JNN

ORIGINAL ARTICLE

pISSN 2635-425X eISSN 2635-4357
https://doi.org/10.31728/jnn.2022.00114

Progression in Lacunar Stroke is Related to Elevated Blood Viscosity

Sang Won Han, MD*; Sun Ki Min, MD*; Taemin Kim, MD*; Jinyoung Oh, MD*; Jin Kim, MD*; Hyun-jeung Yu, MD, PhD†

Department of Neurology, Sanggye Paik Hospital, Inje University College of Medicine*, Seoul; Department of Neurology, Bundang Jesaeng General Hospital†, Seongnam, Korea

Background: This study aimed to determine the relationship between neurological deterioration (ND) and blood viscosity (BV) in patients with lacunar stroke (LS).
Methods: This was a single-hospital retrospective observational study of patients with LS. Patients were categorized into two groups: those with progressive symptoms and those without clinical worsening. Progression was defined as worsening by ≥2 points on the National Institutes of Health Stroke Scale (NIHSS) for motor function or ≥3 points on the total NIHSS score.
Results: In total, 215 patients (26% of the total stroke population during the study period) who had experienced LS were screened for enrolment, and 182 were included in the final analysis. Of these, 40 patients (22%) showed clinical progressive symptoms. Among men, the progressive stroke group visited the hospital earlier with more severe symptoms than the non-progressive stroke group. Logistic linear regression analysis revealed that onset to admission ≤24 hours (odds ratio [OR], 4.03; 95% confidence interval [CI], 1.1-14.71; p=0.035), NIHSS ≥4 at admission (OR, 2.63; 95% CI, 1.03-6.71; p=0.043), systolic BV (OR, 3.57; 95% CI, 1.39-9.16; p=0.008), and diastolic BV (OR, 1.09; 95% CI, 1.02-1.16; p=0.012) were associated with progressive stroke. Whereas in women, only onset to admission ≤24 hour (OR, 17.92; 95% CI, 2.16-148.62; p=0.008) showed association.
Conclusion: We found that admission within 24 hours, higher NIHSS score, and higher BV at admission were associated with an increased risk of ND in male patients with LS. Increased BV may play a role in reducing cerebral collateral circulation, thrombus propagation, or arterial reocclusion in progressive LS.
J Neurosonol Neuroimag 2022;14(1):35-41

Key Words: disease progression; stroke; viscosity

Received: March 15, 2022
Revised: April 20, 2022
Accepted: April 20, 2022

Correspondence:
Hyun-jeung Yu, MD, PhD

Department of Neurology, Bundang Jesaeng General Hospital, 20 Seohyeon-ro 180beon-gil, Bundang-gu, Seongnam 13590, Korea
Tel: +82-31-779-0216
Fax: +82-31-779-0897
E-mail: yhj314@dmc.or.kr

INTRODUCTION

Lacunar strokes (LS), caused by the occlusion of individual penetrating arteries, are small subcortical infarcts in the deep hemisphere or in the brainstem.[1] Although LS accounts for one-quarter of all ischemic strokes and generally has a favorable outcome, 20-30% of patients with LS show neurological deterioration (ND), especially motor deficits, within a few days after stroke onset.[2-4] ND in LS has been shown to be associated with cerebral edema, low collateral blood flow, thrombus propagation, or recurrent embolism.[2,5] Because ND in LS leads to a high rate of functional disability, early identification of patients who are at risk of progression may improve their clinical and therapeutic management.

Blood viscosity (BV) is defined as the measurement of intrinsic resistance applied to blood flow, and describes the blood stickiness and thickness.[6] BV is related to elevated concentrations of blood cells and plasma components, and high aggregability and low deformability of erythrocytes.[6,7] Prior studies have demonstrated that

high BV increases the major thromboembolic risk, and is associated with cerebro-cardiovascular diseases.[6-8] Regarding stroke, several studies have suggested that BV appears significantly elevated more commonly in LS among stroke subtypes.[9,10] It has been postulated that when the blood passes the cerebral small arteries, increased BV can aggravate the flow disturbance and cause luminal occlusion.[9,11]

Considering the underlying pathomechanisms of ND in LS, we hypothesized that increased BV could influence cerebral vessel viscosity, which is related to thrombus propagation and collateral blood flow circulation. Hence, this study aimed to determine the relationship between ND and BV in patients with LS.

