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Research Article / Araştırma

Pneumothorax in Patients with COVID-19 in Tertiary Intensive Care

Üçüncü Basamak Yoğun Bakımda COVID-19'lu Hastalarda Pnömotoraks

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ABSTRACT

Objectives: Objective of the study was to examine the laboratory findings with clinical characteristics and treatments of patients who were hospitalized in a tertiary intensive care unit with the diagnosis of coronavirus disease 2019 (COVID-19) and developed pneumothorax and to determine epidemiology and risks of pneumothorax.

Methods: The study was conducted by retrospectively examining the electronic records of 681 COVID-19 patients who were followed up between 1 April 2020 and 1 January 2021 in 3 tertiary intensive care units (each was 24 beds). Patients demographic and clinical characteristics, laboratory findings, mechanical ventilator parameters and chest imaging were evaluated retrospectively.

Results: Pneumothorax in 22 (3.2%) of 681 with COVID-19 patients was detected and acute respiratory distress syndrome (ARDS) in 481 (70.6). All the study patients met ARDS diagnostic criterias. Mortality rates were 43.4% (296/681) in all patients, 52.8% (254/481) in patients with ARDS, and 86.3% (19/22) in patients with pneumothorax. Pneumothorax occurred in the patients within a mean of 17.4±4.8 days. The computed tomographies of patients were observed common ground-glass opacities, heterogenic distribution with patch infiltrates, alveolar exudates, interstitial thickening in the 1st week of their symptom onset.

Conclusion: We observed that pneumothorax significantly increased mortality in COVID-19 patients with ARDS. We believe that understanding and preventing the characteristics of pneumothorax will make an important contribution to mortality reduction.

Keywords: ARDS, COVID-19, intensive care unit, mortality, pneumothorax

ÖZ

Amaç: Çalışmanın amacı, üçüncü basamak yoğun bakım ünitesinde koronavirüs hastalığı 2019 (COVID-19) tanısı ile yatırılan ve pnömotoraks gelişen hastaların laboratuvar bulgularının klinik özellikleri ve tedavileri ile birlikte incelenmesi, pnömotoraks epidemiyolojisi ve risklerinin belirlenmesidir.

Yöntem: Çalışma; 1 Nisan 2020 ile 1 Ocak 2021 tarihleri arasında üç adet üçüncü basamak yoğun bakım ünitesinde (her biri 24 yataklı) takip edilen 681 COVID-19 hastasının elektronik kayıtları geriye dönük olarak incelenerek gerçekleştirildi. Hastaların demografik ve klinik özellikleri, laboratuvar bulguları, mekanik ventilatör parametreleri ve akciğer görüntülemeleri geriye dönük olarak değerlendirildi.

Bulgular: COVID-19 geçiren 681 hastanın 22'sinde (%3,2) pnömotoraks ve 481'inde (%70,6) akut respiratuar distres sendromu (ARDS) tespit edildi. Tüm çalışma hastaları ARDS tanı kriterlerini karşıladı. Mortalite oranları tüm hastalarda %43.4 (296/681), ARDS'li hastalarda %52.8 (254/481), pnömotorakslı hastalarda ise %86,3 (19/22) idi. Hastalarda ortalama 17,4±4,8 gün içinde pnömotoraks gelişti. Semptomların başladığı 1. haftada hastaların bilgisayarlı tomografilerinde yaygın buzlu cam opasiteleri, yama infiltratları ile heterojenik dağılım, alveolar eksüdalar, interstisyel kalınlaşma gözlendi.

Sonuç: ARDS'li COVID-19 hastalarında pnömotoraksın mortaliteyi önemli ölçüde artırdığını gözlemledik. Pnömotoraksın özelliklerinin anlaşılmasının ve önlenmesinin mortalitenin azaltılmasına önemli katkı sağlayacağına inanıyoruz.

