

Unraveling the role of collateral circulation and serum ELAVL1 in carotid atherosclerosis and ischemic stroke: Insights from clinical observations

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Conflict of interest

None declared

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Abstract

Background. The (embryonic lethal, abnormal vision, drosophila)-like protein 1 (ELAVL1) is a newly discovered protein associated with cerebral ischemic/reperfusion (I/R) injury. However, little is known of ELAVL1 in ischemic stroke patients.

Objectives. To investigate the clinical significance of collateral circulation and serum ELAVL1 in patients with carotid atherosclerosis (CAS) and ischemic stroke.

Materials and methods. The present prospective cohort investigation included 317 ischemic stroke patients and 300 CAS patients admitted between March 2020 and March 2022. Collateral circulation was measured using digital subtraction angiography (DSA) and graded using the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) grading system. Enzyme-linked immunosorbent assays (ELISAs) were used to measure serum ELAVL1, C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- α). The serum levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were also measured.

Results. The serum levels of ELAVL1, CRP, IL-6, TNF- α , and LDL-C were all markedly higher, while HDL-C was significantly lower in ischemic stroke patients compared to the CAS patients. Serum ELAVL1 was markedly higher in ASITN/SIR grade 0–1 patients compared to grade 2–4 patients. Also, ELAVL1 correlated positively with serum CRP, IL-6, TNF- α , TC, and LDL-C, and negatively with HDL-C. Receiver operating characteristic (ROC) curves showed that ELAVL1 and collateral circulation have the potential to be used as biomarkers for the diagnosis of ischemic stroke. Meanwhile, CRP, IL-6, TNF- α , HDL-C, ASITN/SIR grading, and ELAVL1 were independent risk factors for ischemic stroke.

Conclusions. We found that serum ELAVL1 was associated with clinical outcomes of ischemic stroke patients, while the combination of ELAVL1 and collateral circulation could be used as a potential biomarker for ischemic stroke diagnosis.

Key words: ischemic stroke, collateral circulation, carotid atherosclerosis, biomarker, observational study

Background

Stroke is the second leading cause of disability and mortality worldwide, with over 13 million new cases annually.^{1–3} In the past 50 years, the overall incidence rate of stroke has shown a downward trend in high-income countries and an upward trend in low- and middle-income countries.^{4,5} According to the 2022 global stroke statistics report, the proportion of people over 65 years old is proportional to the incidence rate of stroke, indicating that age is one of the critical risk factors for stroke.^{6,7} Among stroke patients, over 85% have an ischemic stroke, for which carotid atherosclerosis (CAS) is one of the most common causes.^{8,9} Generally, ischemic stroke is caused by occlusion of the middle cerebral artery, which leads to neuronal death due to insufficient blood and oxygen supply to the brain, resulting in brain tissue damage.^{10,11}

Ischemia/reperfusion (I/R) injury is an unavoidable pathological injury in stroke patients and a major cause of neurological damage.^{12,13} Stroke-induced I/R injury can lead to permanent brain tissue damage and may cause cognitive impairment.^{14,15} Despite the development of treatment strategies, the underlying molecular mechanisms of ischemic stroke are still unclear.^{16,17} In recent years, many molecular biomarkers for ischemic stroke have been identified.^{18,19} However, new potential biomarkers for ischemic stroke diagnosis and prediction of prognosis are still needed.

The (embryonic lethal, abnormal vision, drosophila)-like protein 1 (ELAVL1) is a newly discovered protein associated with the development of many diseases, including brain I/R injury, the main pathological alteration in ischemic stroke.^{20–22} However, no clinical studies have focused on ELAVL1 in stroke patients. It is widely accepted that collateral circulation is changed and is associated with the clinical outcomes of ischemic stroke patients.^{23–25} Nonetheless, measuring collateral circulation alone might not be accurate enough to predict patients' clinical outcomes.²⁶

Objectives

In the present study, we aimed to investigate the clinical significance of collateral circulation and serum ELAVL1 in patients with CAS and ischemic stroke, focusing on their association with patients' severity and prognosis. The study findings might provide a novel biomarker for CAS and ischemic stroke.

