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Stratifying by Blood Glucose Levels to Predict Hemorrhagic Transformation Risk Post-Rt-PA in Acute Ischemic Stroke

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Objective: Stroke is a leading cause of disability and mortality worldwide, posing a significant public health challenge. While treatment of acute ischemic stroke (AIS) with recombinant tissue plasminogen activator (rt-PA) is effective but increases the risk of hemorrhagic transformation (HT). This study aimed to explore the determinants of HT in AIS patients treated with rt-PA and investigate the association between blood glucose levels and HT risk.

Methods: We conducted a prospective cohort study at the First Affiliated Hospital of Harbin Medical University from January 2018 to December 2021. Patients with AIS and who received rt-PA within 4.5 hours of symptom onset were included. Demographic, clinical, laboratory, and imaging data were collected.

Results: Of the 426 patients, 15% experienced HT post-rt-PA, occurred more frequently in patients with a history of cardiac embolism, higher prethrombolysis NIHSS scores, and elevated fasting blood glucose (FBG) levels. The frequency of HT was higher in non-diabetic patients with FBG levels ≥7.0 mmol/L compared to diabetic patients. Elevated blood glucose levels were significantly associated with HT, regardless of diabetes history.

Conclusion: The findings suggest importance of precise glycemic control during AIS management to improve patient outcomes, particularly in non-diabetic patients. Future protocols for AIS treatment should incorporate these findings to reduce HT risks. Further large-scale studies are needed to confirm these associations and guide clinical practices.

Keywords: Acute ischemic stroke, thrombolytic therapy, rt-PA, hemorrhagic transformation, blood glucose, outcomes

Introduction

Stroke, a leading cause of disability and mortality worldwide, presents a significant public health challenge, particularly in low- and middle-income countries. According to the 2019 Global Burden of Disease Study, stroke is the second leading cause of level 3 mortality, accounting for 143 million disability-adjusted life years globally.[1] This burden is particularly pronounced in regions with limited healthcare resources.[1] In China, the world's most populous nation, stroke is the leading cause of death.[2] Nationally, the incidence of stroke has been steeply rising since 1990, with recent estimates indicating 3.94 million new cases and 2.19 million deaths in 2019.[2–4] In 2022, the prevalence of stroke in China was 2.6%, the incidence rate was 505.2 per 100,000 person-years, the mortality rate was 343.4 per 100,000 person-years, with the incidence and mortality rates in rural areas were significantly higher than those in urban areas.[2] And the burden of stroke disease in China continues to rise.[5]

Treatment of acute ischemic stroke (AIS) with intravenous recombinant tissue plasminogen activator (rt-PA) is effective but not without risk, particularly regarding hemorrhagic transformation (HT). Studies have shown a higher incidence of cerebral hemorrhage in patients receiving rt-PA compared to those receiving the control treatment, with significant mortality rates.[6,7] Factors such as high blood glucose levels and a history of diabetes have been identified as

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significant predictors of cerebral hemorrhage in patients with ischemic stroke.[8–10] Therefore, studying HT after thrombolysis is of paramount importance.

HT represents a significant challenge in the management of AIS following rt-PA therapy, often leading to worse outcomes and increased mortality.[6] Despite advances in acute stroke management, predicting and preventing of HT remain a major barrier for patients' management. The complexity of the factors contributing to HT, including pre-existing comorbidities such as diabetes, complicates risk assessment and management strategies.[8]

In China, the prevalence of diabetes among adults showed a marginal but consistent increase from 2007 to 2017, highlighting this growing public health concern.[11] Given the mounting evidence that hyperglycemia plays a critical role in stroke outcomes, this trend is highly relevant to stroke management. Recent systematic reviews and meta-analyses have established strong correlation between persistent hyperglycemia and increased stroke mortality, particularly in patients without history of diabetes. These findings indicate that stroke patients who are non-diabetic but have persistent hyperglycemia are at a significantly higher risk of mortality than those who are normoglycemic.[12]

Moreover, studies have shown that the stress hyperglycemia ratio (SHR), a measure of acute hyperglycemia, is closely linked to adverse outcomes in patients with AIS. Notably, patients with AIS who had poor outcomes also had significantly higher SHR values. This correlation holds true across various cohorts, underscoring the need for close monitoring and management of blood glucose levels during the acute phase of stroke.[13]

The interplay between elevated blood glucose levels and the risk of HT in ischemic stroke patients, especially after rt-PA thrombolytic therapy, requires careful consideration. Given the rising prevalence of diabetes in China, understanding this relationship is crucial for optimizing stroke management strategies.[11]

A 2023 study involving 190 patients with AIS identified factors such as atrial fibrillation (AF), timing of thrombolysis, prethrombolytic glucose levels, and NIHSS scores, as influencing the risk of HT after rt-PA treatment.[14] A retrospective analysis of 403 patients found that smoking, prolonged activated partial thromboplastin time, low fibrinogen levels, and low platelet counts were associated with the risk of HT.[15]

