ORIGINAL ARTICLE

Factors affecting mortality in COVID-19 patients in intensive care

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ABSTRACT

BACKGROUND: The COVID-19 pandemic affects the whole world, causing high mortality. Some clinical parameters have already been implemented to be followed up to prevent mortality, but there is still a need for further information about optimum follow-up parameters and cutoff values. We aimed to investigate the reliability of the parameters used in patient follow-up by comparing survivors and non-survivors.

METHODS: Patients were divided into two groups as survivors and non-survivors.The parameters used in the follow-up of patients were evaluated for their prognostic value in the course of COVID-19.

RESULTS: Of the 144 patients evaluated in our study, 57 patients were non-survivors (39.7%). Non-survivors were older with an average age of 67.8 years. Of the non-survivors, 59.6% were men. Male gender was found out to be associated with an increased risk concerning prognosis and mortality. The most common accompanying diseases were hypertension, diabetes mellitus, cardiac disease, and chronic obstructive pulmonary disease. In our study, it has been found that lymphocyte counts and levels of troponin, D-dimer, ferritin, and lactate dehydrogenase are important prognostic predictors in estimating mortality risk.

CONCLUSION: The use of prognostic markers appears to provide benefitsin estimating mortality in COVID-19 patients.

Keywords: COVID-19; D-dimer; ferritin; intensive care; lactate dehydrogenase; lymphocyte; mortality; troponin.

INTRODUCTION

COVID-19 pandemic affects the whole world, causing high intensive care needs and high mortality.

The mortality rate is reported to be higher in elderly patients with comorbid diseases such as hypertension (HT), diabetes mellitus (DM), cardiac disease (CD), and chronic obstructive pulmonary disease (COPD).[1,2] The development of acute respiratory distress syndrome (ARDS) is more common and the need for invasive and/or non-invasive mechanical ventilator support is high in COVID-19 non-survivors.[1]

Despite having only mild fever, cough, or muscle pain, some patients have been reported to worsen suddenly in later stages of the disease or during the recovery process.[3] Clinical studies have found out the development of cytokine storm in critical COVID-19 patients. Cytokine storm causes ARDS or multi-organ dysfunction, leading to physiological deterioration, disease aggravation, and death.[3] Parameters associated with cytokine storm can be used in follow-up.

Identification of laboratory parameters that can distinguish between severe and non-severe COVID-19 cases or between those at high or low risk of mortality will increase awareness of the clinical situation.[4]

Some parameters are used in follow-up of COVID-19 patients to prevent mortality, but there is a need for further information about optimum follow-up parameters and cutoff values.

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In our study, COVID-19 patients, who were followed up in the intensive care unit (ICU), were evaluated retrospectively. We aimed to investigate the reliability of the follow-up parameters by comparing the patients who died and survived.

The primary aim of our study is to investigate, in which prognostic markers are more reliable for predicting mortality. The secondary aim of our study was to determine the cutoff values of biomarkers indicating mortality and to determine biomarkers indicating the likelihood of survival.

MATERIALS AND METHODS

The study was performed on patients with the diagnosis of COVID-19 hospitalized in the ICUs of the Anesthesia and Reanimation Clinic of Gaziosmanpaşa Training and Research Hospital in the period between March 23, 2020, and May 19, 2020. To conduct the study, the approval of the Ministry of Health dated May 2, 2020 and numbered 2020-05-02T00-38-07.xml and the approval of the Clinical Research Ethical Committee of Gaziosmanpaşa Training and Research Hospital dated May 19, 2020, numbered 77 were obtained.

Patients, who were older than 18 years old, who were diagnosed with COVID-19, who were admitted to ICU, and who suffered from severe acute respiratory failure were included in the study. A confirmed case of COVID-19 was defined as a patient with a positive result in the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on nasal and pharyngeal swab specimens.[5,6] Patients receiving 5 L/min O_2 through a mask but having SO_2 levels of ≤90% were considered to have severe pneumonia and were included in the study.

Patients with negative RT-PCR test results, patients with initial SaO_2 levels of >90% in ICU, patients admitted to ICU after cardiopulmonary resuscitation, patients transferred to ICU after an operation, patients lost to follow-up due to a transfer to an external center, patients with missing data, and patients still in the 28-day period for following up mortality were not included in the study. In the period between March 23, 2020, and May 19, 2020, 231 patients were followed up in our ICUs. Nine patients, who were admitted from the emergency department or inpatient wards after cardiopulmonary resuscitation; six patients, who were admitted after an operation; 11 patients with SaO_2 levels of >90% on 5 L/min O_2 on the day of ICU admission; four patients with negative RT-PCR test results but positive findings on computed tomography (CT) images; 23 patients, who were transferred to an external center; and 12 patients still in the 28-day follow-up period for mortality were excluded from the study. Thus, 166 patients were included in the study. Of these 166 patients, 22 were excluded from the study due to missing data. Finally, the data from 144 patients were evaluated in the study.

Demographic data such as age, gender, and comorbid diseases of the patients were recorded. The patients were divided into two groups as survivors (Group S) and non-survivors (Group N).

The two groups were compared in terms of length of stay in ICU and the length of receiving invasive and non-invasive mechanical ventilation support.

