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Associations between multiple acute infarctions and intracranial arterial stenosis with functional outcomes in anterior circulation acute ischaemic stroke reperfusion therapy: results from the China National Stroke Registry III

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ABSTRACT

Objective This study aims to observe the correlation between infarction pattern and intracranial arterial stenosis (ICAS) on magnetic resonance and functional outcome in acute ischaemic stroke (AIS) patients after reperfusion therapy.

Design This is a post hoc analysis of the Third China National Stroke Registry (CNSR-III) study.

Setting The data was derived from the CNSR-III study, which was a nationwide clinical registry of ischaemic stroke or transient ischaemic attack based in China.

Participants Patients with anterior circulation AIS who underwent reperfusion therapy were included for analysis. The patients were divided into single acute infarction and multiple acute infarctions (MAIs) based on the diffusion-weighted imaging findings. Additionally, patients were categorised according to the degree of ICAS assessed by magnetic resonance angiography as either ≥50% or <50%.

Primary outcome measures The primary outcome of this study was poor functional outcome at 12 months, defined as a modified Rankin Scale of 3–6.

Results In the included 796 patients, there were 152, 130 and 126 cases of unfavourable functional outcomes at 3 months, 6 months and 12 months, respectively. After adjusting for all potential confounding factors, MAIs were significantly associated with an increased risk of poor functional outcomes at 12 months (OR 1.96; 95% CI 1.27 to 3.02; p=0.0024). Similarly, ≥50% ICAS was also correlated with an increased risk of poor functional outcomes (OR 1.74; 95% CI 1.14 to 2.67; p=0.0110).

Conclusions Both MAIs and ≥50% ICAS were associated with poor functional outcomes in patients with anterior circulation AIS who received reperfusion therapy.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We used the MRI diffusion-weighted imaging sequence to quickly determine the type of infarction and magnetic resonance angiography to assess the degree of vascular stenosis with the functional outcomes during the patients with anterior circulation acute ischaemic stroke who received reperfusion therapy.
⇒ This study uses a conventional imaging method to provide new insights and methods to guide the clinical evaluation of patient prognosis.
⇒ The imaging assessment data were not detailed enough and the sample size was small.
⇒ All the patients were from China; further prospective research is needed to replicate our findings in diverse populations across different countries.

INTRODUCTION

Stroke is a leading cause of mortality and disability worldwide, and its prevalence has been rising in recent years. In China, the age-standardised incidence rate of stroke was around 246.8 per 100 000 persons in 2022.[1 2]

Reperfusion therapy, which includes pharmacological thrombolysis and thrombectomy, is a crucial treatment for acute ischaemic stroke (AIS), attempting to restore blood flow to the ischaemic penumbra as rapidly as possible. However, more than half of the patients still had substantial disability during the 3 months follow-up.[3–6] The prognosis of reperfusion therapy is critical for developing therapeutic treatment regimens for anterior circulation AIS. Therefore, finding rapid and effective methods to assess prognosis is crucial for guiding treatment and improving the ultimate outcome of stroke.

MRI has many advantages, including high sensitivity, strong objective accuracy and non-invasiveness, making it a primary auxiliary diagnostic tool in clinical practice. Magnetic resonance diffusion-weighted imaging (DWI) has been reported to predict functional outcome in AIS treatment by measuring

lesion volume on images.[7–10] However, this method is complex, time-consuming, and has poor consistency of results, making it difficult to adopt widely in clinical settings. Previous studies have lacked a rapid and effective imaging evaluation method. In our study, we used the MRI DWI sequence to quickly determine the type of infarction and magnetic resonance angiography (MRA) to assess the degree of vascular stenosis with the functional outcomes during the patients with anterior circulation AIS who received reperfusion therapy.

