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Impact of blood pressure variability on hemorrhagic transformation post-rt-PA thrombolysis in patients with acute ischemic stroke

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Abstract

Background: The relationship between blood pressure variability and hemorrhagic transformation after recombinant tissue plasminogen activator thrombolysis in patients with acute ischemic stroke is uncertain due to inconsistent methodologies across studies. This study aimed to elucidate the association between 24-h systolic blood pressure extremes post-admission and hemorrhagic transformation while considering the possibility of hemorrhagic transformation occurring beyond the initial monitoring period.

Methods: We enrolled patients admitted to The First Affiliated Hospital of Harbin Medical University for ischemic stroke who were treated with intravenous recombinant tissue plasminogen activator within 4.5 h of symptom onset between January 2020 and December 2022. We analyzed the relationships among admission blood pressure, 24-h post-admission recombinant tissue plasminogen activator (mean, maximum, minimum, extreme difference, standard deviation, and coefficient of variation), immediate and 1-h post-thrombolysis blood pressure, and hemorrhagic transformation occurrence within 36 h post-thrombolysis. The potential for delayed hemorrhagic transformation was also considered during the interpretation of the results.

Results: Among the 138 patients, 39.1% experienced post-thrombolytic hemorrhagic transformation. Multivariate analysis revealed that hemorrhagic transformation was significantly associated with coronary artery disease, cerebral leukoaraiosis, large cerebral infarction, elevated random glucose levels, and 24-h systolic blood pressure extremes at admission. Specifically, 24-h systolic blood pressure extremes showed a significant positive correlation with hemorrhagic transformation (OR = 1.042; 95% CI: 1.000–1.086, $p < 0.05$).

Conclusion: These findings underscore the importance of establishing robust protocols for continuous blood pressure monitoring and intervention strategies tailored to individual risk profiles. Given that hemorrhagic transformation can occur beyond the initial 36 h, clinicians should maintain vigilance for delayed hemorrhagic transformation, particularly in patients with high recombinant tissue plasminogen activator. Strict control of blood pressure, especially minimizing extremes in systolic blood pressure, is essential to ensure the safety of patients undergoing thrombolysis.

Keywords

Acute ischemic stroke, blood pressure variability, hemorrhagic transformation, thrombolysis, rt-PA

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Introduction

Stroke is the second leading cause of death worldwide, accounting for 11.6% of all deaths. Stroke was the third leading cause of death and disability in 2019, accounting for 5.7% of all disability-adjusted life years (DALYs). The Global Burden of Disease study showed that up to

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12.2 million people suffered from stroke globally in 2019, of which 62.4% were ischemic strokes. Approximately 89.0% of all stroke-related DALYs occurred in low- and lower-middle-income countries.[1] Intravenous administration of recombinant tissue plasminogen activator (rt-PA) thrombolytic therapy within 4.5 h of the onset of acute ischemic stroke is currently an effective treatment for the condition.[2,3] Hemorrhagic transformation (HT) after thrombolysis is one of the major serious adverse effects of rt-PA for stroke.[2,4–7] A previous study has shown a 2.72-fold increased risk of symptomatic intracranial hemorrhage after rt-PA thrombolysis in patients with acute ischemic stroke.[4] A meta-analysis of randomized trials showed a 5.67-fold increased risk of HT within 36 h of rt-PA thrombolysis.[5] Early identification of the risk factors for thrombolysis-related HT can help guide clinical treatment and management protocols for patients with ischemic stroke.

Several studies have shown that increased blood pressure variability (BPV) is associated with hemorrhagic conversion after rt-PA thrombolytic therapy in patients with ischemic stroke. A recent study showed that pre-thrombolysis systolic BPV $\geqslant$ 45 mmHg was a predictor of symptomatic cerebral hemorrhage.[8] A multicenter retrospective study in Japan showed a positive correlation between symptomatic cerebral hemorrhage within 36 h after thrombolysis and systolic blood pressure (BP) extremes, standard deviation (SD), coefficients of variation, and continuous variability within 25 h after initiating thrombolysis; this was independent of pre-thrombolytic BP.[9] A secondary study of patients from the European Cooperative Acute Stroke Study (ECASS-II) showed that high baseline, maximum, mean, and variability of the 24-h systolic BP curves after admission were positively associated with an increased risk of parenchymal hemorrhage within the first 7 days in rt-PA-treated patients.[10] A study from China showed that the SD and mean squared deviation of systolic BP within 24 h of thrombolysis were positively associated with symptomatic cerebral and parenchymal hemorrhages.[11] Although most previous studies have confirmed a clear correlation between BPV and HT, some have not found such a correlation. A study from Germany showed that high BPV does not increase the risk of cerebral hemorrhage after intravenous thrombolytic therapy.[12]

Moreover, although several studies have confirmed the correlation between BPV and HT after rt-PA thrombolytic therapy, the number of studies is limited, and the results are inconsistent. Furthermore, there are large differences in the time window for thrombolysis, the index of BPV, and the time period for monitoring HT in patients with acute ischemic stroke among the various studies.

