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Serum asprosin levels in patients with acute ischemic stroke

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Abstract

Objective: This study aimed to investigate the association between serum asprosin and the incidence, severity, etiological subtypes and thrombolysis therapy of acute ischemic stroke (AIS). *Methods:* A total of 130 patients with AIS were included; 50 patients matched for age, sex, and vascular risk factors, and 50 healthy subjects matched only for age and sex were used as the control group. The National Institutes of Health Stroke Scale was used to estimate the severity of stroke. Scores >6 were considered to indicate a moderate-to-severe stroke. The AIS group was divided into 3 etiological subtype groups according to the Toast classification method. The thrombolytic and non-thrombolytic groups were divided according to whether emergency thrombolytic treatment was performed. *Results:* The asprosin level was significantly higher in the AIS group than in the control group ($p<0.001$). Further, the asprosin level was higher in the moderate-to-severe stroke group than in the minor stroke group ($p<0.001$). Logistic regression analysis showed that asprosin was an independent risk factor for AIS and AIS severity. The areas under the receiver operating characteristic curve of serum asprosin for predicting AIS and moderate-to-severe stroke were 0.671 (95% confidence interval: 0.587–0.755; $p<0.001$) and 0.778 (95% confidence interval: 0.698–0.858; $p<0.001$), respectively. There was no statistically significant difference in serum asprosin levels in the etiological subtype of AIS and thrombolytic therapy or not.
Conclusion: Serum asprosin levels are positively associated with the incidence and severity of AIS and can be used as biomarkers for predicting the occurrence of AIS. Serum asproisn levels may not be used to differentiate between different etiologic subtypes of acute ischemic cerebral infarction and thrombolytic therapy or not.

Keywords: Asprosin, acute ischemic stroke, adipokine, risk factor, severity

INTRODUCTION

Acute ischemic stroke (AIS) comprises a series of clinical syndromes of neurological dysfunction caused by the sudden interruption of blood supply to the brain due to various reasons, resulting in acute dysneuria. In China, approximately 2.5 million patients are diagnosed with stroke, annually.[1] Many traditional risk factors for ischemic stroke include age, sex, hypertension, hyperlipidemia, obesity, and peripheral vascular disease. However, despite appropriate preventive and therapeutic measures, the incidence of ischemic stroke remains high, especially that of AIS. Therefore, there is a need to identify additional risk factors, or to establish a diagnostic index, that would help improve prevention and treatment. Adipokines are a recently favored research topic. Studies have found that adipose tissue can not only store fat but also has many endocrine functions, including the secretion of biologically active substances, namely adipokines. Lipocytokines can be roughly divided into two categories: adipose tissue-specific expression factors, such as leptin, chemerin, omentin; and non-specific adipose tissue expression factors, such as tumor necrosis factor-alpha and interleukin-6.[2] Adipokines, produced by adipose tissue[3], are associated with

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atherosclerosis[4], hypertension[5], diabetes mellitus[6], and cardiovascular disease.[7-9] Moreover, some adipokines are also biomarkers of cerebral infarction, such as omentin-1[10], adiponectin[11], visfatin[12], leptin[13], and others. Asprosin is a newly discovered adipokine in white adipose tissue[14], which plays a role in glucose metabolism, insulin resistance, cell apoptosis, and appetite[15-20], among others. The effects of asprosin on the central nervous system, and peripheral tissues and organs, have been thoroughly investigated[21], with studies on its relationship to metabolic disorders, such as polycystic ovary syndrome, non-alcoholic fatty liver disease, coronary heart disease, diabetic cardiomyopathy, diabetic nephropathy, and obesity.[22-28] However, to our knowledge, no studies have explored the correlation between serum asprosin and AIS. Given its demonstrated links to metabolic disorders, this study aimed to evaluate whether serum asprosin level is correlated with the incidence and severity of AIS, to help improve the prevention, treatment, and diagnosis of AIS.

METHODS

Study subjects

This prospective study was performed between June 2020 and November 2020 and included 130 patients with AIS. Computed tomography and/or magnetic resonance imaging were used to confirm AIS within 24 h after admission. The diagnostic code for AIS was in accordance with the definition of the World Health Organization.[29] The exclusion criteria were as follows: (1) the presence of a malignant tumor, (2) autoimmune disease, (3) immunosuppressive therapy, (4) severe organic disease, and (5) severe trauma. Fifty age- and sex-matched healthy participants (control group 1) and 50 age- and sex-matched patients with existing vascular risk factors (control group 2) were recruited from an outpatient population as control groups. Control subjects were excluded if they had a history of stroke. All the above-mentioned subjects underwent routine blood and biochemical tests and other investigations on the first or second day of admission. Stroke subtypes were defined by the TOAST classification.[30] We divided 72 patients with large artery large-vessel disease subtype (Stroke a), 15 cardioembolism stroke subtype (Stroke b), other subtype (Stroke c).

