Screening risk factors of intravenous thrombolysis for acute ischemic stroke: A multicenter retrospective cohort study

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Research Article

Keywords: neurological function, risk factors, ischemic stroke, thrombolytic therapy, electrocardiogram

Posted Date: August 31st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-860548/v1

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Abstract

Objective

To evaluate the risk factors associated with in-hospital unfavorable outcomes after IV thrombolytic therapy in AIS patients.

Materials and Methods

This two-center retrospective study included AIS patients admitted at the advanced stroke centers of two Grade A tertiary hospitals in China between January 2018 and January 2020. The unfavorable outcome was defined as National Institutes of Health Stroke Scale (NIHSS) score ≥ 16, indicating neurological functional deficit. Univariable and multivariable analyses were used to screen out the factors associated with an unfavorable outcome.

Results

A total of 878 AIS patients undergoing IV thrombolytic therapy were included in this study. After multivariable analysis, Age (odds ratio (OR) = 1.101, 95% confidence interval (95%CI) = 1.048–1.157, P < 0.001), NIHSS score immediately after thrombolysis (OR = 1.336, 95%CI = 1.235–1.444, P < 0.001), total cholesterol (OR = 2.51, 95%CI = 1.432-4.4, P = 0.001), electrocardiogram grade 2 (OR = 17.532, 95%CI = 1.765-174.178, P = 0.014), electrocardiogram grade 3 (OR = 25.213, 95%CI = 2.219-286.425, P = 0.009), computed tomography 24 h after thrombolysis (OR = 3.308, 95%CI = 1.325–8.26, P = 0.010), and lower extremity venous color Doppler ultrasound (OR = 5.685, 95%CI = 1.85-17.471, P = 0.002) were risk factors associated with the adverse outcome. Single antiplatelet (OR = 0.089, 95%CI = 0.033–0.237, P < 0.001), double antiplatelet (OR = 0.063, 95%CI = 0.014–0.289, P < 0.001), high-density lipoprotein cholesterol (OR = 0.047, 95%CI = 0.005–0.488, P = 0.010), and apoprotein A1 (OR = 0.034, 95%CI = 0.002–0.573, P = 0.019) were protecting factors for the outcome.

Conclusion

Electrocardiogram, cholesterol, NIHSS, computed tomography, and Doppler ultrasound could predict unfavorable neurological functional outcomes after thrombolysis for AIS. Antiplatelet therapy reduces the risk of unfavorable outcomes.

Introduction

A stroke is an episode of acute neurological dysfunction from either ischemic infarction or a collection of blood within the brain or ventricular system with resultant focal injury of the central nervous system (CNS) [1, 2]. The determination of stroke can be based on clinical evidence of cerebral, spinal cord, or
retinal injury based on symptoms or can be made based on pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal injury in a defined vascular distribution [1, 2]. Strokes are generally classified as ischemic (80%-87% of strokes) or hemorrhagic [1, 2]. The estimated global incidence of stroke is 2–3 per 1000 person-years [3], with older patients and patients with carotid artery stenosis or atrial fibrillation having the highest risk [1, 2]. Worldwide, the prevalence of stroke increased by 21% from 2005 to 2015, affecting approximately 42.4 million people in 2015 [4]. Acute ischemic stroke (AIS) accounts for 69.6%-70.8% of the strokes in China [5, 6]. Stroke is a leading cause of permanent disability [7]. Ischemic stroke can lead to paralysis, aphasia, permanent stay in bed, and death [1, 2]. After the onset of stroke, survivors are at increased risk of poor outcomes and unable to independently conduct their daily activities [1, 2]. These adverse consequences cause considerable expenses in healthcare and losses in the labor force and economy [8].

Reperfusion therapy is the main treatment option for AIS and can comprehensively improve the functional outcome of patients [9, 10]. The most used therapeutic approaches are intravenous (IV) thrombolytic therapy and endovascular treatment. IV thrombolytic therapy in the early stage of acute cerebral infarction is a safe and reliable strategy [9, 11–13]. Recombinant tissue plasminogen activator (rt-PA) and urokinase (UK) are commonly used for IV thrombolytic therapy [9, 11–13]. Still, due to individual differences in age, the severity of stroke before thrombolysis, and past medical history, some patients can have complications such as symptomatic intracranial hemorrhage, vasogenic edema, and even unfavorable neurological outcomes after thrombolysis [9, 11–13].

The National Institutes of Health Stroke Scale (NIHSS) can guide the therapeutic decisions and is a predictor of the outcomes of AIS [14]. Still, the factors associated with unfavorable outcomes after IV thrombolytic therapy for AIS patients need to be determined accurately to adjust the subsequent therapeutic regimens and clinical management. Electrocardiogram (ECG) abnormalities have been suggested to be associated with stroke outcomes, but conflicting results were observed [15–19]. Computed tomography (CT) showing the disappearance of the cortical sulci and hypo-attenuation in the white matter suggests the development of early edema. On CT, the involvement of > 50% of the middle cerebral artery (MCA) territory correlates with risk for malignant infarction, and infarct volume > 220 mL or midline shift > 3.9 mm is reported to be predictive of severe brain edema and herniation [20, 21]. Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) displaying a lesion volume > 145 mL is reported to be predictive of malignant infarction (100% sensitivity, 94% specificity) [20, 21]. Transcranial Doppler ultrasound can be used to evaluate the cerebral blood flow and the outcomes of thrombolysis [22, 23]. Blood lipids levels are not only a risk factor for the onset of AIS but are also predictors for stroke outcomes [24, 25].

Therefore, this study aimed to evaluate the risk factors of adverse outcomes in AIS patients after IV thrombolytic therapy. The identified risk factors could allow the timely adjustment of the clinical decisions.

**Methods**
Study design and patients

This two-center retrospective study included AIS patients admitted at the advanced stroke centers of the Second Hospital of Hebei Medical University and Baoding No. 1 Central Hospital (both were Grade A tertiary hospitals) between January 2018 and January 2020. The present study was approved by the ethics committees of Baoding No. 1 Central Hospital and the Second Hospital of Hebei Medical University (approval number: 2021[012]). The requirement for informed consent was waived.

The inclusion criteria were 1) meeting the current AIS diagnostic and treatment guidelines and IV thrombolytic therapy criteria [9], 2) underwent IV thrombolytic therapy at the stroke center within 6 h after the onset of AIS, and 3) complete clinical, demographic, and laboratory data. The exclusion criteria were 1) in-hospital stroke, 2) wake-up stroke, 3) received bridging therapy or other non-IV thrombolytic therapies within 6 h, or 4) transient ischemic attack.

