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Title Page

Thrombolysis, Time-to-Treatment and In-Hospital Outcomes Among Young Adults with Ischemic Stroke in China

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Key words: ischemic stroke, young stroke, thrombolysis, door-to-needle time

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ABSTRACT

Background and purpose We aimed to determine whether young adults (< 50 years) with acute ischemic stroke (AIS) are more likely to receive intravenous tissue plasminogen activator (IV tPA) and have shorter time to treatment than older stroke patients.

Methods We analyzed data from the Chinese Stroke Center Alliance (CSCA) registry for AIS patients hospitalized between August 2015 and July 2019. Patients were classified into two groups according to age: young adults (< 50 years of age) and older adults (≥ 50 years of age).

Results Of 79 3175 patients with AIS admitted to 1471 hospitals, 9.1% (71 860) were young adults. Compared to older adults, a higher proportion of young adults received IV tPA among patients without contraindicaitons (7.2% vs. 6.1%, adjusted odds ratio [aOR] 1.13, 95% confidence interval [CI] 1.10-1.17) and among patients without contraindications and with onset-to-door time ≤3.5h (23.6 % vs. 19.3%, aOR 1.20, 95% CI 1.15-1.24). We did not observe differences in onset-to-needle time (median hours 2.7h) or door-to-needle time (DNT) (median minutes 60m) between young and older adults. The proportion of DNT≤30 minutes, DNT≤45 minutes, and DNT≤60 minutes in young and older IV tPA treated patients were 16.9% vs 18.8%, 30.2% vs 32.8% and 50.2% vs 54.2%, respectively. Compared to older adults, young adults treated with IV tPA had lower odds of in-hospital mortality (0.5% vs 1.3%,

aOR 0.54, 95% CI 0.35-0.82) and higher odds of independent ambulation at discharge (61.0% vs 53.6%, aOR 1.15, 95% CI 1.08-1.22), and the associations may be partly explained by stroke severity measured by NIHSS score.

Conclusion Young adults with AIS were more likely to receive IV tPA than older adults, though there was no difference between the two groups in time to treatment. Compared with older adults, young adults may had better in-hospital outcomes.

Key words: ischemic stroke, young stroke, thrombolysis, door-to-needle time

Strengths and limitations of this study

1.We are one of the few authors to focus on the age difference in the status and outcomes of intravenous thrombolysis;

2.Our data come from the Chinese Stroke Center Alliance registry, which is a national, hospital-based, multicenter, voluntary, multifaceted intervention and continuous quality improvement initiative and have stronger evidence level;

3.we believe that it is meaningful for further promotion of treatment for strokes, especially for thrombolysis, because of providing a reference for the operator;

4.Since hospital participation in the CSCA is voluntary, participating hospitals are more likely to be larger, tertiary centers with a myriad of resources that smaller hospitals do not have access to;

5.We did not report data on intra-arterial (IA) therapies and puncture times.

ABBREVIATIONS

CSA: Chinese Stroke Association

CSCA: Chinese Stroke Center Alliance

QI: quality improvement

AIS: acute ischemic stroke

BMI: body mass index

mRS: modified Rankin Scale score

aOR: adjusted odds ratios

CI: confidence intervals

IV tPA: intravenous tissue plasminogen activator

IQR: interquartile range

NIHSS: National Institutes of Health Stroke Scale

DNT: door-to-needle time

sICH: symptomatic intracranial hemorrhage

INTRODUCTION

Stroke incidence among adults under 50 years of age has risen in recent years. [1-5] This creates a signficant socioeconomic burden due to high healthcare costs and loss of labor productivity.[5,6] According to the 2019 Chinese Stroke Statistics, 81.9% of stroke patients had ischemic strokes,[7] of which young adults constituted 15–18%.[8] Given this trend, researchers must carefully consider the clinical features and best practices of treatment for strokes in young adults.[8]

Ischemic stroke is a common, preventable, and treatable disease that typically results from thrombotic or thromboembolic blockage of a cerebral artery.[9] Revascularization therapy plays a major role in the process of saving penumbral tissue from infarction.[10] Tissue plasminogen activator (tPA) is the only intravenous drug approved for the treatment of acute ischemic stroke.[11] Treatment of acute occlusive stroke with IV tPA is considered the most regular and important method when given within 4.5 hours of occlusion.[12,13] While epidemiological studies have been done in other countries regarding IV tPA treatment in young AIS patients, there is limited research on this topic in China.[13-17]

The purpose of this study was to compare the characteristics, IV tPA treatment rates, onset-to-needle time, door-to-needle time (DNT) and in-hospital outcomes of young (<50 years of age) and older (≥ 50 years of age) AIS patients in the Chinese Stroke Center Alliance (CSCA). We hypothesized that young AIS patients would be treated more frequently with IV tPA, have shorter treatment time and better in-hospital

outcomes compared to older adults.

METHODS

Data source

CSCA is a national, hospital-based, multicentre, voluntary, multifaceted intervention and continuous quality improvement initiative. The data coordinating center of CSCA resides at the China National Clinical Research Center for Neurological Diseases (NCRCND), Beijing Tiantan Hospital. [18] Trained personnel collected patient demographics, medical history, medications, DNT, and in-hospital outcomes, then entered this information into a database using a web-based Patient Management Tool (Medicine Innovation Research Center, Beijing, China). The tool is characterized by predefined logic features, range checks, and user alerts to identify a potentially invalid format or value entries and to optimize data quality at the time of entry. Training in the use of the tool was provided online and onsite for all users. However, data collected by hospitals were not independently audited by external chart review. In addition, The China National Clinical Research Center for Neurological Diseases serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for care quality feedback and research purposes. We abstracted 838 229 cases and identified 793 175 patients admitted with ischemic strokes from 2015 to 2019.

Study population

In the first stage, our analyses included patients admitted with AIS within 7 days of the onset of symptoms between August 1, 2015 and July 31, 2019 from 1473 hospitals. We excluded patients who had in-hospital strokes (n=7941, 0.95%), were missing IV tPA information (n=17461, 2.08%), had imprecise or undocumented arrival times (n=12), transferred in from an acute care hospital (n=1777, 0.212%), or had contraindications to venous thrombolysis within the time window (n=17863, 2.13%). This yielded a population of patients with ischemic strokes with indications for thrombolysis (n=793175). To analyze DNT and in-hospital outcomes of ischemic stroke, we excluded patients treated with IV tPA more than 4.5 hours after stroke onset (n=1315, 0.17%) and patients who were not treated with IV tPA (n=743719, 93.76%). This yielded a subset of the study population that consisted of 48141 AIS patients from 1290 hospitals (Figure 1).

Outcomes

The IV tPA treatment rate was assessed among two populations. First, IV tPA rate among patients without contraindications to thrombolytic therapy was calculated as the number of IV tPA cases divided by the total number of ischemic stroke cases without any contraindications to thrombolytic therapy. Then IV tPA rate among patients without contraindication to thrombolytic therapy and with onset-to-door time ≤3.5h was calculated as the number of IV tPA cases divided by the total number of ischemic stroke cases without any contraindications to thrombolytic therapy and

arrived at a hospital within 3.5 hours after stroke onset. The contraindications were defined according to guidelines for the early management of patients with acute ischemic stroke from the Heart Association/American Stroke Association and Chinese Society of Neurology. DNT was defined as the time between arrival at the emergency department (ED) and time of intravenous (IV) thrombolysis, and is an important metric in AIS treatment.[19,20] We analyzed DNT as a binary outcome three times with a different cut-off point each time (⩽30, ⩽45, or⩽60 minutes, respectively).

In-hospital outcomes included symptomatic intracranial hemorrhage (sICH), in-hospital mortality, and independent ambulation at discharge. sICH was defined as intracranial hemorrhage (ICH) within 36 hours of admission, documented by CT or MRI, with the treating physician's notes indicating clinical deterioration attributable to hemorrhage. Patients who were able to walk <48 hours after hospital admission were considered to have independent ambulation at discharge.

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges (IQR) and categorical variables as frequencies and percentages. Between-group differences for young vs. older adults were analyzed using the chi-square test, two sample t-test, or corresponding nonparametric tests in cases of skewed distributions that cannot be normalized. For outcomes such as IV tPA treatment and in-hospital outcomes, logistic regression models were performed to determine adjusted odds ratios (aORs) and 95%

confidence intervals (CIs). Multivariate models were adjusted for gender, insurance status, body mass index (BMI), medical history of prior stroke or transient ischemic attack (TIA), coronary artery disease (CAD) or prior myocardial infarction (MI), diabetes mellitus, hypertension, smoking status, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, medication history (hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid lowering drugs), and hospital grade.

There were few missing data for most variables, with the exceptions of the in-hospital NIHSS score (missing 19.4%), DNT (6.3%), glycated hemoglobin (10.6%) and BMI (1.6%). For continuous variables missing less than 15%, the median was used for imputation. Since the NIHSS score is a widely used tool for assessing stroke severity[21] and contributes important information to AIS prognosis,[22] sensitivity analyses adjusting for the NIHSS score were conducted. Because of the large sample size, some statistically significant differences may not be clinically meaningful. We used absolute standardized differences (ASD) to compare differences in baseline characteristics between young and older adults independent of sample size. An ASD larger than 10 was considered statistically significant.[23]

All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA) and the %ggBaseline SAS macro.[24] Two-sided p-values of <0.05 were

considered statistically significant.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Of 838 229 patients with AIS in the CSCA, 793 175 patients enrolled from 1471 hospitals were eligible for inclusion in this study. The median age was 67.0 years (range: 58.0-75.0) and 62.7% were men. A total of 261 760 (33.0%) patients had previous stroke/TIA, 69 810 (8.8%) had coronary artery disease or myocardial infarction (CAD/prior MI), 170 638 (21.5%) had diabetes, 510 928 (64.4%) had hypertension, 294 708 (37.2%) were smokers, and 40 231 (5.1%) had atrial fibrillation/flutter.

Clinical characteristics

A total of 71 860 (9.1%) patients were young adults (<50 years) and 721 315 (90.9%) were older adults (≥50 years). The median age among young adults was 45.0 (IQR 42.0-48.0) years and 68.0 (61.0-76.0) years among older adults. A larger proportion of the young adults were men (76.3% vs 61.3%) and did not have health insurance coverage (12.9% vs 5.7%), compared to older adults. Young adults had a lower prevalence of cardiovascular risk factors compared to older adults, including history of stroke or TIA (22.5% vs 34.0%), CAD/prior MI (4.0% vs 9.3%), diabetes mellitus (15.3% vs 22.1%), hypertension (53.9% vs 65.5%), and atrial fibrillation (1.2% vs

5.5%). Young adults had a lower rate of medication use than older adults, including hypoglycemic drugs (10.9% vs 17.4%), antihypertensive drugs (33.5% vs 48%), antiplatelet drugs (14.6% vs 21.5%), and lipid lowering drugs (11.4% vs 15.3%). However, diastolic blood pressure in young adults was significantly higher than that of older adults (median 90.0, IQR 80.0-100.0 vs median 86.0, IQR 79.0-95.0), and young adults had a significantly higher mean BMI than older adults (median 24.2, IQR 22.6-26.4 vs median 23.7, IQR 21.7-25.4). The proportion of young adults who smoked was also higher than that of older adults (49.9% vs 35.9%) (Table 1).

Table 1. Baseline characteristics of young and old ischemic stroke patients

Baseline characteristics	Total (N=793175 [100%])	Young adults (< 50 years) (N=71860 [9.1%])	Old adults (≥50 years) (N=721315 [90.9%])	ASD*
Patient characteristics				
Age, years				
Mean±SD	66.1±12.0	43.8±5.3	68.3±10.0	306.1
Median (IQR)	67.0 (58.0–75.0)	45.0 (42.0–48.0)	68.0 (61.0–76.0)	
Male , n (%)	496960 (62.7)	54850 (76.3)	442110 (61.3)	32.8
Insurance status, n (%)				
UEBMI	225940 (28.5)	19160 (26.7)	206780 (28.7)	4.5
URBMI	149839 (18.9)	12393 (17.2)	137446 (19.1)	4.9
NRCMS	333979 (42.1)	27587 (38.4)	306392 (42.5)	8.4
Self-pa	50727 (6.4)	9263 (12.9)	41464 (5.7)	25.0
Other	32690 (4.1)	3457 (4.8)	29233 (4.1)	3.4
Arrive mode, n (%)				
Ambulance	89484 (11.3)	7170 (10.0)	82314 (11.4)	4.5
Private car	372727 (47.0)	33340 (46.4)	339387 (47.1)	1.4
Taxi	68801 (8.7)	6743 (9.4)	62058 (8.6)	2.8
Bicycle or tricycle	7237 (0.9)	577 (0.8)	6660 (0.9)	1.1
Helicopter	338 (0.0)	27 (0.0)	311 (0.0)	

Mobile stroke unit	246 (0.0)	24 (0.0)	222 (0.0)	
Other	254342 (32.1)	23979 (33.4)	230363 (31.9)	3.2
Medical history, n (%)				
Previous stroke/TIA	261760 (33.0)	16197 (22.5)	245563 (34.0)	25.8
CAD/prior MI	69810 (8.8)	2906 (4.0)	66904 (9.3)	21.4
Diabetes	170638 (21.5)	10985 (15.3)	159653 (22.1)	17.5
Peripheral vascular disease	13512 (1.7)	718 (1.0)	12794 (1.8)	6.8
Hypertension	510928 (64.4)	38722 (53.9)	472206 (65.5)	23.8
Smoking†	294708 (37.2)	35848 (49.9)	258860 (35.9)	28.6
Atrial fibrillation/flutter	40231 (5.1)	886 (1.2)	39345 (5.5)	24.1
Dyslipidemia	60605 (7.6)	5861 (8.2)	54744 (7.6)	2.2
Carotid stenosis	10161 (1.3)	509 (0.7)	9652 (1.3)	6.0
Medication history, n (%)				
Anticoagulants	31326 (3.9)	2394 (3.3)	28932 (4.0)	3.7
Hypoglycemic drugs	133244 (16.8)	7802 (10.9)	125442 (17.4)	18.7
Antihypertensive drugs	370017 (46.7)	24065 (33.5)	345952 (48.0)	29.8
Antiplatelet drugs	165771 (20.9)	10482 (14.6)	155289 (21.5)	18.0
Lipid lowering drugs	118827 (15.0)	8171 (11.4)	110656 (15.3)	11.5
NIHSS score in hospital‡				
Mean±SD	4.8±5.2	4.0±4.5	4.9±5.3	18.3
Median (IQR)	3.0 (2.0–6.0)	3.0 (1.0–5.0)	3.0 (2.0–6.0)	
Biochemical Indicators				
Glycated hemoglobin§, %				
Mean±SD	6.2±1.7	6.1±1.8	6.3±1.7	11.4
Median (IQR)	5.8 (5.3–6.5)	5.7 (5.2–6.1)	5.8 (5.3–6.5)	
BMI‖				
Mean±SD	24.0±4.3	24.9±4.8	23.9±4.2	22.2
Median (IQR)	23.7 (21.9–25.5)	24.2 (22.6–26.4)	23.7 (21.7–25.4)	
Homocysteine#, μmol/L				
Mean±SD	17.2±13.5	17.5±14.9	17.2±13.4	2.1
Median (IQR)	13.9 (10.4–19.1)	13.4 (10.0–19.0)	13.9 (10.5–19.1)	
Systolic blood pressure**, mmHg				
Mean±SD	150.0±23.0	147.9±24.4	150.2±22.8	9.7
Median (IQR)	150.0 (134.0–164.0)	145.0 (130.0–161.0)	150.0 (135.0–164.0)	
Diastolic blood pressure††, mmHg				
Mean±SD	87.0±13.9	92.3±16.1	86.5±13.5	39.0
Median (IQR)	86.0 (79.0–96.0)	90.0 (80.0–100.0)	86.0 (79.0–95.0)	
Hospital characteristics, n (%)				
Hospital level				

Secondary hospital	303790 (38.3)	23993 (33.4)	279797 (38.8)	11.3
Tertiary hospital	489385 (61.7)	47867 (66.6)	441518 (61.2)	11.3
Hospital region				
Eastern China	365579 (46.1)	32744 (45.6)	332835 (46.1)	1.0
Central China	262618 (33.1)	24477 (34.1)	238141 (33.0)	2.3
Western China	164978 (20.8)	14639 (20.4)	150339 (20.8)	1.0

Abbreviations: UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme; TIA,transient ischemic attack; CAD, coronary artery disease; MI, myocardial infarction; SD: standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; ASD, absolute standardized difference.

