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Coronavirus Pandemic

Prognostic predictors for mortality of patients with COVID-19 in an intensive care unit

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Abstract

Introduction: Fatality due to COVID-19 continues to be a challenge. Timely identification of critical COVID-19 patients is crucial for their close clinical follow-up and treatment. We aimed to identify the mortality predictors of critical COVID-19 patients.

Methodology: We analyzed medical records of 232 out of 300 patients with COVID-19 hospitalized in the intensive care unit (ICU) whose medical records were available in the hospital database. Non-survivors and survivors were compared for parameters. Medical records of demographics, comorbidities, radiological signs, respiratory support, and laboratory tests on the first day of ICU admission were included. The durations of ICU stay and hospitalization were also evaluated.

Results: The patients with Acute Physiology and Chronic Health Evaluation II (APACHE-II) score above 28.5 and the patients with blood urea nitrogen (BUN) above 45.5 mg/dL were significantly more mortal (95% CI: 0.701, $p = 0.0001$; 95% CI: 0.599, $p = 0.022$; respectively). Partial oxygen pressure/fraction of inspired oxygen (P/F) ratio below 110.5 mmHg was a predictor for mortality (95% CI: 0.397, $p = 0.018$). Older age, smoking, crazy paving pattern on computed tomography (CT), and short duration of hospitalization were also predictors of mortality. The patients requiring invasive mechanical ventilation were significantly more mortal whereas the patients requiring high flow oxygen and non-invasive ventilation were significantly more likely to survive.

Conclusions: We recommend evaluating APACHE-II score, BUN value, P/F ratio, age, smoking status, radiological signs on CT, length of hospitalization and modality of respiratory support upon ICU admission to identify critical patients with poor prognoses.

Key words: COVID19; mortality determinants; ICU; APACHE II.

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Introduction

COVID-19 is a severe pneumonia-like illness caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and has emerged as a global health threat due to its rapid spread and fatality [1]. On 11 March 2020, the World Health Organization (WHO) recognized COVID-19 as a pandemic [2]. The origin and intermediate host of SARS-CoV-2 are still unknown. It is transmitted from human to human by respiratory droplets and physical contact. It leads to a wide range of clinical states, from asymptomatic to mild illness with symptoms such as fever, cough, fatigue, sputum, shortness of breath, sore throat, and headache, to moderate diseases such as pneumonia [3]. Approximately 10% of the confirmed cases result in acute lung failure and, in some cases, multi-organ failure involving the heart, kidney, and gastrointestinal tract, leading to a high mortality rate [4,5]. In a study carried out by Chinese physicians, the fatality rate of critical patients was observed at about 50% [6], which is similar to the mortality from severe acute respiratory distress syndrome (ARDS) [7] after 28 days of severe SARS-CoV-2 pneumonia.

The first COVID-19 case was reported in Istanbul, Turkey on March 10, 2020 [8]. This was followed by a gradual increase in the number of COVID-19 cases and deaths in the city. Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital was declared as a pandemic hospital by the Turkish Health Ministry to serve severe COVID-19 patients, the numbers of whom has rapidly increased since March 2020.

Identifying the predictors of mortality for critical patients is crucial for prompt and effective clinical response. There is a lack of information about the prognostic predictors of critical patients with COVID-19. Thus, we aimed to identify the predictors for mortality of patients with COVID-19 in the intensive care unit (ICU) at this reference hospital.

Methodology

The retrospective cohort study was based on patient data collected from the electronic medical records of the hospital. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Turkish Health Ministry and the Ethics Committee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (REF No: 2021-91).

Patients Recruitment

Data of 300 patients with COVID-19 hospitalized in the ICU between March 2020 and February 2021 was scanned from electronic medical records by the reviewers. Data of 232 out of the 300 patients, were evaluated to determine mortality predictors in this study (Figure 1).