SUBJECTS AND METHODS

1. Patients

We performed a retrospective observational study of patients (aged ≥20 years) with ischemic stroke based on a single stroke center hospital database from March 2020 to November 2021. The inclusion criteria were 1) LS according to the Trial of ORG 10172 in the Acute Stroke Treatment classification system,[12] 2) compatible small subcortical lesions on brain computed tomography (CT) or magnetic resonance imaging (MRI), 3) admission within 5 days of stroke onset, and 4) hemoglobin (Hb) level between 10-18 mg/dL. Patients with intravenous (IV) thrombolysis, recurrent stroke during admission, or prior anticoagulant use were excluded from the study.

The patients' characteristics were assessed upon admission. All patients underwent a physical examination and systemic investigations. Neurological examinations, including the National Institutes of Health Stroke Scale (NIHSS) score, were performed daily by trained physicians. The patients were categorized into two groups: those with progressive symptoms, and those without clinical worsening. Progression was defined as worsening by ≥2 points on the NIHSS score for motor function or ≥3 points in the total NIHSS score.[13,14] The NIHSS score at admission was classified as low (NIHSS <4) or high (NIHSS ≥4), reflecting that the latter generally included severe motor weakness. Brain CT or MRI was performed on all patients at admission, and upon progressive symptoms to exclude cerebral hemorrhage and new ischemic lesions. Echocardiography and 24-hour Holter monitoring were performed in selected patients to identify the potential cardiac sources of embolism. During hospitalization, patients were treated with aspirin plus clopidogrel dual antiplatelet therapy (DAPT) if there were no contraindications. In addition, all patients received the best medical treatment, including antihypertensives, antidiabetic drugs, or statins.

2. BV measurement

We used previously published methods of BV measurement in this study.[2] In brief, the whole blood viscosity was calculated by scanning capillary-tube viscometer (SCTV) (Hemovister, Pharmode Inc., Seoul, Korea). SCTV assesses systolic BV (SBV) and diastolic BV (DBV), which characterize viscosities at high and low shear rates, respectively. In this study, BV measured at a shear rate of 300 s^{-1} was selected as the SBV, and at 1 s^{-1} as the DBV.[4] Although it is not mandatory, considering the possible effect of BV on the treatment of ischemic stroke, BV has been measured in ischemic stroke patients in Sanggye Paik Hospital since January 2017. Laboratory tests, including BV, Hb, and hematocrit (Hct) were performed before IV hydration therapy. BV measurements were performed within 24 hours of sample collection. Because the normal BV values were different between men and women (normal reference range: SBV 3.66-5.41 centipoise [cP] and DBV 23.15-36.45 cP in men, and SBV 3.27-4.32 cP and DBV 18.2-27.36 cP in women), the analysis was conducted separately for each sex.

3. Statistical analysis

Variables were verified for normality using the Kolmogorov–Smirnov test. Descriptive data are expressed as numbers (percentages) or mean±standard deviation. Univariate analyses of baseline characteristics were performed using an independent sample *t*-test or the Mann-Whitney *U* test for continuous variables, and the chi-square test for categorical variables. Multivariable logistic regression models were used to analyze the association between univariate variables and progres-

sive symptoms. Receiver operating characteristic (ROC) curve analysis was performed to determine the cutoff value of BV for progressive symptoms. The area under the ROC curve (AUC) and CI were assessed. Two-sided null hypotheses of no difference were rejected at $p<0.05$. Statistical analyses were performed using SPSS version 25.0 for Windows (IBM Co., Armonk, NY, USA).

RESULTS

In total, 215 patients (26% of the total stroke population of the institute during the study period) who had experienced LS were screened for enrolment, of whom 33 (15%) were excluded from the study (12 due to admission after 5 days of stroke onset, nine due to Hb level <10 or >18 mg/dL, eight with IV thrombolysis, two with recurrent stroke during admission, and two with prior anticoagulant use). Consequently, a total of 182 patients were included in the final analysis.