Levels of partial arterial oxygen pressure (PaO_2), partial arterial carbon dioxide pressure ($PaCO_2$), arterial oxygen saturation (SaO_2), pH, base excess (BE), and lactate were measured by arterial blood gas (ABG) analyses; leukocyte, lymphocyte, platelet, and plateletcrit (PCT) counts were measured by hemogram tests, and levels of ferritin, fibrinogen, hs-troponin-I, D-Dimer, lactate dehydrogenase (LDH), triglyceride (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, prothrombin time (PT), partial thromboplastin time (PTT), and C-reactive protein (CRP) were measured by biochemical analyses. Values of these parameters on the 1st day of ICU admission (initial) and the lowest (minimum) and the highest values (maximum) of these parameters measured during the ICU stay were compared. The reliability, cutoff values, sensitivity, and specificity of the parameters in predicting mortality were determined.

Ranges of the normal values of the parameters evaluated in the study are listed below;
- Leukocyte: 4000–12000/µl
- Lymphocyte: 1500–5000/µL
- Platelet: 150–400 103/µL
- PCT: 0.2–0.5 g/L
- Aspartate aminotransferase <50 U/L
- Alanine aminotransferase <50 U/L
- Creatinine <1.2 mg/dL
- Triglyceride <150 mg/dL
- D-dimer <500 µg/L
- Fibrinogen: 200–400 mg/dL
- Lactate dehydrogenase <250 U/L
- C-reactive protein <5 mg/L
- Ferritin <250 ng/mL
- hs-Troponin-I <20 ng/dL
- PT <15 s
- aPTT<32 s

Patients, who had arrhythmia, hypotension, and HT (patients requiring drug treatment for more than 24 h were included), patients with decreased urine output (patients requiring diuretic or dialysis therapy), were retrieved from the patient files, and the data were compared.

Statistical Analysis

Numerical data were summarized as mean±standard deviation along with median interquartile range (IQR), whereas frequency and percentage were used for categorical data. Shapiro–Wilk's test was used to test the normality of nu-

merical data. Groups were compared for demographical and clinical characteristics by Student's t-test, the Mann–Whitney U-test, or Pearson's Chi-square test; where appropriate. The area under the receiver operating characteristic curve (AUC) along with its 95% confidence interval (CI) were used to assess the diagnostic value of laboratory measurements in discriminating between survivors and non-survivors. Optimal cutoff values of laboratory measurements were determined by Youden's index that was the value corresponding to max (sensitivity + specificity-1). Evaluation of the diagnostic validities for the cutoff values was reported with sensitivity, specificity, negative predictive value, and positive predictive value, including the corresponding 95% CIs. All analyses were performed with the R statistical software environment, version 3.6.3. The "coin" and "report ROC" libraries were used for the non-parametric and diagnostic validity analyses, respectively. P<0.05 was considered statistically significant.

RESULTS

A total of 57 (39.6%) patients died out of 144 patients. The mean age was 62.7±14.92 (min: 27–max: 91) years. Patients in the non-survivor group were significantly older than patients in the survivor group (mean age was 59.31±16 years in the survivor group and 67.81±10.48 years in the non-survivor group, p<0.001). There were 34 (59.6%) male patients in the non-survivor group, while there were 52 (59.8%) male patients in the survivor group (p=0.988). While 19 patients (33.3%) had no concomitant diseases; 25 patients (43.9%) had HT, 18 patients (31.6%) had DM, six patients (10.5%) had CD, seven patients (12.3%) had COPD, and six patients (11%) had other diseases in the non-survivor group (Table 1).

The length of stay in ICU was significantly shorter in the non-survivor group (median [IQR]: 7 [4–12]) compared to the survivor group (median [IQR]: 8 [7–13.5]) (p=0.039) (Table 2). There was not a significant difference in the length of invasive mechanical ventilation support between the non-survivor and survivor groups (p=0.606) (Table 2). The non-survivor group had a shorter length of receiving non-invasive ventilation support compared to the survivor group (median [IQR]: 2 [1–2] and 8 [5–10], respectively) (p<0.001) (Table 2).

The time elapsed from the first occurrence of the initial symptoms to the time of hospitalization was similar between the non-survivor and survivor groups with median values of 2 (IQR: 1–5) days and 3 (IQR: 1–6) days, respectively (p=0.061). Patients in the non-survivor group were transferred to ICU on the 2nd (IQR: 1–5) day of hospitalization and the time elapsed until their transfer to ICU was significantly shorter compared to the time elapsed in the survivor group (p-value) (Table 2).

Out of 144 patients, 63 (43.8%) developed hypotension and 16 (11.1%) developed HT (Table 3). The distribution of complications are shown in Table 3.

Initial values of PaO_2 and SaO_2, which were the PaO_2 and SaO_2 values measured at the time of ICU admission, were similar in both groups (median [IQR]: 57 [45–60] for non-survivors, 54 [52.9–60] for survivors, p=0.992, 83 (61.9–90) for non-survivors, and 82.9 (80.5–89.1) for survivors, p=0.513, respectively) (Table 4).

