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The relationship of laboratory parameters and mortality of patients followed in intensive care units with COVID-19

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ABSTRACT

Aim: We aimed to evaluate the parameters associated with mortality in COVID-19 patients followed up in the intensive care unit.

Material and Method: Three hundred twenty-one patients followed up with the diagnosis of COVID-19 were included in the study. Demographic characteristics, laboratory and clinical parameters were compared in patients with and without mortality.

Results: A higher intubation rate (98.6% vs. 10.9%) and longer hospitalization (10.0 vs. 8.0 days) were detected in the non-survivor group ($p<0.001$). The neutrophil count, ferritin, troponin I, INR, PT, LDH, urea, creatinine, procalcitonin, WBC, CRP, AST, neutrophil/lymphocyte ratio, and CRP/albumin ratio were significantly higher in the non-survivor group, whereas the lymphocyte count, albumin, monocyte, and platelet counts were significantly lower. A multivariate logistic regression model identified endotracheal intubation, high platelet count, low LDH, low albumin, and decreased CRP/albumin ratio as risk factors associated with intensive care unit mortality. Albumin had the highest prognostic accuracy with an AUC of 0.681 (95% CI: 0.621-0.742) and the highest sensitivity (84.5%), and the platelet count had the highest specificity (69.2%).

Conclusion: Advanced age, intubation status, and duration of intubation were associated with mortality, and it was thought that an increase in LDH levels and CRP/albumin ratio and a decrease in albumin levels and platelet counts had predictive value in predicting mortality

Keywords: COVID-19, intensive care, mortality, laboratory parameters

INTRODUCTION

Coronavirus disease (COVID-19) emerged in the city of Wuhan in December 2019 and affected the whole world, causing a pandemic. SARS-CoV-2 can cause asymptomatic infection or severe pneumonia and respiratory failure, which can result in death. It can affect all body areas (especially the respiratory system, lymphoid tissue, arterial venous system endothelial cells, urinary tract, glial cells in the brain, intestines, nasal mucosa, skin, heart, bone, spleen and muscle tissue) because it causes disease through the angiotensin-converting enzyme (ACE-2) receptor (1-2).

The most common symptoms of COVID-19 are fever, cough, and shortness of breath, which can progress to organ failure. In respiratory failure, which occurs with clinical worsening in the later stages of the disease, follow-up in the intensive care unit (ICU) is required according to the need for respiratory support (3).

The mortality rate is high in patients with COVID-19, and among the factors affecting mortality, especially advanced age, male sex, hypertension, immunodeficiency due to chronic diseases, and a history of cancer come to the fore. Supporting this, a study from China reported that advanced age, increased D-dimer, and high sequential organ failure assessment (SOFA) scores were associated with mortality in patients with COVID-19 (4). Apart from this, it has been reported that there is a relationship between mortality and male sex, hypertension, cardiovascular diseases and type-2 diabetes in different studies (5-8).

Although the need for mechanical ventilation in patients admitted to the ICU with the diagnosis of acute respiratory distress syndrome (ARDS) differs in case series, it has been reported to be associated with high mortality.

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In this study, we evaluated the laboratory parameters, recorded co-morbid diseases, treatments received during the follow-up in the ICU, intubation status, length of stay in the ICU, and discharge status from the ICU of patients we followed up with the diagnosis of COVID-19 and respiratory failure in the ICU.

MATERIAL AND METHOD

The study was initiated with the approval of the KTO Karatay University Non-Pharmaceutical and Non-Medical Device Researches Ethics Committee (Date: 11.03.2021, Decision No: 2021/002). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was a single-center, retrospective study, and patients with a probable and definite diagnosis of COVID-19 who were followed up in the ICU between July 2020 and January 2021 were included in the study. The probable or definitive diagnosis of COVID-19 was determined according to the diagnostic criteria of the European Centre for Disease Prevention and Control (ECDC). Patients were determined as possible, probable or confirmed cases according to the ECDC criteria. The case definitions are as follows: (1) possible case, any person meeting the clinical criteria; (2) probable case, any person meeting the clinical criteria with an epidemiologic link or any person meeting the diagnostic criteria, including radiologic evidence for COVID-19; (3) confirmed case, any person meeting the laboratory criteria (9).

