



NIHSS–the Alberta Stroke Program Early CT Score mismatch in guiding thrombolysis in patients with acute ischemic stroke

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Abstract

Objective This study investigates the mismatch between the National Institutes of Health Stroke Scale (NIHSS) score and the computed tomography (CT) findings measured by the Alberta Stroke Program Early CT Score (ASPECTS) for predicting the functional outcome and safety of intravenous thrombolysis (IVT) treatment in patients with acute ischemic stroke (AIS).

Methods This prospective observational study includes patients with AIS who underwent CT imaging within 4.5 h of the onset of symptoms. Patients were divided into the NIHSS–ASPECTS mismatch (NAM)-positive and NAM-negative groups (group P and N, respectively). The clinical outcome was assessed using the Modified Rankin Scale (mRS). Safety outcomes included progression, symptomatic intracerebral hemorrhage (sICH), intracerebral hemorrhage (ICH), adverse events, clinical adverse events, and mortality.

Results A total of 208 patients were enrolled in the study. In group P, IVT treatment was associated with a good functional outcome at 3 months ($p=0.005$) and 1 year ($p=0.001$). A higher percentage of patients with favorable mRS (0–2) ($p=0.01$) and excellent mRS (0–1) ($p=0.011$) functional outcomes was obtained at 1 year in group P with IVT treatment. Group N did not benefit from the same treatment ($p=0.352$ and $p=0.480$ at 3 months and 1 year, respectively). There were no statistically significant differences in sICH, ICH, mortality rates, or other risks between the IVT and conventional treatment groups.

Conclusion IVT treatment is associated with a good functional outcome in patients with NAM, without increasing the risks of sICH, ICH, mortality, or other negative outcomes. NAM promises to be an easily obtained indicator for guiding the treatment decisions of AIS.

Keywords Stroke · NIHSS · ASPECTS · CT · Mismatch · Ischemic penumbra · IVT

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Introduction

Acute ischemic stroke (AIS) accounts for approximately 70–80% of strokes and is among the leading causes of death and disability worldwide [1, 2]. Restoration of blood perfusion in the ischemic penumbra is a determining factor in the functional outcome of patients with AIS. Intravenous thrombolysis (IVT) treatment with recombinant tissue plasminogen activator (rt-PA) within 4.5 h of the onset of the stroke is an effective treatment for AIS [3]. However, because of the narrow time window for IVT treatment, patients may not receive the treatment, even if the ischemic penumbra persists for up to 24 h [4]. Therefore, there is an urgent need for effective ways to identify the state of the ischemic penumbra and to evaluate the accompanying risks to extend the time window for safe and effective IVT treatment.

The mismatch between stroke severity and lesions detected by imaging has been shown to predict the

occurrence of ischemic penumbra and to guide AIS treatment [5, 6]. Previous research implied that a clinical–diffusion mismatch could serve as an indicator of infarct growth in patients with AIS [7]. However, as there can be a significant delay associated with magnetic resonance imaging (MRI), owing to the limited availability of this technology, ischemic infarction volume can progress to the point where IVT is no longer an option. Some studies have suggested that computed tomography (CT) findings measured by the Alberta Stroke Program Early CT Score (ASPECTS) are an accurate indicator of the clinical outcome [8, 9]. A previous study implied that clinical–ASPECT mismatch does not identify patients who would benefit from IVT treatment with rt-PA [10]. However, there have been no further studies evaluating whether the combination of ASPECTS and clinical deficits can reliably serve as a surrogate for ischemic penumbra and predict functional outcome, which would help to identify patients who have experienced a stroke who may benefit from IVT treatment beyond the accepted post-stroke time window. To address this question, the present study investigates the correlation between the National Institutes of Health Stroke Scale (NIHSS) score and ASPECTS mismatch (NAM) and the IVT treatment outcome in patients with ischemic stroke. An NIHSS score ≥ 8 has been suggested as a clinical indicator of a large volume of ischemic brain tissue [5], while an ASPECTS ≤ 7 is associated with severe radiological findings [10]. We, therefore, defined NAM as having an NIHSS score ≥ 8 and an ASPECTS ≥ 8 and examined its utility for detecting ischemic penumbra and guiding IVT treatment.

