

ORIGINAL RESEARCH

Prognostic value of serum sirt6 in predicting short-term functional outcome in patients treated with thrombolysis for acute ischemic stroke

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Abstract

Sirtuins 6 (Sirt6) is a defatting acylase that protects against atherosclerosis and ischemic stroke. It has a high clinical reference value in predicting clinical outcomes such as cerebral hemorrhage, cerebral ischemia, and myocardial infarction. This study aimed to investigate the connection between serum Sirt6 levels and short-term prognosis among patients with acute ischemic stroke (AIS) treated with intravenous thrombolysis with tissue-type plasminogen activator (rt-PA). This study involved AIS patients undergoing intravenous thrombolysis by rt-PA, and found that the serum Sirt6 level were significantly lower in the poor prognosis group than in the good prognosis group ($p < 0.05$), while the poor prognosis group's age, neutrophil count, atrial fibrillation, D-dimer level, and pre-thrombolysis National Institutes of Health Stroke Scale (NIHSS) score were significantly higher ($p < 0.05$). With a cut-off value of 689 ng/mL, receiver operating characteristic (ROC) analysis revealed that the area under the curve (AUC) of serum sirt6 for predicting a poor prognosis following intravenous thrombolytic therapy in AIS patients was 0.841, with corresponding sensitivity and specificity of 90.74% and 70.06%. Poor outcome was independently influenced by age, pre-thrombolysis NIHSS score, platelet counts, D-dimer, and Sirt6 level ($p < 0.05$). A nomogram prediction model was created based on multivariate logistic regression results, and its AUC was 0.972. The Hosmer-Lemeshow test ($\chi^2 = 5.766$, $p = 0.673$) and calibration curve analysis showed an acceptable fit for the prediction model. Decision analysis curves were also used to confirm the clinical utility of the model. In conclusion, Serum sirt6 was found to be a novel biomarker for predicting AIS patients treated with rt-PA, and sirt6-based nomograms may become a valuable tool for predicting AIS patients' long-term prognosis.

Keywords

Acute ischemic stroke; Clinical study; Intravenous thrombolysis; Prognosis; Sirtuins 6

1. Introduction

Acute ischemic stroke (AIS) is a common serious cerebrovascular disorder in middle-aged and elderly people, accounting for 87% of strokes, with a disability rate up to 20%~25% and a mortality rate of 10% within a year [1, 2]. AIS is characterized by a cerebral artery obstruction and abnormal local blood circulation in brain tissues. Ischemia and hypoxia of these conditions can lead to brain tissue necrosis, followed by neurological symptoms and indications. An effective and widely used treatment for AIS is intravenous thrombolysis with tissue-type plasminogen activator (rt-PA) [3]. Long-term outcomes are greatly affected by the fact that a few individuals maintain efficacy that is not immediately evident, and in some instances, neurological function even declines [4]. Research on factors affecting neurological function, prognosis, and effectiveness of rt-PA treatment has been a hot topic. Therefore,

it would be helpful to explore the relevant biomarkers in AIS patients after rt-PA intravenous thrombolytic therapy can assist in timely assessment of their prognosis and progress.

Silent information regulator two proteins, or sirtuins (SIRT) modulate histone deacetylase function and are linked and connected to nicotinamide adenine dinucleotide (NAD⁺) [5]. At the genomic level, besides suppressing transcription, they also raise proteins related to energy metabolism and pro-survival processes. Neuroprotective effects of SIRT have been reported in both acute and chronic neurological diseases [6]. Sirtuin 6 (Sirt6), is shown to prevent atherosclerosis and ischemic stroke [7]. Sirt6 serum levels have been shown to be highly predictive of clinical outcomes such as cerebral hemorrhage, cerebral ischemia, and myocardial infarction. This lays the foundation for accurate disease progression detection and early intervention [8]. However, there has been little research on the

relationship between serum sirt6 and intravenous thrombolytic therapy in AIS patients. The modified Rankin scale (mRS), a clinician-reported measure of global disability, is widely used to evaluate stroke patient outcomes. Based on analyses, randomized clinical trials of acute stroke treatments may require smaller sample sizes if the mRS is used as a primary end point [9]. This study aimed to examine the relationship between serum Sirt6 levels and short-term prognosis in AIS patients treated with intravenous thrombolysis with rt-PA, and to assess its diagnostic efficacy for predicting poor prognosis in AIS patients after intravenous thrombolysis. Moreover, a nomogram model was constructed to predict short-term prognosis in AIS patients by analyzing the influencing factors. This study aims to provide a reliable and simple prediction method for AIS patients' short-term prognosis.

