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Laboratory markers used to predict mortality in severe COVID-19

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Abstract

Aim: Herein, we aimed to examine the laboratory parameters of COVID-19 patients and differentiate the parameters that can be used in mortality prediction.

Materials and Methods: The study retrospectively examined the patients who needed intensive care unit due to COVID-19 between March 2020 and December 2020. Three hundred and seventy-four patients who met the study criteria were included in the study. Two main groups were formed: patients discharged from the intensive care unit with no mortality and patients with a mortal course. Patients discharged constituted Group- 1, and patients who died constituted Group- 2. Patients were examined regarding demographic features, clinical, and laboratory characteristics.

Results: Group- 1 consisted of survived patients (n=148, 39.5%), while Group- 2 patients were the patients with mortal course (n=226, 60.4%). In Group-1, 84 (56.8%) of the patients were male, while in Group-2, 127 (56.2%) were male. In the mortality group, procalcitonin, CRP, BUN, D-dimer, troponin, LDH, lactate, and INR values were significantly higher, albumin value was lower ($p < 0.001$). PLT and D-dimer were found as independent variables of mortality according to the logistic regression analysis.

Conclusion: High procalcitonin and D-dimer values obtained with routinely examined rapid and easily accessible blood tests of COVID-19 patients may contribute to mortality prediction.

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Introduction

Coronavirus-2 (SARS-CoV- 2), the COVID-19 agent, is especially destructive in the respiratory tract. Despite vaccination applications, the pandemic still places the world under a heavy economic and health burden. Patients reveal various clinical manifestations, from asymptomatic infection to severe respiratory failure resulting in death. In symptomatic patients, clinical symptoms such as cough, pyrexia (body temperature 37-38 C), nasal congestion, and weakness begin less than a week after being infected [1]. Pneumonia mainly reveals two or three weeks following the infection. [2, 3]. Lymphopenia, the elevation of liver enzymes and lactate dehydrogenase, inflammation markers such as ferritin, C-reactive protein, erythrocyte, and sedimentation rate are common. Although white blood cells, neutrophils, eosinophils, platelets, and other blood cells, including CD8 cell counts, partially predict between mild and severe COVID-19, the certain significance of those parameters is still unclear. Parameters and rates obtained from tests such as hemogram and biochemistry, which are fast, easy, accessible, and routinely studied in the clinic, have been the subject of many studies to detect biomarkers aiming to predict the disease course.

Therefore, biomarkers that can predict the severity of this disease will make an important contribution to personalized treatment. Early awareness of the clinical course will also help reduce mortality. Herein, we aimed to examine the laboratory markers tested in patients diagnosed or suspected of COVID-19 and to develop parameters that can predict mortality.

Material and Methods

Study design and patients

The study was designed as a retrospective study. Şanlıurfa Training and Research Hospital intensive care unit patients who met the criteria with COVID-19 diagnosis between March 2020 and December 2020 were included in the study. The study was conducted after approval from the Ethics Committee of Harran University with the decision

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no HRU/XXX decree under the Declaration of Helsinki. Three hundred seventy-four patients whose data were fully accessed via the hospital information system were examined. Two groups were formed: the patients discharged from ICU and transferred to the pandemic service and the patients who died. Group-1 consisted of patients without mortality (n= 148), and group-2 consisted of patients who died (n= 226).

Data

Patients' age, gender, COVID-19 PCR test result, comorbid diseases, intubation status, the day of the intensive care hospitalization, laboratory values during hospitalization in the intensive care unit, blood types, blood gas parameters (Ph, PO2, PCO2, lactate) intensive care duration were recorded. In addition, neutrophil-lymphocyte ratio (NLR) value and platelet-lymphocyte ratio (PLR) value were calculated according to laboratory values.

Statistical analysis

All the analyses were performed by using Statistical Package for the Social Sciences (IBM SPSS 25.0 Inc., Chicago, IL, USA) computer software. Mean values, standard deviation values, and percentages were used for the expression of the data. The normal distribution was tested with the Kolmogorov Smirnov test. Student t-test was used for the data within the normal distribution. Group analysis of non-parametric data was examined with the Mann-Whitney U test. A logistic regression test was used for univariate analysis and to calculate odds ratios (OR) with a 95% confidence interval (CI). Categorical groups were compared with the chi-square test. Cut-off values were obtained by receiver operating curve (ROC) analysis. A p-value of ˜0.05 was considered as the significance level.