METHODS

Study population

The data was derived from the China National Stroke Registry III (CNSR-III), which was a nationwide multicentre clinical registry study of AIS or transient ischaemic attack (TIA) between August 2015 and March 2018 in China. Details of the CNSR-III study design and protocol have been published elsewhere.[11] Briefly, a total of 15 166 patients who were older than 18 years, hospitalised within 7 days from symptom onset and diagnosed with AIS or TIA were enrolled in the CNSR-III study. In the present study, we included patients with acute anterior circulation AIS who received reperfusion therapy, then excluded the patients with unavailable MRI data, inability to evaluate image quality, or missing data during 1 year following.

Standard protocol approvals, registrations and patient consents

The study protocol was evaluated and approved by the ethics committee of Beijing Tiantan Hospital and each participating site. All patients or their legal representatives provided written informed consent to participate.

Table 1 Baseline characteristics in patients stratified by diffusion-weighted imaging and intracranial arterial stenosis

		Infarction lesions on DWI			ICAS on MRA		
Variables	Total (n=796)	Single acute infarction (n=409)	Multiple acute infarctions (n=387)	P value	<50% (n=521)	≥50% (n=275)	P value
Age, years, median (IQR)	63.00 (55.00–70.00)	62.00 (54.00–68.00)	64.00 (57.00–72.00)	0.0019	63.00 (55.00–70.00)	62.00 (55.00–70.00)	0.5099
Male gender, n (%)	579 (72.73)	286 (69.93)	293 (75.71)	0.0670	373 (71.59)	206 (74.90)	0.3178
SBP, mm Hg, median (IQR)	150.00 (138.00–165.50)	152.00 (141.00–170.00)	146.50 (134.50–161.00)	<0.0001	151.00 (138.50–168.00)	148.00 (137.50–163.00)	0.0332
DBP, mm Hg, median (IQR)	87.00 (79–96)	89.00 (80.00–97.00)	85.00 (77.50–94.00)	0.0013	87.00 (79.50–96.50)	86.00 (78.00–94.50)	0.2438
mRS score on admission, median (IQR)	3.00 (1–4)	2.00 (1.00–4.00)	4.00 (1.00–4.00)	<0.0001	2.00 (1.00–4.00)	4.00 (2.00–4.00)	<0.0001
NIHSS score on admission, median (IQR)	6.00 (3.00–11.00)	5.00 (2.00–8.00)	8.00 (4.00–14.00)	<0.0001	5.00 (3.00–8.00)	9.00 (4.00–13.00)	<0.0001
Medical history, n (%)							
Hypertension	460 (57.79)	243 (59.41)	217 (56.07)	0.3402	299 (57.39)	161 (58.55)	0.7535
Diabetes mellitus	151 (18.97)	89 (21.76)	62 (16.02)	0.0390	101 (19.39)	50 (18.18)	0.6803
Hyperlipidaemia	52 (6.53)	25 (6.11)	27 (6.98)	0.6219	29 (5.57)	23 (8.36)	0.1288
Stroke	120 (15.08)	54 (13.20)	66 (17.05)	0.1291	66 (12.67)	54 (19.64)	0.0090
Coronary artery disease	75 (9.42)	30 (7.33)	45 (11.63)	0.0382	45 (50.00)	30 (55.56)	0.2968
Lifestyle habits, n (%)							
Drinking	357 (44.84)	178 (43.52)	155 (45.19)	0.8524	228 (43.76)	129 (46.90)	0.5350
Smoking	286 (35.93)	138 (33.74)	148 (38.24)	0.1858	186 (35.70)	100 (36.36)	0.8259
Family history of stroke	97 (12.18)	49 (11.98)	48 (12.40)	0.9835	58 (11.13)	39 (14.18)	0.3673
Medication history, n (%)							
Antiplatelet	106 (13.31)	48 (11.74)	58 (14.99)	0.1772	68 (13.05)	38 (13.82)	0.7622
Lipid-lowering	68 (8.54)	34 (8.31)	34 (8.79)	0.8116	45 (8.64)	23 (8.36)	0.8955
Anticoagulant	9 (1.13)	5 (1.22)	4 (1.03)	0.8011	5 (0.96)	4 (1.45)	0.5301

DBP, diastolic blood pressure; DWI, diffusion-weighted imaging; ICAS, intracranial arterial stenosis; MRA, magnetic resonance angiography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

Figure 1 Distribution of mRS score at 3 months, 6 months and 12 months stratified by DWI (A) and criminal ICAS (B). DWI, diffusion-weighted imaging; ICAS, intracranial arterial stenosis; mRS, modified Rankin Scale.