Therefore, this study aimed to investigate the association between 24-h post-admission BP, post-thrombolytic BPV, and HT 36 h after thrombolysis in patients treated with intravenous rt-PA thrombolytic therapy within 4.5 h of acute ischemic stroke onset.

Methods

Study design

We employed a retrospective cohort study design. After standardizing the inclusion and exclusion criteria, we collected and verified hospital records and imaging data of participants admitted to The First Affiliated Hospital of Harbin Medical University between January 2020 and December 2022. This analysis included data from 54 patients in the hemorrhage group and 84 in the matched non-hemorrhage control group, yielding a total of 138 participants.

Study subjects

Participants were selected based on CT/magnetic resonance imaging (MRI) findings within 24 h following intravenous thrombolysis (IVT) with rt-PA. All participants had experienced acute ischemic stroke between January 2020 and December 2022, were admitted to The First Affiliated Hospital of Harbin Medical University, and underwent rt-PA thrombolytic therapy.

Inclusion criteria

Eligible patients were over 18 years of age and met the diagnostic criteria specified in the 2018 Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke.[13] All participants had no contraindications for IVT, such as the use of anticoagulants (including Warfarin, rivaroxaban, and dabigatran) within 1 week before onset. They each received a standard rt-PA dose (0.9 mg/kg) IVT and had initial CT scans confirming the absence of intracranial hemorrhage upon admission. Comprehensive medical history, clinical examinations, and necessary laboratory data were available for each participant.

This study was approved by the Ethics Committee of The First Affiliated Hospital of Harbin Medical University (IRB2023326), and written informed consent was obtained from all participants or their Legally Authorized Representative in the case of patients who had lost their ability to sign due to stroke.

Exclusion criteria

The exclusion criteria were designed to maintain the integrity of the study data. Excluded patients were those who were either receiving non-standard rt-PA doses, had not received thrombolytic therapy at our hospital, or had undergone cerebral angiography or arterial thrombectomy following IVT. We also excluded patients diagnosed with severe cerebral vascular anomalies during hospitalization, such as intracranial aneurysms or moyamoya disease, as well as those with severe infections, autoimmune diseases, malignancies, hematological disorders, or incomplete clinical data. Additionally, to improve the safety of IVT treatment,

patients who had taken anticoagulants within a week of stroke onset were also excluded.

General patient information

We collected personal data including gender, age, weight, medical history (e.g., stroke, hypertension, diabetes, coronary heart disease, atrial fibrillation, and abnormal lipid levels), smoking (defined as smoking more than one cigarette a day for a year) and drinking habits (defined as alcohol consumed daily >50 ml of white wine or >500 ml of beer, and >1 time per week), use of anticoagulants (including Warfarin, rivaroxaban, dabigatran) 6 months before stroke onset, use of antiplatelet agents before onset, history of leukoaraiosis (diagnosis according to the Fazekas grading based on MRI scan of the patient's head after admission), and large area cerebral infarction (defined as complete stroke of the main carotid artery, the main middle cerebral artery, or the cortical branch, resulting in necrosis and softening of the brain tissue in the blood supply area of the artery). Moreover, all patients were assessed using the National Institutes of Health Stroke Score (NIHSS) and divided into two groups: mild stroke (defined as NIHSS < 8), moderate stroke (defined as NIHSS between 8 and 16), and severe stroke (defined as NIHSS > 16).[14]

The diagnostic standards for hypertension and diabetes in this study adhered to the latest national guidelines. Hypertension was defined based on systolic or diastolic BP thresholds and diabetes was defined using specific glucose thresholds, considering both fasting and postprandial values, irrespective of ongoing treatment.

Laboratory and clinical BP data

The laboratory tests encompassed comprehensive panels: complete blood count, coagulation profile (including prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR)), random blood glucose, lipid profile, cardiac enzymes, liver function tests, kidney function tests, and other biochemical markers, such as sodium ions and potassium ions (an ion disorder was defined if either of these two markers was abnormal). Patients' random blood glucose levels were measured at the time of admission, usually within 4.5 h of the onset of symptoms, both in patients with and without diabetes.

