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Characteristics of the platelet profile as a predictor of 30-day clinical outcome in ischemic stroke patients

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ABSTRACT

Objective. Investigate the relationship between platelet profiles, in this case PDW and MPV at hospital admission, which can be predictors of clinical outcome 30 days after ischemic stroke.

Methods. This research is an analytic study with a retrospective cohort method. Secondary data in the form of medical records at the neuro polyclinic of Bethesda Hospital Yogyakarta in 2019 - 2020. The number of subjects was 74, grouped as good outcome (mRS 0-2) and poor outcome (mRS 3-6). Data analysis used was t-test, Pearson's test, Fisher's test, ROC, and multivariable logistic regression model.

Results. In this study, both PDW (p = 0.982) and MPV (p = 0.174) were not significantly associated (p > 0.05) with poor outcomes on the chi-square test. ROC curve analysis showed that the PDW cutoff value was >11.1 fl [(Area Under Curve (AUC) ROC was 0.638, with 95% CI = 0.518-0.746, and p-value 0.835)] and the MPV cutoff value was ≤9,8 fl [(Area Under Curve (AUC) ROC was 0.521, with 95% CI = 0.402-0.639, and p-value 0.137)] which was also not statistically significant (p > 0.05). From these results, multivariable logistic regression analysis was performed which found that MPV ≤9,8 fl was associated with a small 30-day clinical outcome [(Odds Ratio (OR) = 0.110, 95% CI = 0.013-0.953, p = 0.007)]. While PDW >11.1 fl did not have a significant relationship after regression analysis was carried out where p > 0.05 was obtained.

Conclusion. Increased PDW and MPV values at hospital admission did not increase the risk of 30-day disability in ischemic stroke patients.

Keywords: ischemic stroke, PDW, MPV, disability

INTRODUCTION

Stroke is the second leading cause of death in the world, causing disabilities (second highest in developing countries and third highest in developed countries) and significant impact on the economy of those affected [1]. The prevalence of stroke cases increases with age in Indonesia. The prevalence in males is 11.0 per thousand compared to females at 10.9 per thousand. Stroke is also the leading cause of severe disabilities and total dependence in the elderly. BPJS (National Health Insurance) data shows that stroke costs will increase up to IDR 2.56 trillion in 2018 [2]. Yogyakarta province ranks second highest in stroke cases, with a prevalence of approximately 14.6 per thousand [3].

In cases of ischemic stroke, platelets play a role in the early phase of thromboemboli. Activated platelets will release thromboxane A2 and express glycoprotein Ib and IIb/IIIa receptors, which contribute to thrombosis and stroke. Platelet distribution width (PDW) and mean platelet volume (MPV) serve as indicators of platelet activation. PDW indicates the heterogeneity of platelet size, and an increase in PDW indicates platelet activation. MPV serves as a link between thrombosis and inflammation, where thrombosis can increase inflammation, while inflammation also contributes to thrombogenesis [4]. Based on this, PDW and MPV can be used as predictors of clinical outcomes in stroke patients.

METHODS

Patient characteristics

This study is an analytical study using a retrospective cohort method. The study was conducted at the

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neurology clinic of Bethesda Hospital Yogyakarta from January to June 2022. The data used in this study were secondary data in the form of medical records. The study was conducted based on ethical principles and followed ethical standards in research. This study has obtained ethical clearance from the Research Ethics Committee of Bethesda Hospital Yogyakarta with letter number 38/KEPK-RSB/II/22.

The inclusion criteria for the sample are: 1) male or female diagnosed with ischemic stroke based on World Health Organization (WHO) criteria and confirmed by brain computed tomography or Magnetic Resonance Imaging (MRI), 2) age >18 years old, 3) first-time stroke patients, 4) onset of hospital admission <24 hours after ischemic stroke, 5) non-referral patients, 6) have complete medical records and stroke registry at the hospital. The exclusion criteria for the study sample are: 1) patients with a history of permanent disability and/or speech disorders, 2) patients with a history of splenectomy, rheumatoid arthritis, peritonitis, history of malignancy, blood cell diseases, and autoimmune diseases, 3) discharged against medical advice, 4) patients who were not assessed with mRS score at 30 days after ischemic stroke, 5) deceased patients. The sample size calculation was performed using the hypothesis test formula for relative risk. The calculation was done using the openepi software accessed through https://www.openipi.com/SampleSize/SSCohort.htm, which resulted in a minimum sample size of 74.