2. Materials and methods

2.1 Study population

AIS patients receiving intravenous thrombolysis with rt-PA participated in this study. Inclusion criteria: (1) Diagnosed by the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018, (2) first attack, (3) Within 4.5 h of the attack onset, received standardized alteplase intravenous thrombolysis (4) Aged 40–80 years, (5) Complete information and informed consent form signed. Exclusion criteria: (1) Aged ≥ 80 years, (2) Patients treated with intravenous thrombolysis with urokinase, (3) Patients treated with arterial catheter for reperfusion therapy, (4) Patients with comorbid neurological diseases, such as multiple sclerosis, central nervous system (CNS) infections, or dementia, (5) Patients discharged from hospitals without formal secondary prevention of cerebral infarction.

2.2 Data collection

Patients baseline data included age, gender, common cerebrovascular disease risk factors, time of onset, time from onset to thrombolysis, pre-thrombolysis NIHSS scores, and laboratory indicators were collected. After admission to the hospital, 5 mL of venous blood was collected from each patient. Serum was separated after centrifugation at 3000 r/min for 15 min, and stored at -80°C . Serum Sirt6 levels were determined by enzyme-linked immunosorbent assay (ELISA) using commercial kits (MBS2021864, MyBioSource, San Diego, CA, USA).

2.3 Clinical outcome determination

Patients' short-term prognosis was assessed by two professionally trained researchers using the modified Rankin Rating Scale (mRS). In particular, the good prognosis was defined as mRS score ≤ 2 at month 3; the poor prognosis was defined as mRS score ≥ 2 at month 3, stroke recurrence, or death.

2.4 Statistical analysis

Data analysis was performed using SPSS 23.0 (IBM Corp., SPSS Statistics, Armonk, NY, USA) and R 4.0.3 statistical software. Measurement data followed a normal distribution were presented as mean \pm standard deviation, and Student's

t-test was used to compare both groups. Measurement data that did not fit into a normal distribution were presented as median (quartiles) [M (P25, P75)], and Mann-Whitney U test was used to compare both groups. Count data were analyzed using χ^2 test or Fisher's exact probability method. Using multivariate logistic regression analysis, we identified the distinctive variables that influence the short-term prognosis of AIS patients receiving rt-PA intravenous thrombolysis. By using the "rms" analysis package in R statistical software, a nomogram was derived from the screened characteristic markers. An evaluation of the model's effectiveness was carried out by plotting separately the calibration, decision, and receiver operating characteristic (ROC) curves. $p < 0.05$ indicates statistically significant differences.

3. Results

3.1 General information

This study involved 211 AIS patients, of which 54 had poor prognoses and 157 were good. There were no statistically significant differences in gender, alcohol consumption, smoking, hypertension, cerebrovascular disease, diabetes mellitus, time from onset to thrombolysis, leukocyte count, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), triglycerides (TG), random blood glucose (GLU), uric acid (UA), and homocysteine (Hcy) between both groups ($p > 0.05$, Table 1). In the poor prognosis group, age, neutrophil count, serum D-dimer level, pre-thrombolysis NIHSS score, and percentage of patients with atrial fibrillation were significantly higher, while platelet count was significantly lower ($p < 0.05$, Table 1).

3.2 Relationship between serum Sirt6 level and prognosis in AIS patients after intravenous thrombolytic therapy

Significantly lower serum Sirt6 levels were found in the poor prognosis group than in the good prognosis group ($p < 0.05$, Fig. 1A). With a cut-off value of 689 ng/mL, ROC analysis revealed that the AUC of serum Sirt6 for predicting a poor prognosis following intravenous thrombolytic therapy in AIS patients was 0.841 (95% CI: 0.783–0.899), with corresponding sensitivity and specificity of 90.74% and 70.06% (Fig. 1B).

3.3 Multivariate logistic regression analysis

Age, pre-thrombolysis NIHSS score, platelet count, D-dimer, and Sirt6 level were all independent influences on poor prognosis ($p < 0.05$, Table 2).

