ISCHEMIC STROKE MANAGEMENT: FROM SYMPTOM ONSET TO SUCCESSFUL REPERFUSION AND BEYOND

EDITED BY: Peter Sporns, Johanna Ospel and Marios Psychogios
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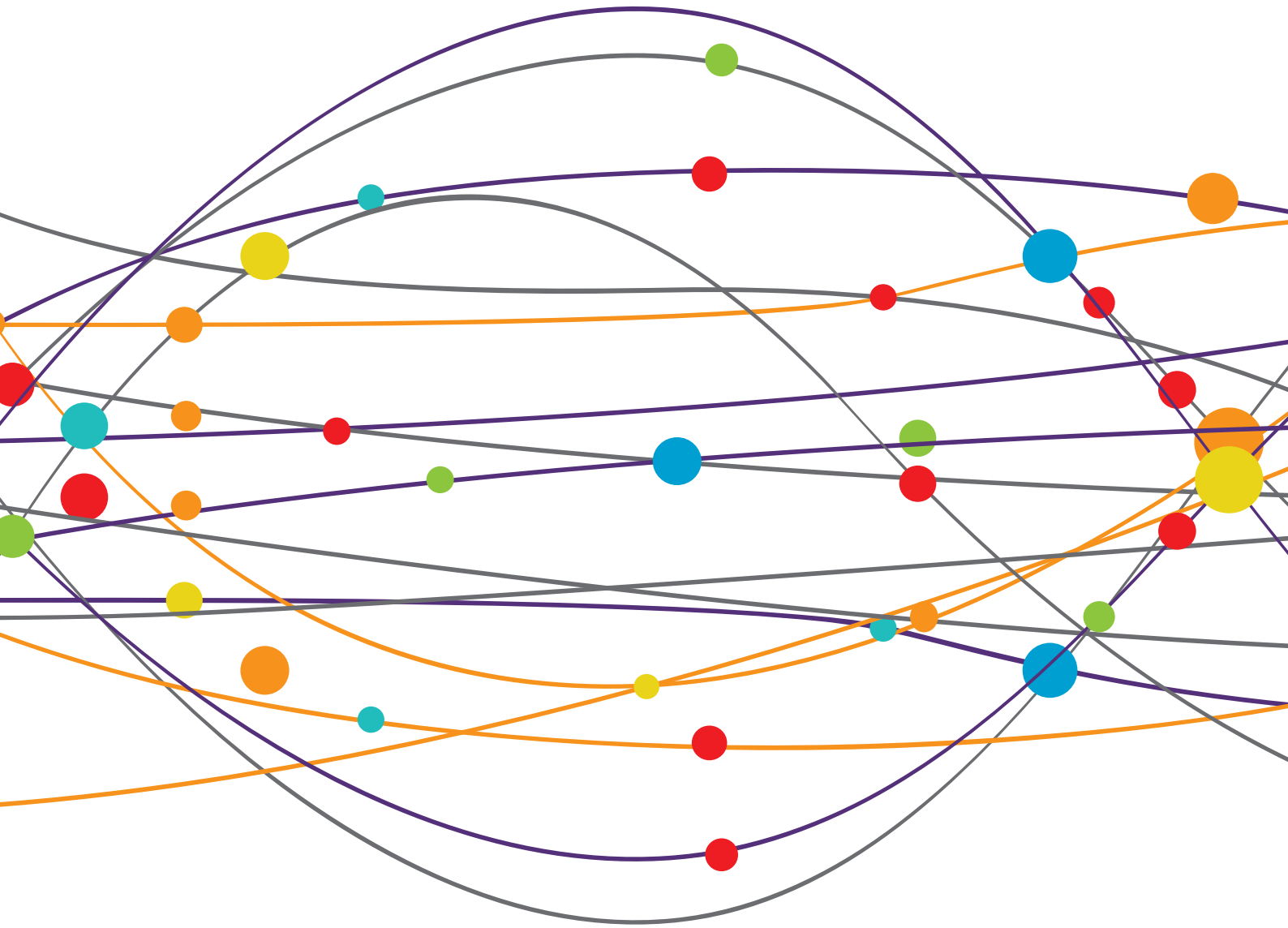

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ISCHEMIC STROKE MANAGEMENT: FROM SYMPTOM ONSET TO SUCCESSFUL REPERFUSION AND BEYOND

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Editorial: Ischemic stroke management: From symptom onset to successful reperfusion and beyond

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KEYWORDS

stroke, thrombectomy, endovascular thrombectomy (EVT), imaging, reperfusion

Editorial on the Research Topic
Ischemic stroke management: From symptom onset to successful reperfusion and beyond

Introduction

Fast and complete reperfusion of the occluded vessel territory is the key to every revascularization therapy in stroke patients, no matter if treated with alteplase or endovascular thrombectomy (EVT) (1–4). However, there is room for substantial improvement in time efficiency and techniques to achieve reperfusion [(3, 5), Advani]. This introduction of the Research Topic "Ischemic Stroke Management: From Symptom Onset to Successful Reperfusion and Beyond" left room for a wide variety of topics for articles, which is reflected by a large number of high-quality articles published in this Research Topic (59). The predefined areas of interest included—but were not limited to—the one-stop management of ischemic stroke patients in the angio-suite, novel methods of pre-hospital patient triage, new procedural techniques and software solutions for effective patient triage, clinical consequences of improved time metrics and prediction of functional outcomes following hyperacute reperfusion therapies. The aim of the Research Topic was to investigate the impact of logistical and procedural improvements on the success of reperfusion and the clinical outcome of ischemic stroke patients.

Looking at the studies published in this Research Topic and starting with pre-hospital triage optimization Cabal et al. report that their new prehospital triage test (FAST PLUS) yielded significant reductions of onset-to-groin times in patients receiving EVT, meaning that median onset-to-groin times reduced from 213 to 142 min in their cohort from the Czech Republic. Weissenborn et al. analyzed workflow and outcome metrics of stroke patients undergoing EVT in their German tertiary stroke center as a starting point for optimization. In their analysis, they found several factors leading to a delay in treatment

(i.e., medical treatment of a hypertensive crisis, epileptic fits, vomiting, or agitation, repeated brain imaging, and transfer from other hospitals). Hence, they concluded that analyses of workflow and treatment results should be carried out regularly to identify the potential for optimization of operational procedures and selection criteria for patients who could benefit from EVT (Weissenborn et al.).

At least as important as prehospital triage and procedural optimization are the technical results of the thrombectomy procedure itself (5, 6). Thus, various articles in this Research Topic investigated technical and procedural developments. In their retrospective study, Guenego et al. described the impact of clot shape on successful middle cerebral artery M1-segment endovascular reperfusion and found that clot shape as determined on T2* imaging, appears to be a predictor of successful reperfusion after EVT because angulated and bifurcating clots were associated with poorer rates of successful reperfusion. Moreover, Candel et al. found that the size of stent retriever matters in acute M1 occlusions treated with aspiration-assisted mechanical thrombectomy. A longer stent retriever with a larger nominal diameter achieved a higher complete and successful first pass effect and higher successful reperfusion compared to a shorter stent retriever (Candel et al.). Another analysis by Etter et al. found that application of a new coating to the delivery wire of the Trevo retriever, with the new device being called the "Trevo NXT" stent retriever, was an effective and safe tool for EVT that could be more easily deployed and was especially effective when used for combined approaches. When looking at the definition for successful recanalization of the thrombectomy procedure, Yoo et al. reported that in their international multicenter trial, first-pass excellent reperfusion (defined as TICI 2c-3), was the technical revascularization endpoint that best predicted functional independence and concluded that this should be an angiographic endpoint for future trials, further consolidating prior evidence from published studies.

Previous studies have shown that histological thrombus composition impacts procedural and technical outcomes of EVT, that thrombus composition is associated with stroke etiology and that the thrombus composition itself can be predicted from admission imaging (7–11). In this issue, Eto et al. report that atherosclerotic components in retrieved thrombi might provide useful clues for diagnosing stroke pathogenesis. Their investigation of the association between onset-to-imaging time and radiological thrombus characteristics suggested that elapsed time from stroke onset plays a limited role in the interpretation of radiological thrombus characteristics and their effect on treatment results and should therefore not confound imaging-based thrombus analysis, at least in the early time window (Tolhuisen et al.). Regarding the visualization of thrombus content, LaGarange et al. reported that MicroCT can be used as an indicator for red blood cells-rich composition of clots, and a combination of MicroCT and electron microscopy revealed further valuable information with regard to clot composition.

Regarding the ongoing debate of intravenous thrombolysis plus EVT vs. EVT alone, Maier et al. report that in patients included in the German Stroke Registry, bridging IVT improved rates of successful reperfusion and long-term functional outcome in mothership patients with anterior circulation large vessel occlusion, which is in line with the results of the recently published SWIFT DIRECT trial. This was further confirmed by a meta-analysis concluding that bridging thrombolysis provides more benefits than EVT alone in terms of clinical functional outcomes without compromising safety in AIS patients with LVOs (Li et al.).

Furthermore, several studies in this article collection further investigated indication criteria in special populations, which were not represented by randomized trials. For example, Kastrup et al. reported that in dependent patients, EVT led to less patients with poor outcomes and smaller infarcts compared to intravenous thrombolysis alone.

Discussion and future challenges

The collection of articles in this Research Topic contributes to the continuous evolvement of further defining patient subgroups that will benefit from hyperacute reperfusion therapies. As an example, there are three currently ongoing randomized controlled trials investigating the benefit of EVT in patients with medium vessel occlusions (DISTAL, NCT05029414, ESCAPE-MeVO, NCT05151172, and DISCOUNT, NCT05030142). Defining imaging and clinical characteristics to identify potential EVT candidates within this patient subgroup will help to treat as many stroke patients as possible with the game-changing endovascular thrombectomy but, on the other hand, also help to prevent harming patients, who are very unlikely to benefit. Further logistic and procedural improvements will pave the way toward treating patients even more effectively and in the end find the optimal and fastest therapy for individual stroke patients.

Author contributions

All authors drafted and revised this editorial. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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ORIGINAL RESEARCH
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Impact of Clot Shape on Successful M1 Endovascular Reperfusion

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Objectives: The susceptibility-vessel-sign (SVS) allows thrombus visualization, length estimation and composition, and it may impact reperfusion during mechanical thrombectomy (MT). SVS can also describe thrombus shape in the occluded artery: in the straight M1-segment (S-shaped), or in an angulated/traversing a bifurcation segment (A-shaped). We determined whether SVS clot shape influenced reperfusion and outcomes after MT for proximal middle-cerebral-artery (M1) occlusions.

Methods: Between May 2015 and March 2018, consecutive patients who underwent MT at one comprehensive stroke center and who had a baseline MRI with a T2* sequence were included. Clinical, procedural and radiographic data, including clot shape on SVS [angulated/bifurcation (A-SVS) vs. straight (S-SVS)] and length were assessed. Primary outcome was successful reperfusion (TICI 2b-3). Secondary outcome were MT complication rates, MT reperfusion time, and clinical outcome at 90-days. Predictors of outcome were assessed with univariate and multivariate analyses.

Results: A total of 62 patients were included. 56% (35/62) had an A-SVS. Clots were significantly longer in the A-SVS group (19 mm vs. 8 mm $p = 0.0002$). Groups were otherwise well-matched with regard to baseline characteristics. There was a significantly lower rate of successful reperfusion in the A-SVS cohort (83%) compared to the S-SVS cohort (96%) in multivariable analysis [OR 0.04 (95% CI, 0.002–0.58), $p = 0.02$]. There was no significant difference in long term clinical outcome between groups.

Conclusion: Clot shape as determined on T2* imaging, in patients presenting with M1 occlusion appears to be a predictor of successful reperfusion after MT. Angulated and bifurcating clots are associated with poorer rates of successful reperfusion.

Keywords: stroke, thrombectomy, endovascular recanalization, magnetic resonance imaging, clot

STATISTICAL ANALYSIS

Adrien Guenego, MD and Matthew Leipzig, BS conducted all the statistical analyses.

INTRODUCTION

Mechanical thrombectomy (MT) is an effective treatment for acute ischemic stroke patients (AIS due to large vessel occlusion (LVO). Rapid and successful reperfusion, defined as thrombolysis in cerebral infarction (TICI) 2b-3, increases the likelihood of a favorable outcome (1, 2). Nevertheless, MT does not result in successful reperfusion in up to 29% of patients (1), and biomarkers that identify patients at risk of failed reperfusion failure are needed.

Clot composition, length, and shape may impact MT success, and imaging predictors of clot response to MT may lead to tailored MT techniques, such as stent-retriever or contact-aspiration, to maximize the likelihood of successful treatment (3, 4). Magnetic resonance imaging (MRI) often demonstrates the thrombus on T2* gradient-echo sequence (GRE) as a region of intravascular hypointense signal abnormality, which is termed the susceptibility vessel sign (SVS). SVS has been used as a measure of clot length to predict response to intravenous thrombolysis (5), to detect small distal occlusions (6), to assess multiplicity of intracranial thrombus fragments (7), and even predict clot composition or stroke etiology (8–13). However, whether SVS depiction of clot shape and extension into vessel branches impacts the likelihood of successful reperfusion has not been investigated. Thrombus that involves a bifurcation or accentuated angle may be more prone to fragmentation and may be more difficult to remove (14).

We hypothesized that SVS may be used to visualize the extent of the clot within the middle cerebral artery branches at the point of vessel occlusion and to determine whether the clot is located in a straight branch (S-SVS) or in an angulated/traversing a bifurcation segment (A-SVS). We determined SVS clot shape, branch occlusion patterns, and the impact of these factors on successful reperfusion and favorable clinical outcomes after thrombectomy for proximal middle cerebral artery occlusions.

METHODS

The study protocol was approved by the institutional review board (IRB) and complied with the Health Insurance Portability and Accountability Act (HIPAA). Patient informed consent was waived by our review board for this single center retrospective analysis of anonymized data acquired prospectively. Adherence to the STROBE criteria (15) was enforced.

Population and Clinical Data

We performed a retrospective cohort study of consecutive patients who underwent MT treatment for acute ischemic stroke at our comprehensive stroke center between May 2015 and March 2018. Patient inclusion criteria were: (1) pre-MT brain magnetic resonance imaging (MRI) that included an axial T2* sequence [gradient-echo (GRE)], diffusion-weighted imaging (DWI) and perfusion weighted-imaging (PWI) that was free of motion degradation or significant artifact, and (2) middle cerebral artery occlusion (M1 or both M1 and M2). Basilar and internal carotid occlusions were excluded to obtain homogeneous groups and avoid the impact of posterior circulation strokes on the overall outcome.

Clinical and stroke treatment data were determined from a prospectively maintained stroke database and from the electronic medical records. Stroke severity was assessed by the National Institute of Health Stroke Scale (NIHSS) at the time of MT triage. All thrombectomies were performed according to the standard departmental protocols under general anesthesia, using combined stent-retriever (diameter of 6 mm) and contact aspiration with a 6F intermediate catheter, balloon-guided catheters were not used at that time, there were five different attendings.

Imaging Data and Analysis

All imaging was performed on either a 1.5T GE Signa or 3.0T GE MR750 MRI scanner using standard departmental protocols and approach, using an 8 channel GE HR brain coil (GE Healthcare, Milwaukee, Wisconsin). T2* gradient-echo axial sequences were performed as: TR 650.0 ms, TE 15.0 ms, slice was 5 mm, slice gap of 0.0 mm, FOV of 24.0 × 24.0 cm.

SVS was assessed on GRE sequences and was defined as "presence of a hypointensity within the proximal middle cerebral artery, in which the diameter of the hypointense signal within the vessel exceeded the contralateral vessel diameter" (16). SVS length was measured in millimeters. A-SVS was defined as SVS that involved an angulated M1–M2 segment or in a MCA bifurcation. Clots entirely within a straight M1-segment and without any significant extension into an angulated M2 branch were defined as S-SVS (**Figure 1**). Patients without SVS were excluded as we couldn't evaluate the clot shape.

MR perfusion-weighted imaging (PWI) data were processed by an automated program (RAPID, iSchemaView, Menlo Park, CA). The ischemic core was defined as the volume of tissue with an apparent diffusion coefficient <620 s/mm^2. The penumbra was defined as the volume of tissue with a Time-to-maximum (TMax) delay of >6 s. Mismatch volume (17) was assessed as the difference between the ischemic core and the penumbra, and the mismatch ratio (18) was calculated as the ratio between the TMax >6 s lesion volume and the core volume. The hypoperfusion intensity ratio (HIR) was used as a measure of tissue collaterals and was calculated as the volumetric ratio of tissue with a TMax >10 s divided by TMax >6 s (18, 19).

Abbreviations: AIS, Acute Ischemic Stroke; A-SVS/S-SVS, patients with an angulated or bifurcation-shaped (A-shaped) Susceptibility Vessel Sign/patients with a straight (S-shaped) Susceptibility Vessel Sign; M1, Proximal Middle Cerebral Artery; mRS, modified Rankin Scale; MT, Mechanical Thrombectomy; NIHSS, National Institute of Health Stroke Scale; POD1, Post-Operative Day 1 post-MT; SVS, Susceptibility Vessel Sign; TICI, Thrombolysis In Cerebral Infarction; TMax, Time to Maximum (sec); CT, Computed Tomography; HIR, Hypoperfusion Intensity Ratio; ICA, Internal Carotid Artery; ICA T, Internal Carotid Artery Termination; IQR, Inter-Quartile Range; LVO, Large Vessel Occlusion; MCA-M1, Proximal Middle Cerebral Artery; MRI, Magnetic Resonance Imaging; tPA, thrombolysis Plasminogen Activator.

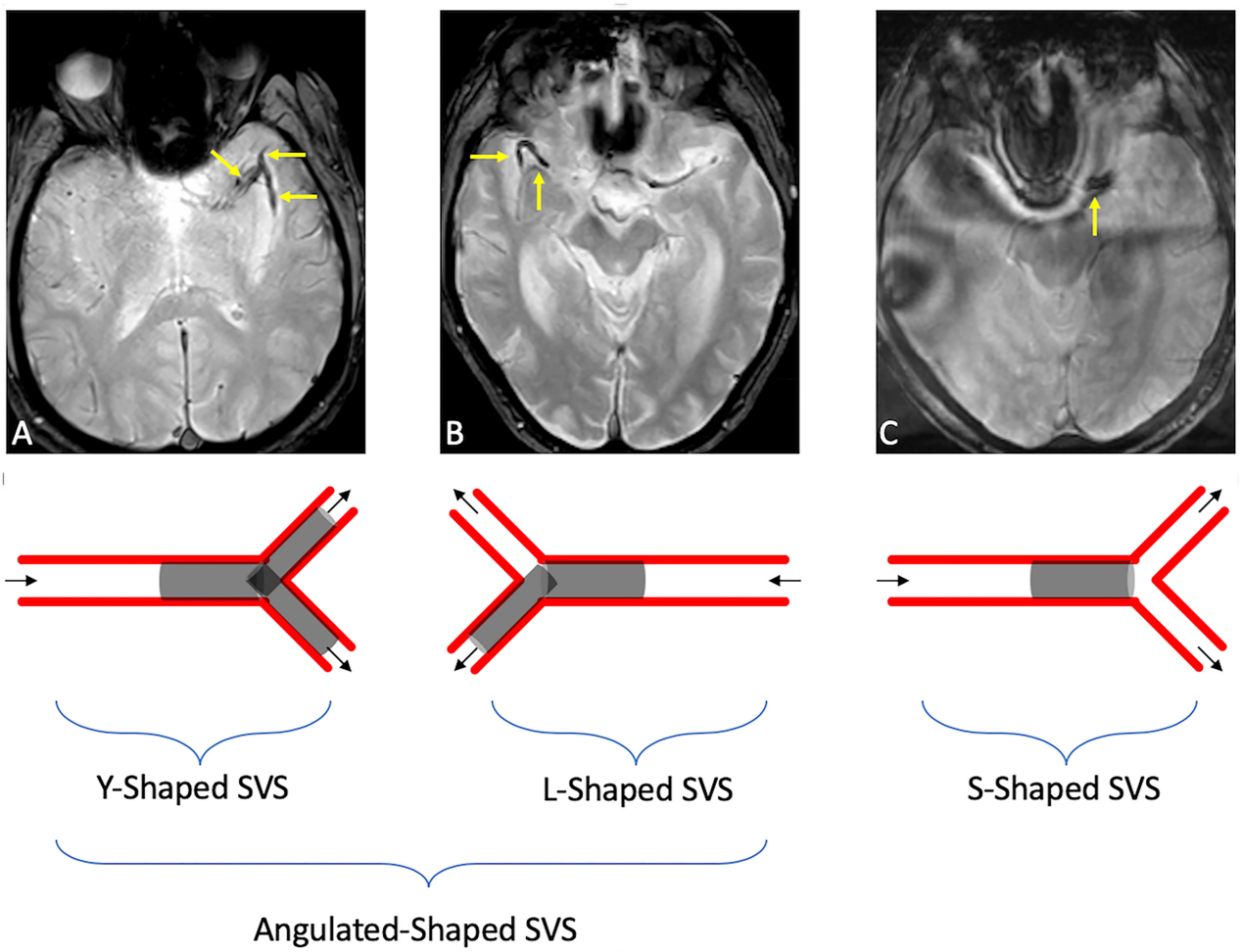

FIGURE 1 | Illustrations of SVS shape in an angulated (A-shaped) branch [either in an MCA bifurcation [a], or an angulated M1–M2 [b]] or in a straight [S-shaped [c]] branch. **(A)** Susceptibility vessel sign in a M1 segment seen as a linear hypo-intensity branch, dividing into two clots within the M2 middle cerebral artery branches. **(B)** Susceptibility vessel sign in a M1 segment seen as a horizontal hypo-intensity in the M1 branch, continuing with a 90° angle in the M1/M2 branch. **(C)** Susceptibility vessel sign in a M1 segment seen as a linear/straight hypo-intensity in the M1 branch (I).

All images were anonymized and blindly analyzed by two neurointerventionalists (A.G. and E.S.S. with 5 and 6 years of experience, respectively). Thrombus length was evaluated from measurements between the proximal and distal extent of the SVS on T2* MR sequences, when the thrombus extended into different branches of the middle cerebral artery, the maximal thrombus length as it extended into one branch vessel was calculated rather than summation of length within all of the involved branches.

Interpretation disagreements were resolved by consensus reading, which was supervised by a third neurointerventionalist (J.J.H. with 10 years of experience).

Outcomes Measures

Primary outcome was the difference in rate of successful reperfusion (defined as TICI ≥2b) after MT.

Secondary outcomes were MT complication rates, MT reperfusion time (minutes), and clinical outcomes. Early clinical outcomes were assessed using NIHSS on day 1 post-MT (POD1), NIHSS shift between baseline and POD1, and discharge NIHSS. Long term clinical outcomes were assessed using the modified Rankin Scale (mRS) 90-days after MT; excellent clinical outcome was defined as mRS 0–1, good clinical outcome was defined as mRS 0–2, and poor outcome was defined as mRS 3–6.

Recorded MT complications included emboli to a new vascular territory, arterial perforation, or symptomatic hemorrhage, which was defined as a parenchymal hematoma (PH1 or PH2) with associated worsening from the baseline NIHSS of at least four points.

Statistical Analysis

Nominal variables were first summarized using frequency descriptive analysis then compared using Fisher's exact test.

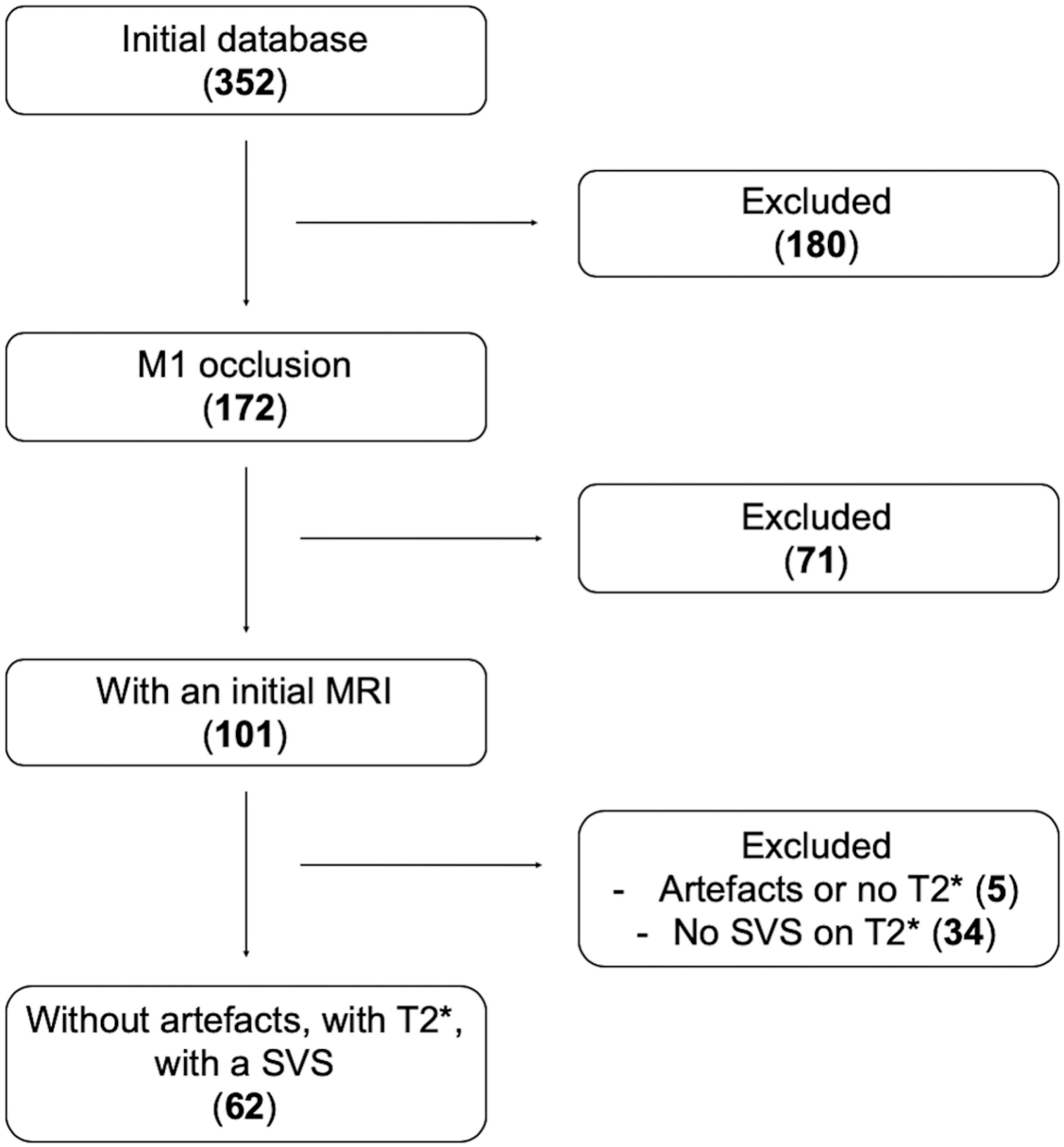

FIGURE 2 | Flow-chart. Number of patients screened then included according to our inclusion criteria: Initial database 352 patients; among them 172 had a proximal MCA (M1) occlusion; 101 of them were screened by MRI, and 71 were screened by CT scan and excluded; 62 patients had A SVS on their GRE imaging.

Continuous variables were summarized using median, quartiles and interquartile range, then tested on univariate analysis using the Mann-Whitney test. Normality of the variables was tested by the Shapiro-Wilk test. Statistical significance was set at the $p = 0.05$ level.

Logistic regression models were designed to assess the association of SVS clot-shape with successful reperfusion (TICI $\geq$2b). To adjust for baseline and MT potential confounders, a multivariate binary logistic regression analysis was conducted.

Factors with a significant association ($P < 0.10$) in the univariate analysis (clot length) were included in the multivariable model and factors associated with patient's outcome in the literature were forced into. Results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs) using S-SVS as reference group.

Other logistic regression models were subsequently designed to assess the association of SVS clot-shape with favorable clinical outcome (mRS 0–2), excellent clinical outcome (mRS 0–1), and mortality (mRS 6).

Initial agreement between the two interventional neuroradiologists was measured using Kappa of Cohen, then disagreements were resolved by consensus reading.

TABLE 1 | Baseline characteristics for patients with an A-shaped SVS compared to those with an S-shaped SVS (S-SVS).

	All	S-SVS	A-SVS	*p*-value
Number of patients	62/62 (100%)	27/62 (44%)	35/62 (56%)	
Age, years (median, IQR)	70 (57–77)	72 (63–79)	67 (55–76)	0.960
Female (%)	33 (53%)	14 (52%)	19 (54%)	1.000
Medical history				
Hypertension (%)	44 (71%)	18 (67%)	26 (74%)	0.51
Diabetes (%)	16 (26%)	8 (30%)	8 (23%)	0.41
Hyperlipidemia	30 (48%)	11 (41%)	19 (54%)	0.33
Atrial fibrillation (%)	31 (50%)	15 (56%)	16 (46%)	0.34
Coronary artery disease (%)	13 (21%)	6 (22%)	7 (20%)	0.49
Prior stroke (%)	8 (13%)	3 (11%)	5 (14%)	0.71
Platelets	195 (163–228)	207 (171–240)	179 (161–212)	0.15
Smoking				0.16
Never (%)	35 (57%)	17 (63%)	18 (51%)	
Prior (%)	19 (31%)	9 (33%)	10 (29%)	
Current (%)	8 (13%)	1 (4%)	7 (20%)	
Stroke details				
Baseline NIHSS (median, IQR)	16 (12–21)	14 (10–20)	17 (13–22)	0.12
Drugs and medications				
Antiplatelet or anticoagulant	28 (45%)	15 (56%)	13 (36%)	0.15
Intravenous tPA (%)	40 (65%)	18 (67%)	22 (63%)	0.48

TABLE 2 | Imaging characteristics for patients with an A-shaped SVS compared to those with an S-shaped SVS.

	All	S-SVS	A-SVS	*p*-value
Number of patients (%)	62/62 (100%)	27/62 (44%)	35/62 (56%)	
MRI characteristics				
Core volume, ml (median, IQR)	15 (6–34)	11 (5–38)	15 (7–31)	0.66
Penumbra TMax >6 s volume, ml (median, IQR)	101 (66–127)	97 (66–117)	104 (68–132)	0.59
Penumbra TMax >10 s volume, ml (median, IQR)	32 (18–54)	28 (15–44)	32 (22–70)	0.38
Mismatch Volume, ml (median, IQR)	71 (51–102)	71 (55–93)	75 (51–107)	0.73
Mismatch ratio (median, IQR)	6 (3–16)	7 (3–17)	5 (3–15)	0.89
HIR (median, IQR)	0.37 (0.23–0.48)	0.32 (0.21–0.42)	0.39 (0.26–0.52)	0.26
Clot length, mm, (median, IQR)	15 (10–20)	8 (10–15)	19 (15–24)	0.0002
Vessel occlusion side				
Left (%)	38 (61%)	19 (71%)	19 (54%)	0.19

All statistical analyses were performed with XLSTAT (Addinsoft, New York City, NY).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Sixty-two patients met inclusion criteria (**Figure 2**). Patients were dichotomized into S-SVS (27 patients; 44%) and A-SVS (35 patients; 56%) groups; reader agreement of SVS classification was substantial (Cohen's Kappa 0.711) (20).

There were no differences between S-SVS and A-SVS with respect to patient age [72 (IQR, 63–79) vs. 67 (IQR, 55–76), $p = 0.960$], female sex (52 vs. 54%, $p = 1.000$), baseline NIHSS [14 (IQR, 10–20) vs. 17 (IQR, 13–22), $p = 0.12$], or frequency of left sided occlusions (71 vs. 54%, $p = 0.19$), respectively (**Table 1**). A-SVS clots were significantly longer compared to S-SVS clots [19 mm (IQR, 15–24) vs. 8 mm (IQR, 10–15), $p = 0.0002$] (**Table 2**). There were no other significant differences between the two groups with regard to neuroimaging variables, which included core infarction volume, penumbra volume, and HIR collateral robustness (**Table 2**). Likewise, MT procedural outcomes were similar between S-SVS and A-SVS groups (**Table 3**). There were no differences in time from groin puncture to reperfusion [36 min (IQR, 25–62) vs. 44 min (IQR, 23–77), $p = 0.70$] or MT complication rates (4 vs. 11%, $p = 0.27$).

All other univariate analysis are described in **Table 3**.

TABLE 3 | Outcomes for patients with an A-shaped SVS compared to those with an S-shaped SVS.

	All	S-SVS	A-SVS	*p*-value
Number of patients (%)	62/62 (100%)	27/62 (44%)	35/62 (56%)	
MT				
TICI 2b/2c/3 (%)	55 (89%)	26 (96%)	29 (83%)	0.09
TICI 2c/3 (%)	31 (50%)	16 (59%)	15 (43%)	0.20
TICI 0 (%)	0 (0%)	0 (0%)	0 (0%)	1
TICI 1 (%)	1 (2%)	0 (0%)	1 (3%)	0.38
TICI 2a (%)	6 (10%)	1 (4%)	5 (14%)	0.16
TICI 2b (%)	24 (39%)	10 (37%)	14 (40%)	0.81
TICI 2c (%)	13 (21%)	7 (26%)	6 (17%)	0.40
TICI 3 (%)	18 (29%)	9 (33%)	9 (26%)	0.51
Complications (%)	5 (8%)	1 (4%)	4 (11%)	0.27
Groin/reperfusion time (min)	40 (24–71)	36 (25–62)	44 (23–77)	0.70
Onset/reperfusion time (min)	419 (306–519)	418 (249–545)	420 (312–484)	0.71
Early clinical outcome				
24 h NIHSS (median, IQR)	10 (5–16)	5 (2–15)	11 (7–18)	0.03
NIHSS SHIFT (median, IQR)	−7 (−11 to −1)	−6 (−10 to −2)	−7 (−11 to 0)	0.67
Discharge NIHSS (median, IQR)	5 (2–13)	3 (2–9)	8 (3–18)	0.004
Long-term clinical outcome (55/62)				
3 months good mRS (0–1–2) (%)	28/55 (51%)	14/25 (56%)	14/30 (47%)	0.49
3 months excellent mRS (0–1) (%)	18/55 (33%)	11/25 (44%)	7/30 (23%)	0.10
3 months mortality (%)	13/55 (23%)	5/25 (20%)	8/30 (26%)	0.56

TABLE 4 | Multivariate analysis.

	S-SVS ($n = 27$)	A-SVS ($n = 35$)	Unadjusted OR (95% CI)	Unadjusted *p*-value	Adjusted OR (95% CI)	Adjusted *p*-value
Technical details						
Successful reperfusion (TICI ≥2b)*	96% (26/27)	83% (29/35)	0.23 (0.03–2.10)	$p = 0.194$	0.04 (0.002–0.58)	$p = 0.02$
Clinical outcomes						
Good clinical outcome (mRS 0–2)**	56% (14/25)	47% (14/30)	0.69 (0.24–1.99)	$p = 0.49$	0.72 (0.21–2.46)	$p = 0.59$
Excellent clinical outcome (mRS 0–1)**	44% (11/25)	23% (7/30)	0.39 (0.12–1.23)	$p = 0.11$	0.35 (0.09–1.46)	$p = 0.15$
Mortality (mRS 6)**	20% (5/25)	26% (8/30)	1.46 (0.41–5.18)	$p = 0.56$	3.22 (0.67–15.49)	$p = 0.14$

**Effect of clot shape, adjusted for baseline NIHSS, clot length, with S-SVS as reference group.*

***Effect of clot shape, adjusted for baseline NIHSS, collaterals [HIR], clot length, baseline infarct volume, with S-SVS as reference group.*

In the multivariable binary logistic regression model (AUC = 0.893), A-SVS was an independent negative predictor of successful reperfusion [OR 0.04 (95% CI, 0.002–0.58), $p = 0.02$, **Table 4**].

There was no impact of A-SVS clot shape in the multivariable binary logistic regression models on good clinical outcome [OR 0.72 (95% CI, 0.21–2.46), $p = 0.59$], excellent clinical outcome [OR 0.35 (95% CI, 0.09–1.46), $p = 0.15$], or mortality [OR 3.22 (95% CI, 0.67–15.49), $p = 0.14$], respectively (**Table 4**).

DISCUSSION

In this study, we found that thrombus morphology measured by SVS-shape influences the likelihood of successful reperfusion after MT. However, SVS morphology did not affect the likelihood of achieving a favorable clinical outcome. Our findings that SVS thrombus morphology is a biomarker of reperfusion have important implications for MT.

Prior studies have used SVS identified on gradient-echo imaging (T2*) (21) to detect (5), localize (22), and measure clot length (5, 22) without contrast administration. Whether SVS is a predictor of reperfusion after MT remains controversial (9, 23). Our findings support the hypothesis that SVS is a biomarker of reperfusion when thrombus morphology is considered. S-SVS are linear clots that do not extend into arterial branch vessels, and clots with this morphology were likely to undergo complete reperfusion compared to angulated clots and clots that extend into branch vessels (A-SVS). Whether a prospective change to MT technique results in higher rates of reperfusion of A-SVS clots requires further study. While clot morphology will not impact the decision to perform a thrombectomy procedure, we hypothesize that it could impact technical strategy, and the routine use of balloon guide sheaths, longer stentretrievers, or even double stentretriever techniques (placement of two devices into two branch points involved with a A-SVS clot) may increase the likelihood of complete reperfusion of A-SVS clots (24, 25).

Patients selection for MT depends on a fast identification of a LVO and on the evaluation of early ischemic changes, and computed-tomography (CT) and magnetic-resonance-imaging (MRI) are recommended for patient evaluation (26). However, MRI is superior to CT for detection of acute ischemia (27), is associated with better outcomes after thrombectomy treatment (28), whereas CT has been associated with an increased risk of futile reperfusion (29). While MRI duration is often reported to be longer in patient's screening for MT (30), MRI did not delay MT (30) nor impact patient's functional outcome in recent studies (30). Use of MRI in AIS screening may then depend on local protocols and optimal institutional workflows.

In contrast to few prior studies that evaluated the importance of clot length on reperfusion (22, 31) our study focused on clot morphology only. In contrast to intravenous thrombolysis stroke treatment, the impact of clot length on successful reperfusion after MT remains controversial (32, 33) and requires further study.

Successful reperfusion has been correlated to clinical outcome in multiple studies (34, 35) and, therefore, one would expect S-SVS to be correlated with a greater likelihood of a favorable clinical outcome. In our study, S-SVS patients had a lower NIHSS the day after thrombectomy and at discharge, but this early recovery did not translate to better outcomes at 90 days. We hypothesize that our study is under powered to detect an outcome difference between S-SVS and A-SVS patients.

Limitations

Our study is limited by its retrospective observational and single center design, which may introduce bias. The relatively small sample size and missing clinical outcomes in 7/62 patients may also introduce bias in our secondary outcome analysis, our findings need to be confirmed in a larger prospective study. The use of GRE MRI to identify SVS and SVS morphology rather than volumetric susceptibility or CT techniques as well as the exclusion of patients without SVS may limit the generalizability of our findings.

CONCLUSION

SVS clot morphology appears to be an independent predictor of successful reperfusion after MT in our cohort.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Stanford Medical Center Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AG, RF, ES, ML, GA, BM, DM, GK, MM, ML, MW, and JH participated to study design, data collection, data analysis, and writing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.642877/full#supplementary-material

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Decomposing Acute Symptom Severity in Large Vessel Occlusion Stroke: Association With Multiparametric CT Imaging and Clinical Parameters

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Background and Purpose: Acute ischemic stroke of the anterior circulation due to large vessel occlusion (LVO) is a multifactorial process, which causes neurologic symptoms of different degree. Our aim was to examine the impact of neuromorphologic and vascular correlates as well as clinical factors on acute symptom severity in LVO stroke.

Methods: We selected LVO stroke patients with known onset time from a consecutive cohort which underwent multiparametric CT including non-contrast CT, CT angiography and CT perfusion (CTP) before thrombectomy. Software-based quantification was used to calculate CTP total ischemic and ischemic core volume. Symptom severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) upon admission. Multivariable regression analysis was performed to determine independent associations of admission NIHSS with imaging and clinical parameters. Receiver operating characteristics (ROC) analyses were used to examine performance of imaging parameters to classify symptom severity.

Results: We included 142 patients. Linear and ordinal regression analyses for NIHSS and NIHSS severity groups identified significant associations for total ischemic volume [$\beta = 0.31$, $p = 0.01$; Odds ratio (OR) = 1.11, 95%-confidence-interval (CI): 1.02–1.19], clot burden score ($\beta = -0.28$, $p = 0.01$; OR = 0.76, 95%-CI: 0.64–0.90) and age ($\beta = 0.17$, $p = 0.04$). No association was found for ischemic core volume, stroke side, collaterals and time from onset. Stroke topography according to the Alberta Stroke Program CT Score template did not display significant influence after correction for multiple comparisons. AUC for classification of the NIHSS threshold ≥6 by total ischemic volume was 0.81 ($p < 0.001$).

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Conclusions: We determined total ischemic volume, clot burden and age as relevant drivers for baseline NIHSS in acute LVO stroke. This suggests that not only mere volume but also degree of occlusion influences symptom severity. Use of imaging parameters as surrogate for baseline NIHSS reached limited performance underlining the need for combined clinical and imaging assessment in acute stroke management.

Keywords: large vessel occlusion, multiparametric CT, CT perfusion, cerebral ischemia, stroke

INTRODUCTION

Multiparametric CT imaging raises the opportunity to comprehensively assess cerebrovascular status in large vessel occlusion (LVO) stroke, including tissue perfusion, topography, collateral flow, thrombus burden or edema formation. These parameters directly translate to morphologic correlates of stroke e.g., penumbra and core volume as well as the temporal course of infarction growth (1–5). For functional assessment of stroke severity the in-person examination using the National Institutes of Health Stroke Scale (NIHSS) comprises the gold standard (6). Taken together imaging and NIHSS are the most crucial factors to guide therapy decision for intravenous thrombolysis (IVT) or endovascular therapy (EVT) (7).

While imaging based parameters and baseline NIHSS were extensively studied regarding their impact on chronic outcome after stroke, the interplay of neuromorphologic and vascular stroke correlates with acute symptom severity remains largely unexplored (8–11). Though a study confirmed the intuitive notion that larger ischemia, causes more severe symptoms, ischemic core and penumbra were not differentiated, leaving their effect on acute neurologic symptoms unclear (10). Other studies on later performed or follow-up MRI found an association between stroke topography and admission symptoms, ignoring LVO status or vascular territory, which complicates translation of these results into the modern thrombectomy era (12, 13).

As clinical application, imaging-based surrogates for acute stroke severity might facilitate and accelerate stroke triage. Due to missing neurologic capacities in hospitals, telestroke networks need to implement video assessment for clinical examination (14, 15). Also, during the COVID-19 pandemic, the in-person examination presents a unique challenge, hence it causes prolonged contact with potentially infected and contagious patients (16). On the other hand, MRI or CT perfusion (CTP) imaging, though crucial for decision making in situations with extended or unclear time window, have been shown to increase pretherapeutic time delays (17).

In this study, we aimed to determine how imaging and clinical factors contribute to acute symptom severity of anterior circulation LVO stroke patients as measured on the NIHSS. Further, we explored the possibility to classify guideline-based NIHSS thresholds by imaging parameters.

MATERIALS AND METHODS

Study Design and Cohort

This retrospective study was approved by the local institutional review board according to the Declaration of Helsinki of 2013 and requirement for written informed consent was waived. Patients with acute ischemic stroke due to anterior circulation large vessel occlusion were selected out of a consecutive cohort of 653 patients between 2015 and 2020, who were prospectively enrolled in the German Stroke Registry (clinicaltrials.gov identifier: NCT03356392) and treated with EVT at our institution.

Inclusion criteria were

- Stroke due to anterior circulation large vessel occlusion [internal carotid artery (ICA), middle cerebral artery (MCA)],
- full imaging dataset including non-contrast CT, CT angiography (CTA) and CTP,
- known time from symptom onset.

We excluded patients with

- premorbid modified Rankin Scale $\geq$2,
- bilateral stroke.

A flowchart of patient selection is provided in the Online Data **Supplementary Figure 1**.

Image Analysis/Measurements

The imaging protocol included non-contrast CT, CTA, and CTP. Examinations were performed on CT scanners of the same vendor (SOMATOM Definition AS+, SOMATOM Definition Flash and SOMATOM Force, Siemens Healthineers, Forchheim, Germany). CTP data were processed using Syngo Neuro Perfusion CT (Siemens Healthineers, Forchheim, Germany) including automated calculation of ischemic core and penumbra volumes according to the manufacturer's thresholds (CBV $<$1.2/100 mL and CBF $<$35.1/100 mL/min) (18). We defined total ischemic volume as sum of penumbra and core volumes. CTA imaging was obtained in a single sweep from the aortic arch to the vertex with a bolus trigger of 100 HU in the aortic trunk. Expert readers (W.G.K., P.R) blinded to all clinical data including admission NIHSS determined Alberta Stroke Program Early CT Score (ASPECTS) on non-contrast CT as well as regional leptomeningeal (rLM) collateral score according to Menon et al. (20 point ordinal score, higher values indicate better collaterals) and clot burden score according to Tan et al. (10 point ordinal score, smaller values indicate more severe

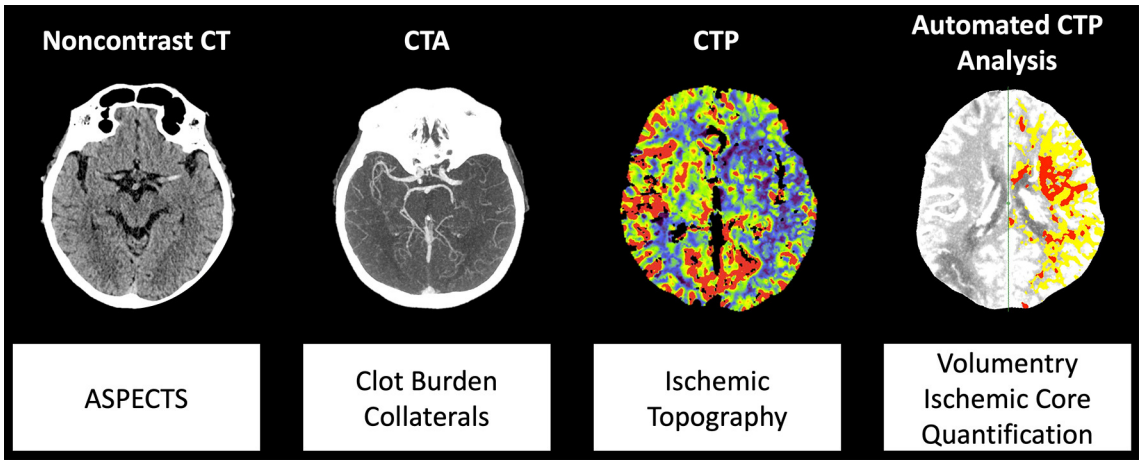

FIGURE 1 | Illustration of multiparametric CT modalities and analyzed parameters. Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CTA, CT angiography; CTP, CT perfusion.

vessel occlusion) on CTA (1, 2, 19). In case of disagreement consensus was reached in a separate session. As measure of inter-reader agreement, we calculated the intraclass correlation coefficient. Stroke topography was assessed on cerebral blood flow maps according to the 10 regions of the ASPECTS template by consensus without double reading. An illustration of multiparametric CT modalities and associated parameters is provided in **Figure 1**.

NIHSS and Clinical Parameters

NIHSS was determined for all 142 patients on admission via in-person examination by on call neurologists. Baseline comorbidities were systematically determined after initial therapy by patient interview or medical records with full datasets available in 138 patients.

Statistical Analysis

Analyses were performed in R version 3.6.2 (R Foundation for Statistical Computing, Vienna Austria) and SPSS Statistics 23 (IBM, Armonk NY 2016, commercial software). Categorical variables are reported as number and percentage. All metric and ordinal variables as median (interquartile range, IQR).

Multivariable linear regression analysis was performed to identify associations of NIHSS with clinical and imaging parameters. To avoid overfitting of the regression models, we tested the multicollinearity of independent variables using the variance inflation factor. For ordinal regression we used a 4-point ordinal scale to classify stroke severity according to the NIHSS (1: minor, NIHSS 0–4; 2: moderate, NIHSS 5–15; 3: moderate to severe, NIHSS: 16–20; 4: severe, NIHSS: 21–42) so that the proportional odds assumption was met (20). Independent model parameters included age, sex, time from symptom onset, stroke side, ischemic core volume, total ischemic volume, non-contrast CT ASPECTS, rLM collateral score and clot burden score. For ordinal regression we used an increment of 10 mL for total ischemic volume in order to facilitate interpretation of the resulting OR.

Additional linear and ordinal regression were performed to incorporate the clinical baseline parameters presence of hypertension, dyslipidemia, diabetes mellitus and atrial fibrillation. Incomplete clinical records led to inclusion of 138 patients in this analysis.

For topography, independent association of hypoperfused ASPECTS regions were tested in separate regression models for each region while adjusting for total ischemic volume and stroke side. *P*-values were corrected using Bonferroni's method.

Receiver operating characteristic (ROC) analyses including calculation of the area under the curve (AUC) were used to determine classification performance of imaging parameters for guideline-based NIHSS thresholds (NIHSS $\geq$6, $\geq$10, $\geq$20, and >25) (21–23). Optimal cut-off values were determined by maximizing the Youden Index. Statistical significance was defined as $p < 0.05$.

RESULTS

Patient Characteristics

In this retrospective study 142 patients with LVO stroke were included. Eighty-one of the patients were male and 61 female. Median age was 74 years, [interquartile range (IQR) 63–81 years]. Median time from symptom onset to CT was 124 min (IQR: 70–213 min). Median NIHSS score at admission was 13 (IQR:7–18). Most frequent site of LVO was the M1 segment of the middle cerebral artery (47.9%), followed by the internal carotid artery (25.4%). Median total ischemic volume was 187.5 mL (IQR:152.5–230.7 mL) and median ischemic core volume was 34.8 mL (IQR:21.7–59.1 mL). All patients were treated with EVT according to our inclusion criteria, additionally 102 patients (71.8%) were treated with intravenous thrombolysis. Detailed patient characteristics are displayed in **Table 1**. Frequency of admission NIHSS values are displayed in the Online Data **Supplementary Tables 1, 2**.

TABLE 1 | Patient characteristics ($N = 142$).

Male sex	81	(57.0%)
Female sex	61	(43.0%)
Median age	74	(63–81)
Male study population	74	(63–80)
Female study population	78	(70–82)
Time from symptom onset to CT (min)	124	(70–213)
NIHSS on admission	13	(7–18)
Hypertension	97	(70.3%)*
Diabetes mellitus	18	(13.0%)*
Hypercholesterolemia	28	(20.3%)*
Atrial Fibrillation	36	(26.1%)*
Treatment		
IV thrombolysis	102	(71.8%)
Endovascular therapy	142	(100%)
Imaging data		
Noncontrast CT-ASPECTS	9	(7–10)
rLM collateral score	16	(12–18)
Clot burden score	7	(4–8)
Total ischemic volume (mL)	187.5	(152.5–230.7)
Ischemic core volume (mL)	34.8	(21.7–59.1)
Mismatch volume (mL)	61.3	(6.1–82.3)
Infarction growth rate (ml/min)	1.5	(0.8–2.9)
Side of stroke		
Right	58	(40.8%)
Left	84	(59.2%)
Occlusion location		
ICA	36	(25.4%)
Carotid T	12	(8.5%)
M1 segment of MCA	68	(47.9%)
M2 segment of MCA	26	(18.3%)

*Values presented are count (percentage) for categorical and median (interquartile range) for ordinal or continuous variables. Time is presented in minutes, all volumes are presented in mL. ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; rLM, regional leptomeningeal. *Available in 138 cases.*

TABLE 2 | Linear regression analysis for association of admission NIHSS and imaging parameters ($N = 142$).

Independent variables	β	*p*-value	VIF
Age	0.17	**0.04**	1.14
Sex	0.04	0.63	1.22
Time from symptom onset to CT	0.06	0.43	1.07
Stroke side	−0.12	0.14	1.13
Core volume	−0.10	0.42	2.56
Total ischemic volume	0.31	**0.01**	2.68
NCCT ASPECTS	−0.11	0.24	1.51
rLM collateral score	0.004	0.97	2.43
Clot burden score	−0.28	**0.01**	1.77

A multivariate linear regression analysis was performed for the indicated parameters. P-values < 0.05 indicate statistical significance. Bold numbers indicate p < 0.05. VIF, variance inflation factor; ASPECTS, Alberta Stroke Program Early CT Score; NCCT, Noncontrast CT; NIHSS, National Institutes of Health Stroke Scale; rLM, regional leptomeningeal.

TABLE 3 | Ordinal regression analysis for association of symptom severity and imaging parameters ($N = 142$).

Independent variables	OR	*p*-value	95%-CI
Age	1.03	0.06	1.00-1.05
Sex	0.91	0.79	0.45-1.84
Time from symptom onset to CT	1.00	0.26	1.00-1.00
Stroke side	2.01	0.05	0.99-4.06
Core volume	0.99	0.30	0.98-1.01
Total ischemic volume/10 mL	1.11	**0.01**	1.02-1.19
NCCT ASPECTS	0.90	0.28	0.74-1.09
rLM collateral score	1.01	0.87	0.91-1.13
Clot burden score	0.76	**0.001**	0.64-0.90

A multivariate ordinal regression analysis was performed for the indicated parameters. Symptom severity was numerically classified by the NIHSS on admission (1: NIHSS 0-4, 2: NIHSS 5-15, 3: NIHSS: 15-20, 4: NIHSS: 21-42). P-values < 0.05 indicate statistical significance. Bold numbers indicate p < 0.05. ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; NCCT, Noncontrast CT; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; rLM, regional leptomeningeal.

Association of NIHSS With Imaging and Clinical Parameters

Multivariable linear regression analysis in 142 patients presented significant independent association of admission NIHSS with total ischemic volume ($\beta = 0.31$, $p = 0.01$), clot burden score ($\beta = -0.28$, $p = 0.01$), and age ($\beta = 0.17$, $p = 0.04$). Ischemic core volume and rLM collateral score as well as time from symptom onset, non-contrast CT ASPECTS or sex did not show significant associations (all $p > 0.05$). No additional associations were found when including the baseline comorbidities hypertension, diabetes, dyslipidemia or atrial fibrillation (all $p > 0.05$). The variance inflation factor was below the critical value of 3.3 (24).

In ordinal regression analysis with NIHSS values ordered by symptom severity from 1 to 4, significant independent association with total ischemic volume per 10 mL [Odds ratio (OR) = 1.11, 95%-CI: 1.02–1.19, $p = 0.01$] and clot burden score (OR=0.76, 95%-CI: 0.64–0.90, $p = 0.001$) was present. Age and stroke side presented a trend toward significance in this analysis (OR=1.03, 95%-CI: 1.00–1.05, $p = 0.06$ and OR = 2.01, 95%-CI: 0.99–4.06, $p = 0.05$). Detailed results are displayed in **Tables 2**, **3**. Analysis including baseline comorbidities are presented in the Online Data **Supplementary Tables 3, 4**. Results using the 4-point scale collateral assessment according to Tan et al. and including occlusion location as independent variable are provided in the Online Data **Supplementary Tables 5–8** (25). Unadjusted bivariate correlation analysis of admission NIHSS and scaled or ordinal parameters is presented in the Online Data **Supplementary Table 9**. ICC presented strong agreement for non-contrast CT ASPECTS, rLM collateral score and clot burden score as displayed in the Online Data **Supplementary Table 10**.

Association of Admission NIHSS With Stroke Topography

Separate regression models for the 10 ASPECTS regions adjusted for total ischemic volume and stroke side resulted in association

TABLE 4 | ROC analysis for classification of NIHSS thresholds by the indicated parameters ($N = 142$).

Threshold parameter	AUC (95% CI)		*p*-value	Y-Index	Y-Index CP	Sensitivity	Specificity
Classification by total ischemic volume (mL)							
NIHSS ≥ 6	0.81	(0.72–0.89)	<0.001	0.54	182.6 mL	0.63	0.91
NIHSS ≥ 10	0.77	(0.69–0.85)	<0.001	0.42	185.9 mL	0.66	0.76
NIHSS ≥ 20	0.68	(0.57–0.78)	0.001	0.41	185.9 mL	0.85	0.56
NIHSS > 25	0.57	(0.33–0.81)	0.569	0.23	208.7 mL	0.57	0.66
Classification by clot burden score							
NIHSS ≥ 6	0.74	(0.64–0.84)	<0.001	0.42	8	0.72	0.70
NIHSS ≥ 10	0.73	(0.65–0.81)	<0.001	0.39	7	0.63	0.76
NIHSS ≥ 20	0.67	(0.56–0.78)	0.003	0.24	7	0.69	0.54
NIHSS > 25	0.66	(0.46–0.87)	0.125	0.24	4	0.43	0.81

A receiver operating characteristic analysis was performed for the indicated parameters. Cut points were determined by the Y-Index. P-values < 0.05 indicate statistical significance. AUC, Area Under the Curve; CI, confidence interval; CP, Cut point; NIHSS, National Institutes of Health Stroke Scale; Y-Index, Youden Index.

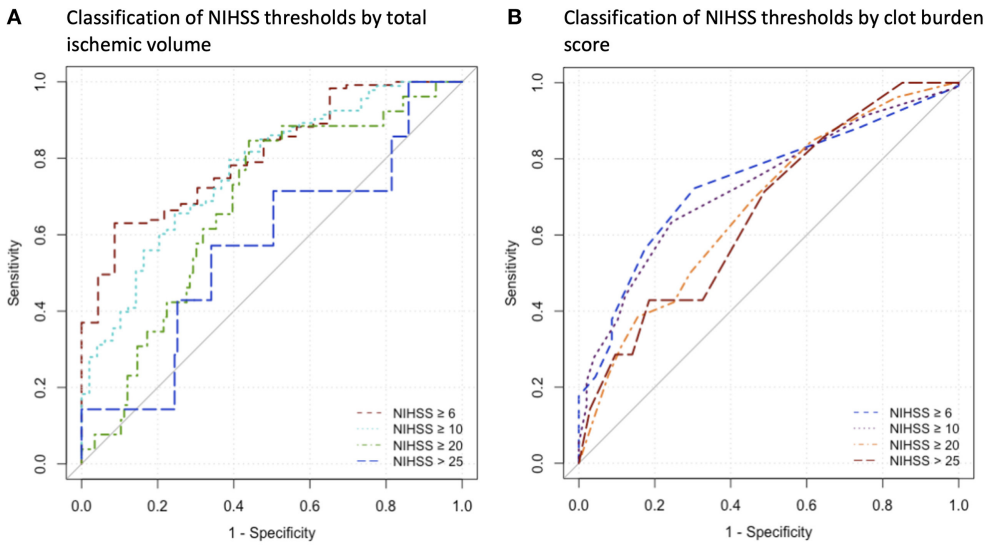

FIGURE 2 | Receiver operating characteristics curves for the indicated parameters. **(A)** Analysis for Classification of NIHSS thresholds by Total Ischemic Volume, **(B)** Analysis for classification of NIHSS thresholds by clot burden score. NIHSS, National Institutes of Health Stroke Scale.

of lentiform nucleus ($\beta = 0.20$, $p = 0.02$) which did not maintain significance after Bonferroni correction for multiple comparisons. Detailed results are presented in the Online Data **Supplementary Table 11**.

Discriminatory Value of Imaging Parameters for Guideline-Based NIHSS Thresholds

The ROC curve analysis in 142 patients for the discriminatory value of total ischemic volume and clot burden score for the NIHSS threshold ≥6 resulted in an AUC of 0.810 ($p < 0.001$) and 0.74 ($p < 0.001$) respectively, with lower performance for the other thresholds of NIHSS ≥10, ≥20, and >25 (AUC < 0.8). Detailed results are displayed in **Table 4**. ROC curves are presented in **Figure 2**.

DISCUSSION

This study presents a comprehensive investigation of multiparametric CT imaging and clinical factors on acute symptom severity in anterior circulation LVO stroke. To our knowledge this is the first study selectively analyzing impact of CTP ischemic core and total ischemic volume while also providing data on the influence of ischemic topography using the routinely applicable ASPECTS template.

Our results indicate that total ischemic volume is a major determinant for acute symptom severity in LVO patients measured by the NIHSS. Notably, there is also an established linear relationship between NIHSS after 24 h and post-treatment infarction volume hinting toward similar mechanisms moderating morphology and symptom severity in the hyperacute and post-therapeutic acute stroke phase (26). We also observed significant association of the clot burden score with NIHSS on

admission similar to other studies (8, 9). Occlusion location did not present independent influence. As possible mechanism we propose that not only ischemic volume but also degree of hypoperfusion, reflected by more severe occlusion, affects acute symptom severity. An interaction that has already been described for initial perfusion deficit and chronic outcome after stroke (27).

Interestingly, neither non-contrast CT ASPECTS nor ischemic core volume exhibited an independent association with symptom severity. As these parameters are closely intertwined, both are particularly useful for predicting morphological and clinical outcomes, yet the effect on acute symptoms seems to be clouded by mere total ischemic volume (28). It is important to note that the inclusion criteria of known time from symptom onset shifted our sample toward an earlier time window. Our study did not reveal correlation of NIHSS and time from symptom onset, though there are observations that NIHSS can worsen during the subacute course of stroke (29). Therefore, our data indicates that the established associations are independent of a defined time window. Later time windows or patients with unknown onset time, however, might still display different dynamics in the translation of ischemic volumes to neurologic symptoms.

Also, collateral status did not impact baseline NIHSS, which is known to affect infarction core growth (5). Accordingly, collateral perfusion would seem to suffice for delaying tissue decline but not for sustaining neurologic function in the acute stroke phase. However, diverging results were found by other studies using less granular collateral scores and disregarding ischemic core volume (9, 30).

Though the NIHSS is known to favor symptoms of the dominant hemisphere, infarction side did not show significant association with symptom severity. These results are in congruence with the findings of Furlanis et al. who found a strong correlation of ischemic volume with baseline NIHSS resulting in similar slopes for right and left hemispheric stroke (10). However, advanced MRI analysis showed left hemispheric stroke led to higher baseline NIHSS (31). Differences in results might partly be explained by the selected study sample containing only LVO patients, requesting dedicated analysis in this important patient group. Also, stroke topography did not significantly impact overall admission NIHSS. Topography seems crucial for chronic stroke symptoms and though there is described location dependency of baseline NIHSS, same locations showed high overlap with lesion volume, which was accounted for in our analysis (13, 15).

Among clinical parameters only age displayed a significant influence on baseline symptom severity with lower NIHSS in younger patients as also found in a prior study (9). Neither sex, nor baseline comorbidities exhibited significant influence.

As potential clinical use, total ischemic volume classified the guideline-based cut-off of admission NIHSS $\geq$ 6 as used in the DEFUSE 3 study with acceptable performance. Other NIHSS cut-off values of 25 from the WAKE-UP trial or 10 and 20 from the DAWN trial were classified with lower performance (22, 23, 32). Accordingly, only differentiation of minor/moderate stroke by total ischemic volume seams feasible. This underlines the importance of proper clinical and imaging examination for evidence-based therapy decisions.

Limitation of this study include the small sample size and retrospective study design. Second, we used a selected dataset of LVO stroke patients with known time from symptom onset and without premorbid disability (pMRS $\leq$ 1). We chose these criteria as we wanted to examine the temporal effects on stroke symptoms during LVO without bias of existing sequelae. Translatability to patients with unknown onset seems reasonable due to the missing impact of time from symptom onset, however, needs further dedicated validation. Also, subgroups with advanced edema formation indicated by low ASPECTS and presumably larger infarction core were underrepresented in our study, requiring further analysis of this highly discussed subgroup in larger samples (33). In light of the small sample size also the borderline non-significant ordinal regression results for impact of ischemic core volume and stroke side need to be interpreted with caution and require reproduction in larger datasets. Third, imaging was performed using scanners and software of a single vendor (Siemens Healthineers, Forchheim, Germany). While volumetry can differ between different software packages, measurements of the used package presented best agreement with the gold-standard RAPID among other packages (18, 34).

CONCLUSION

Our data determined total ischemic volume and clot burden as the most relevant neuromorphologic and vascular correlates for baseline NIHSS in acute LVO stroke, suggesting that not only mere volume but also degree of occlusion influences clinical presentation. On the other hand, ischemic core volume and collateral status did not influence acute symptom severity. All associations were independent from time from symptom onset. Our results indicate only limited potential for classification of symptom severity by CT imaging. This highlights the significance and synergy of clinical and imaging assessment in the acute management of stroke patients. Further studies with a larger dataset are needed to clarify the role of collaterals and side of stroke.

DATA AVAILABILITY STATEMENT

The data supporting the conclusions of this article will be made available by the corresponding author upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkomission der medizinischen Fakultät, LMU Munich. Written informed consent for participation was not

required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LS, ST, WK, and PR: conceptualization. LS, ST, FM, WK, and PR: formal analysis and data curation. LS, ST, WK, PR, and MF: writing—original draft. PR, DP-W, SG, SM, LK, MH, JR, and KD: writing—review and editing. PR, WK, JR, and TL: supervision. All authors: contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.651387/full#supplementary-material

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CASE REPORT
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Case Report: Successful Cerebral Revascularization and Cardiac Transplant in a 16-Year-Old Male With Syndromic *BRCC3*-Related Moyamoya Angiopathy

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Background: *BRCC3/MTCP1* deletions are associated with a rare familial moyamoya angiopathy with extracranial manifestations.

Case: We report the case of an adolescent male presenting with progressive and symptomatic moyamoya angiopathy and severe dilated cardiomyopathy caused by a hemizygous deletion of *BRCC3/MTCP1*. He was treated for renovascular hypertension by left kidney homograft and right nephrectomy in infancy and had other syndromic features, including cryptorchidism, growth hormone deficiency, and facial dysmorphism. Due to worsening of the neurological and cardiac condition, he was treated by a direct superficial temporal artery to middle cerebral artery bypass to enable successful cardiac transplant without cerebral damage.

Conclusions: *BRCC3*-related moyamoya is a devastating disease with severe heart and brain complications. This case shows that aggressive management with cerebral revascularization to allow cardiac transplant is feasible and efficient despite end-stage heart failure.

Keywords: moyamoya angiopathy, revascularization, BRCC3, cardiac transplant, stroke

INTRODUCTION

Moyamoya is a rare cerebrovascular angiopathy characterized by progressive stenosis of the terminal part of the intracranial carotid arteries and/or proximal middle or anterior cerebral arteries. These lesions lead to the development of abnormal and fragile collateral vessels and are responsible for ischemic and hemorrhagic stroke (1). Moyamoya angiopathy can be associated with various conditions, including neurofibromatosis, Down syndrome, radiotherapy, sickle cell

disease, and rare *BRCC3/MTCP1* deletions that associate a rare X-linked moyamoya syndrome with multisystemic manifestations (MIM #300845) (2).

CASE REPORT

Background

The male patient was born prematurely at 34 weeks gestation at a weight of 1,700 g, with a history of intrauterine growth retardation against the background of bridged left renal fibrodysplasia in the mother. Cryptorchidism and mild pulmonary valve stenosis were diagnosed at birth.

He had an older brother, born at 32 weeks gestation, who had spastic diplegia, moderate intellectual disability, perception deafness, and growth hormone deficiency without myocardiopathy. There was no familial history of moyamoya disease.

History

The patient had growth retardation at −2.7DS, with partial growth hormone (GH) deficiency but no hypogonadism (delayed puberty). During infancy, hypertension was discovered during his heart monitoring. Further investigations revealed bilateral stenosis of the renal arteries with a small right kidney. The aortic angio-magnetic resonance imaging (MRI) found evidence of midaortic syndrome with diffuse dysplasia, and stenosis of the inferior renal aorta and bilateral renal arteries. Williams-Beuren syndrome was ruled out.

The hypertension quickly became resistant despite a four-drug regimen. He underwent multiple (right and/or left) angioplasties in childhood without improvement or with rapid restenosis, unsuccessful stent in the left renal artery, then a right nephrectomy for atrophic right kidney. Finally, during adolescence, he underwent a major surgery with insertion of an aorto-aortic Dacron tube and left kidney homograft (on the left common iliac artery). During this surgery, he experienced low systemic flow, which induced left hemiparesis. The cerebral MRI showed severe hypoperfusion of the bilateral corona radiata, with watershed ischemic lesions associated with dysplasia of both internal carotid terminations, suggesting moyamoya angiopathy. The patient recovered well. No surgical revascularization was planned because of the atypical (because of diffuse stenosis and few collaterals) moyamoya syndrome, the absence of recurrent stroke, the normal perfusion sequences, the absence of MRI progression during follow-up and recurrence of neurological symptoms. Reanalysis of *PTEN, SOS1, RAF1*, and *SHOC2* based on the hypothesis of Noonan syndrome, and analysis of *ACTA2*, given the association of moyamoya angiopathy and the clinical presentation, did not identify any pathogenic variants.

The hypertrophic hypertensive cardiomyopathy progressed to mild dilated cardiomyopathy with a left ventricular ejection fraction (LVEF) of 50%.

Three years later, the patient presented with a transient ischemic attack (TIA) without significant modification on MRI (non-contributive perfusion sequences, stable stenosis of M1) and normal blood pressure. He was hospitalized 3 weeks later for faintness associated with cardiac decompensation, hypotension, and worsening of the echocardiographic parameters (LVEF 20%, post-capillary systolic pulmonary hypertension at 55 mmHg, moderate mitral regurgitation). He was no more hypertensive thereafter. The association of moyamoya disease, dilated myocardiopathy, renovascular hypertension, GH deficiency, cryptorchidism, and mild dysmorphism prompted investigation for the *BRCC3/MTCP1* deletion.

Two months later, he developed several episodes of transient left hemiplegia with ischemic lesions in the internal carotid artery area. A cerebral angiogram showed worsening of the M1 stenosis and occlusion of the two anterior cerebral arteries (**Figures 1a,b**). Perfusion MRI showed severe bilateral frontal hypoperfusion of cerebral blood flow, and Tmax cartography (**Figures 1d,e**). Neurologic recovery was excellent except for persistent mild ataxia and melokinetic apraxia.

We discussed at this time the feasibility of revascularization and need of cardiac transplant because he remained in end-stage heart failure despite optimal cardiac therapy. Arterial tension objective was minimum 126/77 mmHg. The feasibility and the risk of surgical cerebral revascularization and the risk of a large stroke during cardiac transplant [because of the cerebral hemodynamic status, embolic complications, arrest, tamponade, and the need for postoperative extracorporeal life support (ECLS)] were weighed. Therefore, in order to improve cerebral perfusion to allow for a cardiac transplantation, we decided to perform direct cerebral revascularization surgery.

A superficial temporal artery to middle cerebral artery (STA-MCA) bypass was performed on the right hemisphere related to the clinical symptoms. We used indocyanine green fluorescence angiography during anastomosis to evaluate the bypass blood flow. Surgery was preceded by an inotropic infusion (levosimendan).

No peri- or postoperative complications occurred. He did not experience further recurrent TIAs. Five months of follow-up imaging with conventional and perfusion-weighted imaging showed that the anastomosis was efficient, with a decrease in frontal hypoperfusion and no additional ischemic lesion. **Figure 1** illustrates the increase in brain perfusion on cerebral blood flow cartography and the shrinkage of delayed perfusion areas (TMAX >6s) on TMAX cartography, which was enabled by the postoperative development of collateral vessels (**Figures 1g,h**).

The patient was registered on the cardiac transplant list 2 months later. New episodes of cardiac decompensation after the neurosurgical intervention required treatment with levosimendan. He underwent a heart transplant a few days before reaching adulthood, at a weight of 30 kg. The last follow-up, 1 year after the transplant, was excellent (**Figure 2**). He began to ride a bike and walk hundreds of meters, he gained weight and muscle, and the last echocardiography showed normal cardiac function (LVEF 62%).

DISCUSSION

Nine *BRCC3*-related moyamoya patients from three families (2–4) have been reported in the literature with a syndromic

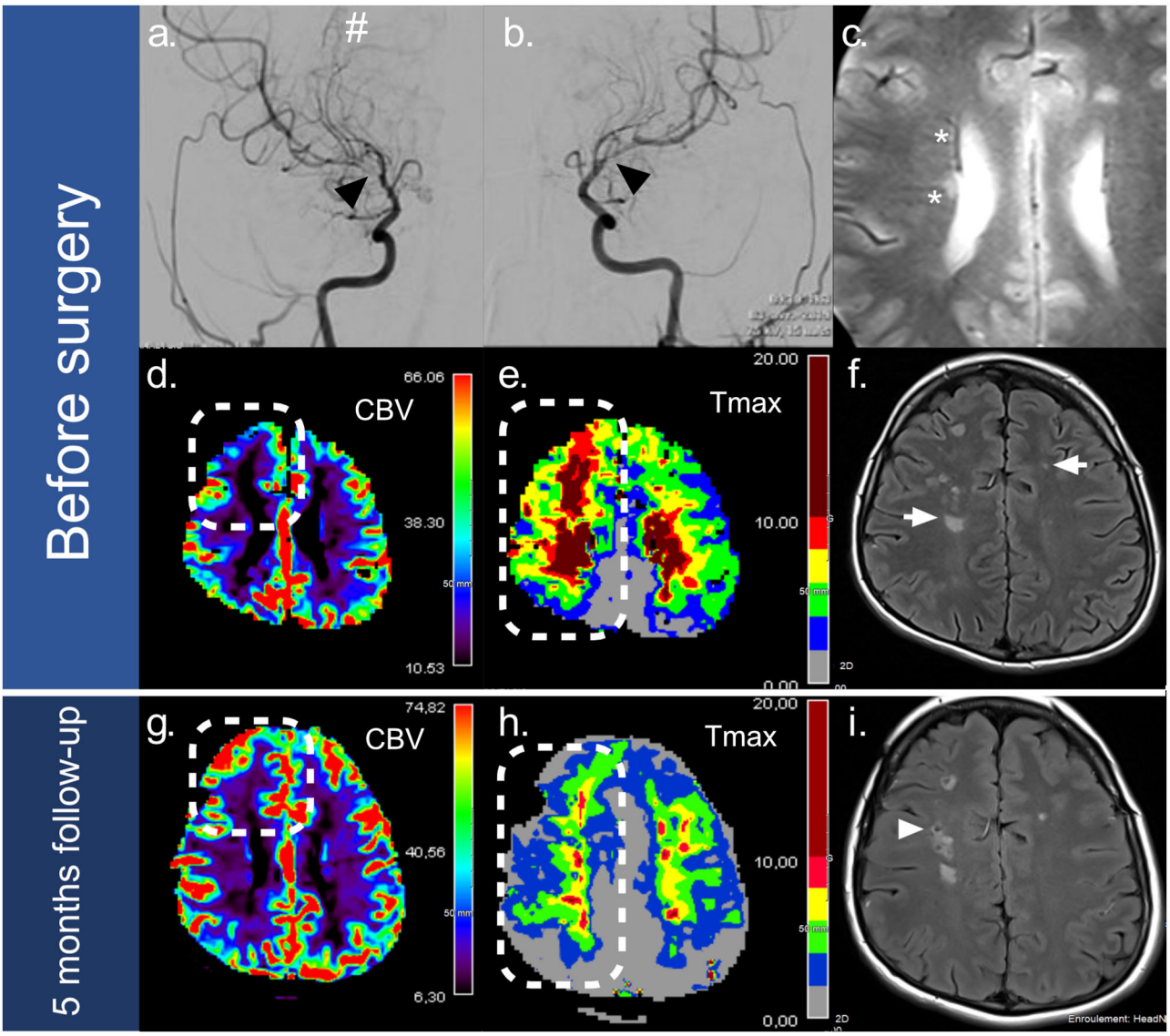

FIGURE 1 | Imaging of moyamoya lesions and 5-month follow-up. Before surgery, moyamoya lesions were observed on the right **(a)** and left **(b)** internal carotid artery angiograms, revealing bilateral stenosis of the internal carotid arteries termination (black arrows), with moyamoya collaterals (#). Magnetic resonance imaging **(c–f)** found asymmetric enlargement of the medullary veins in relation with cerebral hypoperfusion (*) visible on the T2-GE sequence **(c)**, associated with bilateral watershed ischemic lesions on FLAIR **(f)** (white arrow). Perfusion imaging pointed out severe hypoperfusion in the right frontal junctional territory (squared dots) on the cerebral blood flow cartography (CBV) **(d)** and the TMAX cartography **(e)**. A five-month follow-up scan **(g–i)** showed significant improvement of the left frontal lobe perfusion after surgery with: (1) an increase in cerebral blood flow (**d** vs. **g**) (squared dots), and (2) shrinkage of delayed perfusion areas on TMAX >6s (**e** vs. **h**) (rectangular dots). No recurrent ischemic lesions were observed after surgery. Preoperative ischemic lesions progressed into lacunar lesions (**f** vs. **i**) (white arrowhead).

presentation including growth retardation (9/9), moyamoya angiopathy (8/9), hypergonadotropic hypogonadism (7/9), partial GH deficiency (4/5), early-onset cataracts (4/5), dilated myocardiopathy (3/7), renovascular hypertension (3/5), coronaropathy (1/9), and dysmorphism dominated by hypertelorism syndrome with a syndromic presentation including craniofacial dysmorphism and premature graying of hair. The age of onset of the neurological symptoms was variable, from 4 to 32 years. This is the first case, to our knowledge, to have presented diffuse dysplasia and stenosis of the inferior renal aorta and pulmonary valve stenosis. Very little information has been published on the management of these patients.

BRCC3 plays an important role in angiogenesis, and moyamoya vasculopathy with mutation of *BRCC3* is a diagnosis to be kept in mind in the event that prior analysis with a compatible phenotype is negative.

Relevant Medical History			
34 weeks premature. Pulmonary stenosis diagnosed during neonatal period. Cardiac follow-up.			
Age	Events	Diagnosis & treatments	Follow-up
3	Discovery of hypertension	Mid-aortic syndrome, bilateral stenosis of the renal arteries & small right kidney	
4 1/2	Hypertension resistant despite tri-therapy	Angioplasty of bilateral renal arteries	No effect
9	Evolution to cardiac hypertrophy (IVSd Z-score > 2) with preserved LVEF	Follow-up	Mild dilated cardiomyopathy at 13 years old.
10	Non-controlled hypertension (mean pressure > 140/80mmHg)	Introduction of quadri-therapy	Mild diminution of hypertension
13 1 month	Persistent severe hypertension	Right nephrectomy then renal revascularization	Incomplete control of hypertension
13 5 month	Hemicorporeal deficit after surgical wake-up	Cerebral MRI: discovering of moyamoya syndrome	Good recovering. Decreased of medications but need of bi-therapy
16	Viral infection with central facial paralysis and dysarthria	No evolution of cerebral MRI. Normalization of hypertension	Full recovery. Stop of antihypertensive treatments.
16 1 month	Faintness at school	Severe heart failure. No etiology found (infectious, ischemic or metabolic)	Discussion of heart transplant.
16 3 month	Worsening of perfusion MRI and multiple TIA	Cerebral revascularization surgery	No further neurological event
17	End-stage heart failure	Cardiac transplant	1 year follow-up: good cardiac function and improvement of quality of life

FIGURE 2 | Timeline table, resuming evolution of neurological and cardiac disease. The patient's written consent was obtained for publication.

Symptomatic moyamoya angiopathy is often managed with surgical revascularization to improve cerebral perfusion (direct technique with surgical anastomosis or indirect technique with synangiosis). Heart failure is associated with increased mortality in non-cardiac surgery (5, 6). Anesthesia involves many changes in physiology, and the postoperative state is a vulnerable period similar to a cardiac stress test. Prior preparation and complete monitoring during the neurosurgical procedure are also essential, as is the careful choice of anesthetic drugs. The risk of periprocedural stroke is high, notably because of hypotension during the induction of general anesthesia. Nevertheless, we thought that it was the only choice for preventing recurrent hemodynamic stroke and for protecting the brain from ischemia during hemodynamic stress related to cardiac transplant.

On the other hand, cardiac transplantation is also associated with a high risk of stroke and functional decline during the perioperative period (7–9).

This case shows that in the context of this devastating disease, multidisciplinary, and aggressive management with cerebral revascularization followed by cardiac transplant is feasible and efficient despite end-stage heart failure.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

PP wrote the case report. JD made the figure and performed the endovascular part. MA-M and OP performed the genetic part. PB the neurosurgical part. EC and KB were involved in the pediatric management and pediatric supervision. AS helped for the neuroimaging. LC made the supervision. CK rewrite the manuscript and validate each part. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Low-Dose vs. Standard-Dose Intravenous Alteplase in Bridging Therapy Among Patients With Acute Ischemic Stroke: Experience From a Stroke Center in Vietnam

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Background: To date, the role of bridging intravenous thrombolysis before mechanical thrombectomy (MTE) is controversial but still recommended in eligible patients. Different doses of intravenous alteplase have been used for treating patients with acute ischemic stroke from large-vessel occlusion (LVO-AIS) in Asia, largely due to variations in the risks for intracerebral hemorrhage (ICH) and treatment affordability. Uncertainty exists over the potential benefits of treating low-dose alteplase, as opposed to standard-dose alteplase, prior to MTE among patients with LVO-AIS.

Aim: The aim of the study was to compare outcomes of low- vs. standard-dose of bridging intravenous alteplase before MTE among LVO-AIS patients.

Methods: We performed a retrospective analysis of LVO-AIS patients who were treated with either 0.6 mg/kg or 0.9 mg/kg alteplase prior to MTE at a stroke center in Northern Vietnam. Multivariable logistic regression models, accounting for potential confounding factors including comorbidities and clinical factors (e.g., stroke severity), were used to compare the outcomes between the two groups. Our primary outcome was functional independence at 90 days following stroke (modified Rankin score; mRS $\leq$ 2). Secondary outcomes included any ICH incidence, early neurological improvement, recanalization rate, and 90-day mortality.

Results: We analyzed data of 107 patients receiving bridging therapy, including 73 with low-dose and 34 with standard-dose alteplase before MTE. There were no statistically significant differences between the two groups in functional independence at 90 days (adjusted OR 1.02, 95% CI 0.29–3.52) after accounting for potential confounding factors. Compared to the standard-dose group, patients with low-dose alteplase before MTE had similar rates of successful recanalization, early neurological improvement, 90-day mortality, and ICH complications.

Conclusion: In the present study, patients with low-dose alteplase before MTE were found to achieve comparable clinical outcomes compared to those receiving standard-dose alteplase bridging with MTE. The findings suggest potential benefits of low-dose alteplase in bridging therapy for Asian populations, but this needs to be confirmed by further clinical trials.

Keywords: acute ischemic stroke, mechanical thrombectomy, dose, bridging therapy, anterior large artery occlusion, alteplase, intravenous thrombolysis

INTRODUCTION

The role of bridging thrombolysis before mechanical thrombectomy (MTE) has been controversial (1), but it is still recommended in eligible patients (1–4). In a recent meta-analysis of 38 observational studies, bridging therapy appears to be associated with improved functional independence without evidence for safety concerns, and this is compared to MTE for patients with acute ischemic stroke from large-vessel occlusion (LVO-AIS) (5). Randomized controlled trials that assessed whether primary MTE was non-inferior to the bridging strategy of intravenous thrombolysis (IVT) alteplase immediately followed by MTE in AIS patients presenting to thrombectomy capable centers produced mixed results. The SKIP (The Randomized Study of EVT With Vs. Without Intravenous Recombinant Tissue-Type Plasminogen Activator in Acute Stroke With ICA and M1 Occlusion) trial, which included patients with LVO-AIS in Japan, was unable to demonstrate the noninferiority of MTE alone over bridging therapy with low-dose alteplase before MTE (6). Conversely, the DIRECT-MT (Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals) trial conducted in China showed that MTE alone was non-inferior ($\leq$20% margin of confidence) to MTE preceded by standard-dose alteplase with regard to the primary outcome (90-day modified Rankin Scale shift) (7). The DEVT (Direct Endovascular Thrombectomy vs. Combined IVT and Endovascular Thrombectomy for Patients With Acute Large Vessel Occlusion in the Anterior Circulation) trial in China also demonstrated the non-inferiority of primary MTE treatment over the bridging therapy (standard-dose IVT + MTE) in functional independence (noninferiority margin of 10%) (8). However, there may be individual factors in the decision-making process that were not captured in the clinical trials (2). Accumulated trial data so far are insufficient to negate the value of alteplase bridging at thrombectomy capable centers (2), awaiting the results of ongoing trials including the DIRECT-SAFE (DIRECT Endovascular Clot Retrieval Vs. Standard Bridging Thrombolysis With Endovascular Clot Retrieval; NCT03494920) and MR CLEAN-NO IV: Intravenous treatment followed by intra-arterial treatment vs. direct intra-arterial treatment for acute ischemic stroke caused by a proximal intracranial occlusion (9).

In 2010, an open-label, nonrandomized, observational study suggested that low-dose (0.6 mg/kg) intravenous alteplase within 3 h of stroke onset could be safe and effective for the Japanese population (10). Various doses of intravenous alteplase have been used for treating patients with LVO-AIS in Asia, which is largely due to the reduced cost of low-dose IVT and its lower anticipated intracerebral hemorrhages (ICH) rates, compared to standard-dose IVT (11). Findings from the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) trial involving predominantly Asian patients, failed to prove the noninferiority of low-dose to standard-dose intravenous alteplase with respect to death and functional outcomes at 90 days, but there were fewer ICH in the patients receiving low-dose alteplase (6). Since the ENCHANTED study was published, there has been limited evidence comparing clinical outcomes between low- and standard-dose intravenous alteplase in Asian populations. Uncertainty exists over the potential benefits of treating low-dose alteplase, as opposed to standard-dose alteplase, prior to MTE among patients with LVO-AIS presenting directly to a thrombectomy-capable stroke center, particularly for Asian populations.

The aim of the study was to compare clinical outcomes of low-dose vs. standard-dose intravenous alteplase combined with MTE in patients with LVO-AIS.

MATERIALS AND METHODS

Study Design

The study was conducted at the Stroke Center of Bach Mai Hospital, Hanoi, Vietnam. As one of the leading stroke centers nationally, we have been providing acute care to approximately 10,000 episodes of stroke each year. We retrospectively included patients with LVO-AIS at the Stroke center who received bridging therapy between 2017 and 2019. The included patients must meet the criteria for treatment of intravenous alteplase within a 4.5-h window from stroke onset as well as MTE within the 6-h window from stroke onset. We applied the inclusion and exclusion criteria for intravenous alteplase within 4.5 h of onset as recommended in the 2013 American Heart Association/American Stroke Association (AHA/ASA) Guidelines (10) [consistent with the updated 2018 AHA/ASA Guidelines (12)] and the 2015 AHA/ASA Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke (13). At Bach Mai hospital, we have also followed the inclusion and exclusion criteria for treating MTE within 6 h of stroke onset stated in the 2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment (1). At the Stroke Center, bridging

therapy was performed immediately following thrombolysis, and we continued alteplase infusion during thrombectomy even with those who achieved successful recanalization.

The Japanese drug safety authority has approved the use of low-dose alteplase after an open-label, nonrandomized, observational study showed that it could be safe and effective compared to standard-dose alteplase for the Japanese population (10). Given the concerns of intracerebral hemorrhage (ICH), treatment affordability, and lack of clinical evidence for the optimal dose for Vietnamese patients (10), we used low-dose alteplase for thrombolytic therapy before MTE among patients with LVO-AIS at the Stroke Center of Bach Mai Hospital from 2010 to 2018. We later used standard-dose alteplase in combination with thrombectomy for the eligible patients hospitalized in 2019, following the commencement of the ENCHANTED trial (6). Therefore, the patients included in this single-center retrospective study were from two time periods. The 1st period from 2017 to 2018 included the patients who received low-dose intravenous alteplase (0.6 mg/kg; 15% bolus and 85% as infusion over 1 hour), and the 2nd period in 2019 included those receiving standard-dose alteplase (0.9 mg/kg; 10% bolus, and 90% as infusion over 1 h).

All the included patients received computed tomography (CT) and computed tomography angiography (CTA) scans to decide if alteplase should be administered. The patients were immediately referred to the intervention room for MTE if the CTA revealed an anterior large artery occlusion. MTE was performed via a transfemoral approach with either SOLITAIRE (stent retriever system), PENUMBRA (aspiration system), or SOLUMBRA (aspiration plus extraction technique).

This retrospective study was approved by the Ethics Committee of Hanoi Medical University, No 187/HĐĐĐĐHYHN on February 20, 2016.

Clinical Assessments and Measured Outcomes

Patients were assessed by clinicians and their data were obtained at 24, 72 h, 7 days (or at discharge if sooner), 28, and 90 days after hospital admission.

Clinical assessments were performed using the National Institute of Health Stroke Scale (NIHSS), modified Rankin scale (mRS), and brain imaging CT scan, and/ or magnetic resonance imaging [MRI] within 24 h of admission. Information on patient characteristics and care received in the hospital was obtained from the medical records. They included (1) socio-demographics: age, sex; (2) pre-stroke factors: pre-morbid mRS, use of medications, risk factors (body weight, blood pressure, and smoking), and comorbidities (e.g., history of stroke, hypertension, atrial fibrillation, diabetes mellitus, hypercholesterolemia); and (3) stroke-related clinical factors. The clinical factors included stroke severity (initial NIHSS), ischemic stroke subtype according to the Acute Stroke Treatment (TOAST) criteria (14), onset to hospital arrival, door to needle time, needle to groin puncture time, groin to recanalization time, intracranial atherosclerosis, Alberta stroke program early CT score (ASPECT) score (15), and occlusion sites [e.g., internal carotid artery, tandem, and middle cerebral artery (MCA) on cerebral angiography]. Other factors were the MTE technique performed, a need for placement of permanent intracranial stent during MTE to achieve recanalization, and the number of attempts to achieve recanalization. Where available, information on the collateral state was obtained from the medical records. The overall state of collaterals for each patient was assessed based on the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology grading system, with grades of 0 to 1 on CTA scan at baseline denoting poor collateral state (16).

The primary outcome was functional independence at 90 days (defined as mRS 0–2). Secondary outcomes included early neurological improvement, successful reperfusion following the MTE procedure, any ICH complications, and 90-day mortality. Early neurological improvement was defined as a reduction of at least eight points in the NIHSS score or an NIHSS score of 0 or 1 at 72 h after hospitalization (6). Recanalization rates were assessed before thrombectomy and immediately after MTE reperfusion, according to the modified Thrombolysis in Cerebral Infarction scale (mTICI) score (17). An mTICI score of 2b or three was considered as complete reperfusion. Where available, information on the collateral state was obtained from the medical records. The overall state of collaterals for each patient was assessed based on the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology grading system, with grades of 0 to 1 on CTA scan at baseline denoting poor collateral state (16). As the safety outcome, hemorrhagic complications after reperfusion therapy included any ICH, subarachnoid hemorrhage, and other forms of hemorrhage within the cranium identified on brain imaging, or reported by a clinician while in the hospital (6). A sub-parameter of safety outcome was symptomatic cerebral hemorrhage (sICH). An sICH was defined as any hemorrhage identified as the predominant cause of the neurological deterioration (indicated by an NIHSS score that was higher by $\geq$4 points than the value at baseline or the lowest value in the first 7 days or any hemorrhage leading to death) (6). In addition, the hemorrhage must be classified as parenchymal intracerebral hemorrhage type 2 (dense hematoma >30% of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area) (6).

Statistical Analysis

All the data analyses were performed using SPSS software, version 21.0 (IBM, Co., Armonk, NY, USA). Parameters were presented as N (%), mean $\pm$ standard deviation, or median (25 and75th percentile). Differences between the two groups were assessed using the Pearson correlation test for categorical variables and the Student *t*-test or Mann–Whitney *U*-test, where relevant, for continuous variables. The Fisher exact test was applied for continuous variables when the number of observations was <5. A two-sided p-value < 0.05 was considered statistically significant. Multivariable logistic regression models, accounting for potential confounding factors (age, sex, and where possible together with sufficient cases, the variables that showed a p-value <0.1), were used to compare clinical

outcomes and hemorrhagic complications between the two groups (low- vs. standard-dose alteplase) following bridging therapy. We also performed sensitivity analyses that included some relevant covariates not meeting the criteria for being confounders as specified above to see if these factors impacted different outcomes.

RESULTS

In this study, we included 107 patients (63% males; mean age: 63 years) who were treated with intravenous alteplase prior to MTE. They were divided into two groups according to the bridging therapy they received: 73 were treated with a lower dose of intravenous alteplase (0.6 mg/kg) and MTE between 2017 and 2018, and 34 were treated with a standard dose of intravenous alteplase (0.9 mg/kg) and MTE in 2019. **Table 1** shows that there were some differences in baseline demographic and clinical characteristics between the two groups. Compared to the standard-dose group, those with low-dose alteplase before MTE were more likely to have a more severe stroke, indicated by greater initial NIHSS mean score (median difference: 2 points; $p < 0.001$), and longer onset to hospital arrival time [mean difference (MD): 26.6 min; $p = 0.005$; **Table 1**]. Conversely, door to needle and needle to groin times for the standard-dose group, compared to the low-dose group, were about 6 min ($p = 0.094$) and 12 min ($p = 0.042$; **Table 1**), respectively. There were no significant differences between the two groups with regards to the groin to recanalization time, ischemic stroke subtype (**Table 1**), the ASPECTS, and involved vessels in cerebral angiography (**Table 2**). The solitaire device was used more frequently ($p < 0.001$) in the low-dose group (78.1%) than in the standard-dose group (26.5%), while the use of the solumbra technique was more common in the standard-dose than the low-dose group (38.2 and 5.5%, respectively; $p < 0.001$). However, there were no significant differences between the two groups in successful recanalization rates (mTICI score 2b−3) before thrombectomy (high-dose 8.8

TABLE 1 | Baseline demographic and clinical characteristics.

	0.9 mg/kg + MTE (*N* = 34)	**0.6 mg/kg + MTE (*N* = 73)**	***p*-value**
Characteristics	n (%)*or mean ± SD	n (%)*or mean ± SD	
Sex, males	21 (61.8)	46 (63.0%)	0.901
Age (years)	63.6 ± 11.8	62.4 ± 11.4	0.606
Body weight prior to alteplase (kg)	55.8 ± 7.8	56.3 ± 9.1	0.776
Systolic blood pressure (mmHg)	139.5 ± 17.9	137.8 ± 20.7	0.685
Diastolic blood pressure (mmHg)	80.6±9.4	79.5±9.7	0.579
Comorbidities			
Hypertension	15 (44.1)	19 (26.0)	0.076
Atrial fibrillation	2 (5.9)	9 (12.3)	0.497
Previous ischemic stroke	0 (0)	4 (5.5)	0.305
Diabetes mellitus	3 (8.8)	6 (8.2)	0.999
Hypercholesterolemia	2 (5.9)	2 (2.7)	0.590
Current smoker	11 (32.4)	18 (24.7)	0.485
Pre-stroke medications			
Anticoagulation	1 (2.9)	0 (0)	0.318
Antiplatelet agents	0 (0)	0 (0)	
Pre-stroke mRS			
mRS = 0	33 (97.1)	73 (100)	0.318
mRS = 1	1 (2.9)	0 (0)	
Baseline NIHSS score, mean (interquartile range)	14 (11–16)	16 (14–19)	**0.001**
Onset to hospital arrival (minute)	103.2± 45.9	129.8±43.4	**0.005**
Onset to needle time (minute)	157.1± 43.6	175.6 ± 43.3	**0.043**
Onset to needle time, category			
<3 h	22 (64.7)	42 (57.5)	0.531
3–4.5 h	12 (35.3)	31 (42.5)	
Onset to groin puncture (minute)	202.2 ± 53.8	206.3 ± 47.9	0.699
Intracranial atherosclerosis	20 (58.8)	46 (63.0)	0.678
Need of placement of permanent intracranial stent during MTE to achieve recanalization	5 (14.7)	0 (0)	**0.003**
Subtype by TOAST classification			
Large artery disease	17 (50.0)	42 (57.5)	0.466
Cardioembolism	10 (29.4)	20 (27.4)	0.829
Undetermined	7 (20.6)	11 (15.1)	0.477

**Otherwise indicated. Bold denotes statistically significant results. MTE, mechanical thrombectomy; TOAST, trial of ORG 10172 in acute stroke treatment; NIHSS, national institutes of health stroke scale; mRS, modified rankin scale.*

TABLE 2 | Baseline characteristics of acute ischemic stroke on cerebral angiography.

	0.9 mg/kg + MTE (*N* = 34)	0.6 mg/kg + MTE (*N* = 73)	*p*-value
Characteristics	n (%)*	n (%)*	
ASPECTS, median (interquartile range)	8 (7–9)	8 (7–9)	0.754
Involved vessel (occlusion site)			
Internal carotid artery	9 (26.5)	16 (21.9)	0.604
Tandem	4 (11.8)	11 (15.1)	0.647
M1 segment of MCA	16 (47.1)	36 (49.3)	0.828
M2 segment of MCA	5 (14.7)	10 (13.7)	0.889
Door to needle (minute)	53.9 ± 25.1	45.8 ± 13.5	0.094
Door to groin (minute)	98.5 ± 35.5	76.5 ± 20.1	**0.002**
Needle to groin time (minute)	42.9 ± 32.4	30.7 ± 14.9	**0.042**
Mechanical thrombectomy technique			
Solitaire	9 (26.5)	57 (78.1)	**<0.001**
Penumbra	8 (23.5)	11 (15.1)	0.284
Solumbra	13 (38.2)	4 (5.5)	**<0.001**
No device	4 (11.8)	1 (1.4)	**0.034**
Collateral status, grade			
0–1 (poor collateral)	14 (41.2)	0 (0)	**<0.001**
>1	11 (32.4)	34 (46.6)	
Missing data	9 (26.5)	39 (53.4)	
Successful reperfusion before thrombectomy	3 (8.8%)	1 (1.4%)	0.520
Number of attempts to achieve recanalization	1 (1–2)	2 (1–2)	0.075
Recanalization achieved ≤24 h	27 (79.4)	61 (83.6)	0.601
Groin to recanalization time (minute)	40.4 ± 28.6	43.0 ± 25.8	0.403
Onset to recanalization time (minute)	242.7 ± 65.3	249.3 ± 54.6	0.587

**Otherwise indicated. Bold denotes statistically significant results. MTE, mechanical thrombectomy; ASPECTS, alberta stroke programme early CT score; mTICI, modified thrombolysis in cerebral infarction scale; MCA, middle cerebral artery.*

vs. low-dose 1.4%; $p = 0.520$; **Table 2**) and after thrombectomy (97.1 and 95.9%; $p = 0.922$; **Table 3**).

The factors that met our criteria for being included in the multivariable models were age, sex, history of hypertension, initial NIHSS, onset to needle time, needle to groin time, and where applicable, the MTE technique was used. After accounting for potential confounding factors (**Table 3**), it was found that early neurologic improvement, recanalization, 90-day mortality, and functional outcome at 90 days were not statistically significant between the two groups. Those receiving low-dose alteplase before MTE had lower odds of having ICH complications compared to the standard-dose group, but the differences were not statistically significant. The findings were consistent with those from sensitivity analyses accounting for some relevant covariates not meeting the criteria for being confounders (i.e., groin to recanalization time, successful reperfusion before thrombectomy, and a number of attempts to achieve recanalization; **Table 3**).

DISCUSSIONS

Our single-center retrospective study showed no statistically significant differences in clinical outcomes and ICH complications between two groups of LVO-AIS patients treated with low-dose vs. standard-dose bridging alteplase before MTE, after accounting for confounding factors. The findings are consistent with those from the Korean (18)and Taiwanese contexts (19), noting the limited number of cases with bridging therapy (Taiwan, $N = 42$; Korea; $N = 64$; the present study; $N = 107$).

For both groups, MTE was performed immediately following thrombolysis and we continued alteplase infusion during thrombectomy, even with those who achieved successful recanalization. High recanalization rates (>95%) presented in this study are consistent with previous studies conducted in Asian populations. In the SKIP trial conducted in Japan, the rate of successful reperfusion was 92% among those receiving low-dose alteplase bridging with MTE (2, 20). Similar high recanalization rates were observed in the Korean ENCHANTED study on a subset of patients receiving alteplase bridging with MTE (low-dose IVT: 85% vs. standard-dose IVT: 76%) (18) and the Taiwanese study (low-dose IVT: 100% vs. standard-dose IVT: 69%) (19). In a study conducted in Southern Vietnam, among those with standard-dose alteplase bridging therapy, the recanalization rate was approximately 88% (onset to groin time ∼270 min) (21). Our study findings showed no significant time delays occurred between drip and groin puncture time (∼40 min; onset to groin time: up to 206 min), which may contribute to the high recanalization rates in both arms, despite a relatively high rate of large artery disease etiology presented in the study (∼50%). There is a possibility of selection bias in the study.

TABLE 3 | Outcomes and complications of low-dose and standard-dose intravenous alteplase bridging with thrombectomy.

Variable	0.9 mg/kg (*N* = 34) *n* (%)	0.6 mg/kg (*N* = 73) *n* (%)	*p*-value[†]	Unadjusted OR	Adjusted OR (95% CI), model A[‡]	Adjusted OR (95% CI), model B[‡]
Primary outcome						
90-day functional independence (mRS≤ 2)	22 (64.8)	50 (68.5)	0.053	0.84 (0.36–1.99)	1.02 (0.29–3.52)[a]	1.12 (0.31–4.13)[b]
Secondary outcomes						
Early neurologic improvement[*]	14 (41.2)	46 (63.0)	0.204	2.43 (1.06; 5.59)	1.89 (0.54–6.66)[a]	1.91 (0.52–6.98)[c]
Successful recanalization (TICI score 2b−3)	33 (97.1)	70 (95.9)	0.922	0.71 (0.07–7.06)	1.18 (0.10–13.9)[d]	1.24 (0.08–20.5)[e]
Any ICH while in hospital	11 (32.4)	19 (26.0)	0.083	0.74 (0.30–1.79)	0.58 (0.18–1.84)[d]	0.49 (0.15–1.65)[f]
sICH	4 (11.8)	4 (5.5)	0.085	0.43 (0.10–1.85)	0.30 (0.04–2.41)[d]	0.16 (0.02–1.46)[f]
90-day mortality	3 (8.8)	2 (2.7)	0.053	0.29 (0.05–1.83)	0.16 (0.01–2.47)[d]	0.11 (0.01–1.18)[b]

*MTE, mechanical thrombectomy; mRS, modified rankin scale; ICH, intracranial hemorrhage; sICH, symtomatic ICH; NIHSS, national institutes of health stroke scale; OR, odds ratio; NA, not applicable due to insufficient cases. *Early neurologic improvement defined as a reduction of ≥8 points on the NIHSS score, or an NIHSS score of 0 or 1 at 3 days; [†]From Chi-square test; ‡Model A included age, sex, and the variables that showed a p-value <0.1 (where possible together with sufficient cases) as specified in the Methods section. Model B, as a sensitivity analysis, included the factors not meeting the criteria for inclusion in model A but potentially impacting relevant outcomes.*

[a]Adjusted for age, sex, hypertension, initial NIHSS, onset to needle time, needle to groin time, and MTE technique.