Each patient's BP was monitored noninvasively at least four times (once every 6 h) and up to 24 times (once every 1 h) within 24 h after IVT. The data were recorded in the nursing record by a nurse. The mean, maximum, minimum, and range values over a 24-h period were then calculated. The coefficient of variation for both systolic and diastolic pressures was also calculated to assess BPV.

Imaging and diagnostic standards

CT examination was performed in all patients before thrombolysis to exclude hemorrhagic stroke ($n = 138$). If the condition worsens within 24 h after thrombolysis, CT should be re-examined immediately to determine whether developing HT. If the patient's condition is stable, an MRI examination should be performed 24 h after thrombolysis to determine the HT. In this study, 8 out of 58 patients in the HT group were found HT by CT reexamination.

Moreover, we documented occurrences of leukoaraiosis and extensive cerebral infarction and categorized HT according to the ECASS classification system. Hemorrhagic infarction (HI) hemorrhages are divided into four hemorrhagic hemorrhage types: (1) HI H-1: presents as small, spotty, or patchy, bleeding found along the edge of the infarct lesion; (2) Hemorrhagic infraction H-2: either presents as flaky bleeding without space-occupying effect and appears in the area of cerebral infarction or presents as a multiple spot bleeding fusion; (3) Parenchymal hemorrhage (PH)-1: presents as a hematoma area in which cerebral hemorrhage occurs in less than 30% of the cerebral infarction area, and the hemorrhage is accompanied by a slight space-occupying effect; and (4) PH-2: presents as a hematoma area in which cerebral hemorrhage occurs in more than 30% of the cerebral infarction area, and the hemorrhage is accompanied by an obvious space-occupying effect, or the bleeding lesion is far away from the infarction lesion.

Statistical analysis

Normally distributed continuous variables are expressed as mean ± SD. Non-normally distributed continuous variables and ranked variables (NIHSS) are expressed as median (interquartile). Categorical data are presented as frequencies and percentages. Student's *t*-test and the Chi-square test were utilized to assess the differences between groups for continuous and categorical variables, respectively. Multivariate logistic regression analysis was conducted to explore the relationships between HT (dependent variable) and potential risk factors (independent variables). Variables with significant statistical differences ($p < 0.05$) in univariate analysis were selected for inclusion in multivariate analysis. These relationships are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (Version 25.0; SPSS Inc., Chicago, IL, USA).

Results

A total of 162 patients were treated with intravenous rt-PA within 4.5 h of symptom onset during the study periods. In total, 156 patients who met the inclusion criteria were included in the study, after six patients who did not meet the inclusion criteria were excluded (two had undergone thrombectomy, two had transferred to other hospitals, and two had been treated with a non-standard dose of rt-PA). Later, eight patients who lacked BP monitoring data and 10 patients who lacked other data were also excluded. Finally, 138 patients were analyzed in this study (Figure 1).

