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Time-dependent infarct volume affects the benefit of recanalization

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ABSTRACT

Objectives: The benefit threshold of infarct volume from recanalization remains unclear. We assumed that the threshold decreased over time, and then investigated the benefit curve of infarct volume during different time periods.

Methods: We reviewed prospectively collected clinical and imaging data from acute ischemic stroke patients with internal carotid artery and M1 occlusion who underwent angiography before and 24 h after reperfusion therapy. Ordinal analyses of modified Rankin Scale scores were performed and curves were fitted.

Results: Of the included 445 patients, the median age was 71 years and 157 (35.3%) were women. The mean time from onset to treatment (OTT) was 248 ± 142 min. The median baseline infarct core volume was 49 (IQR 22–85) ml. Follow-up angiography revealed recanalization in 265 (59.6%) patients. The fitting curves showed that patients with an OTT ≤3 h would benefit from recanalization no matter how large the infarct volume was, whereas patients with an OTT between 3 and 4.5 h and with an infarct volume ≥ 125 ml, and those with an OTT ≥ 4.5 h and with an infarct volume ≥ 80 ml did not benefit from recanalization.

Conclusions: We established a time-dependent benefit threshold of infarct volume from recanalization, and thus suggested to estimate infarct core volume to select patients for reperfusion therapy in those with an OTT beyond 3 h.

1. Introduction

The natural history of acute ischemic stroke (AIS) patients with large artery occlusion carries a very poor prognosis (Hernandez-Perez et al., 2014). Fortunately, reperfusion therapy, i.e. intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT), extremely improves the clinical outcome in these patients (Goyal et al., 2016). Researchers keep exploring and developing the indications of reperfusion therapy. DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) trials demonstrated benefit extended to 16 to 24 h in selected patients for EVT (Nogueira et al., 2018; Albers et al., 2018). Recently, the Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial also extended the time window up to 9 h for IVT (Ma et al., 2019).

However, a considerable part of stroke patients underwent neurological deterioration, even with timely and complete reperfusion, accompanied by severe hemorrhagic transformation and malignant brain edema. These worsening results are known as reperfusion injury (Mizuma et al., 2018), which may be associated with larger infarct core and longer time from onset to treatment (OTT), based on the clinical observation. DAWN, DEFUSE 3 and EXTEND trials all had restrictions on the size of infarct core when selecting the eligible patients for late window therapy (Nogueira et al., 2018; Albers et al., 2018; Ma et al., 2019). However, so far, it remains unknown whether the interaction between infarct core size and OTT would affect the benefit of reperfusion, especially for the patients within 6 h.

We assume that 1) when the infarct core volume reaches a threshold, patients can hardly benefit from reperfusion/recanalization; 2) the benefit threshold of infarct core volume decreases over time. Therefore, in the current study, we investigated the benefit curve of infarct core volume from recanalization during different time periods, in order to provide some evidences for the decision-making of reperfusion therapy in future clinical trials.

Abbreviations: AIS, acute ischemic stroke; IVT, intravenous thrombolysis; EVT, endovascular thrombectomy; OTT, onset to treatment; CTP, computed tomography perfusion; AOL, Arterial Occlusive Lesion

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2. Subjects and methods

2.1. Study subjects

We retrospectively reviewed our prospectively collected database for consecutive patients with AIS who received reperfusion therapy (IVT and/or EVT) between June 2009 and April 2018. The detailed criteria of patient selection could be found in our registered clinical trial (NCT03367286). We then enrolled patients who (i) had a diagnosis of AIS confirmed by diffusion-weighted imaging (DWI) or computed tomography (CT); (ii) underwent angiography on admission; (iii) showed intracranial internal carotid artery (ICA) or middle cerebral artery (MCA) M1 occlusion on baseline MR/CT angiography; (iv) underwent follow-up MR/CT angiography 24 h after reperfusion therapy; (v) received clinical outcome assessment after 3 months. We excluded patients whose image quality was poor due to motion artifacts.

We retrieved demographic, clinical, and radiological data including age, sex; comorbid conditions such as history of hypertension, diabetes mellitus, and atrial fibrillation; OTT, baseline National Institutes of Health stroke scale (NIHSS) score; baseline infarct core volume, occlusion site, recanalization status 24 h after treatment, and modified Rankin Scale (mRS) score after 3 months. The onset was considered to be the time when a patient was last known to be without ischemic symptoms.

