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The effect of thrombosis-related laboratory values on mortality in COVID-19 infection

Z. ERGENC[1], H. ERGENC[1], A. ÖZTÜRK[2], T. KAYA[3], A. NALBANT[3], C. KARACAER[3], S. GÜNAY[2], M. USANMAZ[4], İ. HAKKI TÖR[5], E. ALKILINÇ[6], S. ARAÇ[7], G. KAYA[8], S. YAYLACI[3], Y. KALPAKÇI[3], D. ÇEKIÇ[3], A. TOÇOĞLU[3], A. ALTAŞ[3], A.B. GENÇ[3]

[1]Department of Internal Medicine, Yalova State Hospital, Yalova, Turkey
[2]Department of Emergency Medicine, Hitit University Çorum Erol Olcok Training and Research Hospital, Çorum, Turkey
[3]Department of Internal Medicine, Sakarya University, Faculty of Medicine, Sakarya, Turkey
[4]Department of Infectious Diseases and Clinical Microbiology, Gazi Government Hospital, Samsun, Turkey
[5]Department of Anesthesiology and Reanimation, University of Health Sciences, Erzurum, Turkey
[6]Department of Pulmonology, Sinop Atatürk State Hospital, Sinop, Turkey
[7]Department of Emergency Medicine, University of Health Sciences, Diyarbakır Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey
[8]Department of Support and Quality Services Directorate, Yalova State Hospital, Yalova, Turkey

Abstract. – OBJECTIVE: COVID-19 may cause thrombosis in both venous and arterial systems. Familiarity with the signs and symptoms of thrombosis and its treatment is essential in treating COVID-19 infection and its complications. D-Dimer and mean platelet volume (MPV) are measurements related to the development of thrombosis. This study investigates whether MPV and D-Dimer values could be used to determine the risk of thrombosis and mortality in the COVID-19 early stages.

PATIENTS AND METHODS: 424 patients who were COVID-19 positive, according to the World Health Organization (WHO) guidelines, were randomly and retrospectively included in the study. Demographic and clinical characteristics such as age, gender, and length of hospitalization were obtained from the digital records of participants. Participants were divided into living and deceased groups. The patients' biochemical, hormonal, and hematological parameters were analyzed retrospectively.

RESULTS: White blood cells (WBC), neutrophils, and monocytes were significantly different in the two groups (*p*-value <0.001), and their values were lower in the living group than in the deceased group. MPV median values did not differ according to prognosis (*p*-value = 0.994). While the median value was 9.9 in the survivors, it was 10 in the deceased. Creatinine, procalcitonin, ferritin, and the number of hospitalization days in living patients were significantly lower than in patients who died (*p*-value <0.001). Median values of D-dimer (mg/L) differ according to prognosis (*p*-value <0.001). While the median value was 0.63 in the survivors, it was found as 438 in the deceased.

CONCLUSIONS: Our results did not show any significant relationship between the mortality of COVID-19 patients and their MPV levels. However, a significant association between D-Dimer and mortality in COVID-19 patients was observed.

Key Words:
COVID-19, MPV, D-Dimer, Prognosis, Mortality.

Introduction

As of the end of December 2019, COVID-19, also known as Coronavirus, has spread worldwide. Many clinical studies have been conducted to predict how the prognosis will progress after the diagnosis. The target organ for COVID-19 is the lung, and the disease may develop acute lung damage that may progress to respiratory and multiple organ failures[1]. Although the most critical complication of COVID-19 infection is a severe lung infection and acute respiratory failure, it also affects other organs of the body, and non-respiratory infections can have significant side effects such as disorder in the blood coagulation system and thrombosis[2-5]. Studies[1-5] have shown that COVID-19 may cause thrombosis in both

Corresponding Author: Hasan Ergenc, MD; e-mail: dr.hasanergenc@hotmail.com

venous and arterial systems, affecting endothelial dysfunction, inflammation, stasis in blood flow, and thrombocyte activation. Familiarity with the signs and symptoms of thrombosis and its treatment is essential in treating COVID-19 infection and its complications.