The baseline characteristics of the enrolled patients are shown in Table 1. Of these, 40 patients (22%) showed clinical progression of stroke symptoms, and 78% remained stable or improved. For males, the study group consisted of 116 patients (22% with progression of stroke symptoms), and the mean age was 68.20±12.01 years. Of these, 69% had a history of hypertension, 36% had a history of diabetes, 49% had a history of dyslipidemia, and 42% were current smokers. Thirty-four patients (29%) regularly used antiplatelets (aspirin alone, 47%; clopidogrel alone, 29%; aspirin plus clopidogrel, 12%; and others, 12%)

Table 1. Baseline characteristics of the study population

	Men				Women			
	Total (n=116)	Progressive (n=25)	Non-progressive (n=91)	*p*-value	Total (n=66)	Progressive (n=15)	Non-progressive (n=51)	*p*-value
Age, years	68.20±12.01	67.50±12.11	68.40±12.04	0.740	72.70±11.35	68.70±11.06	73.90±11.26	0.122
Hypertension	80 (69.0)	19 (76.0)	61 (67.0)	0.391	52 (78.8)	12 (80.0)	40 (78.4)	0.896
Diabetes mellitus	42 (36.2)	10 (40.0)	32 (35.2)	0.656	27 (40.9)	8 (53.3)	19 (37.3)	0.266
Dyslipidemia	57 (49.1)	11 (44.0)	46 (50.5)	0.562	40 (60.6)	11 (73.3)	29 (56.9)	0.369
Stroke	20 (17.2)	5 (20.0)	15 (16.5)	0.68	13 (19.7)	3 (20)	10 (19.6)	0.973
Coronary artery disease	6 (5.2)	1 (4.0)	5 (5.5)	0.765	3 (4.5)	0 (0.0)	3 (5.9)	0.336
Current smoking	49 (42.2)	12 (48.0)	37 (40.7)	0.510	3 (4.5)	0 (0.0)	3 (5.9)	0.336
Prior antiplatelets use	34 (29.3)	5 (20.0)	29 (31.9)	0.248	21 (31.8)	3 (20)	18 (35.3)	0.264
Time to admission, hours	27.3±28.38	11.7±9.55	31.5±30.31	0.002*	28.9±25.34	13.4±8.26	33.4±26.9	0.006*
Onset to admission ≤24 hours	78 (67.2)	21 (84.0)	57 (62.6)	0.043*	37 (56.1)	14 (93.3)	23 (45.1)	<0.0001*
NIHSS score at admission ≥4	37 (31.9)	13 (52.0)	24 (26.7)	0.015*	20 (30.3)	5 (33.3)	15 (29.4)	0.771
Lesion localization				0.793				0.009*
Anterior	63 (54.3)	13 (52.0)	50 (54.9)		43 (65.2)	14 (93.3)	29 (56.9)	
Posterior	53 (45.7)	12 (48.0)	41 (45.1)		23 (34.8)	1 (6.7)	22 (43.1)	
SBP, mmHg	169±31.97	174±37.49	167±30.34	0.323	172±33.81	182±42.51	169±30.65	0.187
DBP, mmHg	92±19.69	97±24.33	91±18.17	0.183	92±16.41	96±17.05	90±16.18	0.259

Values are presented as number (%) or mean±standard deviation.
NIHSS; National Institutes of Health Stroke Scale, SBP; systolic blood pressure, DBP; diastolic blood pressure.
*Significant *p*-value.

at admission. The median time from symptom onset to hospital arrival was 16 hours, and 67% of patients visited the hospital within 24 hours. The median NIHSS score at admission was 3, and 32% of patients presented with NIHSS ≥4. All baseline characteristics were well balanced across the two groups except time to admission (p=0.002), onset to admission ≤24 hours (p=0.043), and NIHSS score ≥4 at admission (p=0.015), suggesting that the progressive stroke group visited the hospital earlier with more severe symptoms than the non-progressive stroke group. For females, 66 patients were enrolled in the study (23% with progression of stroke symptoms), and the mean age was 72.70±11.35 years. There were no differences in the baseline characteristics between the two groups, except for time to admission (p=0.006), onset to admission ≤24 hours (p<0.0001), and lesion localization (p=0.009). The progressive stroke group visited the hospital earlier and had more anterior circulation lesions than that in the nonprogressive stroke group.

