学位論文

Number of Passes of Endovascular Therapy for Stroke With a Large Ischemic Core: Secondary Analysis of RESCUE-Japan LIMIT

（広範囲脳梗塞を伴う急性主幹動脈閉塞に対する血栓回収療法の手技施行回数による転帰への影響の検討： RESCUE-Japan LIMIT の二次解析）

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abstract

Background

The increased risk of intracranial hemorrhage with multiple passes in endovascular therapy (EVT) for large vessel occlusion with a large ischemic core is a concern. We explored the effect of the number of EVT passes on patients in a randomized clinical trial.

Methods

This post hoc study was the secondary analysis of RESCUE-Japan LIMIT, which was a randomized clinical trial comparing EVT and medical treatment alone for large vessel occlusion with large ischemic core. We grouped patients according to the number of passes with successful reperfusion (modified Thrombolysis in Cerebral Infarction score, ≥ 2b) in 1, 2, 3 to 7 passes and failed reperfusion (modified Thrombolysis in Cerebral Infarction score, 0-2a) after any pass in the EVT group, and these groups were compared with medical treatment group. The primary outcome was modified Rankin Scale score of 0 to 3 at 90 days. Secondary outcomes were improvement in National Institutes of Health Stroke Scale score of ≥8 at 48 hours, mortality at 90 days, symptomatic intracranial hemorrhage, and any intracranial hemorrhage within 48 hours.

Results

The number of patients who received EVT with successful reperfusion after 1, 2, 3 to 7 passes and failed reperfusion were 44, 23, 19, and 14, respectively, and 102 received medical treatment alone. The adjusted odds ratios (95% CIs) for the primary outcome relative to medical treatment were 5.52 (2.23–14.28) after 1 pass, 6.45 (2.22–19.30) after 2 passes, 1.03 (0.15–4.48) after 3 to 7 passes, and 1.17 (0.16–5.37) if reperfusion failed. The adjusted odds ratios (95% Cis) for any intracranial hemorrhage within 48 hours relative to medical treatment were 1.88 (0.90–3.93) after 1 pass, 5.14 (1.97–14.72) after 2 passes, 3.00 (1.09–8.58) after 3 to 7 passes, and 6.16 (1.87–24.27) if reperfusion failed.

Conclusions

The successful reperfusion within 2 passes was associated with better clinical outcomes.

Trial Registration

NCT03702413.

Non-standard abbreviations and acronyms

AICH, any intracranial hemorrhage

CT, computed tomography

EVT, endovascular therapy

ICA, internal carotid artery

ICH, intracranial hemorrhage

LIC, large ischemic core

LVO, large vessel occlusion

mRS, modified Rankin Scale

mTICI, modified Thrombolysis in Cerebral Infarction

NIHSS, National Institutes of Health Stroke Scale

OR, odd ratio

SICH, symptomatic intracranial hemorrhage

r-tPA, recombinant tissue-type plasminogen activator

Introduction

Endovascular therapy (EVT) has become the standard of care for acute ischemic stroke with large vessel occlusion (LVO). Several studies have shown that achieving successful reperfusion with a single pass leads to better clinical outcomes.[1-5] However, multiple passes were often required to achieve successful reperfusion. It had been reported that multiple passes to achieve successful reperfusion increased the risk of intracranial hemorrhage (ICH) and worsened clinical outcomes.[6-8] On the contrary, it was also reported that successful reperfusion was more important than the number of passes to obtain better functional outcomes.[9] Thus, it is unknown how many passes should be performed to achieve successful reperfusion to outweigh the benefits of better functional outcomes than the risk of ICH.[10] As far as we know, there have been no reports that examined the effect of the number of passes on outcome only in patients with acute LVO with a large ischemic core (LIC).

Recently, we reported a randomized clinical trial showing the benefit of EVT for patients with LVO with LIC.[11,12] We thus investigated the association between the number of passes in EVT for these patients and clinical outcomes.

