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Independent Predictors of Mortality in ICU Patients with COVID-19

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Abstract

Objective: Early identification of Coronavirus disease 2019 (COVID-19) patients at high mortality risk can improve patient care and prevent deaths. To identify prognostic predictors that increase COVID-19 patient mortality risk in the Intensive Care Unit (ICU).

Methods: Retrospective analysis of clinical characteristics and serological biomarkers of ICU-COVID-19 patients was performed in a tertiary hospital from 24 March 2020 to 20 December 2020. Analysis was conducted on two groups of study participants: survivors and deceased. Multivariate logistic regression was used to determine mortality risk. In order to determine prognostic predictors, the ANOVA test was used to compare the data of serological biomarkers on the day of patients' admission to the ICU and on the 5th day of follow-up.

Results: A total of 335 patients (54.65%) were in the deceased group, and 278 (45.35%) were in the survivors group. A statistically significant difference was found between the deceased and survivor groups regarding mean age ($p<0.001$). According to multivariate analyses of patients' data, age, oxygen saturation, direct bilirubin, and ionized calcium were independent predictors of mortality ($p <0.05$). According to this analysis, age (OR=1.035, p=0.002, 95%CI 1.013-1.058), peripheral capillary oxygen saturation (SpO2) (OR=0.912, $p<0.001$, 95%CI 0,873-0.953), direct bilirubin (OR=6.821, p=0.024, 95%CI 0.282-36.285), ionized calcium (OR=30.524, p=0.035, 95%CI 1.262-738.34) was found that it increased the risk of mortality. In the multivariate logistic regression analysis, it was found that gender, age, and comorbidities had the highest odds ratios in terms of mortality.

Conclusion: The study revealed that advanced age, low SpO2, high direct bilirubin, and elevated ionized calcium levels were independent predictors of mortality for COVID-19 patients in the ICU.

Keywords: COVID-19, Intensive Care Unit, Mortality, Prognostic Predictors

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Yoğun Bakım Ünitesinde Yatan COVID-19 Hastalarının Bağımsız Mortalite Belirleyicileri

Öz

Amaç: Yüksek mortalite riskine sahip Yeni Koronavirüs Hastalığı (COVID-19) hastalarının erken teşhis edilmesi, hasta bakımını artırabilir ve ölümleri önleyebilir. Bu çalışma yoğun bakım ünitesi (YBÜ)ndeki COVID-19 hastalarının mortalite riskini artıran prognostik belirleyicileri belirlemeyi amaçlamıştır.

Yöntemler: YBÜ'de COVID-19 hastalarının klinik özelliklerinin ve serolojik belirteçlerinin retrospektif analizi, 24 Mart 2020'den 20 Aralık 2020'ye kadar olan dönemde bir üçüncü basamak hastanede gerçekleştirildi. Hastaların analizi sağ kalanlar ve ölenler olmak üzere iki grupa ayrılarak yapıldı. Mortalite riskini belirlemek için çok değişkenli lojistik regresyon kullanıldı. Prognostik belirleyicileri saptamak amacıyla, ANOVA testi kullanılarak hastaların YBÜ'ye kabul ve takibin 5. günündeki serolojik belirteç verileri karşılaştırıldı.

Bulgular: Toplam 335 hasta (%54,65) ölen grup içindeyken, 278 hasta (%45,35) sağ kalanlar grubundaydı. Ortalama yaş açısından ölenler ve sağ kalanlar grupları arasında istatistiksel olarak anlamlı bir fark bulundu ($p<0.001$). Hastaların verilerine yönelik çok değişkenli lojistik regresyon analizlere göre yaş, periferik kapiller oksijen saturasyonu (SpO2), total bilirubin ve iyonize kalsiyum mortalitenin bağımsız belirleyicileri olarak saptandı ($p <0.05$). Bu analize göre yaş (OR=1.035, p=0.002, %95 CI 1.013-1.058), Spo2 (OR=0.912, p<0.001, %95 CI 0.873-0.953), total bilirubin (OR=6.821, p=0.024, %95 CI 0.282-36.285), iyonize kalsiyum (OR=30.524, p=0.035, %95 CI 1.262-738.34) mortalite riskini artırdığı bulundu. Çok değişkenli lojistik regresyon analizinde, cinsiyet, yaş ve komorbiditelerin, mortalite açısından en yüksek odds oranlarına sahip olduğu bulundu.

Sonuç: Çalışma, COVID-19 hastalarında ileri yaşın, düşük SpO2, yüksek total bilirubin ve yüksek iyonize kalsiyum seviyelerinin YBÜ'de mortalite için bağımsız belirleyiciler olduğunu ortaya koymuştur.

Anahtar kelimeler: COVID-19, Yoğun Bakım Ünitesi, Mortalite, Prognostik Belirleyiciler.