Materials and methods

Patients and study design

The present study was designed as a prospective cohort investigation and included 317 ischemic stroke patients admitted to our Department between March 2020 and March

2022. Ischemic stroke diagnosis was based on the guidelines of The Chinese Medical Association (2019 update).^{27,28} The inclusion criteria were: 1. all patients were diagnosed with ischemic stroke using imaging methods, including computed tomography angiography (CTA), digital subtraction angiography (DSA) and magnetic resonance imaging (MRI); 2. patients received no anticoagulant therapy within 3 months before the study. The following patients were excluded: those receiving anticoagulant therapy within 3 months of study commencement, patients with hemorrhagic stroke, and patients with other systematic diseases. Additionally, 300 patients with CAS were enrolled as controls within the same study period. Among CAS patients, the following were excluded: patients with severe systematic infections, patients with cancer, and patients with severe cardiovascular, liver or renal diseases. All patients were consecutively enrolled. We recruited all cases who met the inclusion criteria during the study period. The ethical committee of the Brain Hospital of Hunan Province (Changsha, China) approved the study (Ethics Review Board No. 44; 2021).

Measurement of collateral circulation

The collateral circulation was measured with DSA and graded using the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) grading system, where 0–1 means poor compensatory collateral circulation, grade 2 is moderate compensatory circulation, and grade 3–4 is good compensatory circulation.²⁹

Enzyme-linked immunosorbent assay

Blood samples were collected from all patients within 24 h of admission. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum ELAVL1 (kit purchased from MyBioSource Inc., San Diego, USA), C-reactive protein (CRP), interleukin (IL)-6 and tumor necrosis factor alpha (TNF- α). Kits for CRP, IL-6, and TNF- α were purchased from Nanjing Jiancheng Bioengineering Institute, Nanjing, China, according to the manufacturer's instructions.

Data collection

Demographic data, including age, sex, medical history, and complications, were recorded. The serum levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using an automatic Hitachi 7600 biochemical analyzer (Hitachi Corporation, Tokyo, Japan).

Statistical analyses

The data distribution was analyzed using the Kolmogorov–Smirnov method. All measurement data were non-normally distributed and expressed as median (range). Comparison

between the 2 groups employed a Mann–Whitney U test, while χ^2 tests compared rates (without half adjust). Spearman’s analysis was used for correlation analysis. Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic value. Logistic regression was performed to analyze the risk factor of ischemic stroke. All calculations were made using IBM SPSS v. 22.0 (IBM Corporation, Armonk, USA) and GraphPad v. 6.0 (GraphPad Software, San Diego, USA), and $p < 0.05$ was defined as statistically different.

Results

Basic clinical characteristics

The present study included 317 ischemic stroke patients and 300 CAS patients. As shown in Table 1, no significant differences were found between the 2 groups of patients for age, sex, body mass index (BMI), or complications. However, serum CRP, IL-6, and TNF- α levels were markedly higher

in ischemic stroke patients compared to the CAS patients (all $p < 0.05$). For lipid metabolism, TC and TG showed no significant difference, while LDL-C was remarkably higher and HDL-C was significantly lower in ischemic stroke patients ($p < 0.05$). For ASITN/SIR grading, the frequency of grade 0–1 was significantly higher in ischemic stroke patients compared to the CAS patients ($p < 0.05$).

Serum ELAVL1 was associated with collateral circulation

To further investigate the role of ELAVL1 in CAS and ischemic stroke patients, the levels of ELAVL1 in different patients were determined. Serum ELAVL1 was significantly upregulated in ischemic stroke patients compared to the CAS patients ($p < 0.05$, Fig. 1A). Furthermore, serum ELAVL1 was markedly higher in ASITN/SIR grade 0–1 patients than in grade 2–4 patients ($p < 0.05$, Fig. 1B). These results indicated that serum ELAVL1 might be associated with collateral circulation in CAS and ischemic stroke patients.