3.4 Construction of the nomogram model

Nomogram is a visual clinical predictive model that provides a scientific basis for clinical decisions. Through multivariate logistic regression analysis, a visualized nomogram prediction model was developed (Fig. 2). The total score is calculated by adding up the scores corresponding to the risk factor indicators. Probability of poor efficacy of rt-PA intravenous thrombolysis can be determined based on the total score.

TABLE 1. General information.

Group	Good prognosis (n = 157)	Poor prognosis (n = 54)	t/χ^2	p
Age	64.72 ± 9.21	71.09 ± 7.22	4.615	<0.001
Gender				
Male	76	22	0.950	0.330
Female	81	32		
BMI (kg/m ²)	23.03 ± 2.73	23.08 ± 2.72	0.107	0.915
Smoking	81	35	2.838	0.092
Drinking	91	33	0.164	0.685
Time from onset to thrombolysis				
0~3 h	55	25	2.166	0.141
>3~4.5 h	102	29		
NIHSS score	7.39 ± 2.88	10.52 ± 4.02	6.180	<0.001
Hypertension	101	32	0.444	0.505
Diabetes mellitus	90	38	2.866	0.090
Lipid metabolism disorders	90	32	0.062	0.804
Atrial Fibrillation	61	30	4.570	0.033
Leukocyte (×10 ⁹ /L)	7.83 ± 3.01	7.90 ± 3.29	0.158	0.875
Neutrophil (×10 ⁹ /L)	5.17 ± 2.61	5.99 ± 2.39	2.021	0.045
Lymphocyte (×10 ⁹ /L)	1.99 ± 0.93	1.98 ± 0.86	0.097	0.923
NLR	3.99 ± 5.78	4.24 ± 4.10	0.291	0.771
Platelet (×10 ⁹ /L)	254.17 ± 82.61	153.49 ± 71.23	7.990	<0.001
HDL (mmol/L)	1.28 ± 0.29	1.34 ± 0.33	1.367	0.173
LDL (mmol/L)	2.40 ± 0.96	2.28 ± 0.8	0.786	0.433
TC (mmol/L)	4.65 ± 1.16	4.87 ± 1.29	1.152	0.251
TG (mmol/L)	1.99 ± 1.26	2.00 ± 1.07	0.043	0.966
GLU (mmol/L)	8.40 ± 3.64	8.43 ± 3.95	0.047	0.962
UA (μmol/L)	364.77 ± 103.05	356.02 ± 106	0.534	0.594
Hcy (μmol/L)	19.28 ± 13.81	21.80 ± 12.41	1.183	0.238
D-dimer (mg/L)	0.74 ± 0.41	1.91 ± 1.01	12.054	<0.001
Sirt6 (pg/mL)	808.25 ± 280.14	461.83 ± 195.92	8.402	<0.001

Note: NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-to-lymphocyte ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; GLU, random blood glucose; UA, uric acid (UA); Hcy, homocysteine; Sirt6, Sirtuins 6; BMI, body mass index.

3.5 Evaluation of nomogram models

ROC curve analysis (Fig. 3A) demonstrated that the model's AUC for predicting short-term prognosis of intravenous thrombolytic therapy in AIS patients was 0.972 (95% CI: 0.891–0.997), which indicates high predictive validity. Hosmer-Lemeshow test ($\chi^2 = 5.766$, $p = 0.673$) and

calibration curve analysis have confirmed a strong match for the predictive model (Fig. 3B). Decision analysis curves showed a significant difference between the red curve and the gray curve. Hence, predictive models may be beneficial to clinical decision-making (Fig. 3C).

