ORIGINAL RESEARCH

Multidimensional Outcomes of IV Thrombolysis in Minor Ischemic Stroke: Motor, Psychocognitive, and Dependence

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Background: The presence of mild deficit is the most common reason for nonuse of intravenous alteplase in ischemic stroke. We analyzed within a national prospective cohort on whether patients with minor stroke can benefit from intravenous alteplase.

Methods: This observational study included patients with acute ischemic stroke with a National Institutes of Health Stroke Scale (NIHSS) score 0 to 5 at admission. The short-term outcomes at discharge and 3-month were analyzed including the modified Rankin Scale score, gait speed, Montreal Cognitive Assessment, Patient Health Questionnaire-9, General Anxiety Disorder-7 and Stroke Impact Scale-16. Multivariate regression models were performed to evaluate the association between intravenous thrombolysis and clinical outcomes.

Results: A total of 1876 consecutive patients were included in the current analyses with 102 patients (5.4%) received alteplase and 1774 patients (94.5%) were in non-alteplase group. We found that 10.9% patients presented unfavorable functional outcome with a mRS ≥ 2 at 3-month. Patients with alteplase treatment had a more favorable outcome in SIS-16 at discharge (OR, 5.45; 95% CI, 2.22–8.68) and 3-month after stroke (OR, 2.34; 95% CI, 0.17–4.50). There was an association of alteplase with better gait speed in the restricted sample of age >60 (OR,0.14; 95% CI, 0.02–0.25), while an unfavorable effect was found in anxiety (OR, 2.23; 95% CI, 2.23, 0.91–3.55) and depression (OR, 1.54; 95% CI, 0.17–2.91) in female.

Conclusion: Alteplase showed a suggestive benefit in function and motor outcomes in patients with low NIHSS score of 0–5. Meanwhile, female seemed more inclined to post-stroke emotional problems after alteplase treatment, which should be further explored in the future.

Keywords: alteplase, minor stroke, ischemic, outcomes

Background

Over half of patients with acute ischemic stroke have a low National Institutes of Health Stroke Scale (NIHSS) score at presentation.[1,2] A number of these patients were untreated with intravenous thrombolysis (IVT) on account of the presence of mild symptoms in clinical practice.[3] Yet prospective data suggested that 30% patients have residual disability at 3 months after minor stroke.[4,5] A significant proportion of patients with mild and rapidly improving acute ischemic stroke not treated with thrombolytics have suboptimal short-term outcomes.[6] Thus, it is of great significance to explore the benefits of IVT for minor stroke.

Current guidelines on intravenous alteplase in acute ischemic stroke are based on evidence in which alteplase treatment showed an overall benefit of reducing functional disability.[7] However, clinical results of alteplase treatment were inconsistent in patients with mild neurologic deficits. Previous series of studies usually defined functional outcome by the modified Rankin Scale (mRS) to evaluate the efficacy of thrombolysis. Previous study from the Austrian Stroke Unit Registry (ASUR) involving 445 matched pairs, revealing that intravenous thrombolysis was beneficial for mild

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deficit patients with a NIHSS score of 0–5 after 3 months.[8] Nevertheless, the mRS may be unmodified by IVT treatment at some situations. The randomized, double-blind clinical trial from Khatri et al reported that intravenous alteplase appears unlikely to increase the likelihood of favorable outcome compared to aspirin.[9]

Overall, global scales based on the subjective judgment of physicians may not be sufficiently sensitive to capture the changes of disability after minor stroke.[10] Thus, Wendt et al suggested that individual neurologic deficits including language impairment, distal paresis, gait disorder and their impact on functional impairment should be considered in the judgment of a disabling stroke but not just based on the global score.[11] Our study was designed to describe the association between intravenous alteplase and multidimensional outcomes of patients with minor stroke to provide more insights into the effectiveness of thrombolysis.

