ORIGINAL RESEARCH

Prognostic Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio in Acute Ischemic Stroke Patients After Thrombolysis

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ABSTRACT

Context • The neutrophil to lymphocyte ratio (NLR) or platelet to lymphocyte ratio (PLR) is an inflammation marker of acute ischemic stroke, but the predictive value of NLR and PLR before and after thrombolysis for short-term prognosis in acute ischemic stroke patients after thrombolysis remains largely obscure. This study attempts to clarify the predictive value of NLR and PLR before and after thrombolysis for short-term prognosis in acute ischemic stroke patients after thrombolysis.

Design • A retrospective study was carried out in the Affiliated Hospital of Hangzhou Normal University involving 120 patients visiting the neurology department of our hospital from May 2019 to October 2022 and meeting the selection criteria. The participants were assigned to the good prognosis group and the poor prognosis group based on the modified Rankin scale score. Laboratory data collected include NLR and PLR at admission as well as NLR and PLR collected from venous blood within 24 h after thrombolysis.

Results • Age, hyperlipidemia, atrial fibrillation, rheumatic heart disease, and National Institutes of Health Stroke Scale (NIHSS) scores after thrombolysis depicted statistical significance between both groups ($P < .05$). Hyperlipidemia, atrial fibrillation, and NIHSS scores before thrombolysis were independent risk elements for adverse prognosis ($P < .05$). NLR and PLR before and after thrombolysis in the poor prognosis group depicted an elevation relative to that in the good prognosis group ($P < .05$). The area under the curve of NLR or PLR predicting adverse prognosis after thrombolysis depicted an elevation relative to that before thrombolysis ($P < .05$).

Conclusion • The predictive value of NLR and PLR post-thrombolysis for short-term prognosis in acute ischemic stroke patients depicts an elevation relative to pre-thrombolysis; our study provides effective predictive indicators for short-term prognosis in acute ischemic stroke patients. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Acute ischemic stroke (AIS), also known as cerebral infarction, is infarction of brain tissue caused by occlusion of cerebral arteries, accompanied by injury of neurons, astrocytes, and oligodendrocytes, which is the most important vascular event of the central nervous system that causes death and disability in modern society.[1] AIS is the most common type of stroke, accounting for 69.6%-70.8% of strokes in China; the fatality rate of hospitalized AIS patients is 7.8%.[2] The guidelines suggest that if patients meet indications of intravenous thrombolysis and intravascular mechanical thrombectomy, they should first receive alteplase intravenous thrombolysis.[3] Alteplase, as a new thrombolytic drug, can not only strongly dissolve emboli in cerebral vessels, improve cerebral ischemia, and promote the recovery of blood perfusion, but it can also inhibit platelet aggregation and avoid thrombosis.[4] Thus, intravenous thrombolysis is the preferred method for vascular recanalization. Nevertheless, there are still some cases that have further worsened after undergoing thrombolytic therapy.

Inflammatory responses have attracted increasing attention, and multiple reports have validated that inflammatory response exerts a crucial role in the occurrence and development of ischemic stroke.[5-7] Research has demonstrated that neutrophil to lymphocyte ratio (NLR)

level at the time of admission is associated with short-term prognosis of AIS.[8,9] A report on the relationship of early neurological function prognosis and NLR or platelet to lymphocyte ratio (PLR) in AIS patients after thrombolysis depicted that NLR and PLR levels in early neurological function deterioration group depicted elevation relative to those in non-early neurological function deterioration group and early neurological function recovery group.[10] In this study, we have attempted to clarify the predictive value of NLR and PLR before and after thrombolysis for short-term prognosis in AIS patients after thrombolysis.

MATERIALS AND METHODS

Research subjects

The patients who met standards for inpatient therapy in the neurology department of our hospital from May 2019 to October 2022 received continuous collection. Inclusion criteria: In accordance with the diagnostic criteria of the *China Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in 2014*; recombinant tissue plasminogen activator (rtPA) therapy was carried out within 4.5 h post onset; patients or family member agreed and signed informed consent. Exclusion criteria: There was a clear history of infection within 1 week before onset or evidence of infection within 24 h post-thrombolysis; recurrent cerebral infarction patients with pre-onset modified Rankin scale (mRS) scores greater than 2 points; tumor patients; took anti-inflammatory and immunosuppressive drugs; pregnant or lactating women, allergic to the drug ingredients involved in this study; with severe liver damage.