Selection of the patients with COVID-19 registered at the ICU was based on the following criteria: (i) a laboratory-confirmed SARS-CoV-2 infection by a real time polymerase chain reaction (RT-PCR) test and/or specific clinical-radiological findings according to the WHO guidelines [9], and (ii) severe manifestation of COVID-19 requiring treatment in an ICU - characterized as a hospital ward specializing in the care of critical patients with the availability of organ and respiratory support therapies, including medical therapy, oxygen support (e.g., high-flow, nasal cannula), non-invasive ventilation (NIV), and/or invasive mechanical ventilation (IMV).

Data Collection

The data was collected upon ICU admission and included information regarding patient characteristics (e.g., age, gender, comorbidities, smoking status); radiological signs on CT scan; arterial blood gas analyses (PaO_2, partial oxygen pressure/fraction of inspired oxygen [P/F]); and the following laboratory values: inflammatory (procalcitonin, C-reactive protein [CRP], ferritin), coagulation (prothrombin time [PT], D-dimer, fibrinogen), renal (blood urine nitrogen [BUN], creatinine), liver (aspartate aminotransferase [AST], alanin aminotransferase [ALT], lactate dehydrogenase [LDH], total bilirubin), and cardiac (troponin I [TnI]). Additionally, complete blood count (CBC) parameters (leucocyte, platelet, neutrophil, lymphocyte, neutrophil/lymphocyte ratio [NLR], monocyte) were also analyzed.

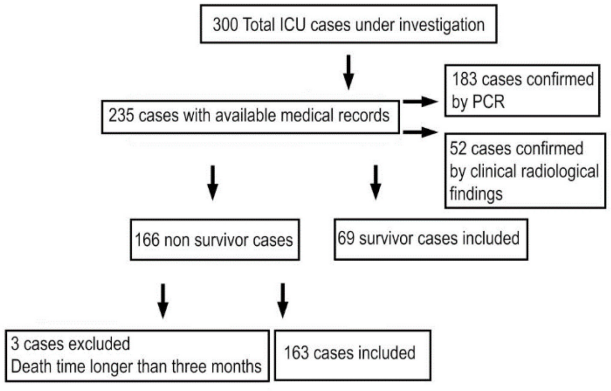
Comorbidities including chronic pulmonary diseases (CPD), such as chronic obstructive pulmonary disease, asthma, and bronchiectasis; chronic liver diseases (CLD), such as hepatitis and liver failure; chronic cardiovascular diseases (CVD), such as coronary artery disease and heart failure; chronic renal diseases (CRD), such as chronic renal failure; malignancy; immunosuppression; diabetes mellitus (DM), and hypertension (HT) - were reviewed. Smoking status was assessed, and patients were classified as one of the following: ever-smoker (both current and former) and non-smoker. Radiological signs on patients' CT scans were detected by two radiologists and two chest physicians simultaneously and categorized according to the following: bilateral ground-glass opacity (GGO), unilateral GGO, consolidation, crazy paving pattern, nodules, reticulation, and pleural effusion.

Moreover, the dates of ICU admission, ICU discharge, and hospital discharge, and patient death were obtained from the electronic medical records of the hospital. Patients' scores on the Acute Physiology and Chronic Health Evaluation II (APACHE-II), an intensive care disease severity scoring system, were also evaluated. Additionally, treatments (e.g., oxygen support, NIV, and IMV) of the patients upon ICU admission were analyzed, and the presence of tracheostomy during patients' ICU stays was reviewed.

Measurements

The biochemical parameters were measured using a clinical chemistry analyzer (Roche Diagnostic/ Cobas 600 c501, Basel, Switzerland). CBC was measured using the Mindray Auto Hematology Analyzer (BC-6800, SH-77002444, Shenzhen, China). The levels of PT, fibrinogen, and D-dimer were analyzed by the Across Auto System analyzer (OCTO-M, OM.96.1020, Istanbul, Turkey).