A prospective study of 1125 patients found that hyperglycemia during acute ischemic stroke was associated with parenchymal hemorrhage and poor outcomes.[16] A study of patients with acute ischemic stroke also showed that the stress hyperglycemia ratio was significantly associated with the risk of hemorrhagic transformation.[17] Another single-center retrospective study found that glucose-to-platelet ratio was a predictor of hemorrhagic transformation in patients with acute ischemic stroke.[18] These findings highlight the complex interplay of various factors that contribute to the development of HT after rt-PA therapy in AIS patients and emphasize the critical role of glycemic status in HT. However, previous studies have paid little attention to the association between blood glucose levels and the risk of HT in AIS patients at different glycemic stratifications.

This hospital-based prospective study explored the determinants of HT in AIS patients treated with rt-PA and examined the association between varying blood glucose levels and HT in both diabetic and non-diabetic stroke patients following rt-PA therapy.

Methods

Study Design

This hospital-based, prospective study was conducted at the Department of Neurology, the First Affiliated Hospital of Harbin Medical University from January 2018 to December 2021. This study evaluated patients with AIS who developed HT after rt-PA thrombolysis that began within the 4.5-hour window following stroke onset.

This study was conducted in accordance with the Helsinki Declaration and received approval from the Ethics Committee of the First Affiliated Hospital of Harbin Medical University (IRB2023326). Written informed consent was obtained from all participants in the study.

Participants

This is a prospective study, and the inclusion and exclusion criteria for participants are as follows:

Inclusion Criteria

1. Meet the AIS diagnostic criteria of the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018; 2. Age > 18 years old, 3 points< NIHSS≤24 points, and receive rt-PA thrombolytic therapy; 3. Past medical history, clinically relevant laboratory examination data and other information are detailed, sufficient and complete. Patients with routine re-examination of NCCT 24 hours after intravenous thrombolysis.

Exclusion Criteria

1. Patients with AIS whose onset time exceeded the 4.5-hour treatment window; 2. Patients who received non-standard rt-PA dosages or who underwent thrombolysis at another hospital; 3. Patients receiving bridging therapy, such as arterial thrombolysis or vascular interventions; patients who underwent endovascular treatment or required fresh frozen plasma therapy or decompressive surgery. 4. Patients diagnosed with intracranial aneurysm, intracranial artery dissection, intracranial arteriovenous malformation, cerebral amyloid angiopathy, or moyamoya disease during hospitalization; 5. Patients with severe infections, malignant tumors, autoimmune disorders, liver or kidney disease, or hematological disorders (Figure 1).

