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Research Article

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Association between diastolic blood viscosity and functional outcomes after acute ischemic stroke

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ABSTRACT

Background: While blood viscosity is recognized as a contributing factor in cerebrovascular disease pathophysiology, the specific role of diastolic blood viscosity (DBV) in functional outcomes after acute ischemic stroke (AIS) remains unclear. This study investigates the relationship between admission DBV levels and 3-month functional outcomes in patients with AIS.
Methods: We analyzed 413 AIS patients admitted within 7 days of symptom onset. We utilized a scanning capillary-tube viscometer to measure whole blood viscosity and categorized DBV into three groups based on established norms. Multivariable logistic regression was employed to assess the association between DBV levels and 3-month outcomes, as determined by the modified Rankin Scale (mRS).
Results: The cohort had a mean age of 70.0 ± 13.2 years and 59.6% were male. Patients with high DBV tended to be younger, predominantly male, with higher body mass index, and more likely to be smokers. These individuals also exhibited higher levels of hemoglobin, low-density lipoprotein, and fasting blood sugar. Despite similar stroke etiology and initial severity, high DBV was significantly associated with poor 3-month outcomes (mRS 3-6; adjusted odds ratio 2.899; 95% confidence interval, 1.119–7.514).
Conclusions: Elevated DBV on admission is linked to worse functional outcome three months after AIS. These findings highlight the importance of incorporating DBV assessments into AIS prognosis and suggest a potential avenue for therapeutic intervention targeting blood rheology to improve cerebral microcirculation and stroke recovery.

Keywords: Blood viscosity; Cerebrovascular disorders; Ischemic stroke; Microcirculation; Prognosis

BACKGROUND

Acute ischemic stroke (AIS) represents a significant health burden due to its high incidence of severe disability and mortality [1]. Among the various pathomechanisms of AIS, blood viscosity has been identified as a critical determinant of blood flow rheology, with profound

Abbreviations

AIS, acute ischemic stroke; ANOVA, analysis of variance; BMI, body mass index; CE, cardioembolism; CI, confidence interval; DBV, diastolic blood viscosity; END, early neurological deterioration; IA, intraarterial; IV, intravenous; LAA, large artery atherosclerosis; LDL, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; OD, other determined; OR, odds ratio; SBV, systolic blood viscosity; SCTV, scanning capillary tube viscometer; SVO, small vessel occlusion; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UD, undetermined; WBV, whole blood viscosity.

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Competing interest

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Kangdong Sacred Heart Hospital (IRB No. 2020-10-011).

Consent for publication

Not applicable.

Authors' contributions

Formal analysis: Lee M, Kim Y; Investigation: Lee M, Kim Y; Methodology: Lee M, Kim Y; Visualization: Lee M, Lee K, Kim Y; Writing - original draft: Lee M, Kim Y; Writing - review & editing: Kim YJ, Bae JS, Lee JH, Lee SH, Kim C, Lee K, Park SH, Kim Y.

effects on the pathophysiology of atherosclerosis, arteriosclerosis, and microvascular dysfunction [2-4]. Previous studies on specific AIS subtypes, such as lacunar infarctions, have demonstrated that elevated blood viscosity, particularly in conditions characterized by lower shear rates such as in smaller diameter arteries, is significantly associated with early neurological deterioration (END), which may eventually lead to poor functional outcomes [5].

Blood viscosity, which can be modulated, plays a pivotal role in microvascular perfusion and is influenced by both systemic and localized vascular conditions [6,7]. Among the types of blood viscosity, elevated diastolic blood viscosity (DBV), measured under conditions reflecting the heart at rest, appears to be more closely linked to small vessel disease. While elevated DBV has been shown to increase the risk of END in lacunar strokes, its direct impact on long-term functional outcomes after AIS has been less extensively studied [3-5]. As DBV represents a distinct aspect of vascular dynamics, understanding its influence on tissue perfusion in ischemic lesions after AIS is critical; this influence could not only induce END but also hinder post-stroke recovery.

The primary aim of this study is to investigate the relationship between DBV and functional outcomes in AIS across a diverse spectrum of stroke types. We hypothesize that higher DBV is associated with worse functional outcomes three months after stroke. By incorporating measures of DBV and assessing their correlation with short-term outcomes, this research seeks to elucidate the prognostic value of DBV in AIS. These insights are fundamental for developing targeted interventions that address the specific needs of AIS patients, leveraging the modifiable nature of blood viscosity in the acute phase of stroke.

