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Correlation of Mean Platelet Volume with D-dimer in Patients with COVID-2019

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ABSTRACT

SARS-CoV-2 binds to ACE2 receptors and causes endothelial injury. Endothelial injury causes the release of tissue factors and triggers the activation of the coagulation cascade, which is characterized by an increase in D-dimer levels. The increase in D-dimer levels reflects the activation of coagulation and fibrinolysis. Endothelial injury leads to platelet adhesion and aggregation. Mean platelet volume is a low-cost, routinely performed parameter available in hematology analyzers at various health facilities. This study aimed to determine the correlation between MPV and D-dimer in COVID-19 patients. This study was an analytical study with a cross-sectional design conducted on 88 subjects aged 18-50 years from COVID-19 patients who were admitted at Dr. M. Djamil Central Hospital in May-September 2021. Mean platelet volume levels were measured using the impedance method and D-dimer levels using the ELISA method. Data were analyzed using the Pearson correlation test, significant if $p<0.05$. The mean age was 33.47 years, range of 18-50 years. Most of the subjects were female, 53 people (62.4%). The mean MPV level was 10.36 (0.87) fL. The mean D-dimer levels were 728.51 (500.99) ng/mL. Correlation analysis showed that mean platelet volume had a weak positive correlation with D-dimer ($r=0.269$, $p=0.013$). This study showed an increase in MPV and D-dimer levels in COVID-19 patients. There is a weak correlation between MPV and D-dimer in COVID-19 patients.

Keywords: Mean platelet volume, D-dimer, COVID-19

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infection caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) with an increasing number of cases and high mortality rates in various countries around the world.[1] The first case of COVID-19 was found in a pneumonia patient in Wuhan, China in December 2019 who was identified as the newly β-Coronavirus.[2] Data from the World Health Organization (WHO) on September 28, 2021, shows that there are 231,703,120 confirmed cases and 4,746,620 deaths worldwide.[3] Total confirmed cases of COVID-19 in Indonesia based on data from September 28, 2021, were 4,209,403 cases with 141,585 deaths. The total number of cases confirmed in West Sumatra Province up to September 28, 2021, was 89,155 cases with 2.37% deaths.[4]

The characteristics of COVID-19 in some patients are the occurrence of severe complications within a short time after infection, such as Acute Respiratory Distress Syndrome (ARDS) or Disseminated Intravascular Coagulation (DIC), sepsis followed by organ failure, and death.[5-7] Patients with ARDS due to COVID-19 are at risk for life-threatening thrombotic complications.[8,9] The initial hypothesis proposed regarding the occurrence of thrombosis is thought to be due to a very high inflammatory response that causes thrombo-inflammation, through mechanisms such as cytokine storm, complement activation, and endothelium dysfunction.[10] Other additional risk factors for thrombotic events in COVID-19 include old age (>65 years), obesity, cancer, pregnancy, heart failure, and a previous history of thromboembolism.[11] Thrombotic events can also occur in severe COVID-19 patients who have no previous risk factors.[12]

The risk of thrombosis can be assessed by examining D-dimers, which are peptide fragments derived from the plasmin-mediated degradation of cross-linked fibrin. The D-dimer examination is used to assess the activation of coagulation and fibrinolysis.[13-16] Data indicated that coagulation disorders, particularly increased levels of very high levels of D-dimer are found in patients who died due to pneumonia caused by COVID-19.[17] Naymagon *et al.* in the United States found an increase in D-dimer levels of more than 1,000 ng/mL as a predictor of poor prognosis in COVID-19 patients.[18] D-dimer on the admission of more than 2,000 ng/mL

or a fourfold increase can effectively predict mortality of COVID-19 patients in the hospital.[19]

