L)	102.0±5.1
Lactate (mmol/L)	2.7±1.5
Ferritin (µg/L)	1023.0±785.2
D-dimer (ng/mL)	1865.4±3529.7
C-reactive protein (mg/L)	139.0±95.9

DISCUSSION

In this study, we evaluated 11 patients who were found to have developed pneumothorax radiologically among 2680 patients we followed up and treated for Covid-19 disease .

Pneumothorax is a clinical pathology that develops secondary to the accumulation of free air between visceral and parietal leaves in the pleural cavity due to various reasons and occurs as a result of lung collapse. It can be spontaneous or can be seen due to secondary causes. [10]

The mechanism of pneumothorax development in Covid-19 disease has not been fully elucidated. The most likely pathophysiological mechanism is necrotic and fibrotic changes occurring at the alveolar level secondary to infection. Increased intra-alveolar pressure caused by invasive and noninvasive mechanical ventilation applied by clinicians to correct hypoxemia observed as a result of loss of elasticity in the lung tissue and deterioration in oxygenation disrupts alveolar integrity and causes pneumothorax. [11-13] In addition, it is known that barotrauma caused by increased intrathoracic pressure during severe cough episodes in patients induces development of pneumothorax in the alveolar structure that is damaged secondary to infection. [14]

The deterioration of the alveolar structure, which predisposes to the development of pneumothorax, can be detected based on radiological findings such as frosted glass appearance, bilateral and peripheral consolidation, linear opacities, “crazy-paving” pattern and “reverse halo” sign. [15] There is a serious correlation between radiological findings and the prognosis of the disease. All of our patients who developed pneumothorax had radiological findings as a result of alveolar damage secondary to Covid-19 during admission to the hospital.

In the management of acute respiratory failure and ARDS that occur in patients with Covid-19 infection, besides invasive and noninvasive mechanical ventilation, high flow nasal oxygen therapy (HFNO) and oxygen therapy with balloon mask constitute the cornerstones of treatment. Although today’s mechanical ventilators have been technologically developed in accordance with the age of the patients, they may cause barotrauma and ultimately pneumothorax during ventilation depending on patient-induced factors or inappropriate ventilation strategies. It is known that ventilation with high tidal volume (> 12ml / kg), high PEEP pressure, high plateau airway pressure and driving pressure values causes alveolar rupture and ultimately pneumothorax by increasing intra-alveolar pressure. [16-19]

In addition to alveolar damage caused by the disease, barotrauma due to mechanical ventilation and oxygenation strategies, the underlying lung diseases of the patient are also predisposing factors in the development of pneumothorax. Examples of such diseases include chronic obstructive pulmonary disease, interstitial lung diseases, ARDS, other pathologies that can cause parenchymal damage, and obstructive diseases such as asthma. [20] It should be noted that there is a possibility of developing pneumothorax even in lower pressure and tidal volumes in patients with comorbid diseases, which are known to be a facilitating factor in the development of pneumothorax, so appropriate mechanical ventilation strategies should be preferred.

We routinely apply protective lung ventilation strategies, which have an important place in the treatment of patients with ARDS, in our clinical practice. [21] Although we applied a lung protective ventilation strategy (low tidal volume (6 ml / kg), low plateau pressure] and our PEEP pressure was not high (7.7 + 4.4), while 8 patients developed pneumothorax during invasive mechanical ventilation. When we examined the time to the development of pneumothorax , we observed that pneumothorax developed after the 10th day of admission to intensive care. The fact that PIP pressures and lung compliance were not recorded in our study is one of the limitations of our study.

We examined the literature, and found studies in which the development of pneumothorax in patients with Covid-19 was reported during treatment with HFNO, during the days after hospitalization, even after discharge or while taking nasal oxygen for treatment. [22-25] Patients whose primary indication for the patient's admission to the hospital was subcutaneous emphysema secondary to pneumothorax, cases that were admitted to the hospital due to isolated pneumothorax and those with PCR (+), who did not have Covid-19 symptoms have been reported in the literature,. [26,27] These patient groups, included patients with minor and self-limiting pneumothorax who did not require intervention, as well as patients who developed tension pneumothorax. [24] In our study, we found that pneumothorax developed in 8 patients during invasive mechanical ventilation and in 3 patients while applying noninvasive high-frequency oscillatory (HFO) and continuous positive airway pressure (CPAP) ventilation. While 10 patients were urgently treated with closed tube drainage, one male patient was followed up conservatively because he did not have a pneumothorax severe enough to require intervention.

Eight of 11 patients who were included in our study and developed pneumothorax had severe ARDS developing on the background of Covid-19. We think that positive pressure invasive ventilation we applied due to severe alveolar injury contributes to the development of pneumothorax in this group.

When we examined the literature, we have encountered different rates in the prevalence of pneumothorax in patients with Covid-19. In the study conducted by Alessandro Belletti, who evaluated pneumomediastinum and pneumothorax together, they stated that pneumothorax developed in up to 24% of their patients. [28]

Nanshan Chen et al. evaluated pneumothorax alone, unlike Alessandro Belletti, and they stated that pneumothorax developed in 1 out of 99 patients (1%). [29] In another study with a large series of 3500 patients, it was reported that pneumothorax developed in 15 patients (0.43%). [30]

Zantah et al. examined over 3000 patients and stated that 6 of 900 patients with PCR (+) developed pneumothorax and the prevalence of pneumothorax development was 0.66%. [31] In our study, we found that 11 out of 2680 patients had pneumothorax and the prevalence of pneumothorax development was 0.41%, similar to the studies in the literature.

When we evaluated our patients with pneumothorax in terms of comorbidities, we think that smoking may contribute to the development of pneumothorax. Because, we found that 4 out of 11 patients who developed pneumothorax had a history of active smoking, and 4 were ex-smokers. Contrary to our study results, Sethi et al. reported that none of the 10 patients with subcutaneous emphysema and pneumomediastinum they followed up in their study had a smoking history. [32] In our literature review, we

could not find any evidence that smoking facilitates the development of pneumothorax in patients with Covid-19, but the fact that 72.6% of our patients who developed pneumothorax in our study had a smoking history indicates that more studies and data are needed.

Finally, the contribution of the presence of secondary infection to the development of pneumothorax during invasive ventilation by increasing the alveolar damage in our patients cannot be denied. The blood culture antibiograms taken from our patients with pneumothorax revealed *Acinetobacter Baumannii* in 6 patients and *Klebsiella Pneumoniae* in 2 patients, while no microorganism growth was detected in 3 patients. When the patients with no bacterial growth were examined, it was seen that they were transferred from an external center and received broad-spectrum antibiotic therapy. When we examined the patients who developed pneumothorax in terms of survey, we found that 10 patients died and only one of our patients could be discharged from the intensive care unit (90.9%). In our literature review, we found that in parallel with our study, the majority of patients who developed pneumothorax during Covid-19 infection died. [33-34]

In conclusion, pneumothorax is a rare finding that can be seen in patients during COVID-19 infection and treatment. In order to prevent the development of pneumothorax, maneuvers that will increase alveolar damage should be avoided in the ventilation strategies used for the correction of hypoxemia and lung protective mechanical ventilation strategies should be adopted. However, it should be kept in mind that pneumothorax may develop in patients during the application of lung protective mechanical ventilation strategies, even during noninvasive ventilation applications.

We recommend that the development of pneumothorax in the treatment of patients with Covid-19 should be recorded as a late-term complication that can lead to increased mortality and morbidity.

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