Clinical Interventions in Aging

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ORIGINAL RESEARCH

Comparison of the Clinical Outcomes Between Reperfusion and Non-Reperfusion Therapy in Elderly Patients with Acute Ischemic Stroke

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Purpose: To investigate the benefit (90-day mRS score) and rate of major complications (early symptomatic intracranial hemorrhage-SICH) after reperfusion therapy (RT) (including intravenous thrombolysis -IVT and mechanical thrombectomy -MT) in patients over 80 years with acute ischemic stroke (AIS).

Patients and Methods: AIS patients aged over 80 admitted to Huizhou Central People's Hospital from September 2018 to 2023 were included in this study. Data on SICH, NIHSS, and mRS were analyzed. A good prognosis was defined as a mRS ≤ 2 or recovery to pre-stroke status at 90 days.

Results: Of 209 patients, 80 received non-RT, 100 received IVT and 29 underwent MT. The non-RT group had the lowest baseline NIHSS while the MT group had the highest (non-RT 6.0 vs IVT 12.0 vs MT 18.0, P <0.001). Higher NIHSS was associated with increased SICH risk (OR 1.083, P=0.032), while RT was not (OR 5.194, P=0.129). The overall SICH rate in the RT group was higher but not significantly different after stratification by stroke severity. Poor prognosis was associated with higher admission NIHSS, stroke due to large artery atherosclerosis (LAA) combined with cardioembolism (CE), and stroke-associated pneumonia (SAP) (OR 0.902, P<0.001; OR 0.297, P=0.029; OR 0.103, P<0.001, respectively). The RT group showed a greater reduction in NIHSS (delta NIHSS) than the non-RT group (non-RT 2.0 vs IVT 4.0 vs MT 6.0, P<0.005). For severe AIS, the IVT group had a better prognosis at 90 days (non-RT 0% vs IVT 38.2%, P=0.039). No 90-day mortality difference was found between groups after stratification.

Conclusion: Stroke severity, rather than RT, is an independent risk factor for SICH in AIS patients over 80. RT in severe stroke patients improves NIHSS at 90 days, suggesting RT is safe and effective in this demographic. Further studies with larger samples are required to confirm these findings.

Keywords: acute ischemic stroke, elderly, intravenous thrombolysis, mechanical thrombectomy, symptomatic intracranial hemorrhage, therapeutic efficacy

Introduction

Stroke is the second leading cause of mortality and the third leading cause of disability worldwide,[1] and it is the first fatal disease in the Chinese population.[2,3] The morbidity of acute ischemic stroke (AIS) in China has increased from 117/100,000 in 2005 to 145/100,000 in 2019.[4] Approximately 30% of patients with AIS are > 80 years old.[1,5] Mainland China's population has entered an aging period. According to the data of the 7th National Population Census in 2021, the proportion of people aged 65 years and above in China is 13.5%, nearly 200 million,[6] which means that the number of AIS patients over 80 years of age will increase with the aggravation of aging.

Timely reperfusion therapy (RT), including intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) for AIS patients is critical in reducing mortality and disability. IVT with recombinant tissue plasminogen activator (r-tPA) improves the prognosis of AIS and has become a standard reperfusion therapy for AIS within 3 h of onset since 1995.[7]

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The therapeutic time window of IVT was extended to 4.5 hours in 2010. Although the European and American guidelines no longer set age limitation as early as 2008 and 2013, respectively, the Chinese guidelines did not lift the age limitation of 18–80 until 2018.[8–11] As another effective reperfusion therapy for patients with AIS due to large artery occlusion, the time window of MT was extended from 6 h in 2015[12–14] to 24 h.[15,16] The use of RT is increasing every year globally, especially in China, but few studies have included patients aged >80 years.[12–16] The limitations of RT in elderly patients are mainly due to concerns regarding symptomatic intracranial hemorrhage (SICH). Ginsberg et al found that approximately 41.4% of SICH cases are fatal.[17]

Whether age is an independent risk factor of SCIH after RT remains controversial. A multicenter study conducted in mainland China that focused on IVT for AIS patients aged 18–80 years old showed that age >70 years was an independent risk factor for SICH.[18] However, two other independent clinical studies conducted in Japan and Australia found that age >80 years did not increase the risk of SICH after IVT.[19,20] This discrepancy may be due to the different research designs. Relatively few studies have focused on RT for AIS patients aged >80 years. In this study, we aimed to investigate the effectiveness and safety of RT therapy in AIS patients aged >80 years and to provide a reference for clinical practice.

Materials and Methods

Participant

This study was reviewed and approved by the Institutional Review Board of the Huizhou Central People's Hospital (kyl2021227). Consecutive AIS patients over 80 years of age within 24 h of onset who were hospitalized in the Department of Neurology at Huizhou Central People's Hospital from September 2018 to September 2023 were prospectively included in the study. Patients were divided into non-RT, IVT, and MT groups based on the therapy they received. Inclusion criteria: ① AIS was diagnosed in accordance with the 2018 Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke;[11] ② The patients in the non-RT group did not receive RT either due to refusal or not eligible for RT; ③ the patients in the IVT group had been diagnosed within 4.5 hours of onset and met the indications for thrombolysis according to the 2018 Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke,[11] and without absolute contraindications; ④ The patients in the MT group had been diagnosed within 24 hours of onset, and met the MT treatment standards according to the 2018 Chinese Guidelines for Endovascular Treatment of Acute Ischemic Stroke;[21] ⑤ Informed consent form for treatment was obtained from every patient or authorized family member before inclusion.

