Received: 28 Dec 2023 | **Accepted:** 17 Sep 2024 **Genel Tıp Derg. Volume** 34/**Issue** 5 (October), 616-623
DOI: 10.54005/geneltip.1411168

ORIGINAL ARTICLE

The Relationship Between Pneumothorax and Lymphopenia in Patients With Covid-19 Pneumonia

Covid-19 Pnömonisi Olan Hastalarda Pnömotoraks ve Lenfopeni Arasindaki İlişki

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How to cite ?

Sahinoglu T. The Relationship Between Pneumothorax And Lymphopenia In Patients With Covid-19 Pneumonia. Genel Tıp Derg. 2024;34(5):616-23.

ABSTRACT

Background: Pneumothorax and lymphopenia are regarded as poor prognostic factors in covid-19 pneumonia. In this study, we aimed to determine whether there is a relationship between pneumothorax and lymphopenia in patients admitted to the intensive care unit due to COVID-19 pneumonia and evaluate whether lymphocyte count can be used to predict the development of pneumothorax.
Methods: We retrospectively reviewed the records of 50 patients with COVID-19 pneumonia who developed pneumothorax and underwent tube thoracostomy at our hospital's intensive care units.
Results: There were 32 women and 18 men, with a mean age of 67.98 years. Of the patients who developed pneumothorax, 78% were intubated. 86% of the patients with pneumothorax died. The mortality risk in patients with pneumothorax decreased 0.198 times as lymphocyte count increased. In ROC curve analysis based on intubation status, a cut-off value 1.02 for lymphocyte count is statistically significant.
Conclusions: In this study, we observed that intubated patients had a high likelihood of developing pneumothorax and that concomitant deep lymphopenia was directly associated with mortality. The results highlight that during intensive care follow-up, it must be kept in mind that poor prognostic factors can interact to result in more serious prognostic implications.

Keywords: COVID-19, Intensive care unit,Lymphopenia, Pneumothorax

ÖZ

Giriş: Pnömotoraks ve lenfopeni, covid-19 pnömonisinde kötü prognostik faktörler olarak kabul edilmektedir. Bu çalışmada, COVID-19 pnömonisi nedeniyle yoğun bakım ünitesine başvuran hastalarda pnömotoraks ve lenfopeni arasında bir ilişki olup olmadığını belirlemeyi ve lenfosit sayımının pnömotoraks gelişimini tahmin etmede kullanılıp kullanılamayacağını değerlendirmeyi amaçladık.
Method: Hastanemiz yoğun bakım ünitelerinde pnömotoraks gelişen ve tüp torakostomi uygulanan COVID-19 pnömonisi gelişen 50 hastasının kayıtlarını retrospektif olarak inceledik.
Bulgular: Yaş ortalaması 67.98 olan 32 kadın ve 18 erkek vardı. Pnömotoraks gelişen hastaların %78' i entübe idi. Pnömotorakslı hastaların %86' sı öldü. Lenfosit sayısı arttıkça pnömotorakslı hastalarda ölüm riski 0,198 kat azaldı. Entübasyon durumuna dayalı ROC eğrisi analizinde, lenfosit sayısı için 1,02' lik bir cut-off değeri istatistiksel olarak anlamlı geldi.
Sonuçlar: Bu çalışmada entübe hastalarda pnömotoraks gelişme olasılığının yüksek olduğunu ve eşlik eden derin lenfopeninin mortalite ile doğrudan ilişkili olduğunu gözlemledik. Sonuçlar, yoğun bakım takibi sırasında, kötü prognostik faktörlerin etkileşime girerek daha ciddi prognostik sonuçlara yol açabileceğinin akılda tutulması gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Kovid-19, lenfopeni, Pnömotoraks, Yoğun bakım

Introduction

COVID-19 infection can be asymptomatic or manifest with potentially fatal pneumonia and/or complications of pneumonia. According to World Health Organization (WHO) data, approximately 15% of patients are admitted to intensive care because of critical illness characterised by complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and multiple organ failure [1]. In intensive care patients who receive invasive or noninvasive mechanical ventilation support, cystic formations in the lung parenchyma resulting from alveolar damage caused by COVID-19 pneumonia can progress to larger blebs [2–4]. Spontaneous or barotraumatic rupture of these blebs causes pneumothorax, which indicates poor prognosis [2–6].

