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Effect of first application laboratory values on the prognosis of COVID-19 patients hospitalized in the intensive care unit

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Abstract. – OBJECTIVE: The aim of the study was to investigate the effect of blood values at first admission to the hospital on predicting mortality in COVID-19 patients hospitalized in the intensive care unit (ICU).

PATIENTS AND METHODS: The blood parameters of 284 intensive care patients, who were diagnosed with COVID-19 *via* the Real-Time Polymerase Chain Reaction (RT-PCR) for SARS-CoV-2 RNA test, at first admission to the hospital, were evaluated. The contribution of these parameters to predicting mortality was analyzed.

RESULTS: No significant relationship was found between complete blood count and mortality. However, it was determined that the ferritin, ALT, D-dimer, and urea levels significantly affected the mortality rates in intensive care patients.

CONCLUSIONS: The ferritin, ALT, D-dimer, and urea levels of patients who were admitted to the ICU due to COVID-19, at first admission to the hospital, were significant in predicting mortality. Therefore, it is recommended that these parameters will be evaluated at the first application.

Key Words:
COVID-19, Intensive Care Unit, Biochemical parameters, D-dimer, Ferritin, ALT, Urea.

Introduction

The new coronavirus disease-2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), results in lung damage and has caused a worldwide pandemic[1]. The disease was first detected in the city of Wuhan in the Hubei Province of the People's Republic of China in December 2019[2]. Due to the high number of asymptomatic cases and the development of transportation routes, its spread across the world occurred quite rapidly, unlike previous pandemics[3,4]. The World Health Organization declared this disease, which has spread to all continents, as a pandemic on March 11, 2020[5]. As of December 2021, the number of cases exceeded 280 million and deaths exceeded 5 million due to the SARS-CoV-2 virus, which spread to 216 countries (https://www.worldometers.info/coronavirus/).

The SARS-CoV-2 virus can cause a three-stage disease that may first cause flu-like symptoms, then, viral pneumonia, and then, fibrosis causing decreased lung compliance. Acute respiratory distress syndrome occurs by causing intense disease in the lung parenchyma. These patients need intensive care and mechanical ventilation. An increase in inflammatory biomarkers, such as C-reactive protein (CRP), ferritin, D-dimer, interleukin-1 (IL-1), and IL-6, indicating a poor clinical course, is observed in the same patient group[6]. There have been many scholars[7] investigating the relationship between biochemical parameters and COVID-19. Ponti et al[8] showed that the use of biochemical markers is significant in predicting the prognosis of COVID-19. As far as is known, there have been no studies evaluating biochemical parameters at first admission to the hospital in hospitalized patients and those who need intensive care. Therefore, this study is unique in terms of its method. Since predicting the mortality of patients admitted to intensive care is critical, it was aimed herein to investigate the prediction of biochemical parameters in evaluating the prognosis of patients hospitalized in the intensive care unit (ICU).

Patients and Methods

This study was approved by Adiyaman University Clinical Research Ethics Committee (approval code: 2022/1-12). Patients over the age of 18 who were hospitalized in the ICU due to COVID-19 were included in the study. The biochemical analysis of the adult patients atfirst admission to the hospital

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Table I. Demographic characteristics of the patients.

Variable	n	%
Sex		
Male	169	59.5
Female	115	40.5
Living Status		
No	182	64.1
Yes	102	35.9

were also included. Patients whose diagnosis of COVID-19 was not confirmed by Real-Time Polymerase Chain Reaction (RT-PCR) for SARS-CoV-2 RNA testing were excluded from the study. The diagnosis and treatment of the patients were made according to the guidelines of the Ministry of Health of the Republic of Turkey[9]. In addition to the PCR test, patients whose thorax computed tomography (CT) imaging was compatible with COVID-19 pneumonia were also included in the study as a diagnostic tool.

