

Roles of certain biochemical and hematological parameters in predicting mortality and ICU admission in COVID-19 patients

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SUMMARY

OBJECTIVE: In this study, we aimed to retrospectively analyze the roles of certain hematological and biochemical parameters in predicting mortality and intensive care unit admission in patients diagnosed with coronavirus disease 2019 (COVID-19).

METHODS: We analyzed the complete blood count and biochemical parameters of 186 COVID-19 patients by using the polymerase chain reaction test. Whether these parameters can be used to predict intensive care unit admission and mortality in the COVID-19 patients was investigated.

RESULTS: The complete blood count and biochemical parameters of COVID-19 patients and in those admitted to intensive care unit were compared. The red cell distribution width, ferritin, lactate dehydrogenase, D-dimer, C-reactive protein, prothrombin time, and creatinine levels were found to be the most significant parameters. We found that these parameters are significant for predicting not only intensive care unit admission, but also the mortality of the patients admitted to the intensive care unit.

CONCLUSIONS: We determined that the most effective parameters to predict intensive care unit admission and mortality in COVID-19 patients are ferritin, lactate dehydrogenase, D-dimer, C-reactive protein, red cell distribution width, creatinine, and intensive care unit. Close monitoring of these parameters and early intervention in alterations are of vital importance.

KEYWORDS: Coronavirus infections. Mortality. Intensive care unit. Blood coagulation. International normalized ratio. Fibrin fibrinogen degradation products. Creatinine. C-reactive protein. Erythrocyte indices.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) first appeared in the city of Wuhan, China, spread to the entire world and caused a global pandemic. The virus, which was subsequently named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has become the most serious health problem due to its rapidly increasing mortality¹. Since much of the data about the clinical outcomes of this disease are yet to be explored, both treatment and follow-up decisions can be challenging. It is

crucial to predict which patients will be admitted to intensive care unit (ICU) and which patient has a high risk of mortality.

The relation of certain hematological parameters, including hemoglobin and red cell distribution width (RDW), with both ICU admission and mortality in COVID-19 has been demonstrated in earlier studies^{2,3}. It has been reported that the hemoglobin level is significantly decreased and RDW is significantly elevated in patients with severe disease. In another study, the researchers reported that the most distinct determinants for

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the differential diagnosis between community-acquired pneumonia and COVID-19 were hemoglobin and RDW values⁴.

Lactate dehydrogenase (LDH) is an enzyme that converts lactate into pyruvate — a reaction that occurs in severe tissue destruction caused by sepsis, malign diseases, and severe infections in many tissues. In a study, the researchers stated that LDH level was an indicator for pneumonia caused by COVID-19, which increases with severe pneumonia and decreases when pneumonia was resolved, but a cutoff value could not be given⁵.

In a recent systematic research and meta-analysis reviewing 15 studies, low platelet count, elevated C-reactive protein (CRP), and LDH were found to be associated with mortality in COVID-19 patients⁶. In another meta-analysis reviewing 10 studies, elevated liver enzymes, including alkaline phosphatase (ALP) and alanine aminotransferase (ALT), decreased albumin, elevated creatinine kinase (CK), and most importantly, elevated LDH were pointed out⁶. Another study argued that procalcitonin (PCT), CRP, and LDH levels demonstrated significant elevations in a pooled laboratory analysis of children with mild and severe COVID-19, and the elevation of CK-MB could predict early cardiac injury in children⁷. In a different study, laboratory markers were compared in patients with severe and mild COVID-19 disease and the authors stated that especially low lymphocyte count, ferritin, D-dimer, CRP, cardiac troponin, and LDH were significant parameters with predictive value⁸.

