ORIGINAL COMMUNICATION

Influence of procedure time on outcome and hemorrhagic transformation in stroke patients undergoing thrombectomy

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Abstract

Background and purpose Data on procedure time (PT) for mechanical thrombectomy (MT) are scarce. Moreover, the relationship among PT, postprocedural hemorrhagic transformation (HT), and functional outcomes in MT patients remains unclear. We investigated whether postprocedural HT mediated the relationship between PT and functional outcomes in patients with stent-retriever thrombectomy.

Methods We retrospectively analyzed consecutive patients who underwent MT at two comprehensive stroke centers. PT was defined as the time from puncture to first successful recanalization or to abortion of the procedure if successful recanalization was not achieved. A favorable outcome was defined as a 90-day modified Rankin Scale score of 0–2. HT was classified using the European Cooperative Acute Stroke Study definition.

Results Among 283 patients (mean age, 67.2 ± 11.9 years; male, 53.7%), 124 (43.8%) patients had a favorable outcome and 27 (9.5%) patients experienced symptomatic intracranial hemorrhage (sICH). Whether in the overall cohort or in the successful recanalization cohort, extended PT was an independent predictor for a poor outcome (per 30 min: OR 1.433, 95% CI 1.062–1.865, $p = 0.019$; OR 1.522, 95% CI 1.062–2.159, $p = 0.020$, respectively) and sICH (per 30 min: OR 1.391, 95% CI 1.030–1.865, $p = 0.029$; OR 1.716, 95% CI 1.161–2.648, $p = 0.009$, respectively). Moreover, postprocedural HT might partially explain the worse function outcomes in patients with an extended PT (the regression coefficient was changed by 28.2% and 28.1%, respectively).

Conclusions The PT is an independent predictor for 90-day outcomes in stent-retriever thrombectomy patients. Postprocedural HT was partially responsible for the worse outcome in patients who experienced a longer PT.

Keywords Hemorrhagic transformation · Mechanical thrombectomy · Outcome · Stroke

Introduction

Mechanical thrombectomy (MT) has become the current standard of care for large vessel occlusion stroke (LVOS) of the anterior circulation [1]. Furthermore, the benefit of MT

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is critically time-dependent [2]. Traditionally, studies evaluating the relationship between time metrics and outcomes in patients undergoing thrombectomy have mainly focused on the time from stroke onset to door or to vessel revascularization [3, 4]. However, a breakdown of various time metrics based on the extent of impact on clinical outcomes has not been well studied.

A previous study showed that the association between the time from stroke onset to reperfusion and outcomes may be determined by the time from imaging to reperfusion [5]. However, compared with the time from imaging to puncture, the time from puncture to reperfusion or procedure time (PT) demonstrates considerable variation due to the complicated and individualized process of recanalization for MT. Moreover, these variations may directly impact clinical outcomes [6]. Previous studies have investigated the relationship between PT and clinical outcomes in patients with LVOS who underwent endovascular treatment [6–8]. However, these studies were based on the older-generation thrombectomy devices.

According to current guidelines, stent-retriever thrombectomy is now recommended as the first-line approach for LVOS of the anterior circulation [9]. The development of new thrombectomy approaches not only improves the speed and extent of MT recanalization but also creates a concurrent need to analyze the impact of the complex intraprocedural time metrics on outcomes. Recently, two publications reported the effect of the PT on outcomes based on modern thrombectomy techniques [10, 11] and showed that a longer PT may lead to lower rates of functional independence and higher rates of procedural complications or symptomatic intracranial hemorrhage (sICH). However, the relationship among PT, postprocedural hemorrhagic transformation (HT), and 90-day outcomes in MT patients is still unclear. Based on the previous findings, we hypothesized that postprocedural HT mediated the relationship between the PT and functional outcomes in patients undergoing stent-retriever thrombectomy. Additionally, we tried to construct the time–benefit curve of the PT and outcomes for stent-retriever thrombectomy patients.

Materials and methods

Patient selection

We retrospectively analyzed the clinical data of patients with LVOS involving the anterior circulation who underwent endovascular treatment at two comprehensive stroke centers (Jinling Hospital between January 2014 and October 2018 and Yijishan Hospital between July 2014 and December 2018). The stroke centers met the following criteria: (1) all operators were required to have performed

at least 50 endovascular procedures annually, including at least 20 MT procedures with the stent retrieval devices; (2) all intervention teams were certified interventionists for intra-arterial intervention on LVOS of the anterior circulation; and (3) all operators were required to have engaged in intervention work for more than 2 years. The study was approved by the local ethics committee.

Patients were enrolled if they fulfilled the following inclusion criteria: (1) age ≥ 18 years; (2) time from stroke onset to puncture (OTP) ≤ 8 h; (3) baseline National Institutes of Health Stroke Scale (NIHSS) score ≥ 6, baseline Alberta Stroke Program Early CT (ASPECT) score ≥ 6 and pre-stroke modified Rankin Scale (mRS) score < 2; (4) the internal carotid artery (ICA) or M1 segment of the middle cerebral artery (MCA) occlusion confirmed by emergency computed tomographic angiography (CTA)/magnetic resonance angiography (MRA)/digital subtraction angiography (DSA); and (5) the initial MT was performed with stent retrievers. The flow chart of inclusion of the study population is displayed in Fig. 1.

