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Original research

Identifying large ischemic core volume ranges in acute stroke that can benefit from mechanical thrombectomy

Takeshi Yoshimoto ¹, Manabu Inoue,^{2,3} Kanta Tanaka ², Kodai Kanemaru,³ Junpei Koge,³ Masayuki Shiozawa,³ Naruhiko Kamogawa,³ Shunsuke Kimura,³ Tetsuya Chiba,³ Tetsu Satow ⁴, Jun C Takahashi,⁴ Kazunori Toyoda,³ Masatoshi Koga,³ Masafumi Ihara¹

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¹Neurology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

²Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

³Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

⁴Neurosurgery, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

Correspondence to

Dr Manabu Inoue, Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan; gakinoue@ncvc.go.jp

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ABSTRACT

Background We aimed to identify the large ischemic core (LIC) volume ranges in acute ischemic stroke patients that can benefit from mechanical thrombectomy (MT).

Methods Consecutive patients within 24 hours of onset of anterior circulation ischemic stroke with large vessel occlusion and ischemic core volumes of 70–300 mL were included from our single-center prospective database from March 2014 to December 2019. Subjects were divided into three groups by baseline ischemic core volume (A: 70–100 mL; B: 101–130 mL; C: >130 mL). We compared modified Rankin Scale (mRS) score 0–2 at 3 months and parenchymal hematoma between patients receiving MT and standard medical treatment (SMT), and determined clinically treatable core volume ranges for MT.

Results Of 157 patients (86 women; median age, 81 years; median ischemic core volume, 123 mL), 49 patients underwent MT. In Group A (n=52), MT patients (n=31) showed a higher proportion of mRS 0–2 at 3 months (52% vs 5%, P<0.05) versus SMT, respectively. Group B (n=36) MT patients (n=14) also had a higher proportion of mRS 0–2 at 3 months (29% vs 9%, P=0.13) versus SMT, respectively. In Group C (n=69), only four patients received MT. The 95% confidence intervals for the probability of mRS 0–2 at 3 months in patients with MT (n=49) versus SMT (n=108) intersected at 120–130 mL.

Conclusions Ischemic core volumes between 70 and 100 mL may benefit from MT. The treatable upper core limit is approximately 120 mL in selected patients with LIC of 70–300 mL.

increased risk of hemorrhagic complications, due to a lack of evidence.^{2 6 7} Although previous randomized controlled trials have referred to LIC (baseline ischemic core volume of ≥ 70 mL) as the exclusion criterion,^{8 9} a specific subset of LIC patients may still benefit from MT. Numerous previous studies showed positive results with MT in LIC on diffusion-weighted imaging (DWI) (>70 mL)^{10–12} or computed tomography perfusion (CTP)^{13 14} among carefully selected patients. In addition, in the Secondary Analysis of the Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT) study, EVT was associated with better functional outcomes than standard medical treatment (SMT) in patients with LIC on CT with an Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) of <6 or on CTP with a volume ≥ 50 mL with a relative cerebral blood flow of <30%.¹⁵ In contrast, a previous pooled analysis showed that a follow-up ischemic core volume between 12 hours and 2 weeks after onset of ≥ 133 mL was highly specific for a modified Rankin Scale (mRS) score of 3–6 at 3 months.¹⁶ Although several studies reported the lower limit of LIC that can be expected to have a favorable outcome with MT, few studies reported the LIC volume range, especially the upper core volume limit for only quantitative automatically-derived DWI volume in the hyper-acute phase, and the actual range of DWI volume that can benefit from MT is equivocal. In this study, we aimed to identify LIC volume ranges using only the DWI core volume, in anterior circulation acute ischemic stroke patients that can benefit from MT compared with SMT.

INTRODUCTION

The efficacy of mechanical thrombectomy (MT) for ischemic stroke due to anterior circulation large vessel occlusion has been established,¹ but limitations related to the baseline volumetric ischemic core remain a factor associated with malignant outcomes. Ischemic core volumes between 70 and 100 mL are suggested reliable cut-offs as “malignant profiles”.^{2–5} Despite the efficacy of new strategies in acute ischemic stroke treatment, endovascular therapy (EVT) is often not applied to patients with large ischemic core (LIC) volumes, who have an

METHODS

Patients

All patients with ischemic stroke admitted to our institute within 7 days from symptom onset or the last-known-well date have been prospectively registered in the National Cerebral and Cardiovascular Center (NCVC) Stroke Registry.⁵ Data for the period from March 2014 to December 2019 were retrospectively reviewed, and patients who met the following criteria were included: (1) 18 years or older; (2) admission within 24 hours of symptom



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onset; (3) occlusion identified at the internal carotid artery (ICA; either intracranial or extracranial) or M1 or M2 segment of the middle cerebral artery (MCA); and (4) ischemic core volume ≥ 70 mL confirmed by magnetic resonance (MR) DWI within 24 hours. Tandem occlusions, such as concomitant occlusions of the extracranial ICA and M2 segment of the MCA, were included. Multivessel occlusion, such as ipsilateral occlusions of the M2 superior trunk of the MCA and M2 inferior trunk of the MCA, were also included. The upper limit of DWI core volume for patient inclusion was set at ≤ 300 mL according to the unilateral hemisphere volume.

This study was approved by the institutional review board of NCVS (approval number M23-073-4). The NCVS Stroke Registry is registered at ClinicalTrials.gov (NCT02251665). Written informed consent for reperfusion therapy, as well as thrombectomy, was obtained from each patient or a relative, if the patient had communication difficulties, and the opt-out method for patient recruitment was used.