Liu et al.⁹ reported that CRP and interleukin 6 (IL-6) levels increased in severe stages of the disease, and CRP >41.8 mg/L may be an independent risk factor for progression in the early stage COVID-19 patients. In a recent study, Wang¹⁰ claimed that elevated CRP accompanies lung lesions and therefore reflects the severity of disease. In an article exploring the hematological findings and complications of COVID-19, Terpos et al.¹¹ reported elevated D-dimer, prolonged prothrombin time (PT), and activated partial thromboplastin time (aPTT), resulting in disseminated intravascular coagulation, in addition to the increase in CRP, IL-6, and LDH levels. Similarly, many recent studies demonstrated neutrophil/lymphocyte ratio as an independent risk factor for the severe COVID-19 disease¹².

It is evident from the studies in the literature that various parameters are used in determining severe and mild COVID-19 infection. However, the parameters that are effective in determining ICU admission and mortality of these patients should be clearly revealed. For these reasons, in this study, we aimed to retrospectively analyze the roles of certain hematological and biochemical parameters in predicting mortality and ICU admission in patients diagnosed with COVID-19 disease.

METHODS

Patients

All the confirmed and hospitalized COVID-19 patients in the University of Health Sciences Izmir Bozyaka Training and Research Hospital between March 2020 and August 2020 were included in this study. Cases were diagnosed according to the interim guidance report of the World Health Organization (WHO)¹³ and to the diagnosis and treatment guidelines of COVID-19 of Ministry of Health in Turkey¹⁴. Patients met all the following conditions:

1. contact history;
2. fever or other respiratory symptoms;
3. typical computed tomography (CT) image findings suggestive of viral pneumonia, and;
4. positive result of real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA. Sputum and throat swab specimens were collected from all patients on admission and tested by RT-PCR for SARS-CoV-2 RNA within 3 hours.

Clinical characteristics and laboratory data

Data of patients with COVID-19, including recent exposure history, clinical symptoms and signs, and laboratory findings, were obtained from electronic medical records. Laboratory assessments included complete blood count (CBC), biochemistry, and coagulation studies. The severity of disease was defined based on the international guidelines for community-acquired pneumonia. The result was cure and discharge, or mortality within 28 days.

This study was approved by the University of Health Sciences Izmir Bozyaka Training and Research Hospital Ethics Committee on Clinical Research (N°. 222/2019).

Statistical analysis

Statistical analyses were performed using SPSS version 17.0 software. The suitability of variables to normal distribution was examined using the analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test). Mean \pm standard deviation was used for descriptive analyses. Deviation is given as frequency and percentage. Descriptive statistics were made by representing demographic characteristics as frequency and percentage values. In continuous data, the Mann–Whitney *U*-test or Student's *t*-test was used to compare binary variables in independent groups, such as mortality or ICU admission (Yes or No). Paired *t*-test or Wilcoxon signed rank test was used to compare biochemical parameters. The Pearson's χ^2 or Fisher's exact chi-square test was used in the analysis of categorical data. The sensitivity and specificity of biochemical parameters that may be the predictors of ICU admission

and survival (or death) were determined by receiver operating characteristic (ROC) analysis. The cases where the p-value was <0.05 were considered statistically significant.

RESULTS

The total number of patients hospitalized due to COVID-19 was 186. Their mean age was 56.0 ± 18.5 years, where the youngest was 18 and the oldest was 96 years old. The mean age of the patients who were admitted to ICU (n=40) was 69.5 ± 16.3 years, while it was 52.3 ± 17.3 years for those who were not admitted (n=146). The difference between these groups was statistically significant ($p < 0.001$, $t = -5.622$). The mean age of those who did not survive (n=30) was 71.8 ± 14.6 years, while the mean age of those who survived (n=156) was found to be 53.0 ± 17.6 years, with a statistically significant difference ($p < 0.001$, $t = 5.482$).

The biochemical parameters of patients who were and were not admitted to ICU were analyzed using the ROC analysis. The cutoff values and sensitivity–specificity ratios of the analyzed biochemical parameters, according to ICU admission, are shown in Table 1. The parameters with the most prognostic values were found to be ferritin, LDH, D-dimer, and CRP.