Data collection

All clinical data were prospectively documented, which included demographics, medical history, baseline NIHSS score, baseline ASPECT score and pre-mRS score. The stroke cause was assessed using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.

Procedural characteristics were evaluated by the operators, including OTP, PT, the collateral circulation score, passes of the retriever and the grade of vessel recanalization. Vessel recanalization was assessed using the modified Thrombolysis in Cerebral Infarction (mTICI) grading system. Successful recanalization was defined as a score of 2b or 3. The PT was defined as the time from puncture to first successful recanalization or to abortion of the procedure if successful recanalization was not achieved [10]. If the patients had an intraprocedural complication, the PT was defined as the time from puncture to the time when the complication was recorded [10]. Collateral circulation was assessed based on the DSA using a 3-point scale score (grade 0, little or no significant filling of the occluded territory or less than one-third of the occluded territory; grade 1, the collateral flow filled less than two-thirds of the occluded territory; and grade 2, the collateralization filled more than two-thirds of the territory or the proximal main stem) [12].

Functional outcomes were assessed using the mRS score at 90 days. A favorable outcome or functional independence was defined as a mRS score of 0–2. The HT was classified using the European Cooperative Acute Stroke Study (ECASS) definition, which is based on CT imaging obtained

Fig. 1 Flow chart of the inclusion of the study population. *ASPECT* Alberta Stroke Program Early CT, *ET* endovascular treatment, *LVOS* large vessel occlusion stroke, *MT* mechanical thrombectomy, *NIHSS* National Institutes of Health Stroke Scale; *OTP* symptoms onset to groin puncture time
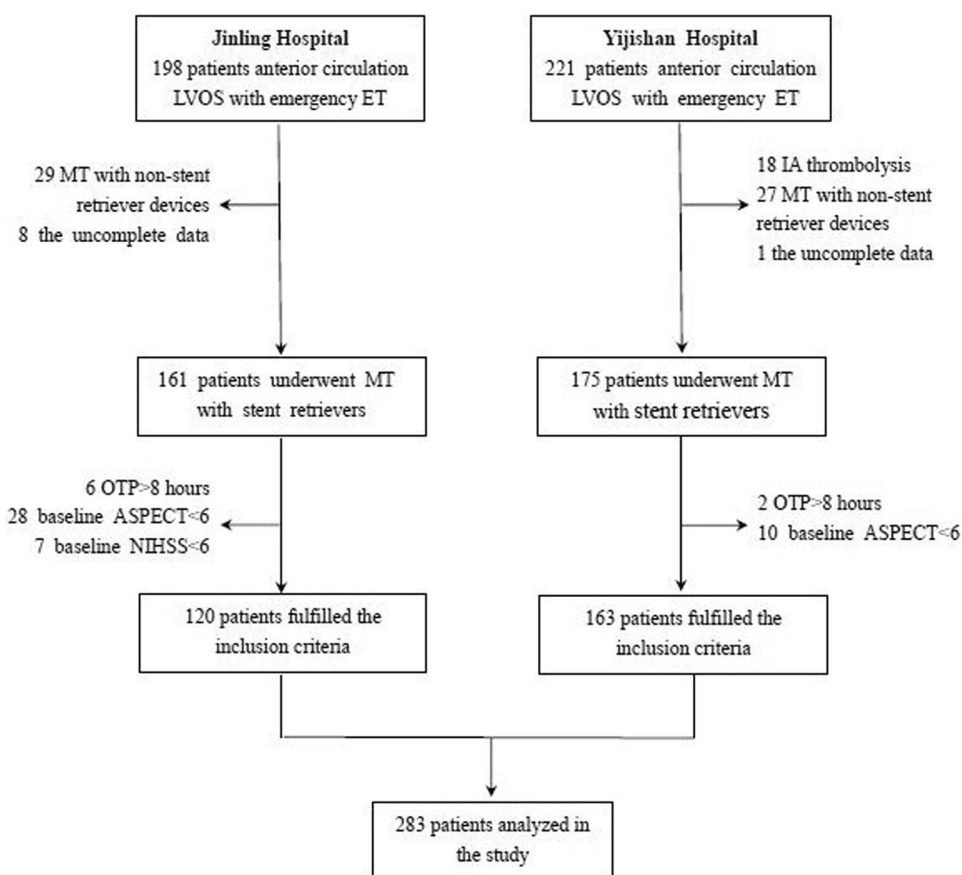
within 24 h of the procedure [13]. The sICH was defined as a type 2 parenchymal hematomas (PH) or as a newly observed intracranial hemorrhage with an NIHSS score that increased by more than four points.