Patients with chronic liver disease, chronic kidney disease, malignancy, chronic obstructive pulmonary disease (COPD) and hematological diseases were excluded from the study. Patients with PCR test and thoracic CT incompatibility were also excluded. Patients who were only followed-up in the ward and those who were outpatients were excluded. Patients whose treatment was started in another center and continued in the ICU in our hospital and those whose biochemical parameters were evaluated in another center were also excluded.

Statistical Analysis

Frequency analysis, descriptive statistics, survival analysis, and receiver operating characteristic (ROC) curve analysis were performed in the statistical analysis phase of the research. Cox regression analysis was applied to investigate the effects of the blood parameters of the patients on the survival time. Individual results were obtained for the adjusted model and the unadjusted model obtained by excluding the effects of age and gender in the Cox regression analysis. The suitability of the Cox regression analysis was tested based on the proportional hazards assumption, while variable selection was tested according to the Akaike information criterion (AIC). In the last stage, the ROC curves were conveyed to determine the cut-off values of the variables obtained as significant according to the Cox regression analysis. The sensitivity, specificity, positive predictive value (PPV), cut-off, and AUC values were obtained using the ROC curves graph. The margin of error was used as 5%, and statistical significance was accepted as p-value<0.05. The entire application was performed using the R-Project program (R Core Team, 2020)[10].

Results

Of the 284 patients included in the study, 169 (59.5%) were male and 115 (40.5%) were women. Moreover, 64.1% of the patients died in the ICU (Table I). The youngest patient in the study was 27 years old, and the oldest was 95. The mean age of the patients was 69.82, and the following mean blood parameters were determined: white blood cell (WBC) count: 10.18, hemoglobin (HB); 12.49, neutrophil; 8.18, lymphocyte; 7.06, glucose; 188.10, urea; 62.20, creatinine; 1.55, aspartate aminotransferase (AST); 57.87, alanine aminotransferase (ALT); 37.33, CRP; 11.32, procalcitonin; 2.28, ferritin; 563.28, and D-dimer; 2,955.63, and

Table II. Descriptive statistics by the blood parameters.

Variable	Mean	SD	Min	Max
Year	69.82	12.26	27.00	95.00
WBC	10.18	6.39	0.38	58.40
HB	12.49	2.43	4.60	18.90
Neutrophil	8.18	5.12	0.17	32.00
Lymphocyte	7.06	67.02	0.16	825.00
Glucose	188.10	103.91	68.00	800.00
Urea	62.20	39.50	11.00	274.00
Creatinine	1.55	1.69	0.48	12.74
AST	57.87	100.15	7.00	942.00
ALT	37.33	64.98	6.00	942.00
CRP	11.32	12.50	0.20	171.00
Procalcitonin	2.28	8.77	0.12	95.00
Ferritin	563.28	445.35	0.15	1,500.00
D-Dimer	2,955.63	6,447.91	254.00	62,400.00
ICP	6.90	6.43	1.00	40.00

SD: Standard deviation, Min: Minimum, Max: Maximum, ICP: Intensive care period.

Table III. Results of the proportional hazard assumption for the Cox regression analysis.

	Chi-square	*p*-value
Model 1	12.642	0.760
Model 2	13.544	0.560

the mean length of stay in the ICU was 6.90 days (Table II).

The proportional hazards assumption was provided for the Cox Regression model established after adjusting for age and gender factor and for the Cox Regression models constructed without the correction effect ($p>0.05$) (Table III).

Table IV shows the results of the Cox regression analysis performed for the purpose of displaying the effects of the blood parameters on the survival time of the patients, which were used for the sex and age factor correction and established without the correction effect. The AIC was used to determine which of the variables related to the blood parameters would remain in the model. The effects of the urea, ALT, and ferritin levels on survival time were statistically significant (p-value<0.05). It was found that a one-unit increase in the urea, ALT, and ferritin levels increased the probability of death by 1.005, 1.003, and 1.000 times, respectively (Table V).