Figure 1. Flowchart describing patient selection. Of the total 300 ICU patients, 235 patients whose medical records were accessed were evaluated. Three non-survivors who did not meet the inclusion criteria were excluded.



End-point of the study

Three-month mortality was reviewed to identify those who died due to COVID-19. Surviving and non-surviving patients were compared in terms of demographic and clinical data, radiological signs, and routine-blood testing parameters.

Statistical Analysis

Statistical Package for Social Science (SPSS) version 21.0 was used for statistical analysis, with the descriptive statistics presented as mean ± standard deviation, frequency, and percentages. In the case of the categorical variables, comparisons regarding mortality status within three months of admission to the ICU were made by the Chi-square test. Comparisons were made by Student's t-test in the case of the continuous variables. A receiver operating characteristic (ROC) curve analysis was used to identify the efficiency of the parameters in predicting the mortality of the ICU patients, and a p value lower than 0.05 was accepted as significant.

Results

Demographic, clinical, and radiological features

The study was conducted on 232 critical patients diagnosed with COVID-19. As shown in Table 1, 69 of the 232 patients (30%) were female. The average age of patients was 65 ± 14 years. The non-survivors were significantly older than the survivors (mean age of 66.6 vs 60 years, respectively, $p < 0.001$). Among the 232 patients, 183 diagnoses (79%) were confirmed by RT-PCR testing, but the RT-PCR results did not influence mortality. The smoking status of the patients was as follows: 98 patients (42%) were non-smokers, 98 patients (42%) were former smokers, and 36 patients (16%) were current smokers. Non-smoker patients had lower mortality ($p = 0.006$).

The frequencies of comorbidities among the non-survivors and the survivors were the same and there

Table 1. Demographic, clinical, and radiological features of ICU patients with COVID-19.

	Total N = 232	**Non-survivors N = 163 (%70)**	**Survivors N = 69 (%30)**	***p***
Age, median ± SD, years	65 ± 14	66.6 ± 12	60 ± 15	< 0.001
Male gender	163 (70)	115 (71)	48 (70)	0.876
RT-PCR confirmation	183 (79)	127 (78)	56 (81)	0.725
Smoking status				
Non-smoker	98 (42)	59 (36)	39 (57)	
Former smoker	98 (42)	80 (49)	18 (26)	0.004
Current smoker	36 (16)	24 (15)	12 (17)	
Smoking status				
Ever-smoker	134 (58)	104 (64)	30 (44)	0.006
Non-smoker	98 (42)	59 (36)	39 (57)	
Comorbidities				
Chronic pulmonary disease	76 (33)	56 (34)	20 (29)	0.449
Chronic liver disease	2 (1)	1	1	0.507
Chronic CVD	87 (38)	66 (41)	21 (30)	0 182
Chronic renal disease	10 (4)	8 (5)	2 (3)	0.727
Malignancy	37 (16)	29 (18)	8 (12)	0.327
Immunosuppression	9 (4)	6 (4)	3 (4)	0.728
Diabetes Mellitus	73 (32)	51 (31)	22 (32)	0.998
Hypertension	121 (52)	87 (53)	34 (49)	0.666
ICU first day admission respiratory support				
High flow oxygen	11 (5)	2 (1)	9 (13)	< 0.001
Nasal cannula oxygen	24 (10)	14 (9)	10 (15)	0.237
NIV	58 (25)	30 (18)	28 (41)	0.001
IMV	165 (71)	137 (84)	28 (41)	< 0.001
Tracheostomy	7 (3)	3 (2)	4 (6)	0.201
APACHE-II, mean ± SD	23.1 ± 10.2	25.4 ± 10.2	17.8 ± 8.1	< 0.001
Length of ICU stay, mean ± SD, days	13.1 ± 12.9	13.4 ± 12.9	12.3 ± 13.1	0.553
Length of hospitalization, mean ± SD, days	17.3 ± 16.3	14.5 ± 13.9	23.9 ± 19.3	< 0.001
Presence of radiological signs	219 (94)	155 (95)	64 (93)	0.535
Bilateral ground glass	197 (85)	137 (85)	60 (87)	0.690
Unilateral ground glass	18 (8)	14 (9)	4 (6)	0.596
Consolidation	146 (63)	106 (65)	40 (58)	0.372
Crazy paving	27 (12)	24 (15)	3 (4)	0.025
Nodules	34 (15)	26 (16)	8 (12)	0.543
Reticulation	52 (22)	39 (24)	13 (19)	0.491
Pleural effusion	27 (12)	22 (14)	5 (7)	0.262

