Platelet Indices and Coagulation Parameters in Critical Patients with Coronavirus Disease-2019

Kritik Koronavirüs-2019 Hastalarında Trombosit İndeksleri ve Pıhtılaşma Parametreleri

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ABSTRACT

Background: The coronavirus disease-2019 (COVID-19) pandemic continues to demonstrate its effects worldwide and critical patients hospitalized in intensive care units (ICUs) because of the disease are still losing their lives. In this single-center retrospective study, it was aimed to 0determine the differences in platelet indices and coagulation parameters at admission in critically ill patients in the ICU.
Methods: This study included 792 critically ill patients with COVID-19 followed in ICUs. The patients were divided into two groups as those who survived (Survivors, group S) and those who did not survive (Nonsurvivors, group NS) and were compared in terms of clinical features, APACHE II and SOFA scores, and laboratory values at first admission to the ICU. In addition, patients were also divided into two groups as those with ≥1 comorbidity and those without comorbidities and compared in terms of platelet indices and coagulation parameters.
Results: Age, APACHE II, and SOFA scores were found to be significantly higher in group NS compared with those in group S (p<0.001). When the groups were evaluated in terms of platelet indices and coagulation parameters, it was found that the patients in group NS had higher MPV (p=0.009), P-LCR (p=0.023), and D-dimer (p=0.021) values. In addition, when the patients were divided into groups in terms of the presence of comorbidity, MPV values were found to be significantly higher in patients with comorbidities (p= 0.049).
Conclusion: Platelet indices can help determine the risk of mortality in critically ill patients with COVID-19 followed-up in the ICU.

Keywords: Coagulation parameters, coronavirus disease-19, mortality, platelet indices

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ÖZET

Amaç: Koronavirüs hastalığı-2019 (COVID-19) pandemisi hala dünya çapında etkisini göstermekte ve hastalık nedeniyle yoğun bakım ünitelerinde yatan kritik hastalar hala hayatını kaybetmektedirler. Bu tek merkezli retrospektif çalışmada yoğun bakım ünitelerindeki kritik hastalarda başvuru anında trombosit indeksleri ve pıhtılaşma parametrelerindeki farklılıkların belirlenmesi amaçlandı.
Yöntem: Çalışmaya alınan hastalar yoğun bakım ünitesinde hayatta kalanlar (grup S) ve hayatını kaybedenler (grup NS) olarak iki gruba ayrıldı ve hastalar yoğun bakım ünitesine ilk girişteki klinik özellikler, APACHE II, SOFA skorları ve laboratuvar değerleri açısından karşılaştırıldı. Ayrıca hastalar ≥1 komorbiditesi olanlar ve komorbiditesi olmayanlar olarak iki gruba ayrılarak trombosit indeksleri ve pıhtılaşma parametreleri açısından karşılaştırıldı.
Bulgular: Grup NS'de yaş, APACHE II ve SOFA puanları grup S'ye göre anlamlı olarak yüksek bulundu (p<0,001). Gruplar trombosit indeksleri ve pıhtılaşma parametreleri açısından değerlendirildiğinde, grup NS'deki hastaların MPV (p=0,009), P-LCR (p=0,023) ve D-dimer (p=0,021) değerlerinin daha yüksek olduğu bulundu. Ayrıca hastalar komorbidite varlığı açısından gruplara ayrıldığında, komorbiditesi olan hastalarda MPV değerleri anlamlı olarak daha düşük bulundu (p= 0.049).
Sonuç: Platelet indeksleri yoğun bakım ünitesinde takip edilen kritik COVID-19 hastalarında mortalite riskinin belirlenmesine yardımcı olabilir.