Methods

Study Design and Population

All supporting data are available from the corresponding author on reasonable request. This study was the secondary analysis of the RESCUE-Japan LIMIT (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism-Japan Large Ischemic Core Trial),[11,12] which was planned after the completion of the main trial and not described in the protocol. RESCUE-Japan LIMIT was a prospective, multicenter, non-industry-supported, open-label, randomized clinical trial evaluating the efficacy and safety of EVT compared with standard medical treatment alone in patients with acute LVO with LIC. This study was conducted in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan and the Declaration of Helsinki. The institutional review boards of Hyogo College of Medicine (approval number 3015) and 45 participating hospitals approved this study, and written informed consent was obtained from patients. We followed the CONSORT (Consolidated Standard of Reporting Trials) statement to report the findings.[13]

The key inclusion criteria of RESCUE-Japan LIMIT were patients with acute ischemic stroke due to LVO of the internal carotid artery (ICA) or horizontal segment of the middle cerebral artery (M1) and an Alberta Stroke Program Early Computed Tomography Score of 3 to 5 on CT or diffusion-weighted magnetic resonance imaging. The patients were aged ≥ 18 years, had a National Institutes of Health Stroke Scale (NIHSS) score of ≥ 6 on admission, modified Rankin Scale (mRS) of 0 to 1 before onset, and could be randomized within 6 hours from the time the patient was last known to be well, or 6–24 hours from the time the patient was last well known to be well, if there were no ischemic changes on fluid-attenuated inversion recovery imaging. Patients who met the inclusion criteria were randomly assigned to receive EVT or standard medical treatment alone in a 1:1 ratio with

the use of a stochastic minimization algorithm with the electronic data capture system, which is used for enrolment, randomization, and data collection. A physician or physical therapist evaluated the mRS score at 90 days without knowledge of the treatment assignment.

Patient stratification

Patients were categorized into 5 groups based on whether EVT or medical treatment was performed, and the total number of passes to achieve successful reperfusion if EVT was received. The number of passes was counted each time when stent retriever or aspiration catheter was used alone or in combination. Balloon angioplasty, intra-arterial thrombolysis, and stenting were treated as rescue therapies and were not counted as the passes. Because those with ≥ 3 passes were rare and a previous retrospective study on the efficacy of EVT for acute LVO with LIC reported that the number of passes > 2 was not effective[14], we grouped those with passes of 3 to 7 into 1 category. Some patients did not achieve successful reperfusion after several passes and were categorized as failed reperfusion.

Measurements and outcomes

In patients who underwent EVT, the physician in charge evaluated the reperfusion status with modified Thrombolysis in Cerebral Infarction (mTICI).[15] Successful reperfusion was defined as mTICI score ≥ 2b, which meant that ischemic territory of the previously occluded target artery was reperfused by ≥50% and failed reperfusion was defined as mTICI score of 0 to 2a.

Consistent with the main report[12], the primary outcome of this study was the achievement of a mRS score of 0 to 3 at 90 days. Secondary outcomes included

improvement in NIHSS score of ≥8 at 48 hours, mortality at 90 days, symptomatic ICH (SICH), and any ICH (AICH) within 48 hours.

Statistical analyses

We described the characteristics of the patients according to the 5 groups (successful reperfusion after 1 pass, 2 passes, 3–7 passes, failed reperfusion, and medical treatment). Categorical variables were expressed as frequencies and percentages, and continuous variables were reported as mean ± SD or median with interquartile range. Comparisons of variables between groups were performed using ANOVA and Kruskal–Wallis test as appropriate, and categorical variables were analyzed using χ^2 test.

We compared the frequencies of clinical outcomes between the 5 groups. We constructed logistic regression models to estimate odds ratios (ORs) and 95% CIs for primary and secondary outcomes of successful reperfusion after 1 pass, 2 passes, 3 to 7 passes, and failed reperfusion compared with medical treatment. We constructed crude models and adjusted models with adjustments for age, sex, initial NIHSS on admission, and use of recombinant tissue-type plasminogen activator (r-tPA) because the number of passes were determined by the treating physician.

