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ORIGINAL RESEARCH

Relationship between peripheral blood inflammation indicators and short-term adverse outcomes in patients with acute ischemic stroke treated with intravenous thrombolysis

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Abstract

This study aimed to assess the correlation between neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and systemic immunoinflammatory index (SII) levels, and short-term prognosis in patients with acute ischemic stroke (AIS) undergoing intravenous thrombolysis with alteplase (rt-PA), and to develop a nomogram model for short-term prognosis prediction. The study collected data from cases of first-episode ischemic stroke treated with intravenous thrombolysis at Wuxi People's Hospital. Patients were categorized into either a poor prognosis group (n = 78) or a good prognosis group (n = 119) based on the modified Rankin Rating Scale score 30 days post-treatment. The results showed that peripheral blood levels of NLR, PLR and SII were significantly elevated in the poor prognosis group compared to the good prognosis group ($p < 0.05$). Receiver operating characteristic (ROC) curve analysis revealed that the area under the curves (AUC) of NLR, PLR and SII for predicting poor prognosis of intravenous thrombolytic therapy in AIS patients were 0.674, 0.770 and 0.779, respectively. Multivariate regression analysis identified blood glucose concentration, pre-thrombolysis National Institutes of Health Stroke Scale (NIHSS) score, prothrombin time (PT), activated partial thromboplastin time (APTT), and SII as independent influencing factors for poor prognosis of intravenous thrombolytic therapy in AIS patients ($p < 0.05$). A nomogram model based on these seven independent influencing factors yielded an AUC of 0.929, with calibration curve and Hosmer-Lemeshow test ($\chi^2 = 2.654$, $p = 0.954$) confirming the model's good fit. Decision analysis curves demonstrated the clinical benefit of utilizing predictive models in aiding clinical decision-making. In conclusion, peripheral blood systemic inflammatory marker SII was identified as a risk factor for poor short-term prognosis in patients treated with intravenous thrombolysis. The constructed nomogram incorporating inflammatory clinical features exhibited efficient and promising clinical utility in predicting early prognosis of AIS patients treated with rt-PA thrombolysis.

Keywords

Alteplase; Intravenous thrombolysis; Acute ischemic stroke; Indicators of peripheral blood inflammation; Nomogram

1. Introduction

Acute ischemic stroke (AIS) is currently one of the most common causes of mortality and a significant contributor of disability worldwide [1]. Its high incidence, mortality rates, and propensity for recurrence place substantial economic burdens on society and families. Intravenous thrombolysis with tissue-type plasminogen activator (rt-PA) is the primary intervention for restoring blood-brain circulation and is widely recognized as effective for AIS treatment [2]. Early administration of intravenous thrombolytic therapy is crucial for reducing mortality and disability in AIS patients. However, despite its benefits, approximately two-thirds of patients fail to benefit from intravenous thrombolysis, and some may experience worsening due to post-thrombolysis hemorrhagic transformation, which hampers neurological recovery [2]. Thus, there is a pressing need to identify easily accessible biomarkers for accurately predicting patient prognosis following rt-PA thrombolysis.

Peripheral blood systemic inflammation markers, including the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and systemic immunoinflammatory index (SII), are presently among the most accessible biomarkers in clinical

diagnostics [3]. In recent years, substantial progress has been made in utilizing MLR, NLR, PLR and SII as valuable indicators for predicting disease progression and guiding interventions. These markers have demonstrated significant clinical utility in predicting outcomes such as cerebral hemorrhage, cerebral ischemia and myocardial infarction [4]. However, the relationship between peripheral blood systemic inflammatory markers and intravenous thrombolytic therapy outcomes in AIS patients, particularly regarding short-term prognosis, remains relatively understudied.

This study aimed to investigate the correlation between NLR, PLR and SII levels and short-term prognosis in AIS patients undergoing intravenous thrombolysis with rt-PA. Additionally, it aimed to evaluate the diagnostic accuracy of these markers in predicting patient prognosis. Furthermore, the study analyzed factors influencing short-term prognosis in AIS patients and developed a nomogram model for predicting such prognosis. The results could offer a reliable and simple prediction approach for predicting the short-term prognosis of AIS patients.