Values are given as count (percent) as appropriate. SD: standard deviation; N: number of patients; RT-PCR: real time polymerase chain reaction; ICU: intensive care unit; NIV: non-invasive ventilation; IMV: invasive mechanical ventilation; CVD: cardiovascular disease; APACHE-II: Acute Physiology and Chronic Health Evaluation II. $p < 0.05$.

were no significant associations between comorbidities and patient mortality (Table 1).

Out of the 232 patients, 219 (94%) exhibited radiological signs compatible with COVID-19 on their CT scans. The most frequent radiological findings in non-survivor and survivor groups were bilateral ground glass and consolidation. A significant association was found between the crazy-paving pattern in radiological reports and high mortality rate ($p = 0.025$), with non-survivors exhibiting a higher number of crazy-paving patterns than the survivors (n = 24 vs 3) (Table 1).

Respiratory support, hospitalization, and survival times

As shown in Table 1, IMV was the most frequently administered supportive treatment to the patients (n = 165, 71%) upon ICU admission. Moreover, NIV was administered in 58 (25%) patients. Nasal cannula and high-flow oxygen support were administered in 24 (10%) patients and 11 (5%) patients, respectively. Patients who required high-flow oxygen support and NIV upon ICU admission had lower mortality rates *(p* = 0.001, $p < 0.001$, respectively), while patients who required IMV upon ICU admission had higher mortality rates *(p* < 0.001). Tracheostomy was performed for seven patients during their ICU stay, and three out of these seven patients died during their stays.

The ICU stay length was longer in the non-survivors than the survivors (mean: 13.4 vs 12.3 days). Moreover, the length of hospitalization (days) was significantly longer for the survivors than the non-survivors (mean: 23.9 vs 14.5, respectively, $p < 0.001$) (Table 1). Additionally, 166 patients died within 12 ± 23 days, and three month-mortality was observed in 163 patients (70%). The median time to death of these 163 patients was 12 ± 23 days. Three patients died after three months; thus, they were excluded from the study since they did not meet the end-point criteria.

In addition, the non-survivors had higher APACHE-II scores than the survivors, (mean: 25.4 vs 17.8, respectively, $p < 0.001$).

Routine-blood testing and arterial blood gases parameters

Routine-blood parameters were recorded upon ICU admission for all patients and then compared between the non-surviving and surviving patients. Various significant differences were found between the groups. The non-survivors had significantly higher BUN values (mg/dL) than the survivors (mean: 50.9 vs 41.7, respectively, $p = 0.013$). A low P/F ratio was significantly associated with mortality ($p = 0.017$), since the non-survivors had a lower P/F ratio (mmHg) than the survivors (mean: 106.4 vs 125.5, respectively).

Moreover, the non-survivors had a higher NLR than the survivors (mean: 18.1 vs 17.1, respectively), but there was no significant association between the NLR and mortality. The TnI values were high among non-survivor and survivor groups. Compared to the survivors, the non-survivors had lower TnI values (pg/mL) (mean: 21.7 vs 19.7, respectively), but this difference was not significant.

Table 2. Routine blood testing and arterial blood gases parameters of patients with COVID-19 on ICU admission.

