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The Impact of Hematological Parameters on Survival for Patients with COVID-19

COVID-19 Hastalarında Hematolojik Parametrelerin Sağ Kalıma Etkisi

***Fatma YILMAZ*[1] *Murat ALBAYRAK*[1] *Abdülkerim YILDIZ*[2]**

***Hacer Berna AFACAN ÖZTÜRK*[1] *Senem MARAL*[1] *Ümit Yavuz MALKAN*[1]**

***Pınar TIĞLIOĞLU*[1] *Merih Reis ARAS*[1] *Buğra SAĞLAM*[1] *Mesut TIĞLIOĞLU*[1]**

ÖZ

Giriş: Coronavirus hastalığı 2019, şiddetli akut solunum sendromu coronavirüs 2'nin (SARS-CoV-2) sebep olduğu viral bir antitedir. Klinik ve laboratuvar belirleyicileri, mortalite riski altındaki hastaları belirleyebilir ve tedaviye rehberlik edebilir. Bu çalışmanın amacı, COVID-19 hastalarında laboratuvar parametrelerini analiz etmek ve hangi parametrelerin mortalite ve hastaneye yatışı etkilediğini belirlemektir.
Araçlar ve Yöntem: Demografik özellikler, tam kan sayımı (CBC) parametrelerini içeren laboratuvar parametreleri, biyokimyasal testler, pıhtılaşma parametreleri, hastanede kalış süresi ve son durum (taburculuk veya ölüm) kaydedildi.
Bulgular: Bu retrospektif çalışma, COVID-19 teşhisi konan 101 hasta üzerinde yapıldı. Analize dahil edilen 101 hasta 52(%51.5) erkek ve 49(%48.5) kadından oluşmaktaydı ve ortalama yaşları 65.7±14.7 idi. İzlem süresi sonunda hayatta kalanlar ve hayatta kalmayanlar arasında karşılaştırmalar yapıldı. Çok değişkenli analiz, ortalama trombosit hacmi (MPV), trombosit dağılım genişliği (PDW) ve laktat dehidrogenazın (LDH) mortalitenin önemli belirleyicileri olduğunu gösterdi. Hastanede kalış süresinin cut-off değeri 10 gün olarak saptandı ve hastalar iki gruba ayrıldı. Tek değişkenli ve çok değişkenli modellerde, hastanede yatış süresinin öngörülmesi için anlamlı bağımsız parametre gözlenmedi.
Sonuç: Mevcut çalışmanın sonuçları, MPV, PDW ve LDH' nin mortaliteyi öngörmede önemli bağımsız değişkenler olduğunu göstermiştir. SARS-CoV -2 ve SARS-CoV'nin aynı reseptörü kullandığı bilindiğinden, mutant varyantlar ve ilk varyant için benzer bir yapı ve reseptör olabilir, dolayısıyla bu öngörücü parametrelerin mutant varyantlarda da etkili olduğu düşünülebilir.

Anahtar Kelimeler: laktat dehidrogenaz; ortalama trombosit hacmi; ölüm oranı; SARS-CoV-2; trombosit dağılım genişliği

ABSTRACT

Purpose: Coronavirus disease 2019 is a viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical and laboratory predictors may provide identification of patients at risk of mortality and guide treatment. This study aims to analyze laboratory parameters in COVID-19 patients and to determine which parameters affect mortality and hospitalization.
Materials and Methods: Demographic characteristics, the parameters including complete blood count (CBC) parameters, biochemical tests, coagulation parameters, duration of hospitalization, and final status (discharge or death) were recorded in patients diagnosed with COVID-19.
Results: This retrospective study was conducted with 101 patients diagnosed with COVID-19. The 101 patients included in the analysis comprised 52(51.5%) males and 49(48.5%) females with a mean age of 65.7±14.7 years. Comparisons were made between survivors and non-survivors at the end of the follow-up period. Multiple analyses showed mean platelet volume (MPV), platelet distribution width (PDW), and lactate dehydrogenase (LDH) to be significant predictors of mortality. The cut-off value of the hospitalization period was found to be 10 days; therefore, the patients were divided into two groups. In the univariate and multiple models, no significant independent parameter was observed for the prediction of hospitalization duration**.**
Conclusion: The results of the current study demonstrated that MPV, PDW and LDH were significant independent variables for the prediction of mortality. As SARS-CoV-2 and SARS-CoV are known to use the same receptor, there may be similar structures and receptors for mutant variants and the first variant, so these predictive parameters can be considered effective in mutant variants.