COVID-19 pneumonia may cause cystic features in the lung parenchyma, which can resolve or progress to larger blebs. This can place patients at risk of rupture, resulting in mediastinal and subcutaneous emphysema

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - intihal.net
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Selcuk University Press
Genel Tıp Dergisi | e-ISSN: 2602-3741
https://dergipark.org.tr/tr/pub/geneltip
https://yayinevi.selcuk.edu.tr/

or secondary spontaneous pneumothorax (SSP). While there is no known cause of primary spontaneous pneumothorax, SSP may develop in the presence of an underlying lung disease. Spontaneous pneumothorax (SP) has been reported as a complication of COVID-19, with published incidences of 1% in hospitalised patients, 3% in patients hospitalised with pneumonia, 6% in mechanically ventilated patients and 1% in deceased patients [7].

Iatrogenic pneumothorax is mainly related to mechanical ventilation. Barotrauma caused by mechanical ventilation is more common in patients with an underlying lung disease, such as chronic obstructive pulmonary disease or ARDS. In COVID-19 patients with severe involvement of the lung parenchyma, pulmonary compliance is reduced due to pathological changes such as oedema, vascular congestion, and inflammation. As a result, it is possible that over-inflation and high Positive end-expiratory pressure (PEEP) in such hypoplastic and fibrotic lungs can lead to alveolar rupture and barotrauma [8].

Due to limited knowledge of lung histopathology in patients with COVID-19, it is unclear how well the diseased lung tissue will spontaneously heal and re-expand without intervention. There have been descriptions of how viral dissemination might be contained using bespoke viral filtration systems to limit contamination. Pneumothorax was more likely in patients with neutrophilia, severe lung injury and a prolonged clinical course [7, 8].

Lymphopenia, regarded as another poor prognostic factor, is a haematological disorder that occurs in COVID-19 patients due to viral pathogenetic mechanisms causing cell and organ damage [9–11]. Lymphopenia is one of the most important markers of the early infection stage in which the virus damages the lung parenchyma and bronchial epithelial cells. Within the scope of this research, we aimed to elucidate whether there was a relationship between pneumothorax and lymphopenia in patients admitted to the intensive care unit due to COVID-19 pneumonia and evaluate whether lymphocyte count can be used to predict the development of pneumothorax.

Methods

The records of 1287 patients with COVID-19 pneumonia who were admitted to the level 2 and 3 intensive care units of Konya Numune State Hospital between July 1 and December 31, 2020. Of these, 50 patients who developed pneumothorax and underwent tube thoracostomy were retrospectively analysed. The clinical COVID-19 diagnosis was confirmed via a real-time polymerase chain reaction (RT-PCR), chest computed tomography (CT) findings, and routine blood test results. The diagnosis of pneumothorax was performed by portable chest X-rays taken at the bedside.

Parameters including the patients' comorbidities; laboratory values such as C-reactive protein (CRP), D-dimer, ferritin, procalcitonin, fibrinogen, white blood cell (WBC) count, and lymphocyte count; positive end-expiratory pressure (PEEP) values during invasive or non-invasive ventilation; extent of involvement on chest CT, and pneumothorax side were documented, and patients who developed lymphopenia and pneumothorax were included in the study. Patients with iatrogenic pneumothorax and patients with accompanying pneumomediastinum were not included in the study

Statistical Analysis

Data were analysed via IBM SPSS Statistics version 23. Normal distribution was assessed using the Shapiro-Wilk test. Chi-square and Fisher's exact tests were used to compare categorical data by groups. Independent samples t-test was used to compare normally distributed data, and the Mann-Whitney U test was used to compare non-normally distributed data according to intubation status. Binary logistic regression analysis was used to examine risk factors associated with mortality. Receiver operating characteristic (ROC) curve analysis was used to determine optimal lymphocyte cut-off values to differentiate according to intubation and mortality status. Analysis results were presented as mean ± standard deviation and median (range) for quantitative data and as frequency (percentage) for categorical data. The level of significance was accepted as $p < 0.05$.

