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Prognostic Value of Diffusion-Weighted Imaging (DWI) Apparent Diffusion Coefficient (ADC) in Patients with Hyperacute Cerebral Infarction Receiving rt-PA Intravenous Thrombolytic Therapy

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Background: The aim of this study was to investigate the potential value of apparent diffusion coefficient (ADC) of diffusion-weighted imaging (DWI) in the prognosis of patients with hyperacute cerebral infarction (HCI) receiving intravenous thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA).


Material/Methods: From June 2012 to June 2015, 58 cases of HCI (<6 h) undergoing rt-PA intravenous thrombolytic therapy (thrombolysis group) and 70 cases of HCI (<6 h) undergoing conventional antiplatelet and anticoagulant therapy (control group) in the same period were collected. DWI was conducted on all the subjects, and ADC maps were generated with Functool software to quantify ADC value. The clinical outcomes of HCI patients were observed for 3 months, and prognostic factors were analyzed.

Results: Before thrombolysis treatment, the lesion area presented high signal intensity on DWI map and low signal intensity on ADC map, and gradually weakened signal intensity on DWI map and gradually enhanced signal intensity on ADC map were observed after thrombolysis. The ADC values of the thrombolysis group were significantly higher than those of the control group after treatment (24 h, 7 d, 30 d, and 90 d) (all $P < 0.05$), and the ADC and rADC values in the thrombolysis group gradually increased over time (all $P < 0.05$). Multiple logistic regression analysis showed that baseline National Institutes of Health Stroke Scale (NIHSS) score, baseline rADC value, and stroke history were the independent factors for the prognosis of HCI patients with thrombolysis (all $P < 0.05$).

Conclusions: The values of ADC and rADC may provide guidance in the prognosis of HCI patients receiving rt-PA, and the baseline rADC value is the protective factor for the prognosis of HCI patients receiving rt-PA.

MeSH Keywords: **Actuarial Analysis • Cerebral Infarction • Prognosis**

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Background

Ischemic stroke annual incidence and the related deaths and disability-adjusted life-years lost are increasing worldwide, resulting in great social-economic burden in low-income and middle-income countries [1]. Cerebral infarction is a type of ischemic stroke resulting from a blockage in the blood vessels supplying blood to the brain. Acute cerebral infarction (ACI) is highly debilitating or lethal, and is characterized by high rates of disability, dementia, and even death [2,3]. Currently, recombinant tissue-type plasminogen activator (rt-PA) is recommended as one of the most effective methods in the treatment of ACI within the limited 4.5-h timeframe [4]. Concerning hemorrhagic risk after intravenous administration of rt-PA, selection of ACI patients with potential benefits in overcoming possible harms caused by thrombolysis is of great importance [5]. Magnetic resonance imaging (MRI) evaluation is widely used for the early diagnosis of ACI, and the clinical implication of useful MRI findings can be comprehensively incorporated into therapeutic decision-making, thus expanding thrombolysis indication and predicting the prognosis [6,7].

It has been demonstrated that multimode MRI is helpful to identify whether patients suffering from hyperacute ischemic cerebral infarction (HCl) are strong candidates for intravenous thrombolytic therapy, giving significant value of MRI-based thrombolysis in HCl [8]. The introduction of DWI makes it possible to obtain images based on the random movement of water molecules, and the diffusion properties of the examined tissue can be quantified by calculating apparent diffusion coefficient (ADC) [9]. A previous study also documented significance of magnetic resonance angiography-DWI mismatch in HCl with respect to the prognosis, and suggested that rt-PA is indicated in patients with MRA-DWI mismatch [10]. DWI-ASPECTS appears to be a reliable tool for predicting outcome in patients treated with rt-PA, and DWI-ASPECTS was reported to be a useful predictor of symptomatic intracerebral hemorrhage for patients with hyperacute stroke [11,12]. In addition, a recent study reported that multiple clinicoradiologic factors of ACI are associated with negative and positive DWI, and DWI is further considered to be helpful in guiding thrombolysis [13]. Previous evidence showed that relative ADC (rADC) may be an independent risk factor for hemorrhagic transformation in patients with ACI [14], but it is not yet clear that thrombolytic therapy is beneficial when HCl patients are selected based on DWI. Therefore, we carried out the present study to investigate the potential value of ADC in the prognosis of patients with HCl receiving intravenous thrombolytic therapy with rt-PA.