2.2. Ethics statement

The protocols of MR and CT perfusion (CTP) guided reperfusion therapy have been approved by our local human ethics committee. All clinical investigation has been conducted according to the principles expressed in the Declaration of Helsinki. A general form of informed consent for the purposes of data collection and further investigation was obtained from all patients or their immediate family members.

2.3. Imaging parameters

MRI was performed on a 3.0T system (Signa Excite HD, General Electric Medical System, Milwaukee, USA) equipped with an 8-channel phased array head coil. DWI sequence was used to generate the apparent diffusion coefficient (ADC) map to measure the infarct core volume (TR = 4000 ms; TE = 69.3 ms; b-value = 1000 s/mm^2; FOV = 24 × 24 cm^2; matrix size = 160 × 160; slice thickness = 5.0 mm; interslice gap = 1.0 mm). Time-of-flight magnetic resonance angiography (TOF-MRA) consisted of 3 slabs with TR = 20 ms; TE = 3.2 ms; flip angle = 15°; FOV = 24 × 24 cm^2; matrix size = 320 × 224; slice thickness = 1.4 mm. Perfusion weighted-imaging was obtained using the standard bolus passage of contrast method by injecting gadolinium (0.1 mmol/kg dose via power injector), its parameters were TR = 1500 ms; TE = 30 ms; slice thickness = 5.0 mm.

Multimodal CT was performed on a 64-slice CT scanner (SOMATOM Definition Flash; Siemens Healthcare Sector, Forchheim, Germany), including unenhanced CT (120 kV, 320 mA, contiguous 5 mm axial slices), and CTP (100 mm in the z-axis, 4 s delay after start of contrast medium injection, 74.5 s total imaging duration, 80 kV, 120 mA, slice thickness 1.5 mm, collimation 32 × 1.2 mm). A 60-ml bolus of contrast medium (Iopamidol; Braccosine, Shanghai, China) was used at a flow rate of 6 ml/s, followed by a 20 ml saline chaser at 6 ml/s. CT angiography (CTA) was generated from CTP.

2.4. Evaluation of imaging and outcome

Infarct core volumes were based on a relative cerebral blood flow (CBF) lesion volume using a < 30% threshold, or a DWI lesion volume with an ADC threshold of $< 620 \times 10^{-3}$ mm/s (Campbell et al., 2011; Purushotham et al., 2015). The mismatch profile was defined as a $T_{max} > 6$ s volume (for both CT and MR perfusion imaging) ≥ 10 ml and ≥ 120% of the infarct core volume. Acute arterial occlusion was determined by the invisibility of the artery on baseline angiography with corresponding symptoms compatible with the involved artery. According to Arterial Occlusive Lesion (AOL) scale (Grade 0: complete occlusion of the target artery; Grade 1: incomplete occlusion or partial local recanalization at the target artery with no distal flow; Grade 2: incomplete occlusion or partial local recanalization at the target artery with any distal flow; Grade 3: complete recanalization and restoration of the target artery with any distal flow) (Zaidat et al., 2013), we defined recanalization with Grades 2 or 3, and no recanalization with Grades 0 or 1. Clinical outcome at 3 months was assessed with mRS and dichotomized into good outcome (0–2) and poor outcome (3–6).

2.5. Statistical analysis

Fisher's exact test was used to compare the dichotomous variables between groups, while independent samples two-tailed *t*-test or Mann-Whitney *U* test was used for the continuous variables, as appropriate. Ordinal analyses of mRS scores were performed. Variables with a 2-tailed *P* value of < 0.1 in univariate analyses were included in the ordinal logistic regression model. In addition, the baseline imaging method (MRI or CTP) and the treatment modality (IVT or/and EVT) were forced into the model, since they might have potential effects on the measurement of infarct core volume and the assessment of clinical outcome. All samples were arranged in order of increasing infarct core volume. The first fifty samples were set as the first group for an ordinal analysis. Then we excluded the first five samples and included the following five samples as the second group, i.e. 1–50, 6–55, 11–60, 16–65… for each group. The median infarct core volume, odds ratios (ORs) and 95% confidence intervals (CIs) for each group were obtained, and then the ORs and 95% CIs were performed with natural log transformations to make the benefit curve much smoother. Thus, the log-transformed lower 95% CI > 0 was considered as clinical benefit for recanalization. Pearson's or Spearman's correlation analysis was used depending on the normality of the distribution. Partial Pearson's correlation analysis was used to adjust the potential confounds. All analyses were performed blinded to participant identifying information. Statistical significance was set at a *P* value of < 0.05. All statistical analyses were performed with SPSS package.