A total of 120 cases meeting the criteria were assigned to the good prognosis group (mRS scores: 0-2 points) and the poor prognosis group (mRS scores: 3-6 points) according to mRS scoring criteria.[11] Good prognosis group: a total of 65 cases; 44 males and 21 females; aged 42-88 years; mean age: (63.80 ± 12.50) years. Poor prognosis group: a total of 55 cases; 36 males and 19 females; aged 37-95 years; mean age: (69.15 ± 10.77) years.

Data collection and measurement

General data (age and gender), cerebrovascular risk elements (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary heart disease, rheumatic heart disease, stroke history, smoking, and alcohol consumption), laboratory data, and National Institutes of Health Stroke Scale (NIHSS) scores before thrombolysis received collection. Laboratory data include NLR and PLR, and the method adopted is as follows: Fasting venous blood of the subjects was collected at admission and within 24 h after thrombolysis, and routine blood examination was performed by Sysmex XN-9000 blood analyzer (Sysmex, Japan). White blood cell count, neutrophil count, lymphocyte count, and platelet count were recorded, and NLR and PLR were calculated.

Alteplase intravenous thrombolytic method

For alteplase injection (Boehringer Ingelheim Pharma GmbH & Co. KG), the total dose was 0.9 mg/kg (maximum dose was 90 mg), of which 10% was injected intravenously within the first 1 min and the rest was continued intravenously for 60 min.

Statistical analysis

All data were statistically processed via SPSS 27.0 statistical software (International Business Machines Corporation, USA). Measurement data were exhibited as mean ± standard deviation ($\bar{x} \pm s$). The t test was adopted for comparison, and counting data were exhibited as rate (%), and the χ^2 test was performed for comparison. The risk elements related to the short-term prognosis of AIS patients after thrombolysis were analyzed using a logistic multivariate regression model. The predictive value of NLR and PLR before and after thrombolysis were analyzed via receiver operating characteristic (ROC) curves for adverse prognosis. The value of NLR and PLR in predicting unfavorable prognosis before and after thrombolysis were evaluated and compared via the area under the curve (AUC) of the ROC curves. All tests were conducted via a two-tailed test. The difference was statistically significant with $P < .05$.

RESULTS

Comparison of general clinical data and pretreatment neurological deficits between both groups

The age, hyperlipidemia, atrial fibrillation, rheumatic heart disease, and NIHSS scores after thrombolysis depicted statistical significance between both groups ($P = .043$, $P = .028$, $P = .005$, $P = .007$, and $P < .001$ respectively), as displayed in Table 1. However, no differences were discovered in gender, smoking, alcohol consumption, hypertension, diabetes mellitus, coronary heart disease, previous history of cerebral infarction, and previous history of stroke between both groups ($P = .796$, $P = .842$, $P = .391$, $P = .657$, $P = .807$, $P = .348$, $P = .507$, and $P = .293$ respectively).

Multivariate logistic regression analysis on the short-term prognosis of acute ischemic stroke patients after thrombolysis

The multivariate logistic regression model illustrated that hyperlipidemia ($P = .021$), atrial fibrillation ($P = .011$), and

Table 1. General Clinical Data and Pretreatment Neurological Deficits in Both Groups

General data	Good prognosis group	Poor prognosis group	χ^2/t	*P* value
Age (years)	63.80 ± 12.50	69.15 ± 10.77	2.070	.043
Gender (male/female)	44/21	36/19	0.067	.796
Smoking	20	16	0.040	.842
Alcohol consumption	12	7	0.735	.391
Hypertension	40	36	0.197	.657
Diabetes mellitus	13	12	0.060	.807
Hyperlipidemia	15	23	4.836	.028
Atrial fibrillation	14	25	7.768	.005
Coronary heart disease	4	6	0.882	.348
Rheumatic heart disease	1	8	7.265	.007
Previous history of cerebral infarction	10	11	0.440	.507
Previous history of stroke	2	4	1.104	.293
NIHSS scores before thrombolysis	7.22 ± 3.05	14.61 ± 6.92	7.780	<.001

Abbreviation: NIHSS, National Institute of Health Stroke Scale.

NIHSS scores before thrombolysis ($P < .001$) were independent risk elements for adverse prognosis (Table 2). However, age and rheumatic heart disease were not independent risk elements for adverse prognosis ($P = .514$ and $P = .079$).

Comparison of NLR and PLR before and after thrombolysis

The median NLR before thrombolysis in the good prognosis group and poor prognosis group were (3.68 ± 1.52) and (5.22 ± 2.04) respectively, illustrating statistical significance ($P < .001$). The median NLR after thrombolysis in the good prognosis group and poor prognosis group were (3.79 ± 1.11) and (7.05 ± 2.69) respectively, illustrating statistical significance ($P < .001$). The median PLR before thrombolysis in the good prognosis group and poor prognosis group were (130.30 ± 47.23) and (154.07 ± 51.88) respectively, illustrating statistical significance ($P = .026$). The median PLR after thrombolysis in the good prognosis group and poor prognosis group were (139.16 ± 41.83) and (207.95 ± 54.97) respectively, illustrating statistical significance ($P < .001$), as displayed in Table 3.

