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ORIGINAL RESEARCH

Analysis of Risk Factors for Poor Prognosis Following Small Artery Occlusion or Lacunar Stroke: A Retrospective Cohort Study

Yan Shi, Yongtao Liu, Jingjing Sun, Bing Zhao, Qingfan Xie

Department of Rehabilitation Medicine, Xingtai People's Hospital, Xingtai City, Hebei Province, People's Republic of China

Correspondence: Qingfan Xie, Department of Rehabilitation Medicine, Xingtai People's Hospital, No. 818 Xiangdu North Road, Xiangdu District, Xingtai City, Hebei Province, 054000, People's Republic of China, Tel +86-03193956196, Email X221021qf@126.com

Objective: To investigate the risk factors and predictive value for poor prognosis following small artery occlusion stroke (SAO) or lacunar stroke.

Methods: A retrospective cohort of 100 SAO patients who received their first intravenous thrombolysis (IVT) treatment with alteplase between March 2019 and March 2021 was collected. Based on the modified Rankin Scale (mRS) score of <3 at 90 days post-admission, patients were divided into a good prognosis group (61 cases) and a poor prognosis group (39 cases) for comparative analysis.

Results: In our retrospective cohort study of 100 SAO patients treated with IVT from March 2019 to March 2021, we found no significant differences in gender, age or BMI between the 61 patients with good prognosis and the 39 with poor prognosis, although smoking habits varied. Statistically differences were observed between the two groups in terms of time from onset to hospital admission for thrombolysis (48.59±20.14 vs 40.03±23.73 min, t=2.202, P=0.030), triglycerides (1.56±0.92 vs 1.20±0.68 mmol/L, t=2.069, P=0.041), and smoking prevalence (42.62% vs 20.51%, χ^2=5.183, P=0.023). Regression analysis indicated that shorter time from onset to hospital admission for thrombolysis (OR=0.978, 95% CI: 0.957–0.993) was a protective factor against poor prognosis post-thrombolysis in SAO patients, while a history of smoking (OR=2.881, 95% CI: 1.115–7.444) was a risk factor for poor prognosis post-thrombolysis. The area under the curve (AUC) for predicting poor prognosis post-thrombolysis in SAO patients based on time from onset to hospital admission was 0.662 (95% CI: 0.552–0.771), with a cutoff value of 36.5 min; the AUC for predicting poor prognosis based on smoking history was 0.614 (95% CI: 0.502–0.726).

Conclusion: An extended duration from onset to hospital admission for thrombolysis and smoking are identified as significant risk factors for poor prognosis following thrombolysis in SAO patients, both of which have substantial predictive value.

Keywords: small artery occlusion stroke, lacunar stroke, risk factors, poor prognosis

Introduction

Cerebral stroke, a leading cause of death and disability worldwide, is categorized into hemorrhagic and ischemic types, with the latter comprising 87% of cases.[1,2] It is the second most common cause of mortality globally, contributing to approximately 10% of all deaths, and its incidence is rising.[3] In China alone, stroke affects up to 13 million people, with 6 to 7 million survivors each year, highlighting the significant healthcare and economic impact of this condition.[4] This underscores the urgent need for effective stroke management strategies to alleviate the growing burden on individuals and healthcare systems.[5]

In ischemic stroke (IS), small artery occlusion (SAO) accounts for about 25%.[6,7] Compared with the severe neurological deficit caused by atherosclerosis, despite being associated with milder initial neurological deficits, SAO strokes confer a substantial risk of recurrent ischemic events and long-term cognitive decline, underscoring the importance of understanding the risk factors for poor prognosis in this patient population.[8] The pathophysiology of SAO is complex and multifactorial, involving processes such as lipohyalinosis and microatheroma formation. While advances have been made in the acute treatment of IS, including the use of intravenous thrombolysis with alteplase, and intravenous injection of alteplase within 4.5 hours after stroke has become the only recommended thrombolytic therapy in the world the outcomes for SAO patients remain variable.