Thrombolysis

The thrombolytic therapy strategies were classified into four types according to the current IV thrombolytic therapy guidelines for stroke [9] and the actual thrombolytic regimens used at the stroke centers. Types 1 and 2 were based on rt-PA. In these two regimens, 10% of the total dose was injected IV within the first 1 min, and the remaining 90% of the dose was continuously infused IV for 1 h. In type 1, the total dose was 0.9 mg/kg. In type 2, the total dose was 0.6 mg/kg. Type 3 and 4 regimens used domestic UK for IV thrombolytic therapy, at 1-1.5 million units (IU) of UK dissolved in 100-200 ml of normal saline and continuously infused over 30 min. In type 3, the UK dose was 1 million IU. In type 4, the dose of UK was 1.5 million IU. The IV thrombolytic therapy regimens were developed by experienced and professionally trained attending physicians or above stroke centers.

If there were no remarkable signs of intracranial hemorrhage on the head CT 24 h after thrombolysis, antiplatelet and anticoagulation therapies could be performed. According to regimens used at the two advanced stroke centers, the antiplatelet therapy could be initiated within 48 h after thrombolysis and was classified into three categories: 1: no antiplatelet therapy; 2: aspirin alone; 3: aspirin combined with another drug. The anticoagulation therapy could be started within 48 h after thrombolysis and was classified as two categories: 0: no anticoagulation; 1: anticoagulation. Anticoagulation referred to all anticoagulation regimens, such as low molecular weight heparin, oral rivaroxaban, or other drugs. Lipid-lowering therapy included statins or other lipid-lowering regimens and was classified into two categories: 0: no lipid-lowering therapy; 1: lipid-lowering therapy.

Data collection
General data included age, sex, body mass index (BMI), history of smoking, and drinking history. Past medical history included hypertension, diabetes, coronary heart disease, arrhythmia, hyperlipemia, and stroke history. Systolic pressure, diastolic pressure, and emergency random peripheral blood glucose (GLU) were detected. Whether the blood pressure or glucose was controlled was recorded.

The emergency laboratory tests included 1) routine blood test: white blood cell count (WBC), red blood cell count (RBC), platelet count (PLT), hemoglobin (HGB), red blood cell distribution width standard deviation (RDWSD), and red blood cell distribution width coefficient of variation (RDWCV), 2) coagulation function: fibrinogen (Fib), prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT), 3) biochemical test: alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), creatine kinase-MB (CKMB), lactate dehydrogenase (LDH), urea nitrogen (UREA), serum creatinine (CREA), and uric acid (UA).

Emergency brain CT was performed before thrombolysis. Reports of brain CT, emergency ECG, and laboratory tests were provided by qualified physicians in the relevant departments. ECG was graded as 1) normal, the report suggested “roughly normal ECG”; 2) mild abnormality, it suggested “mild ST-T change”; 3) severe abnormality, it suggested manifestations other than the above two signs, including atrial fibrillation, atrial flutter, severe ventricular or supraventricular arrhythmia, and severe ST-T changes. CT was classified as 0) no massive cerebral infarction or 1) suggesting massive cerebral infarction. According to the current guidelines for IV thrombolytic therapy [9], massive cerebral infarction was defined as infarct size exceeding 1/3 of the cerebral lobe.

Before thrombolysis, the NIHSS score, modified Rankin Scale (mRS) score, and swallowing function were evaluated by experienced and professionally trained physicians. The mRS was classified as grades 0-6 according to the living ability of patients [26]: 0) no symptoms at all; 1) no significant disability despite symptoms; able to carry out all usual duties and activities; 2) slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance; 3) moderate disability; requiring some help, but able to walk without assistance; 4) moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5) severe disability; bedridden, incontinent and requiring constant nursing care and attention; 6) dead. The baseline swallowing function evaluation was made according to the results of the water swallow test. The patient was asked to sit in a chair and was handed a cup containing 30 mL of warm water. The time required and choking were observed. Grade 1: the patient could drink all the water in one gulp without choking; grade 2: the patient could drink all the water in two or more gulps without choking; grade 3: the patient could drink all the water in one gulp, but with some choking; grade 4: the patient could drink all the water in two or more gulps, but with some choking; grade 5: the patient often choked and had difficulty drinking all the water. The comatose patients were directly recorded as grade 5. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) was made [27]. TOAST was classified as 1) large-artery atherosclerotic stroke (LAA), 2) cardioembolism (CE), 3) small arterial occlusive stroke or lacunar stroke (SAA), 4) ischemic stroke due to other causes (SOE), or 5) ischemic stroke of unknown causes (SUE).
The time from onset to thrombolysis (OTT) and the time from door to needle (DNT) were recorded. OTT time was the length of time from the onset of stroke symptoms to the start of thrombolysis. The onset time of stroke symptoms was determined by the patient’s narrations or the supplementary narrations of their family members accompanying them. DNT was the length of time from the patient's admission with symptoms at the hospital to the start of thrombolysis. According to the relevant international standards, the time of admission was determined as the time for the patient to present to the emergency stroke center [9]. All time points were accurate and united to the min.

Thrombolytic complications were observed after thrombolysis. Thrombolysis complications included bleeding in the skin and mucous membranes or gums, nasal cavity, digestive tract, urinary system or other sites, reperfusion injury, allergies, edema of the tongue or throat, etc., during thrombolysis. It was classified as 0 (no complication) and 1 (presence of complication).

Laboratory tests after thrombolysis included fasting venous blood glucose (FBG), glycosylated hemoglobin (HbA1C), homocysteine (Hcy), thyroid-stimulating hormone (TSH), serum free thyroxine (FT4), serum free triiodothyronine (FT3), antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), and blood lipids: total cholesterol (CHOL), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apoprotein (Apo)A1, ApoB, and lipoprotein(a) (Lp(a)).

Rehabilitation within 72 h after thrombolysis was classified into five categories, 1) no rehabilitation; 2) acupuncture therapy; 3) exercise therapy; 4) acupuncture therapy combined with exercise therapy; 5) other therapies. Rehabilitation was determined by experienced and professionally trained rehabilitation physicians. Brain CT was re-examined 24 h after thrombolysis and classified as 0) no intracranial hemorrhage or 1) presence of intracranial hemorrhage. After thrombolysis, head MRI was performed and classified as 0) no massive cerebral infarction or 1) presence of massive cerebral infarction. Based on the position of infarcts on DWI hyperintense area of brain MRI and the corresponding position of intracranial vessels on magnetic resonance angiography (MRA), infarction position was defined as 1) anterior circulation cerebral infarction (ACCI), 2) posterior circulation cerebral infarction (PCCI), or 3) anterior and posterior circulation. After thrombolysis, carotid duplex ultrasound was performed and defined as 0) no carotid atherosclerosis, namely the results of the carotid duplex ultrasound were unremarkable for the carotid artery, or 1) presence of carotid atherosclerosis, namely the results of carotid duplex ultrasound suggested thickening of intima or plaque formation in the carotid artery. After thrombolysis, the ultrasound cardiogram (UCG) was performed and defined as 0) roughly normal or 1) abnormal, namely the report suggested abnormalities in cardiac structure and/or function. After thrombolysis, lower extremity artery ultrasound was performed and classified as 0) no lower extremity arteriosclerosis, namely the results of the report were unremarkable or 1) presence of lower extremity arteriosclerosis, namely the report suggested the presence of intima-media thickening and/or plaque formation in lower extremity arteries. After thrombolysis, lower extremity venous color Doppler ultrasound was performed and defined as 0) no lower extremity venous thrombosis or 1) presence of lower extremity venous thrombosis.
Clinical outcomes

