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ORIGINAL RESEARCH

Associations of Interleukin 10, Matrix Metallopeptidase 9, and Legumain with Blood Pressure Variability and Neurologic Outcomes in Patients with Ischemic Stroke

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Background: Timely diagnosis and treatment are crucial to improve prognosis of ischemic stroke, making exploring factors associated with prognosis essential. Blood pressure variability (BPV) was reported to be associated with neurologic outcome, and basic researches on cardiovascular diseases found abnormal expression patterns of several factors including interleukin 10 (IL-10), matrix metallopeptidase 9 (MMP-9), and legumain which might be related to abnormal BPV but yet to prove in ischemic stroke. The study aimed to investigate whether IL-10, MMP-9, and legumain are associated with BPV and neurologic outcome of patients with ischemic stroke.

Patients and Methods: Newly diagnosed ischemic stroke patients admitted to the department of neurology, Shidong Hospital of Yangpu District in Shanghai between July 2017 and January 2019 were enrolled. IL-10, MMP-9, and legumain were detected and BPV was assessed within 72 hours after admission. All the patients were followed for neurologic outcomes at discharge and 6 months after admission based on the Modified Rankin Scale (MRS). Correlations of IL-10, MMP-9, and legumain with BPV were examined by Spearman correlation coefficient, and their associations with neurologic outcomes were evaluated by multivariable linear regression.

Results: A total of 349 patients with ischemic stroke were enrolled with an average age of 72.97±11.47 years. Compared with non-progressive ischemic stroke, patients with progressive ischemic stroke had significantly higher IL-10, MMP-9, and legumain on admission. MMP-9 was found to be positively correlated with BPV while no significant correlation was found for IL-10 and legumain with BPV. MMP-9 was associated with progressive ischemic stroke [β=0.23 (95% CI 0.11–0.35) per SD increase for MRS at discharge, and β=0.32 (95% CI 0.20–0.43) per SD increase for MRS at 6 months after admission].

Conclusion: Increased MMP-9 was associated with increased BPV and progressive ischemic stroke for patients with ischemic stroke, which might partially explain the effect of BPV on neurologic outcomes.

Keywords: interleukin 10, matrix metallopeptidase 9, legumain, blood pressure variability, ischemic stroke

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Introduction

Stroke has become one of the major causes of death and serious disability for adults.[1–3] Globally, ischemic stroke accounted for the most (68%) stroke cases,[4] and in the United States this proportion was much higher (87%).[5] The worldwide 30-day case fatality

rate after first ischemic stroke was estimated to be 16–23%.[6,7] For those survived, however, disability could be another serious concern.[8] Obviously, due to its high morbidity and poor prognosis including high mortality and disability, ischemic stroke has become a serious public health problem. The ideal therapy to patients with ischemic stroke is to restore blood flow to the regions of brain that are ischemic but not yet infarcted within the narrow therapeutic window,[9,10] but this is not always achievable, and secondary prevention of ischemic stroke therefore becomes another important issue in the management of ischemic stroke.[11]

Numerous predictors of prognosis were explored which on the one hand might improve the management of ischemic stroke by promoting timely intervention,[12,13] and on the other hand could also increase understanding of mechanisms of the disease. Blood pressure variability (BPV) is one of the factors that related to prognosis of ischemic stroke. Several studies suggested that increased BPV was associated with poor neurologic outcome,[14–16] while the mechanism behind is not fully understood. Researches on hypertension suggested injured endothelium due to highly fluctuating abnormal blood flow related to vascular inflammation,[17,18] and meanwhile accumulating evidence suggested inflammation played a central role in all aspects of stroke including its initiation and progression.[19] These evidences together suggested that increased BPV might aggravate the prognosis of ischemic stroke by inducing vascular inflammation, but relevant research is rare.

Interleukin-10 (IL-10) was found to play an important anti-inflammatory role in response to brain injury and to facilitate the resolution of inflammatory cascades therefore avoiding secondary brain damage.[20] Increased matrix metallopeptidase 9 (MMP-9) might be a potential trigger of the inflammatory response bridging between endothelial cells and vascular smooth muscle cells.[21] Legumain was found to promote atherosclerotic vascular remodeling by enhancing the inflammatory M1 phenotype and oxidized low-density lipoprotein-induced foam cell formation in macrophages.[22] The abnormal expression patterns of these factors might be related to abnormal BPV in ischemic stroke but yet to prove. The study aimed to investigate the associations of IL-10, MMP-9, and legumain with BPV and neurologic outcome of patients with ischemic stroke.

