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Original Research Article

The relation between mean platelet volume and platelet distribution width to COVID-19 severity

I. Kadek Aditya Nugraha[1]*, Kadek Surya Atmaja[2], Ketut Suryana[1], Wayan Wahyu Semara Putra[2]

[1]Department of Internal Medicine, Wangaya Regional Hospital, Denpasar, Bali, Indonesia
[2]Department of Pulmonology and Respiratory Medicine Wangaya Regional Hospital, Denpasar, Bali, Indonesia

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***Correspondence:**
Dr. I. Kadek Aditya Nugraha,
E-mail: kadek_adityanugraha@yahoo.com

ABSTRACT

Background: Wide spectrum of clinical manifestation and severity of COVID-19 led to further studies to find a simple biomarker used to predict the severity of COVID-19. We investigated the role of mean platelet volume (MPV) and platelet distribution width (PDW), widely available parameters, as predictor of COVID-19 severity.
Methods: We conducted a single center analytic observational study to evaluate the relationship between MPV and PDW values and COVID-19 severities. A total of 123 subjects of COVID-19 within October to December 2020 included in the analysis.
Results: Analysis showed a statistically significant difference in MPV, PDW, and D-dimer between COVID-19 severities ($p<0.001$, $p=0.002$, and $p<0.001$). Correlation coefficient between MPV, PDW, and D-dimer with COVID-19 severity were 0.28 ($p=0.002$); 0.22 ($p<0.001$), and 0.81 ($p<0.001$), but there's no correlation between MPV ($p=0.176$) and PDW ($p=0.383$) with D-dimer. The AUC value of the ROC curve of MPV, PDW and D-dimer in predicting severity was 79% ($p=0.001$, 95% CI: 0.696-0.885), 72.5% ($p<0.001$, 95% CI: 0.598-0.852), and 97% ($p<0.001$, 95% CI: 0.937-1.00).
Conclusions: This study found a relationship between MPV and PDW values on the severity of COVID-19. There's no relationship of MPV and PDW to D-dimer concentration.

Keywords: MPV, PDW, D-dimer, COVID-19

INTRODUCTION

In the late 2019, there's a new outbreak of viral pneumonia in Wuhan, China which genetically related to severe acute respiratory syndrome coronavirus (SARS-CoV-2) outbreak in 2002. The novel coronavirus then identified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and its disease named as coronavirus disease 2019 (COVID-19). Due to its rapid and wide transmission, the WHO declared COVID-19 as a pandemic in March 11th 2020.[1]

As January 28th 2021, there are 100,200,107 confirmed case with 2,158,761 (2.15%) mortality worldwide. The spectrum of clinical manifestation in COVID-19 is wide, most common symptoms including fever, dry cough, fatigue, and some can present with productive cough, sore throat, shortness of breath, headache, myalgia/arthralgia, chill, nausea and vomiting, ageusia, anosmia, nasal congestion, diarrhea, abdominal pain, and various non-specific systemic manifestations.[2] Most patient presented with mild-to-moderate severity, but some patients presented with severe symptoms even progressed to critical state manifested as respiratory failure, septic shock, or multiple organ failure in short time. Patients with severe and critical symptoms have worse prognosis and

highest mortality rate.[3] Early recognition with accessible, widely available, and inexpensive laboratory test which can predict severity of COVID-19 patients is important in patient triage and allocating resource in patients treatment.

Platelet is mostly recognized as its role in hemostasis. Recent studies discovered role of platelet in inflammation and immune system regulation. Platelet can carry infectious pathogen, secretes proinflammatory cytokines and chemokines, and expresses various receptor involved in immune regulation. Mean platelet volume (MPV) has been determined as marker of platelet activation in inflammatory process.[4,5] Changes in MPV will directly influence platelet distribution width (PDW) which indicate variation of platelet size. MPV and PDW value are readily available as platelet parameter in complete blood count, and this examination is routinely done in patients with COVID-19. In this study, we aimed to assess the role of MPV and PDW, a widely available and routinely performed test, as predictors of disease severity in COVID-19.