NIHSS score immediately after thrombolysis, NIHSS score 24 h after thrombolysis, and NIHSS score on day 7 of onset were recorded. The study outcome was the adverse outcome of AIS patients after IV thrombolytic therapy. Based on the NIHSS score on day 7 of onset and the literature [28, 29], an NIHSS score ≥16 indicated that the neurological deficit after thrombolysis was extremely severe, and it was considered an unfavorable outcome, while <16 indicated that there was no severe neurological deficit after thrombolysis, which was considered a favorable outcome.

Statistical analysis

Statistical analyses were performed using SPSS 24.0 (IBM, Armonk, NY, USA). Univariable regression analyses were performed to observe the correlation between each variable and the outcome. For continuous variables, the Shapiro-Wilk test was used to test for normal distribution. The normally distributed continuous variables were presented as mean ± standard deviation, and the general linear model-univariable analysis was used for the test. Non-normally distributed continuous variables were presented as the median (IQR), and the non-parametric Mann-Whitney U test was used for statistical analysis. Categorical variables and ranked variables were presented as n (%) and analyzed using binary logistics regression or chi-square test. The variables with P-values <0.20 were selected. After considering whether they met clinical practice and sample size requirements for the number of finally selected risk factors, the multivariable regression analysis was performed. Multivariable regression analysis was performed using binary logistics regression forward stepwise iteration. Setting dummy variables was adopted for the categorical variables and ranked variables of more than three categories in the independent variables. In the screening process, the model automatically calculated a P-value for each variable. The minimum P-value was first included in Model 1, and the other variables were calculated; then, they were included in the model in ascending order. The variables that were ultimately left in the model were those that had an impact on the results. The maximum likelihood method was used to select all the variables in the equation with -2 times the minimum log-likelihood as the factors related to the outcome. The odds ratio (OR) and 95% confidence interval (CI) were calculated.

Results

A total of 878 AIS patients who underwent IV thrombolytic therapy at two advanced stroke centers were included in the present study. After univariable analyses, variables with P<0.20 were pre-selected for the multivariable analysis (Table 1). By comparing the correlation with the clinical professional background and considering the sample size requirements for the number of risk factor variables, the following variables were selected for the multivariable regression analysis: smoking (P=0.001), drinking (P=0.009), coronary heart disease (P=0.191), arrhythmia (P<0.001), thrombolytics type (P=0.047), mRS
(P<0.001), swallowing function (P<0.001), TOAST (P<0.001), infarction location (P=0.027), thrombolytic complication (P<0.001), antiplatelet (P<0.001), lipid regulation (P<0.001), rehabilitation (P=0.064), ECG (P<0.001), CT at admission (P<0.001), CT 24h after thrombolysis (P<0.001), MR (P<0.001), ultrasonic cardiogram (P=0.114), and lower extremity venous color Doppler ultrasound (P<0.001).

After multivariable analysis, the following variables were screened as risk factors associated with the outcome (Table 2): age, NIHSS2, antiplatelet, CHOL, HDL, ApoA1, ECG, CT2, and lower extremity venous color Doppler ultrasound. By comparing OR values and 95% CI, the OR values of age (OR=1.101, 95% CI=1.048-1.157, P<0.001), NIHSS score immediately after thrombolysis (OR=1.336, 95% CI=1.235-1.444, P<0.001), CHOL (OR= 2.51, 95% CI=1.432-4.4, P=0.001), ECG grade 2 (OR=17.532, 95% CI=1.765-174.178, P=0.014), ECG grade 3 (OR=25.213, 95% CI=2.219-286.425, P=0.009), CT 24 h after thrombolysis (OR=3.308, 95% CI=1.325-8.26, P=0.010), and lower extremity venous color Doppler ultrasound (OR=5.685, 95% CI=1.85-17.471, P=0.002) indicated risk factors associated with adverse outcome. The OR values of single antiplatelet (OR=0.089, 95% CI=0.033-0.237, P<0.001), double antiplatelet (OR=0.063, 95% CI=0.014-0.289, P<0.001), HDL (OR=0.047, 95% CI=0.005-0.488, P=0.010), and ApoA1 (OR=0.034, 95% CI=0.002-0.573, P=0.019) indicated protecting factors for the outcome.

**Discussion**

AIS results from a thrombus or embolus block in the cerebral arteries and accounts for a large proportion of all strokes [1, 2]. Early thrombolysis for acute cerebral infarction is a safe and reliable option, but it may have risk [9, 11–13]. Accurately identifying the risk factors for adverse outcomes in AIS patients after IV thrombolytic therapy to timely adjust clinical strategies is crucial for clinical patient management. This study is based on the overall data of two advanced stroke centers that involved factors related to IV thrombolytic therapy. The thrombolytics included rt-PA and domestic UK. Univariable and multivariable analyses were performed to screen out the variables related to the target variable, namely the adverse outcome after IV thrombolytic therapy in AIS patients. By comparing the OR values and their 95% CI, risk factors and protectors were identified. The results suggest that ECG, CHOL, NIHSS, CT, and Doppler ultrasound could predict unfavorable neurological functional outcomes after thrombolysis for AIS. Antiplatelet therapy reduces the risk of unfavorable outcomes.

The increasing age of patients has an important impact on the incidence, mortality, and long-term stroke outcome [30]. Rejno et al. [31] suggested that age could predict the deterioration of neurological functions after stroke. It may be because advanced age leads to the dysfunction of neurovascular units and neurodegenerative changes in stroke patients [32]. In the present study, age was a risk factor for adverse outcome after IV thrombolytic therapy (OR = 1.101, 95%CI = 1.048−1.157), and its clinical significance was that for every increase in one year of age, the risk of in-hospital adverse outcome was increased by 10.1% for AIS patients undergoing IV thrombolytic therapy. NIHSS2 was a risk factor for adverse outcomes after IV thrombolytic therapy (OR = 1.336, 95%CI = 1.235−1.444), and the clinical significance was that for every point increase in the NIHSS score immediately after thrombolytic therapy, the risk of in-hospital adverse outcome was increased by 33.6% after IV thrombolytic therapy. Therefore, the
relationship between the variables age and NIHSS2 and the outcome in the present study was consistent with previous findings.