Anahtar sözcükler: ARDS, COVID-19, mortalite, pnömotoraks, yoğun bakım ünitesi

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Introduction

The frequency of pneumothorax occurrence due to coronavirus disease 19 (COVID-19) in the first series has been reported to be between 1% and 2%.[1-3] The literature published subjecting pneumothorax in COVID-19 patients with acute respiratory distress syndrome (ARDS) are mostly case reports or case series.[4-6] Among the reported series, the number of cases was high only in a multi-center study, but the patients included were not intubated.[7] While pneumothorax in ARDS patients varied between 1.5% and 77% in previous publications, pneumothorax was reported as 10% in COVID-19 related ARDS.[4,8-10] Both the reported case series and the number of cases was deficient, especially in critically ill patients.[4] Experience on this matter needed to be published.

Herein, we report the largest case series with the diagnosis of COVID-19 related pneumothorax in single center tertiary intensive care units and describe their clinical characteristics and outcomes. These results may shed light on preventing pneumothorax by early diagnosis in critically ill patients, and mortality can be reduced.

Methods

This study was approved by the Local Ethics Committee and conducted with the method of retrospective screening of 681 COVID-19 patients hospitalized between April 2020 and January 2021 in the tertiary care unit of the Ankara City General Hospital. Laboratory-confirmed COVID-19 patients (with real time reverse transcription-polymerase reaction) older than 18 years who were followed by Intensive care unit (ICU) and developed a pneumothorax (with/without pneumomediastinum or subcutaneous emphysema) during the course were included in the study. Patients who had pneumothorax for any reason without COVID-19 were excluded from the study.

Pateints demographics, comorbidities, and the Acute Physiology and Chronic Health Evaluation (APACHE) II scores, laboratory tests (complete blood count, biochemical and coagulation tests, C-reactive protein (CRP), procalcitonin, interleukin-6 levels), and outcomes were recorded. Diagnosis of ARDS was based on Berlin standards. Invasive procedures and all respiratory and mechanical ventilator parameters before baroutrauma were recorded. X-ray and chest computed tomography (CT) scans of all patients were examined. Initial chest CT was taken in all patients between the 1st and the 7th day after hospitalization. The follow-up of the patients was usually performed with a portable X-ray.

Statistical Analysis

Statistical analyses were performed using the SPSS software (version; 15 SSPSS Inc. Chicago) for windows. All variables were checked for normal distribution. Variables were reported as mean and standard deviation or as median when appropriate. Continuous variables were compared with Student's t-test or the Mann-Whitney U test. The Chi-square test was used to test for proportions. A $p \leq 0.05$ was considered as statistically significant.

Results

A total of 681 patients were followed up in the ICU with the diagnosis of COVID-19 and 481 (70.6%) of them patients met ARDS diagnostic criterias and 296 (43.4%) of them died during their follow-up. The mortality of ARDS patients was 254 (52.8%). The overall incidence of pneumothorax was 22/681 (3.2%), 22/481 (4.5%) in patients with ARDS. Nineteen of the 22 patients died during hospitalization, with a mortality as high as 19/22 (86.3%). In 3 of 22 patients with pneumothorax, pneumomediastinum was seen subcutaneous emphysema in 5. All patients who developed pneumothorax were treated with invasive mechanical ventilation (Fig. 1).

Twenty-two of patients with pneumothorax met the diagnostic criteria of ARDS. A total of 22 patients, including 16 (72.7%) males and 6 (27.3%) females, were included in the study. The mean age of the patients was 64.6±10.1 (range:48-85) years. Comorbidities accompanying pneumothorax were type 2 diabetes mellitus in 9 (40.9%), hypertension in 9 (40.9%), cancer in 2 (9.1%) , asthma in 1 (4.5%), chronic renal failure in 1 (4.5%), and coronary artery disease in 1 (4.5%), whereas there were no comorbidities in 4 (18.2%) patients. The study population had an APACHE II score of 18.9±8.3 (Table 1).

The mean duration of admission to ICU was 8±2.6 (3-14) days in the patients with pneumothorax. The duration of started to invasive mechanical ventilation was 9.1±3.4 (3-18) days. Pneumothorax occurred in the patients within a mean of 17.4±4.8 (7-29) days. Length of stay of ICU in the patients with pneumothorax was 42.9±22.3 (16-119) days (Table 1).