Patients and Methods

Patients

Newly diagnosed ischemic stroke patients admitted to the department of neurology, Shidong Hospital of Yangpu District in Shanghai between July 2017 to January 2019 were enrolled as study subjects. Detailed inclusion criteria included: 1) admission within 72 hours after the onset of ischemic stroke; 2) conforming to the diagnostic criteria of ischemic stroke based on Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018.[23] Patients with severe chronic illnesses such as cardiovascular diseases, respiratory failure, cirrhosis, or renal insufficiency were excluded. The study was approved by ethics committee of Shidong Hospital of Yangpu District hospital and written informed consent were obtained from all the participants. This study was conducted in accordance with the Declaration of Helsinki.

Detection of IL-10, MMP-9, Legumain, and BPV

After a fast for 8 hours, approximately 10 mL of peripheral blood was obtained using collection tube without additives from each subject within 72 hours after admission. Serum samples were separated by 2300*g*× 20min centrifugation. IL-10, MMP-9, legumain were then detected by enzyme-linked immunosorbent assay using kits from Lianke Biotech Co., Ltd following manufactures' instructions.

TM-2430 ambulatory blood pressure monitor (A&D, Japan) was used for BPV examination. Twenty-four-hour ambulatory blood pressure monitoring was performed for each patient within 72 hours after admission. The cuff of the ambulatory blood pressure monitor is uniformly worn on the left upper arm of the patient, and blood pressure (including systolic blood pressure (SBP), diastolic blood pressure (DBP)) were measured repeatedly every 30 minutes during daytime and every 60 minutes at night-time. During the monitoring period, the patient can move normally, but the patients were asked to remain their left upper arm still during automatic measurement to ensure reliable data.

Baseline Covariates

Information on the following baseline covariates were collected from regular clinical practice, including age, sex, current smoking status, alcohol use, comorbidity (hypertension, coronary heart disease, atrial fibrillation, hyperlipidemia, diabetes, cerebral infarction history, cerebral hemorrhage history), blood test (white blood cells, hemoglobin, platelet, random glucose, fasting blood sugar, hemoglobin A1c, C-reactive protein, international normalized ratio, D-dimer, total cholesterol, HDL cholesterol, LDL cholesterol,

triglyceride, urea nitrogen, creatinine, uric acid, homocysteine, cystatin C), location of ischemic stroke (i.e., anterior circulation or posterior circulation), and subtypes of ischemic stroke (i.e., large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, or stroke of undetermined etiology). NIH Stroke Scale (NIHSS) at admission and at discharge was also collected.

The patients were further categorized as non-progressive ischemic stroke and progressive ischemic stroke. Progressive ischemic stroke was defined as the condition of a patient gradually worsened within 1 week after admission, which was based on an increase of the NIHSS more than 2, or an increase of consciousness score or motor ability score more than 1, or newly appeared neurological deficits.[24,25]

Follow-Up and Study Outcomes

All the patients were followed for 6 months, and neurologic outcomes at discharge and 6 months after admission based on the Modified Rankin Scale (MRS) were selected as the study outcomes.

Statistical Analysis

Continuous variables with normal distribution were presented as mean ± standard deviation, otherwise as median (25%quartile – 75%quartile). Categorical variables were presented as a number and percentage. Comparison of continuous variables between groups was examined by *t*-test or rank sum test when appropriate. Comparison of categorical variables between groups was examined by chi-square test. Correlations between IL-10, MMP-9, legumain, BPV, and MRS (at discharge and 6 months after admission) were examined by Spearman correlation coefficient. Associations of IL-10, MMP-9, and legumain with MRS were evaluated by multivariable linear regression. $P<0.05$ was considered statistically significant. All the statistical analyses were performed by SPSS17.0 software.