3. Results

A total of 445 remaining patients with intracranial ICA or M1 occlusion were included for the final analysis. The median age was 71 years (mean 69 ± 13 years, range 16–98 years) and 157 (35.3%) were women. The median baseline NIHSS score was 14 (IQR 11–18). The mean OTT was 248 ± 142 min (range 53–1320 min). 318 (71.5%) patients received CTP, and 149 (33.5%) had intracranial ICA occlusion. 158 (35.5%) patients received EVT, among whom 30 (19.0%) were mechanical only. The median baseline infarct core volume was 49 (IQR 22–85) ml. Follow-up angiography 24 h after treatment revealed recanalization in 265 (59.6%) patients and no recanalization in 180 (40.4%) patients. The median mRS after 3 months was 4 (IQR 2–5), 3 (IQR 1–4) for patients with recanalization and 4 (IQR 3–5) for those without ($p < .001$), respectively.

The whole cohort was divided into three groups according to the time window for IVT (3 and 4.5 h) (Hacke et al., 2008). Table 1 shows the characteristics of patients with OTT ≤ 3 h. Patients with recanalization had lower baseline NIHSS and mRS after 3 months, higher frequency of EVT and CTP use, and lower frequency of ICA occlusion. Patients with poor outcome were older, had higher frequency of hypertension and ICA occlusion, higher baseline NIHSS, larger infarct core volume, and lower rate of recanalization.

Table 2 shows the characteristics of patients with an OTT between 3 and 4.5 h. Patients with recanalization had higher frequency of atrial fibrillation and EVT, lower rate of ICA occlusion, larger infarct core

Table 1
Univariate analyses in patients with an OTT within 3 h.

Variables	OTT within 3 h (n = 149)					
	Recanalization (n = 87)	No recanalization (n = 62)	P_1	mRS ≤ 2 (n = 52)	mRS > 2 (n = 97)	P_2
Age (year)	72 ± 13	72 ± 12	0.922	68 ± 13	74 ± 12	**0.004**
Female	34 (39.1%)	22 (35.5%)	0.732	18 (34.6%)	38 (39.2%)	0.600
Hypertension	55 (63.2%)	44 (71.0%)	0.380	28 (53.8%)	71 (73.2%)	**0.019**
Diabetes mellitus	19 (21.8%)	15 (24.2%)	0.843	8 (15.4%)	26 (26.8%)	0.152
Atrial fibrillation	55 (63.2%)	36 (58.1%)	0.610	29 (55.8%)	62 (63.9%)	0.380
NIHSS score	13 (10–16)	14 (11–19)	**0.038**	11 (7–14)	15 (12–19)	< **0.001**
OTT (min)	126 ± 34	133 ± 35	0.228	125 ± 35	131 ± 34	0.303
Use of CTP	76 (87.4%)	42 (67.7%)	**0.004**	45 (86.5%)	73 (75.3%)	0.139
Core volume (ml)	53 (30–86)	45 (20 – 110)	0.488	48 (24–64)	62 (29–119)	**0.023**
ICA occlusion	24 (27.6%)	34 (54.8%)	**0.001**	12 (23.1%)	46 (47.4%)	**0.005**
EVT	40 (46.0%)	10 (16.1%)	< **0.001**	19 (36.5%)	31 (32.0%)	0.589
Recanalization	–	–	–	47 (90.4%)	28 (77.8%)	< **0.001**
mRS score	2 (0–4)	5 (4–6)	< **0.001**	–	–	–

OTT = onset to treatment; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; CTP = computed tomography perfusion; ICA = internal carotid artery; EVT = endovascular thrombectomy. Bold indicates p < 0.05.

volume, and lower mRS. Patients with poor outcome were older, had higher rate of ICA occlusion, higher baseline NIHSS, larger infarct core volume, and lower rate of recanalization.