[b]Adjusted for age, sex, hypertension, initial NIHSS, onset to needle time, needle to groin time, groin to recanalization time, MTE technique.

[c]Adjusted for age, sex, hypertension, initial NIHSS, onset to needle time, needle to groin time, groin to recanalization time, MTE technique, recanalization ≤24 h.

[d]Adjusted for age, sex, hypertension, initial NIHSS, onset to needle time, and needle to groin time.

[e]Adjusted for age, sex, hypertension, initial NIHSS, onset to needle time, needle to groin time, groin to recanalization time, successful reperfusion before thrombectomy, and number of attempts to achieve recanalization.

[f]Adjusted for age, sex, hypertension, initial NIHSS, onset to needle time, needle to groin time, groin to recanalization time, and number of attempts to achieve recanalization.

There were significant delays in stroke onset to hospital arrival time whereby about 70% of those with stroke admitted to our stroke unit are not eligible for IVT therapy. In our stroke center, MTE was performed in 160 ischemic stroke patients in 2017, 180 in 2018, 230 in 2019, but most of them were provided with thrombectomy procedures, either within 4.5–8 h of stroke onset or within 4.5 h, but they also had contraindications for intravenous thrombolysis (IVT). These patients were therefore excluded from the study, which had a focus on comparing low-dose vs. standard-dose intravenous alteplase (≤4.5 h) prior to MTE (≤ 6 h).

Our study has several limitations and strengths. This is a single-center retrospective study that included patients receiving either standard- or low-dose alteplase prior to MTE from two different time periods. There could be a risk of selection bias due to the lack of randomization. We attempted to account for the differences in patient characteristics and clinical factors between two groups in our data analyses. However, residual confounding is likely due to poorly measured (e.g., collateral status) or unmeasured confounding factors (e.g., thrombus time) in the study. The sample size was small, which limited our study power particularly for comparing secondary outcomes (e.g., ICH complications) among the two groups of patients. We were also unable to perform sensitivity analyses using alternative statistical methods, such as the propensity score matching approach. To our knowledge, this is one of the rare three studies (18, 19), all based on Asian populations, and the study with the largest sample among the three to compare low-dose and standard-dose in bridging therapy to date. Given potential racial and ethnic differences in patient characteristics and outcomes after reperfusion therapy (e.g., higher risk of ICH and intracranial atherosclerosis), the conclusion of the study can only be applicable to an Asian population. Our study is the first to report the outcomes among Vietnamese patients with different doses of intravenous alteplase prior to MTE using data from a high-volume stroke center with no significant delays in door to groin times and higher reperfusion rate. However, the findings should be interpreted in the context of selected high-volume stroke centers in Asia whereby only a small proportion of patients were eligible for endovascular treatment due to delays in stroke onset to hospital arrival time.

The study findings show no differences in clinical outcomes and ICH complications between low-dose vs. standard-dose bridging alteplase before MTE. The number of treated patients was too low to show non-inferiority of low-dose treatment. The approach of treating low-dose alteplase patients with LVO-AIS may prove beneficial by future studies for cases presenting directly to a thrombectomy-capable stroke center and to Asian populations with higher bleeding risks. Larger randomized trials are needed to demonstrate whether a low alteplase dose retains the same efficacy as the standard dose. The role of

tenecteplase (TNK) in bridging therapy could also prove to improve clinical outcomes in patients requiring bridging therapy. According to the Tenecteplase vs. Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial (22), TNK before thrombectomy demonstrated at least non-inferior to alteplase in restoring perfusion in the territory of a proximal cerebral-artery occlusion and functional outcome than alteplase among patients with ischemic stroke treated within 4.5 h after symptom onset. The Ministry of Health in Vietnam has only approved the use of TNK for patients with acute myocardial infarction. The possible superiority of TNK compared to alteplase suggests that the newer generation of thrombolytic drugs (e.g., TNK) are promisingly alternative thrombolytic for cases with LVO-AIS in future practice, but further clinical trials are required.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This retrospective study was approved by the Ethics Committee of Hanoi Medical University, No 187/HĐĐĐĐHYHN on February 20, 2016.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the study concept and design, acquisition of data, or data analysis, and interpretation of data. The authors also took part in drafting the article, and/or revising the manuscript critically for important intellectual content, read and gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.653820/full#supplementary-material

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OPINION
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Addressing the Stroke Triage Challenge

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Keywords: stroke, paramedic (doctor's assistant), triage – emergency service, ambulance, thrombolytic, thrombectomy, education, acute stroke

The treatment of acute ischemic stroke (AIS) has undergone a revolution. More than two decades have passed since the use of intravenous thrombolysis (IVT) was approved for use within 4.5 h of symptom onset (1). The phrase "Save a minute, save a day" has been used to describe the profound effect of time savings where IVT is administered (2).

Newer works have shown that IVT can also be effective in selected patients up to 9 h after the onset of symptoms (3).

More severe ischemic strokes caused by a large vessel occlusion (LVO) are associated with significantly higher morbidity and mortality rates. Successful Mechanical Thrombectomy (MT) for LVO stroke within 6 h has a number needed to treat (NNT) for an improvement in clinical outcome as low as 2.6 (4). Based on newer trials in 2015 the time frame for MT in patients with a LVO stroke was expanded to 8 h from symptom onset (5). Later the same year, this time frame was expanded to 12 h (6). The latest in this succession of MT trials has shown that carefully selected patients with LVO can benefit from treatment up to 24 h after symptom onset (7). These randomized controlled trials selected patients using advanced radiological imaging to determine the presence of viable penumbra.

Despite the expansion of the treatment window early treatment is crucial. If the time saving in the setting of IVT wasn't profound enough, saving a minute prior to treatment in the setting of Mechanical Treatment (MT) grants a week of disability free life (8). This time saving has now been quantified and puts even more emphasis on efficacious treatment – "Save a minute, Save a week". In setting of acute stroke treatment every minute counts. The afore mentioned trials have shown that a significant number of patients achieve functional independence (mRS 0–2) (6, 9) with the vast majority requiring only modest assistance (mRS 0–3) (10). Time to treatment has been shown to be the key factor associated with better clinical outcome in a large metanalysis (10). The clinical outcomes are significant for each individual patient, but also have a greater socioeconomic impact. The annual cost of care owing to residual stroke morbidity is as great as 90,000 USD, whereas patients achieving functional independence have a significantly lower cost of care, around 15,000 USD (11).

This paradigm shift in treatment has led to an increased burden of duty on paramedics and emergency medical services (EMS) worldwide. The focus being firmly placed on rapid triage and transport of these patients to appropriate stoke treatment centers. Traditionally the FAST (Face, Arms, Speech, Time) acronym has been used to detect a suspected stroke (12). FAST, as a pre-hospital triage tool, has low sensitivity for the detection of a LVO stroke. This has led to the development more specialized stroke triage scales (13, 14). The aim of these newer scales has been to more accurately detect LVO stroke and triage patients to centers offering MT, avoiding unnecessary delay at primary treatment centers. Triaging patients with more severe strokes to comprehensive treatment centers where MT can be performed has been shown to be effective (15). A plethora of these pre-hospital triage scales have been developed showing similar accuracy (16). Centers where Emergency Medical Services (EMS) services employ the use of these newer triages scales have shown time savings and clinical benefit for those patients requiring MT (17).

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These newer pre-hospital scales have however only been put into clinical practice at a limited number of pre-hospital services. In addition to a lack utilization of newer pre-hospital triage scales the time window for urgent triage must be addressed. The majority of triage systems used by the EMS in Scandinavia and Europe prioritize acute ischemic stroke symptoms as urgent within 6 h of symptom onset (18, 19). This, based on the AHA/ASA recommendations, is also the case for severity-based triage used across the USA (20).

This shortened time frame excludes patients eligible for rapid reperfusion therapy from 6 to 24 h of symptom onset; precluding more than 50% of the therapeutic window (18). Similarly, patients with unknown symptom onset or wake up strokes are also not always triaged as urgent. These patients potentially stand to benefit greatly from reperfusion therapy (21).

Mobile Stroke Units (MSU) are an innovative strategy employed with great success in some countries with improved stroke treatment times and clinical outcomes (22). However, this strategy relies on large ambulances with trained personnel being able to effectively access the patient population (23). Furthermore, the cost-effectiveness of this initiative is yet to be established for more generalized use (24). Ultimately, with or without access to MSU, symptom recognition, and correct EMS triage are paramount.

EMS worldwide should aim to implement advanced triage scales into clinical practice. In recent years paramedics have successfully used more advanced diagnostic scales. Some examples of these scales, amongst many others, include CPSSS (25), RACE (14), and ACT-FAST (26). Their use has been validated in the setting of LVO diagnostics; showing an excellent degree of agreement between doctors and paramedics (26). This will not only augment the detection of a suspected stroke, but also help guide the patient to the appropriate treatment center and treatment pathway. The new expanded treatment windows for MT in the setting of LVO stroke should also be implemented into clinical practice. Limiting the urgent triage response to 6 h significantly limits the therapeutic window for these patients and eventual reperfusion therapy. These two factors in combination warrant an overhauling of current pre-hospital stroke triage guidelines.

These newer triage routines have the potential to be implemented in emergency departments in small hospitals where comprehensive stroke treatment isn't offered. Patients showing symptoms of LVO stroke based on the use of newer stroke triage scales arriving at hospitals where MT isn't offered could be transferred directly to comprehensive stroke centers. This would mean that a patient needing MT wouldn't need to undergo a primary evaluation at one hospital before being transferred to a nearest comprehensive stroke center, reducing significant delays before recanalization.

Newer triage routines are being implemented too slowly and patients worldwide are being precluded from treatment daily. The mainstay of this implementation should be based on paramedic education and updating of existing triage algorithms. A better understanding of the recent advances in stroke treatment and implementation of newer pre-hospital triage scales could offer potentially life-saving treatment to many more patients.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Benchmarking the Extent and Speed of Reperfusion: First Pass TICI 2c-3 Is a Preferred Endovascular Reperfusion Endpoint

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Background and Purpose: End-of-procedure substantial reperfusion [modified Treatment in Cerebral Ischemia (mTICI) 2b-3], the leading endpoint for thrombectomy studies, has several limitations including a ceiling effect, with recent achieved rates of ∼90%. We aimed to identify a more optimal definition of angiographic success along two dimensions: (1) the extent of tissue reperfusion, and (2) the speed of revascularization.

Methods: Core-lab adjudicated TICI scores for the first three passes of EmboTrap and the final all-procedures result were analyzed in the ARISE II multicenter study. The clinical impact of extent of reperfusion and speed of reperfusion (first-pass vs. later-pass) were evaluated. Clinical outcomes included 90-day functional independence [modified Rankin Scale (mRS) 0–2], 90-day freedom-from-disability (mRS 0–1), and dramatic early improvement [24-h National Institutes of Health Stroke Scale (NIHSS) improvement ≥ 8 points].

Results: Among 161 ARISE II subjects with ICA or MCA M1 occlusions, reperfusion results at procedure end showed substantial reperfusion in 149 (92.5%), excellent reperfusion in 121 (75.2%), and complete reperfusion in 79 (49.1%). Reperfusion rates on first pass were substantial in 81 (50.3%), excellent reperfusion in 62 (38.5%), and complete reperfusion in 44 (27.3%). First-pass excellent reperfusion (first-pass TICI 2c-3) had the greatest nominal predictive value for 90-day mRS 0–2 (sensitivity 58.5%, specificity 68.6%). There was a progressive worsening of outcomes with each additional pass required to achieve TICI 2c-3.

Conclusions: First-pass excellent reperfusion (TICI 2c-3), reflecting rapid achievement of extensive reperfusion, is the technical revascularization endpoint that best predicted functional independence in this international multicenter trial and is an attractive candidate for a lead angiographic endpoint for future trials.

Clinical Trial Registration: http://www.clinicaltrials.gov, identifier NCT02488915.

Keywords: intra-arterial therapy, reperfusion grading, reperfusion, brain ischaemia, cerebral infacrction, stent retriever, mechanical thrombectomy

INTRODUCTION

The current consensus statement-endorsed benchmark for procedural success after intra-arterial stroke therapy (IAT) is procedure end substantial reperfusion [modified Treatment in Cerebral Ischemia (mTICI) score of 2b or higher], defined as the restoration of anterograde tissue perfusion in more than 50% of the target downstream territory (1, 2). The impressive clinical benefits observed in recent thrombectomy trials reflected improved reperfusion with second generation devices, most notably stent retrievers (3, 4). Since these pivotal trials, there has been a further increase in reported rates of substantial reperfusion (5). In the recent ARISE (Analysis of Revascularization in Ischemic Stroke with EmboTrap) II study, the core lab-adjudicated TICI 2b-3 rate at procedure end was 92.5% (6).

However, there are considerable limitations to using the rate of TICI 2b-3 as a lead technical efficacy endpoint for IAT trials. First, this endpoint counts moderate reperfusion as a success, but when reperfusion is only 50–90% achieved, substantial tissue volumes remain in jeopardy. Second, the outcome of TICI 2b-3 is considered a success regardless of the number of passes required to achieve it, but maximal benefit is likely to be conferred by first-pass success, thus reducing ischemia duration (7). Third, the high rate of TICI 2b-3 seen with modern endovascular technology results in a ceiling effect, making the measure insensitive to further improvements in endovascular technique. Accordingly, a reevaluation of the optimal angiographic endpoint is necessary.

Using core-lab adjudicated data from ARISE II, we aimed to assess the clinical impact of the first-pass effect (FPE) and to identify the optimal definition of angiographic success along two dimensions: (1) the extent of tissue reperfusion, and (2) the speed of revascularization.

Abbreviations: ARISE II, Analysis of Revascularization in Ischemic Stroke with EmboTrap II study; ASPECTS, Alberta Stroke Program Early CT Score; ASTER, Direct Aspiration First Pass Technique for Thrombectomy Revascularisation of Large Vessel Occlusion in Acute Ischaemic Stroke; FP, first pass; FPE, first pass effect; HERMES, Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials Collaboration; IAT, intra-arterial stroke therapy; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; mTICI, modified Treatment in Cerebral Ischemia; ROC, receiver-operating characteristic curve; sICH, symptomatic intracranial hemorrhage; TICI, Treatment in Cerebral Ischemia.

MATERIALS AND METHODS

All data generated or analyzed during this study are included in this published article and its **Supplementary Material**. The ARISE II study design and methods have been previously described (6). The study protocol was approved by the institutional review board/ethics committee at each participating site. All patients or their legally authorized representatives provided written informed consent before enrollment. To analyze a cohort with similar relationships between perfusion deficits and outcomes, only anterior circulation occlusions were included. To limit variability in the size of the at-risk territory, M2 occlusions were excluded, leaving only internal carotid artery (ICA) and middle cerebral artery (MCA) M1 occlusions in the study cohort. Angiographic endpoints were core lab-adjudicated and included TICI scores after each of the first three EmboTrap passes and final TICI score after all interventions. TICI scoring was inclusive of the 2c score (near complete or >90% reperfusion of the downstream territory). Core lab readers were blinded to clinical outcomes.

Statistical Analysis

Baseline characteristics were reported using standard descriptive statistics. Parametric and non-parametric methods were applied where appropriate.

The clinical impact of first-pass reperfusion was measured controlling for final reperfusion grade. For example, among subjects with final TICI score of 3, the subgroup where TICI 3 was achieved on the first pass was compared with the subgroup requiring multiple passes. These subgroups were compared on four efficacy and two safety outcomes. The primary efficacy outcome was 90-day functional independence [modified Rankin Scale (mRS) 0–2]. Additional efficacy outcomes were 90-day freedom from disability (mRS 0–1), 90-day level of disability (ordinal 6-level mRS), and dramatic early improvement [24-h National Institutes of Health Stroke Scale (NIHSS) improvement ≥8 points]. Safety outcomes were symptomatic intracranial hemorrhage (sICH) and 90-day mortality. Endpoints were assessed using the Chi-squared, Fisher's Exact, or Wilcoxon rank sum test as appropriate. This analysis was similarly done for subjects with final TICI 2c and separately 2b. Multiple logistic regression analysis for 90-day mRS 0–2 was performed to assess the impact of first-pass success adjusting for covariates with univariate $P < 0.1$.

To explore the effect of final reperfusion extent on functional outcome, 90-day mRS scores were compared between final

TICI grades using the Jonckheere-Terpstra trend test. Receiver-operating characteristic (ROC) analysis was used to identify the optimal TICI threshold for discriminating 90-day mRS 0–2 and 0–1, and 24-h NIHSS improvement of 8 or more points.

The extent of reperfusion at procedure end that was most strongly associated with outcomes was assessed by comparing: substantial reperfusion (mTICI 2b-3), excellent reperfusion (TICI 2c-3), and complete reperfusion (TICI 3). The extent measure that nominally performed best was then further tested to assess the impact of speed of attainment, by comparing achievement on first, second, third, or fourth or higher passes.

Because the core lab assessed reperfusion after each of the first three passes and at procedure end, all passes beyond the third were aggregated into a single category. The effect of the number of passes on 90-day mRS was evaluated using the Jonckheere-Terpstra trend test. ROC analysis was used to identify the optimal number of passes for predicting 90-day functional independence, 90-day freedom-from-disability and 24-h dramatic neurologic improvement. In all ROC analyses, the optimal operating point was defined as the point with the maximum Youden index (=sensitivity + specificity − 1). Statistical significance was defined as two-tailed P-value < 0.05.

Statistical analysis was performed using MedCalc Software version 19 (Ostend, Belgium). The conclusions were verified by an independent statistician using SAS version 9.4 software (Cary, NC).

ARISE II was sponsored by Neuravi, Inc., currently Cerenovus/Johnson & Johnson. This study is the academic work of the authors. The sponsor played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

TABLE 1 | Baseline characteristics of study population ($n = 161$).

Variable	
Age (years); mean ± SD	66.7 ± 13.3
Female sex; *n* (%)	92 (57.1%)
Baseline NIHSS score; median (IQR)	16 (13–20)
Baseline NCCT ASPECTS; median (IQR) ($n = 124$)	10 (10–10)
Occlusion level; *n* (%)	
ICA	35 (21.7%)
MCA M1	126 (78.3%)
IV tPA treatment; *n* (%)	106 (65.8%)
Hypertension; *n* (%)	107 (66.5%)
Diabetes mellitus; *n* (%)	31 (19.3%)
Atrial fibrillation; *n* (%)	62 (38.5%)
Dyslipidemia; *n* (%)	63 (39.1%)
Smoking; *n* (%)	42 (26.1%)
Previous stroke/transient ischemic attack; *n* (%)	29 (18.0%)
Previous MI/CAD; *n* (%)	35 (21.7%)
Clinical and safety outcomes	
24-h NIHSS score; median (IQR) ($n = 155$)	4 (1–14)
Dramatic neurologic improvement [Baseline to 24-h NIHSS score improvement ≥ 8 points; *n* (%)]	94/155 (60.6%)
90-day disability level mRS; median (IQR) ($n = 156$)	1.5 (0–4)
90-day functional independence, mRS 0–2; *n* (%)	103/156 (66.0%)
90-day freedom-from-disability, mRS 0–1; *n* (%)	78/156 (50.0%)
90-day mortality; *n* (%)	14/156 (9.0%)
sICH; *n* (%)	10 (6.2%)

SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; IV tPA, intravenous tissue plasminogen activator; IQR, interquartile range; MI/CAD, myocardial infarction/coronary artery disease; mRS, modified Rankin Scale; NCCT ASPECTS, non-contrast CT Alberta Stroke Program Early CT Score; sICH, symptomatic intracranial hemorrhage.

RESULTS

Overall Angiographic Results

Two hundred twenty-seven patients were treated with EmboTrap in ARISE II. Nine basilar occlusion patients and 57 M2 occlusion patients were removed for this analysis. Baseline characteristics and outcomes are provided in **Table 1**. Of the 161 patients meeting study entry criteria, 149 (92.5%) patients had substantial reperfusion at procedure end (final TICI 2b-3): 28 (17.4%) final TICI 2b; 42 (26.1%) final TICI 2c; and 79 (49.1%) final TICI 3. The median number of thrombectomy passes was 2 [interquartile range (IQR) 1–3], and the highest number of passes was 9. Median procedural time was 44 (IQR 27–70) min.

Substantial reperfusion (TICI 2b-3) after the first pass was seen in 81 (50.3%) patients: 19 (11.8%) first-pass TICI 2b; 18 (11.2%) first-pass TICI 2c; and 44 (27.3%) first-pass TICI 3. In the remainder, there were 53 (32.9%) first-pass TICI 0–1 and 27 (16.8%) first-pass TICI 2a. Median procedural time from groin puncture to achieving TICI ≥ 2b was 27 (IQR 22–38) min in the subjects who had first-pass TICI 2b-3 vs. 61 (IQR 46–86.5) min in those who achieved TICI 2b-3 after two or more passes ($P < 0.0001$).

First-Pass Success vs. Multiple Passes: Final Angiographic and Clinical Outcomes

Supplementary Material enumerates the breakdown of final TICI results based on the first pass TICI score. When controlling for final reperfusion grade, there were significantly better 90-day ordinal mRS outcomes among patients who achieved their final TICI score on the first pass compared to multiple passes (**Figure 1**). For final TICI 2b, the median 90-day mRS scores were 1 (IQR 0–3) vs. 3 (IQR 2–4) for the first-pass group vs. the multiple-pass group ($P = 0.04$). For final TICI 2c, the median 90-day mRS scores were 0 (IQR 0–2) vs. 2 (IQR 1–4) (first-pass group vs. the multiple-pass group; $P = 0.004$). For final TICI 3, the median 90-day mRS scores were 1 (IQR 0–2) vs. 2 (IQR 1–5) (first-pass group vs. the multiple-pass group; $P = 0.01$). There were no significant differences among the first-pass and multiple-pass groups for sICH and for 90-day mortality, although there were numerically more safety events in the multiple-pass groups in most cases (**Table 2**). After adjusting for age, baseline NIHSS score, baseline Alberta Stroke Program Early Computed Tomography Score (ASPECTS), vessel occlusion level, atrial fibrillation, and final TICI 2c-3 score, first-pass success (i.e., when the final TICI score is achieved on the first pass) was an

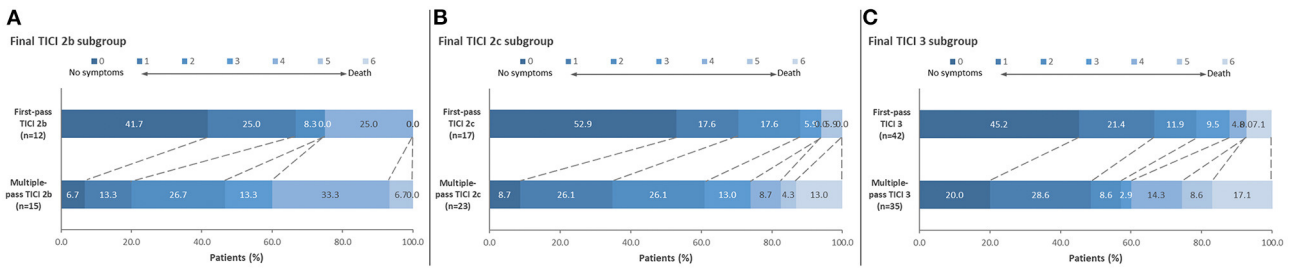

FIGURE 1 | Distribution of 90-day mRS scores comparing first-pass reperfusion vs. multiple-pass reperfusion. Results are shown for **(A)** final TICI 2b: median 90-day mRS scores were 1 (IQR 0-3) vs. 3 (IQR 2–4) for the first-pass group vs. the multiple-pass group ($P = 0.04$); **(B)** final TICI 2c: median 90-day mRS scores were 0 (IQR 0–2) vs. 2 (IQR 1–4) for the first-pass group vs. the multiple-pass group ($P = 0.004$); and **(C)** final TICI 3 patients: median 90-day mRS scores were 1 (IQR 0–2) vs. 2 (IQR 1–5) for the first-pass group vs. the multiple-pass group ($P = 0.01$).

independent predictor of 90-day mRS 0–2 [odds ratio (OR) 3.42 (95% CI, 1.27–9.17), $P = 0.01$]. The associations between the baseline variables and both 90-day mRS 0–2 and final TICI 2c-3 are provided in **Supplementary Material**.

Optimal Final TICI Score for Discriminating Good Clinical Outcome

90-day functional outcome was significantly better with greater final reperfusion extent (**Figure 2**). Median 90-day mRS was 1 (IQR 0–3.25) for final TICI 3, 1.5 (IQR 0–3) for TICI 2c, 2 (IQR 1–4) for TICI 2b, and 3.5 (IQR 2–4.5) for TICI 0-2a ($P < 0.05$; Jonckheere-Terpstra trend test). Final TICI 2c-3 showed the highest nominal accuracy for discriminating 90-day mRS 0–2 (sensitivity 79.6%, specificity 34.0%) and mRS 0–1 (sensitivity 83.3%, specificity 33.3%), and 24-h NIHSS improvement ≥8 points (sensitivity 80.9%, specificity 34.4%).

Optimal Number of Passes for Achieving Final TICI 2c-3

The median number of passes for patients with final TICI 2c-3 was one (IQR 1–3). **Figure 3A** illustrates the relationship between number of passes for achieving TICI 2c-3 and 90-day functional outcome. Median 90-day mRS was 1 (IQR 0–2) for one pass, 1 (IQR 1–4) for two passes, 2 (IQR 1–4) for three passes, and 2 (IQR 1–5) for four or more passes ($P = 0.0001$; Jonckheere-Terpstra trend test). Median procedure time for one pass was 25 (IQR 20–34) min, for two passes was 44 (IQR 35–57.5) min, for three passes was 60 (IQR 48–64) min, and for four or more passes was 76 (IQR 64.5–105) min ($P < 0.00001$; Jonckheere-Terpstra trend test). One pass showed the highest nominal accuracy for discriminating 90-day mRS 0–2 (sensitivity 58.5%, specificity 68.6%) and 24-h NIHSS score improvement ≥8 points (sensitivity 56.6%, specificity 62.5%). Importantly, there were no significant imbalances in the baseline variables between first-pass TICI 2c-3 and non-first-pass TICI 2c-3 (**Table 3**). Two or fewer passes was the optimal threshold for discriminating 90-day mRS 0–1 (sensitivity 80.0%, specificity 46.2%).

Regarding safety, each subsequent pass required to achieve TICI 2c-3 was associated with higher mortality: 90-day mortality was 5.1% (3/59) for one pass, 9.5% (2/21) for two passes, 16.7% (3/18) for three passes, and 21.1% (4/19) for four or more passes ($P = 0.03$, Chi-squared trend test). For comparison, mortality in those without reperfusion (TICI 0-2a) was 16.7%. There was no significant relationship between number of passes and sICH. Rates of sICH were 1.6% (1/62) for one pass, 4.8% (1/21) for two passes, 10.5% (2/19) for three passes, and 5.3% (1/19) for four or more passes ($P = 0.20$, Chi-squared trend test). The sICH rate for TICI 0-2a patients was 25% (3/12).

The impact of the number of passes to final TICI 2c-3 on 90-day outcome is shown separately for patients treated early from stroke onset (≤4 h to groin puncture) vs. late (>4 h) in **Supplementary Material.**

Likelihood of Achieving Final TICI 2c-3 Based on First-Pass Result

There was a significantly higher chance of achieving TICI 2c-3 on the first pass [38.5% (62/161)] compared to after the first pass [27.1% (59/217); $P = 0.02$]. Furthermore, if the first pass did not result in TICI 2c-3 and further attempts were performed, there was a higher chance of achieving final TICI 2c-3 when the first pass yielded a lower reperfusion grade. Rates of final TICI 2c-3 were 71.7% (38/53) for first-pass TICI 0-1, 55.6% (15/27) for first-pass TICI 2a, and 50% (6/12) for first-pass TICI 2b ($P = 0.08$; Chi-squared test for trend). There were more overall passes for lower first-pass TICI scores: median 3 (IQR 3–5) for first-pass TICI 0–1 vs. 3 (IQR 2–3) for first-pass TICI 2a vs. 2 (IQR 2–2.5) for first-pass TICI 2b ($P = 0.0004$; Jonckheere-Terpstra trend test).

DISCUSSION

Core-lab adjudicated ARISE II data confirm the superior clinical benefit of first-pass reperfusion. When adjusting for final TICI score, first-pass success (defined as when the final TICI score of 2b-3 is achieved on the first pass) yielded significantly better 90-day functional outcomes and was an independent predictor of 90-day independence. Furthermore, first-pass TICI 2c-3 was the optimal combination of reperfusion extent and speed for predicting good outcome after IAT. These findings were similar when restricting the analysis to subjects who received 3 or fewer passes with EmboTrap.

TABLE 2 | Dichotomized clinical and safety endpoints for first-pass vs. multiple-pass final TICI scores.

	Final 2b, FP 2b	Final 2b, not FP 2b	*P*-value	Final 2c, FP 2c	Final 2c, not FP 2c	*P*-value	Final 3, FP 3	Final 3, not FP 3	*P*-value
90-day mRS 0–2	9/12 (75%)	7/15 (46.7%)	0.24	15/17 (88.2%)	14/23 (60.9%)	0.08	33/42 (78.6%)	20/35 (57.1%)	0.04
90-day mRS 0–1	8/12 (66.7%)	3/15 (20%)	0.02	12/17 (70.6%)	8/23 (34.8%)	0.03	28/42 (66.7%)	17/35 (48.6%)	0.11
24-hr NIHSS drop 8+ pts	8/13 (61.5%)	6/15 (40%)	0.26	14/18 (77.8%)	12/24 (50%)	0.07	29/40 (72.5%)	21/34 (61.8%)	0.33
sICH	0/13	2/15 (13.3%)	0.48	0/18	3/24 (12.5%)	0.25	1/44 (2.3%)	1/35 (2.9%)	1.00
90-day mortality	0/12	0/15	NC	0/17	3/23 (13.0%)	0.25	3/42 (7.1%)	6/35 (17.1%)	0.17

FP, first-pass; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NC, not calculable; TICI, Treatment in Cerebral Ischemia scale.

The FPE has been variably defined as first-pass TICI 3 and more recently first-pass TICI 2c-3 (8–10). Our study supports the inclusion of 2c scores [defined in ARISE II as >90% anterograde reperfusion (1)] into a standardized FPE definition. Final TICI 2c-3 was achieved in 75.2% of the study cohort compared to 49.1% for TICI 3 alone and provided the best discrimination of good and excellent 90-day functional outcomes (mRS 0–1 and 0–2) and early dramatic neurologic improvement (24-h NIHSS improvement ≥8 points). This mirrors previous reports that have found similar outcomes between TICI 2c and 3 reperfusion (11, 12). In an ancillary analysis of the ASTER trial, the magnitude of benefit for achieving 90-day mRS 0–2 was congruent between TICI 2c and 3 relative to TICI 2b, and combined TICI 2c-3 patients had a significantly higher rate of favorable outcomes compared to 2b patients [OR 1.72 (95% CI, 1.01–2.90)] (12).

Another endpoint used in recent studies is first-pass TICI 2b-3, termed modified FPE (8, 9). A major limitation of this endpoint is that TICI 2b encompasses an overly broad range of reperfusion results (50–89% of the ischemic territory), many of which might be considered suboptimal currently. It is likely for this reason that the majority of first-pass TICI 2b patients [12/19 (63%)] underwent additional passes, questioning the clinical relevance of this first-pass category. There may be potential value of the expanded TICI (eTICI) scale, which subdivides TICI 2b grades into eTICI 2b50 (50–66% reperfusion) and 2b67 (67–89% reperfusion). In the HERMES dataset, the c-statistic for discriminating 90-day mRS 0–2 was slightly higher for eTICI (0.664) compared to the TICI classification employed in ARISE II (0.661), the only difference being the 2b67 categorization (13). Future studies should investigate whether a reformulation of FPE to include eTICI 2b67 results is warranted.

An additional argument against including TICI 2b scores into the FPE definition is the issue of clot fragmentation, which can impede full reperfusion. Our analysis revealed a numerically lower likelihood of achieving TICI 2c-3 when the first pass yielded TICI 2b compared to a lesser score. Among patients who underwent multiple passes, there was a stepwise reduction in final TICI 2c-3 rate from a first-pass TICI score of 0–1 (72%) to 2a (56%) to 2b (50%) ($P = 0.08$). This observation likely owes to the smaller, more distal vessel segments that remain occluded when there is greater partial reperfusion, which are more difficult and riskier to treat. This increased risk may explain why there were fewer passes performed after first-pass TICI 2a and fewer still after TICI 2b compared to TICI 0–1. In this context, both TICI 2a and 2b may be viewed as unwelcome indicators of thrombus fragmentation. Thrombus friability likely plays a central role in cases of distal embolization, and techniques should be targeted to minimize this phenomenon.

The optimal speed for attaining TICI 2c-3 was one thrombectomy pass (first-pass TICI 2c-3), which was observed in 51.2% of final TICI 2c-3 patients and best predicted 90-day good outcome and early dramatic neurological improvement compared to other numbers of passes. There was a worsening of clinical outcomes with each additional pass, consistent with prior work showing that procedural time to reperfusion is a powerful predictor of IAT outcomes (7). With regards to benchmarking device performance, the number of passes is a

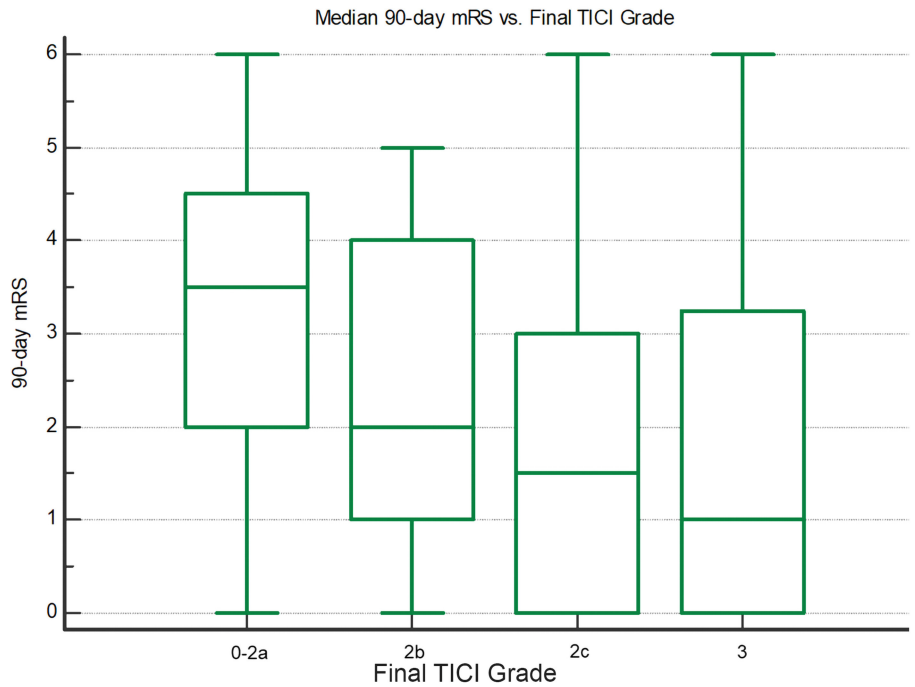

FIGURE 2 | Box-whisker plots showing median 90-day mRS vs. final TICI grade. There are significantly lower mRS scores with greater final reperfusion ($P < 0.05$; Jonckheere-Terpstra trend test).

more suitable measure of device-related revascularization speed than procedure time because it disregards the time required for vessel catheterization, a delay which is unrelated to device action and can be highly variable (14).

A substantial proportion of study patients required three or more thrombectomy passes (37% in the entire cohort, and 31% among those achieving final TICI 2c-3). In refractory cases, an important question facing neurointerventionists is how many passes should be performed before stopping. A recent study of stent retriever thrombectomy reported dismal outcomes after the third pass (7.4% rate of 90-day mRS 0–2 for passes 4 through 8) despite an ∼25% per-pass rate of TICI 2b-3 (15). Conversely, another study of largely stent retrievers (95%) found a significantly higher rate of good outcome in patients who achieved TICI 2b-3 on the fourth pass compared to non-reperfusers (16). Our analysis also suggests clinical value in pursuing more than three passes. First, even though the chance of achieving TICI 2c-3 dropped after the first pass, there was still a 30% per-pass rate of TICI 2c-3 among passes 3 or greater. And when TICI 2c-3 is achieved, there are higher rates of 90-day mRS 0–2 and 0–1 (**Figures 3A–C**) for every pass number, including four or higher, compared to non-reperfusers (final TICI 0-2a). Although many of these per-pass comparisons were not statistically significant, this may be due to small sample sizes. The clinical value of near-complete/complete reperfusion achieved in a delayed fashion is consistent with other studies showing that complete reperfusion mitigates the deleterious effect of treatment delay (16, 17). In addition, there were no obvious safety concerns with pursuing more than three passes. Although mortality increased with each additional pass required to achieve TICI 2c-3, the mortality associated with 4 or more passes (21.1%) was comparable to that seen in non-reperfusers (16.7%). Concerning sICH, there was no significant association with pass number, and the rate of sICH with 4 or more passes (5.3%) was lower than that seen in non-reperfusers (25%). Previous reports are contradictory regarding the relationship between the number of passes and hemorrhagic conversion (18, 19).

Study limitations include use of a single device for the first three thrombectomy passes, which may limit generalizability. However, it is likely that the principal findings regarding the relationship between clinical outcome and the extent and speed of reperfusion are independent of how this reperfusion is achieved. Another limitation is that the study cohort comprised largely ideal treatment candidates, as reflected in their baseline ASPECTS scores (76% with ASPECTS 10). As such, the outstanding outcomes reported here (66% mRS 0–2 and 50% mRS 0–1 at 90 days) do not reflect real-world practice. These limitations stem from the ARISE II study design as a prospective registration trial for FDA approval of EmboTrap. However, this design also lent numerous strengths to the analysis, including rigorous data collection and monitoring, minimal subject attrition (3% at 90 days), and strict core lab adjudication of reperfusion results. Unlike previous thrombectomy studies, the ARISE II core lab prospectively evaluated each of the first

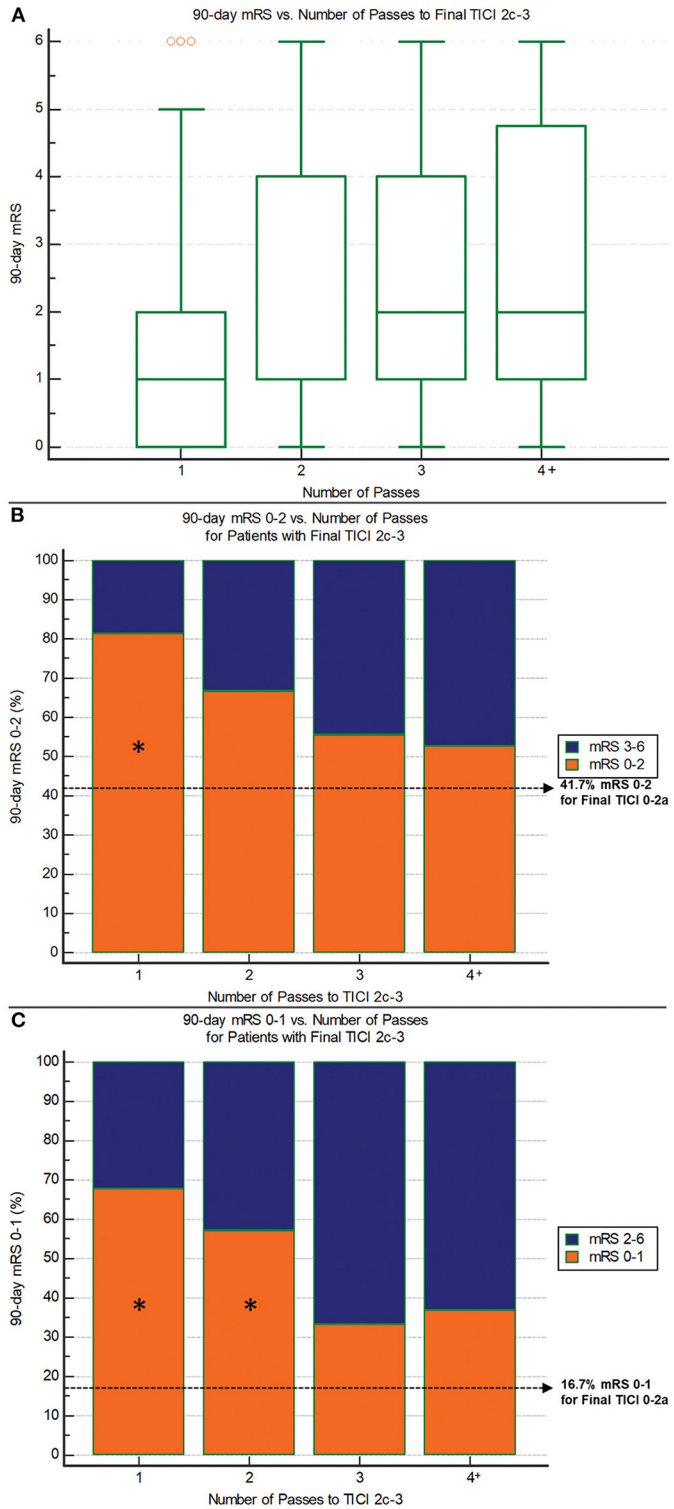

FIGURE 3 | 90-day outcomes vs. the number of passes required to reach final TICI 2c-3 reperfusion. **(A)** 90-day mRS: There are significantly lower mRS scores with fewer passes ($P = 0.0001$; Jonckheere-Terpstra trend test). **(B)** 90-day mRS 0–2: There are progressively lower rates of good outcome with increasing number of passes ($P = 0.005$; Chi-squared test for trend). Asterisk indicates significant difference compared to non-reperfusers (final TICI 0-2a). **(C)** 90-day mRS 0–1: There are progressively lower rates of excellent outcome with increasing number of passes ($P = 0.003$; Chi-squared test for trend). Asterisk indicates significant difference compared to non-reperfusers (final TICI 0-2a).

TABLE 3 | Comparison of baseline variables between first-pass TICI 2c-3 vs. non-first-pass TICI 2c-3.

Variable	FP TICI 2c-3 ($n = 62$)	Non-FP TICI 2c-3 ($n = 59$)	*P*-value
Age (years); mean ± SD	67.2 ± 12.8	66.6 ± 14.0	0.78
Female sex; *n* (%)	36 (58.1%)	36 (61.0%)	0.74
Baseline NIHSS score; median (IQR)	16.5 (12–19)	17 (14–21)	0.36
Baseline NCCT ASPECTS; median (IQR) ($n = 94$)	10 (9.5–10) ($n = 48$)	10 (9–10) ($n = 46$)	0.80
Occlusion level; *n* (%)			
ICA	14 (22.6%)	13 (22.0%)	0.94
MCA M1	48 (77.4%)	46 (78.0%)	
IV tPA treatment; *n* (%)	38 (61.3%)	44 (74.6%)	0.12
Hypertension; *n* (%)	44 (71.0%)	40 (67.8%)	0.71
Diabetes mellitus; *n* (%)	12 (19.4%)	11 (18.6%)	0.92
Atrial fibrillation; *n* (%)	22 (35.5%)	25 (42.4%)	0.44
Dyslipidemia; *n* (%)	22 (35.5%)	26 (44.1%)	0.34
Smoking; *n* (%)	13 (21.0%)	18 (30.5%)	0.23
Previous stroke/transient ischemic attack; *n* (%)	11 (17.7%)	9 (15.3%)	0.71
Previous MI/CAD; *n* (%)	18 (29.0%)	11 (18.6%)	0.18

FP, first-pass; IV tPA, intravenous tissue plasminogen activator; IQR, interquartile range; MI/CAD, myocardial infarction/coronary artery disease; NCCT ASPECTS, non-contrast CT Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TICI, Treatment in Cerebral Ischemia scale.

three thrombectomy passes, yielding novel core lab-adjudicated data concerning reperfusion speed.

CONCLUSIONS

Data from ARISE II underscore the critical impact of procedural time to reperfusion on clinical outcomes after thrombectomy. First-pass TICI 2c-3 provides the optimal measure of both extent and speed of reperfusion for predicting good functional outcome and may serve as a useful benchmark for testing device performance and thrombectomy techniques in future studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board/ethics committee at each participating site. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AY contributed to the conceptualization, methodology, software, formal analysis, and writing of the original draft of the manuscript. AY, TA, JSa, MR, HB, GD, DL, AJ, HM, OZ, and ARISE II Investigators participated in the investigation and provided resources and project administration. JSo contributed to the data visualization. AY, TA, JSa, MR, HB, HM, and OZ provided study supervision. AY, JSo, TA, JSa, MR, HB, GD, DL, AJ, HM, and OZ contributed to the review and editing of the final draft of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.669934/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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Atherosclerotic Components in Thrombi Retrieved by Thrombectomy for Internal Carotid Artery Occlusion Due to Large Artery Atherosclerosis: A Case Report

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Introduction: The correlation between the composition of thrombi retrieved by mechanical thrombectomy (MT) and stroke etiology is inconclusive. We describe a case with atherosclerotic components in thrombi retrieved by MT for acute internal carotid artery (ICA) occlusion.

Case Presentation: A 69-year-old man with acute onset of global aphasia and right hemiplegia was transferred to our institute. His baseline National Institutes of Health Stroke Scale score was 24. Magnetic resonance imaging demonstrated acute ischemic stroke in the left parietal lobe. Magnetic resonance angiography revealed occlusion of the left ICA. MT was attempted for acute left ICA occlusion. The initial angiography showed occlusion of the proximal ICA, while intraprocedural angiography revealed a large thrombus that extended from the cervical ICA to the intracranial ICA. Successful reperfusion was achieved by five passes using stent retrievers and an aspiration catheter. A large volume of red thrombus was retrieved by each pass. The final angiogram showed successful reperfusion with modified Thrombolysis in Cerebral Ischemia grade 2b and severe stenosis in the proximal ICA. Neck magnetic resonance imaging showed severe left ICA stenosis with a vulnerable plaque. Hence, his stroke etiology was determined as large artery atherosclerosis. Histopathological examination of the retrieved thrombi revealed atheromatous components, including cholesterol clefts, foam cells, and a necrotic core.

Conclusions: Atherosclerotic components in retrieved thrombi might provide useful clues for diagnosing stroke pathogenesis. Further studies are warranted to clarify the utility of assessing atheromatous components in retrieved thrombi in diagnosing stroke etiology.

Keywords: mechanical thrombectomy, cholesterol clefts, histopathology, thrombus, large artery atherosclerosis, acute ischemic stroke

INTRODUCTION

Significant advances in the technology of mechanical thrombectomy (MT) have made it possible to perform analysis of the retrieved thrombus in acute ischemic stroke patients with large vessel occlusion (1). Although previous studies have reported the correlation between structural components of retrieved thrombi on histopathology (e.g., red blood cells, fibrin/platelet compositions) and stroke pathogenesis (1, 2), histopathological findings directly linked to the diagnosis of stroke etiology remain to be elucidated. Herein, we describe a case in which atherosclerotic components were found in thrombi retrieved by MT performed for acute internal carotid artery (ICA) occlusion. The histopathological characteristics of the thrombi seen in the present case might be key findings to diagnosing stroke due to large artery atherosclerosis (LAA).

CASE PRESENTATION

History and Clinical Examination

A 69-year-old man with a history of hypertension presented with global aphasia and right hemiplegia of abrupt onset. He was transferred to our institute after 13 h after the last known well-time. His baseline National Institutes of Health Stroke Scale score was 24. Diffusion-weighted magnetic resonance imaging (MRI) revealed acute infarcts in the left parietal lobe. MR angiography revealed the left ICA occlusion (**Figure 1A**). T2*-weighted MRI performed as the routine protocol showed a susceptibility vessel sign at the top of the ICA (**Figure 1B**). Hence, MT was performed after obtaining informed consent for the procedure from the patient's family. Patient's consent was obtained for publication of this report.

Intervention

The initial left common carotid angiography showed occlusion of the proximal ICA (**Figure 1C**). The aspiration catheter was navigated to the cervical ICA through the site of occluded segment of the proximal ICA. Angiography via the aspiration catheter revealed a large filling defect that extended from the cervical ICA to the intracranial ICA (**Figure 1D**). We deployed the stent retriever from the M1 segment of the middle cerebral artery (MCA) into the cavernous portion of the ICA. After the microcatheter was removed, the aspiration catheter was advanced to the intracranial ICA until the drip rate slowed. Then, we pulled the stent retriever and aspiration catheter as a unit into the balloon-guiding catheter. Successful reperfusion was achieved with a total of five passes by the above technique (four passes with Solitaire Platinum® 6 × 40 mm, Medtronic, Irvine, California, USA, and Penumbra ACE 60 aspiration catheter, Penumbra Inc., Alameda, CA, USA; one pass with Trevo® 4 × 20 mm, Stryker Neurovascular, Fremont, California, USA, and Penumbra ACE 60 aspiration catheter). Large red thrombi were retrieved with each pass. The final angiogram showed modified Thrombolysis in Cerebral Ischemia grade 2b reperfusion and stenosis in the proximal ICA (**Figure 1E**). The stenosis rate was 65% according to North American Symptomatic Carotid Endarterectomy Trial criteria (**Figure 1F**).

Postoperative Examinations and Histopathological Findings

After the MT, we performed transthoracic and transesophageal echocardiography, along with electrocardiographic monitoring as the diagnostic workup of the embolic source, to determine if there was any other potential embolic source apart from the stenotic left ICA. However, no cardiac embolic sources were detected. Carotid artery ultrasonography showed severe stenosis with an echolucent plaque in the proximal ICA. Peak systolic flow velocity was 1.9 m/s. We have added neck MRI to evaluate the characteristics of the carotid plaque. Neck magnetization-prepared rapid gradient-echo image and maximum intensity projection images from time-of-flight MR angiography showed high signal intensity in the plaque compared with the sternocleidomastoid muscle (**Figures 1G–I**), indicating a vulnerable plaque. Although there were no embolic sources other than the carotid plaque, the possibility of cardiac source of embolism including covert atrial fibrillation could be completely excluded because of the large volume of retrieved thrombi atypical of LAA.

The specimens retrieved by MT were histopathologically analyzed. The obtained thrombi were fixed in phosphate-buffered formalin solution. Formalin-fixed specimens were embedded in paraffin, cut at 5 μm thickness, and stained with hematoxylin–eosin. Some retrieved thrombi specimens were in addition tested immunohistochemically to confirm the presence of erythrocytes, platelets, and macrophages. Images of the stained thrombi were acquired using a cellSens imaging software (Olympus Corporation, Tokyo, Japan) equipped with a light microscope (Nikon eclipse Ni, Nikon Corporation, Tokyo, Japan). Macroscopically, all retrieved thrombi were dark red in color (**Figure 2A**). Microscopic observation revealed that most of the thrombi were mainly composed of red blood cells (**Figure 2B**), although thrombi composed primarily of platelets were also observed (**Figure 2C**). The thrombus retrieved on the third pass was a red thrombus with diffuse cholesterol clefts (**Figure 2D**) and with foam cells scattered in the thrombus (**Figure 2E**). A necrotic core with aggregation of cholesterol clefts and multinucleated giant cells was also found in the platelet-rich thrombus (**Figure 2F**). Based on clinical and histopathological evaluations, his stroke etiology was determined as LAA.

Aspirin (100 mg/day) and clopidogrel (75 mg/day) were administered for secondary prevention of thromboembolism. His modified Rankin Scale score at 90 days after stroke onset was 1. Clopidogrel was discontinued at 3 months after treatment initiation. He had no recurrent ischemic stroke for 2 years after the index stroke.

DISCUSSION

We described here a patient who underwent MT for acute ICA occlusion due to LAA. Angiography during MT demonstrated a large thrombus extending from the cervical to the intracranial ICA. Histopathological examinations demonstrated that the retrieved thrombi had a variety of characteristics, including cholesterol clefts, foam cells, and a necrotic core. These

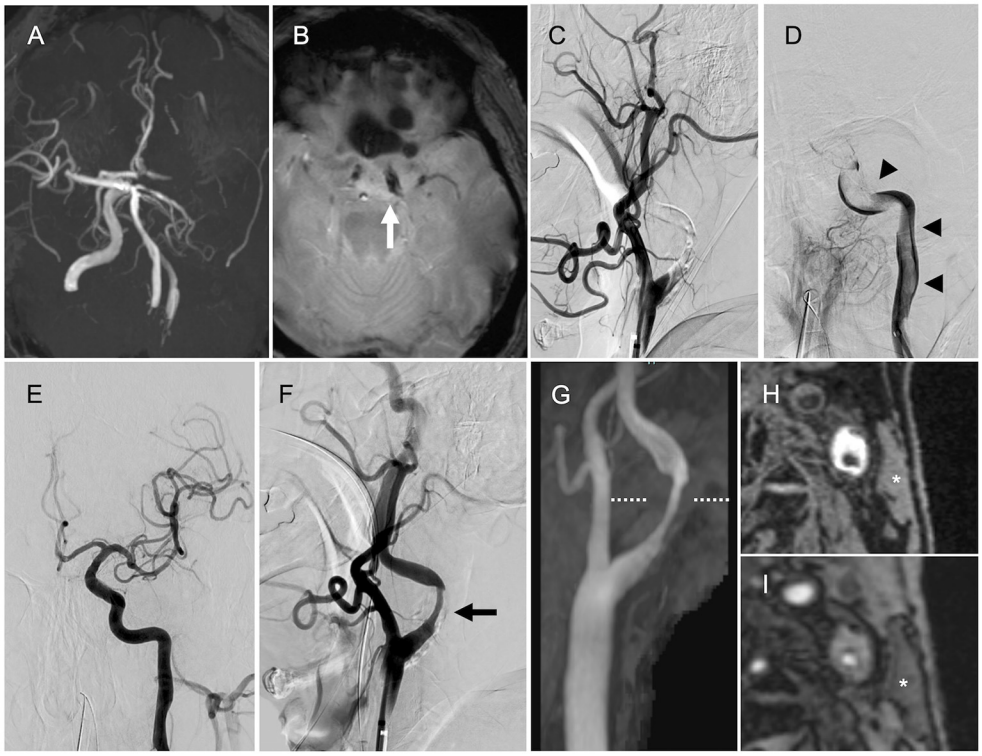

FIGURE 1 | Magnetic resonance imaging (MRI) and angiography findings. **(A)** Magnetic resonance angiography (MRA) showing the left internal carotid artery (ICA) occlusion. **(B)** T2*-weighted MRI showing the susceptibility vessel sign at the top of the ICA (*arrow*). **(C)** Left internal carotid angiography showing the left proximal ICA occlusion (lateral view). **(D)** Angiography via the aspiration catheter in the cervical ICA showing a continuous filling defect (*arrowheads*) from the cervical ICA to the intracranial ICA (anteroposterior view). **(E)** Final angiography showing successful reperfusion (anteroposterior view). **(F)** Final angiography showing the left ICA stenosis (*arrow*, lateral view). **(G)** Neck MRA showing the left ICA stenosis. **(H,I)** Magnetization-prepared rapid gradient-echo image and maximum intensity projection images from time-of-flight MRA (level of the dotted line) showing high signal intensity in the plaque compared with the sternocleidomastoid muscle (*asterisk*).

characteristics of thrombi might be a histological signature of stroke due to LAA.

In percutaneous coronary intervention for acute coronary syndrome, plaque components including vessel wall fragments, a necrotic core, cholesterol crystals, and calcification were found in aspirated coronary materials in 44% of patients (3). In MT for acute ischemic stroke, on the other hand, there is only one report on the existence of the above components in retrieved thrombi (4). Atheromatous tissues were considered to be derived from atherosclerotic plaques or concomitant plaque components retrieved with vessel walls (4). The existence of atherosclerotic components was reportedly rare and less frequently observed in thrombi by recent thrombectomy devices (stent retriever or aspiration catheter) due to less damage to the arterial wall (4–6). Since there are no data on the association between atheromatous tissues in the thrombus and the detailed stroke etiology, its diagnostic role for embolic stroke remains unclear. In the present case, cholesterol clefts were widely distributed in the thrombi retrieved using recent thrombectomy devices, indicating that atheromas were involved in the *in situ* thrombus formation process on the atherosclerotic plaque. Those findings were consistent with the ipsilateral carotid vulnerable plaque. Initially, the possible cardiac source of embolism could not be completely ruled out because of the large thrombus volume. The existence and distribution of atheromas in thrombi reinforced the diagnosis of LAA. Especially in patients who have multiple candidates of embolic sources including atherosclerotic lesions, histopathological examination of retrieved thrombi might be useful to identify the embolic source.

A previous study reported that patients with LAA are likely to have smaller clot burden than those with cardioembolic stroke (6). However, the present case had a large quantity of thrombotic tissue and the character of the thrombi varied considerably, ranging from erythrocyte-rich to platelet-rich. In addition to the initial thrombus that causes vessel occlusion, some thrombi might form after vessel occlusion secondary to blood stasis. We speculate that, in our patient, atherosclerotic plaque rupture caused occlusion of the proximal ICA due to *in situ* thrombus formation, while intracranial ICA occlusion occurred because of artery-to-artery embolism. The large thrombus volume found in the occluded segment of the ICA might have formed secondary to the occlusion. Since massive thrombi can form even in LAA, the amount of thrombus might not be a definitive diagnostic feature when determining stroke etiology.

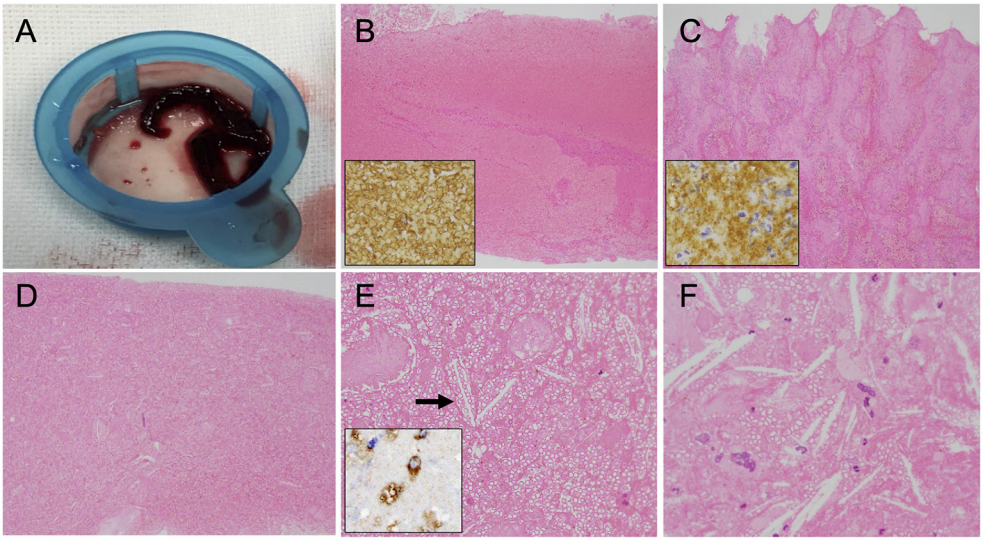

FIGURE 2 | Macroscopic and microscopic findings of the retrieved thrombi. **(A)** Macroscopic appearance of the retrieved thrombi. **(B,C)** Histopathological sections showing the erythrocyte-rich thrombus that was immunopositive for anti-glycophorin A (insert) **(B)** and the platelet-rich thrombus that was immunopositive for anti-glycoprotein IIb/IIIa (insert) **(C)**. Original magnification ×40. **(D)** Many cholesterol clefts are distributed throughout this thrombus specimen. Original magnification ×40. **(E)** Cholesterol clefts (*arrow*) and foam cells in the erythrocyte-rich thrombus. Original magnification ×200. Insert immunohistochemistry with CD68 revealing the presence of macrophages. **(F)** Necrotic core with aggregation of cholesterol clefts and multinucleated giant cells in the platelet-rich thrombus. Original magnification ×400.

CONCLUSION

We described here the histopathological report of thrombi retrieved by MT in case of LAA. In this case, we speculated that thrombi with atherosclerotic components developed at the site of the carotid plaque. Atherosclerotic components in retrieved thrombi might provide relevant information for determining stroke subtype. Further studies are warranted to clarify the utility of atheromatous components in the retrieved thrombi in the diagnosis of stroke etiology.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

FE collected the data and wrote the manuscript. JK collected and analyzed the data and wrote the manuscript. KTa and KH collected the data and revised the manuscript. TY and MS collected the data. KTo supervised the manuscript. MK revised the manuscript. All authors contributed to the article and approved the final version of the manuscript.

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frontiers in Neurology

CASE REPORT
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Case Report: Late Successful Thrombectomy for Ischemic Stroke in a 2-Year-Old Child

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Despite extensive evidence of benefit of thrombectomy in adult ischemic stroke due to large-vessel occlusion in the 6-h window, its role remains uncertain in very young children. We describe hereafter the case of a 2-year-old female child who had a successful thrombectomy 9 h after stroke onset. The patient presented with right hemiplegia, central facial palsy, a normal level of consciousness, and speech difficulties. The PedNIHS score was 11. CT scan without contrast injection displayed spontaneous hyperdensity of the middle cerebral artery (MCA), with only limited early signs of ischemia (ASPECTS 8). CT angiography demonstrated occlusion of the proximal MCA with good collaterals. Thrombectomy was realized. Complete recanalization (TICI 3) was obtained under general anesthesia after two passes of a stent retriever. Time from symptoms onset to full recanalization was 9 h. The acute ischemic stroke was caused by embolic thrombus from a congenital heart disease. Clinical recovery was complete. Three months after the thrombectomy, the young patient was doing well without any neurological sequelae (PedNIHSS 0; modified Rankin Scale: 0). This case report is an example of a decision-making process to perform thrombectomy in a very young child, which included cardio-embolic etiology as a parameter that potentially might have participated to the successful outcome of the therapeutic procedure.

Keywords: thrombectomy, child, congenital heart disease, ischemic stroke, acute stroke

INTRODUCTION

The role of thrombectomy in very young children for acute ischemic stroke due to proximal occlusion of middle cerebral artery (MCA) or internal carotid artery remains uncertain. An institutional local multidisciplinary consensus published that thrombectomy could be considered only in children older than 4 (1). Another challenge for treating these children is that they often present with a long delay from stroke onset to the recognition of stroke signs and subsequent transfer to a comprehensive stroke unit. This usually adds a second exclusion criteria based on delay for thrombectomy in children with stroke.

Our understanding of thrombectomy in this population is however changing, as recent retrospective data (2) have shown that thrombectomy in children is associated with very good outcome. The findings of another large multicentric retrospective study on thrombectomy for acute ischemic stroke in 73 patients aged <18 from 27 centers (The Save ChildS Study) suggested that neurological outcomes of the children were mostly favorable and comparable with those noted in adult trials (3). As for delay, two randomized trials in adults (DAWN and DEFUSE 3) demonstrated that the delay from stroke onset to thrombectomy can be extended beyond the usual 6-h window in patients who present a mismatch between the severity of the clinical deficit and the infarct volume, or between the infarct volume and the perfusion deficit (4, 5). Also, a secondary analysis of the Save Child study, which focused on thrombectomy performed between 6 and 24 h based on the presence of a mismatch between clinical deficit and infarct in 20 patients aged <18, revealed a good functional outcome in these patients (6).

We describe hereafter the case of a 2-year-old female child who had a successful thrombectomy performed 3 h beyond the 6-h window, for an acute ischemic stroke due to MCA occlusion caused by a thrombus originating from a congenital heart disease. The young girl had complete recovery.

PATIENT PRESENTATION, INITIAL DIAGNOSIS, AND OUTCOME

This child suffered from right hemiplegia at 7 p.m. Urgent medical attention was sought 3 h later, and the patient was oriented to the emergency ward of the nearby general hospital where a stroke unit for adults is available. CT scan without contrast injection (not shown) was performed at 11:00 p.m., and displayed spontaneous hyperdensity of the MCA, with only limited early signs of ischemia in the basal ganglia, localized in the deep left MCA territory, scored 8 on the Alberta Stroke Program Early CT Score (ASPECT score).

The child was transferred to the tertiary-care university hospital stroke unit in order to consider thrombectomy. At admission, the patient presented with right hemiplegia, central facial palsy, a normal level of consciousness, and speech difficulties. She was playing with her doll with her left arm only. The Pediatric National Institutes of Health Stroke Scale (PedNIHSS) score was 11. CT angiography demonstrated occlusion of the proximal MCA and good collaterals beyond a 15-mm-long filling defect, taking over the cortical territory (**Figure 1A**).

Because of this favorable pattern with high ASPECT score and good collateral flow, and despite the time elapsed from symptoms onset, the patient was directly transferred to the angio suite where a pediatric cardiovascular anesthesiologist performed general anesthesia. A 4-F sheath was then introduced in the right common femoral artery. A 4-F catheter was navigated into the left internal carotid artery (ICA) over a 0.035-inch Terumo wire (Terumo Medical Corporation, Somerset, NJ). A first angiogram confirmed the occluded proximal M1 segment (**Figure 1B**). An Echelon 10 microcatheter (Medtronic) was navigated into the left MCA over a Traxcess 14 micro-guidewire (Terumo Medical Corporation, Somerset, NJ) and was carefully advanced through the thrombus occluding the M1 segment. A 3 × 23 mm MindFrame Capture LP stent retriever (Medtronic Inc. Minneapolis, MN) was then deployed into the occluded artery. After 4 min, the stent retriever and microcatheter were withdrawn together, while manual aspiration was performed from the 4-F guide catheter in the ICA, using a 20-cc syringe. A small amount of dark clot was trapped into the stent. Control angiogram then revealed occlusion of the terminal ICA. Because the new site of occlusion was more proximal, we considered that dislocated clot was unlikely responsible for the new occlusion and expected vasospasm to have rapidly developed after stent retrieval in this very young patient. Because vasospasm was thus suspected, 0.3 mg of nimodipine half-diluted with serum was manually injected in the 4-F catheter over 5 min. Subsequent angiogram confirmed vasospasm diagnosis, efficiently treated by nimodipine, by showing reopening of the ICA, and partial recanalization of the MCA bifurcation. A second pass of the strentriever was realized using the same technique, and the rest of the clot successfully withdrawn. Final angiogram demonstrated total reopening of the ICA, MCA, and ACA branches, ranked 3 on the Treatment in Cerebral Infarction Score (TICI), meaning complete recanalization (**Figure 1C**). The puncture to total recanalization time, as demonstrated by a TICI 3 score on the last run of DSA, was 43 min, and time from symptom onset to full recanalization was 9 h. Extubation was performed 45 min after the end of the procedure. One hour after thrombectomy, partial recovery of the right motor deficit was already noted. The next day, follow-up brain MRI revealed acute cerebral infarction only limited to areas with early ischemic signs on initial CT in the deep left MCA territory and revealed sequelae of older ischemic lesions in the territory of the right and left MCA (**Figures 1D–F**).

FOCUS ON CONGENITAL HEART DISEASE THAT CAUSED STROKE

The child was known for complex congenital heart disease. Diagnosis of single ventricle had been established prenatally. Two palliative cardiac surgeries had been performed in neonate and at the age of 6 months. The pulmonary artery trunk had been sutured at the end of the second operation (partial cavopulmonary anastomosis). The thrombus that caused the stroke was located inside the pulmonary artery blind trunk (**Figure 2**). Plumonary artery and aorta arose from the same and single ventricle, which is the mechanism by which thrombi are believed to have embolized into the cerebral circulation.

After thrombectomy, the patient was treated with heparin and the intracardiac thrombus, monitored with cardiac echography, progressively disappeared. Clinical recovery was nearly complete, with only persistence of a subtle facial asymmetry, when the patient was discharged. Oral anticoagulant (coumadine) was then prescribed. Three months after the thrombectomy, the young patient was

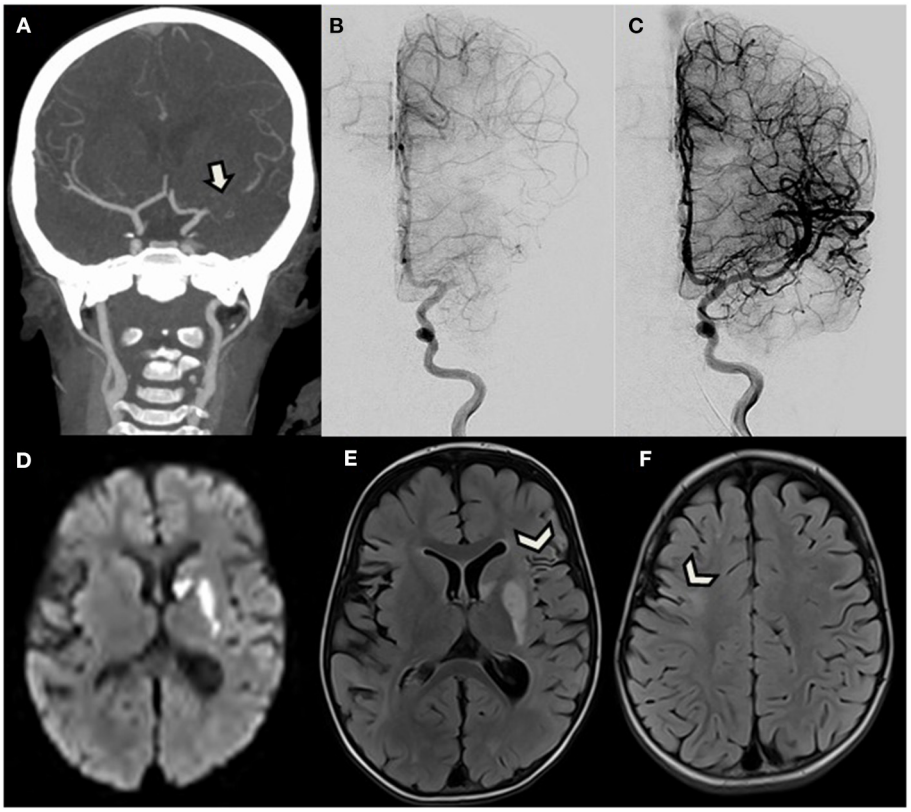

FIGURE 1 | A 2.5-year-old girl with right hemiplegia. **(A)** Reformatted coronal CT angiogram shows proximal left middle cerebral artery occlusion (arrow) with good collateral flow. **(B,C)** Antero-posterior view of digital subtracted angiogram initially confirms CTA findings, and then demonstrates complete reopening after successful thrombectomy. **(D–F)** Brain MRI performed the following day. **(D)** Axial diffusion-weighted image and **(E,F)** FLAIR demonstrate acute ischemic stroke only limited to the basal ganglia, corresponding to the same areas with early ischemic signs on initial CT (not shown), without further extension. Images also reveal sequelae of ancient cortical ischemic lesions scattered in both middle cerebral artery territories (arrowheads).

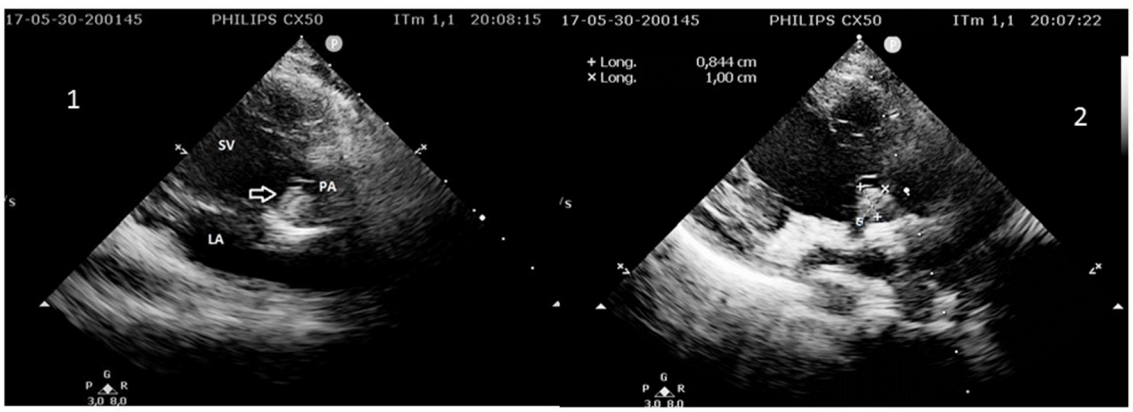

FIGURE 2 | 1. 2D echocardiography showing the mobile thrombus (arrow) inside the pulmonary artery (PA) trunk arising from the single ventricle (SV). LA, left atrium. 2. Measurement of the thrombus in the pulmonary artery (PA) trunk arising from the single ventricle (SV).

doing well without any neurological sequelae (PedNIHSS: 0; modified Rankin Scale: 0) with 85% pulse oximetry. She is under well-equilibrated anticoagulant treatment and is waiting for a third surgery planned to be a total cavopulmonary anastomosis which will be performed during the elementary school.

DISCUSSION

Recommendations concerning thrombectomy in children are scarce, because of lack of randomized trials in this population, especially at very young age. Only few years ago, some authors even advised against this treatment due to lack of sufficient data (7). More recently, a local multidisciplinary consensus recommended to propose thrombectomy only for pediatric patients older than 4 years (1). On the other hand, the prognosis of ischemic stroke in children is not less severe than in adults (8) with more than 70% morbidity (9). Thrombectomy is therefore recognized as an emerging option for selected children, even younger than 5 (10).

The multicentric retrospective study on thrombectomy for acute ischemic stroke in patients aged <18 published last year (The Save ChildS Study) included 73 patients from 27 centers with a median age of 11.3 years (interquartile range: 7–15). Its findings supported off-label thrombectomy in this population (3).

In the case we reported, the child was 2.5 years old and recanalization was achieved 9 h after stroke onset, beyond the recommended time window of 6 h commonly applied for adults who did not benefit from multimodal imaging assessing the ischemic penumbra (11). Still, clinical recovery was complete and the child had no adverse consequences of the treatment.

The outcome in this case report is in line with the findings of a secondary analysis of the Save ChildS Study that included 20 patients aged <18 who had thrombectomy between 6 and 24 h after stroke onset based on mismatch between clinical deficit and infarct (6). In the cited study by Sporns et al., the authors reported a higher proportion of good outcomes as compared to the DAWN and DEFUSE3 studies, and a similar proportion of patients with good outcome in the group treated > 6 h as compared to the group treated < 6 h (6).

Of note, thrombectomy in our case report was performed under general anesthesia, which seems not to be associated with longer time to recanalization or with different outcome in adults (12).

Only two previous cases of thrombectomy in patients <4 years of age have been published in details. These two cases had successful outcomes and occurred as a consequence of cardioembolic strokes in 2- and 3-year-old boys (13, 14). Also, reviews on thrombectomy for ischemic stroke in children found that it was associated with a high recanalization rate and a very good clinical outcome (2, 15). The Save ChildS Study, which retrospectively included 73 patients under 18, found no vascular complications such as vessel rupture or dissection during the endovascular procedure. However, only seven patients with focal or bilateral cerebral arteriopathy were included. For the authors of the paper, an a priori selection bias may have played a role in excluding children with inflammatory cerebral arteriopathy from thrombectomy and may have participated to the observed low rate of hemorrhagic complications (3).

In our case, thrombectomy was achieved 9 h after stroke onset. Thrombolysis was not given because diagnosis was made more than 4.5 h after stroke onset. The criteria of the DAWN and Defuse 3 trials (4, 5), were they to be applied to a pediatric stroke, could not be implemented to our case. The volume of the infarct core and of the ischemic penumbra could not be assessed precisely, as we did not acquire MRI with DWI nor perfusion CT, indeed. However, the association of an ASPECT score of 8 with a proximal occlusion and good collateral flow demonstrated by CTA represents a favorable pattern for thrombectomy, as suggested by dedicated *post-hoc* analysis of the MR CLEAN trial (16).

In the case we describe, the cause of stroke was cardioembolic and was not due to a cerebral vasculopathy, such as moya-moya or transient cerebral arteriopathy, which is a more frequent cause of ischemic stroke in children (10, 17). In line with the few published cases of successful thrombectomy performed in cardioembolic strokes in children, we believe that the supposed cause of stroke should weigh more than age itself in the decision to perform thrombectomy in very young children with large-vessel occlusion. Presumed cardioembolic ischemic stroke with normal underlying cerebral vasculature may carry less risk for thrombectomy than stroke from cerebral arteriopathy.

CONCLUSION

Thrombectomy is feasible in selected cases and may be clinically successful in very young children, even in case of relatively long delay between stroke onset and recanalization. The cardioembolic origin of the depicted stroke due to congenital heart disease, with absence of underlying vasculopathy, has potentially increased the odds of successful recanalization.

SUMMARY

This case report depicts late successful thrombectomy for ischemic stroke caused by congenital heart disease in a 2-year-old child, yielding complete recovery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon request.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for the case-report to be published was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

NN conceptualized the separation between ischemic stroke in small children caused by vasculopathy vs. ischemic stroke in small children caused by cardioembolic disease illustrated in this case-report, and its implication for thrombectomy, made substantial contribution to the acquisition, analysis and interpretation of data, and drafted and revised the manuscript.

LD made substantial contribution to the acquisition, analysis and interpretation of data, depicted the anesthesia procedure, participated to depicting the congenital cardiopathy, and revised the manuscript critically for important intellectual content. EC made substantial contribution to the acquisition, analysis and interpretation of data, depicted the neurological recovery, and revised the manuscript critically for important intellectual content. GC made substantial contribution to the acquisition, analysis and interpretation of data, depicted the anesthesia procedure, and revised the manuscript critically for important intellectual content. JO made substantial contribution to the acquisition, analysis and interpretation of data, and revised the manuscript critically for important intellectual content. PA made substantial contribution to the acquisition, analysis and interpretation of data, depicted the congenital cardiopathy in this patient as well as the clinical follow up, and revised the manuscript critically for important intellectual content. FB made substantial contribution to the acquisition, analysis and interpretation of data, depicted the interventional procedure in this very small patient, participated to drafting the manuscript, and revised the manuscript critically for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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ORIGINAL RESEARCH
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Endovascular Therapy vs. Thrombolysis in Pre-stroke Dependent Patients With Large Vessel Occlusions Within the Anterior Circulation

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Background: In the past few years, several randomized trials have clearly shown that endovascular treatment (ET) in addition to intravenous thrombolysis (IVT) is superior to IVT alone in patients with proximal cerebral arterial occlusions. However, the effectiveness of ET in pre-stroke dependent patients (modified Rankin Scale ≥3) is uncertain.

Methods: Using our prospectively obtained stroke database, we analyzed the impact of pre-stroke dependence on the rates of poor outcome (discharge mRS 5–6), in-hospital death, infarct sizes, and symptomatic intracranial hemorrhage (SICH) in patients with distal intracranial carotid artery M1 and M2 occlusions during two time periods.

Results: From 1/2008 to 10/2012, a total of 544 patients (455 without and 89 with dependence) were treated with IVT, and from 11/2012 to 12/2019 a total of 1,061 patients (919 without and 142 with dependence) received ET (with or without IVT). Irrespective of the treatment modality, the dependent patients had significantly higher rates of poor outcome (55 vs. 32%, $p < 0.001$), death (24 vs. 11%; $p < 0.001$), or SICH (8.2 vs. 3.6%, $p < 0.01$) than independent patients. In dependent patients, ET significantly reduced the rates of poor outcome (49 vs. 64%, $p < 0.01$) and led to smaller infarcts, whereas the rates of in-hospital death (25 vs. 22%; $p = 0.6$) or SICH (8.5 vs. 7.9%, $p = 0.9$) were comparable between both treatment modalities.

Conclusions: Compared with IVT, ET avoids poor outcome and leads to smaller infarcts in dependent patients. However, the overall high rates of poor outcome in this patient population stress the importance to perform decisions based on a case-by-case basis.

Keywords: stroke, thrombolysis, thrombectomy, outcome, endovascular, pre-stroke disability

INTRODUCTION

With the publication of five landmark trials in the year 2015, endovascular treatment (ET), in addition to intravenous thrombolysis (IVT), has become an established treatment for acute stroke patients with proximal large vessel occlusions (1–5). In these trials, the benefit of ET in addition to IVT on outcome was principally observed across all patient groups studied. However, patients with

pre-existing dependency were not included in the aforementioned large, controlled, randomized ET trials. Therefore, current stroke guidelines only state that ET may be reasonable in this patient population (6). Since pre-stroke disability will continue to rise in the coming years (7), the potential impact of ET on outcome in patients with prior disabilities has received increased attention. In fact, several recent case series as well as an analysis of the MR Clean Registry have revealed favorable functional and procedural outcome rates after ET in patients with prior disabilities compared to those without pre-stroke disability (8–11), yet all of these studies lacked a control group, such that the true treatment effect of ET in pre-stroke disabled patients is unknown.

Therefore, we analyzed the impact of preexisting dependency on clinical outcome at the time of discharge as well as the radiological outcome in patients with anterior circulation large vessel occlusions during two time periods using our prospectively obtained database of a high-volume stroke center in which patients with prior disabilities [except for severely affected patients, i.e., bedridden patients with a modified Rankin Score (mRS) of 5] are not routinely excluded from ET or IVT. During the first time period, all patients had been treated with systemic thrombolysis, whereas an endovascular therapy with stent retrievers (with or without systemic thrombolysis) was routinely used during the second time period.

METHODS

Study Population

The study population comprised all acute stroke patients with a proximal large vessel occlusion within the anterior circulation (distal intracranial carotid artery and/or M1 and/or M2 segments of the middle cerebral artery) and who had been treated from January 2008 through December 2019. The main exclusion criteria were (1) distal occlusions beyond the M2 segment, (2) posterior circulation strokes, and (3) bilateral strokes. From January 2008 to November 2012, all patients were treated with systemic thrombolysis alone, mainly using the inclusion and exclusion criteria, as well as a drug dose for thrombolytic treatment of the NINDS study protocol. At our institution, patients can be treated up to 4.5 h after symptom onset, and there is no upper age limit for eligibility.

Endovascular treatment with or without systemic thrombolysis was performed after November 2012 in all patients who presented within 6 h (within 4.5 h in patients additionally treated with rt-PA) of symptom onset (using no upper age limit or specific imaging exclusion criteria).

In each patient, the following demographic data and stroke risk factors were collected: age, gender, arterial hypertension, diabetes, and atrial fibrillation. The time to thrombolysis (or to thrombectomy in patients without prior systemic thrombolysis) from stroke onset was also noted.

Information on the pre-stroke living situation was obtained from the patients themselves, their families, their relatives, or their primary care physicians as well as outpatient medical personnel. Patients who were dependent on the daily help of others before the stroke (either coming from home or coming from a nursing home) were classified as dependent, reflecting a mRS of 3–4; all other patients were classified as independent (mRS 0–2). At our institution, bedridden patients with severe disabilities, i.e., with a mRS of 5, are usually not treated with ET. Since the exact pre-stroke mRS is often misjudged, especially in the emergency setting, dependent patients were not further subcategorized between a mRS value of 3 or 4 (12, 13).

The protocol of our stroke registry had been approved by our local ethics committee. Because of the retrospective character of this study, the lack of treatment influence, and the clinical data having been collected as part of a national quality control program, the study was exempted from informed consent. Using our stroke database, the clinical outcomes of patients treated before December 2014 as well as a subgroup analyses have been published previously (14–17).

Imaging Techniques

Non-enhanced CT (NCT) and CT angiographic acquisitions before treatment were performed on a 4-row Multisection CT scanner (Siemens Volume Zoom, Siemens Medical Solutions, Forchheim/Germany).

NCT was performed with the patient in a head holder in the transverse plane. Using the following parameters, incremental CT acquisitions of the brain were obtained: 120 kVp, 250 mA, 2-s scan time, and 5-mm section thickness.

To allow visualization of the vascular tree from the distal common carotid artery to the intracranial vessels, the CT angiography covered the region from the fifth vertebral body up to the vertex. The following parameters were used: 120 kVp, 200 mAs, 4x 1-mm collimation, 5.5 mm/rotation table feed, and 0.5 s rotation time. A total of 100 ml of contrast material was injected intravenously at a flow rate of 4 ml/s using a power injector. For follow-up studies, repeated CT or MR scans were obtained after 1–3 days after treatment or immediately in case of clinical worsening.

Image Analysis

CT and MR image analyses were performed jointly by a board-certified neuroradiologist (PP, 20 years of neuroimaging review experience) and a stroke neurologist (AK, with 18 years of neuroimaging review experience) on a high-resolution monitor.

Since CTA source images are superior to non-contrast CT images to detect early ischemic changes, they were used to determine the Alberta Stroke Programme Early CT score (CTA-SI-ASPECTS) (16). The follow-up CT or MR scans were used to determine the final ASPECTS as a marker of infarct extent as well as the incidence of symptomatic intracranial hemorrhages (SICH) using the ECASS III definition.

End Points and Analyses

Functional outcome was assessed by a senior vascular neurologist who was certified for NIHSS and mRS scoring (AK, AS). The mRS at the time of hospital discharge was used for early clinical outcome analyses. The main outcome measures were a poor clinical outcome (discharge mRS of 5–6), in-hospital death, infarct sizes, and SICH rates.

In a first step, we compared the clinical and radiological outcomes between pre-stroke dependent (mRS ≥3) and independent (mRS 0–2) patients after either IVT or ET. In a second step, we then analyzed the impact of ET on the clinical and radiological outcomes in pre-stroke dependent patients compared to IVT.

Statistical Analysis

Continuous values were expressed as mean ± standard deviation or as median ± interquartile range (IQR). Nominal variables were expressed as count and percentages. For comparisons of categorical data, two-tailed chi-square statistics with Yates correction and univariate Fisher's exact test were used. Fisher's exact test was used when the predicted contingency table cell values were less than five. Analyses of continuous variables were performed with an unpaired Student's *t*-test or, in case of abnormally distributed data, with a Mann–Whitney *U*-test.

A stepwise, forward, multiple-regression analysis (*P* in 0.05, *P* out 0.1) was applied to determine the independent predictors of a poor clinical outcome (mRS 5–6). The following variables were considered: age, sex, treatment modality, baseline NIHSS, baseline and follow-up SI-ASPECTS, diabetes, hypertension, atrial fibrillation, prior stroke, occlusion site, and SICH. Results are presented as odds ratios (ORs) with 95% confidence interval.

A value of $p < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed with SPSS (version 22, SPSS Inc.).

The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Demographic Data

The IVT group comprised a total of 544 patients, and 1,061 patients had received ET, respectively. Among the IVT patients, 455 (84%) were previously independent and 89 (16%) were dependent before stroke. In the ET group, 919 (87%) patients were functionally independent before the current stroke, whereas 142 (13%) patients were dependent of the help of others before their stroke. **Table 1** shows a summary of the baseline characteristics of the entire study population.

Overall Clinical and Radiological Outcomes

After either IVT or ET, a total of 568/1,605 patients (35%) had a poor outcome (mRS 5–6), and 212/1,605 (13%) died in the hospital. Overall, 68 patients (4.2%) developed a SICH using the ECASS III definition. The rates of poor outcome (55 vs. 32%, $p < 0.001$), in-hospital death (24 vs. 11%; $p < 0.001$), and SICH (8.2 vs. 3.6%, $p < 0.01$) were significantly higher in previously dependent patients than in independent patients. The infarct sizes were comparable between both treatment groups (median 7; IQR: 4–8 vs. median 7; IQR 4–8; $p = 0.5$).

Pre-stroke Dependent Patients

Table 2 shows a summary of the baseline characteristics of pre-stroke dependent patients after either IVT or ET. Notably, the patients treated with ET were significantly younger but more severely affected than those treated with IVT, respectively.

The clinical and imaging outcome data are given in **Table 3**. Compared with IVT, endovascular treatment significantly reduced the rates of poor outcome (49 vs. 64%; $OR_{unadjusted}$, 0.5;

TABLE 1 | Baseline characteristics.

Number of patients	*n* = 1,605
Age	
Mean (years)	74 ± 12
Hypertension	1,306 (81)
Atrial fibrillation	879 (55)
Diabetes	335 (21)
NIHSS	
Median, IQR	14 (10–18)
Pre-stroke mRS (0–2)	1,374 (86)
Pre-stroke mRS (≥3)	231 (14)
Imaging	
Location of occlusion[a]	
ICA	298 (19)
M1 MCA	948 (59)
M2 MCA	359 (22)
Baseline SI-ASPECTS	
Median, IQR	8 (7–10)
Treatment	
Alteplase alone, iv	544
Endovascular therapy (with or without thrombolysis)	1,061

[a] *Most proximal occlusion location.*

NIHSS, National Institutes of Health Stroke Scale; SI-ASPECTS, Source Image Alberta Stroke Program Early CT Score (only for anterior circulation strokes); ICA, internal carotid artery; MCA, middle cerebral artery.

TABLE 2 | Clinical characteristics of previously dependent stroke patients (mRS ≥3) after either thrombolysis or endovascular therapy.

	Intravenous thrombolysis *n* = 89	Endovascular treatment *n* = 142	*p*-value
Age			
Mean (years)	86 ± 7	83 ± 8	$p < 0.05$
Hypertension	81 (91)	130 (91)	
Atrial fibrillation	54 (61)	79 (56)	
Diabetes	21 (24)	43 (30)	
Prior stroke	22 (25)	52 (37)	$p = 0.06$
NIHSS (median, IQR)	15 (11–18)	17 (13–20)	$p < 0.05$
Location of occlusion			
ICA ± M1 MCA	64 (72)	105 (74)	
M2 MCA	25 (28)	37 (26)	
Baseline SI-ASPECTS (median, IQR)	8 (6–10)	8 (6–10)	

NIHSS, National Institutes of Health Stroke Scale; SI-ASPECTS, Source Image Alberta Stroke Program Early CT Score (only for anterior circulation strokes); ICA, internal carotid artery; MCA, middle cerebral artery.

TABLE 3 | Clinical and imaging outcomes after intravenous thrombolysis (IVT) or endovascular treatment (ET) in previously dependent patients at the time of discharge.

	IVT $n = 89$	ET $n = 142$	*p*-value
mRS 5–6	57 (64)	70 (49)	<0.05
Death	22 (25)	31 (22)	0.6
Infarct size[a] (median, IQR)	5 (2–8)	7 (5–9)	<0.01
SICH	7 (8)	12 (8)	0.9

mRS, modified Rankin scale; SICH, symptomatic intracerebral hemorrhage.
[a]Using the follow-up Alberta Stroke Program Early CT Score.

TABLE 4 | Multivariable odds ratios and 95% confidence intervals of poor outcome in dependent patients.

	Odds ratio	CI lower	CI higher	*p*-value
Age[a]	1.02	0.99	1.06	0.3
Atrial fibrillation	0.8	0.49	1.31	0.4
Diabetes	1.53	0.81	2.87	0.2
Prior stroke	1.09	0.57	1.98	0.77
Initial NIHSS[b]	1.12	1.05	1.18	<0.001
ET	0.43	0.24	0.76	<0.01

CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; ET, endovascular therapy.
[a]Per 1 year increase.
[b]Per one point increase.

95% confidence interval, 0.32–0.94; $p < 0.05$). The rates of in-hospital death did not differ significantly between and ET and IVT (22 vs. 25%, $p = 0.6$).

The infarct sizes were significantly smaller after ET than after IVT (median: 7; IQR: 5–9 vs. median: 5; IQR: 2–8; $p < 0.01$), whereas the SICH rates were comparable between both treatment groups (8.5 vs. 7.9, $p = 0.9$).

In the multivariate regression analysis, admission NIHSS and endovascular treatment were significantly associated with a poor clinical outcome (**Table 4**).

DISCUSSION

The main purpose of this study was to analyze the impact of endovascular therapy on clinical and radiological outcomes in patients with pre-stroke disability and proximal large vessel occlusions within the anterior circulation compared with systemic thrombolysis. After either treatment modality, the dependent patients had worse clinical and radiological outcomes than the independent patients. Compared with IVT, endovascular therapy improves the early clinical outcome, avoids poor outcome, and leads to smaller infarcts in patients with prior disabilities.

In our study cohort, 16% of all patients were dependent on the daily help of others before stroke, supporting the notion that these patients represent a significant proportion of the acute ischemic stroke population. Furthermore, 11% of the patients within the MR CLEAN registry were likewise pre-stroke dependent (9). Comparable rates were also found in single-center studies from Israel or from Sweden (11, 18). Studies focusing on patients treated with thrombolysis alone and with unknown vessel status reported proportions of patients with pre-stroke disability ranging from 10 to 30% (19, 20).

Despite the relatively high numbers of patients with acute large vessel occlusions and pre-stroke disabilities in everyday clinical practice, data from randomized trials dealing with the impact of ET compared with IVT in this patient population is scarce and also likely reflects a selection bias. In the Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke trial, only three patients (1.5%) were functionally dependent before their current stroke, while in the Endovascular Recanalization With Solitaire Device vs. Best Medical Therapy in Anterior Circulation Stroke Within 8 h trial, there was only one patient (0.5%), respectively (2, 3).

Recently, several single-center studies and registries have reported the beneficial effects of ET in pre-stroke dependent patients (8, 9, 11, 18). In fact, all of these studies were able to show that pre-stroke disability does not significantly reduce the likelihood to return to the pre-stroke functional level after ET. However, none of these studies had incorporated a control group. We therefore extend these findings and show that ET increases the odds to avoid a poor outcome in this patient population compared with IVT. Taken together, these data support the notion that previously dependent patients should not be routinely excluded from ET.

Despite the overall positive effect of ET on clinical outcome, pre-stroke dependent patients had significantly higher rates of in-hospital death than independent patients irrespective of the treatment modality in our case series. In good agreement with this finding is the fact that the mortality rates at 90 days were significantly higher in patients with a pre-stroke mRS of 2–3 (40%) than independent patients (14%) after endovascular therapy in a recent analysis of two large comprehensive stroke centers in the US (8). In the MR Clean Registry, the mortality rates were twice as high in dependent than in independent patients at 3 months after ET (9). These results emphasize that pre-stroke dependent patients have a higher risk of suffering death after ET, likely reflecting higher rates of comorbidities in this patient population. Although not the focus of our study, but in support of this notion, the pre-stroke dependent patients had significantly more comorbidities than independent patients in the aforementioned MR Clean Registry and analysis of the two comprehensive stroke centers (8, 9). Aside from a higher disease burden caused by preexisting comorbidities, the dependent patients are more likely to have other complications than SICH. In addition, withdrawal of care according to their preferences could also come into play more often.

The overall rates of SICH were 4.1% after ET or 4.4% after IVT, which is within the magnitude of SICH rates observed in the large, randomized trials (2, 4). In contrast to these studies, however, the SICH rates were significantly higher in dependent patients compared to independent patients in our cohort. Higher rates of SICH have also been likewise reported in the MR Clean Registry in a comparable patient population (9).

Notably, ET did not affect the incidence of SICH in patients with prior disabilities, stressing its safety in this patient population.

In this study, we also analyzed the impact of ET on infarct sizes in dependent patients compared with IVT. Using the follow-up ASPECTS as a marker of infarct extent, we observed significantly smaller infarct sizes after ET than after IVT in dependent patients. These data corroborate previous findings, albeit mainly in independent patients, in which the final infarct volumes were significantly smaller after ET than after IVT (21, 22). Although it has clearly been shown that a reduced final infarct volume only partially mediates the positive effect of ET on clinical outcome (21), our primary finding of an improved clinical outcome after ET in dependent patients is thus also supported by the imaging data.

This study has certain limitations. First, the data were obtained retrospectively in a single academic center and in a non-randomized fashion. This limits the generalizability of our results, which need to be corroborated in a randomized controlled trial. Second, the causes for preexisting disability was not obtained in our study, all the more considering that dependent patients likely harbor complex comorbid conditions. Third, we used the mRS at the time of discharge to determine the clinical outcome instead of the widely accepted 90 days. In support of this approach, a reanalysis of the NINDS tPA stroke trial revealed a strong correlation between the day 7 mRS and the 90-day mRS (23). Finally, the impact of recanalization on clinical and radiological outcomes could not be incorporated into our analyses since information on these important variables was not available in the IVT group.

CONCLUSIONS

In everyday clinical practice, a substantial proportion of acute stroke patients with large vessel intracranial vessel occlusions have preexisting disabilities. In these patients, ET can be performed safely and avoids a poor outcome compared with IVT. However, the high death rates in this patient population stresses the importance to perform decisions based on a case-by-case basis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethics Committee of the Ärztekammer Bremen. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AK, CR, and PP contributed to the study design, data acquisition, critical data review and interpretation of data, and contributed to the primary manuscript writing and tables. CR, MP, MA, HH, and AS contributed to data acquisition and interpretation of data. AK, CR, MP, MA, HH, AS, and PP contributed to the critical revision and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Endovascular Treatment of Acute Ischemic Stroke in Clinical Practice: Analysis of Workflow and Outcome in a Tertiary Care Center

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Background and Purpose: Pre- and intra-hospital workflow in mechanical recanalization of large cervicocephalic arteries in patients with acute ischemic stroke still needs optimization. In this study, we analyze workflow and outcome in our routine care of stroke patients undergoing mechanical thrombectomy as a precondition for such optimization.

Methods: Processes of pre- and intra-hospital management, causes of treatment delay, imaging results (Alberta Stroke Program Early Computed Tomography Score, localization of vessel occlusion), recanalization (modified thrombolysis in cerebral infarction score), and patient outcome (modified Rankin scale at discharge and at the end of inpatient rehabilitation) were analyzed for all patients who underwent mechanical thrombectomy between April 1, 2016, and September 30, 2018, at our site.

Results: Finally, data of 282 patients were considered, of whom 150 (53%) had been referred from external hospitals. Recanalization success and patient outcome were similar to randomized controlled thrombectomy studies and registries. Delay in treatment occurred when medical treatment of a hypertensive crisis, epileptic fits, vomiting, or agitation was mandatory but also due to missing prenotification of the hospital emergency staff by the rescue service, multiple mode or repeated brain imaging, and transfer from another hospital. Even transfer from external hospitals located within a 10-km radius of our endovascular treatment center led to a median increase of the onset-to-groin time of ∼60 min.

Conclusion: The analysis revealed several starting points for an improvement in the workflow of thrombectomy in our center. Analyses of workflow and treatment results should be carried out regularly to identify the potential for optimization of operational procedures and selection criteria for patients who could benefit from endovascular treatment.

Keywords: acute ischemic stroke, mechanical recanalization, work-flow, outcome, onset-to-groin-time

Subject terms: ischemic stroke, interventional stroke therapy, quality and outcome.

INTRODUCTION

The implementation of intravenous thrombolysis (IVT) and, more recently, mechanical recanalization of occluded large intracranial arteries into stroke therapy tremendously improved the outcome of acute ischemic stroke (1–8). As with IVT, indications and contraindications for endovascular treatment (EVT) have been continuously challenged and tailored to the patients' demands. The time window for EVT has been extended up to 24 h in patients with a mismatch between clinical deficit and infarct or with a mismatch between ischemic and infarcted tissue (9, 10), and the criteria for eligibility for EVT were expanded to patients with Alberta Stroke Program Early Computed Tomography Score (ASPECTS) <6 and National Institutes of Health Stroke Scale (NIHSS) score <6 (5, 10–14). There are continuous efforts to improve patient selection for thrombectomy and to optimize pre- and intra-hospital procedures. By thorough workflow analysis, weak points in the treatment process can be detected and eliminated, thereby facilitating satisfying treatment results.

We report on the workflow analysis and treatment results of all stroke patients who received mechanical thrombectomy at our tertiary center between April 1, 2016, and September 30, 2018.

METHODS

All consecutive patients with acute ischemic stroke and large vessel occlusion (LVO) who underwent EVT at our site were prospectively enrolled into a local registry. Institutional review board approval was obtained for a retrospective review of these prospectively collected data in a quality assurance database for which consent was waived. Data were prospectively collected by SG, who interviewed the attending physicians within 24 h after the procedure, if possible. In addition, the emergency room (ER) neurologists were requested to document any observed cause of delay in their procedure reports. The indication for EVT was established in consensus between the attending neurologist and the interventional neuroradiologist on a case-by-case basis considering all available clinical and imaging data. Patients were either directly admitted to our hospital or transferred from external hospitals. Intravenous thrombolysis was indicated and applied according to national guidelines (15).

Clinical Data

Age, sex, family status, health insurance, time of symptom onset or last known well, clinical symptoms, Trial of Org 10172 in Acute Stroke Treatment classification, NIHSS at admission, use of anticoagulants or platelet inhibitors before EVT, and cerebrovascular risk factors were documented.

Radiological Data

Intracranial hemorrhage was excluded by cranial computed tomography (CCT) or—especially in the case of unknown time window since stroke onset—magnetic resonance imaging (MRI). LVO was proven by CT angiography (CTA) or magnetic resonance angiography (MRA) and confirmed *via* conventional angiography. ASPECTS and posterior circulation ASPECTS (16) were used to classify the extent of infarction in the CCT or MRIs on admission.

Procedural Data

A team of seven interventional neuroradiologists was available for the EVT on a 24/7 schedule at our site (from 5.00 p.m. to 8.00 a.m. as on-call service). Aspiration catheters, stent retrievers, or both were used on a case-by-case basis. The additional use of intra-arterial thrombolysis, anticoagulants or antiplatelets, and stenting of the occluded or stenotic vessel or the connected upstream vessel was at the discretion of the operator as well. EVT was preferentially done under general anesthesia. Symptom onset-to-groin puncture time, onset-to-needle time, door-to-imaging time, door-to-needle time, door-to-groin time, and onset- and door-to-recanalization time were documented for further analysis as were any circumstances that delayed treatment from the attending neurologist's view (such as delirium, extended vomiting, or severe hypertension demanding treatment before EVT or unavailability of the imaging facilities, for example). "Door time" refers to the time of admission to our center.

Workflow during standardized working hours was compared with that during on-call shifts, as well as the workflow on working days to that on weekends. Additionally, the number of patients seeking neurological treatment at the ER within ±1 h of the arrival of the EVT patients was documented, as was the number of neurologists present at the ER when the patient arrived.

Outcome

Short-term clinical outcome was assessed by NIHSS and modified Rankin scale (mRS) at discharge, long-term outcome by mRS at discharge from the rehabilitation clinic. The radiological outcome was assessed by the modified thrombolysis in cerebral infarction score (mTICI) (17); mTICI scores 2b and 3 were considered favorable. In addition, the need for decompressive hemicraniectomy and occurrence of secondary intracranial hemorrhage were recorded.

Statistical Analysis

Statistical analysis was done using IBM SPSS Statistics 26 (SPSS Inc., Chicago, IL., USA). Normally distributed continuous data were described as mean ± standard deviation and non-normally distributed continuous variables as median with the 25th and 75th percentile. A Gaussian distribution was verified by using the Kolmogorov–Smirnov test. Comparison of non-normally distributed continuous variables was done using the Mann–Whitney *U*-test. Categorical data were analyzed by using the chi-square test. Correlations were analyzed with the Spearman rho test. Risk factors for an unfortunate outcome (mRS 3–5 and mRS 6) were determined by multinomial logistic regression analysis, including all parameters that had been shown to differ significantly between these patient groups and those patients with good outcomes (mRS 0–2). The significance level was set at $p < 0.05$.

