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The expression of peripheral blood inflammatory factors in patients with acute ischemic stroke and its correlation with patients' prognosis

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ABSTRACT

This study aimed to determine the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) in patients with acute ischemic stroke (AIS) and their correlation with the patients' prognosis. For this purpose, a total of 100 patients with AIS admitted to the neurology department of our hospital between March 2019 and February 2022 were selected as the AIS group, and all patients were treated with recombinant tissue plasminogen activator (rtPA) intravenous thrombolysis. According to the Modified Rankin Scale (mRS) scores three months after thrombolysis, patients in the AIS group were grouped into a favourable group (mRS score: 0-2 points) and an unfavourable group (mRS score: 3-6 points). Additionally, 100 healthy individuals who received physical examination over the same time span were enrolled into a health group. The NLR and PLR of each group were compared, and receiver operating characteristic (ROC) curves were drawn to analyze the predictive value of separate tests of NLR and PLR and joint tests of them for unfavourable prognosis of AIS patients who received thrombolytic therapy. Logistic regression analysis was conducted to understand the influencing factors of unfavourable prognosis of the AIS patients who received thrombolytic therapy. The results indicated that the AIS group exhibited significantly higher NLR and PLR levels compared to the health group. The unfavourable group showed notably higher NLR and PLR than the favourable group. Lymphocytes, NLR and PLR were independent risk factors for predicting the prognosis of AIS patients who received thrombolytic therapy. Additionally, NLR and PLR had high diagnostic efficiency in predicting patients' adverse prognoses, and the diagnostic efficiency of their combination is higher than that of single detection. In conclusion, NLR and PLR have certain predictive values for the prognosis of AIS patients who received thrombolytic therapy, and they can serve as indicators for disease monitoring and prognosis evaluation of AIS patients.

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Introduction

Stroke is the primary cause of disability and death worldwide (1). China is the country with the heaviest burden of stroke worldwide, and its incidence is still rising in the past decades (2). Acute ischemic stroke (AIS) is the most frequently seen type of stroke, accounting for 80% of all kinds of stroke, which brings a heavy burden to society and the economy (3). Currently, thrombolytic therapy is the most effective treatment to restore the blood flow of patients, and recombinant tissue plasminogen activator (rtPA) is the most common thrombolytic drug (4). However, there is a lack of economic and effective laboratory indicators for prognosis prediction of patients after rtPA treatment.

In recent years, a growing number of studies have revealed strong correlations between the occurrence, development and prognosis of AIS with inflammatory reactions (5,6). Inflammation may induce secondary brain injury by aggravating blood-brain barrier(BBB) injury, microvascular failure, brain edema, oxidative stress and directly induce neuronal cell death (7). Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are frequently adopted indicators of systemic inflammation and infection (8). It is worth noting that some studies suggest that NLR and PLR probably have better predictive abilities than traditional inflammatory factors (9). Prior research has revealed an association between higher NLR and PLR with worse prognosis of AIS patients (10,11). However, the utilization of NLR and PLR for predicting the prognosis of AIS patients who received thrombolytic therapy is rarely reported.

Accordingly, this study was conducted to explore the clinical significance of NLR and PLR on the prognosis of AIS patients who received thrombolytic therapy. The results of this study may help clinicians to make better use of cheap and easily available indicators to predict the prognosis of AIS patients who received thrombolytic therapy, and make personalized prognosis and active plans accordingly.

Materials and Methods

Research objects

Totally 100 patients with AIS admitted to the neurology department of our hospital between March 2019 and

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February 2022 were selected as the AIS group, and all patients were treated with rtPA intravenous thrombolysis. According to the Modified Rankin Scale (mRS) scores three months after thrombolysis, patients were grouped into a favourable group (mRS score: 0-2 points) and an unfavourable group (mRS score: 3-6 points).

Inclusion criteria: Patients meeting the diagnostic criteria in the 2018 Chinese Guidelines for the Diagnosis and Treatment of AIS, patients who experienced < 4.5h from onset to admission, patients who received rtPA intravenous thrombolysis, patients with complete case data, patients who agreed to join the study and signed the informed consent form, and those > 18 years old.