Table 3 shows the characteristics of patients with OTT ≥ 4.5 h. Patients with recanalization were older with a female predominance, had higher frequency of EVT and CTP use, and lower mRS. Patients with poor outcome were older, had higher baseline NIHSS score, and lower rate of recanalization.

There was no significant correlation between baseline infarct core volume and OTT during any time period (spearman rho = −0.093, p = .248, for OTT ≤ 3 h; spearman rho = 0.056, p = .510, for 3 < OTT < 4.5 h; spearman rho = −0.098, p = .236, for OTT ≥ 4.5 h). Mismatch measurements were taken from 364 patients, neither mismatch volume (partial correlation coefficient = −0.077, p = .144) nor ratio (partial correlation coefficient = −0.019, p = .724) was associated with OTT, after adjusting for baseline infarct core volume. The frequency of EVT raised from 29.9% (for OTT within 4.5 h) to 46.9% (for OTT beyond 4.5 h) over time (p = .001). In addition, CTP was performed more frequently in patients who received EVT (92.4% versus 59.9%, p < .001), mainly because CTP became widely used after EVT was considered as a routine treatment in our stroke center.

Age, baseline NIHSS, ICA occlusion, EVT and CTP use were adjusted in each ordinal logistic regression model. Besides, the history of hypertension was only adjusted in the models within 3 h. Fig. 1 shows the benefit curve of infarct core volume from recanalization with OTT ≤ 3 h. Quadratic curves were fitted for OR (R^2 = 0.703, F = 13.431, p < .001), lower 95% CI (R^2 = 0.744, F = 16.432, p < .001) and upper 95% CI (R^2 = 0.640, F = 10.072, p < .001), respectively. Patients with an OTT within 3 h would always benefit from recanalization no matter how large the infarct core volume was.

Fig. 2 shows the benefit curve of infarct core volume from recanalization with an OTT between 3 and 4.5 h. Quadratic curves were fitted for OR (R^2 = 0.827, F = 33.496, p < .001), lower 95% CI (R^2 = 0.784, F = 25.342, p < .001) and upper 95% CI (R^2 = 0.844, F = 38.016, p < .001), respectively. Patients with an OTT between 3 and 4.5 h might not benefit from recanalization when the infarct core volume was larger than 123.5 ml.

Fig. 3 shows the benefit curve of infarct core volume from recanalization with OTT ≥ 4.5 h. Quadratic curves were fitted for OR (R^2 = 0.614, F = 11.145, p < .001), lower 95% CI (R^2 = 0.622, F = 11.537, p < .001) and upper 95% CI (R^2 = 0.585, F = 9.882, p < .001), respectively. Patients with an OTT beyond 4.5 h might not benefit from recanalization when the infarct core volume was larger than 79.5 ml.

4. Discussion

In the current study, we investigated the effect of infarct volume on the benefit from recanalization at different OTT, and found the benefit threshold of infarct core volume decreased over time. Our findings suggested that patients with an OTT within 3 h would always benefit from recanalization no matter how large the infarct volume was,

Table 2
Univariate analyses in patients with an OTT between 3 and 4.5 h.

Variables	OTT between 3 and 4.5 h (n = 149)					
	Recanalization (n = 85)	No recanalization (n = 64)	P_1	mRS ≤ 2 (n = 45)	mRS > 2 (n = 104)	P_2
Age (year)	69 ± 13	69 ± 13	0.755	64 ± 12	71 ± 12	**0.001**
Female	27 (31.8%)	21 (32.8%)	1.000	12 (26.7%)	36 (34.6%)	0.445
Hypertension	52 (61.2%)	46 (71.9%)	0.222	29 (64.4%)	69 (66.3%)	0.852
Diabetes mellitus	9 (10.6%)	9 (14.1%)	0.614	5 (11.1%)	13 (12.5%)	1.000
Atrial fibrillation	48 (56.5%)	24 (37.5%)	**0.031**	18 (40.0%)	54 (51.9%)	0.213
NIHSS score	15 (12–18)	14 (10–18)	0.106	11 (6–16)	16 (13–18)	< **0.001**
OTT (min)	227 ± 27	229 ± 22	0.549	228 ± 27	228 ± 25	0.857
Use of CTP	57 (67.1%)	35 (54.7%)	0.130	26 (57.8%)	66 (63.5%)	0.583
Core volume (ml)	57 (35–101)	36 (11–86)	**0.023**	38 (11–68)	59 (25–119)	**0.003**
ICA occlusion	15 (17.6%)	28 (43.8%)	**0.001**	6 (13.3%)	37 (35.6%)	**0.006**
EVT	31 (36.5%)	8 (12.5%)	**0.001**	13 (28.9%)	26 (25.0%)	0.686
Recanalization	–	–	–	36 (80.0%)	49 (47.1%)	< **0.001**
mRS score	3 (1–5)	4 (3–5)	**0.003**	–	–	–

