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Distribution and prognosis of acute ischaemic stroke with negative diffusion-weighted imaging

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ABSTRACT

Background and purpose To examine the distribution and prognosis among patients with diffusion-weighted imaging (DWI)-negative acute ischaemic stroke (AIS) and explore the differences between mild (National Institute of Health Stroke Scale (NIHSS) score ≤5) and major (NIHSS score >5) ischaemic stroke in DWI-negative patients.

Methods Patients with AIS with baseline DWI from the Third China National Stroke Registry (CNSR-III), based on a prospective, observational, multicentre cohort study, between August 2015 and March 2018, were included. Patients were classified into negative and positive DWI groups depending on the existence of acute lesions on DWI.

Results Among 12 026 patients who had an ischaemic stroke, 932 (7.7%) had negative DWI. As the NIHSS score increased, the proportion of patients with DWI-negative AIS gradually decreased. Negative DWI was associated with a decreased risk of stroke recurrence (HR 0.63, 95% CI 0.49 to 0.82), combined vascular events (HR 0.72, 95% CI 0.56 to 0.92), mortality (HR 0.60, 95% CI 0.36 to 0.995) and poor functional outcomes (OR 0.57, 95% CI 0.43 to 0.76) within 1 year in all patients. Similar associations were observed in patients with mild AIS (p<0.05 for all) but not in patients with major AIS, excluding poor functional outcomes (OR 0.47, 95% CI 0.28 to 0.81).

Conclusions The proportion of patients with DWI-negative AIS gradually decreased as the NIHSS score increased, and negative DWI was mainly observed in patients with mild AIS. Negative DWI was associated with a better prognosis for all patients with AIS. However, these associations were significant for mild AIS but not for those with major AIS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Limited studies have investigated the prognosis of patients with negative diffusion-weighted imaging (DWI), and most of the studies have focused on minor ischaemic stroke and have reached controversial conclusions.

WHAT THIS STUDY ADDS

⇒ Negative DWI was associated with decreased risks of 1-year recurrent stroke, combined vascular events and poor functional outcomes in patients with acute ischaemic stroke (AIS). And similar association was observed in patients with mild AIS but not observed in patients with major AIS except for poor functional outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The results suggested that for patients with mild stroke, negative DWI could be an imaging marker for a better prognosis, which may help to stratify risk. However, for patients with major stroke, acute treatment and secondary prevention should not be neglected when lesions are not found on DWI.

INTRODUCTION

Stroke is the main cause of disability and death throughout the world, especially in China.[1 2] Early identification of patients with acute ischaemic stroke (AIS) and timely acute treatment are crucial for patient prognosis.[3] Routine brain CT scans are done to exclude intracranial haemorrhage; however, this modality is not sensitive enough for ischaemic stroke. Recently, applications of brain MRI,[4] especially diffusion-weighted imaging (DWI), in evaluating AIS have soared due to its significantly higher sensitivity (88%–100%) and specificity (95%–100%).[5 6] Currently, DWI is recommended by guidelines to obtain the most accurate diagnosis of AIS,[7] and plays a prominent role in the early identification of core infarction.[8] In addition, the existence of lesions on DWI serves as the foundation for tissue-based definitions, which could differentiate between transient ischaemic attack (TIA) and ischaemic stroke.[9]

Following previous studies, a substantial proportion of patients with DWI-negative stroke exists.[10–12] A recent meta-analysis involving 3236 patients from 12 studies found a prevalence of 6.8% for DWI-negative AIS.[10] Some studies have indicated that 40%–60% of patients had negative DWI findings in minor ischaemic stroke.[10 13–15] The occurrence of AIS with negative DWI findings may be attributed to posterior circulation ischaemia,[10 12] small volume infarction[12] and hyperacute ischaemia.[16–18] However, few studies have examined the prognosis of DWI-negative patients, and most of the studies have focused on

minor ischaemic stroke and have reached controversial conclusions.[13 15]

To date, two other major issues need to be clarified: first, although the prevalence of DWI-negative AIS has been studied, the distribution of negative DWI findings among patients with AIS is unclear. The relationship between the distribution of negative DWI and the National Institute of Health Stroke Scale (NIHSS) score is unknown either. Second, research on the prognosis in DWI-negative patients with AIS is limited. Furthermore, the differences between mild stroke (NIHSS score ≤5) and major stroke (NIHSS score >5) are uncertain.