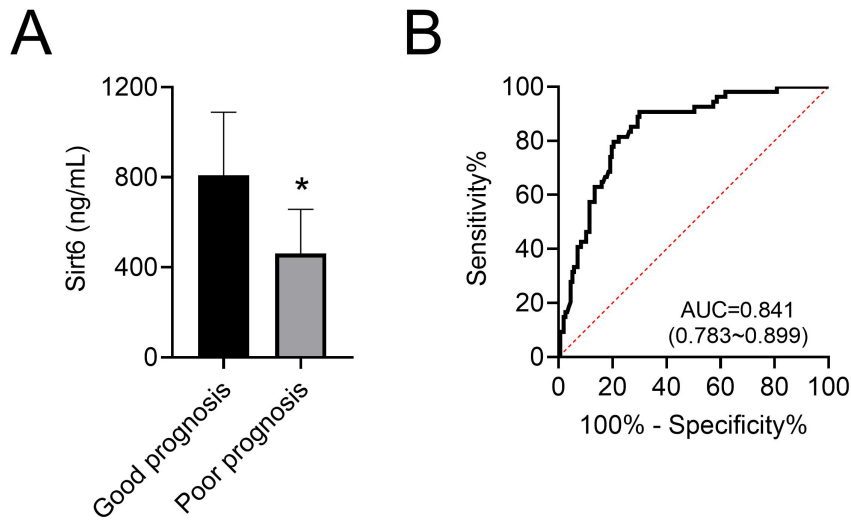


FIGURE 1. Relationship between serum Sirt6 level and prognosis in AIS patients after intravenous thrombolytic therapy. (A) Comparison of serum Sirt6 levels between both groups. (B) ROC analysis of serum Sirt6 levels to predict poor prognosis. Note: AUC, area under the curve; Sirt6, Sirtuins 6. **p* < 0.05 compared with Good prognosis group.

TABLE 2. Multivariate logistic regression analysis.

	B	S.E.	Wald	OR	95% CI	<i>p</i>
Age	0.125	0.041	9.415	1.134	1.046–1.228	0.002
NIHSS	0.394	0.106	13.814	1.483	1.205–1.825	<0.001
Platelet	–0.013	0.005	7.528	0.987	0.970–0.996	0.006
D-dimer	2.468	0.553	19.909	11.798	3.990–34.888	<0.001
Sirt6	–0.006	0.002	15.092	0.994	0.991–0.997	<0.001

Note: NIHSS, National Institutes of Health Stroke Scale; S.E., standard error; OR, Odds Ratio; CI, confidence interval; Sirt6, Sirtuins 6.

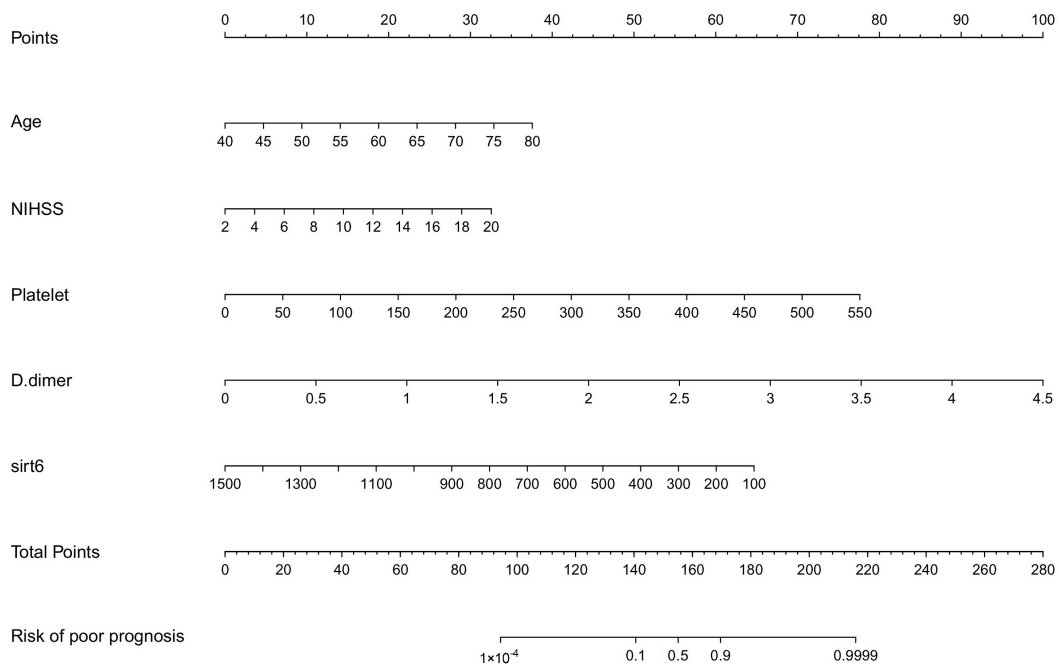


FIGURE 2. A nomogram to predict short-term prognosis. NIHSS, National Institutes of Health Stroke Scale; sirt6, Sirtuins 6.

