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Analysis of prognostic factors and construction of a risk model for patients with acute cerebral infarction treated with dual antiplatelet therapy after optimal hyper thrombolytic time window.

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Keywords: brain infarction; platelet aggregation inhibitors; combination; aspirin thrombolytic therapy; time factors; risk factors.

Abstract. The objective was to identify potential risk factors for the prognosis of dual antiplatelet therapy in patients with acute cerebral infarction (ACI) treated beyond the optimal time window to prevent thrombolysis, and to construct a nomogram to evaluate such risk. The clinical data of 300 ACI patients treated outside the optimal hyperthrombolytic time window and admitted to our hospital from January 2020 to May 2024 were analyzed retrospectively. The association between potential risk factors for poor prognosis after dual antiplatelet therapy was tested by logistic regression. A nomogram was constructed to evaluate the risk of poor prognosis based on the results. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the ability of the model to differentiate types of prognoses. A calibration curve evaluated the consistency of the model, and the fitting of the model was evaluated by the Hosmer-Lemeshow (HL) test. Of the 300 patients, 52 (17.3%) had a poor prognosis. Old age, hypertension history, elevated homocysteine, elevated fibrinogen level and carotid artery stenosis were risk factors associated with poor prognosis in patients with ACI. A nomogram was built based on these risk factors. The AUC, calibration curve, and HL test demonstrated that the selected model was statistically capable of discriminating between good and poor prognosis. In conclusion, advanced age, a history of hypertension, elevated homocysteine, elevated fibrinogen, and carotid artery stenosis are risk factors associated with a poor prognosis for patients with ACI treated beyond the optimal time window. If validated, the nomogram based on these five risk factors could be used to distinguish between cases with poor prognosis and those with good prognosis among these patients.

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Análisis de factores pronósticos y construcción de un modelo de riesgo en pacientes con infarto cerebral agudo tratados con doble terapia antiplaquetaria después del tiempo óptimo para evitar hiper trombólisis.

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Palabras clave: infarto cerebral; inhibidores de la agregación plaquetaria; terapia combinada; aspirina; terapia trombolítica; factores de tiempo; factores de riesgo.

Resumen. El objetivo fue identificar factores asociados con el pronóstico de pacientes con infarto cerebral agudo (ICA) tratados con doble terapia antiplaquetaria después del periodo óptimo para evitar trombólisis, y construir un modelo de riesgo en forma de nomograma. Se analizaron retrospectivamente los datos clínicos de 300 pacientes, tratados después del tiempo hipertrombolítico, que fueron ingresados en nuestro hospital entre enero del 2020 y mayo del 2024. Los factores asociados con el mal pronóstico tras la doble terapia con antiplaquetas se analizaron con regresión logística. De acuerdo a los resultados, se construyó un nomograma para modelar el riesgo de un mal pronóstico. Se utilizó el área bajo la curva de la característica operativa del receptor (ABC) para evaluar la capacidad del modelo para diferenciar entre tipos de pronósticos. La consistencia del modelo se evaluó mediante una curva de calibración y el ajuste del modelo se evaluó mediante la prueba de Hosmer-Lemeshow (HL). De los 300 pacientes, 52 (17,3%) tuvieron un mal pronóstico. El análisis logístico mostró que la vejez, los antecedentes de hipertensión, el nivel elevado de homocisteína, el nivel elevado de fibrinógeno y la estenosis de la arteria carótida fueron factores de riesgo asociados con un mal pronóstico de los pacientes con ICA. Se construyó un nomograma basado en estos factores. La ABC, la prueba de HL, y la curva de calibración mostraron que el modelo seleccionado es estadísticamente capaz de distinguir entre buenos y malos pronósticos. Como conclusión, la vejez, los antecedentes de hipertensión, el nivel elevado de homocisteína, el nivel elevado de fibrinógeno y la estenosis de la arteria carótida son factores de riesgo asociados con un mal pronóstico en pacientes con ICA tratados después del período óptimo. Si es validado, el nomograma basado en estos cinco factores de riesgo podría ayudar a distinguir entre casos de buenos y malos pronósticos en estos pacientes.