*: An absolute standardized difference >10 indicates significant differences between 2 groups.

†: Smoking: having smoking experience or behaviors.

‡: Information was missing for N=154052 patients (19.4%).

§: Information was missing for N=84393 patients (10.6%); median was used for imputation.

||: Information was missing for N=12698 patients (1.6%); median was used for imputation..

#: Information was missing for N= 35781 patients (4.5%).

**: Information was missing for N=245 patients (≈0.0%); median was used for imputation.

††: Information was missing for N=251 patients (≈0.0%); median was used for imputation.

IV tPA treatment rates

Young adults were treated more frequently with IV tPA than older adults among patients without contraindications to thrombolysis (7.2% vs 6.1%, aOR 1.13, 95% CI 1.10-1.17) and among patients without contraindication and with onset-to-door time ≤ 3.5h (23.6 % vs. 19.3%, aOR 1.20, 95% CI 1.15-1.24) . The adjusted OR of treatment with IV tPA was 1.20 (95% CI 1.16-1.24) or 1.24 (95% CI 1.20-1.29) in sensitivity analyses adjusting for NIHSS (Table 2).

Table 2. Multivariable analysis of IV tPA treatment by age group

Treantment	Total (N=793175 [100%])	Young adults (< 50 years) (N=71860 [9.1%])	Old adults (≥50 years) (N=721315 [90.9%])(REF)	Model	OR (95% CI)	P value
IV tPA among patients without contraindications	49456 (6.2)	5181 (7.2)	44275 (6.1)	1	1.19 (1.15-1.22)	<0.0001
				2	1.13 (1.10-1.17)	<0.0001

				3	1.20 (1.16-1.24)	<0.0001
IV tPA among patients without contraindication and with onset-to-door time ≤3.5h	45842 (19.7)	4768 (23.6)	41074 (19.3)	1	1.29 (1.25-1.34)	<0.0001
				2	1.20 (1.15-1.24)	<0.0001
				3	1.24 (1.20-1.29)	<0.0001

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator; OR, odds ratio.

Model 1: Logistic regression model without adjustment.

Model 2: adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated, hemoglobin, diastolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, lipid-lowering drugs, and hospital level.

Model 3: adjusted for were in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, lipid-lowering drugs, and hospital level. Patients (N= 154052) with missing values on NIHSS score were not included in this analysis.

Treatment time

While young adults were more likely to receive IV tPA, there was no significant difference in onset-to-needle time (median 2.7 hours, IQR 2.0–3.5 for both groups) and DNT(median 60.0 minutes, IQR 42.0-90.0 vs median 60.0 minutes, IQR 36.0-84.0) among young and older adults. DNT was also analyzed as a binary outcome at three levels: DNT ≤30, DNT ≤45, and DNT ≤60 minutes. There were no significant differences between the two groups on any DNT level (16.9% vs 18.8%; 30.2% vs 32.8%; 50.2% vs 54.2%) (Table 3).

Table 3. Treatment time in young and old ischemic stroke patients treated with IV tPA

Measures	Total (N=48141 [100%])	Young adults (< 50 years) (N=5044 [10.5%])	Old adults (≥50 years) (N=43097 [89.5%])	ASD*

Onset-to-needle time†,h				
Median (IQR)	2.7 (2.0–3.5)	2.7 (2.0–3.5)	2.7 (2.0–3.5)	
DNT‡ ,min				
Mean±SD	66.8±44.1	70.8±46.8	66.4±43.8	9.7
Median (IQR)	60.0 (36.0–84.0)	60.0 (42.0–90.0)	60.0 (36.0–84.0)	
Treatment time				
DNT≤30 minutes	8938 (18.6)	850 (16.9)	8088 (18.8)	5.0
DNT≤45 minutes	15637 (32.5)	1521 (30.2)	14116 (32.8)	5.6
DNT≤60 minutes	25884 (53.8)	2531 (50.2)	23353 (54.2)	8.0

Abbreviations: CI=confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator; DNT, door-to-needle time ; ASD, absolute standardized difference.

*:An absolute standardized difference >10 indicates significant differences between 2 groups.

†: Onset-to-needle time was missing for 3818(7.9%) patients, with 431(8.5%) in age <50 and 3387(7.9%) in ≥ 50 groups.

‡:DNT was missing for 3027(6.3%) patients, with 342 (6.8%) in age <50 and 2685(6.2%) in ≥ 50 groups.

In-hospital outcomes

In-hospital outcomes including sICH, in-hospital mortality, and independent ambulation at discharge were summarized in Table 4. Multiple logistic regression with adjustments of unbalanced covariates (ASD>10% in Supplemental Table I) showed that young adults had non-significantly lower rates of sICH (0.5% vs 0.9%, aOR=0.74, 95%CI 0.49-1.11) than older adults. However, young adults had significantly lower rates of in-hospital mortality (0.5% vs 1.3%, aOR=0.54, 95%CI 0.35-0.82) and were more likely to be independently ambulating at discharge (61.0% vs 53.6%, aOR=1.15, 95%CI 1.08-1.22).

In sensitivity analyses adjusted for NIHSS scores, young adults had non-significantly lower odds of sICH (aOR=0.77, 95%CI 0.5-1.18), in-hospital mortality (aOR=0.70, 95%CI 0.46-1.09), and non-significantly higher odds of independent ambulation at

discharge (aOR=1.00, 95%CI 0.93-1.08). Sensitivity analysis using different age cut-off point(<35 years and ⩾35 years) showed consistent results with primary analysis (supplemental material table Ⅱ). But when we used another age cut of point (<45 years and ⩾45 years), we had a lower sICH rate (aOR=0.44, 95%CI 0.19-0.99) in the young group (supplemental material table Ⅲ).

Table 4. In-hospital outcomes in young and old ischemic stroke patients treated with IV tPA

Outcome	Total (N=48141 [100%])	Young adults (< 50 years) (N=5044 [10.5%])	Old adults (≥50 years) (N=43097 [89.5%])(REF)	Model	OR (95% CI)	P value
sICH	414 (0.9)	26 (0.5)	388 (0.9)	1	0.57 (0.38-0.85)	0.0057
				2	0.74 (0.49-1.11)	0.1446
				3	0.77 (0.5-1.18)	0.2277
In-hospital mortality	579 (1.2)	24 (0.5)	555 (1.3)	1	0.37 (0.24-0.55)	<0.0001
				2	0.54 (0.35-0.82)	0.0037
				3	0.70 (0.46-1.09)	0.1140
Independent ambulation at discharge	26175 (54.4)	3079 (61.0)	23096 (53.6)	1	1.36 (1.28-1.44)	<0.0001
				2	1.15 (1.08-1.22)	<0.0001
				3	1.00 (0.93-1.08)	0.9490

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator ; OR, odds ratio.

Model 1: Logistic regression model without adjustment.

Model 2: Adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs,and lipid-lowering drugs.

Model 3: Adjusted for in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid-lowering drugs. Patients (N= 2503) with missing values on NIHSS score were not included in this analysis.

DISCUSSION

In this hospital-based observational study of 793 175 AIS patients, we found that young adults (<50 years of age) were more likely to be treated with IV tPA than older adults (7.2% vs 6.1%), which was consistent with our hypothesis. Our study demonstrated that young stroke patients had fewer comorbidities (previous stroke/TIA,

previous CAD/prior MI, diabetes, hypertension, and atrial fibrillation/flutter) at baseline, which may compel providers to feel more secure in administering IV tPA to this group of patients. Even though we did not observe a difference in DNT between age groups, we found that young adults had more favorable in-hospital outcomes than older adults, including lower odds of sICH, in-hospital mortality and higher odds of independent ambulation at discharge, but adjusted for NIHSS scores, the results were not significant, so the associations may be explained by stroke severity measured by NIHSS score.

IV tPA thrombolytic therapy is considered to be the standard therapy in patients with acute ischemic stroke. However, its use has been studied primarily in adults over age 50.[16] Given increasing evidence in the literature that thrombolytic therapy rarely causes hemorrhages in patients with stroke-mimicking conditions, providers may also feel more comfortable administering IV tPA to young adults when it is uncertain whether a stroke or a stroke mimic had occurred.[25] Our research also supports this conclusion. Young adults had similar time to treatment and were more likely to be

treated than older adults, which may reflect increased awareness among patients and clinicians that stroke is a potentially fatal disease affecting people of all ages.

The relationship between time to treatment and mortality was first recognized in clinical studies.[26,27] The importance of this metric was reemphasized in the 2004 American College of Cardiology/American Heart Association practice guidelines, which stated that DNT targets "should not be perceived as an average performance standard but as a goal that an early treatment system in every hospital should seek for every appropriate patient".[28] Consistent with a prior analysis of SITS-ISTR showing no difference in median door-to-needle times between patients 18 to 50 and >50 years of age, there was also not an obvious differentiation in treatment among young or older adults in our study.[15] However, a prior study by Dodds and colleagues found that young adults (18-40 years) with AIS were more likely to experience a delay in evaluation and treatment.[12] Our definition of young adults (age <50 years) differs from theirs (age 18–40 years) and is more applicable in China, which may also explain why we did not find differences in treatment times between the two groups.[29] Another explanation for the lack of differences in treatment times between the two groups may be that DNT mainly depends on hospital level and treatment process rather than age.

In our study, we observed a higher rate of sICH and in-hospital mortality among older adults treated with IV tPA, though the difference was not significant adjusted for NIHSS scores. We cannot entirely separate young age from lower NIHSS score, as

young patients are highly correlated with lower NIHSS scores in clinical practise (4.0±4.5 vs. 4.9±5.3, the Rank Biserial correlation coefficient in this study is 0.10, p<0.001). Therefore, the associations may be partly explained by stroke severity measured by NIHSS score. A Canadian study found that the sICH proportion among younger patients did not differ from those over 50 (3% vs 4.7%, p=0.62).[16] Our finding is consistent with the results of this study. But in two other studies, however, younger patients treated with tPA had a lower sICH rate.[13,15] Although we do not find significant differences between these two groups, we do see a trend towards better outcomes in young people. One possible explanation is that younger stroke patients have fewer comorbidities in their medical history, such as previous stroke or TIA, CAD/MI, diabetes mellitus, hypertension, and atrial fibrillation, as well as milder strokes, all of which are associated with better outcomes.[30] Other factors favoring recovery in young stroke patients include greater brain plasticity and more robust family and social support.[31] There could be several reasons why we didn't reach the same conclusion as the two studies. Firstly, the GWTG-Stroke study had a much larger sample size and used age<40 to define young adults, while the SITS-ISTR study had a much higher NIHSS score and a different definition for SICH. [13,15] When we used different age cut of point (<45 years and ≥45 years), we had a lower sICH rate (aOR=0.44, 95%CI 0.19-0.99) in the young group (supplemental material table Ⅲ). Secondly, this may also reflect, in part, that physicians in China are more conservative in selecting patients for intravenous thrombolysis because of

possible complications. There are several limitations in our study. Since hospital participation in the CSCA is voluntary, participating hospitals are more likely to be larger, tertiary centers with a myriad of resources that smaller hospitals do not have access to. We recognize that findings from CSCA may not be generalizable to AIS patients admitted to hospitals outside of the CSCA. Second, we did not report data on intra-arterial (IA) therapies and puncture times because only a very small number of patients in our study received thrombectomy. We also did not have door-to-imaging data to support the study and there was a relatively high proportion of missing DNT values (6.3% overall, 6.8% in young and 6.2% in older patients). However, we did not observe a significant difference in DNTs between young and older AIS patients. Lastly, we cannot entirely separate young age from lower NIHSS score, as younger age is inherently correlated with a lower NIHSS score. Therefore, better prognosis can not be fully attributed to NIHSS score nor age. But this is a real world study, which represent the current situation of thrombolysis in China. It is based on these data that we are constantly improving the process and quality of thrombolysis.

CONCLUSION

In summary, young adults with AIS are more likely to receive IV tPA than older adults, but there is no difference between the two groups in time to treatment. Young adults may have better in-hospital outcomes compared with older adults, suggesting favorable effects of treatment with IV tPA.

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CONTRIBUTORS

Conceived and led the project: XZ, YW, ZL, YW and YJ. Conception and design: HW, HG, YW and YJ. Data collection and analysis: HW, XY, CW, HG and QZ. Interpret the data: LL, XM and HL. Drafting the article and revising the content: HW, HG, CL, JY and ZL. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

None declared.

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL

This study received approval from the Institutional Review Board/Ethics Committee of Beijing Tiantan Hospital, Capital Medical University with approval number KY 2018-061-02. Participating hospitals received research approval to collect data in CSCA without requiring individual patient informed consent under the common rule or a waiver of authorisation and exemption from their Institutional Review Board.

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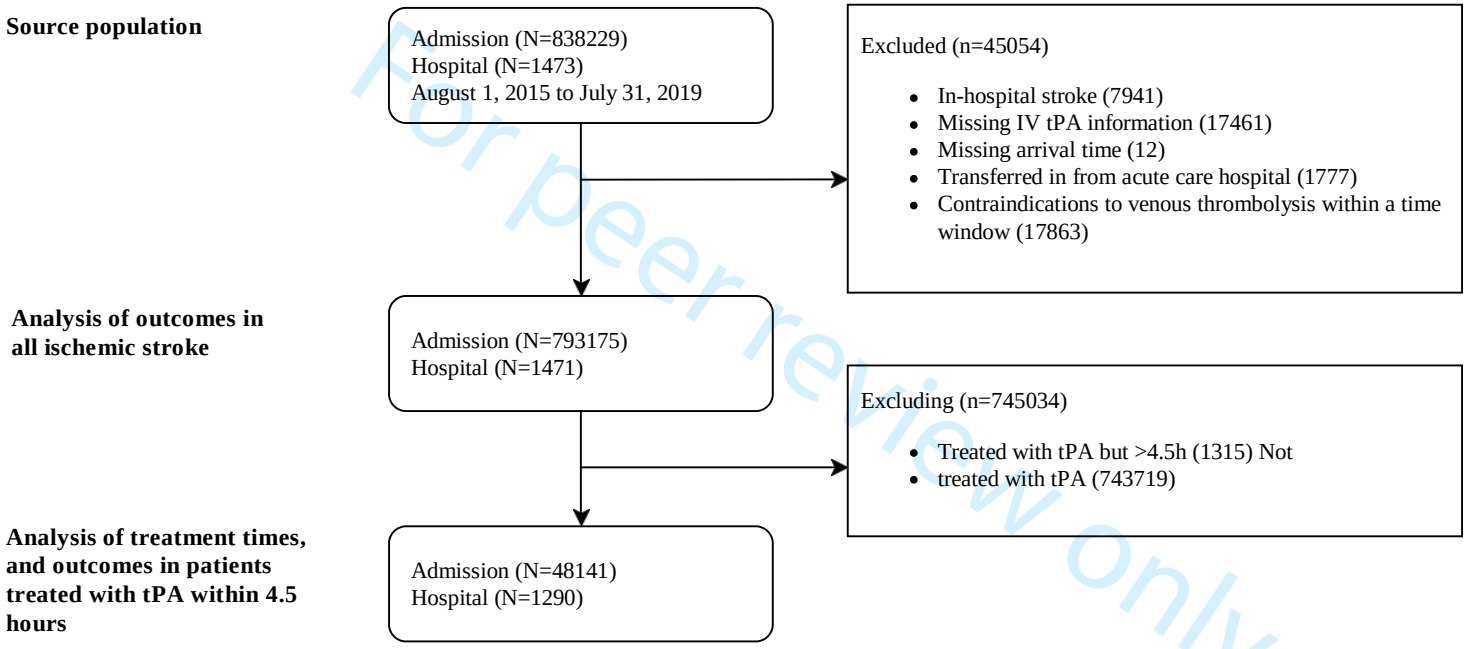
Figure legend

Figure 1. Study flowchart for patients identification.