The lowest PaO_2 (PaO_2 minimum) and the lowest SaO_2 (SaO_2 minimum) values recorded during the ICU follow-ups were

Table 1. Comparison of demographic characteristics and concomitant diseases

Demographic characteristics	Group S	Group N	p-value
	Mean±SD Medium (IQR) n (%)	Mean±SD Medium (IQR) n (%)	
Age (years)	59.31±16.42	67.81±10.48	<0.001[a]
	60 (48;70)	69 (60;76)	
Male/Female, n (%)	52 (59.8)/35 (40.2)	34 (59.6)/23 (40.4)	0.988[c]
Concomitant disease			
HT	36 (41.4)	25 (43.9)	
DM	27 (31)	18 (31.6)	
CD	10 (11.5)	6 (10.5)	
COPD	10 (11.5)	7 (12.3)	
Other	22 (25.3)	6 (11)	
Absent	32 (36.8)	19 (33.3)	

HT: Hypertension; DM: Diabetes mellitus; CD: Cardiac disease; COPD: Chronic obstructive pulmonary disease; SD: Standard deviation. [a]Student's t-test, [c]Pearson's Chi-Square test; Mean, standard deviation, and median (interquartile range) were given for numerical data; frequency and percentage were given for categorical data.

Table 2. Evaluation of the length of mechanical ventilation support, length of stay in ICU and hospital

Length of stay in ICU, hospital and mechanical ventilation support days	Group S	Group N	p-value
	Mean±SD Medium (IQR)	Mean±SD Medium (IQR)	
Length of stay in ICU (days)	11.01±7.69	9.81±7.89	0.039[b]
	8 (7;13.5)	7 (4;12)	
Length of invasive mechanical ventilation support (days)	11.18±9.58	9.07±7.96	0.606[b]
	6 (3;16.75)	6 (4;12)	
Length of noninvasive ventilation support (days)	8.49±4.88	2.1±1.48	<0.001[b]
	8 (5;10)	2 (1;2)	
Time elapsed between the onset of symptoms and hospitalization (days)	3.91±2.93	3±2.39	0.061[b]
	3 (1;6)	2 (1;5)	
Time elapsed between hospitalization and ICU admission (days)	3.71±3.56	2.46±2.09	0.003[b]
	3 (1.5;5)	2 (1;3)	

ICU: Intensive care unit; SD: Standard deviation. [b]Mann-Whitney U test, mean, standard deviation, and median (interquartile range) are presented.

Table 3. Complications during the follow-up of patients

Complications	Group S	Group N	Total	p-value
	n (%)	n (%)	n (%)	
Hypotension				
No	71 (81.6)	10 (17.5)	81 (56.3)	<0.001[c]
Yes	16 (18.4)	47 (82.5)	63 (43.8)	
Hypertension				
No	81 (93.1)	47 (82.5)	128 (88.9)	0.047[c]
Yes	6 (6.9)	10 (17.5)	16 (11.1)	
Arrhythmia				
No	81 (93.1)	44 (77.2)	125 (86.8)	0.006[c]
Yes	6 (6.9)	13 (22.8)	19 (13.2)	
Diuretic requirement				
No	68 (78.2)	14 (24.6)	82 (56.9)	<0.001[c]
Yes	19 (21.8)	43 (75.4)	62 (43.1)	
Dialysis requirement				
No	84 (96.6)	46 (80.7)	130 (90.3)	0.002[c]
Yes	3 (3.4)	11 (19.3)	14 (9.7)	

c: Pearson's Chi-Square test; frequency and percentage are presented.

statistically significantly lower in the non-survivor group compared to the survivor group (PaO_2 minimum was median [IQR]: 42.3 [34.4–50.6] for the non-survivor group and 47.5 [42.2–55.1] for the survivor group, p=0.029). The SaO_2 minimum was 63.7% (51.8–74.9%) for the non-survivor group and 70.54% (68.1–81.35%) for the survivor group (p=0.003) (Table 4). The highest $PaCO_2$ ($PaCO_2$ maximum) values recorded during the ICU follow-ups were statistically significantly higher in the non-survivor group compared to the survivor group (median [IQR]: 83 [62–111] for the non-survivor group, 55.16 [45.7–55.16] for the survivor group, p=0.001). The initial, minimum, and maximum values of the PaO_2/FiO_2 rates were significantly lower in the non-survivor group compared to the survivor group (p<0.001, p<0.001, and p<0.001, respectively) (Table 4).

The parameters used for estimating the prognosis of COVID-19 were evaluated. The leukocyte count was significantly higher in the non-survivor group compared to that found in the survivor group (p<0.001) (Table 5). Lymphocyte counts were low in all patients in both groups at the time of ICU admission. When the two groups were compared; the initial lymphocyte count at ICU admission and the minimum and maximum lymphocyte counts during the follow-up in ICU were significantly lower in the non-survivor group compared to the values in the survivor group (p=0.002, p<0.001, and p=0.002; respectively) (Table 5). The cutoff value was ≤445/μL and sensitivity was 0.92 (95% CI: 0.86–0.98) (Table 6).

The minimum platelet counts and the minimum PCT were statistically significantly lower in the non-survivor group compared to the survivor group (p=0.015 and p=0.029, respectively) (Table 5). A comparison of platelet and PCT between the groups and the corresponding ROC analysis is shown in Tables 5 and 6.