The Mean Platelet Volume (MPV) is the average volume of circulating platelets that describes the state of stimulation and platelet production.[20] The SARS-CoV-2 virus can cause liver damage, presumably through a viral binding mechanism to Angiotensin Converting Enzyme 2 (ACE2) found in cholangiocytes. This leads to cholangiocyte dysfunction and the induction of a systemic inflammatory response.[21] Liver damage will affect the production of thrombopoietin, which plays a role in the megakaryocyte maturation process.[20]

Taha *et al*. found a significant correlation between MPV and D-dimer levels in COVID-19 patients (r=0.454; p<0.01). Taha *et al*. found evidence that MPV reflects platelet activation, and activation of the coagulation cascade and plays a major role in the development of acute renal failure in COVID-19 infection.[22] Another study was conducted by Nugraha *et al.* regarding the relationship between several platelet index parameters and the severity of COVID-19. Nugraha *et al.* examined MPV and D-dimer levels and their correlation with the severity of COVID-19. The results obtained was there is a correlation between MPV and D-dimer levels with the severity of COVID-19, with an r=0.28 (p=0.002) and r=0.81 (p<0.001) respectively, but there was no significant correlation between MPV and D-dimer levels (p=0.176).[23]

The MPV is one of the hematological parameters available in the hematology analyzer and is widely used by health facilities. Mean platelet volume checks are inexpensive and routinely performed. The number of MPV studies on COVID-19 is fewer compared to studies on D-dimer. The objective of this study is to evaluate MPV levels and their correlation with D-dimer in COVID-19 patients.

METHODS

This study was an analytical study with a cross-sectional design. The study was conducted at Dr. M. Djamil General Hospital from May-September 2021. This research received permission from the Health Research Ethics Committee of Dr. M. Djamil General Hospital No.197/KEPK/2021. The study population was COVID-19 patients treated at Dr. M Djamil Hospital who met the inclusion and exclusion criteria. Inclusion criteria age 18-50 years. The exclusion criteria were those who have a history of cardiac disease, stroke, thyroid disease, hematology disease (ITP, aplastic anemia, leukemia), liver disease, renal disease, type 2 diabetes mellitus, hypertension, dengue hemorrhagic fever, any form of malignancy, post-surgery or trauma, post-splenectomy, pregnancy, and post thrombocyte transfusion in <24 hours since admitted. The study was conducted on 88 subjects. The parameters studied were MPV and D-dimer. Quality control was carried out before the tests. Mean platelet volume calculation used the Sysmex XN-1000 automatic hematology analyzer indirectly, using the results of the calculation of plateletcrit (%) divided by the number of platelets (mm^3) multiplied by 107. Plateletcrit and platelets were examined using the impedance principle, which measures the change in the electrical resistance of the cell at a small aperture when the cell passes through the gap. The MPV reference value is 8-10 fL. The D-dimer examination used the ELISA method in Biomerieux VIDAS. The principle of the examination was to combine the two-step enzyme sandwich immunoassay method with the final detection using fluorescence (ELFA). A Solid Phase Receptacle (SPR) is a solid phase coated with monoclonal immunoglobulin. The reference value for D-dimer for ages <50 years is <500 ng/mL. Normality was tested using the Kolmogorov-Smirnov test. The Pearson correlation test was used to determine the correlation between MPV and D-dimer in normally distributed data. Results were statistically significant when p<0.05.

RESULTS AND DISCUSSIONS

The subject characteristics can be seen in Table 1. Most of the subjects were female (62.4%) and the average age was 33.47 years. Subjects experienced increased MPV levels (55.3%) and increased D-dimer levels (63.5%).

