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Hemorrhagic risk factors after rt-PA thrombolysis in acute cerebral infarction

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Abstract. – OBJECTIVE: This study aims to investigate the risk factors of hemorrhagic transformation (HT) after thrombolysis with recombinant tissue plasminogen activator (rt-PA) in patients with acute cerebral infarction (ACI) and establish a logistic regression equation and the risk prediction model.

PATIENTS AND METHODS: One hundred and ninety patients with ACI were divided into the HT group (n=20) and non-HT group (n=170) according to whether HT occurred within 24 hours after rt-PA thrombolysis. The clinical data were collected for analyzing the influencing factors, and a logistic regression analysis model was then established. Besides, patients in the HT group were further grouped into symptomatic hemorrhage (n=7) and non-symptomatic hemorrhage (n=13) according to the type of hemorrhage. The clinical diagnostic value of risk factors in symptomatic hemorrhage after thrombolysis in ACI was analyzed using the ROC curve.

RESULTS: We found that history of atrial fibrillation, time from onset to thrombolysis, pre-thrombolytic glucose, pre-thrombolytic National Institute of Health Stroke Scale (NIHSS) score, 24-hour post-thrombolytic NIHSS score, and proportion of patients with large cerebral infarction were all the influencing factors of HT risk after rt-PA thrombolysis in patients with ACI ($p<0.05$). Logistic regression analysis model was established with an accuracy of 88.42% (168/190), a sensitivity of 75.00% (15/20), and a specificity of 90.00% (153/170). The time from onset to thrombolysis, pre-thrombolytic glucose, and 24-hour post-thrombolytic NIHSS score had higher clinical value in predicting the risk of HT after rt-PA thrombolysis, with the AUCs of 0.874, 0.815 and 0.881, respectively. Blood glucose and pre-thrombolytic NIHSS score were independent risk factors related to symptomatic hemorrhage after thrombolysis in ACI ($p<0.05$). The AUCs for predicting symptomatic hemorrhage alone and in combination were 0.813, 0.835, and 0.907, respectively, with sensitivities of 85.70%, 87.50% and 90.00%, and specificities of 62.50%, 60.00%, and 75.42% respectively.

CONCLUSIONS: The establishment of a prediction model based on the risk factors of HT after rt-PA thrombolysis had a good predictive value in patients with ACI. This model was helpful in guiding clinical judgment and improving the safety of intravenous thrombolysis. Early identification of symptomatic bleeding risk factors provided a reference for clinical treatment and prognostic measures of patients with ACI.

Key Words:
Acute cerebral infarction, rt-PA thrombolysis, Hemorrhagic transformation (HT), Risk prediction model.

Introduction

Acute cerebral infarction (ACI) is a common disease with high mortality and disability rate in clinic, which is mainly induced by ischemia and hypoxia of the brain tissue due to the interruption of blood flow in the local blood supply area, resulting in corresponding neurological symptoms and signs[1]. Once cerebral infarction occurs, cerebral cells in the infarcted area suffer from ischemic damage. With the prolongation of ischemic time, the cells damaged by ischemia gradually necrotize and expand until they develop into irreversible necrosis area[2,3]. Therefore, it is of great significance to restore the cerebral blood flow perfusion in the ischemic area as soon as possible and reduce the degree of neurological deficit to improve the prognosis of patients.

