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To Explore the Relationship Between NLR And the Severity of Acute Ischemic Stroke and The Clinical Prognosis of Patients Receiving Intravenous Thrombolytic Therapy

Liu Hongbo, Zhou Jiehao, Zou Beilei, Yang Yihong*, Li Caixia

Abstract

Objective: To investigate the relationship between the neutrophil lymphocyte ratio (NLR) and the severity of acute ischemic stroke (AIS) and the clinical prognosis of patients receiving intravenous thrombolytic therapy.

Methods: A total of 120 AIS patients admitted to our hospital from January 2018 to January 2020 were selected. According to the "Scoring Standards for the Degree of Clinical Neurological Impairment in Chinese Stroke Patients", all patients were divided into mild AIS group with a score of 0-15 (N = 54), 16-30 were divided into moderate AIS group (n = 33), 31-45 were divided into severe AIS group (n = 33), and then according to the prognosis of intravenous thrombolysis, all patients were divided into prognosis Good group (n = 84), poor prognosis group (n = 36). The peripheral blood neutrophil count and percentage, lymphocyte count percentage, and NLR levels were compared between the three groups of patients with mild AIS, moderate AIS, and moderate AIS, and between the two groups with good prognosis and poor prognosis before treatment. Logistic regression analysis method, Pearson correlation analysis method, receiver operating characteristics (Receiver Operating Characteristics, ROC) area under curve (Area under curve, AUC) were used to analyze the severity of NLR and AIS disease and the clinical prognosis of patients after intravenous thrombolytic therapy Correlation.

Results: As the severity of AIS deepened, the neutrophil count, neutrophil percentage, and NLR in the peripheral blood of patients increased significantly, and the lymphocyte count and lymphocyte percentage decreased significantly (P <0.05); the peripheral blood of patients in the severe AIS group. The blood neutrophil count, neutrophil percentage, and NLR level were significantly higher than the mild AIS group and the moderate AIS group, and the lymphocyte count and lymphocyte percentage levels were significantly lower than the mild AIS group and the moderate AIS group (P <0.05). The results of multivariate logistic regression analysis showed that neutrophil count, neutrophil percentage, and NLR are independent risk factors that affect the severity of disease and poor clinical prognosis of patients after intravenous thrombolytic therapy. Lymphocyte count and lymphocyte percentage is a protective factor (P <0.05). The results of Pearson correlation analysis showed that there was a positive correlation between NLR and AIS patients' disease severity (P <0.05). The peripheral blood neutrophil count, neutrophil percentage, and NLR levels in the good prognosis group were significantly lower than those in the poor prognosis group, and the lymphocyte count and lymphocyte percentage levels were significantly higher than those in the poor prognosis group (P <0.05). The NLR predicts the clinical prognosis of AIS patients after receiving intravenous thrombolytic therapy, AUC=0.803, sensitivity 75.36%, specificity 77.52%, AUC (95%CI) =0.754 ~ 0.893 (P <0.05).

Conclusion: NLR is an independent risk factor that affects the severity of the disease in AIS patients and the poor clinical prognosis of patients after intravenous thrombolysis,

*Emergency department of Fuyang people's Hospital of Anhui Province； *Correspondence author: 15856806657@163.com*

and is positively correlated with the severity of the disease in AIS patients. It has a higher prognosis for patients receiving intravenous thrombolysis in AIS and high prediction accuracy.

Keywords: Neutrophil lymphocyte ratio; acute ischemic stroke; severity; intravenous thrombolysis; prognosis

