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Risk factors affecting the development of pneumothorax in patients followed up in intensive care with a diagnosis of COVID-19

Yasemin Bozkurt Turan[1*]

Abstract

Background Pneumothorax is a little known and reported complication of COVID-19. These patients have poorer general outcomes and greater respiratory support requirements, longer hospitalization times, and higher mortality rates. The purpose of this study was to determine which factors predict mortality in patients with tube thoracostomy diagnosed with COVID-19, admitted to the COVID-19 intensive care unit (ICU), and developing pneumothorax.

Methods This respective, observational study was conducted in all COVID-19 ICUs at the Marmara University Pendik Training and Research Hospital, Türkiye. Patients admitted to the ICU with diagnoses of COVID-19 pneumonia and with chest tubes inserted due to pneumothorax were investigated retrospectively.

Results One hundred patients with tube thoracostomy were included in the study. Their median age was 68 (57–78), and 63% were men. The median follow-up time was 20 [10–29] days, and the median time from initial reverse transcriptase polymerase chain reaction (RT-PCR) results to tube thoracostomy was 17 [9–23] days. Initial RT-PCR results were positive in 90% of the patients, while 8% were negative, and 2% were unknown. Half the patients exhibited pulmonary involvement at thoracic computed tomography (CT) ($n=50$), while 22 patients had COVID-19 reporting and data system (CO-RADS) scores of 5 (22%). Sixty-two patients underwent right tube thoracostomy, 24 left side placement, and 14 bilateral placement. The patients' mean positive end expiratory pressure (PEEP) level was 10.31 (4.48) cm H_2O, with a mean peak inspiratory pressure (PIP) level of 26.69 (5.95) cm H_2O, a mean fraction of inspired oxygen (FiO2) level of 80.06 (21.11) %, a mean respiratory rate of 23.71 (5.62) breaths/min, and a mean high flow nasal cannula (HFNC) flow rate of 70 (8.17) L/min. Eighty-seven patients were intubated (87%), six used non-rebreathable reservoir masks, four HFNC, two non-invasive mechanical ventilation (NIV), and one a simple face mask. Comorbidity was present in 70 patients, 25 had no comorbidity, and the comorbidity status of five was unknown. Comorbidities included hypertension (38%), diabetes mellitus (23%), cardiovascular disease (12%), chronic obstructive pulmonary disease (5%), malignancy (3%), rheumatological diseases (3%), dementia (2%) and other diseases (9%). Twelve of the 100 patients survived. The median survival time was 20 (17.82–22.18) days, and the median 28-day overall survival rate was 29% (20-38%). The multivariate Cox proportional hazards model indicated that age over 68 (HR = 2.23 [95% CI: 1.39–3.56]; $p=0.001$), oxygenation status other than by intubation (HR = 2.24 [95% CI: 1.11–4.52];

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$p = 0.024$), and HCO3- below 22 compared with a normal range of 22 to 26 (HR = 1.95 [95% CI: 1.08–3.50]; $p = 0.026$) were risk factors associated with mortality in patients in the ICU.

Conclusions Age over 68, receipt of oxygenation other than by intubation, and HCO3- values lower than 22 in patients with COVID-19 pneumonia emerged as prognostic factors associated with mortality in terms of pneumothorax.

Keywords COVID-19, SARS-CoV-2, Acidosis, Bicarbonate, Tube thoracostomy, Oxygenation, Pneumothorax

Introduction

Background

COVID-19 infection developing in association with the highly contagious agent SARS-CoV-2 began spreading rapidly across the world from the end of 2019 and subsequently affected millions. The World Health Organization (WHO) declared a viral pneumonia pandemic on 11 March, 2020 [1]. With its high mortality and morbidity rates and various complications, COVID-19 infection developed into the world's most severe pandemic [2].

Between the onset of the pandemic and 12 October, 2023, 771,191,203 confirmed cases of COVID-19 were reported to the WHO, including 6,961,014 deaths [3]. COVID-19 infection is a respiratory disease with a wide spectrum, ranging from asymptomatic disease or mild upper airway infection to severe pneumonia resulting in severe respiratory failure and death, and can also lead to widespread physical and psychological function disorders [4]. Defined as air in the pleural space, pneumothorax is one of the complications of COVID-19 infection [5]. Retrospective studies have reported pneumothorax in 1% of COVID-19 patients requiring hospitalization and in 2% of those requiring admission to the ICU [6–8]. Pneumothorax is a little known and reported complication of COVID-19. These patients have greater respiratory support requirements, longer hospital stays, higher mortality rates, and poorer general outcomes [9].