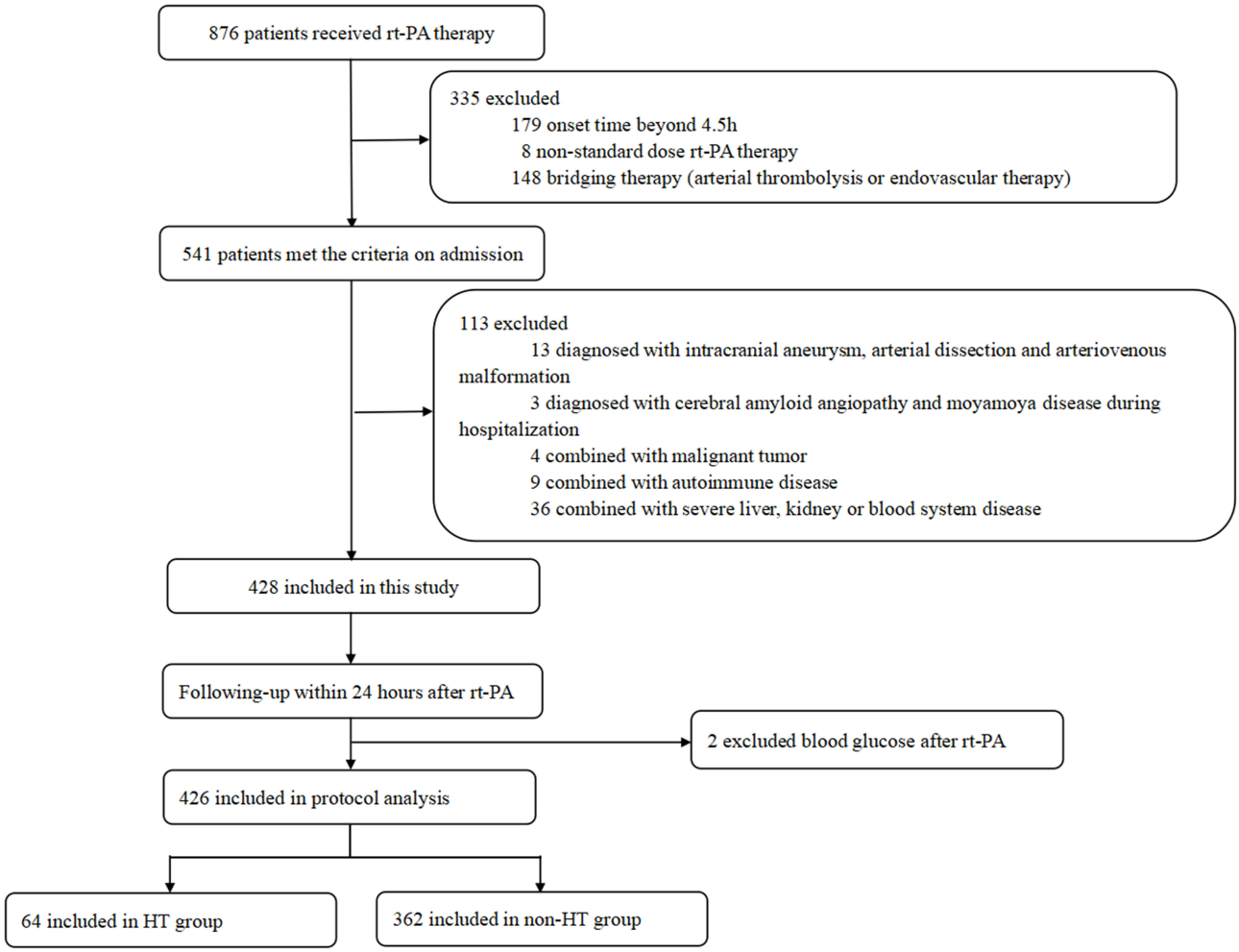

Figure 1 Flow chat of patients' selection A total of 876 patients who received rt-PA therapy were initially assessed. Of these, 335 were excluded due to various reasons: 179 had an onset time beyond 4.5 hours, 8 received a non-standard rt-PA dose, and 148 underwent bridging therapy (arterial thrombolysis or endovascular therapy). After exclusions, 541 patients met the inclusion criteria on admission. An additional 113 patients were excluded for reasons such as intracranial aneurysm, arterial dissection, arteriovenous malformation, cerebral amyloid angiopathy, moyamoya disease, malignancy, autoimmune disease, severe liver, kidney, or blood system disease, and severe infection. Two patients were excluded due to missing blood glucose data after rt-PA. In total, 426 patients were included in the final analysis. Of these, 64 patients were included in the HT group, and 362 were in the non-HT group. All patients were followed up within 24 hours after rt-PA therapy.

Clinical Data Collection

The collected clinical data included the following parameters: demographic information, such as age and sex; previous medical history (stroke, hypertension, diabetes, coronary artery disease, and AF); lifestyle factors, with a focus on smoking and alcohol consumption habits; admission information, including the timing of admission and the interval to thrombolysis; and clinical assessments, such as National Institutes of Health Stroke Scale score (NIHSS) pre- and post-thrombolysis, subtypes (TOAST, Trial of Org 10172 in Acute Stroke Treatment), treatment of hyperglycemia, ASPECTS scores.

Blood samples were collected by a specialist nurse in the ward. Blood routine tests, coagulation parameters, and random blood glucose were collected immediately after admission. Biochemical series, including fasting blood samples, were collected within 24 hours of admission. Blood glucose was measured twice: random blood glucose before thrombolysis and fasting blood glucose after intravenous thrombolysis. If fasting blood glucose was elevated, blood glucose was monitored seven times, and fasting blood glucose and glycated hemoglobin were remeasured.

Laboratory Testing

The laboratory tests included blood glucose level upon admission; glucose, fasting blood glucose (FBG) and glycated hemoglobin levels; counts of white blood cells (WBCs), red blood cells (RBCs), and platelets; coagulation profiles including prothrombin time (PT), activated partial prothrombin time (APTT), fibrinogen level (FIB), thrombin time (TT), D-dimer, and prothrombin time international normalized ratio (PTINR); lipid profiles with measurements of total cholesterol (TC), triglycerides (TG), high-density lipopolysaccharide cholesterol (HDL-C), low-density lipopolysaccharide cholesterol (LDL-C), apolipoprotein A and B (ApoA/ApoB), and lipoprotein a (LP[a]); and assessment of cardiac and liver enzyme levels, including creatine kinase-MB (CK-MB), troponin I (TNI), alanine transaminase (ALT), aspartate transaminase (AST), albumin, and globulin levels. Additional biochemical parameters that were monitored included levels of blood urea nitrogen (BUN), creatinine (CR), uric acid (UA), potassium, and sodium.