INTRODUCTION

Worldwide, 771 million cases and 6,9 million deaths have been reported of COVID-19 according to World Health Organization (WHO) data[1]. Additionally, WHO classified EG.5, known as "Eris," as an "intriguing variant," signifying the need for closer monitoring than other COVID-19 subvariants due to mutations that might enhance its infectivity or severity[2]. Even though COVID-19 is associated with a high mortality rate, the clinical and laboratory determinants of mortality in hospitalized COVID-19 patients remain controversial[3]. Identifying mortality risk predictors early in critical COVID-19 patients can improve management and prevent mortality.

COVID-19 patients' clinical characteristics, serologic biomarkers, and risk factors can be used to determine their severity. Studies have identified the main factors associated with COVID-19 fatalities, such as older age, diabetes mellitus, cardiovascular disease, hypertension, obesity and CBC, platelet count, lymphocyte count, IL-6, and serum ferritin, lower albumin levels, increased D-dimer, ferritin, and serum troponin levels[4-7]. It is possible to estimate the risk of death during hospitalization in COVID-19 patients using demographic, clinical, and laboratory parameters mentioned in the literature. Furthermore, determining the parameters that can be used as independent predictors can be vital to recognizing fatality risks early.

COVID-19 patients with severe symptoms need to be admitted to an intensive care unit, and death rates are very high[8]. The fatality rate from COVID-19 can be reduced if effective and rapid treatment efforts are made early after admission to the ICU for COVID-19 patients at high risk of mortality. The best clinical and laboratory parameters to predict early mortality in COVID-19 patients during ICU admission remain unclear. We aimed to investigate the prognostic predictors that

increase the mortality risk of ICU COVID-19 patients.

METHODS

A retrospective study in ICU COVID-19 patients was conducted between 24 March 2020 and 20 December 2020. The study protocol was approved by the institutional ethical board of a tertiary hospital (Date: 31 December 2021, Decision No: 967).The study recruited 613 COVID-19 patients older than 18 in the ICU of a tertiary hospital. The diagnosis of COVID-19was confirmed by real-time (RT)- polymerase chain reaction(PCR) assay for SARS-CoV-2 from nasopharyngeal and oropharyngeal swabs. COVID-19 patients treated and monitored for at least five days after admission to the ICU were included in this study. In addition to the duration of hospitalization mentioned above, electronic medical records were evaluated for COVID-19 ICU patients. This study excluded ICU patients with negative RT-PCR results.

A comparison of survivors versus deceased COVID-19 patients was conducted by dividing the patients into two groups. Individuals displaying clinical symptoms of pneumonia such as fever, cough, sputum production, and dyspnea, combined with at least one of the following criteria, were categorized as ICU patients: a respiratory rate exceeding 30 breaths per minute, severe respiratory distress, SpO2 below 90% when breathing room air, and the presence of potential COVID-19 pneumonia indicators on CT scans. On admission ICU of all patients, demographic-clinical characteristics (risk factors, vital parameters), ordinary laboratory test results with the inclusion of complete blood count (CBC) along with differentiation, , creatinine, cardiac troponin I, lactate dehydrogenase (LDH), aminotransferases (AST and ALT), blood urea nitrogen, albumin, total bilirubin (Tbil), direct bilirubin (Dbil),D-dimer, ferritin, procalcitonin, C-Reactive Protein (CRP), International normalized ratio (INR), and blood gas results of patients were recorded.

Statistical Analysis

The arithmetic mean and standard deviation were calculated for numerical data, while frequency and percentage were used for categorical data. In order to perform analysis, IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) was used. Analysis of categorical data was conducted using the Chi-square test. Shapiro-Wilks tests were performed on the numerical data to determine their conformity to the normal distribution. The Mann-Whitney U test was utilized in data analysis that did not comply with the normal distribution, and the 95% Confidence Interval (CI) min-max values of these data were shown in parentheses. In univariate logistic regression analyses, clinical patient risk factors were recorded that were noteworthy in standard analyses. A 95% CI was included with the odds ratios (ORs). A logistic regression analysis was used to count variables that continued to be statistically significant after univariate analysis. Mortality risk was determined by multivariate logistic regression. Mortality risk was defined by multivariate logistic regression. To reveal the prognosis predictors; the Anova test was used with repeated measurements comparing the biochemical data of day 1 and day 5. In this analysis, 1st and 5th-day measurements were taken as within-subjects, and two different (survivors vs deceased) patient groups were taken as between-subjects. A p-value below 0.05 was examined remarkably for whole analyses.

RESULTS

This study included a total of 613 patients, consisting of 270 women and 343 men. Among all study patients, two groups were formed survivors [278 (45,35%) patients] and deceased [335(54.65%) patients]. A total of 613

patients were aged 68 ±15 (95 CI: 66,93-69,59%) years. A statistically significant difference in mean age was found between the deceased group and the survivors' group (p<0.001). Comorbidities such as diabetes were statistically significantly higher in the deceased group than in the survivors (p= 0.037). Demographic data, relevant comorbidities, and laboratory are in Table I.

