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Effect of prolonged microcirculation time after thrombectomy on the outcome of acute stroke

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ABSTRACT

Background Although recanalization can be successful, microcirculatory dysfunction is common in acute large vessel occlusive stroke (LVOS). We assessed the microcirculation time by postprocessing software and analyzed its impact on prognosis in patients treated with mechanical thrombectomy (MT).

Methods Patients with acute LVOS treated with MT were retrospectively enrolled consecutively. We measured the time to peak (TTP) and cerebral circulation time (CCT) in regions of interest on digital subtraction angiography using syngo iFlow software (Siemens Healthineers, Forchheim, Germany). A modified Rankin score ≤2 at 90 days was defined as a favorable outcome. Logistic regression was used to analyze the effect of each time parameter on prognosis. Then, we included time parameters in the baseline model to construct receiver operating characteristic (ROC) curves to assess the predictive ability for prognosis.

Results A total of 215 patients were finally included. Of them, 118 (54.9%) had a favourable outcome at 90 days. Multivariate analysis showed that the microvascular cerebral circulation time (mCCT) was significantly associated with poor outcomes (odds ratio (OR) 2.061, 95% confidence interval (CI) 1.414 to 3.005 p<0.001). The area under the ROC curve was significantly enhanced by including mCCT in the baseline model (0.859 vs 0.829, p=0.016, DeLong test).

Conclusions The mCCT immediately after recanalization is a powerful predictive factor for 90-day functional prognosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Microcirculatory dysfunction is one of the important factors affecting the prognosis of mechanical thrombectomy (MT) treatment. Patients with early identification of microcirculatory dysfunction can benefit from closer monitoring and neuroprotective strategies. However, methods to identify microcirculatory function in MT patients remain limited.

WHAT THIS STUDY ADDS

⇒ We assessed microvascular cerebral circulation time (mCCT) using syngo iFlow software to measure digital subtraction angiography (DSA) images immediately after MT as an index to observe microcirculatory function. We obtained a significant improvement in predictive power by incorporating mCCT into the baseline model (adjusting for age, National Institutes of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT Score (ASPECT), collateral circulation, reperfusion status, and Trial of ORG 10,172 in Acute Stroke Treatment (TOAST) classification). The mCCT immediately after recanalization is a powerful predictive factor for 90-day functional prognosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In clinical practice, the ability of the mCCT to identify microcirculatory dysfunction patients after MT is crucial for physicians and will facilitate the selection of appropriate pharmacological treatment strategies and close monitoring.

INTRODUCTION

Cerebral circulation time (CCT) is confirmed to be an important parameter of cerebral blood flow reserve, which reflects the hemodynamic differences between symptomatic and asymptomatic carotid stenosis, hyperperfusion after carotid artery stenting and prediction of acute ischemic stroke in patients with middle cerebral artery stenosis.[1–3] It was first proposed by Greitz to be calculated on digital subtraction angiography (DSA) by measuring the time interval from visualization of the intracranial arteries to clouding of the cortical veins.[4] However, CCT lacks a unified evaluation method.[5 6] The microvascular CCT (mCCT) is the time for blood flow to pass through the microvasculature during the entire CCT. Several studies have shown that prolonged mCCT can reflect microcirculatory dysfunction in aneurysmal subarachnoid hemorrhage by different measurement methods.[7 8] This may be caused by microvascular spasm and microvascular obstruction.[9 10] However, studies of CCT in patients with acute large vessel occlusive stroke (LVOS) are less frequent.

Acute LVOS has a high rate of mortality and disability, and prompt opening of the occluded vessel through mechanical thrombectomy (MT) provides a promising treatment for these patients.[11] However, successful recanalization therapy does not always result in successful tissue reperfusion.[12] Animal studies have found that when the occluded middle cerebral artery is recanalized, part of the microcirculation is not reperfused, and the no-reflow phenomenon in the microcirculation after

revascularization is also common in the human brain.[12 13] In the presence of an ischemic hemisphere, even if the vessel is opened, the ineffective perfusion of microcirculatory blood flow may significantly reduce the benefit of recanalization therapy.[14] Clinical evidence suggests that restoration of microcirculatory flow is a better predictor of clinical prognosis than reopening an occluded artery.[15] Therefore, we hypothesized that CCT could be an important predictor of prognosis in patients with MT.

Recently, Wang *et al* observed that CCT on DSA after recanalization is a predictor of prognosis in acute stroke.[5] However, the mCCT was not assessed in that study. Microvascular transport time has better predictive value than CCT in the whole brain or arterial phase for delayed cerebral ischemia after subarachnoid hemorrhage.[8] However, it has not been elucidated in LVOS.

Thus, in this study, we assessed whether the CCT of microcirculation changes on DSA immediately after MT can be used as a predictor of prognosis in patients with LVOS who are successfully reperfused, and we further explored the clinical factors of mCCT.

METHODS

Study population

A total of 298 patients were seen at Yijishan Hospital for acute anterior circulation LVOS between June 2020 and December 2021. The study was approved by the Ethics Committee of the First Affiliated Hospital of Wannan Medical College (201900039). Patients who met the following criteria were included: (1) pre-stroke modified Rankin Scale (mRS) <2 scores; (2) age >18 years; (3) expanded Thrombolysis in Cerebral Infarction (eTICI) score ≥2b; and (4) within 24 hours of known stroke onset. The exclusion criteria for these patients were as follows: (1) 90-day post-operative loss to follow-up; (2) no post-operative imaging follow-up; (3) multivascular occlusion; (4) anterior cerebral artery occlusion; or (5) inability to calculate the CCT due to poor quality or incomplete DSA imaging. A flowchart for inclusion in the study cohort is shown in online supplemental figure 1.

Baseline variables

Our baseline variables regarding demographic characteristics and clinical information were retrospectively and included sex, age, medical history (hypertension, diabetes, atrial fibrillation), National Institute of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT (ASPECT) score, the Trial of ORG 10,172 in Acute Stroke Treatment (TOAST) classification, and bridging treatment with intravenous thrombolysis.

Surgical information, namely, the time from onset to puncture (OTP), time from onset to recanalization (OTR), anesthesia method, and approaches of procedure was recorded by the surgeon.