The purpose of this study was to conduct a retrospective investigation of the demographic, clinical, laboratory, and radiological characteristic of patients admitted to the COVID-19 ICU, diagnosed with COVID-19, and with chest tubes inserted due to pneumothorax. The objective was to identify which factors predicted mortality in patients with COVID-19 pneumonia with chest tubes inserted due to pneumothorax.

Methods

Study design and population

The research was conducted as a retrospective, observational study in all the Marmara University Training and Research Hospital COVID-19 ICUs, Türkiye. The study was carried out in accordance with the Declaration of Helsinki and the Good Clinical practice guidelines. Patients with tube thoracostomy aged 18 or over admitted to COVID-19 ICUs between 11.03.2020 and, with COVID-19 pneumonia confirmed by nasopharyngeal swab reverse transcriptase polymerase chain reaction (RT-PCR) and developing spontaneous pneumothorax confirmed by clinical diagnosis and thoracic computed tomography (CT) scans were included in the study.

Patients with pneumothorax associated with any underlying disease, with recurrent spontaneous pneumothorax, or with iatrogenic pneumothorax were excluded from the study.

The eight initially PCR-negative patients were individuals diagnosed with COVID-19 pneumonia. Exitus occurred within 24 h of admission to hospital in four patients, and new PCR could not be investigated. PCR was investigated after 24 h in the other four patients, results being positive in three cases and negative in one.

Data collection

Since this study was retrospective, informed and written consent was not obtained from the patients themselves or their relatives. Permission to waive informed consent was obtained from the Marmara University Medical Faculty ethical committee.

Ethical approval was obtained from the Marmara University Medical Faculty ethical committee (no. 09.2022.710) following receipt of permission from the Turkish Ministry of Health. The patient list was obtained from the hospital's data processing unit (with the approval of the chief physician) using the tube thoracostomy code. The following patient data were recorded on admission to the ICU from the hospital's database:

Patients' demographic characteristics during admission to the ICU, comorbidity status, minimum 28-day mortality investigation, RT-PCR results, positive end expiratory pressure (PEEP), peak inspiratory pressure (PIP), fraction of inspired oxygen (FiO2), non-rebreather mask use, high flow nasal cannula (HFNC) use, non-invasive mechanical ventilation (NIV) requirements, simple face mask use, and intubation status.

Thoracic computed tomography (CT) scans and diagnosis of pneumothorax, chest X-ray scans, and the side of the tube thoracostomy.

Ferritin, C-reactive protein (CRP), procalcitonin, LDH, D-dimer, IL-6, white blood cell (WBC), lymphocyte, neutrophil, pH, pO2, IL-6, pCO2, HCO3-, BE, oxygen saturation (SpO2), lactate, neutrophil to lymphocyte ratio

(NLR), fibrinogen, and ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) values.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) case-control checklist was employed during the writing of the paper [10]. Arterial blood gas pH 7.35–7.45, PaCO2 35–45 mmHg, standard bicarbonate 22–26 mmol/L [11], PaO2 75–100 mmHg, and SaO2 95–100% [12] were regarded as normal values.

Statistical analysis

Descriptive statistics were presented as frequency (percentage) for categorical variables and as mean (SD) and median (IQR) values for continuous variables. The overall survival (OS) of the patients referred to the intensive care unit (ICU) was estimated using the Kaplan-Meier method. A multivariate Cox proportional hazards (CPH) model using forward stepwise (likelihood ratio) method was applied for the factors affecting OS. The proportional hazards assumption was tested with Schoenfeld's residuals. The cut-off values of the continuous variables included in CPH model were based on reference values, or median values. Statistically significant ($p<0.05$) covariates in the univariate analysis were included in the multivariate model. Statistical significance was set at 0.05 level and the analysis was carried out on IBM SPSS version 25 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA) and STATA 15 (Stata Statistical Software: Release 15. College Station, TX, USA) software.

Results

Study flowchart

One hundred eighty patients with tube thoracostomy codes were evaluated, and 80 meeting the exclusion criteria were excluded. One hundred patients were thus finally enrolled. The study flowchart is shown in Fig. 1.