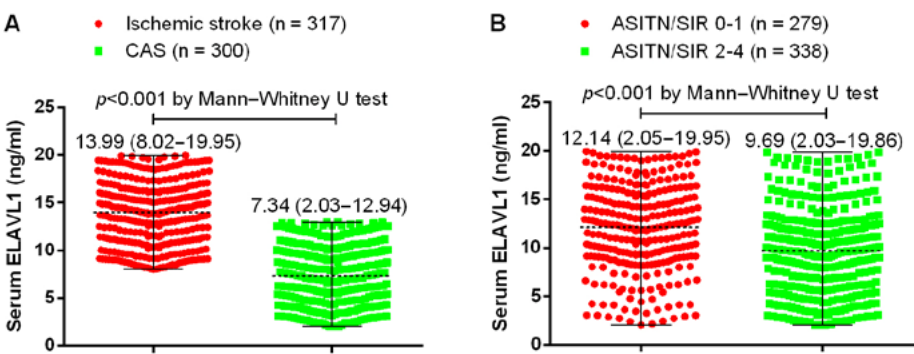


Fig. 1. A. Serum ELAV (embryonic lethal, abnormal vision, drosophila)-like protein 1 (ELAVL1) was evaluated in ischemic stroke patients using an enzyme-linked immunosorbent assay (ELISA) and compared to carotid atherosclerosis (CAS) patients; B. Serum ELAVL1 was evaluated using ELISA in patients with different American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) grades. Lines indicate the median (range)

Table 1. Basic characteristics of all patients

Variables		Ischemic stroke (n = 317)	CAS (n = 300)	p-value
Age [years]		52 (35–70)	51 (35–70)	0.891
Sex (male : female, %)		179 (56.47) : 138 (43.53)	165 (55.00) : 135 (45.00)	0.834
BMI [kg/m ²]		25.12 (18.01–31.99)	24.57 (18.03–31.74)	0.714
Complications, n (%)	diabetes	75 (23.66)	70 (23.33)	0.735
	hypertension	69 (21.77)	57 (19.00)	
	current smoker	141 (44.48)	124 (41.33)	
CRP [mg/L]		27.24 (5.32–49.73)	12.67 (3.02–24.95)	<0.001
IL-6 [pg/mL]		32.29 (5.05–59.90)	16.95 (5.04–29.98)	<0.001
TNF- α [pg/mL]		22.98 (5.01–39.85)	12.24 (5.02–19.85)	<0.001
TC [mmol/L]		4.36 (3.25–5.37)	4.22 (3.26–5.38)	0.189
TG [mmol/L]		1.49 (0.93–2.02)	1.44 (0.94–2.01)	0.659
LDL-C [mmol/L]		3.15 (2.21–4.00)	2.88 (2.17–3.79)	<0.001
HDL-C [mmol/L]		1.10 (0.95–1.23)	1.12 (0.97–1.25)	0.002
ASITN/SIR grading, n (%)	0–1	194 (61.20)	85 (28.33)	<0.001
	2–4	123 (38.80)	215 (71.67)	

The p-values were calculated between CAS and ischemic stroke patients using Student’s t-test of Mann–Whitney U test for normally or non-normally distributed data, respectively. χ^2 test was used for comparing rates. CAS – carotid atherosclerosis; BMI – body mass index; CRP – C-reactive protein; IL-6 – interleukin 6; TNF- α – tumor necrosis factor alpha; TC – total cholesterol; TG – triglyceride; LDL-C – low-density-lipoprotein cholesterol; HDL-C – high-density-lipoprotein cholesterol; ASITN/SIR – American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology.

Serum ELAVL1 was associated with inflammatory cytokines and lipid metabolism

We conducted additional correlation analysis for serum ELAVL1, inflammatory cytokines, and lipid metabolism. As shown in Table 2, serum ELAVL1 was positively correlated with serum CRP, IL-6, TNF- α , TC, and LDL-C, and negatively correlated with HDL-C (all $p < 0.05$), suggesting that serum ELAVL1 was associated with the clinical outcomes of CAS in ischemic stroke patients.