Exclusion criteria: ① AIS onset >24 hours; ② Previous history of severe stroke with residual neurological deficits and modified Rankin Scale (mRS) >2 points before the current episode; ③ A history of severe head injury or stroke within 3 month; ④ Intracranial hemorrhage; ⑤ Intracranial tumors or giant intracranial aneurysms; ⑥ Active bleeding; ⑦ Epileptic seizures; ⑧ Unstable blood pressure in the systemic circulation or using the vasoactive drugs; respiratory failure requires mechanical-assisted ventilation; severe renal insufficiency [with a glomerular filtration rate of <30 mL/(min * 1.73 m^2) or required maintenance hemodialysis]; ⑨ Individuals with severe hypertension which could not be controlled below 185/110 mmHg after pharmacological intervention, or blood glucose could not be maintained between 2.8 and 22.2 mmol/L; ⑩ Platelets <100 × 10^9/L; ⑪ Individuals with unknown time of disease onset, incomplete clinical data, or unable to complete follow-up.

Standard Procedure of Diagnosis and Treatment for AIS

Patients suspected of having AIS were prioritized for evaluation through the "stroke green channel" by senior neurologists when they arrived at the emergency department. Cranial computed tomography (CT) was performed as soon as possible to rule out intracranial hemorrhage. Laboratory tests such as blood electrolytes, blood glucose, blood cell count, coagulation function, liver and kidney function, and electrocardiography were immediately performed. The scales for assessing neurological function, including the National Institutes of Health Stroke Scale (NIHSS) and mRS, were assessed by a neurologist before treatment. Patients with stroke onset ≤4.5 hours and eligible for IVT received r-tPA for thrombolysis at a dose of 0.9 mg/kg (maximum dose 90 mg) with the consent of the patient and/or their authorized

family member. For patients within 4.5 hours of stroke onset but with contraindications or who refused to undergo IVT, or for patients within 4.5–24 hours of onset, head and neck CT angiography (CTA) and CT cranial perfusion were performed immediately to confirm the presence of large vessel occlusion (LVO). Experienced neurointerventional specialists who performed the MT process evaluated patients with LVO for eligibility. Individuals who did not undergo IVT or MT were included in the non-RT group. All patients were admitted to the Department of Neurology and underwent comprehensive management of blood pressure, blood glucose level, and other comorbidities in accordance with the guidelines. Patients receiving RT will be scheduled for a follow-up cranial CT scan 24 h and 72 h after treatment. Once the patient's neurological symptoms deteriorated and the NIHSS score increased by ≥3 points, cranial CT was performed immediately to confirm whether cerebral hemorrhage had occurred. All patients underwent carotid artery ultrasound, cranial MRA, or CTA to achieve the TOAST etiology classification diagnoses, which were defined as large artery atherosclerosis (LAA), small artery occlusion (SAO), cardiac embolism (CE), stroke of other determined etiology (SOD), or stroke of unknown etiology (SUD).[22] For patients with either significant (>50%) atherosclerotic stenosis, occlusion of a major brain artery or branch cortical artery, and concurrent atrial fibrillation (AF) which led to an ambiguous diagnosis of the origin of the embolus, the etiology was defined as LAA combined with CE.

Data Collection and Definitions

All clinical data were obtained from the Big Data Observatory Platform for Stroke, China (BOSC). BOSC was established in 2017 (https://sinosc.org/home/index), and all clinical data of AIS patients who underwent RT within 24 h of onset were uploaded to the system in accordance with national requirements. General clinical data, including age, gender, history of smoking, alcohol use (≥8 units alcoholic consumption per week),[23] previous AIS history, coronary artery disease, AF, heart failure, hypertension, diabetes, blood glucose, liver and kidney function, and blood lipid levels were collected at admission. Indicators related to quality control for different treatment methods, such as onset-to-needle time (ONT) and door-to-needle time (DNT) for the IVT group and onset-to-puncture time (OPT), door-to-puncture time (DPT), and the grading of forward blood flow of mechanical thrombectomy in cerebral infarction (modified Thrombolysis in Cerebral Infarction Score, mTICI) in the MT group were also recorded. Related complications that occurred during hospitalization, such as stroke associated pneumonia (SAP), acute heart disease (acute myocardial infarction, acute heart failure, and cardiac arrest), or brain herniation were also recorded. SAP was diagnosed based on the clinical and laboratory indices of respiratory tract infection for hospital-acquired pneumonia and supported by typical chest X-ray or CT scan findings according to previous studies.[24] Progressive stroke was defined as an increase in NIHSS score of ≥3 within 72 h, excluding intracranial hemorrhage.[25] The patients who did not receive antiplatelet or anticoagulant drugs before onset were defined as no history of antithrombotic therapy.

Evaluation Indicators and Outcomes

According to a previous report, AIS severity was classified into three levels based on the NIHSS: NIHSS of 1–7 points were defined as mild AIS, 8–15 points as moderate AIS, and NIHSS >15 as severe AIS.[26] Evaluation of the safety of RT treatment mainly focused on SICH 72 h after treatment. The main outcome indicators were NIHSS and mRS scores at the 90-day follow-up. An mRS score of 0–2 or with the same condition as before the current episode was defined as good prognosis. Delta NIHSS and delta mRS were defined as the differences between the NIHSS or mRS scores at admission and the NIHSS or mRS scores at the 90-day follow-up. The delta value reduces the impact of NIHSS on admission, which could be more objective in comparing the efficacy between groups with significantly different baseline NIHSS.[27]