Patient characteristics

The demographic and clinical characteristics of the 100 patients with tube thoracostomies who were referred to the ICU are shown in Table 1. The patients' median age was 68 (57–78), and 63% were men. The median follow-up time was 20 [10–29] days, and the median time elapsing from initial RT-PCR results to tube thoracostomy was 17 [9–23] days. The initial RT-PCR results were positive in 90% of the patients, while 8% were negative, and 2% were unknown. Half the patients exhibited pulmonary involvement at thoracic CT ($n=50$), while 22 had a COVID-19 reporting and data system (CO-RADS) score of 5 (22%). Sixty-two patients underwent right-side, 24 left-side, and 14 bilateral tube thoracostomy. The patients had a mean positive end expiratory pressure (PEEP) level of 10.31 (4.48) cm H_2O, a mean peak inspiratory pressure (PIP) level of 26.69 (5.95) cm H_2O, a mean FiO2 level of 80.06 (21.11) %, a mean respiratory rate of 23.71 (5.62) breaths/min, and a mean high flow nasal cannula (HFNC) flow rate of 70 (8.17) L/min. Eighty-seven patients were intubated (87%), six used non-rebreathable reservoir masks, four HFNC, two NIV, and one patient a simple face mask. Comorbidity was present in 70 patients, while no comorbidity was present in 25, and the comorbidity status of 25 was unknown. Comorbidities included hypertension (38%), diabetes mellitus (23%), cardiovascular disease (12%), chronic obstructive pulmonary disease (5%), malignancy (3%), rheumatological diseases (3%), dementia (2%) and other diseases (9%). The patients' median procalcitonin, ferritin, pH, PaCO2, PaO2, SpO2, HCO3-, BE, lactate, WBC, neutrophil, lymphocyte, neutrophil-to-lymphocyte ratio (NLR), LDH, fibrinogen, D-dimer, CRP and ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) values are shown in Table 1.

Survival analysis

The OS of the patients referred to the ICU is shown in Table 2. Twelve of the 100 patients survived. The median survival time was 20 (17.82–22.18) days and the median 28-day OS level was 29% (20 −38%). The patients' Kaplan-Meier survival curve is presented in Fig. 2.

The factors affecting the OS of the patients in the ICU are shown in Table 3. The univariate analysis showed that the age, oxygenation status, hypertension presence, levels of SpO2, HCO3-, BE and lymphocyte were associated with mortality ($p<0.05$). The multivariate CPH model indicated that the age over 68 (HR=2.23 [95% CI: 1.39–3.56]; $p=0.001$), having an oxygenation status other than intubation (HR=2.24 [95% CI: 1.11–4.52]; $p=0.024$), and having HCO3- below 22 compared with a normal range of 22 to 26 (HR=1.95 [95% CI: 1.08–3.50]; $p=0.026$) were risk factors associated with mortality (Table 3).

Discussion

A high mortality rate (88%) was observed in this study of patients with thoracostomy developing pneumothorax and hospitalized in the COVID-19 ICU. Age over 68, receipt of oxygenation other than by intubation, and HCO3- values lower than 22 mEq/L in patients with tube thoracostomy were associated with mortality among patients in the ICU.

Approximately 80% of COVID-19 cases exhibit a mild course, while 15% involve severe pneumonia, and 5% exhibit a critical disease manifestation requiring intensive care and invasive mechanical ventilation [13].

The patients' median PEEP value was 10 [8–12] cmH20, median PIP 26 [22–32] cmH2O, median FiO2 80% (65–100), median respiration rate 22 [20–26] breaths/minute, mean Spo2 92.8% (6.84), median PaO2 79 (69–105) mmHg, median PaO2/FiO2 ratio 106 (77–144) mmHg,