The reperfusion classification was assessed by the eTICI score.[16] Successful reperfusion was classified as eTICI 2b50, eTICI 2b67, eTICI 2c or eTICI 3. Poor collateral circulation was defined as collateral filling ≤50% of the occluded territory, while good collateral circulation was defined as collateral filling >50% of the occluded territory.[17]

For all enrolled subjects, the imaging characteristics were evaluated by two neurologists/interventionalists who were blinded to the clinical information. In case of disagreement, the third expert made the final decision through consultation.

Cerebral circulation time measurement

All patients underwent standard cerebral angiography (transfemoral access) immediately after MT, with an 8 Fr catheter located in the extracranial C2-C4 segment of the internal carotid artery. Six millilitres of contrast agent (iohexol 300, GE Healthcare, Japan) was mechanically injected at a flow rate of 4 mL/s. The 2D DSA series was used at a rate of 4 frames per second to acquire images in anterior-posterior and lateral positions at the beginning of contrast agent injection. This is a routine task in our department. DSA images were transferred to the workstation (*syngo* X-Workplace VB21; Siemens Healthineers) in Digital Imaging and Communications in Medicine (DICOM) format and converted to color-coded images using *syngo* iFlow software (Siemens Healthineers, Forchheim, Germany) to measure time-density profiles.[18]

The regions of interest (ROIs) were placed in the intravenous vertical portion of the internal carotid artery (ROI_{C5}), the cortical segment of the rolandic artery (ROI_{M4}), and the rolandic vein (ROI_{VR}) to calculate the time-density profile.[7] The time to peak (TTP) on the time-density curve for each region of interest was recorded as TTP_{C5}, TTP_{M4}, and TTP_{VR}. CCT is defined as the difference in the time to peak intensity between ROIs.[2] (1) $CCT_{C5\text{-}M4}=TTP_{M4}–TTP_{C5}$; (2) $CCT_{C5\text{-}VR}=TTP_{VR} - TTP_{C5}$; (3) $CCT_{M4\text{-}VR}=TTP_{VR} - TTP_{M4}$ (referred to as the microvascular cerebral circulation time (mCCT)) (figure 1).

Follow-up

The intracerebral hemorrhage (ICH) events analyzed in this study were classified according to the European Cooperative Acute Stroke Study III criteria for any ICH, parenchymal hematoma, and symptomatic ICH within 24 hours after MT.[19] Clinical or telephone follow-up was performed at 90 days of onset; and a favorable functional outcome was defined as an mRS score of 0–2, whereas a poor functional outcome was defined as an mRS score of 3–6.

Statistical analysis

Patients were divided into the favorable and poor outcome groups, ICH and non-ICH group. The distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as the means (standard deviation), and non-normally distributed continuous variables are presented as the medians (interquartile range). Categorical variables are presented as percentages. Continuous variables were analyzed using the t test or the Mann-Whitney U test. Differences in categorical variables were analyzed using the $\chi 2$ test and the Fisher's exact test as appropriate. Variables with $p < 0.05$ in the univariate analysis were included in the multivariate analysis.

Receiver operating characteristic (ROC) analysis was used to assess the ability of TTP_{VR}, $CCT_{C5\text{-}VR}$, and mCCT to distinguish between 90-day favorable and poor outcomes among patients. The DeLong test was used to compare the area under the curve of each model with that of the baseline model (adjusting for age, NIHSS score, ASPECT score, collateral circulation, reperfusion status, and TOAST classification). To explore the factors influencing mCCT, mCCT was divided into the high mCCT group and the low mCCT group based on the cut-off value of the ROC curve. A p value<0.05 was considered statistically significant. Statistical analysis was performed using SPSS 26.0 (IBM, Armonk, NY, USA).

RESULTS

Patient baseline characteristics

During the study period, a total of 298 patients with anterior circulation LVOS were enrolled, and 215 were eventually

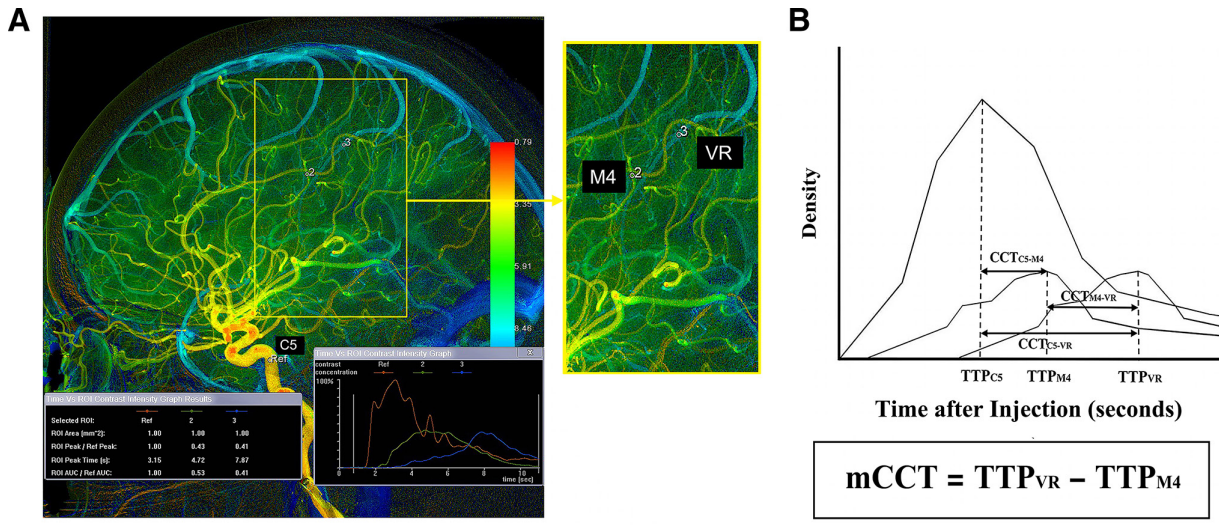

Figure 1 Measurement of time to peak (TTP) and cerebral circulation time (CCT). (A) Regions of interest (ROIs) were set in color-coded images using syngo iFlow software (B) Time-density curve. $CCT_{C5\text{-}M4}$, cerebral circulation time from the vertical intracavernous portion of the internal carotid artery to the cortical segment of the rolandic artery; $CCT_{C5\text{-}VR}$, cerebral circulation time from the vertical intracavernous portion of the internal carotid artery to the rolandic vein; $CCT_{M4\text{-}VR}$, cerebral circulation time from the cortical segment of the rolandic artery to the rolandic vein; TTP_{C5}, time to peak of the vertical intracavernous portion of the internal carotid artery, TTP_{M4}, time to peak of the cortical segment of the rolandic artery; TTP_{VR}, time to peak of the rolandic vein.