This study included 321/398 patients with severe pneumonia followed in the intensive care unıt. Seventy-seven patients were excluded because they did not meet the inclusion criteria. The pneumonia severity of all patients with COVID-19 in this study was classified according to the World Health Organization (WHO) guidelines (10) and the inclusion criteria were as follows: age over 18 years, positive SARS-CoV-2 real-time transcription-polymerase chain reaction (RT-PCR) in nasopharyngeal swab and/or lung tomography compatible with COVID-19 viral pneumonia, and requiring follow-up in the ICU. Patients aged under 18 years, patients in whom COVID-19 was excluded or with missing file records were excluded from the study. Demographic characteristics, medical history, comorbid diseases, clinical findings, intubation status, intubation duration, laboratory findings, drug treatments, and discharge status from the ICU were evaluated retrospectively from the electronic medical records of hospitalized patients.

The relationship of age, sex, and comorbid diseases (hypertension, diabetes mellitus, pulmonary diseases, heart diseases and other comorbidities) with mortality was evaluated.

The treatments administered during the hospitalization period of the patients were evaluated. The contribution of tocilizumab, favipiravir, plasma therapy, and corticosteroid therapy to the patient's survival and their relationship with mortality were evaluated.

In terms of standardization of the data, the blood laboratory parameters of the patients at the first admission to the emergency department were examined. The normal ranges of the investigated parameters were as follows: white blood cell (WBC) count (4.49-12.68 $\times 10^9$/L), lymphocyte count (1.26-3.35 $\times 10^3$/mL), neutrophil count (2.1-8.89 $\times 10^3$/mL), monocyte count (0.25-0.84 $\times 10^3$/mL), platelet count (173-390 $\times 10^3$/mL), troponin (0-19.8 ng/L), D-dimer (0-0.5 µg/mL), lactate dehydrogenase (LDH) (25-248) IU/L), C-reactive protein (CRP) (0-8 mg/L), procalcitonin (0-0.5 µg/L), ferritin (23.9- 336.2 µg/L), albumin (35-52 g/L), aspartate aminotransferase (AST) (3-50 IU/L), alanine aminotransferase (ALT) (3-50 IU/L), urea (17-43 mg/dL), creatinine (0.67-1.17 mg/dL), prothrombin time (8.40-10.6 sec), and activated partial thromboplastin time (APTT) (23.9-33.2 sec). To evaluate the relationship of these parameters with mortality, a comparison was made between the two groups according to the patients' discharge status from the ICU.

Statistical Analysis

Statistical analyses were performed using the SPSS version 21.0 software. Data are presented as median and interquartile range (IQR) for continuous variables, and as numbers and percentages (%) for categorical variables. The normality of data distribution was determined using the Kolmogorov-Smirnov test. Categorical variables were compared using the Chi-square ($\chi 2$) or Fisher's exact test according to their suitability. Continuous variables with normal distribution were analyzed using the independent samples t-test, and those that did not fit were analyzed using the Mann-Whitney U test. A logistic regression model was used to evaluate risk factors associated with mortality. The significance of the relationship was indicated by the odds ratio (OR) and 95% confidence interval (CI). Based on the results of the logistic regression, the prognostic value of the parameters found to be significant was evaluated using receiver operating characteristic (ROC) curve analysis. The best discriminatory cut-off values were calculated using Youden's criteria. A value of $p<0.05$ was considered significant in all tests.

RESULTS

This study included 321 patients with a confirmed diagnosis of COVID-19 who were followed in the ICU. One hundred ten (34%) patients were in the survivor group, and 211 (66%) patients were in the non-survivor group. The mean age of all patients included in the

study was 71.0 (range, 65.0-80.0) years, the mean age in the survivor group was 69.0 (range, 61.0-77.0) years, and in the non-survivor group, it was 72.0 (range, 66.0-82.0) years. Of the included patients, 143 (44.5%) were female and 178 (55.5%) were male. In the survivor group, 42 (38.2%) patients were female and 68 (61.8%) were male. In the non-survivor group, 101 (47.9%) were female and 110 (52.1%) were male. When the survivor and non-survivor groups were compared in terms of age, the mean age was found to be significantly higher in the non-survivor group than in the survivor group (p<0.001). There was no significant difference between the groups in terms of sex. RT-PCR was negative in 44 (13.7%) of all patients and positive in 277 (86.3%). In the survivor group, 18 (16.4%) were negative, 92 (83.6%) were positive, and in the non-survivor group, 26 (12.3%) were negative and 185 (87.7%) were positive in terms of RT-PCR tests.