Table 2. Spearman's correlation among serum (embryonic lethal, abnormal vision, drosophila)-like protein 1 (ELAVL1), inflammatory cytokines and lipid metabolism in all patients

Variables	Spearman's correlation	p-value
CRP	0.354	<0.001
IL-6	0.334	<0.001
TNF- α	0.335	<0.001
TC	0.098	0.015
TG	-0.019	0.632
LDL-C	0.146	<0.001
HDL-C	-0.076	0.049

BMI – body mass index; CRP – C-reactive protein; IL-6 – interleukin 6; TNF- α – tumor necrosis factor alpha; TC – total cholesterol; TG – triglyceride; LDL-C – low-density-lipoprotein cholesterol; HDL-C – high-density-lipoprotein cholesterol.

Diagnostic value of ELAVL1 and collateral circulation for ischemic stroke

The ROC curves were used to determine the diagnostic value of ELAVL1 and collateral circulation for ischemic stroke. The ELAVL1 showed good diagnostic value for ischemic stroke, with an area under the curve (AUC) = 0.904, sensitivity = 79.18%, specificity = 78.67%, and a cutoff value >10.56 ng/mL (Fig. 2A). Collateral circulation (ASITN/SIR grading) also demonstrated diagnostic value for ischemic stroke, with an AUC = 0.625, sensitivity = 61.88%, specificity = 54.20%, and a cutoff value <2.5 (Fig. 2B).

When practicing the diagnostic mode in the patients using the cutoff value, both ELAVL1 and ASITN/SIR grading could be used as diabetic markers. The combination of ELAVL1 and ASITN/SIR grading showed better sensitivity and accuracy (Table 3). All of these results imply that ELAVL1 and collateral circulation have the potential to be used as biomarkers for the diagnosis of ischemic stroke. Figure 3 shows a typical DSA image of the collateral circulation.

Risk factors for ischemic stroke by logistic regression

Finally, we used univariate and multivariate logistic regression to analyze the risk factors for ischemic stroke. In univariate logistic regression, CRP, IL-6, TNF- α , LDL-C, HDL-C, ASITN/SIR grading, and ELAVL1 were risk factors for ischemic stroke. While in multivariate logistic regression, CRP,

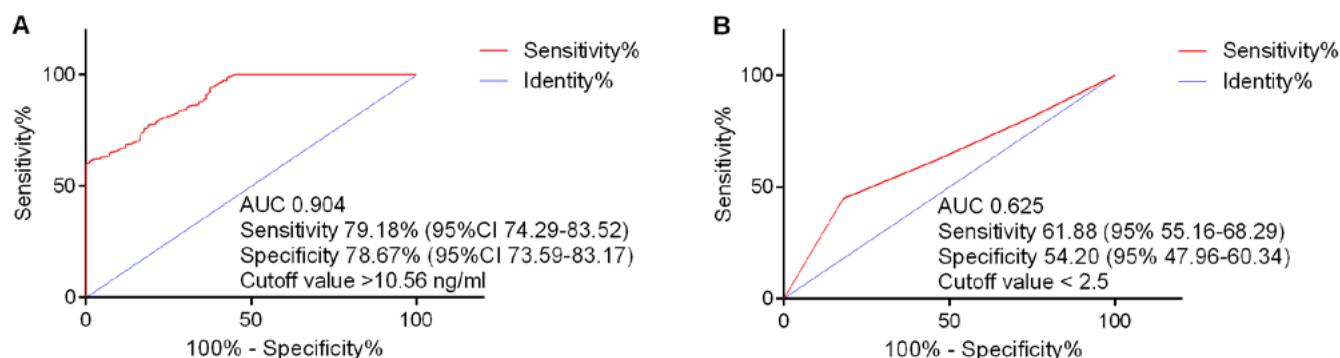


Fig. 2. A. Receiver operating characteristic (ROC) curve of ELAV (embryonic lethal, abnormal vision, drosophila)-like protein 1 (ELAVL1) for the diagnosis of ischemic stroke; B. ROC curve of American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) grading for diagnosis of ischemic stroke