included in this study. The baseline characteristics of the patients are shown in table 1. The median age of all patients was 70 (62-76) years, and 125 (58.1%) were male. Of the patients, 156 (72.6%) patients had an onset within 6 hours and 59 (27.4%) patients had an onset within 6–24 hours. A total of 127 (59.1%) had a history of hypertension, 22 (10.2%) had a history of type 2 diabetes, and 124 (57.7%) had a history of atrial fibrillation. The median NIHSS and ASPECT scores at admission were 13 (11-18) and 9 (7-10), respectively. Of the included patients, 28 (13.0%) had a reperfusion status of eTICI 2b50, 27 (12.6) had a reperfusion status of eTICI 2b67, 33 (15.3) had a reperfusion status of eTICI 2c, and 127 (59.1%) had a reperfusion status of eTICI 3. A total of 118 (54.9%) patients had a favorable outcome (mRS<2) at the 90-day follow-up. The medians of TTP_{C5}, TTP_{M4}, and TTP_{VR} were 2.6 (2.3–2.9) s, 4.2 (3.7–4.8) s, and 7.9 (7.2–8.9) s, respectively. The medians of $CCT_{C5\text{-}M4}$, $CCT_{C5\text{-}VR}$, and mCCT were 1.6 (1.0–2.3) s, 5.2 (4.4–6.3) s, and 3.6 (3.0–4.4) s, respectively.

Assessment of TTP and CCT in relation to outcomes

After adjusting for variables with p <0.05 in the univariate analysis (age, NIHSS score, ASPECT score, collateral circulation, reperfusion status, and TOAST classification), multivariate analysis showed that TTP_{VR} (OR 1.425, 95% CI 1.078 to 1.882, p=0.013), $CCT_{C5\text{-}VR}$ (OR 1.475, 95% CI 1.124 to 1.936, p=0.005), and mCCT (OR 2.061, 95% CI 1.414 to 3.005, p <0.001) were significantly associated with poor functional outcome, while TTP_{C5}, TTP_{M4}, and $CCT_{C5\text{-}M4}$ were not significantly associated with outcome in univariate and multifactorial analyses (table 2). Therefore, we used ROC to assess the predictive ability of TTP_{VR}, $CCT_{C5\text{-}VR}$, and mCCT on outcome.

Predictive ability of mCCT for outcomes

For the prediction of outcome, the areas under the curve for TTP_{VR}, $CCT_{C5\text{-}VR}$, and mCCT were 0.637 (95% CI 0.561 to 0.712, p<0.001), 0.664 (95% CI 0.590 to 0.738, p<0.001), and 0.708 (95% CI 0.638 to 0.777, p<0.001), respectively. The area under the curve for the baseline model was 0.829 (95% CI 0.774 to 0.885, p<0.001). After TTP_{VR}, $CCT_{C5\text{-}VR}$, and mCCT were incorporated into the baseline model to construct the ROC, the area under the curve increased to 0.838, 0.843, and 0.859, respectively, and only mCCT was significantly different from the baseline model (p=0.016, DeLong test) (table 3).

Influencing factors of mCCT

To assess the factors influencing mCCT, we dichotomized mCCT according to the ROC cut-off value of 3.68. OTP and OTR were utilized in model 1 and model 2 and included other variables with a p <0.05 in the univariate analysis, such as reperfusion status and intravenous thrombolysis. Multivariate analysis showed that a higher reperfusion grade was negatively associated with the occurrence of microcirculatory impairment in both model 1 (eTICI 3: eTICI 2b50 OR 0.233, 95% CI 0.097 to 0.563, p=0.001; eTICI 2c: eTICI 2b50 OR 0.285, 95% CI 0.098 to 0.833, p=0.022) and model 2 (eTICI 3: eTICI 2b50 OR 0.227, 95% CI 0.094 to 0.548, p=0.001; eTICI 2c: eTICI 2b50 *OR* 0.285, 95% CI 0.098 to 0.831, p=0.022) (online supplemental tables S1 and S2).

The relationship between ICH and mCCT

Any ICH and parenchymal hematoma were more common in patients with prolonged mCCT (32.3% vs 18.9, p=0.024; 15.1% vs 6.6%, p=0.042), while symptomatic ICH was not significantly different (online supplemental table S1). In the univariate analysis, mCCT was higher in patients with any ICH (3.9 [3.1–4.7] vs 3.4 [2.9–4.2], p=0.025) and parenchymal hematoma (4.2 [3.0–4.5] vs 3.4 [3.0–4.4], p=0.093). When the variables with p values <0.05 by univariate analysis were included in the multivariate analysis, mCCT was not significantly associated with any ICH (OR 1.103, 95% CI 0.796 to 1.528, p=0.556) or parenchymal hematoma (OR 1.085, 95% CI 0.708 to 1.661, p=0.708) (online supplemental tables S3 and S4).

