The Association of Platelet Index with Event of Deep Vein Thrombosis in Acute Ischemic Stroke Patients at Rumah Sakit Umum Pusat Haji Adam Malik Medan

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ABSTRACT

Introduction: Deep Vein Thrombosis (DVT) occurs in stroke with an incidence varying from 10-75%, depending on the diagnostic method and time of evaluation. Platelets play important role in the pathogenesis of thromboembolism. Large size platelets are more metabolically and enzymatically active also hemostatically more reactive and prone to the development of thrombosis. This study aims to determine the association between platelet index and the occurrence of DVT in patients with acute ischemic stroke.
Method: Prospective study with a total of 42 samples acute ischemic stroke patients who were treated ≤ 3 days in the stroke corner of RSUP. H Adam Malik Medan. Compression ultrasonography to diagnose DVT was performed on the lower extremities. Platelet indices assessed were mean platelet volume (MPV), platelet volume distribution width (PDW), and plateletcrit (PCT) based on the results of a complete blood test on admission.
Results: The mean age was 59.7 years with male gender as much as 66.7%. The majority of research subjects had a history of hypertension (42.9%) The mean body mass index was 28, 18 kg/mm². 97.6% were found to have asymptomatic DVT with Well's score of 1 (moderate probability of DVT occurrence). 54.8% of the study subjects with positive DVT results based on compression ultrasound results. There is an association between increased MPV and the incidence of DVT in acute ischemic stroke patients (p = 0.002).
Conclusion: There is an association between an increase in MPV value and the incidence of DVT in acute ischemic stroke patients.

Keywords: Platelet Index, Deep Vein Thrombosis, Acute Ischemic Stroke, Mean Platelet Volume, Platelet Distribution Width, Plateletcrit

INTRODUCTION

The development of a blood clot in a blood vessel is known as thrombosis. [1] A thrombus forms in a deep vein in a condition known as deep vein thrombosis (DVT).[2,3] Venous thromboembolism (VTE) includes DVT. The most dangerous side effect of DVT is pulmonary embolism, which can result in the detachment of a blood clot (or several clots) from a blood vessel, travel through the right side of the heart, and lodge in an artery that delivers blood to the lungs.[4]

DVT is frequent in stroke settings and, if it leads to pulmonary embolism, can be a deadly consequence. Depending on the diagnostic technique and timing of the

evaluation, the incidence of DVT in patients with post-stroke immobilisation ranges from 10–75%. The difference in prevalence between asymptomatic DVT and clinically confirmed DVT after an acute stroke is about 2-10%. After an acute stroke, DVT can develop on day 2, reaching its peak between days 2 and 7, and proximal DVT has a 15% mortality risk if ignored.[5]

Compression ultrasonography is currently the preferred imaging diagnostic for identifying DVT. The diagnostic standard is the absence of compressibility of the venous segment, although the inclusion of Doppler (including colour flow) can be helpful to precisely identify the vessel and to confirm the compressibility of a specific segment. When compared to venography, Doppler ultrasound examination has a 94% accuracy rate in patients with proximal DVT that is symptomatic; however, this rate is lower in patients with calf DVT that is asymptomatic. False negative results with compression ultrasonography can reach 50% and have a sensitivity of 89% and specificity of 97% in DVT in the calf region.[6]

When it comes to the pathogenesis of thromboembolism, platelets are crucial. The smallest yet most reactive component of blood are platelets. Platelets play a number of key roles in the early stages of fibrosis and the preservation of healthy hemostasis. Many pieces of recent research-based data support platelets' multifunctional role. When there is vascular damage, blood platelets are the first component to accumulate. When classical agonists like ADP, TXA2, PAF, and inflammatory cytokines like IL-1, IL-6, and TNF alpha activate them, they can deform and form pseudopodia, localised release of cytoplasmic granular contents, and aggregate. This starts the fibrosis and inflammatory processes. [7]