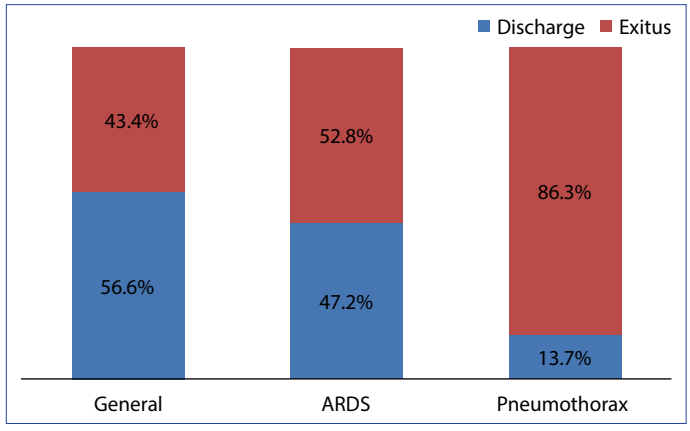

Figure 1. Mortality rates.
ARDS: Acute respiratory distress syndrome.

Table 1. The clinical characteristics of patients

Clinical characteristics	n=22 patients
Age, years (mean±SD)	64.6±9.7
Sex, male/female (%)	16/6 (72.7/27.3)
APACHE (mean±SD)	18.9±8.3
Comorbidities (%)	
Type 2 diabetes mellitus	9 (40.9)
Hypertension	9 (40.9)
Cancer	2 (9.1)
Asthma	1 (4.5)
Chronic renal failure	1 (4.5)
Coronary artery disease	1 (4.5)
Time, days (mean±SD)	
Admitted to the ICU	8±2.6
Start to invasive mechanical ventilation	9.1±3.4
On the day of pneumothorax occurrence	17.4±4.8
Length of stay of ICU	42.9±22.3

APACHE: Acute physiology and chronic health evaluation; ICU: Intensive care unit.

The median CRP level was found to be 65 mg/L (range: 22-180) on the 1st day of hospitalization to the ICU, and 105 mg/L (range: 39-250) on the day of pneumothorax occurrence. The difference was statistically significant ($p<0.05$). The median lymphocyte count in the study group on the 1st day of ICU was 500 /µL with a (range: 260-680), and the median lymphocyte count on the day of pneumothorax occurrence was significantly lower 360/µL (range: 70-650) ($p<0.05$). At the ICU 1st day, the median neutrophil/lymphocyte (NL) rate was 20.4 (range: 7.2-44.3), the median fibrinogen level was 3.2 g/L (range: 0.86-6.2), the median Lactate Dehydrogenase (LDH) value was 447 U/L (range: 268-744), while on the day of pneumothorax occurrence, the median NL rate was 23.7 (range: 8.2-114.5), the median fibrinogen level was 4.68 g/L (range: 1.25-7.74), the median LDH value was 513 U/L (range: 280-2259). These increases were statistically significant (Table 2).

When the patients were evaluated regarding mechanical ventilator parameters, the median positive end-expiratory pressure (PEEP) was 6 cm H_2O (range: 5-9) on ICU 1st day, and the median was 7 cm H_2O (range: 5-9) on the day of pneumothorax occurrence. Yet, at the ICU 1st day, the median Peak inspiratory pressure (PIP) was 29 cm H_2O (range: 27-32), median tidal volume (V_T) was 400 ml (range: 320-500), while on the day of pneumothorax occurrence, median PIP was 29 cm H_2O (range: 27-32), and V_T was 380 ml (range: 340-500). The difference between the respiratory parameters between the 1st day of ICU hospitalization and the day of pneumothorax occurrence was not statistically significant (Table 3). The computed tomographies of patients were observed common ground-glass opacities, heterogenic distribution with patch infiltrates, alveolar exudates, interstitial thickening in the 1st week of their follow-up. All CT findings and clinical summaries of the patients are given in (Table 4). Thorax CT images are shown in (Figs. 2, 3).