The correlation between blood lipids and stroke outcome varies depending on the components of blood lipids. CHOL is a modifiable risk factor, and CHOL levels are closely associated with the first ischemic stroke attack [33]. Globally, since 1990–2013, high cholesterol levels (greater than 185 mg/dl) have led to a 24% increase in stroke-related disability-adjusted life years [34]. CHOL levels are positively correlated with the risk of ischemic stroke. Celap et al. [35] found that APOA5 genotype (TC + CC) was more common in patients with NIHSS score $\geq 21$, suggesting that APOA5 genotype (TC + CC), age, and obesity can be used as risk factors for outcomes in extremely severe stroke patients (NIHSS $\geq 21$). In the present study, CHOL was a risk factor for adverse outcomes after IV thrombolytic therapy (OR = 2.51, 95%CI = 1.432-4.4). Its clinical significance was that for every increase in CHOL by 1 mmol/L, the risk of adverse outcomes after IV thrombolytic therapy was increased by 151%. The correlation between CHOL and outcome in the present study was consistent with that of previous findings.

HDL-C is a powerful and independent negative predictor of cardiovascular and cerebrovascular diseases. The beneficial effect of HDL is largely due to its key role in reverse cholesterol transport, namely the transport of excess cholesterol in peripheral tissues to the liver. There is increasing evidence that HDL also has anti-inflammatory, antioxidant, and vasodilator characteristics, reducing atherosclerosis [36]. Gu et al. [37] surveyed six cohort studies involving 267,500 Chinese subjects and showed that LDL-C and TG levels were positively correlated with ischemic stroke, while HDL-C levels showed a negative correlation. Li et al. [38] suggested that the ATP-binding cassette transporter A1 (ABCA1)/apolipoprotein E (ApoE)/HDL signaling pathway may be involved in the myelination and oligodendrocyte cytogenesis of ischemic brain tissues after stroke, which could repair the white matter damage of the central nervous system caused by stroke and promote the white matter remodeling of ischemic brain tissues, thereby facilitating the recovery of neurological function in the late stage of ischemic stroke. Hence, HDL is associated with the functional outcome of ischemic stroke and might be a protector for the outcome. In the present study, HDL was a protector for adverse outcomes after IV thrombolytic therapy, which was consistent with previous findings. After multivariable analysis, the OR value of HDL was 0.047, 95% CI = 0.005–0.488. The clinical significance was that for every increase in HDL by 1 mmol/L, the risk of adverse outcomes after IV thrombolytic therapy was reduced by 95.3%.

ApoA1 is the main lipoprotein related to HDL in plasma and the main protein component responsible for the transport of cholesterol in HDL [39], which plays an important role in reverse cholesterol transport. ApoA1 has clinical value in the diagnosis of ischemic stroke and differentiation from hemorrhagic stroke [40]. A meta-analysis showed that decreased ApoA1 levels and increased ApoB/A1 ratio were risk factors for ischemic stroke [41]. Studies have found that serum ApoA1 levels are negatively correlated with the prevalence of type 2 diabetes and fasting venous blood glucose levels [42]. The latter two are also common clinical risk factors for cerebrovascular diseases. Previous studies have suggested that ApoA1 levels might be associated with the occurrence of atherosclerotic cerebral infarction and the characteristics of carotid plaque [43]. Ohtani et al. [43] showed that compared with the normal control
group, ApoA1 levels in patients with atherosclerotic stroke were significantly reduced. The serum ApoA1 levels of the low-intensity plaque subgroup were significantly lower than those of the medium-intensity plaque subgroup and the high-intensity plaque subgroup. In addition, the serum ApoA1 level of the mixed plaque subgroup was significantly lower than that of the simple plaque subgroup. ApoA1 is shown to enhance the excretion of cholesterol from arterial wall cells and prevent atherosclerosis [44]. The present study found that ApoA1 was a protector for the adverse outcome of AIS patients after IV thrombolytic therapy (OR = 0.034, 95%CI = 0.002–0.573), and its clinical significance was that for every increase in the ApoA1 level by 1 g/L, the risk of adverse outcome after IV thrombolytic therapy was reduced by 96.6%, which was consistent with previous findings.

IV thrombolytic therapy and endovascular thrombectomy can quickly achieve reperfusion to reduce disability [9, 11–13, 45]. Still, IV thrombolytic therapy has an increased risk of symptomatic intracerebral hemorrhage (sICH) [46]. Non-contrast CT can exclude intracranial hemorrhage, and it is crucial to recheck the head CT as soon as possible after thrombolysis (after 24 h, and before the administration of antiplatelet drugs) [9]. In the present study, CT2 was a risk factor for the outcome (OR = 3.308, 95% CI = 1.325–8.26), and its clinical significance was that the risk of adverse outcome in patients with intracranial hemorrhage on CT scan 24 h after IV thrombolytic therapy was 3.308 times that in those without intracranial hemorrhage, which was consistent with previous findings.

