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Original Research

The Relationship Between Serum Netrin-1 Expression Levels and Prognosis in Revascularized Patients with Acute Ischemic Stroke

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Abstract

Background: This study aimed to explore the relationship between serum netrin-1 expression levels and acute prognosis in patients with acute ischemic stroke (AIS) within 24 hours after revascularization. **Methods**: A total of 121 revascularized patients admitted to the Jinshan Branch of the Shanghai Sixth People's Hospital, China, between July 2019 and July 2021 were selected as study subjects. The primary outcome was the modified Rankin Scale (mRS) score three months after revascularization: patients with an mRS score >2 were classified into the unfavorable prognosis group and others into the favorable prognosis group. Those with serum netrin-1 expression levels greater than the median of all patients were classified into the elevated protein group and others into the decreased protein group. Multivariate logistic regression analysis was used to analyze the independent risk factors for prognosis in patients with AIS after revascularization. **Results**: The differences between the unfavorable prognosis group and the favorable prognosis group in gender, age, coronary heart disease, and netrin-1 levels were not statistically significant ($p > 0.05$). However, the National Institute of Health Stroke Scale (NIHSS) scores and number of patients with comorbid hypertension in the unfavorable prognosis group were significantly higher than in the favorable prognosis group ($p < 0.05$). Multivariate logistic regression analysis showed that NIHSS score before revascularization was an independent risk factor for unfavorable prognosis but that netrin-1 expression levels were not significantly associated with prognosis in patients after revascularization. **Conclusions**: Serum netrin-1 expression levels in the acute phase are not significantly associated with prognosis in patients with AIS after revascularization.

Keywords: revascularization; netrin-1; prognosis; risk factors

1. Introduction

Acute ischemic stroke (AIS) is brain tissue necrosis caused by the interruption of cerebral blood supply arising from abnormal blood and hemodynamics. It has a high fatality and disability rate [1]. AIS brings severe challenges to patients and to society and is the top priority for stroke prevention and treatment both in China and abroad [2]. AIS treatment employs rapid and safe revascularization for blood flow restoration before nerve cell injury becomes irreversible, with the aim of saving the ischemic penumbra and reducing nerve injury [3]. The current methods of revascularization are thrombolysis and thrombectomy [4]. After intravenous thrombolysis, a revascularized patient may still be susceptible to enlarged infarct volume and malignant cerebral edema, with the incidence of hemorrhage being 2–7% [5,6]. Thrombectomy may achieve a revascularization rate of up to 90% but has a favorable prognosis rate within 90 days of only 50% [7]. This is closely related to the further damage caused to the penumbra neurons by ischemia-reperfusion (I/R) after revascularization. Furthermore, effective prevention and treatment methods are still absent in clinical practice [8], and the biomarkers of prognosis after revascularization in patients with AIS still need to be further explored.

Netrin-1 is a secretory protein that acts as axon guidance during embryonic development [9]. Studies have shown that overexpression of netrin-1 in the peri-infarct area can exert a protective effect on the brain by increasing local microvascular density [10]. Recent studies have also suggested that netrin-1 is involved in cerebral protection by binding with deleted in colorectal cancer receptors through the Notch1 signaling pathway, and the promotion of angiogenesis may be one of its mechanisms [11,12]. Netrin-1 has also been found to alleviate I/R injury in brain tissues [13,14]. Additionally, it has been shown in various models that, depending on the driving mechanism of injury, netrin-1 levels are highly dynamic. Netrin-1 is one of the cytoprotective proteins expressed in normal kidneys, and it increases in response to [15] injury. In murine acute inflammation models, Tadagavadi *et al.* [16] noticed a drastic decrease in circulating netrin-1 levels in response to renal I/R injury. Their results indicated that netrin-1 levels first drop before they restore to normal levels or achieve even higher levels than the baseline. However, Rosenberger *et al.* [17] found that netrin-1 was strongly induced during hypoxia and seemed to steadily increase over time. The results are similar to those of various chronic inflammatory models [18]. Therefore, netrin-1 levels might be time de-

pendent.