Definitions

HT was defined as the absence of bleeding in the first head computed tomography/magnetic resonance imaging (CT/MRI) investigation after cerebral infarction, intracranial hemorrhage found detected on the second head CT/MRI investigation, or hemorrhagic infarction determined based on the first head CT/MRI investigation.[19] In this study, AIS patients with HT within 24 hours after intravenous thrombolysis were selected for evaluation.

Diabetes was defined as an FBG level of ≥7.0 mmol/L or the current use of antidiabetic medication. Hypertension was identified based on a systolic blood pressure (SBP) reading >140 mmHg or a diastolic blood pressure (DBP) reading >90 mmHg; smoking status was determined by the daily consumption of at least one cigarette.

All patients were categorized according to the levels of glucose (glucose <11.1 mmol/L or glucose ≥11.1 mmol/L) and FBG (FBG <7.0 mmol/L or FBG ≥7.0 mmol/L).

Statistical Analysis

Categorical data are presented as numbers or percentages. Continuous data (age, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C, albumin, and uric acid) are shown as means with standard deviations (SDs). The independent *t*-test or Mann–Whitney *U*-test was used for continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables to analyze differences between the two groups. Multivariate logistic regression analysis was used to investigate the relationships between HT and risk factors, based on the results of the univariate analysis; these relationships were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$. All statistical analyses were conducted using SPSS software (Version 25.0; SPSS, Chicago, IL, USA).

Results

Demographic Characteristics Among Patients in This Study

During the study period, 426 patients with AIS who were treated with rt-PA were included. Of these, 305 patients (71.6%) were male and 121 (28.4%) were female, with an overall average age of 64.49 years. HT occurred in 15% of AIS

Table 1 Comparison of General Data Between HT Group and Non-HT Group After Alteplase Thrombolysis

Characteristics	HT	Non-HT	Total	P value
Gender:				0.584
Men	44 (14.4)	261 (85.6)	305 (71.6)	
Women	20 (16.5)	101 (83.5)	121 (28.4)	
Total	64 (15.0)	362 (85.0)	426 (100)	
Age, y	68.66±11.33	62.67±10.79	64.49±8.20	<0.001
Past medical history:				
Stroke				<0.001
No	30 (10.2)	263 (89.8)	293 (68.8)	
Yes	34 (25.6)	99 (74.4)	133 (31.2)	
Hypertension:				0.104
No	22 (11.8)	164 (88.2)	186 (43.7)	
Yes	42 (17.5)	198 (82.5)	240 (56.3)	
Diabetes mellitus:				0.072
No	42 (13.2)	276 (86.8)	318 (74.6)	
Yes	22 (20.4)	86 (79.6)	108 (25.4)	
Coronary heart disease:				<0.001
No	41 (11.5)	316 (88.5)	357 (83.8)	
Yes	23 (25.8)	46 (74.2)	69 (16.2)	
Atrial fibrillation				<0.001
No	41 (10.8)	338 (89.2)	379 (89.0)	
Yes	23 (48.9)	24 (51.1)	47 (11.0)	
Drink:				0.874
No	50 (14.9)	286 (85.1)	336 (78.9)	
Yes	14 (15.6)	76 (84.4)	90 (21.1)	9
Smoke:				0.498
No	44 (15.9)	233 (84.1)	277 (65.0)	
Yes	20 (13.4)	129 (86.6)	149 (35.0)	
Dyslipidemia:				0.313
No	25 (17.5)	118 (82.5)	143 (33.6)	
Yes	39 (13.8)	244 (86.2)	283 (66.4)	
TOAST:				<0.001
Large artery atherosclerosis	34 (54.8)	233 (64.5)	267 (63.1)	
Cardioembolism	19 (30.6)	8 (2.2)	27 (6.4)	
Small artery occlusion	9 (14.5)	117 (32.4)	126 (29.8)	
Other determined etiology	0 (0.0)	0 (0.0)	0 (0.0)	
Undetermined etiology	0 (0)	3 (0.8)	3 (0.7)	

Note: Data are presented as number (%), mean±SD.

patients, 14.4% in men and 16.5% in women. The proportions of patients with a specific previous disease history were 31.2% (stroke), 56.3% (hypertension), 25.4% (diabetes), 16.2% (coronary heart disease), 11% (AF), and 66.4% (dyslipidemia). Among these patients, 35% smoked and 21.1% drank alcohol (Table 1).