METHODS

Study population

From the prospective stroke registry of a university-affiliated academic hospital, we enrolled patients diagnosed with AIS who were admitted within seven days of symptom onset between June 2021 and May 2023. Among these consecutive stroke patients, 413 who underwent laboratory testing to measure serum blood viscosity were included in the final analysis (**Supplementary Fig. 1**).

All participants received standard and optimal acute stroke management according to the up-to-date regional and global acute stroke management guidelines during their hospitalization [8-10]. The study protocol was approved by the institutional review board of Kangdong Sacred Heart Hospital (IRB No. 2020-10-011). We obtained informed consent from all participants or their next of kin when the patients were unable to provide consent themselves.

Covariates and outcome variable

We collected baseline demographic and clinical characteristics of participants, including age, sex, and key risk factors such as hypertension, diabetes, dyslipidemia, and atrial fibrillation. We classified stroke types according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [11]. We assessed initial level of neurological impairment using the National Institute of Health Stroke Scale (NIHSS) score at admission. For the outcome, we assessed short-term functional outcomes based on the modified Rankin Scale (mRS) score three months post-stroke. These outcomes were dichotomized into two categories: good outcomes (a 3-month mRS score of 0–2) and poor outcomes (a 3-month mRS score of 3–6).

Systolic and diastolic blood viscosity measurements

Whole blood viscosity (WBV) was measured using the scanning capillary tube viscometer (SCTV) (BVD-PRO1, Bio Visco Inc., Jeonju, Korea) on the first blood sample obtained in the emergency room, prior to the administration of intravenous tissue plasminogen activator or antithrombotics [12]. The SCTV offers advantages over traditional rotational viscometers by enabling the analysis of WBV across a broad range of shear rates from 1 to 1,000 s–1 through a single automated process [12,13]. This technique maintains a constant temperature of 36.5 ± 0.5°C, ensuring accurate viscosity measurements [13].

For each viscosity test, we utilized approximately 3 mL of EDTA-anticoagulated whole blood. The study specifically examined WBV at shear rates of 1/s and 300/s. At a shear rate of 1/s, the viscosity measurement is known as DBV, and at 300/s, it is termed systolic blood viscosity (SBV). For healthy individuals, the reference ranges are 3.66–5.41 cP at 300 s–1 and 23.15–36.45 cP at 1 s–1 [13,14]. In the context of viscosity measurements, the poise (P), which is a unit of dynamic viscosity in the centimeter-gram-second system and defined as one gram per centimeter per second, is commonly used. However, in clinical practice, the centipoise (cP), equal to one-hundredth of a poise, is more frequently employed.

Statistical analysis

We compared demographic, clinical, laboratory, and stroke characteristics according to short-term functional outcomes and DBV groups, which were categorized as low, normal, and high according to established norms. We utilized appropriate statistical methods for our analysis, including the χ^2 test, one-way analysis of variance (ANOVA) with Scheffe's post hoc analysis, and the Kruskal-Wallis test, depending on the data type. To compare the values of SBV and DBV across different TOAST classifications, ANOVA analyses were conducted. Continuous variables were presented as mean ± standard deviation, and categorical variables were expressed as number and percentage.

We further investigated the association of DBV with short-term functional outcomes using binary logistic regression, with the normal DBV range as the reference category. The results of the logistic regression were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). In the multivariable analysis, we adjusted for variables based on prior knowledge, including those with a p-value of less than 0.10 in the univariable analysis. The adjusted variables include age, sex, body mass index (BMI), previous mRS, initial NIHSS, thrombolysis, history of stroke or transient ischemic attack (TIA), hypertension, diabetes, atrial fibrillation, TOAST classification, creatinine, hemoglobin, low-density lipoprotein cholesterol (LDL), fasting blood sugar, systolic blood pressure, and smoking status.

For sensitivity analysis, we excluded patients who were previously taking antiplatelet agents, anticoagulants, or those with a history of any type of cancer. This exclusion was made to reduce potential confounding effects and to assess the robustness of our findings. The same multivariable models were then applied to the remaining cohort to assess the impact of these exclusions on the results.

A *P*-value of < 0.05 was deemed indicative of statistical significance. All analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Between June 2021 and May 2023, our study enrolled 413 patients. The analysis demonstrated that patients with worse functional outcomes three months after AIS were generally older, predominantly female, and had higher premorbid mRS scores. They were also more likely to have pre-existing conditions such as hypertension, diabetes, atrial fibrillation, and a history of smoking, as well as previous strokes or TIAs. Additionally, these patients presented with elevated fasting blood glucose levels and reduced levels of hemoglobin, LDL, and DBV (**Table 1**).