METHODS

This was a single center analytic observational study conducted in Wangaya General Hospital. This study was approved by the Ethics Committee of Wangaya General Hospital with an approval. Patient diagnosed with COVID-19 from October 2020 to December 2020 were enrolled by total sampling. Patients aged 18 years old or older confirmed with COVID-19 by Real-time polymerase chain reaction (RT-PCR), without existing chronic hepatitis, cirrhosis, malignancy, and pregnancy were included. Complete blood count is performed routinely within examination in emergency department on patients who assessed with suspect COVID-19. Oro-nasopharyngeal swab is taken at the same time for RT-PCR analysis to confirm the diagnosis. D-dimer test then routinely performed within a day after diagnosis confirmed by RT-PCR.

Patients' severity is classified as mild, moderate, severe, and critical based on WHO guideline. In this study analysis, patient's severity categorized as mild, moderate, and severe-critical. Patient's age categorized as 18-60 years and more than 60 years group. Co-morbidity is defined as pre-existing chronic disease occurred in the patients, such as diabetes mellitus, cardiovascular disease, hypertension, chronic obstructive pulmonary disease, and chronic kidney disease. Statistical analysis to evaluate the relationship between MPV, PDW, and D-dimer to disease severity of COVID-19 were performed using SPSS version 25.0. The AUC value of the ROC curve for the value of MPV, PDW and D-dimer in predicting disease severity, respectively.

RESULTS

A total of 123 subjects of COVID-19 within October to December 2020 were included in the analysis. Majority of the patients aged between 18-60 years (79.7%). Male patients slightly higher (54.5%) compared with female (45.5%). Most patient admitted with moderate severity (54.5%), then mild (25.2%), and severe (20.3%) at presentation. Co-morbidity presented by the patients are diabetes mellitus (16.3%), Hypertension (13.8%), coronary vascular disease (8.1%), chronic kidney disease (8.1%), and chronic pulmonary disease (2.4%). Mortality rate of admitted patients are 9.8% in this period. Mean value of MPV and PDW based on complete blood count examination were 10.05 (6.8-12.9) fl and 11.44 (7.6-20.2) fl subsequently. Mean concentration of D-dimer was 1941.27(107-12224) ng/ml. The characteristics of this study subjects is presented in Table 1.

Table 1: Baseline charasteristics of the study.

Characteristics	N (%)
Age (years)	
18-60	98 (79.7)
>60	25 (20.3)
Sex	
Male	67 (54.5)
Female	56 (45.5)
Severity	
Mild	31 (25.2)
Moderate	67 (54.5)
Severe-critical	25 (20.3)
Co-morbidity	
Diabetes mellitus	
Yes	20 (16.3)
No	103 (83.7)
Hypertension	
Yes	17 (13.8)
No	106 (86.2)
Coronary vascular disease	
Yes	10 (8.1)
No	113 (91.9)
Chronic kidney disease	
Yes	6 (4.9)
No	117 (95.1)
Chronic pulmonary disease	
Yes	3 (2.4)
No	120 (97.6)
Outcome	
Discharge	111 (90.2)
Death	12 (9.8)
MPV (fl)	10.05 (6.8-12.9)
PDW (fl)	11.44 (7.6-20.2)
D-dimer (ng/ml)	1941.27 (107-12224)

Kolmogorov-Smirnoff normality test performed to analyzed data distribution of MPV, PDW, and D-dimer. Only MPV distributed normally (p=0.2), contrary with PDW (p=0.007) and D-dimer (p<0.001).

One-way analysis of variance (ANOVA) of MPV within disease severity shown statistically significant value (p<0.001), while Kruskal-Walis test of PDW and D-dimer

within disease severity also shown significant value (p=0.002 and p<0.001). MPV and PDW value found to be lower, 9.308±0.79 fl and 10.596 (8.2-20.2) fl, in severe COVID-19 than mild to moderate COVID-19. D-dimer concentration is found to be progressively increasing from mild (mean=351.19), moderate (mean=1180.51), to severe (5951.80) COVID-19 (Table 2 and Figure 1).

Correlation coefficient between MPV, PDW, and D-dimer with COVID-19 severity were 0.28 (p=0.002); 0.22 (p<0.001), and 0.81 (p<0.001) subsequently. Contrary to this result, there's no statistically significant correlation between MPV (p=0.176) and PDW (p=0.383) value with D-dimer concentration in this COVID-19 subjects. ROC curve analysis than performed between MPV, PDW, and D-dimer with COVID-19 severity. Disease severity than further classified into non-severe and severe to establish the analysis.