Statistical analysis

The continuous variables were presented as the mean ± standard deviation (SD) or as the median (interquartile range, IQR), and the categorical variables were expressed as frequency (percentages). The continuous variables were compared using the Student's *t* test or Mann–Whitney *U* test, and the categorical variables were compared using the chi-square test or Fisher's exact test. The association between the PT and clinical outcomes was analyzed using binary logistic regression. Variables were included in the logistic models based on the statistical significance of the univariate analysis ($p \leq 0.05$), with goodness of fit being assessed using the Hosmer–Lemeshow test. Regression coefficients and odds ratios (OR) with two-sided 95% confidence intervals (CI) for each of the variable included in the model were finally calculated.

Mediation analysis was performed to determine whether the HT (ECASS classifications) influences the association between the PT (continuous variable) and functional outcome (the 90-day mRS score) [14]. Mediation analysis consists of a four-step procedure [15]. The Sobel test was used to detect the statistical significance of the mediation effect.

To generate time–benefit curves, we used a logistic regression model to estimate the probability of clinical outcomes based on the PT after adjusting for age, baseline NIHSS score, baseline ASPECT score, and OTP [16]. In addition, curves representing changes in the percentages of the outcomes, passes of the retriever or sICH associated with the PT were performed by GraphPad Prism 7 (GraphPad, La Jolla, California, USA), and a best-fitting curves model was constructed. The models were evaluated using the R^2 and the Runs test for model deviance from actual values [10].

For all analyses, a two-tailed value of $p < 0.05$ was considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient baseline characteristics

A total of 283 patients (mean age, 67.2 ± 11.9 years; male, 53.7%) were included in this study. The baseline NIHSS score, baseline ASPECT score and OTP was 17 (IQR 14–20), 9 (IQR 8–10), and 256 ± 76.6 min, respectively. Successful recanalization was achieved in 227 (80.2%) patients. All enrolled patients underwent a 90-day follow-up. Of the enrolled patients, 124 (43.8%) patients achieved 90-day functional independence, 27 (9.5%) patients had an sICH, and 70 (24.7%) patients died.

Multivariate analysis of the relationship among procedure time, functional outcome, and symptomatic intracranial hemorrhage

In the univariate analysis, the PT was significantly shorter in patients with a favorable outcome than in patients with a poor outcome (66 min vs. 89 min, respectively, $p < 0.001$). Similarly, there was a significantly longer PT in patients with sICH than in patients without sICH (111 min vs. 75 min, respectively, $p = 0.001$). However, there was no significant difference in OTP between the two groups. We used logistic regression models to analyze the predictive effect of the PT for clinical outcomes. The univariate

Table 1 Comparison of variables between patients with and without a favorable outcome in the overall cohort

Parameters	Favorable outcome (n = 124)	Poor outcome (n = 159)	p value	Odds ratio[a] (95% CI)	p value
Age, mean (SD), years	63.5 (12.4)	70.1 (10.9)	< 0.001	1.031 (1.001–1.061)	0.040
Male, n (%)	81 (65.3)	71 (44.7)	0.290		
Medical history, n (%)					
Hypertension	81 (65.3)	115 (72.3)	0.205		
Diabetes mellitus	19 (15.3)	35 (22)	0.155		
Clinical characteristics, median (IQR)					
Baseline SBP, mmHg	132 (120–157)	142 (127–159)	0.020		
Baseline DBP, mmHg	80 (74–89)	80 (73–92)	0.351		
Baseline NIHSS score	15 (12–19)	18 (15–22)	< 0.001	1.118 (1.050–1.190)	< 0.001
Baseline ASPECT score	9 (8–10)	9 (8–10)	0.002	0.917 (0.699–1.204)	0.543
Stroke cause, n (%)			0.003		
LAA	40 (32.3)	41 (25.8)		2.392 (0.776–7.380)	0.129
Cardioembolic	65 (52.4)	110 (69.2)		2.394 (0.776–7.389)	0.129
Undetermined or others	19 (15.3)	8 (5)		Reference	
Occlusion site, n (%)			< 0.001		
ICA	25 (20.2)	72 (45.3)		2.067 (1.071–3.986)	0.030
MCA M1	99 (79.8)	87 (54.7)		Reference	
OTP, mean (SD), min	265 (80.7)	249 (72.8)	0.154		
Procedure time, mean (SD), min	66 (30.5)	89 (47.2)	< 0.001	1.433 (1.062–1.865)[b]	0.019
Intravenous thrombolysis, n (%)	29 (23.4)	35 (22)	0.784		
Tandem occlusion, n (%)	16 (12.9)	16 (10.1)	0.454		
Collateral score, n (%)			< 0.001		
Grade 0	10 (8.1)	50 (31.4)		Reference	
Grade 1	41 (33.1)	71 (44.7)		0.312 (0.129–0.752)	0.009
Grade 2	73 (58.9)	38 (23.9)		0.161 (0.066–0.394)	< 0.001
Passes of retriever > 3, n (%)	26 (21)	62 (39)	0.001	0.836 (0.401–1.743)	0.632
mTICI, 2b/3, n (%)	112 (90.3)	115 (72.3)	< 0.001	0.314 (0.144–0.805)	0.014