Statistics

The data were processed and analyzed using SPSS 22.0. The Shapiro–Wilk Test was performed to determine if a dataset follows a normal distribution. If the p-value was greater than 0.05, it is considered that the data was normally distributed. Normally distributed measurement data were expressed as mean ± standard error; independent sample *t*-test was used for comparison between two groups, while one-way analysis of variance (one-way ANOVA) was applied to compare the means of two or more independent groups. Non-normally distributed econometric data were expressed as medians and percentiles. Comparisons between two groups were performed using the Mann–Whitney *U*-test, while the Kruskal–

Wallis *H*-test was used to compare more than two groups. Categorical variables were expressed as frequencies and percentages. Statistical methods were based on the total number (N) and the number of single cells (T) as follows: ① When $N \geq 40$ and the frequency $T \geq 5$ for all groups, Pearson chi-square test was used; ② When $N \geq 40$ but $1 \leq T \leq 5$, continuous correction chi-square test was used; ③ When $N<40$ or $T<1$, Fisher's exact test was used. Binary logistic regression analysis was used for the risk factor analysis. A two-tailed test ($P<0.05$) indicated significant differences.

Results

After excluding AIS that did not meet the inclusion criteria for this study (patients inclusion flow chart was presented in Figure 1), a total of 209 patients were included in this study, including 96 males (45.9%) and 113 females (54.1%), with an average age of 83.6± 3.8 years old, of whom 80 (38.3%) in the non-RT group (9 cases with an onset of ≤4.5 hours), 100 (47.8%) in the IVT group, and 29 (13.9%) in the MT group (Table 1). Compared to the non-RT group, patients in the MT group had a lower average age (non-RT 84 vs MT 81, *P*=0.004). The IVT group had a higher rate of coronary artery disease and heart failure (IVT 26.0% vs non-RT 13.8%; *P*=0.043). Baseline blood glucose levels in the IVT and MT groups were slightly higher than those in the non-RT group (IVT 7.4 vs non-RT 6.2, $P < 0.001$; MT 7.7 vs non-RT 6.2, *P*=0001). Compared with the other two groups, more patients in the MT group had a history of anticoagulant medication (non-RT 0.0% vs IVT 1.0% vs MT 13.8%, $P<0.05$); however, the overall medication usage for antithrombotic therapy before the current episode of AIS was the lowest in the MT group (non-RT 83.8% vs IVT 81.0% vs MT 62.1%, $P<0.05$). From the perspective of the TOAST etiological classification, the proportion of LAA in the non-RT group (63.8%) was higher than that in the IVT group (40.0%) (*P*=0.002), and the CE rate was lower than that in both the IVT (non-RT 7.5% vs IVT 22.0%, *P*=0.008) and MT group (non-RT 7.5% vs MT 31.0%, *P*=0.002). Patients in the IVT group had more LAA and CE than those in the non-RT group (non-RT 8.0% vs IVT 16.0%, *P*=0.022) (Table 1).

It was noted that patients in the RT group had more severe neurological deficits than patients in the non-RT group at admission, as reflected by both NIHSS (non-RT 6.0 vs IVT 12.0 vs MT 18.0, $P<0.001$) and mRS (non-RT 3.0 vs IVT 4.0 vs

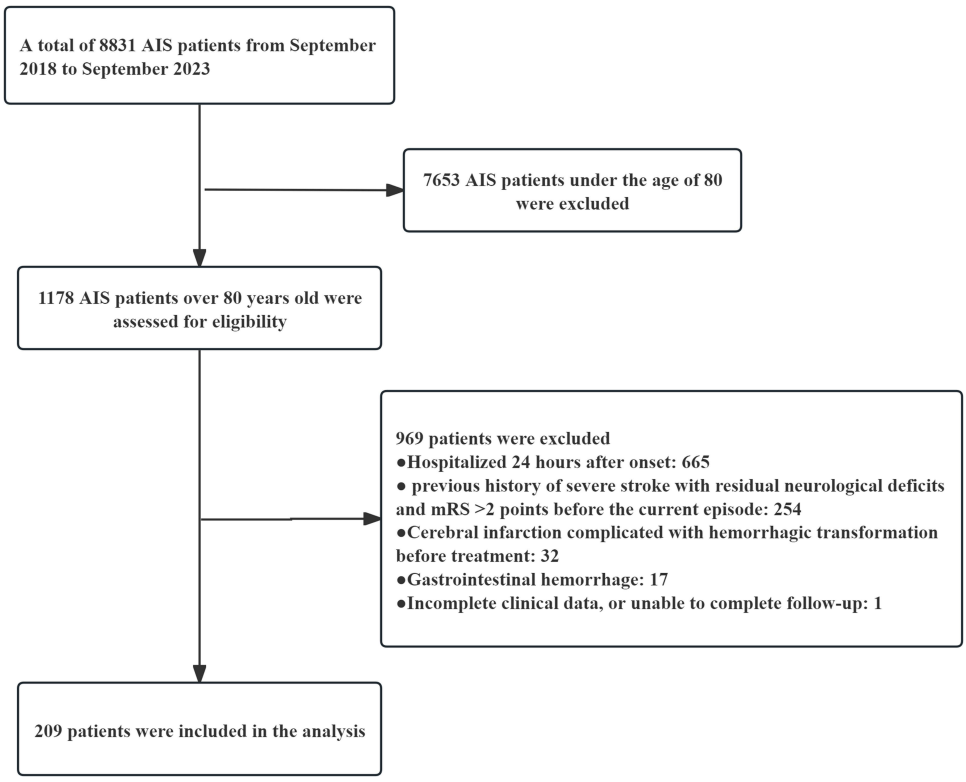

Figure 1 Patients inclusion flow chart.
Abbreviations: AIS, acute ischemic stroke; mRS, modified Rankin Scale.

