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Correlation between D-dimer and first-ever acute ischemic stroke (AIS) severity in Dr. Sardjito General Hospital, Yogyakarta

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ABSTRACT

Acute ischemic stroke (AIS) continuing to be an entity causing morbidity and mortality worldwide. The National Institutes of Health Stroke Scale (NIHSS) is a largely used as clinical assessment instrument to measure neurological deficit of stroke. Studies concerned that D-dimer, a fibrin degradation product, has as a potential biomarker in predicting stroke severity and prognosis. This study aimed to investigate the correlation between D-dimer levels and NIHSS score in patients with a first-ever AIS. This cross-sectional study used the stroke registry data of the Dr. Sardjito General Hospital, Yogyakarta from October 2021 to December 2022. A total 83 patients who met the inclusion and exclusion criteria were involved. The blood D-dimer level was measured during admission. The NIHSS scores were assessed within 24 hr of admission. The correlation between D-dimer levels and NIHSS scores were analysed using Spearman's test. Multiple analysis was performed to evaluate the association of non-dependent risk factors using multiple logistic regression. The mean age of subjects was 60.77±11.08 yr, with a slightly males predominant (54.2%). The mean value of NIHSS score was 6.59 ± 7.00 and D-dimer level was 712.02 ± 1159.2 ng/mL. A significant positive correlation between D-dimer and NIHSS score (r= 0.475; p= 0.01) was observed. Furthermore, D-dimer remained showing an independent association with on-admission NIHSS score (p= 0.026). In conclusion, D-dimer level in stroke patients is associated with more severe on-admission NIHSS score.

ABSTRAK

Stroke iskemik akut (SIA) masih menjadi penyebab morbiditas dan mortalitas di seluruh dunia. *The National Institutes of Health Stroke Scale* (NIHSS) merupakan alat penilaian klinis yang banyak digunakan untuk mengukur defisit neurologis pada stroke. Penelitian menunjukkan bahwa D-dimer, produk degradasi fibrin, berpotensi sebagai biomarker untuk memprediksi keparahan dan prognosis stroke. Penelitian ini bertujuan mengkaji hubungan antara kadar D-dimer dan skor NIHSS pada pasien dengan serangan pertama SIA. Penelitian potong lintang ini menggunakan data registrasi stroke RSUP Dr. Sardjito Yogyakarta pada bulan Oktober 2021 hingga Desember 2022. Sebanyak 83 pasien yang memenuhi kriteria inklusi dan eksklusi diikutsertakan dalam penelitian. Kadar D-dimer darah diukur saat masuk rumah sakit. Skor NIHSS dinilai dalam waktu 24 jam setelah masuk. Korelasi antara kadar D-dimer dan skor NIHSS dianalisis menggunakan uji Spearman. Analisis regrisi logistik dilakukan untuk mengevaluasi hubungan faktor risiko non-dependen. Usia rata-rata subjek adalah 60,77 ± 11,08 tahun, dengan sebgaian besar laki-laki (54,2%). Rerata skor NIHSS sebesar 6,59 ± 7.00 dan kadar D-dimer sebesar 712,02 ± 1159,2 ng/mL. Terdapat hubungan positif nyata antara D-dimer dan skor NIHSS (r= 0,475; p= 0,01). Selain itu, D-dimer tetap menunjukkan hubungan independen dengan skor NIHSS saat masuk (p= 0,026). Simpulan, kadar D-dimer pada pasien stroke berhubungan dengan skor NIHSS saat masuk rumah sakit yang lebih parah.

Keywords:
first-ever ischemic stroke;
acute ischemic stroke;
stroke severity;
D-dimer;
National Institutes of Health Stroke Scalep

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INTRODUCTION

In 2022, the World Stroke Organization (WSO) reported that the global burden of stroke is significant with more than 101 million people currently living with stroke worldwide. Stroke is the second leading cause of death after ischemic heart disease.[1] In Indonesia, stroke prevalence is 0.0017% in rural areas and 0.022% in urban areas with the overall prevalence being 10.9/1,000,000.[2] In 2016, the Indonesian Health Insurance reported that stroke healthcare costs were 1.43 trillion rupiah. It rose to 2.19 trillion rupiah in 2017, and in 2018, it reached 2.57 trillion IDR.[3]

The increase in stroke prevalence is due to an increasing aging population, a sedentary lifestyle, and an increasing incidence of the established risk factors including hypertension, diabetes mellitus, and atrial fibrillation. The burden of ischemic stroke is not limited to its acute impacts but also causes long-term disability, cognitive impairment, and increased mortality.[4] Recognizing the factors associated with stroke severity can benefit optimizing acute management strategies and in developing targeted interventions to prevent long-term complications.

