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Predictive role of admission serum glucose, baseline NIHSS score, and fibrinogen on hemorrhagic transformation after intravenous thrombolysis with alteplase in acute ischemic stroke

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Abstract. – OBJECTIVE: This study aimed to investigate the predictive role of admission serum glucose, baseline NIHSS score, and fibrinogen on hemorrhagic transformation after intravenous thrombolysis with alteplase in acute ischemic stroke.

PATIENTS AND METHODS: A total of 254 patients admitted with acute ischemic stroke who received intravenous thrombolysis with alteplase from January 2016 to December 2017 were selected to collect clinical data. Patients were divided into a hemorrhagic transformation group (n=70) and a no-hemorrhagic transformation group (n=184) based on repeat CT/magnetic resonance imaging (MRI) findings during the acute period. The demographic data, past medical history and laboratory examination indexes of the two groups were compared. Multivariate Logistic regression analysis was used to explore the influencing factors of hemorrhage transformation after intravenous thrombolysis in patients with acute ischemic stroke. ROC curve was used to plot the ability of blood glucose at admission, baseline NIHSS score and fibrinogen alone to predict bleeding transformation after intravenous thrombolysis of alteplase, and then the combined model of the three was constructed and the predictive ability of this model to bleeding transformation was evaluated.

RESULTS: Among 254 patients, 70% (27.55%) had hemorrhage transformation. Except for DNT, red blood cell count, platelet count, fibrinogen, smoking, atrial fibrillation, baseline NIHSS score and admission serum glucose, there were statistically significant differences between the hemorrhagic transformation group and the non-hemorrhagic transformation group ($p<0.05$), and there were no statistically significant differences in other indicators between the two groups ($p>0.05$). The combined model was better than the three models alone in predicting the risk of bleeding conversion ($p<0.05$). Compared with the group without hemorrhagic transformation, the 90d prognosis was worse in the hemorrhage transformation group ($p<0.05$).

CONCLUSIONS: Admission blood glucose, NIHSS score, and fibrinogen are independent risk factors for hemorrhage transformation after intravenous thrombolysis of alteplase in patients with acute ischemic stroke, and the combined model established by them has high predictive efficacy for hemorrhage transformation risk after intravenous thrombolysis of alteplase.

Key Words:

Admission blood glucose, Baseline NIHSS score, Fibrinogen, Combined model, Hemorrhagic transformation, ROC curve.

Introduction

As the most common type of stroke in China, acute ischemic stroke (AIS) accounts for 80-87% and tops the list of ischemic strokes. It is characterized by incidence, disability, mortality and recurrence[1]. Studies have shown that the 1-year mortality rate for patients with acute ischemic stroke patients is 14.4-15.4%, and the disability rate is 33.4-33.8%. Recombinant Tissue Plasminogen Activator (rt-PA) is currently the most effective treatment for acute ischemic stroke, and timed intravenous thrombolysis with rt-PA is the only treatment proven to reduce the disability rate of acute ischemic stroke[2]. However, hemorrhagic transformation after thrombolysis is very common in acute ischemic stroke, and the incidence of hemorrhagic transformation after thrombolysis in patients with acute ischemic stroke is about 2.4-4.9%, with a case fatality rate of up to

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90%[3,4]. Therefore, early and effective prediction is of great significance for the prevention and treatment of hemorrhage transformation after intravenous thrombolysis. A risk prediction model can provide a reference for clinical staff in the implementation of thrombolytic therapy, as a tool for assessing and screening the high risk of bleeding transformation after intravenous thrombolytic therapy.

