Original Article

Association of reactive hyperglycemia, D-dimer, and asymmetric dimethylarginine (ADMA) with outcomes in acute ischemic stroke

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Abstract

Acute ischemic stroke is frequently accompanied by stress-related (reactive) hyperglycemia and may involve coagulation activation and endothelial dysfunction, reflected by D-dimer and asymmetric dimethylarginine (ADMA) levels, respectively. These factors may influence clinical outcomes. The aim of this study was to evaluate the associations of reactive hyperglycemia, D-dimer, and plasma ADMA with stroke outcomes in patients with acute ischemic stroke. A cross-sectional study was conducted among patients with acute ischemic stroke admitted to the neurology ward and stroke unit of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, between May and September 2024. Functional stroke outcome (FSO) was assessed using the Barthel Index, and disability stroke outcome (DSO) was assessed using the modified Rankin Scale (mRS). A total of 123 patients were included. The findings indicate that mean admission blood glucose was significantly higher in the improved FSO group than in the unchanged-worsened group (p=0.004), whereas mean blood glucose did not differ significantly across DSO categories (p=0.194). Mean D-dimer was significantly higher in the unchanged-worsened FSO group than in the improved group (538.6±249.4 vs 398.4±128.5 ng/mL; p<0.001). Across DSO categories, D-dimer showed a significant difference only between the no-disability and moderate-disability groups (p=0.044), without a consistent graded pattern. Mean ADMA levels were not significantly different between FSO groups (p=0.136), but it was statistically significant between DSO categories (slight vs moderate disability), p=0.045. The present analysis indicated that elevated D-dimer, dyslipidemia, heart disease, and GCS were significantly associated with FSO. Systolic blood pressure, diastolic blood pressure, reactive hyperglycemia, and hypertension were significantly associated with DSO severity. Overall, elevated D-dimer was more strongly associated with Barthel Index-based functional outcome, whereas reactive hyperglycemia was associated with mRS-based disability outcome.

Keywords: Reactive hyperglycemia, D-dimer, ADMA, functional stroke outcome, disability stroke outcome

Introduction

Stroke is an acute cerebrovascular disorder characterized by focal neurological deficits resulting from vascular injury to the central nervous system, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. It remains a leading cause of mortality and long-term disability worldwide [1]. Ischemic stroke accounts for approximately 80% of cases and arises

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from arterial occlusion that reduces cerebral blood flow below the threshold necessary for neuronal survival, leading to hypoxia, energy failure, and tissue necrosis [2-4]. Secondary injury processes, including cerebral edema developing within the first 24–72 hours, further exacerbate neuronal damage [5]. Clinically, ischemic stroke manifests as acute focal deficits such as hemiparesis, sensory impairment, cranial nerve involvement, reduced consciousness, aphasia, visual field defects, and other higher cortical dysfunctions [6].

Beyond structural vascular injury, systemic pathophysiological responses substantially influence stroke severity and prognosis. Reactive hyperglycemia is frequently observed during the acute phase in both diabetic and non-diabetic patients and has been identified as an independent predictor of unfavorable outcomes [7,8]. Activation of coagulation and fibrinolytic pathways is another key feature of acute stroke. D-dimer, a fibrin degradation product, reflects thrombus formation and turnover; elevated levels indicate a hypercoagulable state and have been associated with increased stroke severity and adverse outcomes [9]. Endothelial dysfunction further contributes to cerebrovascular pathology. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of endothelial nitric oxide (NO) synthase, reduces NO bioavailability and may promote vascular impairment [9]. Increased ADMA concentrations have been reported in individuals with cardiovascular risk factors, including hypertension, smoking, hypercholesterolemia, diabetes mellitus, and renal insufficiency [11]. Although reactive hyperglycemia, D-dimer, and ADMA have each been individually associated with unfavorable outcomes, their integrated relationship with functional recovery after acute stroke remains insufficiently characterized. In particular, limited data are available regarding the combined impact of metabolic stress, coagulation activation, and endothelial dysfunction on standardized functional outcome measures in clinical practices.

Stroke outcomes commonly assessed using functional stroke outcome (FSO) and disability stroke outcome (DSO), measured with validated instruments, namely the Barthel Index and the modified Rankin Scale (mRS), respectively [10,11]. The Barthel Index is extensively used to assess activities of daily living [12] and has shown strong reliability and validity for evaluating functional recovery and rehabilitation effectiveness in stroke populations [13]. The mRS was initially developed to assess post-stroke handicap but is now predominantly applied to evaluate global disability [14]. The scale has demonstrated good reliability and validity in determining functional outcomes after stroke [15]. Although both tools demonstrate good reliability and validity, they primarily capture functional status and may not fully reflect the underlying biological processes influencing recovery. Integrating clinical scales with relevant biomarkers may therefore improve prognostic stratification and guide individualized management strategies. The aim of this study was to evaluate the association between reactive hyperglycemia, D-dimer levels, and ADMA concentrations with functional and disability outcomes in patients with acute ischemic stroke.