2. Materials and methods

2.1 Patients

The data of patients diagnosed with AIS and treated with rt-PA intravenous thrombolysis were retrieved and assessed. As an enrollment criteria, the patients were required to have received treatment within 4.5 hours of hemorrhage onset, as confirmed by cranial Computed Tomography (CT).

The study included patients who met the following criteria: (1) diagnosis according to the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischaemic Stroke 2018; (2) experiencing the initial onset of the disease; (3) undergoing standardized intravenous thrombolytic therapy with rt-PA within 4.5 hours of symptom onset; (4) aged between 18 and 80 years; and (5) providing informed consent after receiving all relevant information. Patients with any of the following exclusion criteria were not included: (1) presence of comorbid neurological diseases; (2) prior intracranial vascular intervention; (3) concurrent serious systemic illnesses before hospitalization; and (4) lack of formal follow-up for secondary prevention of cerebral infarction post-hospital discharge, including inadequate management of risk factors (such as blood pressure, glucose-lipid metabolism, and smoking cessation), as well as failure to adhere to antiplatelet and antithrombotic drug regimens.

2.2 Data collection

Baseline data such as age, gender, smoking history, alcohol consumption, diabetes history, hypertension history, atrial fibrillation presence, blood glucose concentration, time from symptom onset to intravenous thrombolysis, pre-thrombolysis National Institutes of Health Stroke Scale (NIHSS) score, prothrombin time (PT), activated partial thromboplastin time (APTT), white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM) and platelet count (PLT), were assessed. Additionally, NLR, PLR and SII were calculated as follows: NLR = NEU/LYM; PLR = PLT/LYM; SII = PLT $\times$ (NEU/LYM).

2.3 Clinical outcome

Two experienced researchers assessed each patient's short-term prognosis using the modified Rankin Rating Scale (mRS). A favorable prognosis was characterized by an mRS score of $\leq$2 three months after thrombolytic therapy, while an unfavorable prognosis was indicated by an mRS score of $>$2 after three months of thrombolytic therapy, stroke recurrence or death.

2.4 Statistical analysis

All statistical analyses were performed using SPSS (IBM Corp., SPSS Statistics, Armonk, NY, USA) and R 4.3.2 statistical software. Normally distributed measurement data are presented as mean $\pm$ standard deviation, with the Student's *t*-test employed for intergroup comparisons. Non-normally distributed measurement data were expressed as median (quartiles) (M (P25, P75)), and between-group comparisons were conducted using the Mann-Whitney U test. Categorical data are presented as percentages, and intergroup comparisons were assessed using the χ^2 test. Univariate and multivariate logistic regression analyses were conducted to identify characteristic indicators influencing the short-term prognosis of rt-PA intravenous thrombolytic therapy in AIS patients. A nomogram prediction model was constructed based on the identified characteristic indicators. Receiver operating characteristic (ROC) curves, calibration curves, and decision curves were generated separately to evaluate the model's efficacy. A significance level of $p < 0.05$ was considered statistically significant.

3. Results

3.1 Baseline characteristics

Among the 207 AIS patients treated with rt-PA included in the observational cohort, there was one death attributed to cerebral hemorrhage post-intravenous thrombolysis with rt-PA, two deaths due to cerebral herniation, three instances of stroke recurrence, and four missed follow-up visits. Consequently, data from 197 patients were retrieved and assessed, comprising 78 cases with poor prognosis and 119 cases with good prognosis. No statistically significant differences were observed between the two groups regarding age, smoking history, presence of atrial fibrillation, adverse events, platelet count, red blood cell count, and hemoglobin concentration ($p > 0.05$, Table 1). Conversely, compared to the good prognosis group, the poor prognosis group comprised a higher proportion of males, a greater prevalence of alcohol consumption history, diabetes mellitus, and hypertension, as well as a higher pre-thrombolysis NIHSS score. Additionally, the poor prognosis group demonstrated relatively elevated glucose concentration, longer time interval between symptom onset and thrombolytic therapy initiation, and shorter PT and APTT ($p < 0.05$, Table 1).