Abbreviations: IV tPA, intravenous tissue plasminogen activator.



Supplemental Material

Table Ⅰ. Baseline characteristics of young and old ischemic stroke patients with IV tPA treatment

Baseline characteristics	Total (N=48141 [100%])	Young adults (< 50 years) (N=5044 [10.5%])	Old adults (≥50 years) (N=43097 [89.5%])	ASD*
Patient characteristics				
Age, years				
Mean±SD	65.2±12.1	43.4±5.6	67.8±9.8	305.7
Median (IQR)	66.0 (57.0–74.0)	45.0 (41.0–48.0)	68.0 (60.0–75.0)	
Male, n (%)	31456 (65.3)	3961 (78.5)	27495 (63.8)	32.9
Insurance status, n (%)				
UEBMI	15948 (33.1)	1609 (31.9)	14339 (33.3)	3.0
URBMI	9813 (20.4)	913 (18.1)	8900 (20.7)	6.6
NRCMS	16442 (34.2)	1495 (29.6)	14947 (34.7)	10.9
Self-pa	4083 (8.5)	813 (16.1)	3270 (7.6)	26.5
Other	1855 (3.9)	214 (4.2)	1641 (3.8)	2.0
Arrive mode, n (%)				
Ambulance	14364 (29.8)	1352 (26.8)	13012 (30.2)	7.5
Private car	21213 (44.1)	2240 (44.4)	18973 (44.0)	0.8
Taxi	2539 (5.3)	357 (7.1)	2182 (5.1)	8.4
Bicycle or tricycle	118 (0.2)	7 (0.1)	111 (0.3)	4.5
Helicopter	14 (0.0)	1 (0.0)	13 (0.0)	
Mobile stroke unit	31 (0.1)	4 (0.1)	27 (0.1)	0.0
Other	9862 (20.5)	1083 (21.5)	8779 (20.4)	2.7
Medical history, n (%)				
Previous stroke/TIA	12339 (25.6)	830 (16.5)	11509 (26.7)	25.0
CAD/prior MI	4737 (9.8)	240 (4.8)	4497 (10.4)	21.3
Diabetes	8477 (17.6)	516 (10.2)	7961 (18.5)	23.8
Peripheral vascular disease	628 (1.3)	31 (0.6)	597 (1.4)	8.0
Hypertension	28815 (59.9)	2283 (45.3)	26532 (61.6)	33.1
Smoking†	18835 (39.1)	2567 (50.9)	16268 (37.7)	26.8
Atrial fibrillation/flutter	5692 (11.8)	138 (2.7)	5554 (12.9)	38.7
Dyslipidemia	3195 (6.6)	351 (7.0)	2844 (6.6)	1.6
Carotid stenosis	454 (0.9)	22 (0.4)	432 (1.0)	7.2
Medication history, n (%)				
Anticoagulants	1779 (3.7)	150 (3.0)	1629 (3.8)	4.4
Hypoglycemic drugs	6404 (13.3)	330 (6.5)	6074 (14.1)	25.2
Antihypertensive drugs	20099 (41.8)	1302 (25.8)	18797 (43.6)	38.1
Antiplatelet drugs	7882 (16.4)	467 (9.3)	7415 (17.2)	23.5
Lipid lowering drugs	5614 (11.7)	382 (7.6)	5232 (12.1)	15.1
NIHSS score in hospital‡				
Mean±SD	7.9±6.5	6.4±5.3	8.0±6.6	26.7
Median (IQR)	6.0 (3.0–11.0)	5.0 (3.0–9.0)	6.0 (3.0–12.0)	

(Continued)

Table Ⅰ. Baseline characteristics of young and old ischemic stroke patients with IV tPA treatment

Baseline characteristics	Total (N=48141 [100%])	Young adults (< 50 years) (N=5044 [10.5%])	Old adults (≥50 years) (N=43097 [89.5%])	ASD*
Biochemical Indicators				
Glycated hemoglobin§,%				
Mean±SD	6.2±1.6	5.9±1.5	6.2±1.6	19.3
Median (IQR)	5.8 (5.3–6.4)	5.6 (5.1–6.0)	5.8 (5.3–6.5)	
BMI‖				
Mean±SD	23.6±4.2	24.9±5.5	23.4±4.0	31.2
Median (IQR)	23.4 (21.1–25.5)	24.4 (22.3–26.8)	23.2 (21.0–25.4)	
Homocysteine#, μmol/L				
Mean±SD	16.7±13.1	17.4±14.8	16.6±12.9	5.8
Median (IQR)	13.3 (10.0–18.5)	12.7 (9.6–18.9)	13.3 (10.1–18.5)	
Systolic blood pressure**, mmHg				
Mean±SD	152.5±23.8	148.3±24.6	153.0±23.7	19.5
Median (IQR)	150.0 (136.0–168.0)	145.0 (130.0–163.0)	151.0 (137.0–168.0)	
Diastolic blood pressure††, mmHg				
Mean±SD	87.6±14.5	92.1±16.1	87.1±14.2	32.9
Median (IQR)	87.0 (79.0–97.0)	90.0 (80.0–101.0)	86.0 (78.0–96.0)	
Hospital characteristics, n (%)				
Hospital level				
Secondary hospital	16479 (34.2)	1735 (34.4)	14744 (34.2)	0.4
Tertiary hospital	31662 (65.8)	3309 (65.6)	28353 (65.8)	0.4
Hospital region				
Eastern China	26410 (54.9)	2792 (55.4)	23618 (54.8)	1.2
Central China	15024 (31.2)	1630 (32.3)	13394 (31.1)	2.6
Western China	6707 (13.9)	622 (12.3)	6085 (14.1)	5.3

Abbreviations: IV tPA, intravenous recombinant tissue plasminogen activator; UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme; TIA, transient ischemic attack; CAD, coronary artery disease; MI, myocardial infarction; SD: standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; ASD, absolute standardized difference.

*: An absolute standardized difference >10 indicates significant differences between 2 groups.

†: Smoking: having smoking experience or behaviors.

‡: Information was missing for N = 2503 patients (5.2%).

§: Information was missing for N =4749 patients (9.9%), using the median for imputation.

‖: Information was missing for N =743 patients (1.5%), using the median for imputation.

#: Information was missing for N = 2682 patients (5.6%).

**: Information was missing for N =28 patients (0.1 %), using the median for imputation.

††: Information was missing for N =28 patients (0.1%), using the median for imputation.

Table Ⅱ. In-hospital outcomes in young(< 35 years) and old (≥35 years) ischemic stroke patients treated with IV tPA

Outcome	Total (N=48141 [100%])	young adults (< 35 years) (N=456 [0.9%])	old adults (≥35 years) (N=47685[99.1%])(REF)	Model	OR (95% CI)	P value
sICH	414 (0.9)	4 (0.9)	410 (0.9)	1	1.02 (0.38-2.74)	0.9678
				2	1.45 (0.54-3.94)	0.4612
				3	1.52 (0.56-4.13)	0.4136
In-hospital mortality	579 (1.2)	1 (0.2)	578 (1.2)	1	0.18 (0.03-1.28)	0.0861
				2	0.28 (0.04-2.01)	0.2066
				3	0.27 (0.04-1.97)	0.1953
Independent ambulation at discharge	26175 (54.4)	279 (61.2)	25896 (54.3)	1	1.33 (1.10-1.60)	0.0034
				2	1.09 (0.90-1.32)	0.384
				3	1.15 (0.92-1.42)	0.2173

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator ; OR, odds ratio.

Model 1: Logistic regression model without adjustment.

Model 2: Adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs,and lipid-lowering drugs.

Model 3: Adjusted for in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid-lowering drugs. Patients (N= 2503) with missing values on NIHSS score were not included in this analysis.

Table Ⅲ. In-hospital outcomes in young(< 45 years) and old (≥45 years) ischemic stroke patients treated with IV tPA

Outcome	Total (N=48141 [100%])	young adults (< 45 years) (N=2244 [4.7%])	old adults (⩾45 years) (N=45897[95.3%])(REF)	Model	OR (95% CI)	P value
sICH	414 (0.9)	8 (0.4)	406 (0.9)	1	0.40 (0.20-0.81)	0.0106
				2	0.54 (0.26-1.10)	0.0877
				3	0.44 (0.19-0.99)	0.048
In-hospital mortality	579 (1.2)	8 (0.4)	571 (1.2)	1	0.28 (0.14-0.57)	0.0004
				2	0.43 (0.21-0.87)	0.0197
				3	0.52 (0.26-1.07)	0.077
Independent ambulation at discharge	26175 (54.4)	1356 (60.4)	24819 (54.1)	1	1.30 (1.19-1.41)	<0.0001
				2	1.08 (0.98-1.18)	0.1082
				3	0.97 (0.88-1.08)	0.6096

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator ; OR, odds ratio.

Model 1: Logistic regression model without adjustment.

Model 2: Adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs,and lipid-lowering drugs.

Model 3: Adjusted for in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid-lowering drugs. Patients (N= 2503) with missing values on NIHSS score were not included in this analysis.

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Title Page

Thrombolysis, Time-to-Treatment and In-Hospital Outcomes Among Young Adults with Ischemic Stroke in China: Findings from a Nationwide Registry Study in China

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Key words: ischemic stroke, young stroke, thrombolysis, door-to-needle time

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ABSTRACT

Background and purpose We aimed to determine whether young adults (< 50 years) with acute ischemic stroke (AIS) are more likely to receive intravenous tissue plasminogen activator (IV tPA) and have shorter time to treatment than older stroke patients.

Methods We analyzed data from the Chinese Stroke Center Alliance (CSCA) registry for AIS patients hospitalized between August 2015 and July 2019. Patients were classified into two groups according to age: young adults (< 50 years of age) and older adults (≥ 50 years of age).

Results Of 793 175 patients with AIS admitted to 1471 hospitals, 9.1% (71 860) were young adults. Compared to older adults, a higher proportion of young adults received IV tPA among patients without contraindicaitons (7.2% vs. 6.1%, adjusted odds ratio [aOR] 1.13, 95% confidence interval [CI] 1.10-1.17) and among patients without contraindications and with onset-to-door time ≤3.5h (23.6 % vs. 19.3%, aOR 1.20, 95% CI 1.15-1.24). We did not observe differences in onset-to-needle time (median hours 2.7h) or door-to-needle time (DNT) (median minutes 60m) between young and older adults. The proportion of DNT≤30 minutes, DNT≤45 minutes, and DNT≤60 minutes in young and older IV tPA treated patients were 16.9% vs 18.8%, 30.2% vs 32.8% and 50.2% vs 54.2%, respectively. Compared to older adults, young adults treated with IV tPA had lower odds of in-hospital mortality (0.5% vs 1.3%,

aOR 0.54, 95% CI 0.35-0.82) and higher odds of independent ambulation at discharge (61.0% vs 53.6%, aOR 1.15, 95% CI 1.08-1.22), and the associations may be partly explained by stroke severity measured by NIHSS score.

Conclusion Young adults with AIS were more likely to receive IV tPA than older adults, though there was no difference between the two groups in time to treatment. Compared with older adults, young adults may had better in-hospital outcomes.

Key words: ischemic stroke, young stroke, thrombolysis, door-to-needle time

Strengths and limitations of this study

- We used data from a large-scale, nationwide, hospital-based, multicenter quality improvement initiative.
- Multiple regression models adjusted for different levels of covariates were used to check the robustness of the results ;
- Data on intra-arterial therapies, puncture times, door-to-imaging, and follow-up outcomes after discharge were not collected and reported.

ABBREVIATIONS

CSA: Chinese Stroke Association

CSCA: Chinese Stroke Center Alliance

QI: quality improvement

AIS: acute ischemic stroke

BMI: body mass index

mRS: modified Rankin Scale score

aOR: adjusted odds ratios

CI: confidence intervals

IV tPA: intravenous tissue plasminogen activator

IQR: interquartile range

NIHSS: National Institutes of Health Stroke Scale

DNT: door-to-needle time

sICH: symptomatic intracranial hemorrhage

INTRODUCTION

Stroke incidence among adults under 50 years of age has risen in recent years. [1-5]This creates a significant socioeconomic burden due to high healthcare costs and loss of labor productivity.[5,6] According to the 2019 Chinese Stroke Statistics, 81.9% of stroke patients had ischemic strokes,[7] of which young adults constituted 15–18%.[8] Given this trend, researchers must carefully consider the clinical features and best practices of treatment for strokes in young adults.[8]

Ischemic stroke is a common, preventable, and treatable disease that typically results from thrombotic or thromboembolic blockage of a cerebral artery.[9] Revascularization therapy plays a major role in the process of saving penumbral tissue from infarction.[10]Tissue plasminogen activator (tPA) is the main intravenous drug approved for the treatment of acute ischemic stroke.[11] Treatment of acute occlusive stroke with IV tPA is considered the most regular and important method when given within 4.5 hours of occlusion.[12,13] While epidemiological studies have been done in other countries regarding IV tPA treatment in young AIS patients, there is limited research on this topic in China.[13-17]

The purpose of this study was to compare the characteristics, IV tPA treatment rates, onset-to-needle time, door-to-needle time (DNT) and in-hospital outcomes of young (<50 years of age) and older (≥ 50 years of age) AIS patients in the Chinese Stroke

Center Alliance (CSCA). We hypothesized that young AIS patients would be treated more frequently with IV tPA, have shorter treatment time and better in-hospital outcomes compared to older adults.

METHODS

Data source

CSCA is a national, hospital-based, multicentre, voluntary, multifaceted intervention and continuous quality improvement initiative. The data coordinating center of CSCA resides at the China National Clinical Research Center for Neurological Diseases (NCRCND), Beijing Tiantan Hospital. [18] Trained personnel collected patient demographics, medical history, medications, DNT, and in-hospital outcomes, then entered this information into a database using a web-based Patient Management Tool (Medicine Innovation Research Center, Beijing, China). The tool is characterized by predefined logic features, range checks, and user alerts to identify a potentially invalid format or value entries and to optimize data quality at the time of entry. Training in the use of the tool was provided online and onsite for all users. However, data collected by hospitals were not independently audited by external chart review. In addition, The China National Clinical Research Center for Neurological Diseases serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for care quality feedback and research purposes. We abstracted 838

229 cases and identified 793 175 patients admitted with ischemic strokes from 2015 to 2019.

Study population

In the first stage, our analyses included patients admitted with AIS within 7 days of the onset of symptoms between August 1, 2015 and July 31, 2019 from 1473 hospitals. (supplemental material table Ⅰ)We excluded patients who had in-hospital strokes (n=7941, 0.95%), were missing IV tPA information (n=17461, 2.08%), had imprecise or undocumented arrival times (n=12), transferred in from an acute care hospital (n=1777, 0.212%), or had contraindications to venous thrombolysis within the time window (n=17863, 2.13%). This yielded a population of patients with ischemic strokes with indications for thrombolysis (n=793175). To analyze DNT and in-hospital outcomes of ischemic stroke, we excluded patients treated with IV tPA more than 4.5 hours after stroke onset (n=1315, 0.17%) and patients who were not treated with IV tPA (n=743719, 93.76%). This yielded a subset of the study population that consisted of 48141 AIS patients from 1290 hospitals (Figure 1).