ECG plays an important role in identifying risk factors for stroke, such as atrial fibrillation and left ventricular hypertrophy. Cardiogenic stroke caused by atrial fibrillation accounts for one-third of ischemic strokes [1, 2]. The role of atrial fibrillation in cryptogenic stroke is well-known. In about 25% of patients with ischemic stroke, new atrial fibrillation can be noted through routine enhanced ECG monitoring [47]. Lowres et al. [48] studied the use of iPhone ECG (iECG) in pharmacies for a community screening of unknown atrial fibrillation. They found that the high risk of stroke/thromboembolism in newly confirmed atrial fibrillation patients could be largely prevented. Many other ECG characteristics, namely ECG/structural remodeling-Q wave, QRS/QT interval, bundle block, P wave interval/amplitude/dispersion, other waveform angles and slopes, higher automatism, ectopic beats, atrial tachyarrhythmia, and heart rate and its variability, are also potential predictors for stroke [49]. Gatti Pianca et al. [50] evaluated the relationship between ECG p-wave abnormality and neurological dysfunction in patients with cryptogenic stroke and found that in the ECG criteria, left atrial enlargement assessed by clockwise rotation was more common in disabling stroke. In the present study, ECG was a ranked variable. When setting dummy variables, the first grade-normal ECG was used as the reference and the second grade-mild change as the risk factor for the outcome. The OR value was 17.532 (95%CI = 1.765-174.178), and the clinical significance was that the risk of adverse outcomes in patients with mild ECG changes before IV thrombolytic therapy was 17.532 times that of patients with normal ECG. The third grade-malignant arrhythmia was associated with adverse outcomes (OR = 25.213, 95%CI = 2.219-286.425). Its clinical significance was that the risk of adverse outcomes in patients with malignant arrhythmia in ECG before IV thrombolytic therapy was 25.213 times that of patients with normal ECG. The results of the ranked variables suggested that the impact of each grade on the outcome was not equidistant.
Lower extremity venous thrombosis is severe comorbidity of ischemic stroke. Paralysis after stroke is a common cause of lower extremity venous thrombosis. Pan et al. [51] used some clinical characteristics and accessible biochemical parameters to develop and validate a nomogram for predicting the risk of deep vein thrombosis in patients with acute stroke within 14 days. Liu et al. [52] conducted a study on 679 stroke patients (including 507 with ischemic stroke and 172 with hemorrhagic stroke) and found that 21.1% of patients with ischemic stroke (n = 107) were affected by deep vein thrombosis. The intermuscular veins, especially the fibular veins, were the most susceptible. Ha et al. [53] studied Asian AIS patients with lower extremity deep venous thrombosis and found that female and higher NIHSS scores were independently associated with lower extremity deep venous thrombosis. Compared with D-dimer screening, lower extremity deep venous color Doppler ultrasound of patients with severe neurological deficits might be more conducive to diagnosing deep vein thrombosis in Asian AIS patients. Decreased activities of the lower extremities or joint contractures caused by stroke and other reasons may be the main contributors to deep vein thrombosis of the lower extremities, which can further lead to a prolonged rehabilitation process [54]. After completing the acute phase of treatment, most stroke patients need rehabilitation. It usually takes months or even years for patients to restore their extremity function fully. Paralyzed limbs may be restricted in daily activities such as turning over, getting up, and moving short distances due to decreased activities. After lower extremity venous thrombosis, the rehabilitation exercise of the paralyzed limbs will be further decreased, which will lead to a longer recovery time of the extremity function, and severe neurological deficits, and poor outcome. Therefore, lower extremity venous thrombosis may be a risk factor for poor outcomes after stroke. The present study found that lower extremity venous color Doppler ultrasound was a risk factor for the outcome (OR = 5.685, 95% CI = 1.850-17.471), and its clinical significance was that the risk of adverse outcome in patients with lower extremity venous thrombosis revealed in the lower extremity venous color Doppler ultrasound after IV thrombolytic therapy was 5.685 times that of patients without lower extremity venous thrombosis.

Antiplatelet therapy with drugs such as aspirin is one of the traditional therapies for treating ischemic stroke. Aoki et al. [55] showed that aspirin combined with IV thrombolytic therapy and endovascular treatment played a key role in reducing stroke recurrence. The current domestic and foreign AIS and TIA treatment guidelines strongly recommend antiplatelet regimen using aspirin for antiplatelet aggregation therapy [56–58]. Chinese guidelines for diagnosis and treatment of AIS 2018 recommended that aspirin be administrated within 48 h of stroke onset for patients who do not meet IV thrombolytic therapy or endovascular thrombectomy indications and have no contraindications. The AIS management guidelines issued by the American Heart Association/ASA in 2018 clarified the Class IIa recommendation for dual antiplatelet drugs for the treatment of acute minor stroke [59, 60]. From several prospective randomized controlled trials such as the CHANCE [61] and POINT [62] trials, aspirin combined with clopidogrel can significantly reduce the neurological deterioration in patients with acute non-cardiogenic stroke. A meta-analysis of 16 randomized controlled trials involving 28,032 patients showed that dual antiplatelet therapy was significantly superior to single antiplatelet therapy in reducing the incidence and mortality of stroke and its composite events (i.e., cardiovascular diseases), but bleeding events did not increase
significantly [63]. Dual antiplatelet therapy may exert synergistic effects by inhibiting different platelet pathways. The variable antiplatelet in the present study was a ranked variable and a protector for the outcome. With the first grade, namely no anti-platelet aggregation treatment as the reference, the OR value of the second grade was 0.089, 95% CI = 0.033–0.237. Its clinical significance was that the risk of adverse outcomes in AIS patients receiving anti-platelet aggregation treatment with aspirin alone within 24–48 h after IV thrombolytic therapy was decreased by 91.1% compared with that in those receiving no anti-platelet aggregation treatment. The OR value of the third grade was 0.063, 95% CI = 0.014–0.289, and suggesting that the risk of adverse outcome in AIS patients receiving anti-platelet aggregation treatment with two drugs (one of which was aspirin) within 24–48 h after IV thrombolytic therapy was decreased by 93.7% compared with that in those receiving no anti-platelet aggregation treatment, which was consistent with previous findings.

Regarding the strategies of screening variables into the multivariable regression, the baseline variables considered clinically relevant, or the baseline variables that had a univariable relationship with the outcome were included in the multivariable risk regression model [64]. Given the number of available events, and to ensure the conciseness of the final model, the variables were carefully selected. As candidate variables that might impact the outcome event, first, from the perspective of clinical specialty, its role must be acceptable to people, and it can be reasonably explained from a certain physiological mechanism or pathway. The candidate variables of the present study included demographic data (e.g., sex, age, and BMI), lifestyle (e.g., smoking and drinking), medical history (e.g., hypertension, diabetes, coronary heart disease, arrhythmia, hyperlipidemia, and past stroke), examinations (blood test indicators and other examination items), treatments (thrombolytics type, DNT, and OTT time), and exposure/treatment factors (NIHSS score after thrombolysis, subsequent related antiplatelet, anticoagulation, lipid regulation, and rehabilitation). For the above candidate variables, by referring to the previously published literature, the published and reported variables that had independent effects on the outcome event were summarized and used as key candidate variables for alternatives.

Second, the variables were screened from the results of the univariable analysis. The relationship between traditional univariable analysis and univariable regression analysis was essentially equivalent. Univariable analysis analyzed the differences of single factors among groups and included the t-test, chi-square test, and analysis of variance. Through these univariable analysis methods, distribution differences of the means or percentages between two or among multiple groups can be simply and directly observed. Univariable regression analysis included only one factor into the regression model for fitting when constructing the regression model. Therefore, univariable regression analysis was equivalent to the traditional univariable analysis methods used in the present study. The t-test was equivalent to simple linear regression, while analysis of variance was equivalent to multiple linear regression. Similarly, the results of the analysis of variance and the univariable linear regression were also consistent to a certain extent. Not only the results of univariable linear regression were consistent with the results of the t-test and analysis of variance, the results of univariable logistic regression and chi-square test were also equivalent. Therefore, during screening variables in the present study, the chi-square test was used to conduct univariable analysis of categorical variables and ranked variables, which was essentially
equivalent to univariable regression analysis, and the P values obtained were equivalent and effective. The present study used the Mann-Whitney U-test for non-normally distributed continuous variables and used the general linear model - univariable test method for normally distributed ones. The latter was essentially equivalent to a two independent-sample t-test. The test method used for continuous variables was essentially equivalent to the univariable regression analysis. The P values obtained were also equivalent and effective.