Table I: Demographic data, presence of comorbidities, vital parametres and laboratory parameters of all groups

	All patients (n:613) **n (%) Mean±SD (%95 CI min-max)**	**Survivor (n:278)** **n (%) Mean±SD (%95 CI min-max)**	**Deceased (n:335)** **n (%) Mean±SD (%95 CI min-max)**	**p**
Gender				
Female	270 (44)	124 (44.6)	146 (43.6)	0.838
Male	343 (56)	154 (55.4)	189 (56.4)	
Age (year)	68.26±14.74 (66.93-69.59)	6164±1631 (58.91-64.38)	7101±1311 (69.60-72.42)	0
Underlying Comorbidities	**n (%)**	**n (%)**	**n (%)**	
Hypertension	319 (52)	130 (46.8)	189 (56.4)	0.055
Diabetes Mellitus	178 (29)	66 (23.7)	112 (33.4)	0.037
Chronic obstructive pulmonary disease-asthma	82 (13.4)	42 (15.1)	40 (11.9)	0.431
Coronary Artery Disease/ Heart Failure	107 (17.5)	42 (15.1)	65 (19.4)	0.269
Oxygen Saturation	85.44±9.63 (84.57-86.31)	89.87±5.49 (88.94-90.79)	83.6±10.36 (82.48-84.71)	0
White Blood Cell (4.000-10.000/mm3)	8.29±5.24 (8.82-9.76)	8.30±4.72 (7.51-9.09)	9.7±5.4 (9.12-10.28)	0.004
Neutrophil(2.000-7.000/mm3)	7.7±4.74 (7.27-8.12)	6.56±3.8 (5.92-7.2)	8.17±5 (7.63-8.71)	0.001
Lymphocytes (800-4000/mm3)	1.15±1.89 (0.98-1.32)	1.32±2.53 (0.89-1.74)	1.08±1.54 (0.92-1.25)	0.005
Monocytes	0.4±0.24 (0.38-0.42)	0.4±0.24 (0.35-0.44)	0.4±0.24 (0.38-0.43)	0.695
Eosinophil	0.01±0.05 (0.002-0.01)	0.02±0.05 (0.01-0.03)	0.01±0.05 (0.008-0.02)	0.002
Basophil	0.02±0.03 (0.02-0.02)	0.01±0.01 (0.01-0.02)	0.02±0.03 (0.02-0.03)	0.014
Hemoglobin (11-16 gr/dl)	13.01±2.05 (12.83-13.2)	13.30±2.15 (12.94-13.66)	12.89±2 (12.68-13.11)	0.014
Hematocrit (37-54 %)	40.98±6.1 (40.43-41.53)	41.7±6.22 (40.65-42.74)	40.68±6.04 (40.03-41.33)	0.032
MCV	88.76±7.49 (88.08-89.43)	87.4±6.34 (86.34-88.46)	89.32±7.85 (88.47-90.16)	0.008
Platelet (150.000-450.000/mm3)	209.13±84.07 (201.54-216.72)	218.75±80.68 (205.22-232.28)	205.14±85.24 (195.97-214.3)	0.059
RDW CW	14.3±1.78 (14.14-14.46)	13.97±1.68 (13.69-14.25)	14.44±1.8 (14.24-14.63)	0
RDW SD	47.15±6.08 (46.60-47.7)	45.43±5.69 (44.48-46.39)	47.87±6.1 (47.21-48.52)	0
Albumin (34-48 g/L)	30.44±5.25 (29.96-30.91)	31.92±5.62 (30.98-32.87)	29.82±4.96 (29.29-30.36)	0
ALT (0-41 U/L)	47.45±110.61 (37.46-57.44)	42.05±57.6 (32.39-51.71)	49.7±126.29 (36.1-63.29)	0.899