Outcomes

The IV tPA treatment rate was assessed among two populations. First, IV tPA rate among patients without contraindications to thrombolytic therapy was calculated as the number of IV tPA cases divided by the total number of ischemic stroke cases without any contraindications to thrombolytic therapy. Then IV tPA rate among

patients without contraindication to thrombolytic therapy and with onset-to-door time ≤3.5h was calculated as the number of IV tPA cases divided by the total number of ischemic stroke cases without any contraindications to thrombolytic therapy and arrived at a hospital within 3.5 hours after stroke onset. The contraindications were defined according to guidelines for the early management of patients with acute ischemic stroke from the Heart Association/American Stroke Association and Chinese Society of Neurology. DNT was defined as the time between arrival at the emergency department (ED) and time of intravenous (IV) thrombolysis, and is an important metric in AIS treatment.[19,20] We analyzed DNT as a binary outcome three times with a different cut-off point each time (⩽30, ⩽45, or⩽60 minutes, respectively).

In-hospital outcomes included symptomatic intracranial hemorrhage (sICH), in-hospital mortality, and independent ambulation at discharge. sICH was defined as intracranial hemorrhage (ICH) within 36 hours of admission, documented by CT or MRI, with the treating physician's notes indicating clinical deterioration attributable to hemorrhage. Patients who were able to walk < 48 hours after hospital admission were considered to have independent ambulation at discharge.

Statistical analysis

Continuous variables with normal distribution were expressed as mean and SD, and those with skewed/non-normal distribution as medians and interquartile ranges (IQR). Categorical variables were summarised as frequencies and percentages. Because of

the large sample size, some statistically significant differences may not be clinically meaningful. We used absolute standardized differences (ASD) or Hodges–Lehmann estimator to compare differences in baseline characteristics between young and older adults independent of sample size. An ASD larger than 10% was considered meaningful imbalance.[21]

For outcomes such as IV tPA treatment and in-hospital outcomes, logistic regression models were performed to determine adjusted odds ratios (aORs) and 95% confidence intervals (CIs). Multivariable models with different level of adjustment were used to check the robustness of the results. Covariates in multivariable models including gender, insurance status, body mass index (BMI), medical history of prior stroke or transient ischemic attack (TIA), coronary artery disease (CAD) or prior myocardial infarction (MI), diabetes mellitus, hypertension, smoking status, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, medication history (hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid lowering drugs), and hospital grade.

There were few missing data for most variables, with the exceptions of the in-hospital NIHSS score (missing 19.4%), DNT (6.3%), glycated hemoglobin (10.6%) and BMI (1.6%). For continuous variables missing less than 15%, the median was used for imputation. Since the NIHSS score is a widely used tool for assessing stroke severity[22] and contributes important information to AIS prognosis, [23] sensitivity

analyses adjusting for the NIHSS score were conducted. In addition, results from multiple imputation were also provided.

All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA) and the %ggBaseline SAS macro.[24] Two-sided p-values of <0.05 were considered statistically significant.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Of 838 229 patients with AIS in the CSCA, 793 175 patients enrolled from 1471 hospitals were eligible for inclusion in this study. The median age was 67.0 years (range: 58.0-75.0) and 62.7% were men. A total of 261 760 (33.0%) patients had previous stroke/TIA, 69 810 (8.8%) had coronary artery disease or myocardial infarction (CAD/prior MI), 170 638 (21.5%) had diabetes, 510 928 (64.4%) had hypertension, 294 708 (37.2%) were smokers, and 40 231 (5.1%) had atrial fibrillation/flutter.

Clinical characteristics

A total of 71 860 (9.1%) patients were young adults (<50 years) and 721 315 (90.9%) were older adults (≥50 years). The mean age among young adults was 43.8±5.3 years

and 68.3±10.0 years among older adults. A larger proportion of the young adults were men (76.3% vs 61.3%) and did not have health insurance coverage (12.9% vs 5.7%), compared to older adults. Young adults had a lower prevalence of cardiovascular risk factors compared to older adults, including history of stroke or TIA (22.5% vs 34.0%), CAD/prior MI (4.0% vs 9.3%), diabetes mellitus (15.3% vs 22.1%), hypertension (53.9% vs 65.5%), and atrial fibrillation (1.2% vs 5.5%). Young adults had a lower rate of medication use than older adults, including hypoglycemic drugs (10.9% vs 17.4%), antihypertensive drugs (33.5% vs 48%), antiplatelet drugs (14.6% vs 21.5%), and lipid lowering drugs (11.4% vs 15.3%). However, diastolic blood pressure in young adults was significantly higher than that of older adults (mean±SD 92.3±16.1 vs mean±SD 86.5±13.5), and young adults had a statistically higher mean BMI than older adults (mean±SD 24.9±4.8 vs mean±SD 23.9±4.2). The proportion of young adults who smoked was also higher than that of older adults (49.9% vs 35.9%) (Table 1).

Table 1. Baseline characteristics of young and old ischemic stroke patients

Baseline characteristics	Total (N=793175 [100%])	Young adults (< 50 years) (N=71860 [9.1%])	Old adults (≥50 years) (N=721315 [90.9%])	ASD (%)/H-L Estimator*
Patient characteristics				
Age, years	66.1±12.0	43.8±5.3	68.3±10.0	306.1
Male , n (%)	496960 (62.7)	54850 (76.3)	442110 (61.3)	32.8
Insurance status, n (%)				
UEBMI	225940 (28.5)	19160 (26.7)	206780 (28.7)	4.5
URBMI	149839 (18.9)	12393 (17.2)	137446 (19.1)	4.9
NRCMS	333979 (42.1)	27587 (38.4)	306392 (42.5)	8.4
Self-pa	50727 (6.4)	9263 (12.9)	41464 (5.7)	25.0

Other	32690 (4.1)	3457 (4.8)	29233 (4.1)	3.4
Arrive mode, n (%)				
Ambulance	89484 (11.3)	7170 (10.0)	82314 (11.4)	4.5
Private car	372727 (47.0)	33340 (46.4)	339387 (47.1)	1.4
Taxi	68801 (8.7)	6743 (9.4)	62058 (8.6)	2.8
Bicycle or tricycle	7237 (0.9)	577 (0.8)	6660 (0.9)	1.1
Helicopter	338 (0.0)	27 (0.0)	311 (0.0)	
Mobile stroke unit	246 (0.0)	24 (0.0)	222 (0.0)	
Other	254342 (32.1)	23979 (33.4)	230363 (31.9)	3.2
Medical history, n (%)				
Previous stroke/TIA	261760 (33.0)	16197 (22.5)	245563 (34.0)	25.8
CAD/prior MI	69810 (8.8)	2906 (4.0)	66904 (9.3)	21.4
Diabetes	170638 (21.5)	10985 (15.3)	159653 (22.1)	17.5
Peripheral vascular disease	13512 (1.7)	718 (1.0)	12794 (1.8)	6.8
Hypertension	510928 (64.4)	38722 (53.9)	472206 (65.5)	23.8
Smoking†	294708 (37.2)	35848 (49.9)	258860 (35.9)	28.6
Atrial fibrillation/flutter	40231 (5.1)	886 (1.2)	39345 (5.5)	24.1
Dyslipidemia	60605 (7.6)	5861 (8.2)	54744 (7.6)	2.2
Carotid stenosis	10161 (1.3)	509 (0.7)	9652 (1.3)	6.0
Medication history, n (%)				
Anticoagulants	31326 (3.9)	2394 (3.3)	28932 (4.0)	3.7
Hypoglycemic drugs	133244 (16.8)	7802 (10.9)	125442 (17.4)	18.7
Antihypertensive drugs	370017 (46.7)	24065 (33.5)	345952 (48.0)	29.8
Antiplatelet drugs	165771 (20.9)	10482 (14.6)	155289 (21.5)	18.0
Lipid lowering drugs	118827 (15.0)	8171 (11.4)	110656 (15.3)	11.5
NIHSS score in hospital‡				
Mean±SD	4.8±5.2	4.0±4.5	4.9±5.3	18.3
Biochemical Indicators				
Glycated hemoglobin§, %				
Median (IQR)	5.8 (5.3–6.5)	5.7 (5.2–6.1)	5.8 (5.3–6.5)	11.4
BMI‖				
Mean±SD	24.0±4.3	24.9±4.8	23.9±4.2	22.2
Homocysteine#, μmol/L				
Median (IQR)	13.9 (10.4–19.1)	13.4 (10.0–19.0)	13.9 (10.5–19.1)	2.1
Systolic blood pressure**, mmHg				
Mean±SD	150.0±23.0	147.9±24.4	150.2±22.8	9.7
Diastolic blood pressure††, mmHg				
Mean±SD	87.0±13.9	92.3±16.1	86.5±13.5	39.0
Hospital characteristics, n (%)				
Hospital level				

Secondary hospital	303790 (38.3)	23993 (33.4)	279797 (38.8)	11.3
Tertiary hospital	489385 (61.7)	47867 (66.6)	441518 (61.2)	11.3
Hospital region				
Eastern China	365579 (46.1)	32744 (45.6)	332835 (46.1)	1.0
Central China	262618 (33.1)	24477 (34.1)	238141 (33.0)	2.3
Western China	164978 (20.8)	14639 (20.4)	150339 (20.8)	1.0

Abbreviations: UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme; TIA, transient ischemic attack; CAD, coronary artery disease; MI, myocardial infarction; SD: standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; ASD, absolute standardized difference.

*HL estimator, Hodges–Lehmann estimator; an absolute standardized difference (%) >10% indicates meaningful imbalance between 2 groups.

†Smoking: having smoking experience or behaviors.

‡Information was missing for N=154052 patients (19.4%).

§Information was missing for N=84393 patients (10.6%); median was used for imputation.

|| Information was missing for N=12698 patients (1.6%); median was used for imputation.

#Information was missing for N= 35781 patients (4.5%).

** Information was missing for N=245 patients (≈0.0%); median was used for imputation.

††Information was missing for N=251 patients (≈0.0%); median was used for imputation.

IV tPA treatment rates

Young adults were treated more frequently with IV tPA than older adults among patients without contraindications to thrombolysis (7.2% vs 6.1%, aOR 1.13, 95% CI 1.10-1.17) and among patients without contraindication and with onset-to-door time ≤ 3.5h (23.6 % vs. 19.3%, aOR 1.20, 95% CI 1.15-1.24). Data from sensitivity analyses showed consistent results.(Table 2)

Table 2. Multivariable analysis of IV tPA treatment by age group

Treantment	Rate of IV-tPA	aOR (95% CI) from model 1	aOR (95% CI) from model 2	aOR (95% CI) from model 3	aOR (95% CI) from model 4
IV tPA among patients without contraindications	49456/793175 (6.2)				
Young adults	5181/71860 (7.2)	1.19 (1.15-1.22)	1.13 (1.10-1.17)	1.20 (1.16-1.24)	1.19(1.15-1.22)
Old adults	44275/721315 (6.1)	1.00	1.00	1.00	1.00
IV tPA among patients	45842/232905(19.7)				

without contraindication and with onset-to-door time ≤3.5h					
Young adults	4768/20191 (23.6)	1.29 (1.25-1.34)	1.20 (1.15-1.24)	1.24 (1.20-1.29)	1.23(1.19-1.28)
Old adults	41074/212714 (19.3)	1.00	1.00	1.00	1.00

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator; OR, odds ratio.

Model 1: Logistic regression model without adjustment.

Model 2: adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated, hemoglobin, diastolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, lipid-lowering drugs, and hospital level.

Model 3: adjusted for were in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, lipid-lowering drugs, and hospital level. Patients (N= 154052) with missing values on NIHSS score were not included in this analysis.

model 4: results from multiple imputation.

Treatment time

While young adults were more likely to receive IV tPA, there was no significant difference in onset-to-needle time (median 2.7 hours, IQR 2.0–3.5 for both groups) and DNT (median 60.0 minutes, IQR 42.0-90.0 vs median 60.0 minutes, IQR 36.0-84.0) among young and older adults. DNT was also analyzed as a binary outcome at three levels: DNT ≤30, DNT ≤45, and DNT ≤60 minutes. There were no significant differences between the two groups on any DNT level (16.9% vs 18.8%; 30.2% vs 32.8%; 50.2% vs 54.2%) (Table 3).

Table 3. Treatment time in young and old ischemic stroke patients treated with IV tPA

Measures	Total (N=48141 [100%])	Young adults (< 50 years) (N=5044 [10.5%])	Old adults (≥50 years) (N=43097 [89.5%])	ASD (%)/H-L Estimator *
Onset-to-needle time†,h				
Median (IQR)	2.7 (2.0–3.5)	2.7 (2.0–3.5)	2.7 (2.0–3.5)	
DNT‡ ,min				
Median (IQR)	60.0 (36.0–84.0)	60.0 (42.0–90.0)	60.0 (36.0–84.0)	9.7
Treatment time				
DNT≤30 minutes	8938 (18.6)	850 (16.9)	8088 (18.8)	5.0
DNT≤45 minutes	15637 (32.5)	1521 (30.2)	14116 (32.8)	5.6
DNT≤60 minutes	25884 (53.8)	2531 (50.2)	23353 (54.2)	8.0

Abbreviations: CI=confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator; DNT, door-to-needle time; ASD, absolute standardized difference.

*HL estimator, Hodges–Lehmann estimator; an absolute standardized difference (%) >10% indicates meaningful imbalance between 2 groups.

†Onset-to-needle time was missing for 3818 (7.9%) patients, with 431(8.5%) in age <50 and 3387(7.9%) in ≥ 50 groups.

‡DNT was missing for 3027(6.3%) patients, with 342 (6.8%) in age <50 and 2685(6.2%) in ≥ 50 groups.

In-hospital outcomes

In-hospital outcomes including sICH, in-hospital mortality, and independent ambulation at discharge were summarized in Table 4. Multiple logistic regression with adjustments of unbalanced covariates (ASD% >10% in Supplemental Table Ⅱ) showed that young adults had non-significantly lower rates of sICH (0.5% vs 0.9%, aOR=0.74, 95% CI 0.49-1.11) than older adults. However, young adults had significantly lower rates of in-hospital mortality (0.5% vs 1.3%, aOR=0.54, 95% CI 0.35-0.82) and were more likely to be independently ambulating at discharge (61.0% vs 53.6%, aOR=1.15, 95% CI 1.08-1.22).

In sensitivity analyses adjusted for NIHSS scores, young adults had non-significantly lower odds of sICH (aOR=0.77, 95%CI 0.5-1.18), in-hospital mortality (aOR=0.70, 95%CI 0.46-1.09), and a neutral association with independent ambulation at discharge (aOR=1.00, 95% CI 0.93-1.08). Sensitivity analysis using different age cut-off point (<35 years and ≥ 35 years) showed consistent results with primary analysis (supplemental material table Ⅲ). But when we used another age cut of point (<45 years and ≥45 years), we had a lower sICH rate (aOR=0.44, 95% CI 0.19-0.99) in the young group (supplemental material table Ⅳ).