D-Dimer is one of the components produced after the destruction of fibrin in the blood clot, and its level is measured routinely in vascular thrombosis diagnosis. Any pathological or non-pathological process that raises fibrin production and breakage will also increase the amount of D-Dimer[6]. As a cross-linked fibrin degradation product, D-Dimer is an important biomarker in the study of vascular embolism. However, this marker has low specificity because it increases in cases where the body's homeostasis system is activated, such as pregnancy, inflammation, cancer, trauma, liver disease, heart disease, sepsis, hemodialysis, and cardiovascular resuscitation[6,7].

Mean platelet volume (MPV) measurement is a simple method to measure platelet function and shows the production and stimulation rate of the platelet. Larger platelets are more enzymatically and metabolically active than smaller platelets and have greater prothrombotic potential. Thus, an increase in MPV can be accepted as a characteristic of platelet activity[8]. Studies[9,10] have shown that high MVP is venous thromboembolism (VTE) predictor, especially venous thromboembolism of unknown origin. These findings[11,12] support the belief that platelet activity might play a role in the pathogenesis of venous thromboembolism in COVID-19 infections. This study investigates whether MPV and D-Dimer values could determine the thrombosis and mortality risk in the early stages of COVID-19.

Patients and Methods

This study was conducted in accordance with the ethical rules and after obtaining the approval of Medicana International Samsun Hospital clinical research Ethics Committee (decision No. 7129, 20.04.2021). Out of patients diagnosed with COVID-19 admitted to Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital and Ayancık State Hospital from April 1, 2020, to April 1, 2021, 424 patients were randomly and retrospectively included in the study. All patients included in the study were COVID-19 positive according to the World Health Organization (WHO) guidelines[15]. Demographic and clinical characteristics such as age, gender, and length of hospitalization were obtained from the digital records of participants. The patients' biochemical, hormonal, and hematological parameters were analyzed retrospectively.

Patients with previous diagnoses of cancer, endocrine disorders, liver or kidney failure, autoimmune diseases, infectious diseases, and under 18 were excluded from the study. Written consent was waived since the data of the study were obtained retrospectively from the hospital automation system. Participants were divided into living and deceased groups. All patients were followed-up daily until discharge or death. All study procedures were performed according to the principles of the Helsinki Declaration of 1964 and the subsequent 2013 amendment.

Statistical Analysis

Mann-Whitney U test was used to compare quantitative data between living and deceased groups. The Chi-square test was used to compare death rates according to gender. Binary logistic regression analysis was used to determine the risk factors affecting death. Data were analyzed using SPSS v. 23 (IBM Corp., Armonk, NY, USA). The significance level was taken as a p-value <0.05.

Results

Table I shows the comparison results of biochemical, hormonal, and hematological parameters of participants in living and deceased groups. Table I shows that White Blood Cells (WBC), neutrophils, and monocytes were significantly different in the two groups (p-value <0.001), and their values were lower in the living group than in the deceased group. Lymphocytes were significantly different between the two groups (p-value <0.001) and were higher in the living group than in the deceased group. Hemoglobin (Hb) and platelet count (PLT) were also significantly different (p-value = 0.043 and p-value <0.001) in the two groups and were lower in the living group than in the deceased group. Mean platelet volume (MPV) median values did not differ according to prognosis (p-value = 0.994). While the median value was 9.9 in the survivors, it was 10 in the deceased.

Red Cell Distribution Width (RDW), C-reactive protein (CRP), and glucose were significantly lower in the living group than in the deceased group (p-value <0.001). Albumin (Alb) and Calcium (Ca) values were significantly higher in the

Table I. Comparisons according to groups.