DISCUSSION

In this study, we analyzed the effects of different periods of CCT and TTP on prognosis. We found that TTP_{VR}, $CCT_{C5\text{-}VR}$, and

Table 1 Baseline clinical characteristics of patients with favorable and poor outcome groups

Variables	ALL (n=215)	90d-mRS≤2 (n=118)	90d-mRS>2 (n=97)	P-value
Demographic characteristics				
Age, y, median (IQR)	70(62, 76)	67(58, 75)	73(66, 77)	<0.001
Male, n (%)	125 (58.1)	76 (64.4)	49 (50.5)	0.052
Past Medical History, n (%)				
Hypertension	127 (59.1)	63 (53.4)	64 (66.0)	0.071
Diabetes mellitus	22 (10.2)	10 (8.5)	12 (12.4)	0.374
Atrial fibrillation	124 (57.7)	54 (45.8)	70 (72.7)	<0.001
Clinical data				
Admission SBP, median (IQR)	152(137, 169)	152(137, 168)	152(140, 170)	0.378
Admission DBP, median (IQR)	84(75, 93)	84(76, 93)	83(75, 92)	0.552
Admission NIHSS, median, (IQR)	13(11, 18)	12(10, 16)	16(12, 19)	<0.001
Admission ASPECT, median, (IQR)	9 (7, 10)	9 (8, 10)	7 (5, 9)	<0.001
IV-rtPA, n (%)	32 (14.9)	18 (15.3)	14 (14.4)	1
Occlusion site, n (%)				0.094
ICA	91 (42.3)	42 (35.6)	49 (50.5)	
MCA-M1	107 (49.8)	66 (55.9)	41 (42.3)	
MCA-M2	17 (7.9)	10 (8.5)	7 (7.2)	
TOAST type, n (%)				0.002
LAA	57 (26.5)	38 (32.2)	19 (19.6)	
CE	133 (61.9)	61 (51.7)	72 (74.2)	
Others	25 (11.6)	19 (16.1)	6 (6.2)	
Procedure process				
OTP, median (IQR)	300(220, 390)	290(210, 360)	312(225, 420)	0.097
OTR,median (IQR)	358(270, 450)	345(270, 421)	364(274, 506)	0.166
Collateral, n (%)				<0.001
poor	67 (31.2)	21 (17.8)	46 (47.4)	
good	148 (68.8)	97 (82.2)	51 (52.6)	
First Attempt Approach, n (%)				0.078
Stent retriever	59 (27.4)	39 (33.1)	20 (20.6)	
Direct aspiration	102 (47.4)	47 (39.8)	55 (56.7)	
Stent retriever+aspiration	13 (6.0)	7 (5.9)	6 (6.2)	
Balloon/stenting angioplasty	41 (19.1)	25 (21.2)	16 (16.5)	
eTICI				0.005
2b50 (50–66%)	28 (13.0)	9 (7.6)	19 (19.6)	
2b67 (67–89%)	27 (12.6)	10 (8.5)	17 (17.5)	
2c	33 (15.3)	19 (16.1)	14 (14.4)	
3	127 (59.1)	80 (67.8)	47 (48.5)	
TTP_{C5},sec, median (IQR)	2.6 (2.3, 2.9)	2.6 (2.4, 2.9)	2, 6 (2.1, 2.9)	0.037
TTP_{M4},sec, median (IQR)	4.2 (3.7, 4.8)	4.3 (3.9, 4.8)	4.1 (3.6, 4.7)	0.16
TTP_{VR},sec, median (IQR)	7.9 (7.2, 8.9)	7.8 (7.0, 8.4)	8.2 (7.6, 9.4)	0.001
$CCT_{C5\text{-}M4}$,sec, median (IQR)	1.6 (1.0, 2.3)	1.6 (1.1, 2.4)	1.6 (1.0, 2.3)	0.679
$CCT_{C5\text{-}VR}$,sec, median (IQR)	5.2 (4.4, 6.3)	5.0 (4.2, 5.8)	5.8 (4.7, 6.8)	<0.001
$CCT_{M4\text{-}VR}$,sec, median (IQR)	3.6 (3.0, 4.4)	3.3 (2.9, 3.9)	4.2 (3.3, 4.9)	<0.001

ASPECT, Alberta Stroke Program Early CT; $CCT_{C5\text{-}M4}$, cerebral circulation time from the vertical intracavernous portion of the internal carotid artery to the cortical segment of the rolandic artery; $CCT_{C5\text{-}VR}$, cerebral circulation time from the vertical intracavernous portion of the internal carotid artery to the rolandic vein; $CCT_{M4\text{-}VR}$, cerebral circulation time from the cortical segment of the rolandic artery to the rolandic vein; CE, cardioembolic; DBP, diastolic blood pressure; eTICI, expanded Thrombolysis in Cerebral Infarction; ICA, internal carotid artery; IQR, interquartile range; IV-rtPA, intravenous alteplase; LAA, large-artery atherosclerosis; MCA-M1, M1 segment of the middle cerebral artery; MCA-M2, M2 segment of the middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OTP, onset-to-puncture time; OTR, onset-to-reperfusion time; SBP, systolic blood pressure; SD, standard deviation; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment; TTP_{C5}, time to peak of the vertical intracavernous portion of the internal carotid artery; TTP_{M4}, time to peak of the cortical segment of the rolandic artery; TTP_{VR}, time to peak of the rolandic vein.

Ji Y, *et al*. *J NeuroIntervent Surg* 2023;**15**:1078–1083. doi:10.1136/jnis-2022-019566

Table 2 Univariable and multivariable logistic regression analyses for mRS>2 at 90 days

Independent variable	Unadjusted OR (95% CI)	P-value	Aadjusted OR (95% CI)	P-value
mRS>2 at 90 days				
TTP_{C5} [a]	0.614 (0.349 to 1.077)	0.089	0.704 (0.352 to 1.409)	0.322
TTP_{M4} [a]	0.789 (0.577 to 1.104)	0.173	0.798 (0.540 to 1.179)	0.257
TTP_{VR} [a]	1.487 (1.184 to 1.867)	0.001	1.425 (1.078 to 1.882)	0.013
$CCT_{C5\text{-}M4}$ [a]	0.934 (0.662 to 1.319)	0.700	0.877 (0.576 to 1.334)	0.539
$CCT_{C5\text{-}VR}$ [a]	1.570 (1.253 to 1.967)	<0.001	1.475 (1.124 to 1.936)	0.005
$CCT_{M4\text{-}VR}$ [a]	2.223 (1.619 to 3.052)	<0.001	2.061 (1.414 to 3.005)	<0.001

a: adjusted for age, NIHSS score, ASPECT score, collateral circulation, reperfusion status, and TOAST classification

$CCT_{C5\text{-}M4}$, cerebral circulation time from the vertical intracavernous portion of the internal carotid artery to the cortical segment of the rolandic artery; $CCT_{C5\text{-}VR}$, cerebral circulation time from the vertical intracavernous portion of the internal carotid artery to the rolandic vein; $CCT_{M4\text{-}VR}$, cerebral circulation time from the cortical segment of the rolandic artery to the rolandic vein; mRS, modified Rankin Scale; TTP_{C5}, time to peak of the vertical intracavernous portion of the internal carotid artery; TTP_{M4}, time to peak of the cortical segment of the rolandic artery; TTP_{VR}, time to peak of the rolandic vein.

mCCT were the factors independently associated with 90-day functional independence. We included TTP_{VR}, $CCT_{C5\text{-}VR}$, and mCCT in the baseline model to construct the ROC to assess the predictive ability on prognosis. The area under the curve was enhanced in all cases, but only mCCT was significantly different from the baseline model. Furthermore, we found that a higher eTICI classification was associated with a shorter mCCT.