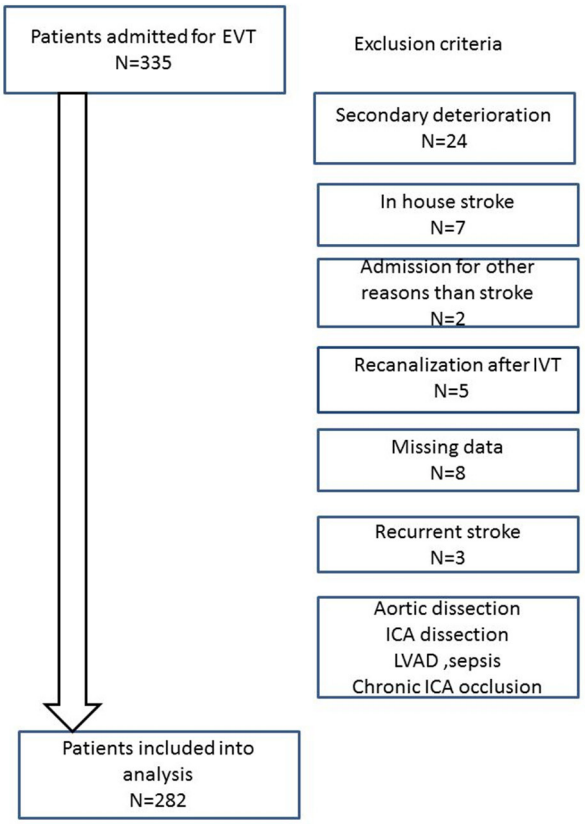

FIGURE 1 | Flowchart displaying the exclusion criteria. Patients with secondary deterioration had presented without neurological symptoms or a rapid improvement in the emergency room but had developed severe neurological deficits hours later. As we aimed to analyze the quality of our prehospital care and flow of our emergency processes, we decided to exclude these patients from further analyses because they are not representative of the "usual" workflow.

RESULTS

Baseline Characteristics

From April 1, 2016, until September 30, 2018, 335 patients with acute ischemic stroke underwent EVT at our institution. Fifty-three patients were excluded from further analysis for various reasons. Details are given in **Figure 1**. A total of 132 of the remaining patients were directly admitted to our hospital, whereas 150 were transferred from external hospitals for further treatment from a distance of up to 100 km. Clinical and imaging baseline characteristics of the included patients can be found in **Tables 1**, **2**.

Transferred patients were younger and more frequently men. Moreover, the time of symptom onset was more often known in this patient group.

The majority of the patients were admitted during standby service (185 of 282; 65.6%) with an equal distribution regarding weekdays. A total of 110 of the 132 patients (83.3%) who were directly admitted were announced in advance by the emergency medical staff.

TABLE 1 | Baseline characteristics of patients directly admitted to MHH vs. patients referred from external hospitals.

	Patients directly admitted to MHH *N* = 132	Patients referred from external hospital *N* = 150	*p*-value
Age (years)	77 (40–94)	75 (23–91)	0.03
Sex (m/f)	59/73	89/61	0.01
Family status single/married/unknown	55/70/7	52/89/9	0.48
Statutory/private health insurance	105/27	114/36	0.45
NIHSS on admission	15 (2–40)	15 (1–40)	0.85
Symptom onset unknown	62/132 (47.0%)	53/150 (35.3%)	0.05
Intravenous thrombolysis	104/132 (78.8 %)	100/150 (66.7 %)	0.08
Diabetes mellitus	37/132 (28.0%)	35/150 (23.3 %)	0.37
Hypertension	92/132 (69.7%)	117/150 (78.0%)	0.11
Hypercholesterolemia	64/132 (48.5%)	73/150 (48.7%)	1.00
Atrial fibrillation	74/132 (56.1%)	82/150 (54.7%)	0.15
Platelet inhibitors	39/132 (29.5%)	42/150 (28.0%)	0.78
Vitamin K antagonist	19/132 (14.4%)	18/150 (12.0%)	0.55
DOAC/LMWH	13/132 (9.8%)	27/150 (18.0%)	0.05
TOAST classification			0.35
Large artery atherosclerosis	11/132 (8.3%)	15/150 (10.0%)	
Cardioembolic	74/132 (56.1%)	78/150 (52.0%)	
Other etiology	7/132 (5.3%)	3/150 (2.0%)	
Unknown etiology	40/132 (30.3%)	54/150 (36.0%)	

M, male; f, female; NIHSS, National Institute of Health Stroke Scale; DOAC, direct oral anticoagulants; LMWH, low molecular weight heparin; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Initial imaging was CCT and CTA in 93 (70.4%), MRI and MRA in 22 (16.7%), and CCT plus MRI in 17 (12.9%) of the 132 patients who were directly admitted to our hospital compared with 100% of CCT/CTA in the transferred patients. The distribution of occlusion sites and ASPECTS was similar in the directly admitted and the transferred patients (**Table 2**), as was the stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment classification (**Table 1**). In 204 cases (72.3%), EVT was accompanied by IVT.

Endovascular Treatment

EVT was performed under general anesthesia in 261 (92.6%) patients and under conscious sedation in 21 (7.4%). An aspiration catheter was used more often in conjunction with a stent retriever (153 patients) than exclusively (93 patients). Intracranial stents were placed in four patients. In 24 patients (8.5%), EVT was not successful due to technical obstacles such as significantly tortuous vessels precluding access to the thrombus or advanced atherosclerosis of the femoral artery precluding arterial access. In 13 patients, rt-PA (recombinant tissue plasminogen activator) (between 5 and 20 mg) was administered intra-arterially during the mechanical recanalization procedure. In 58 patients with tandem occlusions, stenting of the cervical occluded or stenotic vessel was performed in addition to recanalization of the intracranial branch to secure adequate

TABLE 2 | Neuroradiological data.

	Patients directly admitted *N* = 132	Patients referred from external hospital *N* = 150	*p*-value
Occlusion site			
ICA	19 (14.4%)	9 (6.0%)	0.10
ICA + MCA	25 (18.9%)	32 (21.3%)	
MCA	76 (57.6%)	85 (56.7%)	
BA	12 (9.1%)	22 (14.7%)	
VA	0	2 (1.3%)	
ASPECTS on admission	7 (6/9) ($n = 116$)	6 (5/8) ($n = 111$)	0.220
pc ASPECTS on admission	8 (7/10) ($n = 13$)	8 (6/9) ($n = 23$)	0.371
Technical details of EVT			
Aspiration catheter	43/132	50/150	0.37
Aspiration + stent retriever	68/132	85/150	
Intracranial stent	1/132	3/150	
No thrombotic material retrievable	5/132	3/150	
Site of occlusion not accessible	15/132	9/150	
Extracranial stent	23/132 (17.4 %)	35/150 (23.3 %)	0.22
Processing times			
Door-to-imaging time (min)	18 (13/24)	17 (11/23) ($n = 67$)	0.24
Door-to-groin time (min)	81 (64/105)	42 (28.75/68)	<0.001
		Without further imaging ($n = 83$): 30 (25/39)	
		Additional CCT ($n = 34$): 54 (42.5/66.25)	
		Additional MRI ($n = 28$): 81 (65/104)	
		Additional CCT + MRI ($n = 5$): 134 (91.5/225)	
Onset-to-groin-time (min)	145 (114.75/174) ($n = 70$)	255 (206/313) ($n = 99$)	<0.001
Groin-puncture-to-recanalization (min)	76 (45/102)	84.50 (50/120.5)	0.17
Onset-to-recanalization (min)	221 (187.25/277) ($n = 70$)	342 (293/435) ($n = 99$)	<0.001
Door-to-recanalization (min)	156 (127.25/205)	128.50 (94.25/179.25)	<0.001
Recanalization			
mTICI 0	25 (18.9%)	22 (14.7%)	0.70
mTICI 1	3 (2.7%)	5 (3.3%)	
mTICI 2a	8 (6.1%)	14 (9.3%)	
mTICI 2b	52 (39.4%)	56 (37.3%)	
mTICI 3	44 (33.3%)	53 (35.3%)	

ICA, internal carotid artery; MCA, middle cerebral artery; BA, basilar artery; VA, vertebral artery; ASPECTS, Alberta Stroke Program Early CT Score; pc, posterior circulation; EVT, endovascular treatment; min, minutes; CCT, cranial computed tomography; MRI, magnetic resonance imaging; mTICI, modified thrombolysis in cerebral infarction score.

blood flow to the affected area. The door-to-groin time was 64 min in median (25th/75th percentile: 40.0/91.7 min). The EVT procedure lasted 80 min (25th/75th percentile: 47.5/115 min). The onset-to-groin time was 205 min (25th/75th percentile: 149.0/272.5 min) and the onset-to-recanalization time 300 min (25th/75th percentile: 220.0/365.5 min) in those with known symptom onset. Satisfactory recanalization (TICI 2b/3) was achieved in 205 of 282 patients (72.7%).

Table 2 compares the respective data of the directly admitted to the transferred patients. The need for transfer increased the onset-to-groin time by more than 100 min in median, mainly depending on the distance between the hospitals. However, even transport between hospitals within Hannover delayed groin puncture by ∼60 min (**Figure 2**), and deficits in transfer organization were recorded in 28 patients who came from external hospitals (18.7%) but also in 13 of 132 cases (9.9%) who were directly admitted.

Causes for Delay of Endovascular Treatment

Several causes of delay were reported, some avoidable, others inevitable. Brain imaging was delayed in 13 cases due to unavailability of CCT or MRI, preference of MRI, or request of both MRI and CCT by the interventional neuroradiologist. In eight patients, a concurrent intervention delayed the start of EVT. In 67 transferred patients, the interventional neuroradiologist on duty requested additional brain imaging (CCT in 34, MRI in 28, both in 5) to confirm the indication for EVT, usually because the transfer had taken a significant amount of time. The duration of this additional imaging is outlined in **Table 2**. Further reasons for the delay of EVT were lack of a venous line on admission ($n = 17$), delay in ER procedures ($n = 17$), severe hypertension ($n = 16$), interdisciplinary discussion about the indication for EVT in borderline cases ($n = 22$), agitation, seizures or vomiting ($n = 25$), extensive information of patients or relatives ($n = 16$), non-availability of an anesthesiologist ($n = 14$), deficits in communication between departments ($n = 8$), primary admission to another specialty than neurology (neurosurgery, trauma surgery; $n = 5$), and technical problems such as malfunction of the CCT ($n = 6$).

A multiple linear regression analysis using door-to-groin time as the dependent variable and sex, age, family status, admission during regular working hours, NIHSS on admission, ASPECTS on admission, number of delays, and transfer for EVT as independent variables showed that admission outside of working hours (B: −19.29, CI: −28.63 to −9.94) and transfer for EVT (B: −29.64, CI: −38.6 to −20.67) significantly decreased the door-to-groin times, whereas with every single cause for delay noticed, the door-to-groin time increased by 7 min (CI: 4.3 to 11.11 min).

The number of patients who attended the neurological ER within 1 h before and after the admission of the EVT patient had no impact upon the door-to-groin time. However, the door-to-groin time was shorter if the ER was staffed with two neurologists instead of one (median 60 vs. 70 min, $p = 0.037$).

The number of interventions performed by the individual neuroradiologists during the observation period differed notably

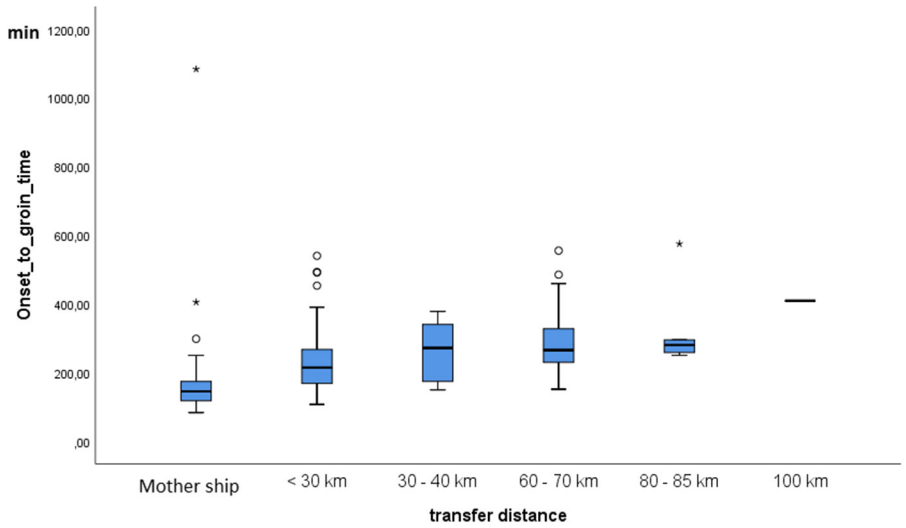

FIGURE 2 | Onset-to-groin time in dependence of transfer distance. MHH, Hannover Medical School. *Represents extreme outliers in the distribution.

(between 27 and 110), as did their median door-to-groin time (49.5–89.0 min; $p < 0.001$). The door-to-groin time decreased with increasing experience of the interventionalist regarding EVT.

Outcome

The NIHSS at discharge was 12 (25th/75th percentile: 3.0/20.25) and was not significantly different between directly admitted (median NIHSS 12.0; 25th/75th percentile: 3.0/21.0) and transferred patients (median NIHSS: 11.0; 25th and 75th percentile: 3.0/18.2) ($p = 0.77$). Median mRS at discharge was 5 for all patients, as well as for the two subgroups (25th/75th percentile: 2/5). Only 79 of the 282 patients (28%) achieved a mRS of 0–2, of those with ASPECTS $\geq$ 6, 33.4%. There was no difference between the directly admitted and transferred patients. Sixty-one patients died in hospital (21.6%): 27 (9.6 %) received palliative care following the demands of the patient's provision, eight patients each died due to space-occupying intracranial hemorrhage or brain stem infarction, five from malignant MCA infarction, five from sepsis, four from aspiration pneumonia, and four from preexisting severe accompanying disease. There was no difference between the two patient groups.

mRS at discharge from rehabilitation (in median at 68.5 days; 25th/75th percentile: 43.7/90 days) was available for 246 patients. Fourteen additional patients had died, increasing mortality for this subgroup from 24.8 to 30.5%. However, the number of patients with mRS 0–2 increased from 57 (23.2%) to 71 (28.9%) (**Figure 3**). Of the patients with EVT in the anterior circulation and ASPECTS > 6, 38.2% achieved a good outcome (mRS 0–2) compared with 20.2% with ASPECTS < 7. Details of risk factors for unfortunate outcomes are described in the **Supplementary Material**.

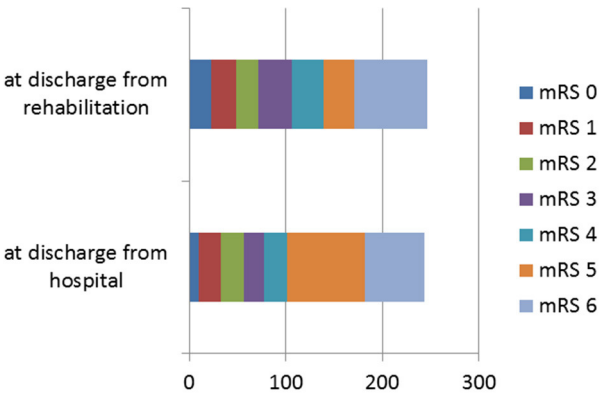

FIGURE 3 | Modified Rankin Scale (mRS) at discharge from hospital and after inpatient rehabilitation for $n = 246$ patients for whom data at both time points were available.

DISCUSSION

The major purpose of our registry was to analyze our in-house management of patients admitted for EVT of acute ischemic stroke. We identified several factors that caused a delay in endovascular treatment. Straightforward patient management was impeded by mandatory medical treatment of a hypertensive crisis, epileptic fits, vomiting, or agitation of the patient. However, the analysis also revealed flaws in the workflow that could be easily addressed.

Despite consensus on the standard procedure, the ER neurologist did not get advance notice of the stroke patient from the emergency medical service in 17% of the cases—a factor that could be easily addressed by reporting to the physician in charge. In approximately one-third of the cases, a delay in the

neuroradiological diagnosis and treatment was documented. In several cases, door-to-groin time was prolonged by request for MRI or more than one imaging technique, which was observed more often in patients with unknown time of symptom onset and with less experienced interventionalists. Another less frequent cause of delay was the lack of immediate availability of CCT or MRI.

Imaging protocols in stroke patients differ significantly. A recently published survey including 50 interventional sites from different countries showed that multimodal CT (not contrast-enhanced CT, CTA, and CT perfusion) was the most frequently used imaging modality on admission (58%), followed by not contrast-enhanced CT plus CTA (32%) and multimodal MRI (12%) (18).

In the THRACE trial, where centers were free to use CT or MRI before randomization, CCT needed significantly less time than MRI (19). Accordingly, Kim and colleagues observed an ∼25-min delay if MRI was used for the evaluation of acute ischemic stroke patients for EVT compared with CCT (3).

Therefore, MRI should be used only to clarify non-standard cases. Current American Heart Association guidelines (20) recommend that patients with acute ischemic stroke within 6 h of last known normal, LVO, and ASPECTS $\geq$ 6 be selected for mechanical thrombectomy on the basis of CT and CTA or MRI and MRA. Additional imaging is reserved for patients with wake-up stroke. We caution against excluding patients from EVT by additional imaging studies that are not indicated. Our results emphasize that additional imaging is time-consuming. Because the benefit of EVT decreases with increasing time from symptom onset, strict adherence to standard operating procedures is imperative.

Standardization of stroke care workflow, continuous hospital staff education, and discussion of possible improvements efficiently reduces door-to-recanalization times and improves patient outcome (21). By implementing a dedicated program, Hassan et al. were able to reduce the door-to-recanalization time by ∼30% (21).

In patients who are transferred for EVT, the so-called door-in-door-out time at the referring center has been shown to be significantly related to clinical outcome (22). Rapid access of the patient to an EVT center is desirable. In our cohort, onset-to-groin time differed in median 110 min between those patients who were directly admitted and those who were transferred for EVT, and onset-to-recanalization differed by 120 min in median. Approximately one-third of the patients were transferred from hospitals located within a radius of <30 km, most of them in a radius of <10 km. Even in these cases, the transfer took in median 60 min. This loss of time could have been avoided by direct admittance to the EVT center. On-site triage based on the severity of stroke and allocation to an EVT center has been repeatedly recommended to reduce the onset-to-treatment times but is only reluctantly accepted (23–25). Centralization of EVT in centers that are available 24/7 would help to standardize the pre- and intra-hospital management of these patients and facilitate treatment by highly experienced personnel.

In addition to workflow, treatment outcomes were also analyzed. Patients treated at our hospital differed significantly from those included in the 2015 thrombectomy trials (1–5). However, they were quite similar to those presented in the German Stroke Registry Endovascular Treatment, except for the frequency of atrial fibrillation, unknown symptom onset, i.v.-thrombolysis, and premedication with anticoagulants, which all were higher in our sample (7). Nevertheless, the outcome was comparable. At discharge from inpatient rehabilitation (in median 68.5 days after stroke), mortality (30.5 vs. 29%) was similar in our patients, whereas good outcome (28.9 vs. 37%) was less frequent. The latter may be due to the difference in median ASPECTS on admission (9 vs. 7). Of note, both the German Stroke Registry Endovascular Treatment and our single-center registry indicate that patients with ASPECTS $\leq$ 6 can achieve

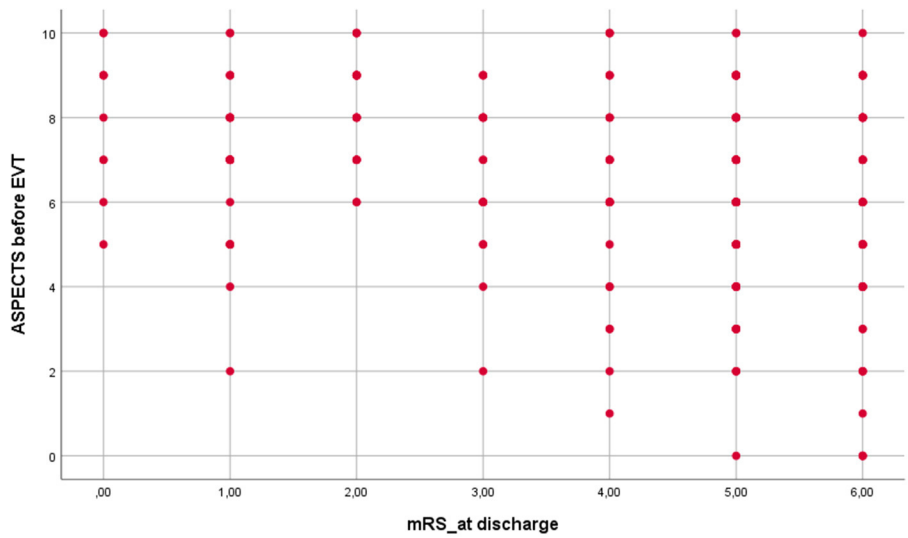

FIGURE 4 | Modified Rankin Scale (mRS) at discharge in relation to Alberta Stroke Program Early CT Score (ASPECTS) on admission (Spearman rho correlation: $r = -0.295$; $p < 0.001$).

a favorable outcome (26) (**Figure 4**). This was also shown by a recent meta-analysis of seven randomized EVT trials (27).

CONCLUSION

EVT has been used successfully to treat LVO for more than 5 years, but there is room for improvement both in the prehospital setting and in the hospital. Although our data were collected monocentrically, our results are likely applicable to other hospitals. We believe that consistent and repeated process analysis is critical to further optimize EVT outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

ETHICS STATEMENT

Ethical review and approval was not required for the study in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KW: conceptualization, methodology, data monitoring, data analysis, original draft preparation, draft review, and editing. SG: data acquisition, data analysis, draft review, and editing. GG and MG: data monitoring, draft review, and editing. RS and HW: draft review and editing. OA-F: data acquisition, original draft preparation, draft review, and editing. FG: conceptualization, methodology, original draft preparation, draft review, and editing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.657345/full#supplementary-material

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Inhouse Bridging Thrombolysis Is Associated With Improved Functional Outcome in Patients With Large Vessel Occlusion Stroke: Findings From the German Stroke Registry

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Background: Endovascular treatment (EVT) for large vessel occlusion stroke (LVOS) is highly effective. To date, it remains controversial if intravenous thrombolysis (IVT) prior to EVT is superior compared with EVT alone. The aim of our study was to specifically address the question, whether bridging IVT directly prior to EVT has additional positive effects on reperfusion times, successful reperfusion, and functional outcomes compared with EVT alone.

Methods: Patients with LVOS in the anterior circulation eligible for EVT with and without prior IVT and direct admission to endovascular centers (mothership) were included in this multicentric, retrospective study. Patient data was derived from the German Stroke Registry (an open, multicenter, and prospective observational study). Outcome parameters included groin-to-reperfusion time, successful reperfusion [defined as a Thrombolysis in Cerebral Infarction (TICI) scale 2b-3], change in National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), and mortality at 90 days.

Results: Of the 881 included mothership patients with anterior circulation LVOS, 486 (55.2%) received bridging therapy with i.v.-rtPA prior to EVT, and 395 (44.8%) received EVT alone. Adjusted, multivariate linear mixed effect models revealed no difference in groin-to-reperfusion time between the groups (48 ± 36 vs. 49 ± 34 min; $p = 0.299$). Rates of successful reperfusion (TICI ≥ 2b) were higher in patients with bridging IVT (fixed effects estimate 0.410, 95% CI, 0.070; 0.750, p = 0.018). There was a trend toward a higher improvement in the NIHSS during hospitalization [ΔNIHSS: bridging-IVT group 8 (IQR, 9.8) vs. 4 (IQR 11) points in the EVT alone group; fixed effects estimate 1.370, 95% CI, −0.490; 3.240, $p = 0.149$]. mRS at 90 days follow-up was lower in the bridging IVT group [3 (IQR, 4) vs. 4 (IQR, 4); fixed effects estimate −0.350, 95% CI, −0.680; −0.010, $p = 0.041$]. There was a non-significantly lower 90 day mortality in the bridging IVT group compared with the EVT alone group (22.4% vs. 33.6%; fixed effects estimate

0.980, 95% CI −0.610; 2.580, $p = 0.351$). Rates of any intracerebral hemorrhage did not differ between both groups (4.1% vs. 3.8%, $p = 0.864$).

Conclusions: This study provides evidence that bridging IVT might improve rates of successful reperfusion and long-term functional outcome in mothership patients with anterior circulation LVOS eligible for EVT.

Keywords: ischemic stroke, LVOS, bridging, endovascular treatment, rtPA

INTRODUCTION

Endovascular treatment (EVT) of large vessel occlusion stroke (LVOS) has been shown to be highly effective and superior to intravenous thrombolysis (IVT) alone in multiple studies (1–3). However, the role of bridging therapy with IVT prior to EVT still is a matter of debate with studies showing no additional effect of IVT (4–6) and studies showing beneficial effects on functional outcome and reperfusion rates (7–9). Within the HERMES trials, most patients received IVT prior to endovascular treatment (MrClean 87%; ESCAPE 72%) (1). The conclusion of these trails to date is that IVT prior to thrombectomy is safe and still should be the standard of care. Limitations of these studies are the differences in study design, a lack of "real world" data with highly selected patient groups, the inclusion of heterogeneous patient groups (mothership, drip and ship, and just ship), and the fact that thrombectomy techniques as well as symptom to reperfusion times significantly improved in the last few years. Moreover, the patient numbers of most studies addressing the effect of bridging thrombolysis are low, and most meta-analysis/analysis from registries included patient data from the pre-HERMES studies era and do not differentiate between patients with drip-and-ship IVT and patients receiving IVT directly prior to EVT ("mothership" patients).

To address the role of these limitations and to clarify the role of IVT prior to EVT, the large, well-designed prospective DIRECT-MT study, including 656 patients enrolled at 41 academic tertiary care centers in China, recently demonstrated non-inferiority of the direct-EVT compared with the bridging-IVT approach with regard to 90 days functional outcome, despite a higher rate of successful reperfusions in the bridging IVT group (10). Why in this study, a higher reperfusion state prior to EVT, and a higher reperfusion rate achieved by EVT in combination with IVT, did not lead to improved functional outcomes in the bridging group, is not entirely clear and still a matter of debate. However, the DIRECT-MT trial had some shortcomings, which need to be considered for the interpretation of the results: First, the median door to needle time in this trial was 59 min. Given the fact that especially the effect of rtPa is highly time dependent, and that goal door to needle times in Europe are in the range of 30 min, the possible effect of rtPa might have been underestimated in this trial, although a higher percentage of successful reperfusions before EVT was observed in the trial. Second, as some patients had to pay for the rtPa treatment, this might even further have influenced the time scale of the iv treatment. Finally, there was a significant difference in patients not undergoing EVT between IVT + EVT vs. the EVT alone group. These facts might explain, why—despite reporting a successful reperfusion rate of >80%—the percentage of patients with favorable functional outcome with 36.6% was lower compared with previous pooled analyses of large thrombectomy trials with 46% favorable functional outcome (1, 10). The differences in functional outcome between the Chinese DIRECT-MT trial and the previous, large western thrombectomy trials are likely to be multifactorial including the difference in the studied ethnical group (Asian vs. Caucasian population with different stroke etiologies and subtypes).

Therefore, the aim of our study was to specifically address the role of in-house (mothership) bridging IVT directly prior to mechanical thrombectomy and to compare reperfusion times and reperfusion rates as well as functional outcome and complications in patients with and without bridging IVT prior to EVT.

MATERIALS AND METHODS

Patient Population and Clinical Characteristics

Available data of patients enrolled in the German Stroke Registry—Endovascular Treatment (GSR-ET 07/2015-04/2018; ClinicalTrials.gov Identifier: NCT03356392) between 2016 and 2019 was analyzed. The GSR-ET is an ongoing, open-label, prospective, multicenter registry of 25 sites in Germany, collecting consecutive patients with LVOS undergoing EVT. This registry includes neuroradiological and neurological data as well as all time metrics relevant to the interventional treatment and clinical outcome of patients presenting with LVOS. In detail, time metrics and imaging characteristics were recorded by a stroke-experienced senior neuroradiologist, while clinical data like prior medical history and medication, National Institute of Health Stroke Scale (NIHSS), and modified Rankin scale (mRS) have been evaluated and recorded by an experienced, stroke-trained neurologist. NIHSS was recorded at initial presentation of the patient in the emergency department and at discharge. mRS was recorded at discharge and at 90 days follow-up. The endovascular approaches (direct aspiration, stent retrieval, i.e., thrombolysis and combinations of these approaches) were based on the judgment of the treating neuroradiologist. For further information and main outcome of the GSR, we refer to the original publication of the main outcome (11).

Treatment Groups

We predefined two treatment groups: the first treatment group received IVT directly prior the EVT within a time window

of <4.5 h and after exclusion of contraindications according to the American Heart Association (AHA)–American Stroke Association (ASA) guidelines (12). In this group, for the thrombolytic therapy only, Alteplase was used and administered right after the native CT-scan if intracerebral hemorrhage had been ruled out (0.9 mg/kg over 1 h with 10% of initial bolus).The second treatment group received EVT alone. Both treatment groups were directly admitted at a thrombectomy center and had not been transferred from another hospital ("mothership" patients). Only patients with anterior circulation LVOS (occlusions of the extra- or intracranial carotid artery or occlusions of the medial cerebral artery in its M1 and M2 segment) were included in the analysis. We excluded patients being inconsistently recorded or had missing data (both regarding IVT treatment and time metrics), non-mothership cases, patients with other occlusions than ICA and MCA occlusions, flow restoration with IVT only prior to EVT, and patients with incomplete IVT treatment independent of the reason.

Outcome Measures

We defined functional (peri-)procedural and safety measures as follows: mRS and mortality at 90 days, change of NIHSS from admission to discharge (ΔNIHSS = NIHSS at admission minus NIHSS at discharge), groin to reperfusion times [time from groin puncture to first angiographic series with Thrombolysis in Cerebral Infarction perfusion scale (TICI) ≥ 2b], rates of successful recanalization (defined as TICI ≥ 2b) as well as any intracerebral hemorrhage, groin hematoma, groin pseudoaneurysm, space occupying edema of medial cerebral artery territory, myocardial infarction, and recurrent stroke.

Statistical Analysis

All variables are summarized by either mean ± SD, median with interquartile range (IQR) or absolute and relative frequencies, as appropriate. Values were compared univariately between the groups using Welch's two-sample *t*-test, Fisher's exact test, or Mann–Whitney U test as appropriate. Linear mixed effect models taking into account the center as random effect, and controlling for the following potential confounders unequally distributed in a univariate analysis with a $p < 0.2$: Onset-to-first TICI ≥ 2b- and onset-to-imaging times, diabetes mellitus, arterial hypertension, atrial fibrillation, premedication with acetylsalicylic acid, clopidogrel, low molecular weight heparin, oral anticoagulants (Apixaban, Rivaroxaban, Dabigatran, Edoxaban, and Marcumar), living status, pre-stroke-modified Rankin score (mRS) and kind of sedation as well as intracranial internal carotid artery bifurcation occlusion, and Alberta stroke program early CT score. These confounders were fit to the data to assess the association between IVT-treatment and the groin-to-reperfusion status and time as well as the functional outcomes. The scores of the mRS were modeled using mixed effect ordinal (cumulative link) regression models (13). Missing values were imputed using multiple imputations.

The 3-month mortality was modeled using a mixed effect logistic regression model. In order to assess a potential power limitation in the fully controlled model, as a sensitivity analysis, a propensity score analysis was performed: logistic mixed effect regression model was fit to the grouping using the potential confounders as fixed effects (and the center as random effect) and the fitted logit scores were used as propensity scores, which were added to the model for the 3-month mortality as covariable. Additionally, we performed an analysis on 1:1 matched samples where samples were matched within centers using a caliper of 0.15. Data from propensity score matched samples were used to plan for a comparison using the Mann–Whitney U-test in a future randomized trial. For the mRS at 3 months, we conducted two power analyses to detect differences between EVT + IVT and EVT – IVT: In the first scenario, the power to detect the observed difference was analyzed. The second scenario assumes a smaller effect of 20% of the patients receiving a smaller mRS in the EVT + IVT group. The significance level was set to alpha = 5% for all statistical tests. All analyses were performed with the statistic software R using the R-package lme4 (14) for the mixed effect logistic regression, the R-package ordinal (15) for the mixed effect cumulative link models, the R-package CMatching (16) for the clustered propensity matching, and the R-package WMWssp (17) for the power analyses for the Mann–Whitney U-test.

RESULTS

Baseline Characteristics

At the time of data analysis, the GSR databank contained 2,637 cases. After discarding cases being inconsistently recorded, cases with missing data, non-mothership cases, and patients with other occlusions than ICA and MCA occlusions, 881 patients remained for the analysis (**Supplementary Figure 1**). From these patients, 486 (55.2%) received bridging-IVT prior to EVT, and 395 (44.8%) received EVT alone. Baseline characteristics of both groups are shown in **Table 1**.

Patients with bridging-IVT had significantly lower pre-stroke mRS ($p < 0.001$) and were less likely to have cardiovascular comorbidities like diabetes mellitus (19.2% vs. 24.1%, $p = 0.083$), arterial hypertension (72.1% vs. 78%, $p = 0.051$), and atrial fibrillation (36.5% vs. 45.5%, $p = 0.007$) as well as were significantly less likely to be on antiplatelets or anticoagulants. In addition, patients with bridging-IVT were more likely to live at home without nursing, while the percentage of patients living in a nursing home was equally distributed. There was no significant difference in symptom onset to imaging—(84 ± 53 min vs. 103 ± 163 min, $p = 0.177$), groin- (159 ± 66 min vs. 168 ± 84 min, $p = 0.281$) and to reperfusion times (205 ± 76 min vs. 217 ± 82 min, $p = 0.146$). Patients with bridging IVT had lower rates of occlusions of the intracranial internal carotid artery bifurcation (15.4% vs. 20.8%, $p = 0.042$); all other sites of vessel occlusion were equally distributed. Alberta stroke programme early CT score (ASPECTS) was higher in the bridging group (9 vs. 8, $p < 0.001$); there were no differences in adverse events between both groups, including any kind of intracerebral hemorrhage (**Supplementary Table 1**).

TABLE 1 | Baseline characteristics of with (EVT + IVT) and without (EVT – IVT) bridging thrombolysis.

	EVT + IVT group (*n* = 486)	EVT – IVT (*n* = 395)	*p*-value
Demographics and clinical data			
Age (mean ± SD)	72 ± 13	73 ± 13	0.330
Sex male (*n*, %)	237 (48.9)	190 (48.1)	0.839
Baseline NIHSS (median score, IQR)	14 (10,18)	15 (10,19)	0.279
Pre-stroke mRS (median score, IQR)	0 (0;1)	0 (0;2)	<0.001
Living status			0.038
Home (*n*, %)	403 (87.0%)	313 (83.7%)	
Nursing at home (*n*, %)	17 (3.7%)	29 (7.8%)	
Nursing home (*n*, %)	43 (9.3%)	32 (8.6%)	
Stroke etiology			<0.001
Cardioembolism (*n*, %)	232 (48.2%)	209 (53.7%)	
Large-artery arteriosclerosis (*n*, %)	125 (26.0%)	91 (23.4%)	
Other determined etiology (*n*, %)	17 (3.5%)	29 (7.5%)	
Undetermined etiology (*n*, %)	90 (18.7%)	57 (14.7%)	
Anesthesia			0.009
CS (*n*, %)	114 (24.4%)	109 (28.6%)	
Switch from CS to GA (*n*, %)	26 (5.6%)	7 (1.8%)	
GA (*n*, %)	327 (70.0%)	265 (69.6%)	
Medical history			
Diabetes mellitus (*n*, %)	93 (19.2%)	95 (24.1%)	0.083
Arterial hypertension (*n*, %)	349 (72.1%)	308 (78.0%)	0.051
History of AF (*n*, %)	176 (36.5%)	179 (45.5%)	0.007
Dyslipoproteinemia (*n*, %)	165 (34.2%)	151 (38.4%)	0.203
Previous and current smoking (*n*, %)	107 (22%)	95 (24%)	0.629
Time metrics			
Onset-to-needle time (mean min ± SD)	101 ± 54	n.a.	n.a.
Onset-to-imaging time (mean min ± SD)	84 ± 53	103 ± 163	0.177
Onset-to-groin time (mean min ± SD)	159 ± 66	168 ± 84	0.281
Onset-to-first TICI≥2b (mean min ± SD)	205 ± 76	217 ± 82	0.146
Imaging data			
ASPECTS at baseline (median, IQR)	9 (8,10)	8 (7,10)	<0.001
Site of vessel occlusion			
Intracranial ICA bifurcation (*n*, %)	75 (15.4%)	82 (20.8%)	0.042
Intracranial ICA non-bifurcation (*n*, %)	22 (4.5%)	22 (5.6%)	0.535
Extracranial ICA (*n*, %)	17 (3.5%)	20 (5.1%)	0.311
MCA, proximal M1-segent (*n*, %)	201 (41.4%)	164 (41.5%)	1.000
MCA, distal M1-segent (*n*, %)	121 (24.9%)	85 (21.5%)	0.263
MCA, M2-segent (*n*, %)	111 (22.8%)	81 (20.5%)	0.413
Medication on admission			
Acetylsalicylic acid (*n*, %)	117 (30.4%)	185 (39.4%)	0.006
Clopidogrel (*n*, %)	8 (1.7%)	18 (4.7%)	0.015
Low molecular weight heparin (*n*, %)	2 (0.4%)	18 (4.7%)	<0.001
Apixaban (*n*, %)	2 (0.4%)	30 (7.8%)	<0.001
Rivaroxaban (*n*, %)	4 (0.9%)	24 (6.2%)	<0.001
Dabigatran (*n*, %)	1 (0.2%)	5 (1.3%)	0.096
Edoxaban (*n*, %)	2 (0.4%)	12 (3.1%)	0.002
Marcumar (*n*, %)	14 (3.0%)	38 (9.9%)	<0.001

EVT, endovascular therapy; IVT, intravenous thrombolysis; SD, standard deviation; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; CS, conscious sedation; GA, general anesthesia; AF, atrial fibrillation; TICI, thrombolysis in cerebral infarction scale; ASPECTS, Alberta stroke programme early CT score; ICA, internal carotid artery; MCA, medial cerebral artery.

TABLE 2 | Unadjusted primary outcome parameter in patients with and without bridging-thrombolysis.

	EVT + IVT group (*n* = 486)	EVT – IVT group (*n* = 395)	*p*-value
Procedural and imaging outcomes			
Groin-to-first TICI≥2b	48 ± 36	49 ± 34	0.766
Final TICI-score			0.612
TICI 0	50 (5.7%)	27 (6.9%)	
TICI 1	12 (1.4%)	6 (1.5%)	
TICI 2a	31 (6.4%)	29 (7.4%)	
TICI 2b	187 (38.7%)	140 (35.8%)	
TICI 3	236 (48.9%)	189 (48.3%)	
Functional outcomes			
NIHSS discharge (median points, IQR)	4 (9)	7 (12)	<0.001
Δ NIHSS (median points, IQR)	8 (9.8)	4 (11)	0.001
mRS at discharge (median score, IQR)	3 (4)	4 (3)	<0.001
mRS after 90 days (median score, IQR)	3 (4)	4 (4)	<0.001
Mortality at 90 days (*n*, %)	96 (22.5%)	119 (33.6%)	0.001

EVT, endovascular treatment; IVT, intravenous thrombolysis; TICI, thrombolysis in cerebral infarction scale, IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; Δ NIHSS = NIHSS admission minus NIHSS discharge.

Unadjusted Analysis of Primary Outcomes

In the unadjusted analysis of the outcome parameters, there was no difference between groin to reperfusion times and reperfusion status on final angiogram between the bridging- and EVT alone group (**Table 2**). Patients with bridging-IVT had lower NIHSS at discharge (4 vs. 7, $p < 0.001$), higher improvement on the NIHSS during in-patient stay (8 vs. 4, $p = 0.001$) as well as lower mRS at discharge and at 90 days follow-up (3 vs. 4, $p < 0.001$). Mortality rates in the bridging-IVT group were lower compared with the EVT alone group [96 (22.5%) vs. 119 (33.6%), $p = 0.001$)].

Adjusted Analysis of Primary Outcomes

After adjustment for multiple confounders, successful reperfusion (defined as TICI ≥ 2b on final angiogram) was associated with bridging-IVT (fixed effects estimate 0.410, 95% CI, 0.070; 0.750, $p = 0.018$), while no difference persisted with regard to groin to reperfusion times between both groups (fixed effects estimate −0.030, 95% CI, −0.070; 0.020, $p = 0.243$) (**Table 3**). Concerning the adjusted analysis of the functional outcome parameters, bridging IVT was associated with lower mRS at discharge (fixed effects estimate −0.340, 95% CI, −0.650; −0.030, $p = 0.031$) and at 90 days follow-up (fixed effects estimate −0.350, 95% CI, −0.680; −0.010, $p = 0.041$).

In addition, patients with bridging-IVT had lower NIHSS at discharge (fixed effects estimate −0.050, 95%CI, −0.130; 0.030, $p = 0.209$) and higher improvement in NIHSS between admission and discharge (Δ NIHSS; fixed effects estimate 1.370, 95% CI, −0.490; 3.240, $p = 0.149$), in which both did not reach statistical significance after correcting for multiple confounders (**Table 3**). Adjusted mortality rates were non-significantly lower

TABLE 3 | Adjusted analysis of outcome parameters and bridging IVT using linear mixed effect models.

	n	Fixed effects estimate	95% CI	*p*-value
Successful reperfusion	704	0.410	0.070; 0.750	0.018
Groin-to-reperfusion time	604	−0.030	−0.070; 0.020	0.243
mRS at discharge	693	−0.340	−0.650; −0.030	0.031
mRS at 90 days	622	−0.350	−0.680; −0.010	0.041
NIHSS at discharge	554	−0.050	−0.130; 0.030	0.209
Δ NIHSS	552	1.370	−0.490; 3.240	0.149
Mortality	622	0.980	−0.610; 2.580	0.346

IVT, intravenous thrombolysis; CI, confidence interval; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; Δ NIHSS, NIHSS admission minus NIHSS discharge, successful reperfusion, TICI, thrombolysis in cerebral infarction scale ≥ 2b on final angiogram.

in the bridging IVT group (fixed effects estimate 0.980, 95% CI −0.610; 2.580, $p = 0.351$). Also, in the propensity score adjusted model, no significant group effect was observed (estimate 0.770, 95% CI 0.451; 1.315, $p = 0.338$). Similarly, in the propensity score matched set, no significant group effect was observed (estimate 0.833, 95% CI 0.534–1.297, $p = 0.418$). An overview and visualization of all model covariates is given in **Supplementary Figures 2A–E**.

DISCUSSION

In this study, we found an association between bridging IVT and higher rates of successful reperfusion as well as improved functional outcome including a "real world" cohort of patients receiving in-house bridging-IVT vs. EVT alone for anterior circulation LVOS in multiple tertiary stroke centers in Germany.

The treatment approach of bridging-IVT has been suspected to exhibit multiple potential advantages compared with EVT alone. These advantages include earlier and more complete reperfusion, especially in delayed intervention and if the thrombus is challenging to reach, dissolution of distal thrombus fragments by IVT as well as reperfusion of the vessel before initiation of the interventional procedure. In contrast, possible delays of EVT, risks for intracerebral hemorrhage, and increased costs have to be taken into account (18). Most retrospective studies and *post hoc* analyses from randomized controlled clinical trials on the question if bridging with IVT is necessary prior to EVT have found benefits compared with EVT alone (19, 20). As all these studies—including the present study—have major limitations inherent to retrospective study designs, the large, multi-center and prospective DIRECT-MT trial has recently been conducted in China. Interestingly, this study also found a higher percentage of successful reperfusion in patients with the combined treatment with IVT and EVT (our study: 87% vs. 83%; DIRECT-MT: 85% vs. 79%), while the groin to reperfusion times (our study: 48 min vs. 49 min; DIRECT-MT: 71 min vs. 60 min) as well as the incidence of brain hemorrhage did not differ significantly between the groups (10). The overall lower reperfusion rate and longer groin to reperfusion time of the DIRECT-MT study compared with our data could be discussed as reasons for a lack of effect on functional outcome (21). Moreover, from a statistical point of view, the margin for non-inferiority in the DIRECT-MT study was generous and the confidence intervals did not exclude a benefit of ∼20% in the group treated with IVT. Recently, the Japanese trial (SKIP study) was published, which also did not show inferiority in the EVT only group (22). However, this trial also showed numerically more patients achieving good reperfusion (>TICI2b) as well as excellent outcome (mRS 0–1) in the IVT + EVT group. Both secondary endpoints were not statistically significant. First, the reason for this could be because of the lower rtPA dose (0.6 mg/kg), which is used in Japan, second, because of the total small sample size (n = 100 in each group), which was originally calculated using the results from trials using 0.9 mg/kg of Alteplase (22). This point is also discussed as a limitation by the authors themselves. Another widely discussed shortcoming of the two abovementioned studies is the raw segmentation of the mRS scheme itself, especially when it comes to smaller, but clinically highly relevant add-on effects like cognitive endpoints (23). We performed a power analysis based on our data for the day 90 mRS with a strictly propensity score matched sample ($n = 332$) for a comparison using the Mann–Whitney U-test. To detect a difference as pronounced as in the data, 350 subjects would suffice. If the effect is smaller, of course, more subjects are necessary: if 20% of the samples end up with a smaller mRS at day 90 with IVT, 2,336 subjects would be necessary. Currently, there are three more trials ongoing [MR CLEAN-NO IV (ISRCTN80619088), SWIFT DIRECT (NCT03192332), and DIRECT-SAFE (NCT03494920)], which are necessary to give more solid information. Additionally, these trials could help to perform a meta-analysis in order to provide more clarity.

The reason why groin to reperfusion times were not shorter in the bridging IVT group, but the rate of successful reperfusion was higher, seems to be contradictory. One would assume that IVT facilitates the clot removal by reducing clot load and softening the thrombus and therefore improving the passage through the thrombus and its removal. The lack of difference between groin to reperfusion times in our study could be explained by the different stroke etiologies in both groups. Most importantly, there were around 5% more cardio-embolic strokes and 2.6% less macroangiopathic strokes in the EVT alone group. While IVT might have facilitating effects in both stroke etiologies, cardio-embolic thrombi removal by EVT in the majority of cases is faster and easier compared with often hard, calcified, and plaque-associated thrombi and emboli (24, 25). One could assume equal effects of IVT in both groups, while time to reperfusion has been shorter in the EVT alone group because of technically easier clot removals in this group requiring less passes and aspirations. The higher rate of successful reperfusion is mechanistically plausible, as rates of reocclusions and residual thrombi are likely to be reduced by IVT after clot removal and the assumption, that proximal parts of the thrombi are being dissolved (reduction of thrombus length) and possibly emboli in new territories could be resolved, though, due to the study design, we were not able to

analyze the original CTA-scans for this purpose, and no data is available if and when follow-up CTA scans were performed.

Multiple effects of IVT improving functional outcomes have been discussed. IVT prior to EVT could lead to the lysis of small, peripheral thrombi impairing the penumbra-perfusion by collaterals. As the majority of large vessel occlusions are likely to be of embolic origin, the occlusion of collaterals by shattered thrombi therefore might be crucial for the functional outcome. Consequently, it could be speculated that the collateralization could have been positively influenced by the systemic administration of IVT, which has been administered after CTA, while this effect was missing in the non-bridging-group. In addition, also sources of emboli like cardiac thrombi are being treated by IVT, and the rate of recurrent strokes could be lower in this group. In this respect, Molina et al. showed that M1 occlusions of cardioembolic source are more likely to be recanalized by IVT compared with other sources of thrombus origin (26).

Strengths and Limitations

Limitations of previous retrospective studies on the role of bridging IVT include monocentric designs, lack of sufficient patient and periprocedural data with potential bias, and the inclusion of heterogeneous patient groups (e.g., inclusion of drip-and-ship patients and non-anterior circulation occlusions) (27). In contrast, the strength of our study is the inclusion of a large cohort of highly selected patients being treated in multiple German thrombectomy centers, receiving full doses of IVT directly prior to EVT for anterior circulation LVOS. Although we adjusted our regression analyses for multiple confounders like comorbidities, pre-stroke medication, peri-interventional factors including time metrics and kind of anesthesia, stroke severity, and pre-stroke functional status, residual confounding is still possible. The most important bias in this respect is represented by the various reasons not to treat with bridging-IVT (selection bias), which were at the discretion of the treating neurologists and neuroradiologist using different clinical (e.g., age of the patient) and imaging-based (e.g., cerebral microangiopathy) factors. Contraindications for IVT include cancer, recent surgery, and current anticoagulation. The first two factors can be major contributing factors for worse functional outcomes, for which in this study no correction could be made, as these data were not recorded in the GSR. However, from a clinical point of view, these patients represent a minority of EVT patients, and therefore, this bias seems to be negligible. In contrast, anticoagulation is highly associated with existing atrial fibrillation, which again is more prevalent in patients with a high number of comorbidities. On the one hand, residual bias concerning other comorbidities significantly influencing the functional outcome of the possibly higher morbidity of patients in the sole EVT group cannot be entirely excluded. On the other hand, in the GSR, only any kind of intracerebral hemorrhage in the post-interventional phase is recorded, not differentiating symptomatic from asymptomatic hemorrhages. This again represents another limitation of our study and should be considered when interpreting the results, even if total rates of intracerebral hemorrhages did not differ between both groups. In addition, the aim of the study was to investigate only patients with and without bridging IVT actually undergoing EVT. Therefore, an additional effect of IVT-related racialization without EVT on functional outcome is possible. Finally, 316 cases have been excluded because of inconsistent or missing data regarding IVT treatment times and additional 38 cases were excluded because of recanalization after IVT prior to EVT. Concerning this significant number of excluded patients, additional selection bias is possible.

In conclusion, our findings provide further evidence for the effectiveness and safety of bridging IVT directly prior to EVT, with all precautions due to the retrospective design. Thus, the findings of the ongoing prospective, randomized trials are highly anticipated and will hopefully finally answer the question, if and for which kind of patient bridging IVT is necessary and in which scenarios is dispensable.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics commission of the university medicine Göttingen; 16/2/16. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IM designed the study, was involved in the acquisition and statistical analysis of the data, drafted and finalized the manuscript, and approved the manuscript before submission. AL was involved in the statistical analysis of the data and approved the manuscript before submission. MBad, IA, AH, and were involved in the acquisition of the data and drafting of the manuscript and approved the manuscript before submission. MBäh contributed to the manuscript and approved the manuscript before submission. DB contributed to the manuscript, involved in the acquisition of the data, and approved the manuscript before submission. M-NP contributed to the manuscript, involved in the acquisition of the data, and approved the manuscript before submission. JL contributed to the manuscript and approved the manuscript before submission. Patient data were collected by the GSR-ET committee. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.649108/full#supplementary-material

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ORIGINAL RESEARCH
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New Prehospital Triage for Stroke Patients Significantly Reduces Transport Time of EVT Patients Without Delaying IVT

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Background and Purpose: Ischemic stroke is a leading cause of mortality and morbidity worldwide. The time from stroke onset to treatment impacts clinical outcome. Here, we examined whether changing a triage model from "drip and ship" to "mothership" yielded significant reductions of onset-to-groin time (OGT) in patients receiving EVT and onset-to-needle time (ONT) in IVT-treated patients, compared to before FAST-PLUS test implementation. We also investigated whether the new triage improved clinical outcomes.

Methods: In a before/after multicenter study, we evaluated the effects of changing the prehospital triage system for suspected stroke patients in the Moravian–Silesian region, Czech Republic. In the new system, the validated FAST PLUS test is used to differentiate patients with suspected large vessel occlusion and triage-positive patients are transported directly to the CSC. Time metrics and patient data were obtained from the regional EMS database and SITS database.

Results: For EVT patients, the median OGT was 213 min in 2015 and 142 min in 2018, and the median TT was 142 min in 2015 and 47 min in 2018. For tPA patients, the median ONT was 110 min in 2015 and 109 min in 2018, and the median TT was 41 min in 2015 and 48 min in 2018. Clinical outcome did not significantly change. The percentages of patients with favorable clinical outcome (mRS 0–2) were comparable between 2015 and 2018: 60 vs. 59% in tPA patients and 40 vs. 44% in EVT patients.

Conclusions: The new prehospital triage has yielded shorter OGTs for EVT patients. No changes were found in the onset-to-needle time for IVT-treated patients, or in the clinical outcome at 3 months after stroke onset.

Keywords: prehospital triage, stroke, paramedic, EVT, large vessel occlusion

INTRODUCTION

Ischemic stroke is a leading cause of mortality and morbidity worldwide (1), and the recognition of stroke symptoms and prehospital stroke management represent critical bottlenecks in acute stroke management. The delay from the onset of stroke symptoms to hospital arrival is largely due to delayed activation by the patient/witness or failure of EMS crew to recognize stroke symptoms (2–4). Delayed hospital arrivals are common and contribute to the fact that only one in four stroke patients present within the time window for receiving tPA (5). Quicker therapy provision is associated with better clinical outcome (6–8); therefore, effective prehospital intervention is important.

One possible means of decreasing prehospital delay is to increase stroke preparedness in the general population; however, previous studies of this topic have shown mixed results (9–11). Another method is to educate paramedics in stroke signs recognition. This method was used in the Czech Republic before the implementation of a new prehospital triage test (12). In 2016, a prehospital stroke scale, the FAST PLUS test, which evaluates for the presence of severe hemiparesis (NIHSS of three to four points for upper and lower limbs), was introduced in the Moravian–Silesian region to differentiate patients with suspected large vessel occlusion (LVO). This test reportedly predicts LVO with 93% sensitivity and 47% specificity (13). If the FAST PLUS result is positive, the paramedic has a tele-consultation with a hospital-based neurologist in a comprehensive stroke center (CSC). If the neurologist agrees, the triage-positive patient is transferred directly to the CSC (mothership approach). If the FAST PLUS test result is negative, the nearest primary stroke center is contacted. With the introduction of the FAST PLUS test, the triage model has been changed from drip and ship (transferring the stroke patient to the nearest stroke center, and if there is LVO, then secondary transfer to CSC is indicated) (**Figure 1**) to mothership (direct transfer of stroke patient with suspected LVO to CSC—i.e., bypassing the nearest PSC) (**Figure 2**).

Currently, there is only a limited body of evidence comparing these prehospital models (mothership vs. drip and ship) (14, 15).

The main aim of our present study was to determine whether changing the triage model from drip and ship to mothership yielded a significant reduction in onset-to-groin time (OGT) among patients receiving EVT and in onset-to-needle time (ONT) among IVT patients, compared to the situation before FAST-PLUS test implementation. The second aim was to determine whether the new triage protocol led to better clinical outcomes.

Abbreviations: CSC, comprehensive stroke center; DGT, door-to-groin time; DNT, door-to-needle time; EMS, emergency medical services; EVT, endovascular treatment; IVT, intravenous thrombolysis; LVO, large vessel occlusion; OCT, onset-to-call time; ODT, onset-to-door time; OGT, onset-to-groin time; ONT, onset-to-needle time; PSC, primary stroke center; SSTS, stockholm stroke triage system; tPA, tissue plasminogen activator; TT, transport time.

METHODS

In this study, we conducted a before/after study comparing the situation before and after a change in prehospital stroke triage system. In 2016, a new prehospital triage test (FAST PLUS test) was introduced to detect stroke patients with possible LVO in the Moravian–Silesian region of the Czech Republic. Before its implementation in routine clinical practice, this test was validated and demonstrated the following: sensitivity 93%, specificity 47%, PPV 41%, and NPV 94% (13). Its inter-rater reliability was assessed and showed moderate agreement between paramedics and neurologists (12).

Population

The Moravian–Silesian region is home to ∼1.2 million inhabitants, with a population density of 220/km^2. It includes five primary stroke centers (PSCs) and one CSC, with a maximum driving distance of ∼50 km to the nearest stroke center and ∼95 km to the nearest CSC. **Figure 3** presents the locations of the PSCs and CSC in this region. In 2015 and 2018, one PSC performed mechanical thrombectomies only for patients from its primary catchment area (300,000 inhabitants).

Emergency and Triage System

There is only one regional Emergency Medical Services (EMS) system, and the majority of stroke patients are transported by ground EMS transport.

Under the mothership model, patients with positive FAST PLUS results are transported directly to the CSC. The transport times of all stroke patients treated with IVT, EVT, or both at all stroke centers in the Moravian–Silesian region were compared between 2015 (before the intervention) and 2018 (after). From the regional EMS database, we got the list of patients transferred with suspected stroke to all stroke centers in the region and all the time metrics of these transfers.

Data Collection

Using the Safe Implementation of Treatment in Stroke (SITS) database, we obtained the time metrics of therapeutic interventions, patient identification, age, sex, baseline NIHSS, and clinical outcome evaluated by modified Rankin scale (mRS) at 3 months after stroke onset, door-to-needle time (DNT) or door-to-groin time (DGT), and stroke onset time. The onset time was completed for every patient, using either the stroke onset time or last seen well time from the SITS database. We calculated the following time metrics (**Figure 4**): onset-to-call time (OCT, time from the first stroke symptoms to EMS call by patient or witness), transfer time (TT, time from the arrival of paramedics at the stroke site to arrival at hospital), onset-to-door time (ODT, from stroke onset to door of hospital), onset-to-needle time (ONT, ODT + time to the first bolus of IVT), and onset-to-groin time (OGT, ODT + time to groin puncture).

The SITS initiative offers a platform for collecting stroke data from stroke centers in more than 80 countries. The registry is internet based, which allows rapid data entry and retrieval, and allows centers to compare their own treatment results on both a national and global scale.

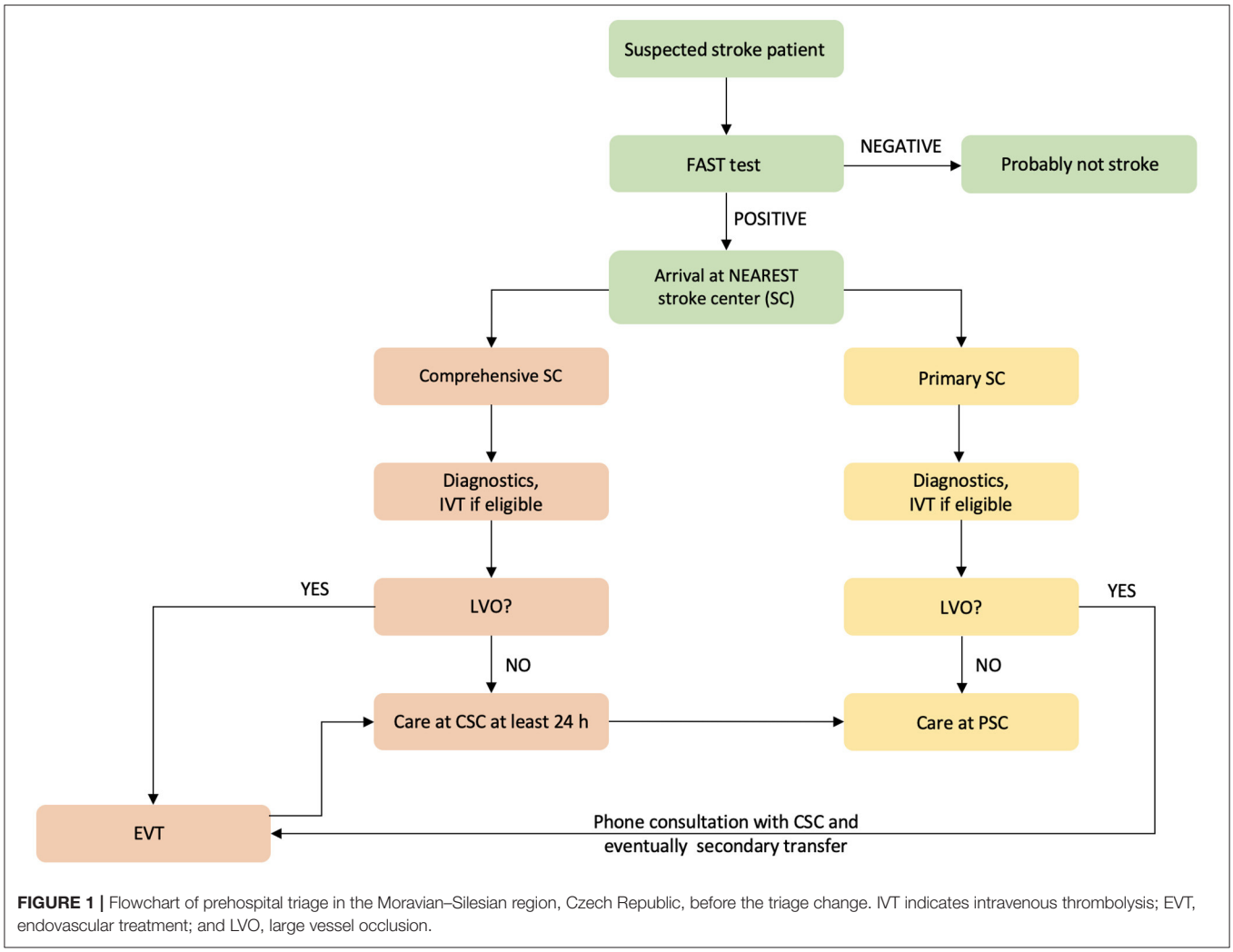

FIGURE 1 | Flowchart of prehospital triage in the Moravian–Silesian region, Czech Republic, before the triage change. IVT indicates intravenous thrombolysis; EVT, endovascular treatment; and LVO, large vessel occlusion.

To achieve the data completeness, an official e-mail has been sent to the chairs and physicians of all included stroke centers, who were responsible for data entering into the SITS database. The centers were officially asked to update all relevant time metrics as well as outcome measures (3-month modified Ranking scale). The centers were not aware of the study neither before it was started or after the study was finished.

All data are available on reasonable request from the corresponding author.

Statistical Analysis

Data were processed using standard statistical analysis methods and reported as median values, means, standard deviations, contingency intervals, and IQR variance. Testing was performed using Kruskal–Wallis-type non-parametric tests. Normality was assessed by Shapiro–Wilk test. Analyses were performed using the "R-project" package of mathematical libraries.

This study was approved by the Ethical Committee of University Hospital Ostrava, Czech Republic, and is registered at ClinicalTrials.gov (identifier: NCT03072524). For this type of study, informed consent is not required.

RESULTS

In 2015, a total of 3,513 patients were diagnosed with acute ischemic stroke, of whom 431 were treated either with tPA or mechanical thrombectomy (EVT)—including 364 (85%) with tPA only and 89 (20%) with EVT ± tPA. In 2018, a total of 3,554 patients were diagnosed with acute ischemic stroke, of whom 691 were treated—654 (95%) with tPA only and 179 (26%) with EVT ± tPA. Between these time periods, the number of patients treated with endovascular intervention doubled from 89 to 179. The 2015 and 2018 populations did not significantly differ in sex distribution: 54% men in 2015 vs. 52% men in 2018 ($P = 0.5$). The median age was 72 years in 2015 and 74 years in 2018 (**Table 1**).

Among tPA-treated patients, the median TT was 41 min (IQR 19.7) in 2015 and 48 min (IQR 20.1) in 2018 ($P < 0.001$), and the median ONT was 110 min (IQR 81) in 2015 and 109 min (IQR 48.7) in 2018. Among EVT-treated patients, the median TT was 142 min (IQR 128.1) in 2015 and 47 min (IQR 19.7) in 2018 ($P < 0.001$), and the median OGT was 213 min (IQR 105) in 2015 and 142 min (IQR 51.5) in 2018 ($P < 0.001$). Among all stroke patients, the median DNT was 45 min (IQR 24) in 2015

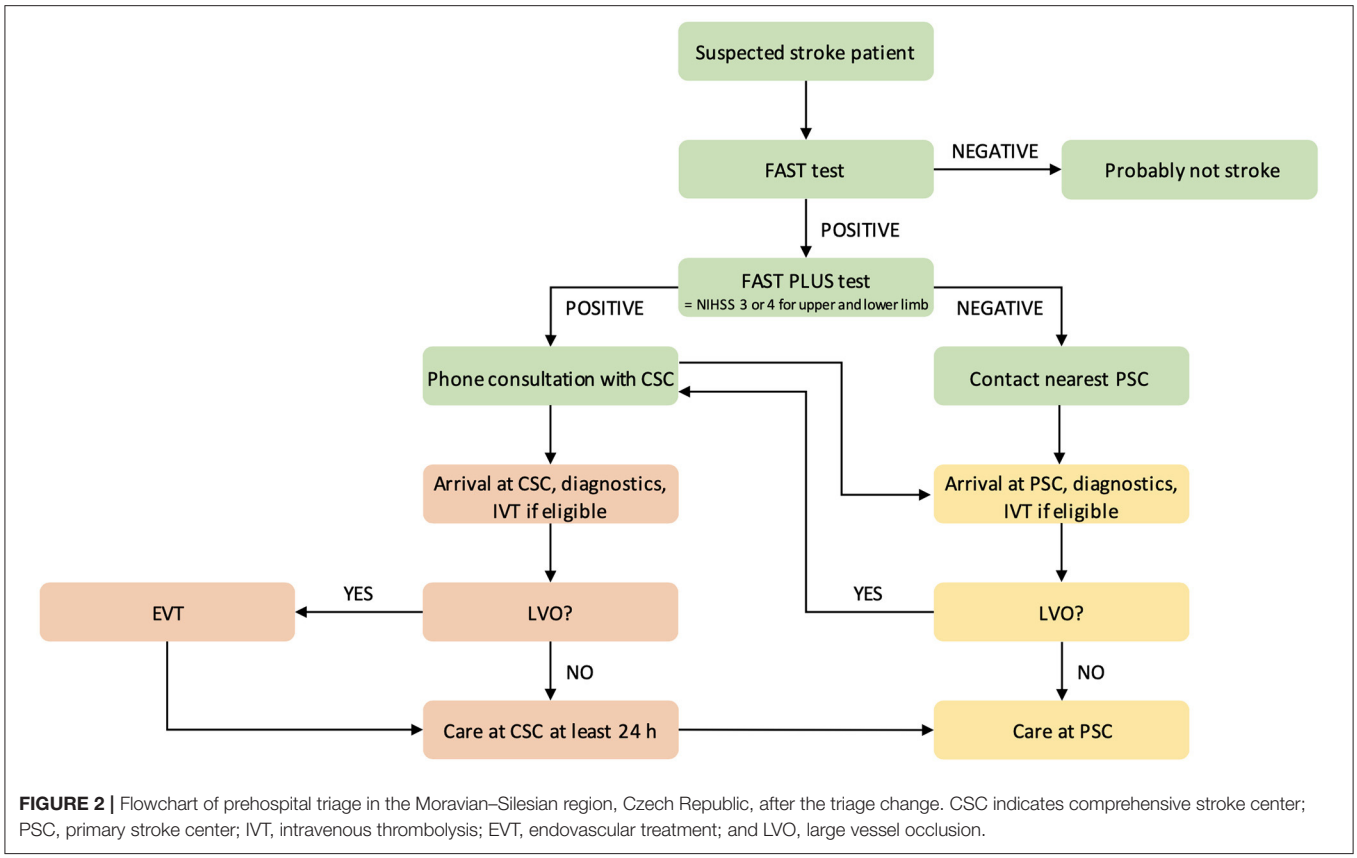

FIGURE 2 | Flowchart of prehospital triage in the Moravian–Silesian region, Czech Republic, after the triage change. CSC indicates comprehensive stroke center; PSC, primary stroke center; IVT, intravenous thrombolysis; EVT, endovascular treatment; and LVO, large vessel occlusion.

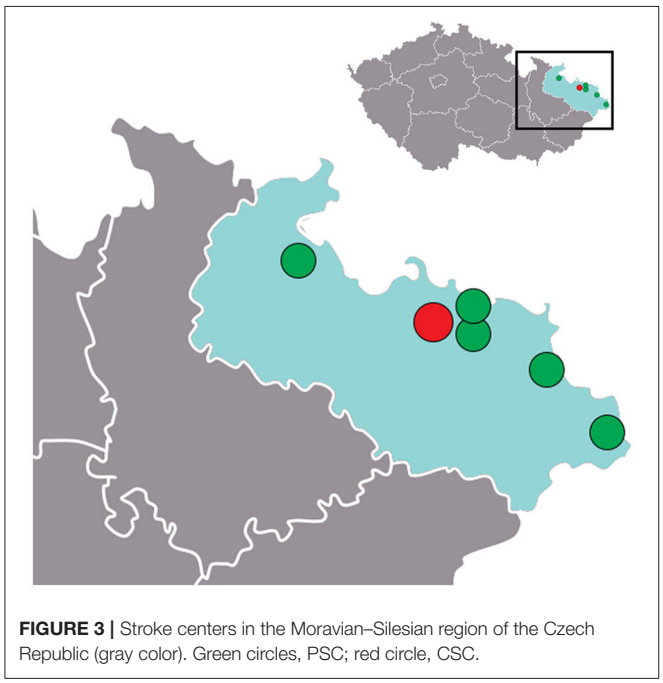

FIGURE 3 | Stroke centers in the Moravian–Silesian region of the Czech Republic (gray color). Green circles, PSC; red circle, CSC.

and 26 min (IQR 15) in 2018 ($P < 0.001$). The median DGT increased from 33 min (IQR 74.2) in 2015 to 60 min (IQR 35) in 2018 ($P = 0.02$).

In 2015, from 53 secondary transferred patients, 49 received EVT (92.4%). In year 2018, 14 out of 21 received EVT (66.7%).

The percentages of patients with favorable clinical outcome (mRS 0–2) were comparable between 2015 and 2018: 60 vs. 59% among tPA-treated patients and 40% vs. 44% among EVT-treated patients (**Figure 5**).

DISCUSSION

Prior to implementation of the new prehospital triage test, it was uncertain whether the bypass of PSC might delay IVT initiation. Among EVT patients, the median TT was three times shorter in 2018 compared to in 2015 ($P < 0.001$). On the other hand, among tPA patients, the median TT was 7 min longer in 2018 (48 vs. 41 min) because triage-positive patients were not taken to the nearest PSC but rather directly to the CSC, which was sometimes farther. Nevertheless, the median ONT (onset-to-needle time) for tPA patients was 110 in both 2015 and 2018 due to the shortening of intrahospital times (median DNT decreased from 45 to 26 min). Moreover, we observed a significant positive change in OGT from 213 min in 2015 to 142 min in 2018 ($P < 0.001$).

Notably, the number of endovascular interventions practically doubled between 2015 and 2018. There are probably multiple reasons for this, including better availability of this therapeutic intervention, increasing clinical experience, and changes of the guidelines for patient selection. The number of secondary

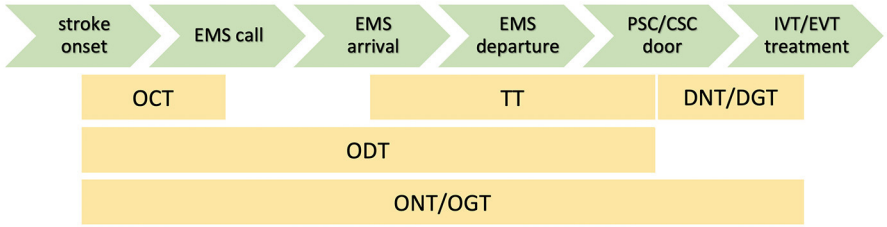

FIGURE 4 | Calculated time metrics. OCT indicates onset-to-call time; TT, transfer time; DNT, door-to needle time; DGT, door-to-groin time; ODT, onset-to-door time; ONT, onset-to-needle time; and OGT, onset-to-needle/groin time.

TABLE 1 | Demographic data and results.

	2015		2018		*P*-value	
	IVT	**EVT**	**IVT**	**EVT**	**IVT**	**EVT**
Total number of treated patients	431		691		NA	
Number of patients, total (% men)	364 (54.4)	89 (56.2)	654 (52)	179 (54.7)	NS	NS
Age	72.5 (16.2)	70 (12)	74 (16)	73 (12)	0.170	0.024
Baseline NIHSS	11 (9.5)	16 (9)	9 (11)	16 (7)	0.003	0.307
Favorable clinical outcome (mRS 0–2), %	60	40	59	44	NA	NA
DNT, min	45 (24)	—	26 (15)	—	<0.001	NA
DGT, min	—	32,5 (74.2)	—	60 (35)	NA	0.023
OCT, min	15 (54.1)	9 (11)	12 (28.3)	7 (17.6)	0.024	0.515
TT, min	41 (19.7)	142 (128.1)	48 (20.1)	47 (19.7)	<0.001	<0.001
ODT, min	93 (111)	179 (184.8)	81 (44.4)	74 (34.9)	<0.001	<0.001
ONT, min	110 (81)	—	109 (48.7)	—	0.118	NA
OGT, min	—	213 (105)	—	142 (51.5)	NA	<0.001

Data presented as median (IQR) unless otherwise indicated.
DNT indicates door-to-needle time; DGT, door-to-groin time; OCT, stroke onset to call of the EMS; TT, transfer time (from the arrival of EMS to a stroke patient to the stroke center); ODT, stroke onset to arrival to the stroke center; ONT, onset-to-needle time (only for IVT patients); and OGT, onset to the catheterization of femoral artery (only for EVT patients).

transfers decreased, but the median DGT increased from 33 to 60 min ($P = 0.02$). This increase was possibly due to the need to perform diagnostic tests at the CSC before endovascular intervention.

In our opinion, the lower median baseline NIHSS in 2018 might be partially explained by the effect of national strategy to support the IVT administration in acute stroke patients. A very recent publication by Mikulik et al. (16) focused on this topic and demonstrated that it is feasible and achievable to treat as many as 20% of all ischemic stroke patients with IVT. Continuous education of neurologists and less fear of IVT administration in low/er NIHSS patients might be another possible explanation for this phenomenon.

Our secondary aim was to determine whether the change of triage method has led to better clinical outcomes. The study by Herm et al. (17) focused on analysis of the DGT within the German Stroke Registry of EVT-treated patients and its impact on functional outcome. Fifty-six percent of the patients were primarily treated in CSC and 44% of the patients were primarily treated in PSC and then transferred to CSC. Median DGT was shorter in the PSC-treated patients (44 min); in CSCs, the median DGT was 79 min. On the other hand, median OGT was 196 min among patients primarily transferred to CSC vs. 278 min for patients primarily treated in PSC. In our study, we have shown very similar findings. The median DGT was 33 min in 2015 and 60 min in 2018 (mothership strategy). The median OGT shortened from 213 min in 2015 to 142 min in 2018. One possible explanation of prolonged DGT, when more patients were primarily treated in CSC, is that the lower number of secondary transports (with diagnostic CT and CT angiography performed in the PSCs) led to a higher number that need to perform diagnostic tests at CSC before EVT. Nevertheless, the percentage of EVT patients with a favorable clinical outcome (mRS 0–2) did not change overtime (44 in 2018 vs. 40% in 2015).

The percentages of patients with favorable clinical outcome treated with IVT (i.e., mRS 0–2 at 3 months) did not change either (60% in 2015 and 59% in 2018).

When comparing the transport situation in the Moravian–Silesian region with the mathematical models presented in the paper by Schlemm et al. (18), there is a similarity with the rural scenario (rectangular shape with one side 120 km and the second side 60 km). Schlemm et al. concluded that if the additional delay to IVT is <50 min, the patient with suspected LVO should be transferred directly to CSC. In the Moravian–Silesian region,

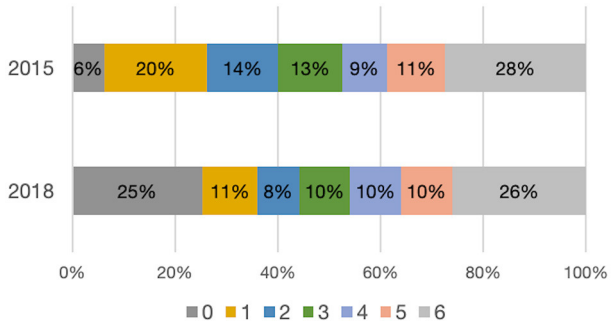

FIGURE 5 | Distribution of mRS values at 3 months for EVT patients in 2015 and 2018.

the longest on-road distance between PSC and CSC is 50 km (for road-based EMS transport, it is <50 min); therefore, our effort to use the mothership model for suspected LVO patients corresponds to the study results of Schlemm et al.

The triage change was also accompanied by the lower number of secondary transfers of stroke patients with LVO between PSC and CSC from 53 in 2015 to 21 in 2018. In 2015, from 53 secondary transferred patients, 49 received EVT (92.4%). In 2018, 14 out of 21 received EVT (66.7%). The main reasons for not performing the EVT in 2018 were complete recanalization on the first DSA run (three patients) and operator/technical difficulties of reaching the occlusion (four patients).

A similar study was recently conducted in Stockholm, with a comparison of the situations before and after implementation of the SSTS (Stockholm Stroke Triage System) for predicting LVO (19). Their study was also region-specific, was conducted over 1 year (October 2017–October 2018), and included patients transported to the hospital for suspected acute stroke. Their primary objective was to evaluate the performance of the SSTS, which is highly similar to the FAST PLUS test. Both tests evaluate upper and lower limb weakness. The only difference is the NIHSS cutoff value, which is ≥3 for each limb with the FAST PLUS, and ≥2 with the SSTS. Implementation of the SSTS yielded the same results as found in our present study: shortening of onset-to-puncture/groin time without delaying IVT. The authors mentioned several study limitations, such as the specific region and logistic circumstances, the large number of patients without emergent CT angiography scans, and not reporting comparisons of clinical outcomes.

The presently observed shortening of OGT is similar to results reported in other PSC bypass studies using the RACE (Rapid Arterial oCclusion Evaluation) scale (20, 21) or LAMS (Los Angeles Motor Scale) score (22). However, these previous studies did not analyze all of the time metrics assessed in our study (e.g., ONT, ODT, and TT).

STUDY LIMITATIONS

This study was conducted in a specific geographic locality with relatively short distances between the PSCs and CSC. We are aware that our data were based on a retrospective analysis of registry data (SITS) and their quality depends on accuracy and completeness.

In addition, the secular trends must be taken into the consideration—change of lifestyle, improved public awareness, or increased lifespan.

CONCLUSIONS

The change in prehospital triage yielded shortening of the OGT among EVT patients, as well as a reduction of the number of secondary transfers from 53 to 21. No changes were observed in the onset-to-needle time among IVT-treated patients or in clinical outcome at 3 months after stroke onset. Mothership triage is supported by the results of our study in case of stroke patients with severe hemiparesis.

DATA AVAILABILITY STATEMENT

The data analyzed in this study was obtained from the Safe Implementation of Treatment in Stroke (SITS) database with the cooperation of those responsible for granting access to this data. Requests to access these datasets should be directed to SITS International, info@sitsinternational.org.

AUTHOR CONTRIBUTIONS

MC, LM, DV, OV, and MB contributed to conception and design of the study. DH and PJ organized the cooperation with paramedics. MC organized the database and cooperated with statistician. MC and OV wrote the first draft and all revised versions of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Influence of Onset to Imaging Time on Radiological Thrombus Characteristics in Acute Ischemic Stroke

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Introduction: Radiological thrombus characteristics are associated with patient outcomes and treatment success after acute ischemic stroke. These characteristics could be expected to undergo time-dependent changes due to factors influencing thrombus architecture like blood stasis, clot contraction, and natural thrombolysis. We investigated whether stroke onset-to-imaging time was associated with thrombus length, perviousness, and density in the MR CLEAN Registry population.

Methods: We included 245 patients with M1-segment occlusions and thin-slice baseline CT imaging from the MR CLEAN Registry, a nation-wide multicenter registry of patients who underwent endovascular treatment for acute ischemic stroke within 6.5 h of onset in the Netherlands. We used multivariable linear regression to investigate the effect of stroke onset-to-imaging time (per 5 min) on thrombus length (in mm), perviousness and density (both in Hounsfield Units). In the first model, we adjusted for age, sex, intravenous thrombolysis, antiplatelet use, and history of atrial fibrillation. In a second model, we additionally adjusted for observed vs. non-observed stroke onset, CT-angiography collateral score, direct presentation at a thrombectomy-capable center vs. transfer, and stroke etiology. We performed exploratory subgroup analyses for intravenous thrombolysis administration, observed vs. non-observed stroke onset, direct presentation vs. transfer, and stroke etiology.

Results: Median stroke onset-to-imaging time was 83 (interquartile range 53–141) min. Onset to imaging time was not associated with thrombus length nor perviousness (β 0.002; 95% CI −0.004 to 0.007 and β −0.002; 95% CI −0.015 to 0.011 per 5 min, respectively) and was weakly associated with thrombus density in the fully adjusted model (adjusted β 0.100; 95% CI 0.005–0.196 HU per 5 min). The subgroup analyses

showed no heterogeneity of these findings in any of the subgroups, except for a significantly positive relation between onset-to-imaging time and thrombus density in patients transferred from a primary stroke center (adjusted β 0.18; 95% CI 0.022–0.35).

Conclusion: In our population of acute ischemic stroke patients, we found no clear association between onset-to-imaging time and radiological thrombus characteristics. This suggests that elapsed time from stroke onset plays a limited role in the interpretation of radiological thrombus characteristics and their effect on treatment results, at least in the early time window.

Keywords: ischemic stroke, endovascular treatment, radiological thrombus characteristics, acute ischemic stroke, computed tomography, thrombus perviousness, thrombus length, thrombus density

INTRODUCTION

Radiological thrombus characteristics are among the few biomarkers that are associated with acute ischemic stroke (AIS) treatment success. Thrombus perviousness, reflecting the extent to which intravenous contrast permeates into a thrombus, was shown to be strongly associated with higher recanalization rates and treatment success of intravenous alteplase (IVT) (1, 2). Thrombus length was reported to negatively affect success rates of both IVT and endovascular treatment (EVT) (3, 4), although no effect on EVT outcomes was found in some other studies (5, 6). Higher thrombus density is related to higher recanalization rates after IVT and EVT (7, 8).

Thrombus characteristics may vary over time. For example, stasis in low pressure systems can cause thrombus growth over time by the accumulation of red blood cells in low-density fibrin networks (9). In contrast, time may allow for natural thrombolysis or IVT to reduce the size of the clot (10–13). In addition, if a patient has good collaterals, decreased blood stasis was reported to limit thrombus growth distal to the clot and improve thrombus exposure to alteplase (14, 15). Clot contraction may also reduce thrombus length, increase thrombus density, and decrease perviousness (16, 17).

Dynamic behavior of thrombi may influence the success of stroke treatment. For example, patients with a prolonged time to AIS treatment and favorable thrombus dynamics may show alteplase-induced or even spontaneous recanalization. This effect has been observed in patients transferred from primary hospitals to comprehensive stroke centers for EVT (18). Alternatively, if the thrombus grows before treatment, the chance of recanalization with IVT reduces, and endovascular procedure time increases (3, 4). Moreover, if radiological thrombus characteristics change over time, elapsed time between the moment of measurement and the start of stroke treatment may affect the association between these values and stroke treatment outcomes.

Despite these possibly relevant effects, the effects of time on thrombus characteristics have been understudied. We therefore aimed to assess the relation between stroke onset to imaging time and thrombus length, perviousness, and density using data from a large national registry.

METHODS

Study Population

This study includes patients from the Multicenter Randomized Clinical trial of Endovascular Treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) Registry (part I) (19) between March 2014 and June 2016. The MR CLEAN Registry is a nation-wide, prospective, observational, multicenter study at 16 comprehensive stroke centers in the Netherlands, including all patients who underwent EVT for AIS since the completion of the MR CLEAN trial (20). IVT was administered before EVT if patients were eligible. The central medical ethics committee of the Erasmus Medical Center Rotterdam, the Netherlands, granted permission (MEC-2014–235) to perform the study as a registry. Source data of this study are available in anonymized form upon reasonable request to the corresponding author.

Inclusion criteria for the current study were: M1 occlusion; age $\geq$18 years; groin puncture within 6.5 h after stroke onset; and treatment in an MR CLEAN trial center. Only patients with thin-slice ($\leq$2.5 mm) CT-angiography (CTA) and non-contrast CT (NCCT) images that were acquired on the same scanner no longer than 30 min apart were included. We used the images acquired at the first point in time. For patients who were transferred from a primary stroke center we used the primary center's radiological images if they were available and of sufficient quality. Otherwise, we used the images acquired at the comprehensive stroke center. Patients were excluded if images contained excessive noise, artifacts, poor contrast opacification on CTA, or uncorrectable registration errors. Patients with calcified thrombi were excluded as well, since the high attenuation of these thrombi can cause streak and partial volume artifacts.

Image Analysis

Measurements of radiological thrombus characteristics were performed in ITK-SNAP (www.itksnap.org) (19) by two neuroradiologists (B.G.D. and H.A.) (4). The NCCT and CTA images for each patient were co-registered with rigid registration, using Elastix® (21), such that thrombus measurements could be performed in both modalities simultaneously. If alignment of the CTA and NCCT was suboptimal, we performed manual registration.

Thrombus length was measured manually using the ITK-SNAP ruler function (22). If contrast pick-up distal to the thrombus was not seen on CTA, the hyperdense artery sign on NCCT was used as a reference point for the distal thrombus end. If the thrombus extended into two arterial branches, the longest thrombus length was included as measurement.

Thrombus perviousness and density were computed from three region of interests (ROIs). On the co-registered NCCT and CTA images, three spherical ROIs with a 1 mm radius were placed in the proximal, middle, and distal parts of the thrombus. Thrombus density was defined as the mean density of these ROIs on NCCT, in Hounsfield Units (HU). Thrombus perviousness was computed by subtracting the mean density of the ROIs on NCCT from the mean density of the ROIs on CTA, resulting in the average thrombus attenuation increase in HU (thrombus perviousness $= \rho_{CTA} - \rho_{NCCT}$).

Collateral score (23), occlusion location, Alberta Stroke Program Early CT Score were assessed on baseline CTA and NCCT by the MR CLEAN Registry core laboratory (19).

Statistical Analysis

The dependent variables were thrombus length (mm), perviousness and density (HU). The independent variable of interest was time from symptom onset or last seen well to imaging per 5 min. Imaging time was defined as the acquisition time of the NCCT images. Baseline characteristics were summarized appropriate to the type of data. Comparisons were made by one-way ANOVA, Kruskal-Wallis, Mann-Whitney-*U*, or Fisher's exact-test appropriate to the type of data. Visual representations of the data were made with scatter and bar plots.

Univariable and multivariable linear regression were used to assess the association between onset to imaging time and thrombus length, perviousness, and density, resulting in beta coefficients (β) with 95% confidence intervals (95% CI). The multivariable models were adjusted for the following baseline pre-specified variables: age, sex, history of atrial fibrillation, IVT administration, and antiplatelets. Model 2 was additionally adjusted for: observed stroke vs. non-observed stroke, CTA collateral score, transfer or direct presentation at a comprehensive stroke center, and stroke etiology according to the modified Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria (cardio-embolic vs. large artery atherosclerosis vs. unknown). The TOAST criteria were scored for a previous study on our data set (15). Because thrombus length and perviousness showed a right-skewed distribution, they were log-transformed for the regression analyses (**Supplementary Figure 1**).

Exploratory sensitivity analyses were performed by comparing the results of univariable models for different subgroups: (a) patients with observed stroke onset vs. patients without observed stroke onset (using last-seen-well time as onset time), (b) patients with vs. without IVT administration prior to EVT, (c) patients with collateral score 0–1 vs. patients with CS 2–3, (d) transfer patients vs. direct presentation to a comprehensive stroke center, (e) patients with different stroke etiologies: cardioembolic stroke, large-artery atherosclerotic stroke and stroke with an undetermined origin.

Missing data in the main and secondary variables of interest were imputed using multiple imputation for regression analyses only, based on relevant covariates and outcomes. A two-sided *p*-value of 0.05 was considered significant. Statistical analyses were performed with Stata/SE 14.2 (StataCorp, TX).

RESULTS

The total MR CLEAN Registry part I population consisted of 1,627 patients, of whom 825 had an M1 occlusion. We included 245 patients in the current study (**Supplementary Figure 2** and **Table 1**). Of these, 90 patients were transferred from a primary to a comprehensive center for EVT. We measured radiological thrombus characteristics on images acquired in the primary center for 44 of these patients. Baseline characteristics of our study population were similar to the overall MR CLEAN Registry population with an M1 occlusion except for a lower frequency of patients transferred from a primary stroke center [90/245 (36%) vs. 441/825 (53%), $p < 0.01$]. Median time from stroke onset to imaging was 83 (IQR 53–141) min. Median thrombus length was 12 (IQR 9–16) mm, median perviousness was 5 (IQR 0.1–11) HU, and median density was 52 (IQR 46–58) HU (**Figures 1A–D**). **Figures 1E–G** show the values of onset to imaging time in relation to thrombus length, thrombus perviousness and thrombus density for all patients.

The regression coefficients of the association of onset-to-imaging time and thrombus length, perviousness, or density are presented in **Table 2**. None of these associations were statistically significant, except for a positive association for thrombus density in the adjusted Model 2 (β 0.10; 95% CI 0.005–0.20 HU/5 min, **Table 2**). The sensitivity analyses showed no statistically significant associations for thrombus length, perviousness, or density in any of the subgroups (**Supplementary Tables 1–4** and **Supplementary Figures 3–7**), except for a significantly positive relation between onset-to-imaging time and thrombus density in patients transferred for EVT from a primary stroke center ($n = 90$) in the adjusted Model 2 only (β 0.18; 95%CI 0.022–0.35 HU/5 min, **Supplementary Table 4**). Patients who were transferred from a primary center had longer median onset to imaging times (median 137 min, IQR 65–181) than those presented directly to a comprehensive center (median 69 min, IQR 48–103, $p < 0.01$). In addition, among IVT-treated transferred patients ($n = 77$), median onset-to-imaging times were shorter among patients whose thrombus characteristics were measured on images acquired in the primary stroke center ($n = 36$; 67 min, IQR 56–100), as compared to the comprehensive stroke center ($n = 41$, 175 min, IQR 138–197; $p < 0.01$). Nonetheless, the longer time for IVT to work did not affect the association between onset-to-imaging time and thrombus characteristics (**Supplementary Table 4**).

DISCUSSION

Our study showed no association between stroke-onset to imaging time and thrombus length, density and perviousness,

TABLE 1 | Baseline characteristics of patients included in the current study, compared to all MR CLEAN Registry patients with an M1 occlusion.

	Current study ($n = 245$)	MR CLEAN Registry patients with M1 occlusion ($n = 825$)	*P*
Baseline clinical variables (data known in *n*=)			
Age, median (IQR)	69 (61–80)	72 (61–80)	0.57
Sex (men), *n* (%)	127 (52)	423 (51)	0.89
NIHSS baseline, median (IQR)	15 (11–20) (243)	16 (11–19) (811)	0.85
SBP, mmHg, median (IQR)	148 (130–162) (238)	150 (131–165) (803)	0.29
Medical history, *n* (%)			
Diabetes mellitus	45 (19) (242)	151 (18) (820)	0.93
Previous stroke	37 (15) (242)	152 (19) (820)	0.29
Atrial fibrillation	48 (20) (240)	195 (24) (812)	0.22
Pre-stroke mRS, *n* (%)			0.45
0–2	204 (85) (240)	707 (86) (814)	
≥3	36 (15) (240)	107 (14) (814)	
Workflow			
Observed onset time, *n* (%)	187 (76)	618 (75)	0.67
Intravenous alteplase, *n* (%)	188 (77)	637 (78)	0.86
Transferred from primary stroke center*, *n* (%)	90 (36)	441 (53)	<0.01
Time from onset to presentation at first hospital, minutes, median (IQR)	55 (40–92) (200)	55 (39–93) (640)	0.87
Time from onset to imaging[$], minutes, median (IQR)	83 (53–141)	69 (51–106) (733)	0.62
Imaging variables			
ASPECTS subgroups, *n* (%)			0.47
0–4	9 (4)	46 (6)	
5–7	56 (23)	186 (23)	
8–10	180 (73)	571 (71)	
Collateral score, *n* (%) (known in)			0.95
0	16 (7) (240)	48 (6)	
1	72 (30) (240)	252 (31)	
2	97 (40) (240)	323 (40)	
3	55 (23) (240)	179 (22)	
Extracranial carotid tandem lesion[#]	28 (11) (192)	136 (16) (689)	0.14
Thrombus length, mm, median (IQR)	12 (9–16)	NA	NA
NCCT thrombus density, HU, median (IQR)	52 (46–58)	NA	NA
Thrombus perviousness, attenuation increase, HU, median (IQR)	5 (0.1–11)	NA3	NA

ASPECTS, Alberta Stroke Program; Early CT Score; CTA, CT-angiography; IQR, interquartile range; HU, Hounsfield Units; mRS, modified Rankin Scale; NA, not applicable; NCCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure. If no (known in) number is shown, data were available for all included patients.

**Images from the primary stroke center were used in 44/90 transfer patients (49%).*

[$] *In current study sample: time of imaging used for measurements. In all Registry M1 occlusion patients: time of first acquired imaging.*

[#] *Tandem lesion was defined as an atherosclerotic occlusion, high-grade stenosis, or dissection ipsilateral to the intracranial occlusion, as assessed on baseline CT angiography.*

suggesting that within the critical time window of treatment no observable changes occur. Thrombus density may slightly increase over time, which was visible in our data in patients transferred from a primary stroke center. Transferred patients had a longer median onset to imaging time, possibly allowing for a higher density difference to develop. This density increase could be caused by the contraction of the thrombus resulting in the compression of erythrocytes in a densely packed structure, though may also have been a chance finding (17). Overall, however, the effects of thrombus contraction (16, 17), thrombus growth (9), and endogenous or alteplase-induced thrombolysis (10–13) seem to balance each other out in the time window we observed.

Only a small number of studies have been reported that focus on the influence of time on thrombus image characteristics. Qazi et al. (24) included onset to imaging time for the analysis of thrombus characteristics in patients with AIS. They have studied the relation between collateral status and thrombus length. Similar to our study, onset-to-imaging time did not influence thrombus length. Also, Pikija et al. (25) have studied the relation

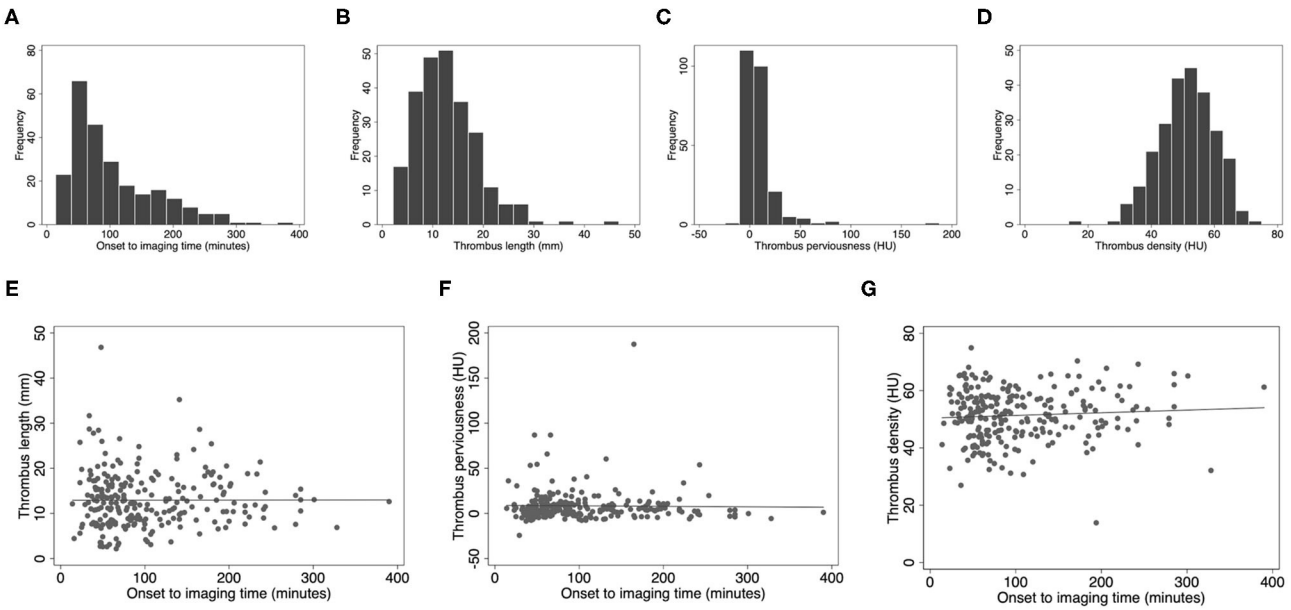

FIGURE 1 | Scatter and box plots of image characteristics. **(A)** Time from symptom onset to imaging distribution, **(B)** thrombus length histogram, **(C)** thrombus perviousness histogram, **(D)** thrombus density histogram, **(E)** onset to imaging time vs. thrombus length, **(F)** onset to imaging time vs. perviousness, **(G)** onset to imaging time vs. non-contrast CT density. HU, Hounsfield Units; mm, millimeter.

TABLE 2 | Beta coefficients of the effect of time from stroke onset to CT imaging (per 5 min) on thrombus characteristics.

Outcome variable	Model 0 Unadjusted		Model 1 Adjusted for pre-specified variables*		Model 2 Adjusted for pre-specified variables* + variables of interest#	
	β	95% CI	*β*	95% CI	*β*	(95% CI)
Thrombus length	0.002	−0.002 to 0.007	0.003	−0.002 to 0.008	0.002	−0.004 to 0.007
Perviousness	−0.005	−0.012 to 0.011	−0.001	−0.012 to 0.012	−0.002	−0.015 to 0.011
Thrombus density	0.046	−0.036 to 0.129	0.047	−0.035 to 0.120	**0.100**	**0.005 to 0.196**

CI, confidence interval; ICA-T, internal carotid artery terminus.

**Pre-specified variables: age, sex, and history of atrial fibrillation.*

#Variables of interest: observed stroke onset, intravenous alteplase, CTA collateral score, direct presentation at thrombectomy-capable center or transfer, stroke etiology (cardio-embolic vs. large artery atherosclerosis vs. unknown). Values printed in bold are statistically significant ($p < 0.05$).

of time with thrombus density. In contrast to our results, their results showed a drop in thrombus density within a 5-h time window for onset to imaging time. Finally, Haridy et al. (26) reported no association between the presence of a hyperdense artery sign (HAS) or relative thrombus density and onset to imaging time within a 24 h time window. Unfortunately, they did not specifically study the relation of time with thrombus density or perviousness. Therefore, we cannot directly compare our results with their study.

Since the assessment of the radiological thrombus characteristics addressed in this study is not part of current treatment decision making in clinical practice and is not included in the national or international stroke guidelines (27), our results do not give rise to changes in the standard clinical care for AIS. For research on radiological thrombus characteristics in relation to stroke treatment outcomes, our results indicate that the elapsed time from symptom onset is of limited influence on the values of these characteristics, and as such would not have to be taken into account in the time window that we investigated.

Our study has limitations. First, a selective group of patients was included. Our study population contained patients who underwent EVT and therefore included severe cases of stroke only. All patients were treated within a short time window, since the onset to hospital time is relative low due to the small surface area and high hospital density of the Netherlands (19, 28). In addition, it is expected that the treatment window for EVT will be extended in the future and onset to imaging time will be prolonged. Increased variation in time from stroke onset may make changes in radiological thrombus characteristics more pronounced (29). In the overall Registry population, the proportion of transfer patients was higher than in our study sample. This may have contributed to our shorter median onset to imaging time: thin-slice CT scans are less often available for transferred patients, which was one of our inclusion criteria.

Second, the dynamic behavior of thrombus size could not be assessed in a controlled environment; we combined data of a heterogeneous group of patients. To reduce the variability, we only selected patients with an occlusion of the M1, though this resulted in a relatively small sample size. Third, thrombus measurements were performed on single-phase CTA. As such, results are dependent on the phase of the CTA. In case of stasis of blood flow and early CTA san timing, the contrast may not reach the exact proximal location of the thrombus, and contrast may not have reached the distal part of the thrombus. This may have resulted in an overestimation of thrombus length and lower perviousness values. Future implementation multiphase CTA may resolve that issue (30). Fourth, we tried to assess the dynamic behavior of thrombi on imaging made at a single point in time. Ideally, thrombus measurements would be performed at two moments in time in the same patient, to address individual rates of thrombus growth or shrinkage. By comparing thrombus characteristics in a large group of patients with varying onset-to-imaging times, we expected other factors influencing thrombus length to be approximately evenly distributed. Fifth, thrombi may be older than the duration of stroke symptoms, and hence be more organized than what one would expect based on the time from stroke onset to imaging. Cardiac thrombi for example may form and age in the heart, break loose, and embolize to cause a stroke (31, 32). However, our results did not vary between stroke etiology subgroups. Sixth, apparent trends in the subgroup analyses may not have translated to statistically significant regression results due to the small number of patients in the subgroups. However, our effect estimates were close to zero and any trends found in the data visualization may have occurred due to chance. Finally, because we only included patients with an M1-occlusion to improve data homogeneity, we could not assess differences in thrombus location and length. Thrombi may contract over time in all directions, instead of only in length, thereby decreasing in diameter and embolizing to a more distal location. Further research with more observations in distal occlusion locations could focus on the association between onset-to-imaging time and the distance from the carotid terminus to the proximal thrombus border.

CONCLUSION

Our results did not show a clear association between onset to imaging time and radiological thrombus characteristics for AIS patients within the observed time window. Only thrombus density slightly increased with longer onset to imaging time intervals due to interhospital transfer. There was no association between time and thrombus perviousness or length. This suggests that elapsed time from stroke onset plays a limited role in the interpretation of radiological thrombus characteristics and their effect on treatment results, at least in the relatively short time window observed in this study.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of patient consent restrictions for reuse of data, but analysis code and results are available upon reasonable request to the corresponding author. Requests to access the datasets should be directed to MK, m.kappelhof@amsterdamumc.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Erasmus Medical Center Rotterdam, the Netherlands (MEC-2014–235). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MT, MK, IJ, and BD collected the data. MT, MK, VG, HM, and MC conceived the study idea and conceptualized the analysis. MK, MT, HM, and MC wrote the manuscript and performed the statistical analyses. All authors discussed the ideas and results and critically revised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.693427/full#supplementary-material

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ORIGINAL RESEARCH
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First-Pass Reperfusion by Mechanical Thrombectomy in Acute M1 Occlusion: The Size of Retriever Matters

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Introduction: Single-pass complete reperfusion using stent retrievers has been shown to improve functional outcome in patients with large vessel occlusion strokes. The aim of this study was to investigate the optimal size of stent retrievers to achieve one-pass complete reperfusion by mechanical thrombectomy.

Methods: The study evaluated the results of aspiration-assisted mechanical thrombectomy of acute isolated occlusion of the middle cerebral artery in the M1 segment with a novel 5 × 40-mm stent retriever compared to the usual 4 × 20-mm device. Reperfusion status was quantified using the Thrombolysis In Cerebral Infarction (TICI) scale. We hypothesized that thrombectomy of M1 occlusions with 5 × 40-mm stent retriever yields higher rates of complete first-pass reperfusion (FP) (TICI ≥2c after one pass) and successful or modified FP (mFP) (TICI ≥2b after one pass) than thrombectomy with 4 × 20. We included isolated M1 occlusions treated with pRESET 5 × 40 (phenox) as first-choice device for thrombectomy and compared with M1 occlusions treated with pRESET 4 × 20. We excluded patients with additional occlusions or tandem stenosis or who received an intracranial stent or angioplasty as a part of the endovascular treatment.