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Studies have shown that the effectiveness of intravenous thrombolysis (that is, clinical cure or significant improvement after three months) is only 32.1%.[9] Further research shows that only 37.8% of patients treated with alteplase have a good prognosis after three months (mRS score 0–2). This shows that many stroke patients have not benefited from intravenous thrombolysis, which highlights the urgent need for in-depth research on the factors affecting the outcome of thrombolysis. The research of Zhang et al identified age, hypertension, diabetes, smoking, time before thrombolysis and NIHSS score before thrombolysis as independent factors affecting clinical prognosis after three months, among which NIHSS score is also an indicator of death risk.[10] A follow-up survey in Europe showed that anemia was independently related to poor thrombolytic results.[11] Australian National University School of Medicine found that hyperglycemia and low hemoglobin levels before thrombolysis are closely related to larger infarct size, malignant stroke progression, poor prognosis and higher mortality.[12] Compared with European and American populations, Asian stroke patients have higher proportion of intracranial arterioles, lower proportion of aortic atherosclerosis, and lower levels of fibrinogen and coagulation factor VIII. These demographic characteristics may affect the therapeutic effect and prognosis of alteplase thrombolysis.[13] Prior research has begun to elucidate some of these factors, but a comprehensive understanding of the determinants of poor prognosis after SAO stroke remains elusive. There is a critical need to identify specific risk factors that predict poor prognosis following SAO to inform tailored treatment strategies and improve patient outcomes.

This study aims to fill this gap by analyzing risk factors for poor prognosis in a cohort of SAO patients who underwent intravenous thrombolysis (IVT). We hypothesize that certain demographic, clinical, and therapeutic factors may be associated with adverse outcomes at three months post-discharge. By identifying these factors, we aim to contribute to the development of predictive models and targeted interventions that could enhance the management of SAO patients and improve their long-term prognosis.

Study Subjects and Methods

Subjects

A retrospective cohort of 100 SAO patients who received their first IVT treatment with alteplase between March 2019 and March 2021 at our hospital was collected using convenience sampling (Figure 1). Based on the modified Rankin Scale (mRS) score of <3 at 90 days post-admission, patients were divided into a good prognosis group (61 cases) and a poor prognosis group (39 cases). The IVT protocol followed the Chinese Stroke Association Guidelines for Clinical Management of Cerebrovascular Diseases[14] and the American standards for intravenous thrombolysis treatment of acute IS.[15]

The inclusion criteria were as follows: (1) age >18 years; (2) meeting the diagnostic criteria for large artery atherosclerotic cerebral stroke according to the "Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018";[3] (3) onset of acute ischemic stroke within ≤24h; and (4) diagnosed with SAO according to the TOAST classification; (5) an mRS score of <3 at discharge.

The exclusion criteria were as follows: (1) bridging endovascular treatment; (2) major surgery within the past two weeks; (3) other unexplained non-atherosclerotic vascular stenosis; (4) severe systemic diseases or other potential life-threatening risks or expected life expectancy of <1 year; (5) target lesion with severe tandem stenosis; (6) severe cardiopulmonary, gastrointestinal, liver, kidney, thyroid, coagulation, or brain function diseases; and (7) secondary thrombolysis due to stroke recurrence within two weeks.

After thrombolysis, the patients were followed up for 3 months (90 days), mainly adopts face-to-face or telephone interviews to ensure the accuracy and integrity of the data, and all patients enrolled in the study were successfully followed up, resulting in a 100% follow-up rate. The short-term prognosis was evaluated by mRS:[10] M *RS* score ≥3, moderate to severe disability or death was poor prognosis; If the mRS score is less than 3 points, the prognosis is good if patients could move on there own without assistance.

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Xingtai People's Hospital (No.2022【089】). Written informed consent was obtained from all participants.