Methods

Study Design and Participants

We designed a retrospective analysis enrolled patients from the Impairment of CognitiON and Sleep after acute ischemic stroke or transient ischemic attack (ICONS) study, which is one subgroup study of The Third China National Stroke Registry (CNSR-III).[12] The CNSR-III is a national prospective multicenter registry for patients with a diagnosis of AIS or TIA within seven days from 201 study sites in China that collected 15,166 stroke patients from August 2015 to March 2018 The detailed design, rationale, and basic description of the CNSR-III study have been described before.[1]

The inclusion criteria of ICONS were the same as CNSR-III, including: (1) age older than 18 years; (2) within 7 days from the onset of ischemic stroke symptoms to enrollment. The exclusion criteria were added to ICONS, including: (1) prior diagnosis of cognitive impairment, schizophrenia, or psychosis disease; (2) illiterate patients; (3) severe aphasia defined as National Institutes of Health Stroke Scale (NIHSS) item 9>2, visual impairment, hearing loss, dyslexia, severe unilateral neglect, or consciousness disorders (NIHSS item 1a >1 or 1b >1). We recruited patients with a diagnosis of minor stroke at admission in this study. The minor stroke was defined as the National Institutes of Health Stroke Scale (NIHSS) score ≤5. Patients were excluded if they met one of the following criteria: (1) premorbid mRS ≥2; (2) can not to walk for 10 m; (3) treated with intravenous urokinase.

Demographics and Clinical Profile

Data on demographics and clinical characteristics were obtained from medical recordings during hospitalization at baseline. All the clinical data were collected by unified trained investigators through the electronic data capture system (EDC). We collected demographic information including age, gender, body mass index (BMI) and education level, medicare, medical history (including hypertension, diabetes mellitus, hyperlipidemia, previous stroke, coronary artery disease, atrial fibrillation, current smoking, current drinking), baseline medication history (including antiplatelet agents, anticoagulant agents, anti-hypertensive, antilipidemic, antidiabetic), arrival and stroke severity (onset to arrival time, baseline NIHSS) and etiology classification of ischemic stroke (TOAST, Trial of Org 10172 in Acute Stroke Treatment).[13] All the patients were divided into two groups: alteplase group and non-alteplase group according to the using of intravenous alteplase or not. The recommended dose of alteplase for Asian people was 0.9 mg/kg (maximum 90 mg).[14]

This study was conducted in accordance with the Declaration of Helsinki and the protocol of CNSR-III and ICONS was approved by the ethics committee of Beijing Tiantan Hospital (IRB approval number: KY2015-001-01).[1] Written informed consents were obtained from all patients or their legal representatives.

Outcomes Assessment

The follow-up standardized tests were done by face-to-face interview at discharge and 3-month after stroke onset.

Motor Outcomes

Motor function was evaluated by gait speed through 10-meter-walking test.[15] Participants were required to walk on a 10-meter walkway at their usual pace and the gait speed was calculated as distance in meters divided by time in seconds.[16] Each test was conducted three times and the average value was kept for the analyses. Participants who used assistive devices were also included.

Psychocognitive Outcomes

The mood of patients was assessed with the Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7).[17,18] The PHQ-9 was used to evaluate depression during the past 2 weeks, with a total score of 27 points and the higher score means severe depression conditions. The GAD-7 was used to assess anxiety during the past 2 weeks, with a total score of 21 points and the higher score means severe anxiety conditions.

The cognitive function data was assessed with Montreal Cognitive Assessment (MoCA),[19] with a total score of 30 points and the higher score means better cognitive conditions.

Functional Outcomes

The functional dependence status was assessed by the modified Rankin Scale (mRS)[20] and Stroke Impact Scale (SIS-16).[21] The mRS was used to measure global functional status with a score range from 0 to 5, which means no symptoms to serious functional impairment. The poor functional outcome was defined as a score of 2 or more on the mRS.[22] The SIS-16 evaluated poststroke physical limitations with a broad score range from 0 to 100, which means fully dependent to fully independent.[23]

Statistical Analyses

All analyses were performed using the SAS, version 9.4, software (SAS Institute, Cary, NC, USA). Baseline character-istics between groups were compared using χ^2 or Fisher exact test for categorical variables, t tests for normally distributed continuous variables and Mann–Whitney U-test for other continuous variables. Multivariate linear regression models were used to evaluate the association between intravenous alteplase and clinical outcomes including gait speed, MoCA, PHQ-9, GAD-7, and SIS-16 at 3-month after stroke, whereas multivariate logistic regression models were used to evaluate the association between intravenous alteplase and the dichotomous outcome (mRS 0–1 vs 2–5). First, unadjusted regression models were examined. The first model adjusted for age, gender, and baseline NIHSS. The second model additionally included education level, medicare, hypertension, diabetes mellitus, hyperlipidemia, previous stroke, current smoking, atrial fibrillation, coronary artery disease, medication history of anticoagulation, medication history of antiplatelet, onset-arrival time and TOAST classification. Prespecified stratified analyses were conducted by age (>60 and ≤60), gender (male and female) and baseline NIHSS (0–2 and 3–5) controlling for the variables in model 2. A two-tailed p value less than 0.05 was statistically significant.