Imaging protocol and analysis

All MR imaging (MRI) scans were obtained before MT using a 3.0-Tesla system (MAGNETOM Spectra; Siemens Healthcare, Erlangen, Germany). The MR protocol included an axial isotropic diffusion-weighted echo-planar spin-echo sequence. DWI was performed using a spin echo-planar sequence (field of view=230 mm, slice thickness=4 mm, number of slices=30, slice gap=5 mm, acquisition matrix=140 × 192). All MR DWI were retrospectively postprocessed on an automated image postprocessing system (RAPID; iSchemaView Inc., Menlo Park, CA, USA). Ischemic core volume was calculated by the apparent diffusion coefficient $< 620 \times 10^{-6}$ mm²/s on b0/b1000 image in MR images.¹⁷

Treatment protocol

All endovascular procedures were performed by neurointerventionalists certified by the Japanese Society for Neuroendovascular Therapy, basically according to the American Heart Association/American Stroke Association Guideline¹⁸ and the Japanese Guidelines for Neuroendovascular Mechanical Thrombectomy (3rd edition).¹⁹ Even if the patients had features that are not strongly recommended from the guidelines, MT was considered by the physicians when benefits outweighed the risks. MT included stent retriever techniques, aspiration techniques, and a combination of stent retriever and aspiration catheters. Any device for EVT approved for clinical use in Japan could be selected. All patients underwent MT under local anesthesia, and sedation was added when required. To classify patients' recanalization status, we used the modified Thrombolysis in Cerebral Infarction (mTICI) scale, with successful recanalization defined as mTICI scale 2b or 3, and complete recanalization as mTICI scale 3. SMT included intravenous thrombolysis (IVT) with alteplase at 0.6 mg/kg according to the standard of care protocol in Japan.²⁰

Clinical data collection

Baseline clinical characteristics for the following variables were collected from the NCVS Stroke Registry: sex, age, prestroke mRS score, medical history (hypertension, dyslipidemia, diabetes mellitus, current smoking, ischemic stroke, and atrial fibrillation), systolic blood pressure on admission, baseline National Institutes of Health Stroke Scale (NIHSS) score, serum glucose at admission, DWI-ASPECTS at admission, ischemic core volume at admission, occluded artery (ICA, M1 segment of

MCA, M2 segment of MCA, tandem occlusion, or multivessel occlusion), time logistics (onset-to-hospital arrival time and onset-to-imaging time), treatment profile (IVT and/or MT), and stroke causative mechanism. Ischemic core volume at admission was measured as described above. Occlusion sites were determined using MR angiography or digital subtraction angiography at admission. The stroke causative mechanism was determined according to the Trial of ORG 10172 in Acute Stroke Treatment criteria by board-certified stroke neurologists.

Outcomes

The primary efficacy outcome was mRS score 0–2 at 3 months, which represented good functional outcome. Other efficacy outcomes were favorable outcome defined as mRS score 0–2 or a return to the same score as prestroke mRS at 3 months, severe disability or death (mRS score 5–6) at 3 months, and death within 3 months. Safety outcomes were defined as parenchymal hematoma (PH), any intracranial hemorrhage (ICH) within 36 hours after symptom onset, symptomatic ICH within 36 hours after symptom onset, and decompressive craniectomy. Symptomatic ICH was defined according to the European Cooperative Acute Stroke Study (ECASS) II criteria (any ICH with a ≥ 4 -point increase in the NIHSS score from baseline) and Safe Implementation of Thrombolysis in Stroke-Monitoring Study criteria (PH2 combined with a ≥ 4 -point increase in the NIHSS score from baseline).²¹

Statistical analyses

Data are summarized as median (IQR) for continuous variables and frequencies and percentages for categorical variables. The DWI core volumes were used to divide the patients into three groups by ischemic core volume at admission (Group A: 70–100 mL;^{5 10–12} Group B: 101–130 mL;^{2 15} Group C: >130 mL¹⁶) according to previous studies, and outcomes for each group were compared between patients who received MT versus SMT. Statistical differences between patients receiving MT and those receiving SMT were assessed using the Mann–Whitney U test or Fisher's exact test, as appropriate. We constructed multivariable logistic regression models of efficacy and safety outcomes for all three groups. For the models, the following variables, which were previously reported to be associated with efficacy and safety outcomes, were set as covariates: female sex,²² age,^{1 10 12} prestroke mRS score,¹ baseline NIHSS score,¹ baseline ischemic core volume,¹ onset-to-imaging time,²³ ICA occlusion,¹ and IVT.^{1 13} Odds ratios (ORs) with 95% confidence intervals (CIs) were also calculated.

Predictive marginal probability adjusted by the above variables for good functional outcome (mRS score 0–2 at 3 months) and PH in patients who received MT or SMT were plotted according to baseline ischemic core volume in the full cohort. The absolute risk reduction was calculated as the difference of the marginal probabilities for the good functional outcome between the patients with MT and those with SMT, for ranges of baseline ischemic core volume. The number needed to treat to achieve good functional outcome with MT was estimated as 1 over the absolute risk reduction.²⁴ In addition, we stratified patients who received MT by mTICI grade to clarify the relationship between recanalization status and clinical response.

All reported P values were two-tailed, with the level of statistical significance set at $P < 0.05$. All analyses were performed using the Stata/IC statistical package, version 15.1 (StataCorp LP, College Station, TX, USA).

Table 1 Clinical characteristics of the groups by baseline ischemic core volume in the full cohort