Ferritin levels were quite high in both groups at ICU admission (median [IQR]: 530 (355.25–801.5) for non-survivors and 384 (149–814) for survivors, p=0.113), but the difference between the two groups was not statistically significant. In the follow-ups, the minimum and the maximum ferritin values were significantly higher in the non-survivor group compared to the survivor group (p=0.010 and p<0.001, respectively)

Table 4. Comparison of arterial blood gas analysis results by patient groups

Arterial blood gas Analysis results	Group S	Group N	p-value
	Mean±SD / Medium (IQR)	Mean±SD / Medium (IQR)	
PaO_2 initial (mmHg)	52.97±9.022 / (52.98;60)	51.86±10.67 / 57 (45;60)	0.992
PaO_2 min (mmHg)	47.52±10.37 / 47.52 (42.2;55.1)	43.5±11.52 / 42.3 (34.4;50.6)	0.029[b]
PaO_2 max (mmHg)	160.24±49.82 / 160.24 (158;191)	164.78±56.6 / 166.4 (128;198)	0.746[b]
$PaCO_2$ initial (mmHg)	40.15±10.61 / 40.15 (34;41.55)	36.41±7.88 / 36.5 (31.4;41.6)	0.032[b]
$PaCO_2$ min (mmHg)	33.79±4.77 / 33.79 (32.3;35)	31.54±6.73 / 32.2 (27.4;35)	0.041[b]
$PaCO_2$ max (mmHg)	55.16±16.36 / 55.16 (45.7;55.16)	90.47±36.94 / 83 (62;111)	<0.001[b]
SaO_2 initial (%)	80.5±12.33 / 82.9 (80.5;89.15)	73.82±20.42 / 83 (61.9;90)	0.513[b]
SaO_2 min (%)	70.54±15.68 / 70.54 (68.1;81.35)	62.12±18.58 / 63.7 (51.8;74.9)	0.003[b]
SaO_2 max (%)	96.65±4.34 / 96.65 (96.65;99)	98.21±2.41 / 99.1 (97.6;99.4)	<0.001[b]
PaO_2:FiO_2 initial	129.76±65.69 / 129.76 (96.1;150)	87.54±49.56 / 76.7 (58;100)	<0.001[b]
PaO_2:FiO_2min	111.93±59.17 / 111.93 (80;111.93)	68.19±30.72 / 60 (44.1;88)	<0.001[b]
PaO_2:FiO_2max	320.32±103.45 / 320.32 (300;350)	262.63±148.16 / 250 (124;380)	0.006[b]

PaO_2: Partial arterial oxygen pressure; $PaCO_2$: Partial arterial carbon dioxide pressure; SaO_2: Arterial oxygen saturation; BE: base excess; FiO_2: Fraction of inspired oxygen; SD: Standard deviation. Initial: Levels at the time of intensive care admission; min: the lowest values; max: the highest values during the intensive care follow-ups. [b]Mann-Whitney U test; mean, standard deviation, and median (interquartile range) are presented.

Table 5. Comparison of leukocyte, lymphocyte, platelet and PCT values by groups

Leukocyte, lymphocyte, platelet, and PCT values	Group S	Group N	p-value
	Mean±SD / Medium (IQR)	Mean±SD / Medium (IQR)	
Leukocyte initial (/µl)	8907.91±5004.19 / 7510 (5600;10220)	9614.04±7080.75 / 8190 (6160;11590)	0.545[b]
Leukocyte min (/µl)	5630.93±2106.76 / 5520 (4190;6780)	7636.32±6335.93 / 6600 (4720;8500)	0.007[b]
Leukocyte max (/µl)	12870.12±6455.84 / 11960 (8250;15430)	21442.75±12436.1 / 16820 (13420;26390)	<0.001[b]
Lymphocyte initial (/µl)	1297.88±936.71 / 1100 (790;1400)	966.18±596.33 / 800 (600;1250)	0.002[b]
Lymphocyte min (/µl)	806.47±350.84 / 700 (560;1010)	479.16±288.97 / 400 (290;550)	<0.001[b]
Lymphocyte max (/µl)	2093.18±1045.99 / 1990 (1370;2480)	1632.23±971.09 / 1280 (870;2100)	0.002[b]
Platelet initial (10^3/µl)	255.81±123.46 / 224 (164;304)	224.97±82.59 / 208 (169;270)	0.295[b]
Platelet min (10^3/µl)	208.13±99.89 / 181 (141;256)	165.18±78.3 / 157 (115;202)	0.015[b]
Platelet max (10^3/µl)	411.18±144.68 / 384 (309;510)	362.97±185.16 / 331 (272;403)	0.007[b]
PCT initial (g/l)	0.24±0.11 / 0.22 (0.17;0.28)	0.21±0.07 / 0.2 (0.17;0.25)	0.130[b]
PCT min (g/l)	0.19±0.08 / 0.18 (0.14;0.24)	0.16±0.06 / 0.16 (0.12;0.2)	0.029[b]
PCT max (g/l)	0.39±0.12 / 0.38 (0.3;0.43)	0.34±0.14 / 0.32 (0.24;0.38)	0.003[b]

PCT: Plateletcrit; SD: Standard deviation. initial: Values at the time of intensive care admission; min: lowest values; max: highest values during intensive care follow-ups; [b]Mann-Whitney U test; mean, standard deviation, and median (interquartile range) are presented.

(Table 7). For ferritin values, the cutoff value was ≥550 ng/mL and sensitivity was 0.87 (95% CI: 0.79–0.96) (Table 6).