Variables

The independent variable of this study was PDW and MPV. The dependent variable was disability 30 days post-ischemia stroke. In this study, the measurement of disability 30 days after ischemic stroke was measured using the modified Rankin Scale (mRS). The disability scores were divided into 2 groups; good outcome and poor outcome. The mRS score in the good outcome group was 0-2 and the mRS score in the poor outcome group was 3-6.

Statistical analysis

Statistical analysis was performed using SPSS version 23 and MedCalc® Statistical Software version 20.111. Differences in baseline characteristics and clinical outcomes between the two groups were compared using t-test for continuous variables, Pearson or Fisher's test for categorical variables. Receiver Operating Characteristics (ROC) was used to determine the optimal cutoff for PDW and MPV, as well as to calculate sensitivity and specificity of the cutoff value in predicting poor outcomes. Multivariable logistic regression model was used to identify the relationship between poor outcome and PDW, MPV, and other variables. Probability value p <0.05 was considered statistically significant.

RESULTS

Based on the selection criteria for inclusion and exclusion in the study, out of 151 available data, a total of 74 were used in this research. There were 65 patients (87.8%) in the good group, while there were 9 patients (12.2%) in the poor group. Basic characteristics and clinical conditions of the study population are presented in Table 1, with a mean age of 60.89 ± 11.348 (mean ± SD), and 47 (63.5%) patients were male. Nine (12.2%) out of 74 patients had a poor outcome.

The median of PDW in the total population was 11.2 fl, with an interquartile range (IQR) of 10.27-12.7 fl. The median of MPV in the total population was 9.9 fl, with IQR of 9.47-10.4 fl. Patients had a clear picture of the infarct location, with the majority of infarcts occurring in the supratentorial region (p <0.05). There were no other significant clinical parameters that differed between patients with good and poor outcomes.

In Figure 1, the PDW cutoff was found to be 11.1 fl, with PDW >11.1 fl resulting in a sensitivity of 66.67% and specificity of 49.23%. The Area Under