3.2 Indicators of systemic inflammation in peripheral blood

The peripheral blood levels of NLR, PLR and SII were significantly higher in patients in the poor prognosis group compared to the good prognosis group ($p < 0.05$, Table 2). ROC curve analysis (Fig. 1) revealed that the area under curves (AUC) for predicting poor prognosis of intravenous thrombolytic therapy in AIS patients were 0.674 (95% CI: 0.588–0.761) for NLR, 0.770 (95% CI: 0.700–0.840) for PLR, and 0.779 (95% CI: 0.715–0.843) for SII. Correlation analysis demonstrated a significant positive correlation between NLR and PLR ($p < 0.05$, Fig. 2), while no significant correlation was observed between NLR and SII ($p > 0.05$, Fig. 2). Additionally, PLR exhibited a significant positive correlation with SII ($p < 0.05$, Fig. 2).

3.3 Univariate and multivariate logistic regression analysis

Univariate regression analysis revealed that gender, history of alcohol consumption, blood glucose concentration, time interval from symptom onset to receiving thrombolytic therapy, pre-thrombolysis NIHSS score, PT, APTT, NLR, PLR and SII were significantly associated with poor prognosis of intravenous thrombolytic therapy in AIS patients ($p < 0.05$, Table 3). However, multicollinearity testing indicated a multicollinearity issue between NLR, PLR and SII. Therefore, NLR and PLR were excluded, with only SII retained in the multivariate regression model. Multivariate regression analysis demonstrated that blood glucose concentration, onset-to-thrombolysis time, pre-thrombolysis NIHSS score, PT, APTT and SII were independent factors associated with poor prognosis following intravenous thrombolytic therapy in patients with AIS ($p < 0.05$, Table 3).

3.4 Construction of the nomogram model

A nomogram was constructed using the "rms" analysis package in R statistical software, and the predictive model generated by multivariate logistic regression analysis was visualized and discriminated (Fig. 3). In clinical practice, physicians can

TABLE 1. Baseline characteristics.

Characteristics	Good prognosis group (n = 119)	Poor prognosis group (n = 78)	t/χ^2	p
Age (yr)	68.18 ± 10.09	67.69 ± 8.75	0.347	0.729
Gender				
Male	59	66	24.939	<0.001
Female	60	12		
Smoking	68	55	3.591	0.058
Drinking Alcohol	45	61	30.925	<0.001
Diabetes	64	60	10.818	0.001
Hypertension	57	60	16.457	<0.001
Atrial fibrillation	11	6	0.144	0.705
pre-thrombolysis NIHSS score	7.83 ± 3.13	11.09 ± 4.15	6.269	<0.001
Blood glucose concentration (mmol)	7.90 ± 3.07	8.91 ± 2.85	2.319	0.021
Time from onset to thrombolysis (min)	130.55 ± 47.44	148.72 ± 48.66	2.602	0.010
Adverse effects	14	8	0.108	0.742
PT (s)	12.07 ± 1.00	11.13 ± 1.07	6.268	<0.001
APTT (s)	33.93 ± 6.30	28.59 ± 6.47	5.762	<0.001
Red Blood Cell Count ($\times 10^{12}$/L)	4.40 ± 0.51	4.42 ± 0.59	0.176	0.860
Hemoglobin (g/L)	136.67 ± 14.72	135.45 ± 15.21	0.560	0.576
WBC	6.53 ± 1.28	6.80 ± 1.15	1.505	0.134

NIHSS: National Institutes of Health Stroke Scale; PT: prothrombin time; APTT: activated partial thromboplastin time; WBC: white blood cell count.

TABLE 2. Indicators of systemic inflammation in peripheral blood.

Indicators	Good prognosis group (n = 119)	Poor prognosis group (n = 78)	t	p
NLR	2.97 ± 1.12	4.04 ± 2.01	4.980	<0.001
PLR	8.76 ± 3.96	12.99 ± 3.79	7.466	<0.001
SII	636.71 ± 274.91	994.55 ± 397.16	7.474	<0.001

NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic immunoinflammatory index.