Image acquisition and analysis

All patients were asked to complete the MRI examinations on either a 3.0 or 1.5 T MRI scanner. The MRI of CNSR-III consisted of the T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery, DWI, three-dimensional time-of-flight MRA (3D-TOF-MRA). The range of intracranial arteries includes: bilateral internal carotid artery intracranial segment, middle cerebral artery M1 and M2 segments, anterior cerebral artery A1 and A2 segments, posterior cerebral artery (PCA) P1 and P2 segments, vertebral artery intracranial segment and basilar artery (BA). At baseline, patients with high signal lesions in the DWI sequence and new infarcts were divided into single acute infarction (SAI) and multiple acute infarctions (MAIs). Uninterrupted lesions visible in contiguous territories were defined as SAI, and more than one lesion topographically distinct were defined as MAIs. Evaluate the degree of criminal intracranial vascular stenosis using 3D-TOF-MRA. Equal to or more than 50% signal loss on MRA was considered significant to the categorisation of a stenosis pattern, then the participants were divided into ≥50% and <50%.

Baseline data collection

Trained research coordinators of CNSR-III collected baseline information following a standard data collection protocol developed by the steering committee. Baseline data included demographics (including age and gender), systolic blood pressure (SBP), diastolic blood pressure (DBP), lifestyle habits (including smoking and drinking status), prestroke modified Rankin Scale (mRS) score, National Institutes of Health Stroke Scale (NIHSS) score, medical history (including hypertension, diabetes mellitus, hyperlipidaemia, stroke and coronary artery disease), family history of stroke, and medication utilisation (including antiplatelet, lipid-lowering and anticoagulant).

Outcome assessment

The primary outcome of this study was unfavourable functional outcome at 12 months, defined as an mRS of 3–6. The secondary outcomes included unfavourable functional outcome at 3 months and 6 months. The follow-up period was 1 year, with face-to-face visits at 3 months and 12 months, and phone interviews conducted by trained research coordinators at 6 months.

Statistical analysis

The baseline categorical variables were described as frequency (percentage), while continuous variables were described as the median (IQR). The χ^2 tests or Fisher exact tests were used for categorical variables, and the Kruskal-Wallis tests were used for continuous variables to compare baseline characteristics differences among groups. Univariable and multivariable logistic regression analysis were conducted to investigate the relationship between (SAI, MAIs) infarction types and (≥50%, <50%) intracranial arterial stenosis (ICAS) with poor functional outcomes (mRS score of 3–6) by calculating ORs and 95% CIs. Adjustments for potential confounding factors with single-factor statistical p values <0.2 were made, including age, gender, SBP, DBP, prestroke mRS score, NIHSS score, medical history of diabetes mellitus, stroke, coronary artery disease and antiplatelet use.

Table 2 Associations between diffusion-weighted imaging infarct pattern and ≥50% intracranial arterial stenosis with poor prognostic function