Given netrin-1's protective effect on brain tissues, a China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) study showed that serum netrin-1 levels can be used to predict the prognosis of ischemic stroke [19]. However, this does not mean that netrin-1 has the potential of being useful in assessing prognosis after revascularization in patients with AIS, and few studies exist on the relationship between netrin-1 and prognosis after revascularization in patients with AIS. As such, the present study prospectively analyzed the relationship between serum netrin-1 levels and prognosis after revascularization in patients with AIS.

2. Materials and Methods

2.1 Study Protocol and Design

A prospective cohort study from July 1, 2019, to July 31, 2021, in the Jinshan Branch of Shanghai Sixth People's Hospital, China, was established. A total of 121 patients with AIS who met the inclusion criteria were enrolled. They were given anti-platelet aggregation and control of risk factors 24 hours after no hemorrhage was found in a cranial computed tomography (CT) scan following revascularization. In case of any hemorrhage in the cranial CT, routine control of risk factors and symptomatic treatment were performed. Stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS) scores at admission.

Inclusion criteria: (1) patient was diagnosed and treated according to the criteria for ischemic stroke of the Fourth National Cerebrovascular Disease Conference of the Chinese Medical Association; (2) patient met the requirements for intravenous thrombolysis and arterial embolectomy in the *Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018*.

Exclusion criteria: (1) patient had sick sinus syndrome or bradycardia; (2) patient had severe hepatic or renal function damage; (3) patient had fibrinogen levels <2 g/L; (4) patient had a history of malignant tumors; (5) patient or their family rejected enrollment; (6) patient had an expected survival time of less than three months for other diseases.

This study was a prospective cohort study. The NIHSS scores were measured on the first day, seventh day, and third month, and the modified Rankin Scale (mRS) scores were measured three months after onset. Venous blood was collected from the elbow, and serum netrin-1 levels were detected using an enzyme-linked immunosorbent assay (ELISA). Routine blood readings, hepatic and renal indicators, blood lipids, coagulation function, D-dimers, skull magnetic resonance imaging or cranial CT, carotid duplex ultrasounds, and electrocardiograms were also conducted and analyzed.

Data in favor of the findings of this study may be available from the corresponding author upon reasonable request.

2.2 Methods

2.2.1 Revascularization

Intravenous thrombolysis: Thrombolytic therapy was administered with alteplase (S20160055, Boehringer Ingelheim, Ingelheim am Rhein, Germany). Following the intravenous injection of 10% 0.9 mg/kg alteplase over the course of 1 min, the remaining 90% was continuously pumped intravenously over the course of 1 h, with the total dose of alteplase being up to 90 mg/kg. Intravenous thrombolysis was followed by neuroprotective therapy, and cranial CT was performed 24 h later. If no hemorrhage was found, 100 mg aspirin enteric-coated tablets were administered for anti-platelet aggregation.

Arterial embolectomy: The location of the cerebral artery occlusion was identified by digital subtraction angiography (DSA) under general anesthesia, and a Solitaire AB stent was delivered via catheter. The catheter was then slowly withdrawn to allow the stent to open naturally, and an intermediate catheter was raised slowly to the thrombosis by using the rivets on the stent. No thrombosis attached to the stent was observed, but any that had been observed would have been sucked out of the intermediate catheter, and the thrombectomy would have been repeated if necessary. Patients were then re-examined by DSA to check the occlusion of blood vessels, and the treatment was terminated when the forward flow reached a thrombolysis in cerebral infarction score of II–III. Cranial CT was performed immediately after surgery, and the patient's blood pressure was strictly controlled. Cranial CT images was performed again 24 h after surgery. In the absence of intracranial hemorrhage, 100 mg/d bayaspirin was administered to prevent thrombosis.

2.2.2 Serum Netrin-1 Determination

Blood samples were collected from all patients within 24 h of admission after fasting for 8 h. The samples were centrifuged at 3000 r/min for 10 mins, before being stored at –80 °C until the laboratory test. An ELISA kit (JLC7710, Shanghai Jingkang Bioengineering Co., Ltd., China) was used to measure serum netrin-1, and the inter- and intra-assay coefficients of variation were $<8.0\%$ and $<10.0\%$, respectively. Laboratory technical personnel were unaware of the general characteristics and clinical outcomes of the study participants. The median netrin-1 level in patients with AIS after revascularization was used as the cut-off point in the elevated protein group and decreased protein group.