Background

Acute ischemic stroke (acute ischemic stroke, AIS) is the most common type of stroke in our country [1], and its pathogenesis is mainly caused by acute blood supply disorder of brain tissue or blockage of cerebral arteries and blood vessels caused by various factors, causing brain tissue deficiency. Hypoxic necrosis of the blood eventually leads to the occurrence of AIS [2]. AIS is a cerebrovascular disease that has a serious adverse effect on life and health. It has a high risk of illness, disability and death, which will cause huge economic pressure on patients and society [3]. Therefore, it is extremely important to accurately assess the degree of AIS disease progression and prognostic outcome to improve the survival rate of patients and reduce the risk of death and disability. At present, the clinical treatment of AIS mainly uses intravenous thrombolysis [4]. Timely intravenous thrombolysis can clear block cerebral blood vessels and restore blood circulation, thereby saving the brain tissue around the lesion in a state of reversible damage, and can also effectively improve the clinical prognosis of patients [5]. In addition, clinical studies have found that inflammation is importantly related to the occurrence and development of cardiovascular and cerebrovascular diseases such as stroke, and neutrophil lymphocyte ratio (NLR) is an emerging inflammatory response that can monitor systemic inflammation. The indicators have also been found to be related to AIS [6]. However, the current researches on AIS at home and abroad [7-8] mostly focus on its treatment methods, nursing measures, etc., and rarely study the relationship between NLR and AIS severity and prognosis. Therefore, this study conducted a study on 120 AIS patients admitted to our hospital from January 2018 to January 2020, aiming to explore the relationship between the severity of NLR and AIS and the clinical prognosis of patients receiving intravenous thrombolytic therapy. It provides a theoretical basis for delaying the disease progression of patients, reducing the risk of death and disability, and improving the prognosis. The report is as follows.

1. Materials and methods

1.1 General information

A total of 120 AIS patients admitted to our hospital from January 2018 to January 2020 were selected, including 79 males and 41 females. The age was 34-85, with an average age of 63.54±8.23 years; family history of AIS: 23 cases with family history and 97 cases without family history. According to the "Scoring Standards for the Degree of Clinical Neurological Impairment in Chinese Stroke Patients" [9], all patients were divided into mild AIS group (n = 54) and 16-30 were divided into moderate AIS group (n = 33), 31-45 were divided into severe AIS group (n = 33). According to the prognosis of intravenous thrombolysis, the patients were divided into a good prognosis group (n = 84) and a poor prognosis group (n = 36). All patients and their families were fully aware of the contents of this study and signed an informed consent form.

1.2 Inclusion criteria and exclusion criteria

Inclusion criteria: (1) All study subjects were diagnosed with AIS [10]; (2) Acute onset, no more than 4.5 hours from onset to consultation; (3) Non-intracranial hemorrhage confirmed by imaging examination; (4) Age over 18 years old; (5) Good compliance. Exclusion criteria: (1) history of severe brain trauma or stroke; (2) head CT and other imaging examinations for pathological brain diseases such as intracranial hemorrhage and vascular malformation; (3) combined with other organ diseases or loss of function; (4) Accompanied by coagulation disorders; (5) There is a history of brain or spinal canal related surgery within one month before admission.

1.3 Intravenous thrombolytic therapy

After admission, all patients undergo neurological physical examinations, blood tests, CT examinations, establishment of venous channels, ECG monitoring and other routine intravenous thrombolytic treatments to prepare and instruct the patients to defecate.

The specific method of intravenous thrombolysis: Dissolve 1 million-1.5 million u of urokinase (Wuhan Hualong Biopharmaceutical Co., Ltd., National Medicine Zhunzi H42021603, specification 10IU) in 100-200 ml of sodium chloride solution (Sinopharm Rongsheng Pharmaceutical Co., Ltd. In the company, National Medicine

Standard H20044024, specification 10ml: 0.9%), intravenous drip is used, and the patient can be guaranteed that the drip can be completed within half an hour. After the instillation is completed, the patient remains to be observed for 10-20 minutes. If the patient's clinical symptoms have not been significantly relieved, intravenous supplementation of urokinase is performed. Dissolve 200,000-500,000 u of urokinase in 100 ml of sodium chloride solution and keep the intravenous infusion time within 10-30 minutes. The total amount of two intravenous drips of urokinase does not exceed 2 million u. After intravenous infusion of urokinase (end of thrombolysis), the patient will be given 500 ml of low-molecular dextran (Shanghai Changzheng Fumin Jinshan Pharmaceutical Co., Ltd., National Medicine Standard H31022786, specification: 250ml) intravenously, once a day, continuous treatment 10 day.