Patients with AIS were divided into a thrombolytic group and a non-thrombolytic group according to whether the patients underwent acute thrombolysis or not. The selection of patients with AIS was performed by an experienced neurologist.

Data collection

Data, including age, sex, and vascular risk factors, such as smoking habits, systolic blood pressure (SBP), diastolic blood pressure (DBP), atrial fibrillation (AF), diabetes mellitus, coronary heart disease, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, total cholesterol, white blood cell (WBC) count, glycosylated serum protein (GSP), uric acid, and homocysteine (HCY), were collected. The National Institutes of Health Stroke Scale (NIHSS) was used to estimate stroke severity.[31] Accordingly, an NIHSS score >6 was defined as moderate-to-severe stroke, and patients with lower scores were classified into the minor stroke group. The NIHSS score of each patient was assessed by a neurologist.

Sample collection and measurement of serum asprosin levels

All subjects' serum from Nanchang University First Affiliated Hospital Clinical Laboratory were abandoned. Blood for testing asprosin levels was drawn within 24 hours of the patient's admission to the hospital. In thrombolysis group, the blood collection for asprosin was before thrombolysis infusion. Asprosin levels were analyzed using a human fibrillin-1 (FBN1) ELISA kit (Cat.: ELK1585; Wuhan, China). The microtiter plate provided in the kit was precoated with an antibody specific to FBN1. Standards or samples were then added to wells of the microtiter plate, which had a biotin-conjugated antibody specific to FBN1. Next, avidin conjugated to horseradish peroxidase was added to each well, and the microtiter plate was incubated. Following this, a tetramethylbenzidine substrate solution was added, and only wells containing FBN1, biotin-conjugated antibody, and enzyme-conjugated avidin exhibited a color change. The enzyme-substrate reaction was terminated by the addition of sulfuric acid. The color change was measured spectrophotometrically at a wavelength of 450 ± 10 nm. The calcitonin FBN1 concentration in the samples was then determined by comparing the optical density of the samples to the standard curve.

Statistical analysis

Data were analyzed using SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA) and GraphPad

Prism (version 8.01; GraphPad Software, San Diego, CA, USA). Continuous variables are presented as the median (interquartile range) or mean ± standard deviation, while categorical variables are presented as percentiles. Differences in variables between the groups were analyzed using the Mann–Whitney *U* test and Kruskal–Wallis one-way analysis of variance (Dunn's multiple comparison test). Logistic regression models were used to assess the independent relationship of serum asprosin concentration between the AIS and control groups, moderate-to-severe stroke group, and minor stroke group. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The diagnostic value of serum asprosin level for the incidence and severity of AIS was estimated by constructing a receiver operating characteristic curve and calculating the area under the curve (AUC). Differences were considered significant at $p<0.05$.

RESULTS

Basic clinical characteristics of the study subjects

Both control group 2 and the AIS group had significantly higher SBP, DBP, WBC, HCY, smoking, GSP, and asprosin levels than control group 1 (Table 1). When comparing the AIS group to control group 2, the AIS group had higher WBC, HCY, creatinine, asprosin, and smoking levels, but lower GSP levels (Table 1). However, there were no significant differences in age, sex, total cholesterol, triglycerides, LDL cholesterol, and uric acid among the three groups.

