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Biochemical parameters and relation to disease severity in COVID-19 patients

COVID-19 hastalarında biyokimyasal parametreler ve hastalık şiddeti ile ilişkisi

Sedat Gülten[1], Uğur Akpulat[2], Selahattin Özcan[3], Esra Özcan[4], Özlem Durak[5], Veysel Garani Soylu[6], Muhammed Mustafa Gülhan[7], Büşra Çalışır[8], Çetin Kılınç[8], Nilay Çöplü[9]

[1]Kastamonu University, Faculty of Medicine, Department of Medical Biochemistry, Kastamonu, Turkey
[2]Kastamonu University, Faculty of Medicine, Department of Medical Biology, Kastamonu, Turkey
[3]Kastamonu University, Faculty of Medicine, Department of Orthopedics and Traumatology, Kastamonu, Turkey
[4]Kastamonu University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation Kastamonu, Turkey
[5]Bucak Public Hospital, Department of Pathology Laboratory, Burdur, Turkey
[6]Kastamonu University, Faculty of Medicine, Department of Intensive Care Science, Kastamonu, Turkey
[7]Düzce Atatürk Public Hospital, Department of Infectious Diseases and Clinical Microbiology, Düzce, Turkey
[8]Kastamonu Training and Research Hospital, Microbiology Laboratory, Kastamonu, Turkey
[9]Kastamonu University, Faculty of Medicine, Department of Medical Microbiology, Kastamonu, Turkey

ABSTRACT

Aim : In this study, we aimed to evaluated whether there is an association between the biochemistry parameters obtained from the first blood test after hospitalization of COVID 19 patients and the prognosis and severity of the disease. Thus, we planned to identify patients with a severe course at an early stage and to help physicians determine the appropriate treatment.

Material and Method: The study included 106 COVID 19 patients confirmed by RT-PCR. Patients were categorized into two groups: those admitted to the hospital ward and discharged with recovery (mild cases) and those admitted directly or eventually to the intensive care unit (severe cases). Biochemical parameters of the groups were compared with the Mann Whitney-U Test, as none of the compared parameters fit the normal distribution.

Results: There was no statistically significant difference between the male-female numbers and ages of the two groups. Statistically significant differences were observed in the length of hospital stay, procalcitonin, hs-troponin I, ferritin, glucose, urea, creatinine, calcium, direct bilirubin, AST, LDH and CRP values ($p<0,05$). However, no significant difference was found in sodium, potassium, chloride, total bilirubin and ALT tests.

Conclusion: The results show that some biochemistry parameters may be used to predict the prognosis of the disease. In particular, procalcitonin, hs troponin I, LDH and CRP values seem to be moderate biomarkers of the prognosis of the disease.

Keywords: COVID 19, biochemical parameters, disease severity

ÖZ

Amaç: Bu çalışmada COVID 19 hastalarının hastaneye yatışları sonrası ilk kan testinden elde edilen biyokimya parametreleri ile hastalığın prognozu ve şiddeti arasında bir ilişki olup olmadığını değerlendirmeyi amaçladık. Böylece ağır seyreden hastaları erken dönemde tespit etmeyi ve uygun tedaviyi belirlemede hekimlere yardımcı olmayı planladık.

Gereç ve Yöntem: Çalışma, RT-PCR ile teyit edilen 106 COVID 19 hastasını içeriyordu. Hastalar iki gruba ayrıldı: Servise yatırılıp şifa ile taburcu edilenler (hafif vakalar) ve doğrudan veya sonunda yoğun bakım ünitesine kabul edilenler (ağır vakalar). Karşılaştırılan parametrelerin hiçbiri normal dağılıma uymadığından grupların biyokimyasal parametreleri Mann Whitney-U Testi ile karşılaştırıldı.

Bulgular: İki grubun erkek-kadın sayıları ve yaşları arasında istatistiksel olarak anlamlı bir fark yoktu. Hastanede kalış süresi, prokalsitonin, hs-troponin I, ferritin, glukoz, üre, kreatinin, kalsiyum, direkt bilirubin, AST, LDH ve CRP değerlerinde istatistiksel olarak anlamlı farklılıklar gözlendi ($p<0,05$). Ancak sodyum, potasyum, klorür, total bilirubin ve ALT testlerinde anlamlı fark bulunmadı.