When the risk factors and accompanying comorbidities of the patients were examined, hypertension (the most common) was found in 144 (44.9%), diabetes mellitus in 83 (25.9%), pulmonary disease in 71 (22.1%), heart diseases in 78 (24.3%), and other additional diseases (e.g. kidney disease, malignancy, rheumatologic diseases) in 133 (41.4%) of 321 patients. There was no significant difference between the survivor and non-survivor groups in terms of co-morbid diseases.

When the medical treatment administered to the patients was evaluated, 304/321 (94.7%) received favipiravir, 252/321 (78.5%) corticosteroids, 181/321 (56.4%) convalescent plasma, and 42/321 (13.1%) had tocilizumab. There was no significant difference between the survivor and non-survivor groups in terms of medical treatment.

A higher intubation rate (98.6% vs. 10.9%) was found in the non-survivor group compared with the survivor group (p<0.001). Also, longer hospital stay (10.0 vs. 8.0 days) was observed. The characteristics of the patients are listed in **Table 1**.

When the laboratory parameters were evaluated, the neutrophil count (p<0.001), ferritin (p<0.001), troponin I (p<0.001), INR, PT (p<0.001), LDH (p<0.001), urea (p<0.001), creatine (p<0.001), procalcitonin (p<0.001), WBC, CRP (p<0.001), AST, neutrophil/lymphocyte ratio (p<0.001), and CRP/albumin ratio (p<0.001) were significantly higher in the non-survivor group, while the lymphocyte count (p<0.001), albumin (p<0.001), monocyte and platelet count were significantly lower (**Table 2**).

Table 1. Baseline characteristics of COVID-19 patients in ICU

Characteristics		All patients n=321	Survivor patients n=110	Non-survivor patients n=211	P value
Age (years) (Median)		71.0 (65.0-80.0)	69.0 (61.0-77.0)	72.0 (66.0-82.0)	0.001
Sex, n (%)	Female	143 (44.5%)	42 (38.2%)	101 (47.9%)	0.098
	Male	178 (55.5%)	68 (61.8%)	110 (52.1%)	
RT-PCR, n (%)	Negative	44 (13.7%)	18 (16.4%)	26 (12.3%)	0.318
	Positive	277 (86.3%)	92 (83.6%)	185 (87.7%)	
Hypertension, n (%)	No	177 (55.1%)	63 (57.3%)	114 (54.0%)	0.579
	Yes	144 (44.9%)	47 (42.7%)	97 (46.0%)	
Diabetes mellitus, n (%)	No	238 (74.1%)	80 (72.7%)	158 (74.9%)	0.676
	Yes	83 (25.9%)	30 (27.3%)	53 (25.1%)	
Pulmonary disease, n (%)	No	250 (77.9%)	87 (79.1%)	163 (77.3%)	0.706
	Yes	71 (22.1%)	23 (20.9%)	48 (22.7%)	
Heart disease, n (%)	No	243 (75.7%)	88 (80.0%)	155 (73.5%)	0.195
	Yes	78 (24.3%)	22 (20.0%)	56 (26.5%)	
Additional disease, n (%)	No	188 (58.6%)	70 (63.6%)	118 (55.9%)	0.183
	Yes	133 (41.4%)	40 (36.4%)	93 (44.1%)	
Tocilizumab therapy, n (%)	No	279 (86.9%)	94 (85.5%)	185 (87.7%)	0.575
	Yes	42 (13.1%)	16 (14.5%)	26 (12.3%)	
Favipiravir therapy, n (%)	No	17 (5.3%)	5 (4.5%)	12 (5.7%)	0.665
	Yes	304 (94.7%)	105 (95.5%)	199 (94.3%)	
Plasma therapy, n (%)	No	140 (43.6%)	45 (40.9%)	95 (45.0%)	0.480
	Yes	181 (56.4%)	65 (59.1%)	116 (55.0%)	
Corticosteroids, n (%)	No	69 (21.5%)	20 (18.2%)	49 (23.2%)	0.297
	Yes	252 (78.5%)	90 (81.8%)	162 (76.8%)	
Intubation, n (%)	No	101 (31.5%)	98(89.1%)	3 (1.4%)	<0.001
	Yes	220 (68.5%)	12 (10.9%)	208 (98.6%)	
Length of ICU (day)		9.0 (5.0-16.0)	8.0 (5.0-14.0)	10.0 (4.0-18.0)	0.218
Length of IMV (day)		3.0 (0.0-9.0)	0.0 (0.0-0.0)	6.0 (2.0-12.0)	<0.001