Results

The patient group consisted of 32 women (64%) and 18 men (36%), with a mean age of 67.98 years (range: 32.00–91.00). Comorbidities were elaborated as diabetes mellitus (DM) in 18% of the patients, hypertension (HT) in 38%, acute kidney injury (AKI) or chronic kidney disease (CKD) in 16%, coronary artery disease (CAD) in 12%, asthma/chronic obstructive pulmonary disease (COPD) in 22%, and other in 28.6% of the patients such as cerebrovascular events (CVE), epilepsy, chronic heart failure (CHF), atrial fibrillation (AF), Parkinson's disease, or substance addiction. Of

the patients who developed pneumothorax, 78% were intubated, 10% received non-invasive mechanical ventilation, and 12% were extubated. In addition, 86% of the patients with pneumothorax died, and the other 14% were discharged. Furthermore, 66% of the patients developed pneumonia according to the chest CT (Table 1).

Table 1. *Frequency distribution of categorical variables*

	Frequency (n)	Percent (%)
Gender		
Women	18	36,0
Men	32	64,0
DM		
No	41	82,0
Yes	9	18,0
HT		
No	31	62,0
Yes	19	38,0
AKI/CKD		
No	42	84,0
Yes	8	16,0
CAD		
No	44	88,0
Yes	6	12,0
Asthma/COPD		
No	39	78,0
Yes	11	22,0
Other concomitant diseases		
No	35	71,4
Yes	14	28,6
Intubated		
No	11	22,0
Yes	39	78,0
Noninvasive mechanical ventilation		
No	45	90,0
Yes	5	10,0
Extubated		
No	44	88,0
Yes	6	12,0
Pneumothorax		
Bilateral	9	18,0
Right	29	58,0
Left	12	24,0
Survival		
Discharged	7	14,0
Exitus	43	86,0
Pneumonia in Thorax CT		
Mild	15	30,0
Moderate	33	66,0
Severe	25	50,0
Very severe	1	2,0

Only pneumothorax cases with chest tube insertion were included in the study. There were no patients without chest tube insertion. Patients had pneumonia and isolated pneumothorax. Patients with accompanying pneumomediastinum were not included in the study. Of the 39 intubated patients, 5 were under non-invasive mechanical ventilation (NIMV), and 6 were extubated. Therefore, patients who could develop pneumothorax secondary to barotrauma were those who were intubated and those under NIMV. However, barotrauma cannot be effective in all their pneumothorax. The mean Peep in those who were intubated was 7.86 cm H2O. There was no risk of barotrauma in those who were extubated or those under nasal oxygen support. In other words, 88% of patients with pneumothorax had a risk of barotrauma.

In the patients' invasive and noninvasive mechanical ventilation settings, the mean PEEP value was 7.86 cm H2O. The mean CRP level was 89.22 mg/L, and the mean lymphocyte count was 0.80×103/mL (reference range: 1.26–3.35×103/mL) (Table 2). Intubated patients who developed pneumothorax had a significantly higher mortality rate (97.4%) (Table 3).

Table 2. *Descriptive statistics of quantitative data*

	Mean	Standard deviation	Median	Minimum	Maximum
Age	67,98	14,06	69,00	32,00	91,00
PEEP	7,86	3,27	9,00	0,00	11,00
CRP	89,22	68,99	80,85	3,17	338,00
D-Dimer	664,64	2434,55	3,64	0,23	12301,00
Ferritin	556,07	324,94	477,60	75,50	1379,00
Lymp-hocyte count	0,80	0,49	0,75	0,17	2,54
Procalci-tonin	1,80	3,00	0,61	0,02	16,37
Fibrinogen	495,82	191,34	478,00	99,00	918,00
WBC	16,80	7,86	14,96	6,97	36,70