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INTRODUCTION

Stroke is a primary chronic noncommunicable disease that seriously endangers health. According to data from the World Health Organization, the annual death rate of stroke accounts for 10.7% of the global death rate [1]. In China, stroke has become one of the major diseases causing death and disability and is the first cause of death and disability in adults, with five characteristics: high incidence, high disability rate, high mortality rate, high recurrence rate and high economic burden [2]. Stroke can cause neurological impairment of patients, seriously affect their long-term prognosis, and lead to the decline

of cognitive function and daily living ability [3], and some patients may have residual limb dysfunction [4]. The most common clinical stroke is ischemic stroke, that is, ACI, which is caused by a disturbance in the brain blood supply, and the main clinical manifestations are ischemic necrosis of localized brain tissue and nerve function deficit. Currently, the treatment of ACI primarily includes intravenous thrombolysis, intravascular intervention, and antiplatelet therapy. For ACI patients within 4.5 hours after onset, intravenous thrombolysis is the preferred method for vascular recanalization [5]. However, a considerable number of patients have insufficient understanding of acute cerebral infarction and miss the time window for effective treatment. When patients miss the optimal time for thrombolytic therapy, clinical treatment options are minimal. Therefore, dual-antiplatelet therapy (i.e., aspirin combined with antiplatelet drugs such as clopidogrel) within the hypercoagulable time window has become an important therapeutic method [6]. By inhibiting platelet aggregation and preventing thrombus formation and expansion, dual antiplatelet therapy can improve brain blood flow and promote nerve function recovery[7]. However, its therapeutic effect and prognosis are influenced by numerous factors, and responses vary significantly among patients. At present, there are relatively few studies on the prognostic factors of dual-antiplatelet therapy in ACI patients after the optimal hyperthrombolytic time window. In addition, most existing risk assessment models are based on thrombolytic therapy, and the risk model for hyperthrombolytic time-window dual therapy is not perfect, which is why it is challenging to meet the clinical demand for individualized prognosis assessment. Therefore, the purpose of this study was to analyze the prognostic factors affecting dual-antiplatelet therapy in ACI patients beyond the hyperthrombolytic time window, and to construct a nomogram which, if validated, will provide clinicians with an individualized prognostic assessment tool, optimize the treatment plan, improve the treatment effect, and reduce the disability rate and mortality.

MATERIALS AND METHODS

General information

Three hundred and ten patients outside the hyperthrombolytic time window, admitted to the Department of Neurology at our hospital from January 2020 to May 2024, were included as initial samples. However, ten patients with incomplete clinical data were excluded, resulting in a total of 300 patients meeting the inclusion criteria. Inclusion criteria: (1) Meet the diagnostic criteria of ACI [8]. (2) Admission within 24h after onset but beyond the time window of intravenous thrombolysis. (3) Aspirin combined with clopidogrel was given within 24 hours after admission. (4) Age ≥18 years. Exclusion criteria: (1) Patients with drug allergies. (2) Patients with cerebral hemorrhage, acute infection and malignant tumor. (3) Patients with coagulation dysfunction or thrombocytopenia. (4) Incomplete clinical data. This study was reviewed and approved by the Tianjin Hospital Ethics Committee.

Treatment method

Patients received routine basic interventions, including improving circulation, controlling blood pressure and blood sugar levels, and stabilizing plaque. At the same time, Clopidogrel (Sanofi Pharmaceutical Company, approval number: H20171238, specification: 75 mg x 7 tablets) was administered orally at a dose of 75 mg once daily. Aspirin (Bayer Healthcare Co., LTD., Sinopol: HJ20160685, specification: 100mg ×30 tablets) 100mg/ time, 1 time/day, orally. A course of treatment lasts for seven days. The patient persisted in the treatment for two courses.