D-dimer values were high in both groups at the time of ICU admission and were statistically significantly higher in the non-survivor group compared to the survivor group (median [IQR] for non-survivor and survivor groups: 1700 [1160–3156.5] and 1180 [635–2697.5], respectively; p=0.007). When the minimum and maximum D-dimer values recorded during follow-ups were compared, a significant difference was found between the groups (1370 [931–2250] and 795.5 [512–1380] for minimum values, respectively, p<0.001 and 5890 [2800–16200] and 2405 [1190–4715] for maximum values, respectively p<0.001) (Table 7). For the D-dimer value, the

Table 6. ROC analysis of paremeters

	Cut-off	AUC	SEN	SPE	PPV	NPV
Lymphocyte min (/µl)	≤445	0.81 (0.73;0.89)	0.92 (0.86;0.98)	0.61 (0.49;0.74)	0.78 (0.7;0.86)	0.83 (0.72;0.95)
Platelet min (10^3/µl)	≤213.5	0.62 (0.53;0.71)	0.41 (0.31;0.52)	0.81 (0.71;0.91)	0.76 (0.64;0.88)	0.48 (0.38;0.58)
PCT min(g/l)	≤0.215	0.61 (0.52;0.7)	0.34 (0.24;0.44)	0.88 (0.79;0.96)	0.81 (0.68;0.94)	0.47 (0.38;0.57)
PCT max(g/l)	≤0.335	0.65 (0.56;0.74)	0.65 (0.55;0.75)	0.63 (0.51;0.76)	0.72 (0.62;0.82)	0.55 (0.43;0.67)
Ferritin max (ng/ml)	≥550	0.75 (0.67;0.83)	0.87 (0.79;0.96)	0.51 (0.4;0.61)	0.53 (0.43;0.64)	0.86 (0.76;0.96)
Fibrinogen max (mg/dl)	≥445.5	0.59 (0.49;0.7)	0.72 (0.6;0.84)	0.48 (0.37;0.59)	0.46 (0.35;0.57)	0.74 (0.62;0.86)
D-Dimer max (µg/liter)	≥2165	0.74 (0.66;0.83)	0.9 (0.82;0.98)	0.5 (0.39;0.61)	0.55 (0.44;0.65)	0.88 (0.79;0.98)
Troponin max (ng/ml)	≥24.5	0.82 (0.76;0.89)	0.95 (0.89;1.00)	0.64 (0.53;0.74)	0.63 (0.53;0.73)	0.95 (0.89;1.00)
LDH max (U/liter)	≥526	0.81 (0.74;0.88)	0.86 (0.76;0.95)	0.63 (0.53;0.73)	0.6 (0.49;0.71)	0.87 (0.78;0.95)
TG max (mg/dl)	≥261.5	0.55 (0.23;0.87)	0.5 (0.15;0.85)	0.93 (0.83;1.02)	0.67 (0.29;1.00)	0.87 (0.75;0.99)
AST max (U/liter)	≥170.5	0.67 (0.58;0.76)	0.39 (0.26;0.51)	0.9 (0.83;0.96)	0.71 (0.55;0.87)	0.69 (0.61;0.78)
ALT max (U/liter)	≥425	0.54 (0.44;0.64)	0.16 (0.06;0.25)	1 (1;1)	1 (1;1)	0.64 (0.56;0.73)
Cre max (mg/dl)	≥1.535	0.86 (0.79;0.92)	0.83 (0.73;0.92)	0.85 (0.78;0.93)	0.78 (0.68;0.89)	0.88 (0.81;0.95)
PT max (sec)	≥16.15	0.7 (0.61;0.79)	0.53 (0.4;0.66)	0.82 (0.74;0.9)	0.65 (0.52;0.79)	0.72 (0.64;0.81)
PTT max (sec)	≥32.1	0.77 (0.69;0.85)	0.74 (0.62;0.85)	0.81 (0.72;0.89)	0.71 (0.6;0.83)	0.82 (0.74;0.91)
CRP max (mg/liter)	≥213.5	0.76 (0.68;0.84)	0.79 (0.68;0.89)	0.61 (0.5;0.71)	0.56 (0.45;0.67)	0.81 (0.72;0.91)

PCT: Platelet crit; LDH: Lactate dehydrogenase; TG: Triglyceride; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Cre: Creatinine; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; CRP: C-reactive protein. AUC: Area under the curve; SEN: Sensitivity; SPE: Specificity; PPV: Positive predictive value; NNV: Negative predictive value. initial: Values at the time of admission to intensive care; min: lowest values; max: highest values during the intensive care follow-ups. Cut-off values are based on Youden's Index: Sensitivity + Specificity – 1; diagnostic values along with the corresponding 95% Confidence Intervals in brackets are presented.

cutoff value was ≥2165 µg/L and sensitivity was 0.9 ([95% CI: 0.82–0.98) (Table 6).

When the troponin values were examined, it was observed that initial troponin values measured at ICU admission were high in both groups and statistically significantly higher in the non-survivor group compared to the survivor group ($p<0.01$) (Table 7). When maximum troponin values recorded during intensive care follow-ups were examined, they were found statistically significantly higher in the non-survivor group compared to the survivor group ($p<0.01$) (Table 7). For troponin, the cutoff value was found to be ≥24.5 ng/dL and sensitivity was 0.95 (95% CI: 0.89–1.00) (Table 6).