Table 3. Comparison of categorical variables according to intubated status

	Intubated		Total	Test statistic	**p-value**
	No	**Yes**			
Gender					
Women	2 (18,2)	16 (41)	18 (36)	---	0,287[F]
Men	9 (81,8)	23 (59)	32 (64)		
DM					
No	9 (81,8)	32 (82,1)	41 (82)	---	1,000[F]
Yes	2 (18,2)	7 (17,9)	9 (18)		
HT					
No	8 (72,7)	23 (59)	31 (62)	---	0,498[F]
Yes	3 (27,3)	16 (41)	19 (38)		
AKI/CKD					

No	9 (81,8)	33 (84,6)	42 (84)	---	1,000F
Yes	2 (18,2)	6 (15,4)	8 (16)		
CAD					
No	9 (81,8)	35 (89,7)	44 (88)	---	0,601F
Yes	2 (18,2)	4 (10,3)	6 (12)		
Asthma/COPD					
No	10 (90,9)	29 (74,4)	39 (78)	---	0,416F
Yes	1 (9,1)	10 (25,6)	11 (22)		
Other concomitant diseases					
No	10 (90,9)	25 (65,8)	35 (71,4)	---	0,143F
Yes	1 (9,1)	13 (34,2)	14 (28,6)		
Pneumothorax					
Bilateral	0 (0)	9 (23,1)	9 (18)		
Right	6 (54,5)	23 (59)	29 (58)	X^2=5,272	0,072
Left	5 (45,5)	7 (17,9)	12 (24)		
Survival					
Discharged	6 (54,5)	1 (2,6)	7 (14)	---	<0,001F
Exitus	5 (45,5)	38 (97,4)	43 (86)		
Pneumonia in Thorax CT					
Mild	4 (36,4)	11 (28,2)	15 (30)		
Moderate	9 (81,8)	24 (61,5)	33 (66)		
Severe	4 (36,4)	21 (53,8)	25 (50)	$X^2$3,181	0,528
Very severe	0 (0)	1 (2,6)	1 (2)		

X^2: chi-square test statistic, F: Fisher's exact tests

The median PEEP value of the intubated pneumothorax patients was 9.00 cm H2O. There was a statistically significant difference in median CRP values of pneumothorax patients according to intubation status (p =0.04). The median CRP level was 17.10 mg/L among the non-intubated patients, compared to 102.00 mg/L among intubated patients (Table 4). There was also a statistically significant difference in mean lymphocyte count between intubated and non-intubated patients (p <0.001). Intubated patients had deeper lymphopenia, with a mean lymphocyte count of 0.67×103/mL while this was 1.26×103/mL in the non-intubated patients. In addition, there was a statistically significant relationship between intubation and procalcitonin values (p =0.001). Median procalcitonin levels were higher in intubated patients compared to non-intubated patients (0.92 versus 0.12 ng/mL) (Table 4).

When the risk factors associated with mortality in patients with pneumothorax were examined by binary logistic regression analysis as a univariate model, the risk of mortality was 45.6 times higher in intubated patients (p =0.001). As age increased, the mortality risk increased 1.087 times (p =0.014). As the PEEP value increased, the mortality risk increased 1.715 times (p =0.001). As expected, the mortality risk decreased