Study Methods

All patients received standard treatment as per the Stroke and Transient Ischemic Attack Prevention Guidelines: American Heart Association/American Stroke Association Guidelines for Healthcare Professionals (2014). Smoking history was defined

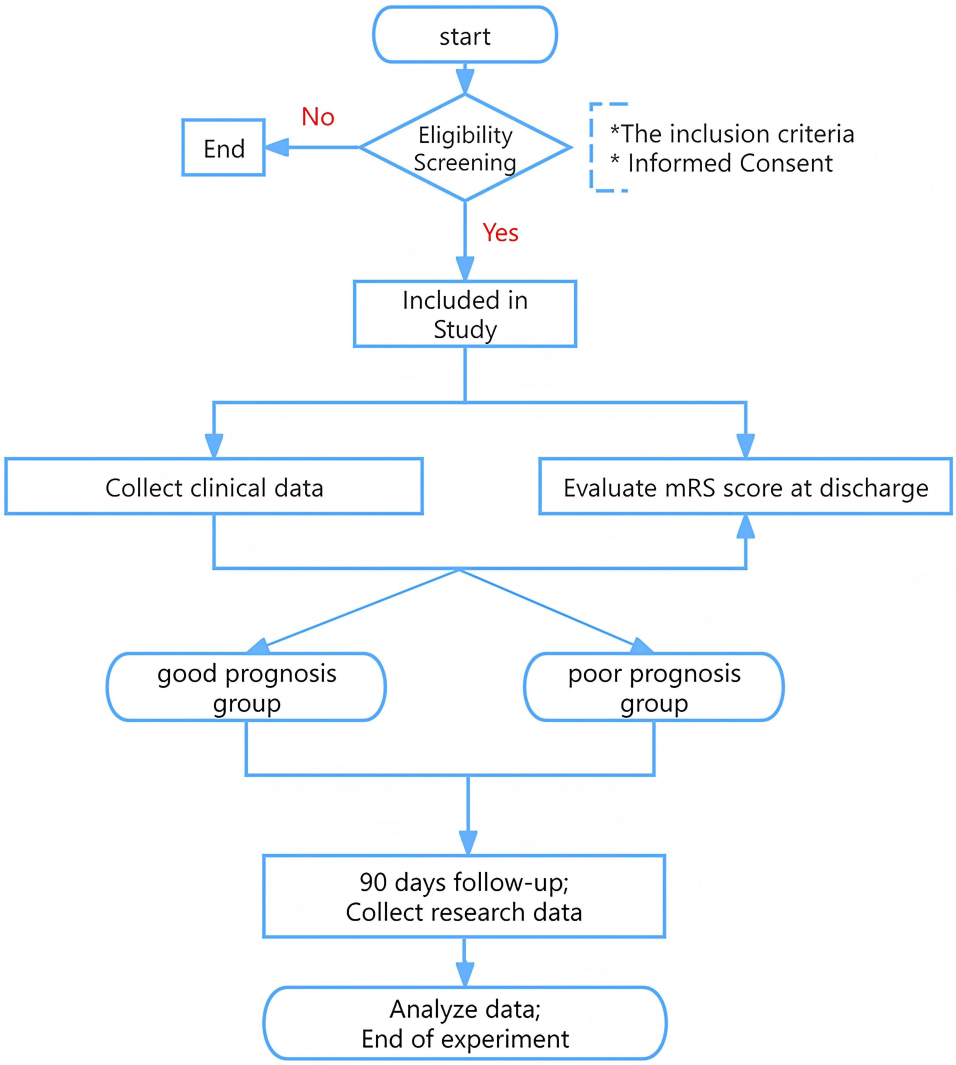

Figure 1 Flowchart of carrying out the experiment.

as smoking >10 cigarettes/d for ≥6 months; alcohol consumption history was defined as intake ≥60 grams/d for ≥1 year. Normal lipid levels were defined as: triglycerides: 0.56–1.70 mmol/L, total cholesterol: 3.11–5.20 mmol/L, high-density lipoprotein: 1.04–1.55 mmol/L, low-density lipoprotein: 2.07–3.37 mmol/L.