In addition, the parameters other than ALT and aPTT may also predict ICU admission (Figure 1).

The biochemical parameters of COVID-19 patients were also analyzed for the risk of mortality using the ROC analysis. The cutoff values and sensitivity–specificity ratios of the analyzed biochemical parameters are shown in Table 2. The parameters with the most prognostic values were found to be RDW, D-dimer, LDH, urea, creatinine, PT, international normalized ratio (INR), CRP, and ferritin. However, the parameters other than ALT and CK may also predict mortality (Figure 2).

In our analyses, hemoglobin and RDW parameters exhibited the most distinct differences. However, the sensitivity and specificity of hemoglobin were remarkably low (for ICU admission, AUC: 0.290, sensitivity: 20.5%, and specificity: 59.3%). On the other hand, RDW values appeared to have higher significance on ICU admission and mortality as the sensitivity and specificity rates were much higher (AUC: 0.710, sensitivity: 71.8, and specificity: 75.9 for mortality; AUC: 0.869, sensitivity: 86.7%, and specificity 79.5% for ICU admission). A cutoff value of 15% and above for RDW appears significant in terms of mortality.

CRP, which is an inflammation marker, is found to be significant for mortality and ICU admission. For mortality, AUC

Table 1. Comparison of parameters at the time of ICU admission

Parameters	Cutoff Value	AUC	p-value	95%CI [min–max]		Sensitivity (%)	Specificity (%)
Hb	13.8	0.290	<0.001	0.185	0.396	20.5	59.3
RDW	13.8	0.710	<0.001	0.602	0.818	71.8	75.9
PDW	12.6	0.678	0.001	0.572	0.784	59.0	77.2
D-dimer*	326.0	0.867	<0.001	0.811	0.924	76.9	80.0
LDH*	316.0	0.870	<0.001	0.812	0.928	54.0	95.4
Glucose	122.5	0.754	<0.001	0.665	0.844	64.1	71.0
Urea	36.5	0.739	<0.001	0.633	0.846	69.2	78.6
Creatinine	1.25	0.304	<0.001	0.207	0.400	16.4	55.0
ALT	33.5	0.499	0.986	0.388	0.610	35.9	74.5
AST	31.5	0.723	<0.001	0.612	0.834	71.8	71.0
PT	12.8	0.692	<0.001	0.577	0.806	69.2	69.7
APTT	31.1	0.448	0.315	0.340	0.555	25.6	67.6
INR	11.4	0.784	<0.001	0.692	0.875	74.4	69.7
CK	159.0	0.389	0.034	0.276	0.503	20.5	80.0
Total Bilirubin	5.5	0.684	<0.001	0.584	0.785	56.4	71.0
CRP*	149.5	0.826	<0.001	0.759	0.893	79.5	76.6
Ferritin*	234.0	0.883	<0.001	0.821	0.945	87.2	84.1

AUC: area under the curve; CI: confidence interval (95%); Hb: hemoglobin; RDW: red cell distribution width; PDW: platelet distribution width; LDH: lactate dehydrogenase; ALT: alanine transaminase; AST: aspartate transaminase; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; CK: creatinine kinase; CRP: C-reactive protein. $p < 0.05$ was considered significant. *Important predictors for intensive care unit admission.

