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Association of critical hypoperfusion biomarkers on CT with futile recanalization and poor outcome after mechanical thrombectomy in acute ischemic stroke

Meng Fu[1,2†], Jun Yang[3†], Xiaonan Dong[4], Changren Huang[5], Zhengzhou Yuan[1], Li Jiang[1], Renliang Meng[1], Yang Xie[1] and Jinglun Li[1*]

Abstract

Background and purpose We aimed to investigate the association between critical perfusion delay and poor outcome among recanalized stroke patients with anterior large-vessel occlusion, and to use pretreatment hypoperfusion biomarkers on CT to predict futile recanalization even after successful thrombectomy.

Methods An ischemic region with time-to-maximum (Tmax) > 12s–10s was defined as critical hypoperfusion, Tmax > 8s as moderate hypoperfusion, and hypoperfusion intensity ratio (HIR, volumetric ratio of Tmax > 10s / Tmax > 6s) represented for severity of critical hypoperfusion and rCBF < 30% for ischemic core. The associations between these CT perfusion characteristics and favorable or unfavorable outcome (mRS 0–2 versus 3–6) were analyzed in univariable regression, and a multivariable model was then used to predict futile recanalization.

Results Seventy-nine stroke patients were included and had good grades of instant recanalization. Forty-two patients (53%) had poor outcomes, and they had a significantly larger volume of critical hypoperfusion as seen with Tmax > 10s and > 12s ($P = 0.032$ and 0.008, respectively), a larger volume of ischemic core ($P = 0.011$) and a higher HIR ($P = 0.002$) than those patients achieving good outcomes. In the univariable analysis, a lower HIR (OR, 0.008; 95%CI, 0.001–0.254, $P = 0.006$) was associated with favorable outcome. The volume size of Tmax > 12s was significantly and positively correlated with the size of ischemic core. A HIR value higher than 0.491 might predict a futile recanalization and poor outcome (AUC = 0.701).

Conclusions The critical hypoperfusion biomarkers on CTP could be useful in triaging endovascular treatment and identifying stroke patients at risk of futile recanalization.

Keywords Ischemic stroke, Anterior large-vessel occlusion, Hypoperfusion, Mechanical thrombectomy, Futile recanalization

†Meng Fu and Jun Yang are co-first authors.

*Correspondence:
Jinglun Li
ljl031611@163.com
[1]Department of neurology, Affiliated Hospital of Southwest Medical University, Luzhou, China
[2]Department of Pediatrics, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China
[3]Central imaging laboratory, Glotope Advanced Pharmaceutical Ltd, Beijing, China
[4]Center For Medical Device Evaluation.NMPA, Beijing, China
[5]Department of neurosurgery, Affiliated Hospital of Southwest Medical University, Luzhou, China

Introduction

Mechanical thrombectomy is considered as an effective treatment for timely recanalization, and can improve hypoperfusion in acute ischemic stroke (AIS) patients with a large vessel occlusion [1–3]. Although studies have demonstrated the effectiveness of mechanical thrombectomy in those patients operated within 24 h of stroke onset [2, 4, 5], the clinical benefit of mechanical recanalization is not reflective of the instant opening of occlusion in the affected brain area. In the actual clinical practice, some recanalized patients still have poor functional outcomes (mRS > 2), and even have post-recanalization hemorrhage or complications. To explore the missing jigsaw piece of such paradox between instant recanalization and unfavorable outcome, computed tomographic perfusion (CTP) or MR perfusion is often used as an easily accessible, timely and reliable technique for assessing penumbra and infarct in stroke studies [6, 7]. Some other studies of perfusion imaging found a good correlation between the baseline volume of hypoperfused region (defined by the time to maximum of the residue function (Tmax) > 6s) and the volume of salvaged penumbra after reperfusion [8, 9].

Tmax is a quantitative surrogate of ischemia in response to tissue hemodynamic change, which can be used to predict the size of ischemia and fate of affected tissue [10, 11]. The DEFUSE, DEFUSE2 and EPITHE studies showed that a greater volume of Tmax > 8s was associated with a lower reperfusion rate and a lower chance of good functional outcome [12, 13]. Therefore, the ultimate fate of ischemic tissue can be significantly directed by both degree and volume of the critical hypoperfusion (Tmax > 10s or greater values), as well as hypoperfusion intensity ratio (HIR, defined as volume of Tmax > 10s / volume of Tmax > 6s) [13, 14], regardless of the time from stroke onset or status of endovascular recanalization. However, influence of such critical tissue hypoperfusion on functional fate of the patients whose occlusions have been successfully recanalized, is still unclear.

In our research, the added value was to investigate effects of critically delayed Tmax (> 10s and > 12s) and HIR on the functional outcomes in the AIS patients whose clotted vessels have already been successfully recanalized during endovascular treatments (mTICI of 2b or 3). We sought to use pretreatment HIR and volumes of critical hypoperfusion to predict futile recanalization, and to explore the paradox between poor outcome and successful endovascular recanalization.