ROC curve of MPV with disease severity resulted in 79% AUC (p=0.001, 95% CI: 0.696-0.885). The best cut-off value to predict MPV with disease severity was 9.95 fl with 76.0% sensitivity and 64.3% specificity.

Analysis of PDW with disease severity resulted in 72.5% of AUC (p<0.001, 95% CI: 0.598-0.852), with best cut-off value predicting COVID severity with PDW value was 10.75 fl (76% sensitivity and 63.3% specificity.

Lastly, analysis of D-dimer with disease severity resulted in 97% of AUC (p<0.001, 95% CI: 0.937-1.00), with best cut-off value of D-dimer was 1391.5 ng/ml (96% sensitivity and 80.6% specificity). The ROC curve of MPV, PDW and D-dimer with COVID-19 severity shown in Figure 2.

Table 2: Comparison of MPV, PDW, and D-dimer based on COVID-19 severity.

Disease severity	Mean MPV (fl)	Mean PDW (fl)	Mean D-dimer (ng/ml)
Mild	10.158±0.87	11.484 (8.3-15.6)	351.19 (107-1490)
Moderate	10.274±0.92	11.730 (7.6-18.6)	1180.51 (198-4037)
Severe-critical	9.308±0.79	10.596 (8.2-20.2)	5951.80 (848-12224)
P value	<0.001	0.002	<0.001

