Xu *et al. Thrombosis Journal* (2025) 23:21
https://doi.org/10.1186/s12959-025-00704-0

Thrombosis Journal

RESEARCH Open Access

Outcomes and risk factors for functional prognosis at 3 months after intravenous thrombolysis with r-tPA in patients with acute ischemic stroke: a retrospective cohort study

Yayun Xu[1†], Haixing Feng[1†], Zhengzheng Huang[1], Yanlei Li[1], Feng Chi[1] and Lijie Ren[1*]

Abstract

Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) is the preferred treatment for acute ischemic stroke (AIS). Nevertheless, only approximately half of patients undergoing IVT experience positive outcomes. The objective of the study was to examine the clinical characteristics of patients with AIS and identify predictors for unfavorable clinical outcomes at 3 months after IVT. This retrospective cohort study comprised 3805 consecutive patients diagnosed with AIS who received IVT. Patients categorized as having a poor outcome were those with a modified Rankin scale score (mRS) of 3–6, while those categorized as having a good outcome had a score of 0–2. Clinical profiles and laboratory examinations were compared among patients with differing outcomes. A logistic regression model was utilized to investigate potential factors correlated with unfavorable outcomes. Of the 3805 patients included in the study, 3176 (83.5%) were found to have a good outcome, while 629 (16.5%) experienced an poor outcome following IVT. Advancing age (OR = 1.037, $P < 0.001$) and higher baseline National Institutes of Health Stroke Scale (NIHSS) scores (OR = 1.156, $P < 0.001$) were significant independent predictors of a poor outcome. The area under curve (AUC) values for age, NIHSS score, and the combined effect of age and NIHSS score in predicting a poor response were 0.644, 0.761, and 0.777, respectively. Our research indicates that advancing age and higher baseline NIHSS score may serve as prognostic indicators for predicting early unfavorable outcomes following IVT in patients with AIS.

Keywords Acute ischemic stroke, Intravenous thrombolysis, Age, Baseline NIHSS score, Response

[†]Yayun Xu and Haixing Feng contributed equally to this work.

*Correspondence:
Lijie Ren
13631605966@126.com
[1]Department of Neurology, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen 518035, P. R. China

Introduction

Stroke is a significant cause of functional impairment and places considerable health and economic burdens on the population of China [1]. With an estimated 3 million new stroke cases annually [2], stroke continues to play a critical role in both mortality and disability rates, despite a decreasing trend in mortality [3]. Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) has demonstrated efficacy in treating acute ischemic stroke (AIS) patients within a 4.5-hour window of symptom onset [4]. Nevertheless, the use of rt-PA is hindered by various limitations, such as ischemia-reperfusion injury and the potential for hemorrhagic complications, which may diminish its therapeutic value in AIS patients [5]. Previous studies have indicated that a substantial proportion of individuals suffering from stroke do not experience positive outcomes following IVT treatment [6]. Consequently, there is a critical need to investigate the potential risk factors and quantifiable biomarkers associated with early unfavorable responses to IVT in patients with AIS.

A prognostic model designed for the early prediction of clinical outcomes in patients undergoing t-PA treatment should incorporate variables that are easily accessible within clinical environments. Currently, there exists a scarcity of prognostic models for stroke recovery, with the predictive capabilities falling short of satisfactory levels. An expanding body of research has shown that various factors, such as older age, male, initial National Institutes of Health Stroke Scale (NIHSS) score, high levels of glucose and HbA1c, and peripheral inflammatory biomarkers, are correlated with unfavorable outcomes in patients with AIS following IVT. Specifically, it has been documented that a combination of age, C-reactive protein (CRP), systolic blood pressure (SBP), and blood glucose levels served as a classifier capable of predicting a poor response to t-PA treatment in a cohort of 145 patients with AIS [7]. Moreover, another study has demonstrated that elevated serum glucose levels at admission independently predict adverse neurological outcomes at 90 days post-treatment in a group of 138 AIS patients receiving IVT [8]. Furthermore, a study involving 212 patients with AIS who received IVT reported a negative correlation between hs-CRP levels exceeding 1.60 mg/L and a favorable thrombolysis response rate [9]. Additionally, recent research identified blood fibrinogen and homocysteine levels as independent risk factors for 90-day functional dependence in 276 AIS patients [10]. However, the existing stroke prognostic models exhibit significant variability in quality, and the prediction models for post-stroke mortality are constrained by limitations such as sample size, scope of clinical variables, and overall clinical applicability [11, 12]. Consequently, there is a pressing need for a predictive model that leverages a multicenter cohort with a substantial sample size to enable early estimation of clinical outcomes for patients with AIS following IVT.

In this study, we conducted a retrospective investigation into various baseline clinical characteristics that may be associated with poor clinical outcomes following IVT in 3805 patients with AIS from 32 designated hospitals in Shenzhen, with the aim to shed light on the potential risk factors of early poor response to IVT in AIS patients.

Methods

Study design and participants

This retrospective cohort study enrolled 3805 patients with AIS who received IVT between January 2022 and December 2023. Patients were consecutively recruited from the Shenzhen Center for Quality Control of Cerebrovascular Disease Treatment database, which aggregates stroke data from 32 designated hospitals in Shenzhen. Subsequent evaluations at 90 days post IVT were performed to assess patient prognoses and ascertain clinical outcomes. The diagnosis of AIS adhered to the criteria established by the World Health Organization and was validated through brain computed tomography or magnetic resonance imaging scans. The indications and contraindications for IVT were determined according to the Chinese guidelines for the diagnosis and treatment of acute ischemic stroke (2018) [13]. Participants were included in the final analysis if they satisfied the following criteria: (1) admission within 4.5 h of symptom onset; (2) administration of IVT with r-tPA; (3) age of 18 years or older; and (4) a baseline NIHSS score of ≤ 25. The exclusion criteria were as follows: (1) patients receiving bridging therapy; (2) patients with malignant tumors, autoimmune diseases, or hematological disorders; (3) presence of acute or chronic infections; (4) severe hepatic or renal insufficiency; and (5) patients with incomplete follow-up data. Written informed consent was obtained for all patients to put information in the registry database and analyze them anonymously. This study was performed in accordance with the ethical principles of the 1964 Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Shenzhen Second People's Hospital (ID number: 20211011010-FS01). The study was registered at the Chinese Clinical Trial Registry (ID number: ChiCTR2200055653; registration date: 2022/01/15), and the patient selection process is depicted in Fig. 1.