Table 1 Comparison of General Characteristics for AIS Patients Aged Over 80 Between Groups with Different Treatment

	Non-RT (n=80)	IVT (n=100)	MT (n=29)	Non-RT vs IVT	Non-RT vs MT	IVT vs MT
				P value		
Gender (male, %)	36(45.0)	47(47.0)	13(44.8)	0.789	0.987	0.836
Age (median, IQR)	84.0(82.0,86.8)	83.0(81.0,85.0)	81.0(80.0,84.0)	0.082	0.004	0.070
Current smoking (n, %)	14(17.5)	14(14.0)	6(20.7)	0.520	0.704	0.381
Alcohol use (n, %)	8(10.0)	7(7.0)	1(3.4)	0.469	0.481	0.794
Previous ischemic stroke (n, %)	16(20.0)	25(25.0)	5(17.2)	0.427	0.962	0.535
Antithrombotic medication history						
Antiplatelet (n, %)	13(16.3)	18(18.0)	7(24.1)	0.757	0.347	0.462
Anticoagulation (n, %)	0(0)	1(1.0)	4(13.8)	1.000	0.004	0.009
No antithrombotic treatment (n, %)	67(83.8)	81(81.0)	18(62.1)	0.632	0.016	0.034
Hypertension (n, %)	60(75.0)	62(62.0)	20(69.0)	0.064	0.529	0.493
Diabetes (n, %)	15(18.8)	21(21.0)	5(17.2)	0.708	1.000	0.856
Blood glucose (median, IQR)	6.2(5.3,7.7)	7.4(6.2,8.8)	7.7(6.7,9.3)	<0.001	0.001	0.328
Hyperlipidemia (n, %)	45(56.2)	49(49.0)	14(48.3)	0.333	0.460	0.945
Location of AIS						
Anterior circulation (n, %)	64(80.0)	80(80.0)	23(79.3)	1.000	0.937	0.937
Posterior circulation (n, %)	16(20.0)	20(20.0)	6(20.7)			
TOAST classification						
LAA (n, %)	51(63.8)	40(40.0)	11(37.9)	0.002	0.016	0.841
SAO (n, %)	15(18.8)	14(14.0)	0(0)	0.389	0.010	0.039
CE (n, %)	6(7.5)	22(22.0)	9(31.0)	0.008	0.002	0.316
LAA with CE (n, %)	8(10.0)	16(16.0)	8(27.6)	0.239	0.022	0.158
Others (SOD &SUD) (n,%)	0(0)	8(8.0)	1(3.4)	0.010	0.097	0.665
Stroke in progression (n, %)	11(13.8)	22(22.0)	5(17.2)	0.155	0.882	0.768
SAP (n, %)	21(26.2)	31(31.0)	23(79.3)	0.485	<0.001	<0.001
Concomitant acute myocardial infarction or acute heart failure attack, cardiac arrest (n, %)	2(2.5)	7(7.0)	3(10.3)	0.302	0.226	0.842
Brain herniation (n, %)	2(2.5)	10(10.0)	3(10.3)	0.088	0.226	1.000
Baseline NIHSS (median, IQR)	6.0(3.0,11.0)	12.0(5.0,18.0)	18.0(15.5,21.5)	<0.001	<0.001	<0.001
Mild AIS (n, %)	48(60.0)	31(31.0)	0(0)	<0.001	<0.001	<0.001
Moderate AIS (n, %)	23(28.8)	35(35.0)	7(24.1)	0.373	0.634	0.272
Severe AIS (n, %)	9(11.3)	34(34.0)	22(75.9)	<0.001	<0.001	<0.001
Baseline mRS (median, IQR)	3.0(2.0,4.0)	4.0(3.0,5.0)	5.0(4.5,5.0)	<0.001	<0.001	<0.001
SICH within 72 hours (n, %)	1(1.3)	7(7.0)	4(13.8)	0.135	0.025	0.438
SICH in mild and moderate AIS (n, %)	1(1.4)	4(6.1)	0(0)	0.320	1.000	1.000
SICH in severe AIS (n, %)	0(0)	3(8.8)	4(18.2)	1.000	0.295	0.535
Good prognosis at 90-day (n, %)	46(57.5)	58(58.0)	6(20.7)	0.946	0.001	<0.001
Good prognosis in mild and moderate AIS (n, %)	46(64.8)	45(68.2)	2(28.6)	0.674	0.141	0.096
Good prognosis in severe AIS (n, %)	0(0)	13(38.2)	4(18.2)	0.039	0.295	0.195
TOAST classification of good good prognosis patients at 90-day						
LAA (n, %)	27(52.9)	24(60.0)	4(36.4)	0.501	0.001	0.292
SAO (n, %)	12(80.0)	14(100.0)	0(0)	0.224	-	-
CE (n, %)	3(50.0)	12(54.5)	2(22.2)	1.000	0.329	0.132
LAA with CE (n, %)	4(50.0)	3(18.8)	0(0)	0.167	0.077	0.526
Others (SOD &SUD) (n,%)	0(0)	5(62.5)	0(0)	-	-	0.264
Mortality at 90-day (n, %)	1(1.25)	9(9.0)	4(13.8)	0.054	0.025	0.686
Mortality in mild and moderate AIS (n, %)	0(0.0)	2(3.0)	1(14.3)	0.230	0.090	0.671
Mortality in severe AIS (n, %)	1(11.1)	7(20.6)	3(13.6)	0.867	1.000	0.759

Abbreviations: RT, reperfusion therapy; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; LAA, large artery atherosclerosis; SAO, small-artery occlusion; CE, cardioembolism; SOD, stroke of other determined etiology; SUD, stroke of undetermined etiology; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; SAP, stroke-associated pneumonia; SICH, symptomatic intracranial hemorrhage; AIS, acute ischemic stroke.