ASPECT Alberta Stroke Program Early CT, *CI* confidence intervals, *DBP* diastolic blood pressure, *ICA* internal carotid artery, *IQR* interquartile range, *LAA* large-artery atherosclerosis, *mTICI* modified thrombolysis in cerebral infarction, *MCA* middle cerebral artery, *NIHSS* National Institutes of Health Stroke Scale, *OTP* symptoms onset to groin puncture time, *SBP* systolic blood pressure, *SD* standard deviation

[a]Odds ratio for poor outcome

[b]Odds ratio of per 30 min

Table 2 Comparison of variables between patients with and without sICH in the overall cohort

Parameters	sICH		*p* value	Odds ratio[a]	*p* value
	With (*n* = 27)	Without (*n* = 256)		(95% CI)	
Age, mean (SD), years	71.7 (9.9)	66.8 (12.1)	0.048	1.026 (0.983–1.071)	0.235
Male, *n* (%)	9 (33.3)	143 (55.9)	0.026	0.336 (0.133–0.850)	0.021
Medical history, *n* (%)					
Hypertension	19 (70.4)	177 (69.1)	0.895		
Diabetes mellitus	5 (18.5)	49 (19.1)	0.938		
Clinical characteristics, median (IQR)					
Baseline SBP, mmHg	145 (117–159)	138 (125–158)	0.746		
Baseline DBP, mmHg	77 (70–86)	80 (74–90)	0.152		
Baseline NIHSS score	20 (15–26)	17 (13–20)	0.004	1.066 (0.991–1.146)	0.085
Baseline ASPECT score	8 (8–10)	9 (8–10)	0.223		
Stroke cause, *n* (%)			0.924		
LAA	7 (25.9)	74 (28.9)			
Cardioembolic	17 (63)	158 (61.7)			
Undetermined or others	3 (11.1)	24 (9.4)			
Occlusion site, *n* (%)			0.457		
ICA	11 (40.7)	86 (33.6)			
MCA M1	16 (59.3)	170 (66.4)			
OTP, mean (SD), min	241 (57.0)	258 (78.3)	0.309		
Procedure time, mean (SD), min	111 (58.9)	75 (38.6)	0.001	1.391 (1.030–1.865)[b]	0.029
Intravenous thrombolysis, *n* (%)	7 (25.9)	57 (22.3)	0.665		
Tandem occlusion, *n* (%)	2 (7.4)	30 (11.7)	0.501		
Collateral score, *n* (%)			0.001		
Grade 0	13 (48.1)	47 (18.4)		Reference	
Grade 1	9 (33.3)	103 (40.2)		0.309 (0.111–0.858)	0.024
Grade 2	5 (18.5)	106 (41.4)		0.303 (0.091–1.007)	0.051
Passes of retriever > 3, *n* (%)	15 (55.6)	73 (28.5)	0.004	1.484 (0.557–3.976)	0.428
mTICI, 2b/3, *n* (%)	18 (66.7)	209 (81.6)	0.063		

ASPECT Alberta Stroke Program Early CT, *CI* confidence intervals, *DBP* diastolic blood pressure, *ICA* internal carotid artery, *IQR* interquartile range, *LAA* large-artery atherosclerosis, *mTICI* modified Thrombolysis in Cerebral Infarction, *MCA* middle cerebral artery, *NIHSS* National Institutes of Health Stroke Scale, *OTP* symptoms onset to groin puncture time, *SBP* systolic blood pressure, *sICH* symptomatic intracranial hemorrhage, *SD* standard deviation

[a]Odds ratio for symptomatic intracranial hemorrhage

[b]Odds ratio of per 30 min

analysis and the multivariate logistic regression analyses between the PT and clinical outcomes are shown in Tables 1 and 2. After adjustment for confounding factors, the extended PT was associated with a decreased likelihood of 90-day functional independence (per 30 min: OR 1.433, 95% CI 1.062–1.865, *p* = 0.019) and an increased likelihood of postprocedural sICH (per 30 min: OR 1.391, 95% CI 1.030–1.865, *p* = 0.029).

In the subgroup analysis, we investigated the relationship between the PT and outcomes in patients with successful recanalization (*n* = 227). Significant variables in the univariate analysis were entered into the multivariate logistic model (Tables 3 and 4). We also found that the extended PT was associated with a decreased likelihood of 90-day functional

independence (per 30 min: OR 1.522, 95% CI 1.062–2.159, *p* = 0.020) and an increased likelihood of postprocedural sICH (per 30 min: OR 1.716, 95% CI 1.161–2.648, *p* = 0.009).