The predictive value of NLR and PLR before and after thrombolysis for adverse prognosis

AUC (95% CI) of pre-thrombolytic NLR is 0.685 (0.599-0.772), post-thrombolytic NLR is 0.807 (0.734-0.879), pre-thrombolytic PLR is 0.632 (0.543-0.721), and post-thrombolytic PLR is 0.795 (0.724-0.866), respectively (Figure 1). The AUC of NLR predicting adverse prognosis of patients after thrombolysis showed a statistically significant increase relative to that before thrombolysis ($P = .034$). Similarly, the AUC of PLR predicting adverse prognosis in patients after thrombolysis also showed an increase relative to that before thrombolysis, illustrating statistical significance ($P < .001$), as displayed in Table 4.

DISCUSSION

In AIS patients undergoing alteplase intravenous thrombolysis, there are some cases with adverse prognoses after intravenous thrombolysis. Thus, clarifying risk elements and predictive indicators of neurological deterioration in AIS patients after thrombolysis is of great significance. Multiple known factors, such as advanced age, diabetes, a longer time window of onset, and a higher baseline NIHSS scores at the time of admission, can affect the clinical outcomes of AIS patients post intravenous thrombolysis. It has been reported that a history of hypertension and diabetes, long duration from onset to thrombolysis, and quite high NIHSS scores pre-thrombolysis are major elements affecting the early efficacy of intravenous thrombolysis.[12] Herein, the multivariate logistic regression model illustrated that hyperlipidemia, atrial fibrillation, and NIHSS scores before thrombolysis were independent risk elements for adverse prognosis, indicating that hyperlipidemia, atrial fibrillation, and pre-thrombolytic NIHSS scores may possess independent relation to the occurrence of short-term adverse prognosis post-thrombolysis, which is consistent with previous studies.[13,14]

Table 2. Analysis of Short-Term Prognosis of Acute Ischemic Stroke Patients After Thrombolysis

Factors	χ^2	*P* value
Age (years)	0.427	.514
Hyperlipidemia	5.345	.021
Rheumatic heart disease	3.078	.079
Atrial fibrillation	6.481	.011
NIHSS scores before thrombolysis	53.368	<.001

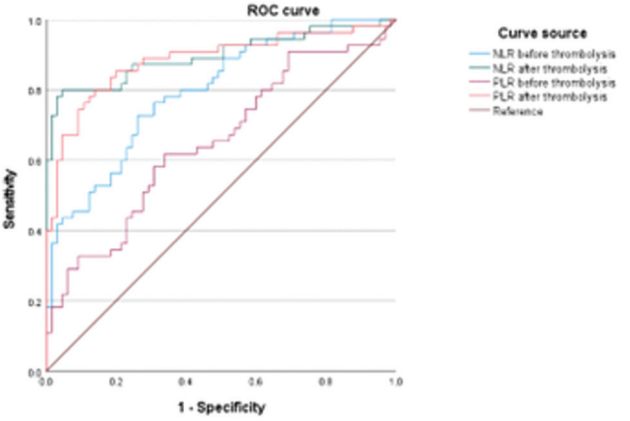
Abbreviation: NIHSS, National Institute of Health Stroke Scale.

Table 3. NLR and PLR Before and After Thrombolysis

Groups	Good prognosis group	Poor prognosis group	*t*	*P* value
NLR before thrombolysis	3.68 ± 1.52	5.22 ± 2.04	6.020	<.001
NLR after thrombolysis	3.79 ± 1.11	7.05 ± 2.69	9.176	<.001
PLR before thrombolysis	130.30 ± 47.23	154.07 ± 51.88	2.281	.026
PLR after thrombolysis	139.16 ± 41.83	207.95 ± 54.97	8.092	<.001

Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Figure 1. ROC Curve of NLR and PLR Before and After Thrombolysis Predicting Adverse Prognosis



Abbreviation: ROC, Receiver Operating Characteristic

Table 4. AUC of NLR and PLR Before and After Thrombolysis Predicting Adverse Prognosis

Groups	AUC		χ^2	*P* value
	Before thrombolysis	After thrombolysis		
NLR	0.795	0.898	4.487	0.034
PLR	0.651	0.884	14.713	<.001