Mean platelet volume, Platelet distribution width (PDW), Plateletcrit (Pct) are platelet indices that are easy to perform during routine blood testing. Mean platelet volume (MPV) is a measure of the average number of platelets in the blood and represents platelet activation. Platelet distribution width (PDW) is the degree of heterogeneity in platelet size. Plateletcrit (Pct) is a parameter obtained by multiplying MPV by platelet count.[8] Large platelets have higher metabolic and enzymatic activity than small platelets. In other words, an increase in mean platelet volume (MPV) increases the risk of thrombosis. In a recent study, PCT values were reported to be higher in patients with retinal vein thrombosis compared with controls.[9]

Several studies have shown that larger mean platelet volume (MPV) is an indication of increased platelet activation in the body. In a study by Sevuk et al., they found that MPV and PDW values were higher in acute DVT patients than in the control group.[10] Based on the above description, it is important to assess the incidence of deep vein thrombosis in ischemic stroke patients to alert clinicians to the possibility of complications in order to prevent the risk disability and death in patients also to the best of the author's knowledge, no one has examined the three parameters of platelet index, DVT, and acute ischemic stroke simultaneously. Therefore, the researchers wanted to study the association between platelet index levels and the occurrence of DVT in acute ischemic stroke patients at RSUP. H Adam Malik Medan.

METHOD

This study is an analytical study with a prospective and cross sectional design to see the association between platelet index and the incidence of DVT in patients with acute ischemic stroke at RSUP. H Adam Malik Medan. The study was conducted after obtaining ethical clearance from the health research ethics commission of the Faculty of Medicine, Universitas Sumatera Utara / RSUP H. Adam Malik Medan until the number of samples was met in May - August 2023. DVT was established based on the results of compression ultrasonography on the lower extremities using a Mindray DP10 ultrasound (Shenzhen Mindray Bio-Medical

Electronics Co.,Ltd, Shenzhen, Guangdong. China) with a 5.0-10.0 MHz linear transducer. The examinations and interpretations were performed by a single radiologist who were blinded to patients' clinical information. The study results were considered positive for DVT when vein compression failed. Sampling was performed using consecutive sampling method on all acute ischemic stroke patients in the stroke corner treatment room at RSUP H. Adam Malik Medan who met the inclusion and exclusion criteria. Based on the sample calculation, a minimum sample of 42 patients was obtained.

Inclusion criteria were patients diagnosed with acute ischemic stroke, admitted to stroke corner ≤ 3 days, and willing to sign informed consent. The exclusion criteria of this study were patients who had a history of using anti-coagulant drugs in the last 3 months, history of transfusion in the last 3 months, history of major surgery in the last 3 months, hematologic malignancies and other cancers in the last 6 months, history of autoimmune and infectious diseases, hepatic cirrhosis and CKD stage 5, incomplete platelet index parameter data (MPV, PDW, and Pct) and head CT-scan radiographic data. The platelet indices assessed were mean platelet volume (MPV), platelet volume distribution width (PDW), and plateletcrit (Pct). The platelet index was recorded based on the results of a complete blood test at the time of admission using the automatic hematology analyzer machine. All patients were rated by the Wells score at the time of the ultrasound examination, and it was used to classify the patient's probability of DVT as low (≤ 0), moderate (1 or 2), or high (>2). The collected data were analyzed and processed using SPSS 25 for Windows software (IBM SPSS Statistics for Windows, Version 25.0. IBM Corp., Armonk, NY). The Shapiro-Wilk normality test is used to assess whether the data was normally distributed. Statistical tests of data to determine the association between MPV and the incidence of DVT used the Chi-Square test. The statistical test of data to determine the association of PDW and PCT with the incidence of DVT used Fisher's exact test because the Chi-Square condition was not met. Statistical significance level was set at $p < 0.05$.

RESULT

This study was attended by 42 acute ischemic stroke patients who met the specified inclusion and exclusion criteria. Table 1 shows the mean age of the study subjects was 59.7 years with male gender of 66.7% and female gender of 33.3%. Based on ethnicity, the majority of research subjects were of Batak ethnicity (64.3%). Based on disease history, the majority of research subjects had a history of hypertension as much as 42.9% followed by diabetes mellitus as much as 11.9% and hypercholesterolemia as much as 4.8%. Research subjects with a history of smoking were found in 2.4% of patients. Based on the results of the study, all research subjects did not have a history of immobilization > 3 days.