One of the potential biomarkers in acute ischemic stroke (AIS) is D-dimer, a product of fibrin degradation. D-dimer reflects thrombosis and hypercoagulability, consistent with stroke pathogenesis.[5] D-dimer increases immediately after AIS and then gradually decreases thereafter.[6] Various medical conditions can cause an increase in D-dimer level, including a history of cancer, active cancer,[7] and COVID-19 infection.[8] Previous studies reported that higher D-dimer levels are associated with a larger infarct volume,[9] more severe neurological deficits, and worse functional outcomes in ischemic stroke patients.[6] These findings suggest that D-dimer may serve as a valuable predictor of stroke severity and guidance of treatment decisions for clinicians.

The National Institutes of Health Stroke Scale (NIHSS) is a widely used scale ranging from 0-42 to assess clinical neurological deficit severity in stroke patients, as well as to assess the patients' response to thrombolytic therapy. A higher NIHSS score reflects more severe neurological deficit. The NIHSS's ability to predict post-stroke outcomes helps clinicians provide accurate information to patients, set realistic treatment goals, and plan patients' discharge.[10] Compared to the first event of stroke, a recurrent stroke leads to a more serious and difficult to treat condition, as well as has a higher mortality rate.[11]

Previous studies generally do not specifically investigate the correlation between D-dimer levels and stroke severity in the first ever acute ischemic stroke, and did not exclude other conditions known to raise D-dimer levels such as cancer and COVID-19 infection; hence, there are many confounding factors that can obscure the genuine correlation between these variables. This study aimed to investigate the correlation between D-dimer levels and stroke severity at admission measured by the NIHSS score, in patients who had a first-ever acute ischemic stroke hospitalized in the Dr. Sardjito General Hospital, Yogyakarta.

MATERIAL AND METHODS

Study design and subjects

This cross-sectional study used the stroke registry data of the Dr. Sardjito General Hospital, Yogyakarta from October 2021 until December 2022. The inclusion criteria were as follows: 1) first-ever ischemic stroke as proven by clinical symptoms evaluated by the neurologist, past medical history from history taking and/or medical record, and head CT scan at admission; 2) arrival to the hospital within 48 hr of stroke symptom onset. Patients with a history of cancer or active cancer, anemia (Hb<10 mg/dL), acute/chronic renal failure,

liver enzymes abnormality, electrolytes disturbance based on the history and physical examination were excluded in this study. Since the data collection was conducted during the pandemic period, we also excluded patients with COVID-19 diagnosis as it is known to elevate D-dimer levels. The status of COVID-19 infection was confirmed using an antigen test based on standardized nasal or oropharyngeal swab examination.

This study was approved by the Medical and Health Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University, Yogyakarta/Dr. Sardjito General Hospital, Yogyakarta with reference number KE/FK/0288/EC. This research is free of charge and the researcher guarantees the confidentiality of the data obtained and only the researcher has access to the raw data.

Data collection

A total 83 patients who met the criteria were included in this study. Several parameters were evaluated, namely demographic and clinical factors, including age, gender, body mass index, hypertension, diabetes mellitus, dyslipidemia, heart disease, smoking history, and stroke severity. Stroke severity measured with the NIHSS score within 24 hr of admission was categorized as mild neurological deficit (0-4 points) and having a good outcome; and moderate to severe (>4 points) neurological deficit and having a poor outcome. Laboratory tests were also carried out within the first 24 hr of admission, including routine hematology tests, fasting blood glucose levels, lipid profile, and D-dimer level. The normal value D-dimer is <500 ng/mL.

Analysis

All statistical analyses were performed using SPSS version 26.0. Continuous variables are shown as mean ± standard deviation (SD). Categorical variables were displayed in terms of frequency and percentage. To examine the relationship between D-dimer levels and stroke severity, we conducted Spearman correlation analysis due to the non-normal distribution of the data. The independent relationship of several confounding variables was evaluated using logistic regression. The correlation analysis presented an odds ratio (OR) and 95% confidence interval (CI). A statistically significant association of variables was demonstrated by a p-value of <0.05.

RESULTS

The mean age of subjects was 60.77 ± 11.08 yr, with a slightly higher proportion of males (54.2%). The largest group was the 51 – 65-year age group (47%). Mild neurological deficits (NIHSS 0-4) were found in 50.9% of subjects. The mean NIHSS score was 6.59 ± 7.00, and the mean D-dimer level was 712.02 ± 1159.2 ng/mL. Most patients had a history of hypertension and dyslipidemia. The overall baseline characteristics of research subjects are presented in TABLE 1.