Materials and methods

Patient selection and study design

This prospective observational study enrolled patients with AIS who were admitted to the Shanghai Ninth People's Hospital between October 2015 and January 2018. The inclusion criteria were as follows: (1) patients with symptoms of AIS, (2) less than 4.5 h from the onset of the stroke to admission, (3) age 18–80 years, and (4) informed consent signed by the patient or their relatives. Exclusion criteria were as follows: (1) history of severe brain trauma or stroke in the previous 3 months, (2) intracranial hemorrhage, (3) previous thrombectomy or other endovascular treatment, and (4) missing clinical 3-month or 1-year Modified Rankin Scale (mRS) scores. A total of 208 patients were included in the study.

We carried out a controlled clinical study, in which we defined group P as patients with an NIHSS score ≥ 8 points and an ASPECTS ≥ 8 points. The remaining subjects were placed into group N. NIHSS and mRS scores were determined by the neurologist who treated the patient, and

ASPECTS was determined by consensus between two stroke neurologists, with one rater blinded to the clinical information of the patients. Each group was further divided into two subgroups according to whether thrombolytic treatment was administered. Therefore, there was a total of four groups: group P with thrombolytic or conventional treatment (PT and PC subgroups, respectively), and group N with thrombolytic or conventional treatment (NT and NC subgroups, respectively). Patients in the thrombolytic treatment group were treated by intravenous administration of rt-PA (0.9 mg/kg). The total dose was divided and 10% was injected within 1 min, and the remaining 90% was continuously administered over the next hour using a pump. A brain CT was performed 24 h later. If there was no obvious intracerebral hemorrhage (ICH), anti-platelet drugs and circulation-enhancing drugs, such as butylphthalide and human urinary kininogenase (included in the Guidelines for Ischemic Stroke in China), were added. Patients in the conventional treatment group were only given anti-platelet and circulation-enhancing drugs.

Outcome measures

The clinical outcome was determined based on the mRS score at the 3-month and 1-year follow-ups, through outpatient visits or telephone calls. The physician who performed the NIHSS and the mRS score assessments was specially trained. Safety outcomes, such as progression, symptomatic ICH (sICH), ICH, adverse events, clinical adverse events, and mortality, were compared between the corresponding subgroups. Progression was defined as an NIHSS score ≥ 2 points higher at discharge than at admission. sICH was defined as any hemorrhage with neurologic deterioration or resulting in death within 2 weeks after admission. Adverse events were progression and ICH, and clinical adverse events were progression and sICH. Mortality was defined as the percentage of deaths between the time of admission and the 1-year follow-up.

Statistical analysis

Data are expressed as mean \pm standard deviation. SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Student's *t* test or the Mann–Whitney *U* test was used to evaluate differences in continuous variables between two groups, while comparisons between three groups were carried out using one-way analysis of variance followed by the Dunnett's test or the Kruskal–Wallis *H* test. Pearson's χ^2 test or Fisher's exact test was used to compare categorical variables. The Kolmogorov–Smirnov test was used to evaluate whether data were normally distributed. All reported *p* values in the study are two-sided, and *p* < 0.05 was considered statistically significant.

Results

Clinical characteristics of the study population

Between October 2015 and January 2018, 345 patients with AIS were recorded in the endovascular registry, of which 208 patients (60.2%) were enrolled in the present study after 18 patients were excluded because of severe brain trauma or stroke in the previous 3 months, 35 for ICH, 10 for thrombectomy or other endovascular

treatments, and 9 for missing follow-up data (Fig. 1). The characteristics and risk factors of the patient subgroups are shown in Table 1. There was no statistically significant difference in the NIHSS score at admission between the PT and PC groups ($p=0.62$) or between the NT and NC groups ($p=0.06$). In addition, there was no significant difference in the mRS score at admission between the PT and PC groups ($p=0.99$) or between the NT and NC groups ($p=0.26$). There were no differences in other variables between each pair of subgroups ($p>0.05$).