Distribution of the levels of the prognostic biomarkers by the groups at the time of ICU admissions and during the follow-ups in ICU is presented in Table 7. The ROC analysis of the maximum values is presented in Table 6.

DISCUSSION

Of the 144 patients evaluated in our study, 57 were non-survivors (39.7%). Non-survivor patients were older with an average age of 67.8 years. Male gender was found to be associated with a higher risk of catching the disease and mortality. Of the non-survivors, 59.6% were male patients. The most common comorbid diseases were HT, DM, CD, and COPD.

In a meta-analysis of 14 studies on a total of 29,990 patients and 1445 deaths of COVID-19, advanced age (over 65 years), male gender, and having HT, CD, DM, or COPD were found to be related to mortality.[7] Another study has shown that patients of old age and patients with comorbidities such as DM, HT, and CD are more likely to develop a critical and severe disease (74%; 20%).[8] Another study on 138 hospitalized patients has shown that 46.4% of the patients had comorbidities and the likelihood of having an underlying disease was higher in ICU patients compared to patients not treated in ICU (72.2% vs. 37.3%, respectively).[9] Zaim et al.,[10] in their study comparing survivor and non-survivor patients, have found that CD and DM were more frequent in non-survivors. In our study, rates of HT, DM, and COPD were found to be higher in the non-survivor group.

In a study on 52 critically ill adult patients, 94% of the patients were reported to receive invasive or non-invasive mechanical ventilation support. All of the patients in our study received invasive or non-invasive mechanical ventilation support.[1] Another study reported that 32.4% of the patients with severe disease received non-invasive mechanical ventilation support, 14.5% received invasive ventilation support, and the length of hospital stay was 12 days.[5] In our study, the mean length of ICU stay was 9.8 days in the non-survivor group and 11.01 days in the survivor group. The number of days in ICU was higher in the survivor group. Furthermore, the number of days of non-invasive mechanical ventilation sup-

Table 7. Comparison of paremeters by groups

Biochemical parameters	Group S	Group N	p-value
	Mean±SD / Medium (IQR)	Mean±SD / Medium (IQR)	
Ferritin initial (ng/ml)	619.77±742.49 / 384 (149;814)	895.38±1593.98 / 530 (355.25;801.5)	0.113[b]
Ferritin min (ng/ml)	307.59±281.33 / 234 (112;382)	625.15±1387.57 / 357 (178.15;617)	0.010[b]
Ferritin max (ng/ml)	839.59±923.09 / 541 (201;1063)	2871.02±3744.72 / 1398 (701.65;2862)	<0.001[b]
Fibrinogen initial (mg/dl)	421.8±106.15 / 408 (361;479)	455.74±129.48 / 436.5 (367;562.75)	0.185[b]
Fibrinojen min (mg/dl)	297.8±92.31 / 303 (223;367)	309.6±118.03 / 287 (230.25;413.75)	0.549[a]
Fibrnojen max (mg/dl)	480.28±116.69 / 460 (408;538)	518.86±130.22 / 489 (432;616.5)	0.072[b]
D-Dimer initial (µg/liter)	3027.45±5825.45 / 1180 (635;2697.5)	4272.9±8064.14 / 1700 (1160;3156.5)	0.007[b]
D-Dimer min (µg/liter)	1361.34±1799.75 / 795.5 (512;1380)	3014.68±7133.12 / 1370 (931;2250)	<0.001[b]
D-Dimer max (µg/liter)	5485.82±12394.12 / 2405 (1190;4715)	14105±20850.01 / 5890 (2800;16200)	<0.001[b]
Troponin initial (ng/ml)	77.98±447.99 / 7.10 (4;19)	153.73±610.24 / 18.95 (9.98;45)	<0.001[b]
Troponin min (ng/ml)	11.17±29.34 / 4.0 (2;9.4)	116.08±593.42 / 13.45 (8.1;29.73)	<0.001[b]
Troponin max (ng/ml)	142.76±512.6 / 14.3 (5.4;58.2)	1573.46±5185.26 / 148.7 (43.05;594.25)	<0.001[b]
LDH initial (U/liter)	373.59±175.07 / 332 (257.5;432)	679.31±879.6 / 545 (413;718.5)	<0.001[b]
LDH min(U/liter)	262.39±83.03 / 259 (211.75;314)	483.02±415.91 / 389.5 (278.75;527.25)	<0.001[b]
LDH max (U/liter)	501.81±224.06 / 474 (317.5;614.25)	1019.49±915.15 / 768 (579.5;1214)	<0.001[b]
TG initial (mg/dl)	147.57±69.35 / 133 (97;170.25)	193.88±134.06 / 158.5 (88.25;274.75)	0.761[b]
TG min (mg/dl)	145.71±70.07 / 133 (97;170.25)	193.88±134.06 / 158.5 (88.25;274.75)	0.703[b]
TG max (mg/dl)	152.29±72.56 / 141 (97;170.25)	253.25±218.8 / 182 (88.25;345.25)	0.648[b]
AST initial (U/liter)	49.41±50.15 / 32 (24.5;57)	62.53±53.21 / 46 (30;78)	0.024[b]
AST min (U/liter)	26.07±11.58 / 23 (18;30.5)	36.21±23.72 / 28 (23;40)	0.002[b]
AST max (U/liter)	95.67±73.55 / 86 (40.5;120)	631.61±1531.86 / 116 (70;265)	<0.001[b]
ALT initial (U/liter)	40.47±43.33 / 22 (16.5;45.5)	51.4±79.22 / 34 (18;52)	0.166[b]
ALT min (U/liter)	27.97±23.75 / 18 (13;30.5)	26.63±15.2 / 22 (14;36)	0.453[b]
ALT max (U/liter)	101.84±84.75 / 78 (35.5;135)	378.91±1090.64 / 69 (47;145)	0.417[b]
Cre initial (mg/dl)	0.99±0.56 / 0.87 (0.63;1.12)	1.21±0.76 / 1.03 (0.77;1.39)	0.018[b]
Cre min (mg/dl)	0.68±0.38 / 0.58 (0.48;0.76)	0.89±0.45 / 0.76 (0.64;1.03)	<0.001[b]
Cre max (mg/dl)	1.44±1.9 / 0.98 (0.78;1.33)	2.72±1.6 / 2.1 (1.61;3.56)	<0.001[b]
PT initial (sec)	13.45±2.14 / 13 (12.2;14)	15.22±6.01 / 13.9 (12.6;15.5)	0.017[b]
PT min (sec)	12.2±1.04 / 12 (11.1;12.95)	13.65±3.79 / 12.5 (11.9;14.1)	0.004[b]
PT max (sec)	15.06±2.5 / 15 (13.1;15.95)	18.32±6.37 / 16.2 (14.6;19.2)	<0.001[b]
PTT initial (sec)	25.58±3.73 / 25.3 (23;27.4)	28.43±5.98 / 27 (24.9;30.1)	<0.001[b]
PTT min (sec)	22.72±2.17 / 22.6 (21.55;24)	25.48±4.15 / 25 (22.9;27.4)	<0.001[b]
PTT max (sec)	30.73±9.04 / 28 (25.9;31.8)	47.14±26.14 / 37.2 (30.8;55)	<0.001[b]
CRP initial(mg/liter)	126.28±90.25 / 102 (53.25;199)	169.42±90.51 / 156 (111.8;231)	0.005[b]
CRP min (mg/liter)	20.25±26.23 / 10 (4.7;23)	95.38±84.41 / 74 (20.8;136)	<0.001[b]
CRP max (mg/liter)	190.94±96.91 / 188 (124.5;259.75)	290.79±95.44 / 289.75 (223.5;354)	<0.001[a]