Data Collection

Data collected included patient age, gender, BMI, blood pressure, imaging number, chief complaint, smoking history, alcohol consumption history, adverse reactions to thrombolysis, comorbidities (hypertension, diabetes, hyperlipidemia, coronary heart disease, atrial fibrillation), mRS, NIHSS scores, and basic lipid profile data such as triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein.

Statistical Analysis

All data were statistically analyzed using the SPSS 26.0 software (SPSS Inc., Chicago, IL, USA). The K–S test was used for the test of normality. Measurement data that followed a normal distribution were expressed as mean ± standard deviation (x±s), and comparisons between groups were made using the independent samples *t*-test. Enumeration data were expressed as frequency (n) or percentage (%), and the χ^2 test was used where applicable. Logistic regression analysis was employed to investigate potential risk factors. The predictive value of various indicators was explored using the Receiver Operating Characteristic (ROC) curve. A

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two-tailed P<0.05 was considered statistically significant. Because this study used convenient sampling, it is impossible to control the sample size. We use Gpower software to calculate the statistical power of each *t*-test and chi-square test between 78% and 84% according to the existing sample size and 0.05 as the statistical threshold. It is acceptable.

Results

General Data

The results indicated statistically significant differences between the two groups in terms of time from onset to thrombolysis (48.59±20.14 vs 40.03±23.73 min, t=2.202, P=0.030), triglycerides (1.56±0.92 vs 1.20±0.68 mmol/L, t=2.069, P=0.041), and smoking prevalence (42.62% vs 20.51%, χ^2=5.183, P=0.023). No significant differences were observed in other aspects (P>0.05), as shown in Table 1.

Logistic Regression Analysis of Suspected Factors for Poor Prognosis in SAO Patients Post-Thrombolysis

Employing the occurrence of poor prognosis as the dependent variable (occurrence=1, non-occurrence=0), and factors that were statistically significant in univariate analysis as independent variables, a logistic regression analysis model was

Table 1 Comparison of General Data

Item	Good Prognosis Group (n=61)	Poor Prognosis group (n=39)	t/χ^2 value	*P* value
Gender (Male/Female)	41/20	25/14	0.103	0.749
Age (years, $\bar{x} \pm s$)	58.93±11.45	59.94±14.15	−0.448	0.655
BMI (kg/m², $\bar{x} \pm s$)	24.05±2.91	23.66±3.47	0.775	0.440
Pre-onset mRS (points, $\bar{x} \pm s$)	1.56±1.22	1.86±1.40	−1.184	0.239
Systolic blood pressure (mmHg, $\bar{x} \pm s$)	147.47±18.22	147.38±15.88	−0.309	0.758
Diastolic blood pressure (mmHg, $\bar{x} \pm s$)	86.14±12.51	85.49±11.32	0.032	0.975
Onset to thrombolysis time (min, $\bar{x} \pm s$)	139.31±54.34	137.97±58.05	0.040	0.968
Admission to thrombolysis time (min, $\bar{x} \pm s$)	48.59±20.14	40.03±23.73	2.202	0.030
Pre-thrombolysis NIHSS score (points, $\bar{x} \pm s$)	4.49±3.58	4.41±2.73	0.493	0.623
Post-thrombolysis NIHSS score (points, $\bar{x} \pm s$)	3.37±3.31	3.2703±2.70	0.415	0.679
24h post-thrombolysis NIHSS score (points, $\bar{x} \pm s$)	3.27±3.40	2.57±2.64	1.240	0.218
7-day post-thrombolysis NIHSS score (points, $\bar{x} \pm s$)	2.10±2.187	1.89±2.61	0.620	0.537
Thrombolysis complications (cases)	14	4	2.597	0.107
Rehabilitation therapy (cases)	33	21	0.001	0.980
Antiplatelet therapy (cases)	60	38	–	1.000
Anticoagulation therapy (cases)	13	8	0.009	1.000
Antihypertensive (cases)	26	11	2.122	0.203
Lipid-lowering (cases)	60	39	–	1.000
Antidiabetic (cases)	6	7	1.384	0.239
Coronary heart disease (cases)	3	5	1.088	0.297
Atrial fibrillation (cases)	0	0	–	1.000
Hypertension (cases)	34	20	0.190	0.663
Diabetes (cases)	9	7	0.181	0.671
Hyperlipidemia (cases)	2	0	–	0.519
Cholesterol (mmol/L, $\bar{x} \pm s$)	4.59±1.07	4.27±0.82	1.168	0.245
Triglycerides (mmol/L, $\bar{x} \pm s$)	1.56±0.92	1.20±0.68	2.069	0.041
High-density lipoprotein (mmol/L, $\bar{x} \pm s$)	1.12±0.32	1.16±0.29	−0.660	0.511
Low-density lipoprotein (mmol/L, $\bar{x} \pm s$)	2.68±0.77	2.43±0.64	1.168	0.246
Uric acid (μmol/L, $\bar{x} \pm s$)	296.66±88.79	295.99±85.06	−0.157	0.875
Homocysteine (μmol/L, $\bar{x} \pm s$)	23.20±32.10	21.67±20.03	−0.078	0.938
Smoking (cases)	26	8	5.183	0.023
Alcohol consumption (cases)	12	5	0.792	0.374