About 20%-40% of patients with acute ischemic stroke will be accompanied by stress-induced glucose elevation, among which 26%-58% of patients have a history of diabetes[5]. Numerous studies[6-9] have shown that elevated blood glucose is one of the independent risk factors for poor prognosis and hemorrhagic transformation after intravenous thrombolysis in patients with acute ischemic stroke. After intravenous thrombolytic therapy in the rat model of acute ischemic stroke with elevated blood glucose, the reperfusion injury in the elevated blood glucose group was more serious, and secondary cerebral hemorrhage and mortality were both higher than those in the normal blood glucose group[10]. Retrospective study has discovered that with every 1 mmol/l increase in blood glucose, there is a 1.1-fold rise in the relative risk of hemorrhage transformation following intravenous thrombolysis. Patients who are admitted to the hospital with blood glucose levels greater than 11.1 mmol/l will experience a 1.05-fold increase in symptomatic intracerebral hemorrhage transformation (sICH) and a 1.07-fold increase in mortality for every 0.6 mmol/l rise in blood glucose[11,12]. However, at present, the sensitivity and specificity of admission serum glucose in the assessment of bleeding transformation after alteplase intravenous alteplase thrombolysis in acute ischemic stroke are low, so admission serum glucose has not been used as a specific index in the clinical evaluation of bleeding transformation. Fibrinogen (FIB), also known as coagulation factor I, is an important glycoprotein involved in the process of blood clotting and hemostasis[13]. A meta-analysis[14] has shown that the increase in plasma FIB level is an independent risk factor for cardiovascular and cerebrovascular events. In addition, scholars have shown that rt-PA activates the conversion of plasminogen to plasminase in patients receiving intravenous thrombolytic therapy, resulting in sharp fluctuations in plasma FIB levels and increasing the risk of symptomatic intracranial hemorrhage in patients[15]. However, there are still few studies on the effect of fibrinogen and admission serum glucose on bleeding transformation after alteplase intravenous thrombolysis. Therefore, this study aimed to investigate the ability of admission serum glucose, baseline NIHSS score, and fibrinogen to predict the risk of hemorrhage transformation after alteplase intravenous thrombolysis in patients with acute ischemic stroke. This study aims to help clinical neurologists to quickly evaluate and guide the decision of whether to perform intravenous thrombolysis in patients with acute ischemic stroke.

Patients and Methods

General Information

A total of 280 patients with acute ischemic stroke combined with alteplase intravenous thrombolysis in the Department of Neurology of Deyang People's Hospital from January 2016 to December 2017 were selected as the study objects.

Inclusion criteria: (1) Patients with symptoms of neurological impairment and diagnosed with acute ischemic stroke. (2) Alteplase intravenous thrombolysis guidelines were met[16]. (3) Symptom onset time < 4.5 h. (4) Age 18 or above. (5) Patients or authorized family members sign informed consent. (6) Hospital stay > 7 days.

Exclusion criteria: (1) Patients with intravenous thrombolysis contraindications for alteplase. (2) Patients with a Modified Rankin Scale (mRS) score of ≥2 points prior to intravenous thrombolysis. (3) Patients with severe heart, liver, or renal insufficiency. (4) Patients with infectious diseases, malignant tumors, blood system diseases, or connective tissue diseases. (5) Patients who are unable to complete the telephone interview.

Data Collection

Collect data from electronic medical records, including age, sex, body mass index (BMI), vascular risk factors (smoking, alcohol consumption, hypertension, hyperlipidemia, glucuria, atrial fibrillation, history of stroke and coronary heart disease), immediate blood pressure on admission, admission serum glucose, modified Rankin scale before stroke (mRS Score), National Institutes of Health Stroke Scale (NIHSS) score, infarct site (left side, right side and anterior and posterior circulation), door-to-needle time (DNT), Onset-to-Needle Time (ONT). Other data analyzed included white blood cell count, hemoglobin, platelet count, red blood cell count, neutrophil

ratio, blood glucose, fibrinogen, international normalized ratio, D-dimer, PT, APTT, uric acid, sodium, and potassium. All blood samples were taken on admission to the hospital but before any medication was administered.

Intravenous Thrombolysis

All patients were given intravenous thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA), manufactured by Boehringer Ingelheim, Germany, under the trade name Atonil. The therapeutic dose of rt-PA was 0.9 mg/kg, the maximum dose was no more than 90 mg, 10% of the dose was first injected intravenously within 1 min, and 90% of the dose was administered by micropump for 60 minutes. Patients should be closely observed during and within 24 hours of intravenous thrombolysis.

Group and Definition of Bleeding Transformation

Patients were divided into the hemorrhage transformation group (HT group) and the no-hemorrhage transformation group (no-HT group) according to reexamination of skull imaging. Evaluation of hemorrhage transformation: head CT findings were reviewed within 24h after intravenous thrombolysis or head CT/MRI findings were reviewed at (10±3) d after onset to assess whether bleeding transformation had occurred. According to the ECASS II (European Cooperative Acute Stroke Study) criteria, there are two types[17]: (1) Hemorrhagic Infarction (HI): punctate hemorrhage along the edge of the infarct area, or patchy hemorrhage within the infarct area with no occupying effect. This includes hemorrhagic infarct type 1 (HI-1, which is a punctate hemorrhage distributed along the infarct foci), hemorrhagic infarct type 2 (HI-2, which is a patchy hemorrhage within the infarct, but without occupying effects), parenchymal hemorrhage (PH, hematoma formation with occupying effect or hemorrhage in the distal compartment of the infarct). The latter includes parenchymal hemorrhage type 1 (PH-1, a hematoma ≤ 30% of the infarct with mild occupying effects) and parenchymal hemorrhage type 2 (PH-2, a hematoma > 30% of the infarct with severe occupying effects, or any hemorrhage outside the infarct area).