Anahtar Sözcükler: Koagülasyon parametreleri, koronavirüs hastalığı-2019, mortalite, trombosit indeksleri

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INTRODUCTION

The pneumonia pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-COV 2), a novel beta coronavirus, resulted in 178,202,610 confirmed cases and 3,865,738 deaths worldwide as of June 21, 2021, according to the World Health Organization's (WHO) data (1). As of June 20, 2021, 2,413,847.050 doses of vaccine have been administered worldwide and vaccination studies are ongoing (1). Despite these developments, there is no treatment method yet that has proven to be effective against the disease. Coronavirus disease-19 (COVID-19) primarily affects the respiratory system; however, it is considered as a multi-system disease because it also affects the cardiovascular, gastrointestinal, neurological, hematopoietic, and immune systems. (2, 3) Although the disease is mostly asymptomatic, it can present with severe respiratory failure, requiring follow-up in the intensive care unit (ICU). (4) Numerous studies have shown that advanced age and the presence of comorbidities are associated with increased mortality in COVID-19 patients. However, the disease can lead to complications such as cardiomyopathy or diffuse intravascular coagulopathy (DIC) in young people, leading to a worsening of the clinical picture. (5, 6)

One of the important systems affected in patients with COVID-19 is the hematopoietic system. Common hematological findings in patients with COVID-19 are lymphopenia and an increase in lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, ferritin, and interleukin-6 (IL-6) levels. (7, 8) In some studies, it has been emphasized that a hypercoagulant state occurs as a result of endothelial damage secondary to hyperinflammation developing in addition to the primary damage of the virus, which leads to the development of thrombotic events. (7, 9–11) In addition, postmortem studies in COVID-19 patients have demonstrated the presence of microvascular thrombosis. (8) Increased D-dimer levels, decreased platelet counts, and prolonged prothrombin time are the most common coagulation pathologies in these patients, and they may have prognostic value. (7, 12)

The present study was designed considering the pathological changes in the coagulation system associated with COVID-19 and the increased risk for thromboembolic events. The primary aim of this study is to retrospectively evaluate whether there is a difference in platelet indices and coagulation parameters between surviving and non-surviving critical COVID-19 patients followed in the intensive care unit. As a secondary aim, we tried to evaluate whether there was a difference by comparing the platelet indices and coagulation parameters of COVID-19 patients with and without comorbidity.

MATERIAL and METHODS

This retrospective cohort study was carried out between 01.05.2020 and 01.12.2020 in Diyarbakır Gazi Yaşargil Training and Research Hospital. The permission from the Scientific Research Platform of the TR Ministry of Health (03.10.2020) and the hospital management (14.10.2020) was obtained for the study. This study was conducted in accordance with the Declaration of Helsinki, 2008 criteria.

Critical patients over 18 years of age, who were diagnosed with COVID-19 between the above mentioned dates, followed-up in the ICU, and in need of serious oxygen support (patients with fever, muscle/joint pain, cough, sore throat, tachypnea (≥30/minute) or dyspnea according to WHO (4) and TR Ministry of Health (13) guidelines, use of extra respiratory muscles, SpO2 level≤90% in room air, bilateral diffuse pneumonia findings on chest X-ray or computed tomography, or PaO2/FiO2<300), or patients who developed complications, such as severe pneumonia, acute respiratory distress syndrome, sepsis/septic shock, and acute renal failure, were included in the study. Patients with COVID-19 who were younger than 18 years of age with mild-to-moderate symptoms, no respiratory distress, no signs of diffuse pneumonia on chest X-ray or computed tomography; patients admitted to the ICU with a diagnosis other than COVID-19; and patients with hereditary or acquired platelet dysfunction were excluded from the study. In addition, patients with missing data in the hospital system or patient file records were also excluded from the study. The clinical conditions of the patients were evaluated using the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores when they were first admitted to the ICU.

The data of the patients were obtained from patient files and the hospital information system. Patients' age, gender, comorbidity, ABO and Rh blood groups, APACHE II and SOFA scores when they were first admitted to the ICU, hemogram parameters (white blood cell, lymphocyte, and platelet counts; platelet/lymphocyte ratio; mean platelet volume (MPV); platelet distribution width (PDW); platelet larger cell ratio (P-LCR); and plateletcrit, coagulation parameters (prothrombin time (PTT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and D-dimer levels), and procalcitonin and ferritin levels were recorded. In addition, duration of hospitalization in the ICU and mortality status were recorded.

The patients were divided into two groups as those who survived (Survivors, group S, n=265) and those who did not survive (Nonsurvivors, group NS, n=527) during their ICU follow-up. Both groups were compared in terms of clinical features, APACHE II and SOFA scores, and laboratory values at first admission to the ICU. In addition, patients were also divided into two groups as those with ≥1 comorbidity and those without comorbidities and compared in terms of platelet indices and coagulation parameters.