Characteristic	Group A			Group B			Group C		
	70–100 mL			100–130 mL			>130 mL		
	MT (n=31)	SMT (n=21)	P value*	MT (n=14)	SMT (n=22)	P value*	MT (n=4)	SMT (n=65)	P value*
Female	11 (36)	16 (76)	<0.05	7 (50)	9 (41)	0.59	4 (100)	44 (68)	<0.05
Age (years)	76 (71–85)	79 (67–87)	0.58	80 (71–85)	77 (71–84)	0.83	77 (65–81)	84 (77–87)	0.09
Prestroke mRS score	0 (0–2)	0 (0–2)	0.79	0 (0–2)	0 (0–4)	0.55	1 (0–2)	0 (0–3)	0.98
Medical history									
Hypertension	19 (61)	14 (67)	0.69	10 (71)	15 (68)	0.84	4 (100)	45 (69)	0.19
Dyslipidemia	11 (36)	9 (43)	0.59	6 (43)	8 (36)	0.70	3 (75)	27 (42)	0.19
Diabetes mellitus	5 (16)	2 (10)	0.49	4 (29)	7 (32)	0.84	1 (25)	9 (14)	0.54
Current smoking	8 (26)	1 (5)	0.05	3 (21)	5 (23)	0.93	2 (50)	6 (9)	<0.05
Ischemic stroke	3 (10)	3 (14)	0.61	5 (36)	9 (41)	0.76	2 (50)	11 (17)	0.10
Atrial fibrillation	21 (68)	9 (43)	0.08	12 (86)	15 (68)	0.24	3 (75)	53 (82)	0.75
Systolic blood pressure on admission (mmHg)	148 (124–165)	144 (136–179)	0.44	151 (131–175)	160 (148–182)	0.39	150 (139–164)	159 (142–176)	0.57
Baseline NIHSS score	21 (18–24)	20 (16–26)	0.79	24 (20–28)	23 (18–26)	0.76	29 (24–36)	26 (21–31)	0.26
Serum glucose (mmol/L)	6.56 (5.78–7.67)	6.94 (6.67–8.50)	0.10	7.56 (6.61–10.72)	7.33 (7.00–10.22)	0.59	8.83 (7.17–10.67)	7.44 (6.17–9.11)	0.30
Baseline DWI-ASPECTS	5 (4–6)	4 (3–5)	<0.05	6 (4–6)	3 (1–5)	<0.05	3 (3–6)	2 (1–3)	<0.05
Baseline DWI ischemic core volume (mL)	80 (74–87)	85 (77–91)	0.06	107 (101–117)	113 (107–124)	0.14	178 (175–194)	182 (150–210)	0.82
Occluded artery									
ICA	13 (42)	7 (33)	0.53	6 (43)	9 (41)	0.91	1 (25)	43 (66)	0.10
MCA M1	10 (32)	8 (38)	0.66	5 (36)	11 (50)	0.40	1 (25)	16 (25)	0.11
MCA M2	2 (7)	4 (19)	0.16	0	1 (5)	0.42	1 (25)	1 (2)	<0.05
Tandem occlusion	6 (19)	2 (10)	0.36	3 (21)	1 (5)	0.17	0	0	--
Multivessel occlusion	0	0	--	0	0	--	1 (25)	5 (8)	0.23
Time logistics									
Onset-to-hospital arrival time (min)	75 (38–264)	330 (47–639)	<0.05	67 (58–173)	367 (150–740)	<0.05	50 (38–81)	379 (102–719)	<0.05
Onset-to-imaging time (min)	94 (57–305)	357 (75–669)	<0.05	94 (81–199)	400 (191–758)	<0.05	77 (61–98)	434 (147–815)	<0.05
Treatment profile									
Intravenous thrombolysis	13 (42)	1 (5)	<0.05	4 (29)	1 (5)	<0.05	2 (50)	1 (2)	<0.05
Stroke causative mechanism									
Large artery atherosclerosis	5 (16)	1 (5)	<0.05	0	3 (14)	0.38	0	2 (3)	0.87
Cardioembolism	24 (77)	11 (52)		10 (71)	15 (71)		4 (100)	55 (85)	
Other	0	8 (38)		2 (14)	2 (10)		0	7 (11)	
Unknown	2 (7)	1 (5)		2 (14)	1 (5)		0	1 (2)	

Data are presented as number (%) or median (IQR).

*Fisher's exact test.

CT, computed tomography; DWI, diffusion-weighted imaging; DWI-ASPECTS, Diffusion-Weighted Imaging-Alberta Stroke Program Early Computed Tomographic Score; ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; SMT, standard medical treatment.

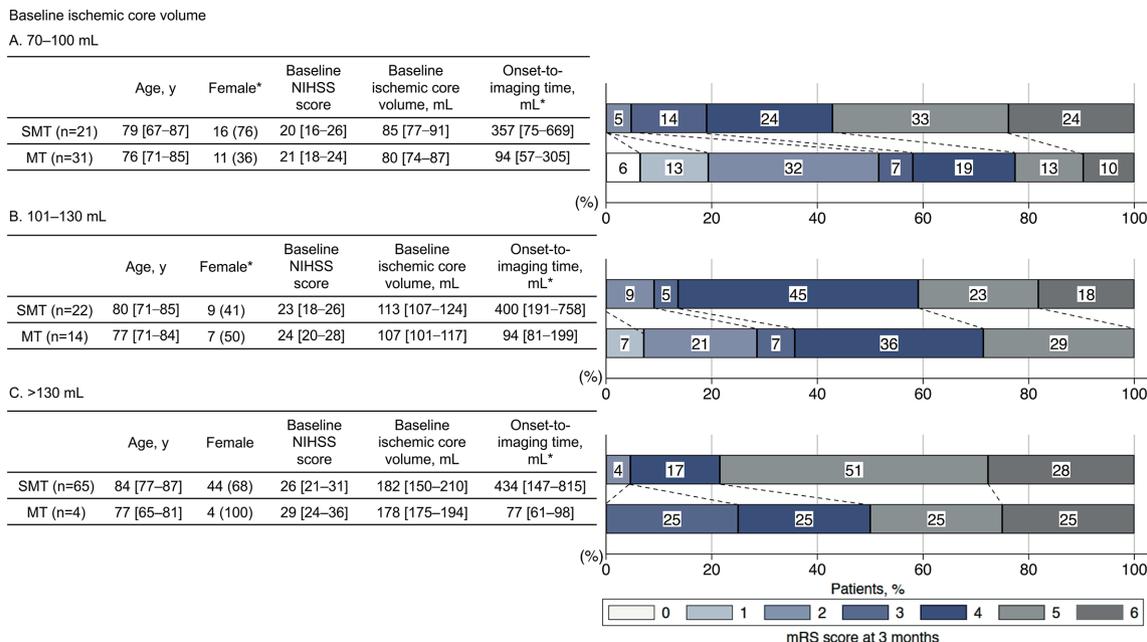


Figure 1 Stroke features and overall distributions of modified Rankin Scale at (MRS) score at 3 months between each group by baseline ischemic core volume. Data are presented as number (%) or median (IQR). Subjects were divided into three groups by baseline ischemic core volume (Group A: 70–100 mL, Group B: 101–130 mL, Group C: >130 mL), and MRS score at 3 months was compared between patients treated with MT and SMT for the three groups. MRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; SMT, standard medical treatment. *P<0.05.

