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Association of Serum Inflammatory Factors with Prognosis after Revascularization Therapy in Patients with Acute Ischemic Stroke

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Abstracts: OBJECTIVE: To investigate the value of serum inflammatory factor levels in acute ischemic stroke patients after revascularization therapy in assessing acute prognosis. METHODS: 94 patients with acute ischemic stroke who underwent revascularization therapy admitted to our hospital from January 01, 2022 to January 01, 2024 were studied. The main evaluation index was modified Rankin Scale score (mRS) after 3 months, and patients with mRS score >2 were categorized into the poor prognosis group, and the rest were the good prognosis group. As well as the treatment of revascularization in all patients was used as a division into a thrombus extraction group and an intravenous thrombolysis group. Logistic regression analysis was applied to explore the independent risk factors for the prognosis of patients treated with recanalization for acute ischemic stroke. RESULTS: Two groups with good (59 cases) and poor (35 cases) prognosis were divided according to the mRS score. There were some differences in age, gender, emergency GLU, INR, whether they had diabetes or hypertension and other contents between the two groups, but the differences were not statistically significant. The NIHSS score, hospitalization days, previous cardiac history, hospitalization days, LDL, fasting glucose, IL-6, and TNF-a at the time of admission were lower than those in the poor prognosis group, and the difference was statistically significant. In the patients in the embolization group, there were some differences in age, gender, emergency GLU, INR, whether they had diabetes or hypertension and other contents between the two groups, but the differences were not statistically significant. The pre-hospital NHISS score, IL-6, and TNF-a of patients in the good prognosis group were lower than those in the poor prognosis group, and the difference was statistically significant. CONCLUSION: IL-6 and TNF-α may be used as predictors of prognosis after revascularization therapy for acute ischemic stroke, and this conclusion also applies to patients in the embolization group.

Keywords: revascularization therapy; IL-6; TNF-a; prognosis; risk factors

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Acute ischemic stroke is an abnormality of cerebral blood supply due to various causes, resulting in necrosis of brain tissues and irreversible changes in neurological function, which is characterized by high morbidity, high disability and high morbidity and mortality, and is a serious danger to human health, greatly aggravating the burden on the family and the society [1]. Rapid and safe revascularization and restoration of blood flow to salvage ischemic hemi-diaphragm tissues before irreversible neuronal damage is achieved is the main therapeutic goal of acute ischemic stroke. Acute ischemic stroke poses a serious challenge to patients and society, and is a top priority for stroke prevention and treatment at home and abroad [2]. Currently, two major types of revascularization therapy are thrombolysis and thrombectomy. The recanalization rate of thrombolysis can reach 90%, but the 90-day prognosis of patients is only 50% [3]. This is closely related to further damage to semidominal band neurons by ischemia-reperfusion after recanalization of the occluded vessel, and therefore, there is still a lack of effective preventive and therapeutic methods in the clinic. Therefore, early prediction of the prognosis of patients with acute ischemic stroke is helpful for early clinical intervention. Therefore, it is important to predict the prognosis of acute ischemic stroke patients after revascularization therapy, and it is clinically significant to investigate the related biomarkers.

Ischemic stroke occurs on top of atherosclerotic plaques, and arterial stenosis occurring on top of carotid atherosclerotic plaques forms thrombi, which is a chronic inflammatory process [4]. In addition, hypo-perfusion and hypoxia may contribute to the release of microglial cells and pro-inflammatory cytokines [5], which promotes the aggregation of peripheral immune cells to the ischemic region of the brain, exacerbates damage to the semi-darkhoric zone and the blood-brain barrier, and leads to cerebral edema, intracranial hypertension, and ultimately exacerbates neuronal damage, resulting in early neurological deterioration and other increased adverse prognostic events for patients [6]. Increasing evidence suggests that neuro-inflammatory responses play a key role in the onset and progression of early neurologic deterioration [7]. Therefore, neuro-inflammation is involved in the onset and development of ischemic stroke.