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Thrombolysis and stenting are both important methods to restore cerebral blood flow perfusion in ischemic regions. Recombinant tissue plasminogen activator (rt-PA) is a kind of protease produced by DNA recombination technology. After intravenous administration, rt-PA combines with fibrin to selectively dissolve local blood clots while activating free plasminogen, thereby improving coronary artery stenosis or occlusion, restoring cerebral blood flow, rescuing neural cells in penumbra, and restoring neural function. At present, rt-PA thrombolysis is the only therapy to improve the prognosis of patients in the acute phase, but hemorrhagic transformation (HT) is an important complication of thrombolytic therapy, including symptomatic and asymptomatic bleeding transformation. The HT induced by rt-PA thrombolysis is mostly related to endothelial cell injury, oxidative stress and inflammatory reaction. On the one hand, rt-PA directly activates microglia to promote the release of inflammatory factors and the occurrence of HT. On the other hand, rt-PA destroys the blood-brain barrier by up-regulating the activity of matrix metalloproteinase-9, and further leads to hemorrhagic transformation. The high cost and relatively strict thrombolytic time window limit the widespread clinical use of rt-PA thrombolytic therapy[4,5]. Therefore, it is of great significance to explore the influencing factors of HT after rt-PA thrombolysis in ACI and improve the safety of rt-PA thrombolysis.

In this study, the patients with ACI diagnosed and treated in our hospital from January 2018 to January 2022 were picked as the subjects and were grouped according to whether HT occurred within 24 hours after rt-PA thrombolysis. The influencing factors of HT after rt-PA thrombolysis in ACI were analyzed. The logistic regression analysis model was established, and its clinical application value was verified. In addition, the risk factors of symptomatic bleeding in HT patients were discussed to provide a theoretical basis for timely clinical intervention.

Patients and Methods

General Materials

One hundred and ninety patients with ACI diagnosed and treated in our hospital from January 2018 to January 2022 were randomly picked as the subjects. Among them, 120 males and 70 females aged between 28-76 years old were included, with an average age of 61.49±10.18. All patients received rt-PA thrombolytic therapy. Inclusion criteria: (1) All subjects met the criteria for diagnosis and treatment of ACI[6]. (2) All patients met the indications of rt-PA thrombolysis, including the onset time within 5 hours, and the brain function continued to be damaged for more than 1 hour. (3) All patients signed the informed consent form and actively participated in the study. (4) The patients had complete clinical and pathological data and could cooperate with the research. (5) The study was approved by the Ethics Committee of our hospital. Exclusion criteria: (1) patients with intracranial hemorrhage. (2) Patients with obviously abnormal liver and kidney function or heart function. (3) Patients who received major surgery 1 month before participating in the study. (4) Patients with coagulation dysfunction. (5) Patients who were allergic to the drugs used in the study. The subjects were graded as HT group (n=20) and non-HT group (n=170) according to whether HT occurred within 24 hours after rt-PA thrombolysis. Among the patients in the HT group, there were 7 cases of symptomatic hemorrhage and 13 cases of non-symptomatic hemorrhage. The selection process of general data is shown in Figure 1.

rt-PA Thrombolytic Therapy

Patients with ACI should receive rt-PA thrombolysis within 1 hour. The rt-PA drug was dissolved with water for injection under sterile conditions[7]. The total dose of rt-PA (Boehringer Ingelheim, Ingelheim am Rhein, Germany, specification: 10 mg, batch number: 20170815) was calculated according to 0.9 mg/kg. Then, 10% of the total dose was injected intravenously, and the remaining 90% was continuously injected intravenously within 1 h.

Collection of Clinical and Pathological Data

The patients' clinical data, including gender (male, female), age, weight, history of atrial fibrillation (yes, no), history of hypertension (yes, no), history of diabetes (yes, no), history of smoking (yes, no), history of alcohol abuse (yes, no), time from onset to thrombolysis, blood glucose before thrombolysis, blood pressure before thrombolysis (systolic and diastolic pressure), The National Institute of Health Stroke Scale (NIHSS) score (NIHSS score before thrombolysis, NIHSS score 24 hours after thrombolysis), the proportion of patients with massive cerebral infarction, white blood cells, platelets, fibrinogen, homocysteine, and creatinine, etc. were detected.