Results

Baseline Characteristics

Among 2625 patients with AIS collected in the CNSR-III-ICONS database, 1925 of them had a final diagnosis of TIA or minor stroke (NIHSS<5), 49 patients were excluded for meeting the exclusion including with premorbid mRS≥2, failed to complete 10-meter-walk test or accepted intravenous urokinase. Thus, a total of 1876 consecutive patients were included in the current analyses (Figure 1). Overall, 102 patients (5.4%) received alteplase and 1774 patients (94.5%) were in non-alteplase group.

The baseline and clinical features of the cohort by alteplase treatment are demonstrated in Table 1. The mean age of the total population was 60.8 years and 26.5% of them was female. Of the study participants, 20.7% of patients had a prior history of stroke and 76.0% of them scored 0 on mRS before the index event (n = 1425). Most of the final diagnosis represented ischemic strokes (90.8%), with a mean NIHSS score at admission of 2. The stroke mechanisms in those with a final diagnosis of ischemic stroke according to the Toast classification included large artery atherosclerosis in 23.0%, cardioembolism in 5.0%, small artery occlusion in 26.3%, other determined cause in 0.9%, undetermined cause in 44.8%.

As noted, the alteplase group had a higher proportion of female than the non-alteplase group (percentage, 36.3% vs 25.9%). They were more likely to have urban worker medical insurance (percentage, 54.9% vs 42.2%) and less likely to have rural cooperation medical insurance (percentage, 11.8% vs 30.0%). Patients treated with alteplase had higher NIHSS score at admission (mean±SD, 2.5±1.5) than non-alteplase (mean±SD, 2.0±1.5). The alteplase group possessed more patients who had a high NIHSS score of 3 to 5 than the non-alteplase group (percentage, 45.1% vs 36.9%). We found no significant differences at baseline in age, BMI, education level, medical history and medication history (p > 0.05).
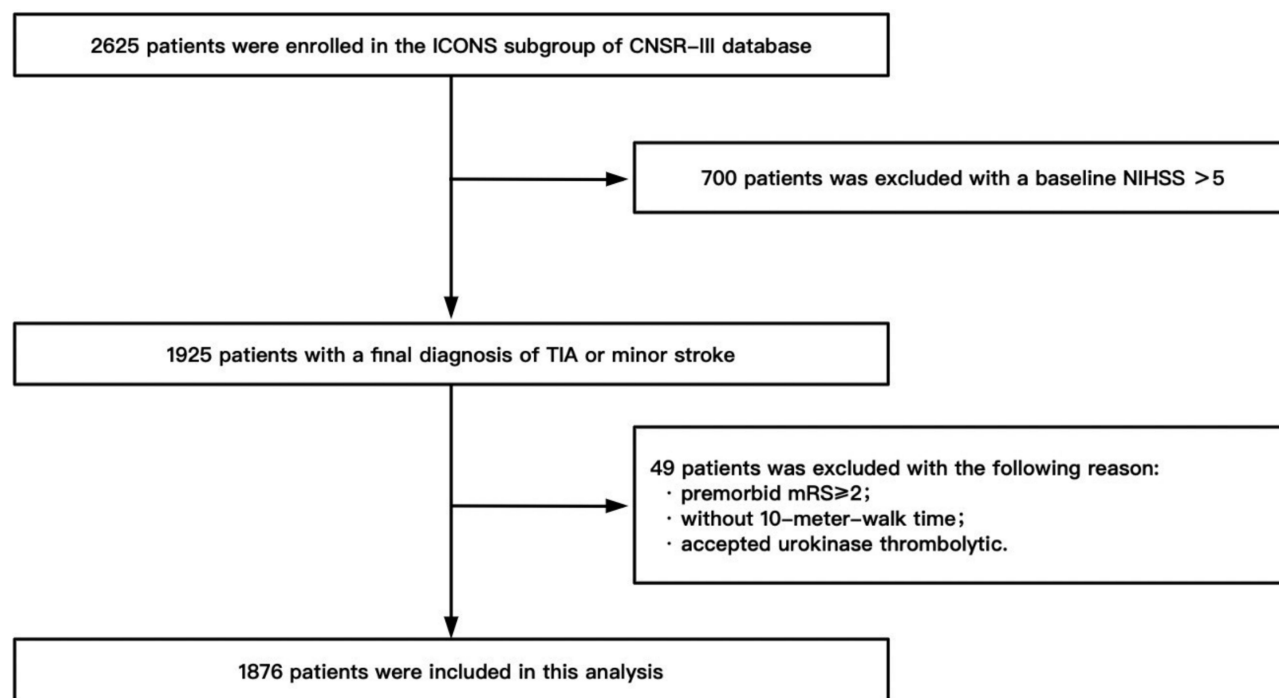
Figure 1 Flow chart of study population.
Abbreviations: ICONS, Impairment of CognitiON and Sleep after acute ischemic stroke or transient ischemic attack in Chinese patients; CNSR-III, The Third China National Stroke Registry; NIHSS, the National Institutes of Health Stroke Scale; mRS, the modified Rankin Scale score.