Keywords: lactate dehydrogenase; mean platelet volume; mortality; platelet distribution width; SARS-CoV-2

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[1]University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Hematology, Ankara, Türkiye.
[2]University of Hitit, Erol Olçok Training and Research Hospital, Department of Hematology, Çorum, Türkiye.

Corresponding Author: Fatma Yılmaz, University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Hematology, Ankara, Türkiye. e-mail: dr.fatmak@hotmail.com

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a new type of coronavirus that is a positive oriented single-stranded RNA virus, and easily transmittable from human to human.[1,2]

Although COVID-19 most often affects the pulmonary system, there may also be extra-pulmonary manifestations affecting most systems, including the hematopoietic, renal, and vascular systems.[3,4] Computed tomography (CT), real-time polymerase chain reaction (RT-PCR) test, and hematological and biochemical parameters are the primary tests for evaluating patients at the time of diagnosis.[5]

Clinical and laboratory predictors of progression may enable risk stratification, differentiation of severe and mild cases, the identification of groups of patients at high and low risk of mortality, and guide treatment. Although recent studies have reported that severe disease and high mortality are associated with lymphopenia,[6] thrombocytopenia,[7] and lactate dehydrogenase (LDH) levels,[8] there is still an unmet need for significant biomarkers to predict hospitalization rate and duration.

The aim of this study was to analyze laboratory abnormalities in patients with COVID-19 and define which parameters affect mortality and hospitalization.

MATERIALS and METHODS

This retrospective study was conducted on 101 patients diagnosed with RT–PCR confirmed infection of SARS-CoV-2, who were admitted to Diskapi Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey, between 1 November 2020 and 1 December 2020. All participants met the case definition criteria for the clinical diagnosis based on the Republic of Turkey Health Ministry diagnosis and treatment guidelines for COVID-19. A record was made of demographic characteristics, chest CT findings, laboratory parameters including complete blood count (CBC) parameters, renal function tests, liver function tests, LDH, coagulation parameters (international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT), hospitalization duration, and final status (discharge or death). All patients were followed until discharge or exitus.

Statistical Analysis

Data obtained in the study were statistically analyzed using SPSS v. 27.0 software.[9] Descriptive statistics were stated as mean±standard deviation (SD), median, percentage (%), minimum and maximum values, or number (n). Categorical variables were expressed as percentage (%). The conformity of variables to normal distribution was assessed with the Kolmogorov-Smirnov test. The Mann-Whitney U-test was used in the analysis of quantitative independent data. The Chi-square test was applied in the analysis of qualitative independent data, and the Fischer test was used when the Chi-square test conditions were not met. The effect level was investigated using univariate and multiple logistic regression analysis. A value of $p<0.05$ was accepted as statistically significant.

Ethical Approval and Informed Consent

All procedures performed in studies involving human participants comply with the ethical standards of the institutional and/or national research committee, and the 1964 Declaration of Helsinki and later amendments or comparable ethical standards. The study was approved by the Clinical Research Ethics Committee of the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (22.03.2021-107/07).

RESULTS

Patient Demographic Data

This retrospective study was conducted on 101 patients diagnosed with COVID-19. In the analysis of 101 patients with a mean age of 65.7±14.7 years, 52(51.5%) were men and 49(48.5 %) were women. The median follow-up duration was 11±6.1 days. The descriptive statistics of the data and distribution of demographic parameters are shown in Table 1.

Predictors of Mortality

Patients were compared in two groups as survivors and non-survivors at the end of the follow-up period. Age,

mean platelet volume (MPV), platelet distribution width (PDW), neutrophil, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), LDH, PT, APTT, and INR values were significantly higher in non-survivors than in survivors. Platelet (Plt) and lymphocyte count were significantly lower in the non-survivors than in survivors. All other parameters were similar in both groups. The comparative analyses of the data collected in survivor and non-survivor groups are shown in Table 2.