Statistical analyses

SPSS 16.0 for Windows program (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous data were expressed as mean and standard deviation, and categorical data were expressed as frequency and percentage. Categorical data were compared using Chi-square and Fisher's exact test, and the results were presented as n %. Normality of numerical data was evaluated using the Shapiro–Wilk test. Normally distributed variables were evaluated using the Student's t test. Mann–Whitney U test was used to compare variables that were not normally distributed. A value of $p<0.05$ was considered significant in all the analyses.

RESULTS

A total of 835 patients were evaluated in the study. Based on the exclusion criteria, 43 patients were excluded from the study, and the study was completed with 792 patients. The mean age of the patients was 69,2±14,1 years, 356 (44,9%) of the patients were female and 495 (62,5%) were male. There was at least one comorbid disease in 495 (62,5%) of the patients included in the study. The most common comorbidities were hypertension (39%) and diabetes mellitus (DM; 26%). A total of 527 of the patients died during their follow-up in the ICU, and the mortality rate was 66,5%. The mean duration of hospitalization in the ICU was 11,16±9,1 days. Details of the demographic and clinical characteristics of the patients are shown in Table 1.

When the patients in groups S and NS were compared in terms of demographic and clinical characteristics, it was found that the patients in group NS had significantly higher age and APACHE II as well as SOFA scores ($p<0.001$). In addition, the patients in group NS had more comorbidities (<0.001) and comorbidities, such as DM, hypertension, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD) were more common in this group (p values <0.001, <0.001, <0.003, <0.001, respectively) than in group S. (Table 1)

Table 1. Demographic and clinical characteristics of patients hospitalized in the intensive care unit due to COVID-19

Characteristic	All patients (n=792)	Survivors (n=265)	Nonsurvivors (n=527)	p value
Age (year)	69,2±14,1	65,7±15,7	71,07±13,0	<0.001
APACHE II score	17,03±7,78	15,3±7,57	17,8±7,75	<0.001
SOFA score	3,66±2,64	3,17±2,1	3,9±2,84	0.001
Sex (n, %)				0,53
Female	356 (44,9)	115 (14,5)	241 (30,4)	
Male	436 (55,1)	150 (18,9)	286 (36,1)	
Blood group (n, %)				0,66
A	357 (45,1)	114 (14,4)	243 (30,7)	
B	155 (19,6)	54 (6,8)	101 (12,8)	
AB	64 (8,1)	19 (2,4)	45 (5,7)	
0	216 (27,3)	78 (9,8)	138 (17,4)	
Rh factor (n, %)				0,77
Negative	109 (13,8)	36 (4,6)	73 (9,2)	
Positive	682 (86,2)	229 (29)	453 (57,3)	
Comorbidities (n, %)				<0.001
No	297 (37,5)	184 (23,2)	113 (14,3)	
Yes	495 (62,5)	81 (10,2)	414 (52,3)	
Diabetes				<0.001
No	586 (74,0)	234 (29,5)	352 (44,4)	
Yes	206 (26,0)	31 (3,9)	175 (22,1)	
Hypertension				<0.001
No	483 (61,0)	209 (26,4)	274 (34,6)	
Yes	309(39,0)	56 (7,1)	253 (31,9)	
COPD				0.003
No	731 (92,3)	255 (32,2)	476 (60,1)	
Yes	61 (7,7)	10 (1,3)	51 (6,4)	
CKD				0.44
No	769 (97,1)	259 (32,7)	510 (64,4)	
Yes	23 (2,9)	6 (0,8)	17 (2,1)	
CVD				<0.001
No	641 (80,9)	246 (31,1)	395 (49,9)	
Yes	151 (19,1)	19 (2,4)	132 (16,7)	

APACHE II = Acute Physiology and Chronic Health Evaluation II score; SOFA = Sequential Organ Failure Assessment score; COPD = Chronic obstructive pulmonary disease; CKD = Chronic kidney disease; CVD = Cardiovascular disease;

Patients in group S and NS were compared in terms of laboratory values and patients in group NS had lower lymphocyte values (p=0.003) and higher MPV (p=0.009), P-LCR (p=0.023), D-dimer (p=0.021), procalcitonin (p<0.001) and ferritin (p=0.012) values. The length of stay in the ICU was significantly higher in group S patients (p=0.01). (Table 2)