Inflammatory indicators such as CRP, IL-6, IL-1β, TNF-α, TPA and others have been studied in various diseases based on the properties of serum indicators such as their convenience, inexpensiveness and easy accessibility [8–9]. CRP and IL-6, as a peripheral marker of inflammation, have been observed to correlate with risk factors for cardiovascular and cerebrovascular events. Moreover, CRP is constantly elevated in the circulatory system of patients with acute ischemic attack. Recent clinical studies have shown a link between CRP, IL-6, D-dimer, TPA and the risk of cardiovascular events. Several studies have pointed out that AIS pathogenesis is associated with an acute inflammatory response, and the use of conventional inflammatory factors such as PCT, IL-6) and other conventional inflammatory factors in the assessment of AIS disease has been reported, but conventional inflammatory factors are susceptible to infection and other factors, and their specificity is relatively poor [10]. Based on the fact that neuroinflammation is closely related to the development of ischemic stroke, it is of great significance to predict the prognosis of patients with acute ischemic stroke by means of blood markers. In the literature, glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), and IL-6 show high levels in the serum of patients with acute ischemic stroke, but there is a paucity of reports on the relationship between the three and the extent of the disease, and the prognosis [11]. Multiple complexity studies have shown that CRP concentration would be a predictive marker of cerebrovascular disease events in patients with stroke, independent of the conventional predictive markers. Meanwhile Gastillo et al. found CRP and IL-6 to be independent risk factors for cerebral infarction in a study of 231 patients with ischemic stroke. However, there are few studies on the function of inflammation-related factors in predicting the prognosis of acute ischemic stroke patients after recanalization therapy, and there are few studies on the relationship between serum inflammation-related factors and the prognosis of acute ischemic stroke patients after revascularization therapy. Based on this, we conducted the present study based on the association between serum levels of inflammation-related indicators such as IL-1/IL-6/TNF-a and prognosis after revascularization therapy in patients with acute ischemic stroke.

1. Information and Methodology:

1.1. Study Program Design

We conducted a retrospective study of acute ischemic stroke patients who received revascularization from January 01, 2022 to January 01, 2024 at the Jinshan Branch of Shanghai Sixth People's Hospital, Shanghai, China. Inclusion criteria: 1) compliance with the diagnostic and therapeutic criteria for stroke of the 4th Conference on Cerebrovascular Diseases of the Chinese Medical Association; 2) NHISS ≥ 10; 3) patients with intravenous thrombolysis with alteplase and arterial thrombolysis with SWIM technique; 4) complete serologic data. Exclusion criteria: 1) those with severe cardiac, hepatic, and renal failure; 3) fibrinogen less than 2 g/L; 4) patients with the presence of malignant tumors; 5) patients who did not undergo revascularization; and 6) patients who were lost to follow-up. Serum inflammation-related indexes such as IL-6, TNF-a and Netrin-1

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were measured by enzyme-linked immunosorbent assay (ELISA), and routine blood tests, blood lipids, coagulation function, liver and kidney indexes, electrocardiograms, cranial MRIs, or cervical vascular ultrasound were also checked. The mRS scores and NHISS scores of the patients were collected after 3 months. This study was approved by the Ethics Committee of the Jinshan Branch of the Sixth People's Hospital, and because it was a retrospective study, informed consent was not applicable.

1.2. Methods

1.2.1. Methods of Revascularization Treatment

Thrombolysis: Thrombolysis with alteplase was used in this study, dose: 10% 0.9mg/kg, injection time: after intravenous push in 1min, the remaining 90% of alteplase was treated with continuous intravenous pumping for 1 hour, and the time of alteplase used was less than 90mg; after thrombolysis, neuroprotective sequential treatment was used, and the head CT was reviewed, time: within 24 hours; finally, those without intracranial hemorrhage were given antiplatelet and other treatments. bleeding is treated with antiplatelet and other therapies.