Table 4. *Comparison of quantitative data according to intubation status*

	No		Yes		Test statistic	p
	Median ± sd	Median (min. - max.)	Median ± sd	Median (min. - max.)		
Age	62,55 ± 14,15	61,00 (32,00 - 91,00)	69,51 ± 13,82	71,00 (36,00 - 88,00)	U=145	0,103
PEEP	2,73 ± 3,13	0,00 (0,00 - 6,00)	9,31 ± 1,20	9,00 (6,00 - 11,00)	U=2,5	<0,001
CRP	52,26 ± 54,89	17,10 (5,13 - 171,00)	99,65 ± 69,55	102,00 (3,17 - 338,00)	U=127	0,040
D-Dimer	4,15 ± 3,27	5,27 (0,36 - 9,68)	850,93 ± 2735,11	3,63 (0,23 - 12301,00)	U=174	0,343
Ferritin	555,28 ± 243,55	582,80 (296,40 - 1098,40)	556,29 ± 347,77	477,60 (75,50 - 1379,00)	U=196	0,755
Lymphocyte count	0,63±1,26	1,20 (0,58 - 2,54)	0,67 ± 0,37	0,72 (0,17 - 1,58)	t=3,944	<0,001
Procalcitonin	0,23 ± 0,31	0,12 (0,02 - 1,12)	2,24 ± 3,27	0,92 (0,06 - 16,37)	U=76	0,001
Fibrinogen	439,18 ± 181,68	403,00 (168,00 - 770,00)	511,79 ± 193,21	481,00 (99,00 - 918,00)	t=-1,114	0,271
WBC	18,15 ± 8,17	14,49 (8,02 - 35,33)	16,41 ± 7,84	15,09 (6,97 - 36,70)	U=182	0,447

t: Independent two-sample t-test statistic, U: Mann-Whitney U test statistic

Table 5. *Examination of risk factors affecting mortality*

	OR (%95 CI)	p
Gender	0,255 (0,028 - 2,309)	0,224
HT	4,32 (0,478 - 39,066)	0,193
AKI/CKD	1,167 (0,121 - 11,254)	0,894
Other concomitant diseases	2,69 (0,293 - 24,66)	0,381
Intubated (No)	45,6 (4,512 - 460,885)	0,001
Noninvasive mechanical ventilation	0,615 (0,058 - 6,477)	0,686
Extubated (No)	0,01 (0,001 - 0,125)	<0,001
Pneumonia in Thorax CT – Mild	2,897 (0,317 - 26,431)	0,346

Pneumonia in Thorax CT - Moderate	0,281 (0,031 - 2,552)	0,260
Pneumonia in Thorax CT - Severe	0,348 (0,061 - 1,993)	0,236
Age	1,087 (1,017 - 1,162)	0,014
PEEP	1,715 (1,264 - 2,327)	0,001
CRP	1,015 (0,998 - 1,034)	0,091
D-Dimer	1,237 (0,873 - 1,755)	0,232
Ferritin	1,002 (0,999 - 1,005)	0,214
Lymphocyte count	0,198 (0,041 - 0,956)	0,044
Procalcitonin	5,041 (0,53 - 47,896)	0,159
Fibrinogen	1,002 (0,998 - 1,007)	0,365
WBC	0,996 (0,9 - 1,101)	0,931

0.198 times as lymphocyte count increased (p=0.044) (Table 5).

In ROC curve analysis based on intubation status, a cut-off value of 1.02 for lymphocyte count had an area under the curve (AUC) value of 0.786 and was statistically significant (p =0.004). At this cut-off value, lymphocyte count had 82.1% sensitivity and 63.6% specificity in the prediction of intubation (Table 6; Figure 1).

Table 6. *Determination of cut-off values of lymphocytes according to intubated and exitus status*

Status	Cut-Off	AUC (%95CI)	p	Sensitivity (%95 CI)	Specificity (%95 CI)	PPV	NPV	Accuracy
Intubated	<1,02	0,786	0,004	0,821	0,636	0,942	0,501	0,780
Exitus	<1,185	0,741	0,043	0,884	0,571	0,979	0,445	0,840
Extubated	>1,02	0,759	0,041	0,667	0,773	0,215	0,945	0,760

PPV: Positive predictive value, NPV: Negative predictive value

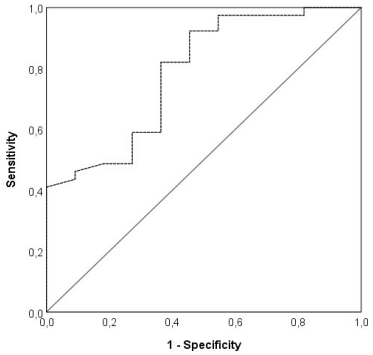

Figure 1. ROC curve of lymphocyte according to intubated status

Discussion

The clinical presentation of COVID-19 ranged from asymptomatic to severe ARDS in the patients in this study, consistent with the findings of Yuan Xu et al. (2021) [6]. A considerable proportion of patients required intubation, especially among those admitted to intensive care units. Pneumothorax in patients who required intubation because of microthrombus-related ARDS and accompanying cytokine storm was a clinical picture associated with high mortality. It was noteworthy that 86% of our patients who developed pneumothorax were deceased.