RESULTS

Patients’ characteristics

The study flow chart is provided in online supplemental figure I. A total of 3531 patients were enrolled from the NCVC Stroke Registry. Data for 157 patients (86 women (54%); median age, 81 years; IQR, 71–86) were available for analysis. Median prestroke mRS score was 0 (IQR, 0–2) and median baseline NIHSS score was 21 (IQR, 14–27). Median DWI-ASPECTS was 3 (IQR, 1–5) and the median baseline ischemic core volume was 128 mL (IQR, 89–189 mL). The distribution of baseline ischemic core volumes over each baseline DWI-ASPECTS is shown in online supplemental figure II. Eighty-nine patients (57%) had ICA occlusion. Median onset-to-imaging time was 254 min (IQR, 85–650), and IVT was implemented in 22 patients (14%) and MT in 49 patients (31%). MT was performed in all patients as the first-line endovascular procedure. MT, including rescue techniques for three patients, led to successful recanalization in 41/49 patients (84%) and complete recanalization in 11 patients (22%). Patients were divided into three groups by baseline ischemic core volume (Group A (70–100 mL), n=52; Group B (101–130 mL), n=36; Group C (>130 mL), n=69). The clinical characteristics of these three groups are summarized in table 1, and the stroke features according to the treatment status are summarized in figure 1. MT and other EVT procedures data are shown in online supplemental table I.

Outcomes

Overall, good functional outcome and favorable outcome were achieved in 15% (26/157) and 18% (29/157) of the patients, respectively; PH was seen in 17% (27/157) of the patients. The overall distributions of the mRS scores at 3 months in each group are shown in figure 1.

Regarding the effectiveness outcomes, in Group A, patients who received MT showed a higher proportion of good functional outcome (mRS score 0–2 at 3 months) (16 (52%) vs 1

(5%); P<0.05; crude OR 21.3, 95% CI 1.97 to 180; adjusted OR (aOR) 55.1, 95% CI 1.92 to 1586) and favorable outcome (17 (55%) vs 1 (5%); P<0.05; crude OR 24.3, 95% CI 2.89 to 204; aOR 81.6, 95% CI 2.13 to 3131) compared with those who received SMT, respectively. In Group B, patients who received MT also tended to show a higher proportion of good functional outcome (4 (29%) vs 2 (9%); P=0.13; crude OR 4.00, 95% CI 0.62 to 25.7; aOR 5.75, 95% CI 0.22 to 151) compared with those who received SMT, respectively. In Group C, only four patients received MT.

Regarding the safety outcomes, in Group A, patients who received MT tended to show a lower proportion of PH (2 (7%) vs 5 (24%); P=0.07; crude OR 0.22, 95% CI 0.04 to 1.27; aOR 1.56, 95% CI 0.00 to 1.31) versus patients who received SMT. No statistical significance was seen for intergroup differences for the other safety outcomes between patients who received MT versus SMT for any of the three groups. Efficacy and safety outcomes for each group by baseline ischemic core volume are summarized in table 2.

Figure 2 illustrates the probability of a good functional outcome (interaction, P=0.86) and PH (interaction, P=0.08) over baseline ischemic core volumes among patients who received MT versus SMT. The 95% CIs for the probability of a good functional outcome in patients with MT and in patients with SMT intersected in the 120–130 mL core volume range (figure 2A). The probability of PH in the patients who received MT in the ischemic core volume range of 70–100 mL tended to be lower than those who received SMT, but overall, the probability of PH increased as ischemic core volume increased (figure 2B).

The absolute risk reduction between patients with MT and those with SMT for ranges of core volume was plotted as shown in online supplemental figure III.

Online supplemental figure IV shows the association between the degree of recanalization and good functional outcome, and PH in the patients who received MT. The degree of recanalization