HT-Associated Factors in the Univariate Analysis

The HT group had a significantly higher mean age and higher rates of previous stroke, coronary heart disease, and AF (Table 1). The D-dimer, TNI, FBG, TC, ApoB, LDL-C, AST/ALT ratio, and globulin levels all differed between the HT and non-HT groups (all, P <0.05; Table 2). Additionally, the HT group showed significantly higher NIHSS scores, pre- and post-thrombolysis; increased door-to-needle time; and higher frequencies of leukoaraiosis (LA), cardiac embolism, drowsiness, trance, stun, cardioembolism of TOAST and elevated random blood glucose levels at admission

Table 2 Comparison of Serological Indexes Between HT Group and Non-HT Group After Alteplase Thrombolysis

Indicators	HT group N=64	Non-HT group N=362	x^2/t	P value
WBC, 10^9/L	9.28±2.62	8.23±4.51	1.808	0.071
RBC, 10^9/L	4.63±0.55	4.68±0.55	0.670	0.503
PLT, 10^9/L	215.84±63.86	220.07±61.98	0.501	0.617
PT, s	11.72±1.10	11.47±1.18	1.578	0.115
PTINR	1.05±0.09	1.49±6.03	1.387	0.166
APTT s	25.16±2.63	25.59±2.51	1.254	0.210
FIB, g/L	3.06±0.95	2.84±1.23	1.627	0.107
TT, s	16.25±1.72	16.13±1.70	0.520	0.604
D-dimer, mg/L	2.24±6.01	0.64±1.05	2.124	0.038
BUN, mmol/L	6.85±2.70	6.64±11.91	0.295	0.768
Cr, umol/L	71.42±25.20	71.05±41.80	0.096	0.923
UA, umol/L	349.53±125.05	343.54±94.73	0.365	0.716
TNI, pg/mL	45.92±143.57	10.12±45.27	1.978	0.052
CKMB, ng/mL	1.14±0.83	1.20±1.17	0.497	0.620
FBG, mmol/L	8.39±3.21	6.29±2.55	4.964	<0.001
TC, mmol/L	5.20±2.02	4.75±1.10	1.737	0.087
TG, mmol/L	1.54±0.97	1.93±1.61	2.638	0.009
ApoA, g/L	1.24±0.24	1.65±8.13	0.957	0.339
ApoB g/L	1.09±0.31	1.01±0.26	1.947	0.055
HDL, mmol/L	1.23±0.29	1.16±0.30	1.729	0.085
LDL, mmol/L	3.26±1.17	2.98±0.87	1.827	0.072
LDL/HDL	2.68±0.88	2.62±0.86	0.513	0.608
ApoA/B	1.24±0.53	1.60±5.93	1.130	0.259
LP, mg/L	261.15±271.14	209.36±242.48	1.547	0.123
BUN/Cr	0.10±0.10	0.10±0.21	0.000	1.000
HCY, mmol/L	17.54±9.70	17.30±13.28	0.172	0.864
ALT, u/L	28.24±19.57	27.21±26.86	0.365	0.716
AST, u/L	29.45±21.88	24.88±31.15	1.434	0.154
AST/AL	1.19±0.64	1.04±0.51	1.778	0.079
Albumin, g/L	40.72±4.40	41.08±4.66	0.574	0.566
Globulin, g/L	30.06±4.72	28.45±5.35	2.257	0.025
GGT u/L	40.21±25.85	43.06±45.86	0.707	0.481
ALP, u/L	85.21±25.21	84.81±25.82	0.115	0.909
K^+, mmol/L	4.01±0.48	4.01±0.42	0.000	1.000
Na^+, mmol/L	138.32±4.54	139.10±4.40	1.301	0.194

Note: Data are presented as mean±SD.

(all P < 0.05). The proportions of patients experiencing massive cerebral infarction, consciousness, and conjugate eye deviation before thrombolysis were significantly lower in the HT group than in the non-HT group (P < 0.05; Table 3). However, no significant correlation was found between ASPECTS scores, hyperglycemia treatment and HT (P>0.05).

HT-Associated Factors in the Multivariate Analysis After Adjusting for Covariates

Multivariate analysis was performed to evaluate the determinants of HT following rt-PA thrombolysis, after adjusting for covariates that were significantly associated with HT in the univariate analysis. Table 4 shows that cardiac embolism, LA, prethrombolysis NIHSS score, and FBG levels were associated with HT after thrombolysis. The risk of HT after rt-PA was 12-fold higher in patients with cardiac embolisms than in those without. Similarly, there was a 3.44-fold higher risk of HT after rt-PA treatment in patients with LA than in those without. For each unit increase in prethrombolysis NIHSS score and FBG level, the risk of HT after rt-PA increased by 11% and 22%, respectively (both, P <0.001).