	Living (n = 245)		Deceased (n = 179)		
	Median (min-max)	Mean ± S. deviation	Median (min-max)	Mean ± S. deviation	*p*-value*
WBC	5.5 (1.9-76.2)	5.92 ± 4.98	9.63 (1.54-41.68)	11.54 ± 7.12	**< 0.001**
Neutrophil	3.9 (1.2-69.9)	4.36 ± 4.65	8.11 (0.73-39.98)	9.92 ± 6.62	**< 0.001**
Lymphocyte	1.1 (0.2-22.7)	1.28 ± 1.56	0.84 (0.1-18.36)	1.12 ± 1.78	**< 0.001**
Monocyte	0.3 (0.05-6)	0.37 ± 0.52	0.4 (0-2.29)	0.46 ± 0.33	**< 0.001**
Hb	12.8 (7.2-17.3)	12.78 ± 1.7	13.3 (3.7-132)	14.32 ± 12.48	**0.043**
PLT	182 (11-656)	186.28 ± 74.65	210 (20-537)	220.52 ± 90.32	**< 0 .001**
MPV	9.9 (6.9-14.5)	10 ± 1.1	10 (7.1-17)	10.06 ± 1.23	0.994
RDW	13.4 (11.8-82.3)	14.04 ± 4.63	46.4 (37.8-92.7)	47.45 ± 6.28	**< 0.001**
Alb	42 (29-51)	41.67 ± 3.73	30 (18-41)	29.46 ± 4.62	**< 0.001**
CRP (mg/L)	19.8 (2-313.5)	44.94 ± 57.81	147 (2-350)	147.43 ± 84.35	**< 0.001**
Glucose	116 (73-387)	132.93 ± 52.81	149 (73-914)	192.83 ± 120.13	**< 0.001**
Ca	8.7 (3.8-12.2)	8.59 ± 0.73	8 (5.6-10.1)	8.03 ± 0.6	**< 0.001**
LDH	257 (23-1,137)	275.14 ± 111.94	411 (110-13,712)	536.73 ± 1,023.12	**< 0.001**
K	4.2 (2.8-101)	4.64 ± 6.23	4.33 (2.21-460)	9.42 ± 47.72	**0.019**
Na	137 (66-4,137)	152.59 ± 256.72	136 (3.83-172)	134.35 ± 15.34	**0.011**
Urea	35 (9.1-146.3)	39.61 ± 19.05	56 (10-267)	69.08 ± 40.48	**< 0.001**
Creatinine	0.9 (0.6-7.1)	1.03 ± 0.55	1.27 (0.61-103)	2.05 ± 7.65	**< 0.001**
Procalcitonin (ng/ml)	0.05 (0-0.83)	0.08 ± 0.11	0.32 (0.01-38)	1.28 ± 3.47	**< 0.001**
Ferritin (ng/ml)	123.9 (4.5-1,650)	214.67 ± 292.28	537 (19-2,826)	766.06 ± 641.36	**< 0.001**
D-dimer (mg/L)	0.63 (0.17-96)	1.95 ± 7.51	438 (9.16-15,938)	1,315.69 ± 2,617.46	**< 0.001**
Hospitalization days	7 (1-26)	8.05 ± 3.85	10 (2-94)	13.83 ± 12.29	**< 0.001**

WBC: white blood cells; Hb: Hemoglobin; PLT: Platelet Count; MPV: mean platelet volume; RDW: red cell distribution width; Alb: Albumin; CRP: c-reactive protein; Ca: Calcium; LDH: Lactate dehydrogenase; K: Potassium; Na: Sodium. *Mann-Whitney U Test, $p < 0.05$.

living group than in the deceased group (*p*-value <0.001). Potassium (K) (*p*-value = 0.019), lactate dehydrogenase (LDH) (*p*-value <0.001), and Urea (*p*-value <0.001) were significantly lower in the living group than in the deceased group. Sodium (Na) was significantly higher in the living group than in the deceased group (*p*-value = 0.011). Creatinine, procalcitonin, ferritin, and the number of hospitalization days in living patients were significantly lower than in patients who died (*p*-value <0.001). Finally, median values of D-dimer (mg/L) differed according to prognosis (*p*-value <0.001). While the median value was 0.63 in the survivors, it was found as 438 in the deceased. Based on the obtained values, the risk factors affecting the death of each variable were investigated, and the results are shown in Table II.