Poor function outcome		Events, n (%)	Unadjusted		Adjusted	
			OR (95% CI)	P value	OR (95% CI)	P value
Infarction lesions on DWI						
12 months	Single acute infarction	41 (10.02)	ref		ref	
	Multiple acute infarctions	85 (21.96)	2.53 (1.69 to 3.78)	<0.0001	1.96 (1.27 to 3.02)	0.0024
6 months	Single acute infarction	42 (10.27)	ref		ref	
	Multiple acute infarctions	88 (22.74)	2.57 (1.73 to 3.83)	<0.0001	1.97 (1.28 to 3.03)	0.0019
3 months	Single acute infarction	54 (13.37)	ref		ref	
	Multiple acute infarctions	98 (25.52)	2.22 (1.54 to 3.21)	<0.0001	1.80 (1.21 to 2.67)	0.0036
ICAS on MRA						
12 months	<50%	62 (11.90)	ref		ref	
	≥50%	64 (23.27)	2.25 (1.53 to 3.30)	<0.0001	1.74 (1.14 to 2.67)	0.0110
6 months	<50%	62 (11.90)	ref		ref	
	≥50%	68 (24.73)	2.43 (1.66 to 3.56)	<0.0001	1.87 (1.23 to 2.86)	0.0035
3 months	<50%	70 (13.54)	ref		ref	
	≥50%	82 (30.26)	2.77 (1.93 to 3.98)	<0.0001	2.15 (1.45 to 3.19)	0.0001

Adjusted for age, gender, SBP, DBP, pre-stroke mRS score, NIHSS score, medical history of diabetes mellitus, stroke, coronary artery disease and antiplatelet use at baseline.
DWI, diffusion-weighted imaging; ICAS, intracranial arterial stenosis; MRA, magnetic resonance angiography; ref, reference.

To examine the robustness of the results, we explored the associations between MAIs as well as ≥50% ICAS and unfavourable functional outcomes within different subgroups. In the subgroup analysis, we divided the patients into subgroups based on age (<60 vs ≥60 years), gender (male vs female), prestroke mRS score (0–2 vs 3–5), and admission NIHSS score (≥4 vs <4).

A significance level of p<0.05 was considered statistically significant. Statistical analysis was conducted using SAS V.9.4 software (SAS Institute, Cary, NC, USA).

Table 3 Subgroup analyses of the association between diffusion-weighted imaging infarct pattern and intracranial arterial stenosis with unfavourable prognostic function at 12 months

Subgroup	Infarction lesions on DWI		P for interaction	ICAS on MRA		P for interaction
	Single acute infarction	Multiple acute infarctions		<50%	≥50%	
Age						
≥60	ref	1.54 (0.68–3.50)	0.8055	ref	1.66 (1.02–2.72)	0.9169
<60	ref	2.28 (1.37–3.81)		ref	1.70 (0.75–3.86)	
Gender						
Male	ref	1.73 (1.04–2.88)	0.3772	ref	1.45 (0.86–2.42)	0.7503
Female	ref	2.76 (1.14–6.71)		ref	2.21 (0.95–5.14)	
mRS score						
0～2	ref	1.64 (0.70–3.80)	0.5940	ref	1.19 (0.44–3.21)	0.4841
3～5	ref	2.14 (1.28–3.58)		ref	1.93 (1.19–3.15)	
NIHSS score						
≥4	ref	1.96 (1.23–3.11)	0.9853	ref	2.26 (1.46–3.51)	0.1011
<4	ref	1.81 (0.44–7.38)		ref	0.74 (0.14–4.01)	

Adjusted for age, gender, systolic blood pressure, diastolic blood pressure, prestroke mRS score, NIHSS score, medical history of diabetes mellitus, stroke, coronary artery disease and antiplatelet use at baseline other than the variable for stratification.
DWI, diffusion-weighted imaging; ICAS, intracranial arterial stenosis; MRA, magnetic resonance angiography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ref, reference.