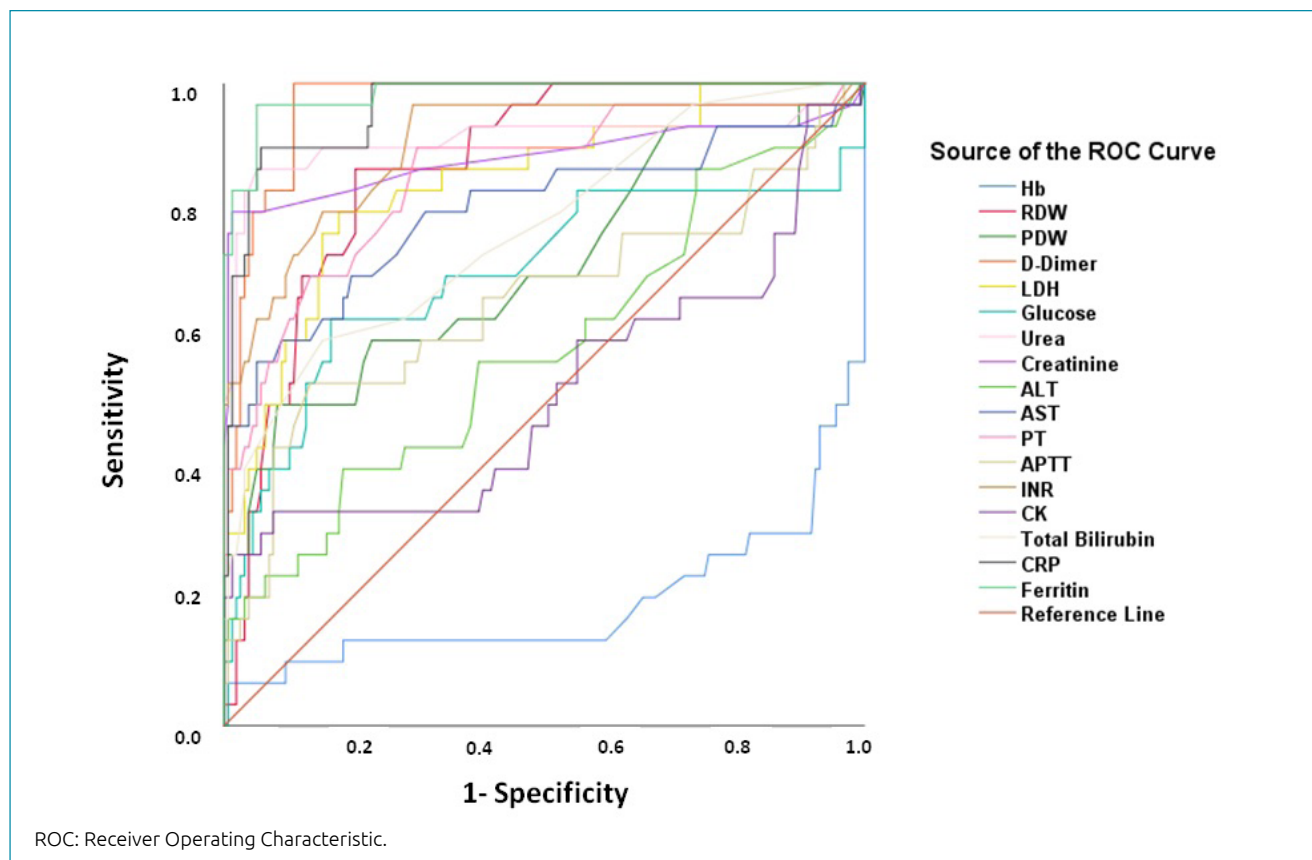


Figure 1. ROC analysis of biochemical parameters related to intensive care unit admission.