As Table II shows, increasing age increases the risk of death by 1.044 (*p*-value <0.001). The risk of death in men is 2.242 times higher than in women (*p*-value <0.001). An increase in WBC value increases the risk of death by 1.335, while an increase in neutrophils increases the risk of death by 1.4 times (*p*-value <0.001). PLT increases 1.005 times, RDW increases 1.361 times, CRP 1.019, Glucose 1.01, LDH 1.008, Urea 1.042, creatinine 3.87, ferritin 1.003, D-Dimer 1.075, and hospitalization time increased the risk of death by 1.133 times. Lymphocyte, Monocyte, Hb, MPV, K, Na, and PCR positivity were not determined as independent risk factors for death (*p*-value > 0.05).

Table III shows that median age values differed according to the groups (*p*-value <0.001). While the median age for the survivors was 69 years, it was determined as 74 years for those who died. In a total of 424 cases included in the study, the rate of women was 47.2%, while the rate of men was 52.8%. While the death rate in females is 32%, it is 51.3% in males, and there is a statistically significant difference between these rates (*p*-value <0.001).

Discussion

This study aimed to show whether MPV and D-Dimer values could be used early in determining coagulopathy and thrombosis that may occur in the early period in COVID-19 patients.

Table II. Examination of risk factors affecting death.

	OR (95% CI)	*p*-value
Age	1.044 (1.026-1.063)	**< 0.001**
Gender	2.242 (1.509-3.332)	**< 0.001**
WBC	1.335 (1.243-1.435)	**< 0.001**
Neutrophil	1.4 (1.293-1.516)	**< 0.001**
Lymphocyte	0.933 (0.807-1.08)	0.354
Monocyte	1.784 (0.945-3.367)	0.074
Hb	1.064 (0.965-1.173)	0.212
PLT	1.005 (1.003-1.008)	**< 0.001**
MPV	1.044 (0.883-1.234)	0.615
RDW	1.361 (1.265-1.464)	**< 0.001**
Alb	0.567 (0.507-0.634)	**< 0.001**
CRP (mg/L)	1.019 (1.015-1.023)	**< 0.001**
Glucose	1.01 (1.007-1.013)	**< 0.001**
Ca	0.25 (0.172-0.364)	**< 0.001**
LDH	1.008 (1.006-1.01)	**< 0.001**
K	1.007 (0.994-1.021)	0.288
Na	0.983 (0.96-1.006)	0.142
Urea	1.042 (1.031-1.053)	**< 0.001**
Creatinine	3.87 (2.392-6.26)	**< 0.001**
Ferritin (ng/ml)	1.003 (1.002-1.004)	**< 0.001**
D-dimer (mg/L)	1.075 (1.042-1.109)	**< 0.001**
Hospitalization days	1.133 (1.088-1.18)	**< 0.001**
PCR (+)	2.263 (0.2-25.565)	0.509

WBC: White Blood Cells; Hb: Hemoglobin; PLT: Platelet Count; MPV: Mean Platelet Volume; RDW: Red Cell Distribution Width; Alb: Albumin; CRP: C-Reactive Protein; Ca: Calcium; LDH: Lactate dehydrogenase; K: Potassium; Na: Sodium.

In this way, the rapid implementation of treatment options for coagulopathy and thrombosis in the early period without clinical deterioration will prevent complications that may occur. Our results showed that D-Dimer was significantly higher in the deceased group than in the living group. However, no significant differences were observed between the WBC of the deceased group and the living group.

Although MPV is known as a marker for infectious and inflammatory diseases, its association with COVID-19 disease remains unknown and conflicting results have been reported[12,13]. In their study, Huang et al[12] showed that higher MPV levels could be associated with a higher risk of pneumonia in COVID-19 patients. In another study, Lippi et al[13] examined the relationship between MPV and the severity of COVID-19 disease and concluded that MPV was significantly associated with disease severity and mortality in COVID-19 patients. Guner Ozenen et al[14] studied the role of MPV and D-Dimer in predicting disease severity in a study of children with COVID-19. Their results showed that D-Dimer was the strongest predictor of hospitalization and disease severity among the studied parameters. However, they found no association between MPV and the severity of COVID-19 disease. Aktas et al[15] examined the MPV role in predicting the prognosis of COVID-19 disease. They found no association between MPV levels and mortality and prognosis in COVID-19 patients. The results of our study were consistent with these findings and showed no significant association between MPV and mortality in COVID-19 patients. This discrepancy in the results may be due to hematological influencing factors or comorbidities that require further study.