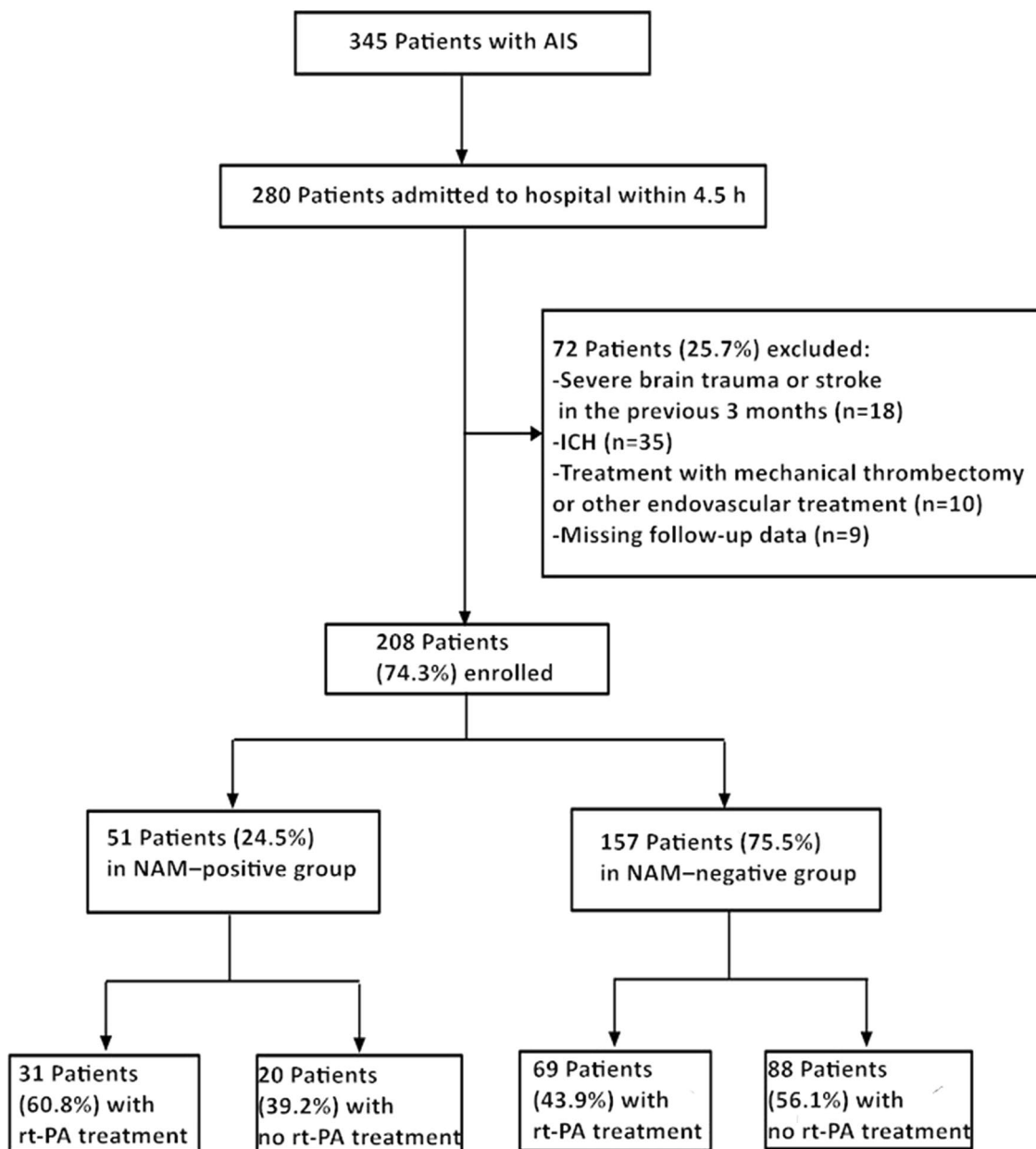


Fig. 1 Patient selection algorithm

Table 1 Clinical characteristics of the study population

	P group			N group		
	PT (n=31)	PC (n=20)	p	NT (n=69)	NC (n=88)	p
Sex, female	15 (48.4%)	6 (30.0%)	0.25	16 (23.2%)	24 (27.3%)	0.59
Age, years	63.48 ± 12.34	67.00 ± 10.9	0.31	61.12 ± 13.19	63.21 ± 12.57	0.32
Hypertension	17 (54.8%)	15 (75.0%)	0.24	41 (59.4%)	65 (73.9%)	0.06
Atrial fibrillation	9 (29.0%)	6 (30.0%)	1.00	8 (11.6%)	7 (8.0%)	0.59
Diabetes	8 (25.8%)	8 (40.0%)	0.36	16 (23.2%)	25 (28.4%)	0.58
Alcoholism	5 (16.1%)	5 (25.0%)	0.49	12 (17.4%)	17 (19.3%)	0.84
Smoking	13 (41.9%)	7 (35.0%)	0.77	32 (46.4%)	48 (54.5%)	0.34
Admission NIHSS	13.19 ± 3.67	13.90 ± 5.61	0.62	3.41 ± 2.98	2.59 ± 1.53	0.06
Discharge NIHSS	7.81 ± 6.25	10.55 ± 6.75	0.14	2.77 ± 2.03	2.24 ± 2.08	0.32
Admission mRS	4.00 ± 1.24	4.05 ± 1.10	0.99	1.88 ± 1.04	1.67 ± 0.89	0.26
ASPECTS	9.58 ± 0.81	9.10 ± 0.75	0.93	9.74 ± 0.70	9.88 ± 0.42	0.16
Platelet	212 ± 44	235 ± 68	0.16	213 ± 87	196 ± 48	0.15
Glucose	8.41 ± 3.73	7.93 ± 2.80	0.66	6.83 ± 2.48	6.72 ± 2.53	0.77
Cholesterol	4.76 ± 1.35	4.98 ± 1.65	0.65	5.08 ± 1.21	11.66 ± 6.28	0.40
Low-density lipoprotein	3.38 ± 1.79	3.15 ± 1.30	0.66	3.17 ± 0.93	3.01 ± 0.95	0.32

Data are presented as mean ± SD, or number (%)

mRS Modified Rankin Scale; N NIHSS–ASPECTS mismatch-negative; NC NIHSS–ASPECTS mismatch-negative with conventional treatment; NIHSS National Institute of Health Stroke Scale; NIHSS–ASPECTS mismatch-negative with intravenous thrombolysis treatment; P, NIHSS–ASPECTS mismatch-positive; PC, NIHSS–ASPECTS mismatch-positive with conventional treatment; PT, NIHSS–ASPECTS mismatch-positive with intravenous thrombolysis treatment

Clinical outcomes

We compared the clinical outcomes of IVT treatment in the NAM-positive and NAM-negative groups (group P and N, respectively). There were significant differences in the mRS scores between the PT and PC groups at the 3-month ($p=0.005$) and the 1-year ($p=0.001$) follow-ups (Table 2).