OTT = onset to treatment; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; CTP = computed tomography perfusion; ICA = internal carotid artery; EVT = endovascular thrombectomy. Bold indicates p < 0.05.

Table 3
Univariate analyses in patients with an OTT beyond 4.5 h.

Variables	OTT beyond 4.5 h (*n* = 147)					
	Recanalization (*n* = 93)	No recanalization (*n* = 54)	P_1	mRS ≤ 2 (*n* = 43)	mRS > 2 (n = 104)	P_2
Age (year)	67 ± 13	62 ± 12	**0.032**	61 ± 15	67 ± 12	**0.017**
Female	40 (43.0%)	13 (24.1%)	**0.032**	12 (27.9%)	41 (39.4%)	0.257
Hypertension	52 (55.9%)	32 (59.3%)	0.732	23 (53.5%)	61 (58.7%)	0.587
Diabetes mellitus	17 (18.3%)	7 (13.0%)	0.491	7 (16.3%)	17 (16.3%)	1.000
Atrial fibrillation	46 (49.5%)	21 (38.9%)	0.233	19 (44.2%)	48 (46.2%)	0.857
NIHSS score	14 (11–18)	13 (8–18)	0.187	11 (7–16)	15 (12–18)	< **0.001**
OTT (min)	397 ± 167	373 ± 138	0.380	400 ± 145	383 ± 162	0.562
Use of CTP	76 (81.7%)	32 (59.3%)	**0.004**	32 (74.4%)	76 (73.1%)	1.000
Core volume (ml)	43 (20–71)	43 (19–78)	0.896	36 (19–57)	48 (23–80)	0.072
ICA occlusion	29 (31.2%)	19 (35.2%)	0.716	12 (27.9%)	36 (34.6%)	0.562
EVT	60 (64.5%)	9 (16.7%)	< **0.001**	20 (46.5%)	49 (47.1%)	1.000
Recanalization	–	–	–	37 (86.0%)	56 (53.8%)	< **0.001**
mRS score	3 (1–4)	4 (3–5)	< **0.001**	–	–	–

OTT = onset to treatment; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; CTP = computed tomography perfusion; ICA = internal carotid artery; EVT = endovascular thrombectomy. Bold indicates p < 0.05.

whereas reperfusion therapy should be carefully considered in those with infarct volume ≥ 125 ml at OTT of 3–4.5 h, or those with infarct volume ≥ 80 ml at OTT ≥ 4.5 h.