Table 4. In-hospital outcomes in young and old ischemic stroke patients treated with IV tPA

Outcome	Rate of outcomes	aOR (95% CI) from model 1	aOR (95% CI) from model 2	aOR (95% CI) from model 3	aOR (95% CI) from model 4
sICH	414/48141 (0.9)				
Young adults	26/5044(0.5)	0.57 (0.38-0.85)	0.74 (0.49-1.11)	0.77 (0.5-1.18)	0.79(0.52-1.20)
Old adults	388/43097(0.9)	1.00	1.00	1.00	1.00
In-hospital mortality	579/48141 (1.2)				
Young adults	24/5044(0.5)	0.37 (0.24-0.55)	0.54 (0.35-0.82)	0.70 (0.46-1.09)	0.65(0.43-1.00)
Old adults	555/43097(1.3)	1.00	1.00	1.00	1.00
Independent ambulation at discharge	26175/48141 (54.4)				
Young adults	3079/5044(61.0)	1.36 (1.28-1.44)	1.15 (1.08-1.22)	1.00 (0.93-1.08)	1.02(0.96-1.10)
Old adults	23096/43097(53.6)	1.00	1.00	1.00	1.00

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator; OR, odds ratio.

Model 1: Logistic regression model without adjustment.

Model 2: Adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs,and lipid-lowering drugs.

Model 3: Adjusted for in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid-lowering drugs. Patients (N= 2503) with missing values on NIHSS score were not included in this analysis.

model 4: results from multiple imputation.

DISCUSSION

In this hospital-based observational study of 793 175 AIS patients, we found that young adults (<50 years of age) were more likely to be treated with IV tPA than older adults (7.2% vs 6.1%), which was consistent with our hypothesis. Our study demonstrated that young stroke patients had fewer comorbidities (previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, and atrial fibrillation/flutter) at baseline, which may compel providers to feel more secure in administering IV tPA to this group of patients. Even though we did not observe a difference in DNT between age groups, we found that young adults had more favorable in-hospital outcomes than older adults, including lower odds of sICH, in-hospital mortality and higher odds of independent ambulation at discharge. However, after adjusting for NIHSS scores, the differences were not significant. Therefore, the benefit among young adults may be explained by stroke severity measured by NIHSS score.

We chose 50 as the cut-off age because several important international studies on thrombolytic therapy in young people also set the cut-off age at 50.[15,16] Using the same cut-off age value would benefit the comparison with other studies and also have advantages for potential systematic review and meta-analysis.

IV tPA thrombolytic therapy is considered to be the standard therapy in patients with acute ischemic stroke. However, its use has been studied primarily in adults over age

50.[16] Given increasing evidence in the literature that thrombolytic therapy rarely causes hemorrhages in patients with stroke-mimicking conditions, providers may also feel more comfortable administering IV tPA to young adults when it is uncertain whether a stroke or a stroke mimic had occurred.[25] Our research also supports this conclusion. Young adults had similar time to treatment and were more likely to be treated than older adults, which may reflect increased awareness among patients and clinicians that stroke is a potentially fatal disease affecting people of all ages.

The relationship between time to treatment and mortality was first recognized in clinical studies.[26,27] The importance of this metric was reemphasized in the 2004 American College of Cardiology/American Heart Association practice guidelines, which stated that DNT targets "should not be perceived as an average performance standard but as a goal that an early treatment system in every hospital should seek for every appropriate patient".[28] Consistent with a prior analysis of SITS-ISTR showing no difference in median door-to-needle times between patients 18 to 50 and >50 years of age, there was also not an obvious differentiation in treatment among young or older adults in our study.[15] However, a prior study by Dodds and colleagues found that young adults (18-40 years) with AIS were more likely to experience a delay in evaluation and treatment.[13] Our definition of young adults (age <50 years) differs from theirs (age 18–40 years) and is more applicable in China, which may also explain why we did not find differences in treatment times between the two groups.[29]

Another explanation for the lack of differences in treatment times between the two groups may be that DNT mainly depends on hospital level and treatment process rather than age.

In our study, we observed a higher rate of sICH and in-hospital mortality among older adults treated with IV tPA, though the difference was not significant adjusted for NIHSS scores. We cannot entirely separate young age from lower NIHSS score, as young patients are highly correlated with lower NIHSS scores in clinical practise (4.0±4.5 vs. 4.9±5.3, the Rank Biserial correlation coefficient in this study is 0.10, $p<0.001$). Therefore, the associations may be partly explained by stroke severity measured by NIHSS score. Although we do not find significant differences between these two groups, we do see a trend towards better outcomes in young people. One possible explanation is that younger stroke patients have fewer comorbidities in their medical history, such as previous stroke or TIA, CAD/MI, diabetes mellitus, hypertension, and atrial fibrillation, as well as milder strokes, all of which are associated with better outcomes.[30] Other factors favoring recovery in young stroke patients include greater brain plasticity and more robust family and social support.[31]

There are several limitations in our study. Since hospital participation in the CSCA is voluntary, participating hospitals are more likely to be larger, tertiary centers with a myriad of resources that smaller hospitals do not have access to. We recognize that

findings from CSCA may not be generalizable to AIS patients admitted to hospitals outside of the CSCA. Second, we did not report data on intra-arterial (IA) therapies and puncture times because only a very small number of patients in our study received thrombectomy. We also did not have door-to-imaging data to support the study and there was a relatively high proportion of missing DNT values (6.3% overall, 6.8% in young and 6.2% in older patients). However, we did not observe a significant difference in DNTs between young and older AIS patients. Lastly, although we provided some possible explanation for the differences between young and old adults group, further researches are needed to explorer the detailed mechanism.

CONCLUSION

In summary, young adults with AIS are more likely to receive IV tPA than older adults, but there is no difference between the two groups in time to treatment. Young adults may have better in-hospital outcomes compared with older adults, suggesting favorable effects of treatment with IV tPA.

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CONTRIBUTORS

Conceived and led the project: XZ, YW, ZL, YW and YJ. Conception and design: HW, HG, YW and YJ. Data collection and analysis: HW, XY, CW, HG and QZ. Interpret the data: LL, XM and HL. Drafting the article and revising the content: HW, HG, CL, JY and ZL. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

None declared.

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL

This study received approval from the Institutional Review Board/Ethics Committee of Beijing Tiantan Hospital, Capital Medical University with approval number KY 2018-061-02. Participating hospitals received research approval to collect data in CSCA without requiring individual patient informed consent under the common rule or a waiver of authorisation and exemption from their Institutional Review Board.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request and after clearance by the local ethics committee.

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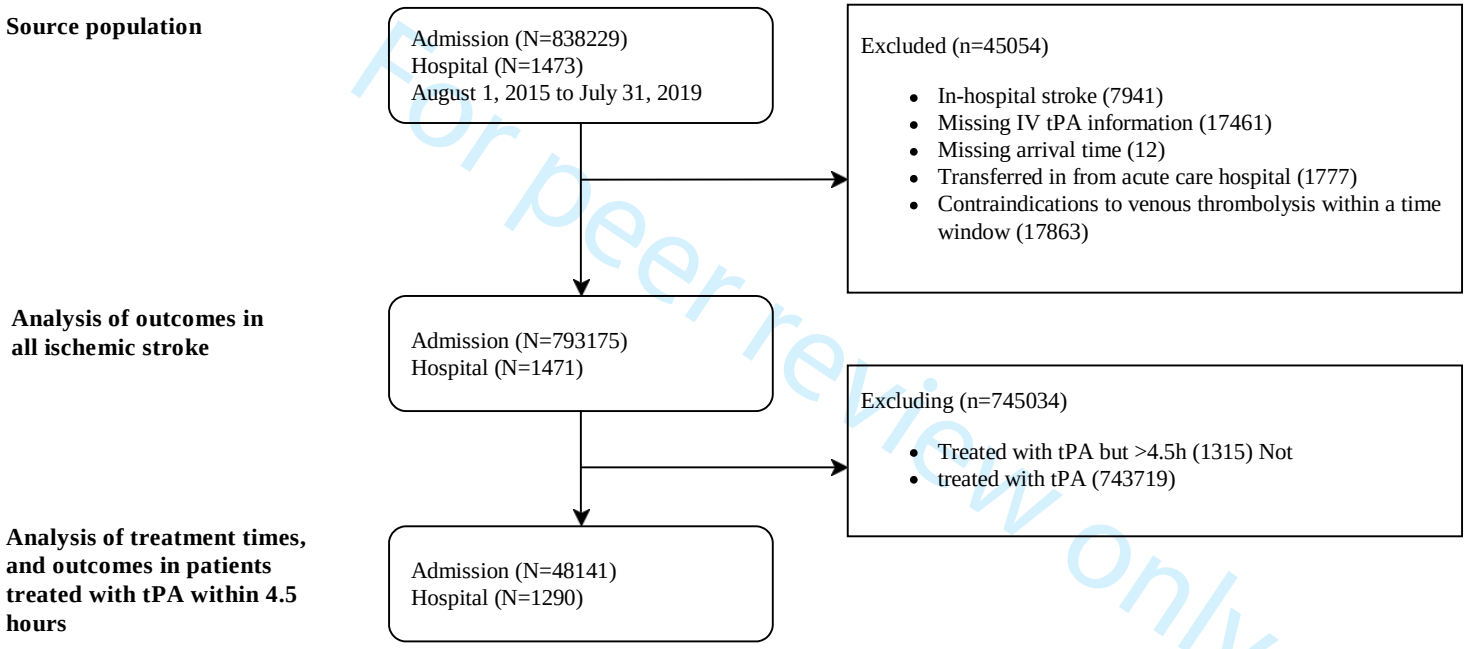
Figure legend

Figure 1. Study flowchart for patients identification.
Abbreviations: IV tPA, intravenous tissue plasminogen activator.



Supplemental Material

Table Ⅰ. Distribution of hospitals in our study

Hospital region	Province or Municipality	Number of hospitals (N=676)	Hospital region	Province or Municipality	Number of hospitals (N=401)	Hospital region	Province or Municipality	Number of hospitals (N=394)
Eastern China	Beijing	16	Central China	Jilin	32	Western China	Inner Mongoria	23
	Tianjin	13		Heilongjiang	41		Guangxi	49
	Hebei	143		Shanxi	44		Chongqing	16
	Liaoning	53		Anhui	29		Sichuan	125
	Shanghai	16		Jiangxi	25		Guizhou	23
	Jiangsu	93		Henan	157		Yunnan	52
	Zhejiang	86		Hubei	39		Tibet	1
	Fujian	52		Hunan	34		Shaanxi	41
	Shandong	81					Gansu	33
	Guangdong	113					Qinghai	9
	Hainan	10					Ningxia	5
							Xinjiang	17

Table Ⅱ. Baseline characteristics of young and old ischemic stroke patients with IV tPA treatment

Baseline characteristics	Total (N=48141 [100%])	Young adults (< 50 years) (N=5044 [10.5%])	Old adults (≥50 years) (N=43097 [89.5%])	ASD*
Patient characteristics				
Age, years				
Mean±SD	65.2±12.1	43.4±5.6	67.8±9.8	305.7
Male, n (%)	31456 (65.3)	3961 (78.5)	27495 (63.8)	32.9
Insurance status, n (%)				
UEBMI	15948 (33.1)	1609 (31.9)	14339 (33.3)	3.0
URBMI	9813 (20.4)	913 (18.1)	8900 (20.7)	6.6
NRCMS	16442 (34.2)	1495 (29.6)	14947 (34.7)	10.9
Self-pa	4083 (8.5)	813 (16.1)	3270 (7.6)	26.5
Other	1855 (3.9)	214 (4.2)	1641 (3.8)	2.0
Arrive mode, n (%)				
Ambulance	14364 (29.8)	1352 (26.8)	13012 (30.2)	7.5
Private car	21213 (44.1)	2240 (44.4)	18973 (44.0)	0.8
Taxi	2539 (5.3)	357 (7.1)	2182 (5.1)	8.4
Bicycle or tricycle	118 (0.2)	7 (0.1)	111 (0.3)	4.5
Helicopter	14 (0.0)	1 (0.0)	13 (0.0)	
Mobile stroke unit	31 (0.1)	4 (0.1)	27 (0.1)	0.0
Other	9862 (20.5)	1083 (21.5)	8779 (20.4)	2.7
Medical history, n (%)				
Previous stroke/TIA	12339 (25.6)	830 (16.5)	11509 (26.7)	25.0
CAD/prior MI	4737 (9.8)	240 (4.8)	4497 (10.4)	21.3
Diabetes	8477 (17.6)	516 (10.2)	7961 (18.5)	23.8
Peripheral vascular disease	628 (1.3)	31 (0.6)	597 (1.4)	8.0
Hypertension	28815 (59.9)	2283 (45.3)	26532 (61.6)	33.1
Smoking†	18835 (39.1)	2567 (50.9)	16268 (37.7)	26.8
Atrial fibrillation/flutter	5692 (11.8)	138 (2.7)	5554 (12.9)	38.7
Dyslipidemia	3195 (6.6)	351 (7.0)	2844 (6.6)	1.6
Carotid stenosis	454 (0.9)	22 (0.4)	432 (1.0)	7.2
Medication history, n (%)				
Anticoagulants	1779 (3.7)	150 (3.0)	1629 (3.8)	4.4
Hypoglycemic drugs	6404 (13.3)	330 (6.5)	6074 (14.1)	25.2
Antihypertensive drugs	20099 (41.8)	1302 (25.8)	18797 (43.6)	38.1
Antiplatelet drugs	7882 (16.4)	467 (9.3)	7415 (17.2)	23.5
Lipid lowering drugs	5614 (11.7)	382 (7.6)	5232 (12.1)	15.1
NIHSS score in hospital‡				
Mean±SD	7.9±6.5	6.4±5.3	8.0±6.6	26.7

(Continued)

Table Ⅱ. Baseline characteristics of young and old ischemic stroke patients with IV tPA treatment

Baseline characteristics	Total (N=48141 [100%])	Young adults (< 50 years) (N=5044 [10.5%])	Old adults (≥50 years) (N=43097 [89.5%])	ASD*
Biochemical Indicators				
Glycated hemoglobin§,%				
Median (IQR)	5.8 (5.3–6.4)	5.6 (5.1–6.0)	5.8 (5.3–6.5)	
BMI‖				
Mean±SD	23.6±4.2	24.9±5.5	23.4±4.0	31.2
Homocysteine#, μmol/L				
Median (IQR)	13.3 (10.0–18.5)	12.7 (9.6–18.9)	13.3 (10.1–18.5)	
Systolic blood pressure**, mmHg				
Mean±SD	152.5±23.8	148.3±24.6	153.0±23.7	19.5
Diastolic blood pressure††, mmHg				
Mean±SD	87.6±14.5	92.1±16.1	87.1±14.2	32.9
Hospital characteristics, n (%)				
Hospital level				
Secondary hospital	16479 (34.2)	1735 (34.4)	14744 (34.2)	0.4
Tertiary hospital	31662 (65.8)	3309 (65.6)	28353 (65.8)	0.4
Hospital region				
Eastern China	26410 (54.9)	2792 (55.4)	23618 (54.8)	1.2
Central China	15024 (31.2)	1630 (32.3)	13394 (31.1)	2.6
Western China	6707 (13.9)	622 (12.3)	6085 (14.1)	5.3

Abbreviations: IV tPA, intravenous recombinant tissue plasminogen activator; UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme; TIA, transient ischemic attack; CAD, coronary artery disease; MI, myocardial infarction; SD: standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; ASD, absolute standardized difference.

*: An absolute standardized difference% >10% indicates meaningful imbalance between 2 groups.

†: Smoking: having smoking experience or behaviors.

‡: Information was missing for N = 2503 patients (5.2%).

§: Information was missing for N =4749 patients (9.9%), using the median for imputation.

‖: Information was missing for N =743 patients (1.5%), using the median for imputation.

#: Information was missing for N = 2682 patients (5.6%).

**: Information was missing for N =28 patients (0.1 %), using the median for imputation.

††: Information was missing for N =28 patients (0.1%), using the median for imputation.