Data collection

Through consulting electronic medical records, clinical data of patients were collected, including age, gender, history of hypertension, diabetes, smoking history,

drinking history, atrial fibrillation history, stroke history, homocysteine (HCY) and fibrinogen (Fib), high density lipoprotein, C-reactive protein (CRP) levels and carotid artery stenosis.

Outcome measurement

The primary measure of this study was the prognosis of patients with ACI. The prognosis was assessed 14 days after the onset of the disease, and the National Institutes of Health Stroke Scale (NIHSS) score was used to evaluate the prognosis of patients after treatment. The NIHSS score ranges from 0 to 42, with higher scores indicating more severe nerve damage. The score is as follows: 0 to 1: normal or nearly normal; 1-4 scores: mild stroke/minor stroke; 5~15 points: moderate stroke; 15-20 points: moderate to severe stroke; Scores 21-42: severe stroke. In this study, a score of 0 to 4 was defined as a good prognosis, and a score of 5 to 42 was defined as a poor prognosis.

Statistical method

The SPSS 23.0 statistical software was used for data analysis. Measurement data were expressed as mean ± standard deviation ($\overline{x}\pm sd$), and inter-group comparison was performed using the t-test of two independent samples. Statistical data were expressed as cases and percentages [n (%)], and the χ^2 test was used for comparison between groups. Logistic regression analysis was used to test for associated factors. $p<0.05$ was considered statistically significant. A sample of 70% of the 300 cases was selected for training to construct the model, while the remaining 30% was selected to evaluate the model's performance. The statistically significant factors were introduced into RStudio software to construct a nomogram. The model's discrimination power was evaluated using the ROC curve and calibration curve. The Hosmer-Lemeshow analysis was used to evaluate the goodness of fit of the nomogram model, and a p greater than 0.05 indicated good consistency.

RESULTS

General data comparison

According to the prognosis assessment, 52 of the 300 patients (17.3%) had a poor prognosis. There were significant differences in age, history of hypertension, homocysteine, fibrinogen, and carotid artery stenosis between the good prognosis group and the poor prognosis group (all $p<0.05$). No significant difference was observed in the comparison of other indicators (all $p>0.05$), as shown in Table 1.

Multifactor analysis

Variables with statistical significance in univariate analysis were included as independent variables, and whether there was a poor prognosis was taken as the dependent variable (yes =1, no =0). The variable assignment table is shown in Table 2. The results showed that old age, history of hypertension, elevated homocysteine level, elevated fibrinogen level, and carotid artery stenosis were risk factors for poor prognosis of ACI patients treated with dual antiplatelet therapy (Table 3).

Construction of a nomogram of prognostic factors in ACI patients

Taking 210 patients in the training set as samples, based on the results of multifactor analysis, the above five statistically significant factors were included in the risk assessment, and a column-line risk model was established (Fig. 1). The specific prediction model formula is as follows: Logit (P)= -42.356 + 0.378 × (Age) + 1.391 × (Hypertension) + 1.503 × (Carotid stenosis) + 1.471 × (Homocysteine) + 1.396 × (fibrinogen). The corresponding scores can be obtained by projecting the corresponding Points of each variable to the "points" axis. The corresponding scores can be added together, and the total scores obtained can be used to asses prognosis.

Verification of the nomogram model

To further verify the predictive efficiency of the model, ROC curves for the training set

and the test set were plotted separately (Fig. 2). The model had a high prediction accuracy in both the training set and the test set, with an ACU of 0.963 (95%CI: 0.920~1.000) and 0.969 (95%CI: 0.927~1.000), respectively. The Hosmer-Lemeshow test showed a good fit (χ^2 =14.933, p = 0.060). The calibration curve (Fig. 3) demonstrates good agreement between the prediction probabilities of the training set and the test set. In addition, the decision curve shows a significant increase in the net benefit of the nomogram (Fig. 4).

Table 1. Comparison of clinical data between the two groups.