Table 2. Laboratory characteristics of patients hospitalized in the intensive care unit due to COVID-19

Characteristic	All patients (n=792)	Survivors (n=265)	Nonsurvivors (n=527)	p value
White blood cells (×103/uL)	12,1 ± 6,4	12,07 ± 6,42	12,15 ± 6,40	0,665
Lymphocyte (×103/uL)	1,14 ± 2,6	1,39 ± 3,4	1,02 ± 2,14	0,003
Platelet (×103/uL)	252,5 ± 104,08	256,8 ± 100,05	250,3 ± 106,0,7	0,165
Platelet lymphocyte ratio (%)	338,8 ± 253,40	318,18 ± 260,7	349,2 ± 249,2	0,076
Mean platelet volume (fL)	9,99 ± 1,06	9,8 ± 0,96	10,06 ± 1,10	0,009
Platelet distribution width (%)	16,3 ± 0,93	16,3 ± 0,38	16,4 ± 1,11	0,221
Platelet larger cell ratio (%)	28,3 ± 8,2	27,2 ± 7,8	28,8 ± 8,41	0,023
Plateletcrit (%)	0,24± 0,09	0,25 ± 0,09	0,24 ± 0,09	0,63
Prothrombin time (s)	14,05 ± 4,12	13,7 ± 2,76	14,21 ± 4,64	0,178
INR	1,32 ± 0,62	1,33 ± 0,91	1,32 ± 0,41	0,286
aPTT (s)	30,13 ± 7,34	29,8 ± 5,26	30,25 ± 8,18	0,298
D-dimer (ng/ml)	1910,7 ± 4538,7	1215,6 ± 2318,9	2260,9 ± 5284,5	0,021
Procalcitonin (ng/ml)	3,18 ± 13,35	1,53 ± 5,25	4,01 ± 15,8	<0.001
Ferritin (µg/L)	837,6 ± 638,39	766,04 ± 628,40	874,12 ± 640,94	0,012
Length of stay in the ICU (day)	11,16 ± 9,11	12,3 ± 10,6	10,5 ± 8,1	0,01

INR: International normalized ratio; aPTT: Activated partial thromboplastin time; ICU: Intensive care unit

When the patients were divided into two groups as those with and without comorbidity and examined in terms of platelet indices and coagulation parameters, it was found that MPV values were significantly higher in patients with comorbidities (p=0.049). There was no statistically significant difference between the groups in terms of other values. (Table 3)

Table 3. The relationship between comorbidity, platelet indices and coagulation parameters in COVID-19 patients

Characteristic	All patients (n=792)	Comorbidity (≥1) (n=495)	Comorbidity (0) (n=297)	p value
Platelet count (×103/uL)	252,5 ± 104,08	251,9±104,8	253,5±102,9	0,68
Platelet lymphocyte ratio (%)	338,8 ± 253,40	338,04±238,4	340,1±276,9	0,79
Mean platelet volume (fL)	9,99 ± 1,06	10,02±1,03	9,94±1,11	0,049
Platelet distribution width (%)	16,3 ± 0,93	16,4±1,14	16,3±0,39	0,94
Platelet larger cell ratio (%)	28,3 ± 8,2	28,6±7,9	27,7±8,7	0,06
Plateletcrit (%)	0,24 ± 0,09	0,25±0,09	0,24±0,09	0,44
Prothrombin time (s)	14,05 ± 4,12	14,02±4,4	14,1±3,62	0,11
INR	1,32 ± 0,62	1,30±0,39	1,36±0,88	0,08
aPTT (s)	30,13 ± 7,34	30,4±8,07	29,6±5,92	0,78
D-dimer (ng/ml)	1910,7 ± 4538,7	2031,7±4746,7	1709,4±4166,6	0,88