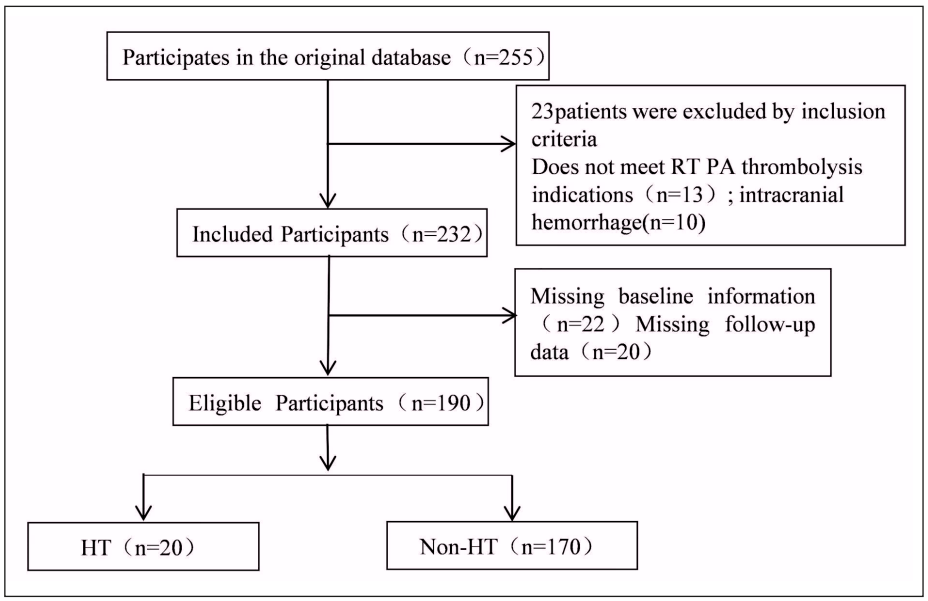

Figure 1. The selection process of general data.

Statistical Analysis

SPSS 21.0 (IBM Corp., Armonk, NY, USA) data statistics software was used for data calculation. Enumeration data were expressed in [cases (%)] and compared using χ^2 test. The measurement data were all in accordance with the normal distribution through the normal distribution test. The measurement data were expressed in the form of () and compared using *t*-test between the two groups. The risk factors related to the risk of HT after rt-PA thrombolysis in patients with ACI were analyzed using a Logistic regression model. A logistic regression equation was established: *p*=ExpΣBiXi/1+ExpΣBiXi. The sensitivity, specificity, and accuracy of the model in predicting the occurrence of HT after rt-PA thrombolysis in ACI were evaluated. ROC curve was adopted to analyze the clinical value of various risk factors in predicting the risk of HT. $p<0.05$ indicated that the difference was statistically significant.

Results

Univariate Analysis of HT Risk after rt-PA Thrombolysis in Patients with ACI

There was no significant difference between HT group and non-HT group in gender, age, history of hypertension, history of diabetes, smoking history, history of alcohol abuse, time from onset to thrombolysis, blood pressure before thrombolysis, platelet, homocysteine and creatinine ($p>0.05$). There were statistically significant differences between the HT group and the non-HT group in terms of weight, history of atrial fibrillation, pre-thrombolysis blood glucose, pre-thrombolysis NIHSS score, 24-hour post-thrombolysis NIHSS score, the proportion of patients with large cerebral infarction, leukocytes and fibrinogen ($p<0.05$, Table I).

Regression Analysis of HT Risk After rt-PA Thrombolysis in Patients with ACI

Logistic regression model analysis was conducted taking the occurrence of HT in patients with ACI after rt-PA thrombolysis as the dependent variable and the statistically significant indicators in Table I as independent variables. The results showed that history of atrial fibrillation, time from onset to thrombolysis, pre-thrombolytic glucose, pre-thrombolytic NIHSS score, 24-hour post-thrombolytic NIHSS score, and proportion of patients with large cerebral infarction were all the influencing factors of HT risk after rt-PA thrombolysis in patients with ACI ($p<0.05$, Table II).