Observation Indicators

(1) A one-way analysis of variance was used to compare any differences in clinical data between the HT and no-HT groups. (2) The risk factors affecting hemorrhagic transformation were clarified by logistic regression analysis. (3) The ability of admission serum glucose, baseline NIHSS score and fibrinogen alone to predict hemorrhagic transformation after intravenous thrombolysis with alteplase was plotted separately using ROC curves, and then a combined model of the three was constructed, and the predictive ability of the model for hemorrhagic transformation was assessed.

Statistical Analysis

SPSS 25.0 software was applied for statistical analysis (IBM Corp., Armonk, NY, USA). Normally distributed measures are expressed as $x\pm s$. Comparisons between groups were made using the *t*-test for comparison of two-sample means. Information on measures that did not conform to a normal distribution was expressed as median and quartiles [M(P25, P75)], and the Mann-Whitney U test for independent samples was used for comparison between groups. Information on categorical variables was expressed as number of cases and percentages [n (%)], and comparisons between groups were made using the χ^2 test or Fisher's exact probability method. Logistic regression analysis was used to determine the independent risk factors for hemorrhage transformation after alteplase intravenous thrombolysis in acute ischemic stroke. ROC curves were used to plot the value of the three separate and combined models in predicting hemorrhage transformation. $p<0.05$ was considered to be statistically significant.

Results

Clinical Data

Of the 280 consecutive patients included in this study, 12 were excluded due to the presence of infection on admission, 3 had poor malignancy, 3 had rheumatic immune disease, 5 had incomplete clinical data and lack of follow-up information, and 3 had low-quality blood samples. Finally, there were ultimately 254 patients with sufficient data to be included in this study, including 145 men and 110 women. The infarct lesion was located on the right side in 95 cases (37.40%), on the left side in 151 cases (59.46%), bilaterally in 1 case (0.39%), and no lesion was seen in 7 cases (2.75%). Infarct lesions were located in the posterior circulation in 43 cases (16.92%), in the anterior circulation in 200 cases (78.76%), no lesions were seen in 10 cases (3.93%) and in both anterior and posterior circulation in 1 case (0.39%).

Table I. Baseline characteristics of 254 patients.

	N = 254
Age (year)	68.04 ± 12.22
Men (n, %)	145 (57.08%)
Baseline NIHSS	9 (6, 14)
Baseline mRS	0 (0, 0)
DNT (minutes)	62 (48, 84)
ONT (minutes)	146 (119.25, 190)
ASG (mmol/l)	7.21 (6.30, 9.07)
Previous history (n, %)	
Hypertension	184 (72.15%)
Diabetes	58 (22.74%)
Hyperlipidemia	40 (15.68%)
CHD (n, %)	18 (7.05%)
Smoke	78 (30.58%)
Stroke	21 (8.23%)
Lesion (n, %)	
Left side lesion	151 (59.46%)
Right side lesion	95 (37.40%)
Double side lesion	1 (0.39%)
Absence of lesions	7 (2.75%)
Anterior circulation	200 (78.76%)
Posterior circulation	43 (16.92%)
Anterior and posterior circulation	1 (0.39%)

DNT: Door to Needle Time; ONT: Onset to needle Time; CHD: Coronary heart disease; ASG: Admission Serum Glucose.

Age ranged from 35-94 years, with a mean of (68.04±12.22) years. Baseline NIHSS score 2-36, median NIHSS score 9 (6, 14). Baseline mRS score 0-3, median mRS score 0 (0, 0). DNT time 3-176 minutes, median DNT 62 (48, 84) minutes. ONT 40-258 minutes, median ONT 146 (119.25, 190) minutes (Table I).

Comparison of 90d Outcome Indicators Between the Two Groups

The median mRS Score at 90 days in the hemorrhage transformation group was 4 (3, 6), and the median mRS Score in the no-hemorrhage transformation group was 1 (0, 3), and the difference was statistically significant (p<0.05) (Figure 1).

Univariate Analysis of Hemorrhagic Transformation

A total of 254 patients were included, with 70 cases (27.55%) hemorrhagic transformation and 184 cases (72.45%) without hemorrhagic transformation. The univariate analysis revealed statistically significant differences in DNT, red blood cell count, platelet count, fibrinogen, smoking, atrial fibrillation, baseline NIHSS score and admission blood glucose between the two groups (p<0. 05). The remaining indicators were not statistically significant between the two groups (Table II).