INR: International normalized ratio; aPTT: Activated partial thromboplastin time

The patients were divided into subgroups according to existing comorbidities and the relationship with platelet indices and coagulation parameters was examined. It was found that PTT (DM 13.6±2.8; non-DM 14.1±4.4; p=0.03) and INR (DM 1.26±0.23; non-DM 1.34±0.71; p=0.018) values were significantly lower in patients with DM compared with those in patients without DM. In addition, P-LCR (Chronic kidney disease (CKD) 31.9±8.4; Non-CKD 28.1±8.2; p=0.022) and MPV (CKD 10.3±1.04; Non-CKD 9.9±1.06; p=0.042) values were significantly higher, platelet count was significantly lower (CKD 209.7±75.7; Non-CKD 253.8±104.5; p=0.047), and aPTT (CKD 36.8±21.1; Non-CKD 29.9±6.5; p=0.03) was significantly longer in patients with CKD compared to those in patients without CKD. There was no significant difference between the patients with and without hypertension, CVD, and COPD in terms of platelet indices and coagulation factors (p>0.05).

DISCUSSION

In this study, we investigated the relationship between platelet indices, coagulation parameters, comorbidity, and mortality in critically ill patients with COVID-19 followed-up in the ICU. We found that patients who did not survive had higher MPV, P-LCR, and D-dimer levels when they were first admitted to the ICU. When patients with and without comorbidities were compared in terms of platelet indices and coagulation parameters, we found that there was no difference in any of the values except the minimal difference in MPV values. When patients were divided into groups as those having ≥1 comorbidity and those without comorbidities and were evaluated, it was found that patients with DM having COVID-19 had shorter PTT and INR values than those in patients with COVID-19 without DM, whereas patients with COVID-19 having CKD had higher P-LCR and MPV values, lower platelet count, and longer aPTT values than those in patients with COVID-19 without CKD.

Platelets play important roles in many events, such as hemostasis, coagulation, preservation of vascular integrity, and inflammatory response, in the human body. Changes in platelet count and activity can be observed in many diseases. (14) Platelet count, MPV, PDW, P-LCR, and plateletcrit are the most commonly used tests to evaluate platelet activity. These tests are easily accessible and inexpensive; this has enabled their evaluation in many diseases. (15)

Studies examining the relationship between COVID-19 and platelet indices report that a hypercoagulant state occurs after hyperinflammation because of the disease. (7, 9) After virus-associated primary vascular endothelial damage, the aggregation and activation of platelets in the damaged area causes further aggravation of inflammation. (15) Some studies emphasize that there may be changes in platelet indices in patients with COVID-19 as a result of this mechanism and that some of these values can be used to indicate the severity of the disease. (14, 16, 17)

The first parameter that is assessed in the evaluation of platelet functions is the platelet count. As platelets play a role in many events in the body, the platelet count tends to increase or decrease in many diseases. A meta-analysis by Lippi et al. examined the effect of thrombocytopenia in patients with COVID-19; a total of 1779 patients with COVID-19 in 9 studies were examined, and the study found that the severity of the disease and the risk of mortality increased in patients with thrombocytopenia. (17) In some of the studies included in this meta-analysis, the accepted values for thrombocytopenia were different, and in some the values were taken at the first admission of the patients to the hospital, while in some of the values during the follow-up. In addition, in this meta-analysis, the researchers evaluated the platelet count together with calculation of weighted mean difference (WMD) and 95% confidence interval (95% CI) of platelet number in COVID-19 patients with or without severe disease. In the present study, when we looked at the values at first admission to the ICU, we did not observe a difference in thrombocyte values in terms of patients who did and did not survive. This result may be due to the fact that we made the evaluation only according to the values during the first hospitalization in the ICU. However, based on our COVID-19 ICU experience of almost 16 months, we can say that thrombocytopenia is observed more frequently in the days following ICU admission in patients who do not survive.

It has been stated that MPV levels, which is one of the platelet indices that are frequently studied in the literature, are outside the normal range in many systemic diseases. (15, 18) Gümüş et al. evaluated 115 pediatric patients and found that MPV values were significantly higher in patients with COVID-19 and that MPV could be a reliable marker in distinguishing asymptomatic children infected with COVID-19 from healthy children. (19) Güçlü et al. grouped and compared 215 patients with COVID-19 as having moderate and severe disease and emphasized that oxygen saturation at hospitalization and difference in MPV between the first and third days of hospitalization were important parameters in predicting mortality in patients with COVID-19. They also stated that a 1-unit increase in difference in MPV between the first and third days of hospitalization increased mortality 1.76 times. (20) Özçelik et al. compared 54 patients with COVID-19 and 43 patients with influenza, and unlike the other two studies, found that MPV values were low in both the viral diseases and that patients with COVID-19 had lower MPV levels compared with those in patients with influenza. (9) Although the patient populations in these studies are different, in line with the first two studies, our results showed that MPV values were higher in critically ill patients who were followed-up in the ICU due to COVID-19 and did not survive. In addition, the MPV values were higher in patients with COVID-19 having CKD compared with those in patients with COVID-19 without CKD.