LDH: Lactate dehydrogenase; TG: Triglyceride; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Cre: Creatinine; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; CRP: C-reactive protein. initial: Values at the time of admission to intensive care; min: lowestvalues; max: highest values during intensive care follow-ups. [a]Student's t-test, b: Mann-Whitney U test; SD: Standard deviation, and median (interquartile range) are presented.

port was higher in the survivor group, PaO_2 minimum values were lower in the non-survivor group, and the PaO_2/FiO_2 rate was lower in non-survivors both at ICU admission and during the follow-ups in ICU.

In a meta-analysis of 21 studies comparing follow-up parameters, the leukocyte count was found to be higher in patients with severe and fatal disease compared to survivors and patients with non-severe disease.[4] In a study evaluating 12 co-

hort studies, leukocyte counts have been shown to increase in severe disease.[2] In our study, leukocyte counts were variable at admission and follow-ups. However, when the maximum values in follow-ups were compared, it was observed that leukocyte values were higher in the non-survivor group.

In our study, lymphocyte counts were low in both groups at the time of ICU admission and significantly lower in the non-survivor group compared to the survivor group. When the minimum values recorded during follow-ups were compared, it was observed that the values were lower in the non-survivor group compared to the values found in the survivor group. For lymphocyte counts, the cutoff value was ≤ 445/µL and sensitivity was 92% in predicting mortality. It has been found out that lymphopenia is an important prognostic marker to be used both in the diagnosis of severe disease and in predicting prognosis. In a study, which evaluated 43 studies on a total of 3600 COVID-19 patients, lymphocyte counts were reported to have decreased.[11] In another study, 85% of the patients had lymphopenia, but it was reported that there was not a difference between survivors and non-survivors.[1] In a meta-analysis of 24 studies on a total of 3099 patients, it was reported that patients with poor outcomes had lower lymphocyte counts compared to patients with favorable outcomes.[12] In several different studies, the prognostic value of lymphopenia in COVID-19 patients was emphasized.[4,6,8,9,13–15]

A meta-analysis study reported lower platelet counts in patients with severe and fatal disease compared to survivors and patients with non-severe disease.[4] In our study, platelet counts were lower in non-survivors compared to survivors.

In the meta-analysis by Henry et al.,[4] it has been reported that ferritin values increased. The authors have recommended that ferritin levels should be used for monitoring patients to follow-up disease course. In our study, ferritin values were observed to be much higher during follow-up in non-survivors compared to survivors. The cutoff value was ≥550 ng/mL and sensitivity was 0.87. We think that ferritin may be an important prognostic marker in estimating mortality.