Methods

Study design and patient cohort

All data in this study were retrospectively collected and analyzed from the Affiliated Hospital of Southwest Medical University. This study was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University with a waiver of informed consent due to the retrospective nature of the study. All methods were carried out in accordance with relevant guidelines and regulation under the 'Ethics approval and consent to participate' .The study enrolled acute ischemic stroke patients who presented in our stroke emergency unit within 24 h from symptom onset, from April 2018 to December 2020. Patients were eligible for inclusion in the study if they were: (1) 18 years of age or older; (2) within 24 h from symptom onset to the therapy; (3) found large vessel occlusion in the anterior circulation (intracranial segments of internal carotid artery, and proximal segment of middle cerebral artery and M1, M2 segment) at admission; (4) all evaluated by baseline non-contrast CT (NCCT) and perfusion CT (CTP); (5) assessed with recanalization status/scale at the end of endovascular treatment on the conventional angiography (i.e. substantial tissue reperfusion defined as modified thrombolysis in cerebral infarction [mTICI] [15] score of 2b or 3); and (6) followed up within 24–72 h using diffusion-weighted imaging (DWI) and/or NCCT. Any patient presented with pregnancy or with severe disability at admission or contraindicated to medication or iodine contrast agent was excluded. All clinical information and characteristics were collected but were blind to the raters who processed and assessed the imaging results.

CT neuroimaging and perfusion parameters

All enrolled patients underwent a NCCT scan and CTP scan before treatment. The CT imaging was done on a 128-slice multidetector CT scanner using default technical settings and protocol for head/neck. NCCT was done with the full brain covered before completing CTP scan. Each CTP scan was composed of 20 sequential scanning cycles with a 3-seconds interval between cycles, and 5-seconds delay of the contrast agent injection.

All CTP data were analyzed using a fully automated post-processing software (Neusoft Medical Systems, China). The software used a deconvolution-based method, specifically singular value decomposition (SVD) [16], for calculating tissue intensity-time curve of the CTP images with selected arterial input, and then generated parametric maps of ischemic core, penumbra and moderate-severe hypoperfusion regions. In brief, ischemic core was defined as the region with a relative cerebral flow threshold of < 30% (rCBF < 30%) to the contralateral brain region. Hypoperfused tissue region or penumbra was defined as a Tmax value of > 6 s. In the cerebral tissue with moderate-severe hypoperfusion, the lesion volumes of such prolonged tissue time delay at Tmax > 8s, > 10s, and > 12s were analyzed, and especially for the volume of Tmax > 12s, which may have potential

to predict unfavorable outcome even when achieved substantial recanalization. In addition, HIR defined as a volumetric ratio of Tmax>10s/Tmax>6s in the hypoperfused lesion, was calculated to measure severity of the hypoperfused epicenter [17]. Data with poor image quality were excluded from the study.

Clinical outcome assessments

The baseline NIHSS score was assessed prior to the treatment for the severity of stroke by a professionally trained and experienced neurologist. The endovascular thrombectomy was performed by an interventional neurology team. All neurologists had at least 4 years of clinical experience of stroke treatments. Functional outcome was evaluated using the modified Rankin Scale (mRS) (range: 0 [no symptoms] to 6 [death]) at 90 days post stroke, and the mRS assessments were done through their outpatient visits, or by phone calls made by the trained neurologists. A score in mRS of 0 to 2 at 90 days is favorable outcome, and poor outcome has a higher score of mRS (score 3–6).

Statistical analysis

All statistical analyses were performed using SPSS version 25.0 (IBM, Chicago, IL). The Shapiro-Wilk test was employed to determine the normality of the data distribution. The chi-square test(for categorical variables), or Mann-Whitney test (for continuous variables without normal distribution), or a Student *t* test (for continuous variables with normal distribution) was used for assessments of clinical and imaging variables between favorable and unfavorable outcome groups. Pearson's correlation analysis was used to measure the association between two variables. We set P values with an α of 0.05 to account for multiple comparisons of the favorable-outcome group versus unfavorable-outcome group.

The associations of age, gender, NIHSS score, presence of hypertension, history of stroke, diabetes mellitus, volume of ischemic core (rCBF<30%), volume of Tmax>6s, 8s, 10s and 12s, HIR value, hemorrhagic transformation with the clinical outcome (mRS at day 90) were assessed using logistic regression. The multivariable logistic regression model was then used when any variable was found significant at $P<0.1$ in the univariable logistic regression. The gender, admission NIHSS, volume of rCBF<30%, volume of Tmax>8s, 10s, 12s and HIR (seven variables) were then selected as the predictors for multivariable association with the favorable or unfavorable outcome, adjusting for the ageand other baseline clinical characteristics. Area under the receiver operating characteristics curve (ROC-AUC) was used for assessing performance of the 7 variable-integrated model or HIR alone in predicting good/poor outcomes. The optimum cut-off value of HIR was then calculated using Youden index.

Results

This study enrolled a total of 125 AIS patients. After excluding some patients with incomplete imaging data ($n=9$), posterior circulation occlusion ($n=12$), missing follow-ups ($n=8$), no substantial tissue reperfusion as seen with mTICI score<2b ($n=15$), not the large vessel vascular occlusion($n=2$), seventy-nine patients (Fig. 1) were finally included in our analysis (Table 1). Twenty-two patients (27.85%) received intravenous thrombolysis before mechanical thrombectomy. No significant differences were observed between favorable and unfavorable outcome group in age, gender, TIA, IV thrombolysis, risk factors, baseline INR, reperfusion score, Trial of Org 10,172 Acute Stroke Treatment (TOAST), occlusive location and hemorrhagic transformation (Table 1). There was a statistically significant difference in mortality between the two groups($p=0.003$).