Establishment and Evaluation of Prediction Model

According to the results in Table II, the Logistic regression prediction model was $p=1/1+\text{Exp}\Sigma(4.156-0.959X_1-1.293X_2-1.315X_3-0.953X_4-1.880X_5-0.953X_6)$. The closer the *p*-value was to 1, the greater the possibility of HT after rt-PA thrombolysis. The comparison table between the

Table I. Univariate analysis of HT risk after rt-PA thrombolysis in patients with ACI ($\bar{x}\pm s$), [cases (%)].

Groups	HT group (n=20)	Non-HT group (n=170)	χ^2/t	p
Gender (%)			2.361	0.124
Male	14 (70.00)	98 (57.65)		
Female	6 (30.00)	72 (42.35)		
Age (year)	66.88±11.35	65.36±10.14	0.885	0.377
Weight (kg)	59.13±7.26	66.26±9.51	4.585	<0.001
History of atrial fibrillation (%)			20.756	<0.001
Yes	13 (65.00)	53 (31.18)		
No	7 (35.00)	117 (68.82)		
History of hypertension (%)			0.870	0.351
Yes	12 (60.00)	115 (67.65)		
No	8 (40.00)	55 (32.35)		
History of diabetes (%)			0.074	0.785
Yes	4 (20.00)	31 (18.24)		
No	16 (80.00)	139 (81.76)		
Smoking history (%)			2.306	0.129
Yes	11 (55.00)	68 (40.00)		
No	9 (45.00)	102 (60.00)		
History of alcohol abuse (%)			1.274	0.259
Yes	11 (55.00)	77 (45.29)		
No	9 (45.00)	93 (54.71)		
Time from onset to thrombolysis (h)	3.76±0.83	2.60±0.72	9.479	<0.001
Pre-thrombolysis blood glucose (mmol/L)	6.64±1.95	3.60±1.69	10.582	<0.001
Blood pressure before thrombolysis (mmHg)				
Systolic pressure	146.84±23.47	149.85±20.25	0.874	0.383
Diastolic pressure	87.18±14.13	86.69±16.47	0.181	0.857
NIHSS score (score)				
Before thrombolysis	15.19±3.13	12.60±3.17	4.894	<0.001
24 hours after thrombolysis	15.87±4.26	6.41±2.65	19.800	<0.001
Proportion of patients with large cerebral infarction (%)	6 (30.00)	11 (6.47)	13.756	<0.001
Leukocytes ($\times10^9$/L)	14.69±5.03	8.81±2.94	10.928	<0.001
Platelet ($\times10^9$/L)	184.12±60.19	193.41±61.14	0.911	0.363
Fibrinogen (mmol/L)	5.96±2.16	3.24±1.83	8.717	<0.001
Homocysteine (mmol/L)	12.79±2.43	13.70±2.89	1.913	0.057
Creatinine (mmol/L)	78.81±8.03	75.79±10.81	1.711	0.088

Table II. Regression analysis of HT risk after rt-PA thrombolysis in patients with ACI.

Factors	B	SE	Wald	p	OR	95% CI
Weight	0.442	1.056	0.181	0.680	1.540	0.172-2.934
History of atrial fibrillation	0.959	0.430	5.052	0.036	2.625	1.129-6.040
Time from onset to thrombolysis	1.293	0.451	8.572	0.002	3.650	1.525-8.681
Pre-thrombolytic glucose	1.315	0.471	7.420	0.005	3.725	1.455-9.571
Pre-thrombolytic NIHSS score	0.953	0.416	5.125	0.020	2.583	1.135-5.757
24-hour post-thrombolytic NIHSS score	1.880	0.574	11.072	0.001	6.668	2.152-11.872
Proportion of patients with large cerebral infarction	0.953	0.416	5.125	0.032	2.572	1.135-5.785
White blood cell	1.175	0.626	3.428	0.064	2.133	0.929-3.299
Fibrinogen	0.970	0.611	2.509	0.112	1.638	0.172-1.985
Constant term	4.156	1.118	10.569	0.001	0.052	—

predicted value and the actual data was obtained using 0.5 as the junction point of the predicted probability value. The results in Table III showed that the Logistic regression analysis model had an accuracy of 88.42% (168/190), a sensitivity of 75.00% (15/20), and a specificity of 90.00% (153/170) in predicting the occurrence of HT after rt-PA thrombolysis in ACI.