Methods

Study design and setting

A cross-sectional study was conducted to evaluate the associations between reactive hyperglycemia, D-dimer levels, and plasma ADMA levels with acute ischemic stroke outcomes. The study was conducted at the neurology ward and stroke unit of Dr. Zainoel Abidin Hospital in Banda Aceh, Indonesia, a provincial referral hospital in Aceh Province. Data collection was performed between May and September 2024. All eligible patients diagnosed with acute ischemic stroke and admitted to the neurology ward and stroke unit during the study period were screened for inclusion. The diagnosis of ischemic stroke was confirmed through clinical evaluation and non-contrast head computed tomography (CT) imaging. Written informed consent was obtained from all participants or, where applicable, from their legally authorized representatives prior to study inclusion. All study procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Study population and eligibility criteria

The study population comprised patients diagnosed with acute ischemic stroke who were admitted during the study period. Eligible participants were adults aged 20–80 years with a confirmed diagnosis of first-ever acute ischemic stroke and hospitalization during the acute

phase. Both male and female patients were included. Patients were excluded if they had a history of recurrent stroke, severe systemic infection (such as sepsis or pneumonia), chronic kidney disease, hematological disorders (including anemia or leukemia), malignancy, or recent head trauma. These exclusion criteria were applied to minimize potential confounding factors that could influence biomarker levels or stroke outcomes.

Sample size and sampling method

Participants were recruited using a non-probability consecutive sampling approach. All patients who met the predefined inclusion and exclusion criteria and provided informed consent were consecutively enrolled until the required sample size was achieved. The minimum sample size was initially calculated based on an estimated population proportion with a 95% confidence level and a margin of error of 10%, yielding a minimum requirement of 50 participants. However, all eligible patients during the study period were included to increase statistical power and improve the precision of the estimates. A total of 123 eligible patients were ultimately enrolled in this study.

Study variables and measurements

The dependent variables in this study were FSO and DSO following ischemic stroke. FSO was assessed using the Barthel Index, which evaluates ten domains of activities of daily living, including feeding, bathing, dressing, toileting, transfers, mobility, stair climbing, bowel control, and bladder control [14]. The Barthel Index score ranges from 0 to 100, with higher scores indicating greater functional independence. In this study, FSO was determined by comparing Barthel Index scores between the first day of admission and the seventh day of hospitalization and categorized as improved if the Barthel Index score increased, and unchanged-worsened if the score remained the same or decreased. DSO was assessed using the mRS on the seventh day of hospitalization or at discharge. The mRS ranges from 0 (no symptoms) to 6 (death) and was categorized into no disability (mRS 0–1), slight disability (mRS 2), moderate disability (mRS 3–4), severe disability (mRS 5), and dead (mRS 6) for statistical analysis.

The independent variables in this study included reactive hyperglycemia, D-dimer level, and plasma ADMA level. Reactive hyperglycemia was defined based on admission blood glucose levels >140 mg/dL. D-dimer levels were measured from plasma samples using standard laboratory methods and categorized as elevated if >500 ng/mL. Plasma ADMA levels were measured using standard laboratory procedures and categorized as elevated if >100 pg/dL.

Additional clinical variables were assessed and recorded as potential covariates, including demographics such as age and sex; Glasgow Coma Scale (GCS) score; blood pressure (systolic and diastolic); lipid profiles (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides); laboratory parameters such as hemoglobin, leukocyte count, platelet count, urea, creatinine, and uric acid; the presence of hypertension, diabetes mellitus, heart disease and dyslipidemia; vascular disorder subtype; as well as the stroke lesion location.

Laboratory procedures

Venous blood samples were collected from all patients within the first 24 hours of hospital admission under aseptic conditions. Blood specimens were obtained after initial clinical stabilization and prior to major therapeutic interventions whenever possible. Admission blood glucose levels were measured using an enzymatic glucose oxidase method with an automated clinical chemistry analyzer (Roche Diagnostics, Mannheim, Germany). Routine hematological parameters were analyzed using an automated hematology analyzer (Sysmex Corporation, Kobe, Japan), and other serum biochemical parameters were measured using standard enzymatic colorimetric assays on a clinical chemistry analyzer (Abbott Laboratories, Abbott Park, IL, USA).

Plasma D-dimer levels were determined using an immunoturbidimetric assay with monoclonal antibody-based detection of cross-linked fibrin degradation products (Siemens Healthineers, Erlangen, Germany). Plasma ADMA levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Elabscience Biotechnology Co., Ltd., Wuhan, China), following the manufacturer's instructions.

Research procedures

All patients presenting with suspected acute stroke underwent a comprehensive clinical evaluation by a neurologist, followed by a non-contrast head CT to confirm the diagnosis of ischemic stroke. Patients who met the predefined inclusion and exclusion criteria were approached for participation. The study objectives and procedures were explained to patients and/or their legally authorized representatives, and written informed consent was obtained prior to enrollment. Following enrollment, baseline demographic and clinical data were recorded, including age, sex, medical history, blood pressure, and GCS score. Venous blood samples were collected within the first 24 hours of admission for laboratory analyses, including blood glucose, D-dimer, ADMA, and other routine hematological and biochemical parameters. FSO was assessed using the Barthel Index on the first day of hospitalization and re-evaluated on the seventh day to determine changes in functional status. DSO was assessed using the mRS on the seventh day of hospitalization or at discharge. All clinical assessments were performed by trained clinicians who were blinded to laboratory biomarker results.