Mediation analysis of the relationship among procedure time, postprocedural hemorrhagic transformation and clinical outcomes

We used the mediation analysis to explore whether postprocedural HT is partially responsible for the worse functional outcomes in patients with a longer PT. After including postprocedural HT as a mediator, we observed a significant partial mediation effect for postprocedural HT on PT-related

Table 3 Comparison of variables between patients with and without a favorable outcome in the successful recanalization cohort

Parameters	Favorable outcome ($n=112$)	Poor outcome ($n=115$)	p value	Odds ratio[a] (95% CI)	p value
Age, mean (SD), years	63.5 (12.2)	71.2 (10.4)	<0.001	1.031 (0.998–1.066)	0.066
Male, n (%)	62 (55.4)	55 (47.8)	0.256		
Medical history, n (%)					
Hypertension	73 (65.2)	89 (54.9)	0.042	1.461 (0.669–3.191)	0.342
Diabetes mellitus	15 (13.4)	29 (25.2)	0.024	1.881 (0.827–4.279)	0.132
Clinical characteristics, median (IQR)					
Baseline SBP, mmHg	132 (120–159)	144 (130–160)	0.010	0.999 (0.983–1.014)	0.850
Baseline DBP, mmHg	80 (74–90)	80 (72–92)	0.539		
Baseline NIHSS score	15 (12–20)	18 (15–22)	<0.001	1.100 (1.028–1.177)	0.006
Baseline ASPECT score	9 (8–10)	9 (8–10)	0.004	0.883 (0.656–1.188)	0.883
Stroke cause, n (%)			0.004		
LAA	36 (32.1)	28 (24.4)		2.983 (0.800–11.120)	0.104
Cardioembolic	59 (52.7)	82 (71.3)		2.727 (0.725–10.256)	0.138
Undetermined or others	17 (15.2)	5 (4.3)		Reference	
Occlusion site, n (%)			0.002		
ICA	23 (20.5)	45 (39.1)		1.523 (0.727–3.188)	0.265
MCA M1	89 (79.5)	70 (60.9)		Reference	
OTP, mean (SD), min	260 (80.5)	249 (76.7)	0.382		
Procedure time, mean (SD), min	62 (27.9)	79 (37.9)	0.001	1.522 (1.062–2.159)[b]	0.020
Intravenous thrombolysis, n (%)	25 (22.3)	25 (21.7)	0.916		
Tandem occlusion, n (%)	13 (11.6)	9 (7.8)	0.336		
Collateral score, n (%)			<0.001		
Grade 0	9 (8)	35 (30.4)		Reference	
Grade 1	35 (31.3)	54 (47)		0.279 (0.106–0.734)	0.010
Grade 2	68 (60.7)	26 (22.6)		0.128 (0.049–0.338)	<0.001
Passes of retriever > 3, n (%)	19 (17)	36 (31.3)	0.012	1.079 (0.459–2.537)	0.861

ASPECT Alberta Stroke Program Early CT, *CI* confidence intervals, *DBP* diastolic blood pressure, *ICA* internal carotid artery, *IQR* interquartile range, *LAA* large-artery atherosclerosis, *MCA* middle cerebral artery, *NIHSS* National Institutes of Health Stroke Scale, *OTP* symptoms onset to groin puncture time, *SBP* systolic blood pressure, *SD* standard deviation

[a]Odds ratio for poor outcome

[b]Odds ratio of per 30 min

effects on the 90-day mRS score. The regression coefficient was changed by 28.2% in the overall cohort and 28.1% in patients with successful recanalization (Fig. 2).

Curve representing changes in the percentage of clinical outcomes with procedure time

The changes in the probability of a poor outcome (90-day mRS score 3–6) and sICH associated with PT are shown in Fig. 3. We found that the predicted probabilities for a mRS score 3–6 were > 50% after 52.8 min of PT (Fig. 3A). Moreover, there was a near linear relationship between the poor outcome and the PT within 100 min. A sigmoidal curve was fitted between the rate of a good outcome and the PT (Fig. 4A, $R^2=0.741$; Runs test, $p=0.788$). Similarly, a significant change was observed after almost 60 min of PT. As shown in Fig. 3B, the rate of sICH gradually increased with the prolongation of the PT. The

incidence of sICH with a PT of more than 119.6 min was higher than the average of this study (9.5%). Similarly, the association between the rate of sICH and the PT was fitted to an exponential growth curve (Fig. 4C, $R^2=0.847$; Runs test, $p=0.853$). However, the number of attempts of the stent retriever and the rate of different outcomes showed a linear relationship (Fig. 4B, $R^2=0.753$; Runs test, $p=0.971$).