Outcomes at Discharge and 3-Month

The clinical outcomes at discharge and 3-month are described in Table 2. In the overall cohort, the neurological functions of patients presented a trend of recovery or improvement in all evaluated dimensions at 3-month compared with discharge. Among patients treated with alteplase, the mean dosage of 56.2±10.7 mg, with a median onset-arrival time of 1.8 hours. None of the individuals was found symptomatic intracerebral hemorrhage (sICH) or life-threatening

Table 1 Baseline Patients Characteristics by Alteplase Treatment

	Cohort N=1876	No Alteplase N=1774	Alteplase N=102	p
Demographics				
Age, yr, mean±SD	60.8±10.8	60.8±10.8	61.2±9.3	0.752
Female	497 (26.5)	460 (25.9)	37 (36.3)	0.021*
BMI, kg/m^2, mean±SD	25.1±3.2	25.1±3.2	24.9±3.9	0.921
Education level				0.181
College or above	195 (10.4)	186 (10.5)	9 (8.8)	
High school	443 (23.6)	412 (23.2)	31 (30.4)	
Junior school	688 (36.7)	656 (37.0)	32 (31.4)	
Primary school	472 (25.2)	443 (25.0)	29 (28.4)	
Not known	78 (4.2)	77 (4.3)	1 (1.0)	
Medicare				
Urban worker medical insurance	804 (42.9)	748 (42.2)	56 (54.9)	0.012*
Urban residents basic medical insurance	462 (24.6)	431 (24.3)	31 (30.4)	0.165
Rural cooperation medical insurance	544 (29.0)	532 (30.0)	12 (11.8)	<0.0001*
Self-payment	62 (3.3)	58 (3.3)	4 (3.9)	0.720
Commercial insurance	5 (0.3)	5 (0.3)	0	0.591
Public health services	18 (1.0)	18 (1.0)	0	0.307

(*Continued*)

Table 1 (Continued).

	Cohort N=1876	No Alteplase N=1774	Alteplase N=102	p
Medical history				
Hypertension	1159 (61.8)	1096 (61.8)	63 (61.8)	0.997
Diabetes mellitus	413 (22.0)	387 (21.8)	26 (25.5)	0.384
Hyperlipidemia	194 (10.3)	181 (10.2)	13 (12.7)	0.412
Previous stroke	389 (20.7)	374 (21.1)	15 (14.7)	0.122
Coronary artery disease	201 (10.7)	189 (10.7)	12 (11.8)	0.724
Atrial fibrillation	81 (4.3)	73 (4.1)	8 (7.8)	0.072
Current smoking	693 (36.9)	659 (37.1)	34 (33.3)	0.438
Current drinking	369 (19.7)	348 (19.6)	21 (20.6)	0.810
Medication history				
Antiplatelet	336 (17.9)	316 (17.8)	20 (19.6)	0.646
Anticoagulant	14 (0.7)	14 (0.8)	0 (0)	0.368
Antihypertensive	847 (45.1)	795 (44.8)	52 (51.0)	0.224
Antilipidemic	228 (12.2)	214 (12.1)	14 (13.7)	0.617
Antidiabetic	324 (17.3)	304 (17.1)	20 (19.6)	0.521
Pre mRS score				0.120
0	1425 (76.0)	1341 (75.6)	84 (82.4)	
1	451 (24.0)	433 (24.4)	18 (17.6)	
NIHSS score at admission, mean±SD	2.0±1.6	2.0±1.5	2.5±1.5	0.003*
0	387 (20.6)	378 (21.3)	9 (8.8)	
1	372 (19.8)	349 (19.7)	23 (22.5)	
2	415 (22.1)	391 (22.0)	24 (23.5)	
3	306 (16.3)	293 (16.5)	13 (12.7)	
4	256 (13.6)	235 (13.2)	21 (20.6)	
5	140 (7.5)	128 (7.2)	12 (11.8)	
Onset-arrival time, median (IQR)	17.0 (4.0–46.0)	20.1 (5.0–48.0)	1.8 (1.0–2.4)	<0.0001*
Discharge diagnosis				0.001*
Acute ischemic stroke	1703 (90.8)	1601 (90.2)	102 (100)	
TIA	173 (9.2)	173 (9.8)	0 (0)	
Toast classification				0.044*
Large artery atherosclerosis	432 (23.0)	399 (22.5)	33 (32.4)	
Cardiogenic embolism	94 (5.0)	86 (4.8)	8 (7.8)	
Small artery occlusion	494 (26.3)	477 (26.9)	17 (16.7)	
Other determined cause	16 (0.9)	15 (0.8)	1 (1.0)	
Undetermined cause	840 (44.8)	797 (44.9)	43 (42.2)	