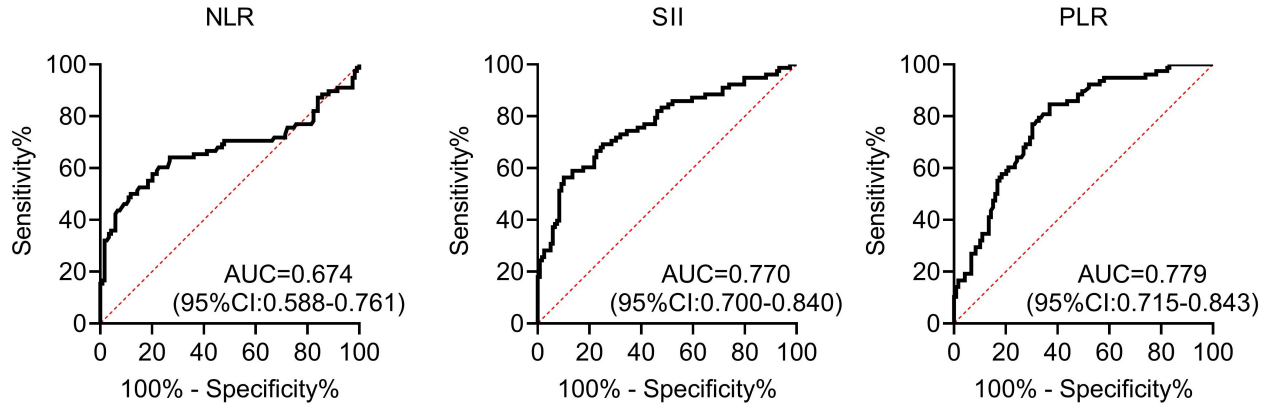

FIGURE 1. ROC curve illustrating the predictive performance of peripheral blood inflammation indexes for poor prognosis following intravenous thrombolytic therapy in patients with acute ischemic stroke. NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic immunoinflammatory index; AUC: area under the curves; CI: confidence interval.

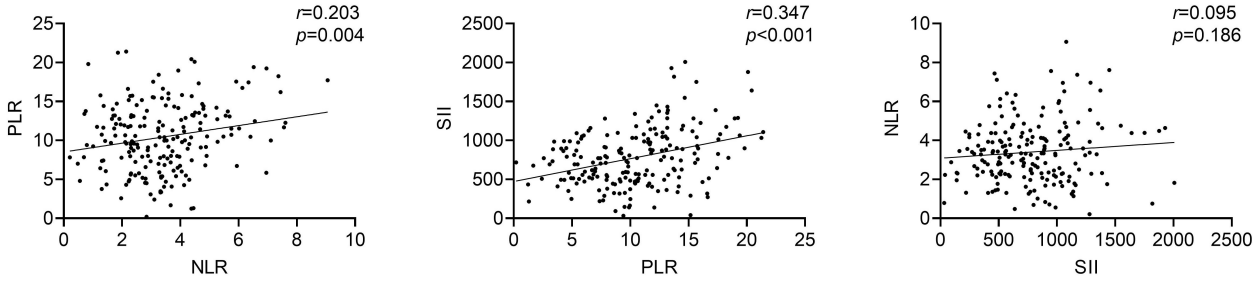

FIGURE 2. Correlation analysis showing the relationships between NLR, PLR and SII in patients with acute ischemic stroke. NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic immunoinflammatory index.

sum the scores corresponding to the risk factor indicators to obtain the total score. Based on this total score, the probability of poor intravenous thrombolytic efficacy can be determined.

3.5 Evaluation of nomogram models

The ROC curve analysis results demonstrated that the model's AUC for predicting treatment effectiveness was 0.929 (95% CI: 0.785–0.931), indicating strong predictive validity (Fig. 4). Calibration curve analysis (Fig. 5) and the Hosmer-Lemeshow test ($\chi^2 = 2.654$, $p = 0.954$) indicated that the predictive model exhibited a good fit. Decision analysis curves revealed a significant difference between the red curve and the gray curve, indicating substantial clinical benefit in utilizing predictive models to aid in clinical decision-making (Fig. 6).