AST (0-40 U/L)	78.94±249.7 (56.38-101.5)	60.46±145.26 (36.10-84.82)	86.63±281.83 (56.29-116.97)	0.013
C-reactive protein (0-5 mg/L)	126.84±82.98 (119.33-134.34)	109.53±84.3 (95.39-123.67)	134.06±81.46 (125.28-142.84)	0.001
Total Calcium (8.8-10.6 mg/dl)	8.79±0.63 (8.73-8.84)	8.8±0.59 (8.7-8.9)	8.78±0.65 (8.71-8.85)	0.68
E-GFR	58.31±28.34 (55.72-60.90)	71.64±27.96 (66.95-76.33)	52.59±26.56 (49.69-55.49)	0
Glucose	169.75±92.85 (161.36-178.14)	158.25±87.32 (143.61-172.9)	174.53±94.78 (164.33-184.74)	0.008
Chlorine (98-107 mmol/l)	103.13±6.03 (102.59-103.68)	102.53±5.31 (101.64-103.43)	103.38±6.3 (102.7-104.06)	0.149
Creatinine (0.72-1.25 mg/dL)	1.56±1.57 (1.41-1.7)	1.14±0.93 (0.98-1.29)	1.73±1.74 (1.54-1.92)	0
Creatine Kinase	467.46±1967.47 (289.32-645.60)	401.25±2396.02 (0.58-803.1)	495.18±1760.79 (305.08-685.28)	0
Lactate Dehydrogenase (135-225 U/l)	470.4±417.45 (432.61-508.2)	388.13±210.08 (352.9-423.3)	504.85±474.35 (453.64-556.06)	0
Potassium(3.5-5.1 mmol/L)	4.24-0.71 (4.17-4.30)	4.1±0.57 (4-4.19)	4.29±0.75 (4.21-4.38)	0.013
Sodium (134-146 mEq/L)	136.88±6.074 (136.33-137.43)	136.69±4.96 (135.85-137.52)	136.97±6.48 (136.27-137.66)	0.672
Indirect Bilirubin	0.31±0.21 (0.29-0.33)	0.3±0.18 (0.27-0.33)	0.31±0.22 0.29-0.33)	0.765
Direct Bilirubin (0-0.3mg/dL)	0.38±0.33 (0.35-0.41)	0,29±0,2 (0,25-0,32)	0.41±0.36 (0.37-0.45)	0
Total Bilirubin	0.68±0.49 (0.63-0.72)	0,63±0,38 (0,56-0,69)	0.7±0.53 (0.64-0.76)	0.081
Urea(16-48mg/dl)	59.85±43.97 (55.87-63.82)	43.02±31.37 (37.75-48.28)	66.85±46.53 (61.84-71.86)	0
INR	1.25±0.23 (1.22-1.27)	1.23±0.2 (1.19-1.26)	1.26±0.24 (1.23-1.29)	0.268
D Dimer(0-243 ng/ml)	1375.8±4274.2 (980.7-1770.9)	535.06±743.41 (408.51-661.61)	1733.9±5040.7 (1176.9-2290.9)	0
Procalcitonin	2.51±8.88 (1,47-3,55)	0.90±2.53 (0.33-1.48)	3.12±10.24 (1.70-4.53)	0
Troponin (0-0.16 ng/ml)	0.32±1.35 (0.19-0.44)	0.15±0.32 (0.09-0.2)	0.39±1.6 (0.21-0.57)	0
Ferritin	946.25±2504.36 (712.67-1179.8)	744.10±775.21 (609.04-879.15)	1029.04±2929.14 (704.3-1353.7)	0.063
pH	7.38±0.16 (7.36-7.39)	7.4±0.06 (7.39-7.41)	7,36±0,18 (7,34-7,38)	0.01
Lactate	2.49±1.92 (2.31-2.67)	2.01±0.9 (1.85-2.16)	2.69±2,17 (2.45-2.93)	0.001
Bicarbonate(HCO3 ACT)	21.95±3.68 (21.61-22.29)	23.39±3.31 (22.82-23.96)	21.36±3.66 (20.96-21.76)	0
Base Exercise	-2.36±4.68 (-2.79-1.92)	-0.65±3.96 (-1.34-0.02)	-3.05±4.78 (-3.58-2.53)	0
Ionized Calcium (Ca2+) (1.15-1.35mmol/lt)	1.11±0.09 (1.10-1.12)	1.09±0.81 (1.08-1.11)	1.12±0.1 (1.11-1.13)	0.015

Categorical data are expressed as n (%) and numerical data as Mean±SD (95% CI min-max).

MCV: Mean Corpuscular Volume, E-GFR: Estimated Glomerular Filtration Rate, RDW CW: Red Cell Distribution Width - Coefficient of Variation, RDW SD: Red Cell Distribution Width - Standard Deviation , INR: International Normalized Ratio, ALT Alanine AminotransferaseAST:Aspartate Aminotransferase

Mortality was associated with age, diabetes, low oxygen saturation, and many hematological and biochemical parameters. In multivariate analyses of these data, age, oxygen saturation, Dbil, and ionized calcium were independent predictors of mortality ($p<0.05$) (Table I).Age, gender, presence of comorbidity, oxygen saturation value at admission ICU, CBC, and all biochemistry and blood parameters were evaluated with Univariate analysis. In Table I,

only statistically significant (p<0.05) parameters were listed. Significant parameters were included in the Multivariate analysis in the second step. Multivariable logistic regression was achieved by adjusting sex, age, and admissible comorbidities with the highest individual OR for mortality. According to the Multivariable Logistic Regression, age (OR=1.035, p=0.002, 95%CI 1.013-1.058), SpO2; (OR=0.912, p<0.001, 95%CI 0,873-0.953), Dbil (OR=6.821, p=0.024, 95%CI 0.282-36.285), Ionized calcium (OR=30.524, p=0.035, 95%CI 1.262-738.34) were found that parameters increased the risk of mortality (OR: odds ratio) (Table II).