Table 2 shows the laboratory findings of the study population. In men, no significant differences were observed in laboratory findings between the groups, except for SBV and DBV. The SBV and DBV were higher in the progressive stroke group (p=0.007 and p=0.006, respectively), showing that the progressive stroke group had increased BV at admission compared to the non-progressive stroke group. Multivariable logistic regression analysis revealed that onset to admission ≤24 hours (odds ratio [OR], 4.03; 95% CI, 1.10-14.71; p=0.035), NIHSS ≥4 at admission (OR, 2.63; 95% CI, 1.03-6.71; p=0.043), SBV (OR, 3.57; 95% CI, 1.39-9.16; p=0.008), and

Table 2. Laboratory findings of the study population

	Men				Women			
	Total (n=116)	Progressive (n=25)	Nonprogressive (n=91)	p-value	Total (n=66)	Progressive (n=15)	Nonprogressive (n=51)	p-value
Hemoglobin, g/dL	14.4±1.48	14.7±1.46	14.3±1.48	0.289	13±1.36	13.9±0.99	12.8±1.37	0.007*
Hematocrit, %	42.86±4.09	43.5±3.71	42.7±4.19	0.381	39.3±4.49	41.7±2.74	38.6±4.68	0.019*
White blood cells, 10^3/μL	7.51±1.89	7.81±1.95	7.43±1.87	0.379	6.81±2.06	7.31±1.69	6.67±2.15	0.292
Platelets, 10^3/μL	232±68.58	233±56.09	232±71.91	0.951	238±61.39	255±64.41	233±60.24	0.234
BUN, mg/dL	16.4±5.11	15.1±3.73	16.8±5.39	0.147	17.1±5.61	15.5±4.02	17.5±5.95	0.233
Creatine, mg/dL	1.05±0.88	0.88±0.17	1.09±0.99	0.300	0.7±0.21	0.66±0.11	0.71±0.23	0.438
Random plasma glucose, mg/dL	160±79.27	160±84.75	160±40.99	0.974	152±74.09	182±110.55	143±57.95	0.205
Total cholesterol, mg/dL	171±53.16	160±84.75	173±55.96	0.294	180±51.15	188±50.82	178±51.54	0.518
LDL-cholesterol, mg/dL	104±34.56	99±29.97	105±35.79	0.480	109±34.88	114±32.89	107±35.61	0.499
HDL-cholesterol, mg/dL	43±10.27	40±9.02	44±10.49	0.096	49±11.15	51±10.58	48±11.34	0.427
Triglyceride, mg/dL	125±64.63	112±44.16	128±69.13	0.289	114±74.39	108±43.11	115±81.62	0.744
INR	1±0.07	0.99±0.06	1±0.07	0.467	0.99±0.11	0.97±0.43	1±0.12	0.352
SBV, cP	4.65±0.56	4.92±0.58	4.57±0.54	0.007*	4.33±0.63	4.73±0.56	4.2±0.6	0.004*
DBV, cP	30.82±8.32	34.90±29.63	29.63±7.57	0.006*	25.86±8.76	31.35±8.57	24.11±8.15	0.004*
hs-CRP, mg/dL	0.36±0.82	0.32±0.74	0.38±0.84	0.734	0.54±1.13	0.51±1.12	0.54±1.17	0.930

Values are presented as mean±standard deviation.
BUN; blood urea nitrogen, LDL; low-density lipoprotein, HDL; high-density lipoprotein, INR; international normalized ratio, SBV; systolic blood viscosity, cP; centipoise, DBV; diastolic blood viscosity, hs-CRP; high sensitive C-reactive protein.
*Significant p-value.