Results

Three hundred seventy-four patients meeting the study criteria were included in the study. The number of patients in Group- 1 was 148 (39.5%), and the number of patients in Group- 2 was 226 (60.4%). The mean age of group-1 was 70 (min: 20-max: 93) years, and group-2 was 70 (min: 20-max: 92) years, and the difference was statistically insignificant (p= 0.001). When we set age 65 as the cut-off value and examined accordingly, it was seen that 82 (55.4%) of the patients without mortality and 152 (67.3%) of the patients who died were over 65 years old. In group-1, 84 (56.8%) patients were male, 64 (43.2%) were female, and in group-2, 127 (56.2%) were male, and 99 (43.8%) were female. The groups did not show significant differences regarding age. When we grouped the patients according to their ethnic origins, 136 (91.9%) were Turkish, 12 (8.1%) were Syrian in Group-1, while in Group-2, 199 (88.1%) were Turkish, and 27 (11.9%) were Syrian. Computed tomography (CT) revealed typical involvement in all patients. When we grouped the patients according to PCR results, there were 75 PCR Negative patients (50.7%), 73 PCR Positive patients (49.3%) in the Group-1, while 98 PCR Negative patients (43.4%), and 128 PCR Positive patients (56.6%) were seen in Group-2. When the patients were evaluated according to their intubation status,

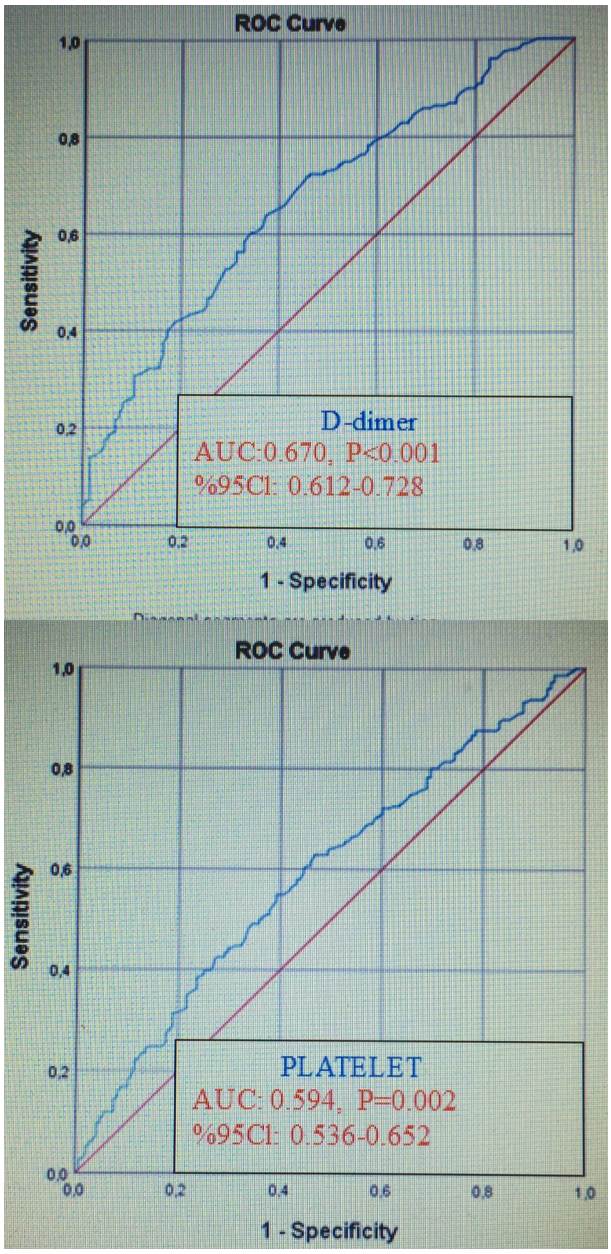

Figure 1. ROC analysis results

it was seen that 138 patients (93.2%) in Group-1 did not need intubation, while 10 (6.8%) patients were intubated. In the mortality group, 18 (8%) patients did not need intubation, while 208 (92%) patients were intubated. The difference between the groups concerning intubation was significant (p< 0.001). In the mortality group, the mean intubation day was the second day (min:0-max:48), the mean intubation time was 7 (min:0-max:65) days, the difference was statistically significant (p< 0.001). When the patients were examined according to their comorbidities, in Group-1, 61 patients (41.2%) had hypertension (HT), 30 patients (20.3%) diabetes mellitus (DM), 50 patients (33.8%) cardiac disease, 44 patients (29.7%) pulmonary disease. Twenty-nine patients (19.6%) had a neurological disease, and seven patients (4.7%) had chronic renal failure (CKD). In Group-2, HT was present in 116 patients (51.3%), DM in 60 patients (26.5%), cardiac disease in 80 patients (35.4%), pulmonary disease in 62 patients (27.4%), neurological disease in 43 patients (19%), and