Our findings indicated significant differences in age, sex, BMI, smoking status, hemoglobin level, and LDL level among the groups categorized by low, normal, and high DBV. Notably, patients with high DBV were typically younger, more likely to be male, had higher BMIs, and were smokers. In contrast, those in the low DBV group were older, predominantly female, had lower BMIs, were less likely to smoke, and exhibited lower levels of hemoglobin and LDL. Both the high and low DBV groups had increased rates of poor functional outcomes

Table 1. Demographic and clinical characteristics according to the 3-month functional outcomes

Variables	Good functional outcome (*n* = 289)	Poor functional outcome (*n* = 124)	*P*-value
Demographic characteristics			
Age	66.7 ± 12.6	77.7 ± 11.2	< 0.001
Sex, male	192 (66.4)	54 (43.5)	< 0.001
Previous mRS	0 [0–1]	1 [0–2]	< 0.001
BMI	24.7 ± 18.4	21.3 ± 6.1	0.006
Stroke characteristics			
Initial NIHSS	24.7 ± 18.4	21.3 ± 6.1	0.006
TOAST classification			0.165
LAA	86 (29.8)	43 (34.7)	
SVO	71 (24.6)	17 (13.7)	
CE	48 (16.6)	26 (21.0)	
OD	8 (2.8)	4 (3.2)	
UD	76 (26.3)	34 (27.4)	
Thrombolysis			< 0.001
None	264 (91.3)	95 (76.6)	
IV tpA	11 (3.8)	11 (8.9)	
IA thrombectomy	5 (1.7)	12 (9.7)	
Combined IV+IA	9 (3.1)	6 (4.8)	
Vascular risk factors			
Hypertension	175 (60.6)	90 (72.6)	0.026
Diabetes mellitus	82 (28.4)	51 (41.1)	0.015
Hyperlipidemia	67 (23.2)	23 (18.5)	0.360
Previous stroke/TIA	40 (13.8)	36 (29.0)	< 0.001
Atrial fibrillation	50 (17.3)	43 (34.7)	< 0.001
Smoking	77 (26.6)	19 (15.3)	0.018
Laboratory findings			
Serum creatinine	1.1 ± 1.2	1.1 ± 0.9	0.844
Hemoglobin	14.0 ± 1.7	13.0 ± 2.4	< 0.001
low-density lipoprotein	108.9 ± 38.5	98.7 ± 42.8	0.017
Fasting blood sugar	117.8 ± 37.8	138.3 ± 60.9	0.001
Systolic blood pressure	151.6 ± 28.0	150.5 ± 25.8	0.696
Blood viscosity			
Systolic blood viscosity	4.4 ± 0.6	4.3 ± 0.7	0.088
Diastolic blood viscosity	27.3 ± 8.4	25.0 ± 10.1	0.028

Values are presented as mean ± standard deviation, number (%), or median [interquartile range].
mRS, modified Rankin scale; BMI, body mass index; NIHSS, national institute of health stroke scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; OD, other determined; UD, undetermined; IV, intravenous; IA, intraarterial; TIA, transient ischemic attack.

Table 2. Demographic and clinical characteristics according to the diastolic blood viscosity level