Thrombus extraction: firstly, under general anesthesia, whole brain angiography was used to clarify the location of the occluded vessel; secondly, the stent was delivered into the vessel location with a catheter (Solitaire AB), then, the catheter was slowly withdrawn after being in place, and the stent was naturally opened, and SWIM technique was used to reduce retrospective offset in all the patients; after that, the stent rivulet force was utilized, and the intermediate catheter was slowly ascended to the thrombus exit; lastly, imaging review was performed, and if necessary, antiplatelet was given. , contrast review, and multiple thrombus retrieval if necessary. Review cranial CT (immediate postoperative period), strict blood pressure control, review cranial CT again (24 hours postoperative period), and use of aspirin 100 mg/d in the absence of intracranial hemorrhage to prevent thrombus formation.

1.2.2. Measurement of Serum Inflammation-Related Indexes

Serum inflammation-related indicators in this study were tested by standard laboratories, all patients' blood samples were collected immediately after admission, centrifuged at 3000 r/min for 10 min, serum was taken and transported on dry ice, and immediately sent to the relevant laboratories for testing, the ELISA test kits we used were from Nanjing built, the laboratory technicians who measured the relevant inflammation indicators in the serum (IL-1/IL-6 /TNF-a/Netrin-1) and other indicators, the laboratory technicians were unaware of the baseline characteristics and the clinical outcomes of the study participants.

1.2.3. NHISS Scores and mRS Scores

The NIHSS scale encompasses consciousness, motor, sensory, speech, eye movement, visual field, ataxia, where the lowest score is 0 and the highest is 42, with scores proportional to neurologic deficits. Currently, an NHISS score of ≤5 is used as a criterion for mild stroke.

The mRS score has a total of 0-6 points, and there are a total of 7 levels: level 1: 0 points, the patient is asymptomatic; level 2, 1 point, the patient does not have obvious functional impairment, and can complete daily life work; level 3, 2 points, the patient has a mild disability, but can perform daily tasks by himself; level 4, 3 points, the patient has a moderate disability, although he can walk independently, but needs help with some of the daily tasks; level 5, 4 points, the patient has a moderate disability, and can walk independently, but needs help with some of the daily tasks; level 5, 4 points, the patient has a moderate disability, and can walk independently. Grade 5, 4 points, the patient has a moderate to severe disability, needs to rely on outside help to complete the work needed in life, and is unable to walk independently; Grade 6, the patient has a severe disability, and is completely dependent on others to complete life; Grade 7, 6 points for death [12].

1.2.4. Prognostic Outcome Assessment

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The primary endpoint indicator was the patients' Modified Rankin Scale, mRS score 0-6 at 3-month follow-up after discharge, where patients with mRS 0-2 were considered to have a good prognosis and 3-6 were considered to have a poor prognosis. The secondary outcome was the proportion of patients with a good prognosis at 3 months of onset based on the baseline NIHSS correction at enrollment.

1.3. Statistical Methods

SPSS21.0 statistical software was applied for statistical analysis and processing, count data were expressed as percentages, and all measurements were expressed as mean ± standard deviation. Continuous variables were compared with the Mann-Whitney U test or Student's t test, and categorical variables were compared by the χ^2 test or Fisher's exact tests. Significant factors were analyzed by logistic regressions to identify independent risk factors associated with the prognosis. Statistical significance for the study was defined as *P*-value ≤ 0.05.

2. Results

2.1. Characterization of Good and Poor Prognosis Groups of Revascularized Patients

A total of 94 patients with acute ischemic stroke were included in this study, of which, two groups were divided into good prognosis (59 patients) and poor prognosis (35 patients) based on mRS score. According to the results, it was suggested that there were some differences in age, gender, emergency GLU, INR, whether they had diabetes or hypertension, and other contents between the two groups, but the differences were not statistically significant (P > 0.05). Notably, there were statistical differences in NIHSS scores at admission, days of hospitalization, and previous cardiac history (P<0.05). Patients in the good prognosis group had lower pre-hospital NHISS scores, patients with history of heart disease, and days of hospitalization than those in the poor prognosis group. Laboratory-related indexes suggested that in the good prognosis group, patients' LDL, fasting blood glucose, IL-6, TNF-a and other indexes were lower than those in the poor prognosis group, and the difference was statistically significant (P<0.05). For details, see Table 1.

