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The Relationship of D-dimer Levels and the Incident of Deep Vein Thrombosis in Acute Ischemic Stroke Patients at Haji Adam Malik General Hospital Medan

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ABSTRACT

Background: Deep Vein Thrombosis (DVT) is the formation of a thrombus in deep veins, often observed in stroke patients due to immobilization and infection during hospitalization. High D-dimer levels are associated with DVT in stroke patients. This study aims to evaluate the association between D-dimer levels as a diagnostic tool for DVT in acute ischemic stroke patients.

Methods: This cross-sectional, retrospective study was conducted from May to August 2023. The study was carried out on acute ischemic stroke patients at Haji Adam Malik General Hospital, Medan, using consecutive sampling. Doppler ultrasound was used as the gold standard, and D-dimer data were analyzed using the SPSS program, employing the Chi-square test or Fisher's exact test.

Results: Of the 49 patients, 35 met the inclusion criteria. Among the patients, 24 (68.6%) were male, 23 (65.7%) were over 50 years old, and 30 (85.7%) had a Body Mass Index (BMI) between 18-24.9. The mean D-dimer value was 2153.43 (±1506.88) ng/mL. All 21 (100%) DVT cases were asymptomatic. According to the Well's score, 15 patients scored 1 (42.8%), 20 patients (57.2%) scored 2, and the probability of DVT is in the moderate range for all 35 patients. The Fisher's Exact Test yielded a p-value of 0.028 ($p<0.05$).

Conclusion: There is a significant relationship between D-dimer levels and the incidence of DVT in patients experiencing acute ischemic stroke.

Keywords: Acute Ischemic Stroke, D-dimer, Deep Vein Thrombosis, Doppler Ultrasound

INTRODUCTION

Deep Vein Thrombosis (DVT) is a condition characterized by the formation of a thrombus within deep veins.[1,2] It is a part of Venous Thromboembolism (VTE). In Asia, the incidence of DVT ranges from 11 to 65 cases per 10,000 population.[3] In Indonesia, the prevalence of DVT reaches 37.1-40.3% in patients who have been bedridden for over three days in a hospital.[4] DVT-related deaths can occur in 6% of cases within a month after diagnosis.[1]

Around 94% of DVT cases occur in the deep veins of the lower extremities, with the remaining cases affecting the upper extremities.[5,6] Several risk factors are associated with an increased risk of DVT, with more than 50% of DVT patients having more than one risk factor.[7] These factors include prolonged surgical procedures, immobilization, prior history of thromboembolism, malignancy, pregnancy, and iatrogenic factors.[8] In addition,

coronavirus disease 2019 (COVID-19) may also increase the risk of DVT.[9]

DVT incidents are common in stroke patients, often resulting from immobilization and infections during hospitalization. Immobilization can lead to venous stasis, increasing the risk of thrombus formation. In contrast, infection can increase DVT risk through systemic coagulation system activation, extended hospital stays, and the formation of neutrophil extracellular traps. Stroke patients are at a 19.1- and 10.3-times greater risk of developing DVT in the first month and 1-3 months post-stroke, respectively.[10] Approximately 11.5% of acute ischemic stroke patients experience asymptomatic DVT, with 85.9% of thrombus detected in distal veins.[11] Even without symptoms, the mortality risk in patients with asymptomatic DVT is nearly three times higher than those without DVT.[6] The Wells' criteria can be used to assess an individual's DVT risk. A Wells score ≥2 indicates a 40% DVT risk, while a score <2 suggests a DVT risk of <15%. In cases with a Wells score <2, a D-dimer test can be conducted to aid in DVT screening. Normal D-dimer results can rule out a DVT diagnosis.[2,12]

D-dimer originates from the breakdown of blood clots by plasmin.[6] It is commonly used in VTE (DVT and pulmonary embolism) and disseminated intravascular coagulation (DIC) cases.[13] Elevated D-dimer levels can also be found in physiological conditions such as pregnancy and old age and pathological conditions like cardiovascular disease, infections, liver disease, chronic inflammatory disease, and kidney disease.[14] Various techniques are available to measure D-dimer levels, including enzyme-linked immunosorbent assays (ELISA), enzyme-linked immunofluorescence assay (ELFA), latex-enhanced immunoturbidimetric (LEI), and whole blood point of care (WBPC). ELFA is the most sensitive method to determine D-dimer levels (sensitivity: 96%; specificity: 46%, turnaround time: 35 minutes), followed by ELISA (94%; 53%; 2-4 hours), LEI (93%; 53%; 15 minutes), and WBPC (83%; 71%; 2-5 minutes).[15]