Table 1. Subject characteristics

Variable	f (%)	Mean (SD)
Gender		
Male	32 (37.6)	
Female	53 (62.4)	
Age (year)		33.47 (7.61)
MPV level (fL)		
Normal	38 (44.7)	
Increased	47 (55.3)	
D-dimer level (ng/mL)		
Normal	31 (36.5)	
Increased	54 (63.5)	

Bauer *et al.* found that the risk of being infected with COVID-19 increased with age per 10 years.[24] Different results were obtained in several studies. The study by Li *et al*. on 425 COVID-19 patients found

that 56% of these patients were male.[25] Zhang *et al.* who studied 140 COVID-19 patients also found that as much as 50.7% of study subjects were male.[26] Males have a greater risk of infection than females.[27] Viral infections show a higher incidence of cases in males.[28] This is presumably because SARS-CoV-2 attacks cells through the same receptor, namely ACE2. Increased expression of ACE2 receptor protein in certain organs correlates with specific organ failure. This is indicated by certain clinical parameters in SARS-CoV-2 patients. Circulating ACE2 levels are higher in male patients, compared to females; and higher in patients with diabetes or cardiovascular disease.[29]

The mean MPV level in this study was 10.36 (0.87) fL with the lowest level being 8.8 fL and the highest level 12.6 fL. This means the MPV level exceeds the normal reference value (8-10 fL) (Table 2). The mean MPV level is also higher than Nugraha *et al.* who found MPV levels in COVID-19 patients to be 10.27 (0.92) fL.[23]

Table 2. Mean value of MPV dan D-dimer level in COVID-19 patients

Variable	Mean (SD)
MPV level (fL)	10.36 (0.87)
D-dimer level (ng/mL)	728,51 (500,99)

Other studies on MPV in COVID-19 generally discussed differences in MPV levels in severe COVID-19 cases. Güçlü *et al.* studied oxygen saturation on the first day of treatment and also compared MPV levels on the first and third days of treatment in adult COVID-19 survivors and non-survivors.[30] Gumus *et al.* compared MPV levels and lymphocyte counts in 55 children with asymptomatic COVID-19 and 60 healthy children. This study found higher MPV levels in asymptomatic pediatric COVID-19 patients.[31]

Platelets play an important role in hemostasis. A recent study has discovered that platelets have a role in inflammation and immune system regulation. Platelets can bind to infectious pathogens, secrete a variety of proinflammatory cytokines and chemokines, and express receptors for various regulatory functions and immune effects.[32] Mean platelet volume has been determined as a marker platelet activation in the inflamatory process.[32,33] Mean platelet volume levels indicate the average size of circulating platelets and describe the stimulation and production of platelets.[34] The SARS-CoV-2 virus can cause damage to various organs, one of which is the liver. The mechanism of liver damage is thought to be due to viral binding to ACE2 receptors present in cholangiocytes causing cholangiocyte dysfunction and induction of systemic inflammatory responses.[21] Liver damage will affect the production of thrombopoietin and interfere with the megakaryocyte maturation process.[20]

The mean D-dimer level in this study was 728,51 (500,99) ng/mL with the lowest level at 149 ng/mL and the highest level at 2,534 ng/mL. The mean D-dimer level in this study exceeds the normal reference value (<500 ng/mL) (Table 2) and is lower than the study conducted by Nugraha *et al.* who found moderate levels of D-dimer in COVID-19 patients of 1,180.51 ng/mL with a range of D-dimer levels of 198-4,037 ng/mL.[23]

Al Mutair *et al*. studied the clinical, epidemiological, and laboratory characteristics of mild and moderate COVID-19 patients in Saudi Arabia. Al Mutair *et al.* found an increase of D-dimer occurring in COVID-19 patients in which D-dimer levels were higher in moderate patients compared to mild patients (690 vs. 570 mg/L).[35] Increased D-dimer levels were associated with the incidence of coagulopathy in the pathophysiology of COVID-19.[23] Increased D-dimer levels trigger thrombotic complications due to hyperactivation of the coagulation cascade. The systemic inflammatory response triggered by a viral infection can cause an imbalance between anticoagulant and procoagulant homeostatic processes.[36]

It can be seen in Table 3 that there is a correlation between MPV levels and D-dimer in COVID-19 patients ($p<0.05$).