Table 2 Efficacy and safety outcomes by baseline ischemic core volume

Group (baseline ischemic core volume)	Group A (70–100 mL)				Group B (101–130 mL)				Group C (>130 mL)			
	MT (n=31)	SMT (n=21)	Crude ORs (95% CI)	aORs* (95% CI)	MT (n=14)	SMT (n=22)	Crude ORs (95% CI)	aORs* (95% CI)	MT (n=4)	SMT (n=65)	Crude ORs (95% CI)	aORs* (95% CI)
mRS score 0–2 at 3 months	16 (52)	1 (5)	21.3 (1.97 to 180)	55.1 (1.92 to 1586)	4 (29)	2 (9)	4.00 (0.62 to 25.7)	5.75 (0.22 to 151)	1 (25)	0	--	--
mRS score 0–2 or a return to the same score as the prestroke mRS at 3 months	17 (55)	1 (5)	24.3 (2.89 to 204.2)	81.6 (2.13 to 3131)	6 (43)	4 (18)	3.38 (0.74 to 15.3)	2.16 (0.24 to 19.6)	1 (25)	0	--	--
Severe disability or death at 3 months	7 (23)	12 (57)	0.22 (0.07 to 0.73)	0.04 (0.01 to 1.82)	4 (29)	9 (41)	0.58 (0.14 to 2.43)	1.37 (0.15 to 12.2)	2 (50)	50 (77)	0.30 (0.04 to 2.31)	1.01 (0.01 to 98.6)
Death within 3 months	3 (10)	5 (24)	0.34 (0.07 to 1.63)	0.29 (0.01 to 9.38)	0	4 (18)	--	--	1 (25)	19 (29)	0.81 (0.08 to 8.26)	0.31 (0.02 to 5.94)
Parenchymal hematoma	2 (7)	5 (24)	0.22 (0.04 to 1.27)	0.02 (0.00 to 1.31)	1 (7)	4 (18)	0.35 (0.03 to 3.47)	0.18 (0.01 to 10.3)	2 (50)	13 (20)	0.44 (0.16 to 1.25)	3.57 (0.19 to 65.9)
Any ICH within 36 hours	14 (45)	6 (29)	2.06 (0.63 to 6.71)	1.56 (0.25 to 9.63)	8 (57)	10 (46)	1.60 (0.41 to 6.18)	1.95 (0.28 to 13.6)	3 (75)	25 (39)	4.80 (0.47 to 48.7)	1.17 (0.05 to 27.9)
Symptomatic ICH ECASS II criteria†	2 (7)	3 (14)	--	--	1 (7)	4 (18)	0.35 (0.03 to 3.49)	0.46 (0.03 to 7.02)	1 (25)	6 (9)	3.28 (0.29 to 48.7)	--
Symptomatic ICH SITS-MOST criteria††	0	5 (1)	--	--	0	2 (9)	--	--	1 (25)	3 (5)	6.89 (0.54 to 87.6)	0.96 (0.01 to 142)
Decompressive craniectomy	1 (3)	2 (10)	0.30 (0.03 to 3.55)	--	0	1 (5)	--	--	1 (25)	3 (5)	6.89 (0.54 to 87.6)	--

Data are presented as number (%).

* Adjusted for female sex, age, prestroke mRS score, baseline NIHSS score, baseline ischemic core volume, onset-to-imaging time, internal carotid artery occlusion, and intravenous thrombolysis.

† Any ICH with a ≥4-point increase in NIHSS score from baseline.

‡ PH2 combined with a ≥4-point increase in NIHSS score from baseline. PH2, blood clots in >30% of the infarcted area with substantial space-occupying effect.

aOR, adjusted odds ratio; CI, confidence interval; ECASS, European Cooperative Acute Stroke Study; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PH, parenchymal hematoma; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; SMT, standard medical treatment.

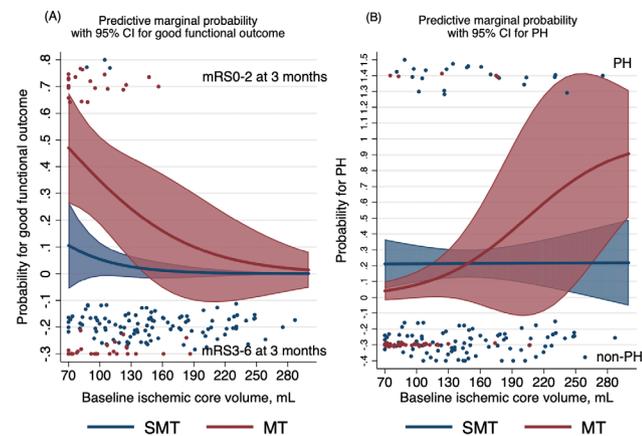


Figure 2 Probabilities of good functional outcome or parenchymal hematoma by baseline ischemic core volume predictive marginal probability of a good functional outcome (mRS 0–2 at 3 months) (A) and parenchymal hematoma (B) with 95% CIs by baseline ischemic core volume, adjusted for female sex, age, prestroke mRS score, baseline National Institutes of Health Stroke Scale score, baseline ischemic core volume, onset-to-imaging time, internal carotid artery occlusion, and intravenous thrombolysis. (A) The upper dot indicates mRS 0–2 at 3 months, while the lower dot indicates mRS 3–6 at 3 months according to baseline ischemic core volume. (B) The upper dot indicates parenchymal hematoma, while the lower dot indicates non-parenchymal hematoma according to baseline ischemic core volume. CI, confidence interval; mRS, modified Rankin Scale; MT, mechanical thrombectomy; PH, parenchymal hematoma; SMT, standard medical treatment.

correlated with good functional outcome, and 64% (7/11) and 41% (11/27) of the patients who achieved complete recanalization and successful recanalization achieved good functional outcome, respectively.

DISCUSSION

The present study demonstrated that MT provided good functional outcomes in patients with ischemic core volumes of 70–100 mL. We also found that even those patients with core volumes of 101–130 mL had the potential to achieve good functional outcomes by MT. The treatable upper DWI core limit was approximately 120 mL in the overall range of 70–300 mL.

The present study was a nonrandomized, observational study, and MT was basically selected according to the American Heart Association/American Stroke Association Guideline¹⁸ and the Japanese Guidelines for Neuroendovascular Mechanical Thrombectomy criteria (3rd edition).¹⁹ Thus, differences in background features, in particular, onset-to-imaging time, between patients receiving MT versus SMT for any group should be well understood to interpret the present results.

With core volume 101–130 mL, patients who received MT did not show a significantly higher proportion of good functional outcomes compared with those who received SMT. Even if the median onset-to-imaging time in MT patients was as short as 90 min, the baseline ischemic core volume appears to have been critical regarding cerebral ischemia. Therefore, the core inflection point for good functional outcomes might be cores of 101–130 mL. From our predictive marginal intersection figure (figure 2A), ischemic core volumes beyond 121–130 mL showed an intersection, indicating that MT and SMT had small

differences regarding achieving good functional outcomes above this volume range.

The widely used core limit of <70 mL is derived from previous IVT trials,^{6,7} but we assume that the core limit for safe recanalization and reperfusion is higher since bleeding complications, including PH, were less likely with EVT combined with IVT compared with IVT alone.