2.2.3 NIHSS and mRS Scores

NIHSS scores consider consciousness, language, movement, sensation, coordinated movement, eye movement, and visual field. The scores range from 0 to 42 and are proportional to the nerve defects of the patient [20].

The mRS has seven levels: 0 = completely asymptomatic; 1 = no obvious dysfunction, capable of daily life

Table 1. Comparison of basic data of patients grouped by favorable and unfavorable prognosis.

Variable		Favorable prognosis group n = 79	Unfavorable prognosis group n = 42	$t/Z/\chi^2$	p
Age/year		69.33 ± 11.51	74.21 ± 10.41	–2.381	0.017
Sex	Female	32 (40.51)	23 (54.76)	2.248	0.134
	Male	47 (59.49)	19 (45.24)	/	/
Vascular risk factors	Smoke	7 (8.86)	3 (7.14)	0.000	1.000
	Diabetes	16 (20.25)	8 (19.04)	0.025	0.874
	Hypertension	52 (65.82)	35 (83.33)	4.162	0.041
	Coronary heart disease	9 (11.39)	5 (11.90)	0.000	1.000
NIHSS/point before recanalization		10.36 ± 7.184 (2–31)	20.65 ± 7.409 (2–36)	–5.886	0.000
Laboratory examination	HDL	1.096 ± 0.254	1.178 ± 0.335	1.256	0.212
	LDL	2.566 ± 0.823	2.264 ± 0.676	–1.656	0.101
	Homocysteine	17.75 ± 15.524	13.73 ± 5.338	–0.291	0.771
	Hba1c	6.891 ± 1.679	6.819 ± 1.724	–0.687	0.492
	Cholesterol	3.927 ± 0.896	3.712 ± 0.979	–1.113	0.268
Protein index	Netrin-1	225.98 ± 35.61	228.55 ± 31.36	–0.569	0.569

NIHSS, national institutes of health stroke scale; HDL, high density lipoprotein; LDL, low-density lipoprotein. Favorable Prognosis: mRS = 0–2. Unfavorable Prognosis Group: mRS = 3–6.

and work; 2 = mildly disabled, able to carry out daily routines; 3 = moderately disabled, able to walk unaided but needs assistance with some daily tasks; 4 = moderately to severely disabled, dependent on external assistance to carry out daily routines, and unable to walk unaided; 5 = severely disabled, relying entirely on others to carry out daily routines; 6 = death.

2.2.4 Evaluation of Outcomes in the Prospective Cohort

The primary endpoint criterion was the portfolio of death and major disabilities (mRS scores of 3–6) at follow-up three months after the onset of the AIS. Patients with mRS scores of 0–2 were considered to have a favorable prognosis, while those with scores of 3–6 were considered to have an unfavorable prognosis.

2.4 Statistical Methods

SPSS Statistics version 21.0 (IBM Corp., Chicago, IL, USA) was used for statistical analysis and processing. The measurement data were expressed as mean ± standard deviation and compared using Student's t-test. The enumeration data were expressed as percentages and compared using a χ^2 test. Logistic regression analysis was used to determine whether netrin-1 levels could be used to independently predict the prognosis of patients with acute stroke 90 days after revascularization. $p < 0.05$ was considered statistically significant.

3. Results

3.1 Comparison of Related Factors Between the Favorable and Unfavorable Prognosis Groups

Of the 121 patients enrolled in the study, 78 (64.5%) underwent intravenous thrombolysis and 43 (35.5%) underwent arterial thrombolysis. The patients were then divided into a favorable prognosis group and an unfavorable prognosis group according to their mRS scores. The differences between the two groups in gender, diabetes, and netrin-1 levels were not statistically significant ($p > 0.05$). However, the NIHSS scores and number of patients with comorbid hypertension were significantly higher in the unfavorable prognosis group than in the favorable prognosis group, and the ages were significantly higher in the favorable prognosis group than in the unfavorable prognosis group ($p < 0.05$; see Table 1).