During the treatment, high dose methylprednisolone was administered to the patients with pneumothorax for a total of 7 days, with a loading dose of 1 g/day for 3 days. The dose given after loading dose was 80 mg/day for 2 days, and then 40 mg/day for 2 days. A chest tube was inserted into all patients, except five patients who developed subcutaneous emphysema. Twenty two patients were treated with invasive mechanical ventilator.

Table 2. Comparison of the laboratory findings

The laboratory findings	Median	Min.	Max.	p
CRP_A	65 mg/L	22	180	0.001
CRP_B	105 mg/L	39	250	
Lymphocyte_A	500/µL	260	680	0.001
Lymphocyte_B	360/µL	70	650	
N/L Rate_A	20.4	7.2	44.3	0.001
N/L Rate_B	23.7	8.2	114.5	
Fibrinogen_A	3.2 g/L	0.86	6.2	0.001
Fibrinogen_B	4.68 g/L	1.25	7.74	
D-dimer_A	3.4 mg/L	0.8	32.4	0.035
D-dimer_B	4.8 mg/L	0.6	35.2	
IL-6_A	16.4 pg/mL	3.1	39.6	0.036
IL-6_B	21 pg/mL	2	48.8	
PCT_A	0.2 ng/mL	0.01	6.03	0.41
PCT_B	0.1 ng/mL	0.02	3.02	
LDH_A	447 U/L	268	744	0.016
LDH_B	513 U/L	280	2259	
Troponin T_A	24 ng/mL	6	320	0.053
Troponin T_B	18 ng/mL	4	628	

Min.: Minimum; Max.: Maximum; A: Start to invasive mechanical ventilation; B: On the day of pneumothorax occurrence; CRP: C-reactive protein; N/L: Neutrophil/lymphocyte; PCT: Procalcitonin; LDH: Lactate dehydrogenase.

Table 3. Evaluations of mechanical ventilator parameters

Mechanical ventilator parameters	Median	Min.	Max.	p
PEEP_A	6 cm H_2O	5	9	0.059
PEEP_B	7 cm H_2O	5	9	
PIP_A	29 cm H_2O	27	32	0.6
PIP_B	29 cm H_2O	27	32	
Tidal volume	400 ml	320	500	0.031
Tidal volume	380 ml	340	500	

Min.: Minimum; Max.: Maximum; A: Start to invasive mechanical ventilation; B: on the day of pneumothorax occurrence; PEEP: Positive end-expiratory pressure; PIP: Peak inspiratory pressure.