	Normal range	Total N = 232	Non-survivors N = 163 (%70)	Survivors N = 69 (%30)	*p*
Leucocyte ($\times 10^9$ per L)	4-10	10.0 ± 16.2	9.9 ± 5.2	10.2 ± 4.1	0.751
Platelet ($\times 10^9$ per L)	150-450	229 ± 106	225 ± 107	240 ± 102	0.336
NLR	1.75	17.9 ± 26	18.1 ± 26	17.1 ± 27	0.921
Lymphocyte ($\times 10^9$ per L)	0.8-4	1.1 ± 26.1	1.1 ± 0.7	1.2 ± 0.8	0.202
Monocyte ($\times 10^9$ per L)	0.12-1.2	1.1 ± 26.2	0.05 ± 0.4	0.5 ± 0.4	0.176
Neutrophil ($\times 10^9$ per L)	2-7	1.1 ± 0.70	13.1 ± 16.4	21.6 ± 41.5	0.310
Troponin I (pg/mL)	0-11.6	20.2 ± 20	19.7 ± 19.7	21.7 ± 21.1	0.604
D-dimer (Quantitative) (mg/L)	0-0.6	2.6 ± 4.6	2.7 ± 4.8	2.4 ± 4.1	0.639
Fibrinogen (mg/dL)	200-400	568 ± 192	555 ± 192	594 ± 193	0.174
Prothrombin time (second)	10-14	13.9 ± 4	14 ± 4.4	13.7 ± 3;3	0.569
Procalcitonin (ng/mL)	< 0.5	1.5 ± 4.7	1.8 ± 5.4	2.4 ± 4.1	0.200
Creatinine (mg/dL)	0.6-1.2	1.7 ± 2.2	1.7 ± 5.4	0.9 ± 2.4	0.858
BUN (mg/dL)	10-50	48.1 ± 25	50.9 ± 27	41.7 ± 18.3	0.013
Lactate dehydrogenase (U/L)	135-225	497 ± 278	488 ± 280	519 ± 274	0.453
Alanine aminotransferase (U/L)	< 41	66 ± 148	42 ± 88	47 ± 64	0.677
Aspartate aminotransferase (U/L)	< 40	43 ± 81	72 ± 177	52 ± 28	0.362
Total bilirubin (mg/dL)	0.1-1.5	0.7 ± 0.6	0.7± 0.7	0.6 ± 0.4	0.298
CRP (mg/L)	Risk: > 5	131 ± 84	133 ± 82	127 ± 89	0.683
Ferritin (ng/mL)	23.9-336.2	527 ± 192	525 ± 393	529 ± 392	0.941
PaO_2 (mmHg)	70-100	61.3 ± 32.9	62 ± 32.8	60.6 ± 33.3	0.826
P/F (mmHg)	300-500	112 ± 55	106.4 ± 52.8	125.5 ± 59.5	0.017

Values are given as mean ± standard deviation as appropriate; NLR: neutrophil/lymphocyte ratio; BUN: blood urea nitrogen; CRP: C-reactive protein; PaO_2: partial oxygen pressure; P/F; PaO_2/FiO_2 (partial oxygen pressure/fraction of inspired oxygen) rate; $p < 0.05$.

D-dimer, fibrinogen, and CRP values were elevated in non-survivor and survivor groups. Specifically, the D-dimer (mg/L) and CRP (mg/L) values were higher in the non-survivors than in the survivors (mean: 2.7 vs 2.4; 133 vs 127, respectively), but no significant correlations were found between the D-dimer and CRP levels, and mortality.