Data collection

Data were inputted into the Shenzhen Center for Quality Control of Cerebrovascular Disease Treatment database by individual centers through a web-based patient data collection interface operated by trained registrars. Demographic characteristics, conventional vascular risk

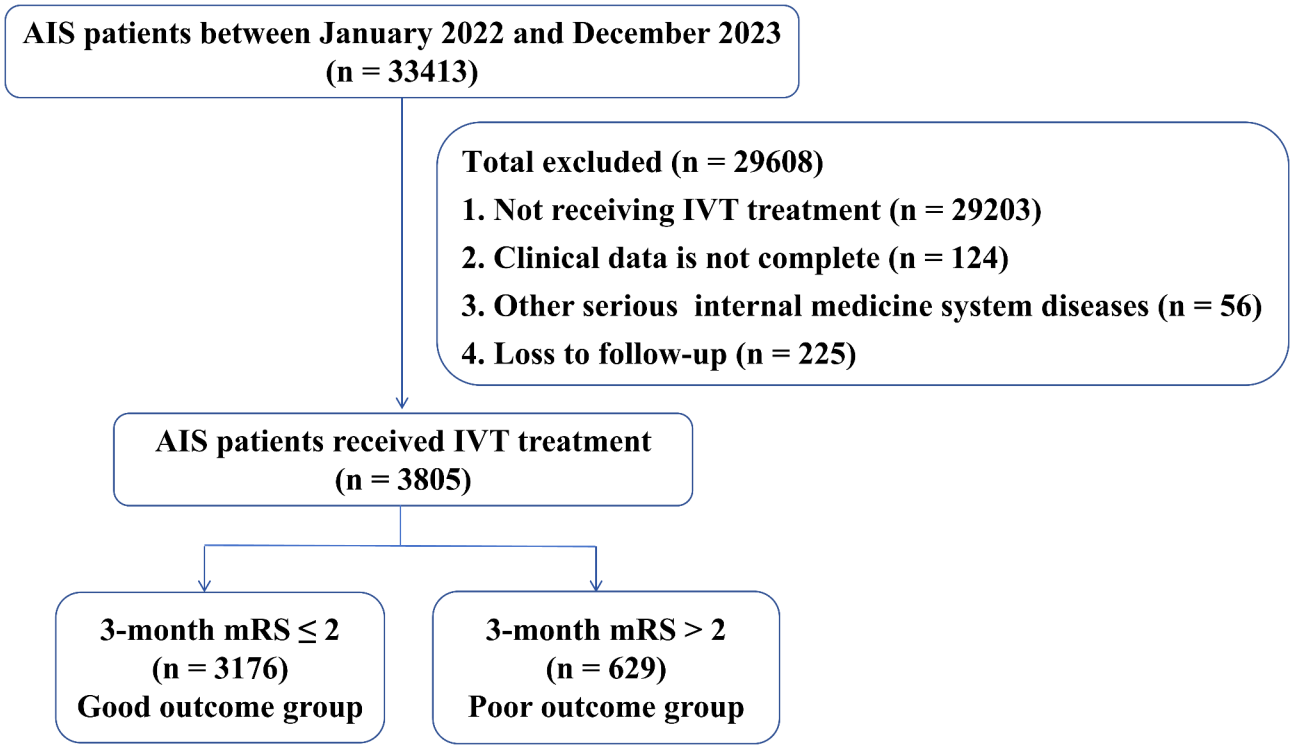

Fig. 1 Study inclusion flow chart. AIS, acute ischemic stroke; rt-PA, recombinant tissue plasminogen activator; mRS, modiffed Rankin Scale Score; HbA1c, glycated hemoglobin; NIHSS, National Institute of Health Stroke Scale

factors (such as hypertension, diabetes, smoking status, alcohol consumption history, and previous stroke occurrence), as well as laboratory data, were extracted from the database for analysis.

Clinical outcomes

Neurologists with specialized training and qualifications assessed all post-stroke clinical outcomes of enrolled patients at the 3-month mark through telephone consultations or outpatient follow-up visits. The modified Rankin Scale (mRS) was utilized to evaluate these outcomes, with a mRS score of ≤ 2 indicating a good outcome and a score of > 2 indicating a poor outcome [14, 15].

Statistical analysis

The data analysis was conducted using SPSS (Version 17.0; SPSS, Inc, Chicago, IL, USA). The Kolmogorov-Smirnov one-sample test was employed to detect normal distributions. Descriptive analyses were performed, with normally distributed quantitative variables reported as means ± standard deviation (SD), and skewed quantitative variables reported as median and interquartile range (IQR; 25–75%). Baseline characteristics differences between groups were assessed using Student's t-test or Mann-Whitney U test for continuous variables, and the Chi-square test for categorical variables. Logistic regression analysis was employed to identify risk factors associated with a poor response. Correlation analysis was performed using Spearman correlation analysis. The discriminatory capacity of each risk factor for predicting a 90-day prognosis was evaluated through the receiver operating characteristic (ROC) curve. Statistical significance was established at a two-tailed *P*-value below 0.05.

Results

Differences in clinical and demographic characteristics of patients with a good outcome and a poor outcome

The demographic and clinical characteristics are presented in Table 1, with 83.5% of patients ($n = 3176$) demonstrating a good outcome to IVT and 16.5% of patients ($n = 629$) showing a poor outcome. The observed disparities between the two groups were as follows: age ($P < 0.001$), sex ($P < 0.001$), BMI ($P = 0.011$), baseline NIHSS score ($P < 0.001$), smoking ($P = 0.027$), diabetes mellitus ($P < 0.001$), previous stroke ($P = 0.044$), diastolic blood pressure ($P = 0.019$), serum glucose level ($P < 0.001$), neutrophil count ($P < 0.001$), lymphocyte count ($P < 0.001$), hs-CRP level ($P < 0.001$), fibrinogen level ($P < 0.001$), D-dimer level ($P < 0.001$), HbA1c level ($P < 0.001$), ALT level ($P < 0.001$), serum uric acid level ($P = 0.001$), and BUN level ($P < 0.001$).