The imaging characteristics were compared between recanalized AIS patients with favorable outcome and with unfavorable outcome (Table 2). The lesion volumes of rCBF<30%, Tmax>10s and >12s in the unfavorable group were significantly higher than those in the favorable group (Fig. 2). Specifically, the median volume of ischemic core was 4.79 mL (IQR 2.41–15.90) versus 13.98 mL (IQR 4.07–31.33) for favorable outcome group and unfavorable group ($p=0.011$), respectively. The median volume of Tmax>10s was 28.27 mL (IQR 9.72–69.8) versus 54.12 mL (IQR 30.20-73.11) for favorable and unfavorable group, respectively ($p=0.032$). The median volume of Tmax>12s was 9.60 mL (IQR 4.69–44.13) versus 33.66 mL (IQR 18.98–54.66) for favorable and unfavorable group, respectively ($p=0.008$). In addition, a higher median HIR was seen in the unfavorable group compared to the favorable outcome group ($p=0.002$, 0.30 (IQR 0.20–0.40) vs. 0.40 (IQR 0.3–0.4), Fig. 2). Spearman correlation analysis (Fig. 3) found that volume of rCBF<30% (ischemic core) was significantly and positively correlated with the volume of Tmax>12s ($r=0.454$).

The pretreatment predictors or factors could be associated with poor/good outcomes even in the successfully recanalized AIS patients, and univariate logistic regression (Table 3) showed an association between volume of Tmax>12s (critically hypoperfused region) and favorable outcome, but only had a marginal significance (OR, 0.986; 95% CI, 0.971-1, $p=0.055$). Similar associations occurred for the volume of rCBF<30% (OR, 0.975; 95% CI, 0.948–1.003, $p=0.083$), volume of Tmax>8s (OR, 0.993; 95% CI, 0.984–1.001, $p=0.086$), volume of Tmax>10s (OR, 0.990; 95% CI, 0.980–1.001, $p=0.073$), admission NIHSS (OR, 0.905; 95% CI, 0.815–1.044, $p=0.059$) ,but remained insignificant. On the other hand, there was a statistically significant association of HIR (OR, 0.008; 95% CI, 0.001–0.254, $p=0.006$) with a favorable outcome (Table 3).

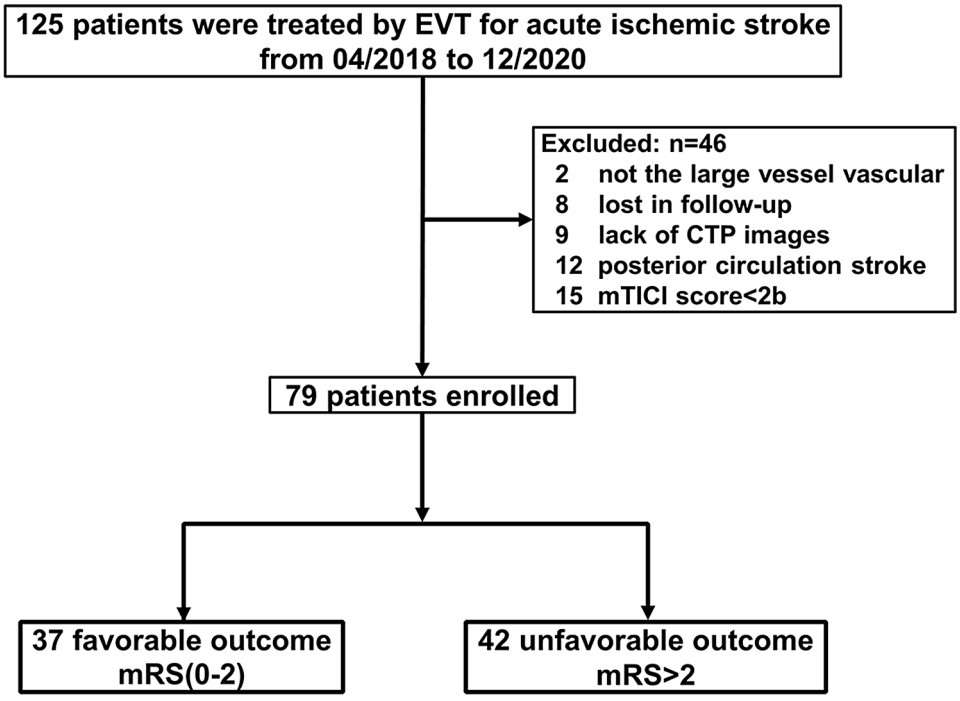

Fig. 1 Study Flowchart and Population

Based on the results of univariate analysis, HIR was selected as a significant imaging predictor to further assess its performance for predicting outcome in the recanalized patients. A receiver operating characteristic curve (ROC) analysis demonstrated an area under the ROC of 0.701; with a sensitivity of 62.9% and a specificity of 69.2% (Fig. 4). The optimum cut-off value of HIR for differentiating favorable or unfavorable outcome, was calculated using the Youden index. The HIR cut-off was determined (HIR ≥ 0.491) to predict an unfavorable functional outcome even when the patients were successfully recanalized (mTICI score = 2b or 3).