Another finding in this study was the importance of the D-Dimer marker in predicting disease severity and mortality in COVID-19 patients. D-Dimer is one of the products of fibrin degradation in the body that can be measured in the blood. With the increase of the fibrin lysis process in coagulation disorders, the amount of this product in the blood will also increase and indicate the severity of the disease. In COVID-19 disease, coagulation cascade activity is increased

Table III. Demographic characteristics.

	Living (n = 245)		Deceased (n = 179)		
	Median (min-max)	Mean ± S. deviation	Median (min-max)	Mean ± S. deviation	*p*-value
Age	69 (21-94)	66.62 ± 13.75	74 (38-93)	72.96 ± 10.29	**< 0.001**[a]
	N	%	N	%	
Gender					**< 0.001**[b]
Female (n = 200)	136	68	64	32	
Male (n = 224)	109	48.7	115	51.3	

[a]Mann Whitney U; [b]Pearson's Chi-Square.

by several mechanisms that are still under investigation, leading to an increase in the amount of D-dimer in patients' blood. According to studies, an increase in D-Dimer in patients' blood worsen the patient's condition. Our results are consistent with these findings[16,17].

Low D-Dimer concentrations can diagnose vascular thrombotic such as pulmonary embolism and deep vein thrombosis (DVT). In other words, increasing amount of D-Dimer indicates the activity of the coagulation process followed by fibrinolysis[18]. The incidence of thrombotic events is one in a thousand people in adults, and risk factors such as infections and inflammatory diseases are involved in this occurrence. Before the COVID-19 pandemic, an increase in D-Dimer in influenza was reported[19] as a pulmonary infection activating the coagulation system.

In COVID-19, D-Dimer increases in parallel with CRP, and unlike the classic disseminated intravascular coagulation (DIC) due to bacterial infection, there is a slight increase in clotting time and active partial thromboplastin time test (APTT) and moderate thrombocytopenia in COVID-19 patients (Platelets $\approx$ 100x10^9/L). Several studies[20-22] in Wuhan, China, have shown that an increase in D-Dimer in COVID-19 patients is associated with increased mortality. Although these studies did not commonly use anticoagulants, observations[23] suggest that patients receiving anticoagulants have lower D-Dimer levels.

Researchers still have no agreement in using D-Dimer values in to manage and monitor COVID-19 patients. Based on experience in COVID-19 patients, a D-Dimer value of cut-off > 1 µg/ml can indicate high risk and poor outcome for the patient. There is no agreement on how to measure D-Dimer and how to function based on the results obtained from its values for receiving anticoagulants in hospitalized patients[22]. The D-Dimer level is directly related to the severity of the disease, the area of lung involvement identified on computed tomography, and the oxygen index. Our results are consistent with these findings[24], in which the median and mean levels of D-Dimer were significantly higher in patients who did not survive.

The specific mechanisms associated with systemic inflammatory responses in COVID-19 infection are not well understood. In COVID-19, misalignment of the coagulation and anticoagulation cascades leads to worsening of the pathological complications of the lung[18]. In influenza, pathogenicity occurs by increasing virus replication, stimulating the immune system, and deviating the immune system, including cellular and protein components. COVID-19 pathogenesis includes extensive alveolar lesion with fibrinous cellular exudate, destruction of squamous lung cells and hyaline membrane formation, pulmonary edema, infiltration of mononuclear inflammatory cells with predominant lymphocytes, similar to what is seen in SARS and MERS[16,17]. Increased D-Dimer value indicates increased fibrinolysis and increased burden of COVID-19 infection. Extensive anticoagulant therapy is directly associated with reduced mortality, especially in patients who breathe mechanically[25,26].