CCT was first proposed by Greitz to be calculated on DSA by measuring the time interval from visualization of the intracranial arteries to clouding of the cortical veins.[4] Then, several studies assessed the CCT via a different method.[5 6] However, CCT lacks a unified evaluation method. Recently, Philipp Gölitz *et al* showed that the microcirculatory transit time has more advantages than the other periods of CCT.[8] Thus, we used post-processing software that subdivided the different measurement points of TTP and different stages of CCT.[7 18] We found that TTP_{VR}, $CCT_{C5\text{-}VR}$, and mCCT were all factors independently associated with 90-day functional independence. However, only mCCT can significantly improve the prediction ability of the baseline prediction model. Our results are similar to those of a previous study.[7 8] Furthermore, we are the first to apply mCCT to the clinical evaluation of patients with MT.

We assessed mCCT using syngo iFlow software to measure DSA images immediately after MT as an index to observe microcirculatory function. This method is more objective than previous methods,[5] and the evaluation consistency is high. In addition, this method is also applicable to non-Siemens systems (such as Hamamatsu Photonics Co., Ltd).[7] Thus, we present a convenient, rapidly accessible post-operative method for reflecting microcirculatory dysfunction.

Several previous studies have shown that restoring reperfusion of the microcirculation plays a crucial role in acute stroke.[20 21] However, most of these observations are based on animal experiments. Recently, Bai *et al* found that optimal tissue reperfusion was associated with a favorable prognosis by analysing preoperative and post-operative CT perfusion images.[22] This result suggests that microcirculatory function may be another important observation in addition to recanalization status.[23] Our study provides a new method for assessing microcirculatory function by measuring microcirculatory transit time after MT. Our data show that mCCT is a critical predictor of the 90-day functional outcome. This finding confirms recent findings and emphasizes the importance of restoring microcirculatory function in acute stroke.[22 24]

According to this result, we consider that the CCT from the cortical segment of the rolandic artery to the rolandic vein correlates with the function of the microcirculation. This is consistent with the findings observed by Masato Naraoka *et al* in subarachnoid hemorrhage.[7] Microvascular injury plays a key role in tissue survival after recanalization by disrupting the integrity of the blood-brain barrier and promoting microcirculatory obstruction.[21] Previous clinical and animal studies have shown that both microthrombosis and microvascular spasm occur in the ultra-early and subacute phases.[13 24 25] Under hypoxic conditions, the lack of ATP to pump intracellular Ca^{+} leads to the activation of contractile mechanisms.[26] In addition, pericyte injury exacerbates microvascular spasms, and the narrow capillary lumen is filled with stagnant red blood cells, leukocytes, and fibrin platelet deposits and forms microthrombi.[27] Therefore, the flow of blood through the microcirculation is slowed down, even to the point of "no flow" regions. On imaging, it was observed that despite successful revascularization, infarct growth continued to occur.[28] This may be due to incomplete restoration of microcirculatory blood flow that may cause ongoing tissue damage even when semi-dark tissue is still present to recanalize the occluded vessel. The results of this study suggest that mCCT may be an important predictor of prognosis after revascularization.

In exploring the factors influencing mCCT, we found that the degree of reperfusion was closely related to microcirculatory dysfunction. Tan *et al* showed that a higher percentage of tissue optimal reperfusion was obtained with an eTICI score of 2c or 3 than with a score of 2b (eTICI score of 2b, 50.0%; eTICI score of 2c, 80.0%; and eTICI score of 3, 81.3%).[23] This is consistent with our findings that optimal microcirculation reperfusion occurs at a higher rate in patients with higher reperfusion grades (eTICI score of 2b50, 32.1%; eTICI score of 2b67, 22.2%; eTICI score of 2c, 63.6%; and eTICI score of 3, 67.7%). This may explain why TICI 3/2c had a better clinical outcome than

Table 3 Predictive value of time to peak and cerebral circulation time on outcome

Independent variable	Area under curve (95% CI)	P-value	Sensitivity	Specificity	P-value with DeLong's test
Baseline model[a]	0.829 (0.774 to 0.885)	<0.001	0.650	0.881	Ref.
TTP_{VR}+Baseline model	0.838 (0.783 to 0.892)	<0.001	0.701	0.873	0.365
$CCT_{C5\text{-}VR}$+Baseline model	0.843 (0.789 to 0.897)	<0.001	0.732	0.848	0.168
mCCT+Baseline model	0.859 (0.809 to 0.910)	<0.001	0.835	0.754	0.016

a: Baseline model adjusted for age, NIHSS score, ASPECT score, collateral circulation, reperfusion status, and TOAST classification

$CCT_{C5\text{-}VR}$, cerebral circulation time from the vertical intracavernous portion of the internal carotid artery to the rolandic vein; mCCT, microvascular cerebral circulation time; TTP_{VR}, time to peak of the rolandic vein.

TICI 2b in a previous study.[29] We consider that mCCT could be another complementary marker in addition to recanalization status in the prognosis of MT patients.

In addition, bridging treatment with intravenous thrombolysis was also associated with microcirculatory dysfunction in a univariate analysis. However, this result was not reproduced in the multivariate analysis. Interestingly, in the CHOICE trial, treatment with alteplase after MT may have improved patient prognosis by improving microcirculatory blood flow compared with placebo.[30] This may be due to some possible physiological differences in the use of thrombolytic drugs before and after reperfusion therapy. Notably, by measuring mCCT, we can screen the patients with impaired microcirculatory blood flow after MT. This approach could provide a rapid selection method for those requiring post-operative thrombolytic drug therapy and may be an interesting clinical practice. In addition, for the efficacy of different thrombolytic drugs in bridging therapy, mCCT may be an important tool in future assessment methods.