Data analysis

Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Prior to inferential analysis, the distribution of continuous variables was assessed for normality using appropriate statistical tests. Comparisons of glucose, D-dimer levels, and ADMA concentrations between unchanged-worsened versus improved FSO were performed using the unpaired Student t-test, while their comparisons between DSO categories based on the mRS were assessed using one-way analysis of variance (ANOVA). Factors associated with FSO and DSO were analyzed using the Chi-squared, unpaired Student t-test, or ANOVA as appropriate. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated if possible. A two-tailed $p<0.05$ was considered statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software (IBM Corp., Armonk, NY, USA).

Results

Characteristics of study samples

A total of 123 patients with acute ischemic stroke were included in this study and their characteristics are presented in **Table 1**. The mean age was 58.9±11.6 years, with a slightly higher proportion of females than males (54.5% vs 45.5%). The mean GCS score was 14.8±0.9. The average systolic and diastolic blood pressures were 158.0±21.6 mmHg and 87.9±13.3 mmHg, respectively. Most patients had hypertension (81.3%) and dyslipidemia (55.3%), while diabetes (42.3%) and heart disease (2.4%) were less frequent. Small vessel disease was the predominant vascular disorder type (80.5%), and most lesions were located in the cortical region (87.8%) (**Table 1**).

Table 1. Characteristics of patients with acute ischemic stroke included in this study (n=123)

Variable	Frequency (%)
Age (year), mean±SD	58.9±11.6
Sex	
Male	56 (45.5)
Female	67 (54.5)
Glasgow Coma Scale, mean±SD	14.8±0.9
Blood pressure	
Systolic (mmHg)	158.0±21.6
Diastolic (mmHg)	87.9±13.3
Laboratory, mean±SD	
Hemoglobin (g/dL)	13.3±1.8
Leukocytes (1000 cells/µL)	9.7±3.9
Platelets (1000 cells/µL)	289.2±88.7
Urea (mg/dL)	34.1±19.3
Creatinine (mg/dL)	0.9±0.4
Total cholesterol (mg/dL)	197.4±42.3
High density lipoprotein (mg/dL)	36.6±11.9

Variable	Frequency (%)
Low-density lipoprotein (mg/dL)	123.2±39.5
Triglycerides (mg/dL)	136.7±48.9
Uric acid (mg/dL)	5.1±1.4
Hypertension	
No	23 (18.7)
Yes	100 (81.3)
Diabetes	
No	71 (57.7)
Yes	52 (42.3)
Heart disease	
No	120 (97.6)
Yes	3 (2.4)
Dyslipidemia	
No	55 (44.7)
Yes	68 (55.3)
Vascular disorder types	
Small vessel disease	99 (80.5)
Large vessel disease	24 (19.5)
Lesion site	
Cortical	108 (87.8)
Subcortical	15 (12.2)
Reactive hyperglycemia	
Yes	65 (52.8)
No	58 (47.2)
D-dimer level	
Elevated	43 (35.0)
Normal	80 (65.0)
ADMA level	
Elevated	6 (4.9)
Normal	117 (95.1)

Comparison of reactive hyperglycemia with functional and disability stroke outcomes measured by the Barthel Index and mRS

Comparisons of admission blood glucose levels across the two stroke outcomes (FSO and DSO) is presented in **Figure 1**. The mean admission blood glucose level was significantly higher in patients with improved FSO than in those with unchanged or worsened FSO (170.6±55.6 mg/dL vs 141.1±35.9 mg/dL; p=0.004) (**Figure 1A**). In contrast, mean admission blood glucose levels varied across DSO categories (no disability: 168.2±61.5 mg/dL; slight disability: 147.9±43.2 mg/dL; moderate disability: 164.8±38.1 mg/dL), but the overall between-group difference was not statistically significant (p>0.05) (**Figure 1B**). No patients were classified as having severe disability (mRS 5) or dead (mRS 6). Taken together, these findings indicate that admission glycemia may have a differential association with short-term functional improvement (Barthel Index-based FSO) versus disability status (mRS-based DSO), and the pattern observed across DSO categories does not suggest a consistent dose-response relationship in this cohort.