Table 3. Diagnostic value of (embryonic lethal, abnormal vision, drosophila)-like protein 1 (ELAVL1) and collateral circulation for ischemic stroke

Methods	True positive	False positive	True negative	False negative	Sensitivity	Specificity	Accuracy
ELAVL1	251	64	236	66	79.18%	78.67%	78.93%
ASITN/SIR grading	232	158	142	85	73.19%	47.33%	60.62%
ELAVL1 + ASITN/SIR grading	300	188	112	17	94.64%	37.33%	66.77%

* Sensitivity = true positive/(true positive + false negative) \times 100%; specificity = true negative/(true negative + false positive) \times 100%; accuracy = (true positive + true negative)/(true positive + false negative + true negative) \times 100%; ASITN/SIR – American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology.

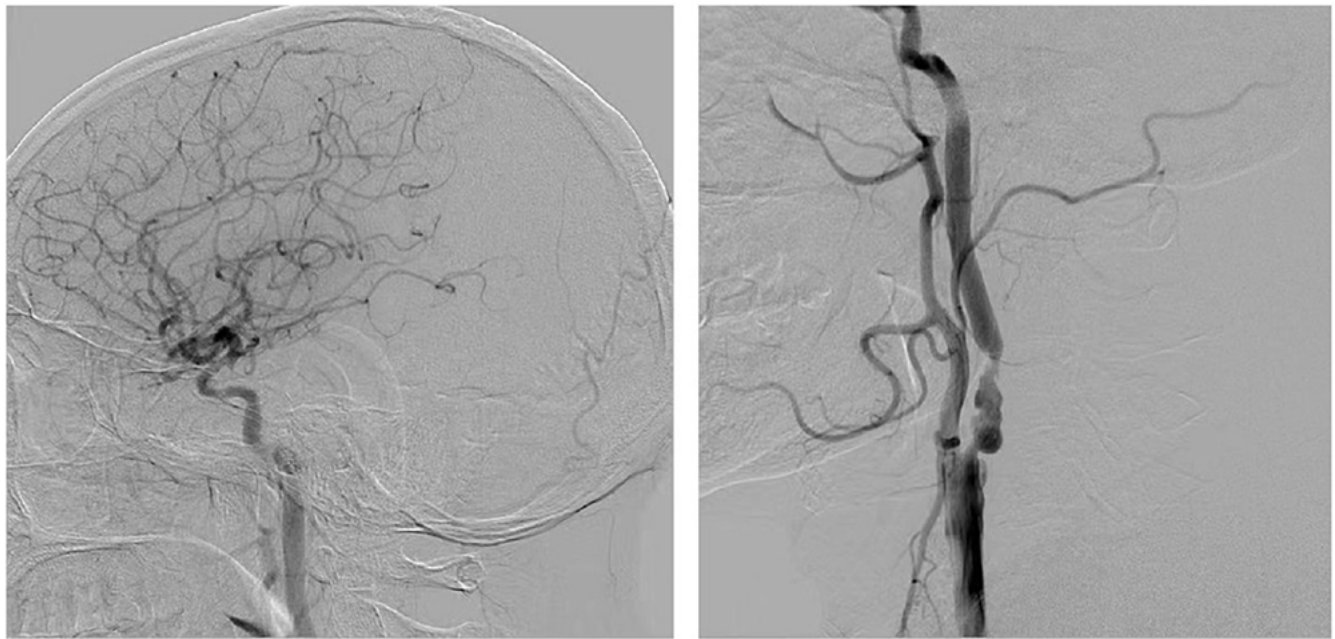


Fig. 3. A typical digital subtraction angiography (DSA) image of collateral circulation from a 52-year-old male patient