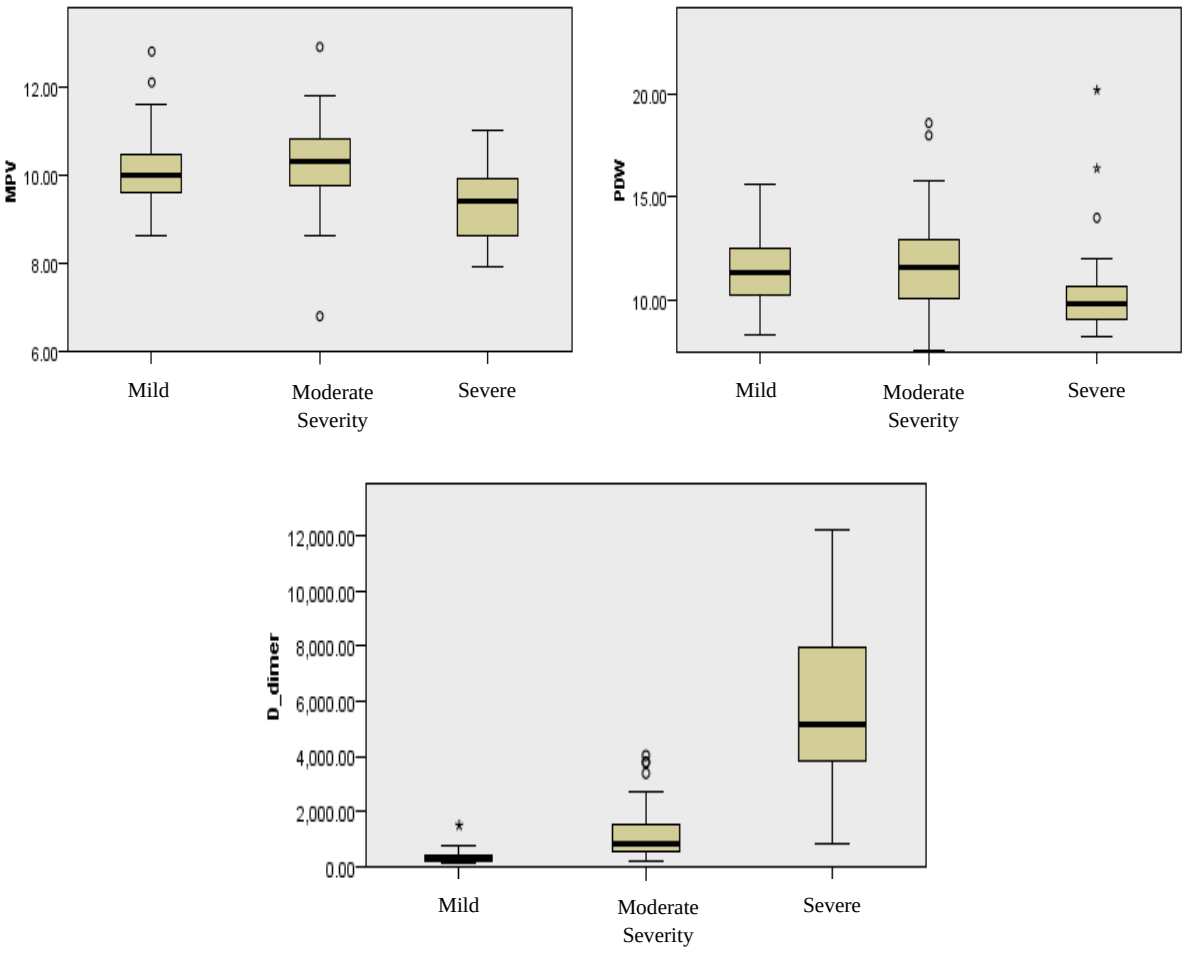

Figure 1: Mean MPV, PDW, and D-dimer by COVID-19 severity.

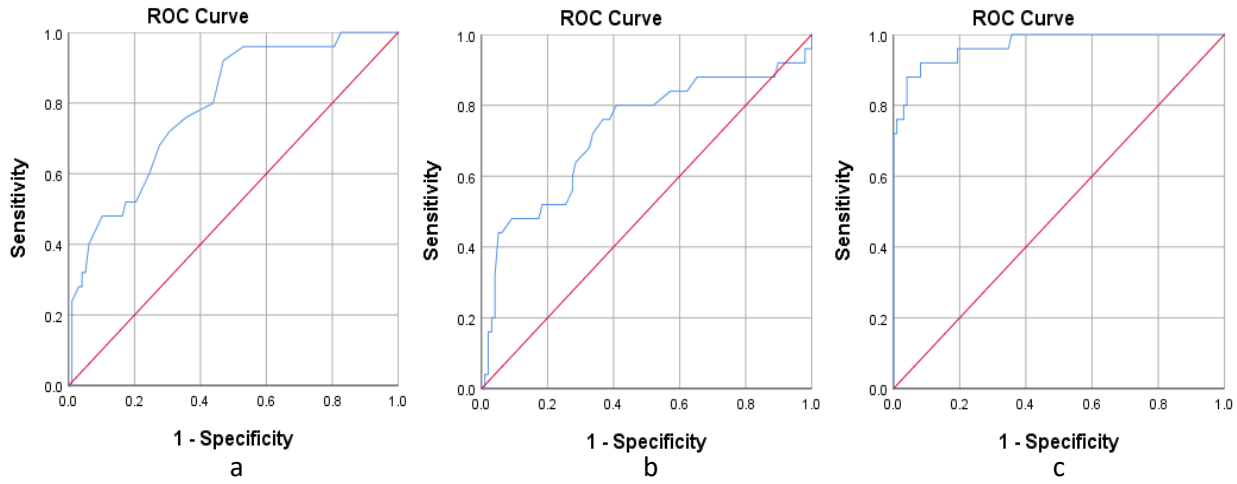

Figure 2: ROC curve of (a) MPV; (b) PDW; and (c) D-dimer with COVID-19 severity.

DISCUSSION

Inflammatory response against SARS-CoV-2 has major role in pathophysiology of COVID-19. Immunological studies shown a high increase of proinflammatory cytokine, known as cytokine storm, is important process in severe COVID-19 cases. Dysregulated, significant increase of proinflammatory cytokine elicit massive inflammatory response that can provoke Acute respiratory disstress syndrome (ARDS) and multiorgan failure which responsible in mortality of COVID-19 patients.[6] Multiple studies have been conducted to look at the role of platelet in inflammation, specifically role of platelet in COVID-19 pathophysiology.[7]

Platelets are the result of fragmentation of megakaryocytes in the bone marrow which will undergo activation in the inflammatory process. Activated platelet will change its shape from discoid into spherical with pseudopodia formation and secreting preformed granule which contain various immune system mediators and proinflammatory molecules. Activated platelets can then interact with leucocytes and endothelial cells directly with contact dependent mechanism or indirectly through immune mediator mechanism.[8] MPV and PDW is routinely evaluated in complete blood count examination. Changes in the MPV value are related to platelet activity so that it can be used as a marker of platelet activity in inflammation. Changes in MPV due to platelet activation in the inflammatory process will directly affect PDW. PDW describes the variation in platelet size.[9]