Table Ⅲ. In-hospital outcomes in young(< 35 years) and old (≥35 years) ischemic stroke patients treated with IV tPA

Outcome	Total (N=48141 [100%])	young adults (< 35 years) (N=456 [0.9%])	old adults (≥35 years) (N=47685[99.1%])(REF)	Model	OR (95% CI)	P value
sICH	414 (0.9)	4 (0.9)	410 (0.9)	1	1.02 (0.38-2.74)	0.9678
				2	1.45 (0.54-3.94)	0.4612
				3	1.52 (0.56-4.13)	0.4136
In-hospital mortality	579 (1.2)	1 (0.2)	578 (1.2)	1	0.18 (0.03-1.28)	0.0861
				2	0.28 (0.04-2.01)	0.2066
				3	0.27 (0.04-1.97)	0.1953
Independent ambulation at discharge	26175 (54.4)	279 (61.2)	25896 (54.3)	1	1.33 (1.10-1.60)	0.0034
				2	1.09 (0.90-1.32)	0.384
				3	1.15 (0.92-1.42)	0.2173

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator ; OR, odds ratio.

Model 1: Logistic regression model without adjustment.

Model 2: Adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs,and lipid-lowering drugs.

Model 3: Adjusted for in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid-lowering drugs. Patients (N= 2503) with missing values on NIHSS score were not included in this analysis.

Table Ⅳ. In-hospital outcomes in young(< 45 years) and old (≥45 years) ischemic stroke patients treated with IV tPA

Outcome	Total (N=48141 [100%])	young adults (< 45 years) (N=2244 [4.7%])	old adults (⩾45 years) (N=45897[95.3%])(REF)	Model	OR (95% CI)	P value
sICH	414 (0.9)	8 (0.4)	406 (0.9)	1	0.40 (0.20-0.81)	0.0106
				2	0.54 (0.26-1.10)	0.0877
				3	0.44 (0.19-0.99)	0.048
In-hospital mortality	579 (1.2)	8 (0.4)	571 (1.2)	1	0.28 (0.14-0.57)	0.0004
				2	0.43 (0.21-0.87)	0.0197
				3	0.52 (0.26-1.07)	0.077
Independent ambulation at discharge	26175 (54.4)	1356 (60.4)	24819 (54.1)	1	1.30 (1.19-1.41)	<0.0001
				2	1.08 (0.98-1.18)	0.1082
				3	0.97 (0.88-1.08)	0.6096

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator ; OR, odds ratio.

Model 1: Logistic regression model without adjustment.

Model 2: Adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs,and lipid-lowering drugs.

Model 3: Adjusted for in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid-lowering drugs. Patients (N= 2503) with missing values on NIHSS score were not included in this analysis.

STROBE Statement—checklist of items that should be included in reports of observational studies

Section/item	Item No	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page1,3,4	Title,Abstract/Para1-2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page3-4	Abstract/Para2-4
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Page7	Introduction/Para1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	Page7-8	Introduction/Para3
Methods				
Study design	4	Present key elements of study design early in the paper	Page8-9	Methods/Para1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page9-10	Methods/Para2-4
Participants	6	(a) ***Cohort study***—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ***Case-control study***—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants	Page8-10	Methods/Para1-4
		(b) ***Cohort study***—For matched studies, give matching criteria and number of exposed and unexposed ***Case-control study***—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page9-10	Methods/Para3-4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page8-11	Methods/Para1-6
Bias	9	Describe any efforts to address potential sources of bias	Page10-12	Methods/Para5-7
Study size	10	Explain how the study size was arrived at	Page8-9	Methods/Para1-2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page10-11	Methods/Para5

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page10-12	Methods/Para5-8
		(b) Describe any methods used to examine subgroups and interactions	Page10-11	Methods/Para5
		(c) Explain how missing data were addressed	Page11-12	Methods/Para7
		(d) ***Cohort study***—If applicable, explain how loss to follow-up was addressed ***Case-control study***—If applicable, explain how matching of cases and controls was addressed ***Cross-sectional study***—If applicable, describe analytical methods taking account of sampling strategy	Page11-12	Methods/Para7
		(e) Describe any sensitivity analyses	Page11-12	Methods/Para7
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page12	Results/Para1
		(b) Give reasons for non-participation at each stage		Figure1
		(c) Consider use of a flow diagram		Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page12-15	Results/Para1-2
		(b) Indicate number of participants with missing data for each variable of interest	Page15	Results/table1
		(c) ***Cohort study***—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	***Cohort study***—Report numbers of outcome events or summary measures over time	Page15-19	Results/Para3-6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page15-19	Results/Para3-6
		(b) Report category boundaries when continuous variables were categorized	Page15-17	Results/Para3-6
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page15-19	Results/Para3-6
Discussion				
Key results	18	Summarise key results with reference to study objectives	Page20-22	Discussion/Para1-5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page22-23	Discussion/Para6

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page19-22	Discussion/Para2-5
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page23	Discussion/Para6
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page24	Funding

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Thrombolysis, Time-to-Treatment and In-Hospital Outcomes Among Young Adults with Ischemic Stroke in China: Findings from a Nationwide Registry Study in China

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Title Page

Thrombolysis, Time-to-Treatment and In-Hospital Outcomes Among Young Adults with Ischemic Stroke in China: Findings from a Nationwide Registry Study in China

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Key words: ischemic stroke, young stroke, thrombolysis, door-to-needle time

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ABSTRACT

Background and purpose We aimed to determine whether young adults (< 50 years) with acute ischemic stroke (AIS) are more likely to receive intravenous tissue plasminogen activator (IV tPA) and have shorter time to treatment than older stroke patients.

Methods We analyzed data from the Chinese Stroke Center Alliance (CSCA) registry for AIS patients hospitalized between August 2015 and July 2019. Patients were classified into two groups according to age: young adults (< 50 years of age) and older adults (≥ 50 years of age).

Results Of 793 175 patients with AIS admitted to 1471 hospitals, 9.1% (71 860) were young adults. Compared to older adults, a higher proportion of young adults received IV tPA among patients without contraindicaitons (7.2% vs. 6.1%, adjusted odds ratio [aOR] 1.13, 95% confidence interval [CI] 1.10-1.17) and among patients without contraindications and with onset-to-door time ≤3.5h (23.6 % vs. 19.3%, aOR 1.20, 95% CI 1.15-1.24). We did not observe differences in onset-to-needle time (median hours 2.7h) or door-to-needle time (DNT) (median minutes 60m) between young and older adults. The proportion of DNT≤30 minutes, DNT≤45 minutes, and DNT≤60 minutes in young and older IV tPA treated patients were 16.9% vs 18.8%, 30.2% vs 32.8% and 50.2% vs 54.2%, respectively. Compared to older adults, young adults treated with IV tPA had lower odds of in-hospital mortality (0.5% vs 1.3%,

aOR 0.54, 95% CI 0.35-0.82) and higher odds of independent ambulation at discharge (61.0% vs 53.6%, aOR 1.15, 95% CI 1.08-1.22), and the associations may be partly explained by stroke severity measured by NIHSS score.

Conclusion Young adults with AIS were more likely to receive IV tPA than older adults, though there was no difference between the two groups in time to treatment. Compared with older adults, young adults may had better in-hospital outcomes.

Key words: ischemic stroke, young stroke, thrombolysis, door-to-needle time

Strengths and limitations of this study

- We used data from a large-scale, nationwide, hospital-based, multicenter quality improvement initiative.
- Multiple regression models adjusted for different levels of covariates were used to check the robustness of the results ;
- Data on intra-arterial therapies, puncture times, door-to-imaging, and follow-up outcomes after discharge were not collected and reported.

ABBREVIATIONS

CSA: Chinese Stroke Association

CSCA: Chinese Stroke Center Alliance

QI: quality improvement

AIS: acute ischemic stroke

BMI: body mass index

mRS: modified Rankin Scale score

aOR: adjusted odds ratios

CI: confidence intervals

IV tPA: intravenous tissue plasminogen activator

IQR: interquartile range

NIHSS: National Institutes of Health Stroke Scale

DNT: door-to-needle time

sICH: symptomatic intracranial hemorrhage

INTRODUCTION

Stroke incidence among adults under 50 years of age has risen in recent years. [1-5]This creates a significant socioeconomic burden due to high healthcare costs and loss of labor productivity.[5,6] According to the 2019 Chinese Stroke Statistics, 81.9% of stroke patients had ischemic strokes,[7] of which young adults constituted 15–18%.[8] Given this trend, researchers must carefully consider the clinical features and best practices of treatment for strokes in young adults.[8]

Ischemic stroke is a common, preventable, and treatable disease that typically results from thrombotic or thromboembolic blockage of a cerebral artery.[9] Revascularization therapy plays a major role in the process of saving penumbral tissue from infarction.[10]Tissue plasminogen activator (tPA) is the main intravenous drug approved for the treatment of acute ischemic stroke.[11] Treatment of acute occlusive stroke with IV tPA is considered the most regular and important method when given within 4.5 hours of occlusion.[12,13] While epidemiological studies have been done in other countries regarding IV tPA treatment in young AIS patients, there is limited research on this topic in China.[13-17]

The purpose of this study was to compare the characteristics, IV tPA treatment rates, onset-to-needle time, door-to-needle time (DNT) and in-hospital outcomes of young (<50 years of age) and older (≥ 50 years of age) AIS patients in the Chinese Stroke

Center Alliance (CSCA). We hypothesized that young AIS patients would be treated more frequently with IV tPA, have shorter treatment time and better in-hospital outcomes compared to older adults.

METHODS

Data source

CSCA is a national, hospital-based, multicentre, voluntary, multifaceted intervention and continuous quality improvement initiative. The data coordinating center of CSCA resides at the China National Clinical Research Center for Neurological Diseases (NCRCND), Beijing Tiantan Hospital. [18] Trained personnel collected patient demographics, medical history, medications, DNT, and in-hospital outcomes, then entered this information into a database using a web-based Patient Management Tool (Medicine Innovation Research Center, Beijing, China). The tool is characterized by predefined logic features, range checks, and user alerts to identify a potentially invalid format or value entries and to optimize data quality at the time of entry. Training in the use of the tool was provided online and onsite for all users. However, data collected by hospitals were not independently audited by external chart review. In addition, The China National Clinical Research Center for Neurological Diseases serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for care quality feedback and research purposes. We abstracted 838

229 cases and identified 793 175 patients admitted with ischemic strokes from 2015 to 2019.

Study population

In the first stage, our analyses included patients admitted with AIS within 7 days of the onset of symptoms between August 1, 2015 and July 31, 2019 from 1473 hospitals. (supplemental material table Ⅰ)We excluded patients who had in-hospital strokes (n=7941, 0.95%), were missing IV tPA information (n=17461, 2.08%), had imprecise or undocumented arrival times (n=12), transferred in from an acute care hospital (n=1777, 0.212%), or had contraindications to venous thrombolysis within the time window (n=17863, 2.13%). This yielded a population of patients with ischemic strokes with indications for thrombolysis (n=793175). To analyze DNT and in-hospital outcomes of ischemic stroke, we excluded patients treated with IV tPA more than 4.5 hours after stroke onset (n=1315, 0.17%) and patients who were not treated with IV tPA (n=743719, 93.76%). This yielded a subset of the study population that consisted of 48141 AIS patients from 1290 hospitals (Figure 1).

Outcomes

The IV tPA treatment rate was assessed among two populations. First, IV tPA rate among patients without contraindications to thrombolytic therapy was calculated as the number of IV tPA cases divided by the total number of ischemic stroke cases without any contraindications to thrombolytic therapy. Then IV tPA rate among

patients without contraindication to thrombolytic therapy and with onset-to-door time ≤3.5h was calculated as the number of IV tPA cases divided by the total number of ischemic stroke cases without any contraindications to thrombolytic therapy and arrived at a hospital within 3.5 hours after stroke onset. The contraindications were defined according to guidelines for the early management of patients with acute ischemic stroke from the Heart Association/American Stroke Association and Chinese Society of Neurology. DNT was defined as the time between arrival at the emergency department (ED) and time of intravenous (IV) thrombolysis, and is an important metric in AIS treatment.[19,20] We analyzed DNT as a binary outcome three times with a different cut-off point each time (⩽30, ⩽45, or⩽60 minutes, respectively).

In-hospital outcomes included symptomatic intracranial hemorrhage (sICH), in-hospital mortality, and independent ambulation at discharge. sICH was defined as intracranial hemorrhage (ICH) within 36 hours of admission, documented by CT or MRI, with the treating physician's notes indicating clinical deterioration attributable to hemorrhage. Patients who were able to walk < 48 hours after hospital admission were considered to have independent ambulation at discharge.

Statistical analysis

Continuous variables with normal distribution were expressed as mean and SD, and those with skewed/non-normal distribution as medians and interquartile ranges (IQR). Categorical variables were summarised as frequencies and percentages. Because of

the large sample size, some statistically significant differences may not be clinically meaningful. We used absolute standardized differences (ASD) or Hodges–Lehmann estimator to compare differences in baseline characteristics between young and older adults independent of sample size. An ASD larger than 10% was considered meaningful imbalance.[21]

For outcomes such as IV tPA treatment and in-hospital outcomes, logistic regression models were performed to determine adjusted odds ratios (aORs) and 95% confidence intervals (CIs). Multivariable models with different level of adjustment were used to check the robustness of the results. Covariates in multivariable models including gender, insurance status, body mass index (BMI), medical history of prior stroke or transient ischemic attack (TIA), coronary artery disease (CAD) or prior myocardial infarction (MI), diabetes mellitus, hypertension, smoking status, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, medication history (hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid lowering drugs), and hospital grade.

There were few missing data for most variables, with the exceptions of the in-hospital NIHSS score (missing 19.4%), DNT (6.3%), glycated hemoglobin (10.6%) and BMI (1.6%). For continuous variables missing less than 15%, the median was used for imputation. Since the NIHSS score is a widely used tool for assessing stroke severity[22] and contributes important information to AIS prognosis, [23] sensitivity

analyses adjusting for the NIHSS score were conducted. In addition, results from multiple imputation were also provided.

All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA) and the %ggBaseline SAS macro.[24] Two-sided p-values of <0.05 were considered statistically significant.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Of 838 229 patients with AIS in the CSCA, 793 175 patients enrolled from 1471 hospitals were eligible for inclusion in this study. The median age was 67.0 years (range: 58.0-75.0) and 62.7% were men. A total of 261 760 (33.0%) patients had previous stroke/TIA, 69 810 (8.8%) had coronary artery disease or myocardial infarction (CAD/prior MI), 170 638 (21.5%) had diabetes, 510 928 (64.4%) had hypertension, 294 708 (37.2%) were smokers, and 40 231 (5.1%) had atrial fibrillation/flutter.

Clinical characteristics

A total of 71 860 (9.1%) patients were young adults (<50 years) and 721 315 (90.9%)

were older adults (≥50 years). The mean age among young adults was 43.8±5.3 years and 68.3±10.0 years among older adults. A larger proportion of the young adults were men (76.3% vs 61.3%) and did not have health insurance coverage (12.9% vs 5.7%), compared to older adults. Young adults had a lower prevalence of cardiovascular risk factors compared to older adults, including history of stroke or TIA (22.5% vs 34.0%), CAD/prior MI (4.0% vs 9.3%), diabetes mellitus (15.3% vs 22.1%), hypertension (53.9% vs 65.5%), and atrial fibrillation (1.2% vs 5.5%). Young adults had a lower rate of medication use than older adults, including hypoglycemic drugs (10.9% vs 17.4%), antihypertensive drugs (33.5% vs 48%), antiplatelet drugs (14.6% vs 21.5%), and lipid lowering drugs (11.4% vs 15.3%). However, diastolic blood pressure in young adults was significantly higher than that of older adults (mean±SD 92.3±16.1 vs mean±SD 86.5±13.5), and young adults had a statistically higher mean BMI than older adults (mean±SD 24.9±4.8 vs mean±SD 23.9±4.2). The proportion of young adults who smoked was also higher than that of older adults (49.9% vs 35.9%) (Table 1).