Several studies have used D-dimer tests to predict DVT tendencies in stroke patients. High D-dimer levels are significantly associated with DVT in stroke patients, increasing the risk by 1.05-4 times.[3,11,16] D-dimer levels gradually rise, peak within two weeks post-stroke, remain high for several weeks, and gradually decline.[16] According to Huang *et al.* (2021), there has been a fourfold increase in D-dimer levels from the baseline in patients with acute ischemic stroke, which can aid in detecting the possibility of DVT.[17] Furthermore, according to the study by Ha SH *et al.* (2020), D-dimer levels increase in patients with acute ischemic stroke and are associated with the underlying mechanisms of stroke.[18] Therefore, it is essential to evaluate DVT incidents in acute ischemic stroke patients as it can increase mortality and cause disability. This study investigates the relationship between D-dimer levels as a diagnostic tool for DVT in acute ischemic stroke patients at Haji Adam Malik General Hospital, Medan.

MATERIALS & METHODS

Study Design

This study was an analytical study with a cross-sectional design and retrospective approach to examine the relationship between D-dimer levels and the incidence of DVT in acute ischemic stroke patients at Haji Adam Malik General Hospital, Medan.

Study Sample

The study population encompassed all acute ischemic stroke patients who received treatment at the Stroke Corner of Haji Adam Malik General Hospital, Medan, from May to August 2023. The study sample included all individuals who met the inclusion and exclusion criteria.

The inclusion criteria were patients diagnosed with acute ischemic stroke with onset within three days, aged >18 years, cooperative, willing to participate and sign the informed consent form, and willing to

undergo a Doppler ultrasound examination. Meanwhile, the exclusion criteria were patients with a history of antithrombotic drug usage and treatments that could affect coagulation, a history of lower extremities within the past 12 weeks, patients with sepsis, pregnant women, patients with malignancy, hepatic cirrhosis, and those with an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2.

Data Extraction

The data collected for this study includes a range of variables: baseline characteristics of the study population (age, gender, body mass index (BMI), and past medical history), Wells' score and the DVT probability of the study population, D-dimer values of the study population, and Doppler ultrasound results.

STATISTICAL ANALYSIS

All data in this study are presented in frequency distribution tables and analyzed descriptively. The Chi-square test was performed using SPSS version 26 to assess the relationship between D-dimer levels and the incidence of DVT in acute ischemic stroke patients. However, Pearson Chi-Square cannot be used when the cell value is <5. As an alternative, Fisher's Exact Test was employed. Statistical significance was defined as $p<0.05$.

RESULT

A total of 35 patients were included in this study. Of these, 24 (68.6%) were male, and 11 (31.4%) were female. Regarding age distribution, 12 patients (34.3%) were under 50, while the remaining 23 (65.7%) were over 50. The study population exhibited a diverse range of BMI values. None of the patients had a BMI below 18.5 kg/m2, while 30 patients (85.7%) fell within the BMI range of 18 to 24.9 kg/m2. Five patients (14.3%) had a BMI between 25 and 29.9 kg/m2, and none had a BMI exceeding 30 kg/m2. Regarding past medical history, one patient (2.8%) had a history of diabetes mellitus, 12 patients (34.2%) had a history of hypertension, and the remaining patients had unknown or unclear medical histories. The baseline characteristics of the study population are presented in Table 1.

Table 1. Baseline Characteristics of Study Population

Age (Years)	**f**	**%**
≤50	12	34.3
>50	23	65.7
Gender	**f**	**%**
Male	24	68.6
Female	11	31.4
BMI (kg/m^2)	**f**	**%**
<18.5	0	0
18.5-24.9	30	85.7
25-29.9	5	14.3
≥30	0	0
Past Medical History	**f**	**%**
Diabetes mellitus	1	2.8
Hypertension	12	34.2
Unknown/unclear	22	63

The Wells' score of the 35 patients in this study is presented in Table 2. Fifteen patients (42.8%) scored 1, and 20 (57.2%) scored 2. Thus, the probability of DVT, according to Wells' score, falls in the moderate range for all 35 patients (100%). No data indicates low or high probability. Regarding DVT symptoms, 21 patients (100%) in this study did not report any complaints related to DVT and were categorized as asymptomatic DVT.