Table 1. Patient's demographic, clinical and laboratory characteristics

Variables			Group-1 Mortality – n: 148	Group-2 Mortality + n: 226	p- value
Age (year)			70 (20-93)	70 (20-92)	0.001
	<65 years		66 (44.6%)	74 (32.7%)	0.021
	≥65 years		82 (55.4%)	152 (67.3%)	
Gender (n,%)	Male		84 (56.8%)	127 (56.2%)	0.915
	Female		64 (43.2%)	99 (43.8%)	
Ethnicity	Turkish		136 (91.9%)	199 (88.1%)	0.235
	Syrian		12 (8.1%)	27 (11.9%)	
PCR	Negative		75 (50.7%)	98 (43.4%)	0.165
	Pozitive		73 (49.3%)	128 (56.6%)	
Entubation	-		138 (93.2%)	18 (8%)	p<0.001
	+		10 (6.8%)	208 (92%)	
Entubation day			0 (0-6)	2 (0-48)	p<0.001
Entubation duration			0 (0-26)	7 (0-65)	p<0.001
Comorbidities	HT	-	87 (58.8%)	110 (48.7%)	0.055
		+	61 (41.2%)	116 (51.3%)	
	DM	-	118 (79.7%)	166 (73.5%)	0.165
		+	30 (20.3%)	60 (26.5%)	
	Cardiac	-	98 (66.2%)	146 (64.6%)	0.749
		+	50 (33.8%)	80 (35.4%)	
	Pulmoner	-	104 (70.3%)	164 (72.6%)	0.630
		+	44 (29.7%)	62 (27.4%)	
	Neurological	-	119 (80.4%)	183 (81%)	0.892
		+	29 (19.6%)	43 (19%)	
	Chronic renal failure	-	141 (95.3%)	210 (92.9%)	0.355
		+	7 (4.7%)	16 (7.1%)	
Laboratory value	WBC (x103/µl)		11.7 (3.26-34.4)	11.6 (0.02-34.64)	0.031
	Rbc (x106/µl)		4.8 (2.6-5.9)	4.4 (2.3-6.5)	0.097
	Hb (g/dl)		12.87±2.06	12.52±2.12	0.102
	Htc (%)		38.82±5.85	37.97±6.7	0.072
	Neutrophil (x103/µl)		9.9 (2-27.1)	9.6 (0.4-32.2)	0.013
	Lymphocyte (x103/µl)		1.1 (0.1-12.5)	0.8 (0.2-9.7)	0.018
	Monocyte (x103/µl)		0.5 (0-2.1)	0.45 (0-11)	0.161
	Platelet (x103/µl)		290 (59-703)	219 (20-552)	0.002
	RDW (%)		13.8 (11.7-22)	14.1 (11.8-20.2)	0.056
	MPV (fL)		10.6 (8.6-13.7)	10.9 (8.4-14.3)	0.047
	Procalsitonin ng/mL		0.2 (0.02-23)	0.24 (0.04-29)	p<0.001
	Ferritin ng/mL		588 (17-16946)	743 (21-38486)	0.013
	NLR		7.42 (0.76-100)	5 (0.76-18.4)	0.001
	PLR		240 (26.82-2500)	125.2 (43.8-545)	0.998
	CRP (mg/L)		94 (2-338)	120 (0.92-435)	p<0.001
	T. Bilirubin (mg/dL)		0.5 (0.1-20)	0.4 (0.1-7.9)	0.094
	D. bilirubin (mg/dL)		0.1 (0-19)	0.2 (0-7.4)	0.008
	AST (IU/L)		34 (11-2213)	43 (10-1243)	0.001
	ALT (IU/L)		24 (7-1697)	26 (5-717)	0.430
	Albumin (g/dL)		3.33±0.44	3.18±0.53	p<0.001
	BUN (mg/dL)		47 (18-193)	54 (12-311)	p<0.001
	Creatinin (mg/dL)		0.95 (0.3-9.4)	1.1 (0.17-6.4)	0.002
	D-dimer (ng/mL)		0.8 (0.15-9.6)	1.8 (0.2-11.1)	p<0.001
	Troponin (ng/L)		14 (3-3355)	28 (3-1421)	p<0.001
	Fibrinogen (mg/dL)		491.24±177.15	487.68±191.27	0.469
	Na (mmol/L)		137 (127-176)	138 (125-171)	0.398
	K (mmol/L)		4.4±0.75	4.32±0.91	0.932
	Ca (mg/dL)		8.5 (7.3-9.5)	8.4 (4.5-10.1)	0.017
	Ph		7.43 (6.9-7.51)	7.38 (6.9-7.56)	0.001
	PO2		47 (17-171)	39 (11-181)	0.021
	PCO2		35 (14-92)	36 (20-95)	0.482
	Laktate		1.7 (0.83-20)	2.3 (0.7-21)	p<0.001
	INR		1.1 (0.8-2.7)	1.1 (0.93-9.9)	p<0.001
Hospital stay (days)			7 (2-30)	12 (1-68)	0.006