Material and Methods

Study subjects

From June 2012 to June 2015, 58 cases of HCl (<6 h) undergoing rt-PA intravenous thrombolytic therapy (thrombolysis group) and 70 cases of HCl (<6 h) undergoing conventional antiplatelet and anticoagulant therapy (control group) in the same period were randomly collected from the Department of Imaging Radiology, People's Hospital of Pudong New Area. The 70 HCl patients receiving no intravenous thrombolysis had contraindications to thrombolytic therapy or these patients and their families refused to accept thrombolytic therapy. There was no significant difference in age, gender, risk factors, stroke history, infarction type, blood pressure, blood sugar, or National Institutes of Health Stroke Scale (NIHSS) score between the thrombolysis group and the control group (all $P>0.05$). Baseline data are shown in Table 1.

Inclusion criteria for all patients were: (1) age, 18–80 years old; (2) clinical symptoms consistent with HCl diagnosis; (3) MRI was completed within 0–6 h after cerebral infarction, and the maximum diameter of abnormal perfusion region on accumulated hemisphere gray-matter perfusion-weighted imaging (PWI) >2 cm; PWI/DWI mismatch region $\geq 20\%$, without intracranial hemorrhage on cranial computer tomography (CT); (4) with initial onset or had no obvious sequelae resulted from previous stroke; (5) NIHSS score >4; and (6) patients or their families agreed and signed the informed consent.

Exclusion criteria for all patients were: (1) high-density lesions (bleeding) on CT examination, or patients without ischemic penumbra on MRI evaluation; (2) severe stroke symptoms (NIHSS >15); (3) stroke symptoms improved rapidly before treatment; (4) had a history of stroke within the previous 6 weeks; (5) had the onset of epilepsy at the beginning of disease; (6) platelet count $<100 \times 10^9/L$ or packed cell volume $<25\%$; (7) blood pressure $>180/110$ mmHg, blood sugar >22.2 mmol/L; (8) with severe liver and kidney dysfunction; (9) had severe white-matter loose or slight bleeding on MRI; (10) patients who took anticoagulant drugs orally, the international normalized ratio (INR) >1.5 ; (11) had a history of cerebral hemorrhage, tumor, subarachnoid hemorrhage, arteriovenous malformations, or aneurysms; (12) had surgical operation, biopsy of substantial organs, lumbar puncture trauma (including head trauma), visceral injury or ulcer, hemorrhagic retinopathy, or other hemorrhagic eye diseases within 1 month; (13) combined with a history of atrial fibrillation; (14) confirmed active/infectious enteritis, ulcerative colitis or intestinal diverticula; and (15) recent acute myocardial infarction-associated pericarditis.

Table 1. Baseline comparison of thrombolysis group and control group before treatment (n, %).

Group	Thrombolysis group (n=58)	Control group (n=70)	P
Age (year)	63.35±8.45	61.14±7.58	0.122
Gender			
Male	39 (67.24%)	44 (62.86%)	0.605
Female	19 (32.76%)	26 (37.14%)	
Hypertension	37 (63.79%)	41 (58.57%)	0.547
Hyperlipidemia	33 (56.90)	45 (64.29%)	0.394
Coronary heart disease	24 (41.38%)	26 (37.14%)	0.625
Diabetes mellitus	21 (36.21%)	27 (38.57%)	0.783
Stroke history	15 (25.86%)	14 (20.00%)	0.430
OCSF			0.274
Complete anterior circulation infarction	19 (32.76%)	32 (45.71%)	
Partial anterior circulation infarction	31 (53.45%)	28 (40.00%)	
Posterior circulation infarction	8 (13.79%)	10 (14.29%)	
NIHSS score	12.93±3.84	13.15±2.86	0.711
Systolic pressure (mmHg)	159.68±17.06	155.43±15.45	0.142
Diastolic pressure (mmHg)	86.18±15.64	82.40±12.13	0.126
Blood sugar (mmol/L)	10.44±3.85	9.35±4.05	0.123

OCSF – Oxfordshire Community Stroke Project; NIHSS – National Institute of Health Stroke Scale.