Table 1. Comparison of basic data of patients in the good prognosis group and the poor prognosis gr.

Variable		Favorable Prognosis Group n=59	Unfavorable Prognosis Group n=35	P
Age/Year		72.85±12.35	75.03±10.32	0.382
Weight/Kg		63.26±9.93	56.26±12.20	0.006
GLU		8.21±4.4.58	9.32±3.60	0.238
INR		0.94±0.09	1.67±2.89	0.072
NHISS / point before recanalization		13.69±4.88	25.20±4.47	0.000
Days of hospitalization /d		11.22±4.73	15.51±9.48	0.004
Sex	Female	22(37.29)	16(45.71)	0.515
	Male	37(62.71)	19(54.28)	
Vascular risk factors	Smoke	42(71.19)	30(85.71)	0.099
	Diabetes	25(42.37)	20(57.14)	0.166
	Hypertension	49(83.05)	31(52.54)	0.467
	Coronary Heart Disease	21(35.59)	23(65.71)	0.006
Laboratory examination	Cholesterol	4.16±1.17	3.69±1.14	0.065
	HDL	1.13±0.23	1.28±0.37	0.023

	LDL	2.81±1.57	2.12±0.89	0.018
	Cysteine	13.73±8.00	14.56±9.15	0.643
	Fasting Glucose	6.79±2.32	9.15±3.66	0.000
	Homocysteine	11.44±4.89	12.57±4.78	0.305
	Hba1c	6.85±2.22	6.73±1.59	0.797
Protein index	Netrin-1	206.19±21.10	207.51±20.66	0.770
	IL-6	21.23±1.59	35.86±4.19	0.000
	PAF	53.85±5.20	52.87±5.61	0.536
	LY6G	865.14±69.69	881.52±78.06	0.295
	TNF-a	433.86±36.09	479.52±30.44	0.000

2.2. Comparison of Risk Factors Related to Patients in the Poor Prognosis Group and Good Prognosis Group

Taking the mRS score of acute ischemic stroke patients 3 months after revascularization treatment as the basis of grouping, patients with 0-2 points were categorized into the good prognosis group, and patients with 3-6 points were categorized into the no prognosis group. Pre-treatment NHISS, serum LDL protein level, serum IL-6, and serum TNF-a were included in the logistic regression analysis. The results suggested that pretreatment NHISS, serum IL-6, and serum TNF-a were risk factors for patients' prognosis at 3 months of treatment ($P<0.05$), while serum LDL protein level was not statistically significant ($P>0.05$). For details, see Table 2.

Table 2. Logistic regression analysis of risk factors affecting the prognosis of patients with revascularization.

Parameter	Regression Coefficients	Standard Error	Odds Ratio	95% Confidence Interval	P-Value	Wald $\chi 2$
NIHSS	0.428	0.094	1.533	1.274–1.845	0.000	20.482
LDL	0.383	0.072	1.467	1.273–1.690	0.010	23.691
IL-6	0.471	0.098	1.623	1.282–1.933	0.035	19.271
TNF-a	0.054	0.015	1.055	1.024–1.088	0.023	12.404

2.3. Characterization of Patients with Acute Ischemic Stroke with Good Prognosis and Poor Prognosis Groups after Thrombolysis

We included a total of 56 patients with acute ischemic stroke with thrombolysis, of which, two groups were divided into good prognosis (21 patients) and poor prognosis (35 patients) according to the mRS score. According to the results, it was suggested that there were some differences in age, gender, emergency GLU, INR, whether they had diabetes or hypertension and other contents between the two groups, but the differences were not statistically significant ($P > 0.05$). It is worth noting that the patients in the good prognosis group had lower pre-hospital NHISS scores, in addition, the laboratory-related indexes suggested that in the good prognosis group, the patients' indexes of IL-6 and TNF-a were lower than those in the bad prognosis group, and the difference was statistically significant ($P < 0.05$). For details, see **Table 3**.