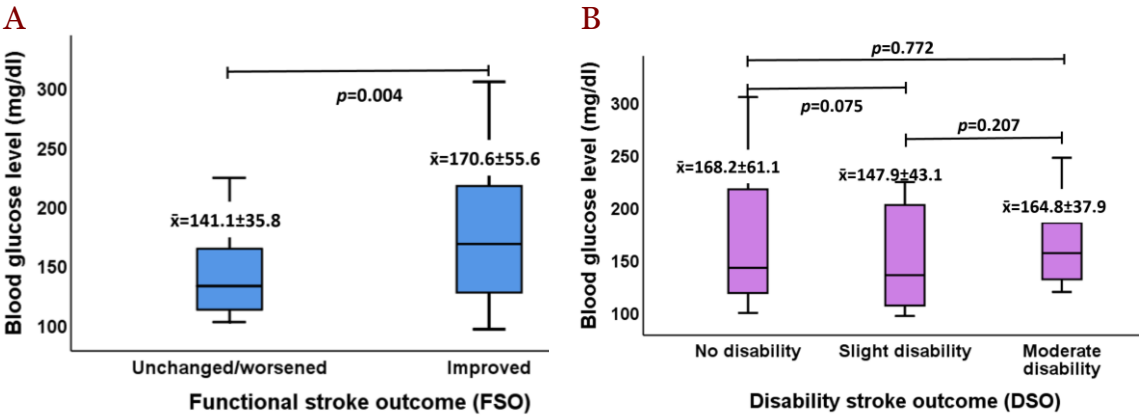

Figure 1. Comparisons of blood glucose level based on functional stroke outcome (FSO) (A) and disability stroke outcome (DSO) (B) in patients with acute ischemic stroke.

Comparison of D-dimer levels with functional and disability stroke outcomes measured by the Barthel Index and mRS

Comparison of D-dimer levels according to the two stroke outcomes (FSO and DSO) is presented in **Figure 2**. Patients in the unchanged/worsened FSO group had significantly higher D-dimer levels than those in the improved FSO group (538.6±249.4 ng/mL vs 398.4±128.5 ng/mL; $p<0.001$) (**Figure 2A**), suggesting that higher coagulation/fibrinolytic activity at admission may be associated with poorer short-term functional recovery. In contrast, although the mean D-dimer levels appeared higher in the moderate disability group (490.7±151.1 ng/mL) compare to the no disability (407.3±139.2 ng/mL) and slight disability groups (453.6±259.2 ng/mL), pairwise comparisons across DSO categories were not statistically significant for no disability vs slight disability ($p=0.240$) and slight disability vs moderate disability ($p=0.424$) (**Figure 2B**). A statistically significant difference was observed only between the no disability and moderate disability groups ($p=0.044$) (**Figure 2B**). Overall, these findings indicate that admission D-dimer may show a clearer relationship with dichotomized functional improvement (Barthel Index-based FSO) than with ordinal disability status (mRS-based DSO), with no consistent graded trend across DSO categories.

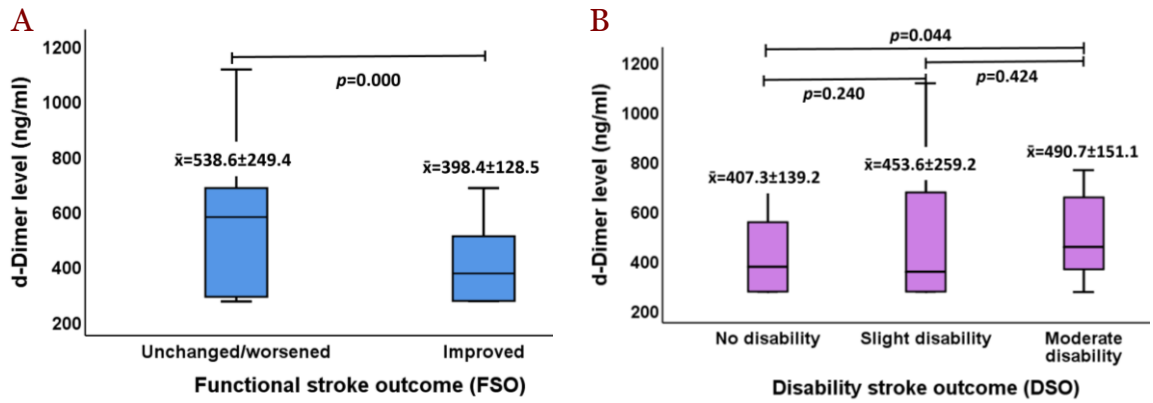

Figure 2. Comparisons of D-dimer levels based on functional stroke outcome (FSO) (A) and disability stroke outcome (DSO) (B) in patients with acute ischemic stroke.

Comparison of ADMA levels with functional and disability stroke outcomes measured by the Barthel Index and mRS

Comparison of ADMA levels across functional and disability stroke outcome groups is presented in **Figure 3**. For FSO, the mean ADMA level was not significantly different between patients with unchanged/worsened and improved FSO (79.0±12.9 pg/dL vs 75.7±9.9 pg/dL, $p=0.136$) (**Figure 3A**).