Results: One hundred thirteen patients were included in the 4 × 20 group and 57 patients in the 5 × 40 group. The 5 × 40 group achieved higher FP compared to 4 × 20 group [61.4% (35 of 57 patients) vs. 40.7% (46 of 113), respectively; adjusted odds ratio (OR) and 95% confidence interval (95% CI) = 2.20 (1.08–4.48), $p = 0.030$] and a higher mFP [68.4%, 39 of 57 patients vs. 48.7%, 55 of 113; adjusted OR (95% CI) = 2.11 (1.04–4.28), $p = 0.037$]. Frequency of successful reperfusion (TICI ≥2b) was similar in both groups (100 vs. 97.3%), but frequency of complete reperfusion (TICI ≥2c) was higher in the 5 × 40 group [82.5 vs. 61.9%, adjusted OR (95% CI) = 2.47 (1.01–6.04), $p = 0.047$]. Number of passes to achieve reperfusion was lower in the 5 × 40 group than in the 4 × 20 group [1.6 ± 1.1 vs. 2 ± 1.4, $p = 0.033$; adjusted incidence rate ratio (95% CI) = 0.84 (0.69–1.03), $p = 0.096$]. Modified Rankin scale at 90 days was similar in 5 × 40 and 4 × 20 groups.

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Conclusions: The size of stent retriever matters in acute M1 occlusions treated with aspiration-assisted mechanical thrombectomy. A longer stent retriever with a larger nominal diameter achieves a higher complete and successful FP and higher successful reperfusion compared to a shorter stent retriever.

Keywords: first-pass, stroke, thrombectomy, reperfusion, stent retriever, large vessel occlusion, pRESET

INTRODUCTION

Mechanical thrombectomy has become standard of care for patients with acute ischemic stroke and large vessel occlusion (LVO). The goal of the thrombectomy is to achieve reperfusion as early as possible to maximize the probability of good functional clinical outcome (1). Although a successful reperfusion, measured after endovascular treatment as a Thrombolysis In Cerebral Infarction (TICI) ≥2b score in the angiography, was the initial goal, a complete reperfusion TICI 3 is associated with greater neurological improvement during hospitalization, better functional outcome at 90 days, and reduced infarct growth (2, 3); moreover, increasing degrees of reperfusion associate better clinical outcome (4). Therefore, achieving TICI 2c or 3 should be the new aim of mechanical thrombectomy for anterior circulation (5).

The first-pass effect (FPE), restoring a complete or near-complete reperfusion (TICI 2c-3) in a single pass, is an independent predictor of good clinical outcome (6–8). FPE is also associated with lower healthcare resources use and lower estimated costs (8), and therefore, it should be pursued as the new goal of the endovascular treatment of LVO with thrombectomy devices. Thrombectomy with stent retriever under aspiration has shown higher rates of first-pass reperfusion (FP) (9) or similar (10) compared to direct aspiration.

There are no recommendations regarding size selection of stent retriever for thrombectomy, and this remains at the discretion of the neurointerventionalist. Larger devices have shown *in vitro* a higher frequency of complete clot removal (11, 12). Use of longer stent retrievers (30–40 mm) was found to be an independent predictor of FP in internal carotid artery (ICA) and middle cerebral artery (MCA) occlusions in comparison to shorter stent retrievers (20 mm) by equal diameter, enhancing the idea that longer retrievers offer a larger surface area of interaction with the thrombus reducing the possibility of leaving a clot behind (13). A longer stent retriever (4 × 40) showed the highest frequency of FP compared with larger diameter (6 × 30) and shorter stents (4 × 20) in ICA, MCA-M1, and MCA-M2 occlusions (14). *In vitro*, it was reported that longer stent retrievers (6 × 40 vs. 6 × 30) achieve higher FP in fibrin-rich clots (15). On the contrary, one study comparing diameter (4 vs. 6 mm) found no difference in reperfusion rate of ICA, MCA, and anterior cerebral artery (ACA) occlusions (16), and others found higher rates of modified FP (mFP) (TICI ≥2b) in the MCA with short stent retrievers (20 mm vs. others) (17).

Our aim is to describe results of thrombectomy of acute isolated M1-MCA occlusions with a new longer size of stent retriever (5 × 40) compared to the usual size used in our center (4 × 20) (18). We hypothesized that thrombectomy of M1 occlusions with a 5 × 40 stent retriever is associated with higher rates of angiographic FP than thrombectomy with a 4 × 20 stent retriever.

MATERIALS AND METHODS

Patient Population

Using a prospective stroke registry, where we collect all the patients referred to our interventional neuroradiology department in order to receive endovascular treatment, we identified the patients with isolated occlusion of MCA in M1 segment treated with pRESET 5 × 40 (phenox, Bochum, Germany), with 5-mm diameter and 40-mm length as first-choice device. The new size of stent retriever is also recommended, as 4 × 20, for 2-mm vessel diameter and was available in our center from December 2019. Until then, we had used pRESET 4 × 20, with 4-mm diameter and 20-mm length as standard stent retriever for thrombectomy in M1 occlusions. Since November 2019, both sizes had been used in our center for thrombectomy in M1 occlusions at the discretion of the neurointerventionalists. We compared patients with acute M1 occlusions treated with 5 × 40 as first-choice device with those patients with M1 occlusion treated with 4 × 20 as first-choice device the previous year (December 2018 to November 2019). For the period where both sizes were available, there was a tendency to use the size 5 × 40. Therefore, we did not find comparable patients treated with the size 4 × 20 during this period, suggesting a selection bias could occur. We excluded patients with additional occlusions or tandem stenosis or who received an intracranial stent or angioplasty as a part of the endovascular treatment.

The new size of stent retriever pRESET 5 × 40 was used between November 2019 and October 2020 in 89 patients with MCA occlusions: 9 were M2-MCA occlusions, and 80 were M1-MCA occlusions. From eligible M1-MCA occlusions: 57 were included in the present study (representing group 5 × 40), and 23 were excluded: 11 because of additional occlusions (9 tandem M1-ICA, 1 tandem A2-M1-ICA, 1 A2-M1) and 12 because an intracranial stent and/or angioplasty was needed (10 patients: proved intracranial stenosis, 2 patients: dissection after thrombectomy or intracranial stenosis). For the comparison group of M1-MCA occlusions treated with pRESET 4 × 20, we selected all the consecutive patients between December 2018 and November 2019. From 126 M1 occlusions treated over the mentioned period with 4 × 20: 113 were included (representing group 4 × 20), and 13 were excluded: 3 because of additional

occlusion, 5 because pRESET LT was used, and 5 because intracranial stenting and/or angioplasty was performed.

Our hospital is a certified comprehensive stroke center, providing endovascular service for 13 regional stroke units. The local ethics committee approved the data collection and analysis. We treat patients initially presented to our hospital or patients referred from other hospitals [with or without previous intravenous (IV) recombinant tissue plasminogen activator (rtPA)]. In our center, all stroke patients with LVO are eligible for mechanical thrombectomy. If there are no contraindications, IV rtPA is administered in eligible patients, according to clinical guidelines (1). We perform computed tomography (CT), CT angiography (CTA), and CT perfusion. Presence or absence of mismatch in CT perfusion is informative and does not preclude the treatment. In the case of unknown onset time, magnetic resonance (MR) with MR angiography (MRA) is the preferred imaging modality. Patients referred from other centers receive CT-CTA or MR-MRA. Patients with acute LVO are considered for endovascular treatment under real life conditions, without exclusion regarding age, baseline National Institute of Health Stroke Scale, time of stroke onset, comorbidities, baseline functional status prestroke, or Alberta Stroke Program Early CT Score (ASPECTS; all included patients had ASPECTS $\geq$4) as long as the joint assessment of neurology and neuroradiology proposed a realistic chance for improvement.

Endovascular treatment is performed with a standardized technique: 8F sheath, 8F guiding catheter, thrombectomy with stent retriever pRESET (phenox) in a 0.021-inch inner-diameter microcatheter [usually Trevo 18 (Stryker) or Velocity (Penumbra)] under proximal aspiration with a distal access catheter (DAC), such as Sofia (MicroVention) or ACE68 (Penumbra) catheters. A VacLok AT Vacuum Pressure Syringe (Merit Medical) aspirates through DAC during thrombectomy maneuver, when we advance DAC over the stent retriever at the same time that thrombectomy is undergone. After removal of the stent retriever, the DAC is left in M1 or M2 segments under aspiration and after a while removed. Sometimes the DAC and stent retriever are removed together under aspiration through the guiding catheter. In the 5 × 40 group, we used as first DAC Sofia Plus 6F (n = 30; 52.6%), Sofia 5F (n = 24; 42.1%), and pHLO (phenox) (n = 3; 5.3%), and in the 4 × 20 group, Sofia 5F (n = 83; 73.5%), Sofia Plus 6F (n = 27; 23.9%), and ACE68 (n = 3; 2.7%). First DAC used differed between groups ($p <$ 0.001). No balloon guiding catheter (BGC) was used. When more passes were necessary, another DAC may have been used at the discretion of the neurointerventionalist. The size of the first stent retriever used was pRESET 5 × 40 mm in the 5 × 40 group and pRESET 4 × 20 mm in the 4 × 20 group. When more than one pass was needed, it could be done with the same stent retriever or with another one according to the preference of the operator, always according to anatomy and technical need. Other stent retrievers used were registered. Intra-arterial (i.a.) rtPA after thrombectomy was allowed: 2 patients (3.6%) with right M1 occlusions received i.a. rtPA after thrombectomy, both in the 5 × 40 group. All procedures were done under general anesthesia. Procedural experience and skills were considered similar between the neurointerventionalists.

Data on demographics, prestroke functional status [quantified by the modified Rankin scale (mRS)], and vascular risk profile were collected. The National Institute of Health Stroke Scale (NIHSS) score before angiography was considered as baseline neurological status. Last time seen well was considered stroke onset if time was unknown or in wakeup stroke. Stroke cause was defined, according to TOAST (Trial of ORG 101172 in Acute Stroke Treatment) classification (19).

Imaging, Clinical, and Angiographic Assessment

Presence of early ischemic changes on admission CT or MRI [diffusion-weighted imaging (DWI)] and in control CT was assessed using the ASPECT score (20). Vessel occlusion was confirmed in primary imaging (CTA or MRA) and in the diagnostic run of the angiography. For patients transferred from other centers, primary imaging and time of imaging were considered from imaging of the referring center. We repeat the imaging after transfer to our center if hemorrhage is suspected by a clinical deterioration of $\geq$4 points in NIHSS. Occlusion of the MCA was differentiated into proximal, when thrombus was seen in proximal or middle segment of M1 segment of MCA and distal, when thrombus was seen in the distal third of the MCA with distal or no lenticulostriate arteries or in MCA bifurcation (21). Origin of the anterior temporal branch from M1 segment was still considered M1 occlusion. Collateral leptomeningeal status was assessed visually in CTA as previously described (22) and graded as follows: grade 1 = absent collaterals, grade 2 = less than the contralateral unaffected side, grade 3 = equal to the contralateral unaffected side, grade 4 = more than the contralateral unaffected side, and grade 5 = exuberant. The scale was dichotomized in "poor collaterals," with less collaterals than contralateral unaffected side (grades 1–2), and "good collaterals," with equal or greater collaterals to contralateral unaffected side (grades 3–4, as no case was graded as 5). In the angiography first run of the affected side, collaterals were assessed according to the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scale (23) graded as grade 0: no collaterals visible at the ischemic site; grade 1 = slow collaterals to the periphery of the ischemic site with persistence of some of the defects; grade 2 = rapid collaterals to the periphery of the ischemic site with persistence of some of the defects and to only a portion of the ischemic territory; grade 3 = collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase; and grade 4 = complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion. The five grades were dichotomized as score 0–2 "poor collaterals" and score 3–4 "good collaterals." If the first run was not performed until the end of venous phase, it was considered not valuable; this occurred in one case in the study.

Angiographic revascularization was assessed using the modified Thrombolysis in Cerebral Infarction (TICI) score in the final run of the angiography, measuring reperfusion in downstream territory of the specific arterial occlusion, as follows: grade 0 = no reperfusion; grade 1 = antegrade reperfusion past

the initial occlusion, but limited distal branch filling with little or slow distal reperfusion; grade 2a = antegrade reperfusion of less than half of the occluded target artery previously ischemic downstream territory; grade 2b = antegrade reperfusion of more than half, but < 90% complete antegrade reperfusion; grade 2c = near-complete reperfusion (90–99%) except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli; and grade 3 = complete antegrade reperfusion, with an absence of visible occlusion in all distal branches (4, 24, 25). TICI ≥2b was considered successful reperfusion, and TICI ≥2c was considered complete reperfusion. A reader reviewed all study cases under blinded conditions and compared the score with the score given the day of treatment. In the cases of discrepancy, a third blinded reader decided the score.

FP complete reperfusion was defined as achieving a complete reperfusion (TICI ≥2c) with a single thrombectomy device pass (6, 14). TICI 2c was included with TICI 3, as substantial evidence suggests that patients with LVO and a TICI 2c reperfusion after treatment follow the same clinical course as patients with a TICI 3 reperfusion (4, 5, 26). FPE was described in patients with a complete TICI 3 reperfusion after a single pass of thrombectomy, but patients with TICI 2c reperfusion were also included in the complete reperfusion category (6), with higher rates of good clinical outcome. mFP or successful FP was defined as achieving successful reperfusion (TICI ≥2b) after a single pass. The numbers of thrombectomy passes were recorded. Vasospasm after thrombectomy, dissection, or perforation was also recorded.

Furthermore, for each patient, we noted the following values: time from stroke onset to IV rtPA, time to groin puncture (stroke onset up to groin puncture), and time to recanalization (time to first assessment of final recanalization). Duration of treatment was the time from groin puncture to last run of angiography.

The clinical outcome was assessed as severity of disability at 90 days according to the mRS. An mRS ≤2 was considered a good clinical outcome (27). Further rates that were recorded were mortality at 90 days, subarachnoidal hemorrhage (SAH), and parenchymal hematoma (PH) [according to ECASS Classification (28)] in imaging 24–36 h after stroke or symptomatic intracranial hemorrhage (SICH) confirmed on neuroimaging (CT or MRI). A SICH was defined as any type of intracerebral hemorrhage on posttreatment imaging with an increase of at least 4 points on NIHSS (ECASS II) (28).

The primary outcome of our study was frequency of FP and mFP. Secondary outcomes were frequency of complete reperfusion (TICI ≥2c), number of passes of thrombectomy, and favorable clinical outcome at 3 months.

Statistical Analysis

Metric variables were reported as mean with standard deviation (SD) or median with interquartile ranges; categorical variables were described by frequencies. Fisher exact test was used for testing the null hypothesis that two categorical variables were independent. Mann–Whitney *U*-test was used to compare whether two groups differed regarding the distribution of a metric variable.

For bivariate outcomes, logistic regression was used to determine which characteristics influence the likelihood of an event happening and Poisson regression to determine the variables with an influence on N passes. For multivariate analysis, variables that show a significant influence on the outcome in the bivariate analysis were chosen (full model). In addition, forward selection with a *p*-value threshold of 0.05 was used for further selection of variables in the multivariate analysis.

The analysis was performed with Stata/IC 16.1 for Unix, and the level of significance was set at a 0.05 level (two-sided).

RESULTS

A total of 113 patients were included in the 4 × 20 group and 57 patients in the 5 × 40 group. Baseline characteristics between the 4 × 20 and 5 × 40 groups, including age, gender, stroke etiology, risk factors, mRS prestroke, NIHSS, ASPECTS, collateral status in CTA and in angiography, and IV rtPA treatment, among others, were comparable and are described in **Table 1**. As shown in **Figure 1** and **Table 2**, the 5 × 40 group achieved significantly higher FP (61.4%, 35 of 57 patients) compared to the 4 × 20 group (40.7%, 46 of 113), unadjusted odds ratio (OR) [95% confidence interval (95% CI)] = 2.32 (1.19–4.51), $p = 0.014$, and adjusted OR = 2.20 (1.08–4.48), $p = 0.030$ (**Table 3**). Also the 5 × 40 group achieved a higher mFP (68.4%, 39 of 57 patients vs. 48.7%, 55 of 113), with unadjusted OR = 2.28 (1.15–4.53), $p = 0.022$, and adjusted OR = 2.11 (1.04–4.28), $p = 0.037$. Frequency of successful reperfusion (TICI ≥2b) was similar in both groups (4 × 20 vs. 5 × 40, 97.3% vs. 100%), but the frequency to achieve complete reperfusion (TICI ≥2c) was higher in the 5 × 40 group [4 × 20 vs. 5 × 40 (61.9% vs. 82.5%)] with unadjusted OR = 2.89 (1.30–6.43), $p = 0.008$, and adjusted OR = 2.47 (1.01–6.04), $p = 0.047$. Multivariate analysis is shown in **Table 3**.

Variables associated with FP in bivariate analysis were thrombectomy with a 5 × 40 stent retriever, better collaterals in the angiography, absence of SAH, type of DAC used, older age, higher ASPECTS on baseline imaging and at 24 h, lower duration of treatment, and time to recanalization. mFP was associated with better collaterals in angiography, absence of SAH, type of DAC, higher ASPECTS after 24 h, lower duration of treatment, and lower time to recanalization. FP was also associated in bivariate analysis with good clinical outcome, OR = 2.28 (1.18–4.38), $p = 0.016$, whereas mFP associated more frequently with a good clinical outcome, OR = 1.94 (1–3.75), without reaching statistical significance.

Variables associated with a complete reperfusion (TICI ≥2c) in bivariate analysis were thrombectomy with a 5 × 40 stent retriever, better collaterals in the angiography, older age, higher ASPECTS at 24 h, lower number of passes with stent retriever, lower time from onset to groin puncture, lower time to recanalization, and lower duration of treatment. Complete reperfusion was not associated with good clinical outcome at 90 days in the whole population [in TICI ≥2c 39.3% vs. not TICI ≥2c 28.3% good clinical outcome, OR = 1.64 (95% CI = 0.81–3.34), $p = 0.227$]. But in patients with a prestroke mRS of 0, achieving a TICI ≥2c is associated with 71.4% of good clinical outcome at 90 days vs. achieving TICI 1–2b, which is associated

TABLE 1 | pRESET 5 × 40 vs. pRESET 4 × 20 in M1-MCA occlusions: baseline characteristics.

	pRESET 4 × 20 (*n* = 113)	**pRESET 5 × 40 (*n* = 57)**	***p*-value***
Age (years), mean ± SD	77.2 ± 11.6	77.6 ± 13	0.513
Gender male/female, n (%)	46 (40.7)/67 (59.3)	27 (47.4)/30 (52.6)	0.417
Cardioembolic etiology of stroke, n (%)	80 (70.8)	39 (68.4)	0.789
AF, n (%)	75 (66.4)	35 (61.4)	0.610
DM, n (%)	25 (22.1)	12 (21.1)	1
Hypercholesterolemia, n (%)	15 (13.3)	9 (15.8)	0.648
Smoker, n (%)	6 (5.3)	6 (10.5)	0.220
Hypertension, n (%)	74 (65.5)	42 (73.7)	0.301
Cardiovascular disease, n (%)	48 (42.5)	24 (42.1)	1
mRS prestroke: mRS ≤2/mRS >2, n (%)	89 (78.8)/24 (21.2)	44 (77.3)/13 (22.7)	0.377
Secondary transport, n (%)	82 (72.6)	45 (78.9)	0.456
Unknown onset, n (%)	42 (37.2)	19 (33.3)	0.735
NIHSS, median [IQR]	14 [11–18]	16 [11–19]	0.193
ASPECTS on baseline, median [IQR] Min–max	9 [8–10] 5–10	9 [8–10] 4–10	0.597
Collaterals CTA			0.103
Grade 1–2: poor collaterals, n (%)	34 (37.8)	25 (53.2)	
Grade 3–4: equal or greater collaterals, n (%)	56 (62.2)	22 (46.8)	
Collaterals angiography			0.241
Grade 0–2: poor collaterals, n (%)	45 (39.8)	17 (30.4)	
Grade 3–4: good collaterals, n (%)	68 (60.2)	39 (69.6)	
M1-MCA occlusion site			
Proximal/distal, n (%)	58 (51.3)/55 (48.7)	35 (61.4)/22 (38.6)	0.254
Left/right, n (%)	51 (45.1)/62 (54.9)	28 (49.1)/29 (50.9)	0.517
IV rtPA, n (%)	40 (35.4)	27 (47.4)	0.139
Time onset to IV rtPA, h, median [IQR]	1.8 [1.2–2.7]	1.7 [1.4–3.2]	0.706
Time imaging-groin puncture, h, median [IQR]	2.1 [1.8–2.7]	2.4 [2–2.8]	0.187
Time onset-groin puncture, h, median [IQR] Min–max	4.2 [3.1–7.4] 1.9–29.2	4.1[3–6.1] 2–13.4	0.513
Time to recanalization, h, median [IQR]	5 [3.8–7.8]	5.1 [3.8–7.2]	0.869
Duration of treatment, h, median [IQR]	0.6 [0.4–0.9]	0.6 [0.4–1]	0.427

**Fisher exact test (qualitative variables); Mann–Whitney U-test (quantitative variables).*

AF, atrial fibrillation; ASPECTS, Alberta Stroke Program Early Computed Tomography Score on baseline imaging; CTA, computed tomography angiography; DM, diabetes mellitus; IQR, interquartile range; MCA, middle cerebral artery; min–max, minimum and maximum; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; IV rtPA, intravenous recombinant tissue plasminogen activator; SD, standard deviation; secondary transport, patients with LVO referred from other hospitals (with or without previous IV rtPA).

with 38.1% of good clinical outcome at 90 days [OR = 4.06 (95% CI = 1.19–13.82), $p = 0.024$].

Regarding use of first DAC (**Figure 2**) and taking into account only Sofia, as the use of the other DACs is anecdotic, in the whole study population, we found higher FP with Sofia 6F (59.6%) vs. Sofia 5F (43%), $p = 0.049$. In the pRESET 4 × 20 group, using Sofia 6F as first DAC compared to Sofia 5F associated higher FP (55.6 vs. 37.3%, OR = 2.10, $p = 0.018$). In the pRESET 5 × 40 group, there was no difference regarding FP between both sizes of DAC. No differences were found between the type of first DAC used and rate of complete reperfusion (TICI ≥2c); although in the whole study population there was a higher frequency of complete reperfusion with Sofia 6F as first DAC used (78.9%) vs. Sofia 5F (64.5%), $p = 0.074$; 4 × 20 and 5 × 40, groups follow the tendency but without statistical significance.

The number of passes to achieve reperfusion was lower in the 5 × 40 group than in the 4 × 20 group (mean ± SD = 2 ± 1.4 vs. 1.6 ± 1.1, $p = 0.033$). In 39 patients of the 5 × 40 group, a single pass was sufficient. More than one pass was needed in 18 patients (31.5%) in the 5 × 40 group and in 55 patients (48.6%) in the 4 × 20 group. In bivariate analysis, a lower number of passes was associated with the use of the 5 × 40 device, successful and complete reperfusion, age, and ASPECTS, whereas a higher number of passes was associated with atrial fibrillation and the presence of SAH in control CT. After adjusting for relevant variables, the number of passes was not associated with thrombectomy with the 5 × 40 retriever [incidence rate ratio = 0.84 (95% CI = 0.69–1.03), $p = 0.096$].

Regarding clinical outcome and safety variables, we did not find differences between the 5 × 40 and 4 × 20 groups in mRS at 90 days, mortality, ASPECTS 24 h after treatment, PH, SICH,

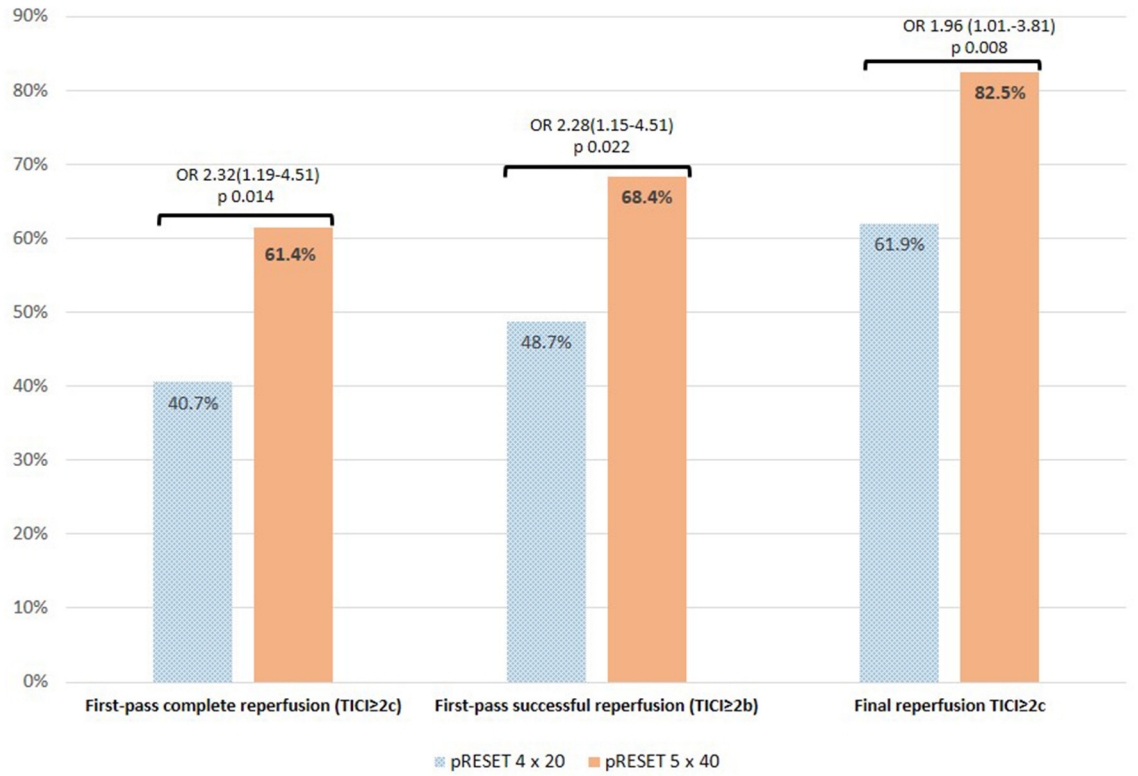

FIGURE 1 | pRESET 5 × 40 vs. pRESET 4 × 20 in M1-MCA occlusions: primary and principal secondary outcomes. Abbreviations: M1-MCA, M1 segment of middle cerebral artery; TICI, modified thrombolysis in cerebral infarction score; first-pass complete reperfusion (TICI ≥2c) and first-pass successful reperfusion (TICI ≥2b) are abbreviated in text as FP and mFP, respectively. Statistics: Fisher exact test; odds ratio (OR) and 95% confidence interval (CI).

or SAH (**Table 2**). Incidence of vasospasm after thrombectomy was similar in both groups (27.4% in group 4 × 20 and 22.8% in group 5 × 40) (**Table 2**). Only one patient in the 4 × 20 group had a perforation of the MCA after the third pass of thrombectomy, and no embolization in a new territory or dissection in any group was reported.

A good clinical outcome at 90 days was achieved in 35.1% of patients in the 5 × 40 group and 36.3% in the 4 × 20 group (p non-significant). Variables associated with good clinical outcome were absence of atrial fibrillation, direct presentation in our hospital, better collaterals in angiography, absence of SAH, FP, younger age, higher ASPECTS prestroke and poststroke, lower NIHSS at baseline, lower number of passes, and lower time from imaging to groin puncture. FP was not independently associated with good outcome at 90 days in the whole study population in multivariante analysis. Taking into account only patients with an mRS prestroke 0–2, achieving an FP-associated good clinical outcome at 90 days occurred in 53.1% of patients, compared with not achieving FP, which resulted in good clinical outcome in only 31% of patients [OR (95% CI) = 2.27 (1.11–4.65), $p = 0.024$].

DISCUSSION

We found a significantly higher FP (TICI ≥2c) for M1 occlusions treated with thrombectomy under aspiration with longer stent retriever compared to shorter stent retriever, 61.4 vs. 40.7%, respectively. FP for all patients in both groups was 69.2%.

Although we assume that frequencies are not directly comparable because of the nature of each study and different patient characteristics, inclusion criteria, and techniques applied, our reported frequencies of FP are higher than in the published literature. FP frequency (TICI ≥2c) described for stent retriever in M1 occlusions was 39.7% (Trevo, almost in 90% of cases) (9). In the data of the NASA registry, for M1 occlusions, FP was 29% (Solitaire) (6), with younger and selected patients, in 2012 and 2013, and in the TRACK registry, FP was 22.3% for M1 occlusions (Trevo 4 × 20) (29). In the ASTER trial, FP in M1 occlusions was 31.2% with stent retriever or aspiration, within 6 h of onset (10). In the STRATIS registry, FP was 40% (Solitaire and Mindframe) (30). Recently, for LVO (including ICA, M1, M2, and posterior circulation), 53% was reported, and for M1, 51% in the ARISE II study [clinical trial with EmboTrap device (Cerenovus, Irvine, CA, USA) (8)]. Including ICA, MCA, and other LVO localizations, although with 85.6% of M1 occlusions, 22.8% of FP was reported in anterior circulation strokes within 6 h of stroke onset treated with only stent retriever, or aspiration or a combination of both (31). Some of these studies (9, 10) include tandem occlusions or intracranial stenosis, or in other studies, it is unknown, and these could be one factor influencing the difference of frequencies as these lesions preclude a FP because of the need for other maneuvers. If we had counted the

TABLE 2 | pRESET 5 × 40 vs. pRESET 4 × 20 in M1 occlusions: safety parameters and clinical and angiographic outcomes.

	pRESET 4 × 20 ($n = 113$)	pRESET 5 × 40 ($n = 57$)	p-value* OR (95% CI)
Safety and imaging			
ASPECTS post, median [IQR], min–max	7 [5–9] 0–10	7 [5–8] 1–10	0.342
PH, n (%)	5 (4.5)§	0	0.168
SICH, n (%)	0§	0	—
SAH, n (%)	18 (16.2)§	6 (10.5)	0.361
Vasospasm, n (%)	31 (27.4)	13 (22.8)	0.581
Primary outcome			
First-pass reperfusion (TICI ≥2c), n (%)	46 (40.7)	35 (61.4)	**0.014** 2.32 (1.19–4.51)
First-pass reperfusion (TICI ≥2b), n (%)	55 (48.7)	39 (68.4)	**0.022** 2.28 (1.15–4.53)
Secondary outcomes			
No. of passes, mean ± SD, min–max	2 ± 1.4, 1–9	1.6 ± 1.1, 1–6	**0.033**
TICI final, n (%)			0.552
0–2a	3 (2.7)	0 (0)	
2b, 3	110 (97.3)	57 (100)	
TICI final ≥2c, n (%)	70 (61.9)	47 (82.5)	**0.008**
mRS at 90 days, n (%)			1
mRS ≤2	41 (36.3)	20 (35.1)	
mRS >2	72 (63.7)	37 (64.9)	
Mortality at 90, days, n (%)	35 (31)	13 (22.8)	0.285

**Fisher exact test (categorical variables); Mann–Whitney U-test (metric variables). Significant p-value marked in bold.*

§Control CT 24 h after treatment was not undergone in two patients of group 4 × 20.

ASPECTS post, Alberta Stroke Program Early Computed Tomography Score 24 h after stroke; IQR, interquartile range; mRS, modified Rankin scale; mTE/aTE, aspiration and mechanic thrombectomy; TICI, modified thrombolysis in cerebral infarction; OR 95% CI, odds ratio und 95% confidence interval; PH, parenchymal hemorrhage; SAH, subarachnoid hemorrhage; SD, standard deviation; SICH, symptomatic intracranial hemorrhage.

patients with dissection or intracranial stenosis, FP frequency would still be high at 39% in the 4 × 20 group and at 50.7% in the 5 × 40 group.

Independent predictors of FP in the literature were use of BGC, better collateral grade (30, 32), site of occlusion with ICA-terminus occlusion as worse predictor and M1 occlusion as better predictor of FP (6, 30, 31), older age, lower systolic blood pressure, a higher DWI-ASPECTS at admission, local anesthesia, and combined first-line device strategy (31). We also found pial collaterals in the angiography, as an independent predictor of FP. Collaterals in acute stroke with LVO correlate with outcome; good collaterals are associated more likely with smaller core infarction, whereas poor collaterals associate larger core infarctions and more rapid infarct growth. Good collaterals also correlate with improved outcome after endovascular treatment and a favorable response to it, with higher recanalization rate and with less core infarct growth (33, 34). Angiographic collaterals were associated in our study with FP, mFP, good clinical outcome at 90 days, and complete reperfusion. Interobserver and intraobserver agreement of collateral circulation grading using the ASITN/SIR score was poor; a simplified dichotomized evaluation was considered more reproducible (23), why we decided to follow this suggestion. A possible explanation to a higher FP frequency with better leptomeningeal collaterals in the angiography could be that they provide a better definition of length of the thrombus, which allows a better position of the stent retriever related to the thrombus; also, good collaterals could avoid thrombus progression as they exert a retrograde pressure over the thrombus.

FP has been reported to be an independent factor for favorable clinical outcome (6, 7), with rates of 90-day better clinical outcome of 61.3% by FP TICI ≥2c (6) and rates of 67% by FP TICI 3 (7), and is associated with lower mortality rate, reduced hemorrhagic transformation, and procedural complications (10). Our study did not find an association between FP and clinical outcome, probably because of clinical characteristics of our population, with a large proportion of patients (21%) older than 85 years, almost 22% of patients with mRS prestroke >2, 10.6% with ASPECTS on baseline imaging ≤6 and long times from stroke onset to groin puncture and to recanalization. We observed that including patients with baseline mRS prestroke >2 influenced this result, as patients in our study with mRS prestroke 0–2 and FP had 53.1% of good clinical outcome at 90 days (good clinical outcome by FP and mRS prestroke 0, 71.4%; by mRS prestroke 1, 57.9%; by mRS prestroke 2, 17.6%), similar to previous publications.

Despite the observed association between size of stent retriever and higher frequency of FP, the size of retriever was not associated in our study with a favorable outcome at 90 days, and in our opinion, the size of the study population could be one reason. Likewise, the STRATIS registry even with a prestroke mRS ≥1 did not find an association between stent retriever size and clinical outcome or mortality by comparable final revascularization between groups (14).

TABLE 3 | Preset 5 × 40 vs. pRESET 4 × 20 in M1-MCA occlusions: multivariate analysis.

	Full model		Stepwise selection*	
First-pass reperfusion (TICI ≥2c)	**OR (95% CI)**	***p*-value***	**OR (95% CI)**	***p*-value***
pRESET 5 × 40 vs. 4 × 20	2.20 (1.08–4.48)	0.030	2.18 (1.07–4.44)	0.032
Age (years)	1.03 (1–1.06)	0.052	1.03 (1–1.06)	0.035
ASPECTS basal	1.18 (0.93–1.49)	0.173	—	—
Collaterals (angiography)	2.35 (1.15–4.76)	0.018	2.73 (1.37–5.43)	0.004
Time to recanalization	0.92 (0.84–1)	0.051	0.91 (0.83–0.99)	0.033
First-pass reperfusion (TICI ≥2b)	**OR (95% CI)**	***p*-value***	**OR (95% CI)**	***p*-value***
pRESET 5 × 40 vs. 4 × 20	2.11 (1.04–4.28)	0.037	2.11 (1.04–4.28)	0.037
Collaterals (angiography)	1.96 (1.01–3.77)	0.045	1.96 (1.01–3.77)	0.045
Time to recanalization	0.91 (0.84–0.98)	0.014	0.91 (0.84–0.98)	0.014
Complete reperfusion, (TICI ≥2c)	**OR (95% CI)**	***p*-value***	**OR (95% CI)**	***p*-value***
pRESET 5 × 40 vs. 4 × 20	2.47 (1.01–6.04)	0.047	2.38 (1.01–5.60)	0.047
Age (years)	2.39 (1.16–4.93)	0.018	—	—
No. of passes	0.64 (0.49–0.85)	0.002	0.62 (0.48–0.82)	0.001
Time to recanalization	0.99 (0.88–1.11)	0.862	—	—
Collaterals (angiography)	2.39 (1.16–4.93)	0.018	2.15 (1.06–4.37)	0.035

**Statistics: logistic regression with forward selection (p-value threshold for adding a variable: 0.05). n = 169 (one patient had no valuable collaterals in angiography).*
ASPECTS, Alberta Stroke Program Early Computed Tomography Score; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; CI, confidence interval; mTICI, modified Treatment In Cerebral Infarction score.

FIGURE 2 | First-pass reperfusion (FP) regarding use of distal access catheter in the whole population and in groups 4 × 20 and 5 × 40. Statistics, Fisher exact test; odds ratio (OR) and 95% confidence interval (CI).

Both clot control and aspiration are necessary for a successful endovascular treatment of LVOs. Clot control with stent retriever depends on multiple factors such as device mechanical characteristics, device behavior during retrieval, and thrombus biomechanics and consistencies (11).

The pRESET 4 × 20 stent retriever has shown a high recanalization rate experimentally *in vivo* (35) and in daily clinical practice (18, 36, 37). *In vitro* experience with the 4 × 20 pRESET and 6 × 30 pRESET has shown a close apposition to the vessel wall during thrombus removal, and highly effective clot removal for both white and red thrombi, with the 6 × 30 demonstrating a 60 and 100% rate of removal for white and red thrombi, respectively, the highest in comparison to other stent retrievers (14). If the specific device characteristics of the pRESET stent retriever play a role in achieving a higher FP, it cannot be elucidated from this study. A clinical comparison between pRESET 4 × 20 and 5 × 40 has to date not been published.

Retriever size could, as mentioned, influence stent properties. Longer and larger stent retrievers provide the potential to catch the clot on multiple planes of attachment in smaller arteries (2–3 mm) like the MCA and keep the engagement at larger vessel diameters in ICA, during clot retrieval (15). Larger-diameter stent retrievers come with higher radial force and a better vessel wall apposition. This results in more stability during the retrieval process (11). Previously, a comparison between 4- and 6-mm diameter Solitaire stent retrievers did not find differences in endovascular treatment outcomes for occlusions of the ICA, MCA, or ACA (16), focusing on reperfusion TICI ≥2b, not ≥2c, and without evaluation of FP. In our opinion, the superiority of the 5 × 40 over 4 × 20 might be rather related to the stent retriever length than to the stent retriever diameter. Longer stent retrievers have previously demonstrated *in vitro* higher rates of complete clot removal (11, 12).

Large white clots with higher fibrin content are stiffer and more difficult to retrieve in comparison to red blood cell–rich clots. Tests *in vitro* with white clot thrombus showed that stent retrievers up to 40 mm did not expand and therefore do not capture this type of thrombus if longer than 6 mm (11); for white thrombus between 2- and 4-mm, stent retrievers could expand, and thrombus was retrieved. *In vitro* studies with 20-mm-long fibrin-rich cloth have shown in M1 occlusion a frequency of FP for Solitaire 6 × 40 of 95%, and for 6 × 30, 67% (if a BGC was used, FP was 100% for both sizes, and if a 0.088-inch sheath and DAC catheter were used, FPs were 83% and 33%, respectively, for 6 × 40 and 6 × 30) (15).

The observed higher frequency of FP with longer stent retrievers in clinical practice has already been described. Longer stent retrievers (4 × 30 to 4 × 40) vs. short (4 × 20) were an independent predictor of mFP (TICI ≥2b) (13) in occlusions of intracranial ICA, M1, and M2 treated with BGC; they also included tandem occlusions; mFP was 62% in long and 50% in short stent retrievers, TICI 2b final was 98% in long and 94% in short stent retrievers with comparable clinical outcomes and comparable SAH. Zaidat et al. (14) reported the highest rate of FP and mFP in ICA, M1, and M2 occlusions with longer stent retrievers (4 × 40) compared to larger (6 × 30) or shorter (4 × 20) without differences in final revascularization or functional outcome. For MCA occlusions, they found the highest rates of mFP and FP with 4 × 40, 71.5 and 49.5%, respectively, and 6 × 30 did not perform better than 4 × 20 (mFP and FP, respectively, 63.2% and 41.6 vs. 59.5% and 41.3%) (14).

On the contrary, comparing lengths of stents (short: 4 × 20 mm and long >20 mm: 4 × 40, 6 × 30, or 4 × 30), Styczen et al. (17) found comparable FP TICI 3 for both short and long stent retrievers in MCA (50.8 vs. 40.7%) occlusions with higher mFP in short vs. long stent retrievers (50.8 vs. 40.7%, $p = 0.024$). But long retrievers achieved a higher rate of successful reperfusion (TICI ≥2b) with higher rate of SAH.

Possible explanations for higher rates of FP with longer stent retrievers are summarized here. As proximal and distal parts of the stent retriever are non-working, longer stent retrievers offer a longer working length, which potentially offer a larger surface for device integration in the clot and uniform distribution of forces along with the clot during traction (13). Using longer stent retrievers allows some degree of imprecision of placement (38) by lack of operator experience and allows for engagement of the entire thrombus in cases of vessel tortuosity/elongation when tension causes a proximal dislocation of the stent retriever by deployment, or if patients without general anesthesia move and make deployment imprecise. Also, a longer stent retriever, with a distal segment beyond the clot in M2, could help to anchor the stent retriever if the operator prefers to remove the microcatheter before the aspiration through DAC during the thrombectomy (38). The part of the retriever placed distal to the thrombus could help to sweep along a clot that does not integrate in the struts. Also, when a push-and-fluff technique is used for better wall apposition resulting in device foreshortening on active deployment, a longer retriever offers a higher security to cover the whole clot (39).

Achieving a reperfusion in only one pass of thrombectomy is our goal, but it is not always possible; therefore achieving a successful or complete reperfusion in the lower number of passes is also determinant. Reperfusion after fewer passes results in better outcomes in comparison to after a higher number of passes (6, 40). Multiple passes of thrombectomy are associated with worse outcomes and higher complication rates (41, 42). Thrombectomy attempts are associated with a risk for distal embolization and vessel damage. In our study, the number of passes is associated independently significant with higher frequency of SAH in control CT. In our study, thrombectomy with a longer stent retriever achieved reperfusion in a lower number of passes than the shorter stent retriever but after adjustment with other relevant variables lost significance. In both groups, the number of passes was low, and this could be one cause for not detecting a difference.

Theoretically, a longer retriever could have more contact to the vessel wall and cause more friction. Safety assessment of longer stents *in vivo* in porcine models has been done for 4-mm-diameter Solitaire devices, 4 × 40 and 4 × 20 (43), and in 6-mm devices, 6 × 40 and 6 × 30 (15), without difference in vascular safety parameters at 90 days. We found similar frequency of vasospasm and SAH after thrombectomy with both stent retriever sizes. No perforation was seen with pRESET 5 ×

40. Our observations show that the longer stent retriever is safe to use for M1 occlusions.

Use of BGC was reported to be a predictor of FP (6, 30). The use of a BGC did not affect angiographic outcomes in other reported studies (29, 31). We achieved good FP results without the use of a BGC. We hypothesized that emboli appear when the microcatheter, stent retriever, and DAC are removed at the same time from M2-MCA to M1-MCA and to ICA as vessel diameter changes. We do not use a BGC for intracranial occlusions, with good angiographic and clinical results. As we almost always try to advance the DAC up to the M1 segment, we remove the stent retriever inside the DAC and leave the DAC under aspiration; then, under aspiration, we also remove the DAC minimizing risk of emboli in new territory as we avoid the loss of engagement of the clot during retrieval (44). Sometimes, we remove the stent retriever and the DAC at the same time under aspiration. Thrombus is retrieved within the stent retriever or within the DAC, after removal, or in both devices. Positioning of a BGC high enough in the ICA is difficult in patients with marked vessel elongation and increases risk of complication specially with a 9F BGD (allowing for the use of a 6F DAC). If the position of the BGC is not high enough, the DAC could be too short to be advanced up to intracranial ICA bifurcation. We agree that the use of BGC could be better in reducing distal emboli, but in our experience, it is not cost-effective.

As we try to advance the DAC over the stent, both stent retriever and aspiration have a role in reperfusion rate in our study. The use of a DAC was not independently associated with FP, although we achieved higher FP with the Sofia 6F in the 4 × 20 group. In the 5 × 40 stent retriever group, there was no difference in using both sizes of DAC (**Figure 2**). In our experience, we think a larger inner diameter DAC brings more lumen for aspiration but also could be associated with difficulties in navigating the DAC distally to the M1 segment. We accept that our FP rate is a result of a combined technique of stent retriever and aspiration, but as treatment in both groups was performed with exactly the same technique, we can assume that the size of stent retriever matters.

The retrospective nature of our study is a major limitation, and selection bias could have occurred. We have designed a prospective, randomized study comparing both size of retriever for M1 occlusions, and we look forward to verify our results. The single-center design could also be a limitation but may demonstrate the benefit of a standardized technique. The strengths of our study include a real life cohort, standardized technique, focus on M1 occlusions, and comparable patients in both groups; to reduce selection bias, all patients treated with 5 × 40 were included and compared to all patients treated with 4 × 20 at 1 year before.

CONCLUSION

The size of the stent retriever matters in acute M1 occlusions treated with aspiration-assisted thrombectomy. A longer stent retriever achieves in one pass a higher first-pass complete reperfusion (TICI ≥2c) and first-pass successful reperfusion (TICI ≥2b) and higher complete reperfusion compared to a shorter stent retriever.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethik-Kommission der Landesäztekammer Baden-Württemberg. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CS: study conception, design of work, acquisition of data, interpretation of data, and drafting of manuscript. MA and VH: acquisition of data and critical revision of manuscript. HB: critical revision of manuscript. HH: study conception, design of work, and critical revision of manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: CS, MA, and VH have consultancy agreements with phenox GmbH. HH is co-founder and shareholder of phenox GmbH.

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ORIGINAL RESEARCH
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Predictors of Early and Late Infarct Growth in DEFUSE 3

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Introduction: The goal of this study is to explore the impact of reperfusion and collateral status on infarct growth in the early and late time windows.

Materials and Methods: Seventy patients from the DEFUSE 3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) with baseline, 24-h, and late follow-up scans were evaluated. Scans were taken with DWI or CTP at time of enrollment (Baseline), with DWI or CT 24-h after enrollment (24-h), and with DWI or CT 5 days after enrollment (Late). Early infarct growth (between baseline and 24-h scans) and late infarct growth (between 24-h and late scans) was assessed for each patient. The impact of collateral and reperfusion status on infarct growth was assessed in univariate and multivariate regression.

Results: The median early infarct growth was 30.3 ml (IQR 16.4–74.5) and the median late infarct growth was 6.7 ml (IQR −3.5–21.6) in the overall sample. Patients with poor collaterals showed greater early infarct growth (Median 58.5 ml; IQR 18.6–125.6) compared to patients with good collaterals (Median 28.4 ml; IQR 15.8–49.3, unadjusted $p = 0.04$, adjusted $p = 0.06$) but showed no difference in late infarct growth. In contrast, patients who reperfused showed no reduction in early infarct growth but showed reduced late infarct growth (Median 1.9 ml; IQR −6.1–8.5) compared to patients without reperfusion (Median 11.2 ml; IQR −1.1–27.2, unadjusted $p < 0.01$, adjusted $p = 0.04$).

Discussion: In the DEFUSE 3 population, poor collaterals predict early infarct growth and absence of reperfusion predicts late infarct growth. These results highlight the need for timely reperfusion therapy, particularly in patients with poor collaterals and indicate that the 24-h timepoint is too early to assess the full impact of reperfusion therapy on infarct growth.

Clinical Trial Registration: http://www.clinicaltrials.gov, Unique identifier [NCT02586415].

Keywords: stroke, infarct growth, reperfused, collaterals, brain imaging (CT and MRI)

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INTRODUCTION

In the DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) trial, endovascular therapy had a very large beneficial effect on long-term functional outcomes. Surprisingly, endovascular treatment did not have an effect on infarct growth. This might be because the follow-up MRI, used to assess infarct growth, was obtained relatively early (24 h) after

randomization (1). In this study we address this limitation by analyzing infarct growth in the subset of patients who underwent an additional scan for clinical purposes beyond the 24-h time point.

Two factors that likely influence infarct growth are reperfusion and collateral blood flow. Reperfusion is a strong predictor of clinical outcome and may influence infarct growth over an extended time period (2, 3). Collateral blood flow is dynamic and can change over time, influencing its impact on infarct growth (4). The hypoperfusion intensity ratio (HIR), derived from CT perfusion (CTP) or MR perfusion imaging, is a measure of collateral status that is associated with infarct growth and with the persistence of a favorable diffusion weighted imaging (DWI)/perfusion weighted imaging (PWI) mismatch profile (5, 6).

The goal of this study is to explore the impact of reperfusion and collateral status on infarct growth in the early (between baseline and 24 h) and late (between 24 h and 5 days) time windows. Our hypothesis is that collateral status is a stronger predictor of early infarct growth while reperfusion status is a stronger predictor of late infarct growth.

MATERIALS AND METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patient Demographics

The inclusion criteria, study design, and primary results of the DEFUSE 3 trial have been reported previously (1). We identified all cases in DEFUSE 3 with an unscheduled late scan, defined as either CT or MR imaging obtained after the 24-h follow-up scan but within 2 weeks of stroke onset. For cases with multiple late scans, we included only the scan closest to day 5. We excluded cases with parenchymal hematoma because the ischemic infarct volume cannot be accurately measured in this setting. Only patients with a baseline, a 24-h, and a late scan were included in this study.

Image Analysis and Definitions

The DEFUSE 3 imaging protocol has been previously reported (1). Infarct volumes were outlined manually on CT and MRI using OsiriX software. Early infarct growth was defined as the change in infarct volume between the infarct core assessed with DWI or CTP on the baseline scan and the infarct volume assessed with DWI or CT on the first follow-up scan, obtained 24 h after randomization. Late infarct growth was defined as the change in infarct volume between the 24-h scan, and the DWI or CT late unscheduled scan. Baseline collateral status was measured using HIR as assessed on baseline CTP and MR perfusion studies and was defined as the proportion of the Tmax >6 s lesion with a Tmax delay of >10 s (5). An HIR ≤0.4 was categorized as good baseline collateral status and HIR > 0.4 categorized as poor baseline collateral status. This binary threshold for HIR was an optimal predictor of collateral status based on digital subtraction angiography (7). Reperfusion was defined as >90% reduction in the volume of tissue with perfusion delay (Tmax > 6 s) between baseline and 24 h, or complete recanalization on the 24-h CT or MR angiogram.

Statistical Analyses

We compared demographic, clinical, and neuroimaging variables using chi-square and Wilcoxon rank-sum tests. The associations between the following candidate predictor variables and early infarct growth were tested in univariate analysis: age, baseline NIHSS score, glucose, time from stroke onset to baseline imaging, time from stroke onset to 24-h imaging, baseline HIR, reperfusion status, and baseline infarct volume. The associations between these same candidate predictor variables and late infarct growth were tested in univariate analysis with the replacement of baseline NIHSS score with 24-h NIHSS score, time from stroke onset to 24-h imaging replaced with time from 24-h scan to late scan, and baseline infarct volume replaced with 24-h infarct. Treatment arm was not assessed as a predictor variable as it strongly correlates with reperfusion status because the majority of patients in the endovascular therapy arm had successful reperfusion. Similarly, gender was not assessed as a predictor variable as it has previously been shown to correlate strongly with HIR in the DEFUSE 3 data (8). For both early and late infarct growth, variables significant at $\alpha < 0.1$ in univariate analyses were entered into a multivariate linear regression model and were retained in the model using a backwards-elimination method if they remained significant at $\alpha < 0.05$. Reperfusion was included in both models because it has a known association with infarct growth (9). We also included an interaction term (reperfusion x baseline collateral status) in the models to test the hypothesis that infarct growth may be more significant in non-reperfused patients with good baseline collaterals. We defined an alpha value of <0.05 as statistically significant and report two-sided results. Alpha values between 0.05 and 0.1 were interpreted as trends of association. Statistical analysis was done using SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Of the 182 patients enrolled in DEFUSE 3, 70 (38%) had a late scan without a parenchymal hematoma and were included in this study. Three cases were excluded due to missing reperfusion data and one was excluded due to poor image quality of the late scan, leaving 66 cases available for full analysis. The late scan imaging modality was CT for 58 patients (83%) and MRI for 12 (17%) patients. The median time from 24-h scan to that of the late scan was 72 h (IQR 52–115). **Table 1** compares the demographic and imaging characteristics of all subjects who were included in this study to the remaining DEFUSE 3 subjects. Patients that were included were more likely in the medical treatment group ($p = 0.01$), did not reperfuse ($p = 0.01$), had worse NIHSS scores at 24 h ($p = 0.04$), and had a higher mortality rate at day 90 ($p = 0.05$). Treatment arm was equally distributed amongst the groups with good vs. poor collaterals with endovascular therapy in 16 (40%) of patients with good collaterals and 11 (37%) of patients with poor collaterals. Treatment arm was not equally distributed amongst the reperfusion and non-reperfusion groups with endovascular therapy in 20 (80%) of the patients with reperfusion and 8 (19%) of the patients who did not reperfuse.

TABLE 1 | Demographic and imaging characteristics of population in this study compared to DEFUSE 3.

	Late scans ($n = 70$)	Rest of DEFUSE 3 ($n = 112$)	p-value
Demographic characteristics			
Age, median (IQR)–yrs	71 (58–80)	70 (60–79)	0.90
Female sex, no. (%)	36 (51%)	56 (50%)	0.85
Glucose, median (IQR)	122 (108–163)	125 (109–151)	0.75
Baseline characteristics			
NIHSS score at baseline, median (IQR)	17 (13–20)	16 (11–21)	0.37
Imaging modality at baseline			
CT	55 (79%)	78 (70%)	0.19
MRI	15 (21%)	34 (30%)	
Time - stroke onset to baseline imaging, median (IQR)–hrs	10 (9–12)	10 (8–12)	0.96
Treatment–medical therapy no. (%)	43 (61%)	47 (42%)	0.01
Reperfusion status–Reperfused no. (%)	25 (36%)	60 (58%)	0.01
Collateral status–Good no. (%)	40 (57%)	63 (57%)	0.96
Hypoperfusion intensity ratio at baseline	0.36 (0.21–0.53)	0.37 (0.21–0.50)	0.95
Infarct volume at baseline, median (IQR) - ml	10.0 (4.6–32.9)	9.4 (2.5–23.5)	0.23
24 h characteristics			
NIHSS score at 24 h, median (IQR)	14 (9–20)	11 (5–19)	0.04
Imaging modality at 24 h			
CT	13 (19%)	17 (16%)	0.60
MRI	57 (81%)	92 (84%)	
Time - stroke onset to 24 h imaging, median (IQR)–hrs	36 (33–39)	37 (33–39)	0.74
Infarct volume at 24 h, median (IQR)–ml	41.2 (26.7–108.8)	36.2 (16.4–92.7)	0.12
Late scan characteristics			
Imaging modality of late scan			
CT	58 (83%)	-	-
MRI	12 (17%)	-	
Time from 24 h to late imaging, median (IQR)–hrs	72 (52–115)	-	-
Death at Day 90–no. (%)	19 (27%)	17 (15%)	0.05

IQR, Interquartile range; NIHSS, National Institutes of Health Stroke Scale; CT, Computerized tomography; MRI, Magnetic resonance imaging; HIR, Hypoperfusion intensity ratio.

As previously mentioned, treatment arm was not included as a variable in the analysis.

For the 66 patients included in the full analysis, the median early infarct growth was 30.3 ml (IQR 16.4–74.5) and the median late infarct growth was 6.7 ml (IQR −3.5–21.6). Patients with poor collaterals showed greater median early infarct growth (58.5 ml; IQR 18.6–125.6) compared to patients with good collaterals (28.4 ml; IQR 15.8–49.3; $p = 0.04$, **Figure 1A**), but showed no difference in late infarct growth (7.0 ml; IQR −2.5–15.8 with poor collaterals vs. 6.6 ml; IQR −4.1–26.5 with good collaterals; $p = 0.62$). In multiple regression analysis, after adjusting for baseline infarct volume and reperfusion status, worse baseline collaterals (higher HIR) showed a trend for increased early infarct growth ($p = 0.06$). In contrast, patients who did not reperfuse had similar volumes of median early infarct growth (38.4 ml; IQR 20.9–79.0; $p = 0.19$) compared to patients with reperfusion (26.7 ml; IQR 14.5–49.3), but showed increased late infarct growth (11.2 ml; IQR −1.1–27.2 without reperfusion vs. 1.9 ml; IQR −6.1–8.5 with reperfusion; $p < 0.01$, **Figure 1B**). In multiple regression analysis, after adjusting for baseline collateral status, the absence of reperfusion remained associated with increased late infarct growth ($p = 0.04$). The interaction term between collateral and reperfusion status was not a significant predictor of either early or late infarct growth.

To ensure that late infarct growth was not exaggerated by differences in imaging modality, a sensitivity analysis excluded patients who had their 24-h infarct volume assessed on CT and their late infarct volume on MRI ($n = 5$). The results of the sensitivity analysis ($n = 61$) were similar to the main results, with early infarct growth showing an association with baseline collateral status and late infarct growth showing a trend with reperfusion status (**Supplementary Table 1**).

DISCUSSION

This study assessed infarct volume at three time points, allowing infarct growth to be investigated independently within discrete early and late time windows. The results suggest that both baseline collateral blood flow and large vessel reperfusion influence infarct growth, but that their effects are best appreciated at different time points. We found that poor baseline collateral status is associated with increased infarct growth between baseline and 24-h imaging. This finding is consistent with other studies that have examined the impact of collateral status on

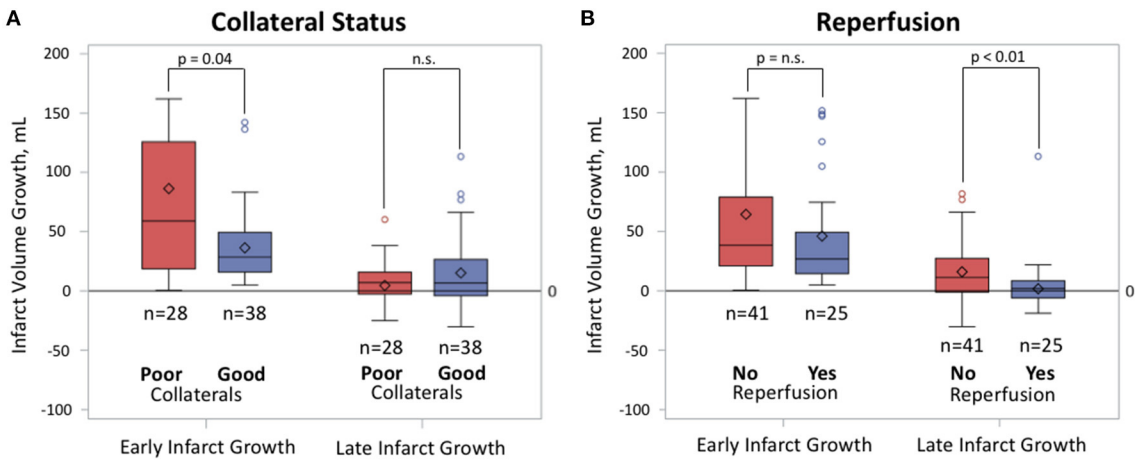

FIGURE 1 | Box plot of early and late infarct growth by collateral status and reperfusion status. Black bars represent medians. Diamonds represent means. Circles represent outliers. **(A)** Good collaterals show a reduction in early infarct growth only. **(B)** Reperfusion shows a reduction in late infarct growth only.

infarct growth in this time window (10). Secondly, we found that absence of reperfusion is associated with increased infarct growth beyond 24-h. This is consistent with Federau et al. (3) who demonstrated that reperfusion status influences infarct growth over an extended time period (5 days) and that the effect of reperfusion on infarct growth is not fully appreciated shortly following endovascular therapy.

In the multivariate analysis predicting late growth, there was a trend for HIR ($p = 0.07$) suggesting that patients with lower HIR (better baseline collaterals) had increased late infarct growth (**Table 2**). This may seem paradoxical as the effect is opposite to the direction in the early window in which good collaterals predict decreased growth. This finding is, however, consistent with Campbell et al. (4) who suggest that good collaterals contribute to a large mismatch between infarcted and hypoperfused tissue, limited early infarct growth, and substantial infarct growth in the late time window if the collaterals fail. This is illustrated in **Figure 2** which shows the DWI and perfusion imaging of a patient with good baseline collaterals who fails to reperfuse. This patient experiences limited early infarct growth but substantial late infarct growth. We speculate that this patient's late infarct growth is the result of failure of collaterals in the absence of reperfusion. While we were unable to assess collateral failure directly as we did not have perfusion imaging with the late scan, other studies have established that collateral status declines over time, and that collateral deterioration is associated with infarct growth (4, 5).

In contrast to patients with good baseline collaterals, the infarcts of patients with poor baseline collaterals grow quickly and reach their final volume early. As a result, these patients typically show only limited growth beyond the first 24 h.

Our results may explain the paradoxical results, reported previously, that in the DEFUSE 3 trial good baseline collateral status was not predictive of improved functional outcome despite showing reduced infarct growth at 24 h (10). Our study, conducted in the subset of the DEFUSE 3 population who underwent a late unscheduled scan, suggests that this finding might be explained by continued infarct growth beyond 24 h, particularly in patients with good baseline collaterals who failed to reperfuse (11).

There are several limitations to this study. First, this study's findings are specific to patients who met DEFUSE 3 selection criteria and therefore have relatively slow infarct progression and small ischemic core volumes at baseline and caution must be used in extrapolating these findings to a more general stroke patient population. Secondly, this study had a limited sample size because it relied upon unscheduled late window scans. This introduces a bias toward patients with worse outcomes who are more likely to undergo repeat scans, which is evidenced by the lower rate of reperfusion, higher 24-h NIHSS score, and higher death rate at day 90 in this study compared to the overall DEFUSE 3 study. However, it is unlikely that this bias influenced the results of our analyses, which were focused on the role of collateral status and reperfusion on lesion growth. Thirdly, the timing of the late scan was variable. This, however, likely did not impact the results as the timing of the late scan was not correlated with late infarct growth. Third, the imaging modality of the late scan was variable. However, a sensitivity analysis removing all cases who underwent CT at 24 h and an MRI, which typically shows larger infarcts, at the later time-point, showed similar results to the overall analysis. Another limitation of this study is that reperfusion was assessed at 24 h and we were unable to account for cases that spontaneously recanalized at a later time point. Finally, this study would have benefited from perfusion data obtained during the follow-up scans which would have allowed us to assess the evolution of collateral status over time.

In conclusion, this study demonstrates that infarct growth depends on different factors during different time windows. In the DEFUSE 3 patient population poor baseline collateral blood flow is a strong predictor of infarct growth in the first 24 h after enrollment, whereas absence of large vessel reperfusion is a strong predictor of infarct growth after 24 h. Our results highlight

TABLE 2 | Multiple linear regression analysis for infarct growth ($n = 66$).

Variable	Early infarct growth		Late infarct growth	
	Growth (ml)	*p*-value	Growth (ml)	*p*-value
Intercept	−6.46	0.69	11.89	0.13
HIR at baseline	83.58	0.06	−29.26	0.07
Reperfusion status (non-reperfuser)	14.02	0.33	14.75	0.04
Infarct volume at baseline (ml)	1.33	0.003	-	-

HIR, Hypoperfusion intensity ratio; Early Infarct Growth defined as growth between baseline and 24 h; Late Infarct Growth defined as growth between 24 h and 5 days.

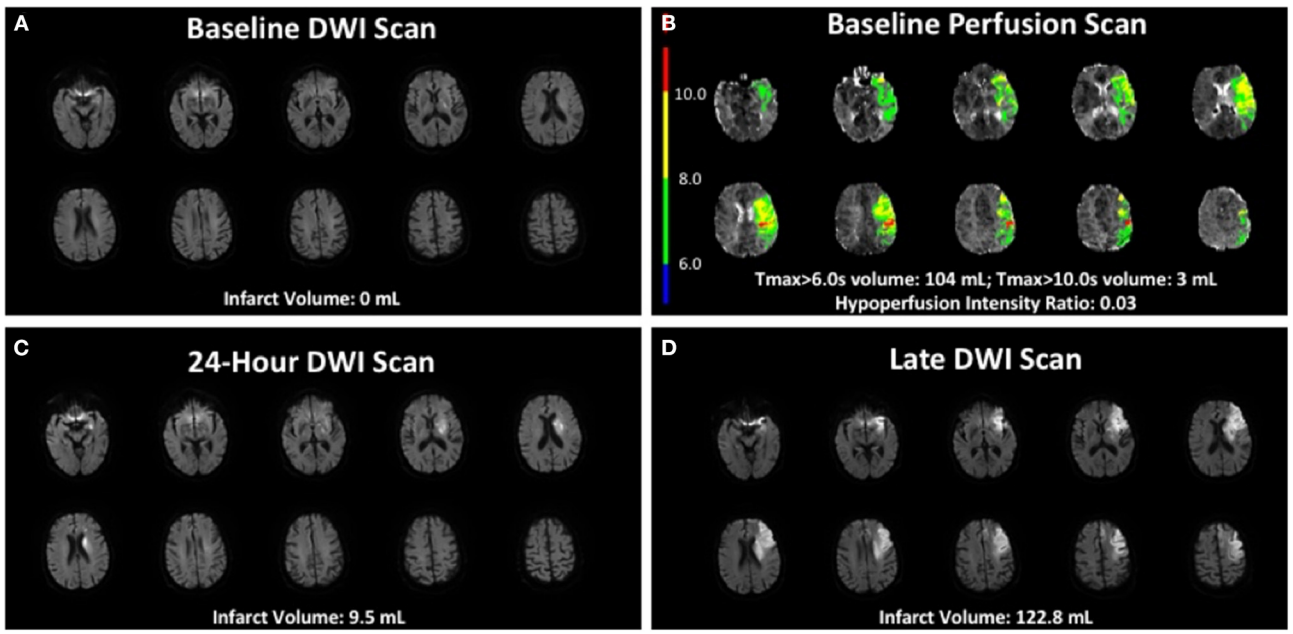

FIGURE 2 | Case example of baseline DWI and perfusion scan, a 24-h DWI scan, and a late DWI scan. Seventy-eight-year-old patient with 12 h of symptoms prior to baseline MRI, with good baseline collaterals but who did not reperfuse with imaging demonstrating minimal early infarct growth and substantial late infarct growth. **(A)** Baseline MRI showed a 0 ml DWI infarct. **(B)** Baseline perfusion imaging showed good collaterals with a hypoperfusion intensity ratio of 0.03. **(C)** 24-h MRI showed a 9.5 ml DWI infarct. **(D)** Late MRI scan occurred 12 days after 24-h scan and showed a 122.8 ml DWI infarct volume.

the need for timely reperfusion therapy, particularly in patients with poor collaterals and indicate that the 24-h timepoint is too early to assess the full impact of reperfusion therapy on infarct growth. Future studies evaluating infarct evolution should consider investigating these factors in discrete early and late time windows.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical approval for this study was obtained from StrokeNet Central Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WT and ML: experimental design. WT, LP, SC, MM, SK, JH, MPM, GA, and ML: analysis/interpretation of data and manuscript writing and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.699153/full#supplementary-material

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Conflict of Interest: GA has equity in and is a consultant for iSchemaView, which produces the software used in DEFUSE 3 for postprocessing of computed tomography and magnetic resonance perfusion studies. He also holds a patent related to that software and has been a consultant for Medtronic. JH is a consultant for Medtronic and MicroVention and a member of the iSchemaView Medical and Scientific Advisory Board. MPM is a shareholder in ThrombX Medical.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Outcomes and Treatment Complications of Intravenous Urokinase Thrombolysis in Acute Ischemic Stroke in China

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Background: Intravenous thrombolysis with alteplase benefits eligible patients with acute ischemic stroke. However, in some countries such as China, alteplase may be too expensive for low-income patients, and also for regions with low economic development. Urokinase is much less expensive than alteplase. This study aimed to assess the outcomes and treatment complications of urokinase in acute ischemic stroke patients, which are poorly understood.

Methods: This multicenter retrospective study included acute ischemic stroke patients who received intravenous urokinase or alteplase from January 2014 to January 2018 at 21 centers in China. Outcomes and treatment complications were analyzed by univariate and multivariate analyses.

Results: Among the 618 patients included in this study, 489 were treated with urokinase and 129 were treated with alteplase. Functional independence, no/minimal disability, mortality, intracranial hemorrhage (ICH), and symptomatic ICH did not significantly differ between the urokinase and alteplase groups in the univariate and multivariate analyses. However, the patients who received alteplase had a lower odds ratio (OR) of extracranial bleeding in the univariate analysis and a lower adjusted OR (aOR) in the multivariate analysis than the patients who received urokinase (OR = 0.410 [95% CI, 0.172–0.977], $p = 0.038$; aOR = 0.350 [95% CI, 0.144–0.854], $p = 0.021$). Furthermore, in patients treated with urokinase, the patients who received high-dose urokinase had a higher OR of extracranial bleeding in the univariate analysis and a higher aOR of extracranial bleeding in the multivariate analysis than patients who received low-dose urokinase (OR = 3.046 [95% CI, 1.696–5.470], $p < 0.001$; aOR = 3.074 [95% CI, 1.627–5.807], $p = 0.001$). Moreover, patients who received low-dose urokinase had similar outcomes and complications compared to patients treated with alteplase.

Conclusions: Patients treated with urokinase had similar outcomes but a higher risk of extracranial bleeding compared to patients treated with alteplase. The risk of extracranial

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bleeding was higher in the patients treated with high-dose urokinase than in the patients treated with low-dose urokinase. Patients who received low-dose urokinase had similar outcomes and complications compared to patients treated with alteplase. In countries such as China where some acute ischemic stroke patients cannot afford alteplase, urokinase may be a good alternative to alteplase for intravenous thrombolysis.

Keywords: urokinase, alteplase, thrombolysis, ischemic stroke, treatment complications, outcomes

INTRODUCTION

Ischemic stroke is a leading cause of death and disability worldwide. Theoretically, intravenous thrombolysis in the early hours after symptom onset can improve the chance of good recovery from ischemic stroke. Alteplase is the only intravenous thrombolytic drug that has been widely confirmed to improve functional outcomes for patients with acute ischemic stroke (1, 2). However, for low-income patients and those from regions with low economic development, alteplase is very expensive, resulting in heavy burdens on patients' families and society; the expense negatively impacts the enthusiasm for thrombolysis. Therefore, there is a pressing need to identify another safe and effective intravenous thrombolytic drug that is less expensive than alteplase.

Like alteplase, urokinase is a plasminogen activator. Urokinase has been approved by the China Food and Drug Administration and recommended in the latest Chinese stroke guidelines to use for intravenous thrombolysis in acute ischemic stroke patients (3). Supported by evidence from two trials with small samples (4, 5), the current Chinese stroke guidelines suggest that eligible acute ischemic stroke patients who are within 6 h of symptom onset can receive 1,000,000–1,500,000 IU intravenous urokinase thrombolysis. Urokinase is much less expensive than alteplase, at less than one-tenth the price. It is widely used in China, especially in regions with low economic development (6). However, the outcomes and treatment complications of intravenous urokinase thrombolysis in stroke patients remain unclear, given the small sample sizes and lack of an alteplase control group in previous urokinase studies (4, 5).

The objectives of this study were to characterize the outcomes and treatment complications in patients with acute ischemic stroke treated with intravenous urokinase within 6 h of symptom onset. We first compared the outcomes and treatment complications of urokinase and alteplase in acute ischemic stroke patients. Furthermore, we investigated the effect of the urokinase dose on outcomes and treatment complications.

METHODS

Study Design and Patients

This multicenter retrospective study included patients from 21 participating centers (**Supplementary Table 1**) in China. Fifteen of these centers are located in regions with low economic development. All the centers have a neurology department; accordingly, these centers have certificated neurologists and neurology nurse specialists.

Supplementary Figure 1 shows a flow diagram of patient selection. The study population comprised patients with a final diagnosis of acute ischemic stroke who received intravenous urokinase or alteplase from January 2014 to January 2018. We excluded patients who did not have a complete medical history, those who were missing a National Institute of Health Stroke Scale (NIHSS) score before thrombolysis, those who were missing a modified Rankin Scale (mRS) score at 3 months, those with an onset-to-treatment time that was longer than 6 h or missing in the urokinase group, those with an onset-to-treatment time that was longer than 4.5 h or missing in the alteplase group, those with a dose that was other than 0.9 mg/kg or missing in the alteplase group, and those with a dose that was other than 1,000,000–1,500,000 IU or missing in the urokinase group.

Measurements

The study population was described with respect to baseline demographics, vascular risk factors, NIHSS score before thrombolysis, and onset-to-treatment time. The outcomes were functional independence at 3 months (defined as an mRS score of 0–2 at 3 months), no/minimal disability at 3 months (defined as an mRS score of 0–1 at 3 months), and death within 3 months. The treatment complications analyzed comprised intracranial hemorrhage (ICH), symptomatic ICH, and extracranial bleeding. ICH was defined as any ICH on computed tomography (CT) scans between baseline and 7 days. Symptomatic ICH was defined according to the National Institute of Neurological Disorders and Stroke (NINDS) criteria as any ICH on CT scans combined with any decline in neurologic status (as measured by the NIHSS) between baseline and 7 days (7). According to the site of bleeding, extracranial bleeding was divided into gastrointestinal bleeding, subcutaneous hemorrhage, gingival bleeding, and other extracranial bleeding. Other extracranial bleeding included hematuria, subconjunctival hemorrhage, epistaxis, and subconjunctival hemorrhage. Major bleeding was defined as per the International Society of Thrombosis and Haemostasis as a decrease in hemoglobin level of 2 g/dL or requiring 2 or more units of packed red blood cells (8). All evaluations of imaging results and neurologic status were performed according to routine clinical practice at the local sites. The 3-month evaluations were conducted as outpatient consultations by clinicians who were highly experienced in outcome assessment. They were instructed not to access the medical records of the patient before the evaluation.

Statistical Analysis

Firstly, patient characteristics were summarized. The variables are presented as count, percentage, or median (interquartile range [IQR]) as appropriate. We used the Mann-Whitney test to compare median data between the groups. Categorical variables were evaluated using the χ^2 test. Secondly, univariable and multivariable logistic regression (Logit [Probability(C)] $\sim$ Treatment + Covariates) was used to detect associations between treatment and outcomes/complications. In the equation, C represented outcomes/complications after treatment, and covariates included age, sex, previous transient ischemic attack or stroke, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, history of smoking, and NIHSS score. The influencing factor of interest was the treatment, including intravenous urokinase and alteplase. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated accordingly, with patients who received urokinase being the reference group. Thirdly, subgroup analyses were performed. We focused on patients who received different urokinase dose (1,000,000 IU vs. 1,200,000-1,500,000 IU) using logistic regression above, with patients who received low-dose urokinase (1,000,000 IU) is the reference group. Besides, we focused on patients who received low-dose urokinase or alteplase using logistic regression above, with patients who received low-dose urokinase (1,000,000 IU) is the reference group. All analyses were performed using SAS v.9.4 (SAS Institute, Cary, NC, USA). Values of $p < 0.05$ were regarded as statistically significant.

RESULTS

Across the 21 participating centers, 597 patients with acute ischemic stroke received intravenous urokinase and 150 received intravenous alteplase between January 2014 and January 2018. Among these patients, 489 treated with urokinase and 129 treated with alteplase met the inclusion criteria (**Supplementary Figure 1**). The baseline clinical characteristics of the patients are described in **Table 1**. The onset-to-treatment time differed between the urokinase and alteplase groups (222 vs. 162 min, $p < 0.001$). Otherwise, the two groups were balanced.

In **Table 2**, outcomes and treatment complications are compared between the urokinase and alteplase groups. The rates of functional independence and no/minimal disability were similar between the two groups in the univariate and multivariate analyses. **Figure 1** shows the distributions of mRS scores at 3 months by thrombolytic drug. Similarly, mortality, ICH, and symptomatic ICH did not significantly differ between the urokinase and alteplase groups in the univariate and multivariate analyses. However, compared to patients who received urokinase, patients who received alteplase had a lower OR of extracranial bleeding in the univariate analysis (OR = 0.410 [95% CI, 0.172–0.977], $p = 0.038$) and a lower adjusted OR (aOR) in the multivariate analysis (aOR= 0.350 [95% CI, 0.144–0.854], $p = 0.021$). We further analyzed the extracranial bleeding according to the site of bleeding. Gastrointestinal bleeding, subcutaneous hemorrhage, gingival bleeding, and other extracranial bleeding did not significantly differ between the urokinase and alteplase groups in the univariate and multivariate analyses. Moreover, regarding major extracranial bleeding, there was also no significant difference between the two groups.

Furthermore, we investigated the effect of urokinase dose on outcomes and treatment complications in patients treated with urokinase. Regarding the urokinase dose, 355 (72.6%) patients were administered 1,000,000 IU (low-dose group), and 134 (27.4%) patients were administered 1,200,000–1,500,000 IU (high-dose group). No patients received 1,000,001–1,199,999 IU urokinase in our study. Outcomes and treatment complications were compared between the low- and high-dose urokinase groups (**Table 3**). The rates of functional independence and no/minimal disability were similar between the two groups in the univariate and multivariate analyses. Similarly, mortality, ICH, and symptomatic ICH did not differ significantly between the low- and high-dose groups in the univariate and multivariate analyses. However, in comparison to low-dose urokinase, patients who received high-dose urokinase were more likely to have extracranial bleeding (7.3 vs. 19.4%; OR = 3.046 [95% CI, 1.696–5.470], $p < 0.001$; aOR = 3.074 [95% CI, 1.627–5.807], $p = 0.001$). Regarding the site of extracranial bleeding, rates of gastrointestinal bleeding (2.8 vs. 8.2%; OR = 3.085 [95% CI, 1.279–7.444], $p = 0.009$; aOR = 4.020 [95% CI, 1.484–10.892], $p = 0.006$) and subcutaneous hemorrhage (2.0 vs. 8.2%; OR = 4.446 [95% CI, 1.686–11.724], $p = 0.003$; aOR = 3.612 [95% CI, 1.278–10.208], $p = 0.015$) were significantly increased in the high-dose group. Furthermore, patients who received high-dose urokinase had a similar rate of major extracranial bleeding in the univariate analysis but a higher aOR in the multivariate analysis compared to patients who received low-dose urokinase (0.8 vs. 3.0%; OR = 3.610 [95% CI, 0.797–16.349], $p = 0.177$; aOR = 9.739 [95% CI, 1.650–57.468], $p = 0.012$).

Moreover, we conducted a subgroup analysis of low-dose urokinase and alteplase. Outcomes and treatment complications were compared between the low-dose urokinase group and the alteplase group (**Table 4**). Functional independence, no/minimal disability, mortality, ICH, symptomatic ICH, and extracranial bleeding were similar between the two groups in the univariate and multivariate analyses.

DISCUSSION

To the best of our knowledge, the present study is the first to compare the outcomes and treatment complications associated with 1,000,000–1,500,000 IU urokinase administered within 6 h from stroke onset and 0.9 mg/kg alteplase administered within 4.5 h from stroke onset in acute ischemic stroke patients. Furthermore, this is also the largest report of ischemic stroke patients treated with intravenous urokinase. We showed that patients treated with urokinase had similar outcomes but a higher risk of extracranial bleeding compared to patients treated with alteplase. Furthermore, patients treated with low-dose urokinase (1,000,000 IU) had a similar functional outcome but a lower risk of extracranial bleeding compared to patients treated with high-dose urokinase (1,200,000–1,500,000 IU). Moreover, patients received low-dose urokinase had similar

TABLE 1 | Baseline clinical characteristics of patients treated with urokinase or alteplase.

Variable	Urokinase (n = 489)	Alteplase (n = 129)	P-value
Age, year, median (IQR)	69 (61–77)	71 (60–76.5)	0.717
Female, *n* (%)	205 (41.9)	56 (43.4)	0.761
Previous TIA or stroke, *n* (%)	97 (19.8)	32 (24.8)	0.217
Hypertension, *n* (%)	253 (51.7)	68 (52.7)	0.844
Diabetes mellitus, *n* (%)	98 (20.0)	28 (21.7)	0.676
Dyslipidemia, *n* (%)	102 (20.9)	33 (25.6)	0.248
Atrial fibrillation, *n* (%)	131 (26.8)	31 (24.0)	0.526
Any history of smoking, *n* (%)	167 (34.2)	48 (37.2)	0.517
Pre-thrombolysis systolic blood pressure, mm Hg, median (IQR)	155 (138–166)	157 (138–173)	0.082
Pre-thrombolysis diastolic blood pressure, mm Hg, median (IQR)	85 (78–93)	87 (79–93)	0.463
Pre-thrombolysis blood glucose, mmol/L, median (IQR)	7.4 (6.1–10.5)	7.3 (6.2–10.9)	0.791
NIHSS score, median (IQR)	10 (5–15)	10 (6–15)	0.943
Onset-to-treatment time, min, median (IQR)	222 (162–294)	162 (123–207)	<0.001

IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

TABLE 2 | Outcomes and treatment complications in patients treated with urokinase or alteplase.

Outcome	Urokinase (n = 489)	Alteplase (n = 129)	OR[a] (95% CI)	P-value	aOR[b] (95% CI)	P-value
Functional independence at 3 months, *n* (%)	295 (60.3)	78 (60.5)	1.006 (0.676–1.496)	0.977	1.012 (0.634–1.616)	0.960
No/minimal disability at 3 months, *n* (%)	238 (48.7)	55 (42.6)	0.784 (0.530–1.159)	0.222	0.726 (0.456–1.154)	0.176
Death within 3 months, *n* (%)	96 (19.6)	20 (15.5)	0.751 (0.444–1.272)	0.285	0.656 (0.356–1.209)	0.176
ICH, *n* (%)	47 (9.6)	11 (8.5)	0.877 (0.441–1.743)	0.707	0.778 (0.366–1.653)	0.513
Symptomatic ICH, *n* (%)	20 (4.1)	6 (4.7)	1.144 (0.450-2.910)	0.778	0.730 (0.243–2.191)	0.575
Extracranial bleeding, *n* (%)	52 (10.6)	6 (4.7)	0.410 (0.172–0.977)	0.038	0.350 (0.144–0.854)	0.021
Gastrointestinal bleeding, *n* (%)	21 (4.3)	2 (1.6)	0.351 (0.081–1.517)	0.229	0.245 (0.054–1.120)	0.070
Subcutaneous hemorrhage, *n* (%)	18 (3.7)	2 (1.6)	0.412 (0.094–1.799)	0.349	0.363 (0.081–1.634)	0.187
Gingival bleeding, *n* (%)	15 (3.1)	2 (1.6)	0.498 (0.112–2.204)	0.526	0.485 (0.107–2.191)	0.347
Other extracranial bleeding, *n* (%)	6 (1.2)	1 (0.8)	0.629 (0.075–5.271)	1.000	0.480 (0.054–4.245)	0.509
Major extracranial bleeding, *n* (%)	7 (1.4)	1 (0.8)	0.538 (0.066–4.412)	0.882	0.459 (0.046–4.614)	0.508

aOR, adjusted odds ratio; ICH, intracerebral hemorrhage; and OR, odds ratio.
[a]Urokinase is the reference group. [b]Urokinase is the reference group. Multivariate analysis was adjusted for age, sex, previous transient ischemic attack or stroke, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, history of smoking, and National Institutes of Health Stroke Scale (NIHSS) score.

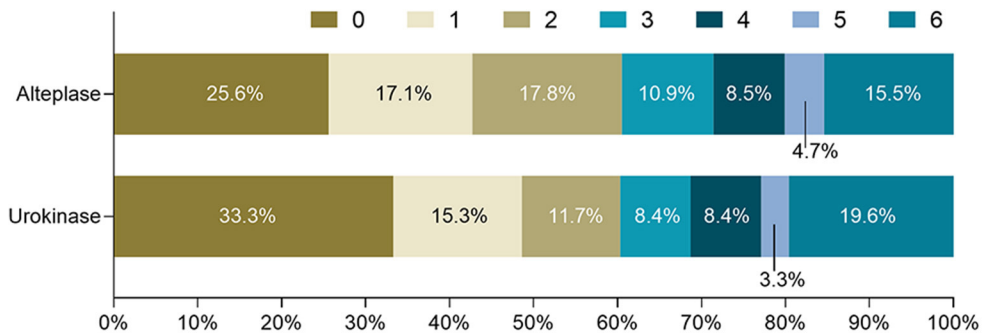

FIGURE 1 | Distribution of mRS scores at 3 months by thrombolytic drug. mRS, modified Rankin Scale.

outcomes and complications compared to patients treated with alteplase.

In recent decades, thrombolytic therapy for acute ischemic stroke has been extensively explored. Intravenous thrombolysis using 0.9 mg/kg alteplase administered within 4.5 h from symptom onset has been widely confirmed to benefit eligible patients with acute ischemic stroke and recommended by the latest international stroke guidelines (2, 3). Unlike patients

TABLE 3 | Outcomes and treatment complications by urokinase dose.

Outcome	Urokinase dose		OR[a] (95% CI)	*P*-value	aOR[b] (95% CI)	*P*-value
	1,000,000 IU, *n* = 355	1,200,000-1,500,000 IU, *n* = 134				
Functional independence at 3 months, *n* (%)	212 (59.7)	83 (61.9)	1.098 (0.730–1.651)	0.654	0.885 (0.534–1.464)	0.634
No/minimal disability at 3 months, *n* (%)	169 (47.6)	69 (51.5)	1.168 (0.785–1.739)	0.443	1.079 (0.647–1.799)	0.771
Death, *n* (%)	72 (20.3)	24 (17.9)	0.858 (0.514–1.431)	0.556	1.175 (0.638–2.164)	0.604
Symptomatic ICH, *n* (%)	14 (3.9)	6 (4.5)	1.142 (0.429–3.035)	0.790	1.818 (0.554–5.969)	0.324
ICH, n (%)	35 (9.9)	12 (9.0)	0.899 (0.452–1.789)	0.762	1.132 (0.516–2.487)	0.757
Extracranial bleeding, *n* (%)	26 (7.3)	26 (19.4)	3.046 (1.696–5.470)	<0.001	3.074 (1.627–5.807)	0.001
Gastrointestinal bleeding, *n* (%)	10 (2.8)	11 (8.2)	3.085 (1.279–7.444)	0.009	4.020 (1.484–10.892)	0.006
Subcutaneous hemorrhage, *n* (%)	7 (2.0)	11 (8.2)	4.446 (1.686–11.724)	0.003	3.612 (1.278–10.208)	0.015
Gingival bleeding, *n* (%)	9 (2.5)	6 (4.5)	1.802 (0.629–5.164)	0.414	2.262 (0.723–7.074)	0.161
Other extracranial bleeding, *n* (%)	4 (1.1)	2 (1.5)	1.330 (0.241–7.345)	1.000	1.761 (0.255–12.150)	0.566
Major extracranial bleeding, *n* (%)	3 (0.8)	4 (3.0)	3.610 (0.797–16.349)	0.177	9.739 (1.650–57.468)	0.012

aOR, adjusted odds ratio; CI, confidence interval; ICH, intracerebral hemorrhage; and OR, odds ratio.
[a]Low-dose (1,000,000 IU) is the reference group. [b]Low-dose (1,000,000 IU) is the reference group. Multivariate analysis was adjusted for age, sex, previous transient ischemic attack or stroke, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, history of smoking, and National Institutes of Health Stroke Scale (NIHSS) score.

TABLE 4 | Subgroup analysis of low-dose urokinase and alteplase.

Outcome	Low-dose urokinase (*n* = 355)	Alteplase (*n* = 129)	OR[a] (95% CI)	*P*-value	aOR[b] (95% CI)	*P*-value
Functional independence at 3 months, *n* (%)	212 (59.7)	78 (60.5)	1.032 (0.683–1.557)	0.882	1.002 (0.612–1.639)	0.995
No/minimal disability at 3 months, *n* (%)	169 (47.6)	55 (42.6)	0.818 (0.545–1.228)	0.332	0.714 (0.438–1.165)	0.177
Death within 3 months, *n* (%)	72 (20.3)	20 (15.5)	0.721 (0.419–1.241)	0.236	0.666 (0.353–1.257)	0.209
ICH, *n* (%)	35 (9.9)	11 (8.5)	0.852 (0.419–1.733)	0.659	0.765 (0.346–1.693)	0.509
Symptomatic ICH, *n* (%)	14 (3.9)	6 (4.7)	1.188 (0.447–3.161)	0.730	0.912 (0.281–2.959)	0.878
Extracranial bleeding, *n* (%)	26 (7.3)	6 (4.7)	0.617 (0.248–1.536)	0.295	0.564 (0.220–1.444)	0.232
Gastrointestinal bleeding, *n* (%)	10 (2.8)	2 (1.6)	0.543 (0.117–2.513)	0.644	0.589 (0.119–2.908)	0.516
Subcutaneous hemorrhage, *n* (%)	7 (2.0)	2 (1.6)	0.783 (0.161–3.818)	1.000	0.758 (0.148–3.893)	0.740
Gingival bleeding, *n* (%)	9 (2.5)	2 (1.6)	0.605 (0.129–2.840)	0.766	0.572 (0.117–2.799)	0.490
Other extracranial bleeding, *n* (%)	4 (1.1)	1 (0.8)	0.686 (0.076–6.191)	1.000	0.526 (0.054–5.145)	0.581
Major extracranial bleeding, *n* (%)	3 (0.8)	1 (0.8)	0.917 (0.094–8.892)	1.000	0.972 (0.063–15.047)	0.984

aOR, adjusted odds ratio; CI, confidence interval; ICH, intracerebral hemorrhage; and OR, odds ratio.
[a]Low-dose urokinase is the reference group. [b]Low-dose urokinase is the reference group. Multivariate analysis was adjusted for age, sex, previous transient ischemic attack or stroke, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, history of smoking, and National Institutes of Health Stroke Scale (NIHSS) score.

treated with alteplase, patients treated with streptokinase, another thrombolytic drug, have a high mortality and symptomatic ICH rate. In patients treated with streptokinase in the Australian Streptokinase (ASK) Trial (9) and Multicenter Acute Stroke Trial-Europe (MAST-E) (10), the mortality was 33.6% to 44.9% and the symptomatic ICH rate was 19.0% to 21.2%. Furthermore, desmoteplase did not improve functional outcomes in the Desmoteplase in Acute Ischemic Stroke 2 (DIAS-2) (11) or Desmoteplase in Acute Ischemic Stroke 3 (DIAS-3) trials (12), with 51.3% of patients who received desmoteplase and 49.8% of patients who received placebo achieving functional independence at 3 months in DIAS-3 (12). Although reliable clinical evidence is limited, urokinase has been widely used in China and recommended in the Chinese stroke guidelines (3). Chinese stroke guidelines recommend 1,000,000–1,500,000 IU urokinase thrombolysis based on the results of two trials with small samples conducted two decades ago (4, 5). The first study was an open-label pilot clinical trial. All of the 409 enrolled ischemic stroke patients received 50,000–1,500,000 IU urokinase. In this trial, 46.6% of patients had European Stroke Scale (ESS) scores $\geq$ 95 at 3 months after stroke onset and 3.9% had symptomatic ICH (4). The second study was a multicenter, double-blind, placebo-controlled randomized clinical trial (RCT). The trial enrolled 465 ischemic stroke patients, of whom 155 were randomly assigned to the 1,500,000 IU urokinase group, 162 to the 1,000,000 IU urokinase group, and 148 to the placebo group. At 3 months after stroke onset, the mRS scores were significantly lower in the 1,500,000 and 1,000,000 IU urokinase group than the placebo group. The symptomatic ICH rates were similar among the three groups (5).

Recently, several comparative studies on the efficacy and safety of alteplase and urokinase for treating acute ischemic stroke have been conducted (13–15). These studies all demonstrated that urokinase and alteplase have similar therapeutic effects. However, the bleeding risks were different. Sun et al. reported that the ICH risk of alteplase was lower than urokinase (14). Bao et al. found that patients treated with urokinase had a lower frequency of bleeding (13). Wang et al. reported that the rates of subcutaneous ecchymosis, gingival bleeding, and ICH were similar between urokinase and alteplase (15). It should be noted that in these studies, the onset-to-treatment time for alteplase was not 4.5 h from symptom onset or the alteplase dose was not 0.9 mg/kg. Furthermore, the sample sizes in these studies were small, and the clinical data collected were limited, i.e., lack of mRS scores.

Among acute ischemic stroke patients treated with intravenous alteplase thrombolysis in the Norwegian Tenecteplase Stroke Trial (NOR-TEST) (16), NINDS (7), European Cooperative Acute Stroke Study III (ECASS III) (17), and Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) (18), 39.2–62.6% had no/minimal disability at 3 months (7, 16–18), and 57.3–78.4% had functional independence at 3 months (16–18). In patients treated with urokinase in the prior RCT urokinase study, the rate of no/minimal disability at 3 months was 44.9% in the 1,500,000 IU urokinase group and 45.5% in the 1,000,000 IU urokinase group, while the no/minimal disability rate in the placebo group was 31.9% (5). In the present study, 48.7 and 42.6% of the patients who received urokinase and alteplase, respectively, had no/minimal disability at 3 months. The rates of functional independence at 3 months were 60.3 and 60.5% in patients who received urokinase and alteplase, respectively. Thus, 1,000,000–1,500,000 IU urokinase administered within 6 h from stroke onset appeared to be at least as effective in achieving a good clinical outcome as 0.9 mg/kg alteplase administered within 4.5 h.

In prior alteplase clinical trials, the mortality of patients who received alteplase was 4.7% to 18.8% (7, 16–18). In prior urokinase trials, the mortality of patients who received urokinase was 10.7–12.2% (4, 5). In the current study, the mortality rate was 19.6% in the urokinase group and 15.5% in the alteplase group, with no significant difference between the two groups. Furthermore, we also did not detect a difference in ICH or symptomatic ICH rates between the urokinase and alteplase groups. Symptomatic ICH was noted in 4.2% of patients in our urokinase group according to the NINDS criteria (7). In the prior urokinase RCT, the rate of symptomatic ICH among patients who received urokinase (1,000,000 or 1,500,000 IU) was 3.8%, which is similar to our study; however, the definition of symptomatic ICH used in the prior RCT was unclear (5). In our study, compared to patients treated with alteplase, patients treated with urokinase exhibited an increased risk of extracranial bleeding. Unlike alteplase, which activates plasminogen only around the thrombus to lyse it with minimal activation of the circulating plasminogen, urokinase activates plasminogen both around the clot and in the circulating plasma, which results in an increased risk of extracranial bleeding (19).

The Chinese stroke guidelines recommend 1,000,000–1,500,000 IU urokinase for thrombolytic therapy as safe and effective (3). However, the guidelines do not state how to determine the patient-specific dose within 1,000,000–1,500,000 IU. Therefore, the specific urokinase dose of each patient was determined by the patients' treating doctors. The decision is typically based on each patient's weight and risk of bleeding. Given the lack of evidence on the bleeding risk of urokinase thrombolysis, the doctors assessed the bleeding risk in accordance with the bleeding risk assessment related to alteplase thrombolysis. In the current study, there were no significant differences in the rates of good outcomes, mortality, symptomatic ICH, or any ICH between the low- (1,000,000 IU) and high-dose (1,200,000–1,500,000 IU) urokinase groups. These findings are consistent with the prior RCT in which the outcome and complication rates were similar between the patients who received 1,000,000 or 1,500,000 IU urokinase (5). However, in our study, compared to the low-dose group, patients treated with high-dose urokinase had an increased risk of extracranial bleeding, which was not investigated in the prior RCT. Furthermore, we conducted a subgroup analysis of low-dose urokinase and alteplase. Outcomes and treatment complications were similar between the two groups.

Our study has several limitations. An important limitation is the retrospective design. The 3-month evaluations were not truly measured by blinded assessors; instead, treating physicians were relied upon to not access patient data before the assessments. Furthermore, the number of patients who received alteplase was lower than the number of patients who received urokinase. Most of our participating centers are located in regions with low economic development, where a large proportion of patients could not afford alteplase or the required onset-to-treatment time for alteplase treatment was exceeded. Furthermore, the patient records were much less complete than we expected. As a result, the information we were able to analyze in our study was limited. For instance, we could not analyze urokinase dose based on patient weight as many of the patient records did not include weight.

In conclusion, our findings indicate that patients treated with urokinase have similar outcomes but an increased risk of extracranial bleeding compared to patients treated with alteplase. Furthermore, the risk of extracranial bleeding was increased in patients treated with high-dose urokinase compared to patients treated with low-dose urokinase. Moreover, patients who received low-dose urokinase had similar outcomes and complications compared to patients treated with alteplase. For acute ischemic stroke patients who cannot afford alteplase, urokinase may be a good choice for intravenous thrombolysis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University. Written informed consent was obtained from all participants for their participation in this study.

AUTHOR CONTRIBUTIONS

XQ, RZ, and HW conceptualized this work. HW, YR, YW, LZ, and YH collected the data. YL and RZ performed the statistical analysis. XQ supervised the study. RZ and XQ prepared the manuscript. JF and PM revised the manuscript. All authors have read and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.685454/full#supplementary-material

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Initial Experience With the Trevo NXT Stent Retriever

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Background: The application of a new coating to the delivery wire of the Trevo retriever has the potential to improve its handling. We therefore report our initial experience with this new stent retriever for mechanical thrombectomy of large and medium vessel occlusions.

Methods: We pooled data of four high-volume European stroke centers over the time period from October 2020 to February 2021. Patients were included in our study if the Trevo NXT stent retriever was used as a first-line device. Primary endpoints were first-pass near-complete or complete reperfusion, defined as mTICI score of ≥2c. Secondary endpoints were final reperfusion, National Institutes of Health Stroke Scale (NIHSS) at 24 h and discharge, device malfunctions, complications during the procedure, and subjective ratings of the interventionalists regarding device functionality.

Results: Eighty patients (39 women, mean age 74 ± 14 years) were eligible for our study. Median NIHSS at admission was 15 (IQR, 8–19), and median Alberta Stroke Program Early CT Score at baseline was 9 (IQR, 8–10). In 74 (93%) patients a primary combined approach was used as first-line technique. First-pass near-complete reperfusion was achieved in 43 (54%) and first-pass complete reperfusion in 34 (43%) patients. Final near-complete reperfusion was achieved in 66 (83%) patients after a median of 1.5 (1–3) passes, while final successful reperfusion was observed in 96% of our cases. We observed no device malfunctions. Median NIHSS at discharge was 2 (IQR, 0–5), and 3 patients (4%) suffered a symptomatic intracranial hemorrhage.

Conclusions: Based on our initial data, we conclude that the Trevo NXT is an effective and safe tool for mechanical thrombectomy especially when used for combined approaches.

Keywords: ischemic stroke, mechanical thrombectomy, stent retriever, primary combined approaches, medium vessel occlusion, large vessel occlusion

INTRODUCTION

Mechanical thrombectomy is considered the standard of care for ischemic strokes caused by large vessel occlusions (LVO) (1). The main techniques can be generally divided into three major categories: (I) use of a stent retriever (SR) and subsequent withdrawal of the device with or without flow arrest by a balloon-guide catheter (BGC); (II) direct aspiration technique using a large-bore aspiration-catheter (ADAPT), placed at the face of the clot; and (III) primary combined approaches (PCA), where both an SR and an aspiration-catheter are used intracranially with additional extracranial aspiration through the guide catheter (2–4).

Among the different techniques for mechanical thrombectomy, various SRs are used in combined approaches. The Trevo ProVue SR is a well-established mechanical thrombectomy device as several studies have confirmed its efficacy in endovascular stroke therapy. In the Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN), Trevo was the most frequently used SR (5). In the Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) randomized trial, which showed thrombectomy to be superior compared to medical management alone, Trevo was the only SR used in the interventional arm (6). The device was also assessed in the Trevo retriever Registry, a prospective post-market study which documented reperfusion success after mechanical thrombectomy and functional outcomes at 90 days. Reperfusion success was defined by a modified thrombolysis in cerebral infarction (mTICI) score $\geq$2b, which was reached in 93% of the study population. Furthermore, functional independence at 90 days (defined as a modified Rankin Scale $\leq$2) was documented in 55% of patients (7).

In this retrospective study, we assessed the new-generation Trevo SR (Trevo NXT) for endovascular therapy of ischemic stroke due to large or medium vessel occlusions. We focused on its efficacy and peri-interventional safety.

MATERIALS AND METHODS

Study Design and Patient Population

We pooled data of four high-volume European stroke centers over the time period from October 2020 to February 2021. Patients were included in our study if the Trevo NXT ProVue SR (Stryker Neurovascular, Kalamazoo, MI, USA) was used as the first-line device. No other inclusion or exclusion criteria were applied.

The National Institutes of Health Stroke Scale (NIHSS) was obtained at baseline, 24 h post procedure and at discharge by a certified stroke neurologist. All angiographies were rated by the treating interventionalist using the mTICI (8) scale. Non-contrast computed tomography (CT) or magnetic resonance imaging (MRI) was regularly performed within 24 h after treatment or immediately in symptomatic patients. Symptomatic intracranial hemorrhage (sICH) was defined as an intracranial hemorrhage that was associated with clinical deterioration, as documented by an increase of $\geq$4 points on the NIHSS. In intubated patients, sICH was defined by the European Cooperative Acute Stroke Study-2 (ECASS-2) criteria as any parenchymal hematoma grade I or larger (9).

As the company claims that the new Trevo NXT can be delivered and retracted through the microcatheter or the aspiration-catheter more easily compared to earlier Trevo generations, we surveyed the involved interventionalists on their subjective experience with the new device. The following questions were used: (a) How easy was advancing the SR through the microcatheter? (b) Could target placement of the SR be achieved? (c) How easy was retrieving the SR into the aspiration-catheter/BGC? and (d) In PCA, could a stable wedge position be achieved, or was the SR accidentally withdrawn into the aspiration-catheter? For questions (a) and (c) we used an evenly distributed ordinal five-point scale (ranging from 1 = very easy, 2 = easy, over 3 = neutral, to 4 = hard, and 5 = very hard), while (b) and (d) were yes/no questions. For this analysis, only cases in which a PCA was used as the first-line approach were included.

The primary endpoint was first-pass complete or near-complete reperfusion, defined as an mTICI $\geq$2c. Secondary endpoints were final reperfusion, NIHSS at 24 h and discharge, occurrence of sICH, device malfunctions, complications during the procedure, and the subjective ratings of the interventionalists.

Endovascular Procedure

Procedures were performed under conscious sedation, local anesthesia, or general anesthesia. Vital findings were monitored by anesthesiologists or stroke neurologists in all patients during the procedures. All procedures were done using a femoral artery access. The treating physician was free to choose the first-line technique, but in most cases the Stent retriever Assisted Vacuum Extraction (SAVE) technique was used as described elsewhere (4).

Device Characteristics

The Trevo NXT ProVue retriever is a further development of its predecessor, the Trevo XP ProVue retriever. While the stent itself was not changed and still offers full radiopaque visibility, the delivery wire received a new hydrophilic coated polymer jacket which enables a smoother and easier delivery and improved retraction into the aspiration-catheter. It is delivered through a 0.021-inch microcatheter (the 3 × 25 mm retriever can also be delivered through a 0.017-inch microcatheter). The device is available in working lengths from 25 to 35 mm and diameters from 3 to 6 mm. The wire length was increased to 200 cm, which improves its compatibility with tri-axial setups.