Table III. Establishment and evaluation of prediction model.

Predicted incidence	Actual incidence		Total incidence
	Occurred	Non-occurred	
Occurred	15	17	32
Non-occurred	5	153	158
Total incidence	20	170	190

The Clinical Value of ROC Curve Analysis of Influencing Factors in Predicting the Risk of HT After rt-PA Thrombolysis

The ROC curve showed that the AUCs of the time from onset to thrombolysis, pre-thrombolytic glucose, and 24-hour post-thrombolytic NIHSS score were 0.874, 0.815, and 0.881, respectively, with a sensitivity of 90.00%, 85.00% and 92.00% respectively, and a specificity of 61.60%, 65.70% and 73.62% respectively (Table IV and Figure 2).

Univariate Analysis of the Transformation Between Symptomatic and Asymptomatic Bleeding

The differences in age, glucose, and pre-thrombolytic NIHSS score were statistically significant between patients with symptom-

Table IV. TThe clinical value of ROC curve analysis of influencing factors in predicting the risk of HT after rt-PA thrombolysis.

Factors	AUC	95% CI	Sensitivity	Specificity	*p*
History of atrial fibrillation	0.669	0.541-0.797	65.00	69.80	0.013
Time from onset to thrombolysis	0.874	0.805-0.944	90.00	61.60	0.000
Pre-thrombolytic glucose	0.815	0.731-0.899	85.00	65.70	0.000
Pre-thrombolytic NIHSS score	0.705	0.597-0.812	70.00	51.46	0.003
24-hour post-thrombolytic NIHSS score	0.881	0.804-0.958	92.00	73.62	0.003
Proportion of patients with large cerebral infarction	0.618	0.472-0.763	60.00	58.62	0.086

Table V. The clinical value of ROC curve analysis of influencing factors in predicting the risk of HT after rt-PA thrombolysis.

	Symptomatic bleeding (n=7)	Asymptomatic bleeding (n=13)	*t*	*p*
Age (year)	71.75±8.25	63.52±6.73	2.414	0.027
Weight (kg)	68.28±12.02	70.90±11.25	0.485	0.633
Blood glucose (mmol/L)	8.25±1.33	6.39±1.78	2.414	0.027
Systolic blood pressure (mmHg)	150.26±12.33	149.84±25.76	0.040	0.968
Diastolic pressure (mmHg)	88.25±5.89	90.26±4.18	0.890	0.385
NIHSS score before thrombolysis	18.50±2.25	13.25±1.48	6.312	0.001
Triglyceride	0.96±0.48	1.06±0.25	0.682	0.504

Table VI. Multivariate analysis of factors influencing the transformation of symptomatic and asymptomatic bleeding after thrombolytic therapy in patients with ACI.

Factors	B	SE	Wald	*p*	OR	95% CI
Age	0.553	0.266	2.023	0.053	2.342	1.442-3.375
Blood glucose	1.482	0.625	5.600	0.017	4.382	1.279-11.258
NIHSS score before thrombolysis	2.273	0.672	11.381	0.001	9.720	2.592-16.358