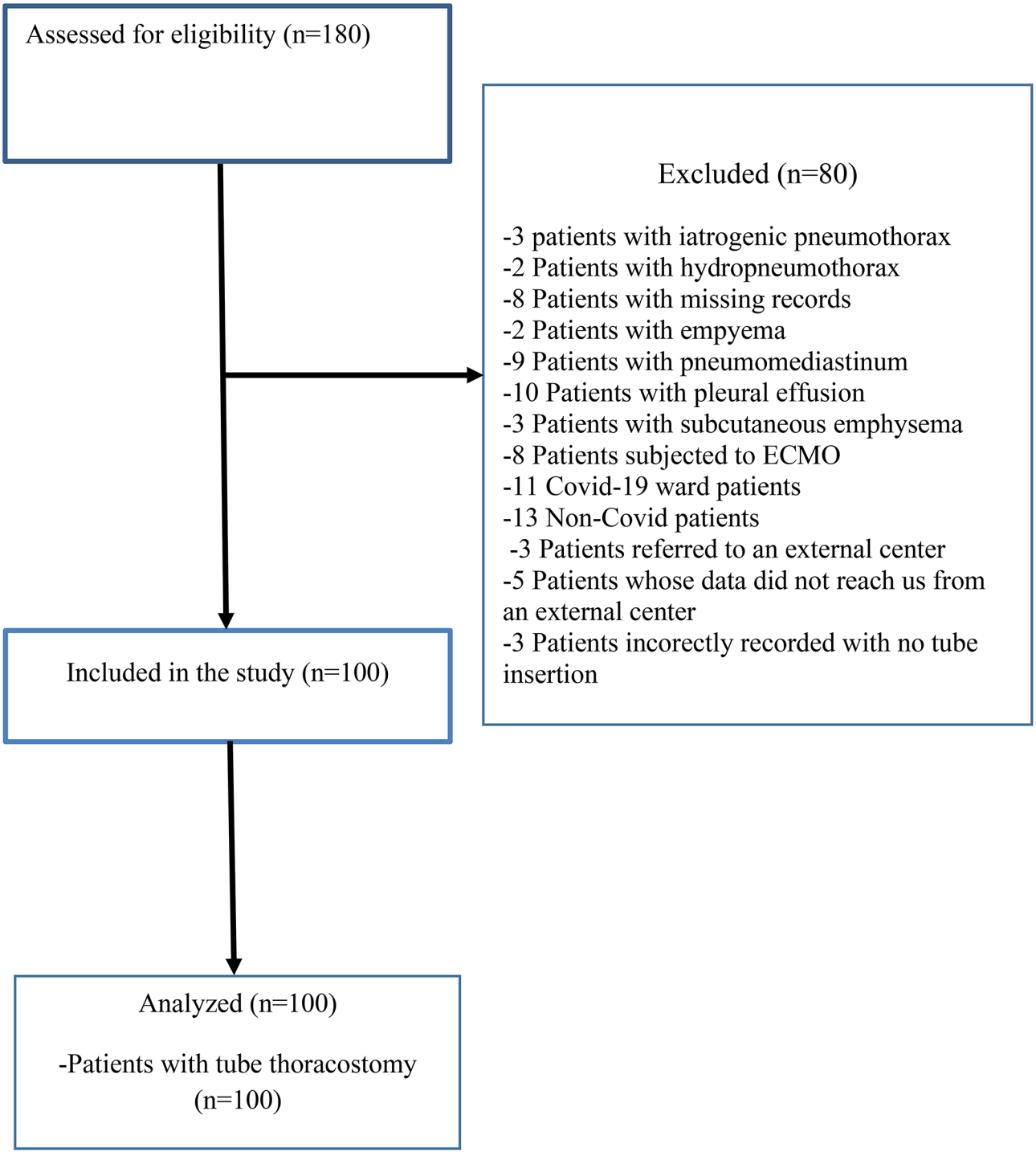

Fig. 1 Study flowchart

and the median PaCO2 value 48 (40–60) mmHg. These results were consistent with those of previous studies [14–17].

Pneumothorax was more common in male patients (63%). The most frequent comorbidities were hypertension in 38% of patients and DM in 23%. These findings were also consistent with other studies [6, 18–20].

PaCO2, BE, fibrinogen, ferritin, LDH, NLR, and lactate levels have been linked to poor prognosis in COVID-19 infection [7, 21–27]. Despite the elevation in these parameters in this study, no statistical significance was observed ($p>0.05$). Low pH values are associated with poor prognosis in COVID-19 infection [28], but no

Table 1 Patient characteristics ($n = 100$)

Variable		*N*	%	Mean (SD)	Median (IQR)
Age		100		66.93 (13.91)	68 (57–78)
Gender	Male	63	63%		
	Female	37	37%		
Follow-up time (days)		100		22.74 (17.41)	20 (10–29)
Duration of RT-PCR result to tube thoracostomy (days)		94		17.67 (11.92)	17 (9–23)
Duration of tube thoracostomy to Event (days)		100		9.96 (11.98)	6 (2–13)
Initial RT-PCR result	Positive	90	90%		
	Negative	8	8%		
	Unknown	2	2%		
CO-RADS Score	1	1	1%		
	2	0	0%		
	3	2	2%		
	4	6	6%		
	5	22	22%		
	CO-RADS score < 5	9	29%		
	CO-RADS score = 5	22	71%		
Presence of pulmonary involvement	Involvement present	50	%50		
	Involvement absent	1	%1		
	Not performed	18	%18		
Tube thoracostomy side	Right	62	62%		
	Left	24	24%		
	Bilateral	14	14%		
PEEP, cm H_2O		75		10.31 (4.48)	10 (8–12)
PIP, cm H_2O		75		26.69 (5.95)	26 (22–32)
FiO_2, %		87		80.06 (21.11)	80 (65–100)
Respiratory rate, breaths/min		75		23.71 (5.62)	22 (20–26)
HFNC		4		70 (8.17)	70 (63–78)
Flow L/min					
Oxygenation	Intubated	86	87%		
	Mask with reservoir	6	6%		
	HFNC	4	4%		
	NIV	2	2%		
	Simple face mask	1	1%		
Diagnosis	Pneumonia	97	97%		
	Pneumonia + Acute Ischemic Stroke	1	1%		
	Pnuemonia + malignancy	1	1%		
	Pneumonia + Postoperative	1	1%		
Comorbidity	Present	70	70%		
	Absent	25	25%		
	Unknown	5	5%		
DM		23	23%		
HT		38	38%		
CVD		12	12%		
Malignity		3	3%		
COPD		5	5%		
Rheumatological disease		3	3%		
Dementia		2	2%		
Other		9	9%		
Procalcitonin, µg/L		100		8.26 (36.99)	1 (0–4)
Ferritin, µg/L		97		1721.23 (3583.24)	1086 (584–1 556)
pH		100		7.19 (0.89)	7 (7–7)
PaCO2, mmHg		100		51.84 (20.52)	48 (40–60)
PaO2, mmHg		100		86.26 (27.11)	79 (69–105)