Statistical Methods

Statistical analysis was performed using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA, https://www.graphpad.com/, 2021). Parametric variables are stated as mean ± standard deviation (SD). Non-parametric or ordinary variables are presented as median and interquartile range (IQR). No interference statistics were performed.

TABLE 1 | Baseline characteristics of the patients.

Characteristics	Values
No. of patients	80
Women, *n* (%)	39 (49%)
Age, mean ± SD	74 ± 14
NIHSS at admission, median (IQR)	15 (8–19)
Pre-stroke mRS, median (IQR)	0 (0–1)
ASPECTS at baseline, median (IQR)	9 (8–10)
Primary approach	
Stent retriever + BGC, *n* (%)	5 (6%)
PCA, *n* (%)	47 (59%)
PCA + BGC, *n* (%)	27 (34%)
Stent retriever only, *n* (%)	1 (1%)
Occlusion location	
ICA-T, *n* (%)	14 (18%)
M1, *n* (%)	38 (48%)
M2, *n* (%)	22 (28%)
BA, *n* (%)	4 (5%)
P2, *n* (%)	1 (1%)
VA, *n* (%)	1 (1%)
Tandem occlusion, *n* (%)	12 (15%)
Outcomes	
NIHSS at 24 h, median (IQR)	4.5 (1.5–11)
NIHSS at discharge, median (IQR)	2 (0–5)
sICH, *n* (%)	3 (4%)
Secondary distal emboli, *n* (%)	4 (5%)
Emboli to new territory, *n* (%)	1 (1%)

ASPECTS, Alberta Stroke Program Early CT Score; BA, basilar artery; BGC, balloon-guide catheter; ICA-T, internal carotid artery terminus; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin scale; PCA, primary combined approach; SD, standard deviation; sICH, symptomatic intracranial hemorrhage; VA, vertebral artery.

TABLE 2 | Angiographic results stratified by occluded vessel and overall vessels.

	ICA-T	M1	M2	Overall
No. of patients	14	38	22	80
First-pass reperfusion				
mTICI ≥2b, *n* (%)	5 (36%)	25 (66%)	11 (50%)	51 (64%)
mTICI ≥2c, *n* (%)	4 (29%)	20 (53%)	10 (46%)	43 (54%)
mTICI 3, *n* (%)	2 (14%)	15 (40%)	8 (36%)	34 (43%)
Final reperfusion				
mTICI ≥2b, *n* (%)	13 (93%)	36 (95%)	22 (100%)	77 (96%)
mTICI ≥2c, *n* (%)	12 (86%)	30 (79%)	19 (86%)	66 (83%)
mTICI 3, *n* (%)	7 (50%)	22 (58%)	13 (59%)	45 (56%)
No of passes, median (IQR)	3 (1–4)	1 (1–2)	1 (1–2)	1.5 (1–3)
Groin puncture–reperfusion time (min), median, IQR	51 (33.8–82.5)	34 (22.3–52.8)	35 (22–57)	39 (23–58.5)

ICA-T, internal carotid artery terminus; IQR, interquartile range; mTICI, modified thrombolysis in cerebral infarction.

TABLE 3 | Per pass reperfusion results.

Pass #	1	2	3	4	5	6
Number of patients	80	34	20	14	8	5
mTICI <2b, *n* (%)	29 (36%)	18 (53%)	12 (60%)	8 (54%)	5 (63%)	3 (60%)
mTICI ≥2b, *n* (%)	51 (64%)	16 (47%)	8 (40%)	6 (46%)	3 (37%)	2 (40%)
mTICI ≥2c, *n* (%)	43 (54%)	12 (35%)	5 (25%)	3 (23%)	1 (12%)	1 (20%)
mTICI 3, *n* (%)	34 (43%)	7 (21%)	2 (10%)	2 (15%)	0 (0%)	0 (0%)

mTICI, modified thrombolysis in cerebral infarction.

RESULTS

Out of 97 received data sheets, 80 patients were enrolled into this study. Ten of the 97 patients were excluded due to ADAPT being the first-line therapy, while in seven patients an SR other than the Trevo NXT ProVue was used for the first maneuver. All baseline characteristics are depicted in **Table 1**. Mean age was 74 ± 14 years, and 39 patients (49%) were female. The median NIHSS at admission was 15 (IQR, 8–19). Occlusion sites were internal carotid artery terminus ("ICA-T") in 14 (18%), M1-segment in 38 (47%), M2-segment in 22 (28%), basilar artery in 4 (5%), P2-segment in 1 (1%), and vertebral artery in 1 (1%) patient. Median Alberta Stroke Program Early CT score (ASPECTS) on initial imaging was 9 (IQR 8–10). The majority of patients was treated either with a PCA (47/80) or PCA with balloon-guide (27/80), while the rest was treated with SR only (1/80) or with SR plus BGC (5/80). Most of the procedures were performed under conscious sedation or local anesthesia (67 patients). General anesthesia was used in the remaining 13 patients (16%).

First-pass complete or near-complete reperfusion (mTICI ≥2c) was achieved in 43 (54%) with complete reperfusion (mTICI 3) in 34 (43%) patients. The final complete or near-complete reperfusion (mTICI ≥2c) was observed in 66 (83%) and complete reperfusion (mTICI 3) in 45 (56%) patients after a median of 1.5 passes (IQR, 1–3). The rate of successful reperfusion (mTICI ≥ 2b) was 64% after one pass and 96% at the end of the procedure (**Table 2**). The overall median time from groin puncture to reperfusion was 39 min (IQR, 23–58.5). We documented 1 (1%) embolus in new territory (initial M1 to A1), and in 4 cases (5%) distal emboli were observed. In 3 patients (4%) an sICH was observed. In 2 cases the intracranial hemorrhage (ICH) was observed immediately on the post-mechanical thrombectomy scan in the angio-suite, while in the third case no immediate scan after MT was performed. It was observed on the first follow-up CT 4.5 h after the intervention. One ICH was mainly an extensive subarachnoid hemorrhage (SAH) in the basal cisterns and hemispheric sulci with small parenchymal hematoma in the left basal ganglia (affecting putamen) and insula; the other 2 ICHs were mainly parenchymal hematomas within the infarct area (both media territory left). In the case with the SAH no intravenous lysis was given, while in the other 2 cases it was given prior to the intervention. None of the sICHs were rated to be related to the intervention. In all cases the handling of the SR was continuously smooth. The median NIHSS 24 h post procedure was 4.5 (IQR, 1.5–11) and 2 (IQR, 0–5) at discharge.

TABLE 4 | Overview of recent studies evaluating stent retrievers.

	Primary used stent retriever	Number of patients	First-pass reperfusion rate (%)		Final reperfusion rate (%)	
mTICI			**≥2b**	**≥2c**	**≥2b**	**≥2c**
Trevo 2000 Registry (7, 13)	Trevo XP	2,008	-	27.8%	92.8%	56.4%[a]
Yi et al. (14)	Trevo XP	98	40.8%		89.7%	
	Solitaire	102	32%		82.3%	
ARISE II (15)	EmboTrap I and II	227	51.5%	40%	92.5%	76%
Ribo et al. (16)	Neva thrombectomy device	30	63%	47%	93%	63%
Velioglu et al. (17)	CatchView thrombectomy device	53	47.2%	-	84.9%	-
Gupta et al. (18)	Tigertriever	160	57.8%	-	95.7%	71.8%
Kurre et al. (19)	pREset stent retriever	271	-	-	84.9%	-
ARTESp (20)	pREset stent retriever	100	-	-	85.3%	-
Kaschner et al. (21)	Aperio thrombectomy device	97	43.9%	15.1%	85.3%	54.8%
Kaschner et al. (22)	Aperio Hybrid stent retriever	48	52.1%	31.3%	95.8%	60.4%
Pfaff et al. (23)	Solitaire Platinum stent retriever	75	38.6%		92%	
Our study	Trevo NXT ProVue retriever	80	63.75%	53.75%	96.25%	82.5%

[a] *Refers to mTICI 3 results.*

mTICI, modified thrombolysis in cerebral infarction.

A total of 158 passes were performed with the Trevo NXT; no device malfunctions were observed. Four complications were reported: 2 SAHs and 2 vasospasms (which resolved after application of nimodipine). Both vasospasms were observed in the segment where the SR was placed [one in the M2-segment of the right middle cerebral artery (MCA) and one in the M2-segment of the left MCA]. In both cases the Trevo NXT 4 × 35 mm SR was used.

A subgroup analysis of the angiographic results after stratification by occlusion site indicated higher first-pass complete or near-complete reperfusion results in the M1- and M2-segments compared to the ICA-T (53%/46% vs. 29%). Furthermore, the number of passes (median 3 for the ICA-T and 1 for the M1/M2) and the groin to reperfusion time (median 51 min for ICA-T vs. 34/35 min for M1/M2) were higher for ICA-T occlusions (see **Table 2** for detailed results). The incremental improvement of the mTICI result declined from pass to pass (**Table 3**).

Advancing the SR was rated "very easy" in 39%, "easy" in 47%, and "neutral" in 14% of our cases, while none of the procedures was rated as "hard." Target placement of the SR was achieved in all cases. Withdrawing the SR toward the aspiration-catheter to reach the wedge position or retrieve it toward the BGC was rated as "very easy" in 51%, "easy" in 42%, and "neutral" in 7%. The wedge position could be sustained in 91% of the procedures.

DISCUSSION

Early and complete arterial recanalization is the most important factor in achieving favorable clinical outcome after ischemic stroke due to LVO (10, 11). Mechanical thrombectomy is the standard of care for LVO and gaining momentum for medium vessel occlusions as well, as multiple randomized trials have demonstrated improved patient outcomes in the interventional arm (1, 12). In cases of tortuous proximal vessels or distal target lesions, pushing the SR through the microcatheter and retrieving the SR within the aspiration-catheter can be challenging. The design of the new Trevo NXT is supposed to help in these situations, due to the hydrophilic coating of the pusher wire. In this retrospective multicenter study, we evaluated the initial results with this new device. One of our main findings was that the rate of first-pass complete or near-complete reperfusion (mTICI ≥2c) was achieved in 54% of cases, which compares favorably to previously published data of the predecessor retriever (**Table 4**) (13, 14). Final mTICI ≥2c was achieved in 83%, and final complete reperfusion (mTICI 3) in 56% of the cases. First-pass mTICI ≥2c was achieved more often than in the Trevo 2000 Registry, where the rate was 28% (13). Regarding final reperfusion rates, mTICI 3 was documented in 56% of the Trevo 2000 Registry cases, which is identical to the final mTICI 3 rates of our study (56%) (7). Data of other newer-generation SRs were mostly comparable to our results: Ribo et al. reported 63% mTICI ≥2b and 47% mTICI ≥2c first-pass reperfusion using the Neva thrombectomy device, although with a small sample size of only 30 patients (16). Slightly inferior results with 52% first-pass mTICI ≥2b and 40% first-pass mTICI ≥2c were reported in the prospective ARISE II study, where the EmboTrap SR was assessed using a larger sample size (n = 227) (15). Results of the Aperio Hybrid SR were recently published, with 52% mTICI ≥2b and 31% mTICI ≥2c first-pass reperfusion in a sample of 48 patients, which are slightly inferior to our reperfusion rates (22). The Tigertriever, which can be radially adjusted, was recently evaluated in the multicentric Tiger Trial (n = 160), yielding similar reperfusion results with first-pass successful reperfusion rates of 58% and final near-complete reperfusion rates of 72% (18). Technical approaches varied within all these studies, limiting the degree to which reperfusion results can be compared. For example, while in this study the primarily used

technique was a combined technique (93% of the cases), this approach was used only in a minority of cases in the Trevo 2000 Registry (7).

Regarding the technical aspects using the Trevo NXT as first-line device, advancing the SR within the microcatheter was described as "easy" in the majority of cases, and target placement of the SR was achieved in all cases. Even in cases of curved proximal vessels or tortuous siphon we were able to push the 4 mm Trevo NXT through a 0.021-inch microcatheter without failing to reach the target position. While treating distal occlusions with the 3 mm Trevo NXT, pushing the device through a 0.017-inch microcatheter was feasible. In our subjective opinion, pushing the new 3 mm device through a 0.017-inch microcatheter was easier compared to previous Trevo generations, although we did not compare the 2 devices in this study. In terms of retrieving the SR into the aspiration-catheter or the BGC, we also received positive feedback from the interventionalists. These findings are consistent with the development of a hydrophilic coated polymer jacket, which was designed to enable a smoother and easier delivery and an improved retraction into the aspiration-catheter. Our experience is that even in tortuous proximal vessels it is much easier to push a rather rigid large-bore aspiration-catheter toward the face of the clot over the new SR after removal of the microcatheter. For physicians using the Solumbra technique (full retrieval of the SR within the aspiration-catheter) as their primary approach, the hydrophilic jacket provides an even smoother retrieval experience compared to older SRs. Nevertheless, we would not recommend this technique to be used as first-line approach, based on the higher occurrence of clot fragmentation and distal emboli (24). A potential disadvantage of the new coating is encountered when pulling the SR toward the tip of the aspiration-catheter for the SAVE maneuver (25): With conventional SRs, there is a point where a wedge position is reached and cannot be lost even with significant pulling power on the SR wire, due to entrapment of the clot between the SR and the aspiration-catheter. Using the new device, we noticed that continuous pull after reaching the wedge position can lead to unintentional withdrawal of the SR within the aspiration-catheter (9% of our cases) resulting in an unintended Solumbra maneuver.

Concerning safety, the Trevo NXT retriever can be regarded as safe. Complication rates were comparable to those of the literature (1). Both cases of SAH were unnoticed during the procedure and could not be clearly attributed to the SR (26).

The main limitation of our study is the retrospective design. Patients were included after initial stroke incident and treatment with mechanical thrombectomy. In addition, angiographic results and complications were rated by the treating physician and not by a core lab, which can lead to heterogenous judgments and potentially influence results. Finally, the Trevo NXT was chosen as the first-line device by the treating physician and not allotted in a randomized setup.

CONCLUSION

Based on our initial data, we conclude that the Trevo NXT is an effective and safe tool for mechanical thrombectomy especially when using combined approaches.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AB, PS, IT, KB, and JO designed the data collection sheets and performed the analysis. MMö, CW, CP-G, MMo, FC, NL, ON, and MW contributed the data and helped to evaluate the data. ME and M-NP wrote the manuscript. All authors reviewed the manuscript critically, gave final approval of the submitted version, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REVIEW
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From Three-Months to Five-Years: Sustaining Long-Term Benefits of Endovascular Therapy for Ischemic Stroke

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Background and Purpose: During the months and years post-stroke, treatment benefits from endovascular therapy (EVT) may be magnified by disability-related differences in morbidity/mortality or may be eroded by recurrent strokes and non-stroke-related disability/mortality. Understanding the extent to which EVT benefits may be sustained at 5 years, and the factors influencing this outcome, may help us better promote the sustenance of EVT benefits until 5 years post-stroke and beyond.

Methods: In this review, undertaken 5 years after EVT became the standard of care, we searched PubMed and EMBASE to examine the current state of the literature on 5-year post-stroke outcomes, with particular attention to modifiable factors that influence outcomes between 3 months and 5 years post-EVT.

Results: Prospective cohorts and follow-up data from EVT trials indicate that 3-month EVT benefits will likely translate into lower 5-year disability, mortality, institutionalization, and care costs and higher quality of life. However, these group-level data by no means guarantee maintenance of 3-month benefits for individual patients. We identify factors and associated "action items" for stroke teams/systems at three specific levels (medical care, individual psychosocioeconomic, and larger societal/environmental levels) that influence the long-term EVT outcome of a patient. Medical action items include optimizing stroke rehabilitation, clinical follow-up, secondary stroke prevention, infection prevention/control, and post-stroke depression care. Psychosocioeconomic aspects include addressing access to primary care, specialist clinics, and rehabilitation; affordability of healthy lifestyle choices and preventative therapies; and optimization of family/social support and return-to-work options. High-level societal efforts include improving accessibility of public/private spaces and transportation, empowering/engaging persons with disability in society, and investing in treatments/technologies to mitigate consequences of post-stroke disability.

Conclusions: In the longtime horizon from 3 months to 5 years, several factors in the medical and societal spheres could negate EVT benefits. However, many factors can be leveraged to preserve or magnify treatment benefits, with opportunities to share responsibility with widening circles of care around the patient.

Keywords: cerebrovascular disease, ischemic stroke, endovascular treatment, long-term outcome, post-acute care

INTRODUCTION

Endovascular therapy (EVT) is a highly efficacious treatment for acute ischemic stroke with large vessel occlusion (LVO), promoting post-stroke functional independence (1). Through successful reperfusion of brain tissue, EVT results in lower post-treatment infarct volumes when performed rapidly (2–4). However, fast and successful EVT alone does not guarantee a good outcome. Several critical factors operate in the post-stroke period that can influence the 3-month recovery of the patient. Some are unmodifiable, like advanced age and comorbidities like cardiovascular disease or cancer (**Figure 1A**) (5). Others are modifiable through attention to the quality of post-acute care, such as the occurrence of post-stroke complications like pneumonia or deep vein thrombosis (5, 6).

Notwithstanding the various potential pitfalls in stroke recovery from EVT to 3 months, the longer time horizon from 3 months to 5 years is fraught with even greater uncertainty. Some patients may experience further recovery from disability beyond 3 months, while some others successfully maintain their independence, with magnification of treatment-related differences in terms of long-term disability and mortality (7). On the other hand, EVT-related benefits may be eroded by recurrent strokes, accrual of non-stroke-related disability, or by non-stroke-related deaths, especially since stroke occurs more often in elderly people with progressive comorbidities. This raises the question of how we may maximally sustain the initial gains from EVT.

In this review, 5 years after EVT became the standard of care for acute ischemic stroke with LVO, we examine the current state of the literature on 5-year post-stroke outcomes, with particular attention to the modifiable factors that influence the evolution of outcome of the patients between 3 months and 5 years post-stroke. This knowledge may help us better ensure that the therapeutic benefits of EVT are sustained to the greatest possible extent until 5 years post-stroke and beyond.

LITERATURE SEARCH

We searched the literature for studies that (1) involved patients with ischemic stroke and (2) examined a post-stroke outcome of interest beyond the 3-month period (search strategy in the **Supplementary Material**). Although we were most interested in studies that examined long-term outcomes after EVT or LVO-associated stroke, there continues to be a paucity of high-quality studies examining longer-term outcomes in this specific population. Therefore, we took a more inclusive approach and considered studies in the general ischemic stroke population as well, since most aspects of post-acute care are not unique to the LVO population. We limited the search to studies of humans published in English. The literature search is up-to-date as of April 30, 2021. We excluded case reports, case series, and opinions or editorials.

Abbreviations: EVT, endovascular treatment; LVO, large vessel occlusion; mRS, modified Rankin Scale; QALY, quality-adjusted life year.

Maximizing Three-Month Outcomes With EVT

The sustenance of EVT benefits between 3 months and 5 years post-stroke is predicated on maximizing 3-month treatment effects in the first place. Therefore, it is worth briefly reviewing key factors of acute stroke care that can optimize 3-month EVT benefits (**Figure 1B**).

Tremendous gains have been made in EVT technology, techniques, and workflow. Improvements in thrombectomy devices (specifically stent retrievers) were crucial to the dawn of successful EVT for stroke (8, 9), and the continued evolution of these devices—with better size choices and longer, more radio-opaque designs—and of EVT training programs holds promise for further enhancing EVT benefits (10–12). Speed is also critical (13); indeed, shortened treatment times from IMS-III (Interventional Management of Stroke trial-III) to the major EVT trials in 2015 helped drive efficacy (14, 15). Further refinement of EVT techniques like CAPTIVE (continuous aspiration prior to intracranial vascular embolectomy) (16) or BADDASS (BAlloon guiDe with large bore DISTAL ACCESS catheter with dual aspiration with Stent retriever as Standard approach) (17) is also crucial to continue improving reperfusion rates. The population benefitting from EVT continues to expand, such as "late-window" patients with salvageable penumbra (18, 19) and potentially patients with more extensive early ischemic changes for whom trials are ongoing (20, 21). Three-month outcomes may be further improved by neuroprotective therapies (22); a promising treatment is nerinetide, which may improve outcomes in patients not receiving alteplase (23). Artificial intelligence and machine learning approaches may further improve outcomes through decision support for stroke identification/triage, imaging interpretation, and patient selection for treatment (24, 25).

Following EVT, attention to post-acute care, ideally on organized stroke units, is essential to prevent or mitigate complications like aspiration pneumonia or deep vein thrombosis, which can rapidly negate EVT benefits (5, 6). Larger, systems-level factors also matter, such as whether care

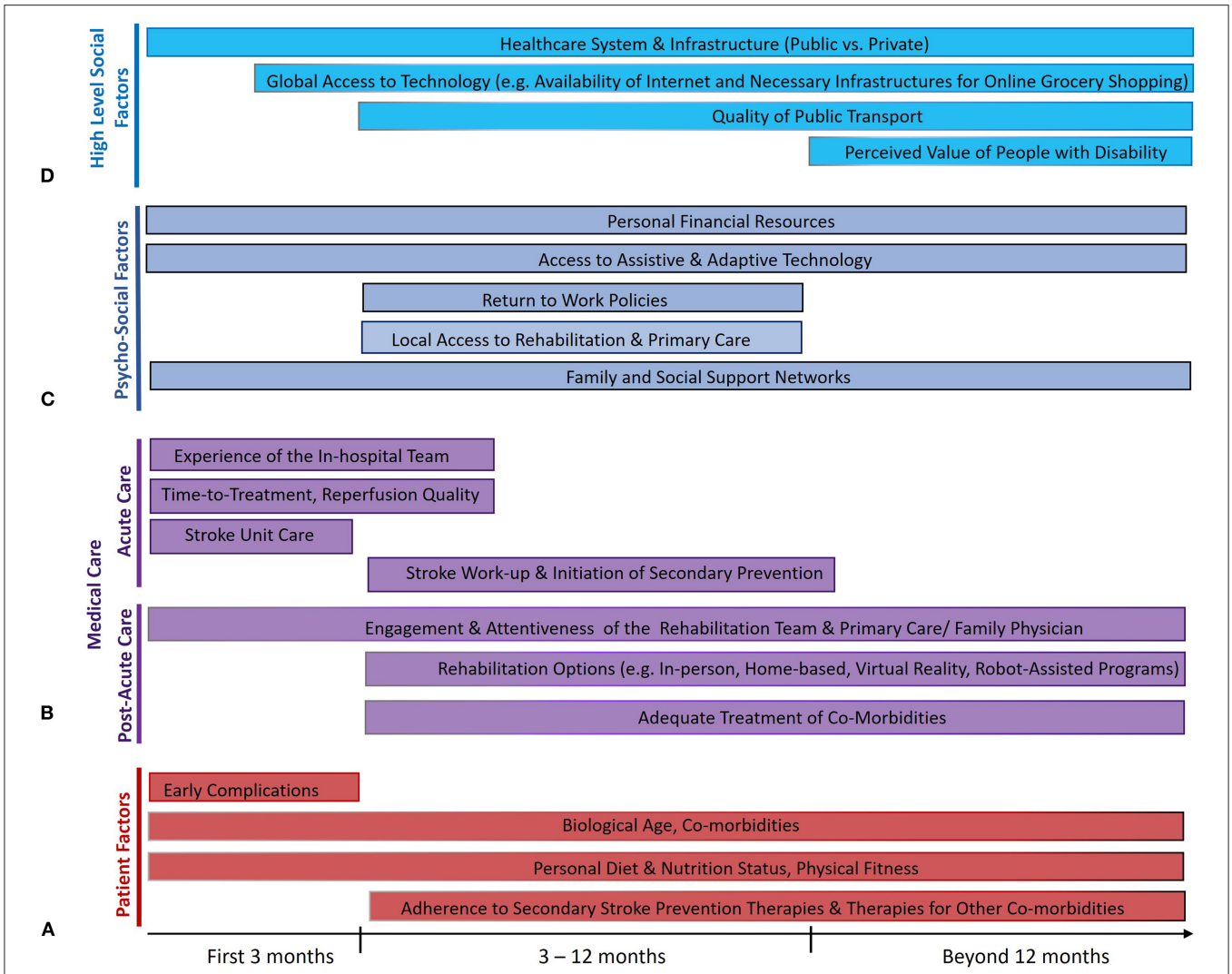

FIGURE 1 | Factors that influence the maintenance of treatment benefits of endovascular therapy (EVT) from 3 months to 5 years after ischemic stroke from large vessel occlusion. Several factors relate to the individual patients themselves **(A)**, some of which are modifiable (like risk of early complications) and rely on effective collaboration between patients and physicians, while several others directly relate to the quality of acute and post-acute medical care **(B)**. Many psychosocioeconomic factors in the life of the patient also play a crucial role **(C)**, as do higher-level societal factors **(D)** that influence the ability of the patient to reintegrate post-stroke and live a fulfilling life. The length of the bars reflects the portion of the post-stroke time period where each factor is thought to play an important role.

occurs in the context of integrated systems of stroke care. Such systems involve concerted efforts across the continuum from prehospital care all the way to post-stroke rehabilitation and secondary prevention (26) and may promote lower 30-day mortality (27). Even in regions with more fragmented systems, the adoption of certain concerted approaches to stroke workflow, such as prehospital notification of incoming "code strokes" and rapid patient triage, stroke team activation, and neuroimaging completion, can improve onset-to-groin-puncture times and thus improve 3-month outcomes (28, 29). The organization of stroke systems in the field to ensure efficient transport of patients with LVO for EVT remains a work in progress (30). Several scales have been developed for prehospital identification of LVO, with attendant limitations (31, 32), and geographical modeling of optimal transport options has emerged as an important technology to guide routing decisions (33, 34).

Relationship Between Three-Month and Five-Year Post-stroke Outcomes

The enduring burden of long-term disability in ischemic stroke has been reported in many cohorts, with about 31–36% of patients being functionally disabled patients 5 years post-stroke (35–38). Three-month modified Rankin Scale (mRS) scores strongly predicted 5-year disability in the population-based Oxford Vascular Study (OXVASC), implying that treatments like EVT that reduce 3-month disability likely promote long-term functional independence (39).

As for mortality, at 1 year post-stroke and beyond, the most frequent causes are respiratory infections and cardiovascular disease (40). Functional dependency, with attendant issues of immobility and incontinence, is associated with complications like infections and pressure sores (41). Observational studies have shown that early post-stroke disability predicts long-term

TABLE 1 | Key observational studies examining the relationship of short-term post-stroke disability or functional outcome to 5-year (or longer-term) mortality.

Study	Main finding
Perth Community Stroke Study (42)	Post-stroke disability on the Barthel Index (<20/20 at around 1 month), particularly urinary incontinence, significantly predicted 5-year death
Prospective admissions-based study at the University of Rome (43)	Only included minor strokes (30-day mRS ≤ 2) and it was found that mRS = 2 was associated with a hazard ratio (HR) of 3.4 for 10-year mortality
Rochester-based retrospective medical record review (40)	On reviewing cause-specific mortality over 10 years or more after first ischemic stroke, it was found that mRS of 4 or 5 was associated with higher mortality.
Riksstroke study (Sweden) (44)	Reported HRs of 1.7, 2.5, and 3.8, respectively, for 3-year mortality for 3-month mRS of 3, 4, and 5 compared with 0–2
Athens Stroke Registry (45)	Patients with worse 3-month mRS scores had higher mortality, after adjusting for comorbid risk factors (relative mortality risk increases of 18, 55, 80, 157, and 472%, respectively, for mRS 1 through 5 vs. 0).
Oxfordshire Community Stroke Project, Lothian Stroke Registery, and the First International Stroke Trial (combined analysis) (46)	Among 7,710 ischemic stroke patients registered between 1981 and 2000 and followed for up to 19 years, functional dependence was a significant predictor of mortality in each cohort, with the median survival being 9.7 years in independent patients and 6.0 years in dependent patients.
Oxford Vascular Study (OXVASC)	Detailed analysis of cause-specific mortality among 1,606 patients found that 54.8% of deaths after 3 months attributable to stroke-related complications occurred after 1 year (39), with each increment of 3-month mRS being associated with higher 5-year mortality (47).

mRS, modified Rankin Scale.

mortality (key studies shown in **Table 1**). These data suggest that early disability reductions from EVT will likely translate into lower long-term mortality, without much erosion by non-stroke-related deaths. Cognitive impairment is a well-recognized post-stroke complication, progressing to dementia in up to one-third of patients (48, 49), with dementia incidence being nearly 50 times higher 1 year post-stroke compared with the general population (50). Post-stroke dementia contributes to dependency (51, 52), institutionalization, and mortality (53). In OXVASC, each 3-month mRS increment was associated with higher 5-year risk of dementia (54).

Healthcare costs also reflect long-term treatment effects. Three-month functional outcome again predicts long-term post-stroke costs. A systematic review of costing studies between 2004 and 2015 found that costs consistently increased with increasing mRS (55). In OXVASC, each increment of worsening 3-month mRS was associated with higher 5-year healthcare/social care costs (47), regardless of premorbid disability (56). Analyses of the North-East Melbourne Stroke Incidence Study (NEMESIS) have shown that 5-year outcomes provide a robust estimate of lifetime post-stroke costs (57). Long-term costs are closely tied to institutionalization, i.e., admission to residential care or nursing homes, affecting 9–15% of patients by 5 years post-stroke (36, 37, 58–60) and over 40% of initially hospitalized patients with severe strokes (61–63). Unsurprisingly, early disability predicts 5-year institutionalization. The Erlangen Stroke Project found that urinary incontinence on the Barthel Index at 7 days conferred a four-fold higher risk of 12-month institutionalization (64). In OXVASC, 1-month/3-month mRS predicted 5-year institutionalization (>35% with mRS of 3–5 vs. <10% with mRS 0–2) (36, 54).

Higher post-stroke disability is also associated with poorer quality of life. Indeed, the 3-year Australian POISE (Psychosocial Outcomes In Stroke) study found that functional independence at 28 days was the strongest predictor of return-to-work within 1 year post-stroke (65). In OXVASC, each 3-month mRS increment was associated with worse quality-of-life ratings and 5-year quality-adjusted life expectancy (QALE) (54, 66). The VISTA (Virtual International Stroke Trials Archive) collaborators found that 3-month mRS scores accounted for 65–71% of variation in health utilities generated using EQ-5D data for different countries (67).

From these observational data, we may extrapolate that 3-month EVT benefits will likely translate into lower 5-year disability, mortality, institutionalization, and care costs and higher quality of life/QALE. This suggests that the 3-month benefits are probably preserved and potentially magnified at 5 years, but a caveat is that many/most of the patients in these cohorts did not have LVOs (although OXVASC reported sensitivity analyses in potentially "treatable" strokes) (39). Preliminary real-world data showing these long-term benefits have come from the analyses of the MR CLEAN (Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands) and REVASCAT (a randomized trial of revascularization with SOLITAIRE FR® device vs. best medical therapy in the treatment of acute stroke due to anterior circulation LVO presenting within 8 h of symptom onset) trials. An analysis of 2-year mRS data from 391 of 500 patients enrolled in MR CLEAN (78.2%) showed an adjusted OR of 1.68 (95% CI 1.15–2.45) for a shift of mRS in favor of EVT (68). One-year mRS data from REVASCAT, available for 205 of 206 patients (99%), showed that 89% of the positive treatment effect was already observed at 90 days (69). In REVASCAT, EVT was also associated with better cognitive performance at 3 months and 1 year on the trail-making—test part B, especially among patients with mRS 0–2 (70).

Interestingly, a recent OXVASC analysis that applied prognostic weights derived for each level of the 3-month mRS to EVT trial data estimated very similar long-term treatment effects as the actual MR CLEAN and REVASCAT analyses. For example, OXVASC estimated a 2.5% lower mortality (95% CI −7.1 to 12.0%) and 0.06 additional QALY (0.003–0.13) in the REVASCAT EVT arm at 1 year, similar to the non-significant 1% mortality difference and 0.12 (0.03–0.22) utility difference reported in the 1-year REVASCAT analysis (69). Similarly, OXVASC estimated a 5.5% lower mortality

(−0.5 to 11.4%) and 0.14 additional QALY (0.06–0.23) in the MR CLEAN EVT arm at 2 years, which was close to the 5% mortality and 0.10 (0.03–0.16) utility differences reported in the 2-year MR CLEAN analysis (68). Buoyed by these robust estimates, the 5-year benefits of EVT were extrapolated using weighted ordinal analyses of pooled 3-month mRS results of all major EVT trials. Endovascular therapy was predicted to confer an 11% lower risk (95% CI 9–14%) of death/dementia/institutionalization, a $10,193 (7,405–12,981) reduction in healthcare/social care costs, and an additional 0.55 (0.43–0.66) QALYs over 5 years vs. control treatments. A subsequent analysis from the HERMES collaboration estimated that every 10 min of earlier EVT results in an average gain of 39 days of disability-free life and increases net monetary benefit by $10,519 for healthcare costs and $10,915 for societal costs over the lifetime of a patient, indicating the long-term benefits of faster EVT (71).

Medical Care-Related Factors Influencing Five-Year Stroke Recovery and Outcomes

Importantly, the strong group-level observational and clinical trial data for the extrapolation of 3-month benefits of EVT to 5 years and beyond by no means guarantee the maintenance of 3-month benefits for individual patients. At the individual level, there are numerous factors occurring as part of the medical care of the patient (both physician- and patient-dependent) that likely influence how the long-term EVT outcome of the patient will play out (**Figure 1B**).

Firstly, the 3-month disability need not guarantee 5-year disability. Whereas, post-stroke recovery was conventionally thought to occur mostly in the first 3 months post-stroke (72), rehabilitation strategies like constraint-induced movement therapy (CIMT) have been shown to be effective in the 3- to 9-month window (73, 74), indicating that patients may demonstrate late functional improvement (75). In OXVASC (76) and in an analysis of three randomized multicenter trials of acute ischemic stroke (2,555 patients), such improvement (by $\geq$1 mRS grades) was observed in about one in four patients with ischemic stroke between 3 and 12 months post-stroke (77). Whereas, analyses of 11 rehabilitation pilot studies demonstrated a gradient of recovery fading to asymptotic levels after about 18 months post-stroke (78), functional improvement was also seen in about 1 in 10 patients in OXVASC between 1 and 5 years post-stroke (76). Although such late improvements, particular between 3 and 12 months, seem more common among those with lacunar strokes (76), patients who demonstrated late improvement in OXVASC, regardless of subtype, had lower 5-year mortality, institutionalization, and healthcare/social care costs (79). These findings should motivate clinicians and patients to maximize late recovery in practice. Robot-assisted rehabilitation holds promise for promoting intensive, interactive, and individualized practice, but methodologically limited studies to date have only shown small effects on motor control and medium effects on strength (80). Augmentation of rehabilitation interventions with virtual reality, particularly involving a gaming component, improves treatment gains by over 10% compared with conventional approaches (81). These approaches may help further promote late recovery in the future.

In addition, attention to secondary stroke prevention and care for post-stroke complications is critical. It is essential to address and control all modifiable cardiovascular risk factors to prevent recurrent stroke. Anticoagulation for atrial fibrillation is one important example, given the high stroke recurrence in the absence of anticoagulation. Some observational studies suggest that early initiation of direct oral anticoagulants post-stroke may be associated with an acceptably low risk of ICH (82, 83); randomized controlled trials are currently investigating the optimal time point to start anticoagulation (e.g., ELAN—NCT03148457, OPTIMAS—NCT03759938, TIMING—NCT02961348) (84). Organized clinical follow-up is associated with lower hospitalization rates several months post-stroke (85–88). There is a wide variation in the availability of secondary prevention services and medical follow-up (89, 90). In a recent American study, 59.3% of patients had primary care follow-up within 1 month post-stroke and only 24% had neurology/stroke service follow-up (87). Similar challenges have been noted in other countries; in Sweden, only 75% of patients in the Riksstroke registry had 90-day follow-up (91). The added benefits of predefined care models and specialized stroke prevention clinics are being systematically studied in clinical trials (92, 93), which may facilitate their wider adoption.

Moreover, patient compliance and lifestyle modification are critical to maintain functional independence. Beyond prescriptions, patients need appropriately tailored information and education to mitigate risk and promote timely recognition of recurrent strokes (94). The quality of patient/caregiver educational strategies is quite variable, with some approaches showing limited effect on long-term outcomes (95, 96). Patients also benefit from organizational and behavioral interventions to meet secondary prevention goals like blood pressure or low-density lipoprotein targets (97, 98). Underscoring the importance of follow-up, patients without 90-day follow-up have lower medication compliance (91). Only around 65% of patients adhere to statins (99, 100), while 60% adhere to anticoagulation (101–103). Barriers to adherence include challenges with self-care, limited knowledge about stroke and its dangers, frequent medication changes, and high treatment burden and complexity (104). Lifestyle modification, especially smoking cessation, is key for secondary prevention. Yet in a recent analysis of the National Health and Nutrition Examination Survey and the Behavioral Risk Factor Surveillance System survey, active smoking had not become less prevalent among stroke survivors over the past 20 years in the United States, in contrast to the general population (105).

Aside from recurrent cardiovascular events, infections are an important cause for readmission post-stroke (106). Such infections, including aspiration pneumonia (39), are associated with increased mortality (107). Particular vigilance is required for patients with dysphagia, associated with pneumonia and increased morbidity/mortality (108). Importantly, swallowing therapy improves long-term survival (109), emphasizing the importance of multidisciplinary care, in this case including speech and language pathologists.

Furthermore, depression affects one-third of patients after stroke and adversely affects long-term outcomes. Optimal treatment options and benefit of antidepressants for daily activities remain uncertain, but early recognition with a combination of pharmacological and non-pharmacological approaches is prudent (110). Recent trials of fluoxetine in the early post-stroke period have shown benefits for mood and emotional control (111, 112) with reduced incidence of new post-stroke depression (112), but no benefits for functional outcomes.

Based on these insights, we can identify a set of "action items" for stroke teams to address between 3 months and 5 years, ideally in tandem with primary care and multidisciplinary teams, to help maximize long-term EVT benefits (**Table 2**).

TABLE 2 | Medical action items for stroke teams to address between 3 months and 5 years post-stroke to ensure maintenance of EVT benefits.

Aspect of stroke care	Goal or action
Stroke rehab	• Educate patients/payers about potential for late functional recovery • Promote multidisciplinary rehab through early supported discharge (113) • Maximize late functional improvement beyond 3 months using proven strategies (like constraint-induced movement therapy) • Promote regular exercise/mobilization and/or positional changes to mitigate long-term complications of immobility
Clinical follow-up	• Provide organized clinical follow-up for stroke survivors at 3 months and beyond through dedicated stroke prevention clinics (86) • Use multiple types of communication and reminders and liaise with primary care physicians to minimize patients that are "lost to clinical follow-up"
Secondary stroke prevention	• Ensure that underlying mechanisms and risk factors have been appropriately investigated and treated using a multidisciplinary approach as needed • Provide education to patients about stroke (to ensure prompt recognition and treatment of future events) and importance of risk factor management • Support lifestyle modification including smoking cessation and attainment of blood pressure and lipid targets using behavioral interventions and longer-term telephone-based follow-ups (114) • Support self-care (e.g., with rehab specialists) and minimize the complexity of medication regimens to promote adherence (104) • Dedicated quality improvement interventions with pharmacists (115) and smartphone-based strategies may help improve medication adherence in certain populations (116, 117)
Infection prevention and control	• Optimize dietary modifications and swallowing therapy/precautions in patients with dysphagia, in concert with speech and language pathologists • Educate patient and caregivers about prompt recognition and treatment of infections • Implement plans for maintenance of hygiene in patients with incontinence, including scheduled changing of indwelling catheters or teaching clean intermittent catheterization if necessary/appropriate
Post-stroke depression	• Educate patient and caregivers about this common complication and monitor for this in follow-up • Prompt identification and use of pharmacological and non-pharmacological management, with input from psychologists and/or psychiatrists as appropriate

Psycho-Social Factors Influencing Long-Term Stroke Recovery and Outcomes

Aside from psychological effects of the stroke itself, there are several relevant psycho-social factors operating in the immediate environment of the patient that play a major role in their long-term recovery and, thus, their long-term EVT benefit (**Figure 1C**).

There is a consistent association of lower socioeconomic status and lower education with higher long-term morbidity/mortality post-stroke (118–120). The growing wealth and income disparity worldwide can be expected to contribute to greater disparities in stroke prevention and outcomes (121, 122). Whereas, socioeconomic or insurance status has been studied mostly in relation to acute/in-hospital care in the United States (123, 124), important data on longer-term care metrics have recently come from European studies. Socioeconomic deprivation was associated with lower survival and greater enduring functional impairment on the Barthel Index at 7 years post-stroke in England (125, 126). Higher education was associated with better motor and functional recovery during rehabilitation in Europe (127) and lower 1-year stroke-related mortality in Finland (128), whereas low income was associated with lower 6-month motor improvement post-stroke in Europe (127) and higher 1-year stroke-related mortality in Finland (128). Some of these differences relate to disparities in accessing good-quality care. For example, patients with socioeconomic deprivation were less likely to receive appropriate post-stroke care during 5 years of follow-up in London, including swallowing assessments, medications for atrial fibrillation, and in Black patients, physiotherapy and occupational therapy (129).

In addition, once patients are discharged from the hospital, their access to rehabilitation programs is highly variable. Insurance policies in countries like the United States often restrict stroke patients from accessing rehabilitation after discharge (75). Even in countries with universal healthcare insurance like the United Kingdom and Canada, patients struggle to access rehabilitation services beyond the first few months post-stroke (130). The aforementioned benefits of late post-stroke recovery should incentivize payers to expand coverage for proven late therapies like CIMT (73) beyond 3 months post-stroke, as such investment can pay off with sustained independence and lower healthcare/social care costs.

However, even with excellent post-acute stroke care, patients may suffer from suboptimal management of non-stroke-related comorbidities due to poor access to primary care or allied health professionals. Timely involvement of primary care physicians is enshrined in guidelines for post-acute care (131), yet options may be limited for patients living in remote/rural areas. Financial barriers also hamper secondary prevention efforts in more subtle ways. Besides making healthy eating habits unaffordable, they create competing priorities for patients trying to attend

appointments; for example, patients may struggle with the double hit of lost income on the day of an appointment and transport/parking costs (130).

Besides, there is a substantial need for family support post-stroke to optimize physical recovery and outcomes (132–134). The experience of a patient of residual disability post-EVT can be dramatically different depending on how invested their families are in helping them thrive at home. Closely tied to this is the social support network of the patient; besides having a more enriching quality of life, patients with more open and vibrant social networks extending beyond their family are also more likely to be brought in for timely medical attention with future emergencies like stroke (135, 136). Social support also influences more intimate aspects of daily life; a poor relationship with the person feeding them (strangers vs. family/friends) can, for example, worsen meal-skipping, malnutrition, frailty, and isolation among stroke survivors (137). Compounded by changing family and social dynamics, social isolation is a major public health issue (138) and results in worse post-stroke outcomes (139, 140).

Access to assistive or adaptive technology is another huge determinant of whether post-stroke impairments cause functional disability. Robots and other technologies designed to compensate for impaired skills may help patients retain functional independence (141). Technological options also influence post-stroke return-to-work, a major component of self-perceived autonomy (142). Only two-thirds of "working-age" patients achieve return-to-work within 4 years of stroke (143, 144), with contributory factors falling into personal (impairment, adaptation, motivation), rehabilitative (availability, appropriateness), and workplace (demands, support, disability management) domains (145). Relatively simple professional supports may help facilitate return-to-work, like practice typing for office jobs (146). Unsurprisingly, socioeconomic disparities again play a role, with patients who worked in higher management positions more likely to return than blue-collar workers or farmers (147).

These psychosocioeconomic factors extend beyond the typically demarcated circle of care of stroke teams, but there are still important action items to consider (**Table 3**). Rather than relying on medical expertise, addressing these challenges requires stroke teams to build collaborations with the family of the patient, social networks, and allied-health community partners and to be effective advocates for patients. One powerful way for stroke teams to help attain these goals is by advocating for and joining integrated stroke systems that empower concerted efforts across the continuum of stroke care (26).

TABLE 3 | Psychosocioeconomic action items for stroke teams to address or advocate for between 3 months and 5 years post-stroke to help maintain EVT benefits.

Issue in patient environment	Goal or action
Access to or adequacy of primary care	• Aim for more seamless communication between hospital and primary care physicians (148) • Try to connect patients with primary care physicians in the community who are accepting new patients as part of discharge planning
Access to or ability to attend specialist clinics and rehabilitation sessions	• Be part of telestroke networks to bridge gaps in access to care, and leverage such opportunities to reduce travel burden for patients and families (149, 150) • Advocate for patients to be covered for rehabilitation by payers, e.g., by focusing on potential cost savings of late functional improvement
Knowledge of and ability to afford healthy lifestyle choices and secondary prevention therapies	• Work in concert with social workers to ensure that patients with financial barriers are best connected to available compassionate or subsidized resources and supplementary income (151) • Develop high-quality educational material that does not assume prior knowledge and can be well-understood by patients of different levels of educational backgrounds
Family support and social networks	• Connect patients with limited support networks with community programs or other social support interventions (152) • Actively seek input from rehab team for homecare, home safety, and best affordable technological supports
Return to work options	• Have a member of the multidisciplinary team (e.g., therapists, social worker) be the point person of the patient to advocate for phased transition into the workplace • Advocate for any return-to-work modifications and assistive technologies to maximize success (153, 154)

High-Level Societal Factors Influencing Long-Term Stroke Recovery and Outcomes

The long-term post-stroke trajectory of a patient is also influenced by much higher-level, upstream societal environmental factors (155). The relevance of such factors is apparent when considering macrogeographical disparities in stroke outcome, evidenced by higher stroke mortality in lower/middle-income countries (LMICs) (120), and microgeographical disparities, evidenced by higher 1-year mortality in disadvantaged parts of a given city (156). Whereas, the general organization of a healthcare system may dictate the access of a patient to care as discussed above, it is worth noting the factors outside the healthcare sphere that influence patient re-engagement post-stroke and, thus, their long-term outcomes (**Figure 1D**).

How a society organizes its public and private spaces can greatly affect the ability of a patient to have a fulfilling life post-stroke. Physical barriers like inaccessible entryways, bathrooms, and door thresholds can lock even mildly disabled patients out of economic and leisurely pursuits (157). In societies where having a car becomes essential, patients who are unable to drive and rely on specialized transport services have a worse quality of life (158). The availability of accessible and affordable public transport may help mitigate these challenges.

In addition, how a society values people with disability in the workplace and the public sphere may determine successful re-engagement post-stroke. Is there a supportive niche for stroke survivors or are they discriminated against? These attitudes also influence the self-perceptions

TABLE 4 | Action items for societies to address to help maintain EVT benefits in stroke survivors at 5 years and beyond.

Societal domain	Goal or action
Accessible public/private spaces	• Provide ramps/railings, minimizing doorway barriers, etc., at all major buildings or businesses
Accessible and affordable transport options	• Incorporate pathways for safe return to driving, such as formal driving assessment and retraining (160) • Equip public transport vehicles with grips and bar handles on both sides, or provide complimentary walkers, canes, or wheelchairs (157) • Provide discounts for patients with disability for taxi rides (if poor transit options) or bus/train passes
Empowering contributions and engagement of persons with disability in society	• Promote representation and accommodation of persons with disability in the workplace and in decision-making positions • Make public spaces inviting for such individuals through clear signage and symbols • Promote openness of institutions like libraries or theaters to help patients plan and enjoy visits (157)
Development of treatments and technologies to mitigate consequences of disability	• Invest in research and development of adaptive technology and long-term restorative therapies • Invest in the widespread adoption of efficacious technology and treatments

and ability of the patient to thrive post-stroke. For example, negative attitudes of employers and colleagues (reflecting prevailing societal attitudes) hamper return-to-work post-stroke (159). The experiences of patients of negative public attitudes toward their need for assistance or accommodations can be especially detrimental to their progress (157).

These high-level factors are clearly beyond the control of an individual physician or stroke team. However, the potential impact of addressing such factors through collaborative efforts (**Table 4**) between policymakers, governments, or private/public partnerships is substantial. In a world of competing demands on resources, this calls for stroke systems to identify and promote highly motivated and visionary health professionals to leadership positions in public and political spheres where they may champion these areas of reform.

DISCUSSION

Endovascular therapy is one of the most efficacious therapies in modern medicine. Current evidence from 2-year follow-up of EVT trials and 5-year follow-up from longitudinal studies of ischemic stroke indicates that the 3-month group-level benefits of EVT will likely be sustained at 5 years, further supporting its long-term cost-effectiveness. In this paper, we have examined the various factors that can potentially modify the long-term outcomes of patients after ischemic stroke, drawing on the best available evidence in the literature. The adoption of regular audits and feedback as quality improvement strategies could help healthcare systems optimize these various aspects of patient care and follow-up across the continuum of stroke care in the months and years after stroke.

Our review has some important limitations. Many of the factors discussed here—such as secondary prevention, rehabilitation, and social reintegration strategies—have not been systematically examined in the EVT or LVO population. In the absence of better data, it is reasonable to extrapolate relevant insights from the general ischemic stroke population to help us optimize longer-term post-EVT care and outcomes in our current practice. Nevertheless, there remains a need for high-quality evidence from prospective cohort studies and longer-term follow-up of EVT trials or LVO cohorts to further validate the benefits of the various action items suggested in our paper. In addition, many of the insights about post-stroke care discussed in this paper have come from observational studies and are yet to be validated in randomized controlled trials. That being said, it is neither practical nor advisable to randomize patients into control arms for several non-pharmacological aspects like physician follow-up or societal accommodations for disability, so it is likely that we will have to continue relying on best-available observational data in many such cases. It is also important to note that various aspects of post-stroke care may not be generalizable to different healthcare systems owing to differences in care delivery and available resources.

When treating individual patients, stroke teams may perceive a loss of control over the long-term outcome of the patients as more time elapses post-stroke. Indeed, in the longtime horizon from 3 months to 5 years, several factors at the medical, psychosocioeconomic, and larger societal–environmental levels could erode EVT benefits. However, several factors at each level can also be leveraged to preserve or magnify treatment benefits, with opportunities to share responsibility with widening circles of care around the patient, involving primary care physicians, family/social supports, and policymakers. The race from stroke onset to EVT is a sprint, but the maintenance of EVT benefits from 3 months to 5 years post-stroke is a marathon.

AUTHOR CONTRIBUTIONS

AG co-conceived the paper, performed literature review, interpreted results, and wrote the first draft of the manuscript. JO and MM co-conceived the paper, performed literature review, interpreted results, and revised the manuscript. WZ, YR, and CM interpreted results and critically revised the manuscript. MG co-conceived the paper, provided supervision, and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.713738/full#supplementary-material

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Added Value of Rescue Devices in Intra-Arterial Thrombectomy: When Should We Apply Them?

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Introduction: Recent trials have demonstrated the superior efficacy of mechanical thrombectomy over other medical treatments for acute ischemic stroke; however, not every large vessel occlusion (LVO) can be recanalized using a single thrombectomy device. Rescue devices were proved to increase the reperfusion rate, but the efficacy is unclear.

Objective: In this retrospective study, we evaluated the efficacy of rescue therapy in different locations of LVO.

Methods: We analyzed the outcomes of mechanical thrombectomy from a prospective registry of consecutive 82 patients in Taipei Medical University Hospital. The reperfusion rate and the functional outcome were compared in patients who received first-line therapy only and patients who need rescue therapy.

Results: An 84.1% reperfusion rate was achieved in our cohort. We applied first-line stent retriever (SR) treatment in 6 patients, among which 4 (66.6%) achieved successful reperfusion. We applied a direct-aspiration first-pass technique (ADAPT) as the first-line treatment in 76 patients, among which 46 (60.5%) achieved successful reperfusion. Successful reperfusion could not be achieved in 30 cases (39.5%); therefore, we applied a second-line rescue SR for 28 patients, and reperfusion was established in 18 (64.3%) of them. These results revealed that the LVO in anterior circulation has a higher chance to respond to SR rescue therapy than posterior circulation lesions (68 vs. 33.3%, $P < 0.001$). Patients who received only first-line therapy exhibited significantly better functional outcomes than those who were also treated with rescue SR therapy (41.2 vs. 16.7%, $P = 0.001$). In addition, patients with LVO in the anterior circulation were found to have a higher probability of achieving functional independence than patients with posterior circulation lesions (10.7 vs. 0.0%, $P < 0.001$). The adjusted multivariate analysis revealed that successful reperfusion and treatment type (first-line or rescue therapy) were significantly related to a modified Rankin Scale (mRS) score at 90 days.

Conclusion: This study reveals that rescue SR therapy improves the reperfusion rate. Patients who require rescue SR therapy have a lower likelihood of functional independence. LVO in the anterior circulation responds better to rescue SR therapy and results in better functional outcomes than posterior circulation lesions.

Keywords: intra-arterial thrombectomy, stroke, rescue, thrombosuction, stent retreiver, large vessel occlusion

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INTRODUCTION

Stroke is one of the leading causes of death and a primary source of disability among older adults worldwide. Ischemic stroke accounts for 80–85% of all strokes, with the anterior circulation stroke being the most frequent one. Intravenous alteplase (IV-tPA) administration is a first-line reperfusion therapy with proven efficacy (1); however, this therapy must be administered within 4.5 h of symptom onset. This short therapeutic time window is one of the most well-recognized limitations of this treatment. In addition, IV-tPA appears to be much less effective at recanalizing occlusions of the major intracranial arteries, but more than one-third of acute anterior circulation strokes are caused by major intracranial arterial occlusions (2). Recent trials and meta-analyses have demonstrated the greater efficacy of mechanical thrombectomy compared with other medical treatments for patients with acute ischemic stroke, with the balance of similar rates of adverse events (3–11). Stent retrievers (SRs), such as the Solitaire (Covidien, Plymouth, MN, USA) and Trevo (Stryker, Kalamazoo, MI, USA) retrievers, are predominantly employed in most trials. A direct-aspiration first-pass technique (ADAPT) is proposed to be a faster thrombectomy technique than the SR technique. Recent trials have demonstrated that ADAPT and the SR technique provide equivalent efficacy in terms of reperfusion rate and functional independence (12, 13); however, none of the aforementioned techniques can guarantee successful reperfusion. According to a meta-analysis comparing ADAPT with the SR technique, the reperfusion [obtaining a thrombolysis in cerebral infraction (TICI) score of 2b or 3] rate can be increased with second-line rescue devices (14); however, it is not clear whether the functional independence rate can also be increased by rescue therapy. In addition, whether the lesion location can affect the efficacy of rescue therapy remains unknown.

The present study investigated the efficacy of first-line and rescue mechanical thrombectomy therapies among patients with acute ischemic stroke. The relationships among the type of procedure, the time required for the procedure, the success of reperfusion, neurological outcome, and lesion location were analyzed.

MATERIALS AND METHODS

Study Procedures

Data of the study cohort were retrospectively collected from a prospective registry of all consecutive patients who were referred for endovascular therapy to Taipei Medical University Hospital between August 2016 and December 2020. The institutional review board approved the use of the data. Patients with acute stroke treated with intra-arterial thrombectomy were recruited. Patients with incomplete clinical or radiographic data were excluded. Demographic variables, National Institutes of Health Stroke Scale (NIHSS) score at baseline, the timing of baseline, procedure time, and detailed procedural information were obtained from medical charts and intervention reports, filed by trained medical researchers and interventionists.

Criteria for thrombectomy eligibility comprised acute ischemic stroke from large vessel occlusion (LVO) within 16 h of symptom onset, an Alberta Stroke Program Early CT Score of >6, including if they had awakened from sleep with symptoms of a stroke. Perfusion imaging was performed for every patient whose time that they had last been well-known was longer than 6 h. Patients were eligible if they had an initial infarct volume (ischemic core) of <70 ml, a ratio of ischemic tissue to initial infarct volume of 1.8 or more, and an absolute volume of potentially reversible ischemia (penumbra) of 15 ml or more (15). The volume of the ischemic core and penumbral regions was estimated using CT perfusion scans and RAPID software (iSchemaView), an automated image post processing system. Penumbra size was estimated from the volume of the tissue to which the arrival of an administered contrast medium [time to a maximum of the residue function (Tmax)] exceeding 6 s (16).

All patients with an internal carotid artery or middle cerebral artery (M1, M2) occlusion and who fulfilled the inclusion and none of the exclusion criteria were eligible for intra-arterial thrombectomy. Patients with vertebral artery or basilar artery occlusion who presented symptoms within 16 h were also included without being required to meet the abovementioned perfusion scan criterion.

Interventions

Patients with acute ischemic stroke were treated according to the American Heart Association/American Stroke Association guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment (15, 17). According to the guidelines, patients eligible for IV-tPA therapy were treated with it before undergoing the endovascular procedure. After LVO confirmation, patients were transported to an angiosuite equipped with a Siemens Artis zee biplane system (Siemens Healthcare, Erlangen, Germany). The procedure was performed under either local or general anesthesia. The selection of anesthesia type was left to the discretion of the attending interventional neuroradiologist and anesthesiologist. The brain vessels were accessed with a 6-F/90-cm guiding sheath (088 Neuron Max, Penumbra Inc., Alameda, CA, USA or Mach1, Boston Scientific, Marlborough, MA, USA). For the first-line ADAPT treatment, an aspiration catheter was navigated into direct contact with the thrombus. The Excelsior XT-27 microcatheter (Stryker Neurovascular, Fremont, CA, USA) over several types of 0.014 inch microwires and an ACE64 or ACE68 Penumbra aspiration system (Penumbra Inc., Alameda, CA, USA) with the original suction pump were employed for this technique. If the ADAPT technique failed to reach the occlusion site or achieve successful reperfusion (TICI 2b or 3) after at least three trials or passes, we applied an SR as the rescue therapy. For the rescue SR treatment, the microcatheter and the SR were navigated through the aspiration catheter used in the ADAPT technique. Continuous aspiration was performed while we retrieved the clots using manual aspiration through a 60 cc syringe attached to the 8Fr guiding catheter and penumbra aspiration tubing through the distal aspiration catheter. A Trevo XP ProVue (Stryker Neurovascular, Fremont, CA, USA) or a Solitaire SR (Medtronic, Dublin, Ireland) was employed in the

first-line of rescue SR treatments. In cases of tight residual stenosis, a combination of procedures including extracranial stent implantation and angioplasty was used as necessary.

Outcome Measures

A modified Rankin Scale (mRS) score for evaluating functional outcome at 90 days was assessed by certified neurologists. Favorable clinical outcome was defined as mRS score $\leq$ 2. Successful reperfusion was defined as a modified TICI score of 2b or 3 on digital subtraction angiography at the end of the procedure. All periprocedural and post procedural complications, including conversion from first-line devices to rescue therapy, were recorded in intervention and patient records. Symptomatic intracranial hemorrhage was defined as parenchymal hemorrhage at any site in the brain revealed by the CT scan, being compatible with documented neurological deterioration. Asymptomatic intracranial hemorrhage was defined as parenchymal hemorrhage at any brain site without deteriorated neurological function.

Statistical Analysis

Descriptive statistics are expressed as means with SD or median with 25–75%. All data were tested with the D'Agostino-Pearson test to check whether samples were normally distributed or not. Non-parametric tests were applied for data that are not normally distributed. Multiple groups (first-line therapy only, successful and failure rescue SR therapy) were compared using the Kruskal-Wallis test and Dunn's multiple comparison test. Binary comparisons utilized chi-square or binomial tests for categorical variables, and the Mann-Whitney *U* test for continuous variables. Multivariate linear regression was performed to evaluate the relationship between mRS score at 90 days with predefined outcome prognosticators: successful reperfusion of not, lesion location (anterior or posterior LVO), and treatment type (first-line only or rescue therapy), adjusting for age, stroke severity (NIHSS) at baseline, symptom to reperfusion time, and IV-tPA therapy or not. Statistical analyses were performed using Prism (release 8.0, GraphPad Software Inc., La Jolla, CA, USA) and StatPlus: mac Pro (AnalystSoft Inc., Walnut, CA, USA). A $p = 0.05$ was considered statistically significant.

RESULTS

Basic Demographics

Our cohort of 82 patients comprised 51 men and 31 women (**Table 1**). Their mean age was 72.1 $\pm$ 11.57 (33–93) years, and their initial median NIHSS score at presentation was 16 (12.0–20.0). In addition, 30.5% of them had atherosclerosis, and 6% of them had arterial dissection. The average time to puncture was 375.1 $\pm$ 241 min, and the overall reperfusion rate was 84.1%.

Detailed Thrombectomy Techniques

We applied first-line SR treatment in six cases, four of which (66.6%) resulted in successful reperfusion (**Figure 1**). We were unable to reach the occlusion site in two cases because of the tortuosity of the cervical carotid artery. We applied first-line ADAPT in 76 cases, 46 of which (60.5%) resulted in successful reperfusion. In 30 patients (39.5%), a TICI score of 2b or 3 was not achieved; therefore, we applied the second-line rescue SR treatment in 28, and reperfusion was achieved in 18 (64.3%) of these cases. We did not implement rescue therapy in the remaining two cases, because their vital signs were not stable and the time since symptom onset already exceeded 8 h after the failure of the first-line treatment. The overall reperfusion rate in the first-line ADAPT group and rescue SR group was 84.2% (53 of 76), which was higher than that in the first-line SR group. We have combined the first-line SR therapy and first-line ADAPT therapy into the first-line therapy only group for the following statistical calculation since there are only six cases in the first-line SR group.

Functional Outcome at 90 Days

The median mRS score was 3.0 (1.0–4.25) in patients that received first-line therapy only, 3.0 (3.0–5.0) in patients that received successful rescue SR therapy, and 6.0 (4.75–6.0) in patients who failed rescue SR therapy. The mRS scores of patients with failed rescue SR therapy were significantly different from those of patients who received first-line only therapy or successful SR therapy ($P = 0.001$ and 0.04, respectively, Dunn's multiple comparison test; **Figure 2**). The overall functional independence rate is 29.2% in our cohort.

With regard to favorable clinical outcome rate in each group (mRS score of 0–2), 38.8% (21 out of 54) of patients receiving first-line therapy only and 10.7% (three out of 28) of patients in the rescue SR therapy group demonstrated functional independence, with an odds ratio of 5.3 (95% CI, 1.4–18.0, $P = 0.001$, **Figure 3**). The proportion of patients who achieved functional independence after successful reperfusion with first-line therapy only was 41.2%; this proportion was 16.7% for rescue SR therapy, with an odds ratio of 3.5 (95% CI, 0.93–12.33, $P = 0.06$).

Procedure Time

The mean puncture to reperfusion time (puncture to reperfusion) for patients who received rescue SR therapy was 78.0 $\pm$ 39.6 min, which was longer than that for patients receiving first-line therapy only (48.6 $\pm$ 33.2 min, $P = 0.01$). The symptom to reperfusion time was significantly longer in the rescue SR group (481.9 $\pm$ 290.4 min) than in the first-line therapy only group (334.2 $\pm$ 208.3 min, $P = 0.02$).

We performed multivariate linear regression to evaluate the relationship between mRS score at 90 days with the predefined outcome prognosticators: successful reperfusion of not, lesion location (anterior or posterior LVO), and treatment type (first-line only or rescue therapy), adjusting for age, stroke severity (NIHSS) at baseline, symptom to reperfusion time, and IV-tPA therapy or not. The result revealed that only successful reperfusion ($p = 0.03$, odds ratio:1.16, 95% CI, 0.09–2.24) and treatment type ($p = 0.04$, OR: 0.97, 95% CI 0.02–1.94) were significantly related to mRS score at 90 days.

Lesion Location in Rescue SR Therapy

For the 28 patients who received rescue SR therapy after failure of the first-line ADAPT therapy, the successful reperfusion rate

TABLE 1 | Patient demographics with clinical and radiographic outcomes.

Clinical Demographics and Disease Outcomes			
Data set	**1st line therapy only (*N* = 54)**	**Rescue SR therapy (*N* = 28)**	***P* value**
Age	72.2 ± 10.8	71.9 ± 13.2	0.9
Gender (M:F)	34:20	17:11	0.7
Baseline NIHSS	15.8 ± 5.9	18.2 ± 7.8	0.2
Intravenous alteplase use	25.9% (17/54)	14.3% (4/28)	0.09
1st line techniques (SR:ADAPT)	6:48	0:28	
Atherosclerosis	25.9% (14/54)	38.3% (11/28)	0.5
Tortuous cervical carotid artery	24.1% (13/54)	28.6% (8/28)	0.7
Arterial dissection	1.8% (1/54)	14.3% (4/28)	0.03
Puncture to reperfusion time*	48.6 ± 33.2	78.0 ± 39.6	0.01
Symptom to reperfusion time*	334.2 ± 208.3	481.9 ± 290.4	0.02
Clinical outcome			
mRS median	3.0 (1.0–4.25)	4.5 (3.0–6.0)	<0.01
mRS 0–2 (%)	38.8% (21/54)	10.7% (3/28)	0.01
Reperfusion rate (TICI 2b &3)	60.5 or 94.4%**	64.3%	
Complication			
Mortality	13.1% (7/54)	21.4% (6/28)	0.32
sICH	14.8% (8/54)	10.7% (3/28)	0.6

NIHSS, National Institutes of Health Stroke Scale; SR, stent-retriever; ADAPT, a direct aspiration first-pass technique: mRS, modified Rankin Scale; TICI, thrombolysis in cerebral infarction. sICH, symptomatic intracranial hemorrhage.

**Puncture to reperfusion time and event to reperfusion time do not include cases fail to be recanalized. **Only include cases who did not receive further rescue therapy.*

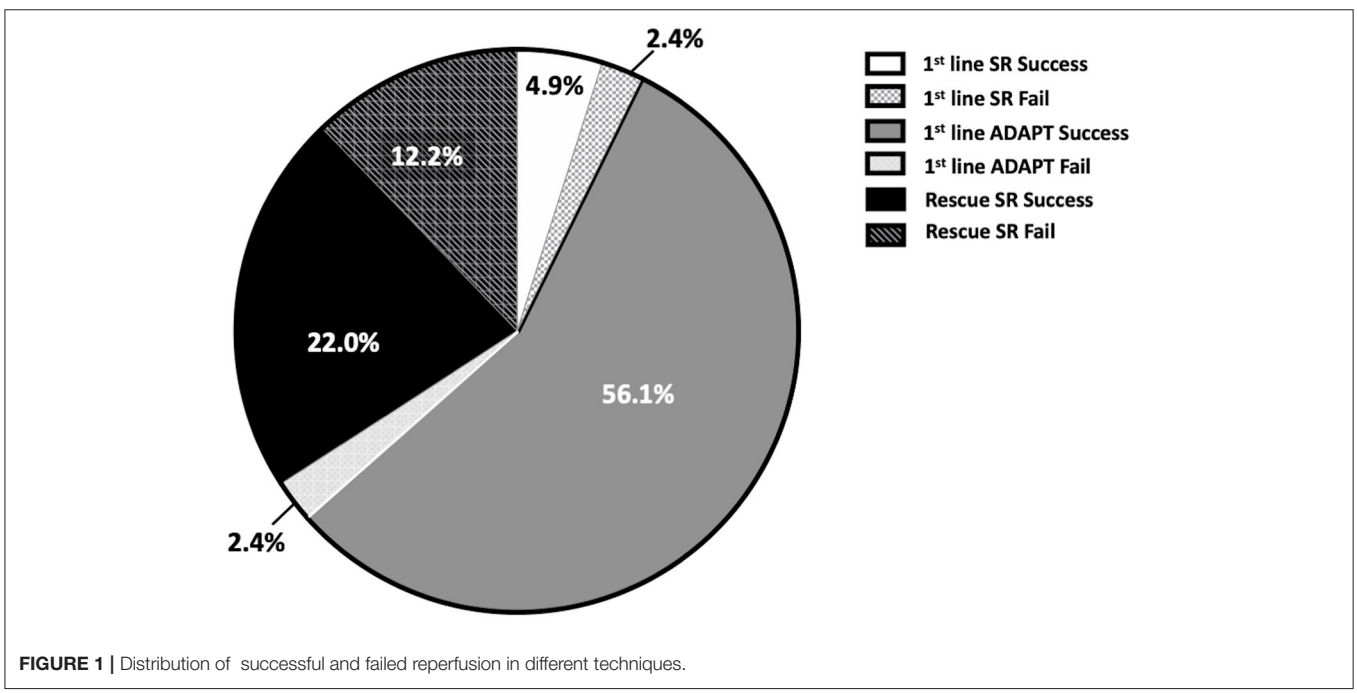

FIGURE 1 | Distribution of successful and failed reperfusion in different techniques.

was 64.3%. These results also revealed that LVO in anterior circulation (internal carotid artery and middle cerebral artery) has a higher chance to be recanalized by rescue SR therapy than posterior circulation lesion (68.0 vs. 33.3%, $p < 0.001$, Binomial test). It is also found that cases with anterior circulation lesions have a higher chance to have functional independence than cases with posterior circulation lesions (10.7 vs. 0.0%, $p < 0.001$) through rescue SR therapy.

Complications and Mortality

The proportion of patients experiencing symptomatic intracranial hemorrhage was 10.7% (3 of 28) in the rescue

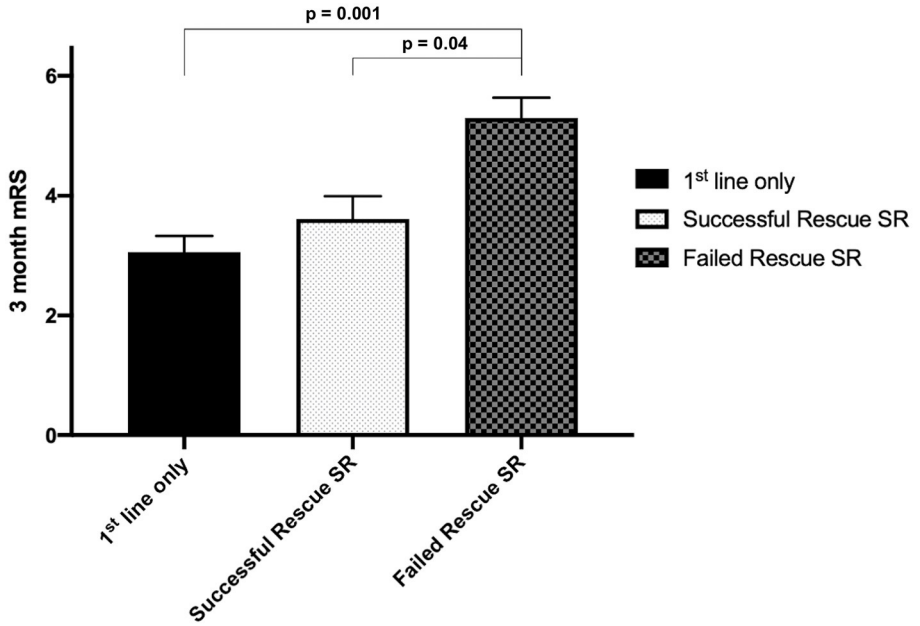

FIGURE 2 | Mean Modified Rankin Scale (mRS) scores at 90 days in different groups. The mean mRS is higher in the failed rescue SR group. A significant difference is noted between patients receiving failed rescue SR therapy and those receiving first-line therapy only.

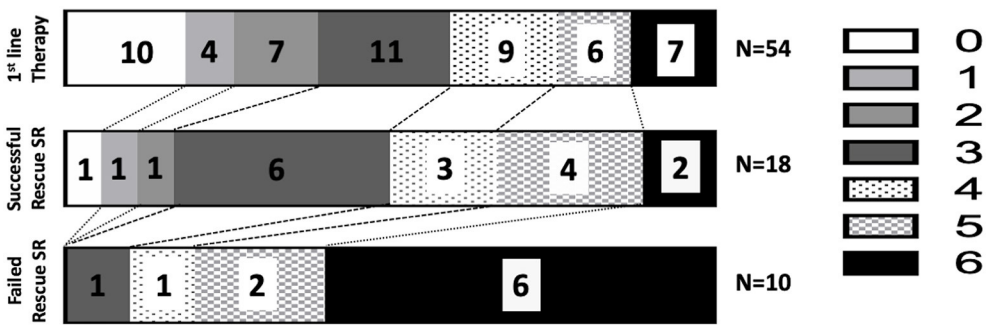

FIGURE 3 | Modified Rankin Scale scores at 90 days in different groups. The functional independence rates (mRS score: 0–2) are 38.8% in the first-line ADAPT group, 16.7% in the successful rescue SR group, and 0% in the failed rescue SR group.

SR therapy group, whereas 14.8% (8 of 54) in the first-line therapy group ($P = 0.6$). The mortality rate was 21.4% (6 of 28) in the rescue SR therapy group, whereas 13.1% (7 out of 40) in the first-line therapy only group ($P = 0.32$). No significant differences were found between the two groups.

DISCUSSION

In this retrospective observational study, we found a significantly higher likelihood of achieving a good functional outcome among patients who only received a first-line SR or ADAPT therapy than those who also received rescue SR therapy (38.8 vs. 10.7%). The adjusted multivariate analyses revealed that successful reperfusion and treatment type were significantly related to mRS score at 90 days. Patients with occlusion in anterior circulation have a better response to rescue SR therapy (68.0 vs. 33.3% reperfusion rate) and better functional outcome (10.7 vs. 0.0% functional independence rate) after rescue SR therapy compared with those with LVOs in the posterior circulation.

In previous reports (14, 18), ADAPT has been demonstrated to recanalize occlusions more quickly than the SR method. Because longer time in occlusion has been shown to put more quantities of tissue at the risk of becoming infarct core (19), we applied the ADAPT technique as first-line therapy in most cases. In this study, the mean procedure time and event to reperfusion time for patients who received rescue SR therapy were significantly longer than those receiving only first-line therapy, suggesting that patients required rescue SR therapy experience, longer tissue ischemia (512.3 min) than those received only first-line therapy (351.5 min). We hypothesize that prolonged tissue ischemia may be a cause of poor functional

outcomes in cases requiring rescue therapy because a meta-analysis of recent clinical trials suggested that earlier reperfusion may result in better functional outcomes (8). However, variation still exists among individuals in the presence of native collaterals; the event to reperfusion time may not be the only indicator of the degree of tissue ischemia. It has been proposed that multiple passes of thrombectomy devices are associated with a higher risk for distal embolization and vessel injury (20). Several reports proved that first-pass reperfusion was associated with a more favorable clinical outcome than multiple passes, irrespective of different thrombectomy techniques (21–23). Therefore, more thrombectomy maneuvers may be one of the causes of worse outcomes in the rescue SR group. In addition, the rescue SR group has a higher proportion of intracranial atherosclerosis disease than the first-line therapy group (38.3 vs. 25.9%). It has been shown that intracranial stenosis is associated with more thrombectomy passes and worse disease outcomes (24, 25). Therefore, the necessity for rescue therapy may be an epiphenomenon, and better functional outcomes in patients who received first-line therapy only could result from multiple underlying causes, ranging from treatment effects to differing stroke pathologies. The application of IV-tPA is another important issue. More patients received IV-tPA treatment in the first-line therapy only group than those in the rescue therapy group (25.9 vs. 14.3%). Though previous reports have proved that alteplase treatment had no impact on the endovascular thrombectomy result (3–7, 26), it can be a confounding factor in this study. More research is required to further clarify these issues.

The functional independence rate in our cohort was not as high as the results in trials that applied the ADAPT technique (12, 13). The less favorable outcomes can be explained by three factors. First, we included patients who presented symptoms for longer than 6 h; such patients were not eligible for the ASTER and COMPASS trials. Although the inclusion criteria we applied were in accordance with those in the DIFFUSE 3 trial (11), many of the patients had larger infarct cores (>50 ml) than those in DIFFUSE 3. Second, we included patients with occlusion in the posterior circulation (vertebral or basilar arteries). Though many studies have demonstrated the efficacy of intra-arterial thrombectomy in the posterior circulation (27, 28), its benefit is still uncertain, even for patients with symptom onset within 6 h (15). We included 10 patients with posterior circulation LVO in our cohort. The successful reperfusion rate in this group was 80.0%; however, the functional independence rate at 90 days was only 20.0%. Third, a balloon guide catheter was not employed in this procedure. Regardless of treatment modality, it has been proved that the application of a balloon guide catheter in intra-arterial thrombectomy can improve the reperfusion rate and the first-pass success rate. In addition, it shortens the procedure time and leads to more favorable outcomes (29, 30). The major reason we did not use a balloon guide catheter is that the device is not reimbursed by the health insurance system in Taiwan.

Patients who received first-line SR or the ADAPT therapy only were a prognosticator detected in our cohort. Many other predictive factors of good functional outcome have been proposed in previous studies, including age, successful revascularization, parenchymal hemorrhage, baseline NIHSS score, anterior choroidal artery infarction, stroke subtype (intracranial atherosclerotic disease or embolism), posterior circulation Acute Stroke Prognosis Early CT Score, diffusion-weighted imaging lesion volume, glucose on admission, and hypersensitive C-reactive protein (31–35). The difference in reported factors may result from the heterogeneity of the study designs and patient demographics. More evidence and research are necessary to provide more accurate prognostic factors for intra-arterial thrombectomy outcomes.

Previous reports have shown that the devices required for aspiration techniques cost from US$4541 to US$5001 less than those for the SR technique (13, 14). ADAPT is considered to be a more cost-effective approach than SR while offering a similar reperfusion rate. When we applied rescue SR therapy after the first-line ADAPT treatment, the mean additional cost of different SRs was approximately US$6878, in the practice environment in the United States (13). Although the rescue SR therapy in this study provided a 64.3% successful reperfusion rate, only 10.7% of the patients recovered to be functionally independent after 3 months. These results also revealed that anterior circulation lesions had better functional outcomes after rescue SR therapy compared with posterior circulation lesions (10.0 vs. 0.0%). Because the choice of thrombectomy device and the decision to perform rescue therapy are both issues concerning value-based care (36), these results suggest uncertainty regarding whether applying rescue SR therapy for LVO in the posterior circulation is rational when the first-line ADAPT treatment cannot restore perfusion. More studies and evidence are warranted to address this issue.

LIMITATIONS

This study has several limitations. First, this is a retrospective observational study with unbalanced patient numbers in the first-line SR and ADAPT groups. Second, SR therapy was the only procedure applied as rescue therapy; other treatments, such as intra-arterial recombinant tissue plasminogen activator, intra-arterial glycoprotein IIb/IIIa inhibitors, and intracranial stenting, were not used in our cohort. Third, we only performed local aspiration along with SR technique in rescue SR therapy; other techniques, such as CASPER (37) and SRLA (38), were not applied in our cohort. Finally, there were only 82 cases in this study, including 10 cases of LVO in the posterior circulation. Limited number in each subgroup is a constrain on the generalizability of result. Further study with a larger cohort is needed to validate this issue.

CONCLUSION

This study revealed that patients with acute LVO stroke who are treated with only first-line SR or ADAPT therapy have significantly better functional outcomes than patients undergoing rescue SR therapy. Patients with occlusion in the anterior circulation have better responses to rescue SR therapy and better functional outcomes compared with patients with LVO in the posterior circulation. More research is required to prove the cost-effectiveness of rescue therapy in different subgroups of LVO patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by TMU Joint Institutional Review Board No: N201804066. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

C-FN, S-JC, and KH contributed to conception and design of the study. C-YC and KH organized the database. KH performed the statistical analysis. KH and T-HY wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Hyperattenuated Lesions on Immediate Non-contrast CT After Endovascular Therapy Predict Intracranial Hemorrhage in Patients With Acute Ischemic Stroke: A Retrospective Propensity Matched Study

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Background and Purpose: This study aimed to analyze the association between hyperattenuated lesions (HALs) and postoperative intracranial hemorrhage (IH) and predict perioperative IH through quantitative analysis of HALs in acute ischemic stroke (AIS) with anterior large vessel occlusion (LVO) after endovascular therapy (ET).

Materials and Methods: This retrospective, propensity-matched study enrolled AIS who received ET from a single-center registry study between August 2017 and May 2020. The enrolled patients were divided into two groups: IH and non-IH, by follow-up postoperative CT. The occurrences of HALs on immediate CT after ET were also recorded. The association between IH and HALs after propensity score matching (PSM) was determined by binary logistic regression models. The receiver operating characteristic (ROC) curve was used to determine the predictive value of the highest CT Hounsfield units (HU) value on immediate CT.

Results: Initially, 1,418 patients who underwent digital subtraction angiography were reviewed and 114 AIS patients with immediate postoperative CT and follow-up CT after ET were enrolled. Forty-nine out of the 114 patients developed IH after therapy. After PSM analysis, patients with IH were more likely to have HALs on immediate CT (Odds Ratio, OR 11.9, $P = 0.002$, and 95% CI: 2.485–57.284). For 80 patients with HALs, ROC analysis of the highest CT value in the HALs territory showed that the cut-off value was 97 HU, the sensitivity was 70.21%, and the specificity was 81.82%.

Conclusions: Patients with HALs after ET are more likely to have perioperative IH. The highest CT value in the HALs area might be used to predict IH.

Keywords: acute stroke, thrombectomy, NCCT, hemorrhage, hyperattenuated lesions

INTRODUCTION

Endovascular interventional therapy, especially mechanical thrombectomy (MT), has extended the treatment window of acute ischemic stroke (AIS) to 16–24 h (1, 2). MT has become the standard treatment for AIS patients with large vessel occlusion (LVO) (3). Cerebral hemorrhage after interventional therapy is a serious complication (4). Early detection of hemorrhagic transformation after interventional therapy can guide blood pressure control (5), sedative use, and antiplatelet therapy (6). In particular, it is important to evaluate the risk of hemorrhage or hemorrhagic transformation after infarction in patients with mTICI $\leq$ 2b and patients with emergency stent implantation and balloon dilatation who need antiplatelet to maintain blood flow. Postoperative non-contrast computed tomography (NCCT)/dual-source CT is used as a routine examination after thrombectomy to distinguish whether there is contrast agent extravasation or hemorrhage (7). Dual-energy CT has superior performance in terms of differentiating contrast agent extravasation from hemorrhage. However, NCCT scans are obtained in centers where dual energy scans are not available. At present, some retrospective cohort studies suggest that the immediate postoperative hyperdensity sign is related to the patient's cerebral hemorrhage (8). However, there is no established quantitative method on postoperative NCCT to predict perioperative intracranial hemorrhage (IH) after endovascular interventional therapy. The purpose of this study is to investigate the association between the HALs and IH after therapy and to perform a quantitative analysis of hyperattenuated lesion (HALs) territory on immediate CT to predict IH after interventional therapy to provide warning of early use of antiplatelet drugs and help perioperative patient management.

MATERIALS AND METHODS

Patients

The patients in this study came from A New Parameter Derived from DSA to Evaluate Anterior Cerebral Perfusion (NCT03607565) of the Department of Neurology of the Xi'an No.3 Hospital and reviewed by the Department of Neurology between August 2017 and May 2020. The inclusion criteria of this study were patients with: (1) cerebral infarction caused by acute intracranial and extracranial anterior circulation large artery occlusion (ICA, MCA M1-M2 segment); (2) endovascular interventional therapy (thrombus aspiration, mechanical thrombus removal, emergency balloon dilation, and emergency stent implantation) was performed; (3) Immediate head CT were performed after intra-arterial therapy; (4) Follow-up CT was performed 2–7 days after endovascular treatment. The exclusion criteria were patients with (1) Head CT with hemorrhagic signs on admission; (2) Vertebral-basal artery infarction; (3) Cerebral infarction caused by blockage of the venous system; (4) Arterial thrombolytic therapy; (5) Incomplete head CT follow-up.

Mechanical thrombectomy and balloon/stenting are different procedures but they both fall into the endovascular treatment (ET) category that removes blood clots. The main mechanism of postoperative hemorrhage transformation is the destruction of the blood-brain barrier. This study is focused on the management of postoperative hemorrhage through the quantitative analysis of HALs on immediate CT but not specific procedures. Therefore, the two groups of patients were not distinguished. This retrospective study was approved by the local Institutional Review Board at the Xi'an No.3 Hospital (No. SYXSLL-2018-010), and the requirement for informed patient consent was waived due to the retrospective nature of this study.

Data Collection

We used the following baseline characteristics of patients from the database: age, sex, previous stroke, side of stroke, initial stroke severity assessed by the National Institutes of Health Stroke Scale (NIHSS), initial CT examination evaluated by Alberta Stroke Program Early CT Score (CT-ASPECTS), intravenous alteplase, hypertension, diabetes mellitus, atrial fibrillation, smoking, tirofiban, thrombolysis in cerebral infarction (TICI), and operational methods.

CT Imaging and HALs Measurement

CT image scanning was completed through two items of equipment (SOMATOM Definition Flash SIEMENS and Optima CT 680 GE) randomly and then uploaded to the picture archiving and communication systems (PACS). The first head CT was performed immediately after endovascular interventional therapy and the time from the acquisition of the last image of the DSA treatment to the immediate head CT was 38 $\pm$ 15 min. The highest CT value of the HALs territory was recorded. The follow-up CT scan was routinely performed 24 h after endovascular treatment, and: (1) If the patient had no IH on 24 h follow-up CT, the head CT should be terminated. (2) If the patient had IH on the 24 h follow-up CT, the head CT was scanned dynamically from 1–7 days after surgery until the IH became stable. The time from the acquisition of the last image of the DSA treatment to the follow-up head CT was 42 $\pm$ 25 h.

HALs are observed on immediate CT after interventional therapy, especially in the area of cerebral infarction. The commercial software that comes with the PACS system was used to draw the areas of high-density signs. Bone structure, choroid, and pineal gland were avoided. The highest CT value in the selected volume represents the most severely damaged area of the blood-brain barrier.

All head CT data were obtained by neuroradiologists with more than 5 years of experience and viewed on PACS. In addition, the IH was confirmed by CT after several follow-ups. Like other neuroimages, all CT images were analyzed separately by a neurologist and a neuroradiologist, and disagreement was resolved by reaching a consensus. If no consensus could be reached, another reviewer made the final decision.

Endpoints

The primary outcome was the association between HALs in immediate CT and early perioperative IH. The second outcome was a receiver operating characteristic (ROC) curve analysis of the highest CT value in HALs territory in patients with HALs to help predict the perioperative IH. Total IH was defined according

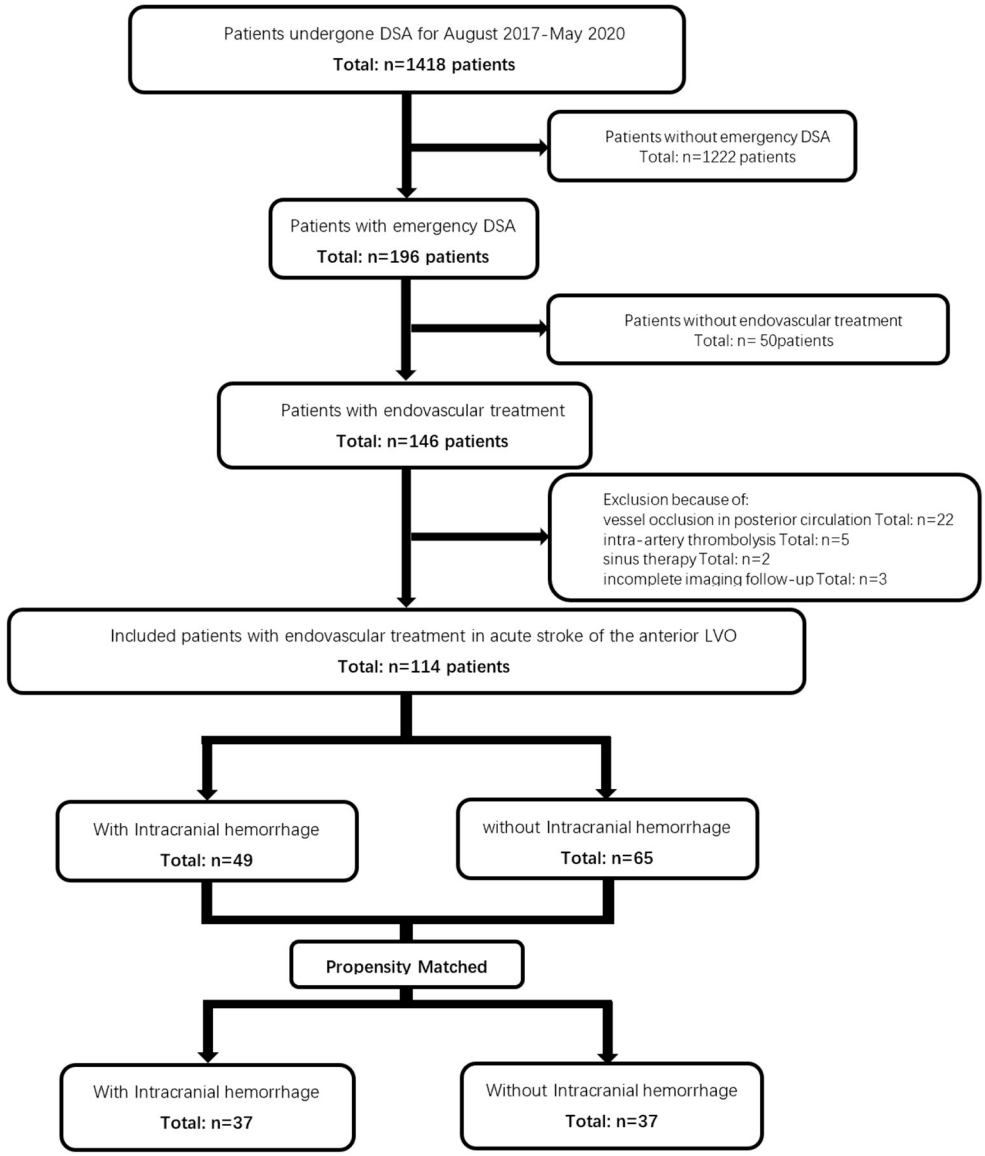

FIGURE 1 | Initially, 1,418 eligible patients were identified from a database. Of those 1,418 patients, 114 patients were enrolled in this study. Among them, 49 patients had an intracranial hemorrhage on follow-up CT while 65 patients did not. In total, 37 matched pairs were identified after the propensity match.

to the European Cooperative Acute Stroke Study (ECASS)II trial (9).

Statistical Analysis

All enrolled patients were divided into two groups: IH and non-IH (control group) groups by follow-up CT after endovascular interventional therapy. Continuous variables were expressed as the mean ± standard deviation or median (inter-quartile range, IQR). Single Student's *t*-test was used to detect the differences between the groups. For categorical variables, frequency and percentage were used to summarize data, and between-group comparisons were performed *via* the Chi-square, Continuity Correction, or Fisher's exact test, as appropriate.

A propensity score matched (PSM) study is a quasi-experimental method in which statistical technique is used to construct an artificial control group. PSM is used to focus on the relationship between IH and HALs in patients whose other clinical characteristics are matched to obtain the OR.

PSM analysis was done using a multivariable logistic regression model based on: age, sex, previous stroke, side of stroke, NIHSS, CT-ASPECT, IV alteplase, hypertension, diabetes mellitus, atrial fibrillation, smoking, tirofiban, TICI score, and operation method. Pairs of patients with IH or non-IH were derived using 1:1 greedy nearest neighbor matching within PS score of 0.2. This strategy resulted in 37 matched pairs in each group. The balance of measured variables between groups

TABLE 1 | Baseline clinical characteristics according to IH.

Variables	All patients			Propensity-matched patients		
	IH ($n = 49$)	Non-IH ($n = 65$)	p	IH ($n = 37$)	Non-IH ($n = 37$)	p
Age, mean ± SD, year	68.6 ± 13.3	65.0 ± 13.0	0.151	69.3 ± 13.5	67.0 ± 14.2	0.466
Male, *n* (%)	32 (65.3)	44 (67.7)	0.072	24 (64.9)	23 (62.2)	1.00
Previous stroke, *n* (%)	7 (14.3)	17 (26.2)	0.124	7 (18.9)	8 (21.6)	1.00
Side of stroke (right), *n* (%)	26 (53.1)	27 (41.5)	0.222	19 (51.4)	19 (51.4)	1.00
NIHSS, median (IQR)	16 (12, 20)	13 (8,19)	0.013*	15 (12,19)	16 (8.5, 20)	0.569
CT-ASPECT, mean ± SD	8.92 ± 1.72	9.46 ± 0.92	0.049*	9.22 ± 1.16	9.35 ± 1.09	0.625
IV alteplase, n (%)	19 (38.8)	21 (32.3)	0.474	16 (43.2)	17 (45.9)	1.00
Vascular risk factors, *n* (%)						
Hypertension	26 (53.1)	41 (63.1)	0.282	20 (54.1)	25 (67.6)	0.359
Diabetes mellitus	8 (16.3)	15 (23.1)	0.374	6 (16.2)	8 (21.6)	0.754
Atrial fibrillation	30 (61.2)	17 (26.2)	0.000*	22 (59.5)	17 (45.9)	0.227
Smoking	13 (26.5)	25 (38.5)	0.181	9 (24.3)	10 (27.0)	1.00
Procedural details, *n* (%)						
Balloon/Stenting, *n* (%)	7 (14.3)	30 (46.2)	0.000*	6 (16.2)	8 (21.6)	0.754
Tirofiban	18 (36.7)	35 (53.8)	0.070	14 (37.8)	19 (45.9)	0.629
TICI=2b/3	43 (87.8)	61 (93.8)	0.255	31 (91.9)	34 (91.9)	1.00
HALs	47 (95.9)	33 (50.8)	0.000*	35 (94.6)	22 (59.5)	0.001*

IH, intracranial hemorrhage; SD, standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; CT-ASPECT, Alberta Stroke Program Early CT score; IV, intravenous; TICI, Thrombolysis in Cerebral Infarction.

**A $p < 0.05$ indicates statistical significance.*

after propensity score-matching was analyzed using a paired Student's *t*-test for continuous measures and McNemar test for categorical variables. Differences in the HALs after propensity score-matching were analyzed using binary logistic regression. Odds ratio (OR) was calculated as an estimate of the risk associated with HALs with 95% confidence intervals (CI). All data were analyzed using SPSS 22.0 (IBM, Armonk, NY, USA) with a significance level of $p < 0.05$ (2-sided).

To predict IH from the highest CT value in HALs territory, a ROC curve analysis was used. Optimal cut-off values to predict IH were calculated by Youden index using MedCalc 15.0 software, and $p < 0.05$ (2-sided) was considered statistically significant.

RESULTS

There were 1,418 eligible patients in the database between August 2017 and May 2020. Among the 196 patients with emergency digital subtraction angiography (DSA), 114 met the study-specific inclusion and exclusion criteria and were enrolled for this study. Among the 82 patients excluded, 50 patients were without endovascular therapy, 22 had vessel occlusion in posterior circulation, five had intra-artery thrombolysis, two had sinus therapy, and three had incomplete imaging follow-ups (**Figure 1**).

Of the 114 patients in the study, 66.7% were male and the mean age was 66.5 ± 13.2. A summary of baseline characteristics of both the entire patients and propensity matched patients (except HALs) is shown in **Table 1**. Patients with IH tended to have high NIHSS score ($p = 0.013$), low CT-ASPECT score ($P = 0.049$), atrial fibrillation ($p < 0.001$), thrombectomy ($p < 0.001$), and HALs ($p < 0.001$).

After performing propensity score matching (except HALs), a total of 37 matched pairs (37 patients from the IH group and 37 patients from the non-IH group) were generated. There were no significant differences in baseline, vascular risk factors and procedural details characteristics for the propensity score matched subjects except for HALs (**Table 1**). The IH group was associated with HALs than the non-IH group in the matched patients ($p < 0.001$).

A summary of characteristics of the patients after propensity matched according to the IH or non-IH is shown in **Table 2**. Patients with IH showed association with higher rates of HALs with OR = 11.9, $p = 0.002$, and 95% CI: 2.485–57.284.

Typical of HALs in patients with acute large vessel occlusion in anterior circulation (**Figure 2**). CASE-1 demonstrates extravasation of only iodine (1A–E): A patient with right M1-segment occlusion and successfully recanalized. The highest CT value was 89 HU on immediate CT and HALs vanished on follow-up CT. CASE-2 shows IH after thrombectomy (2A–E): a patient with right proximal internal carotid artery occlusion that was reperfusion after endovascular treatment. The immediate CT shows a large amount of HALs in the right hemisphere and the highest CT value in the HALs territory was 413 HU. Follow-up CT shows hemorrhage in the right cerebral hemisphere on the 3 days. CASE-3 shows minor IH after thrombectomy (3A–E): a patient with distal occlusion of the internal carotid artery and successfully recanalized. The immediate CT shows HALs in the left ganglia with the highest CT value was 362 HU and the IH showed in the follow-up CT was examined at 24 h.

A ROC curve analysis was used to evaluate the highest CT value in HALs territory to predict the IH in the perioperative period (**Figure 3**). An AUC of 0.816 (95% confidence interval [CI] 0.713–0.894, $p < 0.001$) was obtained. A cut-off value of 97 offered the best accuracy in predicting IH with the sensitivity of 70.21%, specificity of 81.82%, positive predictive value (PPV) of 84.62%, and negative predictive value (NPV) of 65.85%.

TABLE 2 | Univariate logistic regression for predicting IH after propensity score matched.

Variables	Univariate			
	B	OR	95%CI	*p*
Age	0.012	1.012	0.979–1.047	0.478
Sex	−0.117	0.890	0.345–2.294	0.890
Previous stroke	−0.167	0.846	0.272–2.633	0.846
Side of stroke (right)	0.000	1.000	0.402–2.489	1.00
NIHSS	0.021	1.021	0.952–1.095	0.561
CT-ASPECT	−0.110	0.896	0.592–1.354	0.601
IV alteplase	−0.109	0.896	0.358–2.243	0.815
Vascular risk factors				
Hypertension	−0.571	0.565	0.220–1.452	0.236
Diabetes mellitus	−0.354	0.702	0.217–2.268	0.554
Atrial fibrillation	0.546	1.725	0.687–4.335	0.246
Smoking	−0.142	0.868	0.305–2.466	0.790
Procedural details				
Balloon/Stenting	−0.354	0.702	0.217–2.268	0.554
Tirofiban	−0.334	0.716	0.283–1.810	0.480
TICI = 2b/3	0.000	1.000	0.188–5.309	1.00
HALs	2.479	11.932	2.485–57.284	0.002*

OR, odds ratio; CI, confident interval; IH, intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale; CT-ASPECT, Alberta Stroke Program Early CT score; IV, intravenous; TICI, Thrombolysis in Cerebral Infarction.

**A $p < 0.05$ indicates statistical significance.*

DISCUSSION

This present study indicates that, first, the appearance of HALs was closely associated with perioperative IH. Overall, after balancing other baseline characteristics, the risk of having IH in patients with HALs on immediate CT after endovascular treatment was 11.9 times that in patients without. Secondly, in patients with HALs, the highest CT value in the HALs territory might be used to predict the occurrence of perioperative IH, with a sensitivity of 70.21% and a specificity of 81.82% and the cut-off value is 97 HU.

In our study, the probability of IH during the perioperative period was 43.0%, and the probability of HALs on immediate CT after interventional therapy was 70.2%. Previous studies have shown that the probability of postoperative IH fluctuates between 28 and 60.3% (8, 10). The probability of HALs after endovascular therapy fluctuates between 20.8 and 60.8% (8, 10–12), The postoperative HALs in this study are higher than in previous studies. The differences might be explained by: (1) The extravasation of the contrast agent after the operation is mostly metabolized from a few hours to 24 h after operation (11, 12). Therefore, the time of the immediate CT after the operation is relatively important. In this study, the interval between the acquisition of the last image of the DSA and immediate CT was 38 ± 15 min. (2) Patients with thrombus removal in the posterior circulation were excluded in this study because the blood-brain barrier and ischemic tolerance were different than those in the anterior circulation (13).

The risk ratio of IH in patients with HALs was 11.9 times that of patients without after PSM. This data is higher than OR 4.5 (95%CI: 1.22–16.37) in previous reports (10). There are two possible reasons. First, in this study, all types of hemorrhage including symptomatic and non-symptomatic were recorded in follow-up CT. Second, for Chinese patients, intracranial atherosclerotic disease (ICAS) is generally more frequently observed as the cause of LVO than that for patients from the Western world (14). Thus, in such patients, it may have a longer procedure duration and more contrast agent usage. In this study, patients who received balloon dilatation or emergency stent implantation accounted for 32.5% (37/114). Thirdly, randomization was used in this study to eliminate unmatched cases. The reason why reperfusion interval was not included in the analysis in this article is that patients with an onset of more than 4.5 h underwent a mismatch assessment of diffusion-weighted imaging (DWI) and arterial spin labeling (ASL) to identify salvageable brain tissue.