Table 4. All findings and clinical summaries of the patients

S. No.	Sex/age (years)	Comorbidity	Admitted to the ICU	On the day of pneumothorax occurrence	CT findings	Chest drain	Outcome	Length of hospital stay, days
1.	M/68	Cancer	9	26	Bilateral patchy ground-glass opacities, peripheral, more prominent in the lower lobes	Yes	exitus	42
2.	M/64	-	6	29	Diffuse ground-glass opacities, Central and peripheral, intralobular septal thickening	Yes	exitus	47
3.	M/85	Coronary artery disease	11	19	Bilateral ground-glass opacities, central and peripheral, septal thickening	Yes	exitus	31
4.	M/68	Hypertension, Diabetes	8	14	Bilateral ground-glass opacities, central and peripheral, crazy-paving pattern, interseptal thickening	Yes	exitus	19
5.	M, 61	-	14	23	Bilateral Diffuse ground-glass opacities, Peripheral	Yes	exitus	119
6.	M, 54	-	7	20	Bilateral patchy ground-glass opacities, peripheral	Yes	exitus	27
7.	F/64	Asthma	7	15	Bilateral ground-glass opacities, peripheral	Yes	exitus	35
8.	F/68	Hypertension, Diabetes	10	17	Bilateral glass-ground opacification, peripheral, multifocal	Yes	exitus	22
9.	M/69	Hypertension, Diabetes	13	25	Diffuse ground-glass opacities, Central and peripheral	No	exitus	55
10.	F/71	Hypertension	7	17	Bilateral glass-ground opacification, peripheral	Yes	exitus	56
11.	F/55	Diabetes	10	17	Bilateral patchy ground-glass opacities, peripheral, more prominent in the peripheral	Yes	exitus	86
12.	M/50	-	8	17	Bilateral alveolar ground glass opacities, peripheral, more prominent in the peripheral and subpleural areas	Yes	exitus	31
13.	M/77	Chronic renal failure	7	16	Bilateral ground-glass opacities, central and peripheral, crazy-paving pattern, interseptal thickening	Yes	exitus	36
14.	M/58	Hypertension	7	14	Bilateral glass-ground opacification, peripheral	Yes	exitus	46
15.	M/68	Cancer	8	17	Bilateral ground-glass opacities, central and peripheral, crazy-paving pattern	Yes	exitus	34
16.	M/51	Hypertension, Diabetes	3	7	Bilateral glass-ground opacification, peripheral	No	exitus	16
17.	F/80	Hypertension, Diabetes	7	13	Bilateral patchy ground-glass opacities, peripheral crazy-paving pattern, interseptal thickening	No	exitus	40
18.	M/48	Diabetes	10	14	Bilateral glass-ground opacification, peripheral	No	exitus	42
19.	F/63	Diabetes	9	18	Bilateral glass-ground opacification, peripheral		exitus	44
20.	M/73	Hypertension	6	13	Bilateral glass-ground opacification, peripheral	No	discharge	38
21.	M/69	Hypertension	5	16	Bilateral patchy ground-glass opacities, peripheral	Yes	discharge	42
22.	M/58	Diabetes	4	17	Bilateral ground-glass opacities, central and peripheral	Yes	discharge	37

ICU: Intensive care unit; CT: Computed tomography.