Abbreviations: SD: Standard deviation, WBC: White blood cell, Htc: Hematocrit, MPV: Mean platelet volume, RDW: Red Cell Distribution of Width, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, CRP: C-reactive protein, AST: Aspartate Aminotransferaz, ALT: Alanine Aminotransferaz, *: median (range), #: mean SD. *Statistically significant p <0.05

Table 2. Independent variables for mortality

Variables	OR	%95 CI	P-value
Trombocyte(platelet)	0.992	0.987-0.996	0.000
D-dimer	1.230	1.015-1.491	0.035

CRF in 16 patients (7.1%). The results were statistically insignificant.

Procalcitonin, CRP, BUN, D-dimer, troponin, LDH, lactate, and INR values were higher, and albumin value was lower with statistical significance in the mortality group ($p< 0.001$). The patients' demographic, clinical, and laboratory characteristics are summarized in Table 1. The multivariate logistic regression analysis retested demographic characteristics and laboratory parameters that were statistically significant in the univariant analysis between the two groups. In the logistic regression analysis, PLT (OR= 0.992, 95% CI= 0.987-0.996, p= 0.000) and D-dimer (OR= 1.230, 95% CI= 1.015- 1.491, p= 0.035) were detected as independent mortality variables. (Table 2). D-dimer cut-off value in predicting mortality according to ROC analysis of these independent variables were as follows; 1.05 (AUC: 0.670, %95Cl: 0.612-0.728, p: < 0.001), sensitivity was 68.8%, specificity was 56.7%. AUC for platelets: 0.594, %95Cl: 0.536-0.652, p: 0.002 (Figure 1).

Discussion

The damaging effects of COVID-19 still affect the world despite the increased use of antiviral treatments and vaccination. This study aimed to develop markers among the laboratory parameters to predict mortality. The studies performed in intensive care units have emphasized a mortality rate of approximately 100% among patients who needed mechanical ventilation [4]. Our study is even more important since we observed that our mortality rate was 60.4% in our 1 -year intensive care follow-up. We found that the mortality rate was significantly higher in intubated patients.

Regarding the gender-mortality relationship, the M/F ratio was 1.28 in our study. An in-depth Italy sample study examining the Covid-19 effect on 123,300 COVID-19 deaths reported that the mortality rate was more prominent in the male gender. Accordingly, if the mortality rate for female patients was 2.5%, the same rate for males was 3.4%. Nevertheless, the mortality due to COVID-19 was more probable in females than males in a few countries, such as India, one of the worst-affected countries. As of Sept 30, 2020, India had more than 6.4 million proven COVID-19 pa-tients [5], and the COVID-19 mortality rate for males was 2.9%, while it was 3.3% for females [6]. Both Group 1 and Group 2 patients had comorbid diseases, but comorbid diseases were not signifi-cant between the two groups.

The evaluation of laboratory parameters revealed that high levels of procalcitonin, CRP, BUN, D-dimer, troponin, LDH, lactate, INR, and low albumin were significant regarding mortality. The logistic regression analysis revealed that low PLT and high D-dimer were independent variables of mortality. Fan et al. [7] reported that lymphopenia and increased lactate dehydrogenase (LDH) values were in association with higher rates of ICU admission. Patients referred to the ICU had lower lymphocyte and monocyte counts and lower hemoglobin values, while they had higher peak Neutrophil (NEU) counts and higher LDH levels than patients who did not require intensive care. Similarly, in SARS disease, high CRP levels, lymphopenia, leukopenia, and elevated aminotransferase, LDH, and creatine kinase levels have been shown in numerous patients [8]. Liver dysfunction is more frequently observed in severe COVID-19 patients than in those with milder severity, while there was also an elevation in Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels in numerous ICU patients [9]. Infection of liver cells with SARS-CoV-2 should not be ignored since 2- 10% of COVID-19 patients suffer from diarrhea, and viral RNA is determined in both stool and blood samples, suggesting the presence of the virus in hepatocytes (10]. High C-reactive protein (CRP), ferritin and lactate dehydrogenase (LDH) levels were found as in correlation with disease severity and prognosis [11,12].