Table 2. Wells' Score and DVT Probability Level

		f	**%**
Wells' Score	**0**	0	0
	1	15	42.8
	2	20	57.2
	>2	0	0
DVT Probability according to Wells' Score	**Low**	0	0
	Moderate	35	100
	High	0	0
DVT Symptoms	**Symptomatic**	0	0
	Asymptomatic	21	100
Total		35	100

Table 3 presents the D-dimer values of 35 patients with acute ischemic stroke. The mean D-dimer value for patients with acute ischemic stroke is 2153.43 (±1506.88) ng/mL, with minimum and maximum values of 250 ng/mL and 5650 ng/mL, respectively. All patients underwent a Doppler ultrasound examination, confirming DVT in 21 patients. The mean D-dimer value for patients with acute ischemic stroke and DVT is 2702.86 (±1377.98), with minimum and maximum values of 440 ng/mL and 5650 ng/mL, respectively.

Table 3. D-dimer Values

	D-dimer			
	Min.	**Max.**	**Mean (±SD)**	**Unit**
Acute Ischemic Stroke	250	5650	2153.43 (±1506.88)	ng/mL
Acute Ischemic Stroke with DVT	440	5650	2702.86 (±1377.98)	ng/mL

The results of D-dimer and Doppler ultrasound examinations in this study are presented in Table 4. Out of the 35 patients, 29 patients (82.9%) had D-dimer values >500 ng/mL, and six patients (17.1%) had D-dimer values <500 ng/mL. Regarding the Doppler ultrasound examination, 21 patients (60%) had positive results, while 14 patients (40%) had negative results.

Table 4. D-dimer Values and Doppler Ultrasound Results

		f	**%**
D-dimer	**>500 ng/mL**	29	82.9
	<500 ng/mL	6	17.1
Doppler Ultrasound	**Positive**	21	60
	Negative	14	40
Total		35	100

Based on the data analysis in Table 5, the Chi-square test result indicates that the Fisher's Exact Test has a significance value of 0.028 ($p<0.05$). This result suggests sufficient evidence to support the hypothesis that there is a relationship between D-dimer levels and the incidence of DVT in acute ischemic stroke patients in Haji Adam Malik General Hospital, Medan. In other words, based on the analysis conducted, it can be concluded that D-dimer levels have a significant influence on the risk of DVT in the population of patients under investigation.

Table 5. Fisher's Exact Test

		Deep Vein Thrombosis (DVT)		**Total**	**p-value**
		Negative	**Positive**		
D-dimer	**<500 ng/mL**	5	9	14	0.028
	>500 ng/mL	1	20	21	
Total		6	29	35	

DISCUSSION

In this study, 23 respondents (65.7%) were above 50 years old, while 12 respondents (34.3%) were under 50. This result aligns with the previous finding by Kumar *et al.* (2020), which stated that the age group most vulnerable to stroke is those between 61 and 80 years, reaching 47%, and the age group between 41 and 60 years at 46%.[19] According to Mohammedin *et al.* (2021), the age group most affected by stroke is the non-elderly group, aged 50-59 years (49%). In contrast, within the elderly group, the age range of 60-69 years also shows a similar percentage (49%). Differences in the types of stroke can be observed, where Transient Ischemic Attack (TIA) and hemorrhagic stroke occur slightly more often in the non-elderly group compared to the elderly group, at 48.2% vs. 42.3% and 25.5% vs. 20.1%, respectively. Conversely, ischemic stroke occurs more frequently in the elderly group, with a percentage ratio of 57.7% vs 38.2%.[20] Kuriakose and Xiao (2020) noted

that stroke incidence increases with age, doubling after age 55. A concerning trend from 1990 to 2016 was the increased incidence of stroke in individuals under 54 years of age, reaching 18.6% of all stroke cases worldwide, compared to the previous rate of 12.9%.[21] This underscores the importance of considering stroke risk factors and early screening for individuals aged 50 and above. Taking such simple actions may significantly contribute to stroke prevention or reduce mortality in the event of a stroke. This is why the researchers divided the age groups in the sample into <50 years and >50 years.