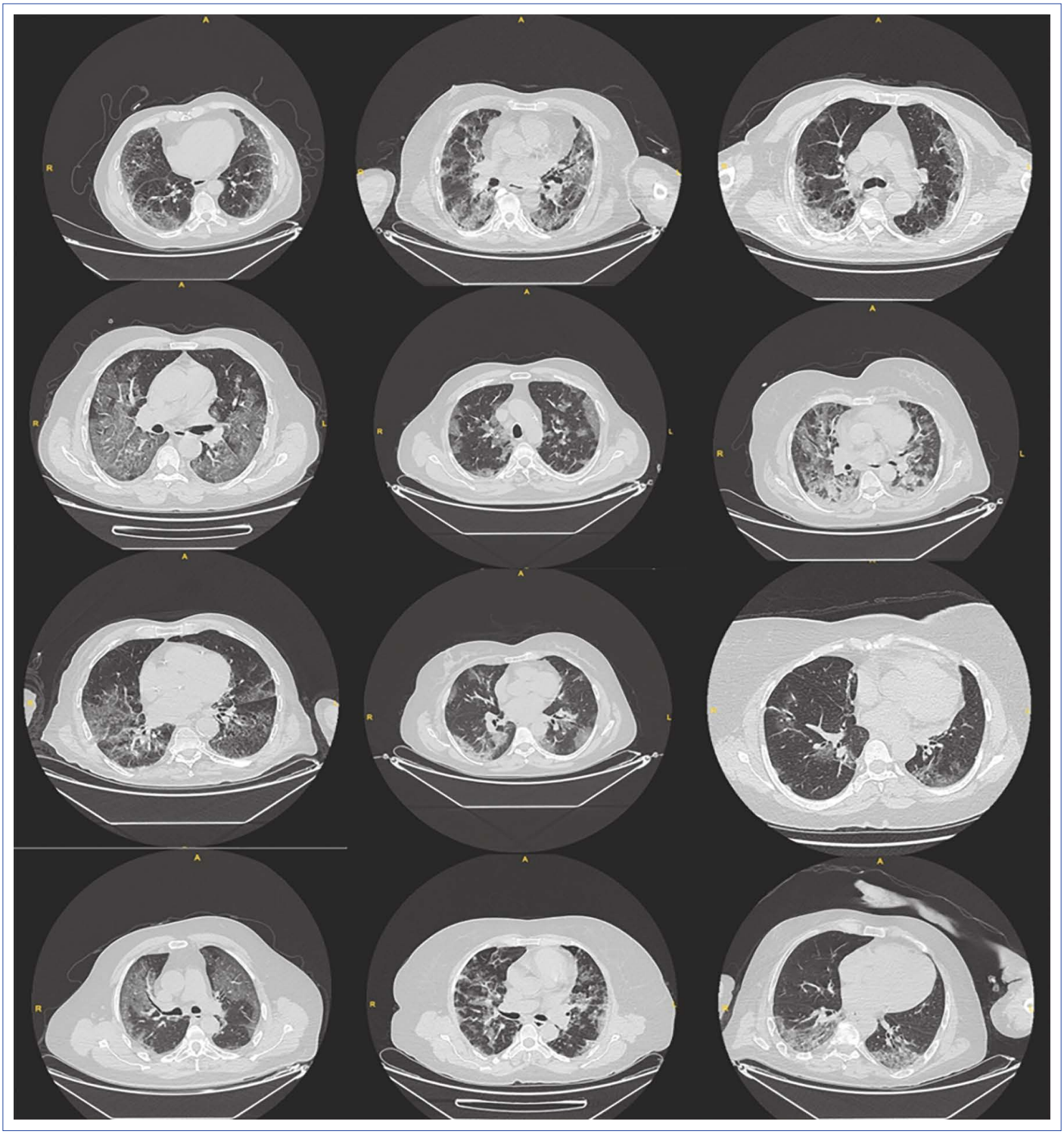

Figure 2. Thorax CT images of patients from 1 to 12.
CT: Computed tomography.

Discussion

Pneumothorax is a fatal complication in patients with ARDS, especially those undergoing invasive mechanical ventilation.[11] In a previous study in which 84 severe ARDS patients were examined, the pneumothorax rate was 48.8%, and the mortality (66% vs. 46%) was higher in patients with pneumothorax.[12] In the presence of COVID-19 and ARDS, this rate was found to be 80%.[4] Since our intensive care is one of our country's reference centers, severe patients were accepted from other intensive care units and