4. Discussion

AIS is the most common type of stroke, and intravenous thrombolysis is recommended for patients within the treatment window and without contraindications [5]. Despite the benefits of intravenous thrombolysis, some patients do not experience significant improvement, negatively impacting their prognosis. Statistics indicate that approximately one-third of patients who receive intravenous thrombolysis may die or become disabled within a year [6]. The NIHSS score is widely used to predict mortality and prognosis in stroke patients and to clinically assess disease severity. However, the NIHSS score has limitations; it does not sensitively reflect the severity of neurological impairment in posterior circulation infarction and overlooks the impact of uncontrollable factors such as age and medical history on prognosis [7]. To improve the prediction of stroke prognosis, researchers have extensively studied biomarkers associated with pathophysiological pathways, including inflammation, oxidative stress, hormones and structural components.

Inflammation plays an essential role in immune responses, and its persistence has been shown to significantly influence the outcome of ischemic stroke, manifesting in nearly every stage of the condition [8]. Various inflammatory immune response indices, such as PLR and NLR, have been associated with AIS [9]. For instance, a meta-analysis conducted by Zhang *et al.* [10] revealed that NLR could predict hemorrhagic conversion and 3-month mortality following ischemic stroke, while elevated PLR was linked to depression after AIS [11]. SII, an immunoinflammatory index combining platelets, lymphocytes, and neutrophils, has also been implicated in adverse events in ischemic stroke patients with coronary artery disease and those undergoing thrombolytic therapy [12]. In this present study, we observed that increased SII, PLR and NLR were all correlated with a poor prognosis following throm-

TABLE 3. Univariate and multivariate logistic regression analysis.

Characteristics	Univariate			Multivariate		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	0.995	0.965–1.025	0.728	-	-	-
Sex	5.593	2.743–11.403	<0.001	-	-	-
Smoking	1.793	0.977–3.292	0.059	-	-	-
Alcohol	5.901	3.072–11.335	<0.001	-	-	-
Diabetes	2.865	1.513–5.423	0.001	-	-	-
Hypertension	3.626	1.916–6.861	<0.001			
Atrial fibrillation	0.747	0.401–1.391	0.358			
Blood glucose concentration	1.121	1.016–1.238	0.023	5.461	1.656–18.011	0.005
Time from onset to thrombolysis	1.008	1.002–1.014	0.011			
Adverse effects	0.916	0.516–1.625	0.763			
pre-thrombolysis NIHSS score	1.277	1.166–1.398	<0.001	1.340	1.142–1.573	<0.001
PT	0.408	0.293–0.568	<0.001	0.282	0.149–0.531	<0.001
APTT	0.870	0.823–0.919	<0.001	0.771	0.694–0.857	<0.001
Erythrocyte Count	1.049	0.618–1.781	0.859			
Hemoglobin	0.994	0.976–1.014	0.574			
WBC	1.197	0.946–1.515	0.135			
NLR	1.593	1.292–1.964	<0.001			
PLR	1.417	1.279–1.570	<0.001			
SII	1.002	1.001–1.003	<0.001	1.004	1.002–1.006	<0.001

OR: odds ratio; CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; PT: prothrombin time; APTT: activated partial thromboplastin time; WBC: white blood cell count; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic immunoinflammatory index.