The scores were lower in the PT (1.55 ± 1.55) than in the PC group (3.15 ± 1.87). There were no differences in the mRS scores between the NT and NC groups at 3 months ($p=0.352$) and 1 year ($p=0.480$). This implies that in the absence of NAM, IVT treatment did not lead to a better functional outcome. We compared the mRS scores over time in groups P and N and found that they decreased over time

Table 2 Clinical outcomes of the study population

	P group				N group			
	PT (n=31)	PC (n=20)	p	RR	NT (n=69)	NC (n=88)	p	RR
mRS at 3 months	2.16 ± 1.51	3.35 ± 1.66	0.005	–	2.58 ± 1.40	2.37 ± 1.22	0.352	–
mRS at 1 year	1.55 ± 1.55	3.15 ± 1.87	0.001	–	1.72 ± 1.36	1.52 ± 1.22	0.480	–
ICH	6 (19.4%)	1 (5.0%)	0.223	4.560	5 (7.2%)	1 (1.1%)	0.087	6.797
sICH	1 (3.2%)	1 (5.0%)	1.000	0.633	1 (1.4%)	0 (0.0%)	0.439	–
Mortality	2 (6.5%)	3 (15.0%)	0.369	0.391	2 (2.9%)	0 (0.0%)	0.192	–
Progression	4 (12.9%)	4 (20.0%)	0.696	0.593	8 (11.6%)	8 (8.0%)	0.586	1.518
Clinical adverse event	5 (16.1%)	5 (25.0%)	0.486	0.577	9 (13.0%)	7 (8.0%)	0.426	1.736
Adverse event	10 (32.3%)	5 (25.0%)	0.579	1.429	13 (18.8%)	8 (9.1%)	0.098	2.321

Data are presented as mean ± SD, or number (%). *p* values in bold type represent statistical significance ($p < 0.05$)

ICH intracerebral hemorrhage; mRS Modified Rankin Scale; N, NIHSS–ASPECTS mismatch-negative; NC, NIHSS–ASPECTS mismatch-negative with conventional treatment; NIHSS National Institute of Health Stroke Scale; NIHSS–ASPECTS mismatch-negative with intravenous thrombolysis treatment; P, NIHSS–ASPECTS mismatch-positive; PC, NIHSS–ASPECTS mismatch-positive with conventional treatment; PT, NIHSS–ASPECTS mismatch-positive with intravenous thrombolysis treatment; RR relative risk; sICH symptomatic intracerebral hemorrhage