Furthermore, we found that prolonged mCCT was more common in patients with any ICH and parenchymal hematoma, whereas mCCT was not significant in the multivariate analysis of any ICH and parenchymal hematoma. This may have been influenced by the small sample size and low hemorrhagic transformation rate. In future studies, we will evaluate the relationship between mCCT and the blood-brain barrier by follow-up MRI with dynamic susceptibility contrast-enhanced perfusion-weighted imaging.[24]

LIMITATION

Our study has some limitations. First, our study is a small-sample-size single-center retrospective study, which is inevitably susceptible to the effects of selection bias. Second, we did not perform healthy-side vessel control as in previous studies because there is no uniform standard in our center for the position of the catheter tap end during healthy-side angiography.[5] This may have led to our results being influenced by individual differences. In addition, due to a retrospective study, infarct volume parameters were not obtained, although mCCT may affect infarct volume growth. Multicenter prospective studies should be conducted to confirm our results.

CONCLUSION

The mCCT on DSA immediately after recanalization, which may reflect microcirculatory function, has certain predictive value for 90-day functional prognosis. A lower eTICI classification was associated with microcirculatory dysfunction. Future studies could evaluate whether patients with prolonged mCCT may benefit from closer monitoring and neuroprotective strategies.

Contributors YCJ, BS, XJH, ZMZ contributed to the study concept and design. HW, YS, KFW, YCJ contributed to acquisition and analysis of data. BS, QY, ZM, JF contributed to image review and drafting figures of the manuscript. YCJ, BS contributed to drafting the text. XJH is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

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Supplementary Materials

Effect of prolonged microcirculation time after thrombectomy on the outcome of acute stroke

Contents

Supplementary Figures

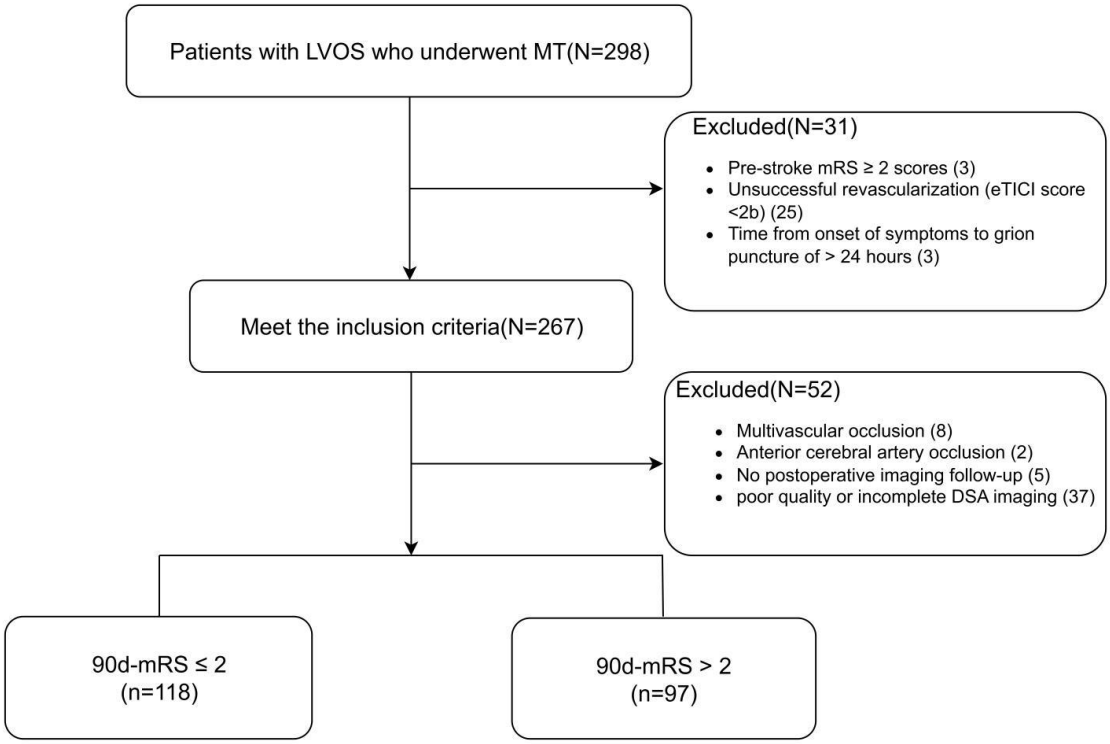

Figure S1 Flow chart of the inclusion of the study population.

LVOS, large vessel occlusive stroke; mRS, modified Rankin Scale; MT, mechanical thrombectomy; eTICI, expended Thrombolysis in Cerebral Infarction

Table S1 Baseline Clinical Characteristics of Patients with High and Low mCCT Groups

Variables	mCCT≤3.68 (n=122)	mCCT>3.68 (n=93)	P-value
Demographic characteristics			
Age, y, median (IQR)	68(60,76)	71(64,77)	0.097
Male, n (%)	76(62.3)	49(52.7)	0.157
Past Medical History, n (%)			
Hypertension	66(54.1)	61(65.6)	0.090
Diabetes mellitus	11(9.0)	11(11.8)	0.500
Atrial fibrillation	67(54.9)	57(61.3)	0.349
Clinical data			
Admission SBP, median (IQR)	150(137,167)	158(139,170)	0.154
Admission DBP, median (IQR)	85(77,92)	82(74,93)	0.681
Admission NIHSS, median, (IQR)	13(11,17)	14(12,18)	0.057
Admission ASPECT, median, (IQR)	9(7,10)	8(7,10)	0.255
IV-rtPA, n (%)	13(10.7)	19(20.4)	0.046
Occlusion site, n (%)			0.663
ICA	49(40.2)	42(45.2)	
MCA-M1	64(52.5)	43(46.2)	
MCA-M2	9(7.4)	8(8.6)	
Tandem occlusion	16(13.1)	7(7.5)	0.189
TOAST type, n (%)			0.253
LAA	32(26.2)	25(26.9)	
CE	72(59.0)	61(65.6)	
Others	18(14.8)	7(7.5)	
Anesthesia mode, n (%)			0.911
General Anesthesia	13(10.7)	11(11.8)	
Local Anesthesia	73(59.8)	53(57.0)	
Conscious Sedation	36(29.5)	29(31.2)	
Procedure process			
OTP, median (IQR)	293(210,360)	312(240,420)	0.029
OTR,median (IQR)	350(260,440)	373(280,506)	0.049
Collateral, n (%)			0.996
poor	38(31.1)	29(31.2)	
good	84(68.9)	64(68.8)	
First Attempt Approach, n (%)			0.252
Stent retriever	40(32.8)	19(20.4)	
Direct aspiration	54(44.3)	48(51.6)	
Stent retriever + aspiration	7(5.7)	6(6.5)	
Balloon/stenting angioplasty	21(17.2)	20(21.5)	
eTICI			<0.001