The purpose of this study was to investigate the distribution and prognosis for patients with DWI-negative AIS, who were further divided into those with mild and major strokes, in the Third China National Stroke Registry (CNSR-III), a large multiple stroke registry in China.

METHODS

Study design and population

We analysed the data obtained from the CNSR-III, which is a nationwide prospective registry for patients with AIS or TIA between August 2015 and March 2018 in China. The protocol for the CNSR-III was previously published.[19] Participants were enrolled consecutively if they were as: (1) age >18 years, (2) diagnosed with ischaemic stroke or TIA within 7 days, and (3) participants or legally authorised agents provided informed consent. Patients with silent cerebral infarction, or declining to attend the registry, were excluded. Patients diagnosed as TIA or stroke mimics were excluded. AIS and TIA were diagnosed using WHO criteria (acute episode of neurological deficit, lasting less than 24 hours in the case of a TIA, more than 24 hours in the case of an ischaemic stroke).[20] In this current study, patients with AIS diagnosed at admission and who completed DWI scans at baseline were included.

Clinical data acquisition

Baseline data, such as demographics, medical history and medication utilisation, were derived from medical records using a standard protocol by uniformly trained researchers. NIHSS scores were gathered through the face-to-face interview on admission. The electronic data capture (EDC) system was applied to collect clinical data. Clinical outcomes were obtained through 3-month face-to-face interviews and 12-month telephone interviews. During follow-up, we keep records of all stroke recurrences, combined vascular events, mortality and poor functional outcome. The new focal neurological deficits caused by ischaemic or haemorrhagic stroke events confirmed by MRI or CT were defined as recurrent stroke. The new onset of stroke, myocardial infarction or cardiovascular death was defined as a combined vascular event. Modified Rankin Scale scores of 3–6 were used to define poor functional outcomes. We divided patients into mild and major ischaemic stroke groups according to NIHSS score (NIHSS score ≤5 vs NIHSS score >5).

Imaging data collection and analysis

All patients without contraindications to MRI had standard brain MRI scans on either a 3.0 T or 1.5 T MRI scanner. Baseline brain scans were acquired during hospitalisation. DWI, apparent diffusion coefficient, T1/T2-weighted, fluid-attenuated inversion recovery, intracranial and extracranial vascular imaging sequences were recommended. The MRI parameters used for the current research were published.[19]

All imaging data were analysed centrally by trained experts and interpreted using the EDC system's standard forms, providing details on the presence and location of infarctions, etc. A visible hyperintense lesion on DWI was defined as acute infarction. According to the presence of acute infarction, we divided the patients into DWI-negative and DWI-positive groups. Patients with persistent focal neurological symptoms for more than 24 hours but no areas of hyperintensity observed on DWI were defined as DWI-negative patients. Two neuroradiologists remained blinded to the patient clinical symptoms while simultaneously interpreting patient images. A third neuroradiologist was brought in to resolve any disagreements.

Aetiological classification

The aetiological classification of ischaemic stroke was conducted using the Trial of Org 10172 in Acute Stroke Treatment criteria.[21] Neurologists and radiologists evaluated each centralised stroke subtype based on a previously established standardised element.[22] Two experts interpreted each case and recorded it on a standardised report form in the EDC system. They remained blind to one another's input data during interpretation. A third expert resolved the discrepancies between the two.

Statistical analysis

Continuous variables are presented as the median and IQR, while categorical variables are described as frequencies and proportions. Student's t-test, the Mann-Whitney U test and the X^2 test were performed for comparing baseline characteristics between groups. Kaplan-Meier survival analysis was used to calculate the 1-year stroke recurrence risk of DWI-negative patients with AIS. Multivariate Cox proportional hazards regression models (adjusting for all possible confounders derived from the univariate analysis) were used to evaluate the association between negative DWI and prognosis in overall patients and those with mild stroke (NIHSS score ≤5) and major stroke (NIHSS score >5). As the timing of the MRI scan is crucial, in addition to the hyperacute phase, a delayed scan time may also be associated with the existence of a negative DWI, as the sensitivity of DWI for stroke decreases rapidly with time, especially after 1 week. Therefore, to minimise the effect of this factor, we also performed a secondary analysis after excluding patients whose scan time was in the hyperacute phase and longer than 7 days. In addition, we attempted to examine the association between negative DWI and prognosis in a more detailed subgroup analysis of patients who had a minor, mild, moderate and severe