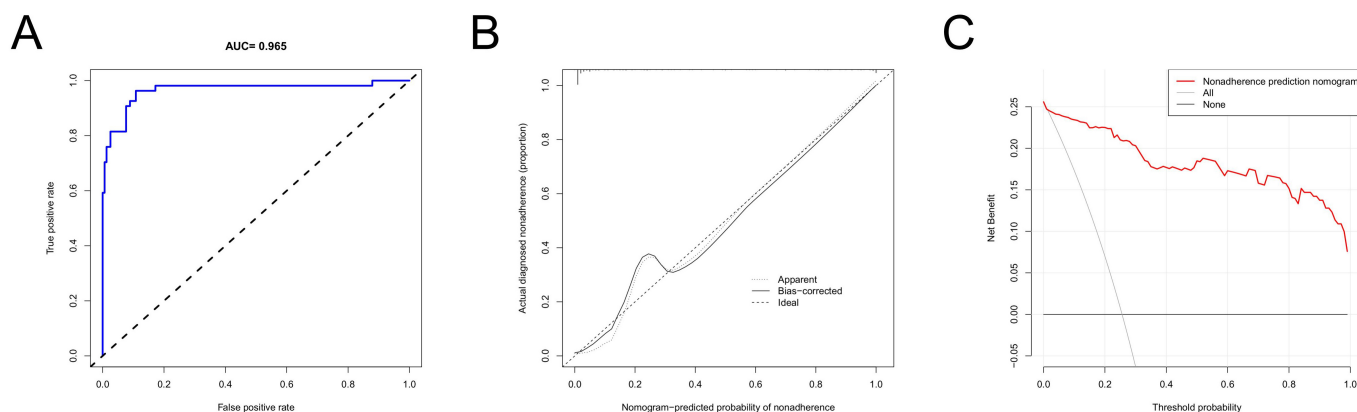


FIGURE 3. Evaluation of nomogram models. (A) ROC curve. (B) Calibration curve. (C) Decision analysis curve. AUC, area under the curve.

4. Discussion

AIS patients are commonly treated with intravenous thrombolytic therapy with rt-PA. Patients who undergo rt-PA intravenous thrombolysis, however, may experience intracranial, cutaneous, urinary, and other hemorrhagic symptoms. These symptoms may impair thrombolytic therapy, and are prone to poor prognosis [10]. This study demonstrated for the first time that low serum Sirt6 levels were associated with poor short-term outcomes in patients receiving intravenous thrombolysis. This study also developed a nomogram model based on serum Sirt6 combined with clinical parameters that predicts short-term outcomes after intravenous thrombolysis.

Various systems of the body can be affected by inflammation, which is part of the immune response. Chronic inflammatory responses have been found to occur throughout almost all stages of ischemic stroke [11]. It is known that Sirt6 functions as an anti-inflammatory protein in inflammatory diseases by regulating the enzymatic activity of tumor necrosis factor (TNF- α) and nuclear factor (NF)- κ B, two of the most significant pro-inflammatory components in the inflammatory response [12]. Sirt6 plays an anti-inflammatory role in the brain by regulating several signaling pathways [8, 13]. A higher expression of Sirt6 was found in ischemic stroke patients with a short-term neurological improvement than those with a poor short-term prognosis, and this difference is correlated with better clinical stroke prognosis [14]. Liberale *et al.* [15] found that serum Sirt6 levels were negatively correlated with the risk of death in AIS patients, suggesting that it could be a prognostic predictor and therapeutic target. This study also indicated that decreased serum Sirt6 was associated with poor prognosis after thrombolytic therapy in AIS patients. There is no doubt that NIHSS score is a valuable quantitative tool for assessing disease severity and clinical prognosis in AIS patients [16]. According to the present study, serum Sirt6 was significantly negatively correlated with NIHSS score among AIS patients. ROC analysis showed that serum sirt6 had a high predictive value for short-term adverse prognosis in AIS patients treated with rt-PA. Additionally, a logistic regression study revealed that a lower serum Sirt6 level was an independent risk factor for a worse outcome in AIS patients receiving rt-PA. Consequently, serum sirt6 might be considered a serum marker for