Table 3 Comparison of Clinical Data Between HT Group and Non-HT Group After Alteplase Thrombolysis

Factors	HT group	Non-HT group	x^2/t	P value
Rt-PA dose, mg	60.37±9.75	62.27±10.74	1.322	0.187
NIHSS:				
Prethrombolysis	13.58±8.298	7.26±5.76	5.849	<0.001
Postthrombolytic	12.95±8.742	5.39±4.97	6.729	<0.001
Difference	−0.62±3.73	−1.87±3.54	2.583	0.010
OTT, min	154.61±50.20	153.18±49.32	0.213	0.831
DNT, min	37.36±20.13	34.00±23.69	1.068	0.286
Leukoaraiosis	36 (56.3)	84 (30.2)	29.351	<0.001
Massive cerebral infarction	26 (40.6)	27 (74.6)	54.918	<0.001
GLU	9.01±3.61	7.65±3.01	2.844	0.006
SBP	156.98±27.64	153.37±23.45	0.984	0.328
DBP	89.14±15.15	90.60±15.00	0.717	0.474
Pulse	78.59±18.46	78.37±15.98	0.099	0.921
Cardiac embolism	17 (26.6)	6 (1.7)	66.045	<0.001
Pre-thrombolytic state of consciousness:				
Consciousness	34 (53.1)	322 (89.0)	50.831	<0.001
Drowsiness	18 (28.1)	28 (7.7)	23.475	<0.001
Lethargy	6 (9.4)	6 (1.7)	9.181	0.002
Coma	6 (9.4)	6 (1.7)	9.181	0.002
Conjugate eye deviation	30 (42.3)	41 (57.7)	49.484	<0.001
ASPECTS scores	7.81 (1.91)	8.29 (1.47)	1.893	0.062
Hypoglycemic therapy				
No	10 (20.4)	322 (85.9)	1.349	0.245
Yes	53 (14.1)	39 (79.6)		

Note: Data are presented as number (%), mean±SD. GLU indicates random blood glucose on admission; SBP indicates Systolic Blood Pressure on admission; DBP indicates diastolic Blood Pressure on admission.

Table 4 Associated Factors of HT in the Multivariate Analysis

Factors	OR (95%CL)	χ^2	P
Cardiac embolism	13.18 (4.37–39.77)	20.935	<0.001
Leukoaraiosis	3.44 (1.80–6.56)	14.066	<0.001
Prethrombolysis-NIHSS	1.11 (1.06–1.15)	21.353	<0.001
FBG	1.22 (1.12–1.34)	18.756	<0.001

Association of Blood Glucose Level with HT Stratified by Diabetes

Table 5 shows the FBG levels associated with HT in patients without diabetes. The frequency of HT was higher in patients with FBG levels ≥7.0 mmol/L (52.6%) compared to those with FBG levels <7.0 mmol/L (7.9%; P <0.001).

Association of Diabetes with HT Stratified by Blood Glucose Level

The association between diabetes and HT was also evaluated and stratified according to blood glucose levels (Table 6). Stratification by blood glucose levels showed a negative correlation in groups with intermediate FBG levels (7.0 ≤ FBG < 11.1 mmol/L). The frequency of HT was significantly higher in patients without diabetes than in those with diabetes (58.1% vs 14.0%; P <0.001).

Table 5 Analysis of the Effect of Blood Glucose Rise on Hemorrhagic Transformation Categorized by Diabetic

Clinical indicators /mmol/L	HT group	Non-HT group	x^2	P
Diabetes:				
			1.700	0.233
GLU<11.1	11 (16.4)	56 (83.6)		
GLU≥11.1	11 (26.8)	30 (73.2)		
			0.631	0.453
FBG<7.0	5 (15.6)	27 (84.4)		
FBG≥7.0	17 (22.4)	59 (77.6)		
Non-diabetes:				
			4.406	0.059
GLU<11.1	38 (12.4)	268 (87.6)		
GLU≥11.1	4 (33.3)	8 (66.7)		
			58.515	<0.001
FBG<7.0	22 (7.9)	258 (92.1)		
FBG≥7.0	20 (52.6)	18 (47.4)		

Abbreviations: GLU: random blood glucose on admission; FBG: Fasting blood glucose.

Table 6 Comparative Analysis of Diabetic/Non-Diabetic Patients at the Same Glucose Level

Clinical indicators /mmol/L	HT group	Non-HT group	x^2	P value
GLU<7.0			0.950	0.401
Diabetes mellitus	3 (17.6)	14 (82.4)		
No-diabetes mellitus	20 (10.1)	179 (89.9)		
7.0≤GLU<11.1			0.017	0.897
Diabetes mellitus	8 (16.0)	42 (84.0)		
No-diabetes mellitus	18 (16.8)	89 (83.2)		
GLU ≥11.1			0.194	0.722
Diabetes mellitus	11 (26.8)	30 (73.2)		
No-diabetes mellitus	4 (33.3)	8 (66.7)		
FBG<7.0			2.192	0.174
Diabetes mellitus	5 (15.6)	27 (84.4)		
No-diabetes mellitus	22 (7.9)	258 (92.1)		
7.0≤FBG<11.1			15.995	<0.001
Diabetes mellitus	6 (14.0)	37 (86.0)		
No-diabetes mellitus	18 (58.1)	13 (41.9)		
FBG ≥11.1			0.060	1.000
Diabetes mellitus	11 (33.3)	22 (66.7)		
No-diabetes mellitus	2 (28.6)	5 (71.4)		

Discussion

In this hospital-based prospective study, we explored the determinants of HT in patients with AIS treated with rt-PA, and the association between varying blood glucose levels and HT in stroke patients with or without diabetes after rt-PA treatment. Cardiac embolism, NIHSS score before thrombolysis, FBG levels, and LA were found to be independent risk factors for HT. The rate of HT in patients with FBG levels of 7–11.1 mmol/L was higher in the nondiabetic group than in the diabetic group.