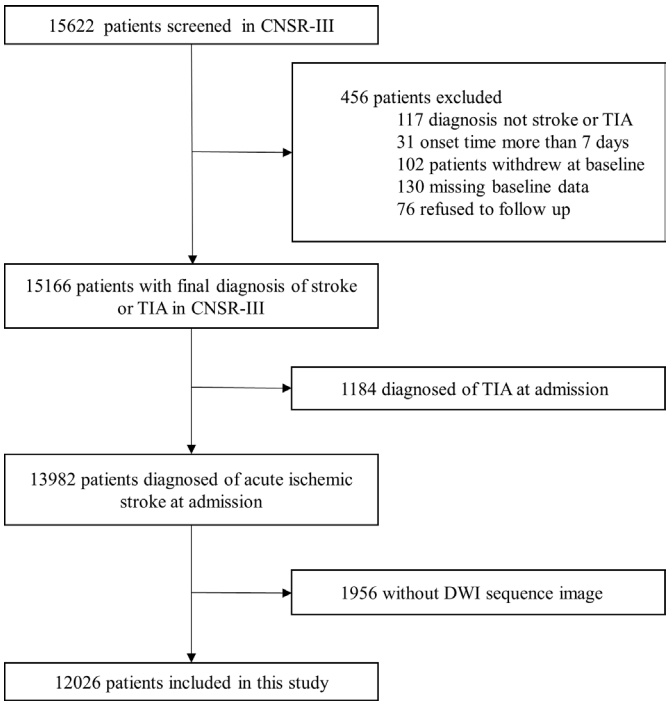

Figure 1 The study population flow chart. CNSR-III, Third China National Stroke Registry; DWI, diffusion-weighted imaging; TIA, transient ischaemic attack.

stroke. All statistical analyses were performed using SAS V.9.4 software (SAS Institute), and a p value of less than 0.05 on both sides was considered significant.

RESULTS

Baseline characteristics

The CNSR-III study initially screened 15 622 patients according to the inclusion criteria. After excluding patients with the diagnosis of TIA or stroke mimics and other causes, the CNSR-III study included a total of 15 166 patients with the final diagnosis of stroke or TIA (figure 1). There were 12 026 patients who had an ischaemic stroke with DWI sequences during hospitalisation enrolled in the current study (figure 1). The enrolled and excluded patients had similar characteristics (online supplemental table 1). The median age was 63 (55–70) years, and 8244 (68.6%) patients were men. There were 932 (7.7%) patients with negative DWI. Compared with patients with positive DWI, negative DWI patients were older, likely to be female, had lower baseline NIHSS scores, had shorter event-to-enrolment time, and likely to have a medical history of stroke, TIA, coronary artery disease, dyslipidaemia, and treatment with recombinant tissue plasminogen activator (rt-PA), and less likely to be smokers or drinkers (table 1). The characteristics of patients with and without positive DWI stratified by stroke severity are further presented in online supplemental table 2.

Figure 2 shows the distribution of patients with negative DWI across different NIHSS scores. The proportion of DWI-negative lesions tended to decrease with increasing NIHSS scores, and for patients with NIHSS scores ≥20, no DWI negativity was observed (figure 2).

One-year outcomes

There were 1159 (9.64%) recurrent strokes, 1222 (10.16%) combined vascular events, 388 (3.23%) death from any cause and 1627 (13.87%) poor functional outcomes.

For all patients, after adjustment for possible confounders in univariate analysis, the patients with negative DWI had significantly reduced risks of stroke recurrence, combined vascular events, mortality and poor functional outcomes (table 2). Similarly, among patients with mild AIS, DWI-negative patients exhibited a decreased risk of stroke recurrence, combined vascular events, mortality and poor functional outcome. However, among patients with major AIS, an association was not observed (p>0.05), except for poor functional outcomes (table 2). The Kaplan-Meier curve estimated the cumulative 1-year stroke recurrence risk (figure 3). During 3-month follow-up, we observed similar results (online supplemental table 3). Even after the exclusion of patients with MRI performed within the first 2 hours from the onset of symptoms and more than 7 days after stroke onset for analysis, consistent results were obtained (online supplemental table 4). Besides, we further did more detailed subanalyses of patients (NIHSS 0–2 vs 3–5 vs 6–13 vs >14) and found that DWI-negative patients with minor strokes had a better prognosis, and this association attenuated as the NIHSS score increased (online supplemental table 5).