Furthermore, seven variables, which had significance at $P < 0.1$ level in the univariable logistic regression, were selected to build up an integrated multivariate regression model for predicting unfavorable outcome. The gender, admission NIHSS, HIR, volume of Tmax > 8s, of Tmax > 10s, of Tmax > 12s and volume of rCBF < 30% were then integrated, and the performance of the integrated prediction model revealed a ROC-AUC of 0.782, with a model sensitivity of 82.1% and specificity of 62.9% (Fig. 5).

Discussion

The association between effectiveness of endovascular therapy in AIS and clinical benefit is complex (Fig. 6), and differences in tolerance of ischemia in white matter and gray matter may be a major confounder affecting early assessment of the outcome of ischemic tissue on CT or MR images [18, 19]. The need of individualized assessment of stroke patients by the neuro-interventionalist is quite obvious, and it can improve the accuracy in selecting candidates for endovascular treatment. However, the reality is lack of such investigation in the recanalized patients using pretreatment radiological biomarkers that are easily accessible in routine practice.

The added value of our study was the comparative investigation of several imaging biomarkers between successfully recanalized patients with and without favorable outcome, while most observational studies included unstratified patients, those with a low recanalization grade who were not expected to have a good reperfusion. Theoretically, a successful recanalization with mTICI of 2b or 3 would indicate a beneficial outcome of the treatment, but our study showed newly added evidence that not all of recanalized AIS participants with mTICI of 2b or 3 reached a good final outcome (i.e. 42 out of 79 patients (53%) had poor outcomes). Other studies show the similar results of the futile recanalization, about 25–50% of patients have futile recanalization [20–22]. To explore the reasons behind such futile recanalization and seek ideal pretreatment biomarkers, we revealed that size of severely hypoperfused regions (at Tmax > 10s and 12s) and ischemic core (at rCBF < 30%), and HIR value were all significantly greater in the poor outcome group than those in the favorable outcome group, suggesting usefulness of pretreatment imaging biomarkers in differentiating patients at risk of futile recanalization from those benefitting from endovascular recanalization.

Table 1 Comparisons of baseline and clinical characteristics between favorable and unfavorable outcome group

Factor	All patients *N* = 79	Favorable mRS ≤ 2 *N* = 37	Unfavorable mRS>2 *N* = 42	X^2/t/U	*P* value
Age, mean ± SD	62.96 ± 11.33	61.56 ± 10.16	64.19 ± 12.32	1.027	0.301
Females/Males, n	34/45	12/25	22/20	3.193	0.074
Hypertension, n (%)	55(69.62)	28(75.67)	27(64.29)	1.207	0.272
Diabetes, n (%)	19(24.05)	8(21.62)	11(26.19)	0.225	0.635
Ischemic heart disease, n (%)	10(12.66)	4(10.81)	6(14.29)	0.215	0.643
Atrial fibrillation, n (%)	27(34.17)	10(27.03)	17(40.48)	1.582	0.209
TIA, n (%)	5(6.33)	3(8.11)	2(4.76)	0.412	0.521
Alcohol intake, n (%)	21(26.58)	8(21.62)	13(30.95)	0.878	0.349
History of smoking, n (%)	27(34.18)	13(35.14)	14(33.33)	0.028	0.866
INR, mean ± SD	1.07 ± 0.19	1.06 ± 0.18	1.08 ± 0.20	0.012	0.913
IV thrombolysis, n (%)	22(27.85)	11(29.73)	11(26.19)	0.123	0.726
Admission NIHSS, Median (IQR)	11(8–14)	11(7–14)	11(10–14)	-1.623	0.105
OTI, Median (IQR)	7.7(4.75-11.00)	7.43(4.32–11.23)	7.88(5.95–10.83)	-0.757	0.449
OTR, Median (IQR)	12.53(8.37–17.5)	11.78(8.5-15.82)	11.75(9-16.55)	-0.418	0.676
Reperfusion grade, n (%)				0.177	0.764
2b	34(43.04)	15(40.54)	19(45.24)		
3	45(56.96)	22(59.46)	23(54.76)		
Location of occlusion, n (%)				0.944	0.624
MCA	59(74.68)	27(72.97)	32(76.19)		
ICA	12(15.19)	7(18.92)	5(11.90)		
T-type	8(10.13)	3(8.11)	5(11.90)		
TOAST, n (%)				3.516	0.172
Large-artery atherosclerosis	53(67.09)	28(75.68)	25(59.52)		
Cardioembolism	23(29.11)	7(18.92)	16(38.10)		
Other determined etiology	2(2.53)	1(2.70)	1(2.38)		
Undetermined etiology	1(1.27)	1(2.70)	0(0)		
Hemorrhagic transformation, n (%)	16(20.25)	7(18.92)	9(21.43)	0.077	0.782
sICH, n(%)	4(5.06)	1(2.70)	3(7.14)	0.142	0.677
Death, n (%)	9(11.39)	0(0)	9(21.43)	8.948	**0.003**