Table 2. Comparison of parameters at mortality

Parameters	Cutoff value	AUC	p-value	95%CI [min-max]		Sensitivity (%)	Specificity (%)
Hb	13.8	0.189	<0.001	0.076	0.301	13.3	67.9
RDW*	15.0	0.869	<0.001	0.811	0.928	86.7	79.5
PDW	12.7	0.714	<0.001	0.601	0.827	60.0	76.9
D-dimer*	488.5	0.965	<0.001	0.941	0.989	96.7	89.1
LDH*	370.0	0.846	<0.001	0.766	0.926	50.0	93.6
Glucose	107.0	0.702	<0.001	0.574	0.829	70.0	65.4
Urea*	55.5	0.913	<0.001	0.829	0.998	86.7	94.9
Creatinine*	1.5	0.792	<0.001	0.702	0.881	43.3	96.2
ALT	48.5	0.586	0.137	0.464	0.708	40.0	81.4
AST	37.0	0.801	<0.001	0.693	0.909	70.0	80.1
PT*	13.6	0.854	<0.001	0.772	0.937	70.0	86.5
APTT	32.1	0.660	0.006	0.532	0.787	60.0	69.2
INR*	1.25	0.901	<0.001	0.831	0.972	70.0	90.4
CK	71.5	0.521	0.717	0.386	0.656	60.0	44.9
Total bilirubin	0.8	0.772	<0.001	0.674	0.871	60.0	84.6
CRP*	160.5	0.964	<0.001	0.936	0.992	70.0	98.7
Ferritin*	538.5	0.984	<0.001	0.967	1.000	96.7	94.9

AUC: area under the curve; CI, confidence interval (95%); Hb: hemoglobin; RDW: red cell distribution width; PDW: platelet distribution width; LDH: lactate dehydrogenase; ALT: alanine transaminase; AST: aspartate transaminase; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; CK: creatinine kinase; CRP: C-reactive protein. p<0.05 was considered significant. *Significant predictors for mortality.

was 0.964, sensitivity was 70.0%, and specificity was 98.7%, while the cutoff value was 160.5 mg/L. For ICU admission, AUC was 0.826, sensitivity was 79.5%, specificity was 76.6%, and the cutoff value was 149.5 mg/L.

LDH, another significant parameter for both ICU admission and mortality, has an AUC of 0.870, sensitivity of 76.9%, and specificity of 82.1% with the cutoff value of 316.0 U/L for ICU admission, and an AUC of 0.846, sensitivity of 80.0%, and specificity of 82.1% with the cutoff value of 370.0 U/L for mortality.

The elevated levels of ferritin were found to be an important risk factor for ICU admission and mortality. For ICU admission, AUC was 0.883, sensitivity was 87.2%, and cutoff value was 234, while for mortality AUC was 0.984, sensitivity was 96.7, specificity was 94.9%, and cutoff value was 538.5. As can be seen, ferritin is much more significant in terms of mortality.

It is observed that D-dimer, LDH, CRP, and ferritin levels predict the risk for both ICU admission and mortality. In terms of D-dimer, AUC was 0.867, sensitivity was 76.9%, specificity was 80.0%, and cutoff value was 326 for ICU admission, while the AUC was 0.965, specificity was 89.1%, sensitivity was

96.7%, and cutoff value was 488.5 for mortality. Considering the AUC values, it can be concluded that D-dimer level is especially more significant for mortality.

The elevated levels of urea, creatinine, PT, and INR had no statistically significant impact on ICU admission, yet they were significant for mortality. In terms of mortality, the cutoff value for urea was 55.5, AUC was 0.913, specificity was 94.9%, and sensitivity was 86.7. The cutoff value for creatinine was found to be 1.5, AUC 0.885, sensitivity 80.0%, and specificity 98.7%. Previous reports in the literature also found that creatinine values increased in severe COVID-19 patients¹⁸. The cutoff values for PT and INR were 13.6 and 1.25, AUC values were 0.854 and 0.901, specificity values were 86.5% and 90.4%, respectively, and sensitivity was 70.0% for both parameters.

DISCUSSION

COVID-19 is a viral infection that possesses a serious public health threat and results in high mortality at present. Worldwide, countries are experiencing serious challenges with the pandemic, both in terms of economy and burden on health systems.