2b50 (50-66%)	9(7.4)	19(20.4)	
2b67 (67-89%)	6(4.9)	21(22.6)	
2c	21(17.2)	12(12.9)	
3	86(70.5)	41(44.1)	
Any ICH within 24h	23(18.9)	30(32.3)	0.024
Parenchymal hematoma within 24h	8(6.6)	14(15.1)	0.042
Symptomatic ICH within 24h	4(3.3)	7(7.5)	0.214

Abbreviations: ASPECT, Alberta Stroke Program Early CT; CE, cardioembolic; DBP, diastolic blood pressure; eTICI, expended Thrombolysis in Cerebral Infarction; ICA, internal carotid artery; ICH, intracerebral hemorrhage, IQR, interquartile range; IV-rtPA, intravenous alteplase; LAA, large-artery atherosclerosis; MCA-M1, M1 segment of the middle cerebral artery; MCA-M2, M2 segment of the middle cerebral artery; mCCT, microvascular cerebral circulation time; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OTP, onset-to-puncture time; OTR, onset-to-reperfusion time; SBP, systolic blood pressure; SD, standard deviation; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment

Table S2 Logistic Regression Analyses for mCCT>3.68 s

Independent variable	Aadjusted OR(95%CI)	P-value
Model1		
OTP	1.001(0.999-1.002)	0.238
IV-rtPA	1.686(0.739-3.847)	0.215
eTICI		
2b50	Reference	
2b67	1.575(0.467-5.313)	0.464
2c	0.285(0.098-0.833)	0.022
3	0.233(0.097-0.563)	0.001
Model2		
OTR	1.001(0.999-1.002)	0.210
IV-rtPA	1.701(0.745-3.886)	0.208
eTICI		
2b50	Reference	
2b67	1.545(0.458-5.215)	0.483
2c	0.285(0.098-0.831)	0.022
3	0.227(0.094-0.548)	0.001

Abbreviations: CI, confidence intervals; eTICI, expanded Thrombolysis in Cerebral Infarction; IV-rtPA, intravenous alteplase; mCCT, microvascular cerebral circulation time; OR, odds ratio; OTP, onset-to-puncture time; OTR, onset-to-reperfusion time

Table S3 Baseline Clinical Characteristics of Patients with and without Intracerebral Hemorrhage

Variables	Any ICH(+) (n=53)	Any ICH(-) (n=162)	P-value	Parenchymal hematoma(+) (n=22)	Parenchymal hematoma(-) (n=193)	P-value
Demographic characteristics						
Age, y, median (IQR)	73(66-77)	69(61-76)	0.020	77(71-79)	69(62-76)	0.017
Male, n (%)	27(50.9)	98(60.5)	0.221	10(45.5)	115(59.6)	0.203
Past Medical History, n (%)						
Hypertension	29(54.7)	98(60.5)	0.458	13(59.1)	114(59.1)	0.998
Diabetes mellitus	3(5.7)	19(11.7)	0.297	2(9.1)	20(10.4)	1.000
Atrial fibrillation	39(73.6)	85(52.2)	0.007	19(86.4)	105(54.4)	0.005
Clinical data						
Admission SBP, median (IQR)	148(134-168)	154(140-169)	0.247	149(128-166)	153(140-169)	0.219
Admission DBP, median (IQR)	84(76-90)	84(75-94)	0.692	87(71-91)	84(75-93)	0.554
Admission NIHSS, median, (IQR)	14(12-17)	13(11-18)	0.230	15(12-18)	13(11-18)	0.114
Admission ASPECT, median, (IQR)	7(4-9)	9(8-10)	<0.001	7(3-9)	9(7-10)	<0.001
IV-rtPA, n (%)	13(24.5)	19(11.7)	0.023	6(27.3)	26(13.5)	0.085
Occlusion site, n (%)			0.061			0.067
ICA	28(52.8)	63(38.9)		11(50.0)	80(41.5)	
MCA-M1	19(35.8)	88(54.3)		7(31.8)	100(51.8)	
MCA-M2	6(11.3)	11(6.8)		4(18.2)	13(6.7)	
TOAST type, n (%)			0.001			-
LAA	5(9.4)	52(32.1)		0(0.0)	57(29.5)	
CE	43(81.1)	90(55.6)		22(100%)	111(57.5)	
Others	5(9.4)	20(12.3)		0(0.0)	25(13.0)	