Table 1 (continued)

Variable	*N*	%	Mean (SD)	Median (IQR)
SpO2, %	100		92.8 (6.84)	95 (91–97)
HCO3-, mEq/L	100		24.45 (6.96)	25 (20–29)
BE, mmol/L	100		-0.2 (7.73)	1 (-5 – +5)
Lactate, mmol/L	100		3.63 (3.45)	3 (2–3)
WBC, $x10^3/\mu L$	100		17693.4 (10231.04)	15,500 (11125–20325)
Neutrophil, $x10^3/\mu L$	100		15,987 (8679.78)	14,450 (10150–19450)
Lymphocyte, $x10^3/\mu L$	100		1126 (3614.35)	500 (300–875)
NLR	100		36.81 (33.67)	25 (16–50)
LDH, U/L	92		856 (1612.98)	610 (457–903)
Fibrinogen, mg/dL	99		577.36 (203.25)	589 (438–693)
D-dimer, mg/L	100		8.39 (43.31)	2 (1–5)
CRP, mg/L	100		131.49 (107.23)	97 (47–199)
PaO2/FiO2, mmHg	87		119.31 (61.94)	106 (77–144)

Table 2 Overall survival of the patients in the ICU

	Number of Events/*N*	Median survival time in days (95% CI)	28-day OS probability (95% CI)
All patients	88/100	20 (17.82–22.18)	0.29 (0.20–0.38)

OS: overall survival

statistical significance was determined in the current ($p>0.05$).

Studies have reported a relationship between pneumothorax and neutrophil count [6, 29], hypoxia and leukocytosis, but none between pneumothorax and CRP, procalcitonin, or D-dimer [19]. Statistical analysis showed that no significance was achieved in these parameters ($p>0.05$).

The mechanism of spontaneous pneumothorax in COVID-19 disease is thought to be associated with viral alveolar membrane damage and cystic and fibrotic changes. The alveolar membrane has a greater tendency to rupture due to inflammation, and this is exacerbated by increased intrathoracic pressure resulting from severe cough or mechanical ventilation. All these factors are thought to be capable of causing pneumothorax [2, 9, 30]. These factors were evaluated as a cause of pneumothorax in the current patient group. No information