Multi-Factor Logistic Regression Analysis of Factors Influencing Hemorrhagic Transformation

With the presence of hemorrhagic transformation occurred as the dependent variable (yes as-

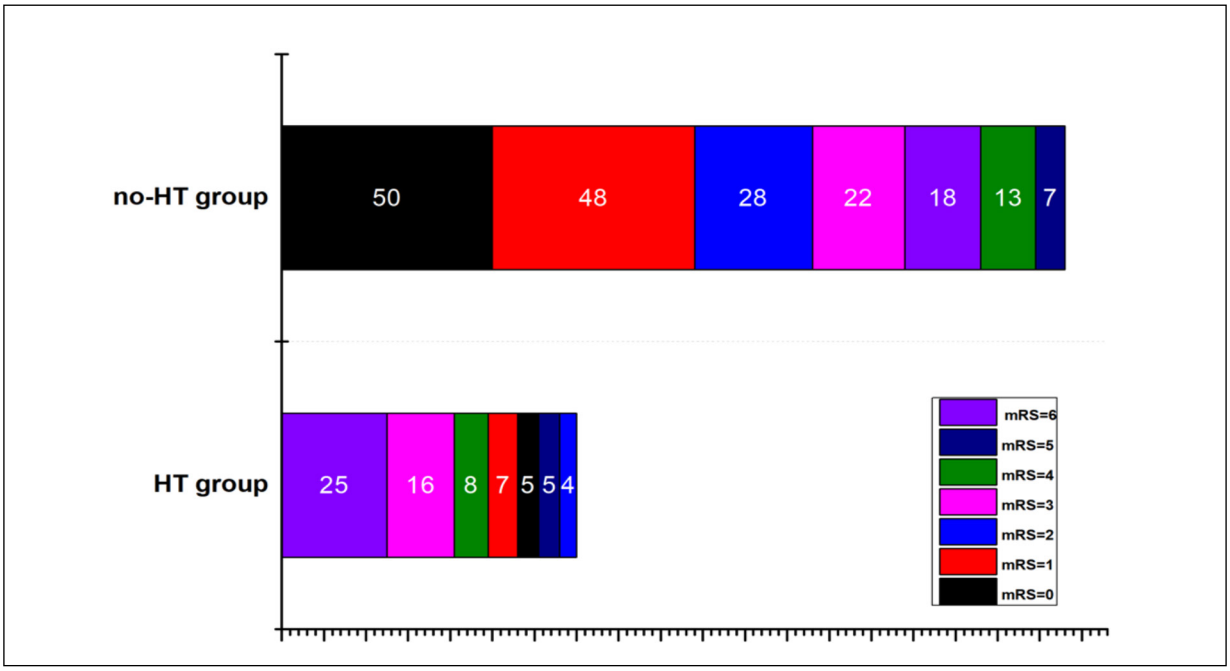

Figure 1. Comparison of 90d prognosis between the two groups.

Table II. Comparison of clinical data.