Table 1. Descriptive statistics of the data and distribution of demographic parameters of the patients

Variables	n(%)
Gender	
Female, n(%)	49(48.5)
Male, n(%)	52(51.5)
Comorbidities	76(75.2)
Hospitalization duration	
<10 days, n(%)	52(51.5)
> 10 days, n(%)	49(48.5)
	Mean±SD
Age	65.7±14.7
WBC, 10^3/µL	9.6±4.0
HGB, g/dL	12.7±1.7
HTC, %	39.0±4.8
PLT, x10^3/µL	322.1±119.8
MPV, fL	10.4±0.9
PCT, %	0.3±0.1
PDW, %	12.1±2.1
Neutrophil, 10^3/µL	7.3±3.7
Lymphocyte,/µL	1431.8±724.2
Monocyte, /µL	665.3±411.8
Eosinophil, /µL	49.4±58.9
Basophil, /µL	31.9±26.6
BUN, mg/dL	51.1±25.0
Creatinine, mg/dL	0.8±0.5
AST, U/L	39.8±84.9
ALT, U/L	52.3±60.2
LDH, U/L	324.4±259.5
PT, sec	10.7±3.4
APTT, sec	31.8±6.2
INR, %	1.2±0.3
Hospitalization duration (days)	11.0±6.1

Table 2. The comparison of parameters between survivors and non-survivors

Variables	Mortality (-) n(%)	Mortality (+) n(%)	P
Gender			
Female, n(%)	43(48.3)	6(50.0)	0.913[x2]
Male, n(%)	46(51.7)	6(50.0)	
Comorbidities, n(%)	66(74.2)	10(83.3)	0.489[x2]
Hospitalization duration			
<10 days, n(%)	48(53.9)	4(33.3)	0.180[x2]
> 10 days, n(%)	41(46.1)	8(66.7)	
Variables	**Mean±SD**	**Mean±SD**	**p**
Age (years)	64.3±14.7	75.3±11.2	0.012 [m]
WBC, 10^3/µL	9.2±3.3	12.3±7.0	0.087 [m]
HGB, g/dL	12.7±1.6	12.0±1.7	0.154 [m]
HTC, %	39.1±4.8	38.1±5.1	0.517 [m]
PLT, 10^3 /µL	330.4±120.4	260.9±98.4	0.019 [m]
MPV, fL	10.3±0.9	11.3±0.9	<0.001[m]
PCT, %	0.3±0.1	0.3±0.1	0.200 [m]
PDW, %	11.9±2.0	13.6±2.4	0.018 [m]
Neutrophil, 10^3/µL	6.9±3.0	10.7±6.1	0.020 [m]
Lymphocyte, /µL	1514.4±720.0	819.2±395.0	0.001 [m]
Monocyte, /µL	648.4±266.4	790.8±977.0	0.384 [m]
Eosinophil, /µL	52.8±61.7	24.2±18.8	0.182 [m]
Basophil, /µL	31.6±26.0	34.2±31.5	0.842 [m]
BUN, mg/dL	47.3±21.2	79.6±32.9	<0.001[m]
Creatinine, mg/dL	0.8±0.2	1.3±1.3	0.033 [m]
AST, U/L	30.3±17.2	110.2±238.8	0.005 [m]
ALT, U/L	49.2±44.1	75.3±129.3	0.769 [m]
LDH, U/L	265.5±87.1	761.8±560.7	<0.001[m]
PT, sec	10.6±3.4	11.7±3.4	0.024 [m]
APTT, sec	31.2±5.9	35.6±7.3	0.023 [m]
INR, %	1.1±0.3	1.3±0.3	0.009 [m]
Hospitalization duration	10.6±5.6	14.3±8.2	0.160 [m]

[m] Mann-Whitney U-test [X2] Chi-square test

In the univariate model, age, MPV, PDW, neutrophils, lymphocytes, BUN, creatinine, LDH, and aPTT were found to be significantly effective in the prediction of mortality. These parameters which were significant in the univariate model were included in the multiple model. The multiple model showed MPV (Figure 1), PDW (Figure 2), and LDH (Figure 3) to be independent significant predictors of mortality Table 3.

Table 3. Logistic regression analysis of factors affecting mortality

Variables	Univariate Model			Multiple Model		
	OR	95 %CI	p	OR	95 %CI	P
Age	1.7	1.01-1.14	0.020			
MPV	2.99	1.53-5.85	0.001	244.78	3.46-17317	0.011
PDW	1.39	1.07-1.81	0.015	0.11	0.02-0.70	0.019
Neutrophil(*10^3)	1.00	1.00-1.00	0.006			
Lymphocyte	1.00	1.00-1.00	0.003			
BUN	1.4	1.02-1.07	<0.001			
Creatinine	14.40	1.68-123.6	0.015			
LDH	1.01	1.01-1.02	<0.001	1.01	1.01-1.02	0.001
APTT	1.10	1.01-1.21	0.030			

MPV: Mean Platelet volume pdw: Platelet distribution width BUN: Blood Urea Nitrogen LDH: Lactate Dehydrogenase APM: Active partial thromboplastin time