Table 2 Logistic Regression Analysis of Suspected Factors for Poor Prognosis in SAO Patients Post-Thrombolysis

Influencing Factors	S.E	Wald χ^2	*P*	*OR*	*OR* (95% CI)
Short admission to thrombolysis time	0.011	3.970	0.046	0.978	0.957~0.993
History of smoking	0.484	4.772	0.029	2.881	1.115~7.444

Table 3 Predictive Value of Various Indicators for Poor Prognosis in SAO Patients Post-Thrombolysis

Item	AUC	95% CI	Sensitivity (%)	Specificity (%)	Cut-Off Value
Admission to thrombolysis time	0.662	0.552~0.771	75.0	51.3	36.5
History of smoking	0.614	0.502~0.726	56.7	79.5	–

constructed. The regression analysis indicated that a shorter time from onset to thrombolysis (*OR*=0.978, 95% CI: 0.957–0.993) was a protective factor against poor prognosis in SAO patients post-thrombolysis, while a history of smoking (*OR*=2.881, 95% CI: 1.115–7.444) was identified as a risk factor for poor prognosis, as shown in Table 2.

Predictive Value of Various Indicators for Poor Prognosis in SAO Patients Post-Thrombolysis

The results demonstrated that various indicators had a certain predictive value for the occurrence of poor prognosis in SAO patient post-thrombolysis. Specifically, the area under the curve (AUC) for the time from onset to thrombolysis in predicting poor prognosis was 0.662, with a 95% CI of 0.552–0.771, and a cutoff value of 36.5 minutes. The AUC for smoking history in predicting poor prognosis was 0.614, with a 95% CI of 0.502–0.726, as detailed in Table 3. The ROC curve is shown in Figure 2.