Image protocol

All patients underwent routine DWI, T₂-weighted imaging (T₂WI), T₁-weighted imaging (T₁WI) and PWI, and all scans were performed on a 1.5-T GE Signa EchoSpeed MR scanner (GE Medical Systems, Milwaukee, WI) with quadrature coils in a gradient switching rate of 120 mT/ms. A single-shot SE-EPI sequence was applied for DWI with the following sequence: repetition time (TR)/echo time (TE), 10,000 ms/114 ms; matrix, 128×128; field of view (FOV), 24×24 cm; 2 diffusion field gradients (b-values, 0 s/mm² and 1,000 s/mm²) with 3 directions of front and rear, left and right, and top and bottom; gradient scanning time, 40 s; slice thickness/gap, 7 mm/2 mm. DWI can simultaneously obtain a EPI-T₂WI image (b=0) and a diffusion-weighted image (b=1000) on the same level.

Imaging analysis

After scanning, the images were analyzed by 2 experienced physicians. The obtained DWI images were processed using a GE ADW4.5 workstation and post-processed by Functool workstation (GE Healthcare, Milwaukee, WI) to obtain the ADC artificial color maps, and cerebral infarction focus expressions in different stages on DWI, T₂WI, and ADC maps were observed. Mean ADC values of the cerebral infarction focus and ADC values in

the center, from center to focus edge, and ipsilateral region were respectively measured on the ADC artificial color maps. Since ADC values are different in different parts of brain tissues in the normal state, and the change of local ADC values cannot effectively reflect the changes of ADC caused by ischemia, rADC was used as an indicator of ADC changes after ischemia, and rADC = the lesion ADC/the ipsilateral ADC ×100%.

Treatment

Patients in the thrombolysis group were given 0.6–0.9 mg/Kg (maximum, 90 mg) of rt-PA (Boehringer Ingelheim GmbH) according to the body weight (expert consensus on the clinical application of rt-PA in the treatment of ischemic stroke). Ten percent of the total dose of rt-PA was given through vein mass injection for 1 min; the remaining 90% with the addition of liquid was administered via intravenous infusion pump for 1 h, and the cannula was then flushed with 0.9% physiologic saline. Heart rate, blood pressure, oxygen saturation, consciousness, pupil reaction, and muscle strength were monitored. Patients in the thrombolysis group were not given anticoagulant or antiplatelet aggregation drugs within 24 h of thrombolysis treatment. Three females were given 0.6 mg/Kg of rt-PA, and the main reason of low dose was that families of these patients worried about the risk of bleeding. The thrombolysis group