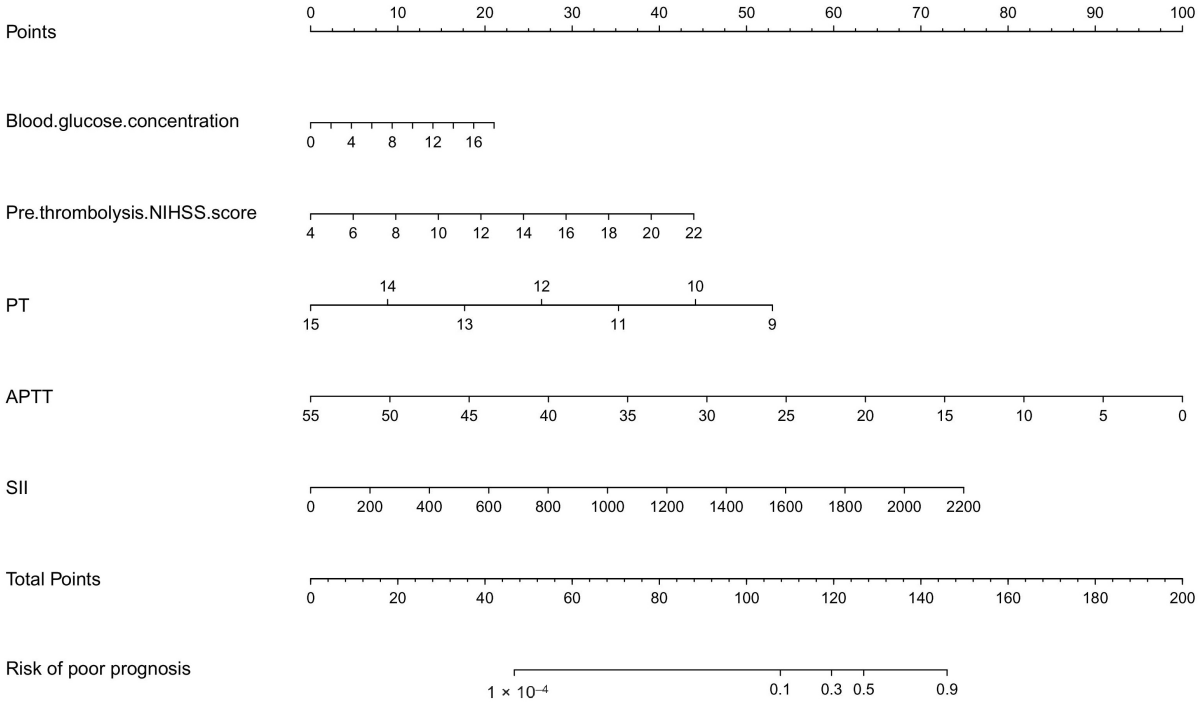

FIGURE 3. Nomogram for predicting short-term prognosis following intravenous thrombolytic therapy in patients with acute ischemic stroke. NIHSS: National Institutes of Health Stroke Scale; PT: prothrombin time; APTT: activated partial thromboplastin time; SII: systemic immunoinflammatory index.

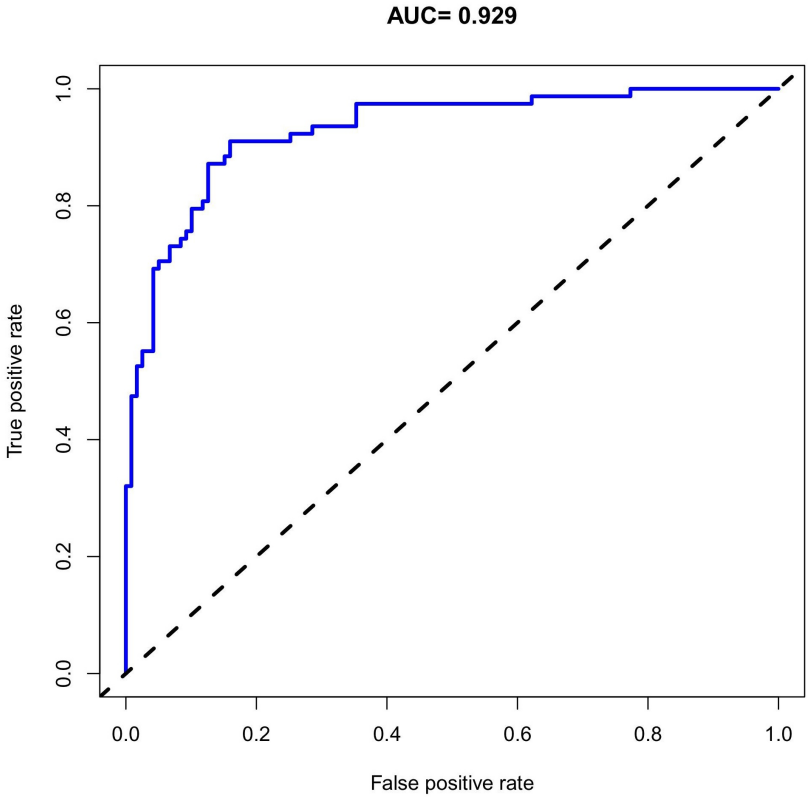

FIGURE 4. ROC curves depicting the prognostic prediction model for intravenous thrombolytic therapy in patients with AIS. AUC: area under the curves.