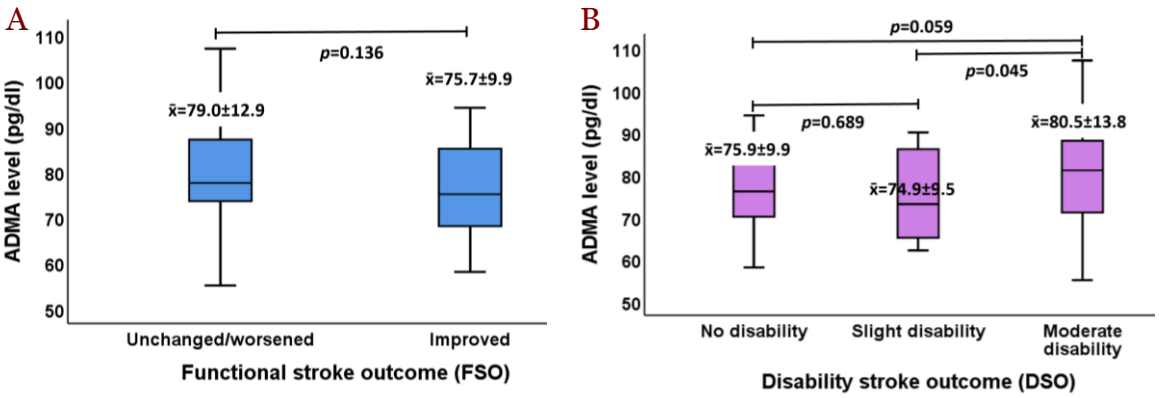

Figure 3. Comparison of ADMA levels based on functional stroke outcome (FSO) (A) and disability stroke outcome (DSO) (B) in patients with acute ischemic stroke.

For DSO, pairwise analysis indicated no significant difference between the no disability and slight disability groups (p=0.689) and between the no disability and moderate disability groups (p=0.059), whereas the difference between the slight disability and moderate disability groups was statistically significant (p=0.045) (**Figure 3B**). Overall, these findings indicate that admission ADMA was not significantly associated with FSO but showed a modest association with DSO in selected category comparisons, without evidence of a consistent gradient across disability levels.

Factors associated with functional stroke outcome measured by the Barthel Index

Factors associated with FSO among patients with acute ischemic stroke are presented in **Table 2**. GCS scores were significantly higher in the improved group compared with the unchanged/worsened group (14.9±0.4 vs 14.4±1.4; p=0.030), indicating that better initial neurological status was associated with favorable functional recovery. Elevated D-dimer level was significantly associated with FSO, with patients exhibiting increased D-dimer having higher odds of an unchanged/worsened outcome (OR=4.1; 95%CI: 1.8–9.4; p=0.001). Dyslipidemia was also significantly associated with FSO (OR=3.6; 95%CI: 1.6–8.2; p=0.002), indicating a greater likelihood of poor functional outcome among affected patients. In addition, heart disease demonstrated a significant association (OR=0.2; 95%CI:0.2–0.4; p=0.024) (**Table 2**). Age, sex distribution, systolic and diastolic blood pressure, reactive hyperglycemia, ADMA level, hypertension, diabetes mellitus, vascular disorder type, and lesion site were not significantly associated with functional stroke outcome (**Table 2**).

Table 2. Factors associated with functional stroke outcome among patients with acute ischemic stroke

Variables	Functional stroke outcome (FSO)		Odds ratio (OR)	p–value [a]
	Unchanged/ worsened (n=36)	Improved (n=87)		
	Frequency (%)	Frequency (%)		
Age (year), mean±SD	59.2±14.5	58.9±10.3		0.887
Sex			0.8 (0.3–1.7)	0.363
Male	15 (12.2)	41 (33.3)		
Female	21 (17.1)	46 (37.4)		
Glasgow Coma Scale, mean±SD	14.4±1.4	14.9±0.4		0.030*
Blood pressure, mean±SD				
Systolic (mmHg)	155.3±23.6	159.1±20.7		0.372
Diastolic (mmHg)	87.3±12.3	88.1±13.7		0.745
Reactive hyperglycemia			0.5 (0.2–1.2)	0.081
Yes	15 (12.2)	50 (40.7)		
No	21 (17.1)	37 (30.1)		
D-dimer level			4.1 (1.8–9.4)	0.001**
Increased	21 (17.1)	22 (17.9)		
Normal	15 (12.2)	65 (52.8)		
ADMA level			2.5 (0.5–13.3)	0.238
Increased	3 (2.4)	3 (2.4)		
Normal	33 (26.8)	84 (68.3)		
Hypertension			0.8 (0.3–2.3)	
No	6 (4.9)	17 (13.8)		0.462
Yes	30 (24.4)	70 (56.9)		
Diabetes			1.0 (0.5–2.3)	
No	21 (17.1)	50 (40.7)		0.546
Yes	15 (12.2)	37 (30.1)		
Heart disease			0.2 (0.2–0.4)	
No	33 (26.8)	87 (70.7)		0.024
Yes	3 (1.6)	0 (0.0)		
Dyslipidemia			3.6 (1.6–8.2)	
No	24 (19.5)	31 (25.2)		0.002**
Yes	12 (9.8)	56 (45.5)		
Vascular disorder types			0.6 (0.2–1.6)	
Small vessel disease	27 (21.9)	72 (58.5)		0.228
Large vessel disease	9 (7.3)	15 (12.2)		