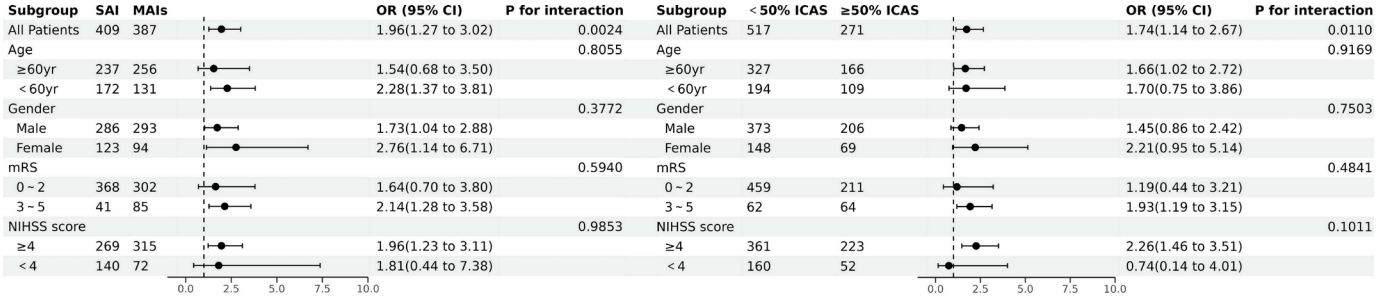

Figure 2 Subgroup analyses of the association between DWI infarct pattern and criminal ICAS with unfavourable prognostic function at 12 months. Adjusted for age, gender, systolic blood pressure, diastolic blood pressure, pre-stroke mRS score, NIHSS score, medical history of diabetes mellitus, stroke, coronary artery disease, and antiplatelet use at baseline other than the variable for stratification. DWI, diffusion-weighted imaging; ICAS, intracranial arterial stenosis; SAI, single acute infarction; MAIs, multiple acute infarctions; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Patient and public involvement

Patients and/or the public were not involved in this study.

RESULTS

Distribution

The data is derived from the CNSR-III, involving 15 166 cases of AIS or TIA patients. Among them, 1352 cases of AIS patients undergoing reperfusion therapy were included in the imaging substudy. Of these, 330 cases with indeterminate imaging quality were excluded, 43 cases lacking baseline DWI and MRA vascular examinations were excluded, 163 cases with posterior circulation infarction were excluded and 20 cases lost to follow-up were also excluded. In the end, a total of 796 patients were included in the final analysis (online supplemental figure S1).

Baseline characteristics

Based on the DWI infarct classification, patients were divided into 409 cases of SAI (51.4%) and 387 cases of MAIs (48.6%). The patients in the MAI group were more likely to have older age, higher NIHSS scores, higher prestroke mRS scores and a history of coronary artery disease at baseline. According to the degree of ICAS on MRA, there were 275 individuals (34.5%) ≥50% ICAS and 521 individuals (65.5%) <50% ICAS. The patients with ≥50% ICAS were more likely to have higher NIHSS scores, higher prestroke mRS scores, higher blood pressure and a history of stroke. Baseline demographic and clinical feature data are presented (table 1).

Associations of DWI infarct pattern and ICAS association with unfavourable prognostic function

This study included a total of 796 patients undergoing reperfusion therapy for acute anterior circulation cerebral infarction. There were 126 (15.83%) participants with unfavourable prognostic function at 12 months, as well as 152 (19.10%) and 130 (16.33%) participants with unfavourable prognostic function at 3 months and 6 months (figure 1).

In univariate analysis, the proportion of poor functional outcomes was higher in MAIs compared with SAI; these differences were statistically significant (p<0.05). After adjusting for potential confounding factors, MAIs were associated with a higher risk of poor functional outcomes at 12 months, with an OR of 1.96 (95% CI 1.27 to 3.02; p=0.0024). In univariate analysis, the proportion of poor functional outcomes was also higher in cases with ≥50% ICAS compared with <50% ICAS. After adjusting for potential confounding factors, ≥50% ICAS was associated with a higher risk of poor functional outcomes at 12 months, with an OR of 1.74 (95% CI 1.14 to 2.67; p=0.0110). These results indicate that MAIs and ≥50% ICAS are independent risk factors for poor functional outcomes in patients undergoing reperfusion therapy for acute anterior circulation infarction (table 2).

Subgroup analysis

The associations remained steady in the subgroup analysis, which was based on age, gender, prestroke mRS score and NIHSS score, all P for interaction >0.05 (table 3 and figure 2).

DISCUSSION

Based on the CNSR-III study, our study indicates that MAIs and ≥50% ICAS were associated with an increased risk of poor functional outcomes at 12 months, as well as 3 months and 6 months during the Chinese anterior circulation AIS received reperfusion therapy.