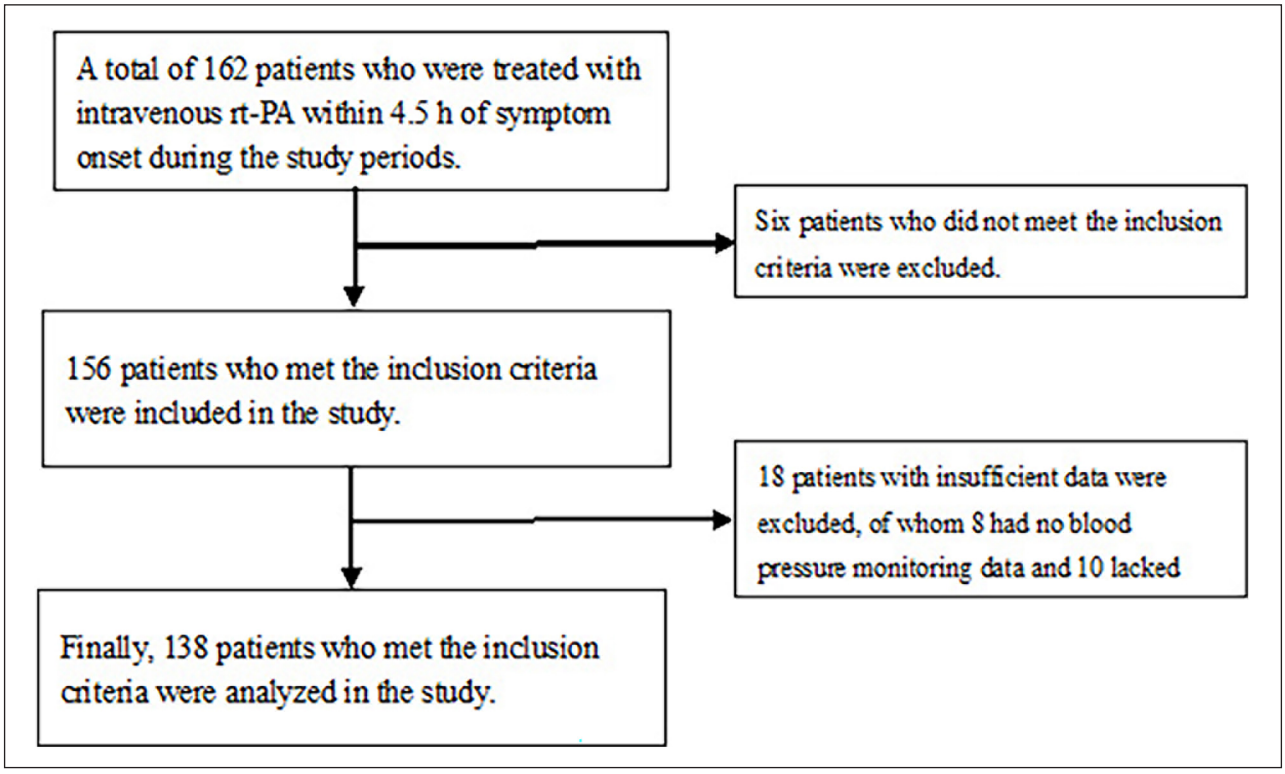

Figure 1. Flow chat of patients' selection.

Characteristics of participants

Of the 138 patients analyzed in this study, 39.1% presented with post-thrombolytic HT, 63% of the participants were men, and the mean age in the study was 66.86 years (Table 1).

Univariate analysis

Table 2 shows the results of the univariate analysis of the non-HT and HT groups. The results of the univariate analysis showed that in the HT group, age, weight, history of stroke, history of coronary artery disease, history of atrial fibrillation, history of drinking alcohol, cerebral leukoaraiosis, large cerebral infarction, NIHSS groups, PT, PT-INR, DDP, random blood glucose, ionic disorder, pulse pressure on admission, 24-h systolic BP on admission maximum, and extreme difference of admission 24-h systolic BP were significantly higher than those in the non-HT group (all $p < 0.05$). However, triglyceride levels in the HT group were significantly lower than those in the non-HT group ($p < 0.01$).

Multivariate analysis

Table 3 shows that post-thrombolysis HT was associated with history of coronary heart disease, cerebral leukoaraiosis, large cerebral infarction, fasting blood glucose, and admission 24-h systolic BP extremes. Admission 24-h systolic BP extremes showed a significant positive correlation with HT (OR = 1.042, 95% CI: 1.000–1.086, $p < 0.05$). However, age, weight, history of stroke, history of coronary heart disease, history of atrial fibrillation, history of drinking alcohol, cerebral leukoaraiosis, large cerebral infarction, PT, PT-INR, DDP, random glucose, triglycerides, ionic disorders, pulse pressure on admission, maximum systolic BP at 24 h of admission, and extreme difference value of systolic BP at 24 h of admission were not significant (all $p > 0.05$).

Discussion

In this study, we investigated the relationship between BPV in patients undergoing intravenous thrombolytic therapy within 4.5 h of the onset of acute ischemic stroke and HT 36 h after thrombolysis. After adjusting for other covariates, admission 24-h systolic BP extremes were found to be an independent risk factor for post-thrombolytic HT, and excessive admission 24-h systolic BP extremes could increase the risk of post-thrombolytic HT. Additionally, we found that coronary artery disease, cerebral leukoaraiosis, large cerebral infarction, and high random blood glucose levels increased the risk of post-thrombolytic HT.

Increased systolic BPV is associated with altered vascular functions such as atherosclerosis and endothelial dysfunction.[14–17] An altered vascular function may be a reason for the increased risk of HT after thrombolysis. Similar to the

Table 1. Characteristics of study participants by gender.