Sonuç: Sonuçlar, hastalığın prognozunu tahmin etmek için bazı biyokimya parametrelerinin kullanılabileceğini göstermektedir. Özellikle prokalsitonin, hs troponin I, LDH ve CRP değerleri hastalığın prognozunun orta düzeyde biyobelirteçleri gibi görünmektedir.

Anahtar Kelimeler: COVID 19, biyokimyasal parametreler, hastalık şiddeti

Corresponding Author / Sorumlu Yazar:
Sedat Gülten, sedat_gulten@hotmail.com

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INTRODUCTION

The first Coronavirus disease 2019 (COVID-19) outbreak occurred in Wuhan, China, in December of 2019 (1,2). The epidemic was declared a public health emergency of international concern by the World Health Organization (WHO) on January 30, 2020 (3). A majority of the world's population has been affected by social distancing measures and the socioeconomic impact of the pandemic (4).

In symptomatic patients, clinical manifestations of the disease, consisting of fever (body temperature 37-38°C), cough, nasal congestion, and fatigue, usually begin within a week after being infected with the virus (5). Pneumonia usually occurs in the second or third week of symptomatic infection (6). The SARS-CoV-2 virus is primarily transmitted between people through respiratory droplets and contact routes. In the early stages of the disease, severe symptoms of acute respiratory infection appear; some patients rapidly develop acute respiratory distress syndrome (ARDS) and other serious complications, eventually followed by multiple organ failure (7). Therefore, early diagnosis and timely treatment of critical cases are very crucial.

The SARS-CoV-2 virus shares approximately 80% overall genome similarity to SARS-CoV and invades host human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor (8). The fatality rate of COVİD-19 is lower than that of severe acute respiratory syndrome (SARS) and much lower than that of Middle East respiratory syndrome (MERS); however, it is far more lethal than the virus that causes the seasonal flu (9). Recent reports have indicated that the hospitalization rate for COVID-19 was 20.7-31.4%, the admission rate to intensive care units was 4.9-11.5%, and the case fatality rate was 1.8-3.4% among unvaccinated people (10). Early identification of potentially severe or critical patients is of great importance in the management of the disease to prioritize health care resources more efficiently (11,12).

In this study, we attempted to predict the prognosis of the disease and the number of days the patient will stay in the hospital with the biochemistry parameters obtained from the first blood taken from the patients after their hospitalization. Thus, we aimed to assist physicians in identifying the patients before manifesting severe symptoms and implement effective treatment early.

MATERIAL AND METHOD

Study Design

In this single-center, retrospective, observational study, we included 106 cases that were confirmed as having positive results by using real-time RT-PCR nucleic acid assay for the SARS-CoV-2 (Cq value <38.0, Bio-Speedy, RT-qPCR Determination Kit, Turkey) in Kastamonu Training and Research Hospital from 18 March 2020 to 16 July 2020. The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Zonguldak Bülent Ecevit University (approval number: 2020-17). Oropharyngeal and nasopharyngeal swab samples were used in the detection of the virus. Data on laboratory tests, age of patients and length of stay in hospital were obtained from the Laboratory Information System. The patients were categorized into two groups as mild cases who were admitted to the hospital ward and discharged with recovery, and severe cases who were admitted directly or eventually to the intensive care unit. Patients under the age of 18, pregnant women and patients with missing tests were not included in the study.

Statistical Analysis

The SPSS 18.0 for Windows program (SPSS Inc., IL, USA) was used for the statistical analysis. Descriptive statistics of the collected data were presented as numbers and percentages for categorical variables and as median (IQR) and mean±standard deviation (SD) for numerical variables. The Mann-Whitney U test was performed for data that did not fit the normal distribution between the groups including procalcitonin, hs-troponin I, ferritin, glucose, urea, creatinine, sodium, potassium, chloride, calcium, total bilirubin, direct bilirubin, ALT, AST, LDH, CRP, length of stay, and age. Spearman Correlation Analysis was used to examine the relationship between continuous variables. P values of <0.05 were considered statistically significant.