Factors	Good prognosis group (n=248)	Poor prognosis group (n=52)	c^2/t	*p*
Age (y)	61.31±3.58*	68.27±5.26*	9.111	<0.001
Gender				
female	104(41.94)**	20(38.46)**	0.214	0.644
male	144(58.06)**	32(61.54)**		
Diabetes				
No	166(66.94)**	29(55.77)**	2.356	0.125
Yes	82(33.06)**	23(44.23)**		
Hypertension				
No	172(69.35)**	23(44.23)**	11.927	0.001
Yes	76(30.65)**	29(55.77)**		
Smoking history				
No	130(52.42)**	27(51.92)**	0.004	0.948
Yes	118(47.58)**	25(48.08)**		
Drinking history				
No	133(53.63)**	28(53.85)**	0.001	0.977
Yes	115(46.37)**	24(46.15)**		
Atrial fibrillation history				
No	207(83.47)**	39(75.00)**	2.088	0.148
Yes	41(16.53)**	13(25.00)**		
Stroke history				
No	168(67.74)**	29(55.77)**	2.733	0.098
Yes	80(32.26)**	23(44.23)**		
Carotid stenosis				
No	184(74.19)**	20(38.46)**	25.223	<0.001
Yes	64(25.81)**	32(61.54)**		
Homocysteine (μmol/L)	6.56±0.98*	8.65±1.56*	9.268	<0.001
High density lipoprotein (mmol/L)	1.31±0.21*	1.26±0.24*	1.506	0.133
C-reactive protein (mg/L)	5.39±0.99*	5.49±1.06*	0.681	0.497
Fibrinogen (g/L)	2.80±0.59*	3.29±0.77*	4.344	<0.001

Note: Data are represented as* mean ± standard deviation, and as ** n (%).

Table 2. Factor assignment table.

Factor	Assign
Age (y)	Original input
Hypertension	0=No,1=Yes
Carotid stenosis	0=No,1=Yes
Homocysteine (μmol/L)	Original input
Fibrinogen (g/L)	Original input

DISCUSSION

Previous studies have confirmed that factors such as inflammation, oxidative stress and ischemia-reperfusion injury can induce acute cerebral infarction [9] and aggravate the progression of the disease. After acute cerebral infarction, most patients present with limb weakness, sensory disorders, swallowing disorders and cognitive function decline, etc.

Table 3. Logistic regression analysis.

Factor	B	SE	Wald	*p*	OR (95%CI)
Age	0.378	0.071	28.544	<0.001	1.46 (1.27-1.68)
Hypertension	1.391	0.600	5.370	0.020	4.02 (1.24-13.03)
Carotid stenosis	1.503	0.582	6.670	0.010	4.50 (1.44-14.07)
Homocysteine	1.471	0.268	30.079	<0.001	4.35 (2.57-7.37)
Fibrinogen	1.396	0.478	8.551	0.003	4.04 (1.59-10.30)
Constant	-42.356	6.274	45.580	<0.001	-

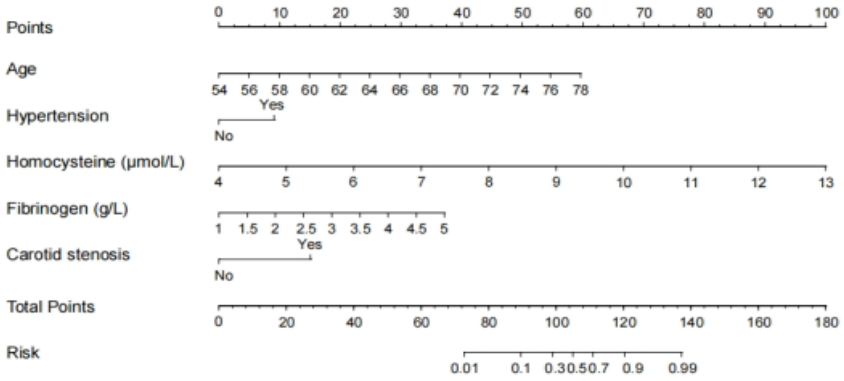


Fig. 1. Nomogram model.