Characteristics	Men	Women	Total
Case, *n* (%)	87 (63)	51 (37)	138 (100)
Age, means (SD)	66.38 ± 10.76	67.69 ± 11.50	66.86 ± 11.01
Stroke, *n* (%)	31 (35.6)	19 (37.3)	50 (36.2)
Hypertension, *n* (%)	54 (62.1)	32 (62.7)	86 (62.3)
Diabetes, *n* (%)	29 (33.3)	14 (27.5)	43 (31.2)
Coronary artery disease, *n* (%)	27 (31.0)	15 (29.4)	42 (30.4)
Atrial fibrillation, *n* (%)	17 (19.5)	11 (21.6)	28 (20.3)
Hyperlipidemia, *n* (%)	1 (1.1)	1 (2.0)	2 (1.4)
Smoking, *n* (%)	40 (46.0)	7 (13.7)	47 (34.1)
Drink alcohol, *n* (%)	25 (28.7)	3 (5.9)	28 (20.3)
Pulse on admission, means (SD)	77.41 ± 13.31	79.63 ± 15.36	78.23 ± 14.09
Using anticoagulants before 6 months of stroke onset, *n* (%)	2 (2.3)	0 (0)	2 (1.4)
Using antiplate drugs before onset, *n* (%)	7 (8.0)	2 (3.9)	9 (6.5)
Cerebral leukoaraiosis, *n* (%)	40 (46.0)	16 (31.4)	56 (40.6)
Large area cerebral infarction, *n* (%)	20 (23.0)	19 (37.3)	39 (28.3)
NIHSS, median (range)	6.00 (0, 25)	8.00 (1, 31)	6.00 (0,31)
NIHSS groups, *n* (%)			
Mild/moderate	80 (92.0)	43 (84.3)	123 (89.1)
Severe	7 (8.0)	8 (15.7)	15 (10.9)
HT, *n* (%)	38 (43.7)	16 (31.3)	54 (39.1)

Table 2. Associated factors of having HT in univariate analysis.

Characteristics	Non-HT group	HT group	$\chi^2/t/z$	*p*-Value
Gender (man/female)	49/35	38/16	2.044	0.153
Age, mean (SD)	64.93 ± 11.05	69.87 ± 10.35	−2.627	0.010
Weight (kg)	66.71 ± 9.96	70.62 ± 9.68	−2.272	0.025
Stroke, *n* (%)	20 (23.8)	30 (55.6)	14.338	<0.001
Hypertension, *n* (%)	48 (57.1)	38 (70.4)	2.449	0.118
Diabetes, *n* (%)	22 (26.2)	21 (38.9)	2.471	0.116
Coronary artery disease, *n* (%)	18 (21.4)	24 (44.4)	8.224	0.004
Atrial fibrillation, *n* (%)	9 (10.7)	19 (35.2)	12.170	<0.001
Hyperlipidemia, *n* (%)	1 (1.2)	1 (1.9)	0.101	0.751
Smoking, *n* (%)	28 (33.3)	19 (35.2)	0.050	0.823
Drink alcohol, *n* (%)	12 (14.3)	16 (29.6)	4.785	**0.029**
Pulse at admission, mean (SD)	77.52 ± 12.46	79.33 ± 16.37	−0.693	0.490
6 months history of anticoagulants, *n* (%)	1 (1.2)	1 (1.9)	0.101	0.751
History of antiplate drugs, *n* (%)	5 (6.0)	4 (7.4)	0.114	0.735
Cerebral leukoaraiosis, *n* (%)	20 (23.8)	36 (66.7)	25.038	<0.001
Large cerebral infarction, *n* (%)	12 (14.3)	27 (50.0)	20.679	<0.001
NIHSS, median (range)	5.00(0, 28)	9.50(1, 31)	3.429	<0.001
NIHSS groups, *n* (%)			5.357	0.021
Mild/moderate	79 (94.0)	44 (81.5)		
Severe	5 (6.0)	10 (18.5)		
WBC 10*9/l	7.83 ± 2.51	8.45 ± 2.23	−1.480	0.141
RBC 10*12/l	4.64 ± 0.61	4.69 ± 0.50	−0.487	0.627
PLT 10*9/l	216.50 ± 61.78	208.76 ± 59.30	0.727	0.469
PT/sec	11.37 ± 1.00	11.89 ± 0.99	−2.975	0.003
PT-INR	1.02 ± 0.09	1.06 ± 0.07	−2.897	0.004
APTT/sec	25.62 ± 2.38	25.67 ± 2.12	−0.122	0.903
FIBg/l	2.85 ± 0.64	3.06 ± 0.86	−1.561	0.122
TT/sec	15.93 ± 1.32	15.64 ± 1.65	1.102	0.273

(Continued)

Table 2. (Continued)