Table 1 Univariate analysis of baseline characteristics and clinical outcome

Characteristics	All patients (*n* = 3805)	Good outcome (*n* = 3176)	Poor outcome (*n* = 629)	*P* value
Age (median [IQR])	59 (51, 69)	58 (50, 68)	66 (55, 76)	< 0.001
Sex (male), N (%)	2676 (70.3)	2276 (71.7)	400 (63.6)	< 0.001
BMI (median [IQR])	24.12 (21.64, 26.25)	24.22 (21.86, 26.28)	23.44 (20.67, 25.97)	0.011
Baseline NIHSS score, median (IQR)	4 (2, 8)	4 (2, 7)	10 (5, 14.25)	< 0.001
ODT, min (median [IQR])	88 (50, 145)	88 (50, 145)	88 (48, 148)	0.915
DNT, min (median [IQR])	35 (26, 49)	35 (26, 48)	35 (27, 50)	0.364
ONT, min (median [IQR])	133 (88, 193)	132 (88, 192)	138 (87, 195)	0.569
Medical history, n (%)				
Smoking	1301 (34.2)	1110 (34.9)	191 (30.5)	0.027
Alcohol drinking	928 (24.4)	786 (24.7)	142 (22.6)	0.246
Hypertension	1130 (29.7)	957 (30.1)	173 (27.5)	0.188
Diabetes	356 (9.4)	268 (8.4)	88 (14.0)	< 0.001
Previous stroke	622 (16.3)	487 (15.3)	135 (21.5)	< 0.001
Blood pressure, median (IQR)				
Systolic blood pressure, mmHg	148 (132, 163)	147 (132, 162)	150 (134, 165)	0.106
Diastolic blood pressure, mmHg	88 (79, 98)	88 (80, 98)	87 (78, 97)	0.019
Laboratory examination, median (IQR)				
Serum glucose, mmol/L	5.90 (5.05, 7.42)	5.80 (5.00, 7.11)	6.71 (5.50, 8.95)	< 0.001
LDL-C, mmol/L	2.90 (2.28, 3.54)	2.92 (2.29, 3.53)	2.82 (2.23, 3.56)	0.163
Neutrophil, 10^9/L	4.80 (3.69, 6.60)	4.71 (3.63, 6.47)	5.32 (4.03, 7.50)	< 0.001
Lymphocyte, 10^9/L	2.00 (1.45, 2.72)	2.05 (1.50, 2.75)	1.82 (1.26, 2.57)	< 0.001
hs-CRP, mg/L	1.68 (0.55, 4.60)	1.51 (0.50, 4.11)	2.50 (0.84, 7.60)	< 0.001
Fibrinogen, mg/dL	2.99 (2.52, 3.57)	2.95 (2.49, 3.52)	3.13 (2.66, 3.84)	< 0.001
D-dimer, mg/L	0.44 (0.22, 1.38)	0.40 (0.22, 1.17)	0.90 (0.30, 2.61)	< 0.001
HbA1c, %	5.90 (5.60, 6.50)	5.90 (5.50, 6.40)	6.10 (5.60, 7.20)	< 0.001
ALT, U/L	20 (15, 29)	21 (15, 29)	19 (14, 25)	< 0.001
Cystatin C, mg/L	1.00 (0.81, 1.34)	1.00 (0.81, 1.34)	1.00 (0.82, 1.33)	0.849
Serum uric acid, μmol/L	348.63 (285.90, 426.00)	351.00 (287.90, 429.25)	337.00 (271.10, 408.70)	0.001
Serum creatinine, μmol/L	74.20 (62.00, 88.50)	74.10 (62.00, 88.00)	74.90 (61.40, 92.00)	0.411
BUN, mmol/L	5.41 (4.34, 6.71)	5.39 (4.31, 6.61)	5.60 (4.46, 7.32)	0.001
Hcy, μmol/L	11.90 (9.5, 15.40)	11.80 (9.40, 15.30)	12.16 (9.90, 16.00)	0.074
Hcy, μmol/L				

BMI: body mass index; ODT: onset to door time; DNT: door-to-needle time; ONT: onset-to-needle time; LDL-C: low-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; HbA1c: hemoglobinA1c; ALT: alanine aminotransferase; BUN: blood urea nitrogen; Hcy: homocysteine

Table 2 Binary logistic regression analysis of potential risk factors related to a poor outcome

	P	Exp (B)	95% CL
Age	< 0.001	1.037	1.018–1.056
Baseline NIHSS score	< 0.001	1.156	1.116–1.197

Variables adjusted for multivariate regression analysis are as follows: sex, BMI, smoking, diabetes, Previous stroke, diastolic blood pressure, serum glucose level, neutrophil count, lymphocyte count, hs-CRP level, fibrinogen level, D-dimer level, HbA1c level, ALT level, serum uric acid level, and BUN level

Logistic regression analysis to identify risk factors associated with a poor outcome

Variables found to be statistically significant in Table 1 were incorporated into a binary logistic regression model to ascertain independent risk factors for a poor outcome to IVT. All potential independent factors successfully passed the collinearity test, with a variance inflation factor below 5. After adjustment for all potential confounders, an increased age (OR = 1.037, 95%CI = 1.018–1.056, $P < 0.001$) and baseline NIHSS score (OR = 1.156, 95%CI = 1.116–1.197, $P < 0.001$) were identified as independent factors for a poor response to IVT (Table 2). Figure 2 shows the violin plots of the age and baseline NIHSS score for the two groups.

Relationship between mRS score and age or baseline NIHSS score in patients with AIS

As shown in Fig. 3, the results of the correlation analysis showed that mRS score at 3 month was positively correlated with age ($r = 0.206$, $P < 0.001$) and baseline NIHSS score ($r = 0.377$, $P < 0.001$) in patients with AIS.

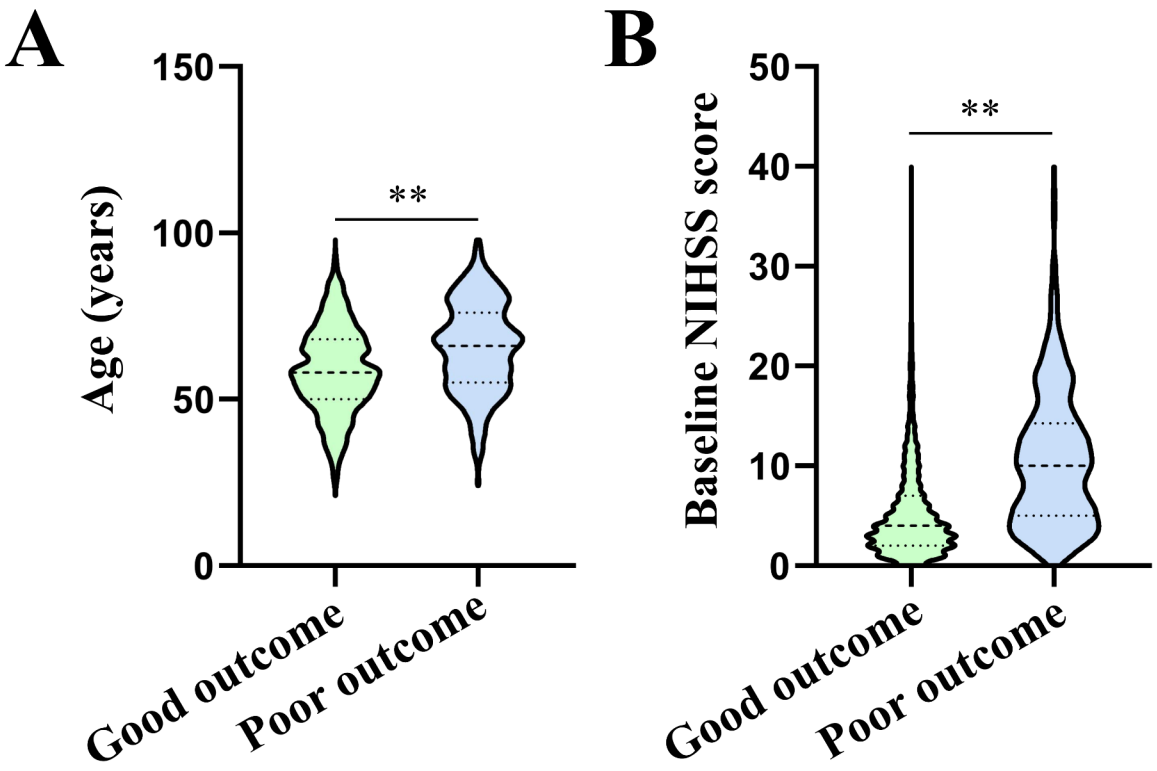

Fig. 2 The violin plot in distribution of age and baseline NIHSS score between good outcome and poor outcome groups. (**A**) the violin plot in distribution of age; (**B**) the violin plot in distribution of baseline NIHSS score