Notes: Values are expressed as n (%), mean ± SD or median (interquartile range). *Means a p value < 0.05.
Abbreviations: BMI, Body Mass Index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

systemic bleeding within 36 hours. Only 1 of the alteplase group had severe complication other than hemorrhages, 7 (6.9%) of these had non-severe complications (Supplemental Table 1).

The Association Between Alteplase and Outcomes at Discharge

We analyzed the association between alteplase and discharge outcomes with 2 multivariable models and prespecified subgroups of age, gender and NIHSS score (Table 3). Significantly, we found an association of alteplase treatment on favorable functional outcome (higher SIS-16 score) at discharge in univariate analysis (β, 3.99; 95% CI, 0.84–7.13). The association still exist after adjusting for age, gender, and baseline NIHSS (Model 1; β, 5.30; 95% CI, 2.29–8.32) or additionally adjusting for education level, medicare, hypertension, diabetes mellitus, hyperlipidemia, previous stroke, current smoking, atrial fibrillation, coronary artery disease, medication history of anticoagulation, medication history of antiplatelet, onset-arrival time, TOAST classification (Model 2; β, 5.45; 95% CI, 2.22–8.68).

Table 2 The Distribution of Outcomes at Discharge and 90 Days

Outcomes	Overall Cohort N=1876	
	At Discharge	**At 90 Days**
mRS score, median (IQR)	1.0 (0.0–1.0)	1.0 (0.0–1.0)
mRS score, 2–5	229 (12.2)	202 (10.9)
Gait speed, m/s, mean±SD	0.9 ± 0.4	1.0 ± 0.4
MoCA, median (IQR)	23.0 (19.0–26.0)	25.0 (21.0–27.0)
PHQ-9, median (IQR)	2.0 (0.0–4.0)	1.0 (0.0–4.0)
GAD-7, median (IQR)	1.0 (0.0–3.0)	0.0 (0.0–2.0)
SIS-16, median (IQR)	100.0 (92.2–100.0)	100.0 (95.3–100.0)

Abbreviations: MoCA, Montreal Cognitive Assessment; PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder-7 scale; SIS-16, Stroke Impact Scale-16.

The Association Between Alteplase and Outcomes at 3-Month

In the above-mentioned multivariable models, similar association between alteplase treatment and higher SIS-16 score was also observed at 3-month after stroke (β, 5.45; 95% CI, 2.22–8.68) in Table 4. The clinical outcomes including motor function, cognitive function and emotion were similar between groups in univariate and multivariable analysis at discharge and 3-month.

Subgroup Analysis

In subgroup analysis restricted to age >60, the associations between alteplase treatment and higher gait speed were observed at discharge (β, 0.13; 95% CI, 0.01–0.25) and 3-month (β, 0.14; 95% CI, 0.02–0.25). When restricting to male, alteplase treatment was associated with lower anxiety score (PHQ-9) at discharge (β, −1.40; 95% CI, −2.37- −0.42), while the association was not observed at 3-month. However, we found alteplase treatment was associated with higher anxiety score (β, 1.54; 95% CI, 0.17–2.91) and depression score (β, 2.23; 95% CI, 0.91–3.55) in female at 3-month. The relationship of alteplase treatment on higher SIS-16 score was consistent between different subgroups of age, gender or NIHSS score (all interaction p > 0.05 at discharge and 3 months). There was no significant difference in the relationship of alteplase treatment on mRS or MoCA outcomes between different subgroups.