DISCUSSION

In this study, we discovered that the proportion of DWI-negative patients gradually decreased as the NIHSS score increased, and the majority of those with negative DWI findings were patients with mild AIS. Moreover, we observed that among all enrolled patients, the prognosis of patients with AIS with negative DWI was better, and DWI-negative patients showed lower risks of recurrent stroke, combined vascular events, mortality and poor functional outcomes. However, although these associations were significant in patients who had a mild stroke, they were not obvious in patients who had a major stroke.

The rate of patients with DWI-negative ischaemic stroke in our study was 7.7%, which was comparable with the 6.8% in a previous meta-analysis of the prevalence of DWI-negative AIS.[10] Our study showed that the proportion of DWI-negative lesions gradually decreased ranging from 17.34% to 0%, as the NIHSS score increased from 0 to 17. This decreasing trend was similar to that observed in the Oxford Vascular Study, although that study only analysed patients with minor strokes (NIHSS score ≤3).[13] Furthermore, among patients with AIS, we found a high proportion of DWI-negative patients with mild stroke (NIHSS score ≤5) and a low proportion of those with major stroke (NIHSS score >5). Despite this, the proportion of

Table 1 Study population baseline characteristics

	DWI– (n=932)	DWI+ (n=11 094)	P value
Age, year	63 (57–72)	63 (54–70)	0.0045
Male	553 (59.33)	7691 (69.33)	<0.0001
NIHSS at admission	2 (1–4)	4 (2–6)	<0.0001
Time from event to enrolment, day	1 (0–3)	2 (1–4)	<0.0001
Time from event to MRI, day	2 (1–4)	2 (1–4)	0.5317
Medical history			
Hypertension	591 (63.41)	7006 (63.15)	0.8740
Diabetes mellitus	208 (22.32)	2583 (23.28)	0.5026
Stroke	257 (27.58)	2396 (21.60)	<0.0001
TIA	31 (3.33)	208 (1.87)	0.0023
Coronary artery disease	116 (12.45)	1081 (9.74)	0.0081
Atrial fibrillation	35 (3.76)	771 (6.95)	0.0002
Dyslipidaemia	88 (9.44)	819 (7.38)	0.0222
Current smoker	237 (25.43)	3593 (32.39)	<0.0001
Heavy drinker	103 (11.05)	1601 (14.43)	0.0045
Treated with rt-PA	152 (16.31)	978 (8.82)	<0.0001
Medication use at discharge			
Antiplatelet	860 (92.27)	10 083 (90.89)	0.1552
Anticoagulants	13 (1.39)	323 (2.91)	0.0070
Antihypertensive agent	395 (42.38)	5556 (50.08)	<0.0001
Lipid-lowering agent	846 (90.77)	10 193 (91.88)	0.2374
TOAST classification			<0.0001
Large artery atherosclerosis	194 (20.82)	3001 (27.05)	
Cardioembolism	50 (5.36)	670 (6.04)	
Small artery occlusion	0 (0.00)	2896 (26.10)	
Other determined aetiology	15 (1.61)	152 (1.37)	
Undetermined aetiology	673 (72.71)	4375 (39.44)	

Variables are shown as median (IQR) or number (%).
Time from event to enrolment is defined as the time from disease onset to patient signing an informed consent form.
DWI, diffusion-weighted imaging; NIHSS, National Institute of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; TIA, transient ischaemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

DWI-negative patients with mild stroke in our study was still much lower than that in the Oxford Vascular Study (86.1% for those with TIA and 34.9% for those with an NIHSS score of 3).[13] We speculate that these differences are due to the composition of the study population. The Oxford Vascular Study was a population-based cohort in which all patients with stroke-related symptoms were enrolled, with low rates of missed diagnosis. In contrast, the CNSR-III comprised a hospital-based cohort. Considering the low awareness and low consultation rate of patients with mild stroke symptoms in China, a substantial number of patients with transient stroke symptoms did not visit the hospital for medical attention.[23] More importantly, these patients were more likely to present as DWI negative.[14] Therefore, this underdiagnosis may contribute to the underestimation of the rate of negative DWI in mild strokes.