1.4 NLR detection method

All patients were collected 5 ml of venous blood on an empty stomach in the morning before intravenous thrombolysis treatment and 6 months after treatment, and blood analyzer (Beijing Haifuda Technology Co., Ltd., GRT-6000 model) and supporting reagents were used for routine blood examination. Inspection indicators include neutrophil count, neutrophil percentage, lymphocyte count, lymphocyte percentage, and NLR calculation in peripheral blood.

1.5 Prognostic criteria

6 months after the end of intravenous thrombolytic therapy, at least two senior physicians (at least the attending physician level) used the modified Rankin scale (mRS) to score the prognosis of all patients. 1) Good prognosis: No more than 2 points; 2) Poor prognosis: 3-6 points.

1.6 Observation indicators

(1) Comparison of peripheral blood neutrophil count and percentage, lymphocyte count percentage, and NLR level in three groups of patients with mild AIS, moderate AIS, and moderate AIS before treatment. (2) The relationship between NLR and AIS disease severity. (3) Comparison of peripheral blood neutrophil count and percentage, lymphocyte count percentage, and NLR level between the good prognosis group and the poor prognosis group 6 months after treatment. (4) The relationship between NLR and clinical prognosis after intravenous thrombolytic therapy.

1.7 Statistical processing

SPSS 22.0 statistical software was used to analyze the data. Among them, the measurement data conforming to the normal distribution are represented by ±s, the comparison between groups is by t test, the comparison between multiple groups is by analysis of variance; the count data is represented by n or %, and the data comparison is by $\chi 2$ test. Logistic regression analysis and Pearson correlation analysis were used to analyze the correlation between NLR and AIS disease severity. Logistic regression analysis and receiver operating characteristics (Receiver Operating Characteristics, ROC) area under curve (AUC) were used to analyze the relationship between NLR and clinical prognosis after intravenous thrombolysis. When $P < 0.05$, the difference is statistically significant.

2. Results

2.1 General information

Gender, age, family history of AIS, body mass index (Body Mass Index, BMI) and other general data of patients in the mild AIS group, moderate AIS group, and severe AIS group, as well as the good prognosis group and the poor prognosis group. In comparison, the differences were not statistically significant ($P > 0.05$), and they were comparable. See Table 1 and Table 2.

2.1.1 Comparison of peripheral blood neutrophil count and percentage, lymphocyte count percentage, and NLR level before treatment in patients of different severity

2.1.2 With the deepening of the severity of AIS, the neutrophil count, neutrophil percentage, and NLR in the peripheral blood of patients increased significantly, and the lymphocyte count and lymphocyte percentage decreased significantly. The difference was statistically significant ($P < 0.05$). Peripheral blood neutrophil count, neutrophil percentage, and NLR levels of patients in severe AIS group were significantly higher than those of mild AIS group and moderate AIS group, and lymphocyte count and lymphocyte percentage levels were significantly lower than those of mild AIS The difference between group and moderate AIS group was statistically significant ($P < 0.05$). See Table 3.

2.2 The relationship between NLR and AIS disease severity

Logistic results showed that neutrophil count, neutrophil percentage, and NLR were independent risk factors that affected the severity of the patient's disease, while lymphocyte count and lymphocyte percentage were protective factors ($P < 0.05$). The results of Pearson correlation analysis showed that there was a positive correlation

between NLR and AIS patients' disease severity, that is, the higher the NLR, the more severe the disease (P <0.05). See Table 4 and Table 5.

Table 1. **Comparison of general information of the three groups of patients**

		Mild AIS group (n =54)	Moderate AISgroup （n = 33）	Severe AISgroup （n = 33）	Statistics	Pvalue
Gender	Male	35	22	22	1.205	0.741
	Female	19	11	11		
Average age (years)		63.52±8.24	63.55±8.23	63.54±8.24	1.325	0.068
AIS Family history	Have	11	6	6	1.318	0.706
	No	43	27	27		
BMI（kg/m^2）		22.84±2.36	22.34±2.64	22.56±2.41	1.024	0.095