Item	T group (70)	no-HT group (184)	$t/z/\chi^2$	p
Men (n, %)	36 (51.42%)	118 (64.13%)	3.43	0.06
Age (year)	69.96 ± 11.24	67.30 ± 12.50	1.63	0.10
Left side lesion (n, %)	42 (60.00%)	107 (58.15%)	0.07	0.78
Anterior circulation (n, %)	60 (85.71%)	140 (76.08%)	2.81	0.09
DNT (minutes)	70 (53.5, 89.5)	60 (47, 79.25)	2.54	0.01
ONT (minutes)	150 (121.25, 190.75)	145.5 (118.75, 187.75)	0.53	0.59
SBP (mmhg)	162.81 ± 28.48	161.07 ± 24.57	0.45	0.65
DBP (mmhg)	90.39 ± 17.77	89.87 ± 15.43	0.21	0.82
Weight (kg)	60.97 ± 10.88	63.09 ± 11.27	1.37	0.17
WBC ($\times 10^9$/l)	7.90 ± 2.85	7.75 ± 3.30	0.32	0.72
RBC ($\times 10^{12}$/l)	4.34 ± 0.63	4.54 ± 0.87	2.02	0.04
PC ($\times 10^9$/l)	182.81 ± 59.14	203.40 ± 54.03	2.53	0.01
Neutrophil ratio (%)	62.68 ± 17.65	63.51 ± 11.51	0.36	0.71
Hematocrystallin (g/l)	134.24 ± 17.04	137.36 ± 14.86	1.34	0.18
PT (s)	12.88 ± 1.27	12.89 ± 1.60	0.05	0.95
APTT (s)	31.44 ± 6.55	32.21 ± 11.25	0.67	0.50
INR	1.01 ± 0.09	1.02 ± 0.14	0.67	0.50
Fibrinogen (g/l)	3.12 (2.60, 3.95)	3.76 (3.32, 4.63)	2.49	0.01
D-D	1.87 (0.62, 3.66)	1.05 (0.48, 2.32)	2.23	0.25
Na (mmol/l)	138.14 ± 2.81	138.65 ± 3.52	1.20	0.23
K (mmol/l)	3.64 ± 0.41	3.67 ± 0.45	0.50	0.61
Previous history				
Smoke (n, %)	13 (18.57%)	65 (35.32%)	6.69	0.01
Hypertension (n, %)	52 (74.28%)	132 (71.73%)	0.16	0.68
Hyperlipidemia (n, %)	12 (17.14%)	28 (15.21%)	0.14	0.70
AF (n, %)	39 (55.71%)	51 (27.71%)	17.37	< 0.05
CHD (n, %)	7 (10%)	11 (5.97%)	0.87	0.68
Diabetes (n, %)	15 (21.42%)	43 (23.36%)	0.10	0.74
Stroke (n, %)	3 (4.28%)	18 (9.78%)	2.02	0.15
Baseline NIHSS	12.5 (10, 17.75)	8 (5, 11)	9.23	< 0.05
Baseline mRS	0 (0, 0)	0 (0, 0)	1.14	0.28
ASG (mmol/l)	7.83 (6.90, 9.74)	7.07 (7.05, 8.73)	2.69	< 0.05
3M-mRS	4 (3, 6)	1 (0, 3)	6.35	< 0.05

DNT: Door to Needle Time; ONT: Onset to needle Time; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; WBC: White Blood Cell Count; RBC: Red Blood Cell Count; BP: Platelet count; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; INR: International Normalized Ratio; D-D: D-Dimer; HCY: Homocysteine; AF: Atrial fibrillation; CHD: Coronary heart disease; ASG: Admission Serum Glucose.

signed = 1, no assigned = 0), indicators that differed on univariate analysis, including baseline NIHSS score, fibrinogen, DNT, platelet count, admission blood glucose, atrial fibrillation, smoking and the inclusion of age and weight as independent variables according to the relevant literature were subjected to binary logistic regression analysis with the entry method selected "Forward LR". Results revealed that greater baseline NIHSS score, lower fibrinogen, and higher admission blood glucose were risk factors for the presence of hemorrhage transformation (all $p<0.05$) (Table III).

Analysis of the Ability to Predict the Risk of Hemorrhagic Transformation

The presence or absence of bleeding was used as the status variable (yes = 1, no = 0). Logistic regression was first used to construct a combined

Table III. Multi-factor logistic regression analysis of factors influencing hemorrhagic transformation.

Item	B	SE	p	OR	95% CI
Baselin NIHSS	0.097	0.027	< 0.05	0.908	0.861-0.956
Fibrinogen	-0.396	0.149	0.008	1.486	1.11-1.988
ASG	0.086	0.044	0.041	0.918	0.842-1.000
Constant	1.658	0.711	0.020	5.251	-

Table IV. Analysis of the ability of each index to predict hemorrhagic transformation.

Item	AUC	SE	*p*	95% CI
Baseline NIHSS	0.727	0.034	< 0.05	0.660-0.794
Fibrinogen	0.313	0.042	< 0.05	0.230-0.396
ASG	0.609	0.039	< 0.05	0.533-0.685
Combine model	0.749	0.037	< 0.05	0.676-0.822

model of baseline NIHSS score, admission blood glucose, and fibrinogen. ROC analysis was performed using the combined model, baseline NIHSS score, admission blood glucose, and fibrinogen as test variables. The results showed that the area under the curve (AUC) of the baseline NIHSS score for predicting the risk of bleeding conversion was 0.727 (0.660, 0.794). The AUC of fibrinogen for predicting the risk of hemorrhagic transformation was 0.313 (0.230, 0.396). The AUC for admission blood glucose to predict the risk of hemorrhagic transformation was 0.609 (0.533, 0.685). The combined model had an AUC of 0. 749 (0. 676, 0.822), a specificity of 75%, a sensitivity of 74.3% and a Jorden index of 0.267 for predicting the risk of hemorrhagic transformation, suggesting that the best ability to predict the risk of hemorrhagic transformation occurred when the baseline NIHSS score was 9, fibrinogen was 3.54 g/l and admission blood glucose 8.7 mmol/l (Table IV and Figure 2).