In our study, we found that patients who had an ischaemic stroke with negative DWI findings had a better prognosis. Established studies aimed at investigating the effect of DWI negativity on the prognosis of patients with AIS are rare and have mainly focused on patients with minor strokes.[10 15 24 25] Some studies have yielded inconsistent results with a limited sample size.[15] The Oxford Vascular Study, a population-based study of TIA or minor stroke, showed that positive DWI was associated with higher long-term stroke recurrence risk for patients with an NIHSS score of 0–1 (OR 3.03, 95% CI 1.29 to 7.08), but not those with an NIHSS score of 2–3.[10] Our study further stratified patients who had a stroke in more

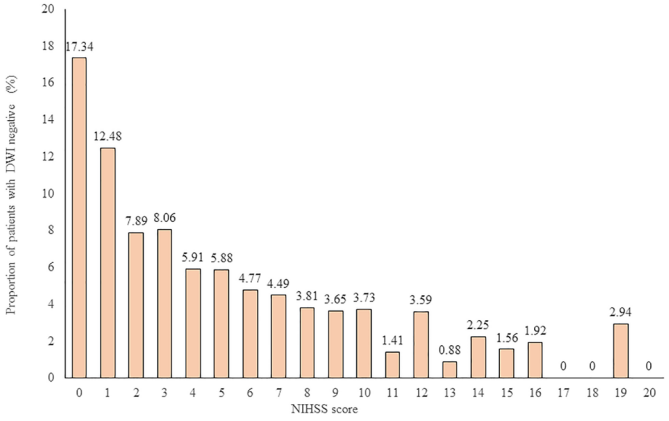

Figure 2 The distribution of proportion of negative DWI patients in different NIHSS scores. Proportion of patients with no acute lesion at baseline DWI in different NIHSS scores. DWI, diffusion-weighted imaging; NIHSS, National Institute of Health Stroke Scale.

detail, and we also found that the association between DWI negativity and stroke recurrence was significant in patients with minor strokes. The TIAregistry.org project, an international registry focused on TIA and minor stroke, identified an elevated recurrent stroke risk in patients with acute infarction, demonstrating that brain imaging could stratify stroke recurrence risk after TIA or minor stroke.[24] Unfortunately, this study did not distinguish between patients with TIA and minor stroke, and no further stratification was performed. The Diagnosis of Uncertain-Origin Benign Transient Neurological Symptoms Study also found that for recurrent stroke, normal MRI scans provided a negative predictive value of 99.8%, but that study only included patients with low-risk focal neurological symptoms.[26]

The key finding in our research indicated that the prognostic value of DWI negativity in predicting recurrent stroke varied between patients with mild and major AIS. According to clinical guidelines, there are differences in the treatment strategies for mild stroke and major stroke in the acute phase. Major stroke should be treated with intravenous thrombolysis and thrombectomy, while mild stroke should be treated with antithrombotic therapy. Therefore, our findings have distinct implications for the current treatment strategies. First, we discovered that in patients with mild stroke, DWI-negative patients had a significantly better prognosis than DWI-positive

Table 2 One-year prognosis of patients with DWI brain imaging (DWI+) and without (DWI–) stratified with stroke severity