Table 2. **Comparison of general information of the two groups of patients**

		Good prognosis group （n = 84）	Poor prognosis group （n = 36）	Statistics	P value
gender	male	55	24	1.193	0.758
	Female	29	12		
Average age (years)		63.55±8.22	63.52±8.25	1.292	0.072
AIS Family history	Have	68	29	1.104	0.863
	No	16	7		
BMI（kg/m^2）		22.59±2.41	22.41±2.52	1.125	0.084

Table 3. **Comparison of peripheral blood neutrophil count and percentage, lymphocyte count percentage and NLR level before treatment in the three groups of patients (±s)**

	Mild AIS group (n = 54)	Moderate AIS group (n = 33)	Severe AIS group (n = 33)	Fvalue	Pvalue
Neutrophil count（10^9/L）	4.65±1.72	7.55±2.26 [a]	10.38±3.54 [a b]	9.352	0.001
Percentage of neutrophils（%）	64.71±10.12	74.39±12.72 [a]	83.25±6.12 [a b]	10.841	0.000
Lymphocyte count (109/L)	1.89±0.72	1.66±0.47 [a]	1.52±0.75 [a b]	8.143	0.002
Percentage of lymphocytes (%)	27.64±9.93	17.43±7.12 [a]	11.25±4.56 [a b]	10.025	0.000
NLR	2.81±1.43	5.07±2.73 [a]	9.36±4.25 [a b]	11.147	0.000

Note: Compared with the mild AIS group, a P <0.05; compared with the moderate AIS group, b P <0.05.

Table 4. **Logistic regression analysis table affecting the severity of disease in AIS patients**

Relevant factors	Regression coefficients	Standard error	Wald	P value	OR value（95%CI）
Neutrophil count	0.615	0.032	10.132	0.000	1.115（1.058~1.823）
Percentage of neutrophils	0.314	0.028	11.654	0.000	1.562（1.224~2.611）
Lymphocyte count	-1.021	0.327	11.307	0.000	0.155（0.064~0.412）
Lymphocyte percentage	-0.364	0.042	12.586	0.000	0.693（0.257~0.915）
NLR	0.672	0.008	15.217	0.000	2.106（1.887~3.085）

Table 5. **Correlation analysis of disease severity between NLR and AIS patients**

index		AISRating level
NLR	R value	0.617
	P value	0.012

2.2.1 Comparison of peripheral blood neutrophil count and percentage, lymphocyte count percentage and NLR level in patients with different prognosis 6 months after treatment

2.2.2 The peripheral blood neutrophil count, neutrophil percentage, and NLR levels in the good prognosis group were significantly lower than those in the poor prognosis group, and the lymphocyte count and lymphocyte percentage levels were significantly higher

than those in the poor prognosis group, and the difference was statistically significant (P <0.05). See Table 6.

Table 6. **Comparison of peripheral blood neutrophil count and percentage, lymphocyte count percentage and NLR level after treatment between the two groups (±s)**

	Good prognosis group （n =84）	Poor prognosis group （n = 36）	T value	P value
Neutrophil count（10^9/L）	4.78±1.42	6.34±2.58 [a]	9.574	0.001
Percentage of neutrophils（%）	68.35±5.12	76.53±8.72 [a]	12.149	0.000
Lymphocyte count（10^9/L）	1.75±0.56	1.57±0.45 [a]	10.811	0.000
Lymphocyte percentage（%）	23.74±5.02	14.61±4.12 [a]	13.129	0.000
NLR	3.42±1.03	5.05±1.79 [a]	11.257	0.000

NLR、The relationship between neutrophil count, lymphocyte count and clinical prognosis after intravenous thrombolytic therapy

Logistic results showed that neutrophil count, neutrophil percentage, and NLR were independent risk factors for poor prognosis in patients with AIS, and lymphocyte count and lymphocyte percentage were protective factors (P <0.05). See Table 7. Among them, NLR predicts the clinical prognosis of AIS patients after receiving intravenous thrombolytic therapy AUC=0.803, the best cut-off point is 2.75, the sensitivity is 75.36%, the specificity is 77.52%, AUC (95%CI) =0.803 (0.754 ~ 0.893) (P <0.05). see picture 1.