MT 5.0, $P<0.001$). After stratifying the severity of cerebral infarction based on the NIHSS score, the RT group had a much lower proportion of mild stroke than the non-RT group (non-RT 60.0% vs IVT 31.0% vs MT 0.0%, $P<0.001$) and a much higher percentage of severe stroke (non-RT 11.3% vs IVT 34.0% vs MT 75.9%, $P<0.001$). There was no significant difference in moderate stroke between the groups (non-RT 28.8% vs IVT 35.0% vs MT 24.1%, $P>0.05$) (Table 1).

In the MT group, twenty-four (82.8%) patients had complete vascular occlusion with a mTICI grade of 0, four (13.8%) had a mTICI grade of 1, and one (3.4%) was rated of 2b before intravascular interventional therapy. After MT treatment, 23(79.3%) patients had a final mTICI grade of 2b or above, and 4 (13.8%) had a grade of 0 (Figure 2). The medications used in the different groups before and after stroke are summarized in Figure 2. Indicators related to quality control for RT, including ONT and DNT in IVT group, OPT and DPT in the MT group, were shown in Figure 2.

Patients in the MT group had a higher probability of developing SAP than those in the non-RT group or IVT group (non-RT 26.2% vs IVT 31.0% vs MT 79.3%, $P<0.001$). There were no significant differences in other baseline data between the three groups, including risk factors for cerebrovascular disease, medical history, and stroke progression (Table 1).

Comparison of SICH Among Different Groups and Analysis of SICH Risk Factors

Overall, although the SICH rate in the MT group was higher than that in the non-RT group (MT 13.8% vs non-RT 1.3%, $P=0.025$), considering that the baseline NIHSS score in the MT group was much higher than that in the non-RT group at admission, we further made a sub-group analysis stratified by NIHSS, which revealed no difference between the different treatment groups (mild to moderate AIS: non-RT 1.4% vs IVT 6.1% vs MT 0%; severe AIS: non-RT 0% vs IVT 8.8% vs

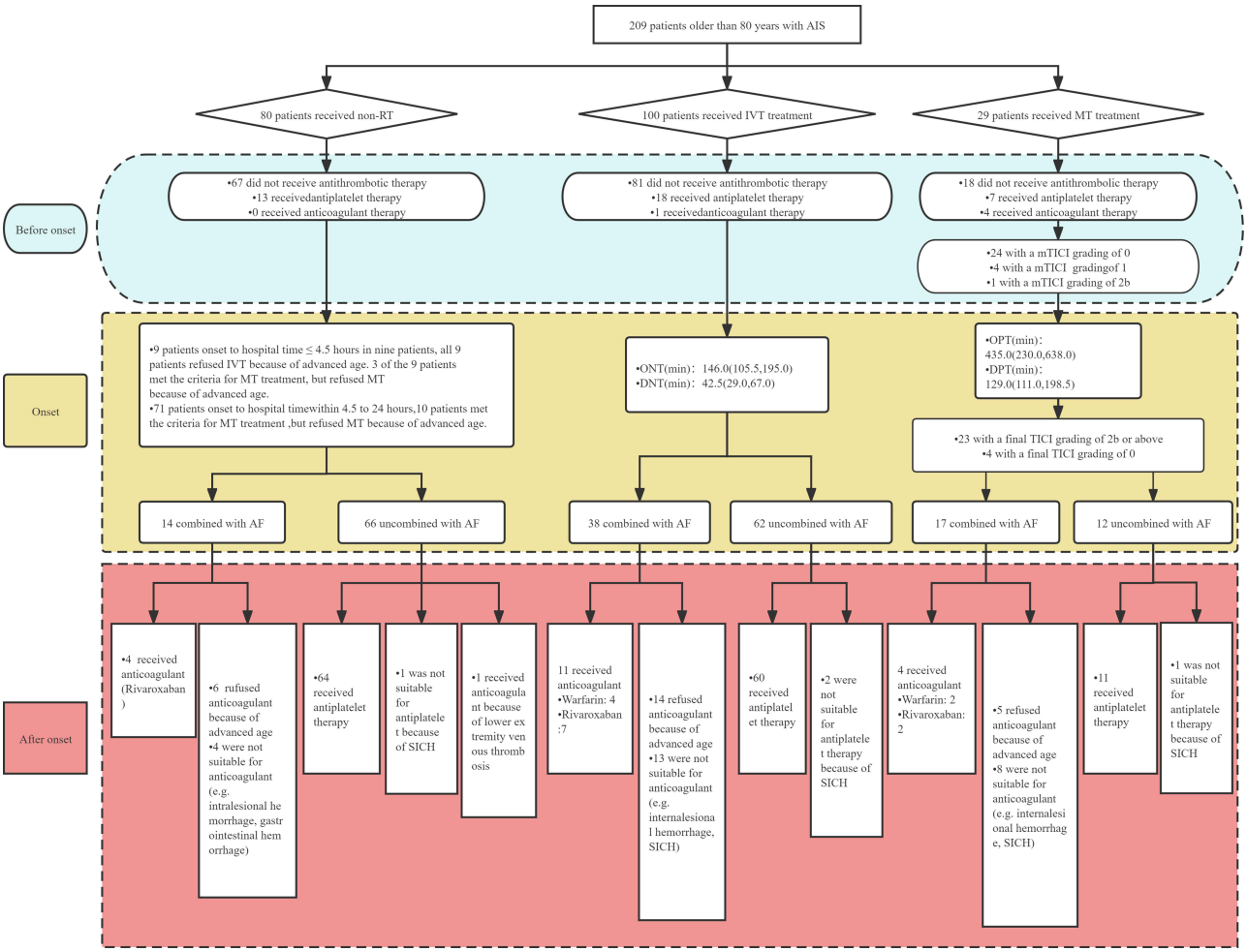

Figure 2 A summary flow chart of treatment process and medications for three different therapeutic schedules.
Abbreviations: RT, reperfusion therapy; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; ONT, onset-to-needle time; DNT, door-to-needle time; OPT, onset-to-puncture time; DPT, door-to-puncture time.