To our knowledge, no previous studies have used the highest CT value on immediate NCCT after endovascular treatment to predict perioperative IH. Some studies have shown that the average HU in HALs territory was significantly higher in the IH group identified by immediate dual energy CT than that in the non-IH group after surgery (377.9 ± 385 HU vs. 83.5 ± 37.9 HU; $P < 0.0001$) (15). The cut-off value of the lesion HU for differentiating IH, which was calculated by ROC analysis, was 80 HU; this value had 100% sensitivity, 63.8% specificity. A hand drawn HALs area lacks repeatability and consistency, thus bringing inaccuracy to the average HU value. The highest CT value represents the severity of the blood-brain barrier damage from stroke blood-brain barrier damage mechanism (16). The appearance of HALs on immediate CT after endovascular therapy might attribute to the following reasons: (1) The extravasation of the contrast agent alone. (2) Contrast-agent-mixed red blood cell extravasation. (3) The rupture of the blood vessel caused a large amount of contrast agent and blood to leak out of the arteries. Ischemia and hypoxia lead to rapid metabolism of glucose reserves, resulting in accumulation of lactic acid in brain tissue, and subsequent changes in cell structure, which in turn leads to the release of pro-inflammatory factors, oxidants, and proteolytic enzymes, which ultimately leads to cell damage and rupture of the blood-brain barrier (16). As the destruction of the blood-brain barrier increases, the exudation of the iodine contrast agent increases (17). When the vascular permeability further increases, the red blood cell mixed with iodine contrast agent leaks out of the blood vessel to cause hemorrhage transformation, and the iodine contrast agent is absorbed and metabolized at the 24 h postoperative follow-up CT (11), while the red blood cells are

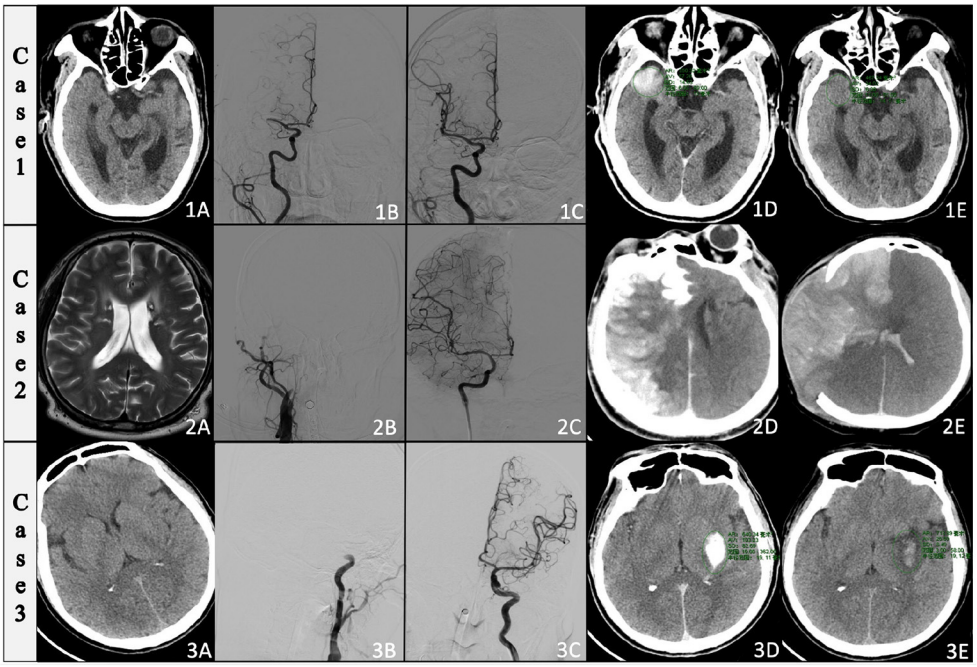

FIGURE 2 | Examples of HALs in patients with acute large vessel occlusion in anterior circulation. CASE-1 demonstrates extravasation of iodine: **(1A)** Head CT before ET, **(1B)** DSA showed right M1-segment occlusion that was successfully recanalized **(1C)**. On immediate CT **(1D)**, there were HALs in the right temporal lobe and the highest CT value was 89 HU. The HALs on follow-up CT performed at 24 h after thrombectomy **(1E)** had vanished. CASE-2 shows IH after thrombectomy: **(2A)** Head CT before ET and DSA demonstrated right proximal internal carotid artery occlusion **(2B)** that was recanalized after endovascular treatment **(2C)**. The immediate CT showed a large amount of HALs in the right hemisphere **(2D)**. We measured the highest CT value in the HALs territory to be 413 HU. The follow-up CT showed hemorrhage in the right cerebral hemisphere on the 3 days **(2E)**. CASE-3 shows minor IH after thrombectomy: **(3A)** Head CT before ET and DSA showed distal occlusion of the internal carotid artery **(3B)** and was successfully recanalized **(3C)**. The immediate CT **(3D)** showed HALs in the left ganglia with the highest CT value of 362 HU. The hemorrhage showed in the follow-up CT **(3E)** was examined at 24 h.

still retained in the brain tissue of the infarct area. Intraoperative blood vessel rupture caused the mixed blood of the iodine contrast agent to leak directly from the blood vessel, resulting in the formation of high-density lesions on immediate CT after the operation, and follow-up CT showed massive hemorrhage. Therefore, we use the highest CT value to predict IH, rather than the averaged CT value, and HALs mostly appear in low-density areas on preoperative CT and high-intensity areas on DWI scans.

At present, the effective method of identifying IH after ET is immediate dual source CT (18). Due to the progress made by the Chinese Stroke Center, thrombectomy has been widely promoted as a suitable treatment method for the Primary Stroke Center. However, the Primary Stroke Center is rarely equipped with dual-source CT. The method proposed in this study can use ordinary CT to predict hemorrhage. At the same time, although ducal energy CT can separate IH or iodine immediately, it does not predict hemorrhage transformation in postoperative and this approach might. Some scholars have pointed out that some patients with immediate dual source CT excluded IH had intracranial hemorrhage transformation in the follow-up CT (23.1% had delayed ICH and 11.5% had delayed PH)(15). The appearance of HALs on immediate CT can be divided into three categories. First, HALs are from hemorrhage combined with contrast agents, such patients would need blood pressure control, sedation after surgery (if necessary), and avoid the use of antithrombotic drugs. Such patients will show hemorrhage on follow-up CT. Second, HALs are from single contrast agent exudation and hemorrhage is highly likely to be transformed. The postoperative management of such patients is the same as in the first case. Third, HALs are from single contrast agent exudation and intracranial hemorrhage transformation is unlikely: these patients benefit from early antithrombotic drugs to prevent re-embolism. Thus, our study focuses on how HALs can be quantitatively analyzed to help with postoperative management, rather than be used to differentiate contrast agent exudation from IH.

This study attempts to identify patients with HALs yet with a low risk of hemorrhage. According to our results, patients with the highest CT value of <97 have a low risk of hemorrhage transformation. This value might be used to help determine patients to apply antithrombotic drugs in the early postoperative period, especially those with mTICI $\leq$ 2b and with emergency stent implantation or balloon dilatation who need antiplatelet to maintain the blood flow.

One limitation of this study is the relatively small sample size of the enrolled patients because only one stroke center was considered. In this case, we only generated 37 pairs of matched data, which resulted in the confidence interval ranging

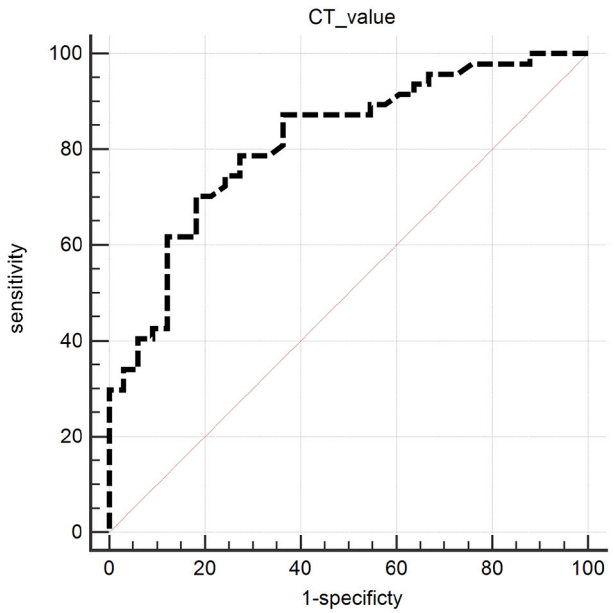

FIGURE 3 | ROC curve analysis of the highest CT value in HALs territory to predict IH. The highest CT value in HALs was a predictive factor for IH with the area under curve (AUC) of 0.816 (95% confidence interval [CI] 0.713–0.894, $p < 0.001$). ROC, receiver-operating characteristic.

from 2.485 to 57.284 and partly limits the generalization of our conclusion. Moreover, more quantitative parameters within the HALs could be calculated and analyzed besides the highest CT value to predict IH. For instance, if the HALs can be lineated automatically with high repeatability and consistency, average CT value within HALs might be used.

CONCLUSION

If the patients with anterior LVO are matched with the baseline characteristics of patients with perioperative IH and non-IH, the incidence of HALs on immediate CT is higher in the IH group. In all patients with HALs, the highest CT value in the HALs area might be used to predict IH in patients during the perioperative period.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board at the Xi'an No.3 Hospital (No. SYXSLL-2018-010). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MC and YT: conception and design. NH: data collection and article draft. GC, YL, HM, HG, XZ, YZ, SL, LZ, YG, WS, PY, and WL: contributed to manuscript review and revision.

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Conflict of Interest: YL was employed by company GE Healthcare China.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy and Safety of a Novel Thrombectomy Device in Patients With Acute Ischemic Stroke: A Randomized Controlled Trial

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Purpose: The Tonbridge stent is a novel retriever with several design improvements which aim to achieve promising flow reperfusion in the treatment of acute ischemic stroke (AIS). We conducted a randomized controlled, multicenter, non-inferiority trial to compare the safety and efficacy of the Tonbridge stent with the Solitaire FR.

Methods: AIS patients aged 18–85 years with large vessel occlusion in anterior circulation who could undergo puncture within 6 h of symptom onset were included. Randomization was performed on a 1:1 ratio to thrombectomy with either the Tonbridge stent or the Solitaire FR. The primary efficacy endpoint was successful reperfusion using a modified thrombolysis in cerebral infarction score (mTICI) of 2b/3. Safety outcomes were symptomatic intracranial hemorrhage (sICH) within 24 ± 6 h and all-cause mortality within 90 days. A clinically relevant non-inferiority margin of 12% was chosen as the acceptable difference between groups. Secondary endpoints included time from groin puncture to reperfusion, National Institutes of Health Stroke Scale (NIHSS) score at 24 h and at 7 days, and a modified Rankin Scale (mRS) score of 0–2 at 90 days.

Results: A total of 220 patients were enrolled; 104 patients underwent thrombectomy with the Tonbridge stent and 104 were treated with the Solitaire FR. In all test group patients, the Tonbridge was used as a single retriever without rescuing by other

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thrombectomy devices. Angioplasty with balloon and/or stent was performed in 26 patients in the Tonbridge group and 16 patients in the Solitaire group ($p = 0.084$). Before angioplasty, 86.5% of those in the Tonbridge group and 81.7% of those in the Solitaire group reached successful reperfusion ($p = 0.343$). Finally, more patients in the Tonbridge group achieved successful reperfusion (92.3 vs. 84.6%, 95% CI of difference value 0.9–16.7%, $p < 0.0001$). There were no significant differences on sICH within 24 ± 6 h between the two groups. All-cause mortality within 90 days was 13.5% in the Tonbridge group and 16.3% in the Solitaire group ($p = 0.559$). We noted no significant differences between groups on the NIHSS at either 24 h or 7 days and the mRS of 0–2 at 90 days.

Conclusion: The trial indicated that the Tonbridge stent was non-inferior to the Solitaire FR within 6 h of symptom onset in cases of large vessel occlusion stroke.

Clinical Trial Registration: ClinicalTrials.gov, number: NCT03210623.

Keywords: acute ischemic stroke, large vessel occlusion, thrombectomy, reperfusion, stent

INTRODUCTION

Five landmark trials have established endovascular thrombectomy as one of the most powerful treatments for acute ischemic stroke (AIS) due to large vessel occlusion in anterior circulation (1–5). The benefits shown in these trials were driven by improved stent-retriever thrombectomy devices combined with patient selection. The Solitaire FR (Medtronic Inc., Irvine, CA, USA) has been one of the most frequently used stent retrievers. Recently, various novel thrombectomy devices have been developed and put into use.

The Tonbridge stent (Tonbridge, Tonbridge Medical Technology, Zhuhai, Guangzhou, China) has been modified into a new design with a longitudinal spiral opening along its tubular surface (**Figure 1**). It has also been modified so that the finished temperature of nitinol increases the radial force, and has a broad size ranging from 3/4/5/6 mm. The maximum length of the series 4/5/6 mm is 30 mm. In *in vitro* tests, the Tonbridge stent had similar maximum friction within the 0.021-in. microcatheter and a slight increase in radial force when compared with the Solitaire FR. An *in vivo* comparative study in beagle models showed that the Tonbridge stent was safe and had a similar number of retriever attempts and similar recanalization rates when compared with the Solitaire FR (6). To evaluate the true efficacy and safety of this new device compared with that of the Solitaire FR in a clinical setting, a multicenter randomized controlled trial was designed and carried out.

METHODS

Study Design and Patients

We conducted a randomized, prospective, controlled, multicenter, single-blind, non-inferiority trial with blinded outcome assessment that enrolled patients with AIS. This study was designed with input from an academic steering committee and overseen by an independent clinical events committee as well as an independent core laboratory. The sponsor of the study, Tonbridge Medical Technology, was responsible for the logistical operations and monitoring of the trial. An independent contract research organization (OSMUNDA Medical Device Service Group, en.osmundacn.com/) and a site management organization (Excellence Future International Consulting Co. Ltd., http://www.chncro.com) were also involved in monitoring the study in order to ensure the quality of the trial. All statistical analyses were conducted by four independent external statisticians (Medical Research & Biometrics Center, National Center for Cardiovascular Disease, China).

We enrolled patients from 17 tertiary care centers, which were each required to have performed at least 30 endovascular thrombectomy procedures during the previous year. The protocol was approved by the respective ethics committee of each participating site. Written informed consent was obtained from all patient participants or their legal representatives prior to enrollment. The trial was designed to enroll 220 patients with the following eligibility criteria: (1) adults aged 18–85 years of age; (2) a baseline National Institutes of Health Stroke Scale (NIHSS) score <30; (3) an angiographically proven occlusion in the internal carotid artery (ICA), middle cerebral artery (MCA) (M1 or M2), or the anterior cerebral artery (MCA) (A1 or A2); (4) a prestroke modified Rankin Scale (mRS) (7) score of <2; and (5) patients able to undergo puncture within 6 h of symptom onset. Key exclusion criteria were the following: a massive cerebral infarction (8, 9); an Alberta Stroke Program Early CT Score (ASPECTS) (10) of <6, or infarct volume ≥70 ml, or >1/3 of blood supplying areas on CT/diffusion-weighted imaging; simultaneous acute bilateral carotid occlusion; uncontrolled hypertension (defined as SBP >185 mmHg or DBP >110 mmHg after medication); concomitant use of oral anticoagulation medications; an INR >3.0; and a platelet count of $<40 \times 10^9$.

Randomization and Blinding

Randomization was performed utilizing a 1:1 ratio to mechanical thrombectomy with either the Tonbridge stent or the Solitaire

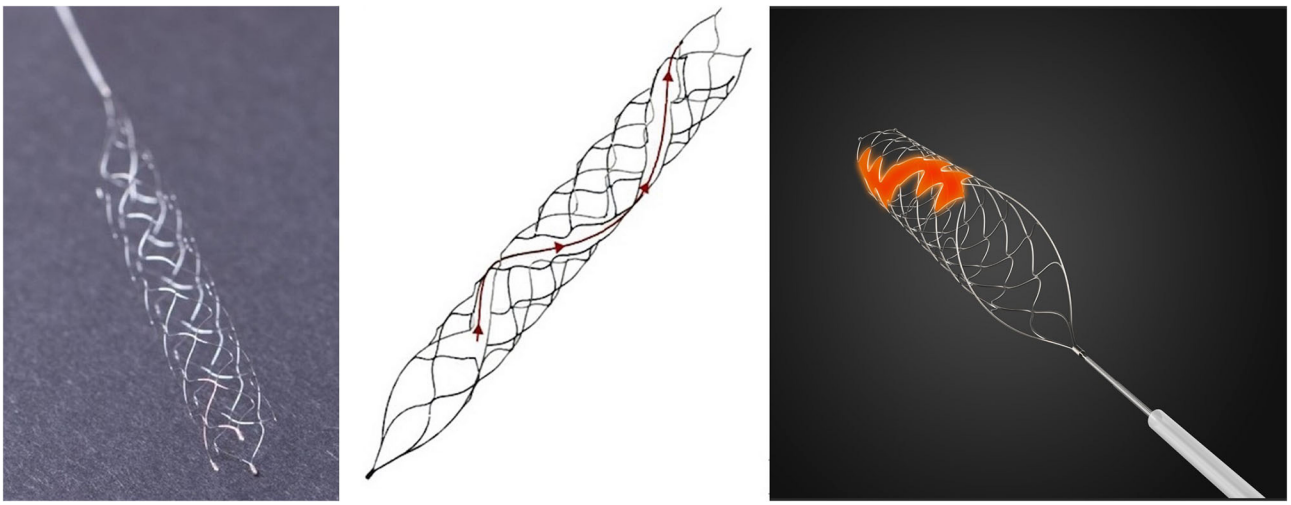

FIGURE 1 | The Tonbridge device and the unique design of the longitudinal spiral opening along its tubular surface.

FR. This was accomplished by employing a web-based system with stratification according to the participating site. Treatment-group assignment was known to the operating physicians but blinded to the patients. Three postprocedure clinical follow-up exams were performed by independent physicians who were unaware of the treatment-group assignment of the patient.

Procedures

According to guidelines, intravenous thrombolysis with rtPA was administered as a bridging therapy in patients who had no contraindications for it. The use of general anesthesia was performed according to standard practices based on local practice. A baseline angiogram was obtained before device deployment in order to assess angiographic inclusion and exclusion criteria. The choice of thrombectomy device was made according to random allocation. The instructions of the manufacturers regarding the Tonbridge stent were very similar to those of the Solitaire FR. Other retrievers, such as the Trevo stent (Stryker, Kalamazoo, MI, USA), or other techniques were allowed after three unsuccessful attempts with the Tonbridge stent. Aspiration with an intermediate catheter was allowed in both stent retriever arms. If there was an underlying stenosis or insufficient reperfusion, salvage measures, including additional balloon (Gateway, Boston Scientific, Natick, MA, USA) angioplasty and/or placement of a permanent stent (Enterprise, Johnson and Johnson, Raynham, MA, USA; Wingspan, Stryker, Kalamazoo, MI, USA) or an Apollo balloon-mounted stent (MicroPort, Shanghai, China), were allowed. If permanent stent deployment was performed, tirofiban (glycoprotein IIb/IIIa inhibitors) was provisionally administered, followed by a loading dose of clopidogrel, and aspirin was immediately administered orally. Daily oral dual antiplatelet therapy was started postprocedure and continued for 3 months. Subsequently, 100 mg of aspirin was prescribed for the rest of the lifetime of the patient (11).

Outcomes

The primary efficacy endpoint was successful reperfusion, defined as achieving modified thrombolysis in cerebral infarction (mTICI) (12) 2b or 3, in AIS patients assessed by an independent angiography core laboratory. All of the images were read by two experienced neuroradiologists, with consensus required in cases of discrepancy. First-pass effect and modified first-pass effect were also compared. First-pass effect was defined as achieving complete recanalization (mTICI 3) with a single thrombectomy device pass. Modified first-pass effect was defined as meeting mTICI 3/2b after the first pass (13, 14). Major safety outcomes included symptomatic intracranial hemorrhage (sICH) within 24 ± 6 h and all-cause mortality within 90 days, which were assessed by an independent clinical events committee. An sICH was defined as any ICH identified by CT scan combined with a four-point increase in NIHSS or death. The secondary endpoints were time from groin puncture to reperfusion, NIHSS at 24 h and at 7 days, favorable clinical outcomes (defined as an mRS of 0–2), and median mRS score at 90 days. The mRS score at 90 days was done by outpatient follow-up or telephone interview.

Statistical Analysis

The primary study hypothesis was that the rate of successful reperfusion in the Tonbridge group would be non-inferior to the rate in the Solitaire group. According to results previously reported in the literature, both devices were assumed to have a successful reperfusion rate of 90%. A clinically relevant non-inferiority margin of 12% was chosen as the acceptable difference between groups simultaneously, under a one-sided significance level alpha of 2.5% and an estimated 10% withdrawal or loss to follow-up rate. Under these conditions, randomizing a total of 220 patients would provide 80% power to demonstrate non-inferiority of the Tonbridge stent to that of the Solitaire FR.

Baseline data are presented as descriptive statistics according to treatment assignment, as appropriate. All statistical analyses followed the intention-to-treat principle. Continuous variables

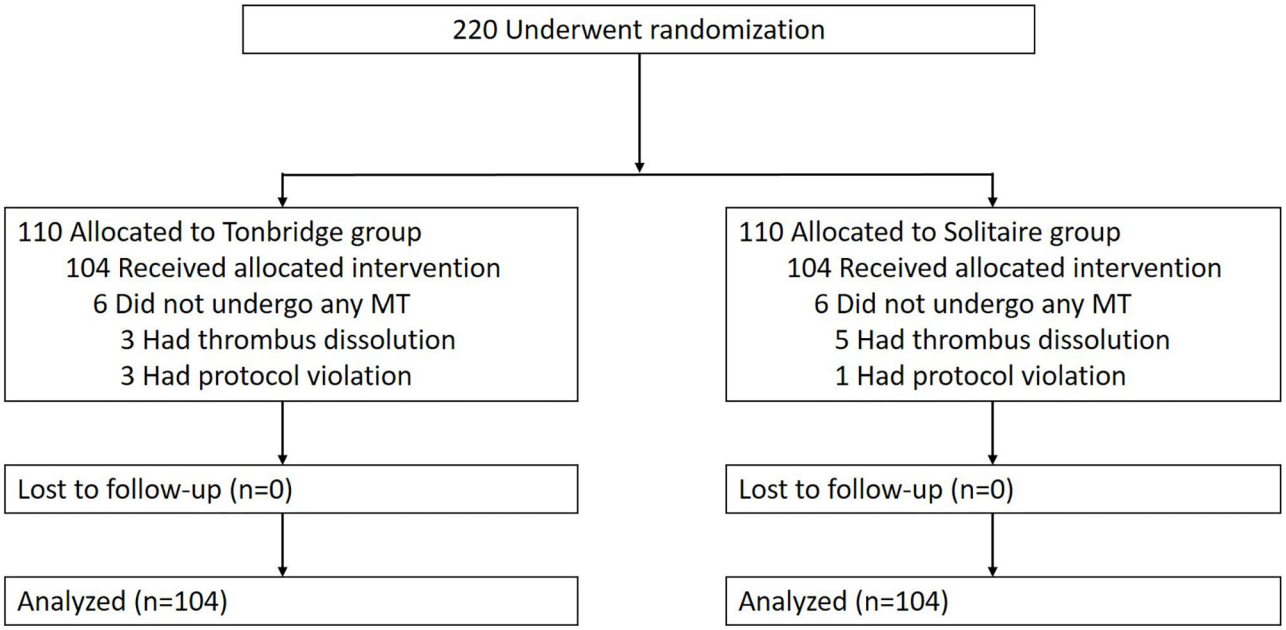

FIGURE 2 | Randomization and treatment of the patients.

are presented as mean ± SD and categorical variables are presented as either counts or percentages. Normally distributed continuous variables were compared using Student's *t*-test. Categorical variables were compared using a chi-squared test or Fisher's exact test. For the primary endpoint, two-sided 95% confidence intervals (CIs) of differences in the rate of successful reperfusion between the groups were estimated by a Cochran–Mantel–Haenszel chi-squared test with adjusting center. The non-inferiority test was based on an asymptotic *Z* test. All the analyses were performed assuming a significance level of two-sided 0.05, using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Between August 3, 2017, and August 27, 2018, a total of 220 patients were enrolled in the trial (**Figure 2**). Eight patients had thrombus dissolution before the devices reached the target vessels, and four had protocol violations. A total of 104 patients were treated with the Tonbridge stent, while 104 underwent thrombectomy with the Solitaire FR. No patients crossed over or were lost to follow-up. The baseline characteristics of the patients are detailed in **Table 1**. The patient median age was 62 years in the Tonbridge group and 61 years in the Solitaire group. There were 52 target vessels in the ICA cases, 133 in the MCA M1 cases, 21 in the MCA M2 cases, and 2 in cases of ACA A2. There were no differences in baseline characteristics observed between the two groups.

Procedural results and outcomes are shown in **Table 2**. In 37 patients (18 in the Tonbridge group and 19 in the Solitaire group), bridging intravenous fibrinolysis was started before thrombectomy. There were no differences in bridging therapy between the two groups. No balloon guide catheters were used in either arm. In all 104 patients in the Tonbridge group, the Tonbridge was used as the single retriever with no rescuing needed using other thrombectomy devices. The use of a retriever in conjunction with aspiration was similar between the two groups. There were no significant differences observed in the median number of passes needed with the assigned study device between the groups. First-pass effect was achieved in 39/208 patients, with no significant differences noted between the Tonbridge group and the Solitaire group (18.3 vs. 19.2%, respectively). There was a similar result in the modified first-pass effect. Angioplasty with balloon and/or stent was performed as a remedial measure to maintain a stable flow in 26 patients in the Tonbridge group and 16 patients in the Solitaire group ($p = 0.084$). Before angioplasty, 90 patients (86.5%) in the Tonbridge group and 85 (81.7%) in the Solitaire group reached successful reperfusion ($p = 0.343$). Median time from groin puncture to successful reperfusion was similar between treatment groups. Finally, more patients in the Tonbridge group than those in the Solitaire group achieved successful reperfusion (92.3 vs. 84.6%, 95% CI of difference value 0.9%−16.7%, $p < 0.0001$).

Regarding other group comparisons, differences in sICH within 24 h (1.9% in the Tonbridge group and 5.0% in the Solitaire group) and all-cause mortality within 90 days (13.5% in the Tonbridge group and 16.3% in the Solitaire group) were not significant. We also noted no significant differences between groups in terms of NIHSS at 24 h and NIHSS at 7 days. Rates of favorable outcome (mRS 0–2) at 90 days were

TABLE 1 | Baseline characteristics of the 208 patients.

Characteristic	Tonbridge group ($n = 104$)	Solitaire group ($n = 104$)	*P*
Age—years, median (IQR)	63.98 (53.96–71.39)	66.50 (55.82–72.76)	0.910
Male sex, no. (%)	62 (59.6%)	61 (58.7%)	0.888
BMI, mean	24.1 ± 3.3	23.8 ± 3.8	0.631
Prestroke mRS 1, no. (%)	10 (9.6%)	14 (13.5%)	0.385
NIHSS—median (IQR)	15 (12–19)	16 (13–19)	0.431
ASPECTS—median (IQR)	9 (8–10)	9 (8–10)	0.580
Systolic blood pressure at hospital arrival—mmHg, median (IQR)	143 (129–160)	143 (127–153)	0.416
Glucose level at hospital arrival—mmol/L, median (IQR)	6.9 (6.0–8.5)	6.8 (6.1–7.8)	0.130
Time from stroke onset to groin puncture—min, median (IQR)	256 (193–315)	248 (187–306)	0.462
Intracranial arterial occlusion, no. (%)			
ICA	21 (20.2%)	31 (29.8%)	0.461
MCA M1 segment	71 (68.3%)	62 (59.6%)	
MCA M2 segment	11 (10.6%)	10 (9.6%)	
ACA A1 segment	0 (0%)	0 (0.0%)	
ACA A2 segment	1 (1.0%)	1 (1.0%)	
Preprocedure mTICI, no. (%)			
0	90 (86.5%)	97 (93.3%)	0.196
1	10 (9.6%)	6 (5.8%)	
2a	4 (3.8%)	1 (1.0%)	
2b	0 (0%)	0 (0%)	
3	0 (0%)	0 (0%)	

BMI, body mass index; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT score; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; mTICI, modified thrombolysis in cerebral infarction score.

58.7% in the Tonbridge group and 61.5% in the Solitaire group ($p = 0.671$).

DISCUSSION

Our randomized controlled trial demonstrated that the Tonbridge stent had a comparable rate of successful reperfusion when compared with the Solitaire FR in a clinical setting for the treatment of AIS due to large vessel occlusion in the anterior circulation. In terms of safety endpoints, sICH within 24 ± 6 h and all-cause mortality within 90 days were comparable for both devices. Clinical outcomes within 7 days and at 90 days follow-up were comparable between the two groups.

Although several approved thrombectomy devices are currently available, improvements designed to increase the effectiveness of reperfusion have continued. The Tonbridge is a novel stent-based clot retriever with a hybrid closed and partially open cell design, which forms a longitudinal spiral opening along its tubular surface. It was designed to allow increases in stent radial force strength and the tensile breaking force of the connection point between the stent and its push wire. In *in vitro* tests, the radial force and flexibility of the Tonbridge stent were superior to those of the Solitaire FR (6). These improvements may have the following potential advantages: the promise of tighter clot engagement and reduced chance of clot fall-off during retrieval; they make the device better adapted to curved vessel lumen; and they prevent connection site break-off during repeated retriever manipulations. Animal experiments revealed a slightly higher rate of recanalization (100 vs. 88.9%), but without statistical significance (6). To determine the value of this novel device in the treatment of AIS, this clinical comparative study was essential.

Our study is one of the few prospective randomized controlled trials that focuses on the efficacy and safety of a new stent-like device. Trials of thrombectomy devices have usually been single-arm studies whose aim was to show the safety of a device for regulatory approval purposes (15–23). In these studies, the data from a single group were usually compared with the data from previous studies of other devices, such as the Solitaire FR or the Trevo. These two devices have been evaluated in numerous trials and prospective registries (16, 18). However, direct comparison of prognoses between single-arm studies and previous registries can produce uncontrolled effects from inhomogeneous baselines and different endpoints. In our study, the two groups had well-balanced baseline characteristics because of the prospective randomization design. To minimize bias, the assessments of key endpoints, including postprocedural mTICI and sICH, were evaluated by an independent core laboratory and clinical events committee.

The Tonbridge stent achieved a similar rate of successful reperfusion as the Solitaire FR before angioplasty. We also

TABLE 2 | Procedural and outcomes data.

	Tonbridge group ($n = 104$)	Solitaire group ($n = 104$)	*P*
Bridging intravenous fibrinolysis, no. (%)	18 (17.3%)	19 (18.3%)	0.856
Retriever in conjunction with aspiration, no. (%)	4 (3.8%)	7 (6.7%)	0.353
Number of passes by retriever, median	1.5	1	0.641
Balloon and/or stent angioplasty, no. (%)	26 (25.0%)	16 (15.4%)	0.084
Primary outcome:			
Final successful reperfusion, no. (%)	96 (92.3%)	88 (84.6%)	<0.0001[a]
mTICI 2b/3 with a first pass, no. (%)	50 (48.1%)	46 (44.2%)	0.578[b]
mTICI 3 with a first pass, no. (%)	19 (18.3%)	20 (19.2%)	0.859[b]
mTICI 2b/3 before angioplasty, no. (%)	90 (86.5%)	85 (81.7%)	0.343[b]
Secondary outcomes:			
Time from groin puncture to successful reperfusion—min, median (IQR)	67.5 (46.5–95.5)	67 (44.0–99.0)	0.970
NIHSS at 24 h, median (IQR)[c]	10 (4–15)	8 (4–16)	0.993
NIHSS at 7 days, median (IQR)[d]	6 (2–13)	4 (1–13)	0.777
mRS 0–2 at 90 days, no. (%)	61 (58.7%)	64 (61.5%)	0.671
mRS at 90 days, median (IQR)	2 (1–4)	2 (1–4)	1.000
Postprocedure mTICI, no. (%)			
0	1 (1.0%)	4 (3.8%)	0.3138
1	3 (2.9%)	3 (2.9%)	
2a	4 (3.8%)	9 (8.7%)	
2b	64 (61.5%)	58 (55.8%)	
3	32 (30.8%)	30 (28.8%)	
Major safety outcomes:			
Symptomatic intracranial hemorrhage within 24 h, no. (%)[e]	2 (1.9%)	5 (5.0%)	0.238
Death within 90 days, no. (%)	14 (13.5%)	17 (16.3%)	0.559

mTICI, the modified thrombolysis in cerebral infarction score; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

[a] *The p-value was for noninferiority and calculated by the CMH chi-square test.*

[b] *The p-value was for difference and calculated by the chi-square test.*

[c] *Data were missing for one patient in the Tonbridge group and four patients in the Solitaire group.*

[d] *Data were missing for seven patients in the Tonbridge group and 11 patients in the Solitaire group.*

[e] *Data were missing for one patient in the Tonbridge group and three patients in the Solitaire group.*

compared first-pass effect and modified first-pass effect between the two groups. These indicators were first described by Zaidat et al. (13) and have subsequently been shown to be independent factors of favorable outcomes (14, 24, 25). In this trial, a first-pass effect was achieved in one-fifth of all patients, which was slightly lower than that reported by Zaidat as well as a recently published systematic review (13, 26). Potential reasons may be a lack of the use of balloon guide catheters, which has been proven to contribute to a greater first-pass effect. Our trial indicates a similar rate of modified first-pass effect to that of previous studies (13, 14, 24–26).

The fact that acute arterial occlusions due to intracranial atherosclerotic disease (ICAD) are more prevalent in Eastern populations was an issue. Recent studies have shown that ICAD-related occlusion accounts for 12%−30% of all large vessel occlusion etiologies in Asia (27–30). However, while the thrombectomy devices could achieve initial reperfusion quickly, reocclusion is often encountered due to subsequent platelet aggregation at the lesion site or elastic recoil. In our study, about one-fifth of patients received angioplasty with a balloon and/or stent in order to maintain successful reperfusion. In line with a study published by Yoon et al., these patients achieved a higher recanalization rate (31). The final successful reperfusion rate we report is higher than those reported in the MR CLEAN, REVASCAT, and ESCAPE trials (1–3) and comparable with those seen in the SWIFT, PRIME, and EXTEND-IA trials (4).

Another concern about the safety of the device was whether the high radial force of the Tonbridge stent would lead to vessel wall injury or hemorrhage. Gascou et al. estimated that >10% of perioperative complications are associated with thrombectomy devices (32), including arterial perforation (0.9–4.9%), subarachnoid hemorrhage (0.6–4.9%), arterial dissection (0.6–3.9%), and vasospasm (3.9–23%) (27, 33). It is well-known that high radial force is associated with higher rates of clot removal (34). However, high radial force is also associated with endothelial vessel wall injury (35, 36). Therefore, minimizing radial force may reduce the incidence of vessel wall injury complications while still maintaining optimal clot retrieval rates. In an *in vitro* test, the radial force of the Tonbridge stent was noted to be slightly higher than that of the Solitaire FR. In the present clinical trial, we did not note any significant differences between the two groups in terms of symptomatic

intracranial hemorrhage, including subarachnoid hemorrhage. These results indicate that the Tonbridge stent has the potential to improve the rate of reperfusion without increasing vessel wall injury complications.

Our study was limited in many aspects by the restrictive nature of a randomized controlled trial design, such as strict inclusion and exclusion criteria, center selection, and operator experience. The image core lab evaluated the DSA only without CTA or MRA, and the analysis item was very limited. We acknowledged that these were all the limitations. Postmarketing clinical registries allow for more inclusive criteria by including a range of clinical sites, operators, and varying patient populations, which will provide valuable information on the generalizability and reproducibility of our results, and allow additional opportunities to explore clinical hypotheses for patients treated outside of this trial.

CONCLUSIONS

In this randomized clinical trial, the Tonbridge stent was non-inferior to the Solitaire FR in the treatment of large vessel occlusion stroke within 6 h of symptom onset.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shanghai Changhai Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YongxZ and WH: manuscript writing and revision. JL and PY: conception and design of the work. All authors: data collection. All authors read and approved the final manuscript.

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SYSTEMATIC REVIEW
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Endovascular Treatment With and Without Intravenous Thrombolysis in Large Vessel Occlusions Stroke: A Systematic Review and Meta-Analysis

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Background: Previous studies have shown conflicting results about the benefits of pretreatment with intravenous thrombolysis before endovascular treatment (EVT) in patients with acute ischemic stroke (AIS) with large vessel occlusions (LVOs). This study aimed to investigate the clinical efficacy and safety of EVT alone vs. bridging therapy (BT) in patients with AIS with LVOs.

Methods: A systematic review with meta-analysis of all available studies comparing clinical outcomes between BT and EVT alone was conducted by searching the National Center for Biotechnology Information/National Library of Medicine PubMed and Web of Science databases for relevant literature from database inception to October 20, 2020.

Results: A total of 93 studies enrolling 45,190 patients were included in the present analysis. In both unadjusted and adjusted analyses, BT was associated with a higher likelihood of 90-day good outcome (crude odds ratio [cOR] 1.361, 95% confidence interval [CI] 1.234–1.502 and adjusted OR [aOR] 1.369, 95% CI 1.217–1.540) and successful reperfusion (cOR 1.271, 95% CI 1.149–1.406 and aOR 1.267, 95% CI 1.095–1.465) and lower odds of 90-day mortality (cOR 0.619, 95% CI 0.560–0.684 and aOR 0.718, 95% CI 0.594–0.868) than EVT alone. The two groups did not differ in the occurrence of symptomatic intracranial hemorrhage (sICH) (cOR 1.062, 95% CI 0.915–1.232 and aOR 1.20, 95% CI 0.95–1.47), 24-h early recovery (cOR 1.306, 95% CI 0.906–1.881 and aOR 1.46, 95% CI 0.46–2.19), and number of thrombectomy device passes $\leq$2 (aOR 1.466, 95% CI 0.983–2.185) after sensitivity analyses and adjustment for publication bias.

Conclusions: BT provides more benefits than EVT alone in terms of clinical functional outcomes without compromising safety in AIS patients with LVOs.

Keywords: acute ischemic stroke, large vessel occlusion, thrombectomy, endovascular treatment, bridging therapy

INTRODUCTION

Stroke is the leading cause of disability and the second major cause of death among adults worldwide, with ischemic stroke accounting for ≥80% of the cases (1, 2). The primary principle of acute ischemic stroke (AIS) treatment is recanalization and reperfusion of the occluded artery. To date, intravenous thrombolysis (IVT) is the recommended standard therapy and first-choice treatment for all eligible patients with AIS within the first 4.5 h after the onset of symptoms, irrespective of the AIS subtype (3). However, in addition to the narrow therapeutic time window and various contraindications and complications of IVT, numerous studies have reported that IVT seems less effective in AIS patients with large vessel occlusions (LVOs) (4–6).

More recently, with the development of mechanical thrombectomy (MT) devices, endovascular treatment (EVT) coupled with standard medical treatment has been demonstrated to be more beneficial than standard medical treatment alone in AIS patients with anterior circulation LVOs (6, 7). EVT, in addition to pretreatment with IVT (bridging therapy, BT), is now recommended for all eligible AIS patients with LVOs within 6 h after symptom onset based on class I level A evidence (3). However, many clinical trials and meta-analyses published from 2016 to 2020 have shown the clinical efficacy of EVT alone without pretreatment with IVT in AIS patients (8–12), giving rise to debates about the benefits of EVT alone.

Arguments in favor of BT suggest that pretreatment with IVT could improve post-MT clinical outcomes by promoting thrombus softening and fibrinolytic processes, thus increasing the likelihood of early successful recanalization (13–15). Moreover, IVT could offer the chance of reperfusion in AIS patients in whom MT failed because of the inability to reach the target occlusion. Furthermore, IVT may lead to recanalization of distal occlusions in some patients, thereby avoiding subsequent MT, or may result in the reperfusion of any remaining distal occlusions after MT (14). Conversely, pretreatment with IVT may increase the risk of bleeding complications, especially intracranial hemorrhage (ICH) (8, 16), and facilitate thrombus fragmentation, which increases the potential for migration from proximal to distal vessels (where EVT is impossible to achieve). Furthermore, pretreatment with IVT may delay the start of subsequent EVT procedures and limit additional interventions, such as antiplatelet and heparin administration (17). Additionally, an analysis performed in the United States indicated that IVT before EVT leads to significantly higher costs (18).

Considering the aforementioned uncertainties, this systematic review with meta-analysis of published studies was conducted to investigate the clinical efficacy and safety of BT vs. EVT alone in AIS patients with LVOs.

METHODS

Data Sources and Search Strategy

The present study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines (19). We conducted an electronic search of eligible studies without language restriction in the National Center for Biotechnology Information/National Library of Medicine (NCBI/NLM) PubMed and Web of Science databases using the following terms: (thrombectomy OR bridging therapy OR embolectomy OR endovascular) AND (thrombolysis OR tissue plasminogen activator OR plasminogen) AND (stroke OR brain ischemia OR cerebrovascular accident). The search covered the period from the inception of the databases to October 20, 2020. The reference lists of all retrieved articles were also manually searched to ensure maximum sensitivity and integrity of the search strategy. A reference manager (EndNote X7; Thompson Reuters, Philadelphia, PA, USA) was employed to remove duplicate references generated from the searches based on the fields "Author," "Year," and "Title." The requirements for ethical approval and patient informed consent were waived for this study by the Ethics Committee of Southeast University owing to the origin of the analyzed data. Data supporting the findings of this study are available from the corresponding author on reasonable request.

Study Selection

The inclusion criteria for eligible studies were as follows: (1) enrolled AIS patients with LVOs; (2) compared outcomes between EVT alone and BT, or investigated the correlation between IVT and outcomes in patients undergoing EVT; and (3) reported raw data on both EVT alone and BT treatments, or odds ratios (ORs) or risk ratios (RRs) and 95% confidence intervals (CIs) for outcomes from regression analyses. The exclusion criteria were as follows: (1) lack of data on outcomes of AIS patients stratified by IVT treatment before EVT; (2) no reported data on the outcomes of interest of this study; (3) conference abstracts, study protocols, guidelines, comments, review articles, case reports, and other meta-analyses; (4) inclusion of pediatric, adolescent, or pregnant patients; and (5) un-extractable data related to outcomes. When duplicated data for each outcome of interest were reported in different studies, we included the study with the larger sample size. The detailed screening process of full-text articles is shown in **Figure 1**.

Data Extraction and Quality Assessment

Two reviewers (SL and D-DL) independently extracted data from qualified studies using predefined electronic forms. The forms were selected by two of the authors (SL and GL) according to the inclusion and exclusion criteria. In case of disagreements, the full-text articles were retrieved to reach a consensus among all authors. As the enrolled studies presented different control sets, we defined "treatment with EVT alone" as the reference and "treatment with BT" as the intervention group. The following study characteristics were robustly extracted: name of the first author, publication year, registry name or data source, prospective or retrospective design, sample size, age of patients, ethnicity, National Institutes of Health Stroke Scale (NIHSS) score on admission, time from onset to groin puncture, time from groin puncture to reperfusion, time from onset to reperfusion, thrombolysis dose, EVT device, location of the occluded artery, time to follow-up, clinical outcome, statistical method, crude

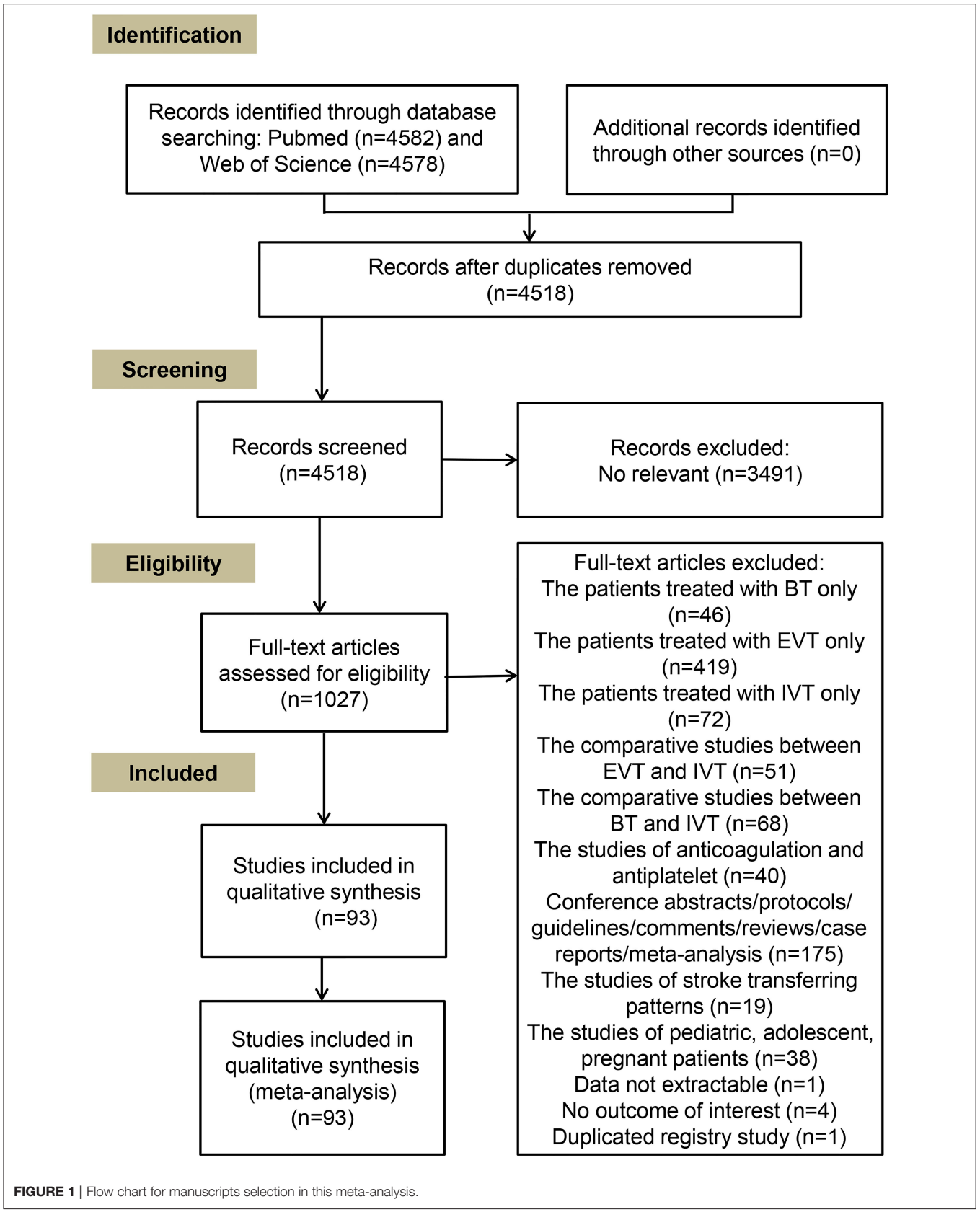

FIGURE 1 | Flow chart for manuscripts selection in this meta-analysis.

and adjusted results (RR, OR, 95% CI, and *p*-value) for clinical outcomes, and confounder adjustment.

The Newcastle-Ottawa Scale (NOS) was used by two of the authors (SL and Q-WD) to independently evaluate the quality of cohort studies and *post hoc* analysis of clinical trials and to investigate potential causes of bias in eligible studies. Differences in NOS scores were settled through discussion and mutual consensus.

Clinical Outcome Evaluation

The primary efficacy outcome in this study was the degree of disability assessed using the modified Rankin Scale (mRS) at discharge and 90 days or the longest available follow-up time point, and categorized as follows: (1) excellent outcome (defined as an mRS score of 0–1), (2) good outcome (defined as an mRS score of 0–2), and (3) favorable outcome (defined as an mRS score of 0–3). The secondary efficacy outcomes included the following: (1) successful reperfusion (defined as thrombolysis in cerebral infarction [TICI]/modified TICI [mTICI]/expanded TICI [eTICI] score ≥2b or thrombolysis in myocardial infarction [TIMI] score ≥2 or their equivalents), (2) complete reperfusion (defined as TICI/mTICI/eTICI/TIMI=3 or their equivalents) after the first-line strategy or at end of the procedure or 24 h after EVT, (3) early recovery (defined as ΔNIHSS score ≥4 at least or NIHSS score 0–2 at 24 h after admission), (4) a dramatic improvement (defined as ΔNIHSS score ≥8), (5) a good improvement (defined as ΔNIHSS score ≥2 at least or NIHSS<5 at discharge or 7 days or 3 months), and (6) number of the thrombectomy device passes ≤2.

The primary safety outcomes were mortality during the hospital stay or at 90 days after onset or the longest available follow-up. The secondary safety outcomes were the proportions of patients with any bleeding at the longest available follow-up, including (1) intracranial hemorrhage (ICH), (2) subarachnoid hemorrhage (SAH), (3) symptomatic intracranial hemorrhage (sICH), (4) asymptomatic intracranial hemorrhage (aICH), (5) hemorrhagic transformation (HT), (6) parenchymal hematoma (PH) type1/2, and (7) hemorrhagic infarction (HI) type1/2. Complications (clot migration, groin hematoma, pneumonia, rescue therapy, vasospasm, vessel dissection, and vessel perforation) and recurrent stroke were also evaluated. The definitions of the various bleeding types and complications are summarized in **Supplementary Table 1**.

Data Synthesis and Statistical Analysis

We calculated the cOR or mean difference (MD) values and 95% CIs with an ordinal logistic regression analysis (Review Manager 5.3 software package; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) using data from studies that did not report relevant crude RR (cRR) or crude OR (cOR) values but provided dichotomous data on the clinical outcomes of AIS patients with LVOs stratified by IVT treatment before EVT. Heterogeneity among the enrolled studies was assessed using Cochran's *Q* and Higgins I^2 statistics. A random-effect model (DerSimonian-Laird) was applied to calculate summary ratios (ORs and RRs) with 95% CIs if Cochran's Q $p < 0.10$ or $I^2 > 50\%$; otherwise, a fixed-effect model (Mantel-Haenszel) was used (20, 21). In case of heterogeneity (Cochran's Q $p < 0.10$ or $I^2 > 50\%$) of any outcome across overall studies, we conducted related subgroup analysis with a random-effect model based on the ethnicity of the studied population, study type, location of the occluded artery, and timing of functional outcome assessment. Subgroups that included fewer than two individual studies were not analyzed. The sensitivity analysis was performed through the sequential elimination of each study to identify the effect of an individual study on the pooled results. Begg's funnel plots and Egger's linear regression tests, with the logarithm of RR in the *y*-axis vs. the logarithm of the standard error of RR in the *x*-axis, were used to graphically show and assess publication bias at a statistical significance level of 0.10. A "trim-and-fill" analysis was conducted to verify and adjust for publication bias if $p < 0.1$ in Egger's linear regression test.

All ratios (ORs and RRs) and corresponding 95% CIs from each study (summarized in **Supplementary Table 1**) were pooled and analyzed using STATA software version 11.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Study Selection and Characteristics

The search strategy in the NCBI/NLM PubMed and Web of Science databases yielded 4,582 and 4,578 results, respectively. A total of 1,027 articles with available full-text were assessed after removing duplicated and non-relevant articles. Thereafter, 934 articles were further excluded owing to unavailability of data use of other treatment methods, analysis of a targeted specific population, and the nature of the study (conference abstracts, descriptive and summative studies, or duplicated registry studies). Finally, 93 studies, including 6 randomized controlled trials (RCTs), met the inclusion criteria and were incorporated in the qualitative synthesis (**Figure 1**). The included studies enrolled 45,190 patients, and ∼54% of the patients were treated with BT and showed anterior and posterior circulation involvement. The mean ± standard deviation age ranged from 57.9 ± 11.8 to 77 ± 14 years; the median (interquartile range) age ranged from 61 (55–66) to 92 (90–93) years, and the admission NIHSS score ranged from 5 to 20. The mean duration from onset to treatment ranged from within 4.5 h to within 24 h and the symptom onset to reperfusion time ranged from 144 to 415 min. The time from symptom onset to reperfusion (MD −26.57, 95% CI −61.25–8.11) (**Supplementary Figure 1A**) and the time from groin puncture to reperfusion (MD 0.24, 95% CI −4.20–4.67) (**Supplementary Figure 1B**) were similar in BT and EVT alone groups. However, the meta-analysis of 12 studies showed that the time from onset to groin puncture was shorter in patients treated with BT (MD −58.37, 95% CI −90.76 to −25.98) (**Supplementary Figure 1C**). The main characteristics of the studies and the reported ORs/RRs for the primary and secondary clinical outcomes are shown in **Supplementary Tables 1–4**.

Study Quality Assessment

Considering that lack of appropriate adjustments for potential confounders may lead to biases in the reported risks and results, we extracted the adjusted results in 66 of the

studies (**Supplementary Table 1**) and listed the related confounders in 61 studies (5 studies had no available data) in **Supplementary Table 5**. Furthermore, the cOR/cRR and adjusted OR/RR (aOR/aRR) values with corresponding 95% CIs for the clinical outcomes were, respectively, synthesized, and the pooled results are provided in **Supplementary Tables 6**, **7**. The overall NOS score of the enrolled studies was 696/837 (83%), and each study had a score of ≥6, which is considered to indicate an overall high quality (**Supplementary Table 8**).

Functional Outcomes

On the basis of the unadjusted analysis, BT was associated with a higher likelihood of a good outcome at 90 days in the meta-analysis of 58 studies (cOR 1.361, 95% CI 1.234–1.502) (**Figure 2A**) and a good outcome at discharge in the synthesis of 8 studies (cOR 1.691, 95% CI 1.203–2.377) than EVT alone (**Supplementary Figure 2A**). These associations remained significant after adjusting for potential confounders (aOR 1.369, 95% CI 1.217–1.540 at 90 days and aOR 2.032, 95% CI 1.022–4.043 at discharge) (**Figure 2B** and **Supplementary Figure 2B**). Furthermore, sequential omission of one study in the sensitivity analyses revealed a significant difference in the achievement of a good outcome at discharge between BT and EVT alone in the unadjusted analysis (cOR 1.691, 95% CI 1.10–2.78), but not in the adjusted analysis (aOR 2.032, 95% CI 0.77–7.24) (**Supplementary Figure 3**). Notably, the subgroup analysis revealed that BT could improve the rate of 90-day good outcome regardless of the nature of the occlusion (anterior or posterior circulation involvement) (**Supplementary Figure 4**). Moreover, both unadjusted and adjusted analyses showed that the rate of an excellent outcome at 90 days was higher in the BT group than in the EVT alone group (cOR 1.354, 95% CI 1.170–1.566; aOR 1.328, 95% CI 1.118–1.577) (**Supplementary Figure 5**). No significant effects of IVT pretreatment on excellent outcome at discharge, good outcome at 6 months or 1 year, and favorable outcome at 90 days were found (**Supplementary Figures 6, 7**). The detailed summaries of the subgroup analyses by study type, location of the occluded artery, and ethnicity are shown in **Supplementary Tables 6, 7**, and in **Supplementary Figures 4**, **8–19**.

Mortality

The pooled results from 41 studies suggested that BT resulted in a lower rate of mortality within 90 days than EVT alone (cOR 0.619, 95% CI 0.560–0.684; aOR 0.718, 95% CI 0.594–0.868) (**Figure 3**). Similar results were also observed for in-hospital mortality (cOR 0.714, 95% CI 0.592–0.862; aOR 0.805, 95% CI 0.741–0.874) (**Supplementary Figure 20**). Meanwhile, the sensitivity analyses with adjusted ORs showed similar in-hospital mortality between the two groups after the exclusion of individual studies (aOR 0.80, 95% CI 0.60–1.07) (**Supplementary Figure 21B**). Furthermore, regardless of the location of the occluded artery, patients undergoing BT had a lower likelihood of mortality within 90 days (**Supplementary Figure 22**). However, in particular, similar rates of mortality within 90 days were noted between the two groups when the analyses were limited to Asian patients (cOR 0.706, 95% CI 0.451–1.106; aOR 0.742, 95% CI 0.497–1.109) (**Supplementary Figure 23**). Additionally, without considering the follow-up time, treatment with BT still resulted in a lower mortality rate at the longest available follow-up (cOR 0.624, 95% CI 0.566–0.688; aOR 0.742, 95% CI 0.640–0.860) (**Supplementary Figure 24**). The results of related stratified analyses are presented in **Supplementary Tables 6, 7** and **Supplementary Figures 22, 23**, **25–30**.

Reperfusion

The unadjusted meta-analysis of 55 eligible studies showed a significantly higher rate of successful reperfusion in the BT group than in the EVT alone group (cOR 1.271, 95% CI 1.149–1.406) (**Figure 4A**), which was consistent with the result of the adjusted analysis of 22 studies (aOR 1.267, 95% CI 1.095–1.465) (**Figure 4B**). Particularly, subgroup analysis by the location of the occluded artery also indicated that BT could increase the rate of successful reperfusion in AIS patients with tandem occluded lesions (cOR 1.552, 95% CI 1.138–2.117) (**Supplementary Figure 31**). Meanwhile, the subgroup analysis involving Asian patients showed no significant difference between the two treatment groups (cOR 1. 206, 95% CI 0.731–1.989; aOR 1.178, 95% CI 0.643–2.159) (**Supplementary Figure 32**). Moreover, no differences between BT and EVT alone were detected in the unadjusted and adjusted analyses for complete reperfusion (cOR 1.084, 95% CI 0.947–1.241; aOR 0.988, 95% CI 0.800–1.219) (**Supplementary Figure 33**). The results of subgroup analyses are detailed in **Supplementary Tables 6, 7**, as well as in **Supplementary Figures 32, 34–38**.

ICH

The incidence of ICH was reported in 46 studies in the unadjusted analyses and in 20 studies in the adjusted analyses, with all studies indicating increased ICH incidence in the BT group (cOR 1.153, 95% CI 1.026–1.295; aOR 1.214, 95% CI 1.040–1.417) (**Supplementary Figure 39**). However, the unadjusted meta-analysis of 36 studies showed a similar incidence of sICH between the BT and EVT alone groups (cOR 1.062, 95% CI 0.915–1.232) (**Figure 5A**). Although BT has been considered to be associated with a higher incidence of sICH in the adjusted analysis (aOR 1.204, 95% CI 1.021–1.421) (**Figure 5B**), the sensitivity analysis revealed that the incidence of sICH did not significantly differ between the BT and EVT alone groups (aOR 1.204, 95% CI 0.95–1.47) (**Figure 5C**). Similarly, the pooled results showed that the BT group had higher rates of HT than the EVT alone group (cOR 1.152, 95% CI 1.021–1.301; aOR 1.355, 95% CI 1.014–1.811) (**Supplementary Figure 40**). However, the sensitivity analysis produced negative results for HT in both groups (cOR 1.15, 95% CI 0.95–1.304; aOR 1.35, 95% CI 0.95–2.05) (**Supplementary Figure 41**). Nevertheless, the incidence of aICH was higher in the BT group, without significant heterogeneity ($I^2 = 3.1\%$, p for Cochran's $Q = 0.402$ in the unadjusted analysis and $I^2 = 0.0\%$, p for Cochran $Q = 0.903$ in the adjusted analysis) (cOR 1.524, 95% CI 1.233–1.882; aOR 1.936, 95% CI 1.384–2.708) (**Supplementary Figure 42**). In addition, treatment with BT was found to be more likely to cause

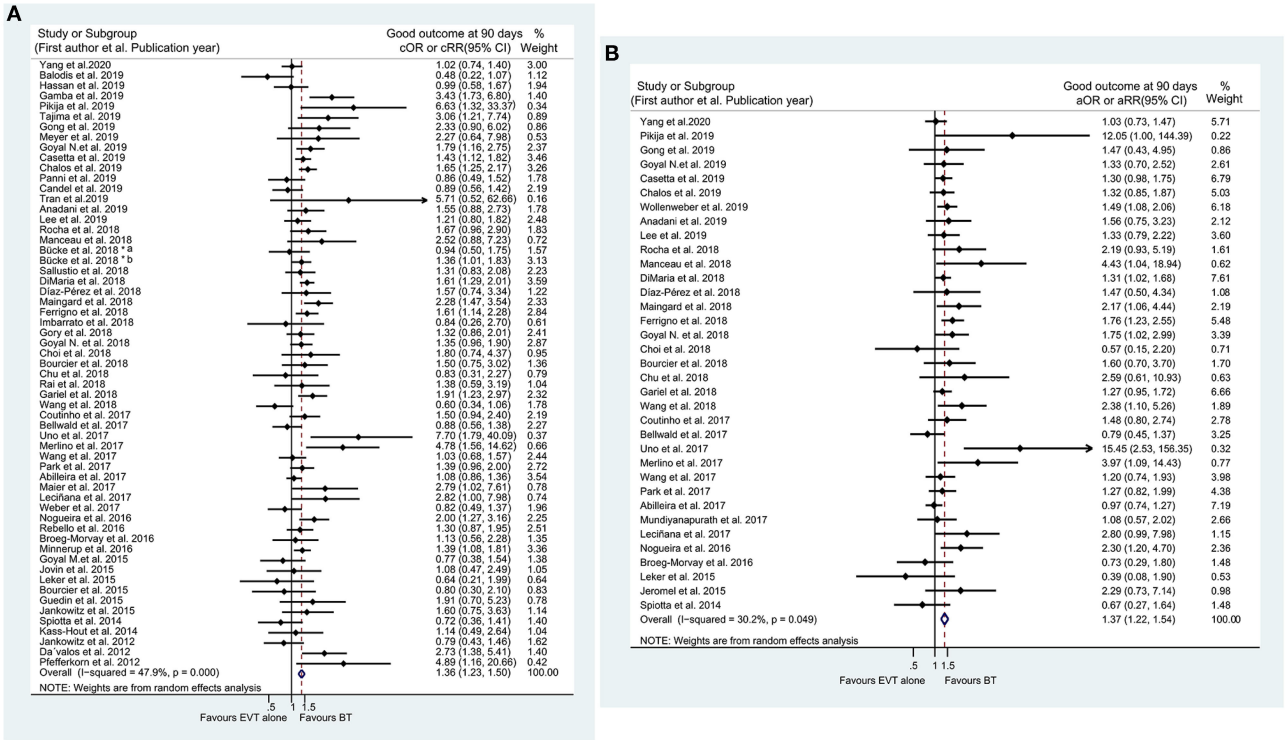

FIGURE 2 | Forest plots of studies assessing good outcome at 90 days in unadjusted **(A)** and adjusted **(B)** analysis. ICA, internal carotid artery. *The acute intracranial vessel occlusion patients with (a) or without (b) concomitant ipsilateral ICA-occlusion or high-grade stenosis were investigated, respectively, in the study by Bücke et al. (22).

bleeding in any part of the body than treatment with EVT alone (aOR 1.215, 95% CI 1.040–1.420) (**Supplementary Figure 43B**). The results of the meta-analysis on SAH, HI, and PH (including the PH-1 and PH-2 subtypes) and those of all related subgroup analyses are presented in **Supplementary Tables 6, 7** and **Supplementary Figures 44–66**.

Symptom Improvement According to NIHSS Scores

In addition to mRS scores, NIHSS scores were also used to evaluate the prognosis with respect to the secondary efficacy outcomes. The unadjusted analysis showed that a dramatic improvement at discharge/7 days was more frequently observed in the BT group than in the EVT alone group (cOR 1.402, 95% CI 1.143–1.719) (**Supplementary Figure 67**), whereas no significant differences in early recovery at 24 h after admission (cOR 1.306, 95% CI 0.906–1.881) and good improvement at discharge/7 days (cOR 2.623, 95% CI 0.993–6.931) or at 3 months (cOR 1.499, 95% CI 0.866–2.595) were observed (**Figure 6A** and **Supplementary Figure 68**). Furthermore, the subgroup analysis indicated similarities between the two groups in the occurrence of a dramatic improvement at discharge/7 days in AIS patients with occluded anterior circulation (cOR 1.621, 95% CI 0.983–2.673) (**Supplementary Figure 69A**). For the adjusted analysis on the above outcomes, only three studies on early recovery at 24 h after admission were included in the meta-analysis. Although the adjusted results showed that BT was associated with a higher probability of early recovery at 24 h after admission (aOR 1.457, 95% CI 1.084–1.957) (**Figure 6B**), the sensitivity analyses suggested an instability of the pooled results (aOR 1.46, 95% CI 0.46–2.19) (**Figure 6C**). The detailed results of subgroup analyses are shown in **Supplementary Tables 6, 7** and **Supplementary Figures 70–72**.

Number of Passes of the Thrombectomy Device

A significant difference in number of thrombectomy device passes ≤ 2 was found in the unadjusted analysis, which showed that patients treated with BT required fewer passes (cOR 1.870, 95% CI 1.344–2.603) (**Figure 7A**). However, the result was debatable because of publication bias confirmed by Egger's linear regression test ($P_E = 0.024$), Begg's funnel plots (**Figure 7B**), and "trim-and-fill" analyses (**Figure 7C** and **Supplementary Table 9**). Moreover, this difference remained not significant in the adjusted analysis (aOR 1.466, 95% CI 0.983–2.185) (**Figure 7D**). Additionally, the unadjusted meta-analysis of three studies on number of thrombectomy device pass = 1 showed similar attempts during the MT procedure (cOR 1.605, 95% CI 0.926–2.781) (**Supplementary Figure 73A**). The results of subgroup analyses are presented in **Supplementary Tables 6, 7** and **Supplementary Figures 73–75**.

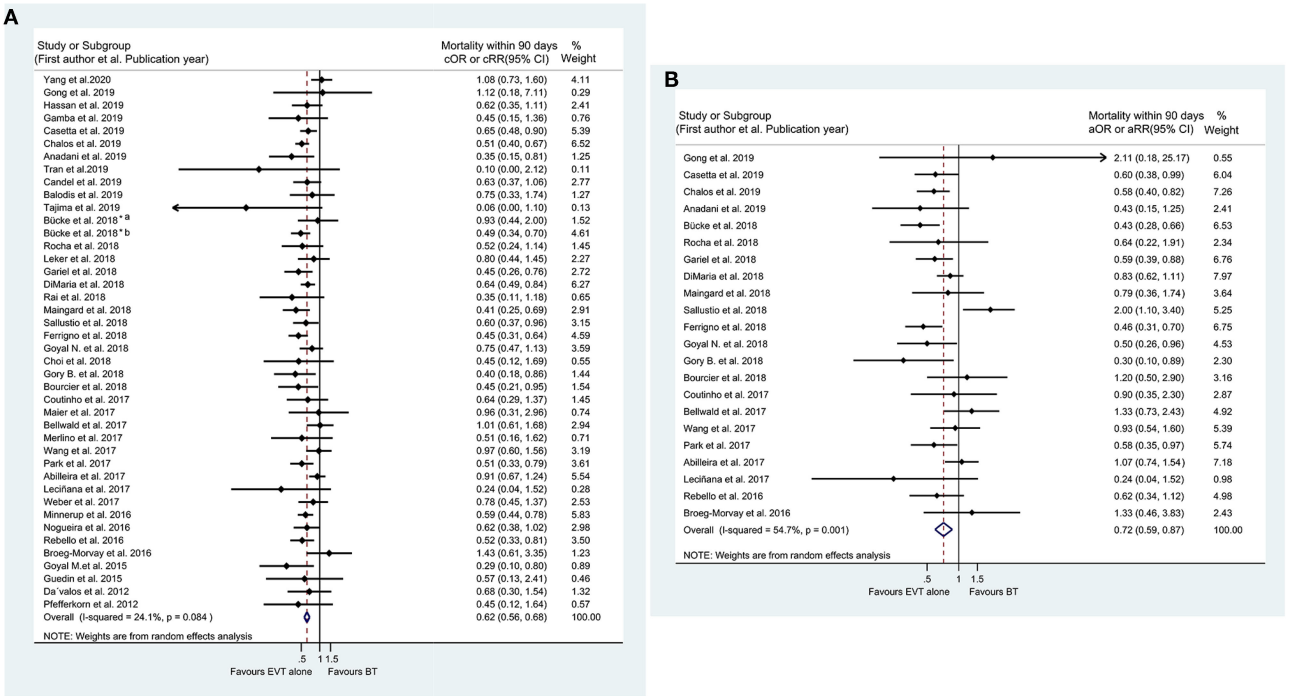

FIGURE 3 | Forest plots of studies assessing mortality within 90 days in unadjusted **(A)** and adjusted **(B)** analysis. ICA, internal carotid artery. *The acute intracranial vessel occlusion patients with (a) or without (b) concomitant ipsilateral ICA-occlusion or high-grade stenosis were investigated, respectively, in the study by Bücke et al. (22).

Complications and Recurrent Stroke

The rates of procedural complications (any complications, clot migration, groin hematoma, rescue therapy, vasospasm, vessel dissection, and vessel perforation), pneumonia, and recurrent stroke were comparable between the BT and EVT alone groups (**Supplementary Tables 6, 7** and **Supplementary Figures 76–95**).

Sensitivity Analysis

Sensitivity analysis was performed by sequentially omitting individual studies and evaluating the pooled results of the remaining studies. In the unadjusted analysis, sensitivity analysis data related to all outcomes except HT were consistently reported with the full pooled results, suggesting the stability and reliability of the analyses (**Supplementary Figure 41**). Sensitivity analyses with adjusted data produced inconsistent results for in-hospital mortality, good outcome at discharge, sICH, HT, and early recovery at 24 h in the BT group. However, no divergent trends were observed in other outcomes (**Figures 5C**, **6C** and **Supplementary Figures 3, 10, 21, 41, 96–115**).

Publication Bias

Begg's funnel plots in the unadjusted and adjusted analyses exhibited slight asymmetry, and Egger's linear regression tests confirmed the presence of publication bias in the analysis of some efficiency and safety outcomes (**Supplementary Figures 116–138**), involving the unadjusted analysis of aICH ($P_E = 0.088$), vessel dissection ($P_E = 0.068$), and number of thrombectomy device passes ≤ 2 ($P_E = 0.024$) and in the adjusted analysis of 90-day good outcome ($P_E = 0.018$), successful reperfusion ($P_E = 0.053$), number of thrombectomy device passes ≤ 2 ($P_E = 0.011$), any procedural complications ($P_E = 0.002$), and clot migration ($P_E = 0.016$). However, after adjustment using the "trim-and-fill" method, the test results for all outcomes remained stable except for the unadjusted analysis of number of the thrombectomy device passes ≤ 2 in the random model (**Supplementary Table 9**).

RCT Analysis

Considering that RCTs could provide a higher level of evidence, we made further comparisons in the six RCT studies included in the present meta-analysis (**Supplementary Table 10**). The unadjusted and adjusted analyses showed a similar rate of 90-day good outcome between the BT and EVT alone groups (cOR 1.293, 95% CI 0.940–1.779; aOR 1.201, 95% CI 0.987–1.461) (**Supplementary Figures 139, 140**). Moreover, no significant effect of IVT pretreatment on 90- day excellent outcome was found (cOR 1.035, 95% CI 0.803–1.334; aOR 1.015, 95% CI 0.781–1.319) (**Supplementary Figures 141, 142**). However, BT treatment resulted in lower mortality within 90 days than EVT alone treatment (cOR 0.567, 95% CI 0.349–0.921; aOR 0.584, 95% CI 0.446–0.765) (**Supplementary Figures 143, 144**), consistent with the above overall results. Moreover, the unadjusted analysis revealed that BT treatment performed better than EVT alone in terms of successful reperfusion (cOR 1.228,

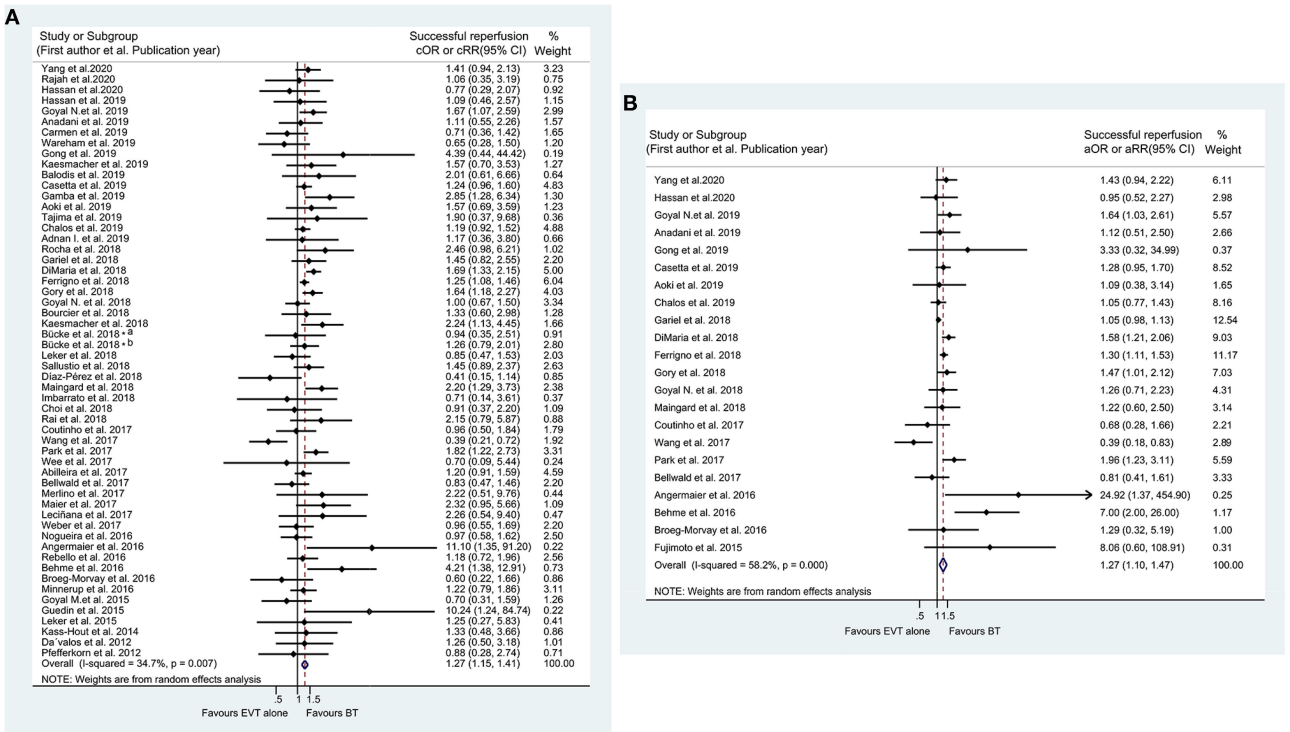

FIGURE 4 | Forest plots of studies assessing successful reperfusion in unadjusted **(A)** and adjusted **(B)** analysis. ICA, internal carotid artery. *The acute intracranial vessel occlusion patients with (a) or without (b) concomitant ipsilateral ICA-occlusion or high-grade stenosis were investigated, respectively, in the study by Bücke et al. (22).

95% CI 1.011–1.492), whereas the adjusted analysis showed no difference between the two treatments (aOR 1.058, 95% CI 0.988–1.133) (**Supplementary Figures 145, 146**). In addition, a similar incidence of sICH was observed between BT and EVT alone, in keeping with the overall pooled results (cOR 1.281, 95% CI 0.864–1.899; aOR 1.323, 95% CI 0.871–2.010) (**Supplementary Figures 147, 148**). The graphical abstract is shown in **Figure 8**.

DISCUSSION

The present meta-analysis based on 93 studies with available full-text source suggested a potential beneficial effect of BT on 90-day functional outcomes and successful reperfusion in AIS patients with LVOs compared with EVT alone. Moreover, the rate of 90-day mortality was lower with BT, without any increase in the incidence of sICH. These benefits were consistently observed in both adjusted and unadjusted analyses. Although the adjusted analysis indicated that BT may be associated with sICH and HT, the sensitivity analysis confirmed a lack of statistical correlation after the exclusion of individual studies. Notably, IVT pretreatment did not result in a delay in the time from onset to groin puncture in EVT. The current study also showed that BT was associated with an increase in any ICH compared with EVT alone, mostly a higher incidence of aICH. Furthermore, significant differences in the occurrence of a dramatic improvement, evaluated using the NIHSS score at discharge/7days, were detected in favor of BT, but not in early recovery at 24 h after admission. In addition, the likelihood of number of thrombectomy device passes ≤2, procedural complications, pneumonia, and recurrent stroke was similar between BT and EVT alone.

A previous study published in 2012 by Dávalos et al. showed that compared with EVT alone, BT with Solitaire FR was associated with better functional outcomes, whereas it was not relevant to successful recanalization, sICH, and mortality (23). Meanwhile, Pfefferkorn et al. also revealed that patients treated with BT were more likely to have a better outcome than those treated with EVT alone, whereas there was no significant difference in successful recanalization and mortality (24). Furthermore, Guedin et al. disclosed that BT could facilitate successful recanalization although it was not associated with better functional outcomes, mortality, and sICH incidence in AIS patients compared with EVT alone (25). In 2018, Ferrigno et al. suggested that pretreatment with IVT tended to improve functional outcomes and successful reperfusion, as well as reduced the mortality rate without increasing the sICH incidence (26). In contrast, Kass-Hout et al. showed that the odds of good functional outcomes, successful reperfusion, lower mortality rate, and sICH were not significantly different between treatments with BT and EVT alone, consistent with the results of Abilleira et al. and Gong et al. (11, 27, 28). Moreover, according to

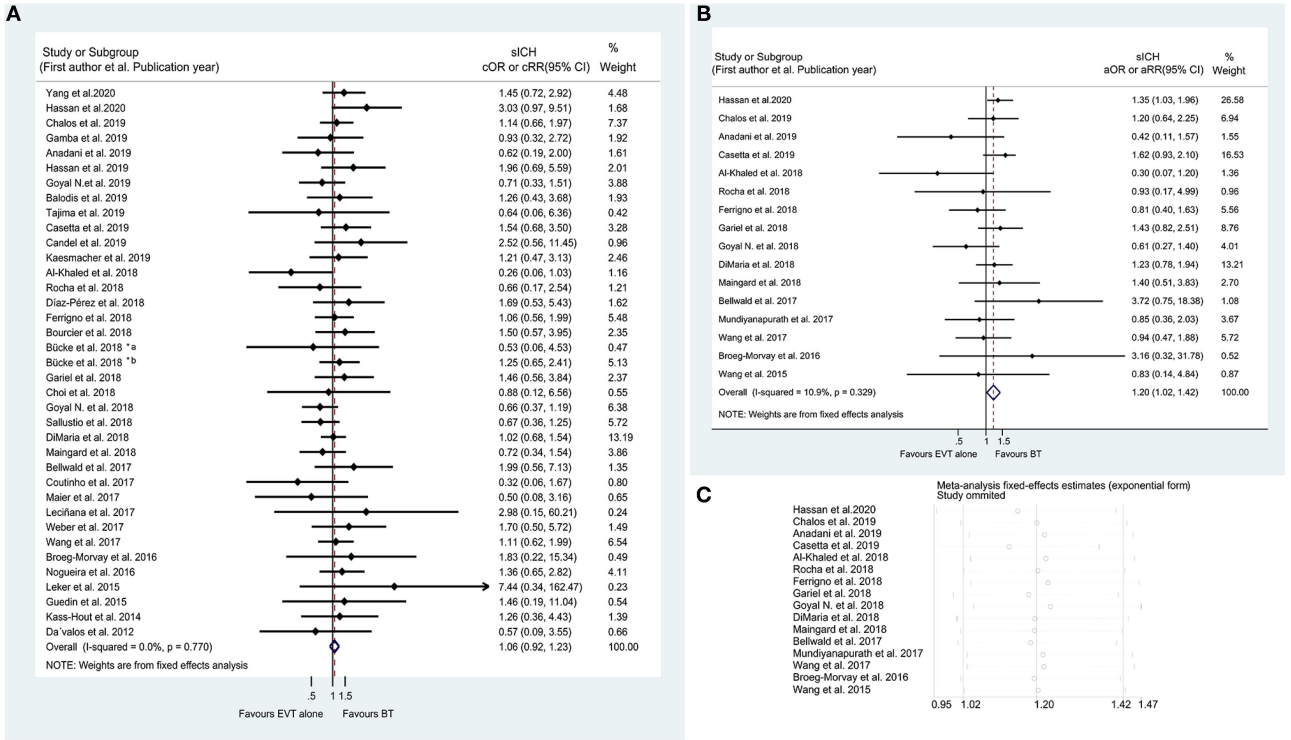

FIGURE 5 | Forest plots of studies assessing sICH in unadjusted **(A)** and adjusted **(B)** analysis with related sensitivity analysis **(C)**. sICH, symptomatic intracranial hemorrhage; ICA, internal carotid artery. *The acute intracranial vessel occlusion patients with (a) or without (b) concomitant ipsilateral ICA-occlusion or high-grade stenosis were investigated respectively in the study by Bücke et al. (22).

the study by Hassan et al. in 2020, BT was not related to the likelihood of good functional outcomes, successful reperfusion, and lower mortality. However, it was associated with a higher incidence of sICH (29). Therefore, whether pretreatment with IVT could benefit AIS patients with LVOs remains unclear. The current meta-analysis indicated that BT was associated with the likelihood of good functional outcomes, successful reperfusion, and lower mortality without time delays and sICH occurrence, thus providing theoretical evidence in favor of BT.

Given the controversial results from different studies, the present meta-analysis considered and summarized the reasons for the discrepancies. First, there was a selection bias due to the treatment indication of IVT (e.g., most patients in the EVT alone group were ineligible for IVT, whereas BT was performed in patients who were eligible for IVT) (9, 10). Second, most studies comparing BT and EVT alone were observational *post hoc* analyses of clinical trials, including RCTs, that divided patients into the EVT and IVT groups (9, 30). Third, the criteria of time from onset to intervention were different for the BT and EVT alone groups, and the indication of the timing of EVT treatment also differed across various studies (e.g., within 6 or 8 h from onset to treatment) (9, 10). Finally, the discrepancies in results could also be attributed to the various MT devices and the different IVT drugs and their doses used in AIS patients in numerous studies (9, 27, 30). Larger RCTs with complete adjustments for confounding factors are needed in the future.

Recently, the DIRECT-MT (Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: A Multicenter Randomized Clinical Trial) study disclosed that among patients who were eligible for both intravenous alteplase treatment and EVT, EVT alone was non-inferior to BT in terms of functional outcomes (12). The results of this RCT were consistent with those of the meta-analysis by Kim et al. (31), which was also supported by the findings of a meta-analysis in tissue plasminogen activator eligible patients (32). Meanwhile, our subgroup analysis with six RCTs indicated that BT and EVT alone performed similarly in improving the functional outcomes. However, compared with EVT alone in RCTs, BT treatment resulted in lower mortality within 90 days, consistent with our overall results. Although other recent meta-analyses and the present study all showed that IVT pretreatment provided additional benefits to those of EVT in terms of clinical outcomes without evidence of safety concerns, a notable point is that these studies did not perform adjustment for various biases, especially when patients eligible and ineligible to IVT were all included in the BT group (33, 34). Therefore, the meta-analysis results should be further validated in well-designed studies in the future.

The studies included in the current meta-analysis mainly focused on anterior circulation occlusion rather than posterior circulation occlusion, and only seven studies compared BT with

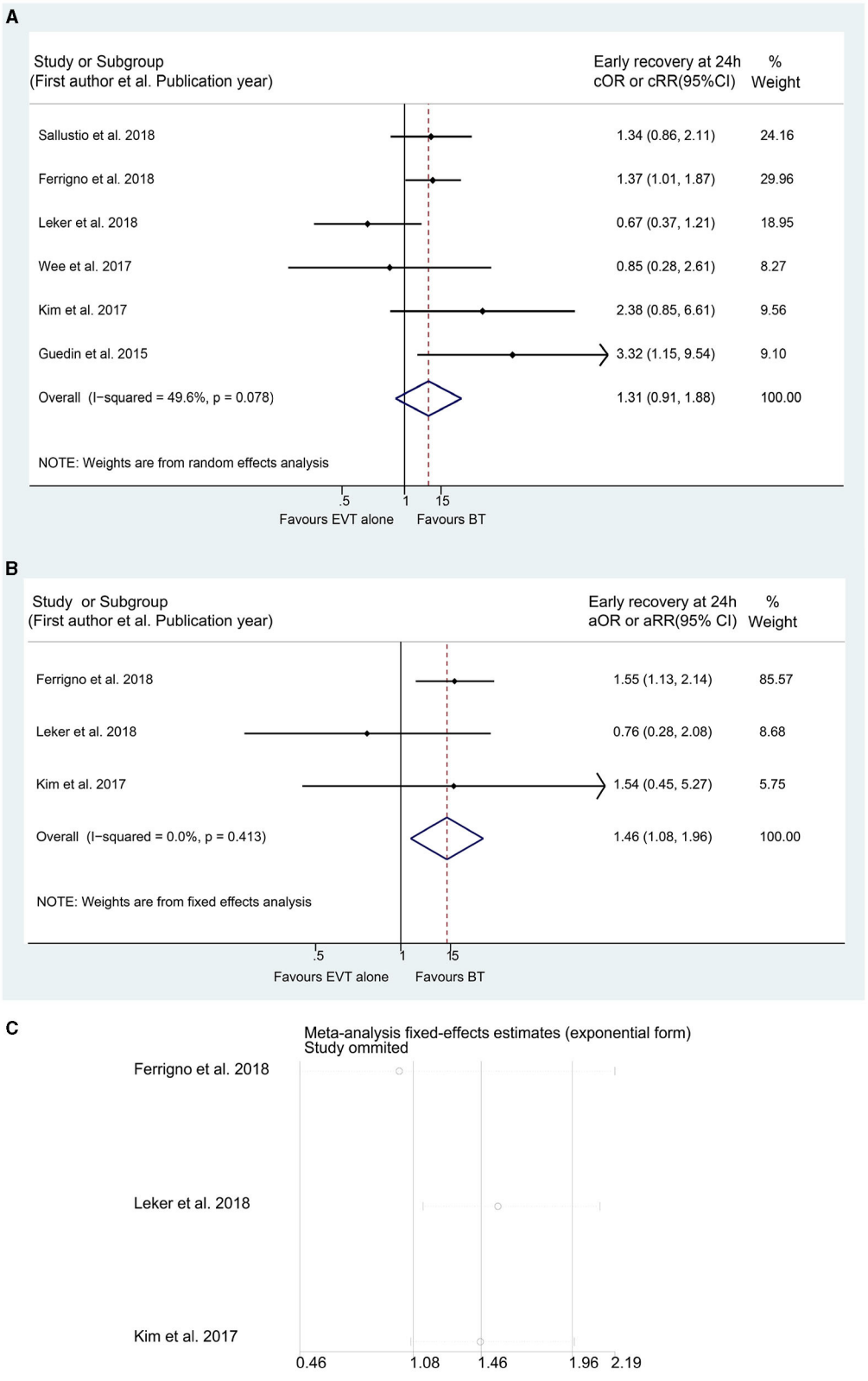

FIGURE 6 | Forest plots of studies assessing early recovery at 24 h in unadjusted **(A)** and adjusted **(B)** analysis with related sensitivity analysis **(C)**.

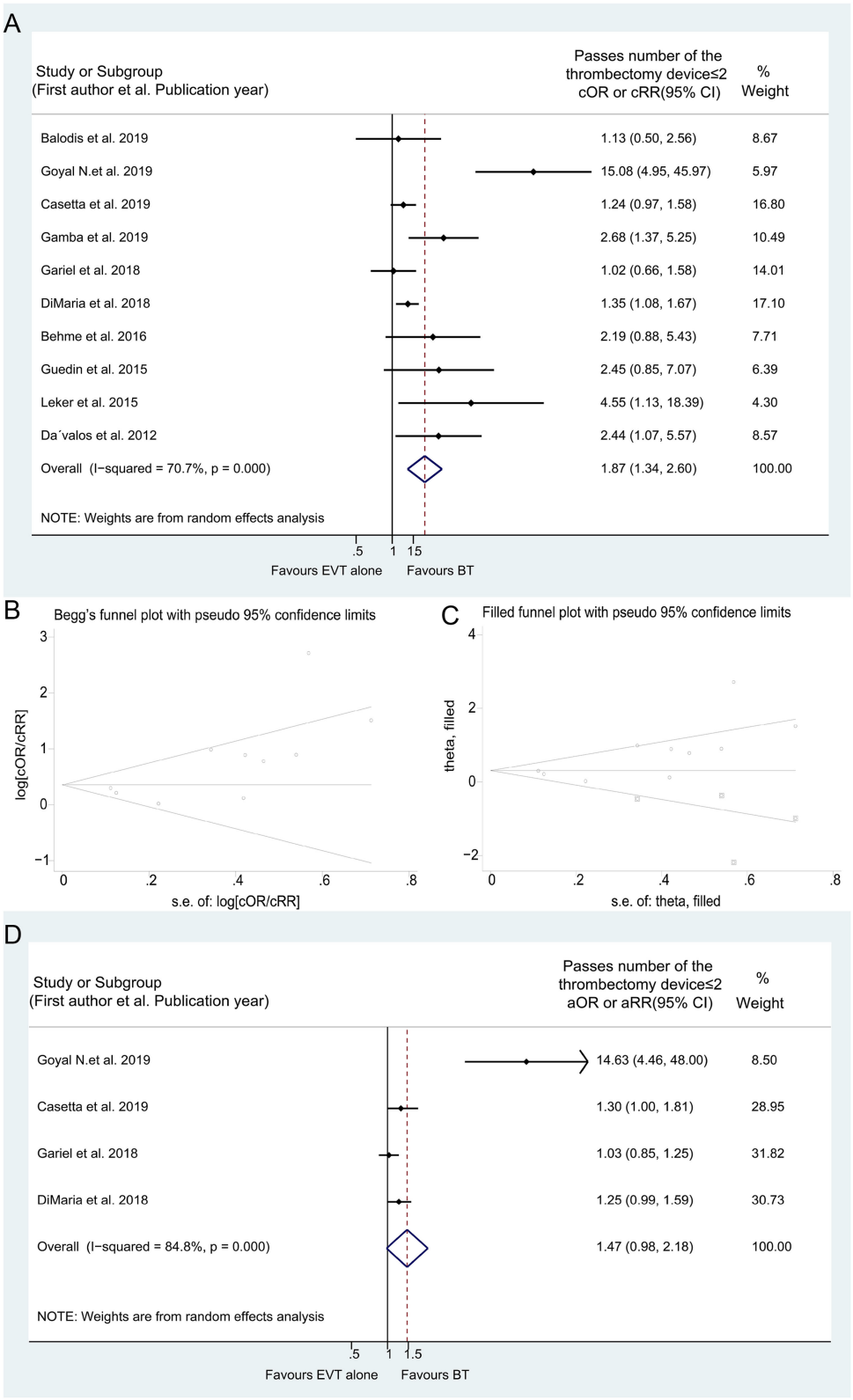

FIGURE 7 | Forest plots of studies assessing number of passes of the thrombectomy device ≤2 in unadjusted analysis **(A)** with related Begg's funnel plots **(B)** and "Trim and fill" analysis **(C)**, and in adjusted analysis **(D)**.

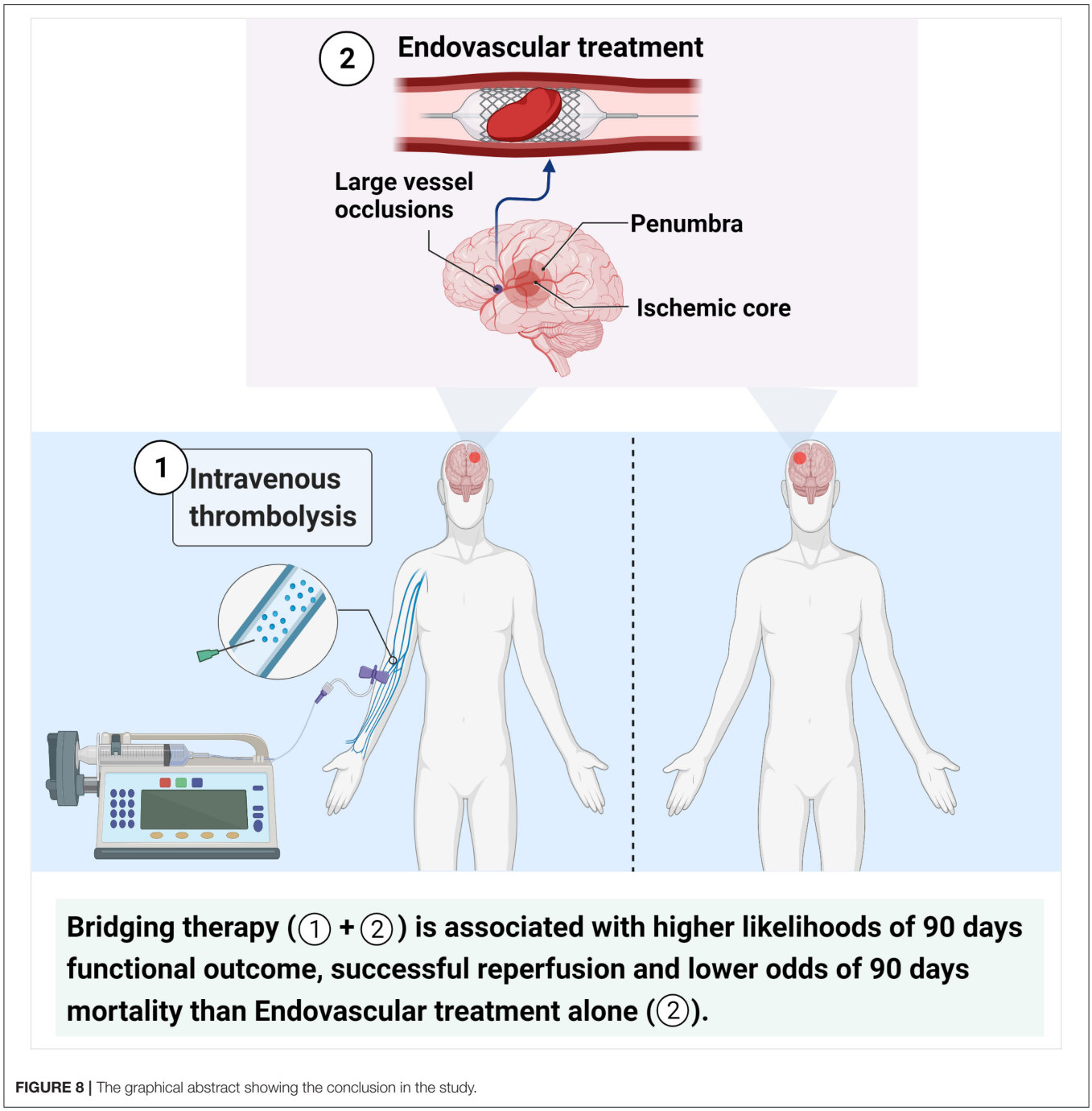

FIGURE 8 | The graphical abstract showing the conclusion in the study.

EVT alone in AIS patients with posterior circulation occlusion (**Supplementary Table 3**). According to the pooled results, BT could improve the 90-day functional outcomes and reduce 90-day mortality and the incidence of any bleeding in posterior circulation occlusion (**Supplementary Figures 4, 22, 56**), which indicates the benefits of BT for AIS patients with posterior circulation occlusion. Subgroup analyses by ethnicity were still conducted for the comparison of each outcome although the proportion of studies performed in an Asian population was low. The synthesized results in the adjusted analysis showed that BT was associated with 90-day functional outcomes, whereas the rates of mortality and successful reperfusion were similar in the BT and EVT alone groups in Asian patients, which differ from the results in Caucasian patients (**Supplementary Figures 9, 23, 32**). Furthermore, the meta-analysis with only three studies on tandem lesions showed that the rate of 90-day good outcome did not significantly differ between the two groups. However, the rate of successful reperfusion seemed to be higher in the BT group than in the EVT alone group (**Supplementary Figures 10, 31**). The number of studies and sample sizes in the above subgroup analyses were relatively small. Hence, more cohort studies are warranted to verify these findings.

Several limitations of the present meta-analysis should be acknowledged. First, selection bias due to IVT indication and unmeasured confounders was not considered in the current meta-analysis despite the pooling of adjusted outcome data from available studies (**Supplementary Table 5**). Second, a pooled subgroup analysis by thrombectomy device type and used drugs, as well as the doses of IVT drugs, was not conducted in this meta-analysis to further investigate the differences in outcomes between the two groups (although these variables are summarized in **Supplementary Table 3**). Third, sensitivity analyses with adjusted data showed inconsistent results for in-hospital mortality, good outcome at discharge, sICH, HT, and early recovery at 24 h, which suggested that the relevant results should be explained on the basis homogeneous studies. Nevertheless, the sensitivity analysis showed stability and reliability of the unadjusted analysis for the above outcomes in addition to HT. Fourth, the definitions of sICH were diverse among the original studies (**Supplementary Table 1**), which might have resulted in heterogeneous outcomes. Finally, publication biases for some unadjusted and adjusted outcomes were detected in the included studies. Nevertheless, after adjusting for publication bias, the results for all outcomes remained stable except for the unadjusted outcome of number of thrombectomy device passes $\leq$2 (**Supplementary Table 9**). Hence, the results from the unadjusted analysis of number of thrombectomy device passes should be interpreted with caution, and the significant association may not be true.

In conclusion, compared with EVT alone, pretreatment with IVT is associated with a higher likelihood of 90-day good and excellent functional outcomes and successful reperfusion, and lower odds of 90-day mortality in patients with AIS with LVOs. Moreover, the occurrence of sICH, 24 h early recovery, and number of thrombectomy device passes $\leq$2 did not significantly differ between the two groups. The results of this study provided evidence for the clinical choice of IVT before EVT, although further studies are needed to confirm these findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

Q-WD and F-LY conceived and designed the study and advised on critically revising the manuscript and interpreting the data. SL and GL selected the extracted the qualified studies from databases. SL and D-DL extracted data with predefined electronic forms. SL, J-SZ, and Q-WD participated in synthesized data and statistical analysis. YL and J-SZ carried out the sensitivity analysis and publication bias. SL and Q-WD performed the NOS score. SL, D-DL, GL, and YL prepared figures and tables. SL drafted the manuscript. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.697478/full#supplementary-material

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STUDY PROTOCOL
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A Prospective Multicenter Registry on Feasibility, Safety, and Outcome of Endovascular Recanalization in Childhood Stroke (Save ChildS Pro)

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Rationale: Early evidence for the benefit of mechanical thrombectomy (MT) in pediatric patients with intracranial large vessel occlusion has been shown in previous retrospective cohorts. Higher-level evidence is needed to overcome the limitations of these studies such as the lack of a control group and the retrospective design. Randomized trials will very likely not be feasible, and several open questions remain, for example, the impact of arteriopathic etiologies or a possible lower age limit for MT. Save ChildS Pro therefore aims to demonstrate the safety and effectiveness of MT in pediatric patients compared to the best medical management and intravenous thrombolysis.

Design: Save ChildS Pro is designed as a worldwide multicenter prospective registry comparing the safety and effectiveness of MT to the best medical care alone in the treatment of pediatric arterial ischemic stroke (AIS). It will include pediatric patients (<18 years) with symptomatic acute intracranial arterial occlusion who underwent either MT or best medical treatment including intravenous thrombolysis.

Outcomes: The primary endpoint of Save ChildS Pro is the modified Rankin Scale score at 90 days post-stroke. Secondary endpoints will comprise the decrease of the Pediatric National Institutes of Health Stroke Scale score from admission to discharge and rate of complications.

Discussion: Save ChildS Pro aims to provide high-level evidence for MT for pediatric patients with AIS, thereby improving functional outcome and quality of life and reducing

the individual, societal, and economic burden of death and disability resulting from pediatric stroke.

Clinical Trial Registration: Save ChildS Pro is registered at the German Clinical Trials Registry (DRKS; identifier: DRKS00018960).

Keywords: stroke, ischemic stroke, arterial ischemic stroke, thrombectomy, mechanical thrombectomy, intravenous thrombolysis, childhood stroke, pediatric stroke

INTRODUCTION

Arterial ischemic stroke (AIS) affects 1.3 to 1.6 per 100,000 children every year in developed countries (1–3), and outcomes are potentially severe, with 70% retaining long-term neurological deficits, 20% suffering recurrent strokes, and 10% of strokes resulting in death of the child (4–6). Risk factors for adult stroke such as atherosclerosis are nearly non-existent in pediatric stroke, so that knowledge and evidence of adult stroke cannot be extrapolated to children. Moreover, a lack of recruitment led to the termination of the prospective randomized TIPS (Thrombolysis in Pediatric Stroke) trial designed to assess the safety of intravenous tissue-type plasminogen activator (iv-tPA) in pediatric patients, highlighting the challenges of randomizing children with acute stroke (7). For mechanical thrombectomy (MT) in adults, several randomized clinical trials published in 2015 have shown the efficacy and safety of endovascular recanalization for large vessel occlusions (LVOs) with large effect size (8). In children, after several case series (9, 10), the retrospective Save ChildS Study recently provided the first systematic evidence for the safety of MT in children (11–13). In this study, the rate of recanalization and adverse events was comparable to large randomized controlled trials in adults, and neurological outcomes of the children were generally favorable. However, definitive conclusions cannot be drawn given the limitations of the Save ChildS Study, which include the lack of a control group of LVO patients not treated by MT and the retrospective design (14). Important questions remain, such as a possible lower age limit to perform thrombectomy in children or the impact of specific etiologies such as cerebral arteriopathies on the safety and efficacy of MT.

With the abovementioned difficulties in recruiting pediatric stroke patients for randomized controlled trials together with the ethical concerns about randomizing children into a non-MT group on the basis of the current knowledge, prospective randomized trials on MT in children are unlikely to succeed. Therefore, a prospective multicenter registry is considered the best option to collect further evidence for performing interventional recanalization in childhood stroke (14, 15).

The primary objective of the Save ChildS Pro registry is therefore to generate evidence for the use of MT in childhood stroke under the hypothesis that MT is safe and results in a high rate of good clinical outcomes compared to the best medical treatment including intravenous thrombolysis. The Save ChildS Pro registry further serves the purpose of defining selection criteria for MT in pediatric patients, especially for potentially vulnerable subgroups such as very young children, children with AIS due to arteriopathy, and children in the late therapeutic window.

METHODS

Design

Save ChildS Pro is a worldwide multicenter prospective registry that aims to compare the safety and effectiveness of MT to the best medical care alone (including intravenous thrombolysis) in the treatment of pediatric AIS. As of January 2020, 50 centers in nine countries (Germany, Switzerland, Austria, Italy, Sweden, United States, Australia, Argentina, Canada) have agreed to participate. Patient data will be entered through a web-based interface (Eppdata).

Save ChildS Pro is registered at the German Clinical Trials Registry (DRKS; identifier DRKS00018960) and has been approved by the ethics committee of the University of Muenster, Muenster, Germany, in accordance with the Declaration of Helsinki, with waiver of informed consent due to anonymization of the submitted data.

Patient Population

Patients presenting with AIS from January 1, 2020, will be considered for prospective study enrolment.
The following inclusion criteria apply:

- clinical diagnosis of acute ischemic stroke
- confirmed diagnosis of arterial occlusion consistent with symptoms, including occlusion of terminal carotid artery, middle cerebral artery (M1, M2, M3 segments), basilar artery, anterior cerebral artery (A1, A2 segments), or posterior cerebral artery (P1, P2 segments)
- endovascular treatment (EVT) attempted (i.e., groin puncture initiated, including all cases where EVT failed or was interrupted) or best medical treatment including intravenous thrombolysis
- age <18 years

The following is the exclusion criterion:

- perinatal stroke

Study Groups

Endovascular Group

Patients treated with MT (i.e., groin puncture initiated, including all cases where EVT failed or was interrupted), according to established clinical practice, belong to the endovascular group.

Best Medical Treatment Group

The best medical treatment group includes patients who are treated with best medical therapy (including systemic thrombolysis), according to established clinical practice.

OUTCOMES

Primary Outcomes

The primary endpoint of Save ChildS Pro is the patient's modified Rankin Scale score (mRS) at 90 days post-stroke assessed with a shift analysis.

Secondary Outcomes

Secondary endpoints will comprise the decrease of the Pediatric National Institutes of Health Stroke Scale (PedNIHSS) score from admission to discharge and rate of complications. The study will undergo an interim analysis after the first 50 patients have been enrolled.

Clinical and Radiological Assessment

The following baseline and disease characteristics will be assessed at the timepoint admission, treatment, 24 h after treatment, discharge from hospital, and at day 90 (±10 days).

Admission

- Patient data (age, year of birth, gender)
- Patient logistics (symptom onset, admission weekday, date and time of admission, date and time of admission imaging, date and time of last known well, date, and time of symptom onset, referral from other hospital)
- Pre-existing diseases
- Medication
- mRS at admission (deficits prior to stroke)
- PedNIHSS
- Imaging findings (type of admission imaging, occluded vessel, computed tomography or magnetic resonance imaging for Alberta stroke program early computed tomography (ASPECT) score, ASPECT score)

Treatment

- Treatment with iv-tPA
  - date and time of iv-tPA
  - dose
- EVT
  - timing (date and time of first angiography image, time of first pass, time of final recanalization result)
  - type of anesthesia
  - occluded vessel
  - stenosis or occlusion in a proximal vessel
  - number of passes
  - morphologic appearance (normal, arteriopathy, other)
  - type of treatment and devices used,
  - treatment complications [vasospasm, intracerebral hemorrhage (ICH), dissection, other]

24 h

- PedNIHSS
- Imaging findings (persistent or new occlusion, type of follow-up imaging, ASPECTS)
- Adverse events (symptomatic ICH, non-symptomatic ICH, dissection, other)

Discharge

- Patient logistics (length of stay, transfer destination)
- PedNIHSS
- mRS
- Pediatric Stroke Outcome Measure (PSOM)
- Stroke etiology (according to the childhood arterial ischemic stroke standardized classification and diagnostic evaluation classification)
- Adverse events (symptomatic ICH, non-symptomatic ICH, hemicraniectomy, external ventricular drainage, other)

Day 90 ± 10

- mRS
- PSOM
- Adverse events (symptomatic ICH, non-symptomatic ICH, hemicraniectomy, external ventricular drainage, pneumonia, recurrent stroke, other)
- Location (care facility, home)

Data Collection

Data will be collected as part of routine clinical care.