Table 1: **Basic characteristics of AIS patients and controls**

Characteristic	Control 1	Control 2	AIS
Age (years)	58 (55, 65)	55 (50, 59)	62 (54, 68)
Sex (male), n (%)	32 (64)	29 (58)	78 (60)
Smoking, n (%)	3 (6)	11 (22)[a]	53 (40)[b,c]
Diabetes mellitus, n (%)	–	11 (22)	26 (20)
Hypertension, n (%)	–	30 (60)	73 (56)
AF, n (%)	–	10 (20)	15 (11)
Coronary heart disease, n (%)	–	3 (6)	8 (6)
Vascular disease, n (%)	–	31 (62)	79 (60)
SBP (mmHg)	123.46 ± 14.0	143.78 ± 16.95[b]	140.08 ± 21.81[b]
DBP (mmHg)	75.90 ± 11.00	84.94 ± 15.18[b]	83.52 ± 15.12[b]
Total cholesterol (mmol/L)	4.46 ± 0.86	4.55 ± 0.80	4.42 ± 0.97
Triglycerides (mmol/L)	1.42 (0.93, 2.07)	1.30 (1.05, 1.77)	1.49 (0.96, 1.22)
HDL (mmol/L)	1.27 ± 0.34	1.21 ± 0.42	1.14 ± 0.38[a]
LDL (mmol/L)	2.65 ± 0.65	2.83 ± 0.68	2.64 ± 0.76
WBC ($\times 10^9$/L)	5.53 ± 1.42	6.26 ± 1.64[a]	7.76 ± 3.34[b,d]
GSP (mmol/L)	1.94 (1.83, 2.04)	2.17 (2.04, 2.53)[b]	2.01 (1.85, 2.48)[b,d]
Uric acid (μmol/L)	348.17 ± 85.33	374.27 ± 82.22	376.22 ± 120.28
Homocysteine (μmol/L)	10 (9, 11)	11 (9, 13)[a]	2 (10, 15)[b,d]
Creatinine (μmol/L)	64.4 (49.1, 75.6)	65.2 (54.5, 78.4)	69.3(58.8, 82.1)[b]
Asprosin (ng/ml)	0.66 ± 0.26	1.15 ± 0.24[b]	1.34 ± 0.30[b,d]
NHISS score >6	–	–	52 (40)

Compared with control group 1: [a]$p<0.05$; [b]$p<0.01$. Compared with control group 2: [c]$p<0.05$; [d]$p<0.01$.
Control group 1: age- and sex-matched patients with previous vascular risk factors; control group 2: age- and sex-matched healthy participants.
AF, atrial fibrillation; AIS, acute ischemic stroke; DBP, diastolic blood pressure; GSP, glycosylated serum protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; WBC, white blood cell.

Differences in asprosin levels between the AIS and control groups

Serum asprosin concentration at admission in the AIS group was 1.34 ± 0.30 ng/mL, which was higher than that in either control group 1 (0.66 ± 0.26 ng/mL; p<0.001) or control group 2 (1.15 ± 0.24 ng/mL; p<0.001) (Figure 1a).

Analysis of the basic clinical characteristics suggested a higher level of serum asprosin in the AIS group (Table 1). Hence, we further analyzed whether asprosin had diagnostic value for AIS using a receiver operating characteristic curve. Results showed that the optimal cutoff value for asprosin as a diagnostic tool for AIS was 1.152 ng/mL, with a sensitivity of 76.9% and a specificity of 50% (AUC: 0.671, 95% CI: 0.587–0.755; Figure 2a).

Logistic regression analysis yielded an OR for asprosin of 10.25 (95% CI: 2.85–36.76; p<0.001) between the AIS group and control group 2 (Table 2). This significant result was maintained after adjusting for age, smoking, diabetes mellitus, hypertension, AF, peripheral vascular disease, uric acid, LDL cholesterol, WBC count, HCY, and GSP (adjusted OR: 7.70, 95% CI: 1.62–36.65; p=0.01) (Table 2). These data suggest that asprosin may be an independent predictor of AIS.

Asprosin level and stroke severity

Forty percent of the AIS group comprised of patients with moderate-to-severe stroke. The asprosin levels of these patients were higher than those of patients in the minor stroke group (1.22 ± 0.25 *vs*. 1.51 ± 0.28 ng/mL; p<0.001) (Figure 1b). Logistic regression analysis suggested a strong positive association between asprosin and moderate-to-severe stroke, with an unadjusted OR of 53.53 (95% CI: 10.43–274.62; p<0.001). Similarly, even after adjusting for age, sex, smoking, diabetes mellitus, hypertension, AF, peripheral vascular disease, SBP, DBP, uric acid, total cholesterol, triglycerides, HDL, LDL, WBC count, HCY, GSP, and creatinine, multivariate regression analysis showed that asprosin was still an independent risk factor for the severity of stroke (adjusted OR: 69.05, 95% CI: 9.77–487.84; p<0.001) (Table 2). Similarly, the AUC value for predicting moderate-to-severe stroke, compared with mild stroke, was 0.778 (95% CI: 0.698–0.858; p<0.001) for circulating asprosin levels (Figure 2b). The estimated optimal asprosin cutoff value was 1.25 ng/L, with a sensitivity of 82.7% and a specificity of 60.3%.