Although AF has been identified as an independent predictor of HT and poor outcomes in stroke patients,[20] our multivariable logistic regression analysis did not find AF to be independently associated with post-thrombolytic HT. However, cardiogenic brain embolism was significantly correlated with HT. The higher incidence of HT in patients with

cardiogenic brain embolisms than in those with other stroke subtypes may explain this discrepancy.[15] Given the diverse composition of thrombi associated with AF, a cautious approach to thrombolytic therapy in patients with AIS and a history of AF is warranted to mitigate the risk of HT. Moreover, our analysis indicated that higher pre-thrombolysis NIHSS scores were also independently associated with an increased risk of HT, underscoring the need for heightened vigilance and preparedness for hemorrhage management in patients with high NIHSS scores.

LA, a sign of chronic small-vessel disease observed on brain imaging, is associated with an increased risk of HT after thrombolytic therapy in patients with AIS. Although LA may double the risk of HT, thrombolysis with rt-PA is still beneficial, particularly in patients aged >60 years, since it does not raise the risk of symptomatic intracerebral hemorrhages.[21–23] Pathological changes in LA, such as endothelial damage and blood-brain barrier disruption, may increase this risk.[24,25] Additionally, HT in patients with LA tends to occur away from the initial infarct area, indicating the influence of small-vessel disease.[26,27] These findings underscore the importance of considering the presence and severity of LA in stroke management.

The relationship between high blood glucose levels and HT after thrombolysis in patients with AIS is still debated. Through a post hoc analysis of data from the European Multicenter Acute Stroke Trial (MAST-E), Assia et al[28] found that a history of diabetes was associated with symptomatic HT after streptokinase thrombolytic therapy. Derex et al[29] showed that the blood glucose levels of patients with HT after t-PA thrombolysis were significantly higher than those of patients without HT. In a study involving 29 subjects, Magdy et al[8] found that the average admission blood glucose level of patients with HT after thrombolytic therapy was significantly higher than that in patients without HT after thrombolytic therapy. However, the results of a multivariate analysis showed no significant correlation between blood glucose levels and HT after thrombolysis. By reviewing the baseline clinical data of 138 stroke patients treated with intravenous rt-PA, Demchuk et al[9] found that high blood glucose levels and diabetes were predictors of symptomatic cerebral hemorrhage in patients treated with rt-PA. In a multicenter prospective cohort study, David et al[10] found that high blood glucose levels and a history of diabetes were significant predictors of HT after rt-PA thrombolysis in patients with AIS. Several studies have found that high blood glucose levels are highly correlated with the risk of HT after intravenous thrombolytic therapy with rt-PA and intra-arterial therapy with urokinase, especially the occurrence of spontaneous intracerebral hemorrhage (sICH),[30,31] and it is believed that patients with serum glucose levels above 11.1 mmol/L at the onset of stroke have an increased risk of secondary bleeding. Moreover, an increase of 0.56 mmol/L more than double the risk of sICH. Results from another multicenter randomized trial also suggest that higher NIHSS scores and high blood glucose levels are predictors of poor three-month outcomes in AIS patients.[32] However, in the NINDS rt-PA Stroke Trial, admission hyperglycemia (defined as 300 mg/dL) was not an independent predictor of symptomatic ICH within 36 hours of treatment.[33] Our findings further confirm that high blood glucose levels are a risk factor for HT after rt-PA thrombolysis in patients with AIS, regardless of their history of diabetes. FBG levels are also associated with HT in patients without diabetes. A higher frequency of HT was found in patients with FBG levels ≥7.0 mmol/L than in those patients with FBG levels <7.0 mmol/L (52.6% vs 7.9%). Furthermore, in the present study, stratification by blood glucose levels indicated that among patients with FBG levels of 7.0–11.1 mmol/L, there was a higher frequency of HT in those without a history of diabetes than in those with diabetes. Thus, a large multicenter clinical trial is needed to confirm the association between FBG levels and HT in patients with AIS treated with intravenous thrombolytic therapy. High glucose levels can lead to endothelial dysfunction and blood-brain barrier disruption,[34–37] perhaps partly explaining the increased incidence of vasogenic edema and HT following reperfusion after thrombolysis in patients with AIS.