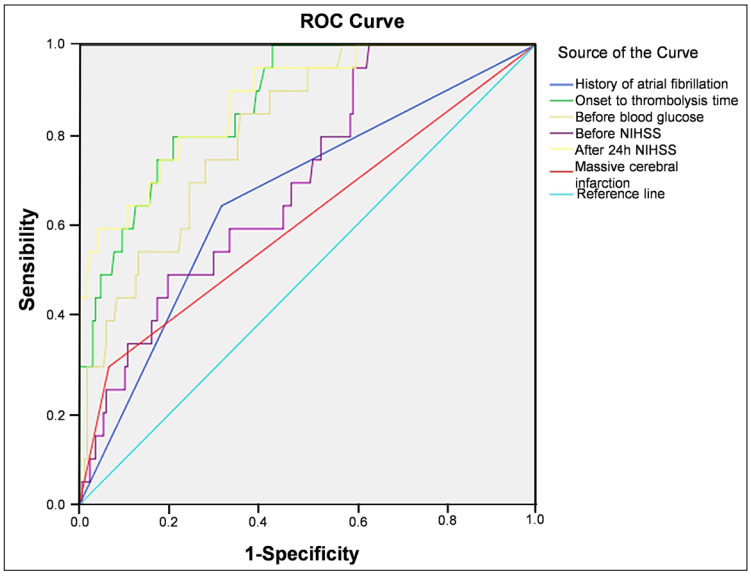

Figure 2. The clinical value of ROC curve analysis of influencing factors in predicting the risk of HT after rt-PA thrombolysis.

atic and asymptomatic hemorrhagic transformation (p<0.05, Table V).

Multivariate Analysis of Factors Influencing the Transformation of Symptomatic and Asymptomatic Bleeding after Thrombolytic Therapy in Patients with ACI

Logistic regression model analysis was conducted taking whether HT was symptomatic bleeding in patients with ACI after rt-PA thrombolysis as the dependent variable, and the statistically significant indicators in Table IV as independent variables. The results showed that blood glucose and pre-thrombolytic NIHSS score were independent risk factors related to symptomatic hemorrhage after thrombolysis in ACI (p<0.05, Table VI).

ROC Curve Analysis About the Clinical Value of Blood Glucose and NIHSS Score Before Thrombolysis in Predicting Symptomatic Bleeding

According to the ROC curve analysis, the AUCs of blood glucose and NIHSS score before thrombolysis alone and in combination in predicting symptomatic hemorrhage were 0.813, 0.835, and 0.907 respectively, with sensitivities of 85.70%, 87.50%, and 90.00%, and specificities of 62.50%, 60.00%, and 75.42% respectively. The predictive value of the combined detection was higher (Table VII and Figure 3).

Discussion

Acute cerebral infarction (ACI) is a common clinical brain function defect syndrome, which has the characteristics of a high incidence rate, high disability rate, high mortality and recurrence rate, and complex pathogenesis. Previous study[8] found that more than 80% of the patients suffered from cerebral ischemia and hypoxia due to stenosis and occlusion of the cerebral artery lumen or blockage of cerebral vessels due to thrombosis. The main method to treat ACI is to restore the blood perfusion of ischemic tissues in time. Thrombolytic therapy is the main method for ACI treatment to restore cerebral blood flow in the ischemic area and reduce the area of cerebral infarction by dredging the blocked cerebral vessels

Table VII. ROC curve analysis about the clinical value of blood glucose and NIHSS score before thrombolysis in predicting symptomatic bleeding.

Factors	AUC	95% CI	Sensitivity	Specificity	*p*
Blood glucose	0.813	0.626-0.825	85.70	62.50	0.024
NIHSS score before thrombolysis	0.835	0.633-0.905	87.50	60.00	0.016
Combined detection	0.907	0.77-0.988	90.00	75.42	0.003

quickly. rt-PA is a serine protease mainly existing in vascular endothelial cells, which was found to effectively dissolve proteins in blood vessels and accelerate the dissolution of fibrin[9]. However, HT is a serious complication after rt-PA thrombolytic therapy. Statistics[10] showed that the risk of HT in patients after rt-PA thrombolysis was much higher compared with the patients with spontaneous HT. Therefore, the establishment of a risk prediction model for the transformation of hemorrhage after thrombolysis in patients with ACI plays an important role in improving the prognosis of patients.