Sarraj *et al*¹⁵ reported that EVT was associated with better functional outcomes, less infarct growth, and smaller final infarct volume compared with medical treatment. Of 10 patients who underwent EVT with core volumes greater than 100 mL, none had a favorable outcome in the SELECT trial. In our study, of 14 patients who underwent EVT with core volumes greater than 100 mL, four patients had favorable outcomes. The characteristics of the four cases were M1 occlusion at a relatively young age (range, 59–71 years), and all onset-to-recanalization times were very short (<100 min). Therefore, although it was rare, we suggest that in young, extremely short onset-to-recanalization patients, patients might have incomplete cytotoxic edema unrelated to core volume measurement, and their functional outcomes may be preserved after complete reperfusion. The analysis of HERMES Collaborations also suggested the benefit, possibly core around 150 mL based on 95% CIs for utility-weighted mRS at 90 days and mRS score 0–2 at 3 months, and younger patients treated rapidly had the most benefit.²⁵ Moreover, in the present study, no statistical significance was seen for symptomatic ICH between patients with MT and SMT. In the meta-analysis, EVT for large core stroke was associated with improved functional independence at 90 days (25% vs 7%, $P < 0.01$) without significant increase in symptomatic ICH (9% vs 5%, $P = 0.09$).²⁶

Although randomized controlled trials (RCTs) such as the TENSION trial (an efficacy and safety of thrombectomy in stroke with extended lesion and extended time window trial; ClinicalTrials.gov Identifier: NCT03094715) and the RESCUE-Japan LIMIT trial (an RCT evaluating endovascular therapy for acute large vessel occlusion with large ischemic core; NCT03702413) are ongoing to clarify the efficacy of EVT with large cores and low ASPECTS, we urge caution regarding using ASPECT scoring for large cores. Although automated core values may represent under- or overestimations compared with visual impressions, our data suggest that the wide median volumetric ranges indicate discrepancies with low ASPECTS scores (online supplemental figure II; range, 70–226 mL in patients with ASPECTS 3–5). Therefore, we suggest selecting large-core patients by volumetric range.

One of the strengths of the present study was that MRI was chosen as the initial imaging modality for all patients. Prior studies have suggested that DWI measurement can detect more patients who are more likely to achieve better outcomes,^{25,27} and the reference standard for delineating the infarct core is suggested to be DWI rather than CT.²⁷ All patients in our study showed significant acceptable but critical LIC volumes, which were evaluated by DWI to more accurately reflect core volume.

This study has several limitations. While our study was a prospective study, the retrospective nature of the analyses was associated with inherent limitations. Another major limitation was the lack of randomization into EVT versus SMT, which likely resulted in selection bias. In particular, patients who received SMT presented for evaluation later than the patients who received EVT, and the SMT patients had longer onset-to-imaging time. Although the multivariate model was conducted to confirm the robustness of the present results, the selection bias between patients with MT and those with SMT was judged to be quite large, and care was required in interpreting ORs. The other

limitation related to selection bias was that patients with more substantial medical comorbidities were less likely to undergo EVT, although it was challenging to adjust this factor since the treatment bias was withdrawn from each operator. Several studies reported the efficacy of MT for large cores according to low ASPECTS scores,^{28 29} however, few studies have measured cores quantitatively. The number of patients treated with ischemic core size >100 mL was rather small in our cohort. Additionally, since only four patients received MT at baseline as a “very large core”, the effectiveness and safety of MT could not be analyzed with this small number. There are many unmeasured cofounders including infarct growth and growth velocity³⁰ in our practical study and we were unable to investigate these “very large core” populations statistically. Finally, the lack of follow-up for time points longer than 3 months is a further limitation.

In conclusion, ischemic cores of 70–100 mL appear to represent a promising target for MT. Patients with cores of 101–130 mL with good physical status appear to have a chance of achieving functional outcomes after MT, and within the range, the treatable upper core limit appears to be approximately 120 mL. Therefore, MT could be considered in some LIC patients.

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ORCID iDs

Takeshi Yoshimoto <http://orcid.org/0000-0003-3178-8171>

Kanta Tanaka <http://orcid.org/0000-0002-3291-5083>

Tetsu Satow <http://orcid.org/0000-0001-8136-5420>

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SUPPLEMENTAL MATERIAL**Identifying large ischemic core volume ranges in acute stroke that can benefit from mechanical thrombectomy**

Supplemental Figure I Study flow chart (Page 2)

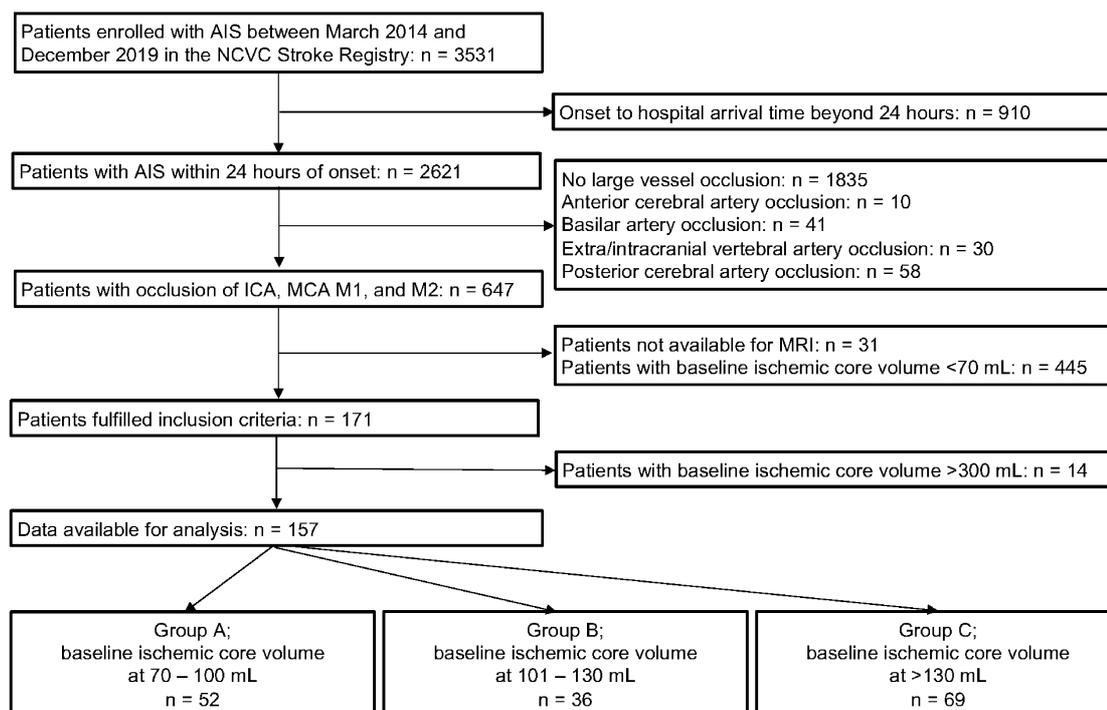
Supplemental Figure II Distribution of baseline ischemic core volume over each baseline DWI-ASPECTS (Page 3)