	DWI–	DWI+	Model 1		Model 2	
Outcome	**Events (%)**	**Events (%)**	**HR/OR (95% CI)**	**P value**	**HR/OR (95% CI)**	**P value**
Total (n=12 026)	(n=932)	(n=11 094)				
Stroke recurrence	63 (6.76)	1096 (9.88)	0.65 (0.51 to 0.84)	0.0009	0.63 (0.49 to 0.82)	0.0006
New ischaemic stroke	57 (6.12)	1011 (9.11)	0.64 (0.49 to 0.83)	0.0009	0.60 (0.46 to 0.79)	0.0002
Recurrent haemorrhage stroke	6 (0.64)	101 (0.91)	0.72 (0.32 to 1.64)	0.4358	0.97 (0.41 to 2.27)	0.9386
Combined vascular event	69 (7.40)	1153 (10.39)	0.68 (0.53 to 0.86)	0.0017	0.72 (0.56 to 0.92)	0.0096
Death from any cause	16 (1.72)	372 (3.35)	0.47 (0.28 to 0.77)	0.0028	0.60 (0.36 to 0.995)	0.0480
Poor functional outcome*	65 (7.19)	1562 (14.42)	0.41 (0.32 to 0.54)	<0.0001	0.57 (0.43 to 0.76)	<0.0001
NIHSS ≤5 (n=8562)	(n=809)	(n=7753)				
Stroke recurrence	51 (6.30)	716 (9.24)	0.65 (0.49 to 0.87)	0.0033	0.60 (0.45 to 0.81)	0.0007
New ischaemic stroke	46 (5.69)	667 (8.60)	0.63 (0.47 to 0.85)	0.0025	0.57 (0.42 to 0.77)	0.0003
Recurrent haemorrhage stroke	5 (0.62)	58 (0.75)	0.85 (0.34 to 2.11)	0.7197	1.10 (0.42 to 2.87)	0.8495
Combined vascular event	57 (7.05)	750 (9.67)	0.70 (0.53 to 0.91)	0.0088	0.72 (0.55 to 0.95)	0.0209
Death from any cause	9 (1.11)	167 (2.15)	0.47 (0.24 to 0.92)	0.0276	0.47 (0.24 to 0.93)	0.0300
Poor functional outcome*	46 (5.82)	609 (8.03)	0.64 (0.47 to 0.88)	0.0052	0.63 (0.46 to 0.88)	0.0060
NIHSS >5 (n=3464)	(n=123)	(n=3341)				
Stroke recurrence	12 (9.76)	380 (11.37)	0.80 (0.45 to 1.42)	0.4448	0.85 (0.47 to 1.52)	0.5764
New ischaemic stroke	11 (8.94)	344 (10.30)	0.80 (0.44 to 1.47)	0.4770	0.85 (0.46 to 1.56)	0.5939
Recurrent haemorrhagic stroke	1 (0.81)	43 (1.29)	0.66 (0.09 to 4.81)	0.6829	0.70 (0.09 to 5.24)	0.7277
Combined vascular event	12 (9.76)	403 (12.06)	0.75 (0.42 to 1.33)	0.3277	0.78 (0.44 to 1.40)	0.4133
Death from any cause	7 (5.69)	205 (6.14)	0.81 (0.38 to 1.73)	0.5897	1.05 (0.48 to 2.26)	0.9107
Poor functional outcome*	19 (16.67)	953 (29.39)	0.41 (0.25 to 0.69)	0.0007	0.47 (0.28 to 0.81)	0.0061

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, NIHSS at admission, event-to-enrolment time, medical history of stroke, TIA, coronary artery disease, atrial fibrillation, dyslipidaemia, current smoker, heavy drinker, treated with rt-PA, anticoagulants, antihypertensive agent and TOAST classification.
*Modified Rankin Scale score was missing for 292 patients at 1 year. Logistic regression analysis was conducted on the remaining population.
DWI, diffusion-weighted imaging; NIHSS, National Institute of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; TIA, transient ischaemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