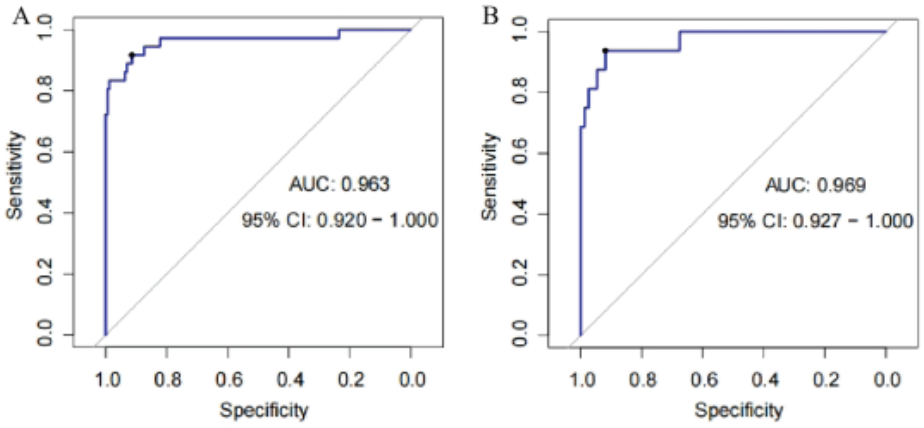
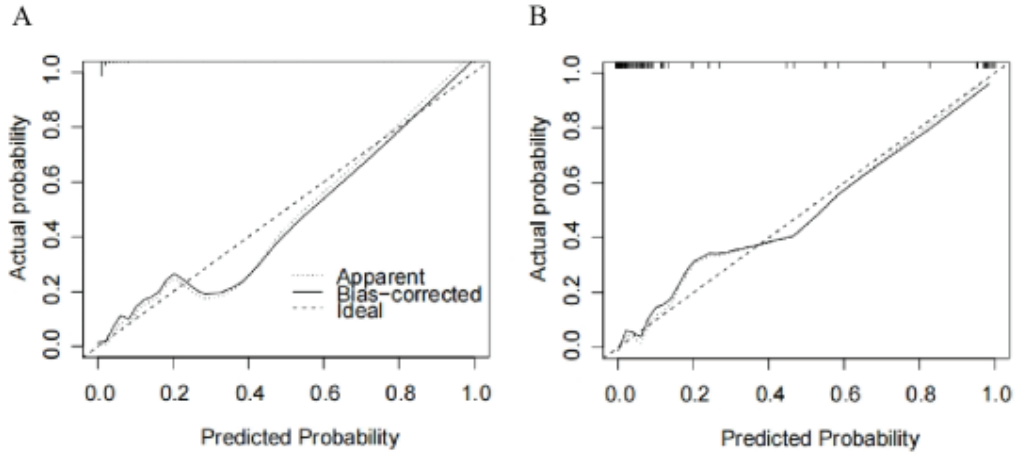


Fig. 2. ROC curve.