* Significant at 0.05 level; Chi-square test for categorical variables, Mann whitney u test for numerical variables. Median (25%-75%). Abbreviations: RT-PCR-Reverse Transcriptase-Polymerase Chain Reaction ICU-Intensıve Care Unıt, IMV- Invasiv mechanic ventilatore

Table 2. Laboratory parameters of COVID-19 patients in ICU

Laboratory parameter	All patients (n=321)	Survivor patients (n=110) (Median)	Non-survivor patients (n=211) (Median)	P value
Neutrophil count (10^3/mL)	8.72 (5.71-13.03)	7.11 (5.03-9.72)	9.97 (6.32-15.09)	<0.001
Lymphocyte count (10^3/mL)	0.80 (0.52-1.17)	0.94 (0.66-1.32)	0.69 (0.46-1.10)	<0.001
Ferritin (µg/mL)	380.0 (191.4-704.0)	272.50 (126.8-531.0)	438.5(235.0-853.0)	<0.001
D-dimer (µg/mL)	1.89 (0.7-9.34)	1.37 (0.55-8.80)	2.49 (0.75-9.41)	0.059
Troponin I (ng/mL)	22.80 (10.5-90.9)	15.35 (7.1-46.6)	33.0 (12.6-140.0)	<0.001
International normalized ratio (INR)	1.14 (1.05-1.3)	1.11 (1.03-1.25)	1.16 (1.07-1.32)	0.006
Prothrombin time (PT) (Second)	13.2 (12.1-15.0)	12.7 (11.9-14.1)	13.5 (12.3-15.4)	<0.001
Partial Thromboplastin Time (APTT) (Second)	29.4 (25.6-34.6)	28.95 (25.30-33.90)	29.4 (25.9-35.0)	0.192
Lactate Dehydrogenase (LDH), U/L	396.0 (293.0-561.0)	354.0 (266.0-456.0)	445.0 (323.0-658.0)	<0.001
Urea (mg/dL)	56.0 (39.0-90.0)	44.5 (32.0-63.0)	64.00 (43.0-110.0)	<0.001
Creatinine (mg/dL)	0.97 (0.72-1.44)	0.82 (0.66-1.08)	1.10 (0.78-1.67)	<0.001
Procalcitonin (U/L)	0.27 (0.11-1.47)	0.14 (0.07-0.39)	0.59 (0.16-2.30)	<0.001
Albumin (g/L)	2.71 (2.26-3.07)	2.91 (2.57-3.40)	2.56 (2.13-2.94)	<0.001
Monocyte (10^3/mL)	0.46 (0.31-0.71)	0.56 (0.39-0.80)	0.44 (0.28-0.68)	0.004
White blood cell count (10^9/L)	9.84 (7.00-14.34)	8.9 (6.19-11.65)	10.78 (7.32-16.37)	0.002
Platelet count (10^3 µ/L)	209.0 (157.0-287.0)	229.0 (163.0-310.0)	200.0 (153.0-271.0)	0.032
C reactive protein (CRP) mg/L)	108.0 (63.6-189.0)	91.65 (33.0-145.0)	118.0 (77.10-227.0)	<0.001
Aspartate aminotransferase (U/L)	40.0 (27.0-66.0)	36.0 (23.0-56.0)	43.0 (28.0-72.0)	0.017
Alanine aminotransferase (U/L)	26.0 (17.0-52.0)	24.5 (17.0-48.0)	27.0 (17.0-59.0)	0.715
Neutrophil/lymphocyte	10.89 (5.57-19.69)	7.45 (4.65-12.33)	13.89 (7.16-24.09)	<0.001
CRP/albumin (10^{-3})	41.17 (23.34-72.68)	30.42 (11.09-51.92)	46.78 (28.14-86.31)	<0.001
Monocyte/albumin (g)	0.18 (0.11-0.27)	0.19 (0.11-0.31)	0.18 (0.11-0.25)	0.295