Furthermore, individuals aged over 40, those with a history of heart and vascular disorders, obesity, and hematological disease, potentially have a higher risk of DVT.[22] This is related to elevated fibrinogen levels, factors VIII and IX, and other coagulation proteins, which do not align with increased anticoagulation factors, disrupting the homeostasis balance. Additionally, other risk factors, such as obesity, commonly found in the elderly population, can increase thrombotic factors. This is attributed to the accumulation of excess adipose tissue, which produces inflammatory cytokines and an active inhibitor of plasminogen, such as plasminogen activator inhibitor 1 (PAI-1).[23,24]

In this study, 24 (68.4%) were male, while 11 (31.4%) were female. This data significantly indicates a male-dominated composition in the study population. Gender is significantly correlated with different stroke events. Women display higher prevalence and incidence rates in certain conditions than men, mainly related to intracranial aneurysms and subarachnoid hemorrhages. In contrast, men have higher rates of intracerebral hemorrhage. For TIA, the risk pattern between women and men can differ based on age groups. In individuals under 30, women have a higher risk than men, but this pattern reverses for individuals above 30.[25] Globally, stroke incidence has increased, affecting both men and women. However, it is essential to note that stroke prevalence tends to be higher in men than women. This discrepancy can be explained by several factors, including the motivation to adopt a healthy lifestyle and smoking habits. Smoking is a significant risk factor for stroke. The smoking habit tends to be more common in the male population than in women, thus explaining the higher prevalence of stroke in men.[26]

Various factors underlie the differences in stroke incidence between men and women. One significant factor is the difference in steroid hormones that function based on gender. For example, estradiol in females strongly affects blood vessel endothelial dilation, resulting in increased blood flow. In contrast, testosterone in males may affect endothelial contraction, reducing blood flow. In addition to hormonal differences, genetic and anatomical factors are pivotal in influencing stroke incidences in both genders. Gender-related differences in vessel size are one of the significant aspects. Heart and artery sizes are generally smaller in women than in men, affecting blood circulation dynamics. This often results in larger atrial sizes in men.[26,27] Gender differences in the prevalence and incidence of DVT have been observed, with results indicating that gender is not an independent risk factor for DVT.[28,29] Some studies have demonstrated that women may possess protective factors that influence reduced DVT incidence.[28]

In this study, approximately 85% of the respondents had a BMI categorized as "normal," while about 14.3% of the respondents fell into the "overweight" category. This result indicates the dominance of a "normal" BMI category in the study population. An elevated BMI, which includes overweight and obese, has been linked to stroke risk, particularly ischemic stroke. Additionally, other studies have shown that the risk of hemorrhagic stroke may increase in men with a BMI below or above normal weight and in obese individuals.[30] Patients who are obese or

have a high BMI have a higher risk of DVT than those within the normal BMI range.[31]

In identifying the past medical history, the results indicate that within the study population, 2.8% of individuals have a history of diabetes mellitus, 34.2% have a history of hypertension, and 63% of other individuals either have an unknown or unclear medical history. VTE has many risk factors similar to cardiovascular diseases, such as atherosclerosis. These risk factors include obesity, hypertension, dyslipidemia, smoking, and diabetes. The risk factors for VTE increase in patients with type 1 and type 2 diabetes.[32] Research suggests that patients with type 2 diabetes may experience increased thrombin production and the concentration of circulating microparticles originating from procoagulant cells. This indicates that the hypercoagulability state, where blood clotting is increased, may play an important pathogenic role in the increased frequency of VTE events in patients with type 2 diabetes.[32]

Patients with hypertension are found to have a twofold higher risk of experiencing VTE after orthopedic surgery.[33] However, no significant association was found between hypertension and VTE occurrences in other studies focused on the age group of ≥70 years. Furthermore, Mendelian randomization studies did not successfully show a correlation between systolic blood pressure and VTE risk. The study results indicate that unmeasured confounding factors may influence the relationship between blood pressure and VTE risk. Therefore, the relationship between hypertension and VTE risk appears complex and requires further investigation to understand the roles of the involved variables.[34]

In this study, the Wells' score obtained from the study population had a value of 15, with a percentage of 42.8% for a score of 1 and 57.2% for a score of 2. Therefore, the probability of DVT based on the Wells' score falls into the moderate range for all 35 (100%) patients. No data indicate low or high probabilities. In the implementation of the Wells' score in patients with low risk (score <1), this method is capable of accurately ruling out the possibility of DVT with a sensitivity and negative predictive value (NPV) of 100%. On the other hand, in patients with moderate to high risk (score ≥2), the Wells' score can predict the likelihood of DVT with a specificity of approximately 90.91%.[35] This makes the method an effective tool in supporting DVT diagnosis.[36] This scoring method is considered a helpful instrument in diagnosing DVT, allowing for more precise subsequent steps, including administering anticoagulant therapy, by referring to established diagnostic algorithms.[37]

In this study, it was found that all 21 respondents (100%) had asymptomatic DVT. Other research reports that asymptomatic DVT occurs in 19% of respondents or 8 out of 42 patients with DVT.[38] Furthermore, other research results show an incidence of approximately 14.7% in asymptomatic DVT, which was conducted on COVID-19 patients not receiving intensive care in the intensive care unit.[80] Asymptomatic DVT often occurs due to blood clots in the distal blood vessels, whereas symptomatic DVT tends to occur in the proximal blood vessels.[39,40]