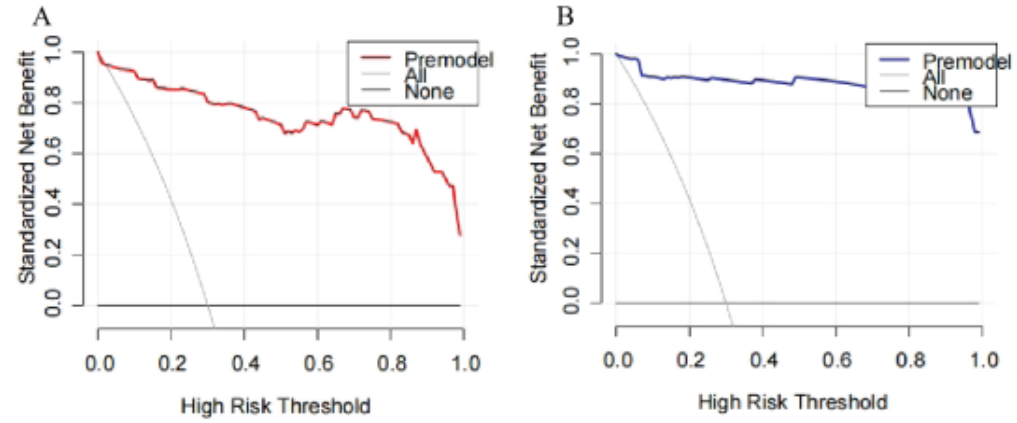
In severe cases, coma or even death may occur. If adequate measures are not taken as soon as possible, a large number of neurons may be damaged [10], thus affecting the neurological function of patients. Intravenous thrombolytic therapy within the time window is an effective means to treat patients with acute cerebral infarction. However, some patients have passed the time window and are not suitable for thrombolytic therapy. Antiplatelet aggregation therapy is a common clinical intervention for acute cerebral infarction [11]. However, its therapeutic effect and prognosis are influenced by numerous factors, and the responses of different patients vary significantly. The results of this study showed that 52 cases (17.33%) of 300 ACI patients who passed the hyperthrombolytic time window had a poor prognosis after dual-antiplatelet therapy, consistent with the report of Liu et al. [12].

The results of this study showed that old age, history of hypertension, elevated homocysteine level, elevated fibrinogen level, and carotid artery stenosis were risk factors for poor prognosis of ACI patients treated with dual antiplatelet therapy.



Note: A: Training set; B: Test set.

Fig. 3. Calibration curve analysis.



Note: A: Training set; B: Test set.

Fig. 4. Decision curve analysis of the nomogram model.

This study found that advanced age was a risk factor for poor prognosis in ACI patients, which was consistent with Zarrintan[13], who pointed out that elderly patients had degraded body function, weakened arterial elasticity, and were more likely to suffer from arterial stenosis and aggravate atherosclerosis. With the increase of age, the structure and function of cerebral vessels undergo significant changes, such as the decrease of the elasticity of blood vessel walls and the aggravation of atherosclerosis [14]. These changes make that in elderly patients after ACI, the brain tissue's tolerance to ischemia and hypoxia decrease, and the ability to recover nerve function weakens. In addition, the ability of cells to repair and regenerate is reduced in older patients, and the plasticity of neurons is diminished, resulting in slower and less effective recovery of neural function compared to younger patients, thereby increasing the risk of a poor prognosis. The history of hypertension is also one of the risk factors affecting the poor prognosis of ACI patients, which is consistent with the results of Zheng's study[15]. Long-term hypertension leads to vascular endothelial damage, platelet adhesion and aggregation, and accelerates the formation of atherosclerotic plaque[16]. In addition, hypertension also promotes the proliferation of vascular smooth muscle cells, which thickens the vascular wall and narrows the lumen, further damaging hemodynamic stability [17]. After a cerebral infarction, narrow and atherosclerotic blood vessels severely impede the supply of blood to ischemic brain tissue. Even if platelet aggregation is inhibited by dual antiplatelet therapy, established vascular lesions and disordered blood flow status still seriously interfere with the restoration of blood supply to the brain, thereby increasing the risk of poor prognosis.