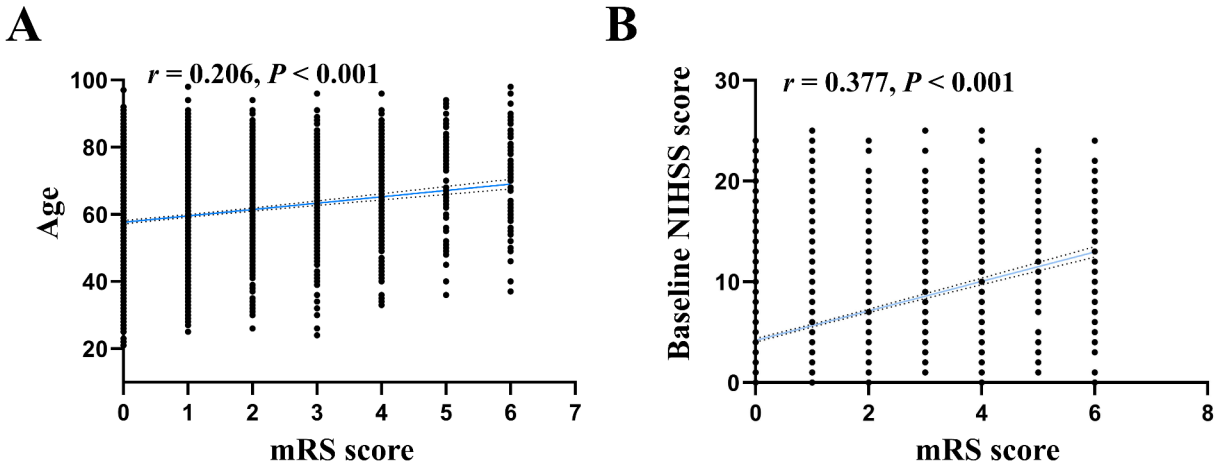

Fig. 3 Positive relationship between mRS score and age or baseline NIHSS score in patients with AIS. (**A**) relationship between mRS score and age; (**B**) relationship between mRS score and age or baseline NIHSS score

ROC curve analysis to assess the overall discriminatory ability in identifying poor responders to IVT

ROC curves were utilized to assess the discriminatory capacity of age and baseline NIHSS score in identifying poor responders to IVT. The AUC for age in discriminating poor responders to IVT was found to be 0.644 (95%CI = 0.620–0.668, $P < 0.001$), with an optimal cutoff of 65.5 and corresponding sensitivity and specificity values of 52.3% and 70.0%, respectively (Fig. 4A). The AUC for the baseline NIHSS score was determined to be 0.761 (95%CI = 0.740–0.782, $P < 0.001$), with a calculated cutoff value of 5.5. The sensitivity and specificity of this cutoff were found to be 72.0% and 68.2%, respectively (Fig. 4B). A single biomarker possesses intrinsic specificity and sensitivity that are inherently limited; however, the integration of multiple biomarkers can enhance

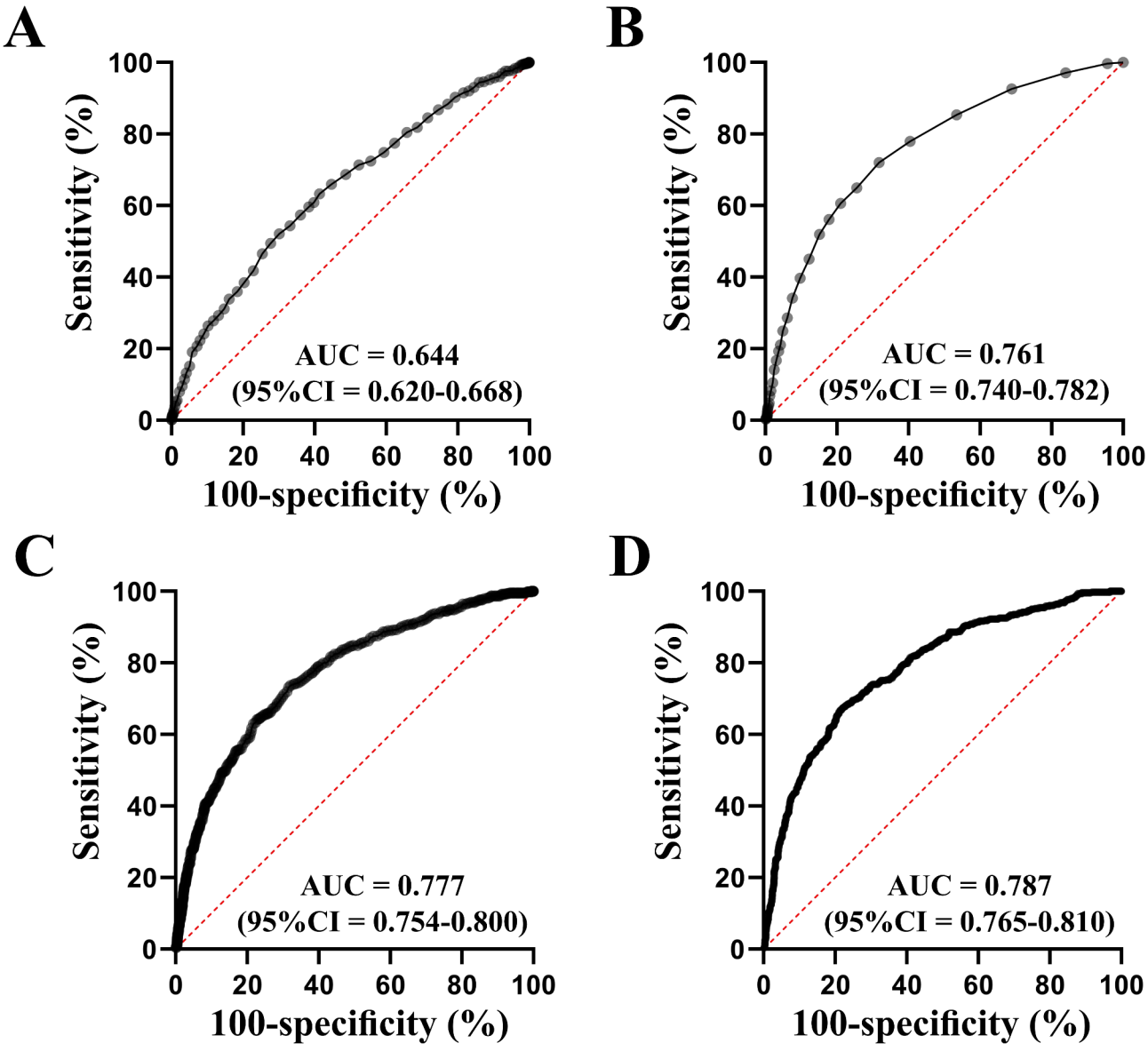

Fig. 4 ROC analysis of age, baseline NIHSS score, and a pannel with multiple potential risk factors for predicting 3-month functional prognosis in AIS patients after IVT. (**A**) ROC analysis of age; (**B**) ROC analysis of baseline NIHSS score; (**C**) ROC curve of a combined panel of age and baseline NIHSS score; (**D**) ROC curve of a combined panel of age, baseline NIHSS score, previous stroke, diastolic blood pressure, lymphocyte, and hs-CRP

clinical performance [16]. Thus, an ROC curve analysis was performed to assess the discriminatory capacity of the combined variables of age and baseline NIHSS score in distinguishing between good responders and poor responders to IVT. The AUC for this combination was calculated to be 0.777 (95%CI = 0.754-0.800, $P < 0.001$; Fig. 4C). In order to further improve the sensitivity and specificity, variables with a P value of < 0.1 in the binary logistic regression model were included in the combined panel in identifying poor responders to IVT. As shown in Fig. 4D, the ROC curve analysis demonstrated that a combined panel of age, baseline NIHSS score, previous stroke, diastolic blood pressure, lymphocyte, and hs-CRP slightly increased the AUC value to 0.787 (95%CI = 0.765–0.810, $P < 0.001$).