Results

Baseline Characteristics of the Study Subjects

Three hundred and forty-nine patients with ischemic stroke were included, of which 265 patients were non-progressive ischemic stroke and 84 patients were progressive ischemic stroke. The average age of the study subjects was 72.97±11.47 years, and 57.88% (202/349) were male. As presented in Table 1, compared with non-progressive ischemic stroke, most baseline characteristics were similar, but patients with progressive ischemic stroke had significantly higher IL-10, MMP-9, and legumain on admission, and more patients had hypertension (85.71% versus 72.08%) and hyperlipidemia (51.19% versus 36.23%). No significant difference was found in location of ischemic stroke and subtypes of ischemic stroke.

Results of baseline BPV are presented in Table 2. Compared with non-progressive ischemic stroke, patients with progressive ischemic stroke had significantly higher SBP at admission, higher average SBP (24h), higher average SBP (day), and higher average SBP (night). Higher CV of average SBP (24h), CV of average SBP (day), and CV of average DBP (day) were also found in patients with progressive ischemic stroke comparing to patients with non-progressive ischemic stroke.

Correlation Coefficient of IL-10, MMP-9, and Legumain with BPV

As presented in Table 3, MMP-9 was found to be positively correlated with CV of average SBP (24h) (ρ=0.3742, P<0.001), CV of average DBP (24h) (ρ=0.2201, P<0.001), CV of average SBP (day) (ρ=0.3162, P<0.001), CV of average DBP (day) (ρ=0.1905, P<0.001), CV of average SBP (night) (ρ=0.1875, P<0.001), CV of average DBP (night) (ρ=0.1340, P=0.012), while no significant correlation was found for IL-10 and legumain with BPV.

CV of average SBP (24h), CV of average SBP (day), and CV of average DBP (night) were also found to be positively correlated with MRS at discharge and at 6 months after admission, but CV of average DBP (24h) was only positively correlated with MRS at 6 months after admission (Table 4).

Associations of IL-10, MMP-9, and Legumain with Neurologic Outcomes

IL-10 and MMP-9 were positively correlated with MRS at discharge and at 6 months after admission, while no significant correlation was found for legumain (Table 5). The correlations were further examined in multivariable linear regression, but only MMP-9 was associated with progressive ischemic stroke [β=0.23 (95% CI 0.11–0.35) per SD increase for MRS at discharge, and β=0.32 (95% CI 0.-20–0.43) per SD increase for MRS at 6 months after admission] after adjusted for age, sex, MRS before admission, and type of ischemic stroke (progressive or not) (Table 6).