Discussion

Intravenous thrombolysis is an effective treatment for acute ischemic stroke and is recommended by the National Institute of Neurological Disorders and Stroke (NIND) and the European Collaborative Study on Acute Stroke (ECASS) in their guidelines[18]. Despite the clear evidence-based efficacy of rt-PA, its potential complications, particularly intracranial hemorrhage, will greatly increase the rate of death

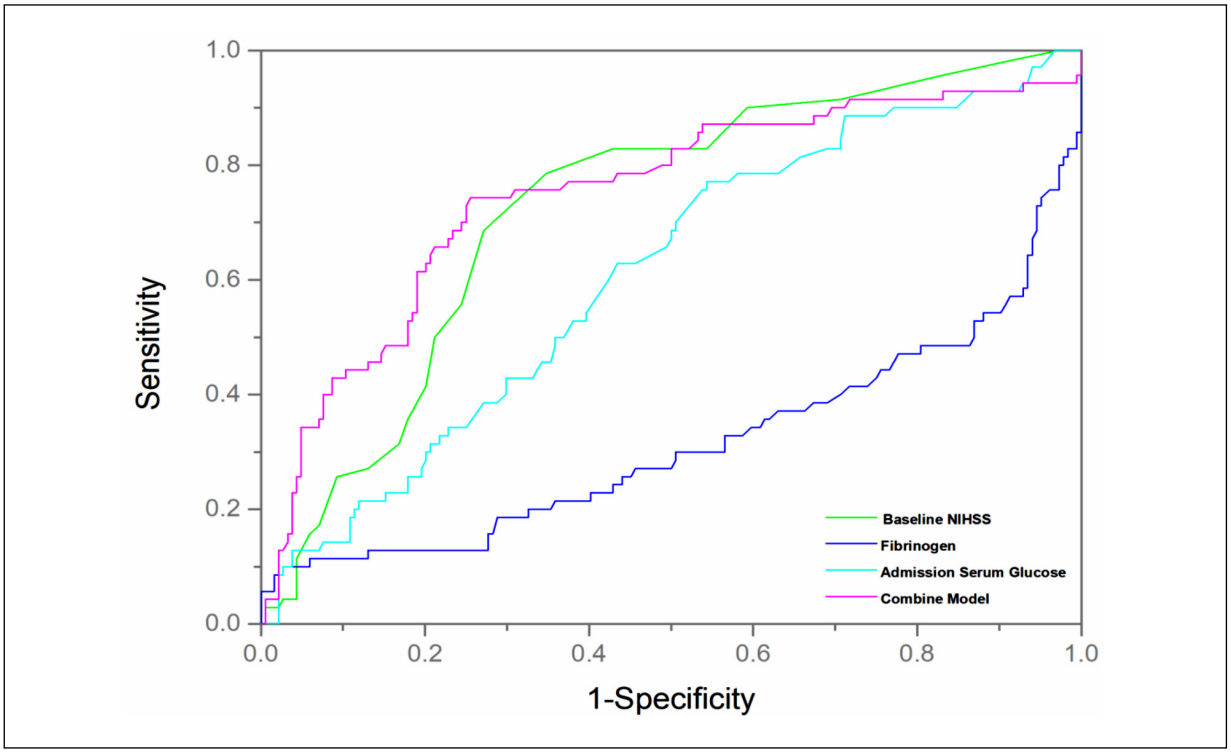

Figure 2. ROC curve.

and disability in patients and are important factors affecting the implementation of intravenous thrombolysis[19]. This study also found that the 90d prognostic outcome mRS score was worse in the HT group compared to the no-Ht ($p<0.05$), which is consistent with previous studies. Hemorrhagic transformation after thrombolysis is a pathological process of increased permeability of blood-brain barrier caused by multiple factors such as ischemic injury, reperfusion injury and coagulation disorder[20]. The mechanism by which hemorrhagic transformation occurs is unclear and the following possible mechanisms are postulated: early in the ischemic phase, damage to the endothelial cell barrier leads to the leakage of water and other small molecules, followed by the degradation of the basal layer barrier, leading to the development of hemorrhage. Secondly, despite its short half-life, rt-PA has a long duration of action on the coagulation system, resulting in reduced fibrinogen levels, prolonged prothrombin time and prolonged partial thromboplastin time, abnormalities that cause coagulation disorders and effects that can last for more than 24 hours after administration[21]. In addition, rt-PA has also been found to disrupt the blood-brain barrier and interact with the matrix metalloproteinase (MMP) system through signaling such as lipoprotein receptor-1, exacerbating dysfunctional MMP and accelerating matrix degradation of the blood-brain barrier[22]. However, the risk factors for hemorrhagic transformation after intravenous thrombolysis with alteplase are not fully understood.