Wang D et al.'s study [13] reported that the ability of procalcitonin elevation in predicting 28 -day intensive care mortality was statistically significant. The study of Mardani et al. [14], examining 200 patients in a single-center, reported that ALT, CRP, NEU, LDH, and BUN values had extreme accuracy in predicting PCR-positive patients. In the same study, the decrease in WBC and lymphocyte counts was evident in PCR-positive patients, but there was no significant difference between our patient groups.

Zhao et al. [15] reported that the most common laboratory findings in COVID-19 patients were decreased lymphocyte count, prolonged APTT, elevated LDH, CRP, and erythrocyte sedimentation rate (ESR). Erol et al. [16] examined 101 patients and showed that CRP, LDH, D-Dimer values were significantly higher, and WBC values were significantly lower in the patient group who died. In our study, similar to these results, we found high CRP, D-Dimer LDH values in Group-2. Although low platelet levels did not make a significant difference between the groups in the study of Erol et al., platelet levels were significantly lower in Group-2 in our study. Deng et al. [17] stated that increased leukocyte counts and decreased lymphocyte count in the survival group were correlated with mortality. Our study did not observe significant differences in both groups' leukocyte counts and lymphocyte counts.

LDH has a known predictive role as a mark of altered glucose metabolism in patients with sepsis [18]. In the study conducted by Gao et al. [19], it was reported that laboratory parameters, such as ALT, CRP, AST, and LDH, can be used to evaluate the course of the disease. Tsui et al. [20] examined 323 cases with severe acute respiratory failure and stated that high LDH level was an important prognostic factor. Similarly, we found significantly high LDH levels in the mortality group.

In our study, we concluded that D-dimer elevation was an independent variable for mortality. Similarly, according to a report published in Wuhan, D-dimer levels of $\geq$ 2.0 ng/mL indicate a higher mortality rate than levels below 2.0 ng/mL [21].

A meta-analysis including 25 studies and 5350 patients

in total published by Huang et al. reported that high CRP, procalcitonin, D-dimer, and ferritin were in association with poor outcomes [22]. COVID-19 infection also manifests with procoagulant factors such as fibrinogen and predominantly high D-dimer levels resulting in a coagulopathy problem and increased mortality. In our study, fibrinogen levels were high in both groups, and the difference was not statistically significant. Likewise, although ferritin values were higher in the mortality group in our study, we could not find a significant difference between the two groups. However, we believe that high ferritin levels were associated with the hyperinflammatory state.

In a meta-analysis of 11 studies and 910 patients reviewed by Aziz et al., a correlation was shown between hypoalbuminemia and severe COVID-19, and it was reported that it would facilitate the early diagnosis of severe disease and help clinicians [23]. In our study, we found that hypoalbuminemia was significant in the mortality group. Similarly, in the study of Erol et al. (16), AST values were higher in the mortality Group than in the survival group, while ALT values did not reveal any significant difference. The AST value was higher in the mortality group in our study, and the difference was not statistically significant (p= 0.001). Zhang et al. (9) showed that 2-11% of COVID-19 patients had liver comorbidity, and 14-53% of cases had abnormal ALT and AST levels during the disease progression. Thus, liver damage appears to be more common in severe cases than mild cases of COVID-19. Yang et al. [24] reported that there was no difference in the incidence of abnormal liver function between the survival (30%) and mortality (28%) groups.

The limitation of our study is that it is retrospective, the number of patients is small, and it is single-centered. In conclusion, full treatment has not been provided yet in the COVID-19 pandemic, which has left its mark on the last century and has caused many deaths. Vaccination and vaccine development studies are still ongoing. Nevertheless, we think that the high procalcitonin and D-dimer values obtained with this study via easily accessible, routinely examined blood tests in COVID-19 patients, may contribute to mortality prediction.

Ethics committee approval

The study was approved by the Harran University Medical Faculty Hospital Local Ethics Committee (approval no: HRU).

Conflict of interest

The authors declared no conflict of interest.

Financial disclosure

The authors declared that this study had received no financial support.

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