Table 7. **Logistic regression analysis table affecting the clinical prognosis of AIS patients after intravenous thrombolytic therapy**

Relevant factors	Regression coefficients	Standard error	Wald	Pv alue	ORvalue（95%CI）
Neutrophil count	0.423	0.107	14.129	0.000	1.621（1.302~1.957）
Percentage of neutrophils	0.221	0.024	17.241	0.000	1.132（1.081~1.282）
Lymphocyte count	-1.804	0.216	13.856	0.000	0.172（0.069~0.457）
Lymphocyte percentage	-0.253	0.035	20.145	0.000	0.829（0.684~0.961）
NLR	0.512	0.005	18.925	0.000	2.127（1.716~2.549）

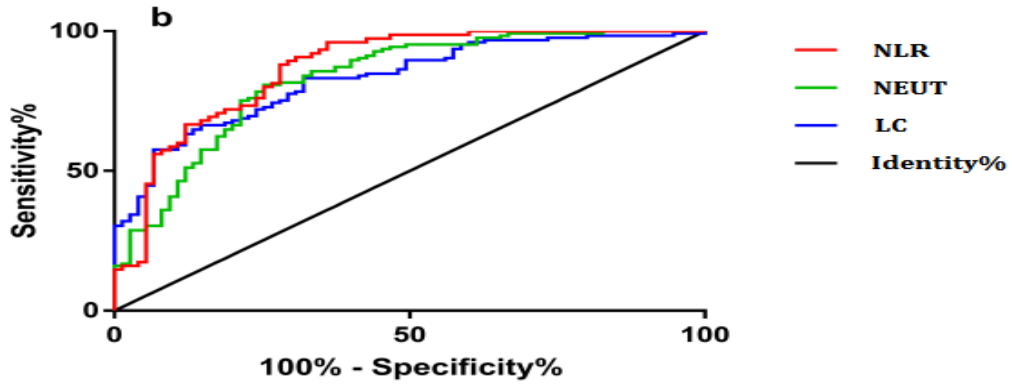

Figure 1. **ROC curve of NLR, neutrophil count, lymphocyte count predicting the occurrence of poor clinical prognosis in AIS patients receiving intravenous thrombolytic therapy. Neutrophil count (NECT), lymphocyte count (Lymphocyte count, LC), neutrophil to lymphocyte ratio (neutrophil to lymphocyte ratio, NLR).**

3. Discussion

AIS belong to the category of stroke, also known as acute cerebral infarction, 80% of which are classified as AIS [11]. AIS are mainly caused by the stenosis or partial stenosis of the carotid and vertebral arteries in the brain, and the lack of blood supply to the brain causes fracture and necrosis of the brain tissue [12]. Its main clinical manifestations are skewed mouth angles, weakness of limbs, slurred speech, etc. It is worldwide one of the

important diseases leading to death and severe disability [13]. The biological indicators include tumor necrosis factor alpha, C-reactive protein, procalcitonin, etc. instead of AIS sensitive biological indicators, but the detection of such indicators is usually cumbersome and difficult. In addition, the detection price is relatively high. In terms of clinical application, it is difficult to be widely applied [14]. Therefore, searching for highly sensitive and easy-to-detect markers is of great value for accurately assessing the severity of AIS and the prognosis of clinical treatment. It is found that NLR has high predictive value in cardiovascular disease risk assessment, and can be used as a reliable marker of acute myocardial infarction and related complications, and the detection cost and difficulty of operation are relatively reduced [15], while AIS and such heart There is a common feature of vascular disease, that is, the complication reaction involved in the occurrence and development of the disease [16]. Therefore, there may also be a correlation between NLR and AIS disease progression and prognosis.