Table 3. Characterization of patients in the embolization group with good prognosis versus those with poor prognosis.

Variable	Favorable Prognosis Group n=21	Unfavorable Prognosis Group n=35	P
Age/Year	77.76±9.35	75.03±10.32	0.325
Weight/Kg	59.71±9.79	56.26±12.20	0.359

GLU		8.00±6.48	9.32±3.60	0.347
INR		0.96±0.10	1.67±2.89	0.289
NHISS / point before recanalization		18.57±5.18	25.20±4.47	0.000
Days of hospitalisation/d		12.57±6.26	15.51±9.48	0.211
Sex	Female	10(37.29)	16(45.71)	0.890
	Male	11(62.71)	19(54.28)	
Vascular risk factors	Smoke	20(71.19)	30(85.71)	0.265
	Diabetes	7(42.37)	20(57.14)	0.084
	Hypertension	18(83.05)	31(52.54)	0.754
	Coronary Heart Disease	11(35.59)	23(65.71)	0.401
Laboratory examination	cholesterol	3.77±1.37	3.69±1.14	0.818
	HDL	1.17±0.26	1.28±0.37	0.248
	LDL	2.49±1.56	2.12±0.89	0.211
	Fasting glucose	7.09±2.06	9.15±3.66	0.022
	Homocysteine	12.69±6.92	12.57±4.78	0.946
	Hba1c	6.7±2.13	6.73±1.59	0.940
Protein index	Netrin-1	203.49±19.46	207.51±20.66	0.475
	IL-6	21.11±1.89	35.86±4.19	0.000
	PAF	53.39±4.98	52.87±5.61	0.730
	LY6G	858.11±64.12	881.52±78.06	0.252
	TNF-a	427.01±32.98	479.52±30.44	0.000

3. Discusion：

Recent studies suggest that the incidence of acute ischemic stroke in China is about 1700/100,000 people. This disease is characterized by rapid onset, high disability and fatality rates, which brings a great burden to our country and even the world society. Currently, revascularization treatments mainly include thrombolysis and thrombus extraction, but the efficacy is still unsatisfactory, and the current clinical practice is still mostly based on prevention. Therefore, it is extremely important to further explore economical and simple assessment indexes to assist in predicting the prognosis of acute stroke patients. Our findings suggest that acute IL-6 and TNF-a are independent risk factors for patient prognosis after revascularization therapy and also have a role in assessing the prognosis of patients after thrombus extraction.

We divided into good prognosis group and poor prognosis group after revascularization treatment by mRS score. By comparing the general characteristics data of patients in the two groups, it was found that pre-treatment NHISS scores and serum LDL protein indexes were higher in the poor prognosis group than in the good prognosis group and the differences were statistically different. This result is consistent with previous findings that the higher the patients' NHISS score, the worse their prognosis. By comparing the neuro-inflammation-related indicators, we found that pre-treatment IL-6 and TNF-α were significantly higher in the poor prognosis group. Further by

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logistic regression analysis, we found that TNF-α, NHISS score, and IL-6 were independent risk factors for the prognosis of acute ischemic stroke patients after 3 months. When the indexes of NHISS, TNF-α, or IL-6 were higher in patients, the likelihood of their poor prognosis was higher.