RESULTS

In the study population, there were a total of 106 COVID-19 patients, 70 in the group with mild cases and 36 in the group with severe cases. There was no statistically significant difference between the male-female ratios of the two groups and between the ages.

Since none of the parameters in **Table 1** fit the normal distribution, the values of the patients in the COVID-19 Care Unit (mild) and Intensive Care Unit (severe) groups were compared with the Mann Whitney-U Test. Statistically significant differences were observed in the length of hospital stay, procalcitonin, hs-troponin I, ferritin, glucose, urea, creatinine, calcium, direct bilirubin, AST, LDH and CRP values. However, no significant difference was found in sodium, potassium, chloride, total bilirubin and ALT tests (**Table 1**).

Table 1. Comparison of data of mild and severe groups of COVID-19 positive patients with Mann Whitney U test

Parameter	COVID-19 Care Unit (76)	Intensive Care Unit (30)	P
	Median (IQR)		
Length of stay (day)	11.0 (8.0;14.0)	15.5 (11.0;20.0)	0.001
Hs troponin I (ng/L)	4.5 (3.0;10.3)	14.5 (7.3;44.3)	<0.001
Procalcitonin (ng/mL)	0.1 (0.0;0.1)	0.2 (0.1;0.4)	<0.001
Ferritin (ng/mL)	113.6 (57.0;239.8)	178.0 (121.0;372.7)	0.006
Glucose (mg/dL)	110.0 (97.0;128.3)	113.5 (102.0;176.0)	0.049
Urea (mg/dL)	31.5 (23.0;42.3)	43.0 (29.0;67.5)	0.004
Creatinine (mg/dL)	0.9 (0.7;1.1)	1.1 (0.9;1.6)	0.002
Sodium (mEq/L)	136.0 (133.0;138.0)	135.0 (132.3;137.8)	0.431
Potassium (mEq/L)	4.0 (3.7;4.2)	4.1 (3.8;4.5)	0.306
Chloride (mEq/L)	102.0 (100.0;103.0)	100.0 (97.0;104.0)	0.295
Calcium (mg/dL)	9.1 (8.8;9.6)	8.6 (8.3;8.9)	<0.001
Total bilirubin (mg/dL)	0.5 (0.4;0.7)	0.6 (0.5;1.0)	0.068
Direct bilirubin (mg/dL)	0.1 (0.1;0.2)	0.2 (0.1;0.3)	0.007
ALT (U/L)	18.0 (14.0;34.0)	21.5 (13.0;40.0)	0.628
AST (U/L)	24.0 (18.8;32.0)	36.0 (23.3;62.0)	0.001
LDH (U/L)	263.5 (216.8;324.5)	326.5 (252.5;512.0)	0.001
CRP (mg/L)	25.3 (10.6;75.5)	98.5 (55.0;149.2	<0.001

IQR the interquartile range, ALT alanine aminotransferase, AST aspartate aminotransferase, LDH lactate dehydrogenase, CRP C-reactive protein.

Cut-off levels of procalcitonin, hs-troponin I, LDH, and CRP of 0.12 ng/mL, 8.5 ng/L, 281.5 U/L, and 61.8 mg/L, respectively, and AUC (area under the curve) levels ranging from 0.7 to 0.8 indicate that they can be a moderate biomarker of the prognosis of the disease from the first day (**Table 2**, **Figure 1**).

Table 2. ROC (receiver operating characteristic) curve analysis values of some biochemical parameters in COVID-19 positive patients