According to the results of Cox regression analysis, which determined the parameters that should remain in the model according to the AIC and were established without the correction effect, the effect of the ALT, urea, and D-dimer levels on the survival time was statistically significant(p-value<0.05). It was found that a one-unit increase in the ALT, urea, and ferritin levels increased the probability of death by 1.007, 1.003, and 1.000 times, respectively (Table VI).

According to the ROC curve established in terms of the effect of the urea, ferritin, ALT, and D-dimer levels on overall survival, the cut-off values were, respectively, and considering the sensitivity and selectivity criteria, found as (0.45, 0.68), (0.18, 0.37), (0.43, 0.57), and (0.48, 0.64). According to the results of the ROC evaluation, in terms of the effect of the urea, ferritin, ALT, and D-dimer levels on overall survival, the correct prediction rate of the test was 0.729, 0.788, 0.701, and 0.705, respectively. Moreover, the area below the ROC curve was statistically significant (p-value<0.05) (Figure 1, Table VII).

Discussion

The mortality rate of the patients treated in the ICU in this study was 64.1%. In a meta-analysis in which Armstrong et al[11] included 52 studies, the mortality rate of the ICU patients was as high as 84%. The mortality rate herein was compatible with the literature.

In this study, the serum ferritin, ALT, urea, and D-dimer levels were associated with the prognosis in COVID-19 patients whose routine blood parameters were evaluated at the time of admission to the hospital and who required admission to the ICU during the treatment process. In a meta-analysis[12] including 25 studies examining the effect of liver function on mortality in patients with COVID-19, it was concluded that high ALT levels may be associated with mor-

Table IV. Results of the Cox regression analysis used as age and sex factor correction and developed without the correction effect.

Variable	Corrected model				Uncorrected model			
	OR	Sub-limit	Upper limit	*p*-value	OR	Sub-limit	Upper limit	*p*-value
WBC	1.009	0.945	1.077	0.794	1.017	0.955	1.083	0.603
HB	0.952	0.891	1.017	0.142	0.958	0.896	1.024	0.206
Neutrophil	0.986	0.908	1.071	0.745	0.974	0.899	1.055	0.519
Lymphocyte	1.002	0.999	1.004	0.229	1.001	0.999	1.004	0.315
Glucose	1.000	0.999	1.002	0.559	1.000	0.999	1.002	0.849
Urea	1.004	1.000	1.009	0.068	1.006	1.002	1.010	**0.003**
Creatinine	1.042	0.931	1.167	0.474	1.016	0.905	1.141	0.788
AST	1.000	0.999	1.002	0.704	1.001	0.999	1.002	0.563
ALT	1.002	1.000	1.005	0.080	1.002	1.000	1.005	0.089
CRP	1.008	0.993	1.023	0.321	1.010	0.996	1.024	0.148
Procalcitonin	0.995	0.977	1.014	0.629	0.994	0.975	1.013	0.529
Ferritin	1.000	1.000	1.001	**0.049**	1.000	1.000	1.001	0.140
D-dimer	1.000	1.000	1.000	0.060	1.000	1.000	1.000	0.050

OR: Odds ratio.

Table V. Results of the Cox regression analysis used as the age and sex factor correction.

Variable	OR	Sub-limit	Upper limit	*p*-value
HB	0.949	0.890	1.011	0.105
Urea	1.005	1.002	1.008	**0.003**
ALT	1.003	1.001	1.005	**0.001**
Ferritin	1.000	1.000	1.001	**0.033**
D-dimer	1.000	1.000	1.000	0.075

OR: Odds ratio.

tality. Lino et al[13] observed that approximately 50% of COVID-19 patients with high serum ferritin levels died. Therefore, the high level of this biomarker indicates the severity of the disease. According to a study by Tang et al[14], D-dimer levels in hospitalized COVID-19 patients may be a good factor in predicting the prognosis of the disease. According to a study[15] developed to estimate in-hospital mortality in COVID-19 patients, the urea level of COVID-19 patients who did not survive was significantly higher when compared to that of the survivors.