DBV (OR, 1.09; 95% CI, 1.02-1.16; p=0.012) were significantly associated with progressive stroke. In men, the cutoff value of the SBV and DBV in progressive stroke were 4.77 cP (sensitivity, 70.8%; specificity, 31.7%) and 32.35 cP (sensitivity, 66.7%; specificity, 65.9%), respectively. The AUC was 0.68 (95% CI, 0.56-0.80; p=0.007) and 0.67 (95% CI, 0.55-0.80; p=0.011) (Fig. 1). Analysis of the female groups showed that Hb, Hct, SBV, and DBV were significantly higher in the progressive stroke group. Multivariable logistic regression analysis revealed that onset to admission ≤24 hours (OR, 17.92; 95% CI, 2.16-148.62; p=0.008) was related to progressive stroke, suggesting that most ND occurred within days after stroke onset. There was also a trend towards increased BV being associated with progressive stroke (SBV OR, 3.25; 95% CI, 0.97-10.97; p=0.057; and DBV, OR, 1.07; 95% CI, 0.99-1.18; p=0.054).

DISCUSSION

In this study, we evaluated the relationship between ND and BV in LS patients. Our study showed that admission within 24 hours, higher NIHSS score, and higher BV at admission were associated with an increased risk of ND in male patients with LS. In women, the onset to admission within 24 hours was associated with progressive stroke, confirming that most ND occurred within days after stroke onset. These data were consistent with previously reported data demonstrating that in 20-30% of LS patients, neurological deficits worsen in hours or days after LS onset.[5,15] In our study, the median time from symptom onset to hospital arrival was 11 hours in the progressive stroke group and 21 hours in the nonprogressive stroke group. Regarding NIHSS score, recent studies have suggested that a higher NIHSS score at admission is associated with an increased risk of ND.[13,16] Eighteen patients (45%) with progressive stroke presented with NIHSS ≥4 in our study. From a therapeutic point of view, patients with NIHSS ≥4 at admission were excluded from the POINT trial.[17] However, one study demonstrated that 5 days of DAPT are associated with improved functional outcomes in progressive LS.[14] Although DAPT efficacy and the mechanisms underlying ND are not yet fully understood, DAPT might improve functional outcomes and reduce clinical fluctuation by reducing thrombus propagation or arterial reocclusion, which is closely related to the mechanism of progressive LS.

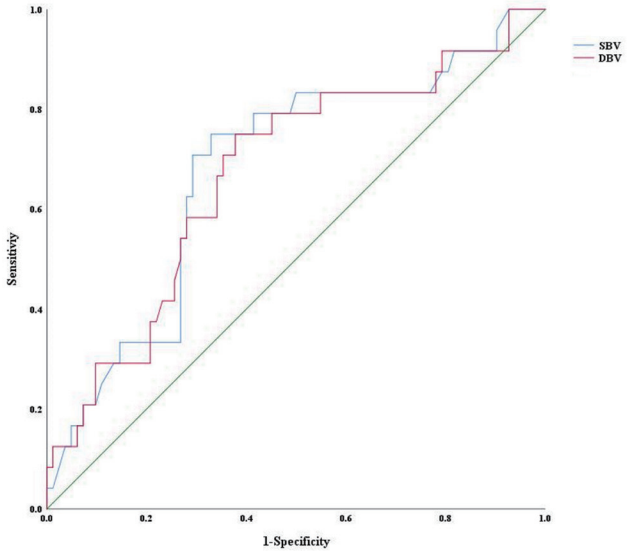

FIG. 1. Receiver-operating characteristic curves to determine the cutoff value of blood viscosity in progressive lacunar strokes. Area under the curve is 0.68 (95% CI, 0.56-0.80) and 0.67 (95% CI, 0.55-0.80) in men. CI; confidence interval, SBV; systolic blood viscosity, DBV; diastolic blood viscosity.

There is still no generally accepted definition of ND for patients with LS. Several studies have used diverse neurological scales and definitions when classifying patients into a progressive stroke group.[5,13-15] One study reported that worsening more than 1 point in NIHSS score is reasonable since the major ND occurred in motor function.[5] Considering the criteria for NIHSS score and clinical fluctuations in LS, we defined progressive stroke as worsening by ≥2 points on the NIHSS score for motor function or ≥3 points in all NIHSS scores.[13,14] We believe that an advanced evidence-based definition of ND in LS is essential to perform good clinical trials and provide the best treatments.