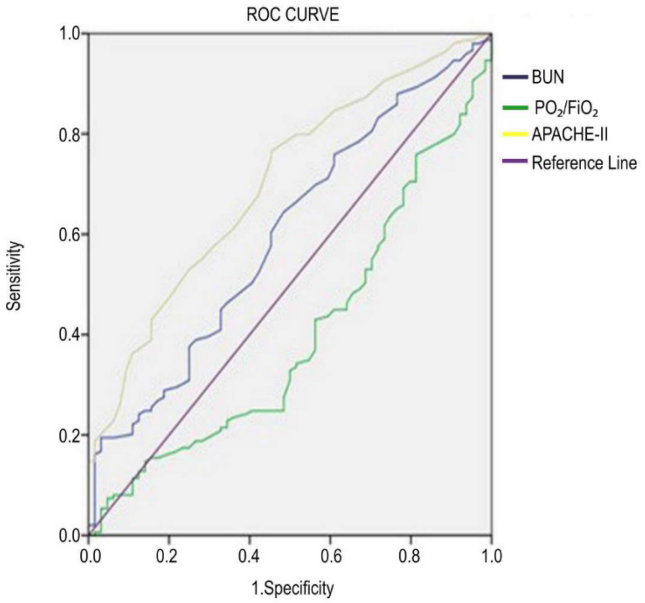
Routine-blood testing and arterial blood gases parameters of patients are shown in Table 2.

ROC curve analysis of parameters

A ROC curve analysis was used to identify the efficiency of the parameters in predicting mortality of the ICU patients (Figure 2). The APACHE-II, BUN, and P/F values exhibited the highest area under the curve (AUC) in the ROC analysis (0.701, 0.599, and 0.397, respectively).

The patients with APACHE-II scores above the cut-off value of 28.5 and those with BUN values above the cut-off value of 45.5 (mg/dL) exhibited significantly higher mortality (p = 0.0001 and p = 0.022, respectively). Moreover, a P/F ratio below the cut-off value of 110.5 mmHg was a predictor of mortality (p = 0.018). The AUC, cut-off, sensitivity, and specificity values for the APACHE-II and laboratory parameters are listed in Table 3.

Figure 2. ROC curves of APACHE-II, BUN and PaO2/FiO2 in predicting mortal SARS-CoV-2 infection on ICU admission. APACHE-II, BUN, and P/F values exhibited the highest AUC in the ROC analysis (0.701, 0.599, 0.397, respectively).



Discussion

It is important to predict the course and outcomes of the COVID-19 disease in the worldwide pandemic. Specifically, the rapid identification of critical COVID-19 patients with poor prognoses upon ICU admission is key to determine which patients need close clinical follow-up and management. A few studies have been published on the mortality predictors of COVID-19 patients in ICU since the outbreak of the pandemic.

To date, many outcomes have been reported regarding the mortality rates of COVID-19 patients in ICUs, some of them reporting 8% [10], 22.7% [11], 38.7% [12], 56% [13], and 66.7% [14] in the literature. In this study, the mortality rate was quite high at 70%. Since we have limited number of beds in the respiratory ICU, we only hospitalize the very severely ill patients. In addition, we consider that the mortality rate was so high because the availability of treatment options was different at various stages of the pandemic and the ICU admission times were different. The most important reason for the poor outcomes reported in the studies may be insufficient resources in the overwhelmed ICUs. Moreover, the fact that such different mortality rates were observed may be attributed to different study designs, the fact that the studies included populations with different ethnicity and number, and the mortality rates were measured at different time intervals.

As reported previously [12,15], older age was a predictive factor for mortality among the critical patients in this study. The ability of the immune system to eradicate the virus diminishes with aging [16]. Specifically, the spleen, thymus glands, and lymph nodes retrograde during aging, which interferes with the natural differentiation of T cells, phagocyte viability, and the secretion of natural killer cells. Additionally, cytokine-storms are more common in the elderly. The imbalance of pro-inflammatory and anti-inflammatory forces in the elderly individuals causes destructive immune dysregulation based on the theory of immunologic discordance [17]. Furthermore, in patients aged > 60 years, there is a significant decrease

Table 3. Efficiency of APACHE-II and laboratory parameters in predicting mortality of patients with COVID-19 on ICU admission.