Barotrauma is the primary cause of pneumothorax in lung parenchyma, which has consolidated pneumonic infiltration and lost compliance [2, 5, 6]. However, as Yuan Xu et al. (2021) stated, pathologies such as blebs caused by alveolar damage secondary to embolism and underlying lung diseases are also thought to play a role in developing pneumothorax [3, 6]. Martinelli et al. (2020) also reported patients with pneumothorax without barotrauma and attributed this to ischemic parenchymal damage and inflammation associated with ARDS [3].

Since the first cases of COVID-19 were described, pneumothorax has been characterised as a potential, though uncommon, complication. Chen et al. (2020) [12] described only one patient with SP out of 99 confirmed COVID-19 cases with a pneumothorax. Yang et al. (2020) [13], in an autopsy study consisting of 92 patients, found just one case with the same diagnosis. Salehi et al. (2020) [14] reviewed computed tomography findings and determined that pneumothorax was uncommon. Ulutas et al. (2022) [7] stated that 1855 COVID-19 patients have been treated; 1498 of these cases were followed up in the ward, and 357 were followed up in the intensive care unit. The first case of pneumothorax was detected incidentally, and no bullae or other pulmonary parenchymal lesions or pulmonary infiltration were detected radiologically.

Chest CT indicated moderate involvement of

pneumonia in 66% of our patients. We think that the development of fibrotic tissues and the increased pneumonic infiltration with disease progression increases the intensity of radiological signs of ground-glass opacity and are also associated with lung damage and pneumothorax that occur. According to Zantah et al. (2020), the disease progresses radiologically from ground-glass density to consolidation and fibrosis. This paves the way for alveolar distension due to ARDS-related alveolar damage, mechanical ventilation, and the subsequent development of pneumothorax [4].

In our study, the mean PEEP value among all pneumothorax patients was 7.86 cm H2O, while the median PEEP value among intubated patients was 9.00 cm H2O. This value is higher than normal and predisposes to barotrauma. Zantah et al. (2020) determined that the prevalence of pneumothorax in patients with ARDS who received mechanical ventilation ranged widely between 14% and 87%. This is also thought to be directly related to the clinical severity of ARDS, barotrauma, and volume trauma, in which high peak inspiratory pressures, high PEEP, high tidal volumes, and minute ventilation values are believed to play a role [4].

It has previously been suggested that the development of pneumothorax during coronavirus infection is an important prognostic marker. However, COVID-19 treatment in patients with pneumothorax may lead to additional comorbidities and complications. Notably, chest-drain insertion for pneumothorax could be considered an aerosol-generating procedure, and severe acute respiratory syndrome coronavirus two viral RNA has recently been detected in the pleural fluid at postmortem [15].

An important complication of mechanical ventilation is barotrauma. Barotrauma appears to be high in COVID-19 patients. Pneumothorax developed in up to 25% of COVID 19 who had barotrauma. However, it develops only in 2% of patients with other causes of ARDS [16, 17]. The percentage of pleural effusion in COVID-19 patients with mild symptoms is only 8% compared to 28% in patients critically ill with COVID-19 infection. Insertion of a chest drain is widely recommended as the gold standard and mainstay of treatment in traumatic pneumothorax. Although controversial for critically ill patients on positive pressure ventilation, it is currently recommended to place a tube thoracostomy when a pneumothorax is observed. Due to the limited knowledge of lung histopathology with COVID-19, it is unknown how well the diseased lung tissue will spontaneously heal and re-expand without intervention [18].