Table 3. Correlation of MPV and D-dimer level in COVID-19 patients

Variable	R	P
MPV level (fL) D-dimer level(ng/mL)	0.269	0.013*

*Pearson correlation test

Table 3 and Figure 1 show a weak positive correlation (r=0.269).

Studies about the correlation of MPV levels with D-dimer in COVID-19 patients in the productive age are still rare. Other studies that described this correlation had different study subjects. Taha *et al.* identified laboratory parameters that correlate with D-dimer levels, one of which is MPV in COVID-19 patients who are at risk for Acute Kidney Injury (AKI) upon admission to the ICU. D-dimer levels were significantly increased in these patients.[22] Different study results were obtained by Nugraha *et al.* who examined the relationship between MPV and the

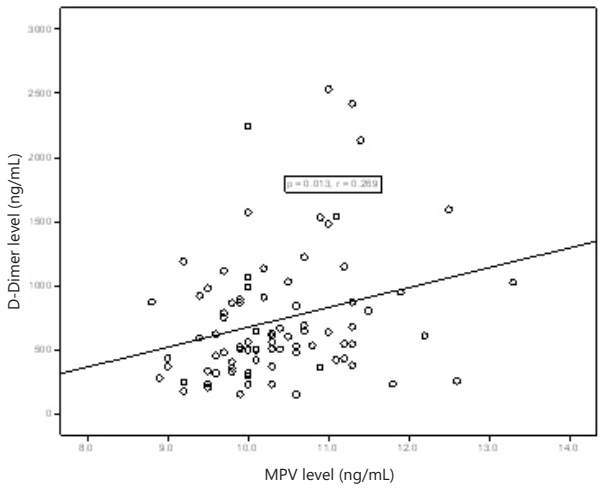

Figure 1. Scatter diagram of a correlation between MPV with D-dimer in COVID-19 patients

severity of COVID-19 on 123 subjects. Nugraha *et al.* found a correlation between MPV and D-dimer levels with the severity of COVID-19, with r=0.28 (p=0.002) and r=0.81 (p<0.001) respectively, but there was no significant correlation between MPV and D-dimer levels (p=0.176).[23]

The increase in MPV in COVID-19 is expected to provide an early warning to clinicians that patients have a risk of thrombosis, especially in patients with comorbidities. Increased D-dimer levels are associated with the incidence of coagulopathy in the pathophysiology of COVID-19.[23] This coagulopathy process causes an increase in D-dimer levels secondary to an increase in the formation of thrombin and fibrinolysis.[37] Another mechanism that plays role in the increase of D-dimer is the direct effect of lung injury in COVID-19. Acute lung injury is characterized by intra-alveolar fibrin deposition, which triggers alveolar epithelial cells to produce urokinase to limit fibrin deposition by converting plasminogen to plasmin and then breaking down fibrin deposits. The degree of lung injury is directly proportional to the severity of the disease, which will increase D-dimer levels.[38]

This study found a weak positive correlation (r=0.269) between MPV and D-dimer in COVID-19 patients. The SARS-CoV-2 virus binds to ACE2 and causes endothelial damage. Endothelial damage causes the release of tissue factors and triggers the activation of the coagulation cascade, which is characterized by an increase in D-dimer. Endothelial damage leads to platelet adhesion and aggregation. The use of platelets increases so that it triggers the production of platelets in the bone marrow and the release of immature platelets in the circulation, which is characterized by an increase in MPV.

CONCLUSIONS AND SUGGESTIONS

This study showed that both MPV and D-dimer have an increased value in COVID-19 patients. There is also a correlation between MPV and D-dimer in patients with COVID-19.

Further studies are needed to evaluate the correlation between MPV and D-dimer in patients with COVID-19 by including lipid profile tests and differentiating the severity of the disease based on WHO criteria. The parameter of MPV can be used alongside D-dimer for better treatment of COVID-19.

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