Table 4. Logistic regression for risk factors of unstable plaque

Variables	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.999	0.984–1.014	0.893	0.985	0.944–1.028	0.488
Sex	1.061	0.772–1.458	0.714	1.388	0.546–3.528	0.490
BMI	0.992	0.955–1.032	0.699	1.041	0.931–1.164	0.479
Diabetes	0.982	0.677–1.425	0.924	0.678	0.243–1.890	0.458
Hypertension	0.843	0.569–1.249	0.395	1.058	0.326–3.435	0.925
Current smoker	0.879	0.639–1.210	0.430	0.562	0.217–1.455	0.235
CRP	0.862	0.840–0.883	<0.001	0.818	0.766–0.873	<0.001
IL-6	0.896	0.879–0.914	<0.001	0.868	0.823–0.916	<0.001
TNF-α	0.843	0.818–0.868	<0.001	0.804	0.746–0.867	<0.001
TC	0.840	0.649–1.089	0.189	1.144	0.560–2.336	0.712
TG	0.896	0.547–1.466	0.661	0.910	0.234–3.536	0.892
LDL-C	0.445	0.322–0.616	<0.001	0.613	0.245–1.536	0.296
HDL-C	26.709	3.701–192.777	0.001	8452.881	24.213–2.95×10 ⁶	0.002
ASITN/SIR grading	1.520	1.348–1.714	<0.001	0.433	0.331–0.566	<0.001
ELAVL1	0.561	0.512–0.615	<0.001	1.560	1.122–2.170	0.008

95% CI – 95% confidence interval; OR – odds ratio; BMI – body mass index; CRP – C-reactive protein; IL-6 – interleukin 6; TNF-α – tumor necrosis factor alpha; TC – total cholesterol; TG – triglyceride; LDL-C – low-density-lipoprotein cholesterol; HDL-C – high-density-lipoprotein cholesterol; ELAVL1 – (embryonic lethal, abnormal vision, drosophila)-like protein 1; ASITN/SIR – American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology.

IL-6, TNF-α, HDL-C, ASITN/SIR grading, and ELAVL1 were independent risk factors for ischemic stroke (Table 4).

Discussion

Stroke is the primary cause of death in China. According to data from China’s National Stroke Epidemiology Survey, the age-standardized incidence rate of stroke in adults

is approx. 1115 cases per 100,000 individuals, with a mortality rate of 115 per 100,000.³⁰ Over the past decade, while the incidence rates have been decreasing in high-income countries, China has seen a gradual increase in stroke incidence, though the mortality rate has remained relatively stable.^{31,32} Ischemic strokes primarily result from occlusion of the cerebral arteries, leading to insufficient blood and oxygen supply to the brain, causing neuronal death and subsequent brain tissue damage.

Currently, ischemic stroke treatment mainly involves thrombolysis, anticoagulation therapy, and surgical interventions.³³ However, the occurrence of I/R injury after treatment often proves difficult to avoid and constitutes a major contributor to neuronal damage. Nonetheless, there are currently no specific drugs or therapies available to effectively address I/R injury and the resulting cognitive impairments following stroke. Thus, timely diagnosis of ischemic stroke is of great significance for patients' treatment and prognosis. In the present study, we demonstrated that serum ELAVL1 was elevated in ischemic stroke patients and correlated with collateral circulation and clinical outcomes. As such, combining collateral circulation and ELAVL1 could be used as a potential biomarker for ischemic stroke diagnosis.

The ELAVL1 is a newly discovered protein associated with the development of many diseases, such as cardiovascular disease (CVD) and cerebral I/R injury. In myocardial I/R injury, ELAVL1 was significantly elevated, and knockdown of ELAVL1 could inhibit ferroptosis and improve I/R injury.³⁴ Du et al. demonstrated that ELAVL1 was upregulated in cerebral I/R injury and facilitated neurobehavioral impairments and brain infarctions after I/R treatment in animal models.²² In an early study, ELAVL1 expression was increased in human hearts and ventricular cardiomyocytes under hyperglycemic conditions and was accompanied by increased inflammation and pyroptosis.³⁵ However, up until now, no study has reported on ELAVL1 in stroke and CAS patients.