MT 18.2%, $P>0.05$)(Table 1). Multivariate binary logistic regression analysis indicated that a high NIHSS score on admission was an independent risk factor for SICH (odds ratio [OR] =1.083, $P=0.032$, Table 2). There was no association between different treatment methods and SICH ($P>0.05$) (Table 2).

Outcomes at 90-Day and Predictive Factors for Good Prognosis

The non-RT group or IVT group had a higher percentage of good prognosis at 90-day than that in the MT group (non-RT 57.5% vs IVT 58.0% vs MT 20.7%, $P\leq0.001$) (Table 1). However, after stratifying by stroke severity, it was found that there was no difference in the good prognosis rate in patients with mild to moderate AIS among the different treatment groups (non-RT 64.8% vs IVT 68.2% vs MT 28.6%, $P>0.05$). Among those with severe AIS, more patients in the IVT group achieved good prognosis at 90-day (IVT, 38.2% vs non-RT, 0.0%; $P=0.039$). Although the good prognosis rate in the MT group was higher than that in the non-RT group, the difference was not statistically significant (MT 18.2% vs non-RT 0.0%, $P=0.295$) (Table 1). There were no differences in 90-day mortality among the three groups, either overall or stratified according to stroke severity (Table 1).

At 90 days of onset, the overall delta NIHSS score in the MT group was higher than that in the non-RT and IVT groups (MT 13.0 vs Non-RT 3.5, $P=0.001$; MT 13.0 vs IVT 3.0, $P=0.002$), and was also the same in the mRS (MT 4.0 vs Non-RT 2.0, $P=0.001$; MT 4.0 vs IVT 2.0, $P=0.001$) (Table 3). There were no differences in NIHSS and mRS scores between the non-RT and IVT groups (Table 3). Owing to significant differences in baseline NIHSS and mRS scores among the different groups, delta NIHSS and delta mRS were used to assess dynamic changes in neurological function for each patient. Interestingly, we found that patients who underwent RT had a more significant improvement in neurological function, manifested in delta NIHSS (IVT 4.0 vs Non-RT 2.0, $P=0.001$; MT 6.0 vs Non-RT 2.0, $P=0.002$) and delta mRS (IVT 2.0 vs Non-RT 1.0, $P=0.008$) (Table 3). Dynamic changes in the mRS scores of each group are shown in Figure 3.

Multivariate binary logistic regression analysis revealed that a higher NIHSS score at admission was associated with poor prognosis (OR=0.902, $P<0.001$) (Table 2).

Table 2 Multivariate Binary Logistic Regression Analysis for the Risk Factors of SICH Within 72 Hours and Good Prognosis at 90-Day

	SICH		**Good Prognosis at 90-day**	
	***OR* (95% CI)**	***P value***	***OR* (95% CI)**	***P value***
RT	5.194(0.618,43.637)	0.129	2.538(1.091,5.903)	0.031
IVT	1.396(0.421,4.631)	0.586	2.044(0.969,4.311)	0.060
MT	2.103(0.536,8.254)	0.287	1.141(0.324,4.021)	0.838
Previous medication				
No antithrombotic treatment	0.339(0.100,1.148)	0.082	0.851(0.357,2.030)	0.717
Antiplatelet	2.526(0.702,9.086)	0.156	1.296 (0.523,3.211)	0.576
Anticoagulation	3.048(0.307,30.235)	0.341	0.503(0.036,7.060)	0.610
Blood glucose	1.003(0.827,1.216)	0.978	1.007(0.904,1.121)	0.905
Posterior circulation infarction	0.335(0.042,2.673)	0.302	2.845(1.367,5.919)	0.005
TOSTA classification				
LAA	0.820(0.247,2.721)	0.745	0.982(0.490,1.967)	0.959
SAO	-	-	5.360(1.338,21.477)	0.018
CE	1.244(0.311,4.969)	0.757	0.686(0.279,1.691)	0.413
LAA with CE	2.321(0.623,8.643)	0.209	0.297(0.100,0.885)	0.029
Others (SOD & SUD)	-	-	1.131(0.295,4.335)	0.858
Baseline NIHSS	1.083(1.007,1.165)	0.032	0.902(0.855,0.950)	<0.001
SAP	-	-	0.103(0.046,0.227)	<0.001

Abbreviations: RT, reperfusion therapy; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; LAA, large artery atherosclerosis; CE, cardioembolism; SOD, stroke of other determined etiology; SUD, stroke of undetermined etiology; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; SAP, stroke-associated pneumonia; SICH, symptomatic intracranial hemorrhage.