Table II: Univariate and multivariatelogistic regression analyses for predictors of mortality in patients with COVID-19 admitted to ICU

	Univariate Analysis				Multivariate Analysis			
			95% CI				95% CI	
Variable	p values	OR	Lower	Upper	p values	OR	Lower	Upper
Age	0	1.045	1.03	1.06	**0.002**	1.035	1.013	1.058
Diabetes Mellitus	**0.038**	1.613	1.027	2.535	**0.07**	1.76	0.955	3.246
Oxygen Saturation	**0**	0.9	0.87	0.931	**0**	0.912	0.873	0.953
White Blood Cell	**0.009**	1.061	1.015	1.11	**0.19**	0.856	0.678	1.08
Neutrophil	**0.001**	1.09	1.036	1.148	**0.17**	1.187	0.929	1.516
Basophil	**0.013**	0.69	0.516	0.924	**0.692**	0.166	0	1182.128
MCV	**0.012**	1.035	1.008	1.063	**0.079**	1.187	0.98	1.438
Platelet	0.11	0.998	0.996	1				
RDW CW	**0.01**	1.191	1.042	1.362	**0.11**	2.339	0.825	6.636
RDW SD	**0**	1.093	1.045	1.142	**0.174**	0.805	0.588	1.1
Albumin	**0**	0.924	0.888	0.961	**0.552**	1.02	0.955	1.09
C-reactive protein	**0.004**	1.004	1.001	1,006	**0.813**	1.001	0.996	1.005
E-GFR	**0**	0.972	0.963	0.981	**0.373**	0.992	0.974	1.01
Creatinine	**0**	1.753	1.28	2.4	**0.125**	1.625	0.874	3.02
Lactate Dehydrogenase	**0.003**	1.002	1.001	1.003	**0.293**	1.001	0.999	1.003
Potassium	**0.006**	1.527	1.126	2.07	**0.585**	0.845	0.462	1.546
Direct Bilirubin	**0**	25.301	6.403	99.968	**0.024**	6.821	1.282	36.285
Urea	**0**	1.02	1.012	1.027	**0.212**	0,.99	0.975	1.006
D DİMER	**0.003**	1	1	1.001	**0.194**	1	1	1
pH	**0.001**	0.006	0	0.125	**0.48**	0.436	0.044	4.362
Ionized Calcium	**0.016**	15.178	1.658	138.938	**0.035**	30.524	1.262	738.335
Lactate	**0**	1.445	1.175	1.778	**0.372**	1.126	0.868	1.459
Bicarbonate (HCO3 ACT)	**0**	0.829	0.771	0.891	**0.799**	0.97	0.767	1.227
Base Exercise	**0**	0.872	0.825	0.923	**0.757**	0.971	0.806	1.17

Age, gender, presence of comorbidity, oxygen saturation, count of blood cells, and all biochemistry parameters were evaluated with Univariate analysis.

Including P values considered statistically significant (P < 0.05) OR: odds ratio MCV: Mean Corpuscular Volume, E-GFR: Estimated Glomerular Filtration Rate, RDW CW: Red Cell Distribution Width - Coefficient of Variation, RDW SD: Red Cell Distribution Width - Standard Deviation

ANOVA tests were used for repeated measurements on the 1st and 5th days to compare the laboratory data of COVID-19 patients treated and followed at least 5 days length of after admission ICU. In this analysis, 1st and 5th-day measurements were taken as within-subjects, and two different (survivors vs deceased) patient groups were taken as between-subjects. p<0.05 was taken as the statistical significance level. From all

parameters; within subjects(*), between subjects(**), Dbil (p:0.054, p:0), Tbil (p:0.106, p:0.041), AST (p:0.064, p:0.009) and creatinine (p:0.7, p:0.005)(Table 3). In spite of the fact that the model parameter values on the 1st and 5th days did not differ statistically significantly, the values in the deceased's group increased, while those in the survivors' group decreased (Table III).Elevated AST levels during admission to the ICU had more statistical significance than ALT levels on the 5th day of admission (p=0.013). Elevated ALT levels did not have a statistically significant difference during admission to the ICU and on the 5th day of admission (p=0.899).

Table III: Variance in repeated measures As measurements within subjects (*), between subjects (survivors vs deceased**).