This study first found that admission blood glucose was an independent risk factor for predicting hemorrhagic transformation after intravenous thrombolysis with alteplase, similar to the findings of mainstream studies[23,24]. It is now believed that blood glucose is significantly associated with prognostic outcomes in acute ischemic stroke and is an important predictor of a variety of models of bleeding conversion after intravenous thrombolysis[25]. The study found that patients with newly diagnosed diabetes and stress hyperglycemia stroke had a higher risk of stroke recurrence compared with stroke patients with previous diabetes and that stress hyperglycemia (measured as the glucose/glycosylated hemoglobin ratio) was associated with an increased risk of stroke recurrence and all-cause mortality in patients with acute ischemic stroke, independent of a previous diagnosis of diabetes already in place[26]. The Prolyse in Acute Cerebral Thromboembolism II (PROACT II) study of intra-arterial application of recombinant urokinase proliferator for acute cerebral thromboembolism showed that stroke patients with baseline glucose >200 mg/dl (11.11 mmol/L) were at increased risk of symptomatic intracranial hemorrhage after thrombolysis[27]. The mechanisms of hyperglycemia-induced hemorrhagic transformation are complex, and some studies[26,41] suggest that hyperglycemia can exacerbate hypoxic necrosis of the arterial wall, leading to disruption of the blood-brain barrier, neurovascular damage, cerebral edema and the development of hemorrhagic transformation. Specific studies are as follows: 1. Acute hyperglycemia will destroy the synthesis of nitric oxide, resulting in interference in the production of pre-thrombotic substances and vasoactive substances[34]. Vasoconstriction affects microcirculation disturbance, increases ischemia, then thrombosis and leads to vascular occlusion[35]. 2. The increase of lactic acid production in CSF induced by hyperglycemia is related to the decrease of ischemic penumbra area[36]. 3. Hyperglycemia and hyperinsulinemia in patients with acute ischemic stroke can reduce fibrinolytic activity and increase the plasminogen activator-inhibitor ratio, thereby reducing the effects of venous r-tPA and recirculation[37]. 4. Studies in animal models of ischemic stroke accompanied by hyperglycemia found that monocytes/macrophages were significantly reduced, and monocytes/macrophages were proved to be neuroprotective cells involved in neurogenesis. This study also showed that glucose metabolites, such as alpha-dicarbonyl, were increased in hyperglycemic mice[38]. 5. Hyperglycemia can cause brain edema by increasing the permeability of the blood-brain barrier and the release of inflammatory mediators[39]. 6. Hyperglycemia will increase the size of existing infarcts, thus aggravating clinical prognosis. Animal studies found that the blood glucose level reached 140-200 g/dl (mild hyperglycemia) and 240-350 mg/dl (severe hyperglycemia) with 30% and 60% glucose solution after suture closure of the middle cerebral artery in animals, respectively. The results showed that there was no statistically significant difference in infarct size between the mild hyperglycemia group and the control group. In the severe hyperglycemia group, the infarct size increased significantly[40]. Therefore, thrombolysis in stroke patients with diabetes mellitus should be performed with good control of baseline blood glucose. It is essential that the patient's

blood glucose is monitored and regulated at all times during thrombolytic therapy and that intravenous thrombolysis with alteplase should not be performed with blood glucose greater than 22.2 mmol/l.

Secondly, the study discovered that fibrinogen was an independent risk factor for hemorrhagic transformation after receiving intravenous thrombolysis with alteplase. Fibrinogen, being the most abundant coagulation protein in plasma, plays a pivotal role in the body's coagulation system, platelet aggregation and adhesion of red blood cells.