Table 1. Baseline characteristics of young and old ischemic stroke patients

Baseline characteristics	Total (N=793175 [100%])	Young adults (< 50 years) (N=71860 [9.1%])	Old adults (≥50 years) (N=721315 [90.9%])	ASD (%)/H-L Estimator*
Patient characteristics				
Age, years	66.1±12.0	43.8±5.3	68.3±10.0	306.1
Male , n (%)	496960 (62.7)	54850 (76.3)	442110 (61.3)	32.8
Insurance status, n (%)				
UEBMI	225940 (28.5)	19160 (26.7)	206780 (28.7)	4.5
URBMI	149839 (18.9)	12393 (17.2)	137446 (19.1)	4.9

NRCMS	333979 (42.1)	27587 (38.4)	306392 (42.5)	8.4
Self-pa	50727 (6.4)	9263 (12.9)	41464 (5.7)	25.0
Other	32690 (4.1)	3457 (4.8)	29233 (4.1)	3.4
Arrive mode, n (%)				
Ambulance	89484 (11.3)	7170 (10.0)	82314 (11.4)	4.5
Private car	372727 (47.0)	33340 (46.4)	339387 (47.1)	1.4
Taxi	68801 (8.7)	6743 (9.4)	62058 (8.6)	2.8
Bicycle or tricycle	7237 (0.9)	577 (0.8)	6660 (0.9)	1.1
Helicopter	338 (0.0)	27 (0.0)	311 (0.0)	
Mobile stroke unit	246 (0.0)	24 (0.0)	222 (0.0)	
Other	254342 (32.1)	23979 (33.4)	230363 (31.9)	3.2
Medical history, n (%)				
Previous stroke/TIA	261760 (33.0)	16197 (22.5)	245563 (34.0)	25.8
CAD/prior MI	69810 (8.8)	2906 (4.0)	66904 (9.3)	21.4
Diabetes	170638 (21.5)	10985 (15.3)	159653 (22.1)	17.5
Peripheral vascular disease	13512 (1.7)	718 (1.0)	12794 (1.8)	6.8
Hypertension	510928 (64.4)	38722 (53.9)	472206 (65.5)	23.8
Smoking†	294708 (37.2)	35848 (49.9)	258860 (35.9)	28.6
Atrial fibrillation/flutter	40231 (5.1)	886 (1.2)	39345 (5.5)	24.1
Dyslipidemia	60605 (7.6)	5861 (8.2)	54744 (7.6)	2.2
Carotid stenosis	10161 (1.3)	509 (0.7)	9652 (1.3)	6.0
Medication history, n (%)				
Anticoagulants	31326 (3.9)	2394 (3.3)	28932 (4.0)	3.7
Hypoglycemic drugs	133244 (16.8)	7802 (10.9)	125442 (17.4)	18.7
Antihypertensive drugs	370017 (46.7)	24065 (33.5)	345952 (48.0)	29.8
Antiplatelet drugs	165771 (20.9)	10482 (14.6)	155289 (21.5)	18.0
Lipid lowering drugs	118827 (15.0)	8171 (11.4)	110656 (15.3)	11.5
NIHSS score in hospital‡	3.0 (2.0–6.0)	3.0 (1.0–5.0)	3.0 (2.0–6.0)	
Biochemical Indicators				
Glycated hemoglobin§, %	5.8 (5.3–6.5)	5.7 (5.2–6.1)	5.8 (5.3–6.5)	
BMI‖	24.0±4.3	24.9±4.8	23.9±4.2	22.2
Homocysteine#, μmol/L	13.9 (10.4–19.1)	13.4 (10.0–19.0)	13.9 (10.5–19.1)	
Systolic blood pressure**, mmHg	150.0±23.0	147.9±24.4	150.2±22.8	9.7
Diastolic blood pressure††, mmHg	87.0±13.9	92.3±16.1	86.5±13.5	39.0
Hospital characteristics, n (%)				
Hospital level				
Secondary hospital	303790 (38.3)	23993 (33.4)	279797 (38.8)	11.3
Tertiary hospital	489385 (61.7)	47867 (66.6)	441518 (61.2)	11.3
Hospital region				
Eastern China	365579 (46.1)	32744 (45.6)	332835 (46.1)	1.0

Central China	262618 (33.1)	24477 (34.1)	238141 (33.0)	2.3
Western China	164978 (20.8)	14639 (20.4)	150339 (20.8)	1.0

Abbreviations: UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme; TIA, transient ischemic attack; CAD, coronary artery disease; MI, myocardial infarction; SD: standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; ASD, absolute standardized difference.

*HL estimator, Hodges–Lehmann estimator; an absolute standardized difference (%) >10% indicates meaningful imbalance between 2 groups.

†Smoking: having smoking experience or behaviors.

‡Information was missing for N=154052 patients (19.4%).

§Information was missing for N=84393 patients (10.6%); median was used for imputation.

|| Information was missing for N=12698 patients (1.6%); median was used for imputation.

#Information was missing for N= 35781 patients (4.5%).

** Information was missing for N=245 patients (≈0.0%); median was used for imputation.

††Information was missing for N=251 patients (≈0.0%); median was used for imputation.

IV tPA treatment rates

Young adults were treated more frequently with IV tPA than older adults among patients without contraindications to thrombolysis (7.2% vs 6.1%, aOR 1.13, 95% CI 1.10-1.17) and among patients without contraindication and with onset-to-door time ≤ 3.5h (23.6 % vs. 19.3%, aOR 1.20, 95% CI 1.15-1.24). Data from sensitivity analyses showed consistent results.(Table 2)

Table 2. Multivariable analysis of IV tPA treatment by age group

Treantment	Rate of IV-tPA	aOR (95% CI) from model 1	aOR (95% CI) from model 2	aOR (95% CI) from model 3	aOR (95% CI) from model 4
IV tPA among patients without contraindications	49456/793175 (6.2)				
Young adults	5181/71860 (7.2)	1.19 (1.15-1.22)	1.13 (1.10-1.17)	1.20 (1.16-1.24)	1.19(1.15-1.22)
Old adults	44275/721315 (6.1)	1.00	1.00	1.00	1.00
IV tPA among patients without contraindication and with onset-to-door time ≤3.5h	45842/232905(19.7)				
Young adults	4768/20191 (23.6)	1.29 (1.25-1.34)	1.20 (1.15-1.24)	1.24 (1.20-1.29)	1.23(1.19-1.28)
Old adults	41074/212714 (19.3)	1.00	1.00	1.00	1.00

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator; OR, odds ratio.

Model 1: Logistic regression model without adjustment.

Model 2: adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated, hemoglobin, diastolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, lipid-lowering drugs, and hospital level.

Model 3: adjusted for were in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, lipid-lowering drugs, and hospital level. Patients (N= 154052) with missing values on NIHSS score were not included in this analysis.

model 4: results from multiple imputation.

Treatment time

While young adults were more likely to receive IV tPA, there was no significant difference in onset-to-needle time (median 2.7 hours, IQR 2.0–3.5 for both groups) and DNT (median 60.0 minutes, IQR 42.0-90.0 vs median 60.0 minutes, IQR 36.0-84.0) among young and older adults. DNT was also analyzed as a binary outcome at three levels: DNT ≤30, DNT ≤45, and DNT ≤60 minutes. There were no significant differences between the two groups on any DNT level (16.9% vs 18.8%; 30.2% vs 32.8%; 50.2% vs 54.2%) (Table 3).

Table 3. Treatment time in young and old ischemic stroke patients treated with IV tPA

Measures	Total (N=48141 [100%])	Young adults (< 50 years) (N=5044 [10.5%])	Old adults (≥50 years) (N=43097 [89.5%])	ASD (%)/H-L Estimator *
Onset-to-needle time†,h	2.7 (2.0–3.5)	2.7 (2.0–3.5)	2.7 (2.0–3.5)	
DNT‡ ,min	60.0 (36.0–84.0)	60.0 (42.0–90.0)	60.0 (36.0–84.0)	
Treatment time				
DNT≤30 minutes	8938 (18.6)	850 (16.9)	8088 (18.8)	5.0
DNT≤45 minutes	15637 (32.5)	1521 (30.2)	14116 (32.8)	5.6

DNT≤60 minutes	25884 (53.8)	2531 (50.2)	23353 (54.2)	8.0

Abbreviations: CI=confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator; DNT, door-to-needle time; ASD, absolute standardized difference.

*HL estimator, Hodges–Lehmann estimator; an absolute standardized difference (%) >10% indicates meaningful imbalance between 2 groups.

†Onset-to-needle time was missing for 3818 (7.9%) patients, with 431(8.5%) in age <50 and 3387(7.9%) in ≥ 50 groups.

‡DNT was missing for 3027(6.3%) patients, with 342 (6.8%) in age <50 and 2685(6.2%) in ≥ 50 groups.

In-hospital outcomes

In-hospital outcomes including sICH, in-hospital mortality, and independent ambulation at discharge were summarized in Table 4. Multiple logistic regression with adjustments of unbalanced covariates (ASD% >10% in Supplemental Table Ⅱ) showed that young adults had non-significantly lower rates of sICH (0.5% vs 0.9%, aOR=0.74, 95% CI 0.49-1.11) than older adults. However, young adults had significantly lower rates of in-hospital mortality (0.5% vs 1.3%, aOR=0.54, 95% CI 0.35-0.82) and were more likely to be independently ambulating at discharge (61.0% vs 53.6%, aOR=1.15, 95% CI 1.08-1.22).

In sensitivity analyses adjusted for NIHSS scores, young adults had non-significantly lower odds of sICH (aOR=0.77, 95%CI 0.5-1.18), in-hospital mortality (aOR=0.70, 95%CI 0.46-1.09), and a neutral association with independent ambulation at discharge (aOR=1.00, 95% CI 0.93-1.08). Sensitivity analysis using different age cut-off point (<35 years and ⩾ 35 years) showed consistent results with primary analysis

(supplemental material table Ⅲ). But when we used another age cut of point (<45 years and ≥45 years), we had a lower sICH rate (aOR=0.44, 95% CI 0.19-0.99) in the young group (supplemental material table Ⅳ).

Table 4. In-hospital outcomes in young and old ischemic stroke patients treated with IV tPA

Outcome	Rate of outcomes	aOR (95% CI) from model 1	aOR (95% CI) from model 2	aOR (95% CI) from model 3	aOR (95% CI) from model 4
sICH	414/48141 (0.9)				
Young adults	26/5044(0.5)	0.57 (0.38-0.85)	0.74 (0.49-1.11)	0.77 (0.5-1.18)	0.79(0.52-1.20)
Old adults	388/43097(0.9)	1.00	1.00	1.00	1.00
In-hospital mortality	579/48141 (1.2)				
Young adults	24/5044(0.5)	0.37 (0.24-0.55)	0.54 (0.35-0.82)	0.70 (0.46-1.09)	0.65(0.43-1.00)
Old adults	555/43097(1.3)	1.00	1.00	1.00	1.00
Independent ambulation at discharge	26175/48141 (54.4)				
Young adults	3079/5044(61.0)	1.36 (1.28-1.44)	1.15 (1.08-1.22)	1.00 (0.93-1.08)	1.02(0.96-1.10)
Old adults	23096/43097(53.6)	1.00	1.00	1.00	1.00

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator; OR, odds ratio.

Model 1: Logistic regression model without adjustment.

Model 2: Adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs,and lipid-lowering drugs.

Model 3: Adjusted for in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid-lowering drugs. Patients (N= 2503) with missing values on NIHSS score were not included in this analysis.

model 4: results from multiple imputation.

DISCUSSION

In this hospital-based observational study of 793 175 AIS patients, we found that young adults (<50 years of age) were more likely to be treated with IV tPA than older adults (7.2% vs 6.1%), which was consistent with our hypothesis. Our study demonstrated that young stroke patients had fewer comorbidities (previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, and atrial fibrillation/flutter) at baseline, which may compel providers to feel more secure in administering IV tPA to this group of patients. Even though we did not observe a difference in DNT between age groups, we found that young adults had more favorable in-hospital outcomes than older adults, including lower odds of sICH, in-hospital mortality and higher odds of independent ambulation at discharge. However, after adjusting for NIHSS scores, the differences were not significant. Therefore, the benefit among young adults may be explained by stroke severity measured by NIHSS score.

We chose 50 as the cut-off age because several important international studies on thrombolytic therapy in young people also set the cut-off age at 50.[15,16] Using the same cut-off age value would benefit the comparison with other studies and also have advantages for potential systematic review and meta-analysis.

IV tPA thrombolytic therapy is considered to be the standard therapy in patients with acute ischemic stroke. However, its use has been studied primarily in adults over age

50.[16] Given increasing evidence in the literature that thrombolytic therapy rarely causes hemorrhages in patients with stroke-mimicking conditions, providers may also feel more comfortable administering IV tPA to young adults when it is uncertain whether a stroke or a stroke mimic had occurred.[25] Our research also supports this conclusion. Young adults had similar time to treatment and were more likely to be treated than older adults, which may reflect increased awareness among patients and clinicians that stroke is a potentially fatal disease affecting people of all ages.

The relationship between time to treatment and mortality was first recognized in clinical studies.[26,27] The importance of this metric was reemphasized in the 2004 American College of Cardiology/American Heart Association practice guidelines, which stated that DNT targets "should not be perceived as an average performance standard but as a goal that an early treatment system in every hospital should seek for every appropriate patient".[28] Consistent with a prior analysis of SITS-ISTR showing no difference in median door-to-needle times between patients 18 to 50 and >50 years of age, there was also not an obvious differentiation in treatment among young or older adults in our study.[15] However, a prior study by Dodds and colleagues found that young adults (18-40 years) with AIS were more likely to experience a delay in evaluation and treatment.[13] Our definition of young adults (age <50 years) differs from theirs (age 18–40 years) and is more applicable in China, which may also explain why we did not find differences in treatment times between the two groups.[29]

Another explanation for the lack of differences in treatment times between the two groups may be that DNT mainly depends on hospital level and treatment process rather than age.

In our study, we observed a higher rate of sICH and in-hospital mortality among older adults treated with IV tPA, though the difference was not significant adjusted for NIHSS scores. We cannot entirely separate young age from lower NIHSS score, as young patients are highly correlated with lower NIHSS scores in clinical practise (4.0±4.5 vs. 4.9±5.3, the Rank Biserial correlation coefficient in this study is 0.10, $p<0.001$). Therefore, the associations may be partly explained by stroke severity measured by NIHSS score. Although we do not find significant differences between these two groups, we do see a trend towards better outcomes in young people. One possible explanation is that younger stroke patients have fewer comorbidities in their medical history, such as previous stroke or TIA, CAD/MI, diabetes mellitus, hypertension, and atrial fibrillation, as well as milder strokes, all of which are associated with better outcomes.[30] Other factors favoring recovery in young stroke patients include greater brain plasticity and more robust family and social support.[31]

There are several limitations in our study. Since hospital participation in the CSCA is voluntary, participating hospitals are more likely to be larger, tertiary centers with a myriad of resources that smaller hospitals do not have access to. We recognize that

findings from CSCA may not be generalizable to AIS patients admitted to hospitals outside of the CSCA. Second, we did not report data on intra-arterial (IA) therapies and puncture times because only a very small number of patients in our study received thrombectomy. We also did not have door-to-imaging data to support the study and there was a relatively high proportion of missing DNT values (6.3% overall, 6.8% in young and 6.2% in older patients). However, we did not observe a significant difference in DNTs between young and older AIS patients. Lastly, although we provided some possible explanation for the differences between young and old adults group, further researches are needed to explorer the detailed mechanism.