Parameter	Cut-off	AUC	95% CI	p
Hs troponin I (ng/L)	8.5	0.778	0.69-0.87	<0.001
Procalcitonin (ng/mL)	0.12	0.765	0.67-0.86	<0.001
Ferritin (ng/mL)	148.7	0.662	0.56-0.77	0.006
Glucose (mg/dL)	110.5	0.617	0.50-0.73	0.049
Urea (mg/dL)	36.5	0.670	0.56-0.78	0.004
Creatinine (mg/dL)	0.97	0.688	0.58-0.79	0.002
Sodium (mEq/L)	135.5	0.453	0.33-0.57	0.433
Potassium (mEq/L)	4.05	0.561	0.44-0.68	0.307
Chloride (mEq/L)	101.5	0.438	0.31-0.57	0.298
Calcium (mg/dL)	8.9	0.203	0.12-0.29	<0.001
Total bilirubin (mg/dL)	0.55	0.609	0.50-0.72	0.068
Direct bilirubin (mg/dL)	0.16	0.657	0.54-0.77	0.008
ALT (U/L)	20.5	0.529	0.41-0.65	0.629
AST (U/L)	28.5	0.695	0.58-0.81	0.001
LDH (U/L)	281.5	0.702	0.60-0.80	0.001
CRP (mg/L)	61.8	0.778	0.69-0.87	<0.001

AUC area under the curve, CI confidence interval, ALT alanine aminotransferase, AST aspartate aminotransferase, LDH lactate dehydrogenase, CRP C-reactive protein.

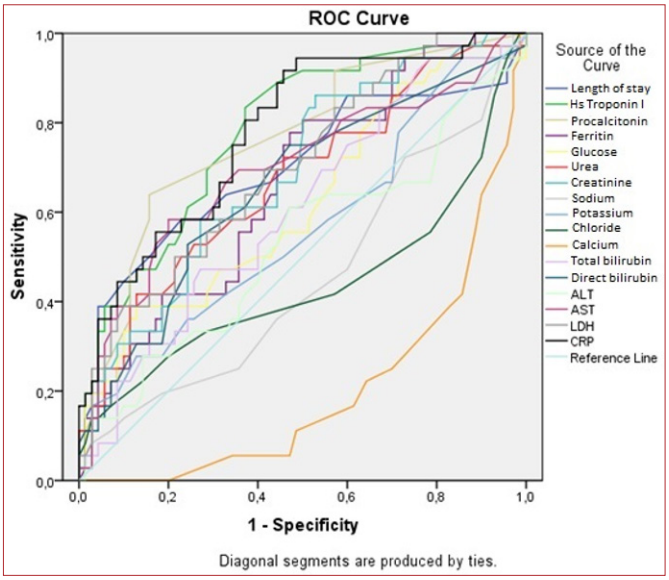

Figure 1. ROC curve analysis of some biochemical data in COVID-19 positive patients

DISCUSSION

In the study, we examined to what extent the age of a patient and the first day values of procalcitonin, hs-troponin I, ferritin, glucose, urea, creatinine, sodium, potassium, chloride, calcium, total bilirubin, direct bilirubin, ALT, AST, LDH and CRP could be effective on the severity of the disease. We investigated the correlation of these values with length of stay.

In a retrospective cohort study of COVID-19 patients from Wuhan, China, high LDH (p<0.001), high procalcitonin (p<0.001), increased serum ferritin (p<0.001), and high interleukin-6 (IL-6) (p<0.001) levels were detected when non-survivors were compared with survivors (13). COVID-19 patients with higher LDH levels have been associated with a higher risk of ARDS (13), intensive care unit (ICU) support (15), and death (14,13). Increased CRP level has been associated with the development of ARDS (14), elevated troponin-T levels and myocardial damage (16), and death (17) in COVID-19 patients. A meta-analysis study demonstrated that increment in procalcitonin levels was associated with an about 5-fold higher risk of severe progression (18). It has been shown that higher serum ferritin is associated with the development of ARDS (HR=3.53, 95% CI: 1.52-8.16, p=0.003); however, there was no statistically significant difference in survival rates (HR=5.28, 95% CI: 0.72-38.48, p=0.10) (14). In their univariate analysis, Zhou et al. reached results supporting an association between higher serum ferritin levels and death, but were unable to provide a multivariate analysis (13). Another emerging biomarker for the course of COVID-19 is IL-6. IL-6 level has been shown to be elevated in 52% of COVID-19 patients (19). Increased IL-6 levels have been associated with an increased risk of death (14), and a gradual increase has been reported during hospitalization in non-survivors (13).