IQR, Interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; INR = international normalized ratio; TIA = transient ischemic attack; OTI = onset-to-image time; OTR = onset-to-reperfusion time; MCA, Middle cerebral artery; ICA, Internal carotid artery; sICH = symptomatic intracerebral hemorrhage. TOAST = Trial of Org 10,172 in Acute Stroke Treatment

Table 2 Comparisons of imaging characteristics between recanalized AIS patients with favorable outcome and with unfavorable outcome

Imaging parameter	All Patients *N* = 79	Favorable mRS ≤ 2 *N* = 37	Unfavorable mRS>2 *N* = 42	U	z	*P* value
Volume of rCBF < 30%, median(IQR)	8.36(3.12–27.17)	4.79(2.41–15.9)	13.98(4.07–31.33)	521.0	-2.556	0.011
Mismatch Volume, median(IQR)	121.345(60.02-150.35)	93.14(42.49-126.59)	127.18(72.74-164.31)	673.0	-1.022	0.307
MismatchRatio, median(IQR)	10(5.6–24)	14(8.3–22)	8.7(5.1–25)	380.5	0.604	0.546
Volume of Tmax > 4s, median(IQR)	189.395(114.14-258.27)	157.53(89.18-208.28)	221.84(166.46-268.71)	687.0	-0.884	0.377
Volume of Tmax > 6s, median(IQR)	130.625(73.94-178.01)	105.98(47.47-167.19)	151.87(120.15-185.17)	639.0	-1.356	0.175
Volume of Tmax > 8s, median(IQR)	73.15(34.96-103.26)	52.29(19.29-101.57)	87.12(61.55-103.26)	586.0	-1.877	0.061
Volume of Tmax > 10s, median(IQR)	47.91(20.7-73.11)	28.27(9.72–69.8)	54.12(30.2-73.11)	558.5	-2.147	0.032
Volume of Tmax > 12s, median(IQR)	31.375(7.4-54.34)	9.6(4.69–44.13)	33.66(18.98–54.66)	507.5	-2.648	0.008
HIR, median(IQR)	0.3(0.2–0.4)	0.3(0.2–0.4)	0.4(0.3–0.4)	408	-3.026	0.002

IQR: Interquartile range; rCBF, relative cerebral blood flow; Tmax, time-to-maximum; HIR, the volumetric ratio of the Tmax > 10s/Tmax > 6s

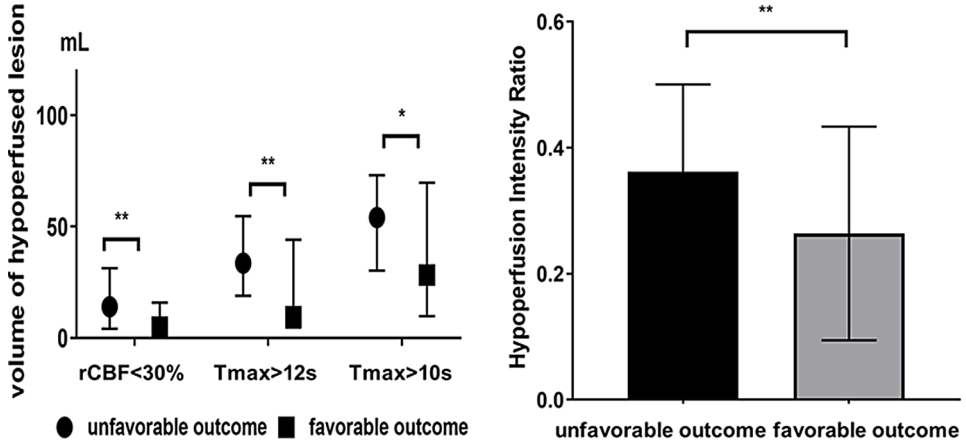

Fig. 2 Imaging characteristics between the two outcome groups of the successfully recanalized AIS patients. The graphs showed that volumetric measurements of hypoperfused regions and ischemic core (Tmax > 10s and 12s, rCBF < 30%) and HIR were all significantly greater in the unfavorable outcome group than those in the favorable group

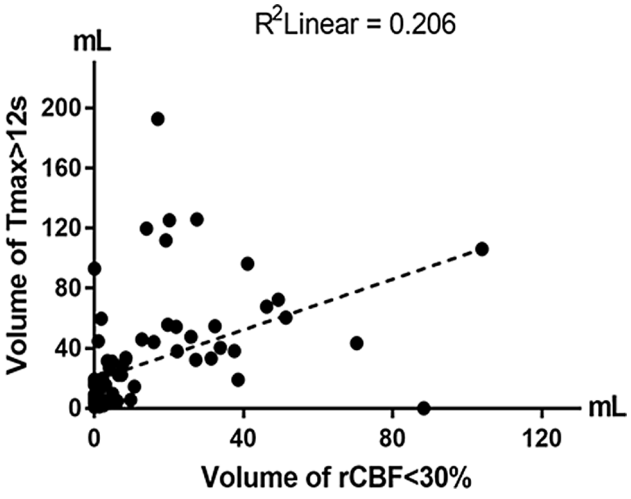

Fig. 3 Spearman correlation plot for volumes of Tmax > 12s and volumes of rCBF < 30%. The correlation coefficient was $r = 0.454$