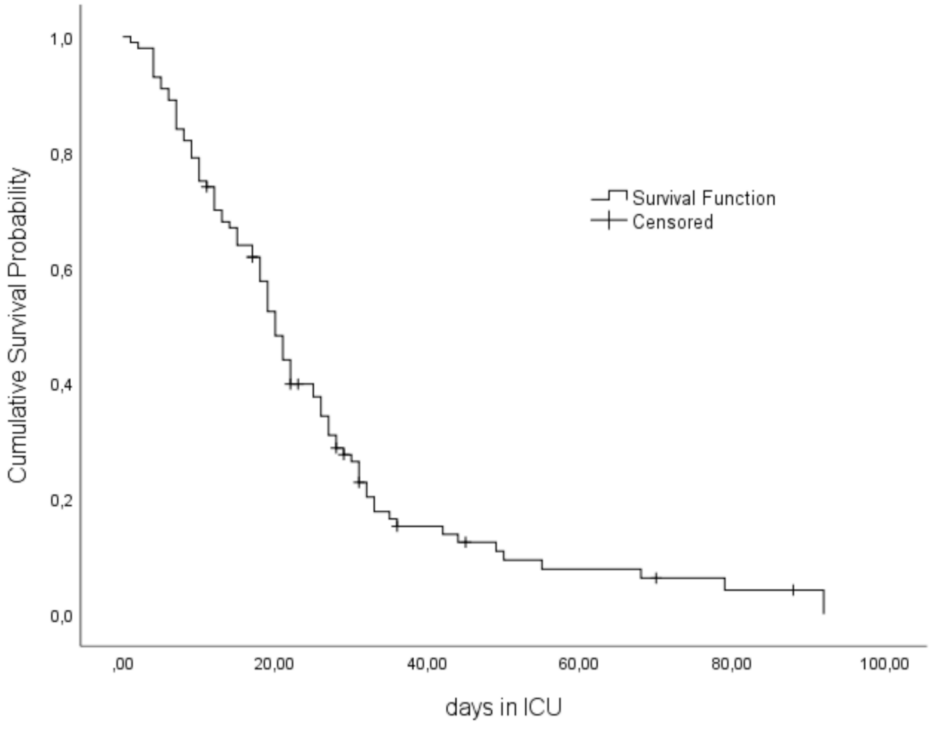

Fig. 2 Kaplan-Meier Survival Curve of the Patients in the ICU

Table 3 Cox Proportional hazards Model

Covariate (ref.)	Univariate		Multivariate[a]	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age ≥ 68 (< 68)	1.85 (1.20–2.84)	**0.005***	2.23 (1.39–3.56)	**0.001**
Male (female)	1.17 (0.75–1.81)	0.486		
Initial RT-PCR		0.243		
Negative (unknown)	2.29 (0.48–10.85)	0.296		
Positive (unknown)	1.16 (0.28–4.74)	0.837		
Tube thoracostomy side		0.895		
Left (bilateral)	1.05 (0.52–2.12)	0.888		
Right (bilateral)	1.14 (0.62–2.09)	0.675		
PEEP, ≥ 10 (< 10) cm H2O	0.96 (0.57–1.61)	0.862		
PIP, ≥ 26 (< 26) cm H2O	1.08 (0.66–1.78)	0.750		
FiO_2, ≥ 80 (< 80) %	1.44 (0.89–2.33)	0.127		
Respiratory rate, ≥ 22 (< 22) breaths/min	1.05 (0.63–1.75)	0.857		
Oxygenation other than intubation (Intubated)	2.38 (1.27–4.47)	**0.014***	2.24 (1.11–4.52)	**0.024**
Comorbidity		0.435		
Present (absent)	1.38 (0.83–2.27)	0.213		
Unknown (absent)	1.13 (0.39–3.30)	0.823		
DM present (absent)	1.43 (0.86–2.36)	0.180		
HT present (absent)	1.78 (1.15–2.77)	**0.011***		
CVD present (absent)	1.35 (0.68–2.65)	0.407		
Procalcitonin, ≥ 1 (< 1) µg/L	1.31 (0.86–1.99)	0.216		
Ferritin, ≥ 1086 (< 1086) µg/L	1.08 (0.70–1.66)	0.731		
pH		0.119		
pH < 7.35 (7.35–7.45)	1.05 (0.64–1.70)	0.853		
pH > 7.45 (7.35–7.45)	0.57 (0.29–1.11)	0.098		
PaCO2		0.337		
PaCO2, < 35 (35–45) mmHg	1.70 (0.85–3.40)	0.133		
PaCO2, > 45 (35–45) mmHg	1.13 (0.68–1.88)	0.634		
PaO2, < 79 (≥ 79) mmHg	1.16 (0.76–1.79)	0.488		
SpO2, < 95 (≥ 95) %	1.63 (1.06–2.50)	**0.026***		
HCO3-		**0.002***		**< 0.001**
HCO3-, < 22 (22–26) mEq/L	1.57 (0.90–2.74)	0.114	1.95 (1.08–3.50)	**0.026**
HCO3-, > 26 (22–26) mEq/L	0.63 (0.36–1.09)	0.099	0.64 (0.36–1.16)	0.145
BE		**0.004***		
<-2 (-2 – +2) mmol/L	1.47 (0.82–2.62)	0.193		
>+2 (-2 – +2) mmol/L	0.65 (0.36–1.18)	0.154		
Lactate, ≥ 3 (< 3) mmol/L	1.40 (0.90–2.18)	0.138		
WBC, ≥ 15 000 (< 15 000) $x10^3$/µL	1.36 (0.88–2.08)	0.163		
Neutrophil, ≥ 14 000 (< 14 000) $x10^3$/µL	1.53 (0.99–2.36)	0.052		
Lymphocyte, < 500 (≥ 500) $x10^3$/µL	1.58 (1.01–2.45)	**0.048***		
NLR, ≥ 25 (< 25)	1.22 (0.80–1.87)	0.354		
LDH, ≥ 610 (< 610) U/L	1.39 (0.90–2.16)	0.140		
Fibrinogen, ≥ 589 (< 589) mg/dL	1.44 (0.94–2.22)	0.093		
D-dimer, ≥ 2 (< 2) mg/L	1.22 (0.80–1.86)	0.364		
CRP, ≥ 97 (< 97) mg/L	1.52 (0.99–2.32)	0.056		
PaO_2/FiO_2, < 100 (≥ 100) mmHg	1.23 (0.78–1.95)	0.370		