Failure of collateral circulation, thrombus propagation, arterial reocclusion, hemorrhagic transformation, stroke recurrence, seizure, brain edema, neuronal excitotoxicity, inflammation, and peri-infarct depolarizations may be associated with ND in LS.[15,18,19] The most plausible explanation tis that local thrombosis superimposes to the ostial atheroma, and thrombus propagation proximal to distal, or distal to proximal segments of a perforating artery.[15,19] Hemodynamic

insufficiency of perforators near the one responsible for the ischemic insult could also contribute to transformation of the penumbra into infarction.[15] It is well known that increased BV reflects an acute phase response to stroke and presents an independent stroke risk factor.[20,21] There are several potential explanations for the relationship between BV and progressive LS.[9,20] Firstly, a reduction in the collateral circulation could be one of the potential mechanisms that lead to progressive LS. Further, cerebral perfusion is inversely related to BV and thus,[20] an increased BV can lead to decreased cerebral perfusion in patients with progressive LS. BV is elevated in the acute phase of ischemic stroke and gradually improves in the chronic phass,[7] and appears to be significantly higher in LS than in other stroke subtypes.[9,11] When the blood passes through the stenotic cerebral perforating arteries, increased BV can aggravate the flow disturbance and cause vascular endothelial remodeling and luminal occlusion. These hemorheological changes can be related to thrombus propagation or arterial reocclusion in progressive LS.[22] Taken together, it can be assumed that increased BV may play an important role in the mechanism of progressive LS.

Our study has several limitations. First, the number of patients with progressive LS may have been underestimated. The frequency of progressive LS is described to be dependent on the time of admission.[5] The ND in LS usually occurred within the first days following stroke onset, but only 63% of patients visited the hospital within 24 hours after stroke onset in our study. Second, BV is elevated in the acute phase of ischemic stroke and gradually decreases over time.[7] The earlier hospital visit in the progressive stroke group and the time differences of measuring BV between the groups may explain the discrepancy in our results. However, Hct, the major determinant of BV, was similar between the groups in men, suggesting that these results were not related to the BV measurement time. Third, several clinical and neuroimaging data have been studied as potential predictors of LS progression. Lesion location (internal capsule, pons, and corona radiata), motor function involvement, and the presence of a few risk factors linked to atherosclerosis are the most consistently reported. Regarding imaging risk factors, previous brain MRI studies have shown that corona radiata or pontine lesions are associated with ND in patients with LS. Although a trend towards concordance with previous studies was observed (p=0.113), our study failed to demonstrate significant imaging data. Finally, the statistical power of the results supporting our conclusion was fairly weak, mainly because of the small sample size and lack of age-matched controls. These limitations should be considered when interpreting our results, and the present findings need to be confirmed in larger trials.

In conclusion, this study showed that admission within 24 hours, higher NIHSS score, and higher BV at admission were all associated with an increased risk of ND in male patients with LS. Increased BV may play an important role in the reduction of cerebral collateral circulation, thrombus propagation or arterial reocclusion in progressive LS. Further studies focusing on a larger sample size with acute onset time are essential to confirm our results.

Ethics Statement

This study was approved by the Clinical Trial Review Committee of Sanggye Paik Hospital (Approval No. SGPAIK 2022-03-011-001). The requirement for written informed consent was waived and the study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki.

Availability of Data and Material

The data supporting the findings of this study are available from HJY, but restrictions apply to their availability, which were used under the license for the current study, and so are not publicly available. However, data are available from the authors upon reasonable request and with permission from the HJY.

Acknowledgments

None.

Sources of Funding

None.

Conflicts of Interest

No potential conflicts of interest relevant to this article was reported.