Given in the univariable analysis, the differences among the results did not reflect the effect of the factor on the outcome event, statistically significant variables in the univariable analyses (P < 0.05) were used as the first echelon of candidate variables, and the inclusion criteria were appropriately extended to P < 0.20 [65], effectively avoiding the omission of some important variables. Although they were not statistically significant in the univariable analysis, their real effects might be underestimated or neglected due to the limitation of the P-value. In addition, the variables with P-value close to 0.2 were carefully considered, incorporating the relevance to the clinical professional background and requirements of the sample size for the number of independent variables screened. For logistic regression, the number of positive outcome events should be at least 15–20 times the number of independent variables finally screened.

When performing multivariable regression analysis, categorical variables with three categories and above need dummy variables because parametric regression was made, which was in the framework of a generalized linear model, and the latter was essentially a linear trend. If there were no dummy variables and the categorical variables with three categories and above were directly included in the multivariable adjustment, then the relationship among the categories had equivalent effects on the outcome during the statistical analysis. It was a linear relationship, but it was a very narrow control of an equidistance. Still, many medical variables were multi-categorical variables, and there was no such equidistant relationship. In order to better explain which variable had a greater impact on the outcome, a reference must be set, namely the dummy variable.

The outcome-related variables screened in the present study conformed to the clinical practice. The severity of stroke can be assessed on a clinical basis according to the degree of neurological deficits (for example, disturbance of consciousness, language and behavioral disorders, visual field defect, dyskinesia). Many studies have conducted quantitative measurements of neurological deficits, and NIHSS scores are increasingly used in clinical practice for assessment. Although many previous studies have shown that the NIHSS score is a reliable predictive tool for the outcome of stroke, which can be used to compare the changes in neurological functions after IV thrombolytic therapy in AIS patients to assess the efficacy [66], its relationship with the outcome varies with the time after the onset of cerebral ischemia [28]. It may be because many patients have undergone a gradual recovery process, and the early symptoms of stroke-related deficits are often changeable. Therefore, NIHSS scores associated with specific disability outcomes tend to shift to lower scores over time. In addition, the correlation between NIHSS score and disability in late-stage is increased over time. Some studies have found that the optimal
predictor of poor outcome 24 h after ischemic stroke is NIHSS score > 22, and the optimal predictor in
days 7–10 is NIHSS score > 16 [28, 29].

The present study has some limitations. First, the follow-up was short. Future studies can extend the
follow-up time to 3 months to half a year after the onset of ischemic stroke. Second, the sample size
should be increased using data from multiple centers.

In conclusion, ECG at admission could predict unfavorable neurological functional outcomes after IV for
AIS patients. CHOL, NIHSS score immediately after thrombolysis, head CT revealing intracranial
hemorrhage 24 h after thrombolysis, and lower extremity venous color Doppler ultrasound showing
venous thrombosis of lower limbs can also predict the risk of unfavorable outcomes. Antiplatelet therapy
may help develop treatment strategies and reduce the risk of unfavorable outcomes.

Declarations

Funding

None

Competing interests

All authors declare that they have no competing interests.

Availability of data and material

All date and Materials are available from the corresponding author.

Code availability

Not applicable

Authors’ contributions

Weiping Wang: Project development, Data management, Manuscript editing

Lu Liu: Protocol development, Data collection, Data analysis, Manuscript writing

Ethics approval

The present study was approved by the ethics committees of Baoding No. 1 Central Hospital and the
Second Hospital of Hebei Medical University (approval number: 2021[012])

Consent to participate

The requirement for informed consent was waived.
Consent for publication

Not applicable

Acknowledgments

The authors would like to thank all study participants who were enrolled in this study.