Although the number of patients who achieved successful reperfusion after ≥3 passes was small, we conducted the sensitivity analyses for primary and secondary outcomes with breakdown of group of passes of 3 to 7 to those with 3, 4, and 5 to 7 passes. To assess the impact of complete or near complete reperfusion within 2 passes on clinical outcomes, we compared the primary and secondary outcomes in patients who achieved mTICI score 2c/3 and 2b within 2 passes. We constructed the same crude and adjusted logistic regression models to estimate the ORs (95% CIs) for these analyses.

All reported P values were 2 tailed, and statistical significance was set at $p < 0.05$.

Statistical analyses were performed using JMP 10.1 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

Among 203 enrolled patients in RESCUE-Japan LIMIT, 101 and 102 patients were assigned to the EVT and medical treatment groups, respectively (Figure 1). After excluding 1 patient who withdrew consent, 100 patients received EVT, and successful reperfusion was finally achieved in 86 patients (Table 1). Baseline characteristics and procedure techniques were generally similar across patients for each number of passes, but there were significant differences from door-to-reperfusion time and from puncture-to-reperfusion time. Two patients without procedure were included in the group of failed reperfusion because the initial contrast showed partial reperfusion mTICI score ≤2a. As the rescue therapies, intra-arterial thrombolysis was performed only in 2 patients with mTICI score ≥2b after 3 to 7 passes (Table S1).

Primary outcome

An mRS score of 0 to 3 at 90 days was achieved in 16 (36.4%) patients who got successful reperfusion after 1 pass (Figure 2). Those who achieved an mRS score of 0 to 3 at 90 days were 11 (47.8%), 2 (10.5%), and 2 (14.3%) patients who got successful reperfusion after 2, 3 to 7 passes, and failed reperfusion, respectively, compared with 13 (12.7%) who received medical treatment (Table 2). The adjusted ORs (95% Cis) for mRS score of 0 to 3 at 90 days of successful reperfusion after 1 and 2 passes were 5.52 (2.33–14.28) and 6.45 (2.22–19.30), respectively, compared with medical treatment (Table 2). Meanwhile, the likelihood of achieving an mRS score of 0 to 3 at 90 days was similar to that of medical treatment if patients had successful reperfusion after 3 to 7 passes (adjusted ORs, 1.03 [95%CI, 0.15–4.48]) or failed reperfusion (adjusted ORs, 1.17 [95%CI, 0.16–5.37]).

The incidence of mRS score of 0 to 3 at 90 days was zero in patients who achieved successful reperfusion after 3 passes (Table S2). There were no significant differences in the mRS score of 0 to 3 at 90 days between patients who achieved mTICI score 2c/3 and 2b within 2 passes (Table S3).

Secondary outcomes

An improvement in NIHSS score≥ 8 at 48 hours was achieved in 20 (45.5%) patients who achieved successful reperfusion after 1 pass (Table 2). Those who got improvement of NIHSS score ≥8 were 6 (26.1%), 4 (21.1%), and 1 (7.1%) patients who got successful reperfusion after 2, 3 to 7 passes, and who failed reperfusion, respectively, compared with 9 (8.8%) who received medical treatment. The adjusted ORs (95% CIs) for improvement of NIHSS ≥8 of successful reperfusion after 1 and 2 passes were 9.28 (3.74–24.85) and 3.68 (1.08–11.95) compared with medical treatment.

Mortality at 90 days occurred in 9 (20.5%), 3 (13.0%), 3 (15.8%), and 3 (21.4%) patients who achieved successful reperfusion after 1, 2, 3 to 7 passes, and who failed reperfusion, respectively, compared with 24 (23.5%) who received medical treatment. SICH within 48 hours occurred in 4 (9.1%), 0 (0%), 2 (10.5%), and 3 (21.4%) patients who achieved successful reperfusion after 1, 2, 3 to 7 passes, and failed reperfusion, respectively, compared to 5 (4.9%) who received medical treatment. Mortality and SICH was not significantly different between the groups.