Studies on COVID-19 patients have reported increased secretion of cytokines [IL-1α, IL-1β, IL-1RA, IL-4, IL-10, IL-13, IL, 17, IL-27, IFN (interferon) -α, and IFN-γ] and chemokines (MCP-1/CCL2) by platelets in COVID-19 patients. The increased secretion of thrombocyte cytokines and chemokines plays a role in local and systemic inflammation, so that it will trigger and aggravate cytokine storm conditions which correlate with the patient's clinical worsening.[10] Rampotas and Pavord found higher MPV in severe COVID-19 (10.65 fl) compared with mild-moderate COVID-19 (10.3 fl). Peripheral blood examination found an increase in dense granule, large proplatelet fragments, and large platelet aggregates in severe COVID-19 patients.[11] Similar findings also reported by Guçlu et al, which found increased MPV (9.85±1.79 vs 9.38±1.42 fl, p=0.04) in severe COVID-19 compared to mild-moderate COVID-19.[12]

In contrast to previous studies, this study found a lower MPV and PDW value in severe COVID-19. The decrease in MPV value in this study can occur through several mechanisms. The inflammatory process will affect the MPV value, either increasing or decreasing, due to the influence of pro-inflammatory cytokines on platelets and bone marrow. Platelet activation will change the shape of the platelets to become larger in size with the formation of pseudopodia. Stimulation of platelet formation by pro-inflammatory cytokines in the bone marrow will form younger and bigger platelets. These younger and larger platelets have more granules, more expression of adhesion molecules, and faster activation abilities.

These conditions will increase MPV and PDW in inflammatory condition. However, at a certain level, the MPV and PDW value can decrease due to the utilization of large activated platelets so that the remaining small platelets will decrease the MPV and PDW values. A decrease in the value of these parameters is also found in various acute conditions such as acute appendicitis and acute cholecystitis. In chronic conditions, decreased MPV and PDW values occur under conditions of increased inflammatory activity during reactivation. During active lung tuberculosis, MPV value is decreased which could be caused by defense reaction of platelet to inhibit pathogens spread by forming microthrombi in tuberculous cavities. Similar findings also occur in reactivation of chronic diseases such as ulcerative colitis, rheumatoid arthritis, and systemic lupus erythematous.[13,14] This study also found that an increase in D-dimer values was associated with the severity of COVID-19, but there's no significant

finding of correlation MPV and PDW with D-dimer elevation in COVID-19 subjects.

Recent meta-analysis also supports this finding. Lippi and Favaloro reported that D-dimer value was constantly higher in severe COVID-19 through studies included in the meta-analysis, with weighted mean difference of 2.97 mg/l (95% CI: 2.47-3.46 mg/l).[15] An increase in D-dimer value is associated with the incidence of coagulopathy in the pathophysiology of COVID-19. Coagulopathy in COVID-19 is characterized by prolonged prothrombin time (PT), increased activity of factor VIII and fibrinogen, von Willebrand factor (vWF) antigen and vWF collagen binding.

The process of coagulopathy in COVID-19 pathophysiology led to elevation of D-dimer secondary due to increase of thrombin formation and fibrinolysis.[10] Other mechanism contributed to elevation of D-dimer due to direct consequence of lung injury in COVID-19. In acute lung injury is characterized by intra-alveolar fibrin deposition. Intra-alveolar fibrin deposition will trigger alveolar epithelial cells to produce urokinase to limit fibrin deposition by converting plasminogen into plasmin, then cleaves fibrin deposits. The degree of lung injury directly proportional with disease severity, which then elevate D-dimer unidirectionally.[16]

There were some limitations to this study. This study only found an association between MPV and PDW on the severity of COVID-19, without being able to provide a causal explanation of the association. This limitation arised because the study design used a cross-sectional design. The next limitation in this study was the analysis of MPV and PDW values was only based on the results when the patient first came and was examined. It was necessary to carry out repeated and periodic evaluations during patient care because of the dynamics of the patient's condition and severity of infection during treatment.

CONCLUSION

Severity of COVID-19 infection is related to the degree of inflammatory response, known as cytokine storm, against SARS-CoV-2 infection. Several parameters have been studied to assess the degree of inflammation in COVID-19 as well as to predict its severity. Apart from having a major role in the hemostasis process, platelets also play a role in the inflammatory process and immune system regulation. MPV and PDW are platelet parameters in routine complete blood counts and are widely available. This study found a relationship between MPV and PDW values on the severity of COVID-19. Further studies are needed to assess both parameters dynamically and periodically during patient care and in the wider population.

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