In our study, D-dimer was found out as another important prognostic factor in estimating mortality with a sensitivity value of 0.9 for levels higher than 2165 µg/L. Similar to our study, a meta-analysis reported increased D-dimer levels in severe disease.[4,8]

In our study, the cutoff value for troponin was ≥24.5 ng/dl with a sensitivity of 0.95. We think that troponin, too, should be used for monitoring to predict non-survivors. A meta-analysis study has reported that troponin levels are higher in non-survivor patients.[4]

Several different studies have shown that LDH values are elevated in COVID-19.[4,8,9,11,13–15] In our study, LDH levels were higher in non-survivor patients with a cutoff value of ≥526 U/L and sensitivity of 0.86. It is thought that LDH levels may be used in estimating mortality.

When triglyceride levels were examined in our study, we found a cutoff value of ≥261.5 mg/dL showing a high diagnostic accuracy with 93% specificity in estimating survivors. Compared to survivors, AST levels were significantly higher in non-survivor patients. In our study, the cutoff value for AST was ≥170.5 U/L and the cutoff value for ALT was ≥425 U/L with specificities of 0.9 and 1, respectively. The diagnostic accuracy was found to be high in estimating survival. The previous studies, too, found that AST and ALT values were high in severe disease.[2,4,8]

In our study, it was observed that creatinine, PT, and CRP levels were significantly higher in the non-survivor group compared to the survivor group. Similarly, the previous studies have shown elevations in creatinine, PT, and CRP levels.[2,4,8,9,11,13–15]

Evidence suggests that, in COVID-19, the host develops a "cytokine storm" reaction similar to bacterial sepsis cases. Furthermore, high levels of inflammatory markers such as high C-reactive protein, D-dimer, and ferritin have been reported to be possibly associated with disease severity and mortality.[16]

The pathophysiology of COVID-19 has not been fully understood, yet, but it is suggested that the disease leads to death through pulmonary involvement. However, determining the severity of lung involvement by CT is not sufficient to predict mortality. Furthermore, it is suggested that the severity of the disease and CT findings are not correlated and PaO_2 values in arterial blood gas analysis are found already very low in patient groups.[17]

Conclusion

It seems beneficial to use prognostic markers to estimate mortality as stated in previous studies. For this purpose, potential prognostic markers that should be used in the follow-up should be determined. In our study, it was found that lymphocyte counts and levels of troponin, D dimer, ferritin, and LDH were important prognostic predictors in mortality estimation. In estimating survival in infected patients; follow-up of AST, ALT, and triglyceride levels as prognostic indicators was found to be important.

The Power of the Study

There is no such study in the literature determined with cut off values. In our study, we have shown the parameters to be used in predicting mortality and survival with cutoff values. We hope that our study will be very helpful in clinical practice and will also be a reference in future studies.

Limitations of the Study

Our study did not have a prospective design. This was not

possible due to the following dynamic processes. Patients achieving adequate peripheral oxygen saturation levels by mask delivery of oxygen were not admitted to ICU but followed up in the wards. Therefore, patients followed up in ICU were deep hypoxemic patients resistant to oxygen therapy. The number of patients referred to external centers was high. Such patients were excluded from the study, because they were lost to follow-up. Furthermore, we could not include patients with missing data in our study. If these patients were included in the study, data analysis could be performed on more patients.

Ethics Committee Approval: This study was approved by the Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (Date: 19.05.2020, Decision No: 77).

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ORİJİNAL ÇALIŞMA - *ÖZ*

Yoğun bakımda takip edilen COVID-19 hastalarında mortiliteyi etkileyen faktörler

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AMAÇ: COVID-19 pandemisi tüm dünyayı etkisi altına almakta ve yüksek mortaliteye neden olmaktadır. Mortalitenin engellenmesi için takipte bazı parametreler kullanılmakta ancak optimum takip parametreleri ve cut-off değerleri hakkında daha fazla bilgiye ihtiyaç bulunmamaktadır. Bizim çalışmamızda ölen ve sağkalan hastalar karşılaştırılarak, takipte kullanılan paremetrelerin güvenilirliğinin araştırması amaçlanmıştır.

GEREÇ VE YÖNTEM: Hastalar hayatta kalan ve ölen hastalar olmak üzere iki gruba ayrıldı. COVID-19 hastalığının prognozunda izlenen parametreler değerlendirildi.

BULGULAR: Çalışmamızda değerlendirilen 144 hastadan 57'si öldü (%39.7). Ölen hastaların yaş ortalması 67.8 idi ve sağkalan hastalardan daha yüksekti. Ölen hastaların %59.6'sı erkekti. Erkek cinsiyetin, hastalık ve ölüm oranı açısından yüksek risk olduğu görüldü. En sık eşlik eden hastalıklar hipertansiyon, diabetes mellitus, kalp hastalığı, kronik obstrüktif akciğer hastalığı idi. Çalışmamızda lenfosit, troponin, D-dimer, ferritin ve laktat dehidrojenaz değerlerinin mortalite tahmininde önemli prognostik belirleyiciler olduğu bulundu.

TARTIŞMA: Mortaliteyi tahmin etmek için prognostik belirteçlerin kullanılması daha faydalı görünmektedir.

Anahtar sözcükler: COVID-19; D-dimer; ferritin; laktat dehidrojenaz; lenfosit; mortalite; troponin; yoğun bakım.

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