Abbreviations: AUC, area under curve; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Inflammatory responses participate in the entire process of ischemic events and cause endothelial damage. Under recruitment of inflammatory mediators, white blood cells infiltrate and aggregate in ischemic brain tissue, directly damaging brain tissue; activation of endothelial cytokines and release of inflammatory cytokines directly damage vascular endothelium, causing vascular contraction and further exacerbating tissue ischemia, hypoxia, and necrosis. Inflammatory response exerts a vital role in AIS occurrence and development. After ischemic brain injury, neutrophils are the earliest inflammatory cells to migrate to the ischemic area, secreting inflammatory mediators, and leading to elevated damage to the ischemic area.[15] Thrombosis can receive induction through different mechanisms, such as

interactions with platelets or coagulation cytokines, and release of proteases.[16] Platelets can facilitate secretion and release of immune mediators, secrete vascular adhesion cytokines, chemokines, etc. by acting on the white blood cells and endothelial cells, and can mediate adhesion and migration of monocytes, jointly causing vascular lesions in the body.[17] Gary et al. have demonstrated that elevation of platelet count may lead to the increase of blood viscosity and facilitate inflammation. Additionally, it is also linked to the formation of atherosclerotic plaque.[18] The elevation in lymphocyte count may have a negative association with systemic inflammatory response.[19] Nevertheless, NLR and PLR can provide richer information and exert a greater role in predicting unfavorable prognosis in AIS patients.[20]

NLR is associated with the prognosis of ischemic stroke patients undergoing intravenous thrombolysis.[21] NLR is a predictive marker for adverse prognosis at 90 days in AIS patients receiving intravenous thrombolysis or intravascular stroke therapy.[22] A meta-analysis has illustrated that in AIS patients undergoing reperfusion, NLR level elevation possessed a positive correlation with symptomatic intracranial hemorrhage transformation, adverse prognosis at 3 months, and mortality at 3 months.[23] Neutrophil or lymphocyte counts change over time after acute cerebral infarction,[24] indicating that NLR and PLR levels vary at different periods after the onset of acute cerebral infarction. Research has depicted that NLR post-thrombolysis has greater clinical significance in predicting prognosis relative to NLR pre-thrombolysis.[25] Herein, NLR before and after thrombolysis in the poor prognosis group depicted an elevation relative to that in the good prognosis group, and the AUC of NLR predicting adverse prognosis after thrombolysis depicted an elevation relative to that before thrombolysis, suggesting that NLR post-thrombolysis has a greater value in predicting adverse prognosis of patients relative to NLR before thrombolysis, which is consistent with previous findings.

In recent years, PLR has become a novel inflammatory marker. High-level PLR has an association with the adverse prognosis of cardiovascular events.[26] Research has depicted that low lymphocyte count and high platelet count can facilitate further development of atherosclerosis.[27] PLR can facilitate atherosclerosis occurrence and development, and atherosclerosis is considered an independent risk element of ischemic cerebrovascular disease. Previous reports have demonstrated a close relationship between peripheral blood PLR and the prognosis of diseases such as angina pectoris and myocardial infarction.[28] Herein, PLR before and after thrombolysis in the poor prognosis group depicted an elevation relative to that in the good prognosis group, and the AUC of PLR predicting adverse prognosis after thrombolysis depicted an elevation relative to that before thrombolysis, which may suggest that PLR post-thrombolysis has a greater value in predicting adverse prognosis of AIS patients relative to pre-thrombolysis. It can provide a predictive marker for evaluating nervous system deterioration in AIS patients post-thrombolysis, helping clinical doctors evaluate the risks of short-term adverse prognosis in such a population. Consistently, Gong et al. have indicated that elevated levels of NLR may predict post-thrombolysis early neurological deterioration in AIS patients.[29] Chen et al. have discovered that both NLR and PLR are independent predictors of 3-months functional outcomes of AIS.[30]

There are some limitations to this study. First of all, the data in this study came from the same hospital, and there was selectivity bias. Second, the study sample size is small. In addition, the follow-up time of AIS patients after thrombolysis was short. Therefore, in future research, it is necessary to expand the sample size and conduct multicenter trials for an improved assessment of the predictive value of NLR and PLR before and after thrombolysis for short-term prognosis of AIS patients post-thrombolysis.

In conclusion, the predictive value of NLR and PLR post-thrombolysis for short-term prognosis in AIS patients depicts an elevation relative to pre-thrombolysis, indicating that NLR and PLR post-thrombolysis may serve as effective predictive indicators for short-term prognosis in AIS patients.

AUTHOR DISCLOSURE STATEMENT

No conflict of interest exists for this study.

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Zhaoyang Ruan and Dongying Wang have contributed equally to this work.

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