In this study, out of a total of 35 patients with acute ischemic stroke, it was found that the mean (±SD) value of D-Dimer was approximately 2153.43 (±1506.88) ng/mL. Similarly, this study found that out of a total of 35 samples, 29 exhibited D-dimer concentrations above the threshold of 500 ng/mL. Comparisons with other research findings reveal that patients with acute ischemic stroke have an average D-dimer concentration of about 6266 ng/mL. In cases of focal infarction, it was 3857 ng/mL in patients with multiple embolic infarcts, 5662 ng/mL in patients with infarctions ranging from 1-19 cc, 6688 ng/mL in patients with infarctions from 20-49 cc, 7025 ng/mL in patients with infarctions of 50-199 cc, and 8440 ng/mL in patients with infarctions exceeding 200 cc.[41] With a mean

(±SD) D-dimer value of approximately 2153.43 (±1506.88) ng/mL, it can be observed that the D-dimer value in this study is lower than in other research. However, differences in the quantity are influenced by factors such as volume, location, and infarction conditions.

D-dimer concentration can increase significantly during the first 6 hours after stroke onset in patients with large artery occlusion and cardioembolic strokes compared to patients with lacunar strokes or those without arterial occlusion.[41] High-risk patients, characterized by severe neurological deficits or immobilization, and acute ischemic stroke patients with low D-dimer concentrations should not be assumed to be at no risk of DVT. Therefore, lower extremity ultrasonography is necessary.[18]

This study found that in patients with acute ischemic stroke who also had DVT, there was one case with a D-dimer level below 500 ng/mL. This patient had a history of type 2 diabetes mellitus (T2DM), possibly related to PAI-1. This protein is crucial in regulating blood clot formation and breakdown within the body.[42] PAI-1 works by regulating the activity of plasminogen activators like urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA).[43] Plasminogen is activated into plasmin to break down fibrin in blood clot formation. PAI-1 inhibits the activation of plasminogen, which can impede blood clot breakdown.[44] Consequently, an increase in PAI-1 can reduce fibrinolysis activity. Patients with T2DM are known to have an increase in PAI-1 levels by 25-280%.[45] This raises the suspicion that in the patient showing low D-dimer levels with the presence of DVT, T2DM might be a contributing factor.

After performing an analysis using Fisher's Exact Test, a p-value of 0.028 ($p<0.05$) was obtained, indicating a significant relationship between D-dimer levels and the incidence of DVT in stroke patients. This finding is consistent with previous study results, such as the study conducted by Ha SH *et al.* in 2020, which also observed an increase in D-dimer levels in patients with acute ischemic stroke and linked it to the stroke mechanism.[18] In other studies, it has also been documented that D-dimer levels have a significant relationship with DVT occurrences in patients with acute ischemic stroke.[46] This aligns with the pathophysiology that occurs during acute ischemic stroke, where coagulation and fibrinolytic systems are activated. This activity is marked by a significantly higher D-dimer concentration in patients with acute ischemic stroke than in healthy individuals. The increase in D-dimer levels reflects an ongoing thrombotic process in the blood vessels. Also, it activates an inflammatory process involving the activation of human cells and the release of proinflammatory cytokines.[47-49] These results enhance our understanding of the role of D-dimer in the risk of DVT in acute ischemic stroke patients and its relevance in the context of the underlying pathophysiological mechanisms of stroke.

CONCLUSION

Based on the results of the data obtained, the conclusions of this study are as follows: (1) There is a significant relationship between D-dimer levels and the incidence of DVT in patients with acute ischemic stroke (p-value 0.0.28), (2) The Wells' score of patients with acute ischemic stroke treated at the Stroke Corner of Haji Adam Malik General Hospital predominantly fall into the score two categories, indicating a moderate probability, (3) The patient characteristics in this study were predominantly male, aged over 50 years, with a normal weight category based on BMI, and a history of hypertension. The mean D-dimer levels in patients with acute ischemic stroke and patients with DVT are 2153.43 (±1506.88) ng/mL and 2702.86 (±1377.98) ng/mL, respectively, (4) The incidence of DVT in patients with acute ischemic stroke treated at the Stroke Corner of Haji Adam Malik General Hospital is 60%, and the incidence of asymptomatic DVT in patients with acute ischemic stroke is 100%.

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