Under the current guideline, no restriction on the size of infarct core volume is needed to select patients for reperfusion therapy including IVT and EVT within 6 h, while CTP, MR-DWI, or MR perfusion is recommended to aid in patient selection for IVT between 4.5 and 9 h and for EVT within 6 to 24 h (Powers et al., 2018), based on the results from DAWN, DEFUSE 3 and EXTEND trials (Nogueira et al., 2018; Albers et al., 2018; Ma et al., 2019). Our findings about the time-dependent benefit threshold of infarct core volume indicated that consideration of infarct volume might not be necessary when OTT is within 3 h, but could be helpful when OTT is beyond 3 h, as no benefit was observed over the threshold of infarct core. Previous studies demonstrated infarct core volume to be a strong predictor for clinical outcome (Gasparotti et al., 2009; Sanak et al., 2006; Yoo et al., 2009; Campbell et al., 2019), and anterior circulation stroke patients with acute DWI lesion volume ≥ 70 ml had a high specificity for poor outcome, with or without therapy (Sanak et al., 2006; Yoo et al., 2009). However, clinical outcome and benefit are not always the same as patients with poor outcome can still benefit from reperfusion or recanalization. Therefore, it is critical to identify the benefit of each individual patient when faced with the decision-making of reperfusion therapy. Our benefit curves thus may provide novel evidences for individualized patient selection in future clinical trials. With the wide use of CTA/CTP in the acute setting of stroke, it may be possible to prospectively observe the benefit threshold of infarct volume for the eligible patients beyond 3 h. In addition, both CTP and MR-DWI are suitable for estimating the infarct core volume. Cereda et al. determined that a relative CBF threshold of < 30% of normal provided the most accurate threshold that did not overcall the DWI lesion (Cereda et al., 2016). Moreover, patients with either IVT or EVT might share the same benefit threshold of infarct core volume for recanalization, since the recent study demonstrated that estimated ischaemic core volume did not modify the treatment benefit of endovascular thrombectomy over standard medical therapy for improved functional outcome (Campbell et al., 2019).

There are some issues need to be clarified. First, recanalization is not equal to reperfusion therapy, because of IVT or EVT failure, or artery re-occlusion. Furthermore, recanalization is not equal to reperfusion (Eilaghi et al., 2013). Successful arterial recanalization does not

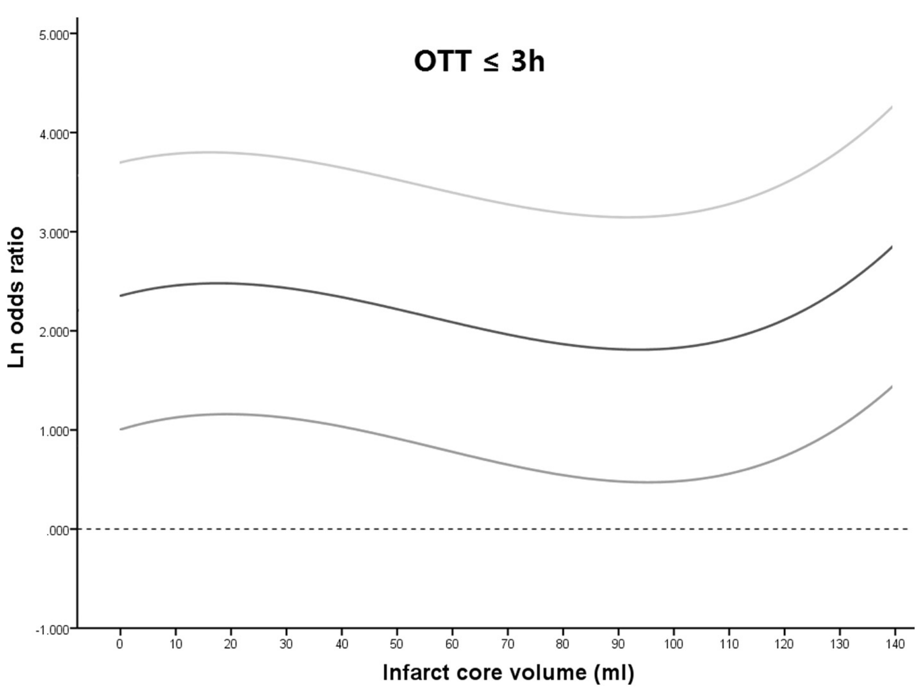

Fig. 1. The benefit curve of infarct core volume from recanalization with a time from onset to treatment within 3 h. Quadratic curves were fitted for odds ratio (R^2 = 0.703, F = 13.431, p < .001), lower 95% confidence interval (R^2 = 0.744, F = 16.432, p < .001) and upper 95% confidence interval (R^2 = 0.640, F = 10.072, p < .001).