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Tables

Table 1. Descriptive statistics of all candidate variables in the complete set and univariable analysis comparing neurological deficit outcome variables.
| Variables                        | n  | Unfavorable outcome (NIHSS score ≥16, n%) | Favorable outcome (NIHSS score <16, n%) | $\chi^2$ | P    |
|---------------------------------|----|------------------------------------------|----------------------------------------|---------|------|
| Sex                             |    |                                          |                                        | 0.055   | 0.815|
| Male                            | 605| 46 (7.6%)                                 | 559 (92.4%)                            |          |      |
| Female                          | 273| 22 (8.1%)                                 | 251 (91.9%)                            |          |      |
| Smoking                         | 413| 19 (4.6%)                                 | 394 (95.4%)                            | 10.791  | 0.001*|
| Drinking                        | 309| 14 (4.5%)                                 | 295 (95.5%)                            | 6.894   | 0.009*|
| Hypertension                    | 549| 45 (8.2%)                                 | 504 (91.8%)                            | 0.419   | 0.518|
| Diabetes                        | 177| 16 (9.0%)                                 | 161 (91.0%)                            | 0.520   | 0.471|
| Coronary heart disease          | 167| 17 (10.2%)                                | 150 (89.8%)                            | 1.711   | 0.191*|
| Arrhythmia                      | 112| 19 (17.0%)                                | 93 (83.0%)                             | 15.272  | <0.001*|
| Hyperlipemia                    | 78 | 5 (6.4%)                                  | 73 (93.6%)                             | 0.213   | 0.644|
| Stroke history                  | 208| 20 (9.6%)                                 | 188 (90.4%)                            | 1.335   | 0.248|
| Thrombolytics type              |    |                                          |                                        | 7.957   | 0.047*|
| 0.6 mg/kg rt-PA                 | 45 | 8 (17.8%)                                 | 37 (82.2%)                             |          |      |
| 0.9 mg/kg rt-PA                 | 659| 44 (6.7%)                                 | 615 (93.3%)                            |          |      |
| 1 million IU UK                | 155| 14 (9.0%)                                 | 141 (91.0%)                            |          |      |
| 1.5 million IU UK              | 19 | 2 (10.5%)                                 | 17 (89.5%)                             |          |      |
| mRS                             |    |                                          |                                        | 196.305 | <0.001*|
| 0                               | 261| 8 (3.1%)                                  | 253 (96.9%)                            |          |      |
| 1                               | 140| 1 (0.7%)                                  | 139 (99.3%)                            |          |      |
| 2                               | 110| 2 (1.8%)                                  | 108 (98.2%)                            |          |      |
| 3                               | 125| 2 (1.6%)                                  | 123 (98.4%)                            |          |      |
| 4                               | 178| 23 (12.9%)                                | 155 (87.1%)                            |          |      |
| 5                               | 64 | 32 (0.5%)                                 | 32 (0.5%)                              |          |      |
| 6                               | 0  | 0                                         | 0                                       |          |      |
| Swallowing function             |    |                                          |                                        | 205.758 | <0.001*|
| 1                               | 671| 17 (2.5%)                                 | 654 (97.5%)                            |          |      |
|   | 2   | 3   | 4   | 5   |
|---|-----|-----|-----|-----|
|   | 63  | 12  | 27  | 105 |
| % | 1.6%| 25% | 11.1%| 41.9%|
|   | 62  | 9   | 24  | 61  |
| % | 98.4% | 75% | 88.9%| 58.1%|
|   | 53.003 | <0.001* |
| LAA | 482 | 47 | 435 | 90.2% |
| CE  | 81  | 19 | 62 | 76.5% |
| SAA | 290 | 2  | 288 | 99.3% |
| SOE | 14  | 0  | 14 | 100% |
| SUE | 11  | 0  | 11 | 100% |
| Infarction position | 7.233 | 0.027* |
| ACCI\(a\) | 594 | 54 | 540 | 90.9% |
| PCCI\(b\) | 173 | 5  | 168 | 97.1% |
| ACCI and PCCI\(c\) | 111 | 9  | 102 | 91.9% |
| Thrombolytic complications | 158 | 28 | 130 | 82.3% | 26.840 | <0.001* |
| Controlled pressure | 454 | 38 | 416 | 91.6% | 0.514 | 0.473 |
| Controlled glucose | 155 | 15 | 140 | 90.3% | 0.984 | 0.321 |
| Antiplatelet | 113.825 | <0.001* |
| Nome | 104 | 35 | 69 | 66.3% |
| Single\(d\) | 571 | 30 | 541 | 94.7% |
| Double\(e\) | 203 | 3  | 200 | 98.5% |
| Anticoagulation | 130 | 20 | 110 | 84.6% | 12.465 | <0.001* |
| Lipid-lowering drugs | 848 | 49 | 799 | 94.2% | 134.333 | <0.001* |
| Rehabilitation | 8.902 | 0.064* |
| None | 512 | 48 | 464 | 90.6% |
| Acupuncture | 126 | 11 | 115 | 91.3% |
| Kinesitherapy | 63 | 1 | 62 | 98.4% |
| Test Description                                      | No   | Yes  | p-value   |
|-------------------------------------------------------|------|------|-----------|
| Both acupuncture and kinesitherapy                   | 123  | 4 (3.3%) | 119 (96.7%) |
| Other therapy                                         | 54   | 4 (7.4%) | 50 (92.6%)  |
| CT at admission                                       | 30.008 | <0.001* |
| No m Cerebral Infarction                              | 849  | 58 (6.8%) | 791 (93.2%) |
| Has Massive Cerebral Infarction                       | 29   | 10 (34.5%) | 19 (65.5%)  |
| ECG                                                   | 64.197 | <0.001* |
| 1                                                     | 210  | 2 (1%) | 208 (99%)  |
| 2                                                     | 566  | 39 (6.9%) | 527 (93.1%) |
| 3                                                     | 102  | 27 (26.5%) | 75 (73.5%)  |
| CT 24 h after thrombolysis                            | 147.542 | <0.001* |
| No intracranial hemorrhage                            | 727  | 20 (2.8%) | 707 (97.2%) |
| Has intracranial hemorrhage                           | 151  | 48 (31.8%) | 103 (68.2%) |
| MR                                                    | 102.89 | <0.001* |
| No massive Cerebral Infarction                        | 672  | 18 (2.7%) | 654 (97.3%) |
| Has massive Cerebral Infarction                       | 206  | 50 (24.3%) | 156 (75.7%) |
| Carotid Duplex Ultrasound                             | 0.21 | 0.647 |
| No arterioarctia                                      | 745  | 59 (7.9%) | 686 (92.1%) |
| Has arterioarctia                                     | 133  | 9 (6.8%) | 124 (93.2%) |
| Ultrasonic Cardiogram (UCG)                           | 2.491 | 0.114* |
| Normal                                                | 775  | 56 (7.2%) | 719 (92.8%) |
| Abnormal                                              | 103  | 12 (11.7%) | 91 (88.3%)  |
| Lower Extremity Artery Ultrasound                     | 5.871 | 0.015* |
| No arteriosclerosis                                   | 685  | 61 (8.9%) | 624 (91.1%) |
| Has arteriosclerosis                                  | 193  | 7 (3.6%) | 186 (96.4%) |
| Lower extremity venous color Doppler ultrasound | 21.214 | <0.001* |
|-----------------------------------------------|--------|---------|
| No venous thrombus                            | 817    | 54 (6.6%) | 763 (93.4%) |
| Has venous thrombus                           | 61     | 14 (23.0%) | 47 (77.0%) |
| ANA                                           | 1.533  | 0.216   |
| Negative                                      | 839    | 67 (8.0%)  | 772 (92.0%) |
| Positive                                      | 39     | 1 (2.6%)   | 38 (97.4%) |
| Age (years)                                   | 878    | 70 (61.76) | 62 (53.69) |
| BMI (kg/m²)                                   | 878    | 24.86 (3.37) | 24.86 (23.18,26.3) |
| OTT (min)                                     | 878    | 74 (59,130) | 97.5 (63,165) |
| DNT (min)                                     | 878    | 177.5 (67.5,240) | 120 (50,210) |
| NIHSS score at admission after                | 878    | 18 (13.22) | 5 (3,10) |
| NIHSS score immediately after thrombolysis    | 878    | 19 (14.5,24.5) | 4 (2,8) |
| NIHSS score 24 h after thrombolysis           | 878    | 20 (15.5,24.5) | 4 (2,8) |
| Systolic pressure (mmHg)                      | 878    | 152 (132,179) | 149 (136,163) |
| Diastolic pressure (mmHg)                     | 878    | 84.5 (72.5,93.5) | 86 (77,95) |
| WBC (10⁹/L)                                   | 878    | 8.72 (7.1,10.71) | 7.5 (6.08,9.4) |
| RBC (10¹²/L)                                  | 878    | 4.54 (4.26,4.89) | 4.62 (4.32,4.99) |
| HGB (g/L)                                     | 878    | 139 (133.5,152.5) | 145 (136,155) |
| PLT (10⁹/L)                                   | 878    | 218.5 (180,249) | 216 (184,252) |
| RDWSD (fL)                                    | 878    | 43.35 (41.5,45.1) | 42 (39.8,44.2) |
| RDWCV (%)                                     | 878    | 13.3 (12.8,13.85) | 12.9 (12.4,13.4) |
| Fib (g/L)                                     | 878    | 3.22 (2.82,3.87) | 2.77 (2.37,3.31) |
| Test       | Value     | Reference Range         | p-value |
|------------|-----------|-------------------------|---------|
| PT (Sec)   | 878       | 11.6 (10.9,12.35)       | <0.001* |
| INR        | 878       | 1.015 (0.97,1.1)        | <0.001* |
| APTT (Sec) | 878       | 27.75 (25.4,30.15)      | 0.359   |
| GLU (mmol/L)| 878       | 6.98 (5.79,9.31)        | 0.129*  |
| ALT (U/L)  | 878       | 19.1 (15.7,26.9)        | 0.455   |
| AST (U/L)  | 878       | 21 (17.3,28.95)         | 0.148*  |
| CK (U/L)   | 878       | 76 (47.5,169)           | 0.791   |
| CKMB (U/L) | 878       | 16 (12.25)              | 0.010*  |
| LDH (U/L)  | 878       | 260.5 (192,365.88)      | 0.500   |
| UREA (mmol/L)| 878      | 6 (5.16,8.2)            | 0.001*  |
| CREA (µmol/L)| 878     | 75 (60.35,94)           | 0.004*  |
| UA (µmol/L) | 878       | 324.61 (279.415,372.3)  | 0.088*  |
| CHOL (mmol/L)| 878      | 4.265 (3.65,5.02)       | 0.027*  |
| TG (mmol/L) | 878       | 1.28 (0.89,1.73)        | 0.082*  |
| HDL (mmol/L)| 878       | 1.035 (0.9,1.24)        | 0.057*  |
| LDL (mmol/L)| 878       | 2.84 (2.1,3.47)         | 0.581   |
| ApoA1 (g/L)| 878       | 1.22 (1.075,1.26)       | 0.011*  |
| ApoB (g/L) | 878       | 0.96 (0.79,1.11)        | 0.530   |
| Lpa (g/L)  | 878       | 15.08 (3.87,27.77)      | 0.548   |
| FBG (mmol/L)| 878       | 6.51 (5.62,8.295)       | 0.071*  |
| HbA1C (mmol/mol)| 878 | 6.46 (5.8,6.46) | 0.100* |
| HCY (µmol/L)| 878       | 18.475 (11.34,20.44)    | 0.434   |
| TSH (µIU/mL)| 878       | 2.05 (0.732,2.05)       | 0.194*  |
| FT4 (pmol/L)| 878       | 15.52 (13.785,15.585)   | 0.856   |
| FT3 (pmol/L)| 878       | 4.25 (3.825,4.25)       | 0.140*  |
Values are presented as median (IQR). Categorical variables are presented as n (%). *Variables with P<0.20 were pre-selected for multivariable analysis.