Table 1 Baseline Characteristics of the Study Subjects

Variables	All Subjects (n=349)	Non-Progressive Ischemic Stroke (n=265)	Progressive Ischemic Stroke (n=84)	P
Age, years	72.97±11.47	73.08±11.34	72.60±11.93	0.739
Male	202 (57.88%)	158 (59.62%)	44 (52.38%)	0.241
Current smoking	112 (32.09%)	86 (32.45%)	26 (30.95%)	0.797
Alcohol use	67 (19.20%)	48 (18.11%)	19 (22.62%)	0.361
Interleukin 10 (pg/mL)	4.81 (2.78–7.72)	4.28 (2.66–7.45)	5.71 (4.08–8.10)	**0.004**
Matrix metallopeptidase 9 (mg/L)	753.82 (639.88–954.83)	715.65 (635.04–891.42)	870.81 (698.83–1345.70)	**<0.001**
Legumain (ng/mL)	5.37 (4.52–7.02)	5.14 (4.49–6.63)	6.01 (4.64–11.41)	**0.002**
Comorbidity				
Hypertension	263 (75.36%)	191 (72.08%)	72 (85.71%)	**0.011**
Coronary heart disease	36 (10.32%)	27 (10.19%)	9 (10.71%)	0.840
Atrial fibrillation	57 (16.33%)	43 (16.23%)	14 (16.67%)	0.924
Hyperlipidemia	139 (39.83%)	96 (36.23%)	43 (51.19%)	**0.015**
Diabetes	155 (44.41%)	110 (41.51%)	45 (53.57%)	0.053
Cerebral infarction history	90 (25.79%)	69 (26.04%)	21 (25.00%)	0.850
Cerebral hemorrhage history	4 (1.15%)	2 (0.75%)	2 (2.38%)	0.245
Blood test				
White blood cells ($\times 10^9$/L)	6.73 (5.58–8.18)	6.59 (5.56–7.98)	6.99 (5.67–8.58)	0.344
Hemoglobin (g/L)	133 (121–145)	132 (120–145)	137 (124–147.5)	0.101
Platelet ($\times 10^9$/L)	206 (171–245)	205 (170–246)	215.5 (172.75–243.25)	0.357
Random glucose (mmol/L)	7.70 (6.30–11.40)	7.60 (6.30–10.70)	8.42 (6.28–13.67)	0.078
Fasting blood sugar (mmol/L)	5.59 (4.88–7.47)	5.49 (4.87–6.99)	5.97 (5.07–8.72)	**0.018**
Hemoglobin A1C (%)	6.20 (5.80–7.70)	6.20 (5.80–7.50)	6.30 (5.60–8.62)	0.764
C-reactive protein (mg/L)	3.20 (1.30–7.80)	3.10 (1.30–7.30)	3.85 (1.25–9.43)	0.709
International Normalized Ratio	0.93 (0.89–0.98)	0.93 (0.89–0.98)	0.94 (0.89–0.98)	0.692
D-dimer (mg/L)	0.41 (0.23–0.98)	0.39 (0.23–0.86)	0.52 (0.22–1.42)	0.230
Total cholesterol (mmol/L)	4.57 (3.82–5.32)	4.49 (3.82–5.23)	4.78 (3.85–5.60)	0.141
HDL cholesterol (mmol/L)	1.12 (0.93–1.33)	1.10 (0.91–1.30)	1.16 (1.04–1.44)	**0.005**
LDL cholesterol (mmol/L)	2.68 (2.13–3.31)	2.66 (2.23–3.28)	2.79 (1.73–3.38)	0.355
Triglyceride (mmol/L)	1.21 (0.92–1.71)	1.19 (0.92–1.66)	1.27 (0.92–1.93)	0.496
Urea nitrogen (mmol/L)	5.52 (4.40–6.70)	5.52 (4.40–6.61)	5.54 (4.36–6.86)	0.665
Creatinine (mmol/L)	72.00 (60.20–86.00)	73.30 (62.80–86.90)	66.45 (54.33–80.55)	**0.003**
Uric acid (mmol/L)	330.45 (273.68–392.32)	332.00 (277.40–395.30)	322.20 (258.65–380.55)	0.176
Homocysteine (μmol/L)	15.40 (12.80–19.30)	15.10 (12.70–18.90)	16.00 (12.88–20.10)	0.516
Cystatin C (mg/L)	0.86 (0.84–0.89)	0.86 (0.83–0.89)	0.86 (0.85–0.89)	0.350
Location of ischemic stroke				0.126
Anterior circulation	225 (64.47%)	165 (62.26%)	60 (71.43%)	
Posterior circulation	124 (35.53%)	100 (37.74%)	24 (28.57%)	
Subtypes of ischemic stroke				0.079
Large-artery atherosclerosis	148 (42.41%)	106 (40.00%)	42 (50.00%)	
Cardioembolism	62 (17.77%)	46 (17.36%)	16 (19.05%)	
Small-vessel occlusion	133 (38.11%)	108 (40.75%)	25 (29.76%)	
Stroke of other determined etiology	1 (0.29%)	0 (0.00%)	1 (1.19%)	
Stroke of undetermined etiology	5 (1.43%)	5 (1.89%)	0 (0.00%)	

Note: A P-value <0.05 was presented in bold.