One previous study has indicated that a volume of 85 mL at Tmax > 8s reduced the effectiveness and safety of reperfusion therapy [12], and each 10 mL increase in lesion volume of Tmax > 10s decreased the probability of functional independence in endovascularly treated patients by 57% [23]. Another imaging biomarker, HIR, is an independent predictor of collateral circulation status, malignant cerebral edema and infarct growth, all of which can affect the fate of endovascular treatment [24, 25], because such treatment does not always come with a good clinical outcome. In our study, some new evidence came from combining both HIR and a new biomarker, volume of Tmax > 12s. This could come to a more supportive conclusion, especially for those successfully recanalized AIS patients during thrombectomy while not showing a beneficial outcome afterwards. The benefit-risk assessment for those recanalized patients should be made as soon as possible when the treatment is done or even before initiation of endovascular recanalization. This study is the first to comprehensively explore the combinative effect of volume with Tmax > 12s and HIR on functional outcomes of AIS patients with endovascular recanalization.

In a recent study, HIR was used as an indicator of whether to perform mechanical thrombectomy in elderly patients over 80 [26]. Other studies have shown that HIR cut-off value was ranged 0.40–0.54, for predicting functional independence after mechanical thrombectomy [25, 27]. In our study, the HIR threshold for differentiating a favorable outcome from poor outcome was defined as 0.491. The minor difference in the HIR cut-offs across our and other studies may be due to the variability of the CTP quantitative analysis, originally derived from image post-processing techniques [19, 28]. Our study shows that HIR is a significant imaging biomarker which affects good or poor clinical outcome after thrombectomy, suggesting a prognostic value of HIR. This observation is similar to another investigation, which demonstrated that a high HIR had infarcts that grew approximately 4.5 times faster than those with a low HIR, and ended with a greater final infarct size and more severe neurological deficits after endovascular treatment [17]. Our findings indicated that patients with a higher HIR were less likely to benefit from reperfusion treatments, and each unit increase in HIR was associated with an 8-fold decrease in the likelihood of favorable outcome. This may be caused by a faster growth of infarct size when HIR has already or nearly breached the threshold of irreversible injury.

In this study, Tmax > 12s, a newly added delay time of ischemic tissue, was used to justify the relationship between severely hypoperfused tissue and functional outcome or size of the infarct core. We chose to use Tmax as such a surrogate because it is a combinative biomarker of time and tissue perfusion, and is superior to

Table 3 Association of factors with favorable outcome (mRS 0–2) in the univariable analysis

Factor	Odds ratio	95% CI	*P* value
Age	0.979	0.941–1.019	0.304
Female sex	0.436	0.174–1.019	***0.076***
Hypertension	1.728	0.648–4.610	0.274
Diabetes	0.777	0.274–2.204	0.636
Ischemic heart disease	0.727	0.188–2.807	0.664
Atrial fibrillation	0.545	0.210–1.411	0.211
TIA	1.818	0.287–11.536	0.526
Alcohol	0.615	0.222–1.707	0.351
History of smoking	1.083	0.427–2.749	0.866
INR	0.674	0.064–6.804	0.726
IV thrombolysis	1.192	0.445–3.193	0.726
Location of occlusion			
MCA			0.628
ICA	1.406	0.307–6.431	0.660
T-type	2.333	0.463–14.613	0.365
TOAST			
Large-artery atherosclerosis			0.182
Cardioembolism	1.160	0.069–19.519	0.918
Other determined etiology	0.438	0.500-8.036	0.578
Admission NIHSS	*0.905*	*0.815–1.004*	***0.059***
OTI	0.964	0.872–1.067	0.481
OTR	0.981	0.939–1.025	0.394
Volume of rCBF < 30%	0.975	0.948–1.003	***0.083***
Mismatch Volume	0.998	0.992–1.003	0.419
Mismatch Ratio	0.989	0.967–1.011	0.320
Volume of Tmax > 4s	0.998	0.994–1.003	0.449
Volume of Tmax > 6s	0.997	0.992–1.002	0.243
Volume of Tmax > 8s	0.993	0.984–1.001	***0.086***
Volume of Tmax > 10s	0.990	0.980–1.001	***0.073***
Volume of Tmax > 12s	0.986	0.971-1	***0.055***
HIR	0.008	0.001–0.254	***0.006***

Abbreviations 95% CI=95% Confidence Interval; ASPECTS=Alberta Stroke Program Early Computed Tomography Score; NIHSS=National Institutes of Health Stroke Scale; OTI=Onset-to-Imaging Time; INR=International Normalized Ratio; TIA=Transient Ischemic Attack. Six variables in italic were significant at the $p<0.1$ level and entered to the multivariable-integrated model for predicting poor/good outcomes; TOAST=Trial of Org 10,172 in Acute Stroke Treatment. T-type=TOAST type

other parameters in characterizing the state of ischemia [10, 29]. The pretreatment volume of Tmax>12s was significantly and positively correlated with the volume of rCBF<30% (r=0.454). The strong correlation indicates that a part of severely hypoperfused region is contained within the ischemic core, which is defined as the region with rCBF<30%. A greater size of Tmax>12s likely represents a quantitative biomarker for predicting a potential risk, even when the reperfusion grade is good in this study. Reperfusion to the ischemic core or severely hypoperfused regions can be a double-edged sword, in our investigation, the patients having good reperfusion after thrombectomy but with a higher HIR and greater volume of Tmax>12s may infer a higher risk of evolving to futile recanalization and even worsening of neurological