To further elucidate the association between age and functional prognosis in AIS patients following IVT, all patients were stratified into two groups based on the optimal cutoff value of age: a low age group (< 66) and a high age group (≥ 66). The distribution of mRS between these two groups is shown in Fig. 5A. The prognosis of the high age group was worse than that of the low age group (mRS > 2, 34.7% vs. 21.6%; χ^2 = 75.485, $P < 0.001$; OR = 1.933, 95%CI = 1.664–2.246).

To further elucidate the association between baseline NIHSS score and functional prognosis in AIS patients

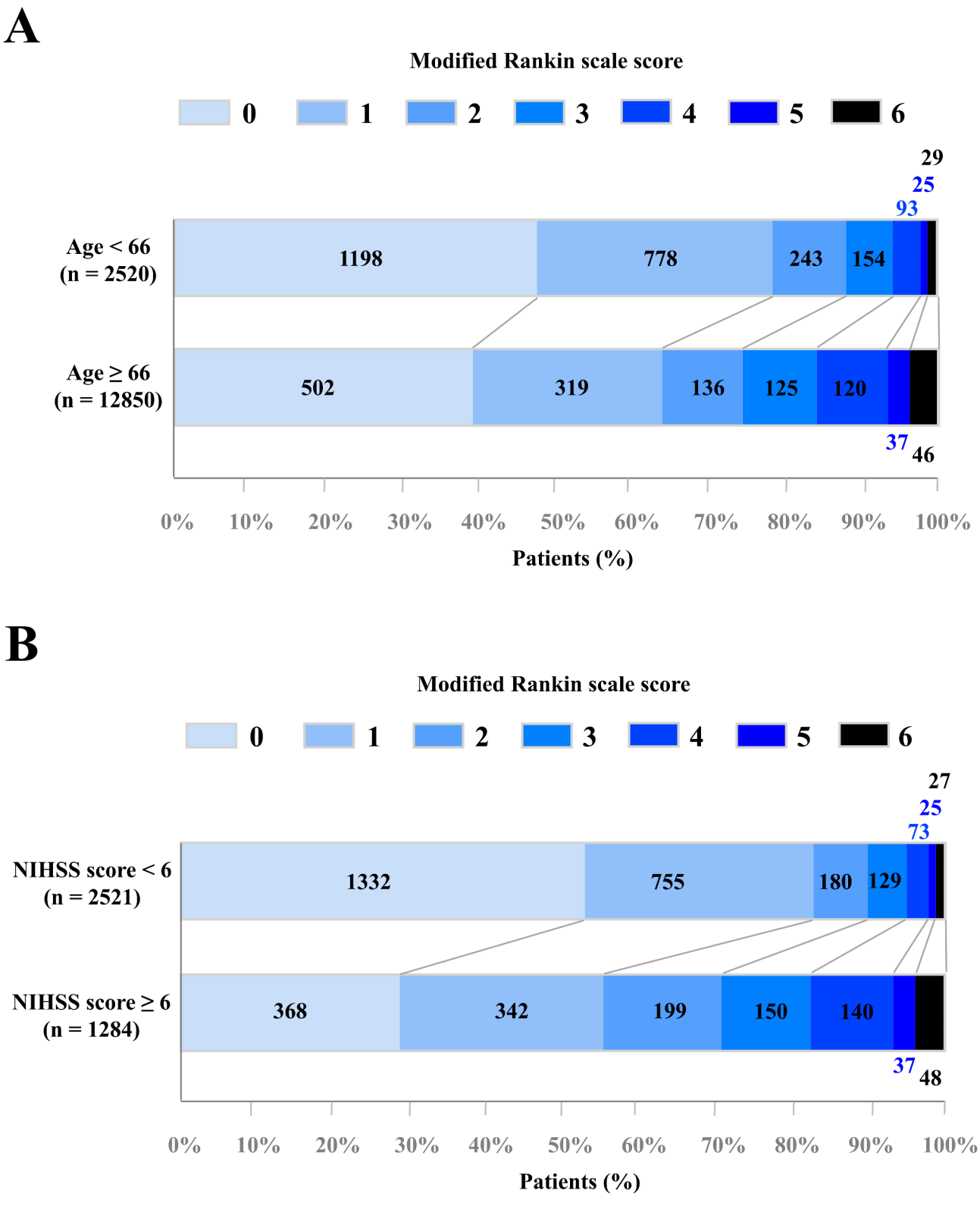

Fig. 5 Distribution of scores on the modified Rankin Scale at 90 days. (**A**) the distribution of mRS scores based on age; (**B**) the distribution of mRS scores based on baseline NIHSS score

following IVT, all patients were stratified into two groups based on the optimal cutoff value of baseline NIHSS score: a low NIHSS score group (< 6) and a high NIHSS score group (≥ 6). The distribution of mRS between these two groups is shown in Fig. 5B. The prognosis of the high NIHSS score group was worse than that of the low NIHSS score group (mRS > 2, 44.7% vs. 17.2%; χ^2 = 330.101, $P < 0.001$; OR = 3.888, 95%CI = 3.343–4.521).

Discussion

The objective of this retrospective investigation was to examine the clinical characteristics of 3805 patients with AIS and identify predictors for unfavorable clinical outcomes at 3 months after IVT. The study yielded three key findings. Firstly, the prevalence of poor outcome in patients with AIS following IVT was determined to be 16.5%. Secondly, logistic regression analysis identified advancing age and higher baseline NIHSS scores as significant risk factors for a poor outcome at 3 months after IVT. Lastly, a combined panel of age and baseline NIHSS scores achieved a moderate accuracy in predicting 3-month functional prognosis.