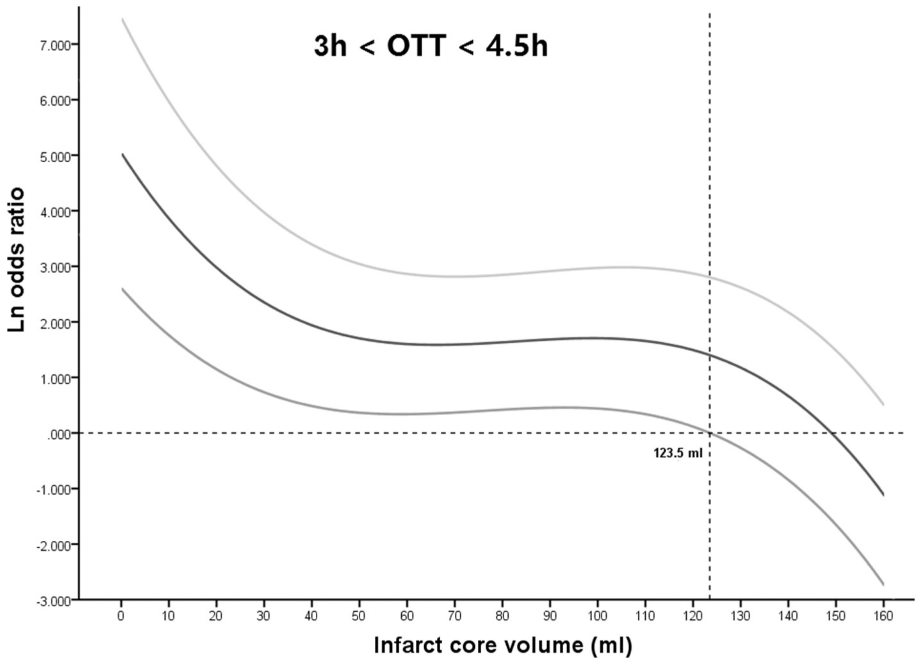

Fig. 2. The benefit curve of infarct core volume from recanalization with a time from onset to treatment between 3 and 4.5 h. Quadratic curves were fitted for odds ratio ($R^2 = 0.827$, $F = 33.496$, $p < .001$), lower 95% confidence interval ($R^2 = 0.784$, $F = 25.342$, $p < .001$) and upper 95% confidence interval ($R^2 = 0.844$, $F = 38.016$, $p < .001$).

necessarily lead to successful tissue reperfusion, for example, the presence of no-reflow phenomenon (Kloner et al., 2018). Although "reperfusion" is the goal of reperfusion therapy, thrombus removal and arterial recanalization are what we can do, no matter whether tissue reperfusion occurs or not. Therefore, the real benefit threshold of infarct volume from reperfusion therapy would be smaller than the threshold in our study. Second, although the R^2 and F values for the quadratic curves were acceptable, the fitting curve might not represent the real relationship between infarct volume and benefit from recanalization. In addition, there were few samples with an OTT beyond 8 h ($n = 16$), which needs to be investigated alone in the future studies. Third, limited data was given in patients with infarct volume ≥ 140 ml as the maximal median infarct volume was around 140 ml. It seems that the possible benefit from recanalization increased in patients with large infarct volume within 3 h, since the slope of the fitting curve gradually increased when the volume was larger than 100 ml in Fig. 1. However, considering the sufficient numbers are not reached at the edge of this threshold, this assumption should be tested in future studies with a large sample size. It remains unclear, why infarct core volume measured with identical techniques and thresholds has a different prognostic value in dependence of OTT. Neither mismatch volume nor ratio was associated with OTT after adjusting for the infarct core volume in the current study. The possible explanation might be that the core area identified by the current imaging methods is partially reversible, and the reversibility depends on OTT.

It's interesting to investigate the influencing factors of recanalization at different OTT. There is no doubt about the increased recanalization rate of EVT. Patients with recanalization had higher