D-dimer level and NIHSS score were measured on an ordinal scale. D-dimer was classified as normal if <500 ng/mL and high if ≥500 ng/mL.[12] The NIHSS score was categorized as a mild neurological deficit if the score was ≤4 and as a moderate-severe neurological deficit if the score was >4.[13]

A positive correlation between D-dimer level and NIHSS was observed based on Spearman test (r= 0.475; p= 0.01) in TABLE 2. Multiple logistic regression to assess the relationship between NIHSS and several markers, namely D-dimer level, age, platelets, leukocytes, and fasting blood glucose (FBG) was presented in TABLE 3. D-dimer remained independently associated with the NIHSS score (p= 0.026).

TABLE 1. Characteristics of subjects (n=83)

Characteristics of subjects	Number
Gender [n (%)]	
• Male	45 (54.2)
• Female	38 (45.8)
Hypertension [n (%)]	67 (80.7)
DM [n (%)]	32 (38.6)
Dyslipidemia [n (%)]	51 (61.4)
Heart disease [n (%)]	26 (31.3)
Smoking [n (%)]	23 (27.7)
Age (mean ± SD yr)	60.77 ± 11.08
• ≤ 35	3 (3.6)
• 36 – 50	10 (12)
• 51 – 65	39 (47)
• > 65	31 (37.3)
NIHSS (mean ± SD ng/mL)	6.59 ± 7.00
• Mild (≤4)	42 (50.9)
• Moderate – severe (>4)	41 (49.1)
D-dimer (mean ± SD ng/mL)	712 ± 1159
• Normal	55 (66.3)
• High	28 (33.7)
Platelets (mean ± SD 10^9/L)	262.3 ± 102.4
Leukocytes (mean ± SD10^3/L)	9.6 ± 4.0
FBG (mean ± SD mg/dL)	136.4 ± 56.6

Note: NIHSS (National Institutes of Health Stroke Scale); FBG (fasting blood glucose).

TABLE 2. Spearman correlation between NIHSS score and D-dimer levels

			Skor NIHSS	D-dimer
Spearman's rho	Skor NIHSS	Correlation coefficient	1.000	.475**
		Sig. (2-tailed)	.	.000
		n	83	83
	D-dimer	Correlation coefficient	.475**	1.000
		Sig. (2-tailed)	.000	.
		n	83	83

**. Correlation is significant at the 0.01 level (2-tailed)

TABLE 3. Logistic regression analysis of NIHSS score and associated variables

Variable	OR	p	95% CI
Age	1.030	0.240	0.981 – 1.081
D-dimer	1.001	0.026*	1.000 – 1.002
Platelets	1.004	0.188	0.998 – 1.009
Leukocytes	1.104	0.218	0.943 – 1.293
FBG	1.009	0.071	0.999 – 1.018

Note: NIHSS (National Institutes of Health Stroke Scale); FBG (fasting blood glucose), OR (odds ratio); CI (confidence interval); *) statistically significant $p<0.05$.

DISCUSSION

This study demonstrated a statistically significant positive correlation between D-dimer levels and NIHSS scores (r= 0.475; p= 0.01). This finding corroborates previous studies reporting that higher D-dimer levels are associated with larger infarct volumes,[9] more severe neurological deficits, and worse functional outcomes in ischemic stroke patients.[6]

Various mechanisms have been proposed to explain the impact of D-dimer levels on AIS outcomes. Elevated D-dimer indicates the process of thrombus formation in the intravascular milieu, including cerebral vessels, reflecting a state of systemic hypercoagulability. In addition, D-dimer can influence the monocytes to release proinflammatory cytokines such as interleukin-6 (IL-6), triggering an inflammation state.[6]

Several mechanisms may explain the correlation between elevated D-dimer levels in AIS and the severity of the stroke, as well as unfavorable outcomes. One possible explanation is the significant involvement of D-dimer in coagulation activity, thrombin generation, and fibrin formation. Elevated D-dimer indicates thrombus formation process in the intravascular milieu, including cerebral vessels, reflecting a systemic hypercoagulability. Moreover, evidence indicates that D-dimer represents a predominant risk factor for venous thrombosis events post-stroke, indicative of a prothrombotic condition that heightens susceptibility to major thrombotic episodes. Alternatively, D-dimer can influence monocytes to release proinflammatory cytokines such as IL-6, triggering an inflammation state. Considering the adverse implications of recurrent vascular disease, subsequent vascular events could lead to functional impairment.[6,14]

Different subtypes of AIS show variable D-dimer levels. The highest levels were observed in cardio-embolic stroke, while the lowest levels were found in the lacunar subtype. This difference can be attributed to the fact that the cardio-embolic source of thrombus is mainly caused by an intravascular stasis state and is considered fibrin-rich. On the other hand, the amount of thrombus in lacunar stroke has a lesser impact on elevating the D-dimer level significantly.[9] Therefore, it is reasonable that higher D-dimer levels are associated with a larger infarct volume and will cause more severe neurological deficits as well.

