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

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Abstract

Objective: Covid-19 may cause thrombosis in both venous and arterial systems. Familiarity with the signs and symptoms of thrombosis and their treatment plays an important role 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 Covid-19 early stages. Methods: 424 patients were randomly and retrospectively included in the study, Covid 19 positive according to the World Health Organization (WHO) guidelines. 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. Results: WBC, neutrophils, and monocytes were significantly different in the two groups ($p < 0.001$), and its values were lower in the living group than in the deceased group. MPV median values do not differ according to prognosis ($p = 0.994$). Creatinine, Procalcitonin, Ferritin, and the number of hospitalization days in living patients were significantly lower than in patients who died ($p < 0.001$). Median values of D-dimer (mg / L) differ according to prognosis ($p < 0.001$). While the median value was 0.63 in the survivors, it was found as 4.38 in the deceased. Conclusion: Our results did not show any significant relationship between the mortality of Covid-19 patients and their MPV levels. However, a significant association of D-Dimer and mortality in Covid-19 patients was observed. Keywords: COVID-19, MPV, D-Dimer, prognosis, mortality

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Methods : 424 patients were randomly and retrospectively included in the study, Covid 19 positive according to the World Health Organization (WHO) guidelines. 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.

Results: WBC, neutrophils, and monocytes were significantly different in the two groups ($p < 0.001$), and its values were lower in the living group than in the deceased group. MPV median values do not differ according to prognosis ($p = 0.994$). Creatinine, Procalcitonin, Ferritin, and the number of hospitalization days in living patients were significantly lower than in patients who died ($p < 0.001$). Median values of D-dimer (mg / L) differ according to prognosis ($p < 0.001$). While the median value was 0.63 in the survivors, it was found as 4.38 in the deceased.

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

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What is already known about this topic?

It is known that Covid-19 disease causes coagulation disorders. This situation significantly affects the morbidity and mortality in Covid-19. It is used as anticoagulant drugs in the treatment of Covid-19.

What does this article add?

In this study, many parameters that will show coagulation in Covid-19 patients were evaluated. It presents important parameters to predict coagulation disorders, which are an important cause of morbidity and mortality in Covid-19.

Introduction

As of the end of December 2019, the Covid-19, also known as Coronavirus, has spread all over the world. Many clinical studies have been conducted to predict how the prognosis will progress after the diagnosis is made. 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 important 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 of the blood coagulation system and thrombosis (2-5). Studies have shown that Covid-19 may cause thrombosis in both venous and arterial systems, affecting endothelial dysfunction, inflammation, stasis in blood flow, and thrombocyte activation (1-5). Familiarity with the signs and symptoms of thrombosis and their treatment plays an important role 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 known as 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 both 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 have shown that high MVP is venous thromboembolism (VTE) predictor, especially venous thromboembolism of unknown origin (9,10). These findings support the belief that platelet activity might play a role in the pathogenesis of venous thromboembolism in Covid-19 infections (11,12). This study investigates whether MPV and D-Dimer values could determine the thrombosis and mortality risk in Covid 19 early stages.

Methods

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. Demographic and clinical characteristics such as age, gender, and length of hospitalization were obtained from the digital records of participants. Biochemical, hormonal, and hematological parameters of these patients 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. Due to the retrospective and anonymous nature of the study, written consent from the participants was waived. Participants were divided into living and deceased groups. All patients were followed up daily until discharge or death. All study procedures were according to the principles of the 1964 Helsinki Declaration and the subsequent 2013 amendment.

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 IBM SPSS V23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). The significance level was taken as $p < 0.05$.

Results

Table 1 shows the comparison results of biochemical, hormonal, and hematological parameters of participants in living and deceased groups. As shown in **Table 1** , WBC, neutrophils, and monocytes were significantly different in the two groups ($p < 0.001$), and its values were lower in the living group than in the deceased group. Lymphocytes were significantly different between the two groups ($p < 0.001$) and were higher in the living group than in the deceased group. Hb and PLT were also significantly different ($p = 0.043$ and $p < 0.001$) in the two groups and were lower in the living group than the deceased group. MPV median values do not differ according to prognosis ($p = 0.994$). While the median value was 9.9 in the survivors, it was obtained as 10 in the deceased.