Table 2 Blood Pressure Variability and Prognosis of the Study Subjects

Variables	All Subjects (n=349)	Non-Progressive Ischemic Stroke (n=265)	Progressive Ischemic Stroke (n=84)	P
Blood pressure variability				
SBP at admission, mmHg	139.94±17.93	138.52±16.90	144.40±20.32	**0.009**
DBP at admission, mmHg	81.37±10.44	81.01±10.14	82.50±11.32	0.255
Average SBP (24h), mmHg	145.42±15.16	144.16±14.06	149.42±17.70	**0.005**
CV of average SBP (24h)	10.98±3.17	10.74±3.04	11.73±3.48	**0.013**
Average DBP (24h), mmHg	80.60±9.27	80.35±9.13	81.37±9.70	0.383
CV of average DBP (24h)	13.50±4.62	13.29±4.33	14.14±5.43	0.144
Average SBP (day), mmHg	146.70±15.28	145.50±14.27	150.50±17.67	**0.009**
CV of average SBP (day)	10.55±3.61	10.26±3.44	11.46±3.96	**0.008**
Average DBP (day), mmHg	81.27±9.53	81.09±9.39	81.82±10.01	0.541
CV of average DBP (day)	13.31±5.13	12.94±4.84	14.49±5.82	**0.015**
Average SBP (night), mmHg	141.72±18.44	140.23±17.18	146.42±21.38	**0.007**
CV of average SBP (night)	10.09±4.36	10.13±4.39	9.98±4.29	0.788
Average DBP (night), mmHg	78.77±11.43	78.37±11.35	80.05±11.62	0.240
CV of average DBP (night)	12.30±5.18	12.20±5.22	12.63±5.09	0.506
NIH Stroke Scale				
At admission	4 (2–6)	4 (2–6)	5 (3–9.25)	**<0.001**
At discharge	3 (2–6)	3 (1–4)	7 (4–10.25)	**<0.001**
Modified Rankin Scale				
Before admission	0 (0–1)	0 (0–1)	0 (0–1)	0.062
At discharge	2 (2–4)	2 (1–3)	4 (2–5)	**<0.001**
After 6 months	2 (1–3)	2 (1–2)	3 (2–4)	**<0.001**
Prognosis*				
Improved at discharge	176 (50.43%)	134 (50.57%)	42 (50.00%)	0.928
Improved at 6 months	253 (72.49%)	202 (76.23%)	51 (60.71%)	**0.006**

Notes: *Improved prognosis was defined by the Modified Rankin Scale ≤2. A P-value <0.05 was presented in bold.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, coefficients of variation.

Discussion

In order to investigate the potential association of three inflammation-related factors (i.e., IL-10, MMP-9, legumain) with BPV and neurologic outcomes of ischemic stroke, in the study, we examined the correlations between IL-10, MMP-9, legumain with BPV and multivariable linear regression was employed to examine the associations of these factors with MRS, an index we selected to represent neurologic outcomes. The main finding of our study is that increased baseline MMP-9, which was positively correlated with BPV, was associated poor neurologic outcomes. This finding suggests that MMP-9 might be a useful prognosis predictor for ischemic stroke, and that the association between increased BPV and poor neurologic outcomes observed in patients with ischemic stroke might be partially related to the increased level of MMP-9.

Abnormal BPV was reported to be associated with poor outcome in acute ischemic stroke.[14–16] For example, Minhas et al[16] found that CV of SBP had a significant linear association with unfavorable shift of mRS at 90 days and CV of DBP over 24 hours post stroke was significantly associated with 3-month poor outcome. This is consistent with what we found in the study, but in our study CV of average DBP (24h) was only correlated with MRS after 6 months rather than MRS at discharge. Although this association looks robust since it has been observed in different studies, it remains unknown whether targeted strategies aimed at improving BPV could bring prognostic benefit in the management of ischemic stroke. One of the obstacles may be the unclear mechanism on how BPV influences prognosis of ischemic stroke. As far as we know, few researches were specifically performed to

Table 3 Correlation Coefficient of Interleukin 10, Legumain, Matrix Metallopeptidase 9 with Blood Pressure Variability