Parameters	Cut-off value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	*p*
APACHE-II	28.5	0.701	64	91	0.0001
BUN (mg/dL)	45.5	0.599	56	68	0.022
P/F ratio (mmHg)	110.5	0.397	65	51	0.018

AUC: area under the curve; APACHE-II: Acute Physiology and Chronic Health Evaluation II; BUN: blood urea nitrogen; P/F; PaO_2/FiO_2 (partial oxygen pressure/fraction of inspired oxygen) rate. $p < 0.05$; significant value.

in the functions of the respiratory immune barrier, particularly the tracheal epithelial ciliary motion, alveolar phagocytosis, ventilation, and the cough reflex, resulting in poor virus clearance [18]. However, no association between gender and mortality was observed in this study, which is in contrast to the findings from previous studies [19,20].

In a previous study, no significant association was found between smoking and increased mortality rate [21]. However, we found that former smoking and current smoking were predictors for mortality in ICU patients, similar to in another study [15]. While smoking may increase pulmonary inflammation and epithelial cell permeability as well as induce mucus overproduction and impaired mucociliary clearance [22], specific effect of smoking on the COVID-19 disease is still polemic. Hypotheses promote both a potentially dangerous effect by the overexpression of the ACE 2 receptor gene [22] and a potentially preventive outcome by decreasing the burden of cytokine-storm in usually critical patients with an extreme immune response to COVID-19 [23]. In addition, risk factors of COVID-19 severity, such as CPD, CVD, and DM, are more frequent among smokers. Thus, overall, the impact of smoking on the mortality of critical patients with COVID-19 is still controversial.

Comorbidities such as HT, DM, and coronary heart disease were related to the high mortality rate in hospitalized patients with COVID-19 in previous studies [20,24]. Chronic Obstructive Pulmonary Disease (COPD), hypercholesterolemia, and Type II DM were determined as predictors for mortality in another study [25]. A systematic review and meta-analysis of 42 studies declared that HT, DM, CVD, COPD, cancer, and acute kidney injury were associated with a higher rate of mortality [26]. In contrast, comorbidities such as HT, CVD, CPD, DM, malignancy, CRD, immunosuppression, and CLD had no influence on mortality in the present study. Since comorbidities were rare in the study group, no significant association was found between comorbidity and mortality.

Francone *et al*. considered GGO as an early-phase radiological sign and crazy-paving pattern as a late-phase radiological sign [27]. They also found patients with a CT score of ≥ 18 to exhibit significantly higher mortality, and CT scores have been observed to be significantly higher among late-phase compared to early-phase patients. Moreover, two previous studies showed that crazy paving on CT was a predictor for poor prognosis in patients with COVID-19 [28,29]. Likewise, in this study, the crazy paving pattern had an association with mortality (p = 0.025), while no association was found between GGO and mortality. Bilateral GGO was the most commonly observed radiological sign in the present study. Crazy paving patterns on the CT scans were observed in a small number of patients (n = 27), and 24 of these patients died.

There is still no curative treatment for COVID-19, and symptomatic and supportive treatments are the major methods of disease management. In this study, it was observed that hypoxemic respiratory failure leading to IMV upon ICU admission was associated with mortality, similar to a previous study [30]. Meanwhile, mortality was found significantly less frequently among patients requiring high flow oxygen support and NIV upon admission to the ICU. These findings indicated that treatment steps were increased in parallel with the clinical worsening of the patients.

In a previous multicenter study [31], patient hospitalization duration was found to be significantly longer among survivors (mean = 26.1 days) than among non-survivors (mean = 15.6 days; $p < 0.001$), and this result was in line with the present study, as the length of hospitalization was longer in the case of the survivors than the non-survivors (mean = 23.9 vs 14.5 days; $p < 0.001$).