Intravenous r-tPA has served as the primary treatment for AIS for more than two decades [17]. Nevertheless, research indicates that certain patients exhibit resistance to r-tPA, while others may encounter a deterioration in their clinical presentation, such as symptomatic intracranial hemorrhage [18, 19]. Multiple studies have indicated that a significant proportion of patients diagnosed with AIS who undergo IVT experience unfavorable outcomes, ranging from 25 to 50% [20–22]. However, the current study observed that only 16.5% of patients failed to achieve favorable outcomes following IVT treatment. The lower incidence of adverse outcomes observed in this study may be attributed to the relatively low baseline NIHSS scores. In the current study, 60.4% (2299 out of 3805) of patients had a baseline NIHSS score of ≤ 5. Similarly, in the study conducted by Tang et al., all patients had acute mild ischemic stroke with a baseline NIHSS score of ≤ 5, and 24.5% experienced an unfavorable outcome at 3 months [21]. On the contrary, in AIS patients with a baseline NIHSS score of ≥ 16, the incidence of adverse outcomes was 71.6% [23]. Another reason to the lower incidence of poor outcomes may be related to the utilization of the Shenzhen stroke emergency map [24]. Prehospital delay has been identified as a significant contributing factor to the low rate of rt-PA thrombolysis for AIS in China [25]. Regional emergency systems have been demonstrated as an effective strategy for enhancing access to thrombolysis. In order to expedite access to rt-PA thrombolysis in Shenzhen, the Shenzhen healthcare administrations implemented a stroke emergency map [26]. This map included the certification of eligible local hospitals, the identification of stroke patients, an acute stroke transport protocol, and the ongoing maintenance of the map [26]. A recent retrospective observational study was conducted to compare consecutive patients with AIS who presented at qualified local hospitals before and after the implementation of the Shenzhen stroke emergency map [24]. The findings indicated a significant increase in the rate of patients receiving rt-PA thrombolysis from 8.3 to 9.7% ($P = 0.003$) following the implementation of the map. Additionally, there was a reduction in both the median onset-to-needle time and door-to-needle time (175.5 min vs. 149.5 min, $P = 0.039$; 71.5 min vs. 51.5 min, $P < 0.001$) [24]. Previous research has indicated that early hospital arrival is associated with improved functional outcomes and reduced mortality following a stroke. Specifically, it has been demonstrated that arriving at the hospital within 6 h of stroke onset correlates with neurological improvement during hospitalization and favorable functional outcomes three months post-stroke in patients with acute ischemic stroke [27, 28]. Notably, each minute reduced in the onset-to-needle time has been shown to contribute an additional 1.8 days of healthy life for stroke patients [29]. It has been reported that 15.2% of AIS patients, with a median onset-to-needle time of 148 min, experienced poor outcomes (mortality) following IVT [30]. Similarly, the present study found that 16.5% of patients, with a median onset-to-needle time of 133 min, experienced poor outcomes following IVT. Therefore, a prospective study should be conducted to assess the difference in poor outcome rates among patients with acute ischemic stroke who receive IVT before and after the introduction of the Shenzhen stroke emergency map.

Age is considered the primary non-modifiable risk factor for AIS [31, 32]. Data from the American Heart Association indicates that the likelihood of experiencing a stroke rises in correlation with advancing age [33]. Individuals over the age of 45 exhibit a twofold increase in stroke occurrence with each successive decade, and the majority of cerebrovascular incidents manifest in individuals over the age of 65 [34]. Age is also a significant factor in stroke outcomes, with advanced age frequently associated with diminished functional recovery [35, 36]. Research has shown that AIS patients receiving IVT who are aged 80 or older have a substantially higher risk of experiencing an unfavorable outcome or mortality within three months of stroke onset compared to those under the age of 60 [37]. This phenomenon is likely attributable to comorbidity and increased stroke severity, both of which are more prevalent in older individuals. Previous studies have well demonstrated a higher prevalence of cerebrovascular risk factors, including hypertension, diabetes mellitus, atrial fibrillation, and dyslipidemia, in the elderly population. This may contribute to elevated mortality rates and unfavorable outcomes in cases of AIS

treated with IVT [38]. In the current investigation, a consistent finding emerged indicating that advanced age was independently associated with a diminished response to IVT in patients with AIS, and a positive correlation was observed between age and mRS score at 3 months post-treatment in this patient population. Analysis of the ROC curve revealed an optimal cutoff age of 65.5 for predicting the occurrence of poor outcomes, with AIS patients aged 66 or older exhibiting approximately twice the risk of experiencing an unfavorable outcome compared to those younger than 66. Collectively, these findings suggest that older age contributed to be the independent factors associated with unfavorable outcomes after IVT in AIS patients, and close attention should be paid to the prognosis of AIS patients of advanced age.

The NIHSS score is commonly employed for evaluating the severity of clinical stroke. Baseline NIHSS has been identified as a significant predictor of unfavorable outcomes in AIS following IVT [22, 39]. Specifically, a study reported that patients with lower NIHSS scores upon admission are more likely to experience favorable outcomes after receiving rt-PA [40]. Moreover, a prospective study involving 269 Chinese AIS patients treated with IVT revealed that higher NIHSS scores were associated with a fivefold increase in the risk of unfavorable functional outcomes [41]. Furthermore, it was found that an admission NIHSS score of less than 7 was a significant predictor of a favorable functional outcome in a cohort of 121 patients with minor stroke who underwent intravenous rt-PA therapy [42]. Additionally, severe strokes, often characterized by NIHSS scores exceeding 20 or 25, are commonly associated with large infarctions and an increased likelihood of hemorrhagic transformation and poorer prognosis [43]. In this study, it was consistently observed that a higher baseline NIHSS score was independently associated with a poor response to IVT in patients with AIS, and mRS score at 3 month was positively correlated with baseline NIHSS score in patients with AIS. The analysis of the ROC curve indicated that a baseline NIHSS score of 5.5 was identified as the optimal cutoff value for predicting poor outcome occurrence, and the prognosis of the high NIHSS score group was worse than that of the low NIHSS score group.

Sex-based biological differences and sex-related sociocultural factors influence the epidemiology, pathophysiology, treatment, and prognosis of cardiovascular diseases [44]. Recent research indicates that women exhibit greater responsiveness to r-tPA [45]. However, the literature remains inconclusive regarding sex-related differences in functional outcomes among patients with AIS following thrombolytic therapy [46, 47]. Recently, data from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China) were collected and analyzed to elucidate new evidence regarding sex differences in prognosis following IVT in Chinese patients [48]. The findings indicated that there is no significant difference in prognosis between women and men after IVT [48]. Consistently, although the proportion of males was significantly lower in the poor outcome group compared to the good response group, subsequent analysis controlling for all potential confounders did not identify sex as an independent predictor of poor response in the present study.

Diabetes is identified as a substantial risk factor for the development of ischemic stroke. A recent meta-analysis of 2565 patients with AIS who underwent IVT therapy has demonstrated a significant correlation between elevated blood glucose levels and symptomatic intracranial hemorrhage, unfavorable clinical outcomes, and increased mortality rates at the 90-day mark [49]. In the current investigation, it was observed that the prevalence of diabetes mellitus and serum glucose levels were notably higher in the poor response group compared to the good response group. However, following adjustment for all potential confounders, diabetes mellitus and serum glucose levels were not found to be independent factors for a poor response. Given the established association between age and the onset of diabetes, it is reasonable to posit that the elevated prevalence of diabetes mellitus and serum glucose levels in the poor response group may be attributed to the older age of individuals in this group.

Recent studies have indicated that inflammation plays a significant role in the initiation and advancement of AIS [50]. It has been demonstrated that white blood cells have a notable influence on functional status 30 days post-stroke, independent of other factors [51]. Moreover, elevated levels of hs-CRP in plasma upon admission are associated with unfavorable outcomes in individuals with acute cerebral infarction [52]. In addition, an elevated level of fibrinogen has been demonstrated as a prognostic indicator for predicting an early inadequate response to IVT in a cohort of 700 patients with AIS [53]. Consistently, it was observed that the neutrophil count, lymphocyte count, fibrinogen level, and hs-CRP level were significantly elevated in the poor response group compared to the good response group. Nevertheless, subsequent analysis controlling for all potential confounders did not reveal these inflammatory biomarkers to be independent predictors of a poor response. The discrepancy between our results and those of prior research may be ascribed to the limited sample sizes utilized in previous studies.