3.2 Comparison of Related Factors Between the Elevated and Decreased Netrin-1 Protein Groups

The median (227.77 pg/mL) serum netrin-1 level in patients with AIS treated with revascularization was used as the cut-off point. Patients with a median serum netrin-1 level >227.77 pg/mL were classified into the elevated protein group, and those with a median serum netrin-1 level ≤227.77 pg/mL were classified into the decreased protein group. The differences between the two groups in age, gender, and NIHSS score were not statistically significant ($p > 0.05$; see Table 2).

3.3 Logistic Regression Analysis of Factors of Unfavorable Prognosis in Patients with AIS Treated with Revascularization

Multivariate logistic regression analysis was performed with favorable prognosis of patients with AIS treated with revascularization as the dependent variable (0 = Yes, 1 = No), and NIHSS score, age, hypertension, smoking history, and netrin-1 levels as independent variables. The results suggested that NIHSS score was a risk factor for

Table 2. Comparison of related factors between the elevated protein and the decreased protein groups.

Variable	Decreased protein group	Elevated protein group	$t/Z/\chi^2$	p
	n = 60	n = 61		
Age (year)	70.77 ± 11.10	71.28 ± 11.66	–0.247	0.805
Sex			0.216	0.642
Female	26 (40.51)	29 (54.76)	/	/
Male	34 (59.49)	32 (45.24)	/	/
Vascular risk factors				
Smoke	6 (8.86)	4 (7.14)	0.436	0.509
Diabetes	12 (20.25)	12 (19.04)	0.002	0.964
Hypertension	46 (65.82)	41 (83.33)	1.338	0.247
Coronary heart disease	9 (11.39)	5 (11.90)	1.368	0.242
NIHSS score/point before recanalization	14.17 ± 8.525 (2–36)	14.07 ± 8.981 (2–31)	0.073	0.942
Laboratory examination				
HDL	1.1205 ± 0.261	1.128 ± 0.294	–0.397	0.693
LDL	2.504 ± 0.762	2.478 ± 0.836	0.160	0.873
Homocysteine	16.07 ± 12.331	17.23 ± 14.347	–0.423	0.672
Hba1c	6.815 ± 1.450	6.911 ± 1.891	–0.813	0.416
Cholesterol	3.884 ± 0.892	3.837 ± 0.961	–0.389	0.699
Prognosis of vascular recanalization after stroke			1.165	0.280
Unfavorable prognosis	18 (30.00)	24 (39.34)	/	/
Favorable prognosis	42 (70.00)	37 (60.66)	/	/

NIHSS, national institutes of health stroke scale; HDL, high density lipoprotein; LDL, low-density lipoprotein.

Table 3. Multivariate logistic regression analysis.

Parameter	Regression coefficients	Standard error	Odds ratio	95% Confidence interval	p-value	Wald χ^2
Age	0.23	0.023	1.023	0.978–1.070	0.316	1.007
Smoke	–0.607	0.885	0.545	0.096–3.089	0.545	0.470
Sex	–0.008	0.689	0.992	0.257–3.828	0.992	0.000
NIHSS	0.163	0.033	1.178	1.103–1.021	0.000	24.218
Hypertension	–1.206	0.593	0.359	0.112–1.146	0.084	2.994
Netrin-1	0.007	0.897	1.007	0.993–1.021	0.344	0.897

prognosis three months after revascularization ($p < 0.05$), while netrin-1 levels and other data were not statistically significant ($p > 0.05$; see Table 3).

4. Discussion

In order to better explore the relationship between netrin-1 levels and the prognosis of patients with AIS after revascularization, in addition to the classification of netrin-1 level by the method described in this paper, the quartile method was also used. However, the results indicated that netrin-1 expression levels in the acute phase were not significantly correlated with prognosis in AIS patients after revascularization. A recent study has stated that there are 1114.8 stroke patients per 100,000 people in China [21]. AIS is characterized by rapid onset and high disability and fatality rates, bringing a significant burden to China and other countries around the world. At present, revascularization is mainly achieved by thrombolysis and thrombectomy [22], but these methods often result in poor efficacy; thus, prevention is still the primary clinical treatment for AIS. Therefore, it is essential to explore economic and simple outcome measures to help predict the prognosis of patients with AIS.