Supplemental Table I Endovascular therapy procedure between groups by ischemic core volume in patients receiving endovascular therapy (Page 4–5)

Supplemental Figure III Treatment effect of mechanical thrombectomy versus standard medical treatment (Page 6)

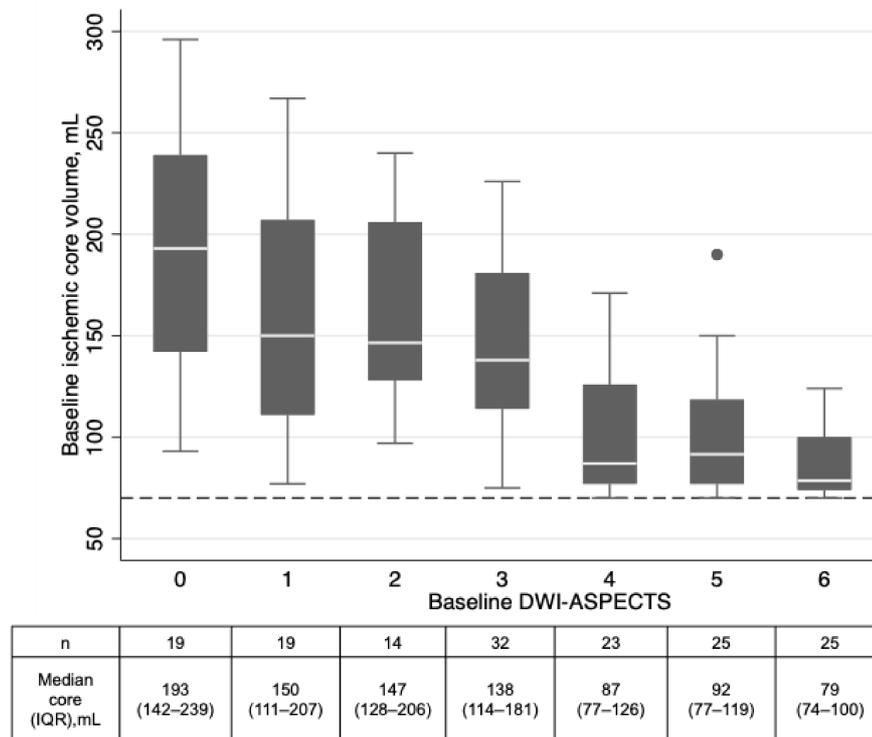
Supplemental Figure IV Associations between degree of recanalization and either mRS score 0–2 at 3 months or parenchymal hematoma in patients who received MT (Page 7)

Supplemental Figure I Study flow chart



Abbreviations: AIS, acute ischemic stroke; ICA, internal carotid artery; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NCVC, National Cerebral and Cardiovascular Center.

Supplemental Figure II Distribution of baseline ischemic core volume over each baseline DWI-ASPECTS



Boxes indicate interquartile range; whiskers, extreme values; horizontal lines in each box, median; horizontal dotted line, 70 mL; round dots, outliers.

Abbreviations: DWI-ASPECTS, Diffusion-Weighted Imaging–Alberta Stroke Program Early Computed Tomography Score

Supplemental Table I Endovascular therapy procedure between groups by ischemic core volume in patients receiving endovascular therapy

Group (baseline ischemic core volume)	Group A (70–100 mL)	Group B (101–130 mL)	Group C (>130 mL)
	(n=31)	(n=14)	(n=4)
First-line mechanical thrombectomy	31 (100)	14 (100)	4 (100)
Simple stent retriever	3 (10)	3 (22)	4 (100)
Aspiration	7 (22)	4 (28)	0
Combination of stent retriever and aspiration catheter*	21 (68)	7 (50)	0
First-line mechanical thrombectomy devices**			
Solitaire stent retriever	15 (48)	8 (57)	4 (100)
Trevo stent retriever	9 (29)	6 (43)	0
EmboTrap revascularization device	1 (3)	0	0
Tron stent retriever	2 (7)	0	0
Penumbra aspiration catheter***	28 (90)	11 (79)	0
Rescue technique			
Carotid artery stenting	2 (7)	0	0
Balloon angioplasty and/or stenting	1 (3)	0	0
Time logistics****, min			
Onset-to-groin puncture time	139 [103–325]	135 [116–224]	86 [73–121]
Onset-to-recanalization time	234 [160–424]	213 [201–373]	154 [117–198]
Groin puncture-to-recanalization time	86 [42–122]	56 [66–97]	40 [33–58]
Number of passes	1 [1–3]	2 [1–2]	1 [1–2]
Successful recanalization*****	26 (84)	11 (79)	4 (100)
Complete recanalization	7 (23)	3 (21)	1 (25)

Data are presented as number (%) or median [interquartile range].

*Combination of stent retriever and aspiration catheter included embolectomy techniques, such as continuous aspiration prior to intracranial vascular embolectomy and blind exchange with mini-pinning technique.

