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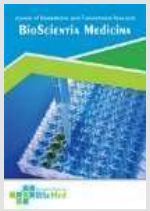

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Differences in D-Dimer Levels in Acute Ischemic and Hemorrhagic Stroke: Observational Study in the Emergency Department of Dr. M. Djamil General Hospital, Padang, Indonesia

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A B S T R A C T

Background: Stroke is the second largest cause of death worldwide with a high morbidity rate of up to 50% of survivors get chronic disability. Rapid diagnosis in patients with suspected acute ischemic or hemorrhagic stroke is very important to determine management and prognosis. D-dimer is an indirect marker of fibrinolysis which functions as a significant marker of activation of coagulation and fibrinolysis. This study aims to determine the differences in D-dimer levels in ischemic and acute hemorrhagic stroke patients in the emergency room (ER) of Dr. M. Djamil General Hospital Padang. **Methods:** Analytical observational research by cross-sectional design was carried out on 56 samples consisting of 28 acute ischemic and 28 acute hemorrhagic stroke samples for the period December 2022-June 2023. D-dimer levels and CTscan checked on each group and analysis is carried out. **Results:** The most common characteristics of research subjects were men, namely 35 patients (62.5%) and aged 51-60 years (32.1%). The mean D-dimer levels for ischemic and hemorrhagic strokes were 794.33 ng/mL (±2.63) and 1288.25 ng/mL (±2.51) with a p-value = 0.055. **Conclusion:** The mean D-dimer in acute hemorrhagic stroke was higher than in acute ischemic stroke but there was no statistically significant difference. The D-dimer examination cannot differentiate the type of stroke that occurred.

1. Introduction

Stroke is the second largest cause of death worldwide with a death rate of around 5.5 million per year. Stroke morbidity rates are high and up to 50% of survivors develop chronic disability. Stroke is a disease with serious economic and social consequences. Stroke is considered a disease in developing countries with 4.85 million stroke deaths and 91.4 million disability-adjusted life years (DALY) each year compared to developed countries with 1.6 million deaths and 21.5 million DALYs.[1] Ischemic stroke has a higher percentage rate compared to hemorrhagic stroke. American Heart Association (AHA) in 2016 reported that the incidence of ischemic stroke reached 87% and the remainder was intracerebral and subarachnoid hemorrhage. Data Stroke Registry in 2012-2014, of 5,411 stroke patients in Indonesia, the majority were ischemic strokes (67%). Of a total of 384 stroke patients who were hospitalized at Dr. Cipto Mangunkusumo National Central General Hospital in 2014, 71.4% had an ischemic stroke. The death rate due to ischemic stroke (11.3%) is relatively smaller than hemorrhagic stroke (17.2%).[2] Ischemic and hemorrhagic strokes have almost the same risk factors, but management is very different. Treatment for ischemic stroke is

thrombolysis and antiplatelets, but should not be done in cases of hemorrhagic stroke where treatment is *immediate and life-saving.*[3] The sooner the patient is treated, the better the patient's quality of life after a stroke, so that fast and accurate diagnosis in super acute conditions is very necessary. Biomarkers can potentially be markers of stroke etiology.[4]

D-dimer is an indirect marker of fibrinolysis and *turnover* Fibrin has unique properties as a biological marker of hemostasis disorders and an indicator of intravascular thrombosis. D-dimer serves as a significant marker of activation of coagulation and fibrinolysis in several clinical cases because it is a soluble fibrin degradation product resulting from the systematic degradation of vascular thrombus through the fibrinolysis mechanism. D-dimer has been evaluated to determine the optimal duration of anticoagulation in patients with venous thromboembolism (VTE), to diagnose and monitor disseminated intravascular coagulation, and to monitor other conditions that put the patient at high risk for bleeding or thrombosis. Limitations of D-dimer testing are the increase in D-dimer in a constellation of clinical scenarios (age, pregnancy, and cancer) and the lack of clinical standardization.[5] Some researchers have found that D-dimer levels can independently predict poor functional prognosis in patients with ischemic stroke while other researchers have reported conflicting results. Research by Zhang et al,. 2019 concluded that high D-dimer levels in patients with acute ischemic stroke within 24 hours of stroke onset were associated with 5-day recurrence based on diffusion-weighted imaging (DWI), 30-day mortality, and outcome poor functional outcomes at 30 and 90 days.[6] Previous research from Rallidis et al. 2008 had conflicting results from Zhang et al research, Rallidis et al,. concluded that D-dimer levels could not predict mortality in the regression model when potentially confounding factors (age > 65 years, atrial fibrillation) were included.[7]