Asprosin level and etiological subtypes of AIS

Figure 3 shows no statistically significant differences between different etiological subtypes of Asprosin concentration in AIS.

Asprosin level and thrombolysis therapy

There was no statistically significant difference in serum asprosin levels between AIS with thrombolysis and no-thrombolysis groups.

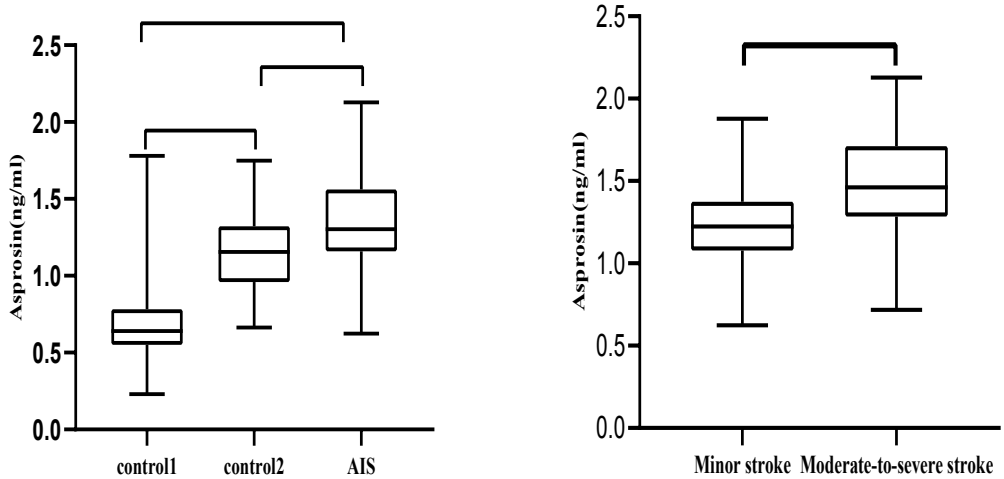

Figure 1 (a) Asprosin concentration in the AIS and control groups. Control group 1: age- and sex-matched patients with previous vascular risk factors. Control group 2: age- and sex-matched healthy participants. (b) Asprosin concentration in minor and moderate-to-severe stroke. Data are presented as the mean ± standard deviation. *p<0.001. AIS, acute ischemic stroke

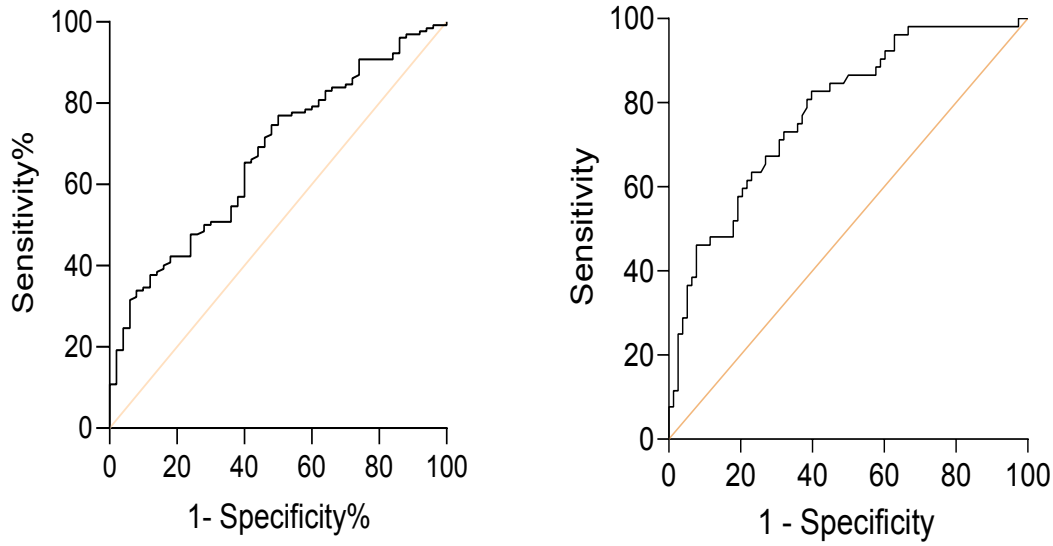

Figure 2. Receiver operating characteristic curve analysis of the diagnostic value of asprosin for acute ischemic stroke and moderate-to-severe stroke (National Institutes of Health Stroke Scale score >6). The area under the curve was calculated to estimate the predictive value of asprosin for (a) acute ischemic stroke and (b) moderate-to-severe stroke