Variables	Functional stroke outcome (FSO)		Odds ratio (OR)	*p*–value [a]
	Unchanged/ worsened (n=36)	Improved (n=87)		
	Frequency (%)	Frequency (%)		
Lesion site			0.6 (0.2–1.8)	
Subcortical	30 (24.4)	78 (63.4)		0.246
Cortical	6 (4.9)	9 (7.3)		
Laboratory, mean±SD				
Hemoglobin (g/dL)	12.6±1.7	13.6±1.7		0.072
Leukocytes (1000 cells/µL)	9.7±3.6	9.7±3.7		0.979
Platelets (1000 cells/µL)	268.4±76.4	297.9±92.3		0.093
Urea (mg/dL)	35.5±24.0	33.6±17.0		0.617
Creatinine (mg/dL)	1.0±0.6	0.9±0.3		0.145
Total cholesterol (mg/dL)	177.8±37.9	205.5±41.6		0.630
High-density lipoprotein (mg/dL)	34.8±9.9	37.4±12.6		0.270
Low-density lipoprotein (mg/dL)	129.3±28.1	130.8±40.2		0.091
Triglycerides (mg/dL)	129.3±48.7	139.7±48.7		0.285
Uric acid (mg/dL)	5.1±1.2	5.1±1.5		0.763

ADMA: asymmetric dimethylarginine.
[a] Analyzed using the Chi-squared test or unpaired Student t-test
* Statistically significant at $p<0.05$
** Statistically significant at $p<0.01$

Factors associated with disability stroke outcome (DSO) measured by mRS

Factors associated with DSO among patients with acute ischemic stroke are summarized in **Table 3**. Systolic and diastolic blood pressure were significantly associated with DSO ($p=0.005$ and $p=0.018$, respectively). Reactive hyperglycemia ($p=0.036$) and hypertension ($p=0.005$) were also significantly associated with disability severity, suggesting that metabolic dysregulation and pre-existing elevated blood pressure are linked to greater stroke-related disability. In contrast, age, sex, and GCS score were not significantly different across DSO categories (**Table 3**). No significant associations were observed for D-dimer level, ADMA level, diabetes mellitus, heart disease, dyslipidemia, vascular disorder type, or lesion site. Similarly, laboratory parameters—including hemoglobin, leukocyte count, platelet count, urea, creatinine, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, uric acid, and blood glucose level—did not differ significantly across DSO groups (**Table 3**).

Table 3. Factors associated with disability stroke outcome among patients with acute ischemic stroke

Variables	Disabilities stroke outcome (DSO)			*p*-value [a]
	No disability (n=61)	Slight disability (n=33)	Moderate disability (n=29)	
	Frequency (%)	Frequency (%)	Frequency (%)	
Age (year), mean±SD	59.6±7.6	58.2±12.5	58.6±16.8	0.837
Sex				0.720
Male	26 (21.1)	15 (12.2)	15 (12.2)	
Female	35 (28.5)	18 (14.6)	14 (11.4)	
Glasgow Coma Scale, mean±SD	14.9±0.4	14.8±0.6	14.5±1.6	0.099
Blood pressure, mean±SD				
Systolic (mmHg)	162.9±20.9	158.3±20.9	147.3±20.5	0.005**
Diastolic (mmHg)	90.5±15.4	88.2±12.7	82.1±4.8	0.018*
Reactive hyperglycemia				0.036
Yes	33 (26.8)	12 (9.8)	20 (16.3)	
No	28 (22.8)	21 (17.1)	9 (7.3)	
D-dimer level				0.197
Increased	20 (16.3)	9 (7.3)	14 (11.4)	
Normal	41 (33.3)	24 (19.5)	15 (12.2)	
ADMA level				0.169
Increased	3 (2.4)	0 (0.0)	3 (2.4)	
Normal	58 (47.2)	33 (26.8)	26 (21.1)	
Hypertension				
No	15 (12.2)	0 (0.0)	8 (6.5)	0.005**
Yes	46 (37.4)	33 (26.8)	21 (17.1)	
Diabetes				
No	32 (26.0)	24 (19.5)	15 (12.2)	0.125
Yes	29 (23.6)	9 (7.3)	14 (11.4)	

Variables	Disabilities stroke outcome (DSO)			*p*-value [a]
	No disability (n=61)	Slight disability (n=33)	Moderate disability (n=29)	
	Frequency (%)	Frequency (%)	Frequency (%)	
Heart disease				
No	58 (47.2)	33 (26.8)	24 (19.5)	0.237
Yes	3 (2.4)	0 (0.0)	0 (0.0)	
Dyslipidemia				
No	26 (21.1)	12 (9.8)	17 (13.8)	0.191
Yes	35 (28.5)	21 (17.1)	12 (9.8)	
Vascular disorder types				
Small vessel disease	52 (42.3)	27 (21.9)	20 (16.3)	0.186
Large vessel disease	9 (7.3)	6 (4.9)	9 (7.3)	
Lesion site				
Subcortical	55 (44.7)	30 (24.4)	23 (18.7)	0.277
Cortical	6 (4.9)	3 (2.4)	6 (4.9)	
Laboratory, mean±SD				
Hemoglobin (g/dL)	13.5±1.9	13.0±1.4	13.3±2.0	0.458
Leukocytes (1000 cells/µL)	9.6±3.9	10.2±3.4	9.6±4.2	0.699
Platelets (1000 cells/µL)	289.3±105.1	313.6±79.2	261.6±43.8	0.069
Urea (mg/dL)	34.6±15.8	31.8±26.1	35.9±17.1	0.681
Creatinine (mg/dL)	0.9±0.4	0.9±0.7	0.9±0.2	0.909
Total cholesterol (mg/dL)	200.5±40.7	200.6±38.7	187.2±48.9	0.748
High-density lipoprotein (mg/dL)	35.8±11.0	37.7±9.4	37.1±15.3	0.881
Low-density lipoprotein (mg/dL)	119.5±42.3	137.6±34.3	114.7±35.3	0.482
Triglycerides (mg/dL)	137.8±38.7	139.8±56.8	130.7±59.1	0.717
Uric acid (mg/dL)	5.0±1.5	4.9±1.2	5.4±1.4	0.697