Discussion

In this study, we described multidimensional outcomes after alteplase treatment in patients with minor stroke or TIA. We found that 10.9% of minor stroke patients with NIHSS score of 0–5 presented unfavorable functional outcome in mRS at 3-month. Patients with alteplase treatment had a more favorable functional outcome in SIS-16 at 3-month after stroke. In a prespecified analysis restricted to age >60, we identified a better outcome of alteplase treatment in gait speed, while an unfavorable effect was found in anxiety and depression in female.

Patients with minor stroke were generally defined as having a low NIHSS score. However, objectively mild deficits do not necessarily mean non-disabling, especially in posterior circulation stroke.[24] Patients may suffer disproportionately impact from minor stroke based on different functional status, profession, or value system. The Potential of rtPA for Ischemic Strokes With Mild Symptoms (PRISMS) trial tested alteplase in minor acute ischemic minor stroke with a new operational definition of nondisabling, which aimed to capture patients who lack evidence of treatment.[9] Although the study was terminated early, it enlightened researchers to focus on patients who might benefit from rtPA treatment and the imbalance of treatment benefits in communities.

We found 10.9% of minor stroke patients presented disability (mRS score ≥2) at 3-month, which was lower than the reported 20–30% in previous observational studies.[4,25,26] But in accordance with the report from the CNSR-III study, 13.2% minor stroke patients experienced all-cause mortality or major disability in 1-year follow-up.[27] Our study provided the association of alteplase with favorable motor function and quality of life at 3-month, which was in accordance with some observational studies. A meta-analysis including seven studies with a total of 1591 minor stroke patients showed that treatment with intravenous thrombolysis was associated with better functional outcome and the

Table 3 Association of Alteplase Treatment with Outcomes at Discharge (No Alteplase as Reference)

Outcomes	mRS Score, 2–5	Gait Speed, m/s	MoCA, Score	PHQ-9, Score	GAD-7, Score	SIS-16, Score
	OR (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Univariate	1.16 (0.61–2.20)	−0.004 (−0.09–0.08)	−0.05 (−1.17–1.07)	−0.56 (−1.35–0.24)	−0.01 (−0.72–0.69)	3.99 (0.84–7.13)*
Model 1	1.51 (0.78–2.94)	0.03 (−0.05–0.11)	0.22 (−0.87–1.30)	−0.73 (−1.52–0.07)	−0.16 (−0.86–0.55)	5.30 (2.29–8.32)*
Model 2	1.74 (0.81–3.72)	0.0006 (−0.09–0.09)	0.35 (−0.76–1.46)	−0.53 (−1.35–0.29)	0.15 (−0.60–0.90)	5.45 (2.22–8.68)*
Model 2 restricted to age >60	0.39 (0.13–1.21)	0.13 (0.01–0.25)*	0.19 (−1.42–1.79)	−0.40 (−1.57–0.78)	−0.41 (−1.47–0.64)	8.58 (3.51–13.65)
Model 2 restricted to age ≤60	0.80 (0.27–2.41)	−0.15 (−0.28- −0.02)*	0.46 (−1.10–2.02)	−0.41 (−1.54–0.71)	0.69 (−0.36–1.74)	2.44 (−1.52–6.40)
Model 2 restricted to Male	0.81 (0.34–1.93)	−0.01 (−0.13–0.10)	0.72 (−0.63–2.07)	−1.40 (−2.37- −0.42)*	−0.42 (−1.29–0.44)	3.91 (0.17–7.65)
Model 2 restricted to Female	0.15 (0.02–1.22)	0.04 (−0.10–0.17)	−0.50 (−2.44–1.44)	0.92 (−0.59–2.43)	1.28 (−0.19–2.75)	9.86 (3.56–16.16)
Model 2 restricted to NIHSS 0–2	0.41 (0.09–1.87)	−0.04 (−0.15–0.08)	0.32 (−1.11–1.75)	−0.35 (−1.40–0.70)	0.31 (−0.65–1.27)	2.36 (−1.57–6.29)
Model 2 restricted to NIHSS 3–5	0.69 (0.28–1.71)	0.04 (−0.10–0.19)	0.53 (−1.23–2.30)	−0.50 (−1.85–0.74)	0.12 (−1.05–1.30)	8.03 (2.45–13.60)

Notes: Model 1: adjusted for age, gender and baseline NIHSS. Model 2: adjusted for all age, gender, education level, medicare, baseline NIHSS, hypertension, diabetes mellitus, hyperlipidemia, previous stroke, current smoking, atrial fibrillation, coronary artery disease, medication history of anticoagulation, medication history of antiplatelet, onset-arrival time, TOAST classification. *Means a p value < 0.05.
Abbreviations: mRS, modified Rankin Scale; MoCA, Montreal Cognitive Assessment; PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder-7 scale; SIS-16, Stroke Impact Scale-16; NIHSS, National Institutes of Health Stroke Scale.