Low lymphocyte levels in critically ill patients indicate that many immune cells have been used and that immunity is suppressed. Lymphocyte damage can be critical in patients' exacerbations, and reduced lymphocyte levels can be used as an important index in assessing disease severity [4]. Lymphopenia is the most common laboratory finding detected on hemograms in COVID-19 patients, starting from the initial stage of infection. Ciaccio et al. (2019) [11] proposed various mechanisms to explain the decreasing lymphocyte levels. As was shown for SARS-CoV, they suggested that the virus could directly infect lymphocytes, especially T cells, and cause depletion of CD4+ and CD8+ cells, thereby suppressing cellular immunity. Evidence that lymphocytes express the angiotensin-converting enzyme (ACE2) receptor on their cell membranes supports such a hypothesis. In addition, Ciaccio et al. argued that the virus could directly destroy lymphatic organs, and proinflammatory cytokines such as interleukin – 6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha) may induce lymphocyte deficiency.

All patients in our study had lymphopenia accompanied by elevated CRP, procalcitonin, ferritin, and D-dimer among their laboratory parameters. Our findings that patients who developed pneumothorax and were intubated had higher mean CRP levels, deeper lymphopenia, and higher procalcitonin values compared to those who were not intubated are also consistent with the literature. It also supports that these parameters are poor prognostic factors in COVID-19 pneumonia. An important finding in the study by Zantah et al. (2020) was that nearly all patients who developed spontaneous pneumothorax had lymphopenia and high inflammatory markers, including CRP, lactate dehydrogenase, ferritin, D-dimer, and IL-6 levels. Cytokine storm is believed to play a role in the pathophysiology of this condition. This form of exaggerated, irregular immune response can lead to the hyperinflammatory form of ARDS and is associated with increased mortality [4].

Most patients who developed SP in the present study found Lymphopenia and elevated inflammatory markers, including C-reactive protein, lactate dehydrogenase, ferritin, D-dimer and interleukin-6 levels. This was consistent with recently published studies that have examined the possible mechanisms of COVID-19-induced lung injury. Cytokine storms have

been thought to play a role in the pathophysiology of the disease. This type of hyperactive and dysregulated immune response may lead to a hyperinflammatory form of ARDS and is associated with critical illness and increased mortality [19, 20].

Higher lymphocyte values were associated with a lower mortality risk in our study. In other words, the prognosis worsened as lymphocyte count decreased. Likewise, pneumothorax is one of the poor prognostic factors in COVID-19 patients. The fact that 97.4% of intubated patients who developed pneumothorax died in our study also supports this. When these poor prognostic factors were evaluated in intubated patients, a lymphocyte cut-off value 1.02 had a statistically significant area under the curve (AUC) of 0.786. This suggests that a lymphocyte value below 1.02 in intubated patients indicates an additional risk of pneumothorax.

In addition, lymphopenia is a biochemical parameter that can accompany the disease from the beginning and is known to be associated with systemic inflammation and cytokine storm. Therefore, in lymphopenic intubated patients, treatment planning should include low-pressure ventilator settings if the lymphopenia count is below 1.02 to prevent the development of pneumothorax. We believe this protective measure will prevent further complications during the intensive care of patients with COVID-19 pneumonia.

A more objective analysis would have been possible with a more equal distribution of intubated patients and those who received noninvasive ventilation. However, due to the course of the disease, it was not possible to balance these numbers among patients who developed pneumothorax. This can be taken into consideration in prospective studies.

The biggest limitation of the study might be attributed to the retrospective design. The relatively small sample size was another obstacle. Patients with positive RT–PCR isolated pneumothorax followed up with chest tubes in 2nd- and 3rd-level intensive care units were rare. Last but not least, the study was conducted in a single centre.

Conclusion

The outcomes of this research indicated that intubated patients had a high likelihood of developing pneumothorax, and concomitant deep lymphopenia was directly associated with mortality. Patient approach and treatment should be considered multifactorial at every stage during intensive care follow-up, and it must be kept in mind that poor prognostic factors can interact to result in more serious prognostic implications.

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