Exclusion criteria: Patients comorbid with malignant tumor, autoimmune disease, coagulation dysfunction, or mental illness, patients comorbid with brain diseases, such as encephalitis, brain trauma, brain tumor, cerebral hemorrhage, etc., patients who took steroids or immunosuppressants in the past 3 months, patients who were allergic to rtPA, patients comorbid with serious diseases, patients whose expected survival time was less than 3 months, patients who suffered infectious diseases within 1 month before admission to the study. All participants signed the informed consent form, and this study was performed with permission from the Medical Ethics Committee of our hospital.

Methods

All patients were treated with 0.9mg/kg rtPA within 4.5h. First, 10% of the total dosage was given intravenously, and the remaining dosage was finished intravenously within 1 h. The general clinical data of the patients were collected, including age, sex, smoking history, hypertension, diabetes mellitus, past stroke history and the time from onset to thrombolytic therapy. Venous blood (5 ml) was acquired from each patient within 24 h after admission for routine blood tests and coagulation function analysis. White blood cell count, neutrophil count, lymphocyte count, platelet count and fasting blood glucose were detected, and NLR and PLR were calculated.

Statistical analyses

This study adopted SPSS23.0 for data analysis. Inter-group comparison of measurement data ($\bar{x}\pm SD$) was conducted using the t-test, and inter-group comparison of counting data (%) was performed using the χ^2 test. Logistic regression was conducted to analyze the influencing factors for the prognosis of patients with AIS. Logistic regression analysis was also conducted to understand influencing factors of unfavourable prognosis of AIS patients who received thrombolytic therapy. Pearson was used to analyze the correlations between NLR, PLR and mRS scores of AIS patients. P<0.05 implies a notable difference.

Results

NLR and PLR increased in AIS cases

Comparison of NLR and PLR between the health group and AIS group revealed notably higher NLR and PLR in the AIS group (P<0.05, Figure 1).

Comparison of clinical features between patients with favourable prognosis and those with unfavourable prognosis

After rtPA treatment, 45 patients had favourable prognoses and 29 patients had unfavourable prognosis. A comparison of the clinical features between the two groups revealed notable differences between them in neutrophils, lymphocytes, NLR and PLR (P<0.05, Table 1).

Analysis of influencing factors for patients' adverse prognosis

Logistic regression analysis was performed with the

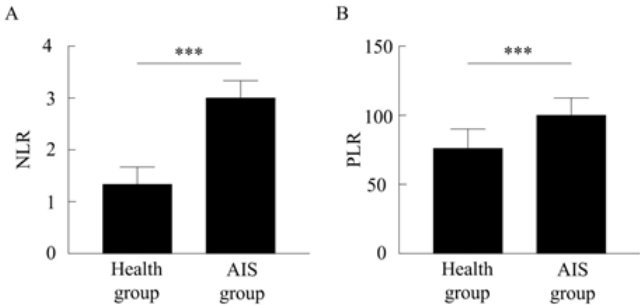

Figure 1. NLR and PLR increased in AIS cases. A: The AIS group showed a higher NLR than the health group. B: The AIS group showed a higher PLR than the health group. *** P<0.001.

Table 1. Comparison of clinical features between patients with favourable prognosis and those with unfavourable prognosis ($\bar{x}\pm sd$), [n(%)].

Group	Favourable group (n=71)	Unfavourable group (n=29)	χ^2/t	P
Male	46 (64.79)	16 (55.17)	0.808	0.369
Age (years)	62.14±9.56	63.11±7.45	0.489	0.626
Hypertension	38 (53.52)	17 (58.62)	0.216	0.642
Diabetes mellitus	29 (40.85)	7 (24.11)	2.494	0.114
History of smoking	40 (56.34)	15 (51.72)	0.177	0.674
Past history of stroke	20 (28.17)	9 (31.03)	0.082	0.774
Time from onset to thrombolysis (min)	122.48±20.76	130.75±22.48	1.765	0.081
White blood cells ($\times10^9$/L)	6.67±1.12	7.11±1.04	1.819	0.072
Neutrophils ($\times10^9$/L)	5.03±1.86	6.58±1.66	3.896	<0.001
Lymphocyte ($\times10^9$/L)	1.86±0.59	1.36±0.68	3.677	<0.001
Platelet ($\times10^9$/L)	178.93±18.65	184.77±19.66	1.399	0.165
Fasting blood glucose (mmol/L)	5.96±1.01	6.11±0.89	0.697	0.488
NLR	2.86±0.56	3.56±0.63	5.468	<0.001
PLR	95.68±11.45	118.46±12.14	8.872	<0.001