Rapid diagnosis in patients suspected of having an acute ischemic stroke is very important for patient management and prognosis. Radiological confirmation is often delayed because of the results computed tomography scan (CT scan) may appear normal in the early stages or in patients with minor symptoms, and magnetic resonance imaging (MRI) is not always available during treatment golden time so that many cases with treatment are delayed. Research regarding the relationship between plasma D-dimer and stroke is still not widely done.[8] Research by Widjaja concluded that examining plasma D-dimer levels can be used as a screening test for CT scans in the diagnosis of ischemic stroke in the acute phase. Researchers obtained D-dimer sensitivity results of 71.4% (cut off ≥500 µg/L), specificity 35.7%, positive predictive value of 62.5% and negative predictive value of 45.5%, likelihood ratio of positive 1.09 likelihood ratio of negative 0.82.[9] Research by Mulyono found that plasma D-dimer levels in hemorrhagic strokes were higher than in ischemic strokes, although there was an increase in both types of stroke. Comparison of D-dimer levels showed a significant difference with p=0.04 with the median D-dimer level for hemorrhagic strokes being 700 (100-4200) while for ischemic strokes being 400 (100-3700).[10] Research on differences in D-dimer levels in acute ischemic and hemorrhagic stroke has not been widely conducted in Indonesia, especially in Padang, so based on the results of the research above, researchers are interested in comparing D-dimer levels in acute ischemic and hemorrhagic stroke patients in the emergency room (ER) of Dr. M. Djamil General Hospital Padang.

2. Methods

This study is a retrospective cohort study by cross-sectional design which aims to determine the average D-dimer levels in acute ischemic and hemorrhagic stroke patients in the emergency room of Dr. M. Djamil General Hospital Padang. The research was conducted at the Central Laboratory Installation and Medical Records Installation at Dr. M. Djamil General Hospital Padang from May to August 2023. The study population was patients with ischemic and hemorrhagic stroke who were diagnosed by clinicians

from December 2022 to June 2023 in the emergency room at Dr. M. Djamil General Hospital Padang. The research sample is part of the population that meets the inclusion and exclusion criteria. Inclusion criteria were patients who underwent D-dimer examination while in the ER and a CT scan head to confirm the diagnosis. Exclusion criteria are pregnant patients, patients with infection or sepsis, patients with heart disease, and patients who are receiving anticoagulant therapy or thrombolysis.

Patients admitted from the emergency room with a diagnosis of stroke in the medical record were selected based on inclusion and exclusion criteria. The sample was divided into two groups, namely the ischemic and hemorrhagic stroke groups. D-dimer and CT scan results data Both groups of samples were taken from medical records and then carried out statistical analysis. Patient characteristic data is processed and presented in the form of a frequency distribution table and numerical data is tested for normality of the data using a Kolmogorov-Smirnov test because the number of samples is >50. Based on this test, abnormal results were obtained, so an attempt was made to obtain a normal distribution through transformation to logarithms and normal results were obtained, so that the difference in the mean D-dimer was analyzed using independent T test. A p-value <0.05 indicates that there is a significant difference.

3. Results

This retrospective cohort study with a cross-sectional design was conducted on 28 hemorrhagic and ischemic stroke patients each diagnosed by clinicians from December 2022 to June 2023 who met the sample criteria. Patient characteristics are shown as follows:

Table 1. Characteristics of the research sample.