CONCLUSION

In summary, young adults with AIS are more likely to receive IV tPA than older adults, but there is no difference between the two groups in time to treatment. Young adults may have better in-hospital outcomes compared with older adults, suggesting favorable effects of treatment with IV tPA.

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CONTRIBUTORS

Conceived and led the project: XZ, YW, ZL, YW and YJ. Conception and design: HW, HG, YW and YJ. Data collection and analysis: HW, XY, CW, HG and QZ. Interpret the data: LL, XM and HL. Drafting the article and revising the content: HW, HG, CL, JY and ZL. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

None declared.

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL

This study received approval from the Institutional Review Board/Ethics Committee of Beijing Tiantan Hospital, Capital Medical University with approval number KY 2018-061-02. Participating hospitals received research approval to collect data in CSCA without requiring individual patient informed consent under the common rule or a waiver of authorisation and exemption from their Institutional Review Board.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request and after clearance by the local ethics committee.

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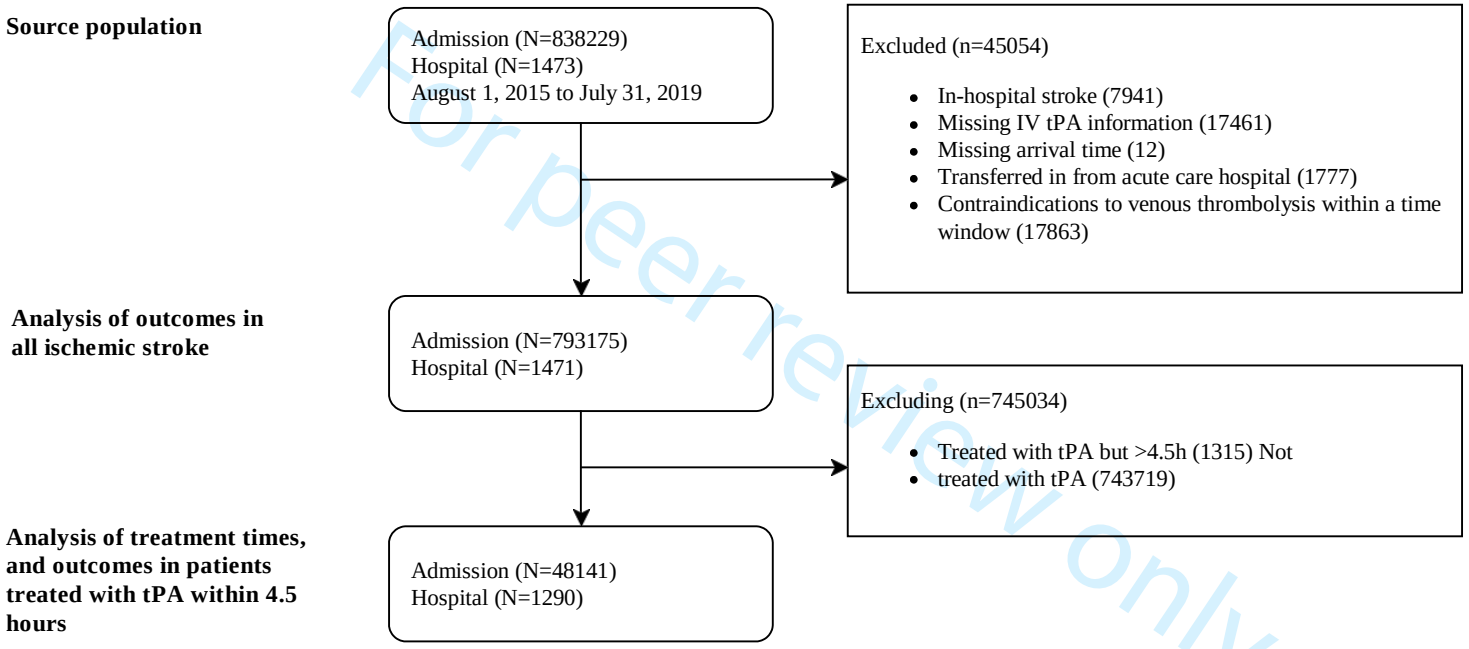
Figure legend

Figure 1. Study flowchart for patients identification.
Abbreviations: IV tPA, intravenous tissue plasminogen activator.



Supplemental Material

Table Ⅰ. Distribution of hospitals in our study

Hospital region	Province or Municipality	Number of hospitals (N=676)	Hospital region	Province or Municipality	Number of hospitals (N=401)	Hospital region	Province or Municipality	Number of hospitals (N=394)
Eastern China	Beijing	16	Central China	Jilin	32	Western China	Inner Mongoria	23
	Tianjin	13		Heilongjiang	41		Guangxi	49
	Hebei	143		Shanxi	44		Chongqing	16
	Liaoning	53		Anhui	29		Sichuan	125
	Shanghai	16		Jiangxi	25		Guizhou	23
	Jiangsu	93		Henan	157		Yunnan	52
	Zhejiang	86		Hubei	39		Tibet	1
	Fujian	52		Hunan	34		Shaanxi	41
	Shandong	81					Gansu	33
	Guangdong	113					Qinghai	9
	Hainan	10					Ningxia	5
							Xinjiang	17

Table Ⅱ. Baseline characteristics of young and old ischemic stroke patients with IV tPA treatment

Baseline characteristics	Total (N=48141 [100%])	Young adults (< 50 years) (N=5044 [10.5%])	Old adults (≥50 years) (N=43097 [89.5%])	ASD*
Patient characteristics				
Age, years	65.2±12.1	43.4±5.6	67.8±9.8	305.7
Male, n (%)	31456 (65.3)	3961 (78.5)	27495 (63.8)	32.9
Insurance status, n (%)				
UEBMI	15948 (33.1)	1609 (31.9)	14339 (33.3)	3.0
URBMI	9813 (20.4)	913 (18.1)	8900 (20.7)	6.6
NRCMS	16442 (34.2)	1495 (29.6)	14947 (34.7)	10.9
Self-pa	4083 (8.5)	813 (16.1)	3270 (7.6)	26.5
Other	1855 (3.9)	214 (4.2)	1641 (3.8)	2.0
Arrive mode, n (%)				
Ambulance	14364 (29.8)	1352 (26.8)	13012 (30.2)	7.5
Private car	21213 (44.1)	2240 (44.4)	18973 (44.0)	0.8
Taxi	2539 (5.3)	357 (7.1)	2182 (5.1)	8.4
Bicycle or tricycle	118 (0.2)	7 (0.1)	111 (0.3)	4.5
Helicopter	14 (0.0)	1 (0.0)	13 (0.0)	
Mobile stroke unit	31 (0.1)	4 (0.1)	27 (0.1)	0.0
Other	9862 (20.5)	1083 (21.5)	8779 (20.4)	2.7
Medical history, n (%)				
Previous stroke/TIA	12339 (25.6)	830 (16.5)	11509 (26.7)	25.0
CAD/prior MI	4737 (9.8)	240 (4.8)	4497 (10.4)	21.3
Diabetes	8477 (17.6)	516 (10.2)	7961 (18.5)	23.8
Peripheral vascular disease	628 (1.3)	31 (0.6)	597 (1.4)	8.0
Hypertension	28815 (59.9)	2283 (45.3)	26532 (61.6)	33.1
Smoking†	18835 (39.1)	2567 (50.9)	16268 (37.7)	26.8
Atrial fibrillation/flutter	5692 (11.8)	138 (2.7)	5554 (12.9)	38.7
Dyslipidemia	3195 (6.6)	351 (7.0)	2844 (6.6)	1.6
Carotid stenosis	454 (0.9)	22 (0.4)	432 (1.0)	7.2
Medication history, n (%)				
Anticoagulants	1779 (3.7)	150 (3.0)	1629 (3.8)	4.4
Hypoglycemic drugs	6404 (13.3)	330 (6.5)	6074 (14.1)	25.2
Antihypertensive drugs	20099 (41.8)	1302 (25.8)	18797 (43.6)	38.1
Antiplatelet drugs	7882 (16.4)	467 (9.3)	7415 (17.2)	23.5
Lipid lowering drugs	5614 (11.7)	382 (7.6)	5232 (12.1)	15.1
NIHSS score in hospital‡	7.9±6.5	6.4±5.3	8.0±6.6	26.7
Biochemical Indicators				
Glycated hemoglobin§,%		5.6 (5.1–6.0)	5.8 (5.3–6.5)	
BMI‖	23.6±4.2	24.9±5.5	23.4±4.0	31.2
Homocysteine#, μmol/L	13.3 (10.0–18.5)	12.7 (9.6–18.9)	13.3 (10.1–18.5)	
Systolic blood pressure**, mmHg	152.5±23.8	148.3±24.6	153.0±23.7	19.5
Diastolic blood pressure††, mmHg	87.6±14.5	92.1±16.1	87.1±14.2	32.9

(Continued)

Table Ⅱ. Baseline characteristics of young and old ischemic stroke patients with IV tPA treatment

Baseline characteristics	Total (N=48141 [100%])	Young adults (< 50 years) (N=5044 [10.5%])	Old adults (≥50 years) (N=43097 [89.5%])	ASD*
Hospital characteristics, n (%)				
Hospital level				
Secondary hospital	16479 (34.2)	1735 (34.4)	14744 (34.2)	0.4
Tertiary hospital	31662 (65.8)	3309 (65.6)	28353 (65.8)	0.4
Hospital region				
Eastern China	26410 (54.9)	2792 (55.4)	23618 (54.8)	1.2
Central China	15024 (31.2)	1630 (32.3)	13394 (31.1)	2.6
Western China	6707 (13.9)	622 (12.3)	6085 (14.1)	5.3

Abbreviations: IV tPA, intravenous recombinant tissue plasminogen activator; UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme; TIA, transient ischemic attack; CAD, coronary artery disease; MI, myocardial infarction; SD: standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; ASD, absolute standardized difference.

*: An absolute standardized difference% >10% indicates meaningful imbalance between 2 groups.

†: Smoking: having smoking experience or behaviors.

‡: Information was missing for N = 2503 patients (5.2%).

§: Information was missing for N =4749 patients (9.9%), using the median for imputation.

‖: Information was missing for N =743 patients (1.5%), using the median for imputation.

#: Information was missing for N = 2682 patients (5.6%).

**: Information was missing for N =28 patients (0.1 %), using the median for imputation.

††: Information was missing for N =28 patients (0.1%), using the median for imputation.

Table Ⅲ. In-hospital outcomes in young(< 35 years) and old (≥35 years) ischemic stroke patients treated with IV tPA

Outcome	Total (N=48141 [100%])	young adults (< 35 years) (N=456 [0.9%])	old adults (⩾35 years) (N=47685[99.1%])(REF)	Model	OR (95% CI)	P value
sICH	414 (0.9)	4 (0.9)	410 (0.9)	1	1.02 (0.38-2.74)	0.9678
				2	1.45 (0.54-3.94)	0.4612
				3	1.52 (0.56-4.13)	0.4136
In-hospital mortality	579 (1.2)	1 (0.2)	578 (1.2)	1	0.18 (0.03-1.28)	0.0861
				2	0.28 (0.04-2.01)	0.2066
				3	0.27 (0.04-1.97)	0.1953
Independent ambulation at discharge	26175 (54.4)	279 (61.2)	25896 (54.3)	1	1.33 (1.10-1.60)	0.0034
				2	1.09 (0.90-1.32)	0.384
				3	1.15 (0.92-1.42)	0.2173

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator ; OR, odds ratio.

Model 1: Logistic regression model without adjustment.

Model 2: Adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs,and lipid-lowering drugs.

Model 3: Adjusted for in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid-lowering drugs. Patients (N= 2503) with missing values on NIHSS score were not included in this analysis.

Table Ⅳ. In-hospital outcomes in young(< 45 years) and old (≥45 years) ischemic stroke patients treated with IV tPA

Outcome	Total (N=48141 [100%])	young adults (< 45 years) (N=2244 [4.7%])	old adults (≥45 years) (N=45897[95.3%])(REF)	Model	OR (95% CI)	P value
sICH	414 (0.9)	8 (0.4)	406 (0.9)	1	0.40 (0.20-0.81)	0.0106
				2	0.54 (0.26-1.10)	0.0877
				3	0.44 (0.19-0.99)	0.048
In-hospital mortality	579 (1.2)	8 (0.4)	571 (1.2)	1	0.28 (0.14-0.57)	0.0004
				2	0.43 (0.21-0.87)	0.0197
				3	0.52 (0.26-1.07)	0.077
Independent ambulation at discharge	26175 (54.4)	1356 (60.4)	24819 (54.1)	1	1.30 (1.19-1.41)	<0.0001
				2	1.08 (0.98-1.18)	0.1082
				3	0.97 (0.88-1.08)	0.6096

Abbreviations: CI, confidence interval; IV tPA, intravenous recombinant tissue plasminogen activator ; OR, odds ratio.
Model 1: Logistic regression model without adjustment.
Model 2: Adjusted for gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, systolic blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs,and lipid-lowering drugs.
Model 3: Adjusted for in-hospital NIHSS score, gender, insurance, BMI, previous stroke/TIA, previous CAD/prior MI, diabetes, hypertension, have smoking experience or behavior, atrial fibrillation/flutter, glycated hemoglobin, diastolic blood pressure, blood pressure, hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and lipid-lowering drugs. Patients (N= 2503) with missing values on NIHSS score were not included in this analysis.

STROBE Statement—checklist of items that should be included in reports of observational studies

Section/item	Item No	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page1,3,4	Title,Abstract/Para1-2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page3-4	Abstract/Para2-4
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Page7	Introduction/Para1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	Page7-8	Introduction/Para3
Methods				
Study design	4	Present key elements of study design early in the paper	Page8-9	Methods/Para1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page9-10	Methods/Para2-4
Participants	6	(a) ***Cohort study***—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ***Case-control study***—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants	Page8-10	Methods/Para1-4
		(b) ***Cohort study***—For matched studies, give matching criteria and number of exposed and unexposed ***Case-control study***—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page9-10	Methods/Para3-4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page8-11	Methods/Para1-6
Bias	9	Describe any efforts to address potential sources of bias	Page10-12	Methods/Para5-7
Study size	10	Explain how the study size was arrived at	Page8-9	Methods/Para1-2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page10-11	Methods/Para5

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page10-12	Methods/Para5-8
		(b) Describe any methods used to examine subgroups and interactions	Page10-11	Methods/Para5
		(c) Explain how missing data were addressed	Page11-12	Methods/Para7
		(d) ***Cohort study***—If applicable, explain how loss to follow-up was addressed ***Case-control study***—If applicable, explain how matching of cases and controls was addressed ***Cross-sectional study***—If applicable, describe analytical methods taking account of sampling strategy	Page11-12	Methods/Para7
		(e) Describe any sensitivity analyses	Page11-12	Methods/Para7
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page12	Results/Para1
		(b) Give reasons for non-participation at each stage		Figure1
		(c) Consider use of a flow diagram		Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page12-15	Results/Para1-2
		(b) Indicate number of participants with missing data for each variable of interest	Page15	Results/table1
		(c) ***Cohort study***—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	***Cohort study***—Report numbers of outcome events or summary measures over time	Page15-18	Results/Para3-6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page15-18	Results/Para3-6
		(b) Report category boundaries when continuous variables were categorized	Page15-17	Results/Para3-6
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page15-18	Results/Para3-6
Discussion				
Key results	18	Summarise key results with reference to study objectives	Page19-21	Discussion/Para1-5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page21-22	Discussion/Para6

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page19-22	Discussion/Para2-6
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page21-22	Discussion/Para6
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page23	Funding

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.