In this study, the clinical data of patients were collected to analyze the related factors affecting HT risk after rt-PA thrombolysis for ACI. The results showed that the history of atrial fibrillation, blood glucose before thrombolysis, NIHSS score before thrombolysis, NIHSS score 24 hours after thrombolysis, and the proportion of patients with massive cerebral infarction were all the influencing factors of HT risk after rt-PA thrombolysis for ACI, and they were also independent risk factors. The reason is that atrial fibrillation is a common cerebrovascular disease and a common cause of cerebral embolism. Statistics[11] showed that cerebral embolism induced by atrial fibrillation accounted for 1/5-1/4 of all patients with ischemic stroke, by comparing the incidence of HT after thrombolytic therapy in cerebral infarction patients combined with or without atrial fibrillation[12]. It was found that cerebral infarction patients combined with atrial fibrillation had a higher risk of HT after thrombolytic therapy. The main reason for this may be that patients combined with atrial fibrillation had a sudden onset and could not form collateral circulation in time, thus leading to a poor prognosis. Timely treatment has a great impact on the outcome. Previous studies[13] found that the prognosis of patients with acute cerebral infarction was greatly improved when thrombolytic therapy was applied within 3 hours of onset. It was reported[14] that the time from onset to thrombolysis might be an important factor in determining the therapeutic effect of patients by reducing mortality and improving the prognosis of patients. The logistic regression prediction model established in this study had the accuracy, sensitivity and specificity of 88.42% (168/190), 75.00% (15/20) and 90.00% (153/170), respectively, in predicting the occurrence of HT after rt-PA thrombolysis in ACI. All the above research results showed that thrombolytic therapy was the most effective treatment method for ACI, which could effectively relieve thrombosis and dredge the occluded blood vessels, restore the blood supply of brain tissue, and protect brain cells. However, the adverse complication of HT seriously affected the curative effect of thrombolytic therapy and increased the mortality and disability rate. The risk prediction model based on risk factors had good prediction ability and certain accuracy, which

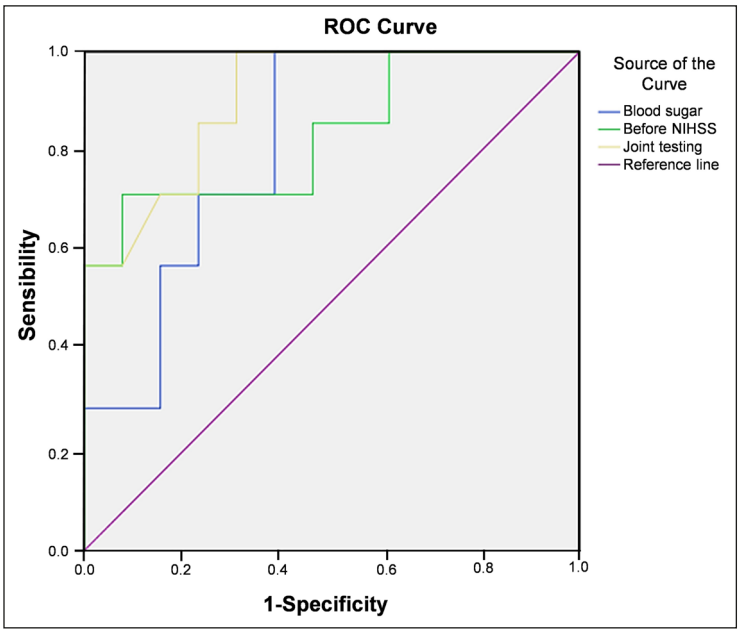

Figure 3. ROC curve analysis about the clinical value of blood glucose and NIHSS score before thrombolysis in predicting symptomatic bleeding.

was helpful in guiding clinical judgment of HT in patients with ACI after thrombolysis.