AICH within 48 hours occurred in 21 (47.7%), 16 (69.6%), 11 (57.9%), 10 (71.4%) patients who got successful reperfusion after 1, 2, 3 to 7 passes, and failed reperfusion, respectively, compared with 32 (31.4%) who received medical treatment. The adjusted ORs (95% Cis) for AICH within 48 hours of successful reperfusion after 1, 2, 3 to 7 passes, and failed reperfusion were1.88 (0.90-3.93), 5.14 (1.97–14.72), 3.00 (1.09–8.58), and 6.16

(1.87–24.27), respectively.

The effectiveness of successful reperfusion after 3 or 4 passes for the secondary outcomes were not observed (Table S2). The incidences of secondary outcomes were similar between patients who achieved mTICI score 2c/3 and 2b within 2 passes (Table S3).

Discussion

We investigated the relationship between the number of EVT passes and clinical outcomes in patients with acute LVO with LIC. If such patients received EVT and achieved successful reperfusion within 2 passes, the mRS score at 90 days was significantly better than those with medical treatment alone without exacerbating the negative effects of AICH. The superiority of successful reperfusion within 2 passes was also observed in terms of 8-scale improvement of NIHSS at 48 hours compared with medical treatment. AICH that occurred within 48 hours was significantly higher in patients who achieved successful reperfusion after ≥2 passes than in those who received medical treatment.

There have been several reports on the number of passes and clinical outcomes in patients with LVO, not limited to those with LIC. Successful reperfusion within 3 passes was reported to be associated with favorable effects on functional outcome.[16, 17] Meanwhile, other reports suggested that functional outcome was better to achieve successful reperfusion regardless of the number of passes.[9] On the contrary, ICH was of great concern when multiple passes were conducted in such patients. Some reports revealed that ICH was increased if ≥ 4 passes were conducted in LVO to achieve reperfusion.[6, 7] Considering the risk of ICH, it is desirable to achieve successful reperfusion within 3 passes, since the number of patients with a good outcome decreases with each pass in general patients with LVO[10] whose ischemic core is relatively small.

Several reasons have been reported for the increased number of passes in EVT. Koge et al[18] reported that ICA tortuosity reduced likelihood of the first pass effect, which was defined as complete reperfusion with the first pass without rescue therapy[1], and increased the time required for reperfusion. It also showed that the combined stent retriever and aspiration catheter technique was more beneficial than either alone in those without tortuous vessels, but not in those with tortuous vessels. Thus, it is possible that the patients who

required multiple passes for successful reperfusion had tortuous ICA despite the high rate of use of combined technique in the first procedure in this study. It was also reported that fibrin-rich hard clots increased the number of passes to achieve effective reperfusion.[19] Another possible cause of multiple passes could be the distal embolization. In this study, intra-arterial thrombolysis was only performed in patients who required 3 to 7 passes to achieve successful reperfusion, which could be due to distal embolization.

To identify patients with risk of increased number of passes of EVT, evaluations of ICA tortuosity and hard clots could be considered. The grading systems were proposed to evaluate the vascular tortuosity for extracranial[20] and intracranial ICA.[21] The grade of ICA tortuosity was associated with the reduction of first pass effect and increase in ICH after EVT. By assessing the ICA tortuosity during angiography before EVT with these grading systems, it could reduce the number of passes for successful reperfusion by selecting bendable stent retrievers with segmented design[22] or aspiration catheter with steam shaped tip.[23] Another factor was clot characteristics, which could increase in passes for successful reperfusion. Hyperdense vessel sign on CT or susceptibility vessel sign on magnetic resonance imaging could evaluate the clots in which red blood cell dominated.[24] If these signs were absent, the clots were considered fibrin-rich and hard. To retrieve such hard clot, special measures such as the Nimbus stent retriever (Cerenovus, Johnson&Johnson, New Brunswick, NJ) could be used to remove the fibrin-rich clots.[25]

In patients with LIC, there was no difference in mRS score 0 to 3 at 90 days between patients who achieved mTICI score 2c/3 and 2b in this study. It suggested that patients with LIC had a smaller residual functional parenchyma than those without, and therefore, even if an mTICI score 2c/3 was not achieved, it could be sufficient to achieve an mTICI score of 2b, including artery that supplied the residual function territory. Therefore, the total number of passes could be reduced when additional passes to achieve mTICI score 2c/3 would not be

necessary for patients with LIC rather than patients without LIC.