Discussion

The major findings of this study were as follows. First, a prolonged PT was significantly associated with a lower rate of 90-day functional independence and a higher rate of sICH, even in patients with successful recanalization. Moreover, worse functional outcomes associated with the prolonged PT could be explained partially by postprocedural HT. Second,

Table 4 Comparison of variables between patients with and without sICH in the successful recanalization cohort

Parameters	sICH		p value	Odds ratio[a]	p value
	With (n = 18)	Without (n = 209)		95% CI	
Age, mean (SD), years	72.9 (10.0)	66.9 (11.9)	0.043	1.029 (0.976–1.084)	0.009
Male, n (%)	5 (27.8)	112 (53.6)	0.036	0.207 (0.058–0.733)	0.015
Medical history, n (%)					
Hypertension	15 (83.3)	147 (70.3)	0.242		
Diabetes mellitus	4 (22.2)	40 (19.1)	0.751		
Clinical characteristics, median (IQR)					
Baseline SBP, mmHg	143 (118–154)	138 (125–160)	0.682		
Baseline DBP, mmHg	75 (69–84)	80 (74–90)	0.039	0.957 (0.920–0.995)	0.026
Baseline NIHSS score	20 (15–26)	17 (13–20)	0.054		
Baseline ASPECT score	8 (8–9)	9 (8–10)	0.103		
Stroke cause, n (%)			0.838		
LAA	4 (22.2)	60 (28.7)			
Cardioembolic	12 (66.7)	129 (61.7)			
Undetermined or others	2 (11.1)	20 (9.6)			
Occlusion site, n (%)			0.744		
ICA	12 (66.7)	62 (29.7)			
MCA M1	6 (33.3)	147 (70.3)			
OTP, mean (SD), min	232 (54.9)	256 (80.1)	0.247		
Procedure time, mean (SD), min	96 (44.3)	68 (32.5)	0.003	1.716 (1.161–2.648)[b]	0.009
Intravenous thrombolysis, n (%)	4 (22.2)	46 (22)	0.983		
Tandem occlusion, n (%)	1 (4.5)	21 (95.5)	0.536		
Collateral score, n (%)			0.002		
Grade 0	9 (50)	35 (16.7)		Reference	
Grade 1	6 (33.3)	83 (39.7)		0.141 (0.036–0.554)	0.005
Grade 2	3 (16.7)	91 (43.5)		0.144 (0.032–0.641)	0.011
Passes of retriever > 3, n (%)	7 (38.9)	48 (23)	0.130		

ASPECT Alberta Stroke Program Early CT, *CI* confidence intervals, *DBP* diastolic blood pressure, *ICA* internal carotid artery, *IQR* interquartile range, *LAA* large-artery atherosclerosis, *MCA* middle cerebral artery, *NIHSS* National Institutes of Health Stroke Scale, *OTP* symptoms onset to groin puncture time, *SBP* systolic blood pressure, *sICH* symptomatic intracranial hemorrhage, *SD* standard deviation

[a]Odds ratio for symptomatic intracranial hemorrhage

[b]Odds ratio of per 30 min

we preliminarily constructed the time–benefit curve of the PT and outcomes for stent-retriever thrombectomy patients.

Previously, several studies have investigated the relationship between the PT and clinical outcomes in endovascular treatment [6–8]. However, the conclusions were based on the older-generation thrombectomy devices. Recently, Alawieh et al. showed that in a direct aspiration at first pass technique (ADAPT) thrombectomy procedures, extended PT may reduce the likelihood of a good outcome [17]. Considering the considerable difference in PT between different thrombectomy devices, the present study further explored the relationship between the PT and functional outcomes in stent-retriever-based thrombectomy. Our data showed that the PT was an important predictor of 90-day functional outcomes. These findings corroborated the results of recent studies [10, 11], and added to the evidence underscoring the benefits of achieving recanalization rapidly in thrombectomy.

Postprocedural HT is a common complication after MT. A previous study showed that extending PT beyond 60 min may increase intraprocedural complications [8]. Moreover, Kass-Hout et al. suggested that a longer PT is an independent predictor for sICH in patients receiving MT [7]. In the study, we further highlighted the effect of extended PT on sICH in patients undergoing stent-retriever thrombectomy and confirmed that worse outcomes associated with prolonged PT may be related to postprocedural HT. To the best of our knowledge, this is the first study to assess the mediation effect of postprocedural HT on functional outcomes based on the PT in thrombectomy patients.

Several mechanisms could explain the results. First, the prolonged PT may be related to difficult catheter access,
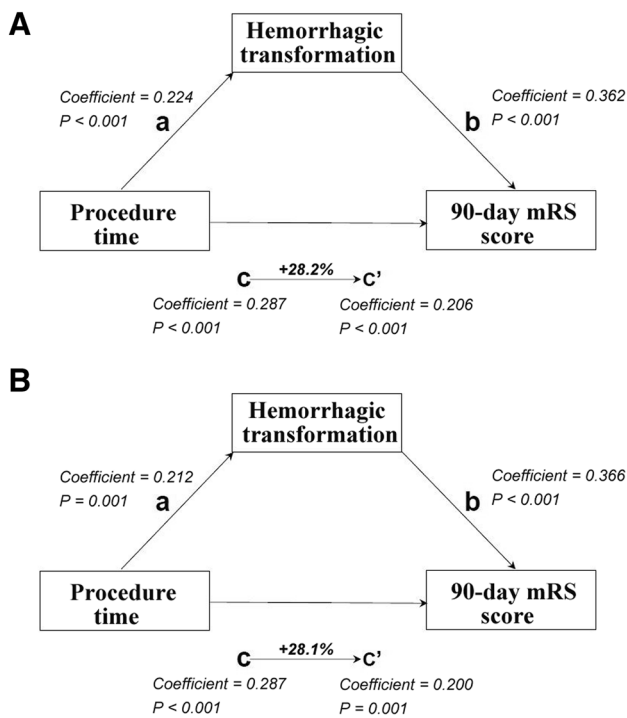
Fig. 2 Each step of the analyses assessing the mediation effect of postprocedural HT on the association of the procedure time with functional outcome (**A** for all patients; **B** for patients with mTICI ≥ 2b). The coefficient and *p* values of the regression of each step are described. The percentage difference of the coefficients (1 − *c*/*c'*) is shown. *mRS* modified Rankin Scale