Table 4 Association of Alteplase Treatment with Outcomes at 90 Days (No Alteplase as Reference)

Outcomes	mRS Score, 2–5	Gait Speed, m/s	MoCA, Score	PHQ-9, Score	GAD-7, Score	SIS-16, Score
	OR (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Univariate	0.91 (0.49–1.69)	0.02 (−0.06–0.11)	−0.25 (−1.24–0.74)	0.09 (−0.68–0.86)	0.35 (−0.33–1.04)	1.57 (−0.69–3.83)
Model 1	1.10 (0.58–2.08)	0.05 (−0.03–0.13)	−0.07 (−1.01–0.88)	−0.02 (−0.79–0.75)	0.29 (−0.40–0.97)	2.40 (0.25–4.54)*
Model 2	1.20 (0.58–2.49)	0.05 (−0.04–0.13)	0.09 (−0.88–1.05)	−0.03 (−0.84–0.78)	0.40 (−0.33–1.14)	2.34 (0.17–4.50)*
Model 2 restricted to age >60	0.29 (0.08–1.03)	0.14 (0.02–0.25)*	−0.31 (−1.84–1.22)	0.10 (−1.06–1.27)	0.90 (−0.15–1.94)	3.50 (−0.19–7.20)
Model 2 restricted to age ≤60	2.34 (0.88–6.23)	−0.05 (−0.18–0.08)	0.45 (−0.75–1.65)	−0.15 (−1.29–0.98)	−0.02 (−1.07–1.02)	1.11 (−1.14–3.37)
Model 2 restricted to Male	0.72 (0.28–1.83)	0.03 (−0.08–0.14)	0.22 (−0.93–1.38)	−0.92 (−1.92–0.08)	−0.52 (−1.41–0.37)	2.41 (0.10–4.71)
Model 2 restricted to Female	1.14 (0.34–3.79)	0.07 (−0.06–0.21)	−0.23 (−2.00–1.54)	1.54 (0.17–2.91)*	2.23 (0.91–3.55)*	2.30 (−2.4–7.05)
Model 2 restricted to NIHSS 0–2	0.92 (0.30–2.85)	0.05 (−0.06–0.17)	−0.30 (−1.53–0.94)	0.18 (−0.83–1.18)	1.03 (0.08–1.98)	0.35 (−2.10–2.79)
Model 2 restricted to NIHSS 3–5	0.81 (0.31–2.10)	0.04 (−0.10–0.18)	0.78 (−0.77–2.33)	−0.28 (−1.63–1.08)	−0.34 (−1.50–0.81)	4.59 (0.61–8.57)

Notes: Model 1: adjusted for age, gender and baseline NIHSS. Model 2: adjusted for all age, gender, education level, medicare, baseline NIHSS, hypertension, diabetes mellitus, hyperlipidemia, previous stroke, current smoking, Atrial fibrillation, coronary artery disease, medication history of anticoagulation, medication history of antiplatelet, onset-arrival time, TOAST classification. *Means a p value < 0.05.
Abbreviations: mRS, modified Rankin Scale; MoCA, Montreal Cognitive Assessment; PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder-7 scale; SIS-16, Stroke Impact Scale-16; NIHSS, National Institutes of Health Stroke Scale.

treatment-related risk of sICH does not contribute to disability or mortality.[28] The Mild and Rapidly Improving Stroke Study (MaRISS) focused on multidimensional outcomes of minor stroke (NIHSS 0–5) and the effect of alteplase at 3-month, a better outcome was identified restricted to the NIHSS of 3–5 group in the SIS-16 but not in mRS.[29] We reassured that alteplase treatment was associated with higher quality of life at discharge and 3-month, which was reflected in higher SIS-16 scores. Although the mRS scale was widely used to evaluate the recovery after stroke, the scale may not reflect the extent and the impact to daily life in disability among people with minor strokes.[30]