DISCUSSION

Asprosin is a fasting-induced hormone produced by white adipose tissue that plays an important role in hepatic glucose release.[15] Its absence in humans leads to a unique pattern of metabolic regulation, including partial lipid metabolism, accompanied by a decrease in plasma insulin and the maintenance of blood sugar; thus, it plays a key role in liver glucose release.[15] To our knowledge, this is the first study to explore the relationship between circulating asprosin levels and AIS. We found that patients with AIS had a higher asprosin level than controls. When compared to patients in the minor stroke group, patients in the moderate-to-severe stroke group also had a higher serum asprosin level. Serum asprosin level was shown to be an independent predictor of the incidence and severity of AIS, even after adjusting for confounders. Additionally, the AUC analysis suggested that asprosin may be of potential diagnostic value for AIS. When comparing asprosin levels in different etiological subtypes of AIS, we found no statistically significant differences in asprosin levels in different etiological subtypes of AIS. We also found no statistically significant difference between asprosin levels and whether

Table 2: Logistic regression analysis for the risk of AIS and its severity

Asprosin (ng/ml)	OR (95% CI) Unadjusted	p-value	Adjusted	p-value
AIS[a]	10.25 (2.85, 36.76)	<0.001	7.70 (1.62, 36.65)[A]	0.01
Moderate-to-severe stroke[b]	53.53(10.43, 274.62)	<0.001	69.05 (9.77, 487.84)[B]	<0.001

Model a: Regression analysis to evaluate serum asprosin as a risk factor for acute cerebral infarction in the risk factors group and the acute ischemic stroke group; [A] ORs adjusted for age, smoking, diabetes, hypertension, AF, peripheral vascular disease, Ura, LDL-C, WBC, and HCY, GSP.

Model b: a regression analysis was conducted to evaluate serum asprosin as a risk factor for moderate and severe ischemic stroke in patients with mild and moderate ischemic stroke; [B]ORs adjusted for age, sex, smoking, diabetes, hypertension, AF, peripheral vascular disease, SBP, DBP, Ura, TC, TG, HDL, LDL, WBC, HCY, GSP, and creatinine.

AF: Atrial fibrillation, AIS: Acute ischemic stroke, DBP: Diastolic blood pressure, HCY: Homocysteine, HDL: High-density lipoproteins, LDL: Low-density lipoproteins, SBP: Systolic blood pressure, TC: Total cholesterol, TG: Triglycerides, UR: Uric acid, GSP: Glycosylated serum protein, WBC: white blood cells, OR: Odds ratio.

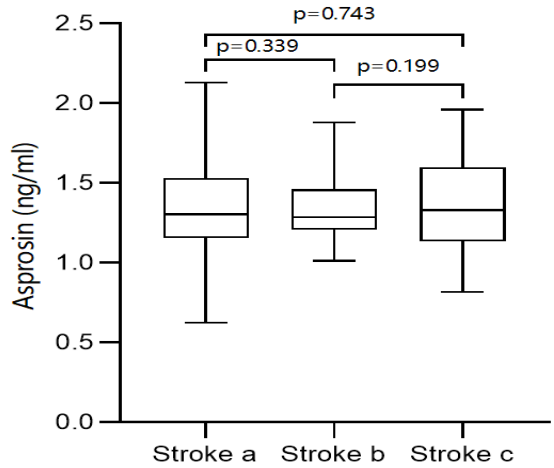

Figure 3. Asprosin concentration in the Stroke a, Stroke b and Stroke c; Stroke a: large-artery atherosclerosis; Stroke b: cardioembolism; Stroke c :small-vessel occlusion,stroke of other determined etiology and stroke of undetermined etiology.

thrombolytic therapy was performed. In summary, our results showed that serum asprosin level may be positively associated with the incidence and severity of AIS.