RDW, CRP, and glucose were significantly lower in the living group than in the deceased group ($p < 0.001$). Alb and Ca values were significantly higher in the live group than in the deceased group ($p < 0.001$). K ($p = 0.019$), LDH ($P < 0.001$), and UREA ($P < 0.001$) were significantly lower in the living group than in the deceased group. Na was significantly higher in the living group than in the deceased group ($P = 0.011$). Creatinine, Procalcitonin, Ferritin, and the number of hospitalization days in living patients were significantly lower than in patients who died ($p < 0.001$). Finally, median values of D-dimer (mg / L) differ according to prognosis ($p < 0.001$). While the median value was 0.63 in the survivors, it was found as 4.38 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 2** .

As **Table 2** shows, increasing age increases the risk of death by 1.044 ($p < 0.001$). The risk of death in men is 2,242 times higher than in women ($p < 0.001$). An increase in WBC value increases the risk of death by 1,335, while an increase in neutrophils increases the risk of death 1.4 times ($p < 0.001$). 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 ($p > 0.05$).

Median age values differ according to the groups ($p < 0.001$). While the median age for the survivors was 69 years, it was determined as 74 years for those who died (**Table 3**). 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 rate of death in females is 32%, it is 51.3% in males, and there is a statistically significant difference between these rates ($p < 0.001$).

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. 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 living groups.

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. Zhong et al. showed in their study that

higher MPV levels could be associated with a higher risk of pneumonia in Covid-19 patients. In another study, Lippi et al. 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 et al. studied the role of MPV and D-Dimer in predicting disease severity in a study of children with Covid-19 (13-15). 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. examined the MPV role in predicting the prognosis of Covid-19 disease (16). 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. The reason for this discrepancy in the results may be 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 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 (17,18).

Low D-Dimer concentrations can be used to diagnose vascular thrombotic such as pulmonary embolism and Deep Vein Thrombosis (DVT). In other words, increasing the amount of D-Dimer indicates the activity of the coagulation process followed by fibrinolysis (19). 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 as a pulmonary infection activating the coagulation system (20).

In Covid-19, D-Dimer increases in parallel with CRP, and unlike the classic DIC due to bacterial infection, there is a slight increase in PT and PTT and moderate thrombocytopenia in Covid-19 patients (Platelets [?] 100x10ˆ9/L). Several studies in Wuhan, China, have shown that an increase in D-Dimer in Covid-19 patients is associated with increased mortality (21-23). Although anticoagulants were not commonly used in these studies, observations suggest that patients receiving anticoagulants indicate lower D-Dimer levels (24).

There is still no agreement among researchers on using D-Dimer values in the management and monitoring of Covid-19 patients. Based on experience in Covid-19 patients, a D-Dimer value of cut-off $> 1\mu g/ml$ 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 (23). The D-Dimer level is directly related to the severity of the disease, the area of lung involvement identified on CT, and the oxygen index. Our results are consistent with these findings, in which the median and mean level of D-Dimer was significantly higher in patients who did not survive (25).

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 (19). 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 (17,18). 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 (26,27).

New Guidelines published by the IFCC emphasize the considering D-Dimer in Covid-19 patients. Studies 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, Disseminated Intravascular Coagulation (DIC) can occur (23). In one study, 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 showed that Covid-19 patients with D-Dimer [?] 2.0 µg/ml have a higher mortality rate than lower doses (28).

In terms of risk factors, studies to date 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 next three days. Studies 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 is also shown that mortality in patients with D-Dimer levels higher than 1µg/ml will be higher (17,18).

In one study, 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 also increase the thrombosis risk. These increase D-Dimer and increase 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 (29).