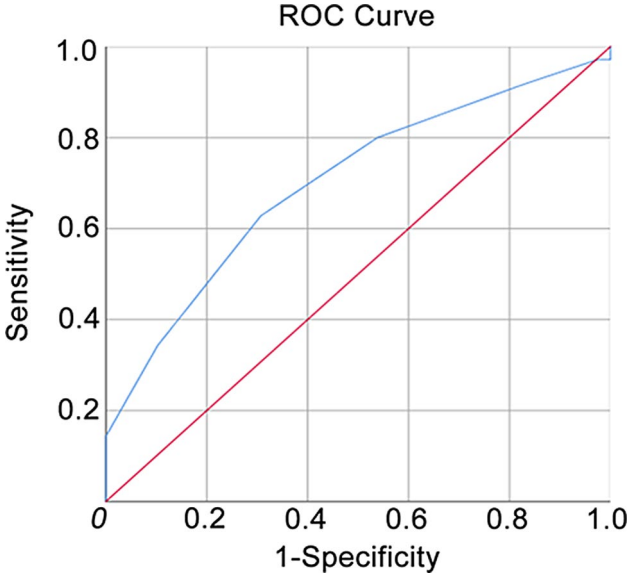

Fig. 4 Performance evaluation using receiver operating characteristic curve (ROC, the blue line) of HIR as significant predictor for predicting unfavorable or favorable outcome in the successfully recanalized AIS patients. The area under the curve was 0.701. The Youden index was used to calculate the optimum HIR cut-off value (0.491) to classify favorable/unfavorable functional outcome

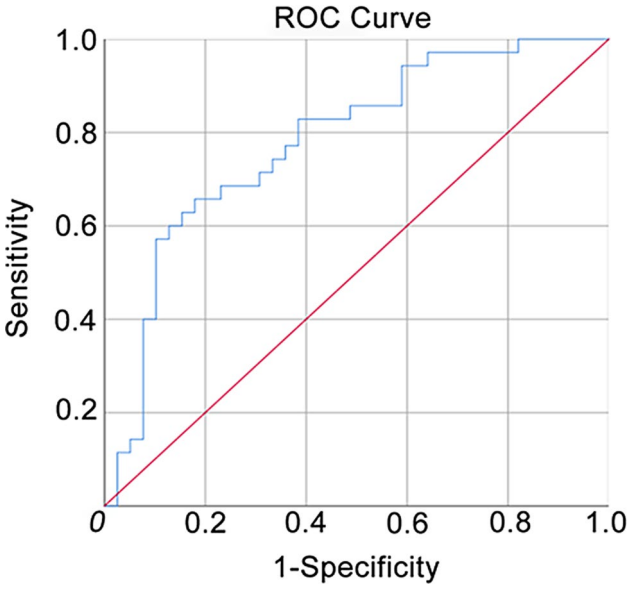

Fig. 5 Performance evaluation using receiver operating characteristic curve (ROC, the blue line) of 7 variable-integrated model for predicting unfavorable or favorable outcome in the successfully recanalized AIS patients. The area under the curve was 0.782. The seven variables used in the model were as follows: gender admission NIHSS, HIR, volume of Tmax > 8s, of Tmax > 10s, of Tmax > 12s and volume of rCBF < 30%

deficit. This observation needs to be further validated in the future studies. On the other hand, the penumbra with Tmax>6s may evolve to Tmax>10s or Tmax>12s within a short time that makes HIR increase rapidly due to an unexpected rate of infarct growth, thus offsetting the