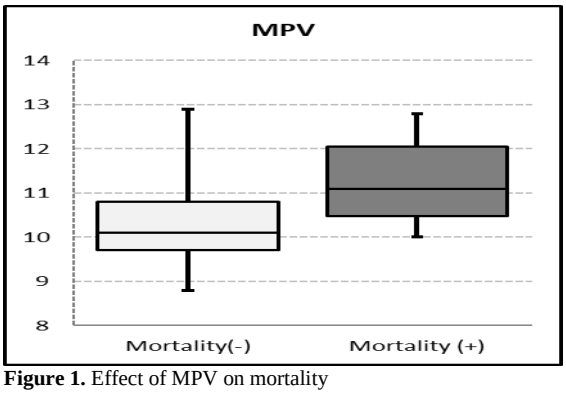

Figure 1. Effect of MPV on mortality

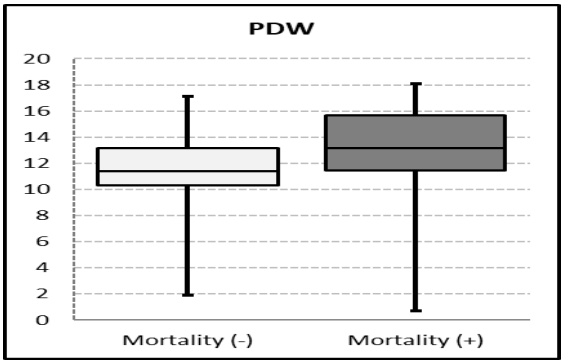

Figure 2. Effect of PDW on mortality

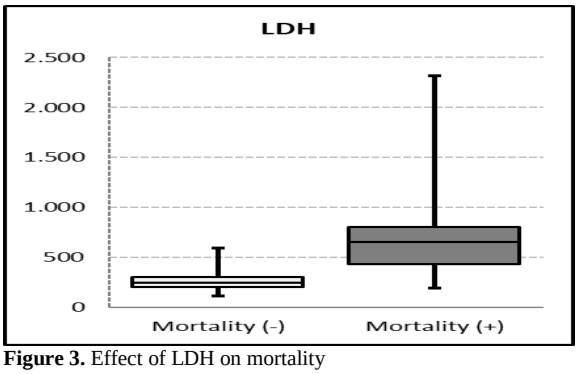

Figure 3. Effect of LDH on mortality

Predictors of Hospitalization Duration

The cut-off value for the length of stay in hospital was found to be 10 days; therefore, patients were separated into two groups of <10 days and >10 days. Parameters were compared in respect of hospitalization duration. LDH was significantly higher in patients with >10 days of hospitalization compared to patients with <10 days. Age, gender, WBC, Hgb, Htc, platelet, MPV, PCT, PDW, neutrophil, lymphocyte, monocyte, eosinophil, basophil, BUN, creatinine, AST, ALT, PT, aPTT, and INR values showed no significant difference (Table 4).

Table 4. The comparison of parameters in respect of hospitalization duration

Variables	Hospitalization<10 Days n(%)	Hospitalization>10 Days n(%)	P
Gender			
Female, n(%)	27(51.9%)	22(44.9%)	0.480 [x2]
Male, n(%)	25(48.1%)	27(55.1%)	
	Mean±SD	**Mean±SD**	
Age (years)	65.3±16.6	66.1±12.6	0.850 [m]
WBC, $10^3/\mu L$	8.9±3.96	10.24±3.95	0.084 [m]
HGB, g/dL	12.7±1.7	12.6±1.7	0.734 [t]
HTC, %	39.0±4.6	38.9±5.2	0.964 [t]
PLT , $10^3/\mu L$	321.7±101.9	322.6±137.3	0.686 [m]
MPV, Fl	10.3±0.8	10.5±1.0	0.163 [m]
PCT, %	0.3±0.1	0.3±0.1	0.752 [t]
PDW, %	11.8±1.9	12.3±2.3	0.364 [m]
Neutrophil , $10^3/\mu L$	6.67±3.54	8.01±3.68	0.052 [m]
Lymphocyte, /µL	1555.8±734.2	1300.2±696.9	0.076 [t]
Monocyte, /µL	666.5±486.3	664.1±319.4	0.794 [m]
Eosinophil, /µL	48.7±61.3	50.2±56.9	0.745 [m]
Basophil, /µL	31.7±29.4	32.0±23.5	0.482 [m]
BUN, mg/dL	48.9±24.2	53.4±25.9	0.355 [m]
Creatinine, mg/Dl	0.9±0.7	0.8±0.3	0.188 [m]
AST, U/L	46.0±117.1	33.2±19.3	0.422 [m]
ALT, U/L	56.8±76.4	47.7±36.0	0.480 [m]
LDH, U/L	304.3±308.1	345.8±196.1	0.009 [m]
PT, sec	10.9±4.2	10.4±2.3	0.407 [m]
APTT, sec	32.6±5.8	30.9±6.5	0.162 [t]
INR, %	1.2±0.4	1.1±0.2	0.074 [m]