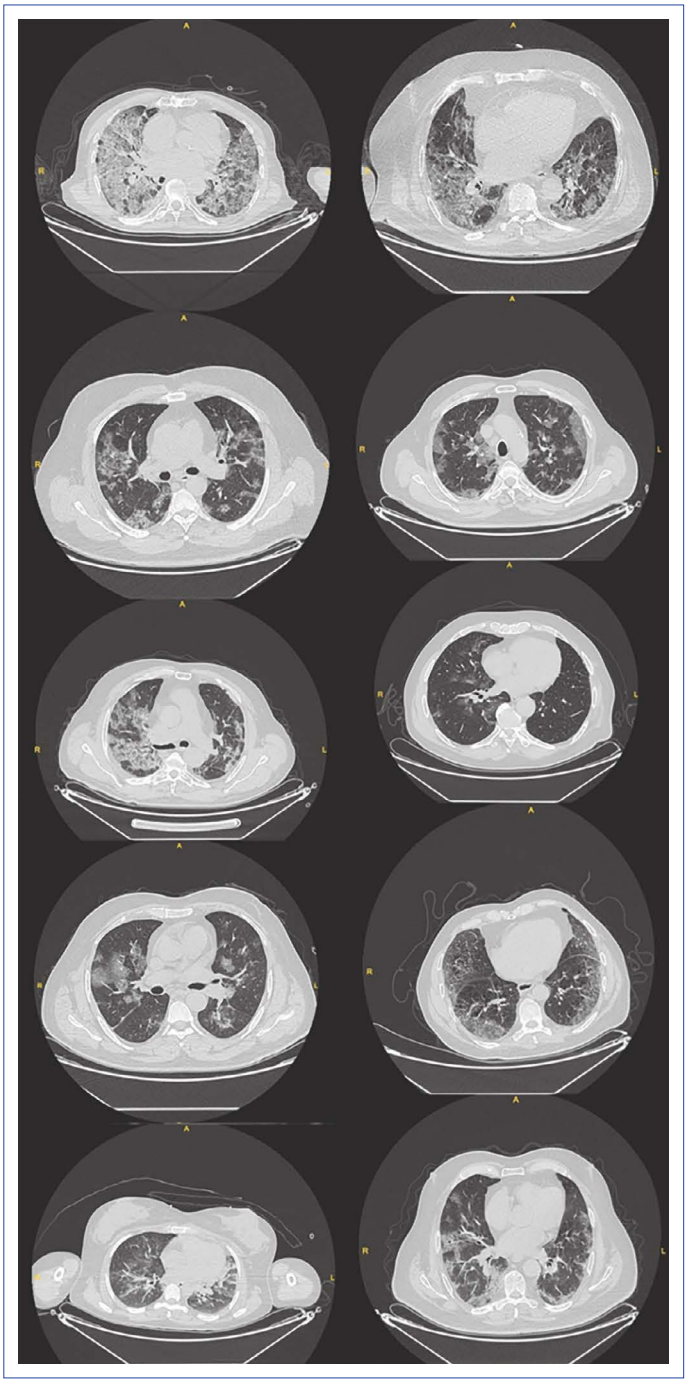

Figure 3. Thorax CT images of patients from 13 to 22.
CT: Computed tomography.

hospitals. Hence, our mortality rate was 43.4% in all patients, 52.8% in patients with ARDS. This rate was found as 87% in the case of pneumothorax with ARDS occurrence. Therefore, we believe that preventing pneumothorax in a tertiary ICU will significantly reduce mortality rates.

In a case series conducted on SARS patients in Hong Kong, it was observed that high neutrophil count and LDH level increased the tendency to pneumothorax.[9] It was also thought that high-dose methylprednisolone administration affected the improvement of the lung tissue and contributed to the pneumothorax occurrence.[9] Hameed et al.[13] reported that high LDH and acute phase reactants were higher in COVID-19 patients who received high-dose prednisolone and developed pneumothorax. We used high dose methylprednisolone in all our patients. We found a significant difference between the baseline LDH level of our patients and the LDH levels at the time of pneumothorax occurrence. In the same manner, we observed that acute phase reactants increased significantly. Increases in acute phase reactants and LDH may be an early indicator for pneumothorax. Besides, we think that it would be beneficial to reconsider high-dose methylprednisolone treatment in this respect in the patient group requiring intensive care.

The duration of ARDS can explain the incidence of pneumothorax in ARDS. ARDS consists of three phases: exudative phase (1-7 days), proliferative phase (8-21 days), and fibrotic phase (>21 days).[14] Gattinoni et al.[12] found the incidence of pneumothorax in late ARDS (longer than 2 weeks) patients as 87% and early ARDS (<7 days) as 30%. Wang et al.[4] reported that pneumothorax occurred 2 weeks after symptom onset in 5 COVID-19 patients with ARDS. In line with the literature, we found that pneumothorax's occurrence time was 17.4±4.8 days in our patients.

ARDS development is one of the most important prognostic factors in COVID-19 patients. In ARDS pathophysiology, neutrophil count is characterized by increased activation of proinflammatory cytokines and complement cascade, which results in microvascular permeability and fluid exudation.[15] Eventually, fluid accumulation, alveolar atelectasis, and fibrin accumulation are seen in the lung.[15] The occurrence of pneumothorax in mechanically ventilated patients is closely related to the underlying pulmonary pathology, and ARDS has been proven to be closely related to the occurrence of this complication.[16] As it has been marvelously described by computed tomographic studies in patients with ARDS, the affected lung parenchyma, seems to have a remarkable heterogenic distribution which causes a multi-compartmental lung, with patchy infiltrates interspersed with normal-appearing lung areas.[11] We performed tomography on our patients in the 1st week of their follow-up (Table 4, Figs. 1, 2). As seen in the literature, we observed common ground-glass opacities, heterogenic distribution with patch infiltrates, alveolar exudates in our patients' tomographic images. Interstitial thickening was observed in patients, although the CT was performed in the early period. Emphysematous appearance and bullous formations occur in the affected lung areas in the late period, explaining the increase in pneumothorax incidence in this period.[10]