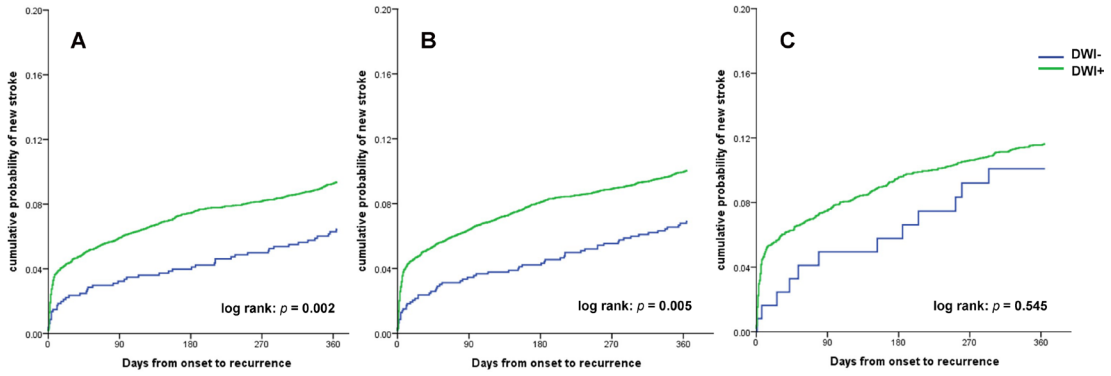

Figure 3 Kaplan-Meier graphs for 1-year risk of recurrent stroke and stratified by stroke severity (NIHSS ≤5 vs NIHSS >5). The 1-year risk of stroke recurrence in overall patients (A), patients who had a mild stroke (B), and patients who had a major stroke (C) with negative DWI and those without. DWI, diffusion-weighted imaging; NIHSS, National Institute of Health Stroke Scale.

patients, suggesting that DWI negativity can be used as an imaging indicator for a good prognosis. The presence of infarction on DWI could be applied for the risk stratification in patients who had a mild stroke. Because of the high stroke recurrence risk in patients who had a mild stroke,[24] it is crucial to perform risk scoring, and the analysis of additional images may contribute to the predictive value of risk scoring.[27] On the other hand, we also found that among patients who had a major stroke, although rare, DWI-negative infarctions also existed. These DWI-negative patients had a similar risk of stroke recurrence as DWI-positive patients. Therefore, for patients with major stroke, standard treatment (especially intravenous alteplase treatment and mechanical thrombectomy) should be given within the appropriate time window, regardless of the presence or absence of infarction, to prevent delayed treatment. Even if stroke mimics are given intravenous thrombolysis, the risk of complications will not increase.[28–30] In addition, it was remarkable that among patients whose NIHSS score was 20 or higher, no DWI-negative patients were identified. These results suggested that in patients with higher NIHSS scores, if DWI is negative, clinicians need to be more cautious in diagnosing AIS.

Strengths of our study included that a prospective, multicentre, hospital-based cohort provided the data for this study. All image interpretation and event adjudication were performed centrally, reducing the potential bias caused by inconsistency among subcentres. This is, to our knowledge, the largest study exploring the prognosis of patients with AIS who are DWI negative. However, some limitations still exist. First, the NIHSS score for the entire population was low, and 71% of patients had mild strokes with an NIHSS score ≤5, which may cause bias. Second, the MR examination times were not uniform but 94.6% of the images were acquired within 7 days of onset. To minimise the effect of MRI scan time, we also performed a secondary analysis after excluding patients whose scans were in the hyperacute phase and longer than 7 days, and obtained essentially unchanged results, suggesting the robustness of our results. Third, the scanners included 1.5 T and 3.0 T devices, so the magnetic field strength was not consistent. Fourth, our findings were primarily based on the Chinese population and cannot be generalised to people of other ethnicities. Finally, although the CNSR-III study excluded most patients diagnosed as stroke mimics, there may also be some stroke mimics left, which could lead to selection bias. Future studies gathering more detailed information about clinical symptoms/syndromes, clinical course and timing of MRI to disentangle different profiles of DWI-negative patients, including different risk factors, clinical prognosis and treatment indications, have considerable clinical significance.

CONCLUSIONS

The rate of DWI negativity in patients with AIS was high, especially in patients who had a mild stroke, and the proportion of DWI negativity tended to gradually decrease as the NIHSS score increased. DWI negativity was associated with low stroke recurrence, most notably in patients with mild stroke, but not in those with major stroke. The results suggested that for patients with mild stroke, DWI negativity could be an imaging marker for a better prognosis, which may help to stratify risk. However, for patients with major stroke, DWI might not be useful for predicting clinical outcomes. Acute treatment and secondary prevention should not be neglected when lesions are not found on DWI.

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Contributors YJW is responsible for the overall content as the guarantor, have access to the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis. YJW, YW and JJ contributed to conception and design of the study. YJW and MW organised the database. YP and MW performed the statistical analysis. YW wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Ethics approval The Ethics Committee of Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centres have approved the CNSR-III protocol. Written informed consent was provided from all patients.

Provenance and peer review Not commissioned; externally peer reviewed.

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.

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