[t]Independent Samples t-test [m] Mann-Whitney U-test [X²] Chi-square test

DISCUSSION

The COVID-19 pandemic that has been affecting the whole world for the last two years and has been shown to be a cause of serious morbidity and mortality, especially in patients with advanced age and comorbidities.[10] However, it has still not been fully clarified whether other patient- and disease-related characteristics have an effect or not on the disease process. Although it is known that changes in parameters, such as hematological parameters,

that can be easily obtained during diagnosis can be seen in the onset and course of the disease, it is not clear whether these factors have an impact on prognosis.

In a case series published by the Chinese Center for Disease Control, overall mortality rate was 2.3%, at 8% in the 70-79 years age group and 14.8 % in patients older than 80 years.[11] Yang et al. and Rodriquez et al. also reported that age and comorbidities were highly related in COVID-19 patients.[10] In the current study, the mortality rate was higher because the median age was older than those in other studies, and comorbidities were present in 83.3% of the non-survivor group. In addition, the patients included in this study were only selected from hospitalized patients. As outpatients with COVID-19 were not included in this study, mortality rate was found to be higher than those in other studies. In this study, the effect of demographic parameters, hematological and biochemical laboratory parameters, and coagulation parameters on the hospitalization duration and final status (discharge or death) of patients hospitalized with COVID-19 were analyzed. In this study, the mean age of all hospitalized patients was 69 years, the mean age of patients who died was 76 years, and the mean age of patients who were treated and discharged was 67 years. Also, the mean age of the patients who did not survive was 9 years higher than that of survivors. The overall mortality rate was 11% as 25% in the 55-70 years age group and 75% in patients older than 70 years.

In the current study, the gender distribution of patients was 48.5% female and 51.5% male. Although 50% of the patients who died and 55.1% of patients hospitalized for more than 10 days were male, gender was not significantly correlated with mortality and hospitalization time. Guan WJ et al. reported that 58% of the patients were male in a study of 1099 patients with COVID-19 in China.[12] S.Richardson et al. reported that 60.3% of patients were male in the study of 5700 patients with COVID-19.[13] This male predisposition could be explained by possible factors, such as a higher proportion of male smokers, lifestyle habits, enzymatic activity, metabolism, drug response or immunological response.[14] Older age and male gender have been identified as risk factors for in-hospital mortality.[3,15]

Hematological laboratory abnormalities are common in patients with COVID-19, including leukopenia, lymphopenia and thrombocytopenia. Lymphopenia has been seen to be a recurrent abnormality in common viral infections. Lymphopenia associated with COVID-19 has a significant prognostic value in patients. In a series of 1099 COVID-19 patients, Guan et al. reported that 33.7% had leukopenia and 83.2% had lymphopenia. Hematological abnormalities were more significant in patients with serious presentation compared to mild presentations: 96.1% versus 80.4% for lymphopenia, and 61.1% versus 28.1% for leukopenia, respectively.[12] Wang et al. reported that 70.3% of patients had lymphopenia, which developed more severely over time until death in non-survivors.[16] Similar to previous studies in the literature, the results of the current study also showed that lymphocyte count was significantly lower in the non-survivors (819.2±395 $10^3/\mu l$) than that in the survivors (1514.4±720 $10^3/\mu l$). SARS-CoV-2 has non-segmented, single-stranded positive-sense RNA (+ssRNA), in two main types: L types and S types. The L type which is seen in 70% of patients is more aggressive and infectious.[17] Leukocyte, lymphocyte and subsets of T-cell levels play a role in the immune response according to the type of virus due to possible viral pathological mechanism.[18]