Table 3 Comparison of the Effectiveness and Outcomes at 90-Day Between Different Treatment Groups

	Treatment			P value		
	Non-RT	IVT	MT	Non-RT vs IVT	Non-RT vs MT	IVT vs MT
NIHSS at 90-day	3.5(1.0,8.0)	3.0(0,12.0)	13.0(5.5,17.0)	1.000	0.001	0.002
mRS at 90-day	2.0(1.0,4.0)	2.0(0,4.0)	4.0(3.0,5.0)	1.000	0.001	0.001
delta NIHSS	2.0(1.0,3.0)	4.0(1.3,9.8)	6.0(2.0,11.0)	0.001	0.002	1.000
delta mRS	1.0(0,1.0)	2.0(0,3.0)	1.0(0,1.5)	0.008	1.000	0.206

Abbreviations: RT, reperfusion therapy; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; delta NIHSS, baseline NIHSS minus NIHSS at 90-day; delta mRS, baseline mRS minus mRS at 90-day.

After adjusting the NIHSS, TOAST classification as LAA combined with CE (OR=0.297, P<0.029) and SAP (OR=0.103, P<0.001) was associated with poor prognosis for AIS patients aged >80 years old at 90-day (Table 2). Receiving RT was positively correlated with good prognosis (OR=2.538, P=0.031) (Table 2).

Discussion

SICH has always been a concern for neurologists during thrombolytic therapy for elderly AIS patients over 80 years of age because SICH may lead to an increase in disability and mortality. Since the Chinese guidelines limited the age for IVT to under 80 years old until 2018, there have been relatively few studies on reperfusion therapy for individuals over 80 years old in mainland China. In 2014, a study based on Chinese AIS patients found no statistically significant difference in SICH between patients aged >80 years who received IVT with r-tPA and those aged <80 years old.[28] IVT did not increase the risk of SICH in elderly patients compared to non-RT patients, which is consistent with previous studies on different ethnic groups.[19,29–32] In this single-center study, we found that approximately 7.0% of AIS patients over 80 years of age who received IVT developed SICH within 72 h of onset, which was similar to the previous report by Xu Dongjuan et al.[28] Meanwhile, the 7.0% incidence of SICH is not higher than the incidence of AIS in patients under the age of 80 years in mainland China, with a reported incidence ranging from 4.87% to 7.3%.[33,34] A regression analysis of SICH also showed that IVT within 72 hours of AIS in patients over 80 years of age was not correlated with SICH, but a high NIHSS score at admission was an independent risk factor for SICH, which was consistent with previous research.[18] The NIHSS score in the IVT group was significantly higher than that in the non-RT group, and the AIS score in the IVT group was more severe. This may be due to severe AIS being more willing to accept IVT, whereas most AIS patients with mild symptoms may be more inclined to refuse IVT.

Although MT has been recommended as an effective reperfusion therapy for patients with AIS due to LVO,[12–14] and the therapeutic time window has been expanded to 24 hours,[15,16] the acceptance of MT in the extremely elderly population remains lower than that in the younger population. A study conducted in 2022 indicated that there was no statistically significant difference in SICH in patients with AIS due to anterior circulatory LVO within 6–24 hours onset who received MT compared with patients who did not receive MT.[35] However, this study did not focus on elderly patients and very few patients aged >80 years were included. To the best of our knowledge, this is the first comparative study to focus on the safety and efficacy of RT (including IVT and MT) in elderly patients with AIS aged >80 years in mainland China. The inclusion criteria for MT in this study were based on the DEFUSE-3 study, which suggests that MT can be considered when there is a mismatch between cerebral core infarction and hypoperfusion and high NIHSS scores are not contraindications.[11] We found that MT within 24 h was not a risk factor for SICH in AIS patients over 80 years of age, whereas a high NIHSS score at admission was an independent risk factor for SICH. Most patients (75.9%) in the MT group had severe neurological symptoms, possibly due to acute occlusion of the large arteries, whereas the proportion of patients with severe AIS was only 11.3% in the non-RT group and 34.0% in the IVT group, which led to the highest overall SICH rate (13.8%) in the MT group. In summary, this study indicates that RT (including IVT and MT) is safe in patients with AIS aged >80 years and does not increase the risk of SICH.