*Statistically significant ($p < 0.05$) variables included in the multivariate CPH. [a]Multivariate model with Forward stepwise method yielded LR Chi-square = 29.210; df = 4; $p < 0.001$ (Total $N = 95$ and N of events = 84)

about whether these patients had previously experienced COVID-19 infection was available.

Pneumothorax is the most frequently reported form of barotrauma, at rates of 72.2–76% [6, 31]. Pneumothorax development has been reported in 1.6% of patients admitted to the intermediate respiratory care unit [18].

Cases of spontaneous pneumothorax have been detected in 0.56‰ of COVID-19 patients presenting to emergency departments, compared to 0.28‰ in patients

without COVID-19 [19]. These findings show that pneumothorax rates are higher in patients with COVID-19.

The overall mortality rate from COVID-19 is 2–3%, although this rises to between 15% [14, 32] and 74% [14, 33, 34] when invasive mechanical ventilation management is required. The mortality rate among patients diagnosed with COVID-19 admitted to hospital and developing pneumothorax is 52.2% [35], and 63.1% in those diagnosed with COVID-19 developing pneumothorax and admitted to the ICU [6]. Mortality rates are thus high in COVID-19 patients with pneumothorax. The mortality rate in the present study was high, at 88%. We attribute this higher mortality rate to the study involving patients admitted to the ICU with tube thoracostomy and to 87% of these receiving invasive mechanical ventilation.

Ct scans show the peripheral distributions of the initial ground-glass opacity changes seen in patients with COVID-19 [36, 37]. Peripherally located bullae may rupture spontaneously or as a result of positive-pressure ventilation [15]. The presence of pulmonary involvement findings in 82 patients in this study may have increased the disposition to pneumothorax. Retrospective examination of the thoracic CT reports showed that some patients were evaluated by means of CO-RADS scores and others in terms of presence or absence of pulmonary involvement. Due to these two different classifications statistical analysis of thoracic CT changes was not possible.

Significantly lower 28-day survival has been reported in COVID-19 patients with pneumothorax aged≥70 years compared to younger individuals (≥70 years 41.7±13.5% survival versus <70 years 70.9±6.8% survival; $p=0.018$) [6], while in the present study 28-day OS levels were also low at 29% (20 −38%). Multivariate analysis revealed that age over 68 (HR (95% CI)=2.52 (1.47–4.34); $p=0.001$) was significantly associated with mortality in patients in intensive care. This was consistent with previous studies [6, 20]. Care in terms of pneumothorax is required during follow-up of elderly patients.

Eight-seven% of the patients were intubated, while HFNC was used in 4%, NIV in 20%, non-rebreathe reservoir masks in 6%, and simple face masks in 1%. Multivariate analysis revealed a significant association between oxygenation other than intubation and mortality (HR (95% CI)=2.65 (1.28–5.45); $p=0.008$). In contrast, Shahsavarinia et al. observed no significant relationship between mortality and positive-pressure ventilation ($P=0.0001$) [20]. Difficult respiration and oxygenation must be considered, and intubation should not be delayed.

Tropism of the virus toward the lungs and kidneys may result in frequent acid-base changes due to pneumonia and kidney failure [16, 38, 39]. Acid-base imbalance can lead to disorders in multiple organs [36]. Studies have reported that 73-79.7% of patients with COVID-19 present with acidosis or alkalosis [16, 22, 40, 41]. COVID-19 patients admitted to the ICU exhibit poorer prognosis, with an 88% mortality rate due to acidosis [41].

A significant relationship between acidosis during pneumothorax and subsequent survival has been reported in COVID-19 patients. Twenty-eight day survival in acidotic COVID-19 patients developing pneumothorax (33.3%±10.8) has been reported to be significantly lower than that in non-acidotic patients (83.3%±7.6) ($p=0.001$) [6].