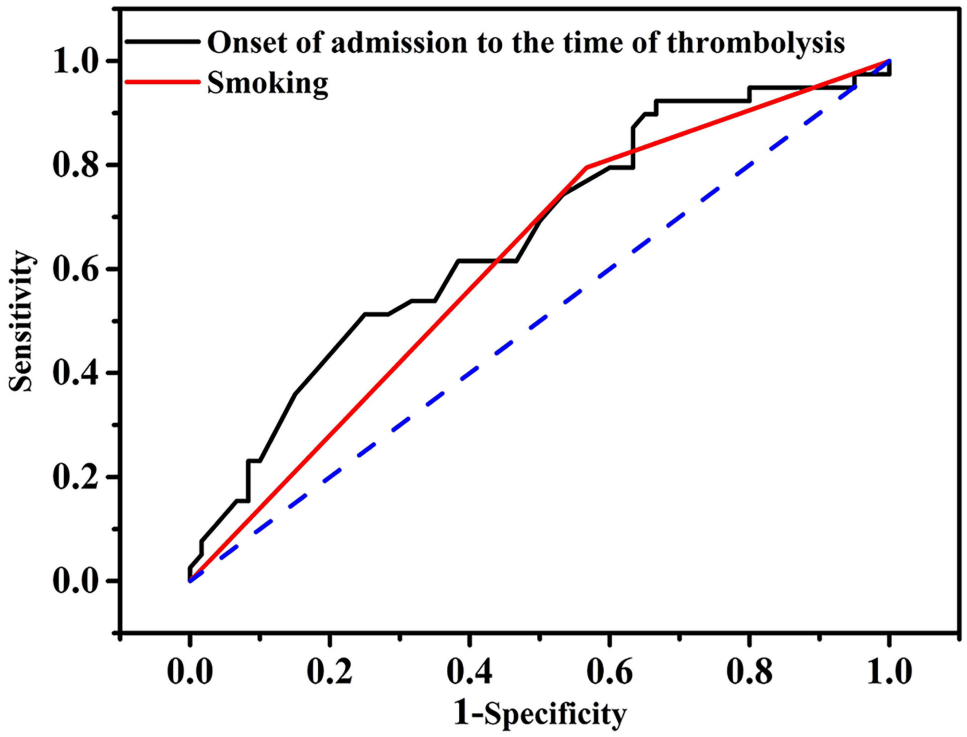

Figure 2 ROC curves of various indicators for predicting poor prognosis in SAO patients post-thrombolysis.

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Discussion

We conducted a retrospective cohort study to analyze risk factors for poor prognosis following SAO or lacunar stroke in 100 patients who received IVT with alteplase. Our findings indicate that factors such as delayed time to thrombolysis and a history of smoking significantly contribute to poor outcomes, aligning with current understanding of stroke prognosis determinants. Lacunar stroke, attributable to the occlusion of a single penetrating artery, constitutes a subset of subcortical stroke. While thromboembolism is a common cause of large artery strokes, the controversial lacunar hypothesis suggests that the key mechanisms of lacunar pathology are microaneurysms and lipohyalinosis, with thromboembolic lacunar strokes being relatively uncommon.[16,17] Despite being associated with inflammatory endothelial dysfunction and blood-brain barrier disruption, the causes of these small vessel changes remain difficult to comprehend. Compared to cortical ischemic strokes, they have a significantly better functional prognosis but place patients at a high risk of recurrent ischemic strokes and cognitive decline.[18] Current understanding of the arteriopathy underlying lacunar infarction (LI) remains limited.[19] Hence, identifying risk factors for poor outcomes in thrombolysis patients without a clear mechanism is imperative for improving patient prognosis. Our study results indicate that the interval from stroke onset to thrombolysis, coupled with a history of smoking, are risk factors for poor prognosis following thrombolysis in LI patients.