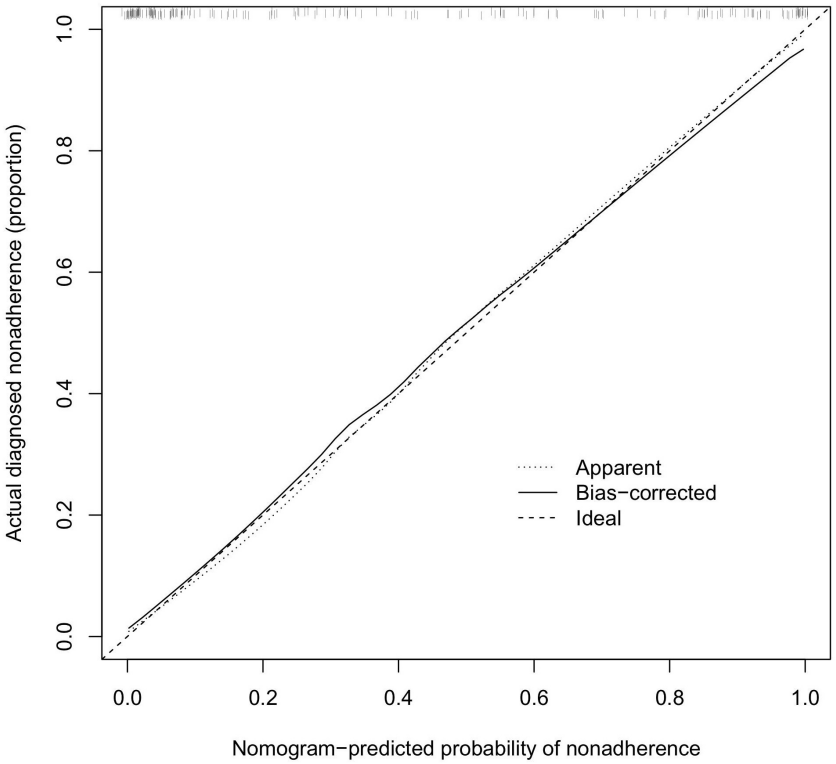

FIGURE 5. Calibration curve analysis for the prognostic prediction model of intravenous thrombolytic therapy in patients with acute ischemic stroke.

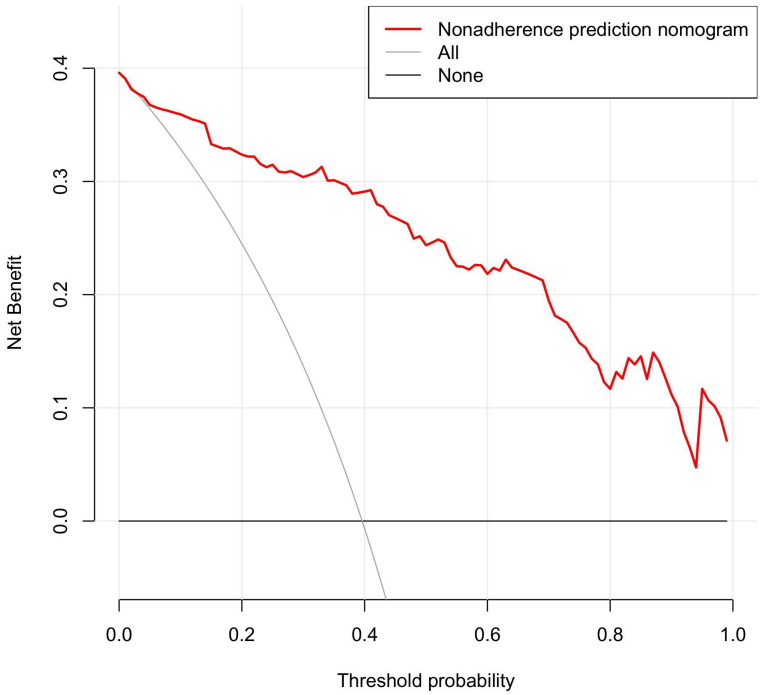

FIGURE 6. Decision analysis curve outcomes for the prognostic prediction model of intravenous thrombolytic therapy in patients with acute ischemic stroke.