Variables	Low DBV (< 23.15, *n* = 144)	Normal DBV (23.15-36.45, *n* = 213)	High DBV (> 36.45, *n* = 56)	*P*-value
Demographic characteristics				
Age	74.3 ± 12.0	68.0 ± 13.5	66.4 ± 12.4	< 0.001
Sex, male	59 (41.0)	147 (69.0)	40 (71.4)	< 0.001
Previous mRS	0 [0–1]	0 [0–1]	0 [0–1]	0.348
BMI	22.2 ± 6.2	23.2 ± 4.3	29.3 ± 40.9	0.014
Stroke characteristics				
Initial NIHSS	4.3 ± 5.3	3.8 ± 4.7	4.1 ± 5.2	0.614
TOAST classification				0.179
LAA	38 (26.4)	77 (36.2)	14 (25.0)	
SVO	35 (24.3)	45 (21.1)	8 (14.3)	
CE	31 (21.5)	31 (14.6)	12 (21.4)	
OD	5 (3.5)	6 (2.8)	1 (1.8)	
UD	35 (24.3)	54 (25.4)	21 (37.5)	
Thrombolysis				0.321
None	120 (83.3)	185 (86.9)	54 (96.4)	
IV tpA	9 (6.2)	12 (5.6)	1 (1.8)	
IA thrombectomy	9 (6.2)	8 (3.8)	0 (0.0)	
Combined IV+IA	6 (4.2)	8 (3.8)	1 (1.8)	
Vascular risk factors				
Hypertension	98 (68.1)	132 (62.0)	35 (62.5)	0.482
Diabetes mellitus	53 (36.8)	62 (29.1)	18 (32.1)	0.312
Hyperlipidemia	34 (23.6)	43 (20.2)	13 (23.2)	0.716
Previous stroke/TIA	30 (20.8)	41 (19.2)	5 (8.9)	0.134
Atrial fibrillation	34 (23.6)	45 (21.1)	14 (25.0)	0.766
Smoking	16 (11.1)	61 (28.6)	19 (33.9)	< 0.001
Laboratory findings				
Serum creatinine				0.118
Hemoglobin	12.4 ± 1.9	14.2 ± 1.6	15.3 ± 1.6	< 0.001
Low-density lipoprotein	94.9 ± 34.5	108.5 ± 38.6	124.3 ± 50.3	< 0.001
Fasting blood sugar	124.4 ± 48.3	121.0 ± 45.3	134.9 ± 48.3	0.149
Systolic blood pressure	147.7 ± 28.9	153.1 ± 25.4	153.6 ± 29.7	0.152
Poor functional outcome	53 (36.8)	53 (24.9)	18 (32.1)	0.051

Values are presented as mean ± standard deviation, number (%), or median [interquartile range].
DBV, diastolic blood viscosity; mRS, modified Rankin scale; BMI, body mass index; NIHSS, national institute of health stroke scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; OD, other determined; UD, undetermined; IV, intravenous; IA, intraarterial; TIA, transient ischemic attack.

compared to the normal DBV group (high: 32.1%; low: 36.8%; normal: 24.9%) (**Table 2**). Further analysis revealed no significant differences in the values of SBV and DBV among the various TOAST classifications (**Supplementary Table 1**).

In univariable logistic regression analysis, the low DBV group exhibited a significantly higher risk of poor functional outcomes (crude OR, 1.758; 95% CI, 1.110-2.784; $P = 0.016$), though this association did not retain statistical significance in multivariable analysis (adjusted OR, 1.053; 95% CI, 0.514–2.159; $P = 0.887$). The high DBV group, however, did not show a significant relationship in the univariable analysis (crude OR, 1.430; 95% CI, 0.753–2.715; $P = 0.274$) but demonstrated a significantly higher risk of poor outcomes in the multivariable models (adjusted OR, 2.889; 95% CI, 1.119–7.514; $P = 0.029$). Beyond these primary exposures of interest, variables such as age, baseline mRS, initial NIHSS score, and history of stroke or TIA also showed significant associations with poor functional outcomes (**Table 3**). In the sensitivity analysis, where patients taking antithrombotics or with a diagnosis of cancer were excluded, the association remained significant (**Supplementary Table 2**). A total of 272 out of 413 patients were included in this analysis.

Table 3. Univariate and multivariable logistic regression analysis for the prediction of poor functional outcome

Variables	Crude OR (95% CI)	*P*-value	Adjusted OR[a] (95% CI)	*P*-value
Normal DBV	Reference		Reference	
Low DBV	1.758 (1.110–2.784)	0.016	1.053 (0.514–2.159)	0.887
High DBV	1.430 (0.753–2.715)	0.274	2.899 (1.119–7.514)	**0.029**
Age	1.085 (1.061–1.109)	< 0.001	1.074 (1.041–1.109)	< 0.001
Sex, male	0.390 (0.253–0.600)	< 0.001	0.652 (0.325–1.315)	0.233
Previous mRS	2.084 (1.692–2.567)	< 0.001	1.553 (1.146–2.105)	**0.005**
BMI	0.925 (0.888–0.963)	< 0.001	0.957 (0.904–1.012)	0.121
Initial NIHSS	1.283 (1.206–1.365)	< 0.001	1.356 (1.224–1.502)	**< 0.001**
Hypertension	1.724 (1.089–2.731)	0.202	1.278 (0.520–2.514)	0.477
Diabetes mellitus	1.761 (1.136–2.738)	0.011	1.292 (0.624–2.674)	0.490
Previous stroke/TIA	2.547 (1.527–4.248)	< 0.001	2.149 (1.012–4.564)	**0.047**
Atrial Fibrillation	2.538 (1.571–4.098)	< 0.001	1.869 (0.715–4.886)	0.202