		Total (n:560) **Mean±SD**	**Survivors (n:266)** **Mean±SD**	**Deceased (n:294)** **Mean±SD**	**p****			**Total (n:560)** **Mean±SD**	**Survivors (n:266)** **Mean±SD**	**Deceased (n:294)** **Mean±SD**	**p****
White Blood Cell (4.000-10.000/mm3)	1. Day	9.04±5.11	8.25±4.64	9.38±5.28	0	**E-GFR**	1. Day	59.34±27.88	71.99±27.76	53.39±25.92	0.01
	5. Day	11.41±6.34	8.68±4.71	12.65±6.60			5. Day	61.37±28.60	78.38±18.98	53.38±28.89	
	p*	0					p*	0.01			
Neutrophil (2.000-7.000/mm3)	1. Day	7.44±4.57	6.52±3.68	7.86±4.86	0	**Blood Glucose**	1. Day	168.21±92.05	157.66±87.78	172.98±93.67	0.177
	5. Day	9.74±5.46	6.88±3.42	11.03±5.72			5. Day	157.19±85.49	136.96±68.40	166.34±90.82	
	p*	0					p*	0.009			
Lymphocytes (800-4000/mm3)	1. Day	1.16±1.97	1.33±2.59	1.08±1.62	0.68	**Chlorine**	1. Day	102.91±5.48	102.46±5.36	103.11±5.53	0.001
	5. Day	1.15±2.66	1.29±3.06	1.09±2.46			5. Day	107.50±10.24	104.40±5.15	108.90±11.58	
	p*	0.814					p*	0			
Monocytes	1. Day	0.40±0.22	0,38±0.19	0.41±0.24	0,587	**Creatinine (0.72-1.25 mg/dL)**	1. Day	1.47±1.39	1.08±0.56	1.65±1.60	0.005
	5. Day	0.44±0.30	0,43±0.24	0.44±0.33			5. Day	1.51±1.46	0.89±0.53	1.79±1.65	
	p*	0.014					p*	0.7			
Eosinophil	1. Day	0.01±0.05	0.02±0.05	0.01±0.06	0.036	**Creatine Kinase**	1. Day	458.69±204.,53	409.33±2449.47	481.26±1839.14	0.46
	5. Day	0.03±0.08	0.05±0.09	0.02±0.07			5. Day	279.05±541.08	122.66±251.77	350.53±617.94	
	p*	0					p*	0.048			
Basophile	1. Day	0.02±0.03	0.01±0.01	0.02±0.03	0.069	**Lactate Dehydrogenase (135-225 U/l)**	1. Day	432.23±284.95	393.85±212.37	449.84±311.41	0.001
	5. Day	0.04±0.04	0.03±0.02	0.04±0.04			5. Day	724.96±1020.18	439.71±189.66	855.79±120362	

	p*	0					p*	0			
Hemoglobin (11-16 gr/dl)	1. Day	13.07±1.99	13.34±2.07	12.95±1.95	0.295	**Potassium (3,5-5,1 mmol/L)**	1. Day	4.21±0.68	4.09±0.57	4.27±0.73	0.806
	5. Day	12.08±1.94	12.46±1.86	11.90±1.96			5. Day	4.23±0.77	4.09±0.60	4.29±0.82	
	p*	0					p*	0.833			
Hematocrit (37-54 %)	1. Day	41.12±5.95	41.83±5.99	40.80±5.91	0.908	**Sodium (134-146 mEq/L)**	1. Day	136.63±5.54	136.63±5.06	136.63±5.75	0
	5. Day	38.82±5.65	39.50±4.96	38.52±5.92			5. Day	142.78±7.74	138.93±4.32	144.51±8.30	
		0					p*	0			
MCV	1. Day	88.49±7.36	87.40±6.45	88.99±7.69	0	**Indirect Bilirubin**	1. Day	0.31±0.21	0.31±0.18	0.32±0.22	0.347
	5. Day	89.17±7.43	86.99±6.45	90.16±7.64			5. Day	1.16±12.53	0.30±0.18	1.55±15.12	
	p*	0.021					p*	0.351			
Platelet(150.000-450.000/mm3)	1. Day	208.94±83.37	218.63±80.03	204.55±84.60	0.001	**DirectBilirubin (0-0.3mg/dL)**	1. Day	0.37±0.30	0.29±0.21	0.40±0.32	0
	5. Day	251.14±110.14	282.32±117.46	237.04±103.83			5. Day	0.41±0.36	0.27±0.14	0.48±0.41	
	p*	0					p*	0.054			
RDW-CW	1. Day	14.28±1.82	13.98±1.72	14.42±1.86	0.003	**Total Bilirubin**	1. Day	0.68±0.47	0.64±0.38	0.69±0.51	0.041
	5. Day	14.57±2.19	14.04±2.34	14.81±2.08			5. Day	0.73±0.54	0.63±0.33	0.78±0.60	
	p*	0					p*	0.106			
RDW-SD	1. Day	46.96±6.01	45.45±5.78	47.64±6.00	0	**Urea (16-48mg/dl)**	1. Day	57.96±43.24	42.31±29.98	65.07±46.40	0
	5. Day	48.16±7.00	44.88±5.87	49.65±6.97			5. Day	72.02±52.76	41.05±28.15	86.08±55.31	
	p*	0					p*	0			
Albumin (34-48 g/L)	1. Day	30.69±5.10	31.93±5.55	30.12±4.78	0.078	**pH**	1. Day	7.38±0.16	7,40±0,06	7.37±0.19	0.043
	5. Day	25.60±4.45	27.43±4.63	24.77±4.11			5. Day	7.34±0.12	7.39±0.06	7.32±0.13	
	p*	0					p*	0.004			
Alanine Aminotransferase (0-41 U/L)	1. Day	40.20±56.87	42.39±58.60	39.21±56.15	0.013	**Ionised Calcium**	1. Day	1.11±0.09	1,09±0.08	1.12±0.10	0.73
	5. Day	91.32±290.66	42.48±37.11	113.42±347.34			5. Day	1.15±0.53	1.12±0.09	1.16±0.63	
	p*	0.013					p*	0.28			
Aspartate Aminotransferase (0-40 U/L)	1. Day	63.66±192.29	61.61±148.37	64.59±209.38	0.009	**Lactate**	1. Day	2.39±1,61	1,99±0,94	2,56±1,78	0.023