In this study, we only investigated patients who came to the hospital within 48 hr after symptom onset, because D-dimer increases immediately after AIS and then gradually decreases thereafter,[6]

while the neurological deficit will persists. A study by Sienkiewicz-Jarosz *et al.*[15] demonstrated D-dimer levels may change variably at different time points after the onset of AIS. They measured D-dimer levels at admission, as well as at 24 and 72 hr after the stroke onset. The study showed that patients with poor outcomes (mRS ≥3) had higher D-dimer levels compared to the good outcome group.[15]

Variable medical conditions can increase the level of D-dimer. A study by Nam *et al.*[7] reported that an increased D-dimer level had a positive correlation with active cancer, history of cancer, and venous thrombo-embolism. Apart from that, according to a meta-analysis conducted by Rostami *et al*.[8] the increase in D-dimer was also found in COVID-19 cases. Early stages of COVID-19 may be associated with high D-dimer, prolonged prothrombin time, and increased fibrinogen levels, which indicates an activation of coagulation and thrombosis pathways. Thus, by excluding patients who have a history of cancer, active cancer, or COVID-19, the impact of such confounding factors that increase D-dimer levels can be addressed.

Patients with recurrent AIS tend to experience more severe neurological deficits than patients with a first AIS.[11] This study only included patients who experienced their first AIS attack, therefore the association between D-dimer level and stroke severity (NIHSS score) was more clearly illustrated.

Individuals who survive an ischemic stroke are significantly at risk of experiencing a recurrent stroke within two years. Of patients who survive an initial ischemic stroke, approximately 85% survive, and 15-30% of them experience a recurrence within the first two years. Recurrent stroke is a concern due to its contribution to increasing patients' mortality, rehospitalization, and long-term disability in the setting of stroke care. Compared with initial stroke occurrence, neurological disorders resulting from recurrent stroke lead to more severe disability, are more complicated in management, and are associated with higher mortality.[11] Consequently, secondary prevention measures after the first stroke are essential for reducing the risk of recurrence.

The multiple logistic regression analysis revealed a predictive relationship of several variables on NIHSS. It showed that the D-dimer level, age, platelets, leukocytes, and FBG indicated a positive association with the NIHSS score based on the OR findings. The value of OR indicates that age, D-dimer level, platelets, leukocytes, and FBG are associated with an increased NIHSS score. However, the only variable showing a statistically significant relationship with NIHSS score was D-dimer level (p= 0.026). This result differs from several previous studies which reported that stroke severity was related to the number of platelets,[16] leukocytes,[17,18] and FBG.[19]

Platelets have an important function in initiating blood clot formation and activating coagulation during the early and developing stages of AIS. Despite their significance, there have been limited clinical research in the last decade investigating the prognostic value of platelets in AIS. Abnormal platelet levels are associated with an increased risk of stroke, stroke-related death, recurrent stroke, and poor clinical outcome.[16]

A study by Nardi *et al.*[17] found that leukocytosis at the time of AIS onset was associated with initial stroke severity but did not have a significant impact on clinical outcomes. The leukocyte count at hospital admission appears to reflect the initial stroke severity and possible stress response without an independent influence on clinical outcome. Based on these findings, it is suggested that efforts focused on reducing the number of leukocytes in the peripheral circulation

during the acute phase of stroke are not recommended.[18]

In the acute stage of stroke, glycemic parameters, such as FBG, are known to be associated with post-stroke clinical outcome. Current guidelines recommend strict glycemic control (normoglycemia) for the management of acute ischemic stroke. A study by Lee *et al.*[19] found that FBG levels were associated with initial stroke severity.

There are several limitations to this study. The small sample size included in the study cannot precisely represent the impact of the exposure in the population. The temporal relationship between exposure and outcome cannot be viewed in this study due to the cross-sectional investigation. In addition, the research was carried out in single institution, therefore it cannot describe the general population.

CONCLUSION

In conclusion, there is a significant positive correlation between D-dimer level and admission NIHSS score severity in first ever acute ischemic stroke patients. After multivariate analysis, the D-dimer level remained significantly associated with the NIHSS score.

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