Characteristics	Non-HT group	HT group	$\chi^2/t/z$	*p*-Value
DDP/mg/l	0.67 ± 0.95	1.44 ± 2.40	−2.235	0.029
Urea mmol/l	6.16 ± 2.52	12.38 ± 40.33	−1.132	0.263
Creatinine umol/l	72.00 ± 39.52	71.90 ± 23.37	0.017	0.986
Uric acid umol/l	335.43 ± 95.16	356.72 ± 128.67	−1.115	0.267
TNIpg/ml	5.87 ± 13.63	37.72 ± 138.96	−1.679	0.099
CKMB/ng/ml	1.30 ± 1.55	1.23 ± 0.65	0.324	0.747
Fasting blood glucose	6.10 ± 1.97	7.87 ± 2.84	−3.990	<0.001
Total cholesterol mmol/l	4.59 ± 1.09	4.43 ± 0.98	0.872	0.385
Triglyceride mmol/l	1.72 ± 1.04	1.32 ± 0.52	2.989	0.003
ApoA g/l	1.25 ± 0.24	3.66 ± 17.66	−1.001	0.321
ApoB g/l	0.99 ± 0.32	0.98 ± 0.32	0.021	0.983
HDLmmol/l	1.21 ± 0.29	1.20 ± 0.27	0.097	0.923
LDLmmol/l	2.89 ± 0.97	2.72 ± 0.87	0.995	0.322
LDL/HDL	2.45 ± 0.81	2.32 ± 0.80	0.905	0.367
A/B	1.39 ± 0.49	1.47 ± 0.64	−0.831	0.408
Lipoprotein a mg/l	203.60 ± 227.87	196.51 ± 224.95	0.179	0.858
Urea/creatinine	0.09 ± 0.03	0.25 ± 1.12	−1.033	0.306
HCY umol/l	17.13 ± 11.42	18.51 ± 11.82	−0.673	0.502
ALT u/l	25.42 ± 16.40	24.25 ± 15.22	0.421	0.674
AST u/l	24.07 ± 12.34	25.11 ± 12.80	−0.475	0.636
AST/ALT	1.09 ± 0.58	1.19 ± 0.48	−1.019	0.310
Albumin g/l	41.43 ± 5.12	41.55 ± 4.06	−0.147	0.884
Globulin g/l	28.79 ± 6.45	29.57 ± 4.60	−0.769	0.443
GGT/u/l	40.07 ± 30.04	40.39 ± 24.98	−0.065	0.948
Alkaline phosphatase (ALP/AKP) u/l	85.31 ± 24.28	87.35 ± 24.08	−0.484	0.629
Potassium mmol/l	4.08 ± 0.49	4.04 ± 0.43	0.447	0.655
Sodium mmol/l	140.23 ± 3.35	139.03 ± 4.38	1.817	0.071
Dyslipidemia, n (%)	25 (29.8)	10 (18.5)	2.195	0.138
Ionic disorder, n (%)	8 (9.5)	12 (22.2)	4.227	0.039
SBP on admission	156.04 ± 20.20	161.91 ± 23.47	−1.563	0.120
DBP on admission	91.33 ± 17.12	90.19 ± 12.70	0.423	0.673
Pulse pressure on admission	64.70 ± 17.09	71.72 ± 19.99	−2.202	0.029
Pulse on admission	77.52 ± 12.46	79.33 ± 16.37	−0.693	0.490
SBP just after thrombolysis	150.14 ± 16.75	153.89 ± 18.79	−1.222	0.224
SBP 1 h after thrombolysis	147.85 ± 15.68	149.80 ± 17.57	−0.660	0.511
Average SBP	143.87 ± 13.81	147.82 ± 13.68	−1.645	0.102
SBP maximum	160.39 ± 17.16	168.43 ± 18.66	−2.593	0.011
SBP minimum	127.83 ± 15.95	128.33 ± 15.20	−0.183	0.855
SBP extreme difference	32.56 ± 15.40	40.09 ± 21.00	−2.272	0.025
Standard value of SBP	12.62 ± 5.45	13.97 ± 6.63	−1.297	0.197
SBP variation	0.09 ± 0.39	0.09 ± 0.04	−0.883	0.379
DBP just after thrombolysis	85.37 ± 11.99	85.30 ± 10.61	0.036	0.971
DBP 1 h after thrombolysis	83.41 ± 11.84	83.08 ± 9.64	0.165	0.869
Average DBP	83.49 ± 8.91	84.25 ± 7.41	−0.520	0.604
DBP maximum	96.69 ± 13.41	97.94 ± 10.66	−0.579	0.563
DBP minimum	70.33 ± 9.53	69.85 ± 9.90	0.285	0.776
DBP extreme difference	26.36 ± 11.89	28.09 ± 11.81	−0.839	0.403
Standard value of DBP	9.50 ± 3.80	9.48 ± 3.50	0.039	0.969
DBP variation	0.11 ± 0.04	0.11 ± 0.04	0.156	0.876