OR, odds ratio; CI, confidence interval; DBV, diastolic blood viscosity; mRS, modified Rankin scale; BMI, body mass index; NIHSS, national institute of health stroke scale; TIA, transient ischemic attack.
[a]Adjusted for age, sex, body mass index, previous mRS, initial NIHSS, thrombolysis, history of stroke, hypertension, diabetes, atrial fibrillation, TOAST classification, creatinine, hemoglobin, low density lipoprotein, fasting blood sugar, systolic blood pressure and smoking status.

DISCUSSION

In this retrospective analysis of a prospective stroke cohort, we identified a significant association between DBV levels and functional outcomes three months after AIS. Specifically, elevated DBV levels were significantly correlated with poorer outcomes, highlighting DBV as an independent risk factor for post-stroke outcomes. Although lower DBV levels initially appeared to correlate with adverse outcomes in the univariable analysis, this association was not significant in the multivariable analysis.

The observed correlation between higher DBV levels and worse functional outcomes is consistent with previous studies that have linked increased blood viscosity to adverse outcomes in ischemic stroke patients. For instance, a study by Lip et al. [15] found that WBV at both high and low shear rates was significantly elevated in AIS patients compared to controls, and this elevation was associated with poorer clinical outcomes. Further, DBV has been found to be elevated in patients with END in lacunar strokes [5]. Given that END is a strong predictor of adverse outcomes in AIS [16-18], elevated DBV likely to contribute to poorer post-stroke outcomes. Elevated DBV may influence the stroke progression in the types of END through increased flow resistance that impedes microvascular tissue perfusion, highlighting a critical pathomechanism in the cascade leading to END [6].

The observed relationship between elevated DBV and worse functional outcomes may also be due to several other mechanisms. Increased viscosity, which is influenced by the characteristics of red blood cells, the concentration of proteins in the blood stream such as fibrinogen, and overall hydration status [19], can impair blood flow, exacerbate the progression of atherosclerosis, and compromise microvascular perfusion, leading to more extensive ischemic damage and potentially impeding post-stroke recovery and worsen functional deficits [4]. Moreover, increased blood viscosity may impede effective collateral blood flow to ischemic regions, reducing the compensatory perfusion that is critical for limiting infarct expansion and neurological deficits [20]. High DBV may also promote thrombosis and increase the risk of occlusion in small vessels, either precipitating new ischemic events or worsening existing deficits from the initial stroke [21]. Additionally, higher viscosity may impede the delivery of therapeutic agents and the clearance of metabolic waste products, further exacerbating the ischemic insult [22].

From a clinical perspective, these findings underscore the potential utility of DBV as a prognostic marker for post-stroke functional outcomes. Incorporating DBV measurements into routine stroke assessments could aid in risk stratification and inform personalized hydration and antithrombotic strategies in the acute stroke phase to improve post-stroke neurological recovery.

Although this study provides valuable insights, it is essential to acknowledge its retrospective nature and the potential for unmeasured confounding factors. Prospective studies with larger sample sizes and longer follow-up periods are warranted to validate these findings and further elucidate the role of DBV in post-stroke recovery trajectories. Other limitations of our study include the following. First, DBV was analyzed within 24 hours of stroke onset, which may reflect acute-phase reactions rather than baseline conditions. Moreover, because blood viscosity and other rheological measurements may change significantly during the first 24 hours following an ischemic event—based on previous studies—this 24-hour cutoff may introduce bias. Second, serial changes in DBV during hospitalization were not monitored. The trajectories of DBV in the acute phase may influence post-stroke outcomes and warrant further investigation. Third, as this study was conducted at a single center in Korea, the results may not be generalizable to other populations.

CONCLUSIONS

Elevated DBV at admission was significantly associated with poor short-term functional outcomes after AIS. These findings underscore the importance of incorporating DBV assessment into AIS prognosis and suggest a potential avenue for therapeutic intervention targeting blood rheology to improve cerebral microcirculation and stroke recovery.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Systolic and diastolic blood viscosity according to the TOAST classification of index stroke event

Supplementary Table 2

Univariate and multivariable logistic regression analysis for the prediction of poor functional outcome in patients who were not taking antithrombotic nor had a diagnosis of cancer

Supplementary Fig. 1

Flowchart of the study enrollment.

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