This study had some limitations. First, all participants were from one local hospital and may therefore not adequately represent the broader AIS patient population. This may affect the generalizability of our findings; additional large-scale clinical trials are required. Second, the absence of detailed pre-thrombolysis medication information, especially regarding anticoagulant use, may have introduced bias. Thus, detailed information on pre-thrombolysis medications, particularly anticoagulants, should be collected in future studies to minimize biases and better understand the impact of treatment history on patient outcomes. Third, we did not include all biomarkers in our studies and lacked follow-up observations of biomarkers, which led to the possibility that we might have omitted certain information. More biomarkers and long-term trends of markers should be included in future studies to further ensure the reliability of experimental results. Fourth, our study only stratified past diabetes history and blood glucose levels, and new stratification studies should be conducted in

future studies in patients with impaired fasting glucose and impaired glucose tolerance to explore in more detail the differences in risk factors for hemorrhagic transformation in different glycemic states. Fifth, our study is the lack of subgroup analyses based on different stroke subtypes and varying levels of stroke severity. While we collected data on TOAST classification and NIHSS, we did not perform a stratified analysis to determine whether the findings apply equally across different stroke subtypes (eg, cardioembolic, large-artery atherosclerosis) or severity levels. This limitation suggests that the results may not be fully generalizable to all stroke patients, especially those with milder or more severe presentations, or those with varying underlying stroke mechanisms. To address this in future research, detailed subgroup analyses based on stroke subtype and severity should be conducted to assess whether the findings are consistent across different groups, thereby making the conclusions more broadly applicable to diverse stroke populations. Moreover, our study did not analysis on post-thrombolysis glucose levels. While we focused on the association between baseline glucose levels and hemorrhagic transformation, we did not evaluate how treatment affected glucose levels during or after thrombolysis. This limitation prevents us from understanding whether changes in glucose levels post-treatment had an impact on HT. In future studies, regular monitoring of glucose levels following thrombolysis should be implemented. Finally, due to the small number of complications in our study, we did not compare complications between the two groups. Research on complications should be added to future studies. More and larger prospective multicenter cohort studies should be conducted in the future to further validate and expand our findings.

Conclusion

This hospital-based, prospective study explored the relationship between blood glucose levels and HT after rt-PA thrombolysis in patients with AIS. The findings revealed that cardiac embolism, pre-thrombolysis NIHSS score, FBG level, and LA are independent risk factors for HT. Compared with the diabetes group, there was a higher rate of HT in patients without diabetes but with FBG levels of 7.0–11.1 mmol/L. The clinical implications of our findings significantly extend to future AIS management and treatment protocols. Specifically, clinicians can predict the risk of hemorrhagic transformation after thrombolysis of rt-PA in AIS patients by monitoring the blood glucose level at the time of admission and related risk factors, and screen out people with high bleeding risk to formulate appropriate treatment and management plans, thereby improving the prognosis of patients. In addition, the active regulation of blood glucose levels in AIS patients and the prevention and management of risk factors can effectively reduce the risk of hemorrhagic transformation after rt-PA thrombolysis in AIS patients, thereby improving clinical outcomes and quality of life. Particularly for non-diabetic patients with high blood glucose levels, there is an urgent need for precise glycemic control during AIS management to improve outcomes and reduce complications in non-diabetic AIS patients receiving thrombolytic therapy with rt-PA.

Abbreviations

AIS, acute ischemic stroke; rt-PA, recombinant tissue plasminogen activator; HT, hemorrhagic transformation; SHR, stress hyperglycemia ratio; AF, atrial fibrillation; NIHSS, National Institutes of Health Stroke Scale score; FBG, fasting blood glucose; WBCs, white blood cells; RBCs, red blood cells; PT, prothrombin time; APTT, activated partial prothrombin time; FIB, fibrinogen level; TT, thrombin time; PTINR, prothrombin time international normalized ratio; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipopolysaccharide cholesterol; LDL-C, low-density lipopolysaccharide cholesterol; ApoA, apolipoprotein A; ApoB, apolipoprotein B; LP[a], lipoprotein a; CK-MB, creatine kinase-MB; TNI, troponin I; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CR, creatinine; UA, uric acid; CT/MRI, computed tomography/magnetic resonance imaging; SBP, systolic blood pressure; DBP, diastolic blood pressure; SDs, standard deviations; ORs, odds ratios; Cis, confidence intervals; LA, leukoaraiosis; MAST-E, European Multicenter Acute Stroke Trial; sICH, spontaneous intracerebral hemorrhage.

Data Sharing Statement

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

Ethics Approval and Informed Consent

This study was conducted under the Helsinki Declaration and received approval from the Ethics Committee of the First Affiliated Hospital of Harbin Medical University (IRB2023326). Written informed consent was obtained from all participants in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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