bolytic treatment in AIS patients, with SII emerging as a more reliable predictor of adverse outcomes compared to NLR and PLR. This association between SII and AIS prognosis may be attributed to immunoinflammatory changes occurring at the onset of AIS. Specifically, AIS triggers immune system activation, leading to the migration of neutrophils to the perivascular area within the brain parenchyma during the early phase (6 to 24 hours) of the condition [13]. Subsequently, neutrophils release an array of inflammatory mediators, including reactive oxygen species, myeloperoxidase, elastase, histone G, and chemokines, culminating in blood-brain barrier disruption and tissue damage [14].

This study revealed that hyperglycemia, onset-to-intravenous thrombolysis time, PT and APTT were independent factors associated with poor short-term prognosis in AIS patients undergoing intravenous thrombolysis alongside NLR, PLR and SII. Elevated blood glucose levels can increase blood viscosity, worsening cerebral tissue hypoxia and promoting lactic acid metabolism, ultimately leading to nervous system damage [15]. Hyperglycemia has been previously linked to poor prognosis in stroke patients and is considered a risk factor for adverse outcomes within 90 days of rt-PA thrombolysis [16]. The NIHSS score holds significant predictive value for hemorrhage risk post-thrombolysis and serves as an independent predictor of poor patient prognosis [17, 18]. Additionally, Kazi *et al.* [19] reported that a higher admission NIHSS score was associated with early neurological deterioration in elderly patients with AIS, consistent with the findings of our study. Both PT and APTT are coagulation-related parameters directly implicated in blood coagulation and thrombosis. APTT has also been linked to bleeding conversion during venous thrombolysis [20]. While age, history of diabetes mellitus [21] and atrial fibrillation [22] have previously been identified as independent predictors of prognosis in intravenous thrombolytic therapy, our study did not find independent correlations between these variables and clinical outcomes in AIS patients treated with rt-PA, which could be attributed to the relatively small sample size of our study.

Nomograms have gained widespread utilization in prognostic prediction and personalized diagnosis and treatment across various diseases [23]. In our study, a total of seven indicators were selected for constructing a prediction model for intravenous thrombolysis efficacy in AIS patients. Unlike previous studies focusing on predicting intravenous thrombolysis efficacy in AIS [24], our study took a step further by developing a nomogram based on fundamental clinical information and routine biochemical indicators of patients. By employing multifactorial logistic regression analysis, we constructed a prediction model aimed at facilitating clinicians in rapidly and easily assessing patient conditions.

Despite the valuable insights gained from this study, there were several limitations that should be acknowledged. Firstly, being a single-center retrospective study, our research drew cases only from one hospital, thus limiting the sample size. Secondly, while our nomogram model exhibited robust discrimination and calibration during internal validation, it lacked external validation. Thirdly, our analysis only incorporated patients' clinical data and laboratory results, neglecting imaging scores that could enhance risk factor assessment and predictive modeling. Therefore, prospective, large-scale multicenter cohort studies are warranted in the future to validate our findings comprehensively.

5. Conclusions

In conclusion, peripheral blood systemic inflammatory index SII was identified as a significant risk factor for poor short-term prognosis in patients undergoing intravenous thrombolysis. Furthermore, our developed nomogram, based on inflammatory clinical features, demonstrates promising predictive efficiency and clinical applicability in predicting the early prognosis of AIS patients treated with rt-PA thrombolysis.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

KJZ—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. KJZ and XQW—supervised the data collection, analyzed the data, interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Wuxi People's Hospital (Approval no. 2022-32). Written informed consent was obtained from all patients included in this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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