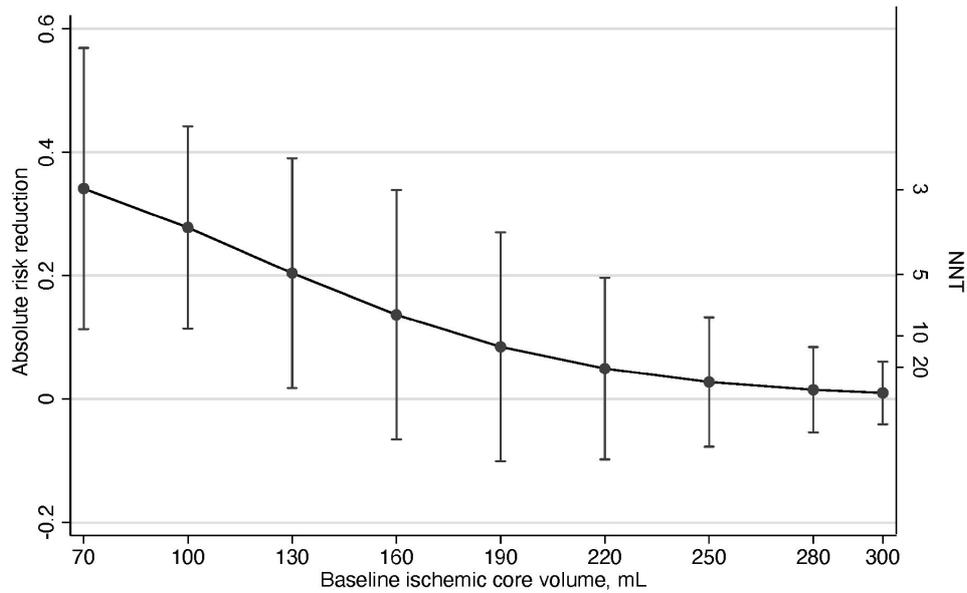
**First-line mechanical thrombectomy devices were the Solitaire stent retriever (ev3, Irvine, CA, USA), Trevo stent retriever (Stryker, Kalamazoo, MI, USA), EmboTrap revascularization device (Cerenovus, Galway, Ireland), Tron stent retriever (Terumo, Tokyo, Japan), and Penumbra aspiration catheter (Penumbra, Alameda, CA, USA).

***Patients receiving a Penumbra aspiration catheter as a distal access catheter were included.

****Time of onset was defined as either the time point at which the symptom appeared or the “last-known-well” date, if time of symptom onset was unknown. Time of recanalization was defined as the time point of confirmed successful reperfusion or when the procedure was terminated with no reperfusion.

*****Successful recanalization was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) scale of 2b or 3, and complete recanalization was defined as an mTICI score of 3.

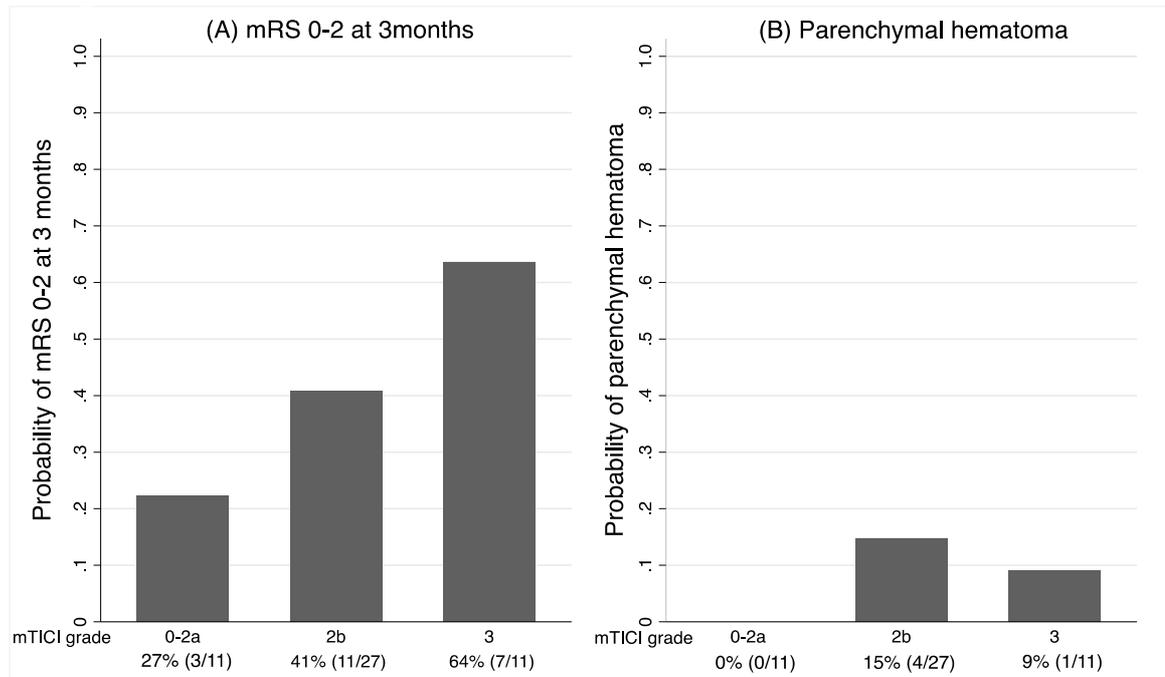
Supplemental Figure III Treatment effect of mechanical thrombectomy versus standard medical treatment



Models adjusted for sex, age, prestroke mRS score, baseline National Institutes of Health Stroke Scale score, baseline ischemic core volume, onset-to-imaging time, internal carotid artery occlusion, and intravenous thrombolysis.

Abbreviations: mRS, modified Rankin Scale; NNT, number needed to treat.

Supplemental Figure IV Associations between degree of recanalization and either mRS score 0–2 at 3 months or parenchymal hematoma in patients who received MT



Abbreviations: mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; MT, mechanical thrombectomy.