In conclusion, our findings in line with previous findings highlight the significant association of D-Dimer in patients with severe Covid-19 and the importance of monitoring it in patients 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 have reported this relationship with different results, which indicates the influence of other factors on this parameter and requires more detailed studies. One of the limitations of this study was the lack of consideration for BMI and common comorbidities affecting hematological parameters. Future studies should consider additional parameters related to hematological factors to elucidate further the association of MPV with Covid-19 severity and mortality.

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Tables

Table 1: Comparisons according to groups

	Living (n = 245)	Living (n = 245)	Deceased (n = 179)	Deceased (n = 179)	P1
	Median (min-max)	Mean ± s. Deviation	Median (min-max)	Mean ± s. Deviation	
WBC	5.5 (1.9 - 76.2)	5,92 ± 4,98	9.63 (1.54 - 41.68)	11.54 ± 7.12	**<0.00**
Neutrophil	3.9 (1.2 - 69.9)	4.36 ± 4.65	8.11 (0.73 - 39.98)	9.92 ± 6.62	**<0.00**
Lymphocyte	1.1 (0.2 - 22.7)	1.28 ± 1.56	0.84 (0.1 - 18.36)	1.12 ± 1.78	**<0.00**
Monocyte	0.3 (0.05 - 6)	0.37 ± 0.52	0.4 (0 - 2.29)	0.46 ± 0.33	**<0.00**
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	**<0.00**
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	**<0.00**
Alb	42 (29 - 51)	41.67 ± 3.73	30 (18 - 41)	29.46 ± 4.62	**<0.00**
CRP (mg / L)	19.8 (2 - 313.5)	44.94 ± 57.81	147 (2 - 350)	147.43 ± 84.35	**<0.00**
Glucose	116 (73 - 387)	132.93 ± 52.81	149 (73 - 914)	192.83 ± 120.13	**<0.00**
Ca	8.7 (3.8-12.2)	8.59 ± 0.73	8 (5.6 - 10.1)	8.03 ± 0.6	**<0.00**
LDH	257 (23 - 1137)	275.14 ± 111.94	411 (110 - 13712)	536.73 ± 1023.12	**<0.00**
K	4.2 (2.8 - 101)	4.64 ± 6.23	4.33 (2.21 - 460)	9.42 ± 47.72	**0.019**
Na	137 (66 - 4137)	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	**<0.00**
Creatinine	0.9 (0.6 - 7.1)	1.03 ± 0.55	1.27 (0.61 - 103)	2.05 ± 7.65	**<0.00**
Procalcitonin (ng / ml)	0.05 (0 - 0.83)	0.08 ± 0.11	0.32 (0.01 - 38)	1.28 ± 3.47	**<0.00**
Ferritin (ng / ml)	123.9 (4.5 - 1650)	214.67 ± 292.28	537 (19 - 2826)	766.06 ± 641.36	**<0.00**
D-dimer (mg / L)	0.63 (0.17 - 96)	1.95 ± 7.51	4.38 (0.91 – 15. 93)	13.15 ± 26.17	**<0.00**
Hospitalization days	7 (1 - 26)	8.05 ± 3.85	10 (2 - 94)	13.83 ± 12.29	**<0.00**

[one]Mann Whitney U test

Table 2 . Examination of risk factors affecting death

	OR (95% CI)	p
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**

	OR (95% CI)	p
Hospitalization days	1.133 (1.088 - 1.18)	**<0.001**
PCR (+)	2.263 (0.2 - 25.565)	0.509

Table 3. Demographic characteristics

	Living (n = 245)	Living (n = 245)	Deceased (n = 179)	Deceased (n = 179)	P
	Median (min-max)	Mean ± s. Deviation	Median (min-max)	Mean ± s. Deviation	
Age	69 (21-94)	66.62 ± 13.75	74 (38-93)	72.96 ± 10.29	**<0.001a**
Gender	n	%	n	%	
Female (n = 200)	136	68	64	32	**<0.001b**
Male (n = 224)	109	48,7	115	51,3	

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