*Significant at 0.05 level; Mann whitney u test for numerical variables. Median (25%-75%)

Based on the above observations, potential risk factors for mortality were examined using logistic regression. Predictors with p values <0.05 in the univariate analysis were included in the multivariate analysis. The multivariate logistic regression model identified endotracheal intubation, high platelet count, low LDH, low albumin, and decreased CRP/albumin ratios as risk factors associated with ICU mortality (T**able 3 and Figure 1**).

Table 3. Risk factors for mortality of COVID-19 patients in ICU

	OR (95% CI)	P value
Age (Year)	0.980 (0.931-1.031)	0.430
Intubation (yes)	4284.786 (303.303-60,531.5)	<0.001
Length of IMV (days)	1.013 (0.970-1.057)	0.560
Neutrophil count (10^3/mL)	0.754 (0.505-1.126)	0.168
Lyphocyte count (10^3/mL)	0.570 (0.146-2.219)	0.418
Ferritin (µg/mL)	1.000 (0.999-1.001)	0.752
Troponin (ng/mL)	1.000 (0.999-1.001)	0.947
International normalized ratio (INR)	5.951 (0.078-452.43)	0.420
Prothrombin time (PT) (Second)	0.918 (0.640-1.317)	0.642
Lactate Dehydrogenase (LDH) (U/L)	0.996 (0.991-1.000)	0.049
Urea (mg/dL)	1.010 (0.993-1.027)	0.239
Creatinine (mg/dL)	0.611 (0.301-1.239)	0.172
Procalcitonin (U/L)	0.992 (0.949-1.037)	0.726
Albumin (g/L)	0.122 (0.015-1.023)	0.049
Monocyte (10^3/mL)	0.419 (0.067-2.632)	0.353
White blood cell count (10^9/L)	1.238 (0.880-1.742)	0.221
Platelet count (10^3µ/L)	1.011 (1.004-1.019)	0.004
C reactive protein (CRP) mg/L)	1.035 (0.997-1.074)	0.068
Aspartate aminotransferase (IU/L)	0.997 (0.986-1.009)	0.641
Neutrophil/lymphocyte	0.932 (0.822-1.057)	0.270
C reactive protein (CRP)/albumin (10^{-3})	0.909 (0.827-0.999)	0.047

*Significant at 0.05 level

ROC curve analysis was performed to evaluate the overall prognostic accuracy of statistically significant parameters in discriminating between survivors and non-survivors. Of all the laboratory parameters, albumin had the highest prognostic accuracy with an area under the ROC curve (AUC) of 0.681 (95% CI: 0.621-0.742) and the highest sensitivity (84.5%), and the platelet count had the highest specificity (69.2%). Details of the ROC analysis are given in **Table 4 and Figure 2**.

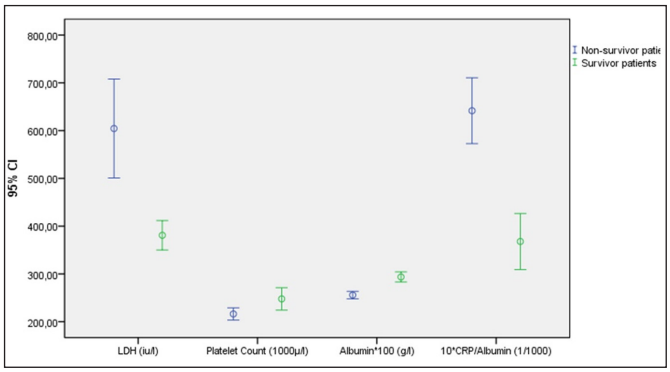

Figure 1. Comparison of significant parameters between survivors and non-survivors.
CI: confidence interval. LDH: lactate dehydrogenase, CRP: C-reactive protein