The results of this study showed that increased homocysteine levels was a risk factor for poor prognosis of patients with ACI treated with dual antiplatelet. Relevant studies have shown that the plasma homocysteine level of ACI patients is significantly higher than that of the general population [18]. The possible reason is that homocysteine is a sulphur-containing amino acid, and its elevated level can damage vascular endothelial cells, promote inflammation and oxidative stress, and accelerate the formation of atherosclerotic plaque. In addition, homocysteine can also directly activate coagulation factors, increase blood coagulation and promote the formation of thrombus [19]. During the hyperthrombolytic time window therapy for cerebral infarction, this tendency of hypercoagulation interacts with vascular lesions, hindering the reperfusion process of ischemic brain tissue, aggravating nerve injury, and leading to poor prognosis. Carotid artery stenosis is a risk factor for poor prognosis of ACI patients treated with dual antiplatelet therapy. It has been reported that plasma homocysteine level is positively correlated with the occurrence and severity of carotid artery stenosis [20]. Carotid artery stenosis significantly reduces the blood supply to the brain, leaving the brain tissue in a fragile state of chronic ischemia and hypoxia. During the occurrence of ACI, the blood supply of ischemic penumbra is severely limited due to carotid artery stenosis, which cannot effectively meet the oxygen and nutrients required for the repair of damaged brain tissue, thus expanding the scope of brain tissue injury and increasing the difficulty of nerve function recovery [21]. When carotid artery stenosis and homocysteine level increase, the two cooperate to aggravate vascular disease and blood hypercoagulability. In the course of dual antiplatelet therapy, this combined effect will weaken the therapeutic effect and make brain tissue ischemia and hypoxia continue to worsen, thereby jointly increasing the risk of poor prognosis of patients. Increased fibrinogen level is also a risk factor for poor prognosis of ACI patients treated with dual antiplatelet therapy, which is consistent with the results of the study [22]. The possible reason is that fibrinogen is a key protein in the process of blood coagula-

tion, and its increased level will enhance the coagulation ability of blood and promote the formation and stability of thrombosis. In ACI patients, elevated fibrinogen levels not only increase the burden of cerebral thrombosis and hinder the recovery of cerebral blood flow, but also further damage brain tissue by activating coagulation factors and inflammatory response [23]. Fibrinogen can also bind to platelets, enhancing the aggregation and activation of platelets, weakening the effect of dual-antiplatelet therapy, and making the disease of cerebral infarction difficult to control effectively.

Additionally, this study constructs a nomogram risk model based on the associated factors. The nomogram can integrate additional clinicopathological parameters to achieve more individualized predictions. It is a calculation chart, rather than complex formulas, presenting the results of regression analysis in an intuitive graphical way. The results of this study showed that the AUC values of the area under the ROC curve of the test set and validation data set of the nomogram model were 0.963 (95%CI: 0.920~1.000) and 0.969 (95%CI: 0.920~1.000), respectively, and the AUC values of the two datasets were >0.75, indicating that the nomogram had good differentiation. The results of this study demonstrate that a model for predicting poor prognosis in ACI patients treated beyond the hyperthrombolytic time window has been successfully established. Following validation in other populations, this nomogram can aid clinicians in informed decision-making regarding ACI.

However, this study still has certain limitations. First, this study is a retrospective analysis with a small sample size, and the conclusions may be biased. Second, due to limitations in the data source, we were unable to include all possible influencing factors, which may limit the comprehensiveness of the constructed model. Future studies can further enhance the reliability of the findings by increasing the sample size and incorporating additional potential influencing factors. At the same time, the nomogram model established in this study exhibits a high degree of differentiation and fit, providing a valuable tool for clinicians in treatment decision-making.

In summary, the factors that affect the prognosis of patients with ACI after the hyperthrombolytic time window include advanced age, history of hypertension, elevated homocysteine level, elevated fibrinogen level, and carotid artery stenosis. The nomogram model, established based on multiple influencing factors, exhibits a high degree of differentiation and fit, providing clinicians with tools to optimize treatment and reduce disability and mortality.

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Consent to publish

The manuscript has neither been previously published nor is it under consideration by any other journal. The authors have all approved the content of the paper.

Consent to participate

We secured a signed informed consent form from every participant.

Ethic approval

The Tianjin Hospital Ethics Committee approved this study.

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Conflicts of interest

The authors declare that they have no financial conflicts of interest.

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Author contribution

JC, developed and planned the study, interpreted the results and edited and refined the manuscript with a focus on critical intellectual contributions. YH, participated in collecting, assessing, and interpreting the data and made significant contributions to the data interpretation and manuscript preparation. ML, provided substantial intellectual input during the drafting and revision of the manuscript.

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