The association between elevated low-density lipoprotein cholesterol (LDL-C) and LI can be explained by the "lipid infiltration hypothesis".[20] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels study showed that patients with cerebral small vessel disease (CSVD), hyperlipidemia, and large artery atherosclerotic strokes had similar rates of stroke recurrence. The administration of atorvastatin at a dosage of 80 mg daily proved equally efficacious in mitigating the risk of stroke recurrence across all three groups, underscoring the potential benefits of statin therapy in patients with CSVD.[21] Besides, Type 2 diabetes mellitus (T2DM) has been recognized as a significant risk factor for ischemic stroke and cognitive decline. Epidemiological studies have shown a correlation between T2DM and lacunar strokes. Research conducted by Bi Xuechao[22] revealed that patients with cerebral small vessel disease exhibited higher insulin levels than those with large vessel disease, with C-peptide levels showing a more significant correlation, especially in patients with LI. Although statins show potential in reducing the recurrence of stroke, our research results show that traditional markers of blood lipid and blood glucose can not predict the bad prognosis. This finding may be attributed to several factors that require a more in-depth discussion in the context of the current scientific literature. Firstly, the immediate lipid-lowering and hypoglycemic treatments administered upon hospital admission for emergency care may have mitigated the acute effects of dyslipidemia and hyperglycemia. However, as highlighted in recent research, the long-term damage to the cardiovascular and cerebrovascular systems caused by chronic exposure to abnormal blood lipids and glucose levels is substantial and cannot be entirely offset by short-term interventions.[23] Secondly, the complex pathophysiology of SAO and lacunar stroke involves multiple factors beyond lipid and glucose metabolism. These include endothelial dysfunction, blood-brain barrier disruption, and microvascular changes such as lipohyalinosis and arteriosclerosis.[24] These pathological changes are likely to contribute to the poor prognosis of SAO patients, independent of lipid and glucose levels. Thirdly, the role of lipid and glucose levels in stroke prognosis may be more nuanced than previously thought. For instance, recent studies have suggested that lipid metabolism plays a complex role in stroke pathophysiology, with certain lipid fractions potentially being neuroprotective.[23] Similarly, the relationship between glycemic control and stroke outcome is influenced by factors such as the duration of diabetes, the presence of complications, and the effectiveness of glycemic management.[25]

The NIHSS score prior to thrombolysis serves as an indicator of stroke severity and is pivotal in prognosticating the outcomes of intravenous thrombolysis. In the NIHSS scale, the scoring weight for posterior circulation ischemia areas is less than for anterior circulation infarctions.[26] Additionally, the NIHSS scale places a significant emphasis on assessing language function, resulting in higher scores for dominant hemisphere ischemia and lower scores for non-dominant hemisphere ischemia, potentially interfering with clinicians' judgment of stroke severity. Elevated NIHSS scores pre-thrombolysis are indicative of poorer prognoses three months subsequent to thrombolysis.[27] Yet, our study found no significant differences in NIHSS scores pre-thrombolysis, post-thrombolysis, 24-h post-thrombolysis, and 7-d post-thrombolysis between the two groups. This may be because it is not sensitive to posterior circulation ischemia and non-dominant hemisphere infarction.

Time is brain. Research by Gąsecki et al suggests that patients with acute ischemic stroke should receive thrombolytic therapy as soon as possible within 4.5 hours of onset, with earlier thrombolysis leading to greater benefits.[28] Furthermore, studies have indicated that smoking is an independent risk factor for the progression of LI, leading to poorer outcomes.[29] Our study results also show that longer time from hospital admission to thrombolysis and smoking are protective factors for poor prognosis after thrombolysis in LI patients, aligning with the aforementioned evidence.

Our results align with current evidence that earlier thrombolysis and avoiding smoking improve outcomes in LI patients. However, this study is limited by its retrospective nature and single-center design, which may restrict the generalizability of the findings. Secondly, this study did not analyze infarct locations, responsible vessels, or differentiate between anterior and posterior circulations, which could be addressed in future research. Thirdly, the retrospective data collection did not allow for dynamic observation of various indicators. Future studies could observe changes in these indicators over time to identify the most predictive time points for prognosis.

Conclusion

To conclude, prolonged time from hospital admission to thrombolysis and smoking are risk factors for poor prognosis following thrombolysis in patients LI. ROC curve analysis indicates that both factors have predictive value for poor outcomes, warranting further investigation into their roles in post-thrombolysis prognosis in LI patients. This could provide a basis for predicting poor outcomes in LI patients after thrombolysis.

Data Sharing Statement

Data not directly reported in this publication can be obtained from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Xingtai People's Hospital (No.2022【089】). Written informed consent was obtained from all participants.

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Disclosure

The authors report no conflicts of interest related to this study.

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