Previous studies have considered infarct volume as an indicator for predicting the prognosis of AIS.[12–18] Measuring the volume of lesions through DWI has been deemed a potential predictor for the functional outcomes after reperfusion therapy for acute cerebral infarction. Tei *et al* found that DWI scores could predict the neurological functional prognosis of patients, but this method cannot be completed in a short period, and the results derived from infarct volume lack consistency.[19] Although artificial intelligence has made some progress, it is not yet widely applicable in clinical settings. Further research is needed to find other simpler and more reasonable alternative evaluation methods.[20] In our study, the results showed that MAIs were an independent risk factor for poor

functional outcomes after reperfusion therapy for acute anterior circulation cerebral infarction. Baseline data in our study indicated statistical significance for risk factors such as hypertension and age between the SAI and MAI groups. The higher the NIHSS score and mRS score on admission, the more severe the neurological impairment and the worse the prognosis. Previous studies have found that an SBP of ≥160 mm Hg on admission and a history of prior stroke predict unfavourable clinical outcomes for non-lacunar infarctions. For high-risk patients, reperfusion therapy should be performed as soon as possible to reduce neurological damage. Additionally, it is essential to strictly control blood pressure and initiate rehabilitation treatment promptly.[16–21] After adjusting for the potential confounding factors including blood pressure and age, we found that MAIs remained an independent risk factor for poor functional outcomes. The common mechanism behind the occurrence of MAIs is often related to extracranial/intracranial major vessel embolism. Previous studies on infarct types have focused more on their correlation with arterial atherosclerosis, and there is limited research on their correlation with functional outcomes.[22 23] Our study results provide new insights and methods to guide clinical assessment of patient prognosis and the development of corresponding treatment plans. Moreover, stratifying the risk of unfavourable functional outcomes in acute anterior circulation stroke based on the number of infarcts (SAIs or MAIs) is convenient and quick in clinical practice.

Previous studies have found that ICAS is associated with the highest recurrence risk among large artery atherosclerosis subtypes in ischaemic stroke (IS).[23–25] In our study, univariate and multivariate regression analysis revealed that ≥50% ICAS was an independent risk factor for poor functional outcomes at 3 months, 6 months and 12 months after reperfusion therapy for anterior circulation AIS. Ois *et al* found that within the first 72 hours after the onset of mild stroke and TIA in patients with ≥50% carotid artery stenosis, 27.6% experienced early recurrent cerebrovascular events.[25] Suo *et al* observed a higher risk of recurrence in patients with acute minor ischaemic stroke or TIA combined with ICAS.[22] In the studies by Lee *et al*, early neurological deterioration in IS patients was associated with ICAS, especially with stenosis in the BA or PCA,[12 26–29] and this association was independent.[29–32] Our results are consistent with previous research, suggesting that assessing responsibility for ICAS using 3D-TOF-MRA can be a complementary approach to traditional risk stratification.

Our study has several limitations. First, infarct types were grouped based on the number of infarcts, and the infarct volume was not measured. Second, we did not analyse the treatments subgroup such as thrombolytic therapy or mechanical thrombectomy, because there were fewer cases of mechanical thrombectomy in our study group. Third, strict inclusion and exclusion criteria were implemented, and the imaging subgroup analysis was based on single-centre data with a small number of patients, which may introduce potential selection bias. Finally, because all patients in our study were from China, further prospective research is needed to replicate our findings in diverse populations across different countries.

Conclusion

In our study, we found both MAIs and ≥50% ICAS were associated with poor functional outcomes in patients with acute anterior AIS who received reperfusion therapy. Both MAIs and ≥50% ICAS in anterior circulation AIS patients should get more attention.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the ethics committee at Beijing Tiantan Hospital (KY2019-109-01). The study protocol of the CNSR-III was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centres. Every participant provided written informed consent before participation. Participants gave informed consent to participate in the study before taking part.

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