Characteristics	Ischemic (n=28)	Hemorrhagic (n=28)	p-value
	N %	N %	
Age			
< 41 years	2 (7,1)	0 (0,0)	0,432*
41 – 50 years	4 (14,3)	5 (17,9)	
51 – 60 years	9 (32,1)	9 (32,1)	
61 – 70 years	10 (35,7)	7 (25,0)	
>70 years	3 (10,7)	7 (25,0)	
Gender			
Male	20 (71,4)	15 (53,6)	0,168^
Female	8 (28,6)	13 (46,4)	
Risk factors			
Hypertension	16 (57,1)	24 (85,7)	0,020*
Diabetes mellitus	3 (10,7)	1 (3,6)	
Hypertension + DM	9 (32,1)	2 (7,1)	
Smoking	0 (0,0)	1 (3,6)	

Description: *= Fisher exact test, ^ = Chi-square test.

Patient characteristics in Table 1 show that the incidence of ischemic stroke tends to increase in the age group <41 years to 61-70 years and decreases at age >70 years. Meanwhile, the incidence of hemorrhagic stroke was seen in the 41-50 year age group, increased in the 51-60 year age group, and decreased in the 61 year and over age group. Based on the Fisher exact test obtained p value = 0.432 (p> 0.05) shows that there is no difference in age between ischemic and hemorrhagic stroke patients. Based on gender, there were 15 male ischemic stroke patients (53.6%) while there were 20 patients with hemorrhagic stroke (71.4%). However, from the results of the Chi square test, a value of p=0.168 (p>0.05) was obtained, which also showed that there was no difference in age between ischemic and hemorrhagic stroke patients. Based on risk factors, it was found that hypertension was more common in hemorrhagic stroke patients

(85.7%) than ischemic stroke (57.1%), while DM was more common in ischemic stroke patients (10.7%) than hemorrhagic stroke (3, 6%). Hypertension and DM were also more common (32.1%) in ischemic than hemorrhagic stroke (7.1%). The results of the Fisher exact test obtained a value of p=0.020 (p<0.05) indicating that there was a significant difference in risk factors between ischemic and hemorrhagic stroke.

Table 2. Mean D-dimer levels in ischemic and hemorrhagic stroke patients.

D-dimer	Ischemic	Hemorrhagic	p-value
Mean ± SD	794,33 ± 2,63	1288,25 ± 2,51	0,055
Kolmogorov-Smirnov*	0,973	0,240	

*p-value after transformation of D-dimer levels to log.

Based on Table 2, it was found that the average D-dimer level in ischemic stroke patients was 794.33 ± 2.63, while in hemorrhagic stroke patients it appears to be higher, namely 1288.25 ± 2.51. After the data was transformed into logarithms and tested for normality of the data distribution, a value of p>0.05 was obtained for both ischemic (p=0.973) and hemorrhagic (0.240) stroke patients, indicating that the data distribution of D-dimer levels between the two types of stroke was normally distributed so that the difference can be analyzed parametrically using the independent t-test. The results of the independent t-test obtained a p value of 0.055 (p>0.05), meaning that there was no statistically significant difference in D-dimer levels between patients with ischemic stroke and hemorrhagic stroke.

4. Discussion

This research was conducted on 56 patients who came to the emergency room at Dr. M. Djamil General Hospital and was chosen by chance random sampling over a 3-month period after applying the inclusion and exclusion criteria. This study aims to see differences in D-dimer levels in acute ischemic and hemorrhagic stroke. D-dimer and CT scan. The head was performed on all these patients. The results of this study showed that the incidence of ischemic stroke tends to increase in the age group <41 years to the age group 61-70 years and decreases in those aged >70 years. Meanwhile, the incidence of hemorrhagic stroke is seen in the 41-50 year age group, increasing in the 51-60 year age group. Based on Fisher's exact test The obtained p value = 0.432 (p> 0.05) shows that there is no difference in age between ischemic and hemorrhagic stroke patients. This is in accordance with Kuriakose and Xiao's statement. 2020 stroke risk factors include age, gender, ethnicity, transient ischemic attack (TIA), and hereditary characteristics. The average age at which stroke occurred was 69.2 years in the United States in 2005. Recent research shows that the 20-54-year age group is at high risk of stroke. This may be due to pre-existing secondary factors.[11] Based on gender, both types of stroke have a higher predilection for males. There were 15 male patients with ischemic stroke (53.6%) while there were 20 patients with hemorrhagic stroke (71.4%). However, from the results of the chi-square test, a value of p=0.168 (p>0.05) was obtained, which also showed that there were no gender differences in ischemic and hemorrhagic stroke patients. Wang et al., 2019 in his research stated that the incidence of stroke was found to be higher in men than women for all types of stroke and their subtypes.[12] Globally, the incidence of stroke is 33% higher in men. This finding is supported by Dahl et al., In 2020, the prevalence of stroke in men was 53.3%.[13] Another research conducted by Sanyasi et al., 2018 also found that ischemic stroke and hemorrhagic stroke were dominated by men (58.1% and 61.4%).[14] However, research conducted by Abdu et al., 2022 obtained different results, namely that the prevalence of stroke in women was found to be higher (51.9%).[15]