In a study comprising 3,212 patients with acute ischemic stroke, it was found that those with hyperfibrinogenemia had a 1.76-fold higher risk of in-hospital death. A subgroup analysis also suggested a significant link between hyperfibrinogenemia and in-hospital mortality[28]. In another prospective study with a follow-up exceeding 10 years, a significant association was observed between high fibrinogen levels at admission and poor long-term prognosis and mortality among patients experiencing acute ischemic stroke. The levels of fibrinogen in this group remained elevated for several months post-stroke, which could be correlated with the β-chain G455A polymorphism of the fibrinogen gene[29]. There is a paucity of studies of rt-PA intravenous thrombolysis in acute ischemic stroke patients with hyperfibrinogenemia in the Asian population. In the present study, we found significantly more grounded fibrinogen levels in the HT group than in the no-HT group. The mechanism by which patients with low fibrinogen are more susceptible to hemorrhagic transformation is unclear and may be related to the fact that some specific populations are abnormally sensitive to rt-PA, causing rt-PA to lose its specificity for selective activation and to degrade large amounts of uncrosslinked fibrinogen in the circulatory system. In addition, fibrinogen degradation products can interfere with activated fibrin function, prevent fibrin from forming cross-linked fibrin, inhibit platelet function and disrupt normal coagulation, resulting in the so-called fibrinogen degradation coagulopathy. The combination of increased vascular wall permeability, disruption of the blood-brain barrier and reperfusion injury after acute ischemic stroke eventually triggers the development of intracranial hematomas[30,31].

Thirdly, this study also found that baseline NIHSS score was also a risk factor for hemorrhagic transformation after intravenous thrombolysis with alteplase in acute ischemic stroke, which is consistent with the findings of existing studies. Ischemic strokes with high NIHSS scores are most often caused by occlusion of the main stem vessels. The likelihood of hemorrhage increases with larger infarct areas and more extensive basement membrane damage. The formation of cerebral edema leads to vessel wall damage, localized brain tissue ischemia and cerebrovascular compression, all contributing to the incidence of reperfusion hemorrhage after thrombolysis[32]. The proportion of symptomatic post-thrombolytic intracranial hemorrhage in patients with a baseline NIHSS score $\leq$10 has been reported to be <3%, whereas this proportion rises by 5% for a baseline NIHSS score $\geq$20 and the risk of post-thrombolytic parenchymal brain hemorrhage increases by 1.35-fold for every 1-point increase in baseline NIHSS score[33]. Although patients with high NIHSS scores and large cerebral infarcts have a greater probability of hemorrhagic transformation after thrombolytic therapy, they are not a contraindication to thrombolysis and still have value for active treatment within the time window.

Due to the substantial clinical risks linked to post-thrombolytic hemorrhagic transformation, anticipating the likelihood of this occurrence can provide valuable guidance for thrombolytic therapy. However, current prediction models tend to utilize a solitary predictor and are primarily predictive models formulated by foreign researchers with a distinct population focus. These models have not been verified in domestic patients and are not wholly applicable to patients with acute ischemic stroke in China. Additionally, numerous models utilize a vast array of indicators, rendering it challenging to evaluate patients holistically within a limited timeframe. Moreover, there is a scarcity of studies that combine basal NIHSS scores, fibrinogen, and admission blood glucose as predictors. Therefore, it is important to develop a risk prediction model that meets the disease characteristics of patients with acute ischemic stroke in China, improves clinical efficiency, and reduces the harm caused by bleeding after intravenous thrombolysis in patients with acute ischemic stroke.

In this study, a combined model of baseline NIHSS score, fibrinogen and blood glucose at admission was constructed by logistic regression analysis, and then, the predictive ability was evaluated by plotting the area under the ROC curve, and it was found that the predictive efficacy of the combined model was better than the predictive

value of the three individually, when the baseline NIHSS score >9, fibrinogen >3.54 g/l and admission blood glucose >8.7 mmol/l. The risk of hemorrhagic transformation after intravenous thrombolysis with alteplase was greater when mmol/l occurred.

Conclusions

In conclusion, the three indicators used in this study are easily accessible in clinical practice, and the combined model has high diagnostic efficacy and can be used to assess the risk of bleeding and 90d functional outcome after intravenous thrombolysis with alteplase in patients with acute ischemic stroke, which is of practical value in guiding clinical treatment and rehabilitation. However, the model does not include neuroimaging factors. The shortcoming of this study is that the sample size is small and further external validation with multicenter and large samples is needed to confirm its predictive performance and utility.

Conflict of Interest
The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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Informed Consent
Informed consent was waived due to the retrospective nature of the study.

Ethics Approval
Ethics approval was obtained from People Hospital of Deyang City Ethics Committee (Approval No: 04-142-K01).

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Authors' Contribution
All authors have made substantial contributions to the conception and design of the study, data acquisition, data analysis and interpretation, drafting of the article or critically revising it for important intellectual content, and final approval of the version to be submitted.

Availability of Data and Materials
The authors confirm that the data supporting the findings of this study are available within the article.

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