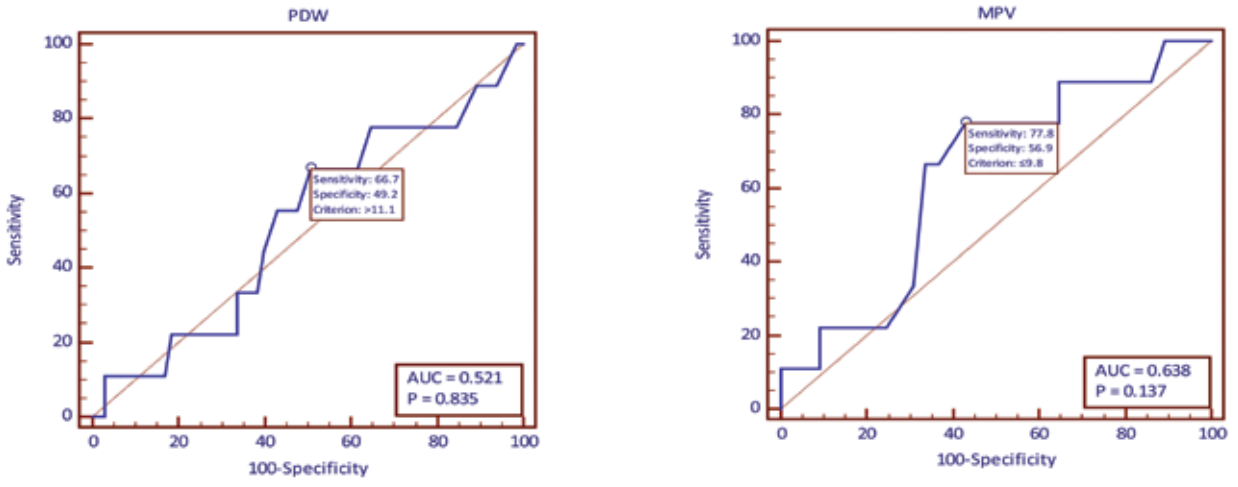

FIGURE 1. ROC curves of PDW and MPV in predicting adverse clinical outcomes

TABLE 1. Basic characteristics and clinical conditions of the subject

Characteristic	Total population (n=74)	mRS 0-2 (n=65)	mRS 3-6 (n=9)	p-value
Demographic data				
Age (years), mean (SD)	60,89 (11,348)	60,38 (11,16)	64,56 (12,66)	0,370
Gender, n (%)				1,000
Man	47 (63,5)	41 (63,1)	6 (66,7)	
Woman	27 (36,5)	24 (36,9)	3 (33.3)	
Komorbid, n (%)				
Hypertension	45 (60,8)	38 (58,5)	7 (77,8)	0,468
Heart disease	14 (18,9)	12 (18,5)	2 (22,2)	0,676
Trombositosis	1 (1,4)	1 (1,5)	0 (0)	1,000
DM	17 (23,0)	15 (23,1)	2 (22,2)	1,000
Dyslipidemia	1 (1,4)	1 (1,5)	0 (0)	1,000
Gastrointestinal bleeding	4 (5,4)	2 (3,1)	2 (22,2)	0,070
Hipokalemia	1 (1,4)	1 (1,5)	0 (0)	1,000
Parameters at admission				
NIHSS inisial, median (IQR)	6 (4-8)	5 (4-6,5)	11 (9-12,50)	0,840
GCS inisial, median (IQR)	15 (15)	15 (15)	15 (15)	-
Location of infarction, n (%)				0,001
Supratentorial	50 (67,6)	43 (66,2)	7 (77,8)	
Infratentorial	2 (2,7)	2 (3,1)	0 (0)	
Supra-infratentorial	2 (2,7)	0 (0)	2 (22,2)	
Unvisualized	20 (27,0)	20 (30,8)	0 (0)	
Laboratory tests				
PDW (fl), median (IQR)	11,2 (10,27-12,7)	11,2 (10,25-12,8)	11,1 (10,3-12,3)	0,982
MPV (fl), median (IQR)	9,9 (9,47-10,4)	9,9 (9,45-10,45)	9,9 (9,4-10,1)	0,174

Curve (AUC) of ROC was 0.521, with 95% CI = 0.518-0.746, and p-value of 0.835. Meanwhile, the MPV cut-off was 9.8 fl, with MPV ≤9.8 fl resulting in a sensitivity of 77.78% and specificity of 56.92%. The AUC of ROC was 0.638, with 95% CI = 0.402-0.639, and p-value of 0.137.

TABLE 2. Multivariable logistic regression analysis

Risk Factors	OR	95% CI	*p-value*
Gastrointestinal bleeding	25,695	1,637 – 403,345	0,021
MPV ≤9,8	0,110	0,013 – 0,953	0,045

The results obtained from the multivariate logistic regression analysis are presented in Table 2. After adjusting for existing confounders, there was a small relationship between MPV ≤9.8 fl and poor clinical outcomes at 30 days [(Odds Ratio (OR) = 0.110, 95% CI = 0.013-0.953, p = 0.045)]. On the other hand, PDW did not have a significant relationship after regression analysis with p>0.05. A confounder in the form of gastrointestinal bleeding was significantly associated with poor clinical outcomes at 30 days (OR = 25.695, 95% CI = 1.637 – 403.345, p = 0.021).

DISCUSSION

The study results showed that the mean age of the study population was 60.89 ± 11.348 (mean ± SD), and 47 (63.5%) patients were male. This is supported by a study by Kim & Vemuganti, which states that age and gender are significant factors in modulating functional outcomes after stroke [5]. Hypertension (60.8%) and diabetes mellitus (23%) were the two most common comorbidities found in the subjects. Hypertension causes changes in the vascular structure that disrupt endothelial relaxation, alter cerebrovascular autoregulation and neovascular coupling (local perfusion as a response to changes in neural activity) that facilitate vascular occlusion and are susceptible to rupture and bleeding, leading to ischemic stroke [6]. Diabetes activates myelopoiesis, facilitating inflammation in the vascular walls, and therefore can lead to atherosclerosis [7]. However, hypertension and diabetes do not have a statistically significant relationship (p > 0.05) for predicting clinical outcomes in ischemic stroke patients. Statistically significant gastrointestinal bleeding occurred, but only four subjects experienced it, and only two had poor clinical outcomes. Ulcers can develop from vagal hyperactivity, which

results in increased gastric acid, pepsin secretion, and gastrointestinal mucosal damage. Sympathetic system hyperactivity after ischemic stroke induces excessive catecholamine release, leading to vasoconstriction that can cause splanchnic hypoperfusion and mucosal ischemia [8]. Gastrointestinal bleeding is a predisposition to thrombosis, increasing the risk of recurrent stroke, mortality, and length of hospital stay [9].