Patients with ARDS who are under mechanical ventilation are at the highest risk for pneumothorax development.[11] Many ventilation parameters, such as tidal volume, PIP, PEEP, and respiratory rate are considered important in the development of barotrauma. It was shown that there is a high correlation between the development of end-inspiratory pressure ($p(_{plat})$), especially when exceeding 35 cm H_2O and pneumothorax.[17] Furthermore, large tidal volume might elicit injury to the pulmonary epithelium; therefore, tidal volume reduction is another parameter presented for the prevention of ventilator-induced injury in ARDS.[18] P_{plat} pressure did not exceed 35 cm H_2O in the patients we followed up. P_{plat} pressure was aimed to be kept below 30 cm H_2O, and only four patients were observed to have over 30 cm H_2O pressure at the time of pneumothorax occurrence. Furthermore, VT was aimed to be kept between 4-6 ml/kg to prevent pulmonary epithelium damage. Neuromuscular blockers and fentanyl were used to minimize oxygen consumption and provide lung-protective settings. High PEEP levels are associated with the persistence of lung air leaks as well as the occurrence of pneumothorax. PEEP level was kept at 5-9 cm H_2O level in our patients. In conclusion, we applied AC protective ventilation in almost all ARDS patients who developed pneumothorax in ICU, but we still could not avoid pneumothorax occurrence.

Data on pneumothorax treatment in ARDS patients are limited. Tube thoracostomy, open thoracotomy, pleurodesis, and thoracoscopic surgical methods are among the treatment methods. It was shown in the previous studies that thoracotomy increases mortality in patients with ARDS.[19] A limited number of successful results have been published using thoracoscopic surgical methods, but further studies are needed on this subject.[20] We placed chest tubes in all of our patients during the treatment, except for five patients with subcutaneous emphysema together with pneumothorax. Furthermore, ECMO was used in one severe ARDS patient whose oxygenation could not be achieved. The patient's survival time who had diffuse lung involvement was extended, but mortality could not be avoided. Nevertheless, we think that administering ECMO can be one of the most promising options in patients who develop ARDS and pneumothorax due to COVID-19, since it reduces lung effort and provides a time gap for the treatment of pneumothorax and the elimination of the virus.

This study had some limitations. The study was conducted retrospectively, and further studies may fill some of the deficiencies of this study. First of all, the number of patients was limited. A multi-center study with a larger sample size may contribute to treatment improvement. Second, the risk factors can be compared by expanding the study population with patients who do not require intensive care conditions, who do not have ARDS, and who have a milder manifestation. Third, since it is difficult to use CT scan as an imaging method in the patients' follow-up, bedside X-ray criteria or USG administration methods can be defined for follow-up. Besides, it can be discussed to administer early treatment to patients to reduce mortality. Furthermore, the relationship between high-dose methylprednisolone treatment and pneumothorax can be examined.

Conclusion

Although lung-protective ventilation parameters were applied, we found that mortality was high in our COVID-19 patients with ARDS. We have seen that the pneumothorax tendency was more common in patients after 2 weeks. We also observed that acute phase reactants and LDH increased significantly on the day of pneumothorax occurrence. According to our findings, pneumothorax with ARDS increased mortality, and we believe that the prevention of pneumothorax will make an important contribution to reducing mortality. Therefore, more comprehensive studies are needed on this subject in the future to prevent and treatment pneumothorax occurrence in critically ill COVID-19 patients.

Disclosures

Ethics Committee Approval: The study was approved by The Ankara City Hospital No 2 Clinical Research Ethics Committee (Date: 10/02/2021, No: E2-21-105).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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