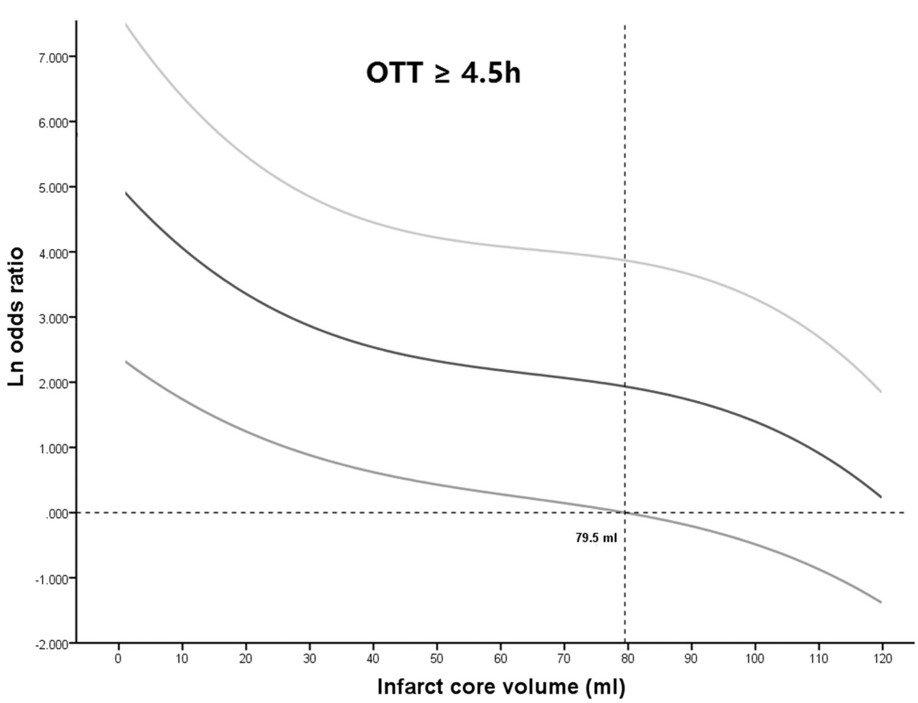

Fig. 3. The benefit curve of infarct core volume from recanalization with a time from onset to treatment beyond 4.5 h. Quadratic curves were fitted for odds ratio ($R^2 = 0.614$, $F = 11.145$, $p < .001$), lower 95% confidence interval ($R^2 = 0.622$, $F = 11.537$, $p < .001$) and upper 95% confidence interval ($R^2 = 0.585$, $F = 9.882$, $p < .001$).

frequency of CTP use, mainly because CTP became widely used after EVT was considered as a routine treatment in our stroke center and was performed more frequent in patients receiving EVT. At an early stage, the clot burden is more important than it's constituent. Patients with lower baseline NIHSS might have a smaller clot, thus achieving recanalization easier. As time goes on, fibrin content gradually decreases, which renders the thrombus resistant to thrombolysis (Brommer et al., 1992). Patients with atrial fibrillation usually had red thrombi that were rich in fibrin and trapped erythrocytes (Jorgensen, 1964), and thus had high frequency of recanalization. These patients always had large baseline infarct volume than those without atrial fibrillation (Tu et al., 2015). Since the high frequency of EVT in the patients with an OTT beyond 4.5 h (46.9% versus 29.9%), the factors that mainly influenced recanalization of IVT became insignificant, such as the presence of ICA occlusion. Meanwhile, older patients had an incremental collateral response (Agarwal et al., 2013), and good pre-treatment collaterals enhanced the rates of successful recanalization in EVT (Leng et al., 2016).

There are some limitations. First, the main results should be better limited within patients who presented an infarct volume below 140–160 ml and with an OTT within 8 h. Second, since our database was built over quite a long period of time, patients received more IVT than EVT. Although the treatment modality was adjusted in each ordinal logistic regression model, conclusions should be repeated in the patients with EVT only, if the sample size permits in the future. Finally, there existed a potential risk of selection bias, due to the retrospective design in a single center. The proportion of women included in the current study is relatively low, which might be partially explained by the sex difference of stroke incidence in China (Wang et al., 2014), besides the selection bias. On the other hand, some severe stroke patients were transferred to intensive care unit or received surgical treatment next day so that they were unable to undergo follow-up angiography within 24 h.

In conclusion, we found a time-dependent benefit threshold of infarct volume from recanalization. We thus suggested to estimate the infarct core volume by using either CTP or MRI for patients who would present an OTT beyond 3 h when selecting eligible patients for reperfusion therapy.

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Author contributions

H.H. and S·Y drafted and revised the manuscript, participated in study concept and design, conducted the statistical analyses, analyzed and interpreted the data. M.L. participated in study concept and design, data interpretation and made a major contribution in revising the manuscript. Y.Z. assisted in designing the MRI sequences and imaging analysis.

Declaration of Competing Interest

All the authors declare no conflict of interest.

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