Variables	Interleukin 10 (pg/mL)		Matrix Metallopeptidase 9 (mg/L)		Legumain (ng/mL)	
	Correlation	P	Correlation	P	Correlation	P
SBP at admission, mmHg	−0.0626	0.244	0.0144	0.789	−0.0160	0.766
DBP at admission, mmHg	−0.0555	0.301	0.0065	0.904	0.0138	0.798
Average SBP (24h), mmHg	0.0139	0.795	0.0507	0.345	−0.0031	0.954
CV of average SBP (24h)	0.0405	0.451	0.3742	**<0.001**	0.0003	0.995
Average DBP (24h), mmHg	0.0214	0.691	0.0498	0.354	−0.0859	0.109
CV of average DBP (24h)	−0.0505	0.347	0.2201	**<0.001**	0.0007	0.989
Average SBP (day), mmHg	0.0125	0.816	0.0523	0.310	−0.0068	0.899
CV of average SBP (day)	0.0498	0.353	0.3162	**<0.001**	−0.0006	0.990
Average DBP (day), mmHg	0.0290	0.589	0.0500	0.352	−0.0842	0.117
CV of average DBP (day)	−0.0543	0.312	0.1905	**<0.001**	0.0144	0.788
Average SBP (night), mmHg	0.0166	0.757	0.0212	0.693	0.0030	0.955
CV of average SBP (night)	−0.0841	0.117	0.1875	**<0.001**	0.0021	0.969
Average DBP (night), mmHg	−0.0086	0.872	0.0073	0.891	−0.0468	0.383
CV of average DBP (night)	−0.0465	0.387	0.1340	**0.012**	0.0119	0.824

Note: A P-value <0.05 was presented in bold.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, coefficients of variation.

Table 4 Correlation Coefficient of MRS with Blood Pressure Variability

Variables	MRS at Discharge		MRS After 6 Months	
	Correlation	P	Correlation	P
SBP at admission, mmHg	0.1030	0.055	0.0969	0.071
DBP at admission, mmHg	−0.0345	0.521	−0.0639	0.234
Average SBP (24h), mmHg	0.1574	**0.003**	0.1383	**0.010**
CV of average SBP (24h)	0.1727	**0.001**	0.1855	**<0.001**
Average DBP (24h), mmHg	0.0754	0.160	0.0504	0.348
CV of average DBP (24h)	0.0951	0.076	0.1053	**0.049**
Average SBP (day), mmHg	0.1450	**0.007**	0.1399	**0.009**
CV of average SBP (day)	0.1671	**0.002**	0.1681	**0.002**
Average DBP (day), mmHg	0.0761	0.156	0.0535	0.319
CV of average DBP (day)	0.0643	0.231	0.0720	0.180
Average SBP (night), mmHg	0.1512	**0.005**	0.1063	**0.047**
CV of average SBP (night)	0.0680	0.205	0.0844	0.116
Average DBP (night), mmHg	0.0564	0.293	0.0267	0.619
CV of average DBP (night)	0.1227	**0.022**	0.1241	**0.020**

Note: A P-value <0.05 was presented in bold.
Abbreviations: MRS, Modified Rankin Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, coefficients of variation.

Table 5 Correlation Coefficient of Interleukin 10, Legumain, Matrix Metallopeptidase 9 with MRS

Variables	Interleukin 10 (pg/mL)		Matrix Metallopeptidase 9 (mg/L)		Legumain (ng/mL)	
	Correlation	P	Correlation	P	Correlation	P
MRS at discharge	0.1927	**<0.001**	0.3770	**<0.001**	0.0376	0.483
MRS after 6 months	0.1789	**<0.001**	0.3816	**<0.001**	0.0459	0.392

Note: A P-value <0.05 was presented in bold.
Abbreviation: MRS, Modified Rankin Scale.

Table 6 Association of Interleukin 10, Legumain, Matrix Metallopeptidase 9 with MRS

Exposure	Crude			Adjust Model 1*			Adjust Model 2§		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
MRS at discharge									
Interleukin 10 (per SD increase)	0.25	0.11–0.40	**<0.001**	0.12	−0.01–0.25	0.065	0.04	−0.07–0.16	0.438
Matrix metallopeptidase 9 (per SD increase)	0.62	0.49–0.75	**<0.001**	0.39	0.26–0.52	**<0.001**	0.23	0.11–0.35	**<0.001**
Legumain (per SD increase)	0.14	−0.01–0.29	0.060	0.15	0.03–0.28	**0.018**	−0.07	−0.18–0.05	0.274
MRS after 6 months									
Interleukin 10 (per SD increase)	0.26	0.12–0.41	**<0.001**	0.11	−0.01–0.23	0.071	0.04	−0.06–0.15	0.437
Matrix metallopeptidase 9 (per SD increase)	0.72	0.59–0.85	**<0.001**	0.45	0.34–0.57	**<0.001**	0.32	0.20–0.43	**<0.001**
Legumain (per SD increase)	0.11	−0.04–0.26	0.1382	0.12	0.01–0.24	**0.037**	−0.07	−0.18–0.04	0.224