Anesthesia mode, n (%)			0.484			0.508
General Anesthesia	8(15.1)	16(9.9)		4(18.2)	20(10.4)	
Local Anesthesia	28(52.8)	98(60.5)		12(54.5)	114(59.1)	
Conscious Sedation	17(32.1)	48(29.6)		6(27.3)	59(30.6)	
Procedure process						
OTP, median (IQR)	335(260-420)	290(205-360)	0.010	330(290-367)	300(210-390)	0.075
OTR,median (IQR)	386(315-510)	347(260-423)	0.008	392(351-453)	350(268-447)	0.046
Collateral, n (%)			0.027			0.012
poor	23(43.4)	44(27.2)		12(54.5)	55(28.5)	
good	30(56.6)	118(72.8)		10(45.5)	138(71.5)	
First Attempt Approach, n (%)			0.052			0.158
Stent retriever	17(32.1)	42(25.9)		5(22.7)	54(28.0)	
Direct aspiration	30(56.6)	72(44.4)		14(63.6)	88(45.6)	
Stent retriever + aspiration	2(3.8)	11(6.8)		2(9.1)	11(5.7)	
Balloon/stenting angioplasty	4(7.5)	37(22.8)		1(4.5)	40(20.7)	
eTICI			0.641			0.212
2b50 (50-66%)	7(13.2)	21(13.0)		5(22.7)	23(11.9)	
2b67 (67-89%)	9(17.0)	18(11.1)		4(18.2)	23(11.9)	
2c	9(17.0)	24(14.8)		1(4.5)	32(16.6)	
3	28(52.8)	99(61.1)		12(54.5)	115(59.6)	
mCCT,sec, median (IQR)	3.9(3.1-4.7)	3.4(2.9-4.2)	0.025	4.2(3.0-4.5)	3.4(3.0-4.4)	0.093

Abbreviations: ASPECT, Alberta Stroke Program Early CT; CE, cardioembolic; DBP, diastolic blood pressure; eTICI, expended Thrombolysis in Cerebral Infarction; ICA, internal carotid artery; ICH, intracerebral hemorrhage, IQR, interquartile range; IV-rtPA, intravenous alteplase; LAA, large-artery atherosclerosis; MCA-M1, M1 segment of the middle cerebral artery; MCA-M2, M2 segment of the middle cerebral artery; mCCT,

microvascular cerebral circulation time; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OTP, onset-to-puncture time; OTR, onset-to-reperfusion time; SBP, systolic blood pressure; SD, standard deviation; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment

Table S4 Logistic Regression Analyses for Intracerebral Hemorrhage

Independent variable	Aadjusted OR(95%CI)	P-value
Any ICH		
Age	1.014(0.975-1.056)	0.483
Admission ASPECT	0.756(0.645-0.885)	0.001
IV-rtPA	3.605(1.384-9.392)	0.009
TOAST		
LAA	Reference	
CE	6.040(1.789-20.394)	0.004
Others	2.636(0.613-11.324)	0.193
OTR	1.002(1.000-1.004)	0.019
Collateral	1.417(0.607-3.305)	0.420
mCCT	1.103(0.796-1.528)	0.556
Parenchymal hematoma		
Age	1.017(0.956-1.082)	0.593
Atrial fibrillation	3.072(0.661-14.290)	0.152
Admission ASPECT	0.725(0.597-0.881)	0.001
OTR	1.001(0.999-1.004)	0.372
Collateral	0.951(0.320-2.825)	0.928
mCCT	1.085(0.708-1.661)	0.708

Abbreviations: ASPECT, Alberta Stroke Program Early CT; CE, cardioembolic; CI, confidence intervals; ICH, intracerebral hemorrhage; IV-rtPA, intravenous alteplase; LAA, large-artery atherosclerosis; mCCT, microvascular cerebral circulation time; OR, odds ratio; OTR, onset-to-reperfusion time; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment

Table S5 Kendall's W test for TTP and CCT

Independent variable	Kendall's W	P-value
TTP_{C5},sec	0.952	<0.001
TTP_{M4},sec	0.965	<0.001
TTP_{VR},sec	0.948	<0.001
$CCT_{C5\text{-}M4}$,sec	0.946	<0.001
$CCT_{C5\text{-}VR}$,sec	0.945	<0.001
$CCT_{M4\text{-}VR}$,sec	0.919	<0.001

Abbreviations: $CCT_{C5\text{-}M4}$, cerebral circulation time from the vertical intracavernous portion of the internal carotid artery to the cortical segment of the rolandic artery; $CCT_{C5\text{-}VR}$, cerebral circulation time from the vertical intracavernous portion of the internal carotid artery to the rolandic vein; $CCT_{M4\text{-}VR}$, cerebral circulation time from the cortical segment of the rolandic artery to the rolandic vein; TTP_{C5}, time to peak of the vertical intracavernous portion of the internal carotid artery, TTP_{M4}, time to peak of the cortical segment of the rolandic artery; TTP_{VR}, time to peak of the rolandic vein.

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9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

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11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/3/2022

Your Name: Bin Shi

Manuscript Title: Effect of prolonged microcirculation time after thrombectomy on the outcome of acute stroke

Manuscript Number (if known): jnis-2022-019566

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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6	Payment for expert testimony	☒ **None**	
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ICMJE DISCLOSURE FORM

Date: 11/3/2022

Your Name: Quan Yuan

Manuscript Title: Effect of prolonged microcirculation time after thrombectomy on the outcome of acute stroke

Manuscript Number (if known): jnis-2022-019566

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ICMJE DISCLOSURE FORM

Date: 11/3/2022

Your Name: Kangfei Wu

Manuscript Title: Effect of prolonged microcirculation time after thrombectomy on the outcome of acute stroke

Manuscript Number (if known): jnis-2022-019566

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ICMJE DISCLOSURE FORM

Date: 11/3/2022

Your Name: Jia Fang

Manuscript Title: Effect of prolonged microcirculation time after thrombectomy on the outcome of acute stroke

Manuscript Number (if known): jnis-2022-019566

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ICMJE DISCLOSURE FORM

Date: 11/3/2022

Your Name: Hao Wang

Manuscript Title: Effect of prolonged microcirculation time after thrombectomy on the outcome of acute stroke

Manuscript Number (if known): jnis-2022-019566

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ICMJE DISCLOSURE FORM

Date: 11/3/2022

Your Name: Zhuang Miao

Manuscript Title: Effect of prolonged microcirculation time after thrombectomy on the outcome of acute stroke

Manuscript Number (if known): jnis-2022-019566

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ICMJE DISCLOSURE FORM

Date: 11/3/2022

Your Name: Yi Sun

Manuscript Title: Effect of prolonged microcirculation time after thrombectomy on the outcome of acute stroke

Manuscript Number (if known): jnis-2022-019566

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ICMJE DISCLOSURE FORM

Date: 11/3/2022

Your Name: Xianjun Huang

Manuscript Title: Effect of prolonged microcirculation time after thrombectomy on the outcome of acute stroke

Manuscript Number (if known): jnis-2022-019566

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