However, the specific mechanism of action of asprosin in AIS has not been investigated. Several studies have suggested a relationship between asprosin and metabolic syndromes and diseases. Thus, asprosin levels can potentially affect the occurrence of stroke. First, asprosin can activate the G-protein-cAMP-PKA signaling pathway in the liver, resulting in liver glycogen degradation, thereby increasing blood glucose[15], possibly through its interaction with the OLFR734 olfactory receptor.[32] Hyperglycemia has been suggested to promote oxidation, produce oxygen-free radicals, and cause blood vessel damage or atherosclerosis.[33] Second, in an animal study[15], intraperitoneal injection of a single dose of asprosin-specific monoclonal antibody resulted in a decrease in asprosin levels and simultaneous hyperinsulinemia, indicating that asprosin levels were positively correlated with insulin resistance. In this regard, Rulin *et al*.[34] and Alan *et al*.[25] reported high asprosin levels in women with polycystic ovary syndrome, while a previous study[35] showed that insulin resistance can not only stimulate the intracellular signal transduction pathway, leading to vascular inflammation and vascular endothelial dysfunction but may also cause atherosclerosis through endoplasmic reticulum stress induction and rapid macrophage apoptosis. Third, serum asprosin can pass through the blood-brain barrier and stimulate orexigenic AgRP+ neurons, resulting in appetite stimulation, thus increasing fat content, body weight, and lipid metabolism.[17] Accordingly, Wang *et al*.[28] and Ugur *et al*.[27] reported that obese adults had higher serum asprosin levels. A meta-analysis including 4.43 million participants revealed that overweight and obese people are prone to suffer from ischemic stroke.[36] Finally, several studies[23,25,37] have shown that asprosin can induce liver glycogen degradation and participate in the inflammatory response via cAMP as a secondary messenger. A previous study[38] showed that inflammation plays a crucial role in atherosclerosis, and it is currently believed that both inflammation and inflammatory cells or factors can lead to and are closely related to atherosclerosis progression. In an animal study[15], asprosin injection was shown to promote blood glucose release, resulting in hyperinsulinemia. A clinical study[22] demonstrated that high circulating asprosin levels were associated with a high

Table 3: Analysis for asprosin concentration in the thrombolytic group and non-thrombolytic group

Group	Number	Asprosin (ng/ml)	P
thrombolysis	20	1.33±0.29	0.486
Non-thromboysis	110	1.38±0.34	

syntax score. An animal study of cardiomyocytes found that asprosin can be a protective factor against diabetic cardiomyopathy, by reducing cardiomyocyte apoptosis.[20] This indicated that asprosin has a self-protective mechanism against diabetic cardiomyopathy. Another study[18] found that asprosin can exert specific effects in mesenchymal stromal cells, with therapeutic potential for myocardial infarction. Hence, the relationship between asprosin and cardiovascular disease is not clear and needs to be confirmed in future studies. Although this study described an association between serum asprosin and AIS, the pathogenetic mechanism behind this association requires further investigation in clinical and animal studies. In summary, the following hypotheses have been proposed: first, asprosin may directly participate in the progression of atherosclerosis by causing vascular endothelial injury through inflammatory reactions and further contribute to ischemic stroke (IS); second, asprosin can increase blood glucose, obesity, blood lipids, insulin resistance, and other metabolic abnormalities through the pathological mechanisms described above, thereby increasing the risk of IS.

In this study, the age- and sex-matched groups with previous vascular risk factors increase the certainty that asprosin can be used as a biomarker for stroke. However, some limitations of this study should be discussed. First, the causal relationship between asprosin and AIS could not be confirmed because of the study's cross-sectional design. However, the study showed for the first time that circulating asprosin levels may be closely associated with AIS, thus providing the basis for future research. Second, serum asprosin levels were not monitored at different time points during AIS. Third, the relationship between serum asprosin levels and stroke outcomes was not assessed. Fifth, changes in serum asprosin levels before and after thrombolytic therapy for AIS were not assessed. Finally, this study only included Chinese individuals and relatively small sample sizes; therefore, future studies with larger sample sizes and different nationalities are needed to confirm our findings.

In conclusion, in this study, we report that serum asprosin levels are positively associated with the incidence and severity of AIS, suggesting that asprosin may be a useful biomarker for predicting AIS. Serum asproisn levels may not be used to differentiate between different etiologic subtypes of acute ischemic cerebral infarction and thrombolytic therapy or not.

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DISCLOSURE

Ethics: The study design was approved by the ethics committee of our institution.

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Conflict of interest: None

Data availability: The data that support the findings of this study are not publicly available because of privacy or ethical restrictions.

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