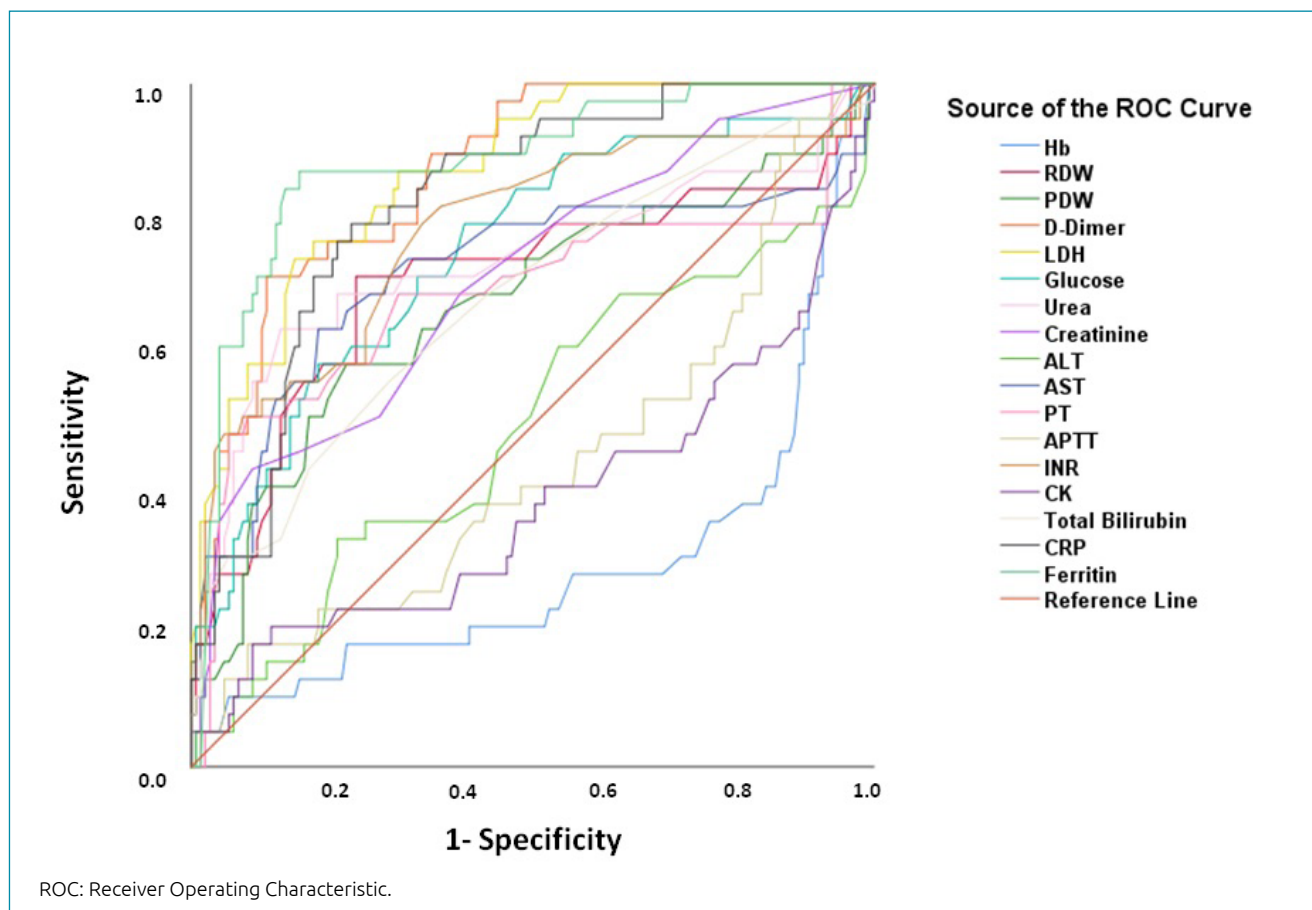


Figure 2. ROC analysis of biochemical parameters related to mortality.

New disease-related findings are being revealed day by day and the treatment-related algorithms are continuously updated.