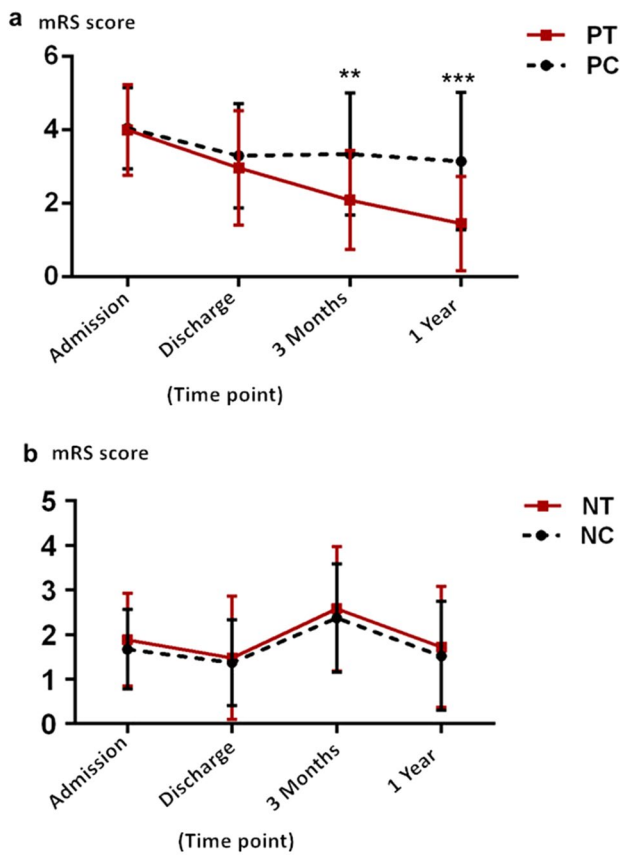


Fig. 2 mRS score at admission, discharge, and at the 3-month and 1-year follow-ups. **a, b** mRS score of PT and PC groups (P group; **a**) and NT and NC groups (N group; **b**). ** $p < 0.01$; *** $p < 0.001$

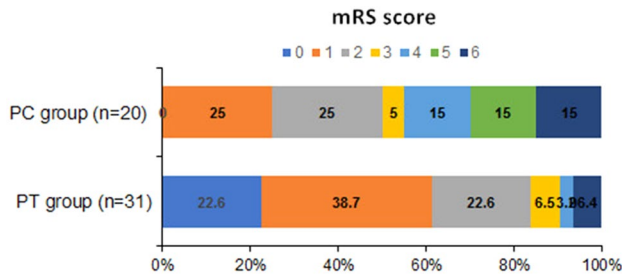


Fig. 3 Distribution of mRS scores at the 1-year follow-up in the P group

in the PT group ($p < 0.001$) when compared with the PC group ($p = 0.299$) (Fig. 2a), indicating a better long-term outcome in the former group. However, there was no declining trend in the mRS score over time in the NT and NC groups (Fig. 2b).

At 1 year follow-up, in group PT, a favorable functional outcome (mRS score ≤ 2) was achieved in 26 patients (83.9%), compared with 10 (50%) in group PC ($p = 0.01$). In group PT, an excellent functional outcome (mRS score ≤ 1)

was achieved in 19 patients (61.3%), compared with 5 (25%) in group PC ($p = 0.011$) (Fig. 3). These results suggest that thrombolytic therapy in group P is associated with a favorable or excellent functional outcome.

In terms of safety outcomes, there was no significant difference in the incidence of ICH between the PT and PC groups (19.4% vs 5.0%, $p = 0.223$) or between the NT and NC groups (7.2% vs 1.1%, $p = 0.087$). sICH occurred in one patient in each of the PT and PC groups (3.2% and 5.0%, respectively), with no significant difference between the two groups ($p = 1.000$). Five patients (9.8%) in group P died, including two (6.5%) in group PT and three (15%) in group PC ($p = 0.369$). Two patients (2.9%) in group N died, group [both in the NT group ($p = 0.192$)]. There were no differences in progression, adverse events, or clinical adverse events between the PT and PC groups or between the NT and NC groups ($p > 0.05$) (Table 2).