In patients with acute LVO with LIC, the effect of the time required for successful reperfusion on clinical outcomes was likely to be greater than that in patients without LIC. Many LVO patients with LIC despite early onset are considered to have poor collateral blood circulation and early progression of cerebral infarction. Therefore, the impact of time required per pass was likely to be greater. Actually, the smaller the total number of passes to achieve successful reperfusion, the shorter the time from door to reperfusion and from puncture to reperfusion, which was significantly different in this study. As a result, successful reperfusion after 3 passes may not have contributed to improved clinical outcomes.

Furthermore, several mechanisms should also be considered as a negative impact of multiple passes.[5] Repeated traumatic shearing forces and accumulated vascular damage by multiple passes could increase ICH.[26,27] As already mentioned, it was reported that AICH and SICH increased with >3 passes in patients not limited to extensive infarcts.[6,7] However, in this study, although AICH was significantly increased in patients who achieved an mTICI score ≥2b with ≥2 passes compared with patients who received medical treatment, there was no significant difference in SICH between the number of passes. One reason why SICH did not increase was that patients with acute LVO with LIC have a smaller residual functional parenchyma than those without LIC as noted above. If hemorrhagic changes do not occur around the residual functional parenchyma, they are likely asymptomatic. This could be the reason why the frequency of SICH was similar to that of multiple passes, in addition to the low frequency of SICH. This does not mean that it is nothing to be concerned about unless there is SICH. AICH including asymptomatic ICH and SICH has been reported to worsen clinical outcomes.[28,29] Therefore, the increase in AICH after 2 passes should be considered important.

Study Limitation

This study had several limitations inherent to the original study design. First, 174 (86.1%) patients were identified using diffusion-weighted imaging Alberta Stroke Program Early Computed Tomography Score to assess LIC, and diffusion-weighted imaging Alberta Stroke Program Early Computed Tomography Score was more accurate for identifying acute infarction than non-enhanced CT.[30] Second, r-tPA was administered to 55 (27.2%) patients. The use of r-tPA should contribute to reperfusion efficacy and the risk of ICH. The effect of the number of passes in a setting with the standard use of r-tPA should also be considered. Third, this study included patients who were within 6 hours of onset or those who were presumed to have early onset based on magnetic resonance imaging. Because patients with LIC >6 hours after onset are considered to have more cases of slow progression of cerebral infarction than those with ≤6 hours of onset, clinical outcomes may be significantly improved even in patients in whom successful reperfusion is achieved with >3 passes. Finally, the sample size was too small to evaluate the efficacy and safety of the number of passes. Further large-scale studies or pooled analyses should be performed to explore more reliable effect of number of passes on clinical outcomes in LVO patients with LIC.

Conclusion

The secondary analysis of the randomized clinical trial indicated that the number of passes to achieve successful reperfusion should be ≤ 2 in patients with acute LVO with LIC in terms of an mRS score of 0 to 3 at 90 days and AICH within 48 hours.

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Supplemental Material

Tables S1-S3

CONSORT Checklist

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Figure Legends

Figure 1. Study flowchart

mTICI, modified Thrombolysis in Cerebral Infarction

Figure 2. Distributions of modified Rankin Scale at 90 days by total number of passes with successful reperfusion, failed reperfusion, and medical treatment

mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction

Tables

Table 1. Baseline characteristics by total number of passes with mTICI ≥ 2b, failed reperfusion, and medical treatment