Table 4. Cut-off, sensitivity, specificity, and area under the curve levels of age, intubation day, LDH, and platelet count of COVID-19 patients in ICU

Characteristic	Cut-off	Specificity (%)	Sensitivity (%)	AUC (95% CI)	P value
LDH (IU/L)	392.5	66.4%	59.2%	0.655 (0.595-0.716)	<0.001
Platelet count (103µ/L)	247	69.2%	45.5%	0.573 (0.506-0.640)	0.032
Albumin (g/L)	2.44	46%	84.5 %	0.681 (0.621-0.742)	<0.001
CRP/albumin (10-3)	31.02	51.8%	70.1 %	0.676 (0.615-0.736)	<0.001

*Abbreviations: CRP- C Reactive Protein, LDH- Lactate Dehydrogenase

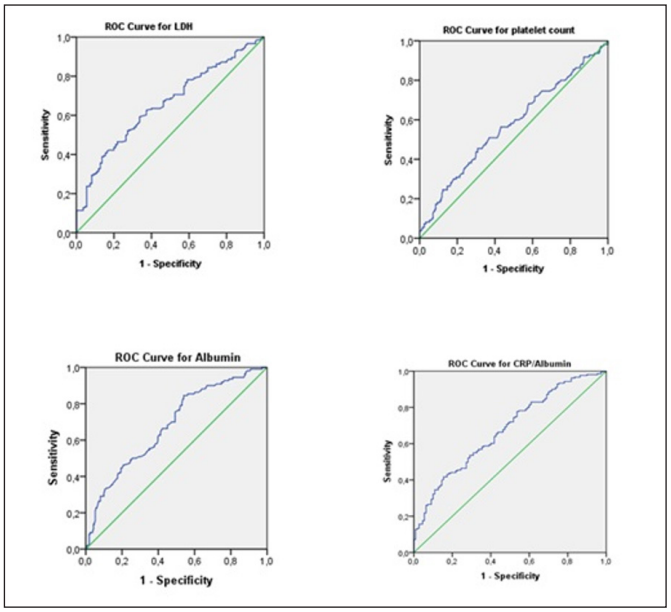

Figure 2. ROC curve of LDH, platelet count, albumin, and CRP/albumin in patients

DISCUSSION

According to our clinical experience, it was observed that conditions such as delay in admission to the hospital, delaying or rejecting treatment, comorbid diseases, old age, and immunodeficiency were the determining factors of ICU need.

Older age as a risk factor, which is thought to be related to mortality in patients followed up in the ICU due to COVID-19, is a common finding of many studies. In a multicenter study conducted to reveal the relationship of age with mortality, higher mortality in older adults compared with healthy older adults was associated with co-morbid conditions. It was argued that advanced age was an independent risk factor for COVID-19 mortality (11-12). In our study, it was noted that the patients in the non-survivor group were older than the patients in the survivor group [72.0 (66.0-82.0) vs. 69.0 (61.0-77.0)], and advanced age was found to be associated with mortality (p=0.001).

Another striking situation in the literature is that mortality is higher in males than in females. Biologic-based differences between the two sexes, hormonal changes, and sexual dimorphism in the expression of the ACE receptor responsible for the pathophysiology of the disease are thought to contribute to this situation. In our study, no association was found between sex and mortality (13-14).

It was suggested that there was a relationship between comorbid diseases, especially hypertension, pulmonary disease history, diabetes mellitus, and mortality. However, in our study, no relationship was found between comorbid diseases and mortality. This finding indicated that the effect of comorbid diseases on mortality might be masked by the effect of age. Similarly, in a study conducted in Wuhan, patients were classified according to disease severity and comorbid diseases were not found to be associated with disease severity (15-17).