IL-6 plays a key role in the acute inflammatory response and regulates the production of acute phase proteins such as C-reactive protein.IL-6 promotes the inflammatory response by activating endothelial cells and accelerating the synthesis of fibrinogen, and it is therefore possible that this inflammatory factor may have an important role in the pathogenesis of vascular inflammation. Several studies have demonstrated that IL-6 is elevated in ischemic states, which is mainly due to the production of large amounts of antigens in brain tissues after cerebral ischemia, resulting in a strong immune response and the activation of inflammatory factors [13]. Numerous clinical and experimental studies have confirmed and emphasized the important role of immunoinflammation mediated by TNF-α and IL-6 in the pathophysiological changes of acute ischemic stroke. Molecular signals generated by cerebral ischemia can activate the innate immune system, leading to amplification of the inflammatory cascade and tissue damage [14]. Previous studies have also indicated that interleukins promote the expression of other inflammatory factors, enhance the inflammatory response, and act on infarcted arterioles to enlarge the infarct size and exacerbate the severity of blood stasis in ischemic brain injury. The results of a DNA methylation-based study on the differential expression of IL-6 gene in coronary heart disease with blood stasis showed that the methylation of the first seven gene sites of the IL-6 gene transcriptional start site was significantly higher in the group with blood stasis compared with the group without blood stasis. It has also been shown that IL-6 plays an important role in cerebral ischemia not only as an intermediate link in the inflammatory process in the acute phase of stroke, but also as a neurotrophic factor in the later stages of cerebral ischemia [15]. In addition, TNF-α is closely related to the occurrence and development of acute cerebral infarction. The release of TNF-α can activate the co-processing of complement and coagulation system, reduce the expression of thrombomodulin in the endothelium, which controls the coagulation system, and promote the release of tissue factor, which can activate the exogenous coagulation pathway to form the hyper-viscosity state of the blood and promote the formation of atherosclerosis and thrombosis [16]. All these evidences suggest that IL-6 and TNF-α play important roles in the pathogenic process of acute ischemic stroke patients. Combined with the results of the present study, IL-6 and TNF-α may serve as predictors of prognosis after revascularization therapy in acute ischemic stroke.

Further, we divided the patients with thrombolysis and intravenous thrombolysis into two groups. In this study, the prognosis of patients with intravenous thrombolysis was good after 3 months, and among the patients in the thrombolysis group, 21 patients had a good prognosis. By dividing the patients in the thrombolysis group into good and poor prognosis groups, we found that the patients in the good prognosis group had lower pre-hospital NHISS scores, and that IL-6 and TNF-a were lower than those in the poor prognosis group, and the difference was statistically significant. Accordingly, we concluded that NHISS score, IL-6 and TNF-a are possible predictors of prognosis after thrombolysis in patients with acute ischemic stroke.

With the establishment of stroke centers and innovations in revascularization techniques, the population of patients with acute ischemic stroke who receive timely treatment is rapidly increasing [17], and therefore, studies on the prognosis of recanalization therapy in stroke patients are of great importance. However, when a metric may be suitable for predicting the prognosis of stroke patients, whether it can also be used to predict the prognosis of recanalization therapy for acute stroke patients is something that needs to be further explored. Therefore, research on prognostic assessment indicators for stroke patients may need to be considered jointly from both treated and untreated aspects. This article has some limitations, 1) a retrospective study with selection bias and a low sample size; 2) the article only assessed IL-6 and TNF-α as risk factors for prognosis after revascularization therapy in patients with acute ischemic stroke, and did not stratify the obtained IL-6 and TNF-α.

4. Conclusion:

Our results suggest that emergency IL-6 and TNF-a are independent risk factors for patients' prognosis after revascularization therapy, and also have a role in assessing the prognosis of patients after thrombus removal. Based on the retrospective study conducted in this paper, and the overall number of cases included is small, the results of the study have to be further considered, and there is a certain selection bias, in order to further improve the credibility of the study as well as the accuracy of the letter, the later study will be on the basis of the increased sample size for in-depth investigation, and prospective study.

Author Contributions: Conception and design of the research—DZT. Acqui sition of data—DZT, SHY, XLL, ZL. Analysis and interpre tation of the data—DZT, CLY. Statistical analysis— DZT, CLY,XXC. Obtaining financing—DZT. Writing of the manuscript—DZT. Critical revision of the manuscript for intellectual content—JGL,CLY, All authors read and approved the final draft.

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Conflict of Interest: The authors declare no conflict of interest.

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