In a previous study, APACHE-II score was found to be significantly predictive for mortality of ICU patients with COVID-19 [32]. Similarly, APACHE-II score had the highest specificity (91%) above the cut-off value of 28.5 among the other mortality predictors in this study. APACHE-II has 12 physiologic measures and supplementary subjects based on patient age and the presence of chronic disease [33]. These supplementary subjects have been declared as mortality predictors for COVID-19 in previous studies. Consequently, the APACHE-II score is an exhaustive and effective predictor for mortality even when used alone, as supported by the present study.

BUN ≥ 20 mg/dL is a minor criteria used to identify ICU patients with community-acquired pneumonia before the development of organ failure [34]. BUN has been previously found to be a prognostic predictor for severe patients with COVID-19 [35]. In another study of COVID-19 patients admitted to the emergency department, the AUC value of BUN level was found to be 0.771, and BUN > 16.05 mg/dL had an 83.3% sensitivity and a 58.5% specificity for predicting mortality [36]. In the present study, it was found that patients with COVID-19 pneumonia with a BUN value > 45.5 mg/dL exhibited significantly higher mortality.

Moreover, the AUC value of the BUN level was 0.599, with BUN having a 56% sensitivity a 68% specificity for predicting mortality. A 100-point increase in the P/F ratio decreased the risk of mortality by 44% (HR, 0.66; 95% CI, 0.61-0.71; $p < 0.001$), while a low P/F ratio was declared as a predictor for mortality of ICU patients with COVID-19 in a previous study [24]. Similarly, patients with P/F < 110.5 mmHg exhibited higher mortality, and those with a P/F ratio below this cut-off value had 65% sensitivity and 51% specificity in terms of predictive value in the present study.

In a previous study, the incidence of in-hospital death significantly increased across NLR tertiles (2.44% vs 6.17% vs 31.71% for tertile 1, tertile 2, and tertile 3, respectively) [37]. In this study, although the NLR of the non-survivors was found to be higher than that of the survivors, no significant correlation was observed between NLR and mortality. High CRP [20,38-41] and D-dimer [38-42] levels were found to be the predictors of the in-hospital mortality of COVID-19 patients in previous studies. Similarly, a single-center study including critical COVID-19 patients showed that elevated levels of CRP and D-dimer were the indicators of mortality [43]. In our study, although high CRP and D-dimer values were correlated with mortality, they were not statistically significant associations. The correlation of relevant parameters with the APACHE II score, which was related to the severity of the disease, was examined and no correlation was identified. These outcomes of the laboratory findings might be due to the small sample size of the single-center study.

The limitations of this study include its retrospective design and the patient population, whose detailed anamnesis could not be obtained due to their states of consciousness. Furthermore, since our study was single-center in design, multicenter studies should be conducted in the future to represent the general population.

Conclusions

We recommend the evaluation of APACHE-II, BUN, and P/F to identify critical COVID-19 patients with poor prognoses. Additionally, older age, smoking status, and the presence of crazy paving pattern on the CT scan can be practically used to predict patient mortality upon ICU admission. In this study, critical COVID-19 patients requiring IMV upon ICU admission were found to exhibit higher mortality, while critical patients requiring high-flow oxygen and NIV upon ICU admission were found to exhibit higher survivability. In addition, an association between short length of hospitalization and the high mortality rate of critical patients was observed in the present study. Overall, we recommend that more multicenter studies on the predictors for mortality of critical patients with COVID-19 should be performed.

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Authors' Contributions

Concept: HA, HKO, STO; Design: HA; Supervision: HA, HKO, STO, SA; Resources: HA, HKO, EAO, NB; Data Collection and/or Processing HA, STO, EAO, NB, FTA; Analysis and/or Interpretation: HA, FTA, EAO, NB; Literature Review: HA, EAO, NB, SA; Writing: HA; Critical Review: HA, STO, FTA, SA. All co-authors have seen and approved the final version of the paper and have agreed to its submission for publication.

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