Funding

Eppdata will provide data services for free in the beginning; later on, acquisition of funding is planned.

Data Ownership

Each participating center remains owner of its data. Upon request, data can be retracted from the database.

Publication Policy

Inclusive (multiauthor): those doing the work will receive the credit, every center that contributes a relevant number of cases will have the right of coauthorship in publications.

Number of Sites

Not limited.

Study Design

Non-interventional, open-label, prospective, multicenter, observational registry study.

Statistical Analyses

Summary tables for patient demographics and baseline characteristics will be provided, and comparisons will be made between study arms for the endovascular and best medical treatment groups. The primary and secondary outcomes will be summarized and compared between study groups for the endovascular and best medical treatment groups.

In general, summaries will be presented by occlusion location within treatment group in the relevant analysis populations. Descriptive statistics for dichotomous/categorical variables will include the number and percent of subjects in each category (including missing), by treatment group. Descriptive statistics

for continuous variables will include the number of non-missing and missing variables, minimum, lower quartile, median, upper quartile, maximum, mean, and standard deviation, stratified by treatment group. Regarding comparisons between treatment groups, χ^2 test (Fisher exact test where appropriate) will be utilized for the comparison of categorical variables, and the *t* test (or the Mann–Whitney *U*-test when appropriate) will be utilized for the comparison of continuous variables. Data for the primary outcome will be presented by treatment group. Confidence intervals for dichotomous or ordinal endpoints will be reported on the odds ratio scale.

CONCLUSION

Save ChildS Pro is a worldwide multicenter prospective registry to compare the safety and effectiveness of endovascular thrombectomy to the best medical care alone (including intravenous thrombolysis) in the treatment of pediatric AIS. Save ChildS Pro will provide high-level evidence regarding effectiveness and safety of thrombectomy for pediatric AIS, improving the ability to determine which children are likely to benefit from this therapy.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Münster. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PS and MW contributed to conceptualization and design. All authors drafted the manuscript, critically revised it and collect the data.

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REVIEW
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Evidence-Based Updates to Thrombectomy: Targets, New Techniques, and Devices

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Endovascular thrombectomy (EVT) has been validated in several randomized controlled trials in recent years for its efficacy in the treatment of acute ischemic strokes (AIS) and is now the standard of care according to international guidelines. However, in about 20% of EVT procedures, recanalization is not achieved, and over 50% of patients who undergo EVT still do not have good functional outcome. In this article, we provide an extensive review of the latest evidence and developments in the field of EVT, with particular focus on the factors that improve patient outcomes. These factors include new and adjunctive techniques such as combination of direct aspiration and stent retriever, intra-arterial urokinase or 2b/3a inhibitors, rescue stenting, as well as novel devices including balloon guide catheters and the newer generations of aspiration catheters and stent retrievers. We also examined the latest notion of using first-pass effect (FPE) as the target to achieve during EVT, which has been associated with an improved functional outcome. While the field of EVT has been rapidly evolving, further research is required in specific AIS patient populations such as those with large ischemic core, late presentation beyond 24 h, posterior circulation strokes, and with distal medium vessel occlusion or tandem lesions to better assess its efficacy and safety.

Keywords: acute stroke, ischaemic, thrombectomy, stent retriever, aspiration, devices, reperfusion

INTRODUCTION

In recent years, several randomized clinical trials in acute ischemic stroke (AIS) have validated and cemented the efficacy of endovascular thrombectomy (EVT) in proximal anterior circulation occlusions (1–6). This revolutionary treatment modality has now emerged as the standard of care in international guidelines and is considered level 1 class A evidence (7, 8). Although EVT has strong evidence for the treatment of AIS, it is unable to achieve recanalization in approximately 20% of AIS patients (9, 10). Moreover, up to half of the patients who undergo EVT still do not have a good functional outcome at 3 months, and this includes patients who do have good reperfusion (6). Nonetheless, the field continues to evolve rapidly, with constant innovations. In this review, we

attempt to summarize the latest evidence-based developments to the field of EVT in the context of AIS, in an attempt to determine what will allow us to improve patient outcomes.

TARGETS

eTICI as Measurement of Success in Thrombectomy

The initial measure of EVT success was extrapolated from cardiology radiological results with the thrombolysis in myocardial infarction score (TIMI). This was quickly adapted into a more cerebral circulation-based thrombolysis in cerebral infarction (TICI) score and subsequently the modified thrombolysis in cerebral infarction score (mTICI) where a mTICI 2b or greater score, equivalent to >50% reperfusion of the affected territory, is considered a successful reperfusion for EVT (11).

Recently, a group of authors examined the data from the HERMES trials and proposed a revised TICI grading scale, the expanded TICI (eTICI). This is a 7-point grade from eTICI 0 to eTICI 3 which assessed the degree of reperfusion in a more quantitative manner by splitting the TICI 2b into more granular divisions (12). In brief, eTICI grade 0 is equivalent to no reperfusion or 0% filling of the downstream territory; eTICI 1 reflects thrombus reduction without any reperfusion of distal arteries; eTICI 2a is reperfusion of less than half or 1–49% of the territory; eTICI 2b50 is 50–66% reperfusion (**Figure 1A**), eTICI 2b67 is 67–89% reperfusion, exceeding TICI 2B but below TICI 2C (**Figure 1B**), eTICI 2c is equivalent to TICI 2C which represents 90–99% reperfusion or near complete; and eTICI 3 is complete or 100% reperfusion, similar to TICI 3. The authors found that after adjustment of covariates, eTICI remained an independent predictor of outcome on multivariate analysis of the mRS shift, and more importantly, adjacent categories of 2a, 2b50, and 2b67 are important distinctions with clinical implications.

In previous established consensus recommendations for reperfusion target in endovascular thrombectomy, successful reperfusion was defined as exceeding 50% of the territory (13). Now with evidence that within the >50% reperfusion category, further subdivisions into 50–66%, 67–89%, and 90–99% help to identify meaningful differences in clinical outcomes, the authors of the paper therefore proposed to adopt eTICI 2b67 as the ideal threshold for defining successful reperfusion. Moving forward, considerations should be made to adopt a more granular scale which has better prognostic value and clinical utility.

First-Pass Recanalization: A New Target for Thrombectomy

With the advent of better equipment and improved devices for EVT, there have been increasingly better rates of successful reperfusion. Accordingly, the standard of care is constantly being re-evaluated to determine what is an achievable benchmark for AIS LVO patients. Recently, there has been a move to nominate a single pass-reperfusion standard as the target to achieve during EVT. Several studies and a recent meta-analysis have shown that there is clinical rationale behind this first-pass reperfusion with improved functional outcomes and such successful initial attempts have been termed first-pass effect (FPE) (14). In the aforementioned meta-analysis which composed 21 studies and 2,747 patients, FPE patients not only displayed better functional outcomes but also had lower mortality rates than patients who did not have FPE. Interestingly, they also showed that complete reperfusion with a single pass (FPE-mTICI 3) was associated with better 3-month outcomes compared with FPE-mTICI 2B (mRS 0–2, 66 vs. 46%; OR, 0.46; 95% CI, 0.037–0.57), better mortality rates (8 vs. 14%) and less intracranial hemorrhage (22 vs. 31%). However, it should be said that while FPE is desirable and clinical outcomes worsen with more attempts, the goal of thrombectomy is to recanalize the vessel, and recanalization after multiple passes is better than no recanalization at all (15).

Besides being used clinically, FPE mTICI ≥2B is increasingly being used to evaluate thrombectomy devices as a new benchmark. This is because in the latest trials, devices achieve >90% reperfusion rates, and there is very little differentiating them (16–18). A new threshold, FPE mTICI ≥2B or even FPE mTICI 2c-3, with its marked clinical improvement, is a potential way to evaluate these devices and tease apart their small differences, as we strive to achieve perfect stroke outcomes.

TECHNIQUES

Direct Aspiration vs. Stent Retriever: ASTER and COMPASS Trial

The two most common EVT techniques for reperfusion are *via* a stent retriever or aspiration with a large bore catheter. It remains a matter of debate as to which technique is superior, The Contact Aspiration vs. Stent Retriever for Successful Revascularization (ASTER) study was a randomized, open-label, blinded end-point superiority trial designed to address this problem. In this study, 381 patients were recruited, with 192 patients assigned first-line direct aspiration and 189 assigned to first-line stent retriever use. Successful reperfusion was achieved at similar rates with direct aspiration (85.4%) and stent retrievers (83.1%), $p = 0.53$. Nonetheless, this was a failed superiority trial that was underpowered to demonstrate a significant difference between the two techniques (17).

After the failure of the ASTER trial, the similar reperfusion rates between modalities led a North American group to change track and conduct a non-inferiority trial in 15 North American sites to once again compare the efficacy between large bore direct aspiration and stent retrievers. In this trial entitled COMPASS, 270 patients without a large early infarct core (ASPECTS > 6) and who presented within 6 h of onset were enrolled. Ultimately, 134 received direct aspiration as first-line treatment and 136 received stent retriever use as first-line treatment. Direct aspiration achieved 52% good functional outcomes at 3 months which was comparable with the 50% achieved by first-line stent retriever use and reached non-inferiority in the analysis ($p = 0{\cdot}0014$) (18). This trial was the landmark trial to provide level 1 evidence in support of direct aspiration, and the study authors also discussed that even in the event of failure of direct aspiration, the large

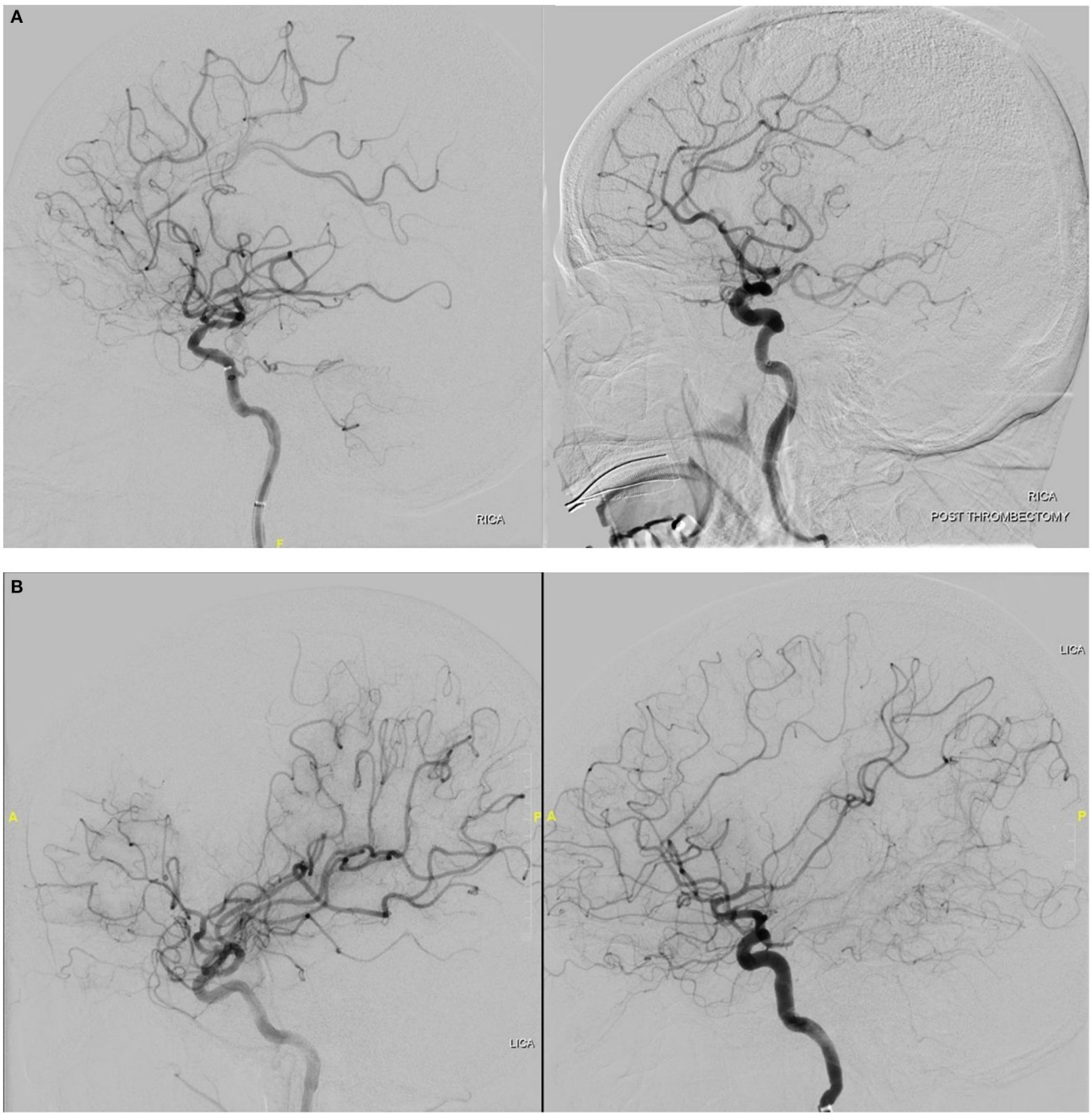

FIGURE 1 | (A) Cerebral digital subtraction angiography showing eTICI 2b50 recanalization in a patient with right MCA occlusion. **(B)** Cerebral digital subtraction angiography showing eTICI 2b67 recanalization in a patient with left MCA occlusion.

bore catheter is still at the clot face and a stent retriever can be quickly deployed over the thrombus. This resulted in the initial direct aspiration arm showing a significantly shorter procedural time than stent retriever use. There was also a mention of the additional benefit that aspiration catheters tend to be more affordable than stent retrievers. Nonetheless, the authors stressed that EVT technique should be tailored to the individual patient and clot characteristics for maximal efficacy.

Combined Techniques

Thrombectomy in many centers are now performed with the combination of a stent retriever and a distal aspiration catheter as well as a balloon guide catheter. These range from the stent retriever-assisted vacuum-locked extraction (SAVE) technique, the BAlloon guiDe with large bore Distal Access catheter with dual aspiration with Stent Retriever as Standard (BADDASS) approach, the aspiration–retriever technique for stroke (ARTS), a

stent retrieving into an aspiration catheter with proximal balloon technique (ASAP), or proximal balloon occlusion together with direct thrombus aspiration during stent retriever thrombectomy (PROTECT-PLUS) (19–24). These are several different variations on the same techniques for thrombectomy, all of which report a high rate of reperfusion, higher first-pass recanalization rates, lower number of attempts, and/or a lower rate of distal embolization. While it may be more expensive to use more equipment, this is offset by the improved first-pass recanalization rate and shorter procedure times which lead to better outcomes.

Adjunctive Intra-Arterial Treatment: Urokinase, tPA, and 2b/3a Inhibitors

The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial is an early study conducted before the use of stent retrievers or aspiration catheters. It provided some grounds for intra-arterial infusion of recombinant pro-urokinase resulting in recanalization in approximately 2/3 of stroke patients with MCA occlusions (25). However, there was a five times greater risk of symptomatic intracranial hemorrhage (SICH) with pro-urokinase and production was stopped before it could obtain US FDA approval as a thrombolytic agent. It has since gradually fallen out of use in the USA, although it is still commonly used in other parts of the world.

The use of thrombolytic agents in conjunction with other thrombectomy methods has rarely been described. If urokinase has the ability to treat microthrombi, it may be able to improve forward flow and perfusion which in turn could contribute to a reduction in infarct size and rate of SICH (26). In one study where urokinase was used in 15 patients in conjunction with thrombectomy, reperfusion was improved in eight patients (53.3%) (27). In other studies, the risk of bleeding and SICH did not appear to be increased with adjunctive tPA or urokinase (28–31). A larger study including 100 patients out of a total cohort of 991 patients who received intra-arterial urokinase administered during mechanical thrombectomy was recently published. While patients who had unsuccessful thrombectomy were included, the most common reason for instillation of intra-arterial (IA) urokinase in this study was incomplete reperfusion, which was defined as mTICI <3 and seen in 53 (53%) patients. The 100 patients treated with IA urokinase during EVT did not demonstrate an increased risk of SICH or mortality. Interestingly in the 53 patients with incomplete reperfusion, there was a significantly higher rate of mRS 0–2 at 3 months (27). This study provides the groundwork for the potential use of urokinase in incomplete reperfusion and may help in improving the chance for reperfusion in distal eloquent occlusions or tortuous distal anatomy. Ultimately, it will need to be validated in larger studies such as the upcoming Multi-arm Optimization of Stroke Thrombolysis (MOST) study (32).

DEVICES

Balloon Guide Catheter

The balloon guide catheter (BGC) is a simple upgrade from the typical guide catheter with a large lumen (6–9F) and an inflatable balloon on the distal tip of the catheter. It is used to generate flow arrest of blood and even flow reversal when negative pressure is applied to remove emboli generated during the EVT procedure and prevent embolic complications. This has been shown *in vitro* where experiments with a vascular phantom occlusion model showed that use of a BGC resulted in 50% reduction of soft clot fragments compared with a conventional guide catheter (33). Similarly, in an animal porcine model, a BGC provided reproducible flow arrest with the balloon inflated, and this translated into reliable flow reversal with manual aspiration using a regular syringe. In comparison, manual aspiration with a syringe in a similar sized conventional guide catheter resulted in oscillatory flow or even an occluding collapse of the walls of the distal vessel (34).

The benefits of BGC thrombectomy has been shown in multiple different studies. In the investigator-initiated TRACK registry which audits the Trevo device, 536 anterior circulation stroke patients of whom 279 (52.1%) had BGC placement showed that mTICI 2b-3 scores were higher in the BGC group (84 vs. 75.5%; $p = 0.01$) with better 3 months outcomes (57 vs. 40%; $p = 0.0004$) and mortality rate (13 vs. 23%; $p = 0.008$). This was despite aspiration catheter or intermediate catheter use being more common in the non-BGC group (35). In the NASA and STRATIS registries (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke), a similar effect was seen for 3-month functional outcomes. Moreover, in these two registries, the FPE was more often seen with the use of a BGC (36, 37). A meta-analysis of studies with BGC use which included 2,022 patients showed that BGC use was indeed associated with a higher chance of FPE (OR, 2.1; 95% CI, 1.65–2.55) (38).

As there were certain challenges with compatibility of BCGs and large-bore distal aspiration catheters, the industry is keen on designing novel aspiration catheters that are compatible with their BCGs (e.g., novel 7Fr Catalyst fits into 8Fr Flowgate or Flowgate2 BGC). The ASTER trial documented a trend toward better mTICI 3 and better clinical outcomes in BGC-treated patients using direct aspiration (17). In the PROTECT trial with 200 patients, the group using both direct aspiration and a BGC had shorter procedure times (29 vs. 40 min; $p = 0.002$), higher rate of successful recanalization (100 vs. 78%; $p = 0.001$) and a higher rate of complete reperfusions (70 vs. 39%; $p < 0.001$) compared with sole distal aspiration during MT (22). However, larger studies are needed for confirmatory evidence to substantiate the benefits of BGC use in direct aspiration for EVT. Finally it must be mentioned that despite all purported benefits, there have been no randomized controlled trials conducted to confirm the benefits of BGC use. This is largely due to the large sample size required to show the difference and the funding required for such a trial (39).

New Aspiration Catheters

The force of aspiration is directly proportional to the inner diameter (ID) of the catheter. Prior scientific examination has similarly established the powerful relationship of ID to pressure loss and flow rate in small vessels (40–42). To take advantage of this principle, three new larger bore 0.071- to 0.072-in aspiration catheters were recently introduced for stroke thrombectomy.

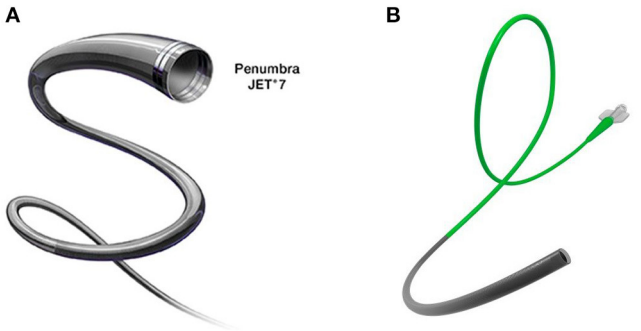

FIGURE 2 | (A) Jet 7 aspiration catheter from Penumbra with a 0.072-in (1.83 mm) inner lumen for greater aspiration force. **(B)** React 71 aspiration catheter from Medtronic (Fridley, MN, USA) with an overlapping nitinol coil and braid design for better navigability and pushability.

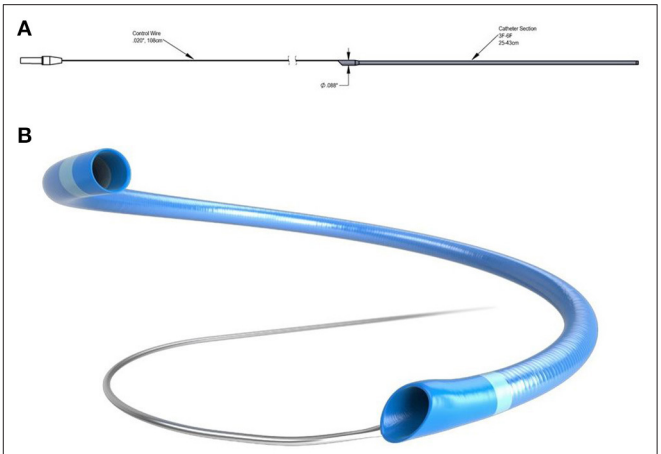

FIGURE 3 | (A,B) 6F R4Q aspiration catheter system from MIVI (Eden Prairie, MN, USA) where the proximal portion is replaced by a wire to increase aspiration flow rates.

These catheters are named the Jet 7, the Vecta 71, and the React 71 (**Figures 2A,B**). All three catheters are the largest bore direct aspiration catheters on the market that can fit within the current guide catheters and are able to generate a larger aspiration force. An early study looking at the navigability and efficacy of these aspiration catheters showed that they were able to reach the face of the clot in a high proportion (87%) of cases: 100% with React 71, 93% with Vecta 71, and 43% with Jet 7 ($p = 0.002$) (43). The rate of mTICI 2b-3 reperfusion was also high in all three catheters and was achieved in 92% of cases: 95% with React 71, 89% with Jet 7, and 89% with Vecta 71. These large bore catheters achieved a 39% FPE rate in this small series which provided early evidence for the use of these new catheters.

Most recently, a novel type of aspiration catheter has been introduced. The Anaconda advanced thrombectomy system (Biomed) is an aspiration catheter system that comprises a delivery catheter and a novel funnel-shaped aspiration catheter which can expand to fit the size of the vessel it is deployed in (44). The funnel shape is achieved by a stent mounted at and covered by the distal end of the catheter, which is deployed and can expand up to a maximum of 5 mm diameter, thus providing flow arrest for vessels of this size or smaller. This allows it to cause flow arrest akin to a BGC and consequently perform clot aspiration with a larger force as well as enable the catheter to accommodate larger clots and prevent distal emboli from fragments. It is, however, designed to be primarily used in conjunction with a stent retriever which is pulled inside the funnel that is subsequently closed and withdrawn. In an early study conducted by the company producing the device, the authors showed better first-pass reperfusion rates and fewer passes for revascularization compared with a BGC + stent retriever combination. Future independent studies will be needed to demonstrate the clinical efficacy of this new catheter device and its superiority to current aspiration thrombectomy technology.

The efficacy of aspiration catheters together with shorter procedural times and cost-effectiveness have pushed the development of even larger bore aspiration catheters. Currently, 8F 0.088-in (I.D.) aspiration catheters (Millipede 088, Perfuze Ltd;) and (0.088 in, Route 92 Medical, Inc., San Mateo, CA) have been proven feasible to navigate in preclinical models of the M1 segment and the basilar artery and to be superior in clot extraction compared with smaller bore catheters (45). However, in this study, there is no published clinical data on safety and efficacy profiles of these catheters from use in patients.

Aspiration catheters typically have a tapered design where the distal tip of the aspiration catheter is slimmer than the proximal shaft, to both increase suction capability while allowing for the possibility of distal access. In the end, there is a balance between the size of the inner diameter and the wall thickness of the aspiration catheter. The R^4Q aspiration catheter (MIVI Neuroscience, Inc., Eden Prairie, MN) is designed to sidestep these limitations by substituting the proximal three-quarters of the catheter shaft with a stainless-steel wire (46). The 6F R^4Q aspiration catheter system (**Figures 3A,B**) comprises a proximal pusher wire of 0.018 in and 117 cm length connected to a distal catheter of 25 cm length. It uses the guide catheter which this device is inserted into, to function as the proximal half of the catheter shaft, while the R^4Q aspiration catheter functions as the distal half of the aspiration catheter. The use of the guide catheter shaft allows it to have a larger catheter diameter with commensurately larger aspiration power. The R^4Q catheters come in 6F, 5F, 4F, and 3F sizes to fit to different vessel sizes. Unlike typical aspiration catheters, the suction is applied directly to the guide catheter and the R^4Q can be retracted into the guide catheter. These properties have the potential to translate into clinical aspiration thrombectomy advances and the initial clinical experience with the R^4Q system in a small cohort of 32 patients shows good reperfusion rates and a high rate of first-pass effect, which will need to be further validated in larger cohorts (47).

Cyclical Aspiration Pumps

Thromboaspiration for stroke thrombectomy is typically conducted by generating a static continuous vacuum either with a pump or a large syringe. In a study on cyclical aspiration,

a SOFIA Plus catheter (MicroVention Inc., Aliso Viejo, CA) had static (29 inHg) or cyclical (18–29 inHg, 0.5 Hz) aspiration employed using the digital CLEAR Aspiration System (Insera Therapeutics, Sacramento, CA) and eight thrombus aspiration experiments were conducted for each aspiration type in a flow model. The study showed that by varying the pressure dynamics through cyclical aspiration, it increased aspiration force on the occlusion as well as resulted in more successful clot clearance when compared with static aspiration (48). The cause of this improved ingestion may be due to the initial clot softening from dynamic compression or that dynamic friction is less than the static friction that occurs when the thrombus is stuck at the tip of the catheter. This was validated in a different study using various types of catheters with different inner diameters (0.054–0.088 in), where the use of cyclic aspiration (18–29 inHg, 0.5 Hz) resulted in better clot ingestion into the aspiration catheter and effectively reduced the rate of distal emboli (49). More recently, in one of the first clinical experience with cyclical aspiration for large-vessel strokes, investigators performed thrombectomy using the CLEAR^{TM} Aspiration System (Insera Therapeutics Inc., Dallas, TX) which yielded promising results. The authors reported high rate of TICI 3 FPE, which was achieved in 68.4% of the study cohort (26 of 38 patients), near-complete reperfusion (TICI 2c/3 FPE) in 76.3% (29/38), and substantial reperfusion (TICI 2b-67/3 FPE) in 78.9% (30/38). In addition, final revascularization results for the entire cohort (in one or multiple attempts) were TICI 3 in 86.8% (33/38), TICI 2c/3 in 94.7% (36/38), TICI 2b-67/3 in 97.4% (37/38), and TICI 2b/3 in 100% (38/38) (50). The high FPE rate also translated into neurological improvement and better functional outcome with 92.1% of the cohort achieving NIHSS improvement of at least 4 points at 24 h and 81.6% having good outcomes (mRS 0–2) at discharge. There were no symptomatic intracerebral hemorrhages and at 90 days, the all-cause mortality was low at 5.3%.

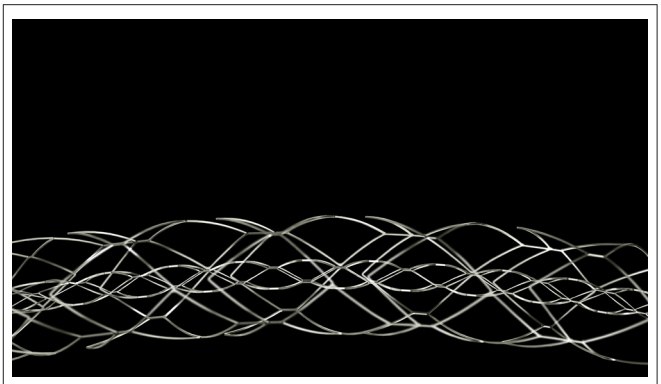

FIGURE 4 | EmboTrap reperfusion device (third-generation stent retriever) from Cerenovus (Miami, FL, USA).

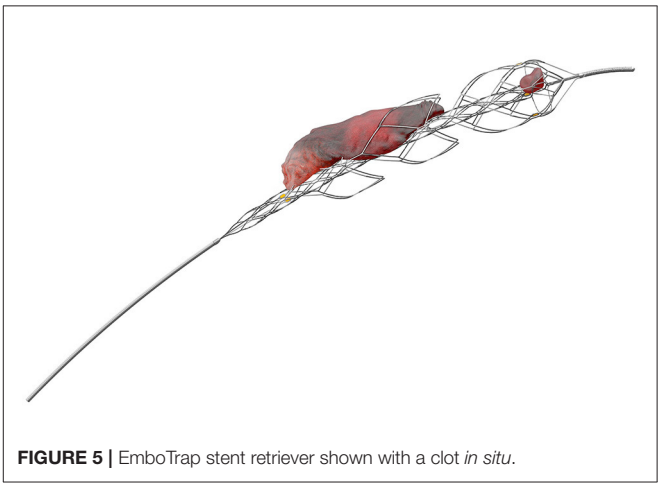

FIGURE 5 | EmboTrap stent retriever shown with a clot *in situ*.

Third-Generation Stent Retrievers

The second-generation Solitaire and Trevo stent retrievers have been widely used and contributed greatly to the fact that EVT is now the standard of care for LVO AIS. However, this technology for stent retrievers has also evolved over time with a recent explosive improvement in the technology. It should be mentioned that despite this, randomized controlled trials showing an improvement in recanalization, functional outcomes, and reduced complications compared with existing stent retrievers have yet to be performed.

The EmboTrap reperfusion device (Neuravi/Cerenovus) is a third-generation stent retriever with a dual-layer structure furnished with articulating petals and a distal capture zone, supposed to enable better grip on the clot and entrapment of clot fragments generated by the EVT procedure (**Figure 4**).

The efficacy of the Embotrap stent was validated by an open-label, single-arm, multicenter, prospective clinical trial conducted by the company which produced the stent, entitled Analysis of Revascularization in Ischemic Stroke with EmboTrap (ARISE II) which enrolled 227 patients (16). The mTICI ≥2b reperfusion within three passes was achieved in 80.2%, while the final mTICI ≥2b reperfusion rate was 92.5%. Good functional outcome of mRS 0–2 at 90 days was achieved by 67% of the cohort, with a mortality rate of 9%. Following this study, Embotrap was granted FDA approval for use in stroke thrombectomy. There are currently newer versions of the device, namely, the Embotrap 2 and Embotrap 3 in the market (**Figure 5**).

Another third-generation stent retriever is the three-dimensional (3D) revascularization device (Penumbra Alameda, CA, USA). A multicentric randomized control trial with 198 patients was performed to evaluate the safety and efficacy of this device in combination with an intermediate catheter (51). Out of the 198 recruited patients, 98 underwent thrombectomy with the 3D stent retriever (**Figure 6**) in conjunction with an intermediate catheter and was able to achieve mTICI 2b-3 reperfusion in 81.9% of the patients. This rate was significantly higher than the comparison arm, where direct aspiration alone with an intermediate catheter achieved only 69.8% mTICI 2b-3 reperfusion in 100 patients.

A new-generation stent retriever is the Versi, a nitinol stent retriever with two to four articulating segments expanding and reconfiguring under traction, during withdrawal, thus presumably facilitating clot trapping. An investigator-led clinical trial compared the third-generation Embotrap and Versi stents

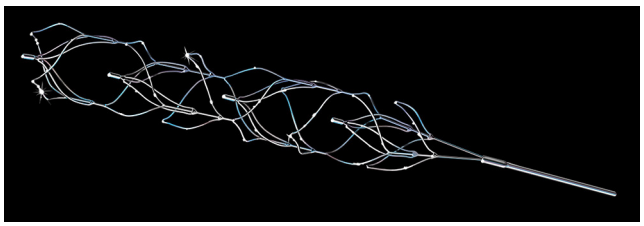

FIGURE 6 | Three-dimensional revascularization device from Penumbra.

with the earlier generation Solitaire and Trevo stent retrievers (52). They employed different flow models with various degrees of tortuosity to evaluate the different stent retrievers. The authors reported that the Versi had significantly better recanalization rates than the second-generation stent retrievers, while the Embotrap also had higher recanalization rates although not reaching statistical significance. The authors were able to discern that more severe tortuosity limited the effectiveness of earlier generation stent retrievers but not effectiveness of third-generation stent retrievers. The finding could explain increased efficacy of third-generation stent retrievers. Nonetheless, this was a study performed in several flow models and remains to be validated in animal models as well as in clinical trials.

Another multisegmental stent retriever is known as the NeVa thrombectomy device. The NeVa device was designed to have an elevated radial force and has Drop Zones that help in the extraction of thrombi that adhere firmly to the artery wall. It is compatible with 0.021 in. microcatheters and is available in multiple sizes: M1-S (4 × 22 mm), M1 (4 × 30 mm), and T (4.5 × 37 mm) with the M1-S having no proximal "flow restoration zone" (53). The final segment is fashioned into a closed-ended basket, which retains the thrombus that has fallen into the Drop Zone openings. In an early single-center clinical trial with 118 patients, the rate of successful recanalization was 95.8% with first-pass mTICI 2b/3 rates achieved in 56.8% of the patients and mTICI 2c/3 rates in 44.9% of the patients. Favorable functional outcome (modified Rankin Scale 0–2) was seen in 42.4% of the population. The authors reported a 3.3% SICH rate with the rate of embolization into new territory at 1.7% (53).

Another novel clot retriever is the Tigertriever (Rapid Medical, Yokneam, Israel) equipped with a handle-controlled mechanism allowing the operator to incrementally adjust the diameter of a nitinol-braided stent as well as collapse it. The feature of diameter adjustment is hypothesized to result in better wall apposition, robust clot integration, and variable exertion of radial force in different vascular segments (54, 55). Three versions of the Tigertriever device are available: The standard version (Tigertriever) has a net length of 32 mm (unexpanded form) and can expand up to 6 mm diameter, can be delivered through a microcatheter with an internal diameter of 0.021 in. In addition, a smaller version (Tigertriever 17) has a net length of 23 mm (unexpanded form) and can be delivered through a microcatheter with an internal diameter of 0.017 in. It can expand up to 3 mm diameter. Finally, there is a new Tigertriever 13 which can fit through a 0.013-in. microcatheter. The Tigertriever device is CE approved since 2016 and completed several phase 1 trials (54–57). The investigators of the multicenter TIGER trial recently published their preliminary result. The Treatment With Intent to Generate Endovascular Reperfusion (TIGER) trial is a single-arm, prospective, multicenter trial comparing the Tigertriever to outcome in six recent pivotal studies (TREVO 2, SWIFT, MR CLEAN, ESCAPE, REVASCAT, and SWIFT PRIME) evaluating the Solitaire and Trevo stent-retriever devices. In the 160 enrolled patients treated with the Tigertriever, the primary efficacy end-point of mTICI 2b-3 reperfusion within three passes without use of rescue therapy was achieved in 84.6% in the main-study phase group compared with the 73.4% historical rate (non-inferiority $p < 0.0001$; superiority $p < 0.01$). Successful reperfusion (mTICI ≥2b) was achieved in 95.7% of the cohort and excellent reperfusion (mTICI 2c-3) in 71.8%. The primary safety composite end point rate of mortality and symptomatic intracranial hemorrhage was 18.1% compared with the 20.4% historical rate (non-inferiority $p = 0.004$; superiority $p = 0.57$). In the secondary outcome analysis, functional independence (mRS score 0–2) was attained by 58.0%, a rate superior to the 43.5% in the pooled comparator trials ($p = 0.006$) (58). The Tigertriever also appears promising in the treatment of distal, medium vessel occlusions (DMVOs) or as rescue treatment. In a cohort of 115 patients with both primary and secondary (after failed or incomplete EVT) DMVOs, as well as distal vessel thromboembolic complications during cerebral aneurysm or AVM embolization, mechanical thrombectomy performed with Tigertriever achieved successful recanalization in 86 patients (74.7%) (59).

ADJUNCTIVE TECHNIQUES

Rescue Stenting

While the advent of the latest stent retrievers and large bore aspiration catheters have an increase of 90% reperfusion rates in LVO thrombectomy (**Figure 7**), there still exists a subset of patients whereby the EVT procedure fails to recanalize the vessel. Although there are several possible factors, one of the key reasons for failure of EVT is underlying intracranial atherosclerotic stenosis (ICAS). ICAS is commonly diagnosed during the EVT procedure by repeated recanalization and then acute re-occlusion of the vessel. In a Korean series of failed EVT, this occurred in up to 77% of the patient cohort (60). There are currently no guidelines on the optimum treatment in patients who failed thrombectomy and one possible technique is to perform permanent stenting to try to salvage the situation, in an attempt to keep the vessel patent. This is termed "rescue stenting" and was shown to be effective in an initial study of 45 failed thrombectomy patients, where the 17 patients with rescue stenting had better outcomes and less thirorcococn cerebral herniation than the 28 non-stenting patient (61).

Rescue stenting was validated in a large retrospective analysis of patients from 16 Korean stroke centers (62). In this study, patients with anterior circulation LVO who failed to recanalize following EVT were split into rescue stenting and nonrescue stenting groups. Out of 148 failed EVT patients, 48 received

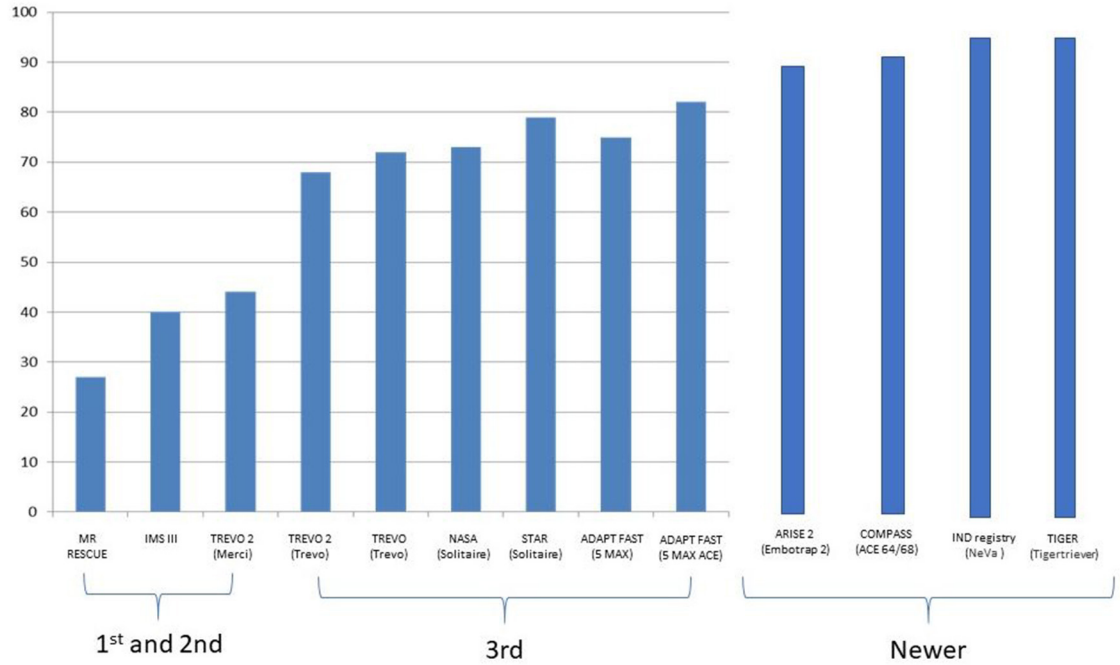

FIGURE 7 | Increasing MTICI 2b-3 reperfusions rates being reported with each successive generation of devices.

rescue stenting while 100 did not; 31/48 rescue stenting patients (64.6%) had successful mTICI 2b-3 reperfusion with rescue stenting, while none of the 100 patients without rescue stenting achieved reperfusion. Good functional outcome at 3 months was observed in 39.6% of the rescue stenting group and in 22.0% of the non-rescue stenting group ($p = 0.031$) without an increase in SICH or mortality. Of note, in the rescue stenting group who had successful reperfusion, 54.8% achieved good outcome despite the initial EVT failure, equivalent to the functional outcomes with mTICI 2b-3 reperfusion in the initial EVT attempts of 55.4%. A meta-analysis on rescue stenting which included articles from 2015 to 2019, similarly found that in a sample of 352 patients, there was improved outcomes in the stenting arm compared with the refractory occlusion arm (OR, 2.87; 95% CI, 1.77–4.66; $p < 0.001$; I^2, 0%) with reduced mortality although there was some heterogeneity between studies for mortality (OR, 0.39; 95% CI, 0.16–0.93; $p = 0.03$; I^2, 43%). The rates of SICH were not significantly different between both arms (63).

In a recent multinational study on emergency rescue stenting in AIS involving seven neurovascular centers (64), good outcome was observed in 73 of 163 (44.8%) patients with recorded outcomes at 90 days. This is considerably better than the rates of 7% to 22% in cohorts with re-occlusion or persistent occlusion reports without rescue stenting. However, the rate of SICH in this analysis (11%) was higher than in the aggregated thrombectomy studies without intracranial stenting of 4.4%, and this was more common in anterior circulation occlusions than posterior circulation occlusions. A lower number of thrombectomy attempts before rescue stenting was also associated with better functional outcomes.

The choice to perform rescue stenting is difficult, as the permanent placement of a stent requires either acute glycoprotein 2b/3a inhibitors or dual antiplatelet treatment to prevent acute re-occlusion from in-stent thrombosis. In acute stroke patients with already sizable amounts of ischemic or infarcted tissue, these medications contribute to a potentially higher risk of symptomatic intracranial hemorrhage. Currently, there is little data and lack of consensus regarding antiplatelet management for intracranial stenting during thrombetomy. There is considerable variation in opinions even among the experts in this field. In an attempt to establish consensus on perioperative and postoperative antiplatelets management using the DELPHI method, a panel of 19 experts were surveyed. While the panel agreed that antiplatelet management in this setting should be standardized regardless of the size of the ischemic "core" on initial brain imaging or final perfusion result or treatment with intravenous alteplase, and that intravenous followed by oral aspirin is a possible choice, it failed to achieve consensus on several other important questions such as timing of initiation of therapy and the need for second antiplatelet agent and the choice of the second antiplatelet agent (65). Therefore, more data are needed to investigate the timing of initiation and choice of antiplatelet management in patients who undergo stenting in the setting of endovascular thrombectomy. Interestingly though, observational studies which have evaluated rescue stenting have demonstrated that the use of glycoprotein 2b/3a inhibitors did

not significantly increase rates of SICH maintaining stent patency (61, 62, 66–70).

Fibrin Capsule of a Clot Broken by the Stent Retriever Followed by 2b/3a Inhibitors

For distal clots or clots past a tortuous intracranial segment, one technique is to deploy a stent retriever over the clot followed by administration of thrombolytics or glycoprotein 2b/3a inhibitor to dissolve the clot. The stent retriever is then resheathed in the microcatheter and removed, as there is a risk of avulsion of pial perforators with withdrawal of a deployed stent retriever. A small publication of 18 cases that initially failed thrombectomy, had a Solitaire stent retriever used as such with concomitant IA tirofiban, a glycoprotein 2b/3a inhibitor, administered. It showed successful reperfusion in 14 out of 18 patients (77.7%) with good functional outcomes seen in 50% of the cases (69).

A more recent publication used a scanning electron microscope to review the structure of 199 thrombi extracted during thrombectomy procedures (71). Despite the heterogeneity of clot composition and organization, thrombi demonstrated a similar outer shell made of compacted fibrin, Von Willebrand factor, and platelets. This prevented the tPA from reaching the inner core of the thrombus, and hence preventing lysis. This study provides a potential explanation on how deploying a stent retriever is able to break the outer shell of the thrombus and expose the inner core to the 2b/3a inhibitor.

IMMINENT QUESTIONS TO ANSWER

Large Ischemic Core

While the current guidelines are clear that EVT should be performed for patients without a large early infarct or with an ASPECTS of six or more, there is a substantial proportion of patients who present to the hospital with an AIS with a sizable ischemic core. While the evidence is not clear, these patients may still derive some benefit from EVT. Pending the outcomes of randomized controlled trials, core-lab adjudicated pooled analyses of existing studies may shed preliminary insight into this crucial question. In one such study pooling data from seven randomized trials with a total of 1,764 patients, of which 871 were in the EVT arm and 893 in the best medical treatment arm, it was demonstrated that EVT was associated with better functional outcomes across a wide range of pretreatment imaging types on ordinal shift analyses (72). This included all ASPECTS groups except for ASPECTS 0–2 where the low sample size could not demonstrate statistical significance. However, this should be interpreted with caution, as in patients with a large ischemic burden or ASPECTS 4 or less, EVT was associated with significantly more SICH. Similarly, in the secondary analysis of the Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT) trial, EVT was associated with better functional independence (mRS 0–2) compared with medical management alone (OR, 3.27; 95% CI, 1.11–9.62; $p = 0.03$). EVT was also associated with less infarct growth, and smaller final infarct volume than medical treatment (73). Such analyses provide a strong foundation to support further investigation of the use of EVT for patients with large infarcts and poor ASPECTS at baseline. These initial results led to the ongoing SELECT-2 trial which is designed to evaluate thrombectomy compared with medical management in distal ICA and MCA M1 occlusions with a large core on either CT (ASPECTS 3–5) or advanced perfusion imaging (rCBF < 30% or ADC < 620 or 50 ml or more) and is expected to be completed at the end of 2021 (74). Other ongoing clinical trials, such as TENSION (NCT03094715), TESLA (NCT03805308), and IN EXTREMIS (75, 76) are also recruiting patients and will provide conclusive evidence on the use of EVT in patients with a large ischemic core at presentation.

Clinically Mild Strokes With LVO

A different group of patients are those who present with LVOs but mild strokes clinically. These are typically defined at NIHSS threshold of <5, where the risk of the EVT procedure needs to be weighed carefully against the potential benefit. A pooled data analysis of six comprehensive stroke centers with 300 patients having LVO and NIHSS 0–5, with 80 patients undergoing EVT and 220 patients undergoing best medical therapy was published (77). Of note is that the best medical treatment group allowed for rescue EVT if there was subsequent neurological deterioration. While the groups were not similar, EVT was associated with better functional outcomes (OR, 3.1; 95% CI, 1.4–6.9) and in a propensity matched analysis, the superiority of EVT over best medical treatment persisted (84.4% vs. 70.1%; $P = 0.03$).

Recently, another meta-analysis pooled patient data from 16 centers from 2013 to 2017. This study evaluated 251 patients with LVO and mild stroke of which 138 were treated with EVT and 113 with best medical treatment. The study revealed that the 3-month functional outcomes were better in the best medical treatment group compared with the EVT group (77.4% vs. 88.5%; $p = 0.02$) (78). The rate of asymptomatic ICH was also lower in the best medical management group as compared with the EVT group (4.6% vs. 17.5%; $p = 0.002$). The two groups did not differ in the rate of reperfusion or in safety outcomes.

We look forward to upcoming RCTs to further elucidate if mild strokes with LVO should be treated *via* EVT. One of these RCTs is ENDOLOW, which investigates anterior circulation occlusions with NIHSS scores 0–5 and is enrolling patients in Canada, the USA, Germany, and Sweden (79). The IN-EXTREMIS trial also includes a substudy, which evaluates ischemic stroke patients with NIHSS <6 and LVO occlusions and similarly will be aiming to answer this important question (76).

Very Late Presenting Patients: Acute Stroke Beyond 24 h

Evidence has recently emerged from the AURORA study, which pooled data from six randomized trials to examine effect of EVT in anterior circulation proximal LVO stroke from 6 to 24 h from time last seen well, that there is benefit of EVT in achieving reduced disability on functional outcome in terms of mRS in this group of patients, with an adjusted common odds ratio of 2.54 (95% CI, 1.82–3.54; $p < 0.0001$). In addition, the Number Needed to Treat to reduce mRS by 1 point was three patients.

Furthermore, no significant differences in mortality or SICH were seen between EVT and control groups (80). This further substantiates the results of previous trials which elucidated that carefully selected patients benefit from thrombectomy up to 24 h (81, 82). However, there remains a pool of patients who present after 24 h. At present, there are no clinical trials or guidelines that detail how we can manage these patients. Kim et al. examined the benefit of EVT in patients presenting very late. In their subgroup analysis of 150 patients who presented more than 16 h from their last known well time, EVT was performed only in 24 patients but a propensity matched analysis showed it was associated with increased odds of having favorable functional recovery at 3 months (adjusted OR, 11.08 (95% CI, 1.88–108.60). In a further subgroup of patients 24 h from last known well, EVT was associated with favorable outcomes as well (adjusted OR, 10.54; 95% CI, 2.18–59.34) (83). These preliminary studies substantiate the understanding that in patients with good collaterals, there is a chance to maintain the penumbra beyond 24 h.

EVT in Posterior Circulation Strokes

There is much uncertainty related to treating posterior circulation stroke caused by basilar artery occlusion (BAO) with mechanical thrombectomy. The Basilar Artery International Cooperation study (BASICS) and endovascular treatment vs. standard medical treatment for vertebrobasilar artery occlusion (BEST) clinical trials are the only randomized clinical trials to date designed specifically to study the outcome of EVT in patients with basilar stroke within 6–8 h of onset (84, 85). However, the benefits of thrombectomy in the anterior circulation have not been replicated in basilar occlusions. These trials enrolled 300 patients and 131 patients respectively with more patients receiving IV tPA in the BASICS trial (80 vs. 30%). Favorable functional outcome was defined as mRS 0 to 3 at 90 days, and this occurred in 44.2% in the endovascular group and 37.7% in the medical care group (risk ratio, 1.18; 95% CI, 0.92 to 1.50) in the BASICS trial, and 42% in the endovascular group vs. 32% in the medical group (adjusted OR, 1.74; 95% CI, 0.81–3.74) in the BEST trial. In addition, SICH occurred in 4.5% of the patients after endovascular therapy and in 0.7% of those after medical therapy (risk ratio, 6.9; 95% CI, 0.9 to 53.0) in the BASICS trial and 8% in the endovascular arm and 0% in the control arm ($p = 0.06$) in the BEST trial. Nonetheless, it is worth noting that the investigators concluded that results of these trials may not exclude a substantial benefit of endovascular therapy as reflected by the wide confidence interval for the primary outcome. This is especially so considering that AIS secondary to BAO are often devastating for patients due to its high morbidity and mortality rates.

There are no randomized trials on thrombectomy in more distal posterior occlusions, and most of the pivotal trials excluded such patients. Strambo et al. examined the outcome of EVT in patient with isolated PCA occlusion vs. best medical therapy (BMT). They reported that complete recanalization at 24 h was achieved in 68% of patients undergoing EVT vs. 34.5% in BMT group (OR = 4.11; 95% CI = 1.35–12.53). This translated into a 15% absolute difference in the proportion of good outcome at 3 months in favor of the EVT group (55 vs. 40.5%), and a 25% absolute difference in visual field normalization at 3 months (50 vs. 25.4%) as well as a significantly better cognitive outcome with EVT (50 vs. 16.1%). In terms of complications, the frequency of SICH and 3-month mortality was similar in both groups (86). The Thrombectomy for Primary Distal Posterior Cerebral Artery Occlusion Stroke or TOPMOST study was a multicentric case-control propensity-matched studies for primary occlusion of the PCA treated with EVT. In 184 matched patients, the NIHSS decreased by a mean of 2.4 points at discharge in the medical group and 3.9 points in the thrombectomy group (mean difference, −1.5 points; 95% CI, 3.2 to −0.8; $p = 0.06$); this was balanced by an incidence of 4.3% SICH in both arms (87).

Direct to Thrombectomy Table—No IV tPA

Time is an important variable that affects functional outcome in acute stroke thrombectomy and any delay in treatment initiation negatively impacts patients' functional outcomes (6).

While IV tPA has the ability to recanalize acute stroke occlusions, this has been eclipsed by the much superior recanalization rate of EVT. There is now a school of thought that instead of administering IV tPA, whether at an intervening primary stroke center or the comprehensive stroke center, patients with acute ischemic stroke from an LVO should go directly to endovascular thrombectomy. An RCT carried out in Japan entitled the SKIP trial comprised 200 AIS patients with anterior circulation occlusions presenting within 4 h of onset (88). At 3 months, the rate of good functional outcome was similar between the direct thrombectomy (59%) and combined bridging approach (57%). Furthermore, the mortality rate was similar between both arms as well. However, it was unable to prove noninferiority of direct to thrombectomy over bridging IV tPA (0.6 mg/kg Japanese standardized dose) because it was underpowered with a modest sample size. While the rate of asymptomatic hemorrhage was not significantly different between both arms and the rate of SICH was similarly non-significantly different, the combined rate of any ICH was significantly lower for the EVT group.

There were two other bridging IV tPA in thrombectomy trials which were similar in design to the SKIP trial but conducted across multiple stroke centers in China. The DIRECT-MT trial, in which 656 patients were enrolled, revealed that endovascular thrombectomy alone was non-inferior to combined intravenous alteplase and endovascular thrombectomy with regard to the functional outcome at 90 days (adjusted common odds ratio, 1.07; 95% confidence interval, 0.81 to 1.40; $p = 0.04$ for non-inferiority). Of note, the non-inferiority margin was set at a high value of 20% margin of confidence in this trial (89). In the DEVT trial, the non-inferiority test also demonstrated that the endovascular thrombectomy alone was non-inferior to the combined IV thrombolysis and endovascular thrombectomy group ($z = 2.7157$, p for non-inferiority $= 0.003$) (90). This trial was terminated after first interim analysis in May 2020 as outcome measured crossed the pre-specified efficacy boundary. In this study, there was no significantly different rate of symptomatic ICH between groups; however, the rate

of any ICH is significantly higher in the bridging r-TPA and thrombectomy group.

It is also worth noting that these trials were performed in east Asian populations, and further evidence is needed in a more diverse population, the SWIFT-DIRECT, MR CLEAN NO-IV (91), and DIRECT-SAFE trials are upcoming international RCTs that can provide more information on the adoption of thrombectomy alone approach against bridging IV tPA (92).

Stroke Secondary to Distal Medium Vessel Occlusion

Endovascular thrombectomy is an evidence-based, guideline-recommended treatment for acute ischemic stroke secondary to large vessel occlusion in the anterior circulation. However, endovascular treatment of DMVO is still unproven in view of the higher risk-benefit ratio with less severe clinical deficits and increased risk of iatrogenic complications. The exact definition of medium-sized vessel also requires consensus, as vessel size and anatomy may be subjected to interobserver variability, although a definition of medium vessel occlusion has been proposed using both anatomical characteristics and functional deficit (93).

Medium vessel occlusion was defined as occlusions of the M2/M3 middle cerebral artery/A2/A3 anterior cerebral artery and P2/P3 posterior cerebral artery segments in a study with pooled data from two multicenter prospective cohorts. In this study, only 50.0% of patients with DMVO achieved an excellent outcome (mRS score, 0–1) at 90 days and 67.4% achieved an independent outcome (mRS score, 0–2). The authors did find that intravenous alteplase was significantly associated with lower mRS scores in mRS shift analysis, but there was no significant association with excellent outcome (mRS score, 0–1). Moreover, even in the alteplase group, early recanalization was achieved in <50% of study cohort, suggesting insufficient efficacy of intravenous alteplase as a stand-alone treatment for DMVO strokes (94).

There is some preliminary evidence from a meta-analysis of data from 12 nonrandomized studies which suggested that endovascular thrombectomy for patients with occlusions of M2 segment of Middle Cerebral Artery that can be safely accessed is associated with high recanalization rates and good clinical outcomes (95). In addition, a more recent meta-analysis of data from the HERMES Collaboration showed that for patients with M2 occlusions, treatment effect favored EVT over control (adjusted OR, 2.39;, 95% CI, 1.08 to 5.28; $p = 0.03$) for mRS 0–2 at 90 days, with number needed to treat for one patient to have functional independence (mRS 0–2) being 5.4 (96). There are also several single-center studies which provided encouraging evidence on the effect of endovascular thrombectomy in treating DMVO (97, 98), and there is hope that reperfusion rates with EVT could improve further with the use of smaller diameter next-generation stent retrievers and aspiration devices. We also wish to emphasize that direct aspiration thrombectomy in distal vessels such as the M3 or M4 has a risk of avulsion injury to the perforators and further studies are needed to determine their safety and effectiveness.

Tandem Occlusions

A tandem occlusion (TO), i.e., a thromboembolic obstruction in the intracranial cerebral vasculature in combination with an extracranial carotid artery occlusion, can occur in up to one-sixth of ischemic stroke patients (99). They tend not to have good recanalization rates with IV tPA and endovascular treatment is therefore advocated (100). In fact, subgroup analyses of the ESCAPE and MR CLEAN studies have suggested that patients with TO have better outcomes with early or concurrent treatment of the extracranial occlusion rather than later in a staged procedure (101, 102). Despite this, the optimal endovascular procedure in acute TO generally remains unclear. The controversy now is the optimal method of treating TO in acute stroke, i.e., is it better to initially bypass the extracranial occlusion and remove the intracranial occlusion first before returning to tackle the extracranial stenosis (the "retrograde" approach)? or is it preferable to attempt primary recanalization of the extracranial occlusion first, before moving on to treat the intracranial occlusion (the "antegrade" approach)?

The usual antegrade approach uses primary stenting to jail the extracranial stenotic atheromatous plaque, which should prevent showering of distal emboli (103). A theoretical drawback of the antegrade approach is the procedural time used for carotid stent placement which delays the time to intracranial reperfusion, which might result in an increase of the final infarct volume (104, 105). Furthermore, stent retriever-based thrombectomy techniques have the potential of entanglement between the struts of the stent retriever and carotid stent during withdrawal if the guiding catheter could not be advanced through the carotid stent. The retrograde approach achieves intracranial recanalization faster and some purport that this gives better functional outcomes (106); however, it may be difficult to pass through the proximal occlusion, and subsequent emboli from the proximal occlusion can sometimes re-occlude the intracranial circulation.

Type of Anesthesia for Thrombectomy

Anesthesia support is necessary for patients undergoing EVT particularly in complex anatomy, difficult cases, or in restless aphasic patients. The modality of anesthesia may have significant implications in outcomes for mechanical thrombectomy and each has its own proposed benefits. General anesthesia (GA) may improve procedural safety by keeping the patient still and protecting the airway, while conscious sedation (CS) has the benefit of neurologic monitoring with hemodynamic stability, and a quicker puncture time (107). It has been difficult to determine which is better for thrombectomy as the literature is very heterogeneous. The initial retrospective studies often based their anaesthesia choice on patient characteristics and what the operator was comfortable with. A retrospective study of 1,174 patients from 2009 to 2013 concluded that GA was inferior to CS; however, there was limited data on the important factors such as blood pressure and the NIHSS; moreover, their outcomes studied were only mortality and length of stay (108). Conversely, another retrospective database study of 2,512 patients concluded the opposite: that CS was superior to GA for stroke interventions. However, it too had many important factors lacking (109).

In the more recent randomized trials attempting to address this topic, the GOLIATH (110), ANSTROKE (111), and SIETSA (112) trials reported GA and CS to be equally safe. In these trials, there was a prespecified target of systolic blood pressure of >140 mmHg prior to revascularization. A later analysis of these three studies showed that a blood pressure of 70 mmHg or less was associated with a significantly worse functional outcomes. GA in those same studies had a higher incidence of mean arterial pressure decreases of 20% or more (113). The worse outcomes of GA with EVT may be explained by decreases in blood pressure and there may be a need to maintain the blood pressure when choosing the type of anesthesia. A more updated meta-analysis which included studies up to 2020 seems to support the RCT findings. This meta-analysis looked at 1,711 subjects undergoing GA and 1,961 subjects using CS. They found no significant difference between the two modalities for functional outcomes, recanalization, mortality, or complications although there was a trend toward SICH for GA (114).

Finally, local anesthesia alone without sedation is emerging as a possible alternative to conscious sedation. In a meta-analysis of 7,797 patients, there was no difference in functional outcomes between GA and LA or between CS and LA; however, there was a trend toward excellent functional outcome (mRS ≤ 1) in the LA group vs. the GA group (OR = 1.44; 95% CI, 1.00 to 2.08; $p = 0.05$; $I = 70\%$) and a trend toward improved mortality in the LA group vs. the GA group (adjusted OR = 1.24; 95% CI, 1.00 to 1.54; $p = 0.05$; $I = 0\%$). The authors conclude that further anesthesia trials should have LA analyzed as a separate arm (115).

CONCLUSION

The field of thrombectomy in acute stroke continues to evolve rapidly, and periodic reviews of the literature are important. We present several of the evidence-based improvements to the procedure and pertinent issues that require further data to settle the controversy.

AUTHOR CONTRIBUTIONS

MJ was involved in data gathering, data analysis, drafting of the article, and is agreeable to be accountable for all aspects of the work. BT, PB, AG, CY, TT, FA, C–HS, SH, and TA was involved in the drafting of the article and the final approval. LY was involved in the conception and design of the project, data gathering, data analysis, drafting of the article, the final approval, and is agreeable to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

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Acute Secondary Prevention of Ischemic Stroke: Overlooked No Longer

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Recent studies of interventions initiated acutely following onset of minor ischemic stroke or transient ischemic attack (TIA) have disclosed early stroke recurrence rates that are substantially higher than long-term recurrence rates and that can be reduced by acute antiplatelet treatment interventions. These observations, bolstered by analysis based on kinetic modeling of the time course of recurrence following initial events, suggest that acute stroke patients experience an underlying vulnerable state that quickly transitions to a more stable state. Some evidence also supports the benefits of early treatment with direct-acting oral anticoagulants in cardioembolic stroke and of continuation or early initiation of statin therapy in atherosclerotic stroke. Treatment of ischemic stroke should address the transient vulnerable state that follows the initial event, employing measures aiming to avert early recurrence of thromboembolism and to promote stabilization of vulnerable arterial plaque. These measures constitute *acute secondary prevention* following ischemic stroke.

Keywords: acute stroke, ischemic stroke, antiplatelet, statin therapy, timing of intervention, anticoagulation timing

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INTRODUCTION

In the hospital care of acute ischemic stroke patients, initial clinical management is tightly focused on interventions aimed to reverse ischemia through induced reperfusion and to limit early complications of brain infarction. Investigations are undertaken to rapidly explore potential mechanisms of stroke, and planning for discharge quickly begins, with selection of the appropriate rehabilitation program to meet the patient's needs. Careful consideration of preventing a subsequent stroke is often relegated to the ambulatory setting. Instead, secondary prevention needs to be considered acutely, as the highest risk for recurrent stroke is typically in the first several days following an initial ischemic event (1, 2). Risks of early recurrence depend on the subtype of ischemic stroke and on individual patient features, and acute interventions to prevent recurrence need to be targeted to the specifics of each case.

ANTIPLATELET TREATMENT IN MINOR STROKE OR TRANSIENT ISCHEMIC ATTACK

Early secondary stroke prevention trials generally had enrollment windows extended for months following the ictus, missing early detection of stroke recurrence. Exceptions were the Chinese Acute Stroke Trial (3) and the International Stroke Trial (4), which examined early initiation

of aspirin within 48 h following ischemic stroke, demonstrating modestly high early recurrence rates that were reduced by aspirin. More recently, trials of acute treatment of minor ischemic stroke or TIA with augmented antiplatelet regimens, such as CHANCE (Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events) (5), SOCRATES (Acute Stroke Or Transient IsChaemic Attack TReated With Aspirin or Ticagrelor and Patient OutcomES) (6), POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) (7), and THALES (Transient IscHaemic Attack Treated With TicAgreLor and ASA for PrEvention of Stroke and Death) (8), with randomization and tracking of subjects occurring within 12–24 h of stroke onset, have demonstrated a clear and consistent finding: the stroke recurrence rate is highest within the first few days following stroke, slowing to a second phase of lower recurrence rate, sustained over subsequent months. In each of these trials of acute antiplatelet regimens, the majority of outcome events, predominantly consisting of ischemic strokes, occurred within the first 7 days, in both control and active treatment groups (see **Table 1**). Further, the effects of dual antiplatelet therapy with aspirin and clopidogrel (in CHANCE and POINT) or with ticagrelor (in THALES) over aspirin monotherapy appeared to be confined to a reduction of the rate of early recurrence, with plots of subsequent survival free of stroke after the first few weeks running in parallel in dual antiplatelet therapy and aspirin monotherapy groups.

Analyses of the CHANCE and POINT trials have confirmed that the benefits of dual antiplatelet therapy over aspirin alone accrued entirely in the first few weeks following stroke, while the small excess bleeding risk accompanying dual antiplatelet therapy continued at an approximately constant rate over the entire duration of the study period (9, 10). For these reasons, several authors have recommended adoption of a dual antiplatelet therapy regimen modified from that of the POINT trial, extending for only a 3-week period rather than 3 months, to gain the early benefit without the extended increased hemorrhage risk.

The aforementioned antiplatelet trials were selected for patients with minor stroke or TIA, arguably enriching strokes of atherosclerotic origin by excluding strokes due to cardioembolism. A *post-hoc* analysis of the CHANCE trial data found that the risk of recurrent stroke was substantially greater in those patients with intracranial atherosclerosis as the probable mechanism of stroke and that risk reductions of dual antiplatelet therapy were numerically confined to this group, though the interaction of subgroup with treatment effect did not reach significance (11). Furthermore, pre-specified analyses of the SOCRATES and THALES trials showed a superiority of ticagrelor (alone or added) over aspirin alone for prevention of stroke recurrence that was confined to the subgroup of subjects with identified ipsilateral atherosclerotic disease (12, 13). A plausible interpretation is that embolic events due to unstable or ulcerated atherosclerotic arterial plaques are particularly associated with high rates of recurrent embolism for a brief period, perhaps until ulceration heals or intraplaque inflammation quiets, explaining both the transient high rate of early stroke recurrence and the efficacy of augmented antiplatelet therapy.

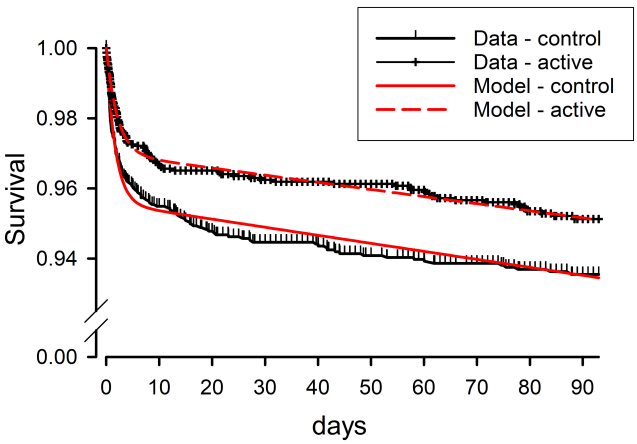

FIGURE 1 | Clinical survivor function data from the POINT trial for active treatment (clopidogrel + aspirin) and control (aspirin) as-treated groups, compared to results predicted by fitting of these data by a mathematical model based on kinetic analysis. Survival free from the composite primary endpoint of ischemic stroke, myocardial infarction, or death is plotted vs. time from study entry, within 12 h of the initial minor stroke or TIA. The kinetic model postulates two clinical states for patients following initial stroke or TIA, one state vulnerable to a high rate of recurrence of ischemic events, but short-lived, and the other state stabilized, with ischemic events recurring at a low rate. Modified from Brorson and Bulwa (14).

While the front-loading of stroke recurrence demonstrated in these trials has been repeatedly recognized, there has been less explicit recognition of a clear implication: that subjects in the acute stroke prevention trials must be distributed between more than one clinical state to produce this sort of temporal pattern. If all subjects were in a single state with constant risks of stroke recurrence, the kinetics of survival free of stroke recurrence would follow a simple exponential decline. Instead, the two phases of recurrence rates seen in trial outcome data require a two-state kinetic model, postulating a transient vulnerable state and a long-term stabilized state. Such a model produces a close mathematical match to the temporal kinetics of Kaplan–Meier curves from the POINT trial (**Figure 1**). It also gives estimates for the kinetic rates of event recurrence in the vulnerable and stabilized states and for the rate of transition from the vulnerable to stabilized state (14). Notably, the predicted kinetic rates for stroke recurrence in the vulnerable state are ∼100-fold greater than the rates in the stabilized state, underscoring the imperative to direct acute preventative treatment to the mechanisms producing the vulnerable state.

ANTICOAGULATION IN CARDIOEMBOLIC STROKE

The following question then arises: whether in cardioembolic stroke there is a similar two-phase time course of stroke recurrence, with a high early rate followed by a constant lower rate over subsequent months and years. Older trials

TABLE 1 | Evidence for front-loading of stroke recurrence in selected stroke treatment trials, based on intention-to-treat data for the primary trial outcome event definition (MI: myocardial infarction).

Trial	*N*	Treatments (following load)	Event rates			Fraction in 7 days	Hemorrhage rates
			7 days	30 days	90 days		90 days
CHANCE Primary outcome: any stroke	2,586	Aspirin 75 mg QD	8.7%	10.2%	11.7%	0.74	0.3%
	2,584	Clopidogrel 75 mg plus aspirin 75 mg QD × 21 days	5.9%	7.3%	8.2%	0.72	0.3%
SOCRATES Primary outcome: stroke, MI, or death	6,610	Aspirin 100 QD	4.9%	5.8%	7.5%	0.65	0.6%
	6,589	Ticagrelor 90 BID	3.9%	5.2%	6.7%	0.58	0.5%
POINT Primary outcome: stroke, MI, or vascular death	2,449	Aspirin 50–325 mg QD	4.6%	5.9%	6.5%	0.71	0.4%
	2,432	Clopidogrel 75 mg QD plus aspirin	2.9%	4.1%	5.0%	0.58	0.9%
THALES Primary outcome: stroke or death	5,493	Aspirin 75–100 mg QD	5.3%	6.6%	(–)	0.80	(0.1% at 30 days)
	5,523	Ticagrelor 90 mg BID plus aspirin	4.2%	5.5%	(–)	0.76	(0.5% at 30 days)
Yaghi et al. (23) (stroke in atrial fibrillation; observational) Primary outcome: stroke, TIA, or arterial embolism	862	DOACs	1.7%	3.1%	4.2%	0.40	
	389	Warfarin	3.3%	5.3%	8.0%	0.41	

Approximate event recurrence rates are derived from published graphical data and are used to estimate the fraction of events over the entire 90- or 30-day trial duration that occurred within the first 7 days. In each of these studies, ischemic stroke constituted the majority of outcome events.

of anticoagulation for atrial fibrillation or cardiomyopathy did not selectively enroll patients in the immediate period following stroke, missing any opportunity to detect an early high-risk phase of stroke recurrence (15–17). A large single-center case series showed a substantial rate of 3.9% of recurrent embolism within 7 days in cardioembolic stroke patients strongly predicting in-hospital mortality (18). Thus, while data are limited regarding early recurrence rates following cardioembolic strokes, there may be reason for urgency in starting anticoagulation therapy for secondary prevention. Current guidelines only recommend that in the setting of atrial fibrillation, it is reasonable to start anticoagulation within 4–14 days of the onset of symptoms (19), but it is also reasonable to delay anticoagulation past 14 days in patients with higher risks (20).

The optimal timing of anticoagulation with direct-acting oral anticoagulants (DOACs) following ischemic stroke in atrial fibrillation is the focus of ongoing trials. Existing evidence shows that anticoagulation with DOACs in the early period (3–5 days) following ischemic stroke at least can be applied with a low frequency of associated symptomatic intracranial hemorrhage events (21, 22). Analysis of multicenter observational data comparing different strategies for anticoagulation following atrial fibrillation-associated stroke supports the use of DOACs over warfarin and supports direct initiation of oral treatment rather than bridging with heparin or heparinoids (23). These data show a noticeable front-loading of recurrent ischemic stroke, especially in the warfarin-treated patients, with events occurring in ∼3% of subjects in the first 7 days after stroke, compared to 8% at 90 days (see **Table 1**). Bleeding events occurred predominantly with bridging with heparin or heparinoids in the first weeks following stroke, with a 3.1% bleeding risk within 30 days. Thus, the currently available data suggest an elevation of early embolism recurrence after atrial fibrillation-associated ischemic stroke, which may be safely countered by early initiation of direct oral anticoagulants, without heparin bridging. Further studies are in progress aiming to better define the optimal timing of initiation of anticoagulation (21).

CERVICAL CAROTID ARTERY DISEASE MANAGEMENT

Cervical carotid artery disease raises an additional dilemma regarding acute secondary prevention: unstable plaque in the internal carotid artery is well-recognized to lead to a very high risk for recurrent stroke, particularly in the early period following initial stroke or TIA (24), and yet risks of hemorrhagic transformation of recent infarction raise concerns

regarding early carotid revascularization with endarterectomy or stenting procedures. At one time, surgeons approached acutely symptomatic carotid stenoses with caution, frequently delaying surgery for 3 weeks or more, theoretically allowing restoration of cerebrovascular reactivity in the recently ischemic tissue before revascularizing the symptomatic carotid. However, secondary analysis of the European Carotid Surgery Trial and North American Symptomatic Carotid Endarterectomy Trial data for effects of timing of surgery following symptoms showed that in patients with symptomatic stenosis, risk reductions provided by surgery fell substantially when surgery was delayed beyond 2 weeks (24). Risks of surgery are no higher in neurologically stable patients with recent TIA or nondisabling stroke when operated on early, within the first 1 week from the event, as compared to those undergoing endarterectomy later (25). American Heart Association guidelines recommend that it is reasonable to perform carotid revascularization, when indicated, within 2 weeks of a TIA or minor nondisabling stroke (20).

A subgroup of cervical carotid stroke patients has a distinctive pattern of crescendo TIA or stroke-in-evolution, often due to hypoperfusion resulting from severe carotid stenosis, with progressive symptoms unresponsive to medical stabilization, and a high risk of severe stroke outcome. These observations have driven a trend toward earlier carotid revascularization in selected cases of unstable ischemia, with acceptable complication risks reported in a large observational study of carotid endarterectomy performed within 48 h of onset of TIA or stroke-in-evolution (26). However, a systemic review of published studies indicates that early intervention in such cases clearly comes at the cost of higher absolute risks of stroke and death (25). Risks and potential benefits of carotid intervention depend on the particular clinical context, including clinical or radiographic evidence for unstable plaque or hypoperfusion due to occlusion, and therefore, decisions regarding the performance and timing of revascularization need to be individualized for each patient.

CRYPTOGENIC STROKE

One-quarter to one-third of ischemic strokes remain unexplained after standard inpatient etiologic evaluations. Many of these cases have features strongly pointing to an embolic mechanism of stroke. These cases have been categorized as "Embolic stroke of undetermined source," or ESUS, and the supposition that many of these events are occurring due to cardioembolism has led to testing of anticoagulation as a potentially more efficacious method of secondary prevention than aspirin. Thus far, randomized trials have not shown any superiority of DOACs over aspirin for secondary prevention following ESUS (27, 28). These trials had long windows of enrollment following the initial stroke of up to 6 months, and thus, they do not provide insight into the rate of early recurrence of stroke. Further study is needed to determine if active short-lived mechanisms producing the initial stroke in ESUS may also contribute to increased rates of early stroke recurrence in this setting.

EFFECTS OF LIPID-LOWERING THERAPY

Though the role of statins in long-term secondary prevention in stroke of presumed atherosclerotic mechanism is well-established, data regarding early initiation of statin therapy are limited. A large retrospective study showed that patients on statins prior to stroke hospitalization had improved post-stroke survival, especially when statins were restarted with 2 days of the stroke, whereas statin withdrawal at the time of the stroke was associated with increased mortality (29). A small randomized trial comparing a 3-day interruption in statin treatment to statin continuation at the time of stroke showed higher rates of early neurological deterioration and of dependency at 3 months with statin withdrawal (30). Two small randomized trials have attempted to test the effect of early vs. late initiation of statin therapy after stroke. Starting atorvastatin 80 mg at day 3 vs. at day 30 made no significant difference in the growth of infarction volume (31). Various statins started within 24 h vs. after 7 days following stroke in the ASSORT (Administration of Statin on Acute Ischemic Stroke Patient) trial did not significantly affect disability at 90 days or the rate of ischemic stroke recurrence (32). Thus, prospective trials have not yet defined the best timing for initiation of statins following stroke. Despite the lack of definitive evidence, existing data suggest that statin therapy should not be withdrawn at the time of stroke. Instead, in patients previously on treatment, statins should be continued at the time of stroke, and in patients with appropriate indications not previously treated with statins, they should be initiated within 1 or 2 days of the stroke.

DISCUSSION

Driven by recent clinical trials examining the early hours following the initial stroke, management of acute stroke and TIA has begun to address *acute secondary prevention*. Clear evidence has established the efficacy of dual antiplatelet therapy with clopidogrel and aspirin and has suggested a possible role for ticagrelor. In atrial fibrillation-related stroke, early institution of anticoagulant therapy with DOACs may also safely prevent an initial wave of stroke recurrence. Statin treatment during and after stroke admission is associated with lowered mortality and dependency following the stroke and is generally indicated for long-term secondary prevention. Further investigations will need to explore ways to promote plaque stabilization following initial atheroembolic events from ruptured plaque, perhaps the chief entity accounting for the vulnerable state transiently following an initial ischemic event. Efforts aimed at preventing early stroke recurrence have long-term consequences for patients, including averting cognitive impairment, a frequent consequence of incident and recurrent lacunar stroke (33, 34). Hospital care

for acute stroke patients must begin to emphasize evidence-based *acute secondary prevention* in the transition between acute treatments and long-term preventative care.

AUTHOR CONTRIBUTIONS

ZB and JB developed the concept for this article. JB wrote the first draft and edited further drafts. ZB and SM reviewed and revised the article. All authors agree to be accountable for the content of the work.

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Experiences With Intravenous Thrombolysis in Acute Ischemic Stroke by Elderly Patients–A "Real World Scenario"

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Objectives: This retrospective single-center study aimed to investigate the risk factors, outcomes and complication rates in patients older vs. younger than 80 years treated with intravenous alteplase.

Methods: Data of 1,253 thrombolysed patients were analyzed between January 1, 2004 and August 31, 2016. Vascular risk factors, stroke severity based on the NIHSS score, functional outcome using modified Rankin Scale (mRS), mortality and symptomatic intracerebral hemorrhage (SICH) were compared between two subgroups (<80 and ≥80 years).

Results: 1,125 patients were included, 199 (17.6%) among them were aged over 80 years, majority (63.3%) were female ($p < 0.00001$). Mean age was 68.2 ± 12.4 years, i.e., 64.7 ± 10.8 years and 84.3 ± 3.4 years in the younger and the older groups, respectively ($p < 0.001$). Atrial fibrillation and pre-stroke anticoagulation among patients over 80 years was more likely ($p < 0.0005$ and $p = 0.02$, respectively). NIHSS scores on admission and at 24 h were higher in elderly patients ($p < 0.0001$). ASPECT score at 24 h was less favorable in elderly patients ($p = 0.007$) and was associated with worse outcome. At 3 months, 59.8% of the patients from the older group had an unfavorable outcome ($p < 0.0001$), however 34.7% had independent outcome. The one-year- survival was significantly worse in the older group ($p < 0.0001$). The incidence of SICH was lower among older patients. In a logistic regression model, atrial fibrillation, heart failure, diabetes mellitus and smoking were proven as a significant independent risk factors for worse outcome.

Conclusion: Although, the outcomes were less favorable in patients over 80 years of age, our results support the feasibility of using intravenous thrombolysis among patients over 80 years of age.

Keywords: ischemic stroke, thrombolysis, elderly, outcome, symptomatic intracerebral hemorrhage

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INTRODUCTION

Stroke is the second most common cause of death and a major cause of disability worldwide (1). According to the WHO statistics, 15 million people suffer a stroke in the world annually. Of these, 5 million die, and another 5 million are left permanently disabled, placing a burden on the family and community (2). Age is the most remarkable non-modifiable risk factor for stroke and a major predictor of clinical outcome (3). In fact, the incidence of stroke is rapidly increasing with age in both genders, doubling each decade after age 55 (4). Intravenous alteplase (recombinant tissue plasminogen activator [IV-rtPA]) is the only approved and validated treatment for pharmacological revascularisation in acute ischaemic stroke. However, despite the high prevalence of stroke in the elderly, data on the safety and efficacy of thrombolysis in the >80 years population were limited for long. In the first major IV-rtPA study, the NINDS trial, treatment of ischaemic stroke with alteplase was not specifically investigated in patients aged over 80, and in further studies, like ECASS-II, this population was excluded. This age restriction came from the potential higher risk of cerebral bleeding and caused uncertainty about the risk-benefit profile in these patients (5). Earlier studies seem to show that high age is an independent predictor of symptomatic intracerebral hemorrhage (SICH) in patients treated with IV-rtPA and the incidence of SICH increases with age (3, 6). However, more and more data support that patients from this age group still seem to benefit from this treatment. Several observational studies have demonstrated the conclusions above, though the outcome at 3 months has been worse for the older patients than for their younger counterparts, the elderly do not seem to have an increased risk for SICH after IV-rtPA (7–9). One of the largest controlled comparisons of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials suggests that increasing age is associated with poorer outcome, but the association between thrombolysis treatment and improved outcome is maintained in very elderly people (10). The conclusion of all these studies is that age alone should not be the reason to exclude patients from treatment with IV-rtPA.

Altogether more than one-third of acute strokes occur among people aged ≥80 years, and due to increasing life expectancy the incidence of stroke will continue to rise in this age group. This problem particularly affects the Central-Eastern European countries where the stroke is more frequent, the mortality rate is higher, and the risk factors such as obesity, hypertension and alcohol abuse are more prevalent than is western Europe (11). However, intravenous alteplase is a safe and effective treatment for acute ischemic stroke within 4.5 h, until 2020, it was only approved for patients aged 18–80 years, and can be used in patients over 80 years on an individual benefit-risk basis (12). In order to select the most eligible elderly patients for thrombolysis, we need to identify the risk factors associated with worse outcome.

In the current work, we present a single-center report on patients over 80 years receiving rt-PA after acute ischaemic stroke. The aim of this study was to compare the risk factors, functional outcomes and complication rates in patients older vs. lower than 80 years old. A real-life scenario was conducted.

METHODS

Subjects, Patients

An analysis of 1,253 patients treated with IV-rtPA was conducted at the stroke unit of tertiary center using the thrombolysis database. The data have been collected prospectively for the period between January 1, 2004, and August 31, 2016. Patients are admitted from a 90 km radius of the center, with a catchment area of 600,000 inhabitants and 600–700 acute stroke hospitalizations per year. All the patients were treated and the parameters recommended in the ESO guideline were monitored in the Neurological Intensive Care Unit, (13–15). Some cases, where treatment indications did not follow the guidelines (13, 14), were excluded, and 1,125 patients' data were analyzed. Among them, 199 (17.6%) were aged over 80 years. From the 1,253 thrombolysed patients only 41 had mRS ≥2 before admission, six patients from ≥80 years group and 35 patients from <80 years group. These patients were excluded from further analysis. Unfortunately, 154 patients were lost during the long-term follow up (**Figure 1**). The patients were divided into two subgroups: patients aged under 80 years and patients aged 80 years or over. For all patients treated over 80 years, permission was obtained from the National Institute of Pharmacy and Nutrition.

Database

The following parameters were recorded: age, gender, logistic data (stroke onset-to treatment, door-to-imaging, door-to-treatment). Risk factors for stroke, past history, hypertension, diabetes mellitus, atrial fibrillation, prestroke anticoagulation, congestive heart failure and smoking habits were also evaluated. Furthermore, all the patients were tested for blood glucose, cholesterol and triglyceride levels, as well as systolic and diastolic blood pressure on admission. Stroke severity was assessed in accordance with the National Institutes of Health Stroke Scale (NIHSS) by the neurologist currently on duty in the stroke unit on admission and 24 h later. All the patients underwent brain imaging with computed tomography on admission, at 24 h after thrombolytic therapy and in case of later neurological deteroriation. Blood pressure, laboratory parameters and onset to treatment time were expressed as mean ± standard deviation. NIHSS scores were presented as medians (1,;3. quartile).

Imaging

Patients with acute stroke were admitted directly to the CT laboratory, where neurological examination, blood sampling and imaging were performed. Non-contrast computed tomography was performed on admission. Arterial occlusion (trunk or at least one branch of any large artery) was identified by CT-angiography. To evaluate hemorrhagic changes, CT was repeated 1 day after treatment and in case of clinical deterioration. Hemorrhagic infarction (HI) or parenchymal hematoma (PH) were defined according to the European Cooperative Acute Stroke Study (16, 17). We used three definitions for symptomatic intracerebral hemorrhage (SICH) as follows: the SITS, the ECASS and the RCT NINDS criteria (17–19). The Alberta Stroke Programme Early CT Score (ASPECTS) was determined unblinded to patient characteristics and was stratified to <7 (group I severe) and ≥ 7

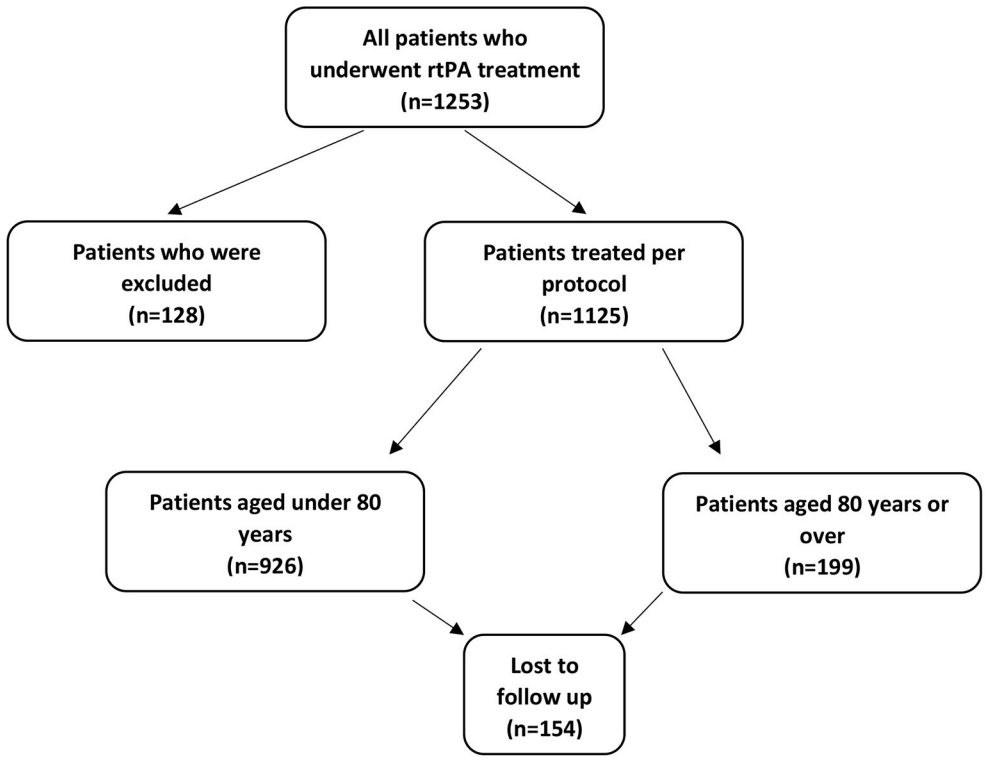

FIGURE 1 | Flow chart of participants (rtPA: recombinant tissue plasminogen activator).

(group II mild), within the mild group patients scoring 10 and less, were examined separately (20, 21).

Treatment

Intravenous thrombolysis was administered according to valid guidelines (13, 14). Intravenous rtPA (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose was given as a bolus followed by a 60-min infusion. Elevated blood pressure was decreased below 185/110 mmHg according to guideline recommendations. Neurological status, side effects (allergic reactions, minor bleedings), pulse, blood pressure, temperature and oxygen saturation were monitored continuously.

Long-Term Outcome

The modified Rankin Scale (mRS) was used to assess 3 months' outcome. The outcome was dichotomized to favorable (mRS 0-2) and unfavorable (mRS>2) points (22). At 1 year, the outcome was dichotomized to "dead" and "alive" status.

Beside these patients data, we compared the long-term outcome in patients over 80 years who underwent thrombolysis with the non-thrombolysed patients of the same age using the data from an Eastern European stroke epidemiological study, the MUD (Marosvásárhely-Ungvár-Debrecen) database (23). This database was chosen as a medical historical control. Only outcomes could be compared, since imaging workup in 1999–2000 differed from the present, and CT scans were not stored digitally.

Statistical Analysis

Statistical analysis was carried out using the SPSS for Windows 19.0 program suite (SPSS Inc. Chicago, USA). Descriptive statistics was performed. Two-group analysis was assessed with Pearson χ^2 test for categorical variables. For continuous variables, Mann –Whitney U test was used. The level of significance was set at $p < 0.05$. Logistic regression models were used to identify the independent predictors of 3-month disability and 1-year case fatality. The analysis was performed with the multivariate general linear model (GLM). In the models, disability at 3 months (mRS >2), and case fatality at 1 year were the dependent variables, and the factors found to be associated with outcome by univariate analyses were entered as confounding variables. The variables were excluded from the analysis one by one, and the variable with $p > 0.05$ and closest to 1.0 was removed, until all features left in the model had $p < 0.05$.

RESULTS

Baseline Characteristics

The baseline characteristics of the patients are summarized in **Table 1**. The patients' age ranged between 17 and 99 years. The mean age of the total population was 68.2 ± 12.4 years, i.e., 64.7 ± 10.8 years and 84.3 ± 3.4 years in the younger and the older groups, respectively, ($p < 0.001$). The majority of the patients in the general population were males (56.3%). There was a significant difference in gender ratio ($p < 0.00001$):

TABLE 1 | Baseline patient characteristics.

Characteristic	Total (n = 1,125)	Age group ≥80 years (n = 199)	Age group < 80 years (n = 926)	p-value
Age (years), mean ± SD	68.2 ± 12.4	84.3 ± 3.4	64.7 ± 10.8	**<0.001**
Gender, male, *n* (%)	633 (56.3)	73 (36.7)	560 (60.5)	**<0.00001**
Risk factors				
Hypertension, *n* (%)	863 (76.7)	176 (88.4)	687 (74.2)	NS
Smoking, current, *n* (%)	281 (24.9)	10 (5)	271 (29.3)	**<0.00001**
Smoking, previous, *n* (%)	138 (12.3)	18 (9)	120 (12.3)	**<0.00001**
Smoking, total, *n* (%)	420 (37.3)	28 (14)	391 (42.2)	**<0.00001**
Diabetes mellitus, *n* (%)	235 (20.9)	36 (18%)	189 (20.4)	0.062
Hyperlipidemia, *n* (%)	398 (35.3)	53 (26.6)	345 (37.3)	**<0.0001**
Atrial fibrillation, *n* (%)	198 (17.6)	69 (34.7)	129 (13.9)	**<0.0001**
Congestive heart failure, *n* (%)	153 (13.6)	35 (17.6)	118 (12.7)	0.048
Prestroke anticoagulation, *n* (%)	104 (9.2)	27 (13.6)	77 (8.4)	0.02
Vital parameters on admission				
Systolic blood pressure (mmHg), mean ± SD	156.9 ± 23	156.8 ± 25.66	157 ± 23.6	NS
Diastolic blood pressure (mmHg), mean ± SD	86.9 ± 14,4	84.3 ± 17	87.5 ± 14.2	**0.003**
Serum glucose level (mmol/l), mean ±SD	7.5 ± 2,9	7,3 ± 2,4	7.6 ± 3	**<0.0001**
Cholesterol level (mmol/l), mean ± SD	4.1 ± 2,2	3,8 ± 2,2	4.2 ± 2,2	**0.005**
Triglyceride level (mmol/l), mean ± SD	1.2 ± 1,1	1.15 ± 0,54	1.56 ± 1	**<0.00001**
NIHSS score on admission, median (1;3 quartile)	10 (6;15)	14 (8;18)	10 (5;15)	**< 0.0001**
Onset to treatment time (min), median ± SD	158 ± 51.3	150 ± 43.2	150.5 ± 51.3	NS

in the older group the percentage of female patients (63.3%) was higher than that in the younger group (39.5%). The risk factors for stroke differed between older and younger patients. Hypertension was the most remarkable risk factor in both groups and was more prevalent among older patients, but the difference was not statistically significant. The history of current or past smoking was the second most common risk factor (42.2%) and was significantly more likely among younger patients. Atrial fibrillation was significantly more prevalent among patients over 80 years than among younger study participants ($p < 0.00001$). Most of the younger subjects (60.9%) did not receive anticoagulation therapy before stroke, but the patients over 80 had previously been treated with oral anticoagulants much more often than in the younger ones ($p = 0.02$). Among the elderly, congestive heart failure was more common, near the significance level ($p < 0.07$) statistically. Regarding other risk factors, such as diabetes mellitus, hyperlipidemia and previous stroke, there were no significant differences between the two groups. Baseline stroke severity was significantly higher ($p < 0.0001$) among patients over 80 years than the younger ones. The median (1;3 quartile) NIHSS scores on admission being 14 (8, 18) and 10 (5, 15), respectively. Time from symptom onset to treatment did not differ significantly in the two groups.

CT Characteristics

CT characteristics on admission and at 24 h compared with on admission-NIHSS, 24 h-NIHSS and 3 months-mortality in patient groups under and above 80 years are summarized in **Table 2** and **Table 3**. Significant correlation can only be declared between ASPECT score and outcome at 24 h because of the small numbers of patients in different categories, despite the trends seen in the table. Groups were created according to ASPECT Score on admission CT scan and CT scan done at 24 h.

TABLE 2 | CT characteristics of patients above and under 80 year.

	Total	age ≥80 years	age <80 years	p-values
Location of stroke				
Anterior circulation, *n* (%)	973 (86.5)	181 (91)	792 (85.5)	
Posterior circulation *n* (%)	152 (13.5)	18 (9)	134 (14.5)	
Large artery occlusion *n* (%)	619 (55)	125 (63)	494 (53.4)	0.09
ASPECT score on admission, *n* (%)				0.319
≥7		180 (99.5)	778 (98.2)	
<7		1 (0.5)	14 (1.8)	
ASPECT score at 24 h, *n* (%)				0.007
≥7		73 (40.3)	399 (50.4)	
<7		108 (59.7)	393 (49.6)	

Most strokes were located in the anterior circulation in both age groups. Probability of developing a large artery occlusion was higher among the elderly (63 vs. 53.4%), but the difference is not

TABLE 3 | CT characteristics on admission and at 24 h compared with on admission-NIHSSS, 24 h-NIHSSS and 3 months-mortality in patient groups under and above 80 years.

	Ratio		NIHSS on admission (1.;3.quartile) median		Ratio of mild (NIHSS 1–7) strokes on admission (pts%)		NIHSS at 24 h (1.;3.quartile) median		Ratio of mild (NIHSS 1–7) strokes at 24 h		3 months case fatality	
	≥80 years	<80 years	≥80 years	<80 years	≥80 years	<80 years	≥80 years	<80 years	≥80 years	<80 years	≥80 years	<80 years
ASPECT Score on admission												
10	92.3%	90.9%	(9;18) 14	(5;14) 9	20.8%	40.8%	(4;18) 11	(3;13) 7	38.1%	53.7%	31.5%	1.2%
9–7	7.1%	7.3%	(10;19) 13	(7;15) 11	15.4%	28.7%	(11;20) 16	(5;16) 11	15.4%	36.7%	23%	15%
<7	0.5%	1.8%	(23;23) 23	(12;19) 16	0%	5.5%	(22;22) 22	(7.5;17) 12.5	0%	22.2%	100%	11.1%
ASPECT Score at 24 hours												
10	22.5%	35.3%	(6.25;14.5) 10.5	(4;10) 6	35%	65.4%	(2.75;6) 4	(1;6)3	62.5%	44.1%	10%	6%
9–7	18%	15.1%	(6.75;11) 18	(6;14) 9	28.1%	40.2%	(2;10.25) 13.75	(3;12)7	62.5%	56.4%	3.1%	4.7%
<7	59.5%	49.6%	(10.25;19) 16	(8;17) 13	10.4%	17.8%	(9;19) 15	(6;12) 17	20.7%	4.5%	46.2%	18.7%

significant ($p = 0.09$). Most of the patients had ASPECT score ≥7 on admission in both age groups. However, median (1;3 quartile) NIHSS score on admission was higher (14 [9:18] vs. 9 [5:14]) and ratio of mild strokes (NIHSS score 1–7) was less frequent (20.8 vs. 40.8%) in the older group. At 24 h, 59.6% of patients over 80 years had ASPECT score <7 ($p = 0.007$) accompanied with higher median (1;3 quartile) NIHSS score and less ratio of milder strokes in both ASPECT group.

Nevertheless at 24 h there was an improvement, which was significant, and according to the Mann–Whitney *U* test the improvement was more pronounced in patients ≥80 than in the younger ones ($p < 0.0001$). The mean rank of on admission NIHSS Score by patients under 80 was 599.7 and at 24 h 601.5, while by patients ≥80 years on admission 755.2, at 24 h 731.75. So altogether the elderly patients had scored more on the NIHSS Scale, but the improvement was better by them.

TABLE 4 | Median NIHSS scores and changes in NIHSS at 24 h in patient groups above and under 80 years.

	age ≥80 years	age <80 years	*p*-values
NIHSS score at 24 h, median (1;3 quartile)	11 (4.5;18)	7 (3;14)	***<0.0001***
Changes in NIHSS score at 24 h			
>2 points worsening, *n* (%)	34 (17)	136 (14.7)	***0.034***
≤2 points worsening, *n* (%)	25 (12.6)	99 (10.7)	0.27
unchanged, *n* (%)	40 (20.1)	160 (17.3)	0.19
≥2 points improvement, *n* (%)	79 (39.7)	439 (47.4)	***0.00016***
<2 points improvement, *n* (%)	21 (10.6)	92 (9.9)	0.38

Outcome

Tables 4–6 and **Figures 2–3** summarize the data of clinical outcomes. At 24 h, the patients over 80 had higher NIHSS scores than the ones under 80, the median (1;3 quartile) NIHSS scores seen at 11 [4.5;18] and 7 (3, 14), with the difference also being statistically significant ($p < 0.0001$). More than two points of worsening in NIHSS score were seen in 17% of patients over 80 years which is significantly worse ($p = 0.034$) deterioration compared to the younger ones (14,7%). In addition, significantly less patients ($p = 0.00016$) achieved at least two points improvement in NIHSS score over the age of 80 compared to the younger group (39.7 and 47.4%, respectively) (**Table 4**) At 3 months, 59.8% of the patients in the older group had unfavorable outcomes (mRS: 3-6), which was significantly worse ($p < 0.0001$) compared to the younger age group (43.2%). However, 34.7% of the patients over 80 had independent outcomes (mRS: 0-2), and more than two thirds of them were able to continue their pre-stroke activities (mRS: 0-1). There was an unfavorable trend regarding the 90-day outcomes for the over-80 patients treated for atrial fibrillation compared to patients of the same age group without atrial fibrillation. While in the former group 27.7% of patients had favorable outcomes, the particular proportion was 41.5%, among the patients without atrial fibrillation. The difference was not significant. The one-year survival in the older group was 41.7%, while the proportion in the younger group was 63.9%, the difference being statistically significant.

In a logistic regression model of the patients under 80 years, atrial fibrillation and heart failure were significant independent risk factors for worse outcomes at 3 months, whereas among the elderly subjects diabetes mellitus was also a risk factor for a worse outcome (**Table 5**). At 1 year, smoking and diabetes mellitus were significant risk factors in the younger group, while no independent risk factor was found among the elderly at 1 year follow-up (**Table 6**).

We compared the mortality rates for the patients over 80 years of age having undergone thrombolysis, to the MUD (Marosvásárhely-Ungvár-Debrecen / Târgu Mureş - Uzhhorod - Debrecen) database's non-thrombolyzed patients of the same age at 3 months and 1 year. The results are as follows: at 3

TABLE 5 | mRS score at 3 months and 1-year mortality in patient groups above and under 80 years.

		Age group			
	Total	**≥80 years**	**<80 years**	**Missing data, *n* (%)**	***p*-value**
mRS score at 3 months					**<0.0001**
Favorable outcome (mRS:0–2), *n* (%)	561 (49.9)	69 (34.7)	492 (53.1)	48 (4.2)	
Moderate disability (mRS:3–4), *n* (%)	222 (19.7)	31 (15.6)	191 (20.6)	48 (4.2)	
Severe disability/death (mRS:5–6), *n* (%)	297 (26.4)	88 (44.2)	209 (29.6)	48 (4.2)	
Mortality at 1 year	299 (26.6)	93 (199)	206 (22.2)	154 (13.7)	**<0.0001**

TABLE 6 | Predictor of outcome with logistic regression mode.

Predictor of outcome <80 years			**Predictor of outcome over 80 years**		
Disability at 3 months					
	Exp(B) (95% CI)	**p**		**Exp(B) (95% CI)**	***p***
Atrial fibrillation	0.524 (0.363-0.756)	**0.001**	**atrial fibrillation**	0.550 (0.396-0.763)	**<0.001**
Heart failure	0.547 (0.362-0.826)	**0.004**	**heart failure**	0.033 (0.44-0.911)	**0.014**
			diabetes mellitus	0.725 (0.536; 0.981)	**0.037**
Survival at 1 year					
Diabetes mellitus	0.705 (0.504;0.988)	**0.042**	**None**		
Actual smoking	0.585 (0.432;0.791)	**<0.001**	**None**		

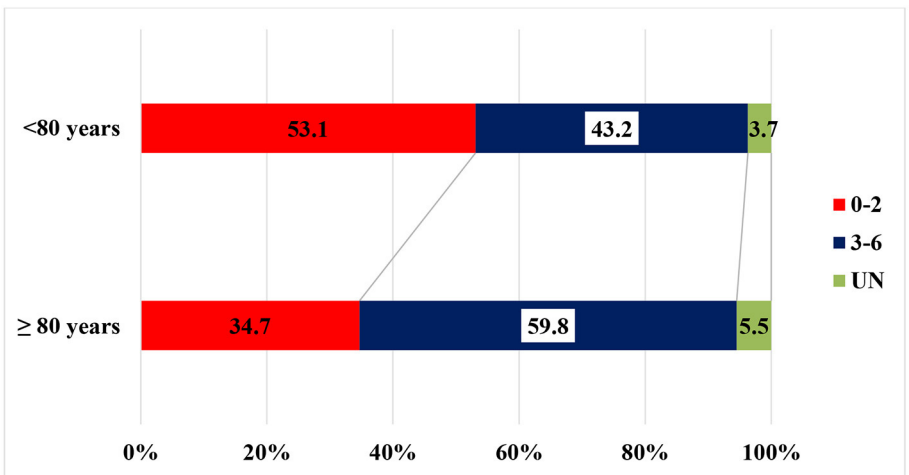

FIGURE 2 | Outcome at 3 months based on mRS score.

months, in the over-80-group, the mortality rate was 30.1%, and in the under-80 it was 33.3% while, at 1 year, the relevant figures were 46.7 and 56.8%, respectively), but the difference was not significant.