results of most previous studies, the present study confirmed that high BPV increased the risk of HT after rt-PA thrombolytic therapy. Our findings showed that the risk of post-thrombolytic HT was associated with excessive 24-h systolic BP extremes after admission, independent of BP at the time of thrombolysis and post-thrombolysis. However, it is important to interpret these findings with caution, as HT can occur after the first 36 h post-thrombolysis or longer, such as 7 days

Table 3. Associated factors of having HT in multivariate analysis.

Characteristics	References	OR (95% CI)	*p*-Value
Age, year	—	0.945 (0.886, 1.007)	0.083
Weight, kg	—	1.035(0.975, 1.099)	0.257
Coronary artery disease	No	0.190 (0.056, 0.639)	0.007
Atrial fibrillation	No	0.871 (0.206, 3.678)	0.851
Drink alcohol	Never	0.428 (0.107, 1.715)	0.231
Cerebral leukoaraiosis	No	0.108 (0.032, 0.369)	<0.001
Large cerebral infarction	No	0.225 (0.059, 0.863)	0.030
PT, sec	—	1.656 (0.477, 6.135)	0.450
PT-INR	—	0.006 (1.4353E-9, 21687.208)	0.503
DDP, mg/L	—	1.476 (0.960, 2.271)	0.076
Random blood glucose, mmol/L	—	1.360 (1.058, 1.747)	0.016
Triglyceride, mmol/L	—	0.567 (0.276, 1.163)	0.121
Ionic disorder	No	0.309 (0.064, 1.498)	0.145
Pulse pressure on admission	—	1.019 (0.983, 1.057)	0.310
SBP maximum	—	0.983 (0.939, 1.030)	0.483
SBP extreme difference	—	1.043 (1.001, 1.088)	0.046
Severe stroke	Mild/moderate	1.721 (0.330, 8.982)	0.519

after thrombolysis. This delayed occurrence might influence clinical outcomes and should be considered when interpreting the results of our study. Clinicians should remain vigilant for HT beyond the first 36 h, particularly in patients exhibiting high BPV or other risk factors identified in our study, such as cerebral leukoaraiosis and large cerebral infarction.[10,18] Consistent with the results of this experimental study, the report from ECASS-II indicated that a high baseline, maximum, mean, and variability in the 24-h post-admission systolic BP curve in rt-PA-treated patients was positively associated with an increased risk of parenchymal hemorrhage within the first 7 days.[10] However, the results of a study by Kellert et al.[12] showed that post-thrombolysis BPV was not associated with cerebral hemorrhage. Conversely, Endo et al. showed a positive correlation between symptomatic cerebral hemorrhage within 36 h after thrombolysis and BPV within 25 h after the start of thrombolysis, but not with pre-thrombolytic BP.[9] A study from China showed a positive correlation between the SD and mean squared deviation of systolic BP within 24 h after thrombolysis and symptomatic cerebral and parenchymal hemorrhages.[11] This may be due to the different time windows for thrombolysis, time periods for BP monitoring, and time periods for hemorrhage conversion monitoring between the studies. More studies are needed to clarify these potential correlations in the future.

Our study also found that patients with cerebral leukoaraiosis had a higher risk of HT after thrombolysis. Previous studies have similarly confirmed this finding, with a meta-analysis of 11 studies showing an increased risk of symptomatic cerebral hemorrhage (0.55-fold) after thrombolysis for acute ischemic stroke in patients with cerebral leukoaraiosis and an increased risk of symptomatic hemorrhage (1.53-fold) in patients with severe cerebral leukoaraiosis, as compared with control patients.[19] A meta-analysis of 17 studies showed that moderate-to-severe cerebral leukoaraiosis could increase the risk of post-thrombolytic hemorrhage conversion by 2.47-fold.[20] The mechanism by which cerebral white matter laxity leads to HT is unclear, and cerebral white matter lesions are thought to play an indirect and interactive role in post-thrombolytic HT, which may be related to endothelial dysfunction and the process of blood-brain barrier damage.[19,21–23]