In a retrospective single-center study, the majority of severe patients showed significantly higher CRP levels compared to non-severe patients (33.2 mg/L versus 57.9 mg/L, p<0.001) (20). Another retrospective cohort study found that patients with CRP levels > 41.8 mg/L were more likely to progress to severe COVID-19 disease (21). Both studies suggested that CRP levels are a strong indicator of the presence and severity of COVID-19 infection. However, compared with erythrocyte sedimentation rate (ESR), CRP levels have been shown to be significantly higher in the early stages of severe cases and have proven to be a more sensitive biomarker to reflect disease development (22). It has been shown that CRP values are more reliable for earlier determination of disease severity than computerized tomography (CT) scans, since the AUC in the ROC analysis was 0.87, with a sensitivity of 83% and a specificity of 91% (22).

In a single-center study comparing ICU patients and non-ICU patients, significantly higher LDH levels were found in ICU patients (248 U/L vs. 151 U/L, p=0.002). It has been suggested that LDH may be a predictive marker for disease severity, as high LDH levels persist for the number of days after hospitalization in ICU patients (218 U/L vs. 160 U/L, p=0.002) (23). In a multicenter study involving a higher number of patients, it was reported that increased LDH level was associated with tissue damage and degree of inflammation (5). Moreover, when LDH levels were compared with CT scans, an increase in LDH level has been shown to reflect the severity of pneumonia (24).

It has been revealed that the univariable odds ratio for death when hs troponin I concentrations were above the 99th percentile upper reference limit was 80.1 (95% CI 10.3–620.4, p<0.001). The odds ratio was higher than the odds ratios all other biochemical parameters tested, including D-Dimer (25). In another study of 416 hospitalized patients with COVID-19, hs troponin I has reported to be elevated in 1 out of 5 patients at the time of hospitalization (26).

In a study of 701 patients, it has been revealed that coagulation pathway abnormalities were more common in patients with elevated baseline serum creatinine levels. It has also been shown that these patients are more likely to need mechanical ventilation or to be admitted to intensive care (27). Another study found that high creatinine levels were also associated with in-hospital mortality by univariate Cox regression analysis (HR 2.99, 95% CI: 2.00, 4.47) (28).

A study examining the relationship between CRP and COVID-19 has demonstrated that patients with CRP > 41.8 mg/L were more likely to develop severe disease. Higher procalcitonin levels in the patients with severe disease progression have suggested that the patients may have concomitant bacterial infections. Because of the small sample size in the study, the researchers recommended that their findings be confirmed in a larger cohort (28).

In our study, a statistically significant difference was found between mild and severe COVID-19 patients in terms of length of hospital stay (p=0.001), procalcitonin (p<0.001), hs-troponin I (p<0.001), ferritin (p=0.006), glucose (p=0.046), urea (p=0.004), creatinine (p=0.002), calcium (p<0.001), direct bilirubin (p=0.007), AST (p=0.001), LDH (p=0.001) and CRP (p<0.001) values. Among all these parameters, a positive correlation was found only between serum urea levels and length of stay (r=0.329 p=0.001). The sensitivity and specificity of procalcitonin at the 0.12 ng/mL cut-off were 67% and 86%, respectively; the sensitivity and specificity of hs-troponin I at the cut-off of 8.5 ng/L were 69% and 87%, respectively; at the 281.5 U/L cut-off of LDH, the sensitivity and specificity were 60% and 80%, respectively, and at the 61.8 mg/L cut-off of CRP, the sensitivity and specificity were 69% and 87%, respectively. It seems that they can be a moderate biomarker of the prognosis of the disease from the first day, with the relevant cut-off levels and AUC levels between 0.7 and 0.8. In addition, the reference range for hs-troponin I is 0-20 ng/L in male adults, while the reference range in female adults is 0-12 ng/L. Unlike the other three parameters, the cut-off we found is within the reference range (CRP reference range 0-5 mg/L, procalcitonin reference range 0-0.65 ng/mL, LDH reference range 0-200 U/L).

Limitations of the Study

One of the main limitations of the study is that it has been carried out retrospectively. Therefore, with more patients, prospective studiesand are required to reach more definite conclusions about the functionality of these parameters in diagnosing the disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Zonguldak Bülent Ecevit University (approval number: 2020-17).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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