ADMA: asymmetric dimethylarginine.
[a] Analyzed using Chi-squared test or ANOVA t-test
* Statistically significant at $p<0.05$

Discussion

This study evaluated the associations of reactive hyperglycemia, D-dimer, and plasma ADMA with short-term stroke outcomes in patients with acute ischemic stroke using two complementary outcome measures, namely Barthel Index-based FSO and mRS-based DSO. The main findings indicated that elevated D-dimer was significantly associated with poorer Barthel Index-based functional outcome, reactive hyperglycemia was associated with mRS-based disability outcome, and plasma ADMA was not significantly associated with either outcome in this cohort.

The association between D-dimer and Barthel Index-based FSO is biologically plausible and clinically relevant. D-dimer is a fibrin degradation product derived from cross-linked fibrin and represents the final product of plasmin-mediated fibrinolysis [16]. Elevated plasma D-dimer levels have been widely reported in thromboembolic conditions, including pulmonary embolism and venous thromboembolism, and may reflect enhanced coagulation activity and fibrin turnover, indicating ongoing thrombosis and vascular occlusion [16]. In addition, elevated D-dimer levels may contribute to thromboembolism formation and propagation, thereby exacerbating cerebral ischemia and infarct progression [16]. D-dimer has also been shown to activate inflammatory pathways by stimulating immune responses and increasing pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin (IL)-1, IL-6, and IL-8 [17]. These mechanisms may partly explain why patients with higher D-dimer levels in the present study were more likely to have unchanged/worsened functional status during hospitalization.

The present findings are consistent with previous studies reporting that higher D-dimer levels are associated with increased stroke severity, larger infarct volume, and worse clinical outcomes [18,19]. Elevated plasma D-dimer levels on admission have also been identified as an independent predictor of short-term poor outcomes in patients with acute ischemic stroke, and high levels have been associated with increased risk of mortality and severe disability at three months, particularly in patients with atrial fibrillation [18]. In the present study, however, the relationship was clearer for Barthel Index-based FSO than for mRS-based DSO. Although mean D-dimer levels tended to be higher in patients with greater disability, the pattern across DSO categories was not consistently graded, and only selected between-group comparisons reached statistical significance. This discrepancy may reflect differences in what each scale captures. The

Barthel Index is more sensitive to short-term changes in activities of daily living during hospitalization, whereas the mRS provides a broader disability classification and may be less sensitive to early functional fluctuations over a short follow-up period [20]. The mention of D-dimer in other thrombotic conditions, such as deep vein thrombosis and pulmonary embolism, underscores its value as a coagulation/fibrinolysis marker, although those conditions are not the direct focus of the present stroke cohort [21].

Reactive hyperglycemia also showed an important but nuanced relationship with outcome. Acute stroke is often accompanied by elevated blood glucose levels, even in patients without a prior history of diabetes mellitus [22]. This phenomenon is largely attributed to stress-induced activation of the hypothalamic-pituitary-adrenal axis, leading to increased cortisol secretion and enhanced gluconeogenesis, which subsequently results in transient hyperglycemia [23]. Reactive hyperglycemia has been reported in approximately 30–40% of patients with acute ischemic stroke and in 43–59% of patients with hemorrhagic stroke [24]. Previous studies have shown that reactive hyperglycemia typically peaks within the first two days following stroke onset, gradually decreases thereafter, and stabilizes within several days [25]. Stress-induced hyperglycemia has been associated with increased infarct size, blood-brain barrier disruption, oxidative stress, and inflammatory responses, all of which may contribute to unfavorable neurological outcomes [7,8].

In the present study, reactive hyperglycemia was significantly associated with DSO, suggesting that early metabolic dysregulation may be linked to greater disability severity. However, the interpretation of FSO requires caution. While mean admission blood glucose differed significantly between Barthel Index outcome groups, categorical reactive hyperglycemia was not significantly associated with FSO in the cross-tabulated analysis. This may indicate that the relationship between glycemia and early functional change is complex and potentially non-linear and may depend on how glucose exposure is modeled (continuous vs categorical), baseline stroke severity, timing of sampling, or concurrent treatment effects during hospitalization. The observation that admission glucose patterns differed between Barthel Index-based and mRS-based outcomes further supports the value of using more than one clinical outcome metric when evaluating prognostic biomarkers in acute stroke.