Our findings also showed that a large cerebral infarction was associated with post-thrombolytic HT; this is consistent with a previous meta-analysis that showed that patients with a large cerebral infarction had a 6.56-fold increased risk of post-thrombolytic HT.[20] A study of acute ischemic stroke combined with atrial fibrillation showed that large cerebral infarcts increased the risk of post-stroke hemorrhage in patients with stroke combined with atrial fibrillation.[24] An MRI-based study showed that the cerebral infarct volume on diffusion-weighted imaging was a predictive variable for post-thrombolytic hemorrhage conversion.[18] Patients with large cerebral infarcts usually have more severe edema and vascular hypoxia, which may contribute to their HT.[18,20]

Excessive glucose levels increase the risk of post-stroke hemorrhage conversion in patients with acute stroke, as demonstrated in several trials. Demchuk et al.[25] reviewed baseline clinical data from 138 stroke patients treated with intravenous rt-PA and found that baseline serum glucose levels were an independent predictor of symptomatic cerebral hemorrhage and all hemorrhages after thrombolysis, with serum glucose >11.1 mmol/L being associated with a 25% rate of symptomatic hemorrhage. Similarly, the results of a meta-analysis of 120 studies showed that serum glucose level was a predictor of symptomatic cerebral hemorrhage after intravenous thrombolytic therapy for acute ischemic stroke.[26] Excessive glucose levels disrupt energy

metabolism, decrease ATP and nicotinamide adenine dinucleotide levels, increase matrix metalloproteinase 3 activity in the post-stroke brain, and promote the onset of acidosis, which may further induce HT.[27–30]

Finally, our findings showed that a history of coronary artery disease can increase the risk of HT after thrombolysis in stroke patients; a correlation between a history of coronary artery disease and HT after thrombolysis has been less frequently found in previous studies. Cheng et al.[31] showed that dynamic changes in troponin levels were associated with HT after thrombolysis, suggesting that pre-existing myocardial injury may increase the risk of HT. Moreover, it has been shown that arterial stiffness is an independent risk factor for HT and is associated with atherosclerosis, in which coronary artery disease may play an indirect role.[32,33]

This study has some limitations. First, the patients included in this study were from the same tertiary hospital; therefore, the representation of patients is limited. Second, clinical data recording was incomplete for a few patients owing to the retrospective study design. Therefore, larger prospective cohort studies are needed to validate the findings of the present study. Third, information on stroke Trial of Org 10172 in Acute Stroke Treatment classification and modified Rank Scale were missing in this study, which may impact the evaluation of the associated factors of HT. We plan to increase the sample size and add more detailed patient information in future research. Finally, the absence of a priori sample size calculation is a limitation of this study. As this research was conducted retrospectively, we did not perform a formal sample size estimation before collecting data. The final sample size of 138 patients was determined based on the number of eligible cases during the study period. This may have implications for the statistical power of our findings and their generalizability to a broader population. Future prospective studies with predetermined sample size calculations are necessary to validate our findings and ensure sufficient power to detect clinically significant differences.

Conclusion

This study highlights the significant association between excessive 24-h systolic BP extremes after admission and the risk of HT within 36 h of rt-PA thrombolysis in patients with acute ischemic stroke. Our findings reinforce the critical role of meticulous BP management in this patient group, particularly focusing on minimizing extremes in systolic BPV immediately after admission. However, given that HT can occur later (including, 7 days after thrombolysis) than the 36-h period we examined, it is essential to adopt a cautious interpretation of these results. Clinicians should remain vigilant for HT beyond the first 36 h, particularly in patients exhibiting high BPV or other risk factors identified in our study, such as cerebral leukoaraiosis and large cerebral infarction. Our findings underscore the importance of establishing robust protocols for continuous BP monitoring and intervention strategies tailored to individual risk profiles. To ensure the safety of patients undergoing thrombolytic therapy, it is crucial to strictly control BP and especially minimize extremes in systolic BP. Further studies with longer follow-up durations are needed to fully elucidate the role of BPV in HT and provide more comprehensive guidelines for managing BP in the acute stroke setting.

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Author contributions

ZZ was involved in conception and design, and data interpretation for this article. SL, JG, HZ, YX, YZ, YL, and JS were involved in data collection, case diagnosis, and confirmation for this article. SL was involved in manuscript drafting. SL was involved in data analysis for this article. ZZ was involved critical review for this article.

Availability of data and materials

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

Declaration of conflicting interests

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Ethics approval

The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Harbin Medical University (IRB2023326).

Informed consent

Written informed consent was obtained from all participants or their Legally Authorized Representative in the case of patients who had lost their ability to sign due to stroke.

Consent for publication

Not applicable to this study.

Trial registration

Not applicable.

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