Table 1. Characteristics of Research Subjects

Characteristics	N = 49
Age, (years)	59.7 ± 12.74
Sex, n (%)	
Man	28 (66,7)
Woman	14 (33.3)
Ethnic, n (%)	
Batak	27 (64,3)
Javanese	4 (9,5)
Others	11 (26,2)
Previous history of disease, n (%)	
Hypertension	18 (42,9)
Diabetes Melitus	5 (11,9)
Hypercholesterolemia	2 (4,8)
History of immobilization > 3 days, n (%)	0 (0)
BMI, (kg/mm^2)	28, 18 ± 32.44

Platelet index	
MPV (fL)	9,6 ± 0,97
PDW (%)	10,1 ± 2,35
PCT (%)	0,25 ± 0,11
DVT Positive Result based on compression ultrasonography, n (%)	23 (54,8)
DVT complaints, n (%)	
Asymptomatic	41 (97.6)
Symptomatic	1 (2.4)
Well's Score, n (%)	
0	0 (0)
1	41 (97.6)
2	0 (0)
>2	1 (2.4)
Probability of DVT based on Well's Score, n (%)	
Low probability	0 (0)
Moderate probability	41 (97.6)
High Probability	1 (2.4)

Based on anthropometric examination, the mean BMI of the research subjects was 28,18 kg/mm2. Based on the platelet index examination, the mean MPV value was 9.6 fL, the mean PDW value was 10.1%, and the mean PCT value was 0.25%. Based on complaints of clinical symptoms of DVT, 41 samples (97.6%) found in this study did not have complaints about DVT so they were included in the asymptomatic DVT category. Based on Well's Score calculation, 41 samples (97.6%) with a value of 1 and a moderate probability of DVT occurrence. Based on the results of compression ultrasonography, 23 people (54.8%) of research subjects were found with positive Deep Vein Thrombosis (DVT) results.

From the results of the study, it is known that in the study subjects with an increase in Mean Platelet Volume (MPV) as many as 22 people where 17 people with positive Deep Vein Thrombosis (DVT) results based on compression ultrasonography examination. Based on the Chi-Square test analysis, the p value is 0.002 which shows that there is an association between an increase in Mean Platelet Volume (MPV) with the incidence of deep vein thrombosis in acute ischemic stroke patients.

From the results of the study, it is known that in the research subjects with an increase in Platelet Distribution Width (PDW) and PCT as many as 1 person where 1 person with a positive Deep Vein Thrombosis (DVT) result based on compression ultrasonography examination. Based on the Fisher's Exact test analysis, the p value is

1.000 which indicates that there is no association between the increase in Platelet Distribution Width (PDW) and PCT with the incidence of deep vein thrombosis in acute ischemic stroke patients.

DISCUSSION
Based on the results of the study, the average age of the research subjects of acute ischemic stroke patients was 59.7 years with male gender of 66.7% and female 33.3%. This is similar to the results of Adly Sadik et al research which found the average age of acute ischemic stroke patients> 55 years. In that research found that the mean age was 58.3 years from 46 patients with acute ischemic stroke treated at Kasr Al Ainy Teaching Hospital, Cairo University. [11] Research by Zafar et al found that acute ischemic stroke occurred in 64.4% of patients with male gender and 35.6% of patients with female gender and the average age of acute ischemic stroke patients with male gender was 59.3 + 13.6 years, while in female gender the average age was 66.8 + 14.9 years (p = 0.00). [12]

Based on the results of this study, history of hypertension was found in 42.9% of the study subjects, followed by diabetes mellitus as much as 11.9% and hypercholesterolemia as much as 4.8%. These results differ from the demographic characteristics in the Arslan et al study which examined 3,968 patients diagnosed with acute ischemic stroke where hypertension, hyperlipidemia, and Diabetes mellitus (DM) were the most risk factors

with 71.7% of the study subjects having a history of hypertension, 56.6% having a history of hyperlipidemia 35.6% and having a history of DM. 2.1%. Based on the results of this study, history of smoking was found to be 2.4%. This result is almost the same as the Arslan et al study where smoking history was also found to be very low (2.1%).[13]