Many studies[15,16] have shown that blood glucose level has an important relationship with poor prognosis of stroke. In patients with acute ischemic stroke receiving thrombolytic therapy, hyperglycemia was closely associated with HT. Under the stimulation of hyperglycemia for a long time, cerebral vascular endothelial cells are seriously damaged, and the permeability of the blood-brain barrier is markedly enhanced, thus inducing the occurrence of HT. NIHSS score is the most commonly used scoring method to evaluate patients' neurological function in clinical practice. A higher NIHSS score means the degree of neurological function defect in patients is higher[17]. In addition, NIHSS score also indirectly indicates the size of the infarct area after the onset of the disease. A higher NIHSS score indicates a larger cerebral infarction area of the patient, which increases the permeability of the vascular wall, thus inducing reperfusion bleeding after thrombolytic treatment[18]. At present, the risk factors of HT after rt-PA thrombolysis in ACI have been discussed in the field of cerebrovascular disease. These risk factors are correlated, and single-factor prediction has a certain clinical value. In this study, ROC curve analysis confirmed that the time from onset to thrombolysis, blood glucose before thrombolysis, and NIHSS score 24 hours after thrombolysis had certain clinical value in predicting the risk of HT after rt-PA thrombolysis in ACI. The results confirmed that in patients with ACI receiving rt-PA thrombolytic therapy, targeted treatment measures could be formulated according to relevant risk factors to adjust the rt-PA intravenous thrombolytic dose and treatment plan and improve the safety of intravenous thrombolytic therapy. At present, HT is graded as asymptomatic bleeding transformation and symptomatic bleeding transformation according to whether there are clinical symptoms[19]. Asymptomatic bleeding transformation means that there were no obvious clinical symptoms, but bleeding lesions were found through the imaging examination. The European Collaborative Study on Acute Stroke (ECASS) defined[20,21] symptomatic bleeding as a lesion with worsening clinical symptoms that can be explained by CT, and the NIHSS score $\geq$4 points. Symptomatic hemorrhagic transformation is the most serious type of HT and a predictor of poor prognosis. This study found that blood glucose and NIHSS score before thrombolysis were independent risk factors for symptomatic hemorrhage after thrombolysis in ACI and had certain predictive values for symptomatic hemorrhage transformation.

Conclusions

The history of atrial fibrillation, the time from onset to thrombolysis, blood glucose before thrombolysis, NIHSS score and the proportion of patients with massive cerebral infarction were all influencing factors of HT risk after rt-PA thrombolysis for ACI. The prediction model based on the risk factors of HT after rt-PA thrombolysis in patients with ACI had a good predictive value, which was helpful in guiding the clinical judgment of HT after thrombolysis in patients with ACI and improved the safety of intravenous thrombolysis. In addition, blood glucose level and NHISS score before thrombolysis were independent risk factors for patients with symptomatic bleeding with good predictive value. Early identification could provide guidance for the clinical screening of symptomatic bleeding patients and provide a reference for clinical treatment and prognostic measures of patients with ACI. This study still has some limitations. The establishment of the prediction model was a single-center retrospective study. A relatively small sample size may lead to some deviation, so it is necessary to further increase the sample size to reduce bias. In addition, many risk factors are related to the complex pathological mechanism of HT, and there might be some missing factors in the present study. A randomized controlled multicenter study with a larger sample size should be conducted to improve the accuracy and feasibility of the risk prediction model.

Conflict of Interest

The authors declare that they have no competing interests.

Ethics Approval

This study was approved by the Ethics Committee of General Hospital of Southern Theatre Command. Ethics approval acceptance number: NZLLKZ2020110.

Informed Consent

Informed consent was obtained from participants for the participation in the study, and all methods were carried out in accordance with relevant guidelines and regulations.

Authors' Contributions

G.-Q. Luo confirmed the authenticity of all the raw data and edited the manuscript. L. Liu processed the data and participated in writing, reviewing and editing the manuscript. Q. Liu and Z.-Y. Yang conducted the statistics, software and validation of data. All authors read and approved the final manuscript.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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