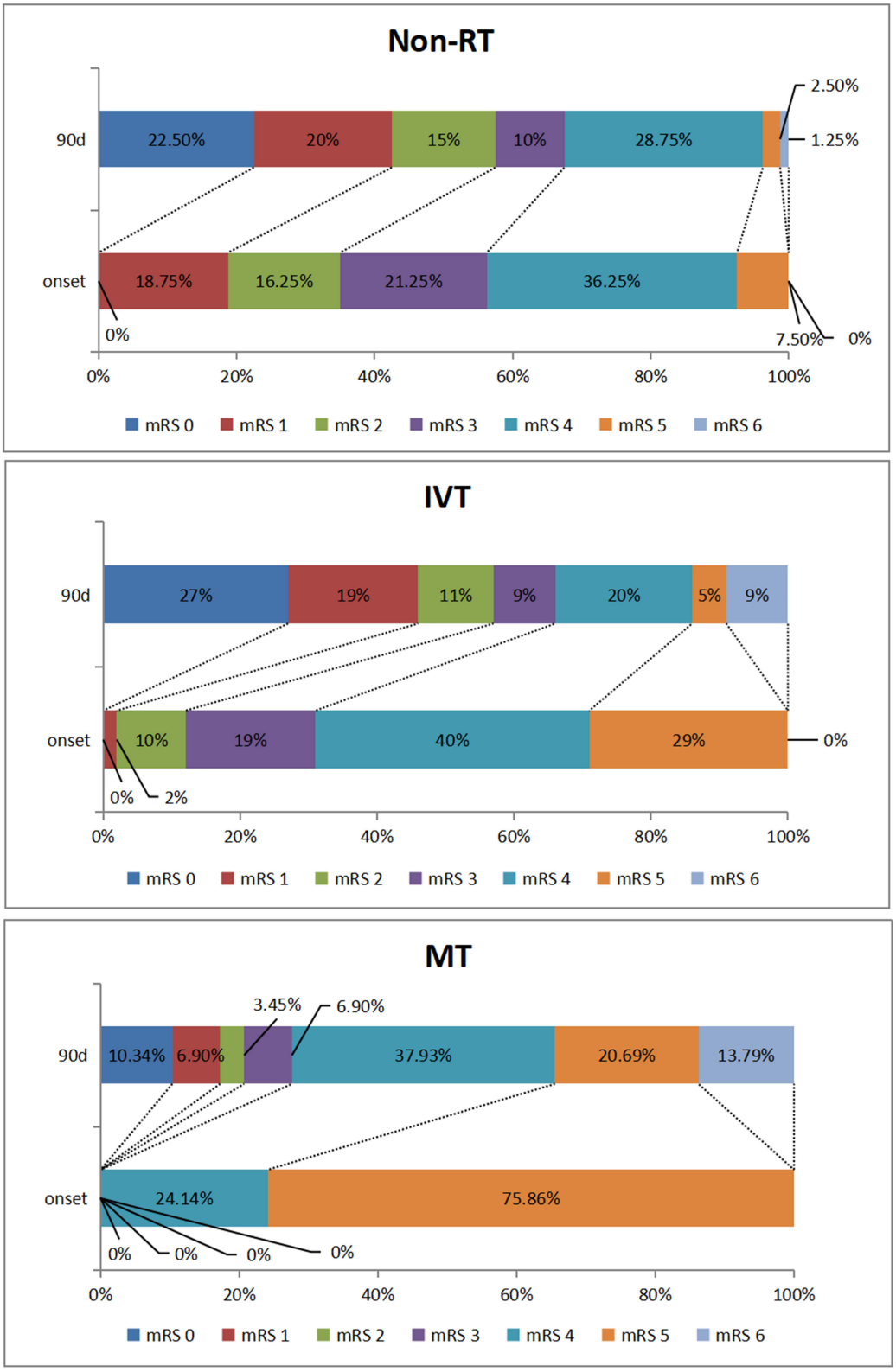

Figure 3 Dynamic changes of mRS before and after treatment at 90-day in different treatment groups.
Abbreviations: RT, reperfusion therapy; IVT, intravenous thrombolysis; MT, mechanical thrombectomy.

From the perspective of efficacy, although the overall 90-day good prognosis was higher in the non-RT and IVT groups, no difference was found for mild to moderate AIS after stratification according to the admission NIHSS. It is worth noting that for patients with severe AIS, timely IVT or MT treatment can achieve a much higher percentage of good prognosis than non-RT treatment. The analysis of dynamic changes in NIHSS and mRS scores further confirms the above conclusion: on the 90th day after MT treatment, the NIHSS score could be reduced by an average of 6 points, in which the IVT group decreased by 4 points, and only decreased by 2 points in the non-RT group. Our study showed that timely vascular recanalization is still the most effective treatment for patients with AIS over 80 years of age.

This study indicates that a high NIHSS score at admission, etiology classification of TOAST combined with LAA and CE, and SAP are risk factors for poor prognosis at 90-day in AIS aged >80 years. The NIHSS reflects neurological deficits and the severity of AIS, and it is not surprising that the higher the NIHSS score, the worse the prognosis. Kim et al[36] pointed out that AIS with LAA had a better prognosis than AIS with the TOAST classification of CE, which may be related to the formation of collateral circulation adapting to chronic occlusion of vessels and chronic ischemia. AIS patients with CE often experience sudden onset of arterial occlusion without sufficient time to produce collateral circulation. We found that patients with LAA combined with AF had poor outcomes, with no significant differences between the treatment groups. Patel et al[37] noted that not all strokes in patients with AF are caused by cardiac embolism, and about 40–50% of cases are caused by intracranial thrombosis or embolism from other sources. The nature of the thrombus and the cause of stroke are usually unclear because the current examination of stroke usually does not include histopathology. Further studies are needed to analyze the pathogenic processes, pathological mechanisms, and prognosis of patients with dual causes.

The inflammatory response caused by SAP exacerbates post-stroke brain injury and is an important cause of mortality after stroke.[24,38] The incidence of SAP in the non-RT (26.2%) and IVT (31.0%) groups was similar to those reported by Xu et al[39] and Smith et al.[40] One of the main causes of SAP is aspiration due to post-stroke consciousness disorders and swallowing dysfunction.[41] The MT group had more severe infarction and more patients with basilar artery occlusion, resulting in more patients with consciousness disorders and swallowing difficulties, which led to a significantly higher incidence of SAP in the MT group (79.3%) than in the other two groups.

Limitations

This study had several Limitations that require further clarification. This was a single-center study, and the sample size was small, especially in the MT group, which may have affected statistical validity. This study took five years to complete, during which the MT materials were continuously updated and iterated. New materials have more advantages, which may be confounding factors in SICH. Since organizational and process-of-care factors are major determinants of timely access to reperfusion interventions in AIS,[42] especially in the elderly who are generally at a disadvantage, the lack of consideration for the process of care was one of our limitations that needs to be clarified.

Conclusion

IVT and MT are safe for patients with AIS over 80 years of age and do not increase SICH. A high NIHSS score at admission is the main risk factor for SICH within 72 h and a predictor of poor outcome at 90-day. Compared with non-RT, patients receiving IVT or MT can achieve a greater reduction in NIHSS at 90-day, reducing disability, especially in patients with severe AIS. More research and a larger sample size are required to verify these conclusions.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Huizhou Central People's Hospital and Guangdong Medical University (kyl2021227).

Data Sharing Statement

The datasets used in this study are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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