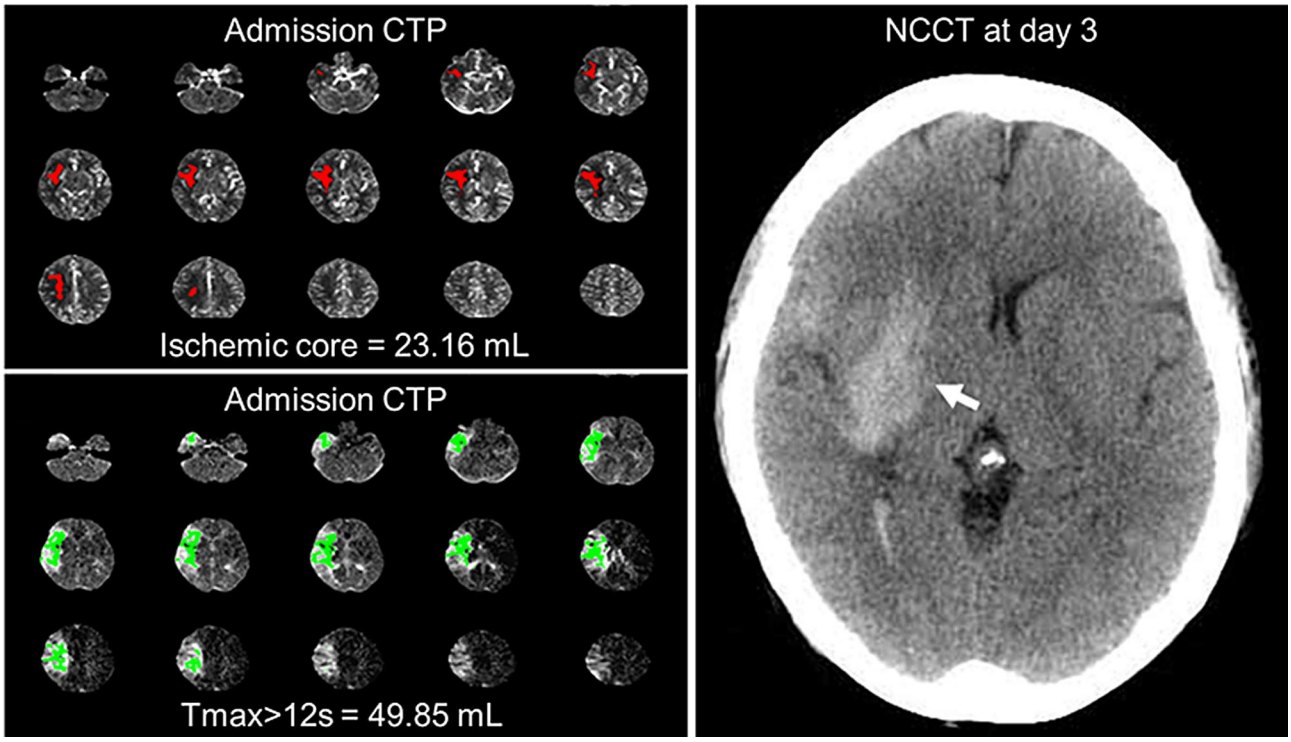

Fig. 6 A recanalized AIS patient who had unfavorable outcome. A-51-year-old woman presented with a weakness in her left limb for 6.7 h after last known to be well. The admission NIHSS (National Institutes of Health Stroke scale) was 10 and the hypoperfusion intensity ratio (HIR) was 0.5. (Top left) The admission CT perfusion (CTP) scan showed the volume of ischemic core (rCBF < 30%) was 23.16mL; (Bottom left) and the volume of critically hypoperfused region (Tmax > 12s) was 49.85mL. (Right) A hemorrhagic transformation in the right frontotemporal insula (white arrow) was seen on the brain NCCT at day 3 after endovascular thrombectomy, and the follow-up NIHSS was 13. Clinical outcome revealed a mRS of 3 at day 90

benefits of recanalization and then affecting overall outcome of the patients. Additionally, given the dependency of hypoperfusion parameters and the deconvolution algorithm on post-processing software, it is crucial to consistently use the same software with appropriate algorithms, and having a single blinded interpreter process all perfusion images can help minimize inter-rater variability, thereby ensuring more accurate and reliable results.

Our study had some limitations. First, the data in a single center limited the support for our findings, and a multicenter study is needed. Second, the sample size of the study was small, and collaterals and infarct growth need to be tracked and elucidated in the future. Third, the evolution of ischemic tissue and core in the region of severe hypoperfusion with Tmax > 12s may need more evidence to better understand mechanism of those patients who did not gain benefits from endovascular recanalization. Fourth, due to the limitations of our sample size, this study was unable to thoroughly explore the differences in ischemic volume characteristics and their impact on outcomes between white and gray matter, cortical and deep gray matter, or between the frontal lobe and MCA regions. In addition, since Tmax tends to overestimate both the ischemic penumbra and non-viable tissue [30], conclusions based solely on Tmax should be interpreted with caution when selecting EVT patients and evaluating their prognosis. It is essential to incorporate other perfusion parameters, such as mean transit time(MTT) and CBF, for a more individualized assessment.

Conclusion

In summary, patients with a larger volume of Tmax > 12s and higher HIR value in the hypoperfused cerebral tissue were less likely to achieve a good functional outcome even when they had successful endovascular recanalization. For endovascular treatment of AIS occurred within 24 h, individualized analysis of hypoperfusion characteristics can help neuro-interventionists and neurologists select more appropriate candidates. More prospective and multicenter evidence are required and pretreatment biomarkers may be effective in stratifying those recanalized AIS patients and reducing futile recanalization, thus improving overall functional outcome after thrombectomy.

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Author contributions
Name roles Meng Fu Writing - original draft, Data curation , Project administration Jun Yang Writing - review & editing, Project administration, Methodology Xiaonan Dong Writing - review & editing, Methodology, Formal analysis Changren Huang Data curation, Project administration Zhengzhou Yuan Data curation, Project administration Li Jiang Data curation, Project administration Renliang Meng Data curation, Project administration Yang Xie Data curation, Project administration Jinglun Li Writing - review & editing, Data curation, Project administration, Methodology All authors reviewed the manuscript.

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Data availability
Data will be available after all authors have given their consent.

Declarations

Ethics approval and consent to participate
All data in this study were retrospectively collected and analyzed from the Affiliated Hospital of Southwest Medical University. This study was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University with a waiver of informed consent due to the retrospective nature of the study. All methods were carried out in accordance with relevant guidelines and regulation under the 'Ethics approval and consent to participate'.

Consent for publication
All authors have reviewed and agreed with the content of the manuscript.

Competing interests
The authors declare no competing interests.

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