The efficacy of alteplase treatment in patients with minor stroke is difficult to interpretation cause the term of minor deficit was defined based on different cut-off points of NIHSS score.[6,25,31] We defined the minor stroke in accordance with IST-3 and other recently published studies.[9,26] Similar to previous studies, the alteplase treated group had higher baseline NIHSS scores compared with the non-alteplase group.[10] Although possible covariates were adjusted in the following multivariable analysis, there may be residual confounding in the initial treatment decision.[29] As above-mentioned, more than fifty percent patients included in our study had a baseline NIHSS score of 0–2, and approximal ninety percent achieved a nondisabled outcome (mRS 0–1) at 3-month. The eligibility criterion of "minor" might be essentially close to the definition of the favorable outcome of an mRS score of 0 −1.[32] Therefore, it may create a ceiling effect for alteplase to show treatment benefit based on mRS outcome. Previous study has identified that the efficacy of reperfusion treatment depends on the disabling degree of the symptoms at admission.[10] In addition, poor outcomes in minor stroke could be related to inadequate detection of functional impairment, such as cognitive or neuropsychological deficits.[4] The positive outcome in the SIS-16 showed that this scale may better catch the severity of functional dependence than the scale based on subjective judgment of physicians.[33]

The Get With The Guidelines Stroke (GWTG-S) registry including 42,394 patients with a baseline NIHSS score of 0–5 untreated with alteplase reported that 27.2% could not ambulate independently at discharge.[6] Similar study in Chinese population reported that 11.1% among 6752 minor stroke patients received alteplase had independent mobility difficulty at discharge.[34] We observed that alteplase treatment was associated with favorable motor function in gait speed in minor stroke patients with age >60, with no significantly increased risk of sICH. As reported in a pooled analysis of 9 cohort studies, gait speed was associated with survival in community-dwelling older adults, with a pooled hazard ratio of 0.88 (per 0.1m/s).[35] The potential cause of the observed benefit in older patients may be that the gait speed declines with age,[36] therefore the improvements in gait speed from treatment may be easier to spot in older adults.

In our study, female seemed to have higher scores on the anxiety and depression evaluation after alteplase treatment. Female gender was a significant predictor of post-stroke depression in prospective cohort studies.[37] In patients under-going percutaneous transluminal coronary angioplasty, female was more susceptible to intrusive thought with feelings of anxiety and increased sensitivity.[38] Some other factors such as social pressures and life stressors may have different effects on depression and anxiety in different genders.[39] This finding implied that post-stroke depression and anxiety should not be underestimated, especially when invasive treatment was applied. And its management calls for a multifaceted approach including social, psychological, and biological dimensions.[40]

The treatment-related adverse events were not further analyzed in this study because none of the patients presented with symptomatic intracerebral hemorrhage or death during hospitalization. That may be speculated by the large proportion of non-alteplase treated patients in our study, though the proportion of minor stroke patients treated with thrombolysis has increased recently.[41] However, the patients in our cohort were managed strictly according to the guidelines, patients accepted thrombolytic therapy would receive electrocardiograph monitoring for at least 24 hours and be reviewed with neuroimaging prior to antiplatelet or anticoagulant medication. Furthermore, previous study also reported a low rate of sICH in the same population.[29,42]

Our study provided a more nuanced view of multidimensional 3-month outcomes in minor stroke and innovatively analyzed the gait speed as an essential outcome related to life quality to discuss the efficient of thrombolysis. There were also some limitations. First, the potential selection bias cannot be excluded in nonrandomized data. However, CNSR-III multicenter registry enrolled patients prospectively from 201 hospitals that cover 22 provinces and 4 municipalities in China.[1] The registry is part of a governmental quality assessment program and was essentially representative of Chinese clinical practice. Second, the neuroimaging markers were not analyzed in our study. Some abnormal parenchymal imaging and large-vessel occlusion were effective predictors of greater disability after minor stroke or TIA,[43,44] their

relationship to other functional outcomes may also be significant. Finally, since this was an observational registration study, further surveys including interventional trials are needed to test our preliminary results. In particular, randomized controlled trials should be performed to exclude the bias by indication.

Conclusion

Our study identified a suggestion of benefit from alteplase treatment in patients with low NIHSS score of 0–5. An expected efficacy of alteplase was also found in motor function in the older subgroup. Meanwhile, female gender seemed more inclined to post-stroke emotional problems after alteplase treatment, which should be further explored in the future. Thus, we suggest adopting multidimensional tools to correctly evaluate outcomes of patients with mild deficit. Further, randomized clinical trials are needed to confirm these preliminary findings.

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Disclosure

The authors report no conflicts of interest in this work.

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