The main reason for gender-related stroke differences is due to differences in sex steroid hormones, especially the hormone estrogen. The hormone estradiol in women has a dilating effect on

the vascular endothelium and increases blood flow, while the hormone testosterone in men has the opposite effect. Genetic and anatomical factors are also known to contribute to differences in stroke epidemiology. Apart from that, there are differences in lifestyle such as physical activity, food intake, social life, and smoking which ultimately influence the incidence of stroke in certain genders.[15] Based on risk factors, it was found that hypertension was more common in hemorrhagic stroke patients (85.7%) than ischemic stroke (57.1%), Fisher exact test results obtained p=0.020 (p<0.05) indicating there were differences in factors significant risk between ischemic and hemorrhagic stroke. Most previous studies discussing the relationship between hypertension and stroke risk often report a stronger relationship between hypertension and the incidence of hemorrhagic stroke than ischemic stroke.[16] This is supported by Sanyasi's research et al., 2018 who found that hypertension was the most common risk factor for hemorrhagic et al stroke (71.4%) compared to ischemic stroke (48%) and was statistically the only risk factor that significantly increased the risk of hemorrhagic stroke.[14]

Sanyasi et al., 2018 in his research stated that hypertension increases the risk of hemorrhagic stroke by 3,680 times, and if blood pressure reaches >160/90 mmHg, the risk of hemorrhagic stroke increases 7 times compared to normotensive sufferers.[14] As per the literature, hypertension is a very important risk factor for hemorrhagic stroke, although it contributes to atherosclerotic disease which can also cause ischemic stroke. A history of hypertension can damage arteries throughout the body and result in the rupture of blood vessels and blockages of arteries in the brain.[17] Risk factors for DM in this study were found to be more common in patients with ischemic stroke (10.7%) than hemorrhagic stroke (3.6%). The results of this research are similar to research conducted by Sanyasi et al., 2018 which found a higher prevalence of DM in ischemic stroke patients (21.6%) compared to hemorrhagic stroke (9.3%).[14] Another research conducted by Mosenzon et al., 2023 also found a higher incidence of DM in ischemic stroke compared to hemorrhagic stroke (33% and 26% respectively). These findings are based on the fact that dyslipidemia, hyperglycemia, and insulin resistance that occur in DM patients result in various physiological changes, including the formation of low-density lipoprotein (LDL) are atherogenic, advanced glycation end products, and activate pro-inflammatory signals that impact the arterial wall, thereby leading to the development of atherosclerotic lesions.[18]

The mean D-dimer level in hemorrhagic stroke patients was higher, namely 1288.25 ± 2.51 compared to ischemic stroke (794.33 ± 2.63). Statistical analysis showed a p-value of 0.055 (p>0.05), which means that there was no significant difference in D-dimer levels between ischemic stroke and hemorrhagic stroke patients. This research is similar to research conducted by Mulyono which found that plasma D-dimer levels in hemorrhagic strokes were higher than in ischemic strokes, although there was an increase in both types of stroke. Comparison of D-dimer levels showed a significant difference with p=0.04 with the median D-dimer level for hemorrhagic strokes being 700 (100-4200) while for ischemic strokes being 400 (100-3700).[10] The results of this research are different from research conducted by Abebe et al., 2023 who obtained a higher mean D-dimer value in ischemic stroke compared to hemorrhagic stroke (each of 0.79 ± 0.31 and 0.57±0.22 µg/ml).[19] D-dimer is a fibrin degradation product that reflects coagulation and fibrinolytic processes that can vary over time. This process may correlate with the degree of vascular injury. High D-dimer concentrations have been shown to be associated with cardiovascular events and major bleeding.[20] In addition, D-dimer is known to be associated with biomarkers of nerve damage in severe stroke and can predict progression and death in acute stroke.[19]