Obesity is one of the most common modifiable risk factors for ischemic stroke.[14] According to the results of this study, the average study subject was obese with an average BMI of 28.18 kg/mm2. As reported by the Danish Stroke Registry, a higher BMI is associated with a faster rate of ischemic stroke. Khan et al. evaluated the association between BMI and lifetime risk of cardiovascular disease and mortality in a population without cardiovascular disease at baseline of 3 million person-years. Research shows that being overweight is associated with the development of cardiovascular disease and that obesity is associated with reduced longevity and cardiovascular survival. In addition, obesity increases the risk of hypertension, diabetes and dyslipidemia, which are non-modifiable risk factors for stroke. [15]

In this study, 41 samples with a Well's score of 1 and a moderate probability of DVT (97.6%) had no complaints of DVT and were therefore classified as asymptomatic DVT. Another study reported that symptomatic DVT occurred in 19% of the sample, or 8 of 42 patients with DVT.[16] The results of another study showed an incidence of asymptomatic DVT of approximately 14.7%, performed in patients with COVID-19 who did not receive intensive care in an intensive care unit.[17] The incidence of asymptomatic DVT is often due to the presence of clots located in the distal portion of the vessel, whereas symptomatic DVT tends to occur in the proximal portion of the vessel. [18]

In this study, 97.6% of asymptomatic patients were found to have a moderate probability value based on Well's score assessment with positive DVT findings in 54.8% of patients. Based on the diagnosis approach algorithm in patients suspected of DVT, patients can be given anticoagulants as additional therapy in patients with a moderate probability of DVT and abnormal compression ultrasonography results. [19] However, at RSUP. H. Adam Malik, there is no clinical practice guideline related to the flow of compression ultrasonography examination in patients with acute ischemic stroke and its relation to the administration of anticoagulants if abnormal results are found. Therefore, further research is needed as a reference related to the creation of clinical practice guidelines related to the flow of examination for diagnosis enforcement and guidance on the administration of anticoagulants as additional therapy in asymptomatic patients with a moderate probability of DVT and abnormal compression ultrasonography results according to the diagnosis approach algorithm in patients with suspected DVT and its relation to patient prognosis.

In this study, patients were examined within 3 days after treatment and based on compression ultrasonography results, deep vein thrombosis (DVT) was positive in 23 subjects (54.8%). Another previous study found that the incidence of DVT varied in immobilized patients after stroke, with an incidence of 10–75%, depending on the diagnostic method and timing of evaluation. [5] The incidence of DVT in this study was higher than in the study by Mori et al that examined acute stroke patients, in which the incidence of DVT occurred in 17.6% of patients in 1,129 patients treated. study. [20] Research by Ko et al. involving 52 patients with acute ischemic stroke found an incidence of proximal DVT in 3 patients (5.8%) based on two compression ultrasonography examinations within 7 to 14 days and 15 to 28 days after acute ischemic stroke.[21] The incidence of DVT after acute stroke varies approximately 2-10% between asymptomatic DVT and clinically proven DVT. The development of DVT after acute stroke can occur on day 2, peaking between days 2 and 7, and proximal

DVT carries a 15% mortality risk if left untreated.[5]

The results of this study show that DVT can occur simultaneously with ischemic stroke when both have the same pathogenesis of thrombosis or ischemic stroke, which can lead to paralysis, paralysis or immobility of the lower limbs is a risk factor for VTE in the Well's score. In addition, ischemic stroke is also a risk factor in VTE risk assessment using the Padua score.[22] In certain cases, arterial disease may directly contribute to VTE. For example, there is a transient increased risk of VTE after myocardial infarction or stroke, possibly due to a combination of leg congestion in immobilized patients and systemic activation of inflammation and hemostasis following tissue damage. The most likely biological explanation for the association between VTE and arterial thromboembolism is the similarity of risk factors.[23]

This study shows an association between an increase in platelet index, specifically mean platelet volume (MPV), and the incidence of deep vein thrombosis in patients with acute ischemic stroke. calculated, based on the results of the chi-square test with p -value 0.002 (p < 0.05). An increase in MPV indicates an increase in platelet diameter, which can be used as a marker of the rate of platelet production and activation.[24] Mean platelet volume (MPV) has been identified as a risk factor for stroke and thrombosis. [25] Several studies have shown that larger mean platelet volume (MPV) is an indication of increased platelet activation in vivo. [26]