patient's prognosis as the dependent variable and the influencing factors of P<0.05 in Results 2.1 as the independent variable. The results showed that lymphocytes, NLR and PLR were independent risk factors for prognosis prediction of AIS patients who received thrombolytic therapy (Table 2).

Predictive value of NLR and PLR for adverse prognosis of AIS patients who received thrombolytic therapy

A receiver operating characteristic (ROC) curve (Figure 2) for the diagnostic value of each index to the patient's unfavourable prognosis was drawn. According to the results, NLR and PLR had high diagnostic efficiency in predicting patients' adverse prognoses, and the diagnostic efficiency of their combination was higher than that of single detection (Table 3 and Figure 2).

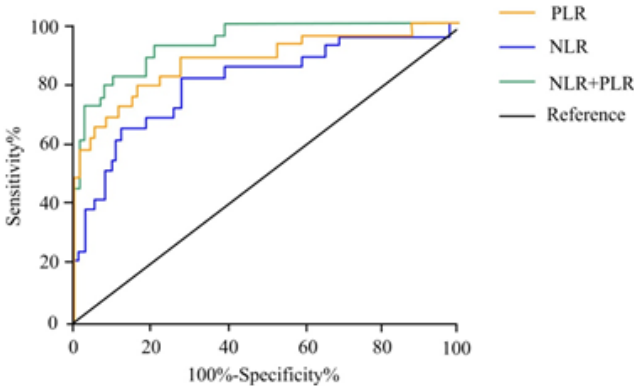

Figure 2. ROC curve.

Correlation analysis of NLR, PLR and prognosis of patients

Pearson correlation analysis revealed positive associations of NLR and PLR with mRS scores (P<0.001, Figure 3).

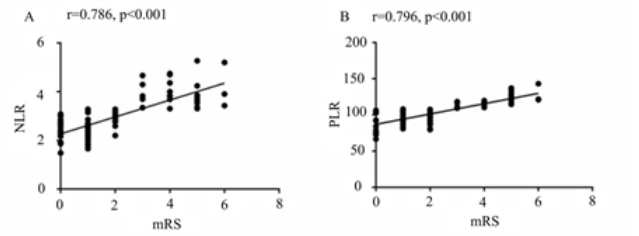

Figure 3. Correlation analysis of NLR, PLR and prognosis of patients A: NLR was positively associated with mRS score. B: PLR was positively associated with the mRS score.

Discussion

Immunity and inflammation are considered to be the key factors of stroke pathology. The immune process involves all stages of acute stroke, including initial arterial occlusion, brain parenchyma injury, subsequent tissue repair and infectious complications (12). It has become the main direction to detect immune inflammation-associated indicators as the severity of AIS to evaluate the prognosis. A growing number of studies have verified the association of neutrophils with thrombosis. Neutrophils can induce various toxic proteases such as histone, elastase and myeloperoxidase, thus damaging endothelial cells and increasing vascular permeability (13). Neutrophils will be activated immediately after stroke, which may result in massive infarction, destruction of BBB and hemorrhagic transformation (14). With the ability to regulate inflammation and immune response, platelets take a crucial part in arterial circulation thrombosis (15). The interaction between platelets and vascular endothelial cells can induce local inflammation of blood vessels and trigger microcirculation disturbance, thus promoting the gradual progress of atherosclerosis (16). Additionally, excessive platelet activity may trigger thrombosis and vascular obstruction, which in turn leads to AIS (17). Lymphocytes, produced by lymphoid organs, are important cellular components of the body's immune response (18). The decrease in the number of lymphocytes reflects the pathological stress state of the body, and a low count of it indicates unfavourable prognosis (19). NLR and PLR are compound ratios of different inflammatory parameters, so they may be able to provide more information about immune activities during the onset of ischemic stroke. Secondly, the ratios are more stable than a single blood parameter that may be affected by multiple variables, such as dehydration, overhydration and blood sample treatment (20). In addition, they are convenient and inexpensive because they can be calculated from the blood cell count.