Recent studies have often focused on the prognostic relationship between outcome measures before revascularization in patients with AIS, such as C-reactive protein/albumin ratio [23], serum MM9 expression level [24], plasma homocysteine level [25], and serum PRDX1 level [26]. However, there are very few reports on the relationship between the outcome measures and prognosis of revascularized patients with AIS.

With the establishment of stroke centers and the improvement of revascularization, a rapidly increasing number of patients with AIS are being treated [27]. Therefore, it is vital to study the prognosis of stroke patients undergoing revascularization. While an outcome measure may be applicable to predicting the prognosis of patients with AIS, the possibility of an outcome measure being used to predict the prognosis of revascularized patients with AIS must also be explored. Therefore, the outcome measures of prognosis in patients with AIS should be studied in both revascularized patients and patients who have not undergone revascular-

ization.

Preliminary basic studies have proven the protective effect of netrin-1 in animal cerebral ischemia models, but the applicability of these findings to humans needs to be studied further. The CATIS study suggested that elevated serum netrin-1 levels were closely associated with the improved prognosis of patients with AIS, indicating that netrin-1 could be used as a prognostic marker. It should be noted that the patients in the CATIS study all suffered a stroke before revascularization [19]. The present study was designed to investigate serum netrin-1 levels and prognosis three months after revascularization in 121 patients with AIS. By comparing the clinical data of the patients in the favorable prognosis group and the unfavorable prognosis group, it was found that there was no significant correlation between serum netrin-1 levels and prognosis, and multivariate logistic regression analysis suggested that netrin-1 levels were not a major influencing factor of prognosis. These findings differ from those of the CATIS trial. Moreover, the NIHSS scores of stroke patients enrolled in the CATIS trial were in the range of 4–10, while those in the present study were as high as 36. The reason for this difference may be that the cases enrolled in the present study included patients who required thrombectomy, so their NIHSS scores would be higher than those in other trials.

In previous studies, netrin-1 levels appeared to have different baseline values in different diseases. This suggests that netrin-1 levels may be time dependent in acute injury. Yim *et al*. [28] suggested that serum netrin-1 levels were lower in some small sample studies, such as atherosclerosis, type 2 diabetes, etc. However, in the CATIS trial, netrin-1 levels were high. The results of the present study suggest that netrin-1 levels are not associated with prognosis in patients with AIS after revascularization, and netrin-1 levels in the present study were low compared to those in the CATIS trial. Therefore, it can be suggested that there is a critical value relationship between netrin-1 levels and prognosis. When a patient's netrin-1 level exceeds this critical value, their prognosis is proportional to their netrin-1 level, and the higher their netrin-1 level, the better their prognosis. Conversely, when a patient's netrin-1 level is below the critical value, their netrin-1 level is not significantly associated with their prognosis.

The present study had some limitations. First, it was a single-center study and was based on a single measurement of netrin-1, so the results may be biased. Second, factors like the type of ischemic stroke, the time of I/R, and the occurrence of complications after treatment could possibly cause bias. Third, the power calculation was not reported. To further improve the credibility and accuracy of this study, the sample size should be increased for further research.

5. Conclusions

Serum netrin-1 levels may be a potential biomarker for the prognosis of patients with AIS, but no significant correlation was found between the serum netrin-1 levels and prognosis of patients with AIS treated with revascularization.

Author Contributions

Conception and design of the research—DZT. Acquisition of data—DZT, CFH, LZ, ZL. Analysis and interpretation of the data—DZT, GJL, CLY. Statistical analysis—DZT, CLY. Obtaining financing—DZT. Writing of the manuscript—DZT. Critical revision of the manuscript for intellectual content—ZL. All authors read and approved the final draft.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of Jinshan branch of Shanghai Sixth People's Hospital (No: jszxyy201911). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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Conflict of Interest

The authors declare no conflict of interest.

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