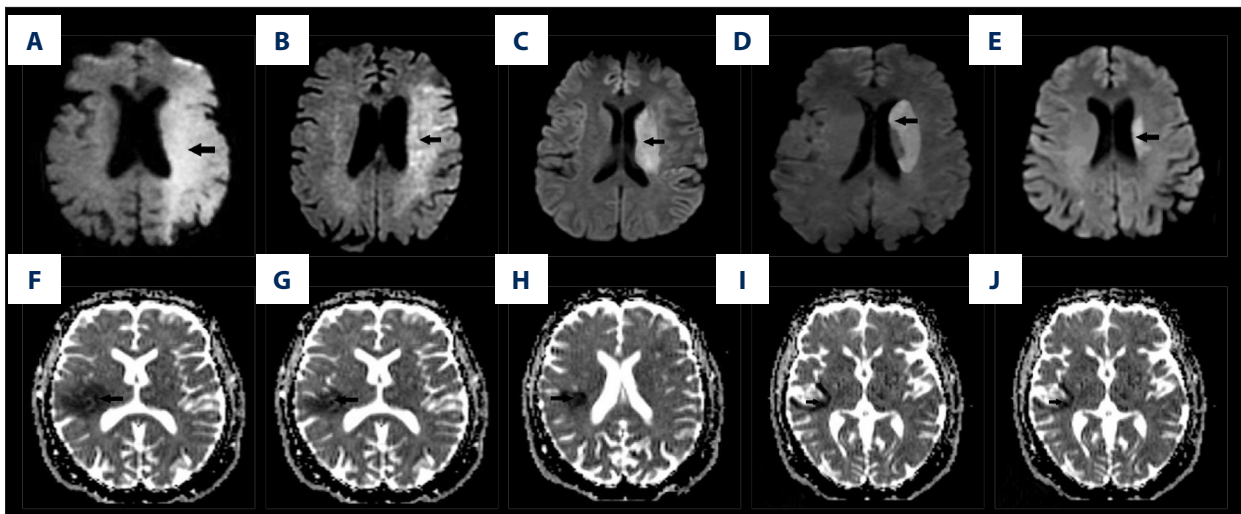


Figure 1. DWI maps and ADC maps at different time points in HIC patients receiving rt-PA intravenous thrombolysis: DWI maps: (A) Before treatment; (B) 24 h after treatment; (C) 7 d after treatment; (D) 30 d after treatment; (E) 90 d after treatment; and ADC maps: (F) Before treatment; (G) 24 h after treatment; (H) 7 d after treatment; (I) 30 d after treatment; (J) 90 d after treatment. The arrow indicates the lesion area. DWI – diffusion-weighted imaging; ADC – apparent diffusion coefficient; rt-PA – recombinant tissue plasminogen activator; HCl – hyperacute ischemic cerebral infarction.

was divided into a 0–3 h subgroup and a 3–6 h subgroup according to the time window. Patients in the control group underwent conventional antiplatelet and anticoagulant therapy.

Clinical observation and curative effect evaluation

The ADC value of the lesion area and the ADC value of the contralateral corresponding region were recorded before treatment and 24 h, 7 d, 30 d, and 90 d after treatment, and the rADC was calculated. NIHSS was used for the evaluation of neurological function [15], modified Rankin Scale (mRS) score for the evaluation of the recovery results of daily life ability after treatment [16], NIHSS score was recorded before treatment and 24 h, 7 d, 30 d and 90 d after treatment, and mRS score was recorded 90 d after treatment. NIHSS reduction ≥ 8 , NIHSS=0–1 or mRS ≤ 1 are considered as good clinical outcomes [17].

Statistical analyses

Continuous variables are expressed as mean \pm SD (standard deviation). Continuous variables in normal distribution were compared with the *t* test. The generalized estimating equation (GEE) was used to analyze the repeated measurement data. Multiple comparisons were corrected with Sidak method. Logistic regression analysis was used to analyze the prognostic factors. Stata12.0 was used for statistical analysis. A 2-tailed *P* value of 0.05 indicates statistical significance.

Results

DWI maps and ADC maps

Before thrombolysis, the lesion areas of HCl patients were clear on the DWI maps and ADC maps, and presented high signal intensity on DWI maps and low signal intensity on ADC maps. Gradually decreased lesion areas and gradually weakened signal intensity on DWI maps were observed 24 h, 7 d, 30 d, and 90 d after thrombolysis (Figure 1A–1E). Gradually decreased lesion areas and gradually enhanced signal intensity on ADC maps were observed (Figure 1F–1J).

Comparison in ADC value

There was no obvious difference in lesion ADC and rADC values between the thrombolysis group and control group before treatment ($P > 0.05$). The ADC and rADC values of the thrombolysis group 24 h, 7 d, 30 d, and 90 d after thrombolytic therapy were significantly higher than those of the control group (all $P < 0.05$) (Table 2).

ADC and rADC values in different time windows

The observation of lesion ADC value and rADC value of patients receiving thrombolysis within 0–3 h after the onset and patients within 3–6 h showed that lesion ADC and rADC values in the 0–3 h group and the ADC values in the 3–6 h group had increased gradually at 24 h, 7 d, 30 d, and 90 d after thrombolysis, and there were significant differences in the lesion ADC and rADC values among different time points (all $P < 0.05$).

Table 2. ADC values in the thrombolysis group and the control group.

Time points	Thrombolysis group (n=58)		Control group (n=70)		P value	
	Lesion ADC	rADC (%)	Lesion ADC	rADC (%)	P ₁	P ₂
Before treatment	0.65±0.08	64.55±13.49	0.63±0.09	61.36±11.70	0.454	0.154
After treatment						
24 h	0.78±0.10	83.28±13.38	0.71±0.11	75.14±14.21	<0.001	0.001
7 d	1.01±0.11	102.10±17.42	0.86±0.11	88.10±16.09	<0.001	<0.001
30 d	1.61±0.16	157.63±18.30	1.25±0.13	120.29±18.97	<0.001	<0.001
90 d	1.91±0.26	182.38±39.08	1.52±0.21	142.73±31.48	<0.001	<0.001

P₁ – comparison in lesion ADC values between the thrombolysis group and the control group; P₂ – comparison in rADC values between the thrombolysis group and the control group; ADC – apparent diffusion coefficient; rADC – relative apparent diffusion coefficient.