AIS patients undergoing rt-PA treatment to indicate poor outcome. The correlation between Sirt1 and functional regression in AIS patients was examined by Liu *et al.* [17], and future studies may examine similar variables. To improve the clinical prognosis of patients undergoing intravenous thrombolysis, risk factors linked to a poor prognosis must be identified and managed promptly. Numerous factors influence the prognosis of patients receiving intravenous thrombolysis. This study found that patients receiving intravenous thrombolysis who suffer a bad short-term outcome have a higher age. The impact of thrombolytic therapy is impacted by the fact that elderly individuals often have a range of fundamental illnesses, organ function decreases, and immunocompromised [18]. Prior to thrombolysis, patients with a high NIHSS score had a roughly 1.5-fold increased chance of having a poor prognosis compared to patients with a low NIHSS score. Patients are primarily assessed for their neurological deficits using the NIHSS score, and a higher NIHSS score at the onset of the disease indicates that the larger the infarct area or the poorer the compensatory function of the side branch of the infarct site, and the worse the thrombolysis effects [19]. Hemorrhage after thrombolysis is strongly predicted by the NIHSS score, which is an independent risk factor for poor patient prognosis [20, 21]. Similar to this study, Kazi *et al.* [22] reported that a higher admission NIHSS score was a risk factor for early neurological deterioration in elderly AIS patients. Low platelet counts and elevated D-dimer levels are independent risk factors for SAP. Platelets play a hemostatic role by adhering and aggregating on damaged blood vessels, while promoting vascular plaque and thrombus formation in the vascular inflammatory response [23]. According to a meta-analysis [24] platelet counts were significantly lower in AIS patients than controls. In thrombolysis, excessive platelet consumption decreased the platelet count [25]. Consequently, the lower the platelet count, the higher the risk of thrombus formation during this episode and the slower the recovery of neurological function in the early period after intravenous thrombolysis with rt-PA. D-dimer is produced by the degradation of cross-linked fibrin, and its elevated level suggests hypercoagulability and secondary hyperfibrinolysis *in vivo*, and hypercoagulable state of blood is a characteristic manifestation of acute cerebral infarction [26]. Stroke-related immunosuppression and hypofunction

are more pronounced at higher levels of D-dimer, as is SAP incidence [27]. An evaluation of risk and identification of predictors are necessary to avoid a poor prognosis. By targeting relevant risk factors, poor prognoses can be reduced. A nomogram represents a statistical prediction model that integrates different variables to predict the likelihood of a clinical event [28]. Predictive models based on nomograms have been widely used in clinical studies [29, 30]. In this study, the above independent risk factors were included in the constructed prediction model and an optimal C-index of 0.972 was derived. Moreover, nomogram-based prediction models were also effective in predicting poor outcomes in patients receiving intravenous thrombolysis. This study suggests that a nomogram constructed based on serum Sirt6 levels and clinical characteristics can be used effectively to predict prognosis in patients underwent intravenous thrombolysis.

This study was a retrospective analysis with a limited sample size, and its data collection methods might have been inadequate since it was an analysis based on retrospective data. A larger sample size and prolonged follow-up period will be necessary in the future to investigate the correlation between Sirt6 and the prognosis of patients treated with intravenous thrombolysis further. As well, this study only evaluated serum Sirt6 levels at admission, which is not yet considered the best evaluation metric. Dynamic identification of serum indicators is necessary for disease surveillance. Further, the nomogram model was used for internal validation, and its extrapolation cannot be verified. Therefore, large-scale prospective and multicenter studies are still necessary to confirm the findings.

5. Conclusions

In conclusion, lowered Sirt6 levels in the blood of patients receiving intravenous thrombolysis might lead to a poor short-term prognosis. With strong predictive effectiveness and practical application value, a nomogram based on serum Sirt6 level and clinical features might be used to predict the early outcome of AIS patients undergoing rt-PA therapy. Therefore, serum Sirt6 may be a novel biomarker for predicting AIS patients receiving rt-PA therapy, and the sirt6-based nomogram may be a valuable tool for predicting AIS patients' short-term outcome.

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

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

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Yan'an People's Hospital (Approval no. 2024LW011). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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