a ACCI: anterior circulation cerebral infarction; b PCCI: posterior circulation cerebral infarction; c ACCI and PCCI: both anterior and posterior circulations have infarcts. d: Single: single drug for anti-platelet aggregation; f: Double: two or more drugs for anti-platelet aggregation. ECG was graded as 1) normal, the report suggested “roughly normal ECG”; 2) mild abnormality, it suggested “mild ST-T change”; 3) severe abnormality, it suggested manifestations other than the above two signs, including atrial fibrillation, atrial flutter, severe ventricular or supraventricular arrhythmia, and severe ST-T changes. CT was classified as 0) no massive cerebral infarction or 1) suggesting massive cerebral infarction.

mRS: modified Rankin scale; TOAST: Trial of Org 10172 in Acute Stroke Treatment; LAA: large artery atherosclerosis; CE: cardioembolism; SAA: small artery atherosclerosis; SOE: stroke of other determined etiology; SUE: stroke of undetermined etiology; CT: computed tomography; ECG: electrocardiogram; MR: magnetic resonance; BMI: body mass index; OTT: onset to thrombolysis time; DNT: door to needle time; NIHSS: National Institutes of Health Stroke Score; WBC: white blood cells; RBD: red blood cells; HGB: hemoglobin; PLT: platelets; RDWSD: red cells distribution width – standard deviation; RDWCV: red cell distribution width – coefficient of variation; Fib: fibrinogen; PT: prothrombin time; INR: international standardized ratio; APTT: activated partial thromboplastin time; GLU: emergency random peripheral blood glucose; ALT: alanine transaminase; AST: aspartate transaminase; CK: creatinine kinase; CK-MB: creatinine kinase-MB; LDH: lactate dehydrogenase; CREA: creatinine; UA: uric acid; CHOL: total cholesterol; TG: triglycerides; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; ApoA1: apoprotein A1; ApoB: apoprotein B; Lpa: lipoprotein(a); FBG: fasting blood glucose; HbA1c: glycated hemoglobin; HCY: homocysteine; TSH: thyroid-stimulating hormone; FT4: thyroxine; FT3: triiodothyronine.

Table 2. Multivariable logistic regression analysis of factors related to the neurological deficit outcome.
| Variables                                      | β    | P     | OR   | 95% CI | Lower | Upper |
|-----------------------------------------------|------|-------|------|--------|-------|-------|
| Variables                                    |      |       |      |        |       |       |
| Age                                           | 0.096| <0.001| 1.101| 1.048  | 1.157 |
| NIHSS score immediately after thrombolysis    | 0.289| <0.001| 1.336| 1.235  | 1.444 |
| Antiplatelet                                  |      | <0.001|      |        |       |       |
| No (reference)                                |      |       |      |        |       |       |
| Single                                        | -2.418| <0.001| 0.089| 0.033  | 0.237 |
| Double                                        | -2.762| <0.001| 0.063| 0.014  | 0.289 |
| CHOL                                          | -3.053| 0.001 | 2.510| 1.432  | 4.400 |
| HDL                                           | -3.383| 0.010 | 0.047| 0.005  | 0.488 |
| ApoA1                                         | -3.141| 0.019 | 0.034| 0.002  | 0.573 |
| ECG                                           |      |       |      |        |       |       |
| 1 (reference)                                 |      |       |      |        |       |       |
| 2                                             | 2.864| 0.014 | 17.532| 1.765  | 174.178|
| 3                                             | 3.227| 0.009 | 25.213| 2.219  | 286.425|
| CT 24 h after thrombolysis                    | 1.196| 0.010 | 3.308| 1.325  | 8.260 |
| Lower extremity venous color Doppler ultrasound| 1.738| 0.002 | 5.685| 1.850  | 17.471|

Data are OR with 95% CI, based on forward-stepwise logistic regression to determine the independent factors.

ECG was graded as 1) normal, the report suggested “roughly normal ECG”; 2) mild abnormality, it suggested “mild ST-T change”; 3) severe abnormality, it suggested manifestations other than the above two signs, including atrial fibrillation, atrial flutter, severe ventricular or supraventricular arrhythmia, and severe ST-T changes.

OR: odds ratio; 95% CI: 95% confidence interval; NIHSS: National Institutes of Health Stroke Scale; CHOL: total cholesterol; HDL: high-density lipoprotein cholesterol; ApoA1: apoprotein A1; ECG: electrocardiogram; CT: computed tomography.