Table 3. The mean ADC value and rADC value of patients receiving thrombolysis within 0–3 h and within 3–6 h after the onset at different time points.

Time points	0–3 h (n=38)		3–6 h (n=20)	
	Lesion ADC	rADC (%)	Lesion ADC	rADC (%)
Before treatment	0.65±0.07	65.82±12.53	0.63±0.10	62.13±15.19
After treatment				
24 h	0.78±0.11*	83.27±13.60*	0.78±0.09*	83.30±13.30*
7 d	1.02±0.13*#	105.28±18.65*#	0.98±0.07*#	96.06±13.22*
30 d	1.61±0.15*##@	159.43±17.10*##@	1.61±0.18*##@	154.23±20.41*##@
90 d	1.95±0.23*##@&	190.63±37.59*##@&	1.82±0.28*##@&	166.72±37.88*##@
Wald-Chi-Square	2220.48	996.29	741.18	315.60
P value	<0.001	<0.001	<0.001	<0.001

* Compared with before treatment, P<0.05; # Compared with 24 h after treatment, P<0.05; @ Compared with 7 d after treatment, P<0.05; & Compared with 30 d after thrombolysis, P<0.05; ADC – apparent diffusion coefficient; rADC, mean ADC ratio.

However, there were no obvious differences in the rADC values between 7 d and 24 h, or between 90 d and 30 d after thrombolysis in patients receiving thrombolysis within 3–6 h after the onset (both P>0.05). The mean ADC and rADC values were not significantly different between the patients receiving thrombolysis within 0–3 h after the onset and the patients within 3–6 h before treatment or each time point after treatment (all P>0.05) (Table 3).

Prognosis of patients with rt-PA intravenous thrombolysis

Results of univariate analysis of prognosis indicated that age, stroke history, baseline NIHSS score, and baseline rADC value may influence the prognosis of HIC patients with rt-PA thrombolytic therapy (all P<0.05) (Table 4). Age, stroke history, baseline NIHSS score, and baseline rADC value were included in multiple logistic regression analysis, and the results showed that baseline NIHSS score and stroke history were independent risk factors, while baseline rADC value may be a

protective factor for prognosis of HIC patients receiving rt-PA intravenous thrombolysis (all P<0.05). However, age was not associated with the prognosis of HIC patients receiving rt-PA thrombolytic therapy (Table 5).

Discussion

Stroke MRI provides comprehensive prognostically relevant information regarding the brain in hyperacute stroke, and may be used as a single imaging tool in acute stroke to identify and monitor candidates for thrombolysis [18]. Multiparametric protocol MRI has significant potential value to identify patients suffering from HCl who are strong candidates for intravenous thrombolytic therapy [19]. Radiological findings in the present study suggested that gradually decreased lesion areas along with enhanced signal intensity on ADC maps were observed 24 h, 7 d, 30 d, and 90 d after thrombolysis. Consistently, the ADC and rADC values of HCl patients were gradually increased

Table 4. The univariate analysis of prognosis in HCl patients after rt-PA intravenous thrombolysis.

Parameter	Good prognosis group (n=42)	Poor prognosis group (n=16)	P
Age (year)	61.63±8.09	67.87±7.89	0.011
Gender (Male/Female)	26/16	13/3	0.161
Stroke history	6 (14.29%)	9 (56.25%)	0.001
Hypertension	28 (66.67%)	9 (56.25%)	0.461
Diabetes mellitus	17 (40.48%)	4 (25.00%)	0.273
Hyperlipidemia	22 (52.38%)	11 (68.75%)	0.261
Coronary heart disease	17 (40.48%)	7 (43.75%)	0.821
OCSF			0.627
Complete anterior circulation infarction	13 (30.95%)	6 (37.50%)	
Partial anterior circulation infarction	24 (57.14%)	7 (43.75%)	
Posterior circulation infarction	5 (11.90%)	3 (18.75%)	
Baseline NIHSS score	12.06±3.58	15.23±3.64	0.004
Blood sugar pre-treatment (mmol/L)	10.40±4.00	10.56±3.55	0.889
Systolic pressure pre-treatment (mmHg)	160.67±18.31	157.09±13.42	0.481
Diastolic pressure pre-treatment (mmHg)	87.90±15.55	81.67±15.44	0.177
Baseline rADC	67.20±13.89	57.59±9.66	0.014

HCl – hyper-acute cerebral infarction; rt-PA – recombinant tissue plasminogen activator; NIHSS – National Institute of Health Stroke Scale; ADC – apparent diffusion coefficient; OCSF – Oxfordshire Community Stroke Project.