Although no treatment has been found with proven effectiveness and safety for SARS-CoV-2 in scientific studies, no statistically significant relationship was found in terms of mortality with the treatment options received by our patients. During the hospitalization period in the ICU, favipiravir, convalescent plasma therapy, tocilizumab, and pulse steroid treatment were administered according to the recommendations of the Turkish Ministry of Health, the COVID-19 Adult Patient Treatment guideline, and according to their clinical status (18).

The efficacy of corticosteroid treatment is controversial; previous studies have shown that it does not contribute to reducing mortality, delay viral clearance, and increases secondary infections in SARS-CoV and MERS-CoV outbreaks. In a meta-analysis in which 10 studies were systematically evaluated in 2019, it was shown that systemic corticosteroids increased the length of hospital stay and increased the incidence of secondary bacterial or fungal infections in patients with influenza (19). When convalescent plasma therapy is used within 7 days at the latest after diagnosis and before intubation is required, it provides a reduction in the risk of disease progression. However, there is insufficient evidence for efficacy and safety in patients with severe pneumonia. It is suggested that late in the course of the disease, in intubated individuals, and during the cytokine storm period, it may do more harm than good (20-21).

It is known that SARS-CoV-2 causes an increase in plasma interleukin (IL)-6 levels during the active period of the disease. Tocilizumab stops the emergence of cytokine effects by preventing the virus from binding to IL-6 receptors. In a study evaluating 21 patients who were given tocilizumab, it was suggested that treatment given during severe disease with clinical worsening reduced

mortality and accelerated recovery (22-23). However, in our study, no positive contribution was observed in patients who were administered tocilizumab, which suggested that there might have been a delay in starting treatment due to the procedures for initiating treatment.

Intubation has become mandatory in patients whose hypoxia continues with non-invasive mechanical ventilation and high-flow nasal cannula oxygenation (HFNC) during a stay in the ICU. Of our patients, 71.4% (257/321) were intubated, and 98.6% of the non-survivor patients were intubated (208/211). The relationship between mechanical ventilation and mortality was found to be statistically significant in patients followed up as intubated (OR: 4284.79 (303.303-60531.46) (p<0.001) (**Table1**-**Table 3**) (p<0.001). In a study in which the observational experiences of patients with COVID-19 in Italy were reported, it was reported that most of the critically ill patients admitted to the ICU needed mechanical ventilation (>80%) and the mortality rate was high (~50%) (17,24). In different case series it was reported, respectively, that the need for intubation in critical patients were (75%), (71%) and the mortality rate of patients in the ICU was 67% (25-26).

In addition to demographic data, changes in laboratory parameters, clinical worsening, and predicting mortality have a very important role in terms of treatment plans. In our study, in the comparative evaluation made among survivors in the ICU, an increase in the neutrophil count (p<0.001), and a decrease in the lymphocyte count (lymphopenia) (p<0.001) were found to be statistically associated with mortality. In a study evaluating the effects of hematologic parameters on admission to the ICU, supporting our study, it was reported that severe lymphopenia was one of the markers indicating early admission to the ICU (27). Guan et al.'s (28) study concluded that severe lymphopenia was associated with the development of ARDS. However, in a retrospective study of 108 patients, increased D-dimer levels and severe lymphopenia were reported to predict mortality (29). Apart from this, increased levels of troponin (p<0.001), urea (p<0.001), creatinine (p<0.001), AST (p=0.017), procalcitonin (p<0.001), ferritin (p<0.001), and prolongation of prothrombin time (p<0.001) were found to be statistically associated with mortality in our study. In an Italian cohort study similar to our study, an increased neutrophil count, increased serum creatinine levels, increased C-reactive protein (CRP) and lactate dehydrogenase levels, and decreased platelet and lymphocyte levels were reported to predict mortality (30-32). In our study, we observed that the neutrophil/lymphocyte ratio was also statistically significant in predicting mortality (p<0.001). Similarly, it was illustrated that the neutrophil/lymphocyte ratio could be an indicator of disease severity, and in the same study, it was reported that renal markers were associated with hospital mortality, similar to our study (32).