NLR is used as an evaluation index of systemic immune status, and is associated with the prognosis of a variety of cancers and immunosuppressive diseases [17]. Jiao Xiu [18] scholars found that the ratio of platelets to lymphocytes and NLR are independent risk factors for the aggravation of AIS. They can be used as good indicators for predicting the severity of AIS and are positively correlated with the severity of the disease. An increase in the value of NLR can indicate the severity of AIS and increase the risk. Scholars such as Qiu Yuxia [19] found that serum albumin and NLR were significantly correlated with the severity of traumatic cerebral hemorrhage patients, and NLR was positively correlated with the disease grade score, and patients in the severe group had NLR on day 1, 3, and 7 both were significantly higher than the mild group and the moderate group. The results of this study showed that as the severity of AIS deepened, the blood neutrophil count, neutrophil percentage, and NLR increased significantly, and the lymphocyte count and lymphocyte percentage decreased significantly. The NLR level of patients in severe AIS group significantly higher than the mild AIS group and the moderate AIS group; NLR is an independent risk factor that affects the severity of the disease in patients. NLR is positively correlated with the severity of the disease in AIS patients, indicating that there is a significant correlation between NLR and the progression of AIS. As a predictor of the severity of the disease, the reasons may be: 1) When AIS occurs and transforms the disease to aggravation, vascular endothelial cells and white blood cells in the brain tissue activate each other to produce a large amount of oxygen free radicals, damage neurons, and destroy the blood-brain barrier aggravates the stress response and complication in the patient's body, and the stress state will cause the concentration of glucocorticoids and catecholamines to increase, which will greatly reduce the level of lymphocytes, increase the level of neutrophils, and cause the NLR to increase. The aggravation continues to expand; 2) Transformation into AIS progresses, and the stress state is aggravated, which affects the differentiation of hematopoietic differentiation, resulting in a decrease in the level of lymphocytes and an increase in the level of neutrophils. This is similar to the research of Jiao Xiu, Qiu Yuxia and other scholars.

Intravenous thrombolysis is a commonly used clinical treatment of AIS, mainly by opening bilateral cerebral blood vessels, dividing the infarct area, restoring blood circulation in the brain and brain neuron cells in a state of reversible damage, and reversing the axial penumbra [20]. Scholars such as Jin Jiamin [21] found that elevated NLR has a better predictive value for the poor prognosis of patients with cerebral infarction thrombolytic therapy, and the sensitivity is 69.8%, the specificity is 74.7%, and the AUC is 0.772. A study by Lu Su et al. [22] found that there is a significant correlation between NLR and poor neurological prognosis after intravenous thrombolysis in patients with AIS (OR = 3.74, 95% CI = 0.997-4.713). The results of this study showed that the NLR level of patients in the good prognosis group was significantly lower than that in the poor prognosis group. NLR is an independent risk factor for poor prognosis in AIS patients. NLR predicts the clinical prognosis of AIS patients after intravenous thrombolytic therapy. AUC = 0.803, the best cut-off point was 2.75, the sensitivity was 75.36%, the specificity was 77.52%, and AUC (95% CI) = 0.803 (0.754~0.893), indicating that NLR is significantly related to the clinical prognosis after AIS intravenous thrombolytic therapy, and it is useful for evaluating the prognosis of patients The higher the prediction accuracy, the higher the level, the higher the risk of poor prognosis. The reason may be that after intravenous thrombolytic therapy, the patient’s NLR increased, the level of lymphocytes decreased, and the level of neutrophils increased, resulting in immunosuppression, which stimulated a strong inflammatory response in the patient’s body, and the brain tissue needed to spend to produce

cytokines and cytokines. Two types of inflammatory factors cause leukocytes in the blood to penetrate into local brain tissues, and promote the activation of microglia and stellate cells, and further aggravate brain damage. In addition, symptomatic hemorrhage in the brain after thrombolytic therapy Transformation into anterior circulation cerebral infarction increases the risk of reperfusion injury, and re-implantation injury can produce a large amount of oxygen free radicals, which can damage the structure of the cerebral vascular membrane, resulting in a poor prognosis for the patient. This is similar to the research of Jin Jiamin and other scholars such as Lu Su.

In summary, NLR is an independent risk factor that affects the severity of the disease in patients with AIS and poor clinical prognosis after intravenous thrombolytic therapy, and is positively correlated with the severity of disease in AIS patients, and can more accurately predict intravenous thrombolytic therapy in patients. The post-clinical prognosis status can be widely used clinically.

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