Table 5. Logistic regression analysis of prognostic indicators.

Indicators	Regression coefficient*	Standard error	Odds ratio (95%CI)	P
Age	-0.10	0.05	0.91 (0.81~1.01)	0.074
Stroke history	-1.98	0.94	0.14 (0.02~0.87)	0.035
Baseline rADC	0.09	0.04	1.09 (1.00~1.19)	0.049
Baseline NIHSS	-0.42	0.16	0.66 (0.48~0.90)	0.008

NIHSS – National Institute of Health Stroke Scale; rADC – relative apparent diffusion coefficient; 95%CI – 95% confidence interval; * using good prognosis as outcome variables.

within 3 months after receiving rt-PA intravenous thrombolytic therapy, indicating that ADC and rADC value can be used as the basis for predicting the outcome of thrombolytic therapy. DWI plays an important role in the diagnosis of perinatal arterial ischemic stroke, a non-linear increase in ADC values in the core of the ischemic tissue (iADC) and rADC values was observed over time, and large middle cerebral artery strokes resulted in lower iADC and rADC values [20].

We also found that patients with HCl who received the rt-PA intravenous thrombolytic therapy within the first 3 h presented with better prognosis, and gradually increased ADC values were observed with rt-PA administered at different time

windows within 6 h, suggesting that the ADC values may be closely related with the prognosis of HCl patients with rt-PA administration. It has been reported that thrombolytic therapy given up to 6 h after stroke reduces the proportion of dead or dependent people, and those treated within the first 3 h derive substantially more benefit than with later treatment [21]. However, a previous study recommended a limited timeframe within 4.5 h [4], while other studies found that rt-PA intravenous thrombolytic therapy within 4.5–6 h after ACI was still effective and safe regarding therapeutic effect and mortality [22,23]. Partially consistent with our results, the rADC increased faster in patients with acute middle cerebral artery infarct with initial intravenous thrombolysis, which seems to have an effect

on the time course of ADC [24]. Acute cerebral ischemic injury in DWI was presented as hyperintense signal changes, reflecting a decline in the ADC, which depends on the stage of cytotoxic edema and water content, while elevated ADC was observed in the chronic stage [25]. In our study, rADC showed a gradual increase from the 7th day to the 90th day after treatment, with a rather uniform time course. As previously reported, 2 phases in the time course of rADC changes have been found, including persistent reduction of rADC within the first 4 d after stroke onset and a subsequent increasing trend of rADC at later subacute-to-chronic time points (≥ 7 days) [26]. Additionally, a reduction in rADC has been also reported from the first hours of stroke and persistent to the 3rd day, followed by increased rADC from the 4th day to the point of pseudo-normalization on day 9 [27].

Multiple logistic regression analysis showed that NIHSS score, stroke history, and baseline rADC value were independent factors for the prognosis of HIC patients receiving rt-PA intravenous thrombolysis. NIHSS score, a tool to objectively quantify the impairment caused by stroke, has been considered as an indicator for tPA treatment and has been found to be an excellent predictor of patient outcomes [28]. As previously published, the baseline NIHSS score strongly predicts the likelihood of a patient's recovery after stroke, and NIHSS change appears to be a useful outcome measure for acute stroke

trials [29,30]. Consistently, our results showed that the NIHSS score in HCl patients with good clinical outcome was obviously higher than those with poor clinical outcome. Additionally, prior stroke and severe stroke at admission were prognostic factors for poor functional outcome [31,32]. In addition, the ADC results obtained from the core and the penumbra of the infarction area are believed to be beneficial in the estimation of the infarction prognosis and in the planning of a treatment protocol in ischemic stroke patients [33].

Conclusions

These preliminary findings revealed that the values of ADC and rADC may provide important guidance in the prognosis of HCl patients receiving rt-PA, and the baseline rADC value is the protective factor for the prognosis of HCl patients receiving rt-PA. Due to the small sample size of this study, further studies with larger sample sizes are needed to observe the relationship regarding ADC value and rADC values in different time windows after thrombolytic treatment.

Competing interests

We declare that we have no conflicts of interest.

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