PCO2 levels begin to rise as COVID-19 progresses and respiratory functions are impaired [40], and respiratory acidosis develops as a result of hypercapnic respiratory failure [16].

Metabolic acidosis and a low bicarbonate concentration (<21 mEq/L) derive from multiple organ failure and are associated with high mortality in patients with severe COVID-19 [23]. Consistent with the previous literature, an HCO3- value lower than 22 mEq/L was associated with mortality ($p=0.026$). Therefore, since a low HCO3- value is a good and easily available marker for high mortality in patients with pneumothorax this can be of considerable benefit in routine clinical practice.

In this study, 24% of pneumothorax-related tube thoracostomies were in the left lung, 62% in the right lung, while 14% were bilateral. The 62% right tube thoracostomy rate was similar to those in other studies (48-81%) [19, 31, 42, 43]. This may be due to the right bronchus exhibiting more vertical extension [44]. However, another study reported equal left and right pneumothorax rates of 47% [35]. This may have been due to regional or genetic differences. The median time elapsing between RT-PCR confirmation and tube thoracostomy was 17 days. This was also consistent with the literature [18, 45, 46].

The mean time between tube thoracostomy and ex/alive departure from the ICU was 9.96±11.98 days. This was longer than the mean duration of tube thoracostomy of 6.7±4.5 days reported in another study [42]. The longer duration in the present study may be due its involvement of intensive care patients.

One of the limitations of this study involve its single-center character and low patient number. However, despite being conducted in a single center, this research is important since it includes all that center's results, its being conducted in a tertiary teaching and research hospital in which large numbers of patients are treated, and the institution being a central hospital of crucial importance to Istanbul. A second limitation is that the administration of oxygen therapy due to the hypoxic state may have affected the arterial blood gas results and thus have given rise to bias in the study findings. A third limitation is that the incidence of pneumothorax was not investigated. Fourth, since the study was conducted

retrospectively, the time when pneumothorax occurred could not be established, and measurements could not be performed. A final limitation is that is that since COVID-19 vaccination could not be completed during the study period and did not cover the entire population, and since the patients' known vaccination rate was very low (55 of the 100 patients were unvaccinated, 13 were vaccinated, and vaccination status in 32 was uncertain), the association between the risk of pneumothorax and vaccination was not investigated.

Nonetheless, there are also a number of strengths to this research. Several studies have included hospital and emergency department patients, while the present research investigated only patients developing pneumothorax with tube thoracostomy admitted to the ICU of a training and research hospital throughout the pandemic. In contrast to those other studies, the current research was based on the RT-PCR confirmation test, rather than on the time of admission or onset of symptoms.

HCO3-, identified as a prognostic risk factor for pneumothorax, was evaluated as a simple and practical parameter easily available from arterial blood gas.

In conclusion, age over 68, oxygenation other than by intubation, and an HCO3- values less than 22 mEq/L in patients developing pneumothorax associated with COVID-19 pneumonia and with tube thoracostomy emerged as prognostic risk factors associated with mortality in terms of pneumothorax.

Since the mortality rate in tube thoracostomy patients with pneumothorax diagnosed with COVID-19 and hospitalized in the ICU remains high, prognostic risk factors should be identified and strategies implemented to reduce the risk of pneumothorax and improve survival in these cases.

Abbreviations

RT-PCR	Reverse transcriptase polymerase chain reaction
CT	Thoracic computed tomography
CO-RADS	COVID-19 reporting and data system
FiO2	Fraction of inspired oxygen
PEEP	Positive end expiratory pressure
PIP	Peak inspiratory pressure
HFNC	High flow nasal cannula
NIV	Non-invasive mechanical ventilation
BE	Base excess
CRP	C-reactive protein
ICU	Intensive care unit
WHO	World Health Organization
NLR	Neutrophil to lymphocyte ratio
PaO2/FiO2	Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology
OS	Overall survival
CPH	Cox proportional hazards
HT	Hypertension
DM	Diabetes mellitus
CVD	Cardiovascular disease
IBM SPSS version 25	IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA
STATA 15	Stata Statistical Software: Release 15. College Station, TX, USA

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Since this study was retrospective, informed and written consent was not obtained from the patients themselves or their relatives. Permission to waive informed consent was obtained from the Marmara University Medical Faculty ethical committee. Ethical approval was obtained from the Marmara University Medical Faculty ethical committee (no. 09.2022.710) following receipt of permission from the Turkish Ministry of Health.

Consent for publication
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Competing interests
The authors declare no competing interests.

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