Other commonly seen abnormalities are related to changes in plt count and plt indices. Thrombocytopenia is one of the most commonly encountered abnormalities in COVID-19 patients. In the current study, the Plt value was significantly lower in the non-survivor group than in the survivor group. Thrombocytopenia was reported in 36.2% of patients by Guan W-j,[19] and in 72.5% of patients by Chang D.[20] Platelet distribution width (PDW) and mean platelet volume (MPV) are platelet volume indices (PVIs). Mean platelet volume shows the size of platelets and platelet activation.[21] Mean platelet volume levels increase with severe inflammation, and changes in MPV levels have been used in the diagnosis or prediction of diseases such as infective endocarditis, brucellosis, sepsis and cellulitis and other infections.[22-25] PDW is evaluated as the coefficient of variation in platelet size and platelet morphology,[26] and has been shown to be a potential predictive factor for diagnosis of COVID-19 with a cut-off value of 12.7 fL.[27] MPV and PDW were found to be higher in non-survivors. Güçlü

et al. reported that for every unit increase in MPV, mortality increased 1.76-fold.[28] The mechanism of affect in platelet indices in COVID-19 patients is multifactorial. One of the mechanisms is that the bone marrow becomes infected. Other mechanisms are platelet destruction by the immune activation, or platelet aggregation in the lung tissue.[29] In the current study, the results of the multiple model showed that MPV and PDW values were significant independent factors for the prediction of mortality.

Tao et al. reported that anemia was independently associated with progression to severe COVID-19. Mehta P et al. reported that hyperferritinemia, which might be due to viral hyperinflammation, was associated with mortality.[30] In contrast to those studies, Wang et al. reported that most elderly patients hospitalized with COVID-19 had lower hemoglobin levels than the normal range, but there was no significant difference between survivors and non-survivors in terms of hemoglobin levels.[31] Unlike these studies, Justin L. et al. reported that anemia was not associated with progression to severe COVID-19.[32] In the current study, the results were similar to those of the above-mentioned studies, as the hemoglobin levels of hospitalised COVID-19 patients were lower than the normal range and not significantly different between survivors and non-survivors because the median age was older than in other studies as in the study by Wang et al. Other comorbidities that could lead to anemia were higher in both groups.

In the literature, elevated LDH levels have been indicated with poor prognosis in patients with various viral infections.[33] Henry BM reported that elevated LDH values were related to 6-fold increased odds of critical disease and 16-fold increased odds of mortality in COVID-19 patients.[8] In the current study, similar significant-independent efficiency of LDH was observed in predicting mortality in the multiple model.

Elevated BUN and creatinine were significantly higher in the non-survivor group than in the survivors in the current study but were not significant for the prediction of mortality or hospitalization duration. Acute kidney injury (AKI) is commonly observed in patients with COVID-19.[34] Both elevated BUN at admission and increased BUN within the first 24 hrs have been associated with increased mortality.[35] Differences between the current study findings and those of other studies are most likely explained by the current study patients being followed up in the wards, not in the intensive care unit. One possible mechanism of AKI is that the systemic immune response to SARS-COV-2 leads to a cytokine storm. Another possible mechanism is the direct effect of the virus. In addition, SARS-CoV-2 RNA has also been identified in kidney tissue and urine in COVID-19 patients.[36] ACE2 is mainly expressed in the proximal tubules and glomeruli. Wang et al. found that entry of SARS CoV-2 through ACE2 receptors may result in kidney injury.[16]

With the emergence of mutant variants, the COVID-19 pandemic continues to be serious. The most important step in determining cases with high mortality risk and requiring hospitalization at the first admission of the patients. This stage is very important in terms of the rapid initiation of treatment, early use of advanced treatment methods, and the effective use of hospital facilities and healthcare personnel. The results of the current study demonstrated that patients with higher MPV, PDW and LDH at the time of diagnosis have poor prognoses and should, therefore, be managed more carefully. As it is known that SARS-CoV-2 and SARS-CoV use the same receptors, there may also be a similar structure and receptors in the mutant variants as in the first variant. Therefore, these predictive parameters may be considered as effective in mutant variants as in the first virus. Nevertheless, further studies are needed to show the effectiveness of these parameters.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

The study was approved by the Clinical Research Ethics Committee of the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (22.03.2021-107/07).

Authors' Contributions

Concept/Design: FY, AY, MA, SM. Data Collection and/or Processing: BS, MT, PA, MRA. Data analysis and interpretation: ÜYM, AY, FY, MT. Literature Search: SM,

ÜYM, BS, PA. Drafting manuscript: MRA, PA, FY, BS. Critical revision of the manuscript: HBAÖ, MA, MT, MRA. Supervision: MA, AY, ÜYM, SM.

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