There are many studies in the literature which report that CBC abnormalities, especially low lymphocyte and platelet counts, and neutrophil/monocyte ratio affect prognosis. In this study, hemoglobin and RDW values were more distinctly different. However, the sensitivity and specificity of hemoglobin were remarkably low. On the other hand, the RDW values appeared to have higher significance on ICU admission and mortality as the sensitivity and specificity rates were much higher. A cut-off value of 15% and above for RDW appears significant in terms of mortality. In one study, it was shown that the RDW level with AUC value of 0.870 can be helpful in differentiating COVID-19 from community-acquired pneumonia².

In terms of biochemical parameters, D-dimer, LDH, CRP, and ferritin levels determined the risk of ICU admission while D-dimer, LDH, urea, creatinine, PT, INR, CRP, and ferritin predicted the risk of mortality.

In a study from Wuhan, China, Zhou et al.¹⁵ reported that D-dimer is an independent risk factor for disease course and is significantly increased in severe pneumonia cases. In another study by different researchers in the same area, it was reported that the clinicians should be alert in the early period when D-dimer is $>1 \mu\text{g/mL}$ ¹⁶. Similarly, Li et al.¹⁷ showed that the mean D-dimer level was $0.6 \mu\text{g/mL}$ (0.2–5.0) in severe cases.

A meta-analysis revealed that LDH levels were higher in severely ill patients than nonsevere patients as with the case in ICU than non-ICU patients¹⁸. Similarly, Wu et al.⁵ evaluated 10 severe and 77 nonsevere patients with COVID-19 pneumonia and found that the mean LDH level was $442 \pm 17.47 \text{ U/L}$ in nonsevere cases and $1040 \pm 158.3 \text{ U/L}$ in severe cases. The researchers mentioned that the high LDH level was mostly due to the very wide normal range of the kit used⁵. In this study, the cutoff values were 316 and 370, while others report the levels of 401–435 U/L.

In a study that assessed the clinical parameters showing the severity of COVID-19, Shang et al.¹⁹ reported that mean CRP level was 43.15 in severe cases and 10.05 in mild cases. In another study, the authors found that mean CRP level was 40 mg/L in

COVID-19 survivors, while it was 125 mg/L in those who died⁸. In a study on CRP levels in the early disease period, the CRP was found to be 54.15 ± 1.06 in the group with severe condition and 105 ± 12.73 in the group with critical condition¹⁰. Although our findings on CRP values are consistent with the literature, it should be noted that the majority of those studies, excluding meta-analyses, had relatively lower sample size than that of our study.

In a study, Velavan et al.⁸ claimed that ferritin is increased in COVID-19 patients with hemophagocytic lymphohistocytosis and more cytokine storm. Consistently, Terpos et al.¹¹ stated that the ferritin level increases very high in ARDS development. There were also authors who claimed that there was a relationship between death and ferritin levels.

Velavan et al.⁸ also noted that the PT was increased in patients admitted to ICU and aPTT was increased in nonsurvivors. Although the cutoff values of the parameters are close to normal values, the high AUC values indicate that they may still be significant despite their being relatively low for mortality.

Our findings indicated that the RDW levels of patients diagnosed with COVID-19 significantly predicted both ICU admission and mortality. We also showed that PT, INR, urea, and creatinine values were significant in terms of predicting mortality along with D-dimer, LDH, CRP, and ferritin. With the predictions of these values, fast and aggressive interventions can be made in the treatment plans.

The major limitation of this study was the relatively low sample size, considering the size of the pandemic and the total number of patients is growing beyond 150 million worldwide. With this study, we aimed to analyze the roles of certain hematological and biochemical parameters in predicting mortality and ICU admission in patients diagnosed with COVID-19, and revealed the cutoff values for these predictive parameters.

AUTHORS' CONTRIBUTIONS

FB: Investigation, Project Administration, Supervision, Methodology.

ŞÇ: Data Curation, Validation, Visualization, Formal Analysis.

ID: Resources, Software, Funding Acquisition, Conceptualization.

OB: Writing – Original Draft, Writing – Review & Editing

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