There are studies[7,16,17] showing that serum ferritin, which is used as an inflammation marker, D-dimer as a fibrin breakdown product, alanine aminotransferase (ALT) as a liver function indicator, and urea as a protein breakdown product increase in COVID-19 patients. In this study, the elevation of these four parameters was also associated with the mortality prediction in the ICU patients. Similar to the current study, the blood biochemistry study of Malik et al[16], with 211 patients hospitalized with suspected COVID-19, also revealed that the serum ferritin, D-dimer, and ALT levels can be used as a guide in showing the progression and severity of COVID-19.

A retrospective study examining the risk factors of hospitalized patients in the city of Wuhan, where the first cases of COVID-19 were seen, revealed that elevated levels of serum ferritin, D-dimer, lactate dehydrogenase (LDH), WBC, lymphocyte count, procalcitonin, creatinine, troponin I, IL-6, PT, and ALT were associated with mortality[17]. The results of a study by Zhou et al[17] were consistent with the results presented herein, in terms of finding that the serum ferritin, D-dimer, and ALT levels were related. However, there were no results regarding urea, since it was not included in their study. However, the WBC and lymphocyte count and procalcitonin levels showed a difference herein, because it was not possible to show the relationship between the parameters that were evaluated at first admission to the hospital and mortality.

Serum ferritin is an important acute phase reactant as well as an important cofactor in iron metabolism. Therefore, it can be an important prognostic indicator in patients with COVID-19. In a meta-analysis conducted by Henry et al[18], which included21 studies and examined33 laboratory parameters of 3377 patients, it was observed that inflammation, heart, liver, kidney and coagulation factors increased significantly in those who had severe disease. Although many of the 33 parameters were associated with the severity of the disease, the WBC, lymphocyte, and platelet count, and IL-10 and serum ferritin levels were stronger parameters in patients with severe disease[18]. The current study revealed that serum ferritin was a prognostic parameter, and this is consistent with the results of the meta-analysis. However, the difference in the WBC count and lymphocyte ratio may have been due to the differences between the studies included in the meta-analysis and the patient demographicsherein[19].

Bilgir et al[7] evaluated 182 patients treated in the service and ICU and showed that the serum ferritin, LDH, urea, creatinine, D-dimer, CRP, prothrombin time (PT), and international normalized ratio (INR) values, which are hematological and biochemical parameters, were associated with

Table VI. Results of the Cox regression analysis developed without a correction effect.

Variable	OR	Sub-limit	Upper limit	*p*-value
ALT	1.007	1.004	1.010	**<0.001**
Urea	1.003	1.001	1.005	**<0.001**
D-dimer	1.000	1.000	1.000	**0.008**