Notes: *Adjusted for age, sex, and MRS before admission. §Adjusted for age, sex, MRS before admission, and type of ischemic stroke (progressive or not). A P-value <0.05 was presented in bold.
Abbreviations: MRS, Modified Rankin Scale; SD, standard deviation; CI, confidence interval.

explore the mechanism in ischemic stroke. Based on evidence from researches on hypertension,[17,18] we assumed that abnormal BPV triggered vascular inflammation could be a possible mechanism and selected three vascular inflammation-related biomarkers (i.e., IL-10, MMP-9, legumain) as proxies to explore. Although the study design of our study is only for examination of correlations, results of the study might provide inspirations for further exploration. In the study, we could see that compared with non-progressive ischemic stroke, there were more patients with hypertension and hyperlipidemia for those who were categorized as progressive ischemic stroke. This again suggested BPV triggered vascular inflammation could be a reason for poor prognosis in ischemic stroke, since the three biomarkers we investigated were also reported to be involved in the regulation of vascular inflammation in hypertension and atherosclerosis.[22,26–28]

Some limitations should be noticed in our study. First, the study included a small sample size, which might result in a limited statistical power. Due to this concern, in the multivariable linear regression model, we only included several confounding factors and therefore the results could also be biased by residual confounding. Second, as an observational study, the relation we found among MMP-9, BPV and prognosis does not equal to a causation relation. In the study, it could be observed that patients with progressive ischemic stroke had a lower creatinine, which suggested inflammation in kidney disease could also be involved in the association between MMP-9 and prognosis. Further researches are needed to explore the role MMP-9 played in abnormal BPV and poor neurologic outcomes in ischemic stroke. It also remains unknown whether other inflammation-related factors are involved since there are several other proinflammatory factors associated with ischemic stroke.[29,30] In addition, in the study, we only used MRS as a proxy for neurologic outcome, which also needs to be validated using other outcome variables in future studies.

Conclusion

Increased MMP-9 was associated with increased BPV and poor neurologic outcomes for patients with ischemic stroke, which might partially explain the effect of BPV on neurologic outcomes.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose.

References

1. Koton S, Schneider AL, Rosamond WD, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. *JAMA*. 2014;312(3):259–268. doi:10.1001/jama.2014.7692
2. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. *Circ Res*. 2017;120(3):439–448. doi:10.1161/CIRCRESAHA.116.308413
3. Johnson CO, Nguyen M, Roth GA, et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(5):439–458. doi:10.1016/S1474-4422(19)30034-1

4. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health*. 2013;1(5):e259–e281. doi:10.1016/S2214-109X(13)70089-5
5. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American heart association. *Circulation*. 2020;141(9):e139–e596.
6. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol*. 2003;2(1):43–53. doi:10.1016/S1474-4422(03)00266-7
7. Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. *Neurol Clin*. 2008;26(4):871–95, vii.
8. Kelly-Hayes M, Beiser A, Kase CS, Scaramucci A, D'Agostino RB, Wolf PA. The influence of gender and age on disability following ischemic stroke: the Framingham study. *J Stroke Cerebrovasc Dis*. 2003;12(3):119–126. doi:10.1016/S1052-3057(03)00042-9
9. Zivin JA. Factors determining the therapeutic window for stroke. *Neurology*. 1998;50(3):599–603. doi:10.1212/WNL.50.3.599
10. Bhaskar S, Stanwell P, Cordato D, Attia J, Levi C. Reperfusion therapy in acute ischemic stroke: dawn of a new era? *BMC Neurol*. 2018;18(1):8.
11. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke*. 2019;50(12):e344–e418.
12. Seners P, Baron J-C. Revisiting 'progressive stroke': incidence, predictors, pathophysiology, and management of unexplained early neurological deterioration following acute ischemic stroke. *J Neurol*. 2018;265(1):216–225. doi:10.1007/s00415-017-8490-3
13. Maulden SA, Gassaway J, Horn SD, Smout RJ, DeJong G. Timing of initiation of rehabilitation after stroke. *Arch Phys Med Rehabil*. 2005;86(12 Suppl 2):S34–S40. doi:10.1016/j.apmr.2005.08.119
14. Mistry EA, Mehta T, Mistry A, et al. Blood pressure variability and neurologic outcome after endovascular thrombectomy: a secondary analysis of the BEST Study. *Stroke*. 2020;51(2):511–518. doi:10.1161/STROKEAHA.119.027549
15. de Havenon A, Stoddard G, Saini M, et al. Increased blood pressure variability after acute ischemic stroke increases the risk of death: a secondary analysis of the virtual international stroke trial archive. *JRSM Cardiovasc Dis*. 2019;8:2048004019856496.
16. Minhas JS, Wang X, Lavados PM, et al. Blood pressure variability and outcome in acute ischemic and hemorrhagic stroke: a post hoc analysis of the HeadPoST study. *J Hum Hypertens*. 2019;33(5):411–418. doi:10.1038/s41371-019-0193-z
17. Dharmashankar K, Widlansky ME. Vascular endothelial function and hypertension: insights and directions. *Curr Hypertens Rep*. 2010;12(6):448–455. doi:10.1007/s11906-010-0150-2
18. Tsuda K. Associations between inflammation and endothelial dysfunction in resistant hypertension. *Am J Hypertens*. 2016;29(11):e4. doi:10.1093/ajh/hpw082
19. Shekhar S, Cunningham MW, Pabbidi MR, Wang S, Booz GW, Fan F. Targeting vascular inflammation in ischemic stroke: recent developments on novel immunomodulatory approaches. *Eur J Pharmacol*. 2018;833:531–544. doi:10.1016/j.ejphar.2018.06.028
20. Garcia JM, Stillings SA, Leclerc JL, et al. Role of interleukin-10 in acute brain injuries. *Front Neurol*. 2017;8:244. doi:10.3389/fneur.2017.00244
21. Ramella M, Boccafoschi F, Bellofatto K, et al. Endothelial MMP-9 drives the inflammatory response in abdominal aortic aneurysm (AAA). *Am J Transl Res*. 2017;9(12):5485–5495.
22. Ozawa N, Sato Y, Mori Y, et al. Legumain promotes atherosclerotic vascular remodeling. *Int J Mol Sci*. 2019;20(9):2195. doi:10.3390/ijms20092195
23. Neurology hSo, Society CS. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. *Chin J Neurol*. 2018;51(9):666–682.
24. Davalos A, Toni D, Iweins F, Lesaffre E, Bastianello S, Castillo J. Neurological deterioration in acute ischemic stroke: potential predictors and associated factors in the European cooperative acute stroke study (ECASS) I. *Stroke*. 1999;30(12):2631–2636. doi:10.1161/01.STR.30.12.2631
25. Kwan J, Hand P. Early neurological deterioration in acute stroke: clinical characteristics and impact on outcome. *QJM*. 2006;99(9):625–633. doi:10.1093/qjmed/hcl082
26. Lima VV, Zemse SM, Chiao CW, et al. Interleukin-10 limits increased blood pressure and vascular RhoA/Rho-kinase signaling in angiotensin II-infused mice. *Life Sci*. 2016;145:137–143. doi:10.1016/j.lfs.2015.12.009
27. Caligiuri G, Rudling M, Ollivier V, et al. Interleukin-10 deficiency increases atherosclerosis, thrombosis, and low-density lipoproteins in apolipoprotein E knockout mice. *Mol Med*. 2003;9(1):10–17. doi:10.1007/BF03402102
28. Florence JM, Krupa A, Booshehri LM, Allen TC, Kurdowska AK, Hribal ML. Metalloproteinase-9 contributes to endothelial dysfunction in atherosclerosis via protease activated receptor-1. *PLoS One*. 2017;12(2):e0171427. doi:10.1371/journal.pone.0171427
29. Shaafi S, Sharifipour E, Rahmanifar R, et al. Interleukin-6, a reliable prognostic factor for ischemic stroke. *Iran J Neurol*. 2014;13(2):70–76.
30. Bokhari FA, Shakoori TA, Butt A, Ghafoor F. TNF-alpha: a risk factor for ischemic stroke. *J Ayub Med Coll Abbottabad*. 2014;26(2):111–114.