Research on the relationship between PDW and clinical outcomes in stroke is still limited, although it has been confirmed that both MPV and PDW increase during platelet activation. Platelet activation can result in pseudopodia formation, causing heterogeneous platelet size and increasing PDW values [10]. Increased PDW may reflect the formation of a new thrombus, seen from the higher production of larger active platelets [11]. Lower PDW suggests that an old thrombus may have already formed. Patients with a new thrombus with higher PDW show better neurological recovery outcomes [12]. Previous studies have shown that high PDW indicates a higher risk of adverse vascular events, while current studies have found a positive correlation between PDW and stroke clinical outcomes.

MPV is an indicator of platelet activation associated with systemic inflammatory response. Higher MPV in ischemic stroke is associated with severe neurological impairment [13]. Large platelet volume is a risk factor for poor outcomes [14]. There is a relationship between increasing platelet volume and increasing levels of dependence [15]. It is concluded that increased MPV is associated with worse outcomes [16].

The correlation between poor clinical outcomes and increased levels of mean platelet volume (MPV) in stroke patients can be explained as follows. First, an increase in MPV levels tends to have an increased thrombogenic ability (larger platelets containing denser granules), express higher levels of adhesion molecule thromboxane B2, and secrete more serotonin and β-thromboglobulin [17]. MPV is also determined by the maturity and ploidy of progenitor cells and remains constant throughout its lifespan [18]. Therefore, it is reasonable to state that a hypercoagulable state caused by increased MPV occurs before the onset of ischemic stroke [19]. Second, MPV is a link between thrombosis and inflammation. Thrombosis can increase inflammation, and inflammation, in turn, contributes to thrombogenesis. Inflammatory cytokines such as interleukin (IL-6 and IL-3) increase platelet production by increasing the number of megakaryocytes [20]. Thus, it is reasonable to speculate that the proinflammatory state before ischemic stroke can explain the higher MPV levels.

Several other studies show different results regarding the relationship between MPV and stroke. MPV is not associated with overall patient morbidity and mortality [21]. Oz et al. stated that MPV is not a reliable marker to predict the occurrence of stroke [22]. Our findings show no correlation between MPV scores and MRS, and cannot demonstrate a correlation between poor outcomes and increased MPV levels. Consistent with our data, Ntaios et al. concluded that MPV is not associated with stroke severity [23].

The explanation that can explain the contradictions between the above studies are as follows: first, an increase in PDW and MPV is associated with incubation time, and there may be differences in treatment. Second, differences in counting instruments, which affect the accuracy of PDW and MPV measurements. Third, the time between stroke onset and blood sampling. Fourth, differences in ethnicity, age, genetic factors, environment, and instruments used, which can affect the estimation and interpretation of PDW and MPV results [21]. Fifth, the administration of antiplatelet therapy and vitamin B12 affects the clinical outcomes of patients, so only a few subjects had poor clinical outcomes, but this study did not perform a test.

This study has several limitations. First, the clinical outcome studied was only disability. Second, the disability assessment used was only one, namely mRS, and the mRS score used was on the 30th day, ideally using mRS on the 90th day. Third, this study had a retrospective cohort design, data collection could not be planned or controlled in more detail beforehand. Fourth, patients with poor clinical outcomes tended to be few, thus reducing statistical power.

CONCLUSIONS

In conclusion, based on the results of the study, it was found that increased PDW and MPV values upon admission to the hospital did not increase the risk of 30-day disability in ischemic stroke patients. Further studies with similar topics could be conducted on severe ischemic stroke patients with clinical outcomes not only limited to disability, and should also include complete laboratory results and management performed on patients.

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