Uric acid, a scavenger of oxygen radicals, is a crucial antioxidant that helps maintain the stability of blood pressure and mitigates oxidative stress. A significant correlation has been identified between serum uric acid levels and favorable prognosis following stroke [54]. More recently, an inverted U-shaped nonlinear relationship

has been observed between uric acid levels and favorable as well as excellent outcomes at 3 months in patients with AIS who underwent IVT [55]. In the present study, serum uric acid levels were significantly lower in the poor outcome group compared to the good response group. However, after adjusting for all potential confounders, this indicator was not identified as an independent factor for poor response, consistent with findings from another study [56]. Consequently, further research is required to elucidate the relationship between serum uric acid levels and functional prognosis in patients with AIS after IVT.

Limitations

Several limitations of this study warrant discussion. Firstly, the study populations consisted of hospital-based cohorts, suggesting the need for validation of the model in unselected patients across various clinical settings. Secondly, the relatively short observation time compared to the recovery period of stroke may not fully capture the prognosis of stroke. Thirdly, the exclusive enrollment of Chinese patients treated with IVT necessitates further testing of the results in non-Chinese populations, and future research should consider longitudinal cohort studies with larger sample sizes.

Conclusion

In conclusion, our study suggests a correlation between advancing age and higher baseline NIHSS score with an unfavorable initial response to IVT in patients with AIS. Additionally, the combination of age and baseline NIHSS score may enhance the predictive accuracy of IVT response. Nevertheless, further research is warranted to validate these findings and investigate potential therapeutic interventions.

Author contributions

Y.X. and H.F. were mainly involved in study design, data analysis, data interpretation, and manuscript preparation. Z.H. and Y.L. were mainly involved in data acquisition and data analysis. F.C. and L.R. were mainly involved in study design. All authors read and approved the final manuscript.

Funding

This work was supported by the Shenzhen Team on the Fusion of Health Management and Prevention of Neurological Diseases (6099007), Science and Technology Innovation Commission of Shenzhen (ZDSYS20200811142600003), Shenzhen Talent Introduction Fund (4004013), Natural Science Foundation of Guangdong Province (2023A1515010169), the China Postdoctoral Science Foundation (No. 2024M752130), and Shenzhen Clinical Research Center for Neurological Diseases (LCYSSQ20220823091204009).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

This study was performed in accordance with the ethical principles of the 1964 Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Shenzhen Second People's Hospital (ID number: 20211011010-FS01).

Informed consent

Informed consent was obtained from all subjects and/or participants. This manuscript contains no individual person's data, and therefore can be published without consent from the participants.

Declaration of competing interest

The authors declare no potential conflicts of interest.

Received: 11 December 2024 / Accepted: 24 February 2025
Published online: 10 March 2025

References

1. Wu S, Wu B, Liu M, et al. Stroke in China: advances and challenges in epidemiology, prevention, and management. Lancet Neurol. 2019;18(4):394–405.
2. Guan T, Ma J, Li M, et al. Rapid transitions in the epidemiology of stroke and its risk factors in China from 2002 to 2013. Neurology. 2017;89(1):53–61.
3. Walter K, What. Is Acute Ischemic Stroke? JAMA. 2022;327(9):885.
4. Herpich F, Rincon F. Management of acute ischemic stroke. Crit Care Med. 2020;48(11):1654–63.
5. Zhang H, Jin B, You X, et al. Pharmacodynamic advantages and characteristics of traditional Chinese medicine in prevention and treatment of ischemic stroke. Chin Herb Med. 2023;15(4):496–508.
6. Deng G, Xiao J, Yu H, et al. Predictors of futile recanalization after endovascular treatment in acute ischemic stroke: a meta-analysis. J Neurointerv Surg. 2021;14(9):881–5.
7. Yue YH, Li ZZ, Hu L, et al. Clinical characteristics and risk score for poor clinical outcome of acute ischemic stroke patients treated with intravenous thrombolysis therapy. Brain Behav. 2019;9(4):e01251.
8. Huang P, Yi X. Effect of admission serum glucose on the clinical prognosis of patients with acute ischemic stroke receiving Alteplase intravenous thrombolysis. Int J Immunopathol Pharmacol. 2023;37:3946320231204597.
9. Cheng XD, Wang DZ, Zhang Q, et al. Predictive role of pre-thrombolytic hs-CRP on the safety and efficacy of intravenous thrombolysis in acute ischemic stroke. BMC Neurol. 2023;23(1):244.
10. Xu Y, Qu X, Ren T, Wang L, Gao Y. Predictive value of fibrinogen levels for 90-day functional outcomes after intravenous thrombolysis in patients with acute ischaemic stroke. J Clin Neurosci. 2023;111:6–10.
11. Counsell C, Dennis M. Systematic review of prognostic models in patients with acute stroke. Cerebrovasc Dis. 2001;12(3):159–70.
12. Wang W, Kiik M, Peek N, et al. A systematic review of machine learning models for predicting outcomes of stroke with structured data. PLoS ONE. 2020;15(6):e0234722.
13. Chinese Society of Neurology, Chinese Stroke Society. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. Chin J Neurol. 2018;51:666–82.
14. Wang Xuan, Wang YY, Gao Q, et al. Development and validation of a nomogram to provide individualized predictions of functional outcomes in patients with convulsive status epilepticus at 3 months: the modified END-IT tool. CNS Neurosci Ther. 2023;29(12):3935–42.
15. Zeng YY, Zhang WB, Cheng L, et al. Cardiac parameters affect prognosis in patients with non-large atherosclerotic infarction. Mol Med. 2021;27(1):2.
16. Gruson D, Bodovitz S. Rapid emergence of multimarker strategies in laboratory medicine. Biomarkers. 2010;15(4):289–96.
17. Karaszewski B, Wyszomirski A, Jabłoński B, Werring DJ, Tomaka D. Efficacy and safety of intravenous RtPA in ischemic strokes due to Small-Vessel occlusion: systematic review and Meta-Analysis. Transl Stroke Res. 2021;12(3):406–15.
18. Liu C, Xie J, Sun S, et al. Hemorrhagic transformation after tissue plasminogen activator treatment in acute ischemic stroke. Cell Mol Neurobiol. 2020;42(3):621–46.
19. Yaghi S, Eisenberger A, Willey JZ. Symptomatic intracerebral hemorrhage in acute ischemic stroke after thrombolysis with intravenous Recombinant tissue plasminogen activator: a review of natural history and treatment. JAMA Neurol. 2014;71(9):1181–5.