REFERENCES

1. Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease: a clinical review. *Neurology*. 2019;92:1146-1156.
2. Gan R, Sacco RL, Kargman DE, Roberts JK, Boden-Albala B, Gu Q. Testing the validity of the lacunar hypothesis: the Northern Manhattan Stroke Study experience. *Neurology*. 1997;48:1204-1211.
3. Nakamura K, Saku Y, Ibayashi S, Fujishima M. Progressive motor deficits in lacunar infarction. *Neurology*. 1999;52:29-33.
4. Sacco S, Marini C, Totaro R, Russo T, Cerone D, Carolei A. A population-based study of the incidence and prognosis of lacunar stroke. *Neurology*. 2006;66:1335-1338.
5. Audebert HJ, Pellkofer TS, Wimmer ML, Haberl RL. Progression in lacunar stroke is related to elevated acute phase parameters. *Eur Neurol*. 2004;51:125-131.
6. Pop GA, Duncker DJ, Gardien M, Vranckx P, Versluis S, Hasan D, et al. The clinical significance of whole blood viscosity in (cardio)vascular medicine. *Neth Heart J*. 2002;10:512-516.
7. Park JH, Kim JY, Baik JS, Park JH, Nam HS, Han SW. Prior antithrombotic use is significantly associated with decreased blood viscosity within 24 hours of symptom onset in patients with acute ischemic stroke. *J Neurocrit Care*. 2019;12:85-91.
8. Késmárky G, Kenyeres P, Rábai M, Tóth K. Plasma viscosity: a forgotten variable. *Clin Hemorheol Microcirc*. 2008;39:243-246.
9. Song SH, Kim JH, Lee JH, Yun YM, Choi DH, Kim HY. Elevated blood viscosity is associated with cerebral small vessel disease in patients with acute ischemic stroke. *BMC Neurol*. 2017;17:20.
10. Furukawa K, Abumiya T, Sakai K, Hirano M, Osanai T, Shichinohe H, et al. Increased blood viscosity in ischemic stroke patients with small artery occlusion measured by an electromagnetic spinning sphere viscometer. *J Stroke Cerebrovasc Dis*. 2016;25:2762-2769.
11. Kim T, Oh J, Han JE, Park JH, Baik JS, Kim JY, et al. The relationship between changes in systemic blood viscosity and transcranial Doppler pulsatility in lacunar stroke. *J Neurosonol Neuroimag*. 2020;12:67-72.
12. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke*. 1993;24:35-41.
13. Berberich A, Schneider C, Herweh C, Hielscher T, Reiff T, Bendszus M, et al. Risk factors associated with progressive lacunar strokes and benefit from dual antiplatelet therapy. *Eur J Neurol*. 2020;27:817-824.
14. Berberich A, Schneider C, Reiff T, Gumbinger C, Ringleb PA. Dual antiplatelet therapy improves functional outcome in patients with progressive lacunar strokes. *Stroke*. 2019;50:1007-1009.
15. Del Bene A, Palumbo V, Lamassa M, Saia V, Piccardi B, Inzitari D. Progressive lacunar stroke: review of mechanisms, prognostic features, and putative treatments. *Int J Stroke*. 2012;7:321-329.
16. Mantero V, Scaccabarozzi C, Botto E, Giussani G, Aliprandi A, Lunghi A, et al. Outcome in lacunar stroke: a cohort study. *Acta Neurol Scand*. 2018;138:320-326.
17. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379:215-225.
18. Regenhardt RW, Das AS, Lo EH, Caplan LR. Advances in understanding the pathophysiology of lacunar stroke: a review. *JAMA Neurol*. 2018;75:1273-1281.
19. Lee MJ, Moon S, Cho S, Chung JW, Seo WK, Bang OY, et al. Mechanisms involved in lacunar infarction and their role in early neurological deterioration. *J Neurosonol Neuroimag*. 2020;12:26-32.
20. Stavropoulos K, Imprialos KP, Bouloukou S, Boutari C, Doumas M. Hematocrit and stroke: a forgotten and neglected link? *Semin Thromb Hemost*. 2017;43:591-598.
21. Coull BM, Beamer N, de Garmo P, Sexton G, Nordt F, Knox R, et al. Chronic blood hyperviscosity in subjects with acute stroke, transient ischemic attack, and risk factors for stroke. *Stroke*. 1991;22:162-168.
22. Oh J, Han JE, Kim T, Park JH, Baik JS, Kim JY, et al. The relationship between the transcranial Doppler pulsatility changes and the CYP2C19 genotype on clopidogrel treatment. *J Neurosonol Neuroimag*. 2020;12:33-39.