New guidelines[22] published by the IFCC emphasize the considering D-Dimer in COVID-19 patients. Studies[22] on SARS-CoV-2 have shown a strong association between disease severity and D-Dimer outcome in COVID-19 patients so that in very severe cases, DIC can occur. In one study[16], an increase in the amount of D-Dimer was considered a predictor of the development and exacerbation of respiratory distress in COVID-19, which may be due to the development of pulmonary embolism, especially in severe cases of COVID-19. Wuhan studies[27] showed that COVID-19 patients with D-Dimer $\geq$ 2.0 µg/ml had a higher mortality rate than lower doses.

In terms of risk factors, studies[22] have shown that age, gender, and days of hospitalization are not associated with an increased risk of pulmonary embolism (PE). Patients who show higher levels of D-Dimer are more likely to develop PE in the following three days. Other studies[19-21] have shown that in severe COVID-19 pneumonia, the risk of developing PE is associated with increased D-dimer levels. The potential link between COVID-19 and vascular embolism is still unclear. It has also been shown[16,17] that mortality in patients with D-Dimer levels higher than 1,000 µg/ml will be higher.

In one study[20], comparative studies between bacterial pneumonia and COVID-19 patients showed an increased D-Dimer level in both diseases, but in COVID-19, the increase was much higher. In patients with COVID-19, coagulation system activity increases due to raised blood viscosity after fever and excessive sweating. Risk factors such as long-term hospitalization, old age, and obesity increase thrombosis risk[21-23]. These increase D-Dimer and the need for anticoagulants. As inflammation decreases and the patient recovers, the level of D-Dimer decreases

in most patients, while in some of these patients, the amount of D-Dimer remains high, contrary to expectations. This justifies the continued use of anticoagulants in these patients to prevent venous thrombosis[28]. One of the limitations of this study was the lack of consideration for body mass index (BMI) and common comorbidities affecting hematological parameters.

Conclusions

In conclusion, our findings, in line with previous findings[16,17], highlight the significant association of D-Dimer in patients with severe COVID-19 and the importance of monitoring it to prevent exacerbation of the disease by anticoagulants. Our results also did not show any significant relationship between the mortality of COVID-19 patients and their MPV levels. Various studies[12-15] have reported this relationship with different results, which indicates the influence of other factors on this parameter and requires more detailed studies. Future studies should consider additional parameters related to hematological factors to elucidate further the association of MPV with COVID-19 severity and mortality.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethics Approval
Ethics Committee approval of this study was obtained from Health Sciences University Samsun Training and Research Hospital Clinical Research Ethics Committee (Protocol code: GOKA/2021/8/7).

Informed Consent
Informed consent was waived due to the retrospective nature of the study.

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ORCID ID
Zeynep Ergenc: 0000-0001-7598-4508; Hasan Ergenc: 0000-0003-0519-0264; Ahmet Öztürk: 0000-0002-9678-2195; Tezcan Kaya: 0000-0003-0483-2333; Ahmet Nalbant: 0000-0003-4756-3575; Cengiz Karacaer: 0000-0002-7164-4810; Mustafa Usanmaz: 0000-0002-5369-2560; Serkan Günay: 0000-0002-8343-0916; İbrahim Hakkı Tör: 0000-0003-0246-3220; Ersin Alkılınç: 0000-0002-6456-6623; Songül Araç: 0000-0001-6830-3639; Gülsüm Kaya: 0000-0003-2517-5512; Selçuk Yaylacı:0000-0002-6768-7973; Yasin Kalpakçı: 0000-0001-6944-9808; Deniz Çekiç: 0000-0002-7114-9334; Aysel Toçoğlu: 0000-0002-9078-6996; Ayfer Altaş: 0000-0002-1082-2716; Ahmed Bilal Genç: 0000-0002-1607-6355.

Authors' Contribution
ZE, HE, AO, TK, AN, CK, MU, SG, IHT, EA, SA, GK, SY, YK, DÇ, AT, AA and ABG took the lead in writing the manuscript. ZE, HE, AO, TK, AN, CK, MU, SG, IHT, EA, SA, GK, SY, YK, DÇ, AT, AA and ABG designed the model and the computational framework and analyzed the data. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

Availability of Data and Materials
The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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