20. Ahmed N, Wahlgren N, Grond M, et al. Implementation and outcome of thrombolysis with Alteplase 3-4.5 h after an acute stroke: an updated analysis from SITS-ISTR. Lancet Neurol. 2010;9(9):866–74.
21. Tang H, Yan S, Wu C, Zhang Y. Characteristics and outcomes of intravenous thrombolysis in mild ischemic stroke patients. Front Neurol. 2021;12:744909.
22. Romano JG, Smith EE, Liang L, et al. Outcomes in mild acute ischemic stroke treated with intravenous thrombolysis: a retrospective analysis of the get with the Guidelines-Stroke registry. JAMA Neurol. 2015;72(4):423–31.
23. Chen X, Xu X, Li Y, et al. Association between fibrinogen-to-albumin ratio and functional prognosis of 3 months in patients with acute ischemic stroke after intravenous thrombolysis. Brain Behav. 2024;14(1):e3364.
24. Ye S, Hu S, Lei Z, et al. Shenzhen stroke emergency map improves access to rt-PA for patients with acute ischaemic stroke. Stroke Vasc Neurol. 2019;4(3):115–22.
25. Gao Z, Liu Q, Yang L, Zhu X. Identification of high-risk factors for prehospital delay for patients with stroke using the risk matrix methods. Front Public Health. 2022;10:858926.
26. Ren L, Li C, Li W, et al. Fast-tracking acute stroke care in China: Shenzhen stroke emergency map. Postgrad Med J. 2019;95(1119):46–7.
27. Matsuo R, Yamaguchi Y, Matsushita T, et al. Association between Onset-to-Door time and clinical outcomes after ischemic stroke. Stroke. 2017;48(11):3049–56.
28. Lee EJ, Kim SJ, Bae J, et al. Impact of onset-to-door time on outcomes and factors associated with late hospital arrival in patients with acute ischemic stroke. PLoS ONE. 2021;16(3):e0247829.
29. Meretoja A, Keshtkaran M, Saver JL, et al. Stroke thrombolysis: save a minute, save a day. Stroke. 2014;45(4):1053–8.
30. Majhadi L, Leys D, Bodenant M, et al. Mortality in patients treated by intravenous thrombolysis for ischaemic stroke. J Neurol. 2013;260(6):1637–48.
31. Rakhimova I, Semenova Y, Khaibullin T, et al. Cryptogenic stroke and embolic stroke of undetermined source: risk factors and approaches for detection of atrial fibrillation. Curr Cardiol Rev. 2021;18(4):e211221199213.
32. Roy-O'Reilly M, McCullough LD. Age and sex are critical factors in ischemic stroke pathology. Endocrinology. 2018;159(8):3120–31.
33. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke Statistics-2023 update: A report from the American heart association. Circulation. 2023;147(8):e93–621.
34. Kelly-Hayes M. Influence of age and health behaviors on stroke risk: lessons from longitudinal studies. J Am Geriatr Soc. 2010;58(Suppl 2):S325–8.
35. Kim TH, Vemuganti R. Effect of sex and age interactions on functional outcome after stroke. CNS Neurosci Ther. 2014;21(4):327–36.
36. Weimar C, König IR, Kraywinkel K, Ziegler A, Diener HC, German Stroke Study Collaboration. Age and National institutes of health stroke scale score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models. Stroke. 2003;35(1):158–62.
37. Wnuk M, Drabik L, Derbisz J, Słowik A. Prognostic significance of age in patients with acute ischaemic stroke treated with intravenous thrombolysis. Neurol Neurochir Pol. 2022;56(1):81–8.
38. Asdaghi N, Butcher KS, Hill MD. Risks and benefits of thrombolysis in the elderly. Int J Stroke. 2012;7(2):142–9.
39. Strambo D, Zambon AA, Roveri L, et al. Defining minor symptoms in acute ischemic stroke. Cerebrovasc Dis. 2015;39(3–4):209–15.
40. Huang YH, Zhuo ST, Chen YF, et al. Factors influencing clinical outcomes of acute ischemic stroke treated with intravenous Recombinant tissue plasminogen activator. Chin Med J (Engl). 2013;126(24):4685–90.
41. Wu Z, Zeng M, Li C, et al. Time-dependence of NIHSS in predicting functional outcome of patients with acute ischemic stroke treated with intravenous thrombolysis. Postgrad Med J. 2019;95(1122):181–6.
42. Kim DH, Lee DS, Nah HW, Cha JK. Clinical and radiological factors associated with unfavorable outcome after intravenous thrombolysis in patients with mild ischemic stroke. BMC Neurol. 2018;18(1):30.
43. Fugate JE, Rabinstein AA. Absolute and relative contraindications to IV rt-PA for acute ischemic stroke. Neurohospitalist. 2015;5(3):110–21.
44. Regitz-Zagrosek V, Kararigas G. Mechanistic pathways of sex differences in cardiovascular disease. Physiol Rev. 2017;97(1):1–37.
45. Savitz SI, Schlaug G, Caplan L, Selim M. Arterial occlusive lesions recanalize more frequently in women than in men after intravenous tissue plasminogen activator administration for acute stroke. Stroke. 2005;36(7):1447–51.
46. Marko M, Miksova D, Haidegger M, et al. Trends in sex differences of functional outcome after intravenous thrombolysis in patients with acute ischemic stroke. Int J Stroke. 2024;19(10):1147–54.
47. Spaander FH, Zinkstok SM, Baharoglu IM, et al. Sex differences and functional outcome after intravenous thrombolysis. Stroke. 2017;48(3):699–703.
48. Zhou H, Chen W, Pan Y, et al. Effect of sex differences on prognosis of intravenous thrombolysis: data from the thrombolysis implementation and monitor of acute ischemic stroke in China (TIMS-China). Stroke Vasc Neurol. 2021;6(1):10–5.
49. Wang Y, Jiang G, Zhang J, et al. Blood glucose level affects prognosis of patients who received intravenous thrombolysis after acute ischemic stroke? A meta-analysis. Front Endocrinol. 2023;14:1120779.
50. Maida CD, Norrito RL, Daidone M, et al. Neuroinflammatory mechanisms in ischemic stroke: focus on cardioembolic stroke, background, and therapeutic approaches. Int J Mol Sci. 2020;21(18):6454.
51. Lasek-Bal A, Jedrzejowska-Szypulka H, Student S et al. The importance of selected markers of inflammation and blood-brain barrier damage for short-term ischemic stroke prognosis. J Physiol Pharmacol. 2019;70(2).
52. Cai Z, He W, Zhuang FJ, Chen Y. The role of high high-sensitivity C-reactive protein levels at admission on poor prognosis after acute ischemic stroke. Int J Neurosci. 2018;129(5):423–9.
53. Deng M, Song K, Tong Y, et al. Higher fibrinogen and neutrophil-to-lymphocyte ratio are associated with the early poor response to intravenous thrombolysis in acute ischemic stroke. Front Neurol. 2024;15:1291950.
54. Lee SH, Heo SH, Kim JH, et al. Effects of uric acid levels on outcome in severe ischemic stroke patients treated with intravenous Recombinant tissue plasminogen activator. Eur Neurol. 2013;71(3–4):132–9.
55. Zhang P, Wang R, Guo ZN, et al. Baseline uric acid levels and intravenous thrombolysis outcomes in patients with acute ischemic stroke: A prospective cohort study. J Am Heart Assoc. 2024;13(7):e033407.
56. Wang C, Zhou M, Kang T, et al. The prognostic value of combined uric acid and neutrophil-to-lymphocyte ratio in acute ischemic stroke patients treated with intravenous thrombolysis. BMC Neurol. 2024;24(1):183.

Publisher's note