Discussion

The results of this prospective observational study show that in patients with AIS and NAM, i.e., group P, IVT treatment given within 4.5 h resulted in neurological improvement and a favorable clinical outcome at 3 months and 1 year, without an increased risk of ICH, sICH, or mortality. In contrast, patients without a mismatch, i.e., group N, did not benefit from IVT treatment when compared with conventional therapy. In addition, IVT treatment resulted in a higher percentage of patients with an excellent functional outcome (mRS score ≤ 1) when compared with conventional treatment in group P.

The time window for IVT treatment in patients with AIS is 4.5 h [11]. However, recent studies have demonstrated that IVT treatment beyond 4.5 h has clinical benefits in some patients with salvageable brain tissue [12, 13]. Therefore, there is a need for ways to identify patients with ischemic penumbra who are candidates for IVT treatment beyond 4.5 h. Several methods have been proposed for evaluating ischemic penumbra. Diffusion-weighted imaging (DWI)–perfusion-weighted imaging (PWI) mismatch, DWI–fluid-attenuated inversion recovery mismatch, or NIHSS–DWI–ASPECTS mismatch is indicative of ischemic penumbra, and these cases were shown to benefit from rt-PA treatment [6, 14, 15]. However, MRI is inaccessible in many places, time-consuming, and complicated, which limits its clinical utility within the AIS timeframe. Other trials have reported that CT perfusion (CTP) is useful for identifying the final infarction core and measuring hypoperfusion volume, which can predict the functional outcome of patients with AIS [16, 17]. CTP imaging does not involve whole-brain imaging or a lengthy procedure. Non-contrast CT images evaluated with ASPECTS, which is the most common

approach in clinical practice, overcome the limitations of other methods with its availability and simplicity, without the need for time-consuming image processing. Especially in unusual times, such as the coronavirus period, CT is more accessible in remote areas. ASPECTS has been used to accurately predict infarction volume and functional outcomes in patients with AIS receiving endovascular therapy [18, 19]. NIHSS has also been validated for selecting candidate patients for IVT treatment [20]. Therefore, we speculate that a more accurate prediction of functional outcome can be achieved by combining the NIHSS score with the imaging results measured by ASPECTS. We found that IVT treatment within 4.5 h resulted in a lower mRS score at 3 months and 1 year when compared with conventional treatment in NAM-positive patients. However, in NAM-negative patients, the type of treatment had no effect on the mRS score at these time points. Regarding the safety of IVT treatment, a higher percentage of patients experienced ICH in group PT than in group PC (6% vs 1%), but the difference was not statistically significant. This implies that thrombolytic therapy benefits NAM-positive patients without increasing the associated risks. The better long-term functional outcome of IVT treatment in group P than in group N may be attributable to the presence of salvageable brain tissue, i.e., the ischemic penumbra, in the former patients. NAM is indicative of a disparity between the severity of clinical symptoms and imaging findings, implying the existence of an ischemic penumbra that was not detected by CT at the time of admission. Therefore, an ischemic penumbra is a selection criterion for IVT treatment beyond the limited AIS time window.

This study had some limitations. First, the patients were admitted within 4.5 h of AIS, and we did not examine those who received IVT treatment after 4.5 h. However, a previous study reported that in cases with a DWI–PWI mismatch, the proportion of salvageable brain tissue is independent of the time since the ischemic event [14]. Second, given the single-center design and small sample size of our study, further research is needed to confirm our findings.

Conclusions

In conclusion, we demonstrated, for the first time, that IVT treatment resulted in neurologic improvement and a better functional outcome at 3 months and 1 year in patients with AIS and NAM-positive. Nevertheless, there is no significant difference in the outcome of NAM-negative patients whether to receive IVT treatment. These results suggest that NAM can serve as a marker for ischemic penumbra to select patients who would benefit from IVT treatment beyond the 4.5 h post-stroke time window and to predict

their functional outcome, thereby improving the long-term prognosis of patients with AIS.

Author contributions GSB, HSX, and PPD conceived and designed the study. PPD, NW, and XJC collected the data. NW, FLC, and PPD contributed to the statistical analyses. PPD and NW wrote the manuscript. GSB, HSX, NW, and XJC critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Availability of data and materials Raw data and information for patients in this study are not publicly available to protect their privacy, but are available from the corresponding author on reasonable request and with the permission of the local ethics committee.

Declarations

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval The study was approved by the Ethics Committee of Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiao Tong University. Patients or their relatives provided written, informed consent. The ID of the IRB was Ethical Review of the Shanghai Ninth Hospital 2018-89-T80.

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