In recent years, a growing number of studies have found greatly increased NLR and PLR in the stroke population, and have also revealed strong associations between the poor prognosis of stroke patients with relatively high NLR and PLR. For example, some research results show that high NLR indicates that AIS patients receiving mechanical thrombectomy are more likely to have unfavourable prognoses (mRS score: 3-6 points) (21). Studies have also

Table 2. Logistic regression analysis of acute ischemic stroke after rtPA treatment.

Group	β	SE	Wald χ^2	P	OR	95% CI
Neutrophil	1.256	0.684	3.318	0.068	3.501	0.918- 13.478
Lymphocyte	0.654	0.279	5.275	0.022	1.924	1.083-3.325
NLR	0.587	0.216	5.432	0.002	1.185	1.078-3.012
PLR	0.690	0.257	7.231	0.007	1.192	1.201-3.289

Table 3. Predictive value of NLR and PLR for adverse prognosis of AIS patients who received thrombolytic therapy

Diagnostic index	AUC	95%CI	Standard error	Cut-off value	Sensitivity (%)	Specificity (%)
NLR	0.811	0.712-0.911	0.051	3.264	82.76	71.83
PLR	0.874	0.799-0.962	0.042	105.70	79.31	83.10
NLR+PLR	0.940	0.894-0.986	0.024	-	82.76	90.14

indicated that high NLR and PLR are independent risk factors for hemorrhagic transformation in AIS patients with large-artery atherosclerosis (22,23). In addition, relatively high NLR and PLR are bound up with reperfusion failure after endovascular treatment of AIS (10). In this study, the AIS group showed higher NLR and PLR than the health group, and the unfavourable group showed notably higher NLR and PLR than the favourable group. In addition, Logistic regression analysis revealed that NLR and PLR were independent risk factors for prognosis prediction of AIS patients who received thrombolytic therapy. According to Pearson correlation analysis, NLR and PLR were strongly positively correlated with mRS scores. Moreover, ROC curves were drawn. ROC curve-based analysis revealed that the area-under-the-curve (AUC) values of NLR, PLR and NLR+PLR for predicting the adverse prognosis of AIS patients who received thrombolytic therapy were 0.811, 0.874 and 0.940, respectively, which is similar to prior research. Chen et al. (24) revealed that the AUC values of NLR and PLR on the poor prognosis of AIS patients (mRS after 90 days: 3-6 points) were 0.776 and 0.697 respectively. Gong et al. (25) showed that the AUC values of NLR and PLR on the adverse prognosis of AIS patients (the increase of NIHSS score within 24h after thrombolysis is $\geq$ 4 points) are 0.763 and 0.703 respectively. The results indicate that NLR and PLR can serve as biomarkers for poor prognosis prediction of AIS patients who received thrombolytic therapy, and their combined prediction effect is more effective.

The study has some limitations. First of all, this study has been conducted only in a single center of our hospital, and there are not many research subjects recruited, which results in some limitations in the results. It is imperative to conduct a more extensive multi-center study on AIS patients to further improve the reliability of the results. Secondly, NLR and PLR values are collected only once after thrombolytic therapy, but dynamic changes may occur during the development of AIS. Moreover, there is more than one neurologist who evaluates the severity of patients, which may cause bias in the evaluation of mRS, even though these neurologists had received standardized training. It is hoped that these limitations can be addressed in the follow-up research.

To sum up, NLR and PLR greatly increase in AIS patients, and high NLR and PLR indicate the unfavourable prognosis of AIS patients who received thrombolytic therapy. The two are promising to be biological indicators for prognosis prediction of AIS patients who received thrombolytic therapy.

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