Variables	mTICI ≥ 2b after 1 pass	mTICI ≥ 2b after 2 passes	mTICI ≥ 2b after 3-7 passes	Failed reperfusion	Medical treatment	P Value
Number of patients, n (%)	44 (21.8)	23 (11.4)	19 (9.4)	14 (6.9)	102 (50.5)	-
Number of passes						
0, n (%)	0	0	0	2 (14.3)	102 (100)	-
1, n (%)	44 (100)	0	0	2 (14.3)	0	-
2, n (%)	0	23 (100)	0	5 (35.7)	0	-
3, n (%)	0	0	7 (36.8)	3 (21.4)	0	-
4, n (%)	0	0	7 (36.8)	1 (7.1)	0	-
5, n (%)	0	0	2 (10.5)	0	0	-
6, n (%)	0	0	2 (10.5)	1 (7.1)	0	-
7, n (%)	0	0	1 (5.3)	0	0	-
Age - years, mean (SD)	76.6 (9.8)	74.3 (12.4)	77.9 (8.4)	79.3 (7.8)	75.7 (10.2)	0.73
Male, n (%)	24 (54.6)	16 (69.6)	7 (36.8)	7 (50.0)	58 (56.9)	0.30
Medical history						
Hypertension, n (%)	28 (63.6)	18 (78.3)	15 (79.0)	10 (71.4)	70 (68.6)	0.66
Diabetes mellitus, n (%)	12 (27.3)	4 (17.4)	4 (21.1)	3 (21.4)	20 (19.6)	0.86
Hyperlipidemia, n (%)	13 (29.6)	4 (17.4)	5 (26.3)	3 (21.4)	24 (23.5)	0.85

Atrial fibrillation, n (%)	26 (59.1)	11 (47.8)	13 (68.4)	9 (64.3)	60 (58.8)	0.73
Current smoker, n (%)	8 (18.2)	3 (13.0)	4 (21.1)	3 (21.4)	21 (20.6)	0.94
Initial NIHSS, median (IQR)	24 (19-27)	20 (15-24)	22 (18-29)	18 (16-23)	21 (17-25)	0.04
Initial ASEPCTS, median (IQR)	3 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	4 (3-4)]	0.83
ASPECTS on MRI	39 (88.6)	20 (87.0)	15 (79.0)	13 (92.9)	87 (85.3)	0.80
Stroke classification						
Cardioembolic, n (%)	36 (81.8)	16 (69.6)	17 (89.5)	14 (100)	76 (74.5)	0.37
Atherothrombotic, n (%)	3 (6.8)	1 (4.4)	0	0	8 (7.8)	
Cryptogenic, n (%)	4 (9.1)	6 (26.1)	2 (10.5)	0	13 (12.8)	
Others, n (%)	1 (2.3)	0	0	0	5 (4.9)	
Occlusion site						
ICA, n (%)	25 (56.8)	9 (39.1)	6 (31.6)	6 (42.9)	49 (48.0)	0.38
MCA M1 segment, n (%)	29 (65.9)	17 (73.9)	14 (73.7)	13 (92.9)	70 (68.6)	0.38
MCA M2 segment, n (%)	0	0	0	0	3 (2.9)	0.56
Tandem lesion of ICA and M1segment, n (%)	10 (22.7)	3 (13.0)	1 (5.3)	5 (35.7)	20 (19.6)	0.22
IV rt-PA, n (%)	12 (27.3)	4 (17.4)	5 (26.3)	5 (35.7)	29 (28.4)	0.79
Contact aspiration alone, n (%)	9 (20.5)	1 (4.4)	1 (5.3)	0	NA	0.06
Stent retriever alone, n (%)	3 (6.8)	3 (13.0)	2 (10.5)	1 (7.1)	NA	0.84
Combined technique, n (%)	32 (72.7)	19 (82.6)	16 (84.2)	11 (78.6)	NA	0.70
No procedure, n (%)	0	0	0	2 (14.3)	NA	0.006
Onset to reperfusion time - minutes,	295	305	355	NA	NA	0.26

median (IQR)	(198-498)	(205-375)	(249-717)			
Door to reperfusion time-minutes, median (IQR)	107 (75-136)	110 (70-148)	161 (142-204)	NA	NA	0.0001
Puncture to reperfusion time-Minutes, median (IQR)	25 (20-37)	37 (20-55)	88 (55-118)	NA	NA	< 0.0001

mTICI, modified Thrombolysis in Cerebral Infarction; SD, standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; MCA, middle cerebral artery; IV rt-PA, intravenous recombinant tissue plasminogen activator; NA, not applicable