	5. Day	134.40±457.29	42.66±34.97	175.90±545.83			5. Day	2.87±2.53	1.95±0.83	3.24±2.87	
	p*	0.064					p*	0.045			
C-reactive protein (0-5 mg/L)	1. Day	12.90±80.83	109.60±84.70	127.48±78.52	0.003	**Bicarbonate (HCO3 ACT)**	1. Day	22.14±3.51	23.63±3.21	21.55±3.45	0.305
	5. Day	112.45±81.65	79.48±62.08	127.42±85.10			5. Day	22.03±4.85	23.95±3.64	21.28±5.05	
	p*	0.003					p*	0.938			
Calcium (8.8-10.6 mg/dl)	1. Day	8.79±0.62	8.80±0.58	8.79±0.64	0.152	**Base Exercise**	1. Day	-2.14±4.53	-0.49±3.98	-2.80±4.57	0.515
	5. Day	8.73±0.60	8.81±0.57	8.69±0.61			5. Day	-2.12±5.97	-0.13±4.60	-2.91±6.27	
	p*	0.24					p*	0.724			

MCV: Mean Corpuscular Volume, E-GFR: Estimated Glomerular Filtration Rate, RDW CW: Red Cell Distribution Width - Coefficient of Variation, RDW SD: Red Cell Distribution Width - Standard Deviation

DISCUSSION

Several studies have found significant increases in fatalities, respiratory failure, and ICU admissions among hospitalized COVID-19 patients during the pandemic[3,4,8,9]. The poor clinical outcomes of COVID-19 patients who are identified early (such as mortality, intubation, ICU admission, etc.) can be reduced through effective, rapid treatment efforts. The clinical characteristics, risk factors, and laboratory parameters can be used to determine the severity of COVID-19.

This study identified useful parameters as independent predictors of mortality in COVID-19 patients at ICU admission. Among COVID-19 ICU patients hospitalized in the ICU, age, oxygen saturation, direct bilirubin, and ionized calcium were predictive of mortality. During ICU admission, these parameters significantly increased mortality risk; Spo2 (OR=1,096, 95%CI 1.049-1.145, p<0.001), advanced age (OR=1.035, 95%CI 1.013-1.058, p=0.002), direct bilirubin (OR=6.821, 95%CI 0.282-36.285, p=0.024) and ionized calcium (OR=30.524, 95%CI 1.262-738.34, p=0.035). During admission to the ICU and on the fifth day, Dbil, Tbil, AST, and creatinine levels were found to be remarkable predictors of mortality.

SpO2 is a parameter that we use to evaluate respiratory functions and provides the clinician with a noninvasive measurement opportunity thanks to its correlation with partial arterial oxygenation. Studies have shown that advanced age and low oxygen saturation value increase ICU admission and mortality[10-11]. SpO2 has been found to be an important predictor of COVID-19 severity in another study[12]. In line with the literature, we found that mortality was more likely to occur in older adults and those with low Spo2.

Several viral infections are associated with changes in serum ionized calcium levels according to Crespi et al[13]. As a result of COVID-19, serum calcium levels decrease. The presence of hypocalcemia was associated with a longer hospital stay (especially in the ICU) and higher mortality rates in studies of COVID-19[13-15]. Cappellini et al[16] found that the total and ionized calcium levels of patients with COVID-19 were lower, arguing that this was a strategy developed by cells so that the virus would not utilize calcium. In severe COVID-19 patients,

Crespi et al[14] suggest that ionized hypocalcemia is a host defense as a result of pathogen adaptation. Based on our findings, we believe that deceased patients are unable to develop their host defense mechanisms as a result of their adaptation to pathogens. In accordance with the literature, we found that ionized calcium levels were statistically significantly higher in deceased patients than in survivors. The deceased and survivors showed no significant difference in total calcium levels, but the survivors had lower ionized calcium levels.