In the present research, we demonstrated ELAVL1 up-regulation in ischemic stroke patients for the first time, which was associated with inflammation and lipid metabolism, and correlated with collateral circulation. Furthermore, higher levels of ELAVL1 were associated with worse clinical outcomes, consistent with *in vitro* and animal studies using ischemia models. Besides myocardial injury, ELAVL1 also facilitates cellular injury in other diseases. A recent study reported that ELAVL1 knockdown led to the suppression of pyroptosis by inhibiting NLRP3 (NLR family pyrin domain containing 3) in the HK-2 renal tubular cell model of diabetic nephropathy.³⁶ In kidney I/R injury, ELAVL1 promoted ferritinophagy in HK-2 cells and thus aggravated ferroptosis and oxidative stress.³⁷ Similar results are also shown in Parkinson's disease.

Researchers found that elevated ELAVL1 and NLRP3 induced pyroptosis, while downregulation of ELAVL1 inhibited pyroptosis, pyroptosis-induced inflammation and oxidative stress.³⁸ These studies imply a correlation between ELAVL1 and inflammation/oxidative stress, which was also seen in our work, where we demonstrated ELAVL1 was positively correlated with serum CRP, IL-6 and TNF- α . Thus, we speculate that the upregulation of ELAVL1 in ischemic stroke patients is also related to increased inflammatory responses and oxidative stress. However, we did not measure oxidative stress in this study.

Collateral circulation has been widely investigated in stroke patients. It was reported that patients with good

DSA collaterals had markedly smaller hypoperfusion volumes and perfusion mismatch volumes, which was also associated with the hypoperfusion intensity ratio.³⁹ In another study, Sui et al. demonstrated that ASITN/SIR grading was associated with the National Institutes for Health Stroke Scale (NIHSS) and prognosis of wake-up stroke patients.⁴⁰ In a meta-analysis, the authors demonstrated that collateral circulation status and final infarct volume (FIV) are independent outcome predictors for ischemic stroke patients.⁴¹ A more recent study investigated the short-term prognosis of wake-up stroke patients and found that patients with ASITN/SIR grade 2–3 had lower NIHSS and modified Rankin scores (mRS) and higher Barthel index (BI) scores after treatment, indicating collateral circulation is associated with the prognosis of wake-up stroke patients.⁴⁰ However, a recent study demonstrated that inter- and intraobserver agreement of collateral circulation grading using the ASITN/SIR score was poor,²⁶ suggesting that ASITN/SIR grading alone might not be accurate enough for predicting clinical outcomes of ischemic stroke patients.

In addition to ischemic stroke, ASITN/SIR grading is also used to measure collateral circulation in intracranial arterial stenosis and subarachnoid hemorrhage.^{42,43} In our study, we also found that the frequency of 0–1 ASITN/SIR grading was markedly higher in ischemic stroke patients. Besides, we observed that ELAVL1 was negatively associated with ASITN/SIR grades, and when combined, they have the potential for ischemic stroke diagnosis. These findings may provide a potential and novel method for the prediction/diagnosis of ischemic stroke.

Limitations

The study had some limitations. The sample size was small, and the patients were all from a single center. Furthermore, the molecular mechanisms of ELAVL1 in ischemic stroke need to be illustrated in future studies. To further understand the role of ELAVL1 in ischemic stroke, we will conduct studies using both myocardial I/R injury animal models and cellular models. Also, expanding the sample size in clinical investigations is needed in the future.

Conclusions

Serum ELAVL1 was associated with clinical outcomes of ischemic stroke patients. The combination of ELAVL1 and collateral circulation could be used as a potential strategy for the diagnosis of ischemic stroke. All of these results might provide a novel method for the diagnosis of ischemic stroke patients. Since timely treatment is critical, especially in acute ischemic stroke, we think that early diagnosis is of great significance. Thus, novel serum markers may help physicians gather more information on the patients'

condition and better understand the risk for patients susceptible to stroke. However, more clinical and basic studies are still needed to provide deeper insights into the role of ELAVL1 in ischemic stroke.

Data availability


All original data can be obtained from the corresponding author on proper request.


Consent for publication


Not applicable.

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