MPV is a simple, rapid and inexpensive test parameter that essentially reflects platelet size. Because of the important role of platelets in hemostasis, many studies have evaluated MPV values in patients with arterial and venous thrombotic disorders. Overall, available evidence suggests that MPV may increase significantly with acute episodes of coronary heart disease, venous thromboembolism, portal vein thrombosis, stroke, erectile dysfunction, and preeclampsia. . In many of these conditions,

high MPV values may also be associated with unfavorable outcomes.[26] Cil et al. found that MPV values were significantly associated with DVT and were found to be independent predictors of in-hospital demonstration of DVT. [27]

The possible role of MPV in patients with venous thromboembolism (VTE), including deep vein thrombosis (DVT) or pulmonary embolism (PE), was recently published in a meta-analysis by Kovacs et al. Overall, patients with VTE had higher MPV compared with samples without (mean difference, 0.69 fL; 95% CI, 0.39-0.98 fL), which translated into an AUC of 0.72 (95% CI, 0.63-0.81) and pooled sensitivity and specificity of 0.77 (95% CI, 0.70-0.84) and 0.57 (95% CI, %, 0 ,46-0.68), respectively.[28]

In this study, it was found that the average PDW value was 10.1%, and the average Pct value was 0.25% and based on the results of the Fisher`s Exact test, there was no association between the increase in Platelet Distribution Width (PDW) and Plateletcrit (Pct) with the incidence of deep vein thrombosis in acute ischemic stroke patients with a p value of 1.000 (p> 0.05). This result is in contrast to a study conducted by Abanoz found that Pct value, which can be obtained easily and cheaply from routine blood parameters, can be a predictor in patients suspected of having DVT where out of 139 patients with DVT found MPV, C-reactive protein (CRP), D-Dimer and Pct values were significantly higher in group diagnosed with DVT (P values; P =0.001, P=0.018, P<0.001, P<0.001, P<0.001, respectively). In the ROC analysis of the study, the cut-off value for Pct was 0.1989 (AUC=0.732, P<0.001, sensitivity 70.8%, specificity 66.7%).[29] In another study by Xiong et al examining 103 cases of DVT found preoperatively showed that elevated platelet count and Pct were independent risk factors for preoperative DVT in elderly total joint arthroplasty (TJA) patients.[30]

The association of PDW and Pct with the incidence of DVT remains controversial.

Research by Ada et al found from 72 patients who experienced DVT found PDW and MPV tended to increase rapidly in the acute phase of deep vein thrombosis and decreased in the subacute and chronic phases. The study also found that there were no statistically significant changes in platelet count and plateletcrit.[31] In Wijaya et al`s study, which was similar to this research, also found differences in PDW in the DVT group and non-DVT group were found to be statistically insignificant with p=0.081 (p>0.05).[32] Differences in several studies on the association between Pct and PDW can be caused by different types of samples and research methods.

This study has several advantages and disadvantages. The advantage of this study is that it is the first study to prospectively examine the association between platelet index levels and the occurrence of DVT in acute ischemic stroke patients. Examination of platelet index, especially the increase in MPV value, which is easily obtained in daily clinical practice from complete blood test results, can be considered as an early detection tool in predicting the occurrence of DVT in acute ischemic stroke patients. However, one of the shortcomings of this study is that it did not compare the results of compression ultrasonography with angiography (venography or phlebography), which is the gold standard examination in confirming the diagnosis of DVT. In addition, this study only involved one institution to narrow the field of research, this can cause application limitations because there is a possibility that research in other locations will provide different results due to the influence of other factors. However, so far the results of this study still show results that are in line with other studies. Therefore, this study still requires further large-scale research so that it can be used as a reference in daily clinical practice including its association with management and prognosis in patients.

CONCLUSION
Increased mean platelet volume (MPV) values showed a significant association with the incidence of Deep Vein Thrombosis (DVT) in patients who experienced acute ischemic stroke.

Authors' Contributions
All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

Declaration by Authors

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