A large multicenter retrospective study by Fu et al[17] found elevated liver biochemistry levels in COVID-19 patients. It was also recommended that abnormal total bilirubin at admission is associated with poor prognosis[17]. Among bile duct cells, type II alveolar epithelial cells, and ACE-2-expressing bile duct cells, Wentao et al[18] reported that ACE2 significantly affects COVID-19 infection. In recent studies on COVID-19, it was realized that expression of ACE2 in cholangiocytes can directly damage the bile ducts and cause a potent mechanism of infection by the virus by using ACE2 as a receptor. It has also been suggested that high total bilirubin may be associated with bile duct cell damage rather than direct hepatic cell damage caused by SARS-CoV-2[19,20].

As an antioxidant, anti-inflammatory, and other vital physiological properties, bilirubin is widely recognized as a preventive bioactive particle[21,22]. A recent study found that bilirubin not only defends against inflammation but also has potent antiviral properties that may be useful in fighting COVID-19[23]. According to Patel et al[24], elevated serum bilirubin levels were associated with poor outcomes, such as death, in septic patients. Researchers discovered that the prognosis of septic patients was dependent on direct bilirubin rather than total bilirubin. Additionally, direct bilirubin has a better predictive value than total bilirubin in patients with septicemia[25]. In this study, we determined that direct bilirubin and total bilirubin increase the risk of mortality and that direct bilirubin can also be used as a prognostic predictor in the follow-up process. The direct bilirubin levels during admission to the ICU and on the fifth day were statistically significant parameters. This revealed the importance of direct bilirubin both during admission and follow-up. In addition, although total bilirubin was not detected as a mortality predictor during admission, and also stands out in clinical follow-up in this study.Bilirubin, an indicator of mortality, can be a useful tool for predicting death from COVID-19 pneumonia, according to this study, which is relevant to the literature.

A common side effect of SARS-CoV-2 infection is liver damage. The damage may have been caused by three different factors, including; direct cytopathic effect on hepatocytes, hypoxic damage caused by the disease, and hepatocyte damage caused by drugs used in treatment[18]. This study found that elevated AST levels were statistically significant during admission to the ICU, whereas elevated ALT levels had no statistically significant difference during admission and 5th-day measurements. While AST levels declined in survivors, they increased in the deceased group during follow-ups. It shows that AST levels can be used to predict prognoses. In a study by Wisniewska et al[26] AST levels were found to be remarkably higher in severe COVID-19 patients, but no difference was found in ALT levels. They suggested that liver injury is secondary to inflammatory response and hypoxia rather than viral injury and that the contribution of AST from sources other than the liver, particularly muscle, should also be considered. As Fang et al[27] noted in their study, early elevated AST levels were associated with indicators of disease severity, suggesting that immune-mediated inflammation might be crucial to liver impairment in COVID-19 patients. Since AST levels were statistically significant during admission, decreased in the

surviving group, and increased in the deceased group in our study, we found that AST levels are more useful than ALT levels.

COVID-19, classified as a severe respiratory disease, exerts its effects on multiple organ systems, including the heart, brain, vessel endothelium, and kidneys[28]. Patient prognosis was efficiently predicted by creatinine levels in COVID-19[28,29]. According to a meta-analysis by Kazemi et al[29], it indicates a direct correlation between the severity of COVID-19 and the levels of creatinine. According to a meta-analysis, creatinine levels are remarkably related to raised disease severity and might be a useful prognostic factor[30]. Consistent with existing literature, our study identified a significant correlation between disease severity and creatinine levels. Notably, the creatinine levels during ICU admission and on the fifth day did not exhibit statistically significant differences among patients. However, a highly significant disparity in creatinine levels was observed between survivors and deceased patients.

As a result of considering risk factors, clinical features, and serological tests, it is possible to identify risk factors associated with fatal outcomes. In addition, it is possible to identify severe COVID-19 patients early and improve COVID-19 patients' outcomes. Studies in the literature may not be able to examine all possible risk factors comprehensively. Each study considers a different number and type of risk factors. As a result of these disadvantages, we used multivariate analysis of patient data with models in our study, and we found that ionized calcium, oxygen saturation, and direct bilirubin were independent predictors of mortality.

Limitations

The study had some limitations. Retrospective research was conducted in a single ICU with a relatively small group of patients. However, imaging features and ICU treatments for COVID-19 lung involvement were not recorded, along with risk factors, clinical features, and serological tests. It is estimated that new information and articles on COVID-19 ICU mortality are published almost daily; therefore, the results of our study cannot be regarded as comprehensive. To confirm the reliability of the independent prediction parameters for fatality in COVID-19 patients, large-scale, long-term, and prospective studies are needed.

CONCLUSION

This study showed that low saturation, advanced age, high direct bilirubin, and high ionized calcium levels are associated with higher mortality rates during ICU admission. Additionally, it found that direct bilirubin, total bilirubin, AST, and creatinine parameters could be used as mortality predictors during the ICU follow-up period.

Ethics Committee Approval: The study protocol was approved by the institutional ethical board of a tertiary hospital (Date: 31 December 2021, Decision No: 967).

Conflict of Interest: The authors declared no conflicts of interest.

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