which may be related to older age or more comorbidities [18]. These factors could increase the risk of HT after endovascular therapy [19]. Second, for stent-retriever MT, the longer PT represents more attempts or rescue treatments to achieve recanalization, which may result in an increased risk of intraprocedural and procedural complications [20]. Third, the longer PT may lead to the progression of ischemia, which may diminish the benefits of recanalization and increase the risk for HT [19]. In this study, even in patients with successful recanalization, prolonged PT significantly affected the prognosis. Therefore, the impact of the PT on prognosis is not limited to 'time delay' itself, but is multifactorial.

Establishing a standardized intraprocedural time metric for MT will likely help to improve clinical outcomes and assist in refining the application of endovascular thrombectomy [21, 22]. In this study, we found that the probability of 90-day functional independence was less than 50% after a PT of more than 52.8 min. Moreover, the probability of a 90-day poor outcome had a steep increase within the first 100 min after the procedures. According to these findings, we suggested that the 'golden 60' may serve as the first metric for MT using the stent retriever. In addition, our data demonstrated that postprocedural HT is an important mediator of the prognosis in prolonged PT patients. This finding is important because it provides a potential warning to the operators. The result of our study showed that after more than 119.6 min of PT, the rate of sICH would be higher than the average from the current study. Therefore, the 'warning 120' may serve as the second metric for MT using the stent retriever. The metric could assist the operators in determining whether the procedure should continue, especially for a prolonged PT in patients with a high HT risk. Although these results were consistent with the findings reported in previous studies [8, 23], they still need to be validated in other large cohorts.

A Korean study demonstrated that the number of attempts may be a surrogate for PT [23]. However, the breaking point
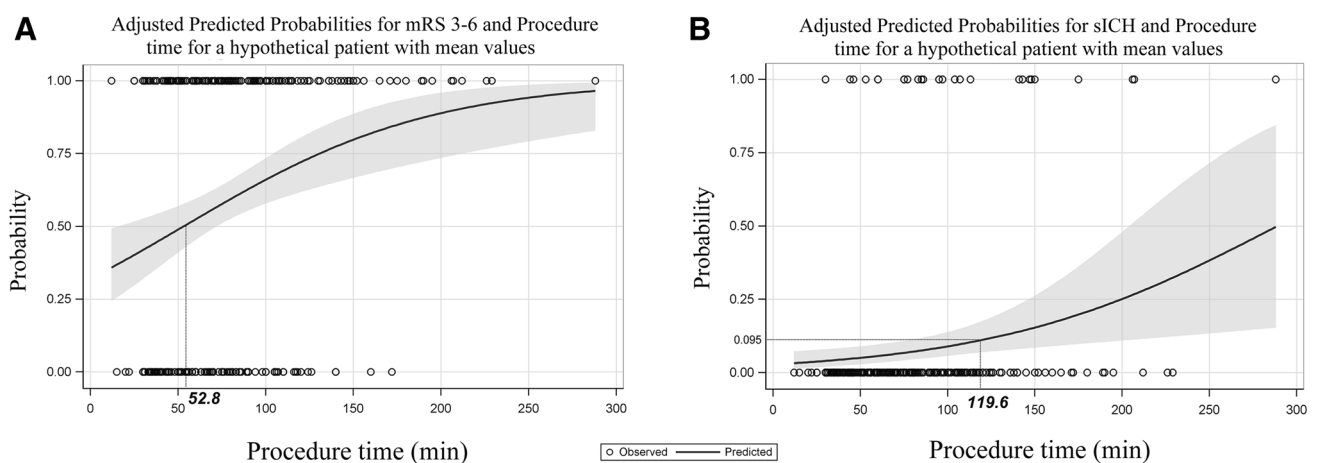

Fig. 3 The adjusted predicted probabilities of the association between the procedure time and a poor outcome (mRS score 3–6, **A**) or sICH (**B**). The regression curve estimates the probability of outcomes for an average patient (mean age, 67.2 years; baseline NIHSS score, 17.4; baseline ASPECT score, 8.7; OTP, 256.2 min). The gray area indi-cates the 95% confidence interval. *ASPECT* Alberta Stroke Program Early CT, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *OTP* symptoms onset to groin puncture time, *sICH* symptomatic intracerebral hemorrhage