Another platelet index used to evaluate platelet functions is P-LCR; P-LCR is the percentage of all platelets with a volume greater than 12 fL circulating in the blood. P-LCR values were found to be lower than normal in myeloid failure and higher than normal in diseases, such as immune thrombocytopenic purpura, DM-related retinopathy, and nephropathy. (15) It was also emphasized that, together with MPV and PDW, P-LCR values are biomarkers that can be used to detect the causes of thrombocytopenia. (21) In the present study, we found that P-LCR values were higher in critically ill patients who were followed-up in the ICU due to COVID-19 and did not survive. These results suggest that MPV and P-LCR values at first admission to the ICU may be useful parameters in predicting mortality in critically ill patients with COVID-19.

In addition to platelet indices, it has been stated that there may be prolongation of PTT and aPTT, which are coagulation parameters, and increased in the levels of D-dimer and fibrin degradation products; lymphopenia; elevated biochemical values of LDH, CRP, ALT, and AST; and increase in procalcitonin and ferritin values in patients with COVID-19. Different studies reported that these values could be used in the follow-up of critical patients. (7, 8, 10, 22) In the present study, D-dimer, procalcitonin and ferritin values, together with lymphopenia, were found to be higher in critically ill patients with COVID-19 compared with those in discharged patients, which was consistent with the results of studies in literature. In contrast to the results of studies in the literature, there was no difference in PTT and aPTT in the present study; this may be due to the fact that the laboratory data included in the study covered only the values on the first day of hospitalization. Prolongation of PTT and aPTT may be observed in the later stages of the disease, especially in patients with severe symptoms.

When the relationship between comorbidity and platelet indices was examined, different studies emphasized that there were changes in platelet indices in many different diseases, such as immune thrombocytopenia purpura, DM, septic shock, heart diseases, and various tumors. (15) Age and the presence of comorbidity increase the severity of the disease and mortality in patients with COVID-19. (23) However, we could not find any study in the literature examining the relationship between comorbidity and platelet indices and coagulation parameters in patients with COVID-19. In this regard, we believe that the findings of the study are important as, to the best of our knowledge, it is the first study to examine the relationship between comorbidity, platelet indices, and coagulation parameters in patients with COVID-19. According to the results obtained, we found that COVID-19 was more lethal in patients with advanced age and comorbidities, consistent with the results in literature. In addition, we found that MPV values were higher in critically ill patients with COVID-19 having ≥1 comorbidities compared with those in patients with COVID-19 without comorbidities. When comorbid diseases were examined in more detail, it was found that patients with COVID-19 having DM had shorter PTT and INR values; whereas patients with COVID-19 having CKD had higher P-LCR and MPV values, lower platelet count, and longer aPTT values. Therefore, platelet indices and coagulation parameters should be closely monitored in ICUs, especially in the follow-up of these two patient groups.

he most important limitation of the present study was that it was a single-center retrospective study. Conducting prospective studies involving more than one center will further contribute to the body of evidence on the subject. Another limitation of the study was that the values obtained only on the first day of admission to the ICU were examined. Different results could be obtained by examining and comparing the values obtained on other days during the ICU follow-up of patients with COVID-19.

In conclusion, platelet indices can help determine the severity of the disease and the risk of mortality in critically ill patients with COVID-19 followed-up in the ICU. Evaluation of critical patients with COVID-19 using these easily accessible and inexpensive tests will contribute to the prediction of thromboembolic complications that may occur due to this disease, which still has a significant impact worldwide, and help reduce the risk of mortality. The comprehensive clinical and experimental studies with larger series on this subject are needed.

Conflict of interest

No conflict of interest was declared by the authors.

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