In contrast, plasma ADMA levels were not significantly associated with either Barthel Index-based FSO or mRS-based DSO in this study. ADMA has been proposed as a prognostic biomarker with additive value beyond traditional cardiovascular risk factors and novel biomarkers such as brain natriuretic peptide [26]. ADMA is an endogenous inhibitor of eNOS and plays a central role in endothelial dysfunction by reducing NO bioavailability [27,28]. The synthesis and degradation of ADMA are tightly regulated by redox-dependent enzymatic processes [29]. Under conditions of increased oxidative stress, such as hypertension, diabetes mellitus, and atherosclerosis, circulating ADMA levels may increase due to enhanced synthesis or reduced degradation [29]. Angiotensin II has been shown to elevate ADMA levels in vascular smooth muscle cells by inhibiting its degradation, increasing its synthesis, and reducing its cellular extrusion [30]. ADMA generated in smooth muscle cells may subsequently impair NO production in adjacent endothelial cells, thereby promoting vasoconstriction and endothelial dysfunction [31]. ADMA is produced through the methylation of L-arginine residues by protein arginine methyltransferase-1 and is predominantly degraded by dimethylarginine dimethylaminohydrolase into L-citrulline and dimethylamine [32]. Experimental studies have also demonstrated that ADMA contributes to atherosclerotic processes by inducing oxidative stress, activating NADPH oxidase, increasing superoxide production, and impairing NO-mediated vasodilation [29,32]. Despite this strong pathophysiological rationale, its prognostic value for short-term stroke outcome was not demonstrated in the present cohort.

Several factors may explain the absence of an observed association between ADMA levels and clinical outcomes in this study. First, ADMA may be more strongly related to chronic vascular risk burden rather than early functional or disability outcomes during acute hospitalization. Second, a single time-point measurement may not adequately capture dynamic endothelial responses after stroke onset. Third, the relatively low proportion of patients with elevated ADMA levels in this cohort may have limited the statistical power to detect significant associations.

In addition to the biomarker findings, this study identified several clinical variables associated with outcome, including GCS, dyslipidemia, and heart disease for FSO, and blood

pressure-related variables and hypertension for DSO. These findings reinforce that stroke outcome is multifactorial and influenced by interactions among neurological status at presentation, vascular comorbidity, hemodynamic factors, and systemic biological responses. Therefore, biomarkers such as D-dimer and glucose are likely to provide the greatest value when interpreted alongside clinical parameters rather than in isolation.

This study has several clinical implications. Early assessment of D-dimer and admission glucose may help support risk stratification in acute ischemic stroke, particularly in settings where rapid advanced imaging or more complex biomarker panels are not always available. The findings also suggest that different biomarkers may be more informative for different dimensions of outcome (functional improvement vs disability classification), highlighting the importance of selecting outcome measures that match the intended prognostic question.

Several limitations should be considered when interpreting these results. First, the cross-sectional observational design limits causal inference. Second, outcomes were assessed over a short in-hospital period (day 7/discharge), so the findings may not fully reflect longer-term recovery trajectories. Third, biomarker measurements were based on a single early sample, which may not capture temporal changes after stroke onset. Fourth, this was a single-center study, which may limit generalizability to other populations and care settings. Finally, residual confounding remains possible, particularly given the complexity of acute stroke management and heterogeneity in stroke pathophysiology. Despite these limitations, this study provides useful evidence from a tertiary referral setting in Indonesia regarding the differential prognostic relevance of coagulation-, metabolic-, and endothelial-related biomarkers in acute ischemic stroke. Future studies with larger multicenter cohorts, repeated biomarker measurements, and longer follow-up are needed to clarify temporal patterns and to determine whether combining D-dimer, glycemic indices, and endothelial dysfunction markers improves prognostic performance beyond conventional clinical assessment.

Conclusion

In patients with acute ischemic stroke, D-dimer and reactive hyperglycemia showed differential associations with short-term clinical outcomes depending on the outcome measure used. Elevated D-dimer was associated with poorer Barthel Index-based functional stroke outcome, while reactive hyperglycemia was associated with mRS-based disability stroke outcome. In contrast, plasma ADMA was not significantly associated with either Barthel Index-based functional outcome or mRS-based disability outcome in this cohort. These findings suggest that coagulation- and metabolic-related biomarkers may provide complementary prognostic information in acute ischemic stroke, particularly when interpreted alongside clinical parameters and according to the specific outcome domain being assessed. Further multicenter studies with larger sample sizes, repeated biomarker measurements, and longer follow-up are needed to validate these findings and clarify their clinical utility in early stroke risk stratification.

Ethics approval

This study was conducted following approval from the institutional Ethics Committee of Dr. Zainoel Abidin Hospital (No. 166/ETIK-RSUDZA/2024). Written informed consent was obtained from all participants or their legally authorized representatives prior to enrollment. All procedures were performed in accordance with the principles of the Declaration of Helsinki.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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