Fig. 4 A, likelihood of achieving a good versus poor outcome at 90 days as a function of procedure time ($R^2 = 0.741$; Runs test, $p = 0.788$); **B** rates of a good or poor outcome with the number of attempts ($R^2 = 0.753$; Runs test, $p = 0.971$); **C** rates of symptomatic intracerebral hemorrhage with procedure time ($R^2 = 0.847$; Runs test, $p = 0.853$)
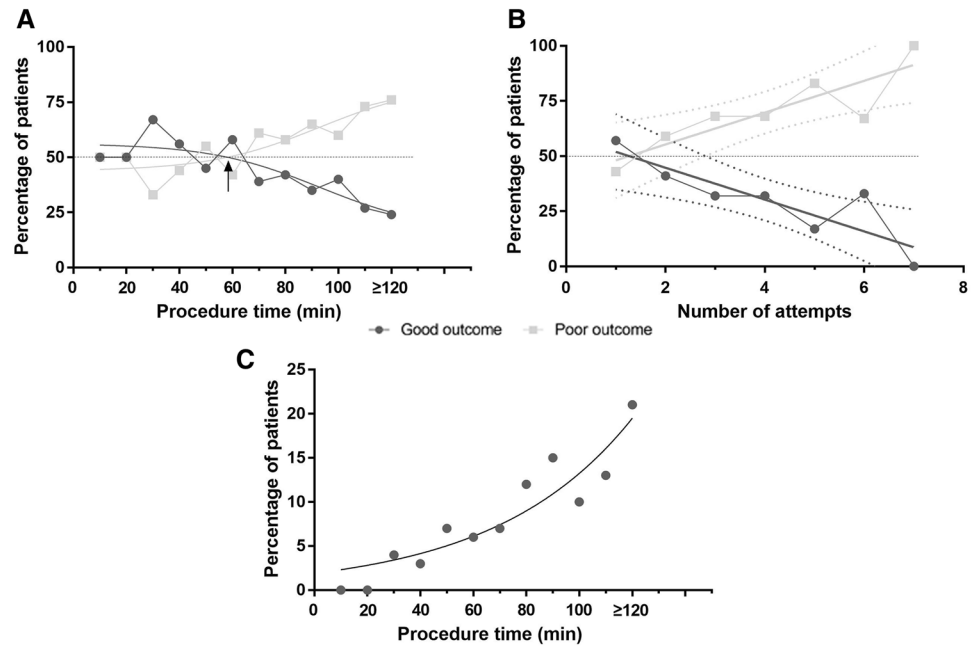
of the number of attempts was significantly different in different studies [19, 23, 24]. Furthermore, a recent study showed that the PT remained a significant predictor even if the number of attempts was included as a variable [10]. We speculated that the difficult anatomy and various types of rescue therapy may affect the relationship among the number of attempts, the PT, and functional outcomes. Further analyses centered on this question should be performed in the future to individualize treatment strategies and determine the best approach to achieving rapid recanalization in each patient.

Notably, these cutoff points were determined by constructing a time–benefit curve, which did not represent an optimal intraprocedural time metric for stent-retriever thrombectomy. Every procedure needs to be considered individually. Moreover, the process of successful recanalization is variable. Thus, we considered that the metrics are doubly important in the setting of the procedure. First, the 'golden 60' can help establish standardized procedural protocols, which could help the operators choose the best approaches based on patient- and treatment-related factors to achieve recanalization as soon as possible. Second, for patients whose PT has exceeded the 'warning 120', the operators would need to reassess the risks and benefits of continuing the procedure.

This study has several limitations. First, our study was a retrospective, medium sample-size study. A multicenter prospective study will be required to confirm our results. Second, this study did not include all outcome-related variables for mediation analysis, such as infarct volume. Thus, selection biases might have occurred. Third, we did not further analyze the relevant factors affecting PT, due to the retrospective nature

of the data. In addition, since this study enrolled only patients in which stent retriever devices were used as first pass, the results could not be extended to patients with other thrombectomy techniques [17]. However, our study provided additional support for the time metric in MT patients using the stent-retriever. Furthermore, to the best of our knowledge, this study was the first to assess the mediation effect of postprocedural HT on functional outcomes based on the PT in MT patients using the stent retriever.

Conclusion

Our data indicated that a longer PT is an independent risk factor for poor 90-day outcomes in patients undergoing stent-retriever thrombectomy. Postprocedural HT was partially responsible for a worse mRS score at 90 days in patients with a prolonged PT. Our findings provided novel information to help improve the process and the determination of procedural decisions for stent-retriever thrombectomy.

Compliance with ethical standards

Conflicts of interest There are no conflicts among the authors. All authors read and approved the final submission of the manuscript.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the insti-

tutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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