564 Table 2. Clinical outcomes

565

Variables	Incidence n (%)	Crude ORs (95%CIs)	P Value	Adjusted ORs (95%CIs)	P Value
		mRS of 0-3 at 90 days			
Medical treatment (n = 102)	13 (12.7)	-	-	-	-
mTICI ≥ 2b after 1 pass (n = 44)	16 (36.4)	3.91 (1.69-9.27)	0.002	5.52 (2.23-14.28)	0.0002
mTICI ≥ 2b after 2 passes (n = 23)	11 (47.8)	6.45 (2.30-17.45)	0.0004	6.45 (2.22-19.30)	0.0007
mTICI ≥ 2b after 3-7 passes (n = 19)	2 (10.5)	0.81 (0.12-3.28)	0.78	1.03 (0.15-4.48)	0.97
Failed reperfusion (n = 14)	2 (14.3)	1.14 (0.17-4.84)	0.87	1.17 (0.16-5.37)	0.86
		Improvement of NIHSS of 8 or more at 48 hours			
Medical treatment (n = 102)	9 (8.8)	-	-	-	-
mTICI ≥ 2b after 1 pass (n = 44)	20 (45.5)	8.61 (3.58-22.22)	<0.0001	9.28 (3.74-24.85)	<0.0001
mTICI ≥ 2b after 2 passes (n = 23)	6 (26.1)	3.65 (1.10-11.52)	0.03	3.68 (1.08-11.95)	0.04

mTICI ≥ 2b after 3-7 passes (n = 19)	4 (21.1)	2.76 (0.68-9.69)	0.15	3.28 (0.78-12.09)	0.10
Failed reperfusion (n = 14)	1 (7.1)	0.79 (0.04-4.77)	0.83	0.90 (0.05-5.63)	0.92
		Mortality at 90 days			
Medical treatment (n = 102)	24 (23.5)	-	-	-	-
mTICI ≥ 2b after 1 pass (n = 44)	9 (20.5)	0.84 (0.34-1.93)	0.68	0.67 (0.26-1.60)	0.38
mTICI ≥ 2b after 2 passes (n = 23)	3 (13.0)	0.49 (0.11-1.58)	0.49	0.55 (0.12-1.89)	0.55
mTICI ≥ 2b after 3-7 passes (n = 19)	3 (15.8)	0.61 (0.13-2.03)	0.44	0.46 (0.10-1.63)	0.24
Failed reperfusion (n = 14)	3 (21.4)	0.89 (0.19-3.12)	0.86	0.97 (0.19-3.76)	0.97
		SICH within 48 hours			
Medical treatment (n = 102)	5 (4.9)	-	-	-	-
mTICI ≥ 2b after 1 pass (n = 44)	4 (9.1)	1.94 (0.46-7.70)	0.35	2.09 (0.48-8.67)	0.31
mTICI ≥ 2b after 2 passes (n = 23)	0	NA	NA	NA	NA

mTICI ≥ 2b after 3-7 passes (n = 19)	2 (10.5)	2.28 (0.31-11.58)	0.37	2.02 (0.27-10.60)	0.45
Failed reperfusion (n = 14)	3 (21.4)	5.29 (0.98-24.79)	0.052	5.45 (0.98-27.01)	0.053
		AICH within 48 hours			
Medical treatment (n = 102)	32 (31.4)	-	-	-	-
mTICI ≥ 2b after 1 pass (n = 44)	21 (47.7)	2.00 (0.97-4.14)	0.06	1.88 (0.90-3.93)	0.09
mTICI ≥ 2b after 2 passes (n = 23)	16 (69.6)	5.00 (1.94-14.13)	0.0008	5.14 (1.97-14.72)	0.0007
mTICI ≥ 2b after 3-7 passes (n = 19)	11 (57.9)	3.01 (1.11-8.47)	0.03	3.00 (1.09-8.58)	0.03
Failed reperfusion (n = 14)	10 (71.4)	5.47 (1.69-21.16)	0.004	6.16 (1.87-24.27)	0.003

mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; SICH, symptomatic intracranial hemorrhage; AICH, any intracranial hemorrhage; OR, odds ratio; CIs, confidence intervals

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