In a retrospective study evaluating survivor patients of COVID-19 via thrombocyte values, one of the hematologic parameters, it was observed that thrombocytopenia was an independent risk factor for mortality in Cox proportional hazard regression analysis. They also reported that a 50 ×109/L decrease in platelet counts increased mortality by 40% (HR: 0.60, 95% CI: 0.43-0.84). In a multicenter study, low platelet levels were also reported to increase the risk of mortality (32-34).

LDH, which plays a role in the glucose metabolism pathway in cell metabolism, is known to be released when necrosis due to lung damage develops in COVID-19 pneumonia and is a marker showing cell damage and disease severity. However, in an observational study evaluating whether LDH values were an independent risk factor in patients with severe COVID-19, it was shown that LDH levels had a strong predictive value in detecting early lung injury and that they were positively correlated with the P/F ratio and computed tomography scores (17,28,32,35). In our study, LDH levels were found to be associated with mortality in patients with COVID-19. According to the ROC curve analysis, the value of 392.5 IU/L was determined as the best cut-off point for LDH. The sensitivity was 59.2% for people with LDH levels above 392.5 IU/L and the specificity was 66.4% for people with ≤392.5 IU/L. In a study evaluating 123 patients in Italy, it was reported that LDH (r=0.62, r2=0.38; p<0.001) and CRP (r=0.55, r2=0.31; p<0.001) levels were strongly correlated with respiratory performance (PaO2/FiO2), and it was emphasized that LDH and CRP had a strong predictive value in detecting respiratory failure . CRP values above 130 mg/L were found to be associated with mortality. In our study, a statistically significant increase in CRP levels was found in the non-survivor group compared with the survivor group (p<0.001) (36-37)

In our study, a relationship between a decrease in albumin levels and mortality was shown. In addition, when clinically important variable logistic regression analysis was performed, it was observed that the albumin ratio was AUC 0.681 (95% CI: [0.621-0.742]; p<0.001), and albumin had high sensitivity in predicting mortality (84.5%). Albumin is a harbinger of nutritional disorders in prolonged hospitalizations due to liver and kidney effects. In a retrospective study in which 427 patients with COVID-19 were evaluated comparatively in two groups (survivors or non-survivors), albumin levels were found to be associated with mortality (38). In a different study conducted in Wuhan, increased CRP and decreased albumin were reported to be correlated with disease progression (39). In our study, when a

statistically significant and clinically significant variable logistic regression analysis was performed in patients with COVID-19, it was found that the CRP/albumin ratio had a statistically significant predictive value in predicting mortality. According to the ROC curve analysis, 31.02 was determined as the best cut-off point for the CRP/albumin ratio, with a sensitivity of 70.1% for individuals with a CRP/albumin ratio above 31.02 and a specificity of 51.8% for individuals with ≤31.02. They defended the importance of CRP/albumin (CAR) ratio in predicting mortality in a retrospective cohort study evaluating mortality-related parameters of 875 patients in the ICU (40).

There were some limitations to our study, such as being a single-center study ,small sample size ,not having a placebo group, being a retrospective study, evaluating the blood tests at the first admission to the emergency department, and not evaluating the follow-up blood test values during the clinical worsening or recovery period of the patients. In the study the number of patients with mild and moderate pneumonia was insufficent and statitical evaluation could not be made between the groups. In addition, due to the fact that vaccition studies had not started in Turkey at the time the study was planned ande case were collected, no evaluotion was made regarding the vaccine.

CONCLUSION

In conclusion, demographic characteristics, especially advanced age, intubation status, and duration of intubation were associated with mortality in patients in our study. Neutrophilia, lymphopenia, thrombocytopenia; increased neutrophil/lymphocyte ratio; increased ferritin, troponin and CRP levels; decreased albumin levels; increased CRP/albumin ratio; prolongation of prothrombin time; increased renal function tests, and increased AST levels were observed. It was thought that an increase in the CRP/albumin ratio, a decrease in the albumin level, and a decrease in the platelet count had predictive value in predicting mortality. To determine parameters that affect mortality in patients with COVID-19 followed in the ICU, and to support our findings, multicenter prospective clinical studies with large numbers of patients are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the KTO Karatay University Non-Pharmaceutical and Non-Medical Device Researches Ethics Committee (Date: 1.03.2021, Decision No: 2021/002).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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