D-dimer is a protein fragment produced from the degradation of fibrin, a key protein in the blood clotting process. D-dimer levels in the blood reflect the balance between coagulation (blood clotting) and fibrinolytic (fibrin dissolution) activities. Elevated D-dimer levels

indicate excessive coagulation and fibrinolytic activation, which can be triggered by a variety of conditions, including vascular injury, thrombosis, and hemorrhage. D-dimer is formed from two covalently bound fibrin fragments, namely D fragment and D fragment. D fragment is produced by plasmin, a protease enzyme that breaks down fibrin. The D fragment is bound to the D fragment via a stable covalent bond, producing a D-dimer. The D-dimer structure is stable and resistant to further degradation, making it ideal as a biomolecular marker for fibrinolytic activity. D-dimer can be measured in blood plasma by various methods, including immunoassay and enzyme-linked immunosorbent assay (ELISA). The coagulation and fibrinolytic processes are important mechanisms for maintaining hemostasis, namely the balance between sufficient blood clotting to prevent bleeding and sufficient fibrinolytic to prevent the formation of unwanted blood clots. Under normal conditions, D-dimer levels in the blood are low because coagulation and fibrinolytic activities are balanced.

Injury to the blood vessel wall triggers activation of coagulation to form a blood clot and stop bleeding. Activation of this coagulation produces fibrin, which is then degraded by plasmin into D-dimer. Thrombosis occurs when a blood clot forms in an uninjured blood vessel. D-dimer is produced as a result of the degradation of fibrin in blood clots. Significant bleeding can trigger coagulation activation to stop the bleeding. This can cause an increase in D-dimer levels. Infection can trigger coagulation and fibrinolytic activation, causing an increase in D-dimer levels. Some types of cancer can cause increased D-dimer levels. Research shows that increased D-dimer levels are associated with an increased risk of cardiovascular events, such as myocardial infarction (heart attack) and stroke. This is thought to be because high D-dimer levels reflect excessive activation of coagulation, which can increase the risk of blood clot formation in the arteries. High D-dimer levels may also be associated with a risk of major bleeding, especially in patients with underlying conditions such as trauma, cancer, or liver disease. This is thought to be because high D-dimer levels reflect excessive fibrinolysis, which can cause excessive fibrin degradation and increase the risk of bleeding. D-dimer can be used to help diagnose TEV (venous thromboembolism), such as deep vein thrombosis (DVT) and pulmonary embolism (PE). High D-dimer levels in patients with symptoms of TEV can help establish the diagnosis. D-dimer levels can be used to monitor the effectiveness of TEV treatment. A decrease in D-dimer levels indicates that treatment is effective, whereas an increase in D-dimer levels may indicate treatment failure or recurrent thrombosis. D-dimer levels can be used to predict the risk of complications in patients with ACS (Acute Coronary Syndrome). High D-dimer levels are associated with an increased risk of death and recurrent myocardial infarction. D-dimer levels can be used to predict the risk of bleeding in patients with trauma or critical illness. High D-dimer levels are associated with an increased risk of major bleeding.[17-20]

5. Conclusion

There were no differences in the characteristics of ischemic and hemorrhagic stroke patients based on age and gender. Meanwhile, based on risk factors, hypertension tends to be found to be higher in patients with hemorrhagic stroke and diabetes mellitus is more dominant in patients with ischemic stroke. The mean D-dimer level in hemorrhagic stroke patients is high (1288.25 ± 2.51), however, statistical analysis showed there was no significant difference between D-dimer levels in hemorrhagic and ischemic stroke patients. It is recommended that further research be carried out which also takes into account the factors that influence D-dimer levels in stroke patients.

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