OR: Odds ratio

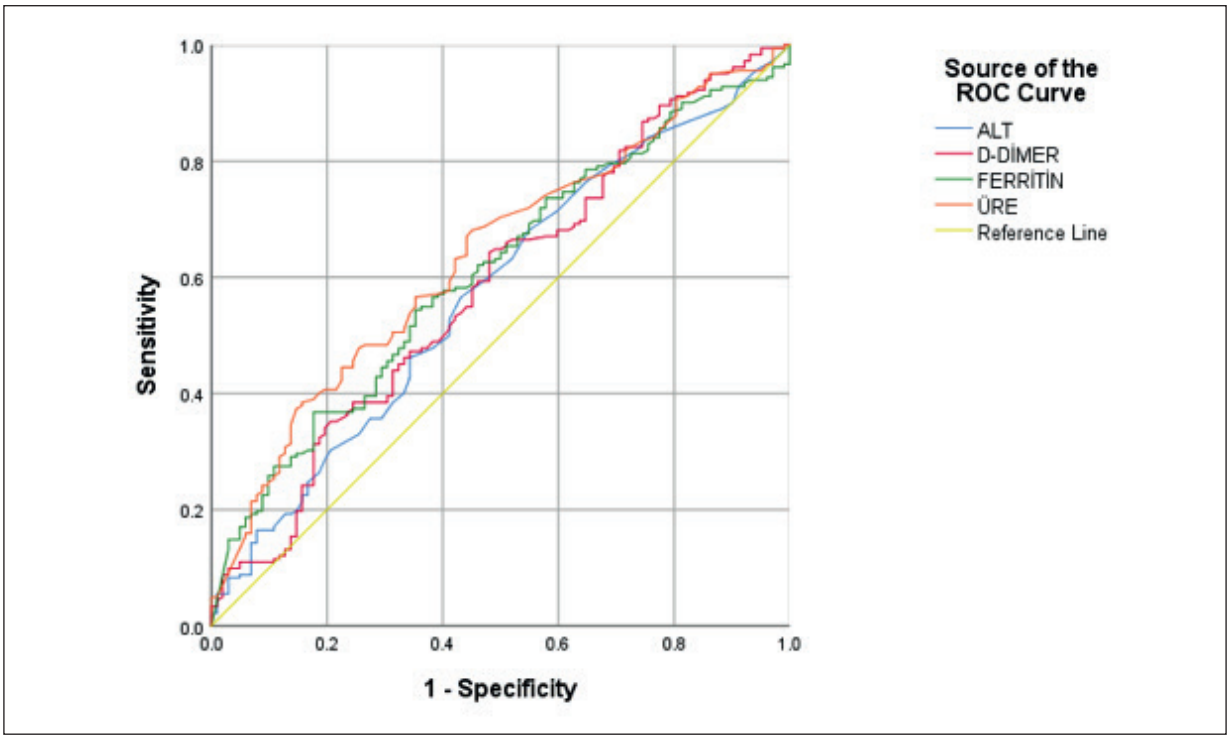

Figure 1. ROC curve developed for the effect of the urea, ferritin, ALT, and D-dimer levels on overall survival.

mortality. Since the routine blood parameters at first admission to the hospital were evaluated in this study, due to its method, the effect of the LDH, PT, and INR values on mortality was not investigated. However, it was shown that the serum ferritin, urea, and D-dimer levels were strong prognostic parameters associated with mortality.

The limitations of this study included the relatively small number of patients, the fact that it was a single-center study, it included only one-time and first-admission sampling for the biochemical analysis, and the inadequate recording of morbidity and characteristics of enrolled patients. Another limitation of the study was that we only evaluated some of the most frequently used blood parameters in the tertiary hospital in Turkey. Some commonly used blood parameters were not evaluated.

Conclusions

Pandemics that affect all humanity have always had an important place in world history due to their tragic consequences. Numerous studies have been carried out regarding how to cope with the COVID-19 pandemic, the first pandemic of the 21st century, to ensure that humanity is less affected. In this study, it was determined that the D-dimer, ferritin, ALT, and urea levels, which were evaluated at first admission inpatients hospitalized in the ICU due to COVID-19, are significant in predicting mortality.

Conflict of Interest

We have no financial or proprietary interest in any instrument or product used in this study. There aren't any conflicts of interest to declare.

Table VII. Results of ROC evaluation developed for the effect of the urea, ferritin, ALT, and D-dimer levels on overall survival.

Variable	Cut-off	PPV	SEN	SPC	AUC	*p*-value
Urea	41.500	0.729	0.681	0,451	0.637	**<0.001**
Ferritin	752.500	0.788	0.368	0.176	0.610	**<0.001**
Alt	22.500	0.701	0.566	0.431	0.576	**0.017**
D-Dimer	1125.000	0.705	0.643	0.480	0.586	**0.008**

SPC: Selectivity, SEN: Sensitivity, PPV: Positive predictive value.

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