Safety

Regarding the hemorrhagic complications of thrombolytic therapy, intracranial hemorrhage occurred in 125 patients (9%), while SICH was detected in 36 patients (3.2%). Intracranial

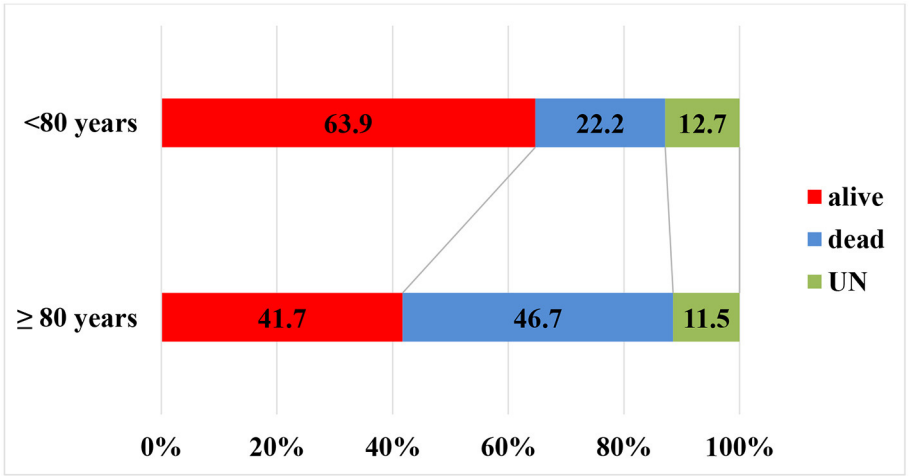

FIGURE 3 | Outcome at 1 year.

hemorrhage and SICH did not differ significantly between the elder and younger patients (**Table 7**).

TABLE 7 | Occurrence of intracranial hemorrhage and symptomatic intracerebral hemorrhage in patient groups under and above 80 years.

	Total	Age ≥80 years	Age <80 years	*p*-values
ICH, *n* (%)	125 (9%)	19 (9.4%)	106 (11.5%)	0.28
SICH, *n* (%)	36 (3.2%)	4 (2.1%)	32 (3.5%)	0.25

DISCUSSION

As life expectancy increases, the proportion of the elderly population is constantly growing. In absolute terms, the number of older persons has doubled over the last 20 years and will more than triple again over the next 30 years (24). The aging society puts a heavy burden on healthcare, not sparing the stroke care either, especially in very old age. Though, more and more studies come to light on the safety of IV-rtPA treatment in acute ischemic stroke among patients over 80 years, the uncertainty still exists in clinical practice. In this single center study, we analyzed the data of 1,125 patients who underwent intravenous thrombolysis, comparing the baseline characteristics and clinical outcomes between patients over and under 80 years.

Consistent with previous studies (25–28), our findings showed that hypertension was the most important risk factor in both subgroups, and it was more prevalent in older patients. Therefore our study points out that optimizing antihypertensive treatment and maintaining blood pressure below the target level may lower the risk for stroke. As described in previous studies (29, 30), older patients were significantly more likely to develop atrial fibrillation than the younger ones. Atrial fibrillation is associated with a five-fold increase in the risk for ischemic stroke, but anticoagulant therapy may reduce the risk of recurrent stroke by ∼by 60% (31, 32). Despite the finding that more than one-third of the patients over 80 years had atrial fibrillation, only 13.6% were previously medicated with oral anticoagulants. Atrial fibrillation was a significant prognostic factor for more severe functional status in univariate model. More detailed in a logistic regression model, there was a difference between the risk factors among patients under and over 80 years. Atrial fibrillation and heart failure were significant independent risk factors for worse outcomes at 3 months among the younger subjects, whereas diabetes mellitus was also a risk for worse outcome among the elderly. At 1 year, smoking and diabetes mellitus were significant risk factors in the younger group, while no independent risk factor was found among the elderly at 1 year follow-up. These findings suggest that by proactively searching for atrial fibrillation and providing effective anticoagulant therapy, the risk of stroke can be reduced and better functional outcome can be achieved. Regarding other vascular risk factors, the prevalence of diabetes and hyperlipidemia did not show significant differences between the two groups, but the history of current or past smoking was more common in younger age. These findings suggest that changing unhealthy lifestyles is of great importance in the prevention of ischemic stroke in both age groups.

Multiple studies have proven that both admission and 24-h stroke severity are poor prognostic factors for long-term outcome (7, 33). An important result of our study shows that older patients tend to experience stroke of higher severity than younger patients previously reported (median NIHSS score of 14 vs. 10), (33, 34). Furthermore, patients over 80 years of age also had significantly higher NIHSS scores at 24 h than younger patients did. Nevertheless according to the Mann–Whitney *U* test, by the elderly patients the improvement was better. These results suggest that thrombolytic therapy has a positive effect in patients above 80 years.

Regarding the correlation of CT parameters and outcome, we found that on admission ASPECT score was similar in the

groups of patients above and under 80 years ($p = 0.319$), but despite this the on admission NIHSS score was higher in the elderly and less patients had milder strokes on admission. Large artery occlusion was more frequent in the elderly ($p = 0.09$), and although there was no sign of hyperacute ischemia, it had an effect on ASPECT at 24 h. ASPECT score at 24 h was less favorable in elderly patients ($p = 0.007$). Not surprisingly with the help of 24 h- ASPECT Score prognosis could be estimated closer than with the on-admission ASPECT Score. Interestingly the ratio of mild strokes at 24 h is less in ASPECT Score <7 by younger patients. This might emphasize the importance of functional collaterals in older ones. Analyzing the 3 months mortality, a higher rate can be detected among elderly patients especially, if the ASPECT Score is <7 points, younger patients have a better chance to survive at 3 months even with more severe CT abnormalities.

As for the long-term outcome, the functional status at 3 months turned out to be significantly worse in the older age group. This result is consistent with most of the recent studies which have shown lower rates of favorable and independent outcomes at day 90 among patients over 80 years of age (35–37). Despite the above, older patients still benefited from IV-rtPA because more than one-third of them were able to live independently. It should also be noted that the modified Rankin Scale not only estimates function loss due to stroke, but it the prevalence of disability increases with age, regardless of stroke (38). Although in our study prestroke disability did not differ in different age groups, but if the on admission-ASPECT Score and/or 24-h ASPECT Score was <7, the case fatality was extremely worse in the elderly patients. Similarly, the one-year mortality rate does not only reflect deaths due to stroke, as its prevalence increases with age regardless of stroke (39). The comparison of our results with the MUD database also supports the safety of thrombolysis because the mortality rates do not differ among over 80-year-old patients after thrombolysis compared with the non-thrombolyzed patients of the same age.

The occurrence of the ICH, SICH was similar in patients below and above 80 years. This is especially important, if we consider that the ratio of the large artery occlusion was more frequent in patients above 80 years. This confirms the safety of thrombolysis in elderly patients. Concerning the risk of therapy, in our study SICH occurred in 3.2% which is somewhat less than reported in major rtPA trials (NINDS 6.4%, ECASS II 8.9%) (17, 18). A hypothesized higher risk for intracerebral hemorrhage is often cited as the reason for excluding very old patients from thrombolytic treatment. Amyloid angiopathy, decreased renal rtPA clearance, and frail vasculature in the elderly are asserted as explanations for a possibly increased risk of suffering an intracerebral hemorrhage (40). However, many other studies had previously reported that the occurrence of SICH did not differ significantly between younger and older groups of patients (7, 41–43). Our results are in line with these studies as we have found that the prevalence of SICH tended to be lower in older than younger patients (2.1 and 3.5% respectively, not significant). Further investigation is needed to determine the underlying cause.

Of course, we are aware of the limitations of our study. Although the number of study participants is small, the most important and relevant risk factors have been identified. Nevertheless, the advantage is the real-world scenario.

In conclusion, according to our results, patients with acute ischemic stroke and over 80 years seem to have an increased risk for unfavorable outcome and a higher mortality rate compared to their younger counterparts. However, intravenous thrombolysis is an effective and safe treatment in this age group, as more than one-third of the patients were capable of living independently and the rate of SICH was lower compared to younger patients. Although, the outcomes were less favorable in patients over 80 years of age, our results support the feasibility of using intravenous thrombolysis among patients over 80 years of age. Consequently, these data support that age by itself should not be a reason to exclude patients over 80 years old from IV-rtPA treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional and Institutional Ethics Committee of University of Debrecen Clinical Center (protocol number: 5473-2020). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KF, IF, and LH led the initiative and revised the drafted document. KF, LH, and MH selected abstract, extracted data, and drafted the manuscript. SM, LH, KF, and MH is involved in investigation, data curation, data analysis, and writing the original draft. IF and KF were involved in supervision. All authors are involved in the conceptualization, methodology, review and editing, and approved the final version.

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Left Atrial Dilatation and Reduced Left Ventricular Ejection Fraction Are Associated With Cardioembolic Stroke

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Objective: Left atrial (LA) dilatation and heart failure are independent risk factors for ischemic stroke. The goal of this study is to evaluate the association between LA dilatation and reduced left ventricular ejection fraction (EF) with cardioembolic stroke.

Methods: Four hundred fifty-three patients with ischemic stroke admitted to the University of California, Irvine between 2016 and 2017 were included based on the following criteria: age >18 and availability of echocardiogram. Stroke was categorized into cardioembolic and non-cardioembolic. EF was categorized into normal: 52–72% (male), 54–74% (female), mildly abnormal: 41–51% (male), 41–53% (female), moderately abnormal: 30–40%, and severely abnormal: <30%. LA volume was categorized into normal ($\leq$34 ml/m^2) vs. enlarged ($\geq$35 ml/m^2). Other variables included gender, hypertension [systolic blood pressure (SBP) $\geq$ 140 or diastolic blood pressure (DBP) $\geq$ 90], and known history of atrial fibrillation (Afib).

Results: Two hundred eighteen patients had cardioembolic, and 235 had non-cardioembolic stroke. Among patients with cardioembolic stroke, 49 (22.4%) and 142 (65%) had reduced EF and enlarged LA, respectively, as compared with 19 (8.1%) and 65 (27.7%) patients with non-cardioembolic stroke ($p < 0.0001$). The odds of cardioembolic stroke were 2.0 (95% CI: 0.1–6.0) and 8.8 times (95% CI: 1.9–42.3) higher in patients with moderately and severely reduced EF, respectively, than in patients with normal EF. The odds of cardioembolic stroke was 2.4 times (95% CI: 1.5–3.9) higher in patients with enlarged LA than in patients with normal LA size. Compared with patients with normal LA and EF, patients with combined enlarged LA and reduced EF had significantly higher rates of Afib (43.4 vs. 9.0%, $p < 0.0001$) and cardioembolic stroke (78.3 vs. 43.4%, $p < 0.0001$).

Conclusions: LA dilatation along with reduced EF is a reliable predictor of Afib and cardioembolic stroke. Further studies are warranted to determine the benefit of anticoagulation for secondary stroke prevention in such patient population.

Keywords: cardioembolic stroke, left atrial dilatation, reduced ejection fraction, atrial fibrillation, heart failure

INTRODUCTION

The etiology of ischemic stroke impacts prognosis and management. Based on the TOAST criteria, ischemic stroke is classified into five categories: cardioembolic, large-artery atherosclerosis, small vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology. Cardioembolic stroke includes patients with arterial occlusion due to an embolus presumably arising in the heart. Up to 25% of ischemic strokes are cardioembolic in nature with atrial fibrillation (Afib) being the most common underlying etiology (1–4). Detection and diagnosis of Afib often requires long-term monitoring, which is costly with variable detection rates reaching only 30% in 3 years (5, 6). In addition to abnormal atrial rhythm detection, structural assessment of atrial size may prove as a potential diagnostic tool. In particular, left atrial (LA) volume index > 32 ml/m^2 in patients without Afib has been demonstrated to be predictive of first-ever ischemic stroke (7). Additionally, LA enlargement has been shown as an echocardiographic indicator of Afib (8, 9). Studies have shown that in the presence of LA dilatation, the likelihood of Afib detection will be higher, and that every 5 mm incremental increase in LA size raises the risk of developing Afib by 39% (10–12). Furthermore, studies have shown that LA dilatation is correlated with cardioembolic compared with atherosclerotic stroke (13).

Heart failure (HF) is another potential independent cardioembolic risk factor accounting for etiology of ∼9% of ischemic strokes with a 9–10% risk of recurrent stroke per year in patients with HF (14, 15). Moreover, these patients are at a greater risk of developing Afib, and conversely, patients with Afib are more likely to develop HF (16). Even among patients with cryptogenic stroke, which makes up to 20–30% of all ischemic strokes, low burden occult Afib has been shown to be one of the underlying etiologies with its frequency increasing in patients older than 60 years of age (17). Discovery of the culprit cardioembolic source despite the most thorough diagnostic testing often remains a challenge; however, its identification is imperative as it will ultimately guide the decisions regarding anticoagulation vs. antiplatelet treatment for secondary stroke prevention.

Of note, patients with HF often have other comorbidities, such as hypertension or ischemic heart disease, which also increase the risk of ischemic stroke (14, 18). However, even after adjusting for those risk factors, there remains 2–3 times higher risk of stroke in patients with HF (19). Additionally, ischemic stroke in HF patients is associated with higher mortality rate and longer hospital length of stay (15). Investigations in HF patients with reduced ejection fraction (EF) without Afib have identified moderate and severe HF [New York Heart Association (NYHA) classes III and IV], insulin-dependent diabetes mellitus, high body mass index, and previous history of stroke as independent stroke risk factors (20). Stratification based on these risk factors demonstrated that these patients may have a rate of stroke risk approximating patients with Afib and not treated with anticoagulation. Accordingly, in patients with a combination of HF and Afib, even paroxysmal in nature, the risk of stroke is higher, and therefore consideration of these risk factors will allow for individualization of stroke prevention measures.

The Heart Failure Society of America recommends consideration of anticoagulation for stroke prevention in patients with EF below 35%. However, studies have failed to prove the benefit of anticoagulation over antiplatelet therapy in this patient population (21). It is unclear if patients with LA enlargement and low EF without Afib will benefit from anticoagulation therapy. In this study, we aimed to evaluate the association between LA dilatation and reduced EF with cardioembolic stroke.

MATERIALS AND METHODS

Ethics

Ethics approval for the study including human participants was obtained from the UCI institutional review board.

Six hundred eighty-three consecutive patients diagnosed with ischemic stroke between 2016 and 2017 at the University of California, Irvine were reviewed. Inclusion criteria included: age ≥ 18, diagnosis of ischemic stroke based on magnetic resonance imaging (MRI) findings, and availability of transthoracic echocardiography (TTE) within 3 months of stroke diagnosis. As shown in **Figure 1**, from 683 records, 230 were excluded due to lack of MRI or echocardiogram.

The diagnostic work-up for all ischemic stroke patients typically involved MRI of the brain if no contraindications, vessel imaging with either computed tomography angiography (CTA) or magnetic resonance angiography (MRA), TTE, transesophageal echocardiography (TEE) in cases indicated after TTE, and continuous cardiac telemetry monitoring for a minimum of 24–48 h. Further work-up for underlying hypercoagulable state, hematological, rheumatological, or other etiologies was pursued per stroke team discretion.

Stroke was dichotomized into cardioembolic (based on MRI findings and identified cardiac source including: evidence of intracardiac thrombi or endocarditis, history of Afib, or if there was high suspicion for cardioembolic stroke) vs. non-cardioembolic (atheroembolic, small-vessel, stroke of other determined etiology, or non-embolic stroke of undetermined source based on the MRI findings and other stroke work-up). LA volume was measured with the biplane area-length method and categorized as 34 ml/m^2 or lower (normal) vs. 35 or greater ml/m^2 (abnormal). Other variables that were taken into consideration included: gender, blood pressure that was dichotomized into hypertension defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg vs. normal blood pressure defined as SBP < 140 mmHg and DBP < 90 mmHg upon presentation, EF: 52–72% normal (male), 54–74% (female), 41–51% mildly abnormal (male), 41–53% (female), 30–40% moderately abnormal (same in both genders), <30 severely abnormal (same in both genders), and known history of Afib.

Continuous variables including age and National Institute of Health Stroke Scale (NIHSS) score were presented as median + IQR using the Kruskal–Wallis tests as they were not normally distributed. Chi-square test was used to investigate

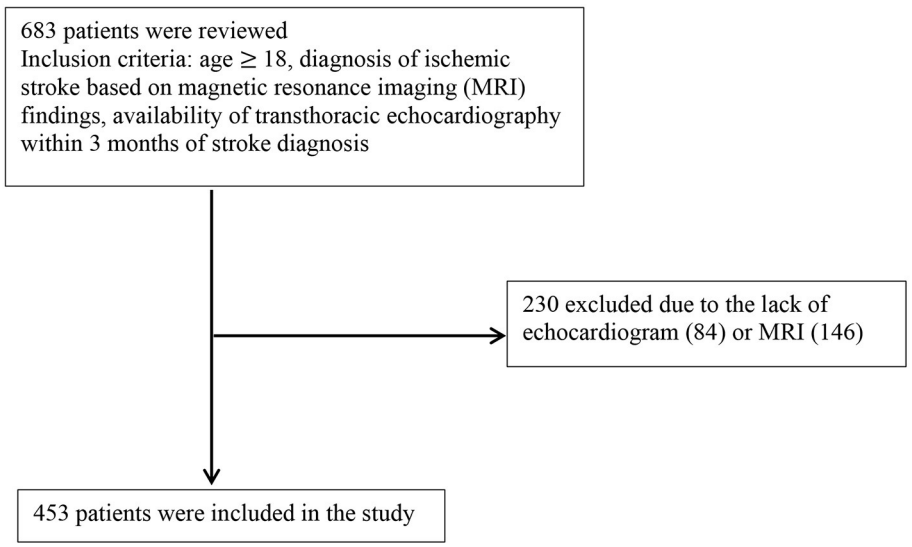

FIGURE 1 | Flow diagram for inclusion and exclusion criteria.

TABLE 1 | Demographic characteristics based on cardioembolic vs. non-cardioembolic stroke.

	All patients (*N* = 453)	Non-cardioembolic (*N* = 235, 51.9%)	Cardioembolic (*N* = 218, 48.1%)	*p*-value
Age, median (IQR)	68.9 (23)	65.2 (23)	72.9 (20)	<0.0001
Gender				
Male	255 (56.3%)	139 (59.1%)	116 (53.2%)	0.20
HTN				
SBP ≥ 140 or DBP ≥ 90	365 (80.5%)	198 (84.3%)	170 (78.0%)	0.08
Atrial fibrillation	112 (24.8%)	9 (3.8%)	103 (47.2%)	<0.0001
EF category, median (IQR)	33 (19)			<0.0001
Normal		216 (91.9%)	169 (77.5%)	
Mildly decreased		10 (4.3%)	16 (7.3%)	
Moderately decreased		7 (3.0%)	16 (7.3%)	
Severely decreased		2 (0.8%)	17 (7.8%)	
Enlarged left atrium	207 (45.7%)	65 (27.7%)	142 (65.1%)	<0.0001
NIHSS, median (IQR)	6 (12)	4 (5)	11 (15)	<0.0001

EF, ejection fraction; HTN, hypertension; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure.

the distribution of the categorical variables among patients with cardioembolic vs. non-cardioembolic stroke, patients with Afib vs. those without Afib, and also those with reduced EF and LA dilatation vs. normal EF and LA size. Logistic regression model was employed to determine the association between variables and stroke types, while non-cardioembolic stroke was considered as the control group. All statistical analyses were performed using SAS version 9.4. Alpha is 0.05, or a p-value < 0.05 is considered statistically significant.

RESULTS

Demographic characteristics of participants are presented in **Table 1**. From a total of 453 patients, 218 were categorized into cardioembolic and 235 into non-cardioembolic strokes. Patients with cardioembolic stroke were significantly older with a median age of 72.9 years (vs. 65.2 years, $p < 0.0001$). There was no difference in terms of gender distribution or prevalence of hypertension between the two categories of cardioembolic and non-cardioembolic strokes.

While 103 (47.2%) patients with cardioembolic stroke had known history of Afib, this was only 9 (3.8%) among patients with non-cardioembolic stroke ($p < 0.0001$). Among patients with non-cardioembolic stroke, 91.9% had normal EF compared with 77.5% of patients with cardioembolic stroke. Among patients with non-cardioembolic stroke, 4.3, 3.0, and 0.8% had mildly, moderately, and severely decreased EFs, respectively, vs. corresponding 7.3, 7.3, and 7.8%, respectively, in patients

TABLE 2 | Multiple logistic regression model.

Covariate	Odds ratio	95% confidence interval
Age	1.02	1.002–1.035
Gender		
Male	1.08	0.676–1.732
HTN		
SBP ≥ 140 or DBP ≥ 90	0.73	0.408–1.319
Atrial fibrillation	14.78	7.005–31.204
EF category		
Mildly decreased	1.30	0.469–3.584
Moderately decreased	2.04	0.070–5.959
Severely decreased	8.85	1.852–42.266
Enlarged LA	2.44	1.519–3.929

The association between cardioembolic stroke and other covariates. EF, ejection fraction; HTN, hypertension; LA, left atrium; SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 3 | Demographic characteristics of patients with Afib vs. those without Afib.

	N = 453	Non-AF (*N* = 341)	AF (*N* = 112)	*p*-value
Age, median (IQR)	72 (23)	67 (22)	78 (16)	<0.0001
Gender				
Male	255	202 (59.2%)	53 (47.3%)	0.03
HTN				
SBP ≥ 140 or DBP ≥ 90	368	282 (82.7%)	86 (76.8%)	0.16
EF category	453			0.01
Normal		300 (88.0%)	85 (75.9%)	
Mildly decreased		14 (4.11%)	12 (10.71%)	
Moderately decreased		14 (4.11%)	9 (8.04%)	
Severely decreased		13 (3.81%)	6 (5.36%)	
Enlarged LA	207	122 (35.8%)	85 (75.9%)	<0.0001

Afib, atrial fibrillation; EF, ejection fraction; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 4 | LA enlargement and reduced EF in patients with Afib and cardioembolic stroke.

	N = 270	Normal LA and EF (*N* = 224)	Enlarged LA and reduced EF (*N* = 46)	*p*-value
Afib	40	20 (8.9%)	20 (43.4%)	<0.0001
Cardioembolic stroke	99	63 (28.1%)	36 (78.3%)	<0.0001

Afib, atrial fibrillation; EF, ejection fraction; LA, left atrium.

with cardioembolic stroke ($p < 0.001$). The prevalence of enlarged LA was 27.7% in non-cardioembolic stroke vs. 65.1% in cardioembolic stroke ($p < 0.0001$). The median NIHSS scores in cardioembolic and non-cardioembolic stroke were 12 and 6, respectively ($p < 0.0001$).

Table 2 demonstrates the association between cardioembolic stroke and other covariates including age, gender, blood pressure, Afib, EF and enlarged left atrium. Cardioembolic stroke is weakly associated with older age (95% CI: 1.002–1.035). Patients with severely reduced left ventricular function (EF < 30%) are at 8.85 times risk of developing cardioembolic stroke compared with those with normal EF (95% CI: 1.852–42.266). Patients with enlarged left atrium have 2.44 odds of cardioembolic stroke compared with those with normal LA size (95% CI: 1.519–3.929). History of Afib is associated with significantly higher odds of cardioembolic stroke (95% CI: 7.005–31.204). Gender and history of hypertension were not associated with cardioembolic stroke after adjusting for other variables.

Table 3 shows the demographic characteristics of patients with known history of Afib and those without Afib. Patients with Afib are significantly older (78 vs. 67 years; $p < 0.001$), less likely to be male (47.3 vs. 59.2%; $p = 0.03$), less likely to have normal EF (75.9 vs. 88.0%; $p = 0.01$), and more likely to have enlarged left atrium (75.9 vs. 35.8%; $p < 0.0001$) than patients without Afib.

To investigate the association of combined LA dilatation and reduced EF with Afib and cardioembolic stroke, we divided patients into two groups: normal LA size and normal EF vs. enlarged LA and reduced EF. In this subgroup analysis as shown in **Table 4**, patients with combined enlarged LA and reduced EF had significantly higher rates of Afib (43.4 vs. 8.9%, $p < 0.0001$) and cardioembolic stroke (78.3 vs. 28.1%, $p < 0.0001$) than patients with normal LA and EF.

DISCUSSION

In this retrospective cohort study, we investigated the association of enlarged LA and reduced left ventricular EF with cardioembolic stroke. This analysis revealed that patients with enlarged LA and severely reduced EF (<30%) are independently associated with 2.4 and 8.8 times higher, respectively, risks of developing cardioembolic stroke than patients with normal values of these parameters. Also, a greater percentage of patients with enlarged LA and reduced EF had Afib and cardioembolic stroke when compared with those with normal LA size and normal EF.

In this study, we used the biplane area-length method to calculate the LA volume, which has been shown to be a more accurate measurement than LA diameter with excellent inter-rater reliability (interclass correlation 0.94) (22). LA enlargement in patients without prior history of Afib is an independent risk factor for first time and recurrent stroke (8, 9). Additionally, LA diameter > 0.5 mm has been shown to be correlated with a 4-fold increased risk of new-onset Afib (12, 23).

Patients with Afib are more likely to develop HF, and conversely, HF patients are at a greater risk of developing Afib (24). HF is also associated with increased activity of procoagulant factors and increased thromboembolic events, as well as increased risk of stroke even in the absence of Afib (25–27). Among HF patients without Afib, the stroke risk in patients with or without reduced EF is the same; however, in the presence of Afib, the stroke risk is higher in those with reduced EF than

in those with preserved EF (20, 27). In other words, HF in the presence of Afib is associated with 5 times higher odds of stroke compared with 3.5 in patients with HF and no evidence of Afib (28).

Studies on the risk of stroke in HF patients have used different criteria to include HF patients (25). Those investigations utilizing different EF categories have shown that patients with severely reduced EF and high CHA_2DS_2-VASc score have a particularly higher risk of ischemic stroke (29, 30). These previous reports support our findings in that severely reduced left ventricular function is associated with higher risk of stroke. Furthermore, we demonstrated significantly higher rates of combined enlarged LA and severely reduced EF among patients with Afib and cardioembolic stroke. Therefore, we propose that the presence of echocardiographic evidence of combined enlarged LA and severely reduced EF (<30%) obviates the necessity for diagnosis of Afib in consideration of anticoagulation for secondary stroke prevention.

Multiple studies have evaluated the benefit of anticoagulation over antiplatelet for stroke prevention in patients with HF and sinus rhythm. Although findings were suggestive of a small benefit with anticoagulation, warfarin was not superior to aspirin due to higher risk of bleeding (31–33).

The NAVIGATE ESUS [New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial vs. ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (ESUS)] trial showed that in patients with an ESUS, there was no significant difference in stroke recurrence between the rivaroxaban and aspirin groups (34). However, in the predefined subgroup of patients with a LA diameter of more than 4.6 cm, there was a significant reduction in recurrent stroke among patients who were treated with rivaroxaban (1.7 vs. 6.5% per year; hazard ratio, 0.26; 95% CI, 0.07–0.94; $p = 0.02$) (35).

Long-term monitoring with loop recorder for Afib can be very costly. Our results suggested that the combination of LA enlargement with decreased EF is an independent predictor of Afib and cardioembolic stroke and may present an indication for anticoagulation for secondary stroke prevention.

Our study has limitations. First, we excluded a significant number of patients due to presumed lacunar infarcts and the unavailability of echocardiogram, which is most of the time requested as part of the work-up when MRI findings are highly suggestive of embolic type of stroke. We did not include a number of variables, such as body mass index and the presence or absence of valvular disease, which may affect the LA size and left ventricular function. Lastly, this is a single center retrospective study. Further studies are warranted to investigate the association between the combination of enlarged LA with reduced EF with cardioembolic stroke and the benefit of anticoagulation for secondary stroke prevention.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of California Irvine Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MH contributed to the concept development, literature review, data and statistical analyses, manuscript draft preparation, and final revision. SM-N contributed to the literature review, data and statistical analyses, and final revision. SL contributed to the data and statistical analyses and final revision. WY contributed to the discussions of important intellectual contents, manuscript draft preparation, critical revision, and final revision. MS contributed to the concept development, data and statistical analyses, manuscript draft preparation, critical revision, and final revision. All authors contributed to the article and approved the submitted version.

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Initial Experience Performing Mechanical Thrombectomy With the CatchView Mini Device for Distal M2 Segment Middle Cerebral Artery Occlusions

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Background: Mechanical thrombectomy (MT) has become the standard of care for acute ischemic stroke due to large vessel occlusion; however, its safety and efficacy in patients with distal strokes remains unclear. In this study, we investigated the safety and efficacy of MT for distal middle cerebral artery (MCA) occlusions using the CatchView Mini (CVM; Balt, Montmorency, France).

Methods: This was a prospective single-center analysis of patients with a single MCA-M2 occlusion treated with the CVM device. Consecutive patients were prospectively enrolled from October 2018 to March 2020. Efficacy outcomes included successful recanalization [modified Thrombolysis in Cerebral Infarction (mTICI) 2b/3], procedure times, and number of device passes. Clinical outcomes included National Institutes of Health Stroke Scale Score (NIHSS) at discharge, 90-day functional independence (modified Rankin Scale 0–2) and safety outcomes included hemorrhagic complications, and 90-day mortality.

Results: A total of 45 patients (mean age: 74.0 ± 12.6; 53.3% [24/45] female) were included in the study. Upon admission, 33.3% (15/45) of patients were mRS 3–5; and mean NIHSS was 13.2 ± 4.2 Mean time from symptom onset to final angiography was 250.0 ± 83.4 min with a mean intervention duration of 34.0 ± 12.6 min. The mean number of device passes was 1.8 ± 1.5 final mTICI 2b/3 was achieved in 91.1% (41/45) of patients. Eight hemorrhagic complications (17.8%, 8/34) occurred, none of which were symptomatic. At 90-days, 57.8% (26/45) patients were functionally independent and the rate of mortality was 15.6% (7/45).

Conclusions: The present analysis demonstrates a low risk profile and high recanalization success for patients with distal M2 occlusions treated with the CVM device.

Keywords: stroke, thrombectomy, stent, hemorrhage, endovascular treatment

INTRODUCTION

Major randomized clinical trials have established the superiority of mechanical thrombectomy (MT) to medical management in patients with acute ischemic stroke due to large vessel occlusion of the anterior circulation (1–7). Newer generation MT devices have allowed operators to navigate more distally and with higher technical precision, expanding the potential therapeutic applications of MT. Yet, current evidence supporting the safety and efficacy of MT for distal occlusion is limited given the exclusion of these patients in major clinical trials. A recent meta-analysis of patients with occlusion of the M2 segment of the middle cerebral artery (MCA) demonstrated a benefit of MT over best medical care for 90-day modified Rankin Scale (mRS) score, but other apparent benefits were not statistically significant (8). M2 occlusions have also been associated with a higher rate of revascularization after treatment with intravenous tissue plasminogen activator (rTPA) compared to more proximal occlusions (9). Accordingly, available international guidelines do not recommend MT for distal occlusions based on the current level of scientific evidence (10).

The CatchView Mini (CVM; Balt, Montmorency, France) is a new version of the low-profile, laser-cut nitinol Catch+ Mini (Balt, Montmorency, France) stent retriever (SR) that boasts improved visibility and device length, as well as an overlapping structure that yields good adaptability to arterial conformation with less rectification during the clot extraction. The aim of this research was to examine the safety and efficacy of MT for occlusions of the M2 or more distal segments of the MCA. We investigated clinical, radiologic, and safety outcomes after MT with the CVM device.

METHODS

Study Design and Patient Selection

The study was a prospective single-center analysis of clinical, radiologic, and safety outcomes after MT as primary treatment for occlusions of the M2 or more distal segments using the CVM. The study enrolled consecutive patients from October 2018 to March 2020. The M2 branch was defined in accordance with anatomic boundaries, in which the M2 segment begins at the genu of the MCA and extends laterally toward the Sylvian fissure. Patients with proximal occlusions were excluded. The study was approved by the institutional ethics board and all patients provided written informed consent. In that cases in which the patient couldn't sign the informed consent, a Legally Authorized Representative signed it.

Baseline Characteristics

Patient baseline evaluation assessed age, sex, anticoagulant treatment, cardiovascular risk factors, pre-stroke mRS, initial National Institutes of Health Stroke Scale (NIHSS), and Alberta Stroke Program Early Computed Tomography Score (ASPECTS), the presence of CT perfusion mismatch, and treatment with intravenous recombinant tissue plasminogen activator (rTPA) before thrombectomy.

Endovascular Procedure

All procedures were performed using a biplane angiography machine. An 8F balloon catheter was positioned in the internal carotid artery. Navigation to the target vessel was accomplished using a 0.014-inch Traxcess guidewire (Microvention, Aliso Viejo, CA) in a Headway duo microcatheter (Microvention, Aliso Viejo, CA). After passage through the clot, intraarterial contrast medium was injected to verify the position of the microcatheter distal to the clot. In cases of primary occlusion of a small vessel feeding eloquent brain areas, the CVM (20 mm length) was used as a front-line device. No adjunctive treatments were used. The ST was deployed by withdrawal of the microcatheter and contrast was injected to evaluate flow after placement of the device. Two to three minutes thereafter, the proximal balloon guiding catheter was inflated to arrest blood flow and the open ST was removed with aspiration (**Figure 1**).

Procedural and Clinical Outcomes

Procedural variables included the modified Thrombolysis in Cerebral Infarction (mTICI) score as a measure of target artery reperfusion (11). All angiograms were adjudicated by an independent physician and successful recanalization was defined as a mTICI score of 2b/3 (complete or near-complete recanalization). We also analyzed the mean treatment time (stroke symptom onset to final angiography), mean intervention time (arterial puncture to final angiography), and mean number of device passes. Vasospasm after retraction of the device was also noted and defined as >50% stenosis on follow-up angiography. Other analyzed variables included vessel perforation, contrast extravasation, and embolism in a new vascular territory.

Clinical outcomes included mean NIHSS score at discharge and 90-day functional independence (mRS score of 0–2 at 90 days). Clinical safety outcomes included 90-day mortality, intracranial hemorrhage, and symptomatic intracerebral hemorrhage (SICH) defined as any type of hemorrhage with an increase of $\geq$4 in NIHSS score. Hemorrhagic complications were identified in accordance with the European Cooperative Acute Stroke Study III criteria (12).

Statistical Analysis

Descriptive statistics were generated using SPSS 17.0 software. Categorical variables are presented as absolute values and percentages and continuous variables are presented as means and standard deviations.

RESULTS

Patient baseline characteristics are described in **Table 1** and study outcomes are presented in **Table 2**.

Baseline Characteristics

The study included 45 patients who presented with a single M2 occlusion on initial angiography. The population was 53.3% female (24/45) with a mean age of 74.0 $\pm$ 12.6 years; 46.7% (21/45) of patients were older than 80 years of age. Most occlusions (66.7% [30/45]) were located on the left side. The most common cardiovascular risk factor was hypertension, present

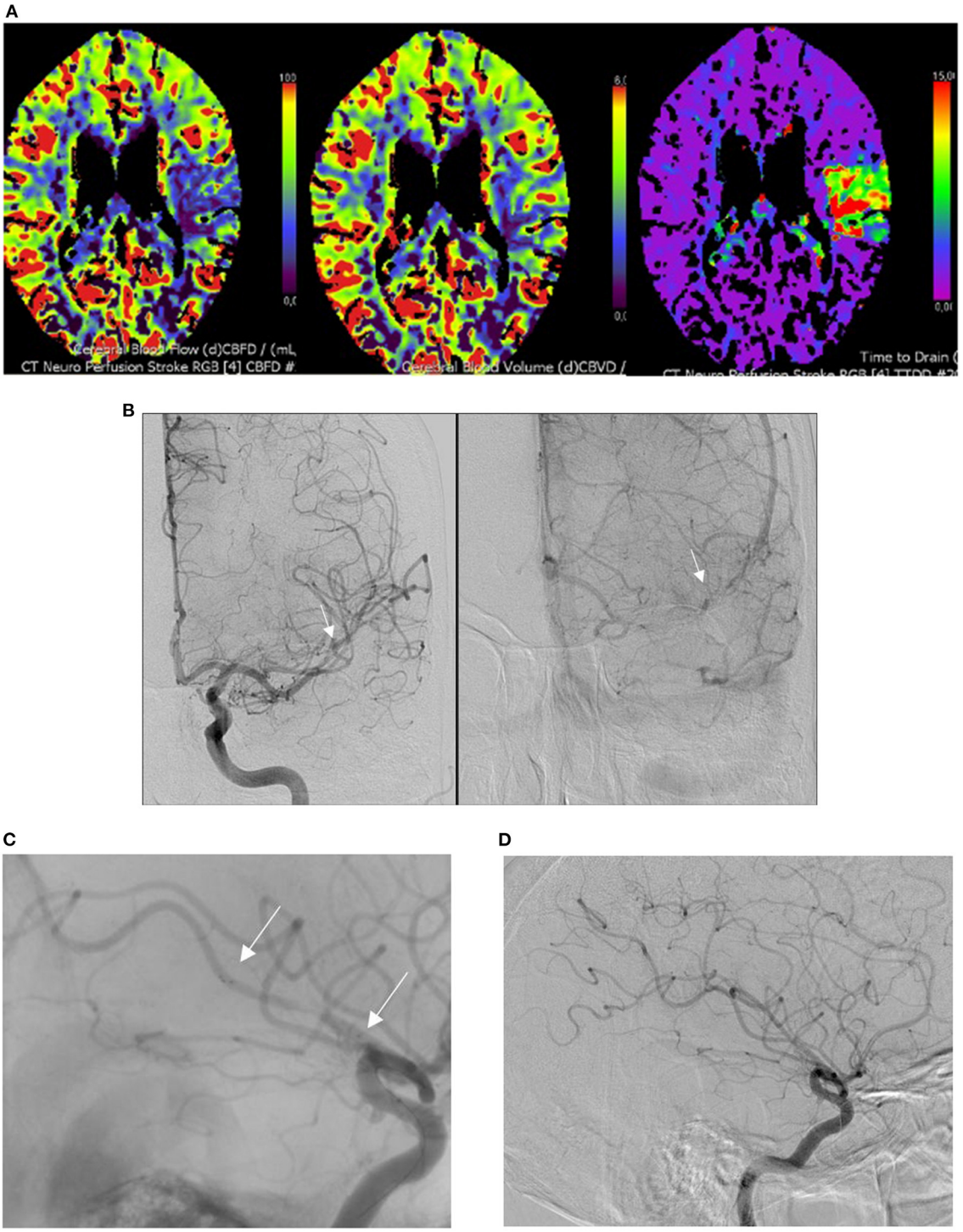

FIGURE 1 | M2 occlusion treated with the CatchView Mini device. **(A)** Perfusion computed tomography demonstrating a decrease in blood flow with normal volume and an increase in mean transit time in the territory of the left M2 segment of the middle cerebral artery. **(B)** Visualization of the M2 occlusion on angiography (anteroposterior view, white arrows). **(C)** Visualization of the distal and proximal ends of the opened CatchView Mini stentriever device inside of the clot on angiography (white arrows). **(D)** Final angiography post-procedure demonstrating complete recanalization of the occluded vessel.

in 73.3% (33/45) of patients, followed by atrial fibrillation in 68.9% (31/45) of patients. At admission, 33.3% (15/45) of patients had a mRS score of 3–5; mean NIHSS score was 13.2 ± 4.2; and mean ASPECTS score was 9.0 ± 1.0. Computerized tomography (CT) perfusion was performed in 93.3% (42/45) of patients; of these, 50.0% (21/42) exhibited

TABLE 1 | Patient baseline characteristics.

Characteristic	Overall (*N* =45)
Age	74.0 ± 12.6
Female	24 (53.3%)
Cardiovascular comorbidities	
Hypertension	33 (73.3%)
Atrial fibrillation	31 (68.9%)
mRS	
0–2	30 (66.7%)
3–5	15 (33.3%)
NIHSS	
0	0 (0%)
1–4	0 (0%)
5–15	33 (73.3%)
16–20	12 (26.6%)
Mean (SD)	13.2 ± 4.2
ASPECTS	9.0 ± 1.0
CT perfusion mismatch (*N* = 42)	21 (50.0%)
IV rTPA	14 (31.1%)
Occlusion side	
Right	15 (33.3%)
Left	30 (66.7%)
Midline	0 (0%)

Data are N (%), mean ± SD, or median (minimum-maximum). ASPECTS, Alberta Stroke Program Early CT Score; IV rTPA, intravenous recombinant tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.

TABLE 2 | Procedural and clinical characteristics.

Characteristic	Overall (*N* = 45)
Treatment time[a] (min)	250.0 ± 83.4
Intervention time[b] (min)	34.0 ± 12.6
Device passes	1.8 ± 1.5
1	28 (62.2%)
2	9 (20%)
3	4 (8.8%)
Final TICI 2b/3	41 (91.1%)
Hemorrhagic complications	
Subarachnoid hemorrhage	3 (6.7%)
Type-1 intraparenchymal hemorrhage	5 (11.1%)
Procedural complications	
Vessel perforation	0 (0.0%)
Contrast extravasation	0 (0.0%)
Embolism in new vascular territory	0 (0.0%)
NIHSS at discharge	5.0 ± 6.6
0	14 (31.1%)
1–4	13 (28.8%)
5–15	12 (26.6%)
16–20	1 (2.2%)
90-day mortality	7 (15.6%)
90-day mRS 0–2	26 (57.8%)

Data are N (%), mean ± SD, or median (minimum–maximum).
[a] Treatment time is defined as the time from stroke symptom onset to final angiography.
[b] Intervention time is defined as the time from arterial puncture to final angiography.
mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction.

perfusion mismatch. CT perfusion could not be performed in 3 cases due to patient agitation. Fifteen patients (33.3% [15/45]) were receiving anticoagulant treatment and 14 (31.1% [14/45]) were treated with at least a bolus of intravenous rtPA before the procedure. Fourteen patients (31.1% [14/45]) were treated under general anesthesia.

Procedural Characteristics and Efficacy Outcomes

The mean time from symptom onset to final angiography was 250 min with a mean intervention time of 34 min. The mean number of device passes was 1.8. No patients necessitated rescue therapy. Target artery reperfusion was assessed in all 45 patients and yielded a recanalization rate (TICI 2b/3) of 91.1% (41/45).

Safety and Clinical Outcomes

There were eight (17.8% [8/45]) hemorrhagic complications (3 subarachnoid hemorrhages and 5 type-1 intraparenchymal hemorrhages), but none were symptomatic. There were no instances of vessel perforation, contrast extravasation, or embolism in a new vascular territory. The mean NIHSS score at discharge was 5 and the 90-day mortality rate was 15.6% (7/45). Twenty-six patients (57.8% [26/45]) were functionally independent (mRS 0–2) at 90 days.

DISCUSSION

In the present study, a majority of patients treated with the CVM device for an M2 occlusion achieved successful reperfusion (TICI 2b/3). MT was also associated with a low risk of complications and a 90-day mortality rate consistent with those reported in previous clinical trials. Taken together, our findings support the safety and efficacy of MT with the CVM for distal occlusion of the MCA.

The rate of successful recanalization in this study was notably higher than that reported after intravenous alteplase in a study of patients with M2 segment MCA occlusions (37.1%) (13) and in the HERMES meta-analysis (59.2%) (8). A high rate of reperfusion in the present study may be in part attributable to our treatment protocol, which implements a proximal balloon guiding catheter together with a new-generation, long (20 mm), low-profile ST that offers better flexibility, adaptability, and navigability for treating small and tortuous vessel occlusions than STs typically used to treat proximal occlusions. Previous research suggests that ST length influences recanalization success (14). Moreover, the CVM is fully compatible with the low-profile Headway Duo microcatheter (1.3F distally, 0.012″ internal lumen), which has been previously demonstrated to reduce the likelihood of clot migration during MT (15).

We similarly observed good clinical outcomes in our study, with more than half patients exhibiting functional independence (mRS 0–2) at 90 days post-procedure. In the HERMES meta-analysis, the direction of clinical benefit generally favored endovascular treatment over medical treatment (mRS 0–2 at 90 days 58.2 vs. 39.7%, respectively), but the results were not statistically significant for all outcomes (8). A larger benefit observed in our study may be due to differences between studies in the included patient population and the use of different treatment protocols, as the HERMES analysis included a broad variety of intra-arterial therapies. Moreover, the meta-analysis results may have been underpowered given the small, pooled sample size of patients with M2 occlusion. Finally, divergence between our results and those of the meta-analysis may have been related to differing definitions as to what constitutes M1 occlusion vs. M2 occlusion from an anatomical perspective (9).

MT with the CVM in our study produced a low rate of complications. There were no observed cases of SICH and relatively few cases of subarachnoid hemorrhage and type-1 intraparenchymal hemorrhage. Additionally, there were no cases of vessel perforation or extravasation. These results are consistent with those reported by the HERMES meta-analysis, which did not identify any SICH or major procedural complications in the endovascular treatment group vs. a cumulative rate of 7.9% in the control arm (8). In contrast, a meta-analysis by Saber et al. (16) reported a 10% rate of SICH after MT for distal occlusion. A higher rate of SICH in the aforementioned study may reflect the risk associated with the use of devices designed for proximal occlusion to treat smaller or more fragile vessels. Furthermore, Baharvahdat et al. (17) examined the rates of post-thrombectomy subarachnoid hemorrhage based on occlusion location and described a higher rate in the M2 group compared to the M1 group (25 vs. 12%; $P = 0.010$); however, this difference was not associated with significant long-term clinical consequences. In our series, we detected a lower rate of subarachnoid hemorrhage with no observed worsening of the patients' clinical condition.

MT in our study was not associated with vessel vasospasm in any patient. Vessel vasospasm was detected in a significant number of patients (22.5%) who underwent treatment with a ST in the SWIFT trial (18) and in more than half of the patients in the Baby Trevo series (19) without clinical sequelae, which may indicate that this is not a hazardous event. Nonetheless, intra-arterial vasodilator infusion either prophylactically or to treat angiographic vasospasm produced good results in these studies. Finally, it is noteworthy that the 90-day mortality rate observed in our study is comparable to that reported in previous trials [11.9% (8) and 15.8% (16)].

The present study has several limitations. First, we included a relatively small sample size. Given a paucity of corroborating evidence for the safety and efficacy of our treatment protocol, additional data is necessary to support MT as a therapeutic option for distal MCA occlusion in international guidelines. Second, the present research was a prospective case series and, therefore, lacked randomization and a control arm for comparison. It is important to acknowledge that a careful risk benefit assessment is important, especially in a context of distal occlusion. Future efforts should include a randomized controlled trial of MT vs. medical therapy for M2 occlusion; however, this may not be feasible due to the lack of clinical equipoise, as MT is now routinely performed for M2 occlusion in contrast with guideline recommendations. Finally, it is important to underscore that our study findings were likely bolstered by use of the CVM device, which offers key advantages for the treatment of distal occlusions relative to STs employed for the treatment of proximal occlusions.

CONCLUSIONS

Our analysis demonstrates that, in a context of distal M2 occlusion, MT with the CVM device is associated with a low risk profile and a high rate of recanalization success.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hospital Universitario Central de Asturias: Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PV: responsible for the integrity of the study, study design, data collection, analysis and interpretation of data, statistical treatment, literature research, text writing, critical revision, and approval of the final version. EM: critical revision, approval of the final version, and responsible for the integrity of the study. JJ and JC: text writing, data collection, study design, and approval of the final version. MG-D, LB, FG-A, and JP: critical revision and approval of the final version. All authors contributed to the article and approved the submitted version.

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Endovascular Device Choice and Tools for Recanalization of Medium Vessel Occlusions: Insights From the MeVO FRONTIERS International Survey

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Background: Endovascular treatment (EVT) for stroke due to medium vessel occlusion (MeVO) can be technically challenging. Devices and tools are rapidly evolving. We aimed to gain insight into preferences and global perspectives on the usage of endovascular tools in treating MeVOs.

Methods: We conducted an international survey with seven scenarios of patients presenting A3, M2/3, M3, M3/4, or P2/3 occlusions. Respondents were asked for their preferred first-line endovascular approach, and whether they felt that the appropriate endovascular tools were available to them. Answers were analyzed by occlusion location and geographical region of practice, using multinomial/binary logistic regression.

Results: A total of 263 neurointerventionists provided 1836 responses. The first-line preferences of physicians were evenly distributed among stent-retrievers, combined approaches, and aspiration only (33.2, 29.8, and 26.8%, respectively). A3 occlusions were more often treated with stent-retrievers (RR 1.21, 95% CI: 1.07–1.36), while intra-arterial thrombolysis was more often preferred in M3 (RR 2.47, 95% CI: 1.53–3.98) and M3/4 occlusions (RR 7.71, 95% CI: 4.16–14.28) compared to M2/3 occlusions. Respondents who thought appropriate tools are currently not available more often chose stent retrievers alone (RR 2.07; 95% CI: 1.01–4.24) or intra-arterial thrombolysis (RR 3.35, 95% CI: 1.26–8.42). Physicians who stated that they do not have access to optimal tools opted more often not to treat at all (RR 3.41, 95% CI: 1.11–10.49). Stent-retrievers alone were chosen more often and contact aspiration alone less often as a first-line approach in Europe (RR 2.12, 95% CI: 1.38–3.24; and RR 0.49, 95% CI 0.34–0.70, respectively) compared to the United States and Canada.

Conclusions: In EVT for MeVO strokes, neurointerventionalists choose a targeted vessel specific first-line approach depending on the occlusion location, region of practice, and availability of the appropriate tools.

Keywords: acute ischemic stroke, endovascular thrombectomy, aspiration thrombectomy, medium vessel occlusions, endovascular treatment (EVT), MeVO, stroke, neurointervention

INTRODUCTION

Given the high efficacy of endovascular treatment (EVT) for acute ischemic stroke due to large vessel occlusion (LVO) and recently recognized substantial morbidity associated with stroke due to medium vessel occlusions (MeVO; distal M2/3, A2/3, P2/3 vessel segments) (1), EVT is now increasingly considered as a treatment for MeVO stroke (2), despite the lack of high-level evidence for MeVO EVT (3, 4). The smaller caliber, more distal location, and longer and more tortuous course of the affected vessels of MeVO compared to LVO makes EVT for MeVO stroke more challenging. Thinner, more fragile arterial walls could increase the risk of dissection, perforation, and vasospasm—complications that could offset any benefit of EVT (3, 4).

Currently, EVT tools and techniques are rapidly evolving, resulting in improved efficacy and safety of MeVO EVT. Several authors report promising results of primary aspiration as a first-line approach in MeVO stroke (5–9). Mini stent-retrievers are designed specifically for more distal occlusion locations, and novel approaches like the blind exchange mini-pinning (10, 11) technique may lead to higher rates of first-pass recanalization and a lower incidence of symptomatic intracranial hemorrhage compared to the use of mini stent retrievers alone (10).

However, in light of these developments, and in the absence of guideline-based treatment recommendations, clinical practice with regard to EVT techniques for MeVO stroke may vary greatly between countries or individual physicians. Currently, there are little data on the variability in MeVO EVT approaches. Therefore, we sought to determine global patterns in preferences and utilization of EVT devices in MeVO stroke. In addition, we explored interventionalists' access to the appropriate EVT devices, and whether they thought that appropriate tools already exist and are available to them in their current practice.

METHODS

We conducted an international, cross-sectional, anonymous, invitation-only survey: MeVO-FRONTIERS (MeVO-Finding Rationales and Objectifying New Targets for IntervEntional Revascularization in Stroke). Approximately 1,400 stroke physicians from 44 countries were invited to participate in this survey through Qualtrics (www.qualtrics.com). There were no restrictions for respondents based on country, years of experience, career stage, or hospital setting. The current study analyzes the survey questions on EVT technique and includes responses from interventionalists who identified themselves as neuroradiologists, neurosurgeons performing endovascular procedures, and interventional neurologists.

Response data were obtained from November 12, 2020 to December 31, 2020. Data are available from the corresponding author upon request. Approval by the local research ethics board of the University of Calgary was obtained (REB20-2086).

Survey Design

The survey consisted of seven narrative MeVO cases with illustrative images and three to six clinical case vignettes per scenario. The case vignettes included patient demographics, clinical symptoms, radiological images, and imaging-derived information like CT-perfusion volumes or early ischemic changes on non-contrast CT. At the end of each case, physicians were asked what their preferred first-line EVT approach for that particular case would be. Answer options were (a) stent-retriever alone, (b) aspiration alone, (c) combined stent-retriever and aspiration, (d) intra-arterial thrombolysis, or (e) no treatment. Participants were then asked whether they thought that optimal tools for treating MeVOs with EVT currently exist (Yes/No/There is substantial scope for improvement) and whether the appropriate material for MeVO EVT is available in their institution (full survey questions shown in **Supplementary Methods**). Prior to accessing the case scenarios, physicians provided basic personal data (age group, gender, subspecialty, years of experience in stroke treatment, annual center stroke treatment volume, and geographic region).

Statistical Analysis

Respondents' baseline characteristics were described using appropriate descriptive statistics. Univariable multinomial regression clustered by participant was used to assess the effect of occlusion site and respondent characteristics on preferred first-line EVT approach. Incidence rate ratios (IRRs) with 95% confidence intervals (CI) were reported.

For the following analysis, first-line approach was dichotomized into dummy variables (e.g., stent-retriever vs. others, aspiration vs. others, etc.). Then, preferred first-line EVT approach by occlusion site (M2/3, M3, M3/4, A3, P2/3) and region of practice (USA and Canada, Europe, rest of the world) were analyzed using binary logistic regression clustered by participant to calculate risk ratios (RRs) with 95% confidence intervals. M2/3 occlusion and responses from practitioners from the USA and Canada were chosen as reference values.

Multinomial regression analysis was used to determine treatment approach preference based on the existence and availability of specific endovascular tools and whether the interventionists thought they had adequate access to them in their current practice. In the multinomial regression model, the

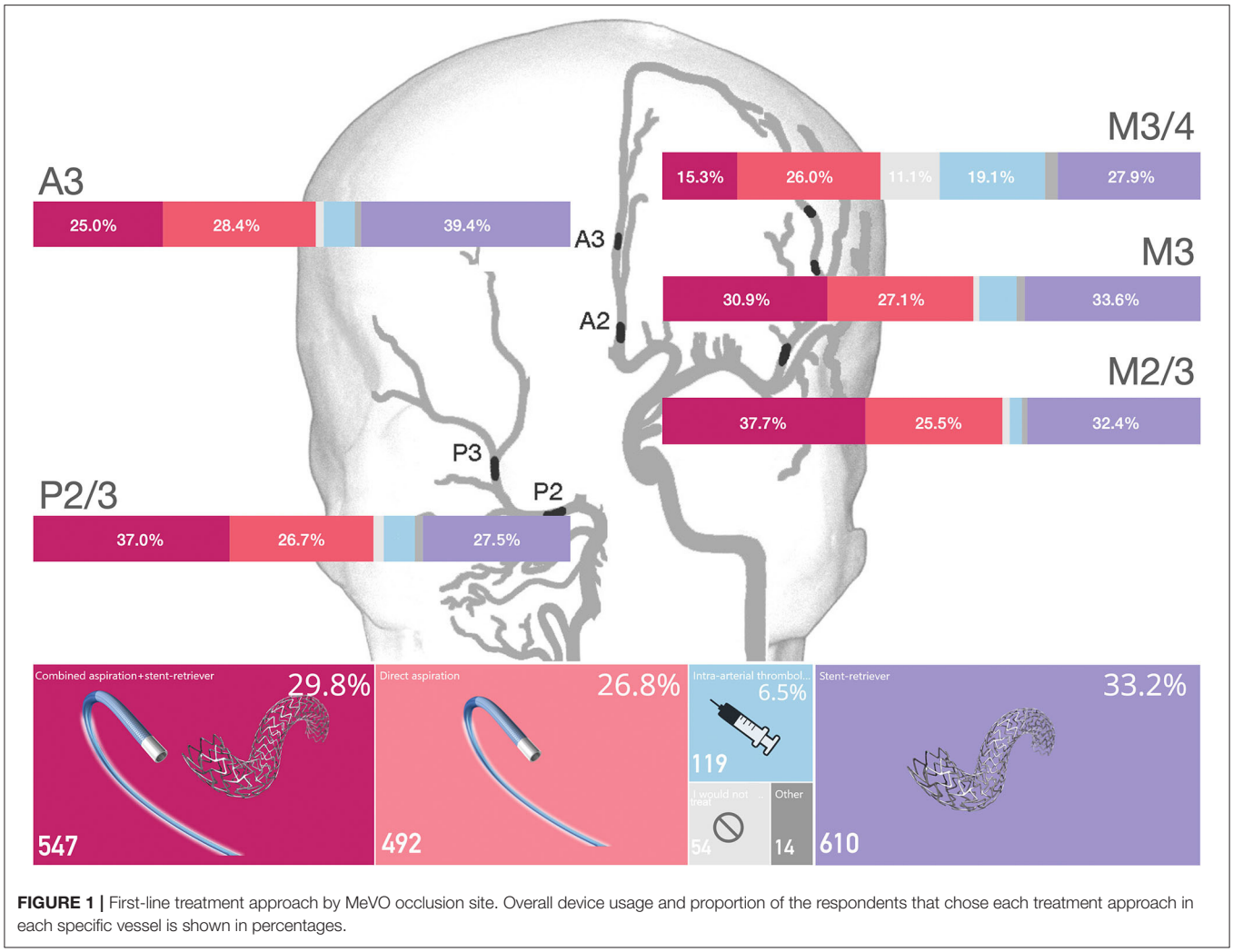

FIGURE 1 | First-line treatment approach by MeVO occlusion site. Overall device usage and proportion of the respondents that chose each treatment approach in each specific vessel is shown in percentages.

combined technique (stent retriever together with the contact aspiration) was chosen as the reference value and responses "Yes, tools exist" and "Yes, tools are available" were taken as base outcome.

The significance level was set at $p < 0.05$. Data analyses were performed in Stata 16.1 (StataCorp, College Station, TX, USA). Figures were created using the Microsoft PowerBI Platform.

RESULTS

In total, 263 of 366 stroke physicians who participated were neurointerventionists and were included in the current study. Seven clinical scenarios (two M2/3 and two A3 cases; one M3, M3/4, and P2/3 case) resulted in 1,836 responses on treatment approaches for MeVOs. Detailed respondent characteristics are listed in **Supplementary Table 1**.

Overall, physicians opted for first-line stent-retrievers alone in 33.2% (610/1,836) of cases, a combined approach in 29.8% (547/1,836), aspiration only in 26.8% (492/1,836) cases, and intra-arterial thrombolysis in 6.5% (119/1,836) cases. In 2.9% (54/1,836) of cases, no treatment was preferred, and in 0.8% (14/1,836) of responses, another endovascular approach was preferred (e.g., combined aspiration and stent-retriever with additional intra-arterial thrombolysis, or guidewire/microcatheter manipulation only). There were no differences in the preferred first-line approach among physicians based on their age, gender, years of experience in neurointervention, career stage, or annual institutional EVT volumes (**Supplementary Table 2**).

First-Line Device Preference by Occlusion Site

First-line treatment approach for each occlusion site is shown in **Figure 1** and **Table 1**. Preference for stent-retrievers alone did not differ between middle cerebral artery (MCA) occlusions (M2/3, M3, M3/4; **Supplementary Table 2**). In A3 occlusions, stent-retrievers were the most commonly preferred approach [39.4%, 207/525 responses; RR 1.22, 95% CI 1.08–1.37 (reference category: M2/3)]. For P2/3 occlusions, the combined approach (stent-retriever and aspiration) was frequently chosen (37% in

TABLE 1 | Likelihood of preferred first-line approach (stent-retriever, combined stent-retriever and aspiration, aspiration, intra-arterial thrombolysis, or other) per occlusion site (reference: M2/3).

	Overall (n = 1,836) RR (95% CI)	M3 (n = 262) RR (95% CI)	M3/4 (n = 262) RR (95% CI)	A3 (n = 525) RR (95% CI)	P2/3 (n = 262) RR (95% CI)
First-line treatment approach for MeVO occlusion site compared to M2/3 occlusion*					
SR	1.01 (0.98–1.04)	1.04 (0.92–1.17)	0.86 (0.72–1.03)	**1.22 (1.08–1.37)**	**0.85 (0.73–0.99)**
Combined (SR + contact aspiration)	**0.93 (0.90–0.97)**	**0.82 (0.72–0.94)**	**0.40 (0.31–0.52)**	**0.66 (0.56–0.78)**	0.98 (0.86–1.12)
Contact aspiration	1.02 (0.98–1.06)	1.06 (0.92–1.22)	1.02 (0.86–1.20)	1.11 (0.97–1.27)	1.05 (0.90–1.22)
IAT	**1.12 (1.04–1.22)**	**2.47 (1.53–3.98)**	**7.71 (4.16–14.3)**	**1.92 (1.04–3.56)**	**2.31 (1.30–4.12)**
No treatment	1.10 (0.97–1.25)	0.86 (0.24–3.07)	**8.30 (3.54–19.5)**	1.43 (0.53–3.87)	1.43 (0.52–3.97)
Other#	1.07 (0.78–1.46)	2.00 (0.54–7.42)	1.34 (0.18–10.1)	1.00 (0.20–4.97)	2.00 (0.54–7.42)

*Risk ratios shown are from dichotomized comparisons, e.g., stent-retrievers vs. all other, contact aspiration vs. all other, etc. The "overall" column shows the risk ratio for preferring the row's first-line approach, for an increasingly distal occlusion location (from M2/3 to P2/3). *M2/3 occlusion was chosen as reference value. # "Other" category included free-text alternative answers, like combined stent-retriever, aspiration and intra-arterial thrombolysis, or intra-arterial thrombolysis and aspiration. 95% CI, 95% confidence interval; A3, third segment of anterior cerebral artery; IAT, intra-arterial thrombolysis; M2/3/4, second/third/fourth segments of middle cerebral artery; P2/3, second/third segment of posterior cerebral artery; RR, risk ratio; SR, stent-retriever. Bold values represent statistically significant findings ($p < 0.05$).*

P2/3). The combined technique was preferred less often in more distal MCA target occlusions (37.7% in M2/3 occlusions, 30.9% for M3, 15.3% for M3/4) with relative RRs indicating diminished use for very distal occlusions (**Table 1**). In more distal occlusions, respondents were also more likely to choose intra-arterial thrombolysis as a first-line approach (overall: RR 1.12; 95% CI 1.04–1.22) or to not treat with EVT at all (in M3/4: RR 8.30; 95% CI 3.54–19.48).

Geographic Variations in Endovascular Device Choice

Stent-retriever alone was the most frequently chosen first-line approach in Europe [37.3%, 340/912 responses, RR 2.09, 95% CI 1.38–3.18 (reference category: USA and Canada)] and the rest of the world (43.3%, 179/413 responses, RR 2.43, 95% CI 1.57–3.78).

In the USA and Canada, contact aspiration alone was the most frequently preferred first-line approach (43.3%, 221/511 responses); in contrast to that, it was significantly less often chosen by Europeans [RR 0.49, 95% CI 0.34–0.70 (reference category: USA and Canada)] and practitioners from the rest of the world (RR 0.44, 95% CI 0.27–0.71).

Combined aspiration and stent-retrievers were chosen by European practitioners in 35.3% of cases (322/911 responses), which was significantly a more frequent choice when compared to the USA and Canada respondents (RR 1.41, 95% CI 1.10–1.96). There was no difference in choice of combined aspiration and stent-retriever between interventionalists in the USA and Canada and the rest of the world (25.1%, 128/511 vs. 23.5%, 97/413, respectively). There was no significant difference in the preference of intra-arterial thrombolysis or other endovascular techniques based on the region of practice (**Table 2**).

Influence of Availability and Access to Optimal MeVO EVT Tools

Overall, 162 (61.5%) participants felt that the current endovascular devices to treat MeVO stroke could be improved. Only 79 (30.0%) participants thought that the optimal tools already existed, and 22 (8.4%) thought that the appropriate tools currently do not exist. The interventionists who thought that the optimal tools to treat MeVO stroke do not exist were more likely to prefer stent-retrievers alone as a first-line approach [40.5%; RR 2.07, 95% CI 1.01–4.24 (ref category: tools exist)] and were more likely to treat MeVOs medically with IA tPA [12.43%; RR 3.25, 95% CI 1.71–6.12 (ref category: tools exist)].

Two-hundred-and-three (77.2%) neurointerventionists indicated that they had access to the best available tools, and 60 (22.8%) stated that they did not (always) have access to the ideal tools. Those without access to the optimal tools more frequently chose no EVT at all as a first-line approach [RR 3.41, 95% CI 1.11–10.49 (reference category: having the access to the best available tools)] (**Table 3**).

DISCUSSION

This survey study found that the first-line device preferences of neurointerventionists for EVT in MeVO stroke vary based on the exact location of the occlusion, physician's region of practice, whether they think that adequate tools exist, and whether they have access to these tools in their current practice.

The optimal strategy for recanalizing MeVOs is currently not known, and the data on the efficacy of first-line aspiration vs. stent-retriever techniques are heterogenous and exclusively from non-randomized studies (12–15). Use of stent-retrievers, either alone (16–19) or combined with aspiration (10, 11), seems to be a widespread approach for MeVO EVT. Stent-retrievers alone or combined stent-retrievers and aspiration were the most commonly chosen first-line approaches, with the combined approach being preferred less often in more distal occlusions and stent-retriever alone more often in A3 occlusions.

EVT device choice in MeVO stroke is likely largely determined by the device's safety profile. Because the affected vessels in MeVO strokes are smaller, more distal, and more fragile, the risk of complications such as vasospasm, manipulation-related subarachnoid hemorrhage, and dissection is increased (3). These risks should be mitigated in order for EVT to result in a net benefit for the patients undergoing recanalization. Current

TABLE 2 | Likelihood of preferred first-line endovascular treatment approach across world regions (reference: USA and Canada).

	Overall (n = 1,836) RR (95% CI)	Europe (n = 912) RR (95% CI)	Rest of the world (n = 413) RR (95% CI)
Endovascular technique choice by world region compared to the USA and Canada**			
SR	1.45 (1.22–1.72)	**2.09 (1.38–3.18)**	**2.43 (1.57–3.78)**
Combined (SR + contact aspiration)	0.99 (0.84–1.18)	**1.41 (1.10–1.96)**	0.94 (0.60–1.48)
Contact aspiration	**0.60 (0.46–0.78)**	**0.49 (0.34–0.70)**	**0.44 (0.27–0.71)**
IAT	0.96 (0.56–1.64)	0.59 (0.29–1.19)	0.97 (0.42–2.28)
No treatment	1.00 (0.49–2.02)	**0.21 (0.08–0.55)**	1.08 (0.47–2.47)
Other	1.11 (0.23–5.34)	0.45 (0.05–4.06)	1.24 (0.14–11.11)

*"Overall" column shows the risk ratio for preferring the row's first-line approach, for an ordinal world region outcome (from USA and Canada to Europe to the Rest of the world). **USA and Canada were chosen as reference value. SR, stent-retriever; IAT, intra-arterial thrombolysis; RR, risk ratio; 95% CI, 95% confidence interval. Bold values represent statistically significant findings ($p < 0.05$).*

TABLE 3 | Likelihood of preferred first-line approach (stent-retriever, combined stent-retriever and aspiration, aspiration, intra-arterial thrombolysis, or other) by physicians' opinion on whether the appropriate tools to treat MeVO exist, or whether they have access to the best available tools.

	No (n = 22) RR (95% CI)	Room for improvement (n = 162) RR (95% CI)
Do appropriate tools exist for MeVOs*		
SR alone	**2.07 (1.01–4.24)**	1.11 (0.72–1.73)
Aspiration	1.56 (0.69–3.49)	1.23 (0.77–1.96)
IAT	**3.25 (1.26–8.42)**	0.98 (0.50–1.90)
No treatment	2.06 (0.60–7.14)	1.30 (0.55–3.10)
	No (n = 18) RR (95% CI)	**Not in all cases (n = 42) RR (95% CI)**
Access to best available tools in current practice*		
SR alone	1.53 (0.69–3.36)	0.95 (0.58–1.55)
Aspiration	2.21 (0.93–5.29)	1.20 (0.68–2.13)
IAT	1.71 (0.64–4.57)	0.91 (0.68–2.13)
No treatment	**3.41 (1.11–10.49)**	0.83 (0.33–2.06)

**"Yes" was taken as the base outcome and combined technique (stent-retriever plus contact aspiration) was chosen as reference value. Other category was included in the analysis but excluded from the table for simplicity. SR, stent-retriever; IAT, intra-arterial thrombolysis; RR, risk ratio; 95% CI, 95% confidence interval. Bold values represent statistically significant findings ($p < 0.05$).*

large bore aspiration catheters may increase the risk of vascular damage, which is reflected in the decreased preference for first-line aspiration in more distal MCA occlusions in our study. Indeed, most intermediate catheters are 5–6Fr in diameter, and thus, they may be too large for MeVOs, considering the average diameter of the M2 middle cerebral artery segments is around 1.4–2.3 mm (20). Furthermore, when navigating the aspiration catheter to distal occlusion sites, there is the possibility of the device getting stuck at a vessel branch point, e.g., the middle cerebral artery bifurcation, although this risk can be mitigated by the use of wedge-shaped microcatheters (21), or coaxial microcatheters better size-matched to the aspiration catheter so as to reduce the step in transition. When using a primary combined approach on the other hand, limited lengths of currently available intermediate and microcatheters may render distal occlusions unreachable.

For stent-retrievers, the tortuosity and angle of the arteries may affect safety because of increased shearing at branch points during stent retrieval as well as and displacement of the arterial tree, both of which may result in subarachnoid hemorrhage. Use of stent-retrievers may hence be more desirable in straight arteries, such as the A3 where there is less tortuosity compared to the MCA branches (22).

Combined aspiration and stent-retrieval was shown to reduce the risk of distal embolization in large vessel occlusion stroke in some studies, with subsequent improved reperfusion quality and clinical outcomes (21). We found that a substantial number of physicians preferred this combined approach in the more proximal MeVO locations (M2/3 and P2/3). Recently proposed techniques such as blind exchange mini-pinning (11), in which the aspiration catheter is advanced introduced over the bare pusher wire once the stent-retriever is deployed, can circumvent problems related to catheter length and, at the same time, provide effective aspiration during the retrieval process. Techniques and specific tools for medium-sized arteries, such are mini stent-retrievers, are under development (17, 23); thus, it can be expected that more data on the safety and efficacy of these techniques will emerge soon.

Access to neurovascular tools and materials plays an important role in EVT decisions and first-line device choice for treating MeVOs as observed in this study. When practitioners thought that the appropriate tools do not exist, they more often chose to treat with stent-retrievers alone or opt for intra-arterial thrombolysis as a first-line approach. Those that felt they did not have access to the best available tools in their practice often chose not to treat at all.

Overall, interventionalists from Europe more often opted for stent-retrievers or combined stent-retrievers and aspiration as a first-line approach, whereas direct aspiration only was the more frequently preferred first-line approach in the USA and Canada. Availability of material and devices in different regions as well as local experience with these tools could potentially account for this variation in physicians' preferences as suggested in previous studies (24), in which the willingness to treat M2 occlusions

increased under assumed ideal conditions in some regions. There is variability in the distribution and supply of stent retrievers across the world with some centers having access only to earlier generation devices, although device availability per country and center is hard to check and changing quickly. Physicians with no access to the optimal devices more often opted either to use stent-retrievers alone or not treat with EVT at all forgoing endovascular treatment that could potentially benefit the patient.

LIMITATIONS

Our study has several limitations. First, decisions in endovascular treatment are highly dependent on details of patient anatomy and factors such as patient motion during EVT. Radiologic images were presented with all case scenarios to make them as realistic as possible; however, details in these images or cases may limit the generalizability of our study results to real clinical practice. Secondly, the landscape of EVT materials and tools changes fast, hence the results represent a snapshot in time and availability would differ as the tools continue to evolve in each region. In addition, the survey did not ask for the specific device brands that were available at respondents' institutions. As such, we do not know the exact EVT materials on which our results reflect, other than the devices that are currently approved in general for EVT. Our intention was to provide a general overview of the field. Thirdly, our respondent sample was collected through personal and professional networks of the study authors, which may introduce selection bias in the results (e.g., overrepresentation of teaching hospitals). Models of financial compensation for MeVO EVT may also have differed between respondents' practice settings.

CONCLUSION

In this study, neurointerventionalists chose a targeted vessel-specific approach when treating MeVOs. Stent-retrievers alone or combined stent-retriever and aspiration were the most commonly used first-line approach, with the combined approach being preferred less often in more distal occlusions and stent-retriever alone more often in A3 occlusions as a first-line approach. Interventionalists from Europe used stent-retrievers and combined stent-retriever and aspiration more often as a first-line treatment, whereas direct aspiration only was more frequently preferred in North America. Physicians without access to the optimal devices more often used stent-retrievers alone or chose not to treat endovascularly at all, forgoing potential benefit.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The Conjoint Health Research Ethics Board of the University of Calgary reviewed and approved this study (REB20-2086). Written informed consent to participate in this study was provided by the participants. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

NK: study conception, data collection, graphical analysis, design of the work, interpretation of data, and manuscript drafting. PC, MG, and MK: study conception, data collection, design of the work, statistical analysis, interpretation of data, and manuscript drafting. JO: study conception, data collection, design of the work, interpretation of data, and manuscript editing. NSi: study conception, data collection, design of the work, statistical analysis, interpretation of data, and manuscript editing. MA: study conception, interpretation of data, and critical manuscript revision. JR: critical manuscript revision. JF and MC: study conception, data collection, design of the work, interpretation of data, and critical manuscript revision. NSa: study conception, data collection, and critical manuscript revision. RA: manuscript revisions. MH: manuscript drafting and critical manuscript revisions. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.735899/full#supplementary-material

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Sedation Mode During Endovascular Stroke Treatment in the Posterior Circulation—Is Conscious Sedation for Eligible Patients Feasible?

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Background and Purpose: To compare safety and efficacy of conscious sedation (CS) vs. general anesthesia (GA) in endovascular stroke treatment (EST) of the posterior circulation (PC).

Methods: Retrospective single-center analysis of patients receiving EST for large-vessel occlusion (LVO) in PC between January 2015 and November 2020. Exclusion criteria were severe stroke syndromes (NIHSS > 20), decreased level of consciousness, intubation for transport, and second stroke within 3 months of follow-up. The primary endpoint was a favorable clinical outcome 90 days after stroke onset (mRS 0–2 or 3 if pre-stroke mRS 3). Secondary endpoints were the rate of EST failure and procedural complications.

Results: Of 111 included patients, 45/111 patients (40.5%) were treated under CS and 60/111 (54.0%) under GA. In 6/111 cases (5.4%), sedation mode was changed from CS to GA during EST. Patients treated under CS showed a lower mRS 90 days after stroke onset [mRS, median (IQR): 2.5 (1–4) CS vs. 3 (2–6) GA, $p = 0.036$] and a comparable rate of good outcome [good outcome, *n* (%): 19 (42.2) CS vs. 15 (32.6) GA, $p = 0.311$]. There was no difference in complication rates during EST (6.7% CS vs. 8.3% GA) or intracranial bleeding in follow-up imaging [*n* (%): 4 (8.9) CS vs. 7 (11.7) GA), $p = 0.705$]. The rate of successful target vessel recanalization did not differ (84.4% CS vs. 85.0 % GA).

Conclusions: In this retrospective study, EST of the posterior circulation under conscious sedation was for eligible patients comparably safe and effective to patients treated under general anesthesia.

Keywords: endovascular stroke therapy, mechanical thrombectomy, posterior circulation, anesthesia management, conscious sedation, acute ischemic stroke

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KEY POINTS

- Endovascular Stroke Treatment for patients with ischemic stroke in the posterior circulation is safe and effective when compared to treatment under general anesthesia with a low rate of failed recanalization and complications.
- Eligible patients show a comparable rate of good functional outcome 90 days after stroke onset.

INTRODUCTION

The mode of sedation during endovascular stroke treatment (EST) is a matter of debate in recent years, mainly regarding EST for large-vessel occlusions (LVO) in the anterior circulation. While conscious sedation (CS) can be time-saving and allows a faster treatment process between imaging and groin puncture, general anesthesia (GA) guarantees immobility of the patient, airway protection, and safe ventilation. Also, uncontrolled blood pressure during the procedure can have an impact on patient outcome. During GA blood pressure tends to be overall lower but is more controllable (1).

In patients with LVO of the anterior circulation, three randomized-controlled trials showed an equal clinical outcome for patients treated under CS or GA for LVO in the anterior circulation (2–4). More recently, a meta-analysis of the three studies mentioned above indicated that patients treated under GA may even have a better clinical outcome (5).

In comparison with the high-level evidence for the benefit of EST in the anterior circulation, there is a lack of evidence for treating patients with ischemic stroke and LVO of the posterior circulation. The BEST trial showed a higher rate of favorable outcome for patients with vertebrobasilar occlusions treated with EST compared to best medical treatment (BMT), but the high crossover rate after randomization represents a major limitation of the trial (6). In the Basilar Artery International Cooperation (BASIC) study (7), which randomized 300 patients until December 2019, EST failed to outperform BMT alone. In this underpowered study, the estimated risk reduction of mortality (16%) was not reached in the intervention arm. However, the intervention arm showed a risk reduction of 6.5% (44.2% compared to 37.7%). Subgroup analyses showed a favorable outcome for patients older than 70 years treated with EST and for patients with bridging i.v. thrombolysis before EST. After all, it remains uncertain if a convincing randomized trial for evidence of EST in the posterior circulation can be conducted. Indirect evidence for the benefit of EST in the posterior circulation remains, like the very high mortality rate, when the occlusion remains despite treatment (8). There is also indirect evidence from comparing outcome parameters and technical success rates with EST of the anterior circulation, where EST of the posterior circulation seems equally safe and effective (9, 10).

When it comes to sedation mode during EST of the posterior circulation contrarily to the anterior circulation, for EST in the posterior circulation, endotracheal intubation and treatment under GA are often deemed mandatory (11). Vertebrobasilar occlusion impairs the brainstem's blood perfusion resulting in disorientation, decreased level of consciousness, and loss of protective reflexes. Thus, patients with acute vertebrobasilar artery occlusions are often comatose on presentation and need to be intubated. Also, with loss of protective reflexes there is often a higher risk of aspiration and apnea requiring airway protection (12). However, some patients with LVO of the posterior circulation present with mild to moderate stroke syndromes (NIHSS 5–20) and clinically stable enough for EST under CS. Opposed to the broadly investigated sedation mode of anterior circulation stroke patients, it remains unclear if treating these patients under CS is comparably safe and effective.

The aim of this study was to compare eligible patients with acute ischemic stroke of the posterior circulation treated with state-of-the-art EST under CS compared to treatment under GA.

Abbreviations: CS, conscious sedation; EST, endovascular stroke treatment; GA, general anesthesia; ICH, intracranial hemorrhage; LVO, large vessel occlusion; mTICI, modified treatment in cerebral ischemia; pc-ASCPETS, posterior circulation alberta stroke program early CT score.

METHODS

For this study, a retrospective single-center analysis of an institutional review board–approved stroke database was performed. The tertiary stroke center's database with prospectively obtained patients was searched for patients receiving EST for LVO in the posterior circulation under CS between January 2015 and November 2020.

Study Endpoints, Patient Selection, and Study Groups

The primary endpoint of this study was a favorable clinical outcome 90 days after stroke onset (mRS 0–2 or 3 if pre-stroke mRS = 3). Secondary endpoints were the rate of successful target vessel recanalization and complication rate including intracranial hemorrhage in follow-up imaging. Exclusion criteria were a severe stroke syndrome (NIHSS > 20) or decreased level of consciousness, intubation before transport to stroke center, simultaneous LVO of the anterior circulation, or re-stroke within 3 months of follow-up. The two study groups were defined as patients with LVO of the posterior circulation treated under CS compared to patients with LVO of the posterior circulation treated under elective GA.

Performance of Modern EST for LVO in the Posterior Circulation

Decision for EST was made based on a consensus by the neurologist and neurointerventionalist after initial stroke imaging with CT or MRI. Intravenous thrombolysis was administered according to national and international guidelines. The choice of the sedation mode in the complete study cohort was made according to the patient's compliance, severity of the stroke syndrome, and level of consciousness. The bias of selecting more severely harmed patients preferably for general anesthesia was reduced in this study by the abovementioned exclusion criteria (severe stroke syndrome, decreased level of consciousness, intubation before transport).

In the standard approach for EST, a transfemoral access is conducted followed by placing a guide catheter in the subclavian artery (7F/80 cm Flexor Shuttle, Cook Medical, Bloomington, IN, USA). Subsequently, a distal access catheter is introduced to the vertebral artery (e.g., Sofia 5F, MicroVention, Aliso Viejo, CA, USA). The first-line approach (performing direct thromboaspiration or stent-retriever-thrombectomy in combination with continuous distal aspiration using a distal

aspiration catheter), as well as the choice of material used for EST, is at the discretion of the treating neurointerventionalist. The following stent-retriever types were used (descending order of frequency of use): Solitaire (Medtronic, Dublin, Ireland), Trevo (Kalamazoo, MI, USA), pRESET (phenox, Bochum, Germany). Follow-up imaging is performed 24 h after EST with either CT or MRI.

Anesthesia Protocols During EST (CS and GA)

Peri-interventional management in both groups was conducted entirely by neurointensivists trained in the interventional setting and a specialized neurocritical care nursing team, according to standard operating procedures derived from guideline recommendations and established over years and continuously adapted to local conditions (2, 13, 14).

Data Acquisition

Source data were generated from a prospectively collected stroke database. Additionally, all data included in the present analysis were validated retrospectively to minimize incorrect or missing data (CW, MM). The pre- and post-interventional stroke imaging was reviewed to assess the posterior circulation Alberta Stroke Program Early CT Score (pc-ASPECTS) and post-interventional intra-cranial bleeding.

Statistical Analysis

Data are shown as median with interquartile range (IQR) or means with standard deviation (SD), as appropriate. Normal distribution was tested for each variable using the Shapiro–Wilk test. Two-sided t tests, χ^2 test, or Mann–Whitney U test was performed as appropriate to compare groups. The level of significance was set at.05 for all p-values. The statistical analyses were performed by using software (SPSS Statistics 21.0.0.0; IBM, Armonk, NY). For the outcome analysis, the groups were compared in univariate and 1:1 matched-pair analysis without propensity score or other applied statistical models (15). Matching criteria were neurological deficit on admission (matching NIHSS $\pm$ 4 points), matching pre-stroke mRS, and reperfusion result based on the modified Treatment in Cerebral Ischemia (mTICI) Classification.

RESULTS

Of the 224 patients treated with EST for acute ischemic stroke in the posterior circulation between January 2015 and November 2020, 101 were excluded due to severe stroke syndromes (NIHSS $>$ 20) and consequently mandatory GA. Of the remaining 123 patients, 11 patients were excluded due to simultaneous LVO in the anterior circulation ($n = 6$), endotracheal intubation before transportation to our facility ($n = 4$), or re-stroke within 3 months ($n = 1$). In six included cases, the sedation mode was

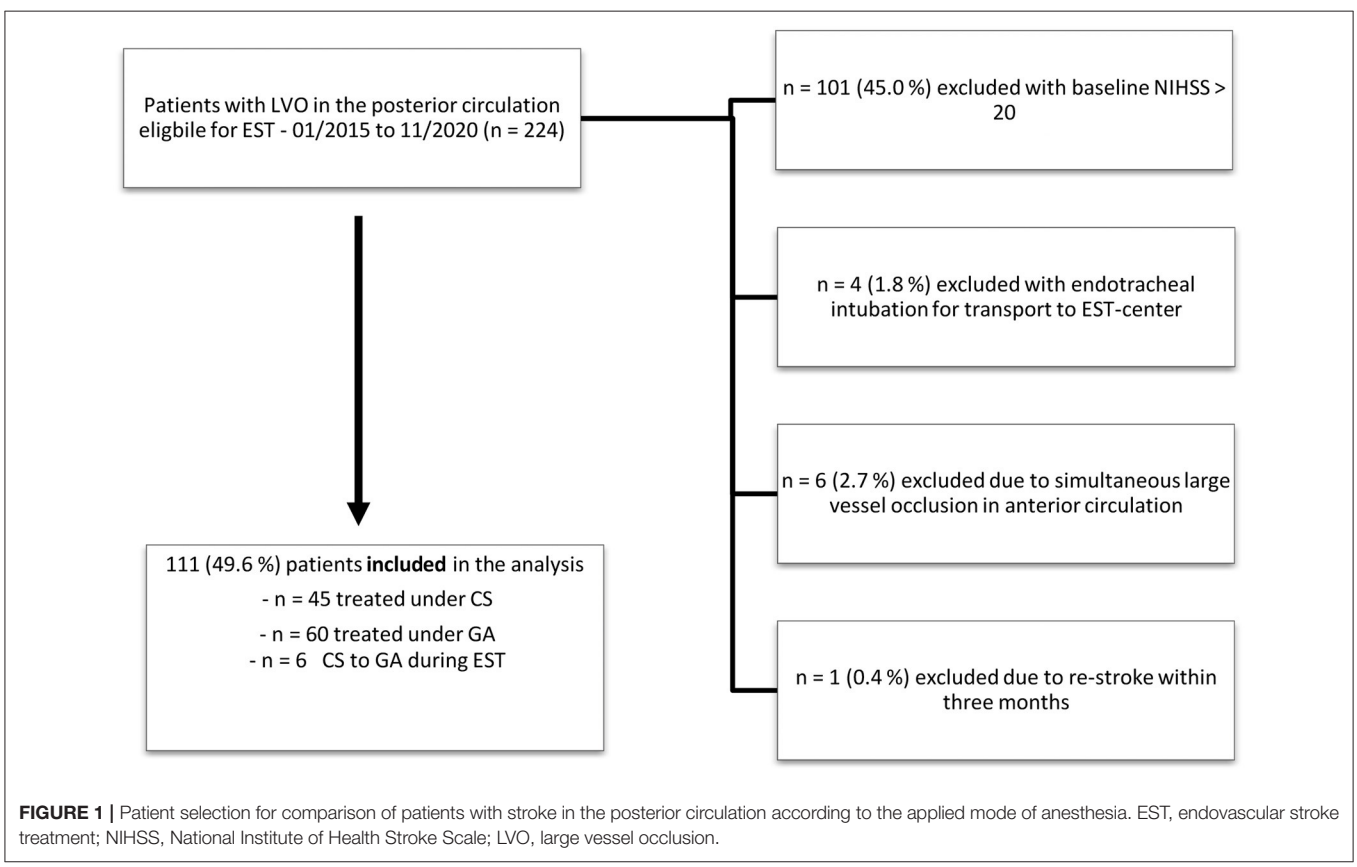

FIGURE 1 | Patient selection for comparison of patients with stroke in the posterior circulation according to the applied mode of anesthesia. EST, endovascular stroke treatment; NIHSS, National Institute of Health Stroke Scale; LVO, large vessel occlusion.

changed from CS to GA during MT. In four cases, the change in sedation mode was performed to guarantee patient immobility for stent-assisted PTA of the basilar artery. In two cases, GA was required due to patient agitation—see **Figure 1**.

Outcome Analysis

In this study, univariate analysis showed that patients treated under CS were less likely to be male [*n* (%): 21 (46.7) CS vs. 41 (68.3) GA, $p = 0.025$] and showed more often a basilar artery tip or posterior artery occlusion as target vessel occlusion [23 (51.1) CS vs. 17 (28.3) GA, $p = 0.017$]. They also had a higher baseline pc-ASPECTS (10 (8–10) CS vs. 9 (7–10) GA, $p = 0.023$), had a shorter time interval from stroke imaging to groin puncture [45 (31–62) CS vs. 64 (45–100) GA, $p = 0.004$], and required less intracranial stenting due to underlying atherosclerotic stenosis of the target vessel [*n* (%): 3 (6.7) vs. 13 (21.7), $p = 0.034$]. While the baseline mRS (0 (0–1) CS vs. 0 (0–2) GA, $p = 0.649$) as well as the NIHSS on admission [7 (4–12) CS vs. 8 (5–14), $p = 0.209$)] were comparable between the two groups, in the matched-pair outcome analysis, patients treated under CS showed a lower mRS 90 days after stroke onset [2.5 (1–4) CS vs. 4 (2–6), $p = 0.008$] and a comparable rate of good functional outcome [*n* (%): 19 (42.2) CS vs. 18 (30.0) GA, $p = 0.143$].

Patient data are presented in **Table 1**.

Recanalization Result and Procedural Complications

The two study groups showed no difference in successful target vessel recanalization [*n* (%): 38 (84.4) CS vs. 51 (85.0) GA, $p = 0.762$] or failure of recanalization [*n* (%): 2 (4.4) CS vs. 5 (8.3) GA]. With an overall low complication rate in this study, there was no difference in complication rates between the groups [3 (6.7) CS vs. 5 (8.3) GA, $p = 0.501$]. The total number of thrombectomy attempts was alike [median (IQR): 1 (1, 2) CS vs. 1 (1, 2) GA, $p = 0.753$] as well as the rate of ADAPT technique for first recanalization attempt [9 (20.0) CS vs. 10 (16.7) GA, $p = 0.931$]. The study groups also did not differ regarding intracranial hemorrhage in follow-up imaging [4 (8.9) CS vs. 7 (11.7) GA, $p = 0.705$].

DISCUSSION

The optimal mode of anesthesia in EST is still under debate. While retrospective analyses rather showed a benefit for CS, three randomized controlled trials addressing EST of the anterior circulation did not find a difference but rather a benefit in favor of GA (5). In contrast, for patients with acute ischemic stroke in the posterior circulation, evidence for the best choice of sedation mode during EST is sparse.

In this study, for the majority of patients (85%) a successful recanalization of the target vessel occlusion could be reached and the technical success rate is comparable to earlier studies on EST in the PC as well as to studies concerning EST in the anterior circulation (9). The success rate does not differ depending on the sedation mode during EST in this study cohort. Also, the complication rate is low for both study groups (6.7% CS vs. 8.3% GA). While the matched-pair outcome analysis is

TABLE 1 | Group comparison of patients treated for LVO of the posterior circulation with EST under conscious sedation (CS) or general anesthesia (GA).

	CS ($n = 45$)	GA ($n = 60$)	*P*-value
Patient characteristics			
Age, median (IQR)	75 (66–82)	76 (64–81)	0.933
Sex—male, *n* (%)	21 (46.7)	41 (68.3)	**0.025**
Diabetes mellitus, *n* (%)	8 (17.8)	9 (15.0)	0.789
Blood glucose level on admission, median (IQR) [mg/dl]	123 (107–150)	119 (104–144)	0.924
Hypertension	36 (80.0)	45 (75.0)	0.896
Atrial fibrillation	16 (35.6)	12 (20.0)	0.093
Hypercholesterinemia	14 (31.1)	17 (28.3)	0.935
Pre-stroke mRS, median (IQR)	0 (0–1)	0 (0–2)	0.649
NIHSS on admission, median (IQR)	7 (4–12)	8 (5–14)	0.209
Time windows			
Unknown symptom onset ("wake up stroke") *n* (%)	15 (33.3)	24 (40.0)	0.484
Transfer for treatment *n* (%)	21 (46.7)	31 (51.7)	0.612
Intra-venous thrombolysis *n* (%)	16 (35.6)	23 (38.3)	0.856
Time from onset to imaging, median (IQR) [min]	142 (62–557)	228 (79–622)	0.084
Time from imaging to groin puncture, median (IQR) [min]	45 (31–62)	64 (45 – 100)	**0.004**
Time from groin puncture to final EST-result, median (IQR) [min]	55 (32–88)	68 (47–123)	0.177
Imaging and Interventional characteristics of EST			
Basilar artery occlusion, *n* (%)	20 (44.4)	49 (81.7)	**<0.001**
Tip of the basilar artery/posterior artery, *n* (%)	23 (51.1)	17 (28.3)	**0.017**
Dominant V4 segment of vertebral artery, *n* (%)	2 (4.4)	4 (6.7)	0.631
Intra-cranial stenting of target vessel	3 (6.7)	13 (21.7)	**0.034**
ADAPT as first thrombectomy attempt, *n* (%)	9 (20.0)	10 (16.7)	0.931
Thrombectomy attempts in total, median (IQR)	1 (1–2)	1 (1–2)	0.753
Successful revascularization (mTICI 2–3), *n* (%)	38 (84.4)	51 (85)	0.762
Failure of revascularization (mTICI 0–1), *n* (%)	2 (4.4)	5 (8.3)	0.501
Procedural complications			
Intraprocedural complications	3 (6.7)	5 (8.3)	0.743
Intracranial vasospasms, *n* (%)	1	1	
Vessel perforation, *n* (%)	0	0	
Vessel dissection, *n* (%)	0	2	
Thrombus embolization, *n* (%)	2	2	
Follow-up imaging			
pc-ASPECTS baseline, median (IQR)	10 (8–10)	9 (7–10)	**0.023**
pc-ASPECTS follow-up, median (IQR)	8 (7–10)	7 (5–9)	**0.012**
Intracranial hemorrhage, *n* (%)	4 (8.9)	7 (11.7)	0.705
Symptomatic intracranial hemorrhage	2	3	0.586

(Continued)

TABLE 1 | Continued

	CS ($n = 45$)	GA ($n = 60$)	*P*-value
Clinical outcome (matched-pair analysis)			
mRS discharge, median (IQR)	3 (2–4)	4 (3–5)	**0.005**
NIHSS discharge, median (IQR)	2.5 (1–11)	6.5 (2–23)	**0.034**
mRS 90 days after stroke onset, median (IQR)	2.5 (1–4)	3 (2–6)	**0.036**
Good outcome (mRS 0–2 or 3 if pre-stroke mRS 3) 90 days after stroke onset, *n* (%)	19 (42.2)	15 (32.6)	0.311
Mortality 90 days after stroke onset, *n* (%)	4 (8.9)	14 (31.1)	**0.002**

Bold values are statistically significant p-values (< 0.05).

supposed to reduce the bias of treating clinically more affected patients in general anesthesia, the functional outcome is better for patients treated under CS. However, the study groups differ concerning baseline pc-ASPECTS, requirement of intracranial stenting, and exact location of target vessel occlusion with more basilar artery occlusions in the GA group. Thus, the presumably better functional outcome of patients treated under CS has to be seen under the light of the potential bias to treat more complicated cases under elective GA. Nevertheless, our study allows the conclusion, that EST under CS for eligible patients is time saving as well as safe and effective and thereby challenges the concept currently active in many stroke centers of intubating every patient with large vessel occlusion in the posterior circulation before EST.

There are only a few studies addressing the sedation mode during EST of the posterior circulation so far. Smaller observational studies from 2014 and before concentrated mainly on EST of the anterior circulation including patients with acute ischemic stroke of the posterior circulation to a varying degree. Precise conclusions for the posterior circulation could not be drawn (16, 17). Two larger-sized retrospective studies concentrating on sedation mode for EST in the posterior circulation showed differing results. Bouslama et al. dismissed CS during EST as an independent predictor for a favorable outcome in a retrospective study of $n = 214$ patients (18). Jadhav et al. showed comparable outcomes for EST under CS vs. GA, when analyzing $n = 63$ patients with vertebrobasilar occlusions treated under CS matched for admission glucose and NIHSS with patients treated under GA (19). These studies did not exclude patients intubated for transport, do not offer information about the rate of intracranial stenting in the study population, and included patients from early EST times before the third-generation stent retrievers were developed. With addressing the above-named shortcomings of predecessor studies, our study supports the results of Jadhav et al., that CS for EST in the PC is safe and effective.

The conversion rate from CS to GA during EST with $n = 6/111$ (5.4%) is comparable to studies of the anterior circulation, which showed a conversion rate of 6.3 to 11.5% (3, 5). Conversion from CS to GA was mainly conducted, when an intracranial stenting became necessary. Intracranial stenting under conscious sedation in the posterior circulation was very rarely performed in this study (in three patients). Jadhav et al. included $n = 16$ patients with intracranial stenting under CS. Generally, it is described that intracranial stenting under CS is feasible (20). However, there is still a relative lack of evidence for EST of the posterior circulation overall and especially regarding intracranial stenting in consciously sedated patients (9), a fact that contributes to differing therapy protocols in different stroke centers.

LIMITATIONS

Limitations of this study are mainly related to the single-center retrospective design. Most likely, patients with complex vascular findings were treated under GA affecting the outcome analysis. The authors of this study want to state that they are well aware of the heterogeneity seen in this study cohort, which comes with analyzing posterior circulation ischemic stroke patients, where many stroke concepts of the anterior circulation (e.g., the penumbra concept) cannot be applied. Nevertheless, these study results show the feasibility of conscious sedation for treating eligible stroke patients and invite to develop better standard operating procedures for posterior circulation stroke patients. To achieve this, more studies addressing differences of stroke in the posterior circulation are needed. This study could serve as basis for prospective, randomized clinical trials and shows aspects, which need further investigation like sedation mode during intracranial stenting in EST of the posterior circulation.

CONCLUSION

Performing endovascular stroke treatment of the posterior circulation under conscious sedation was safe and effective for eligible patients in this study. Compared to patients treated under general anesthesia, the rate of successful target vessel recanalization as well as the complication rate was alike. The clinical outcome comparison tends to favor treatment under conscious sedation, which reflects more likely a basic group difference of the two study groups than a veritable effect.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Medizinischen Fakultät Universitätsklinikum Heidelberg. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CW substantially contributed to the manuscript's concept development, data acquisition, statistical analysis and writing the manuscript. MC, LJ, and SS substantially contributed to data acquisition and manuscript revision. AP and FS substantially contributed to data acquisition, statistical analysis

and manuscript revision. MB and MM substantially contributed to the manuscript's concept development and manuscript revision. All authors contributed to the article and approved the submitted version.

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Dual-Antiplatelet Therapy May Not Be Associated With an Increased Risk of In-hospital Bleeding in Patients With Moderate or Severe Ischemic Stroke

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Background and Purpose: Dual antiplatelet therapy (DAPT), compared to single antiplatelet therapy (SAPT), lowers the risk of stroke or death early after TIA and minor ischemic stroke. Prior trials excluded moderate to severe strokes, due to a potential increased risk of bleeding. We aimed to compare in-hospital bleeding rates in SAPT and DAPT patients with moderate or severe stroke (defined by NIHSS $\geq$4).

Methods: We performed a retrospective cohort study of ischemic stroke over a 2-year period with admission NIHSS $\geq$4. The primary outcome was symptomatic intracranial hemorrhage (ICH) with any change in NIHSS. Secondary outcomes included systemic bleeding and major bleeding, a composite of serious systemic bleeding and symptomatic ICH. We performed analyses stratified by stroke severity (NIHSS 4–7 vs. 8+) and by preceding use of tPA and/or thrombectomy. Univariate followed by multivariate logistic regression evaluated whether DAPT was independently associated with bleeding.

Results: Of 377 patients who met our inclusion criteria, 148 received DAPT (39%). Symptomatic ICH was less common with DAPT compared to SAPT (0.7 vs. 6.4%, $p < 0.01$), as was the composite of major bleeding (2.1 vs. 7.6%, $p = 0.03$). Symptomatic ICH was numerically less frequent in the DAPT group, but not statistically significant, when stratified by stroke severity (NIHSS 4–7: 0 vs. 5.9%, $p = 0.06$; NIHSS 8+: 1.5 vs. 6.6%, $p = 0.18$) and by treatment with tPA and/or thrombectomy (Yes: 2.6 vs. 9.1%, $p = 0.30$; No: 0 vs. 2.9%, $p = 0.25$). DAPT was not associated with major bleeding in either the univariate or the multivariate regression.

Conclusions: In this single center cohort, symptomatic ICH and the composite of serious systemic bleeding and symptomatic ICH was rare in patients on DAPT. Relative to single antiplatelet therapy DAPT was not associated with an increased risk of in-hospital bleeding in patients with moderate and severe ischemic stroke.

Keywords: dual antiplatelet therapy, moderate stroke, severe stroke, secondary prevention, bleeding risk, bleeding rate, hemorrhagic transformation

INTRODUCTION

Three randomized controlled trials found that early dual antiplatelet therapy (DAPT), compared to single antiplatelet therapy, lowers the risk of stroke or death after TIA or minor ischemic stroke with only a small absolute increase in the risk of major bleeding (1–3). As a result, guidelines recommend a short course of treatment with DAPT for patients after high risk TIA and minor non-cardioembolic ischemic stroke (4).

Patients with moderate or severe ischemic stroke were excluded from these trials because of a perceived increased risk of hemorrhagic complications. Nonetheless, these patients are at high short-term risk of recurrent ischemic stroke, death, and other major vascular events (5).

Recent studies evaluating the safety of DAPT in moderate to severe ischemic stroke have had limitations. Two studies using a nationwide registry in Korea compared patients with non-minor strokes who were treated with DAPT to those on Aspirin alone. They found that hemorrhagic stroke rates did not significantly differ between groups, and that recurrent vascular events were lower in the DAPT group (6, 7). These studies did not report details about the type of hemorrhagic transformation, did not report systemic bleeding, and were conducted in a homogenous patient population which might limit generalizability.

With this background, we completed a single center retrospective cohort comparing the safety of single and dual antiplatelet therapy in moderate and severe ischemic stroke, defined by a National Institute of Health Stroke Scale (NIHSS) of 4 or greater. We hypothesized that bleeding rates in patients on DAPT would be similar to patients on single antiplatelet therapy.

METHODS

This was a single center retrospective cohort study. After institutional review board approval, we searched our hospital's stroke registry to identify all patients admitted between January 1st 2017 and November 1st 2019 with ischemic stroke who were age >18 years, and who had an admission NIHSS ≥4.

TABLE 1 | Baseline characteristics.

	SAPT ($n = 229$)	DAPT ($n = 148$)	*P*-value
Age, mean	66.4	67.3	0.58
Sex, % female	53.3	44.6	0.10
Medical history (%)			
Hypertension	73.4	86.5	<0.01
Hyperlipidemia	50.7	62.8	0.02
Diabetes mellitus	32.8	43.9	0.03
Coronary artery disease	15.7	27.0	<0.01
Active smoking	25.8	28.4	0.58
Chronic kidney disease	13.1	17.6	0.23
Congestive heart failure	10.5	12.2	0.61
Atrial fibrillation	11.8	3.4	<0.01
Antiplatelet prior to admission (%)			
None	61.6	38.5	<0.01
SAPT	35.8	39.9	0.43
DAPT	2.6	21.6	<0.01
Admission NIHSS, median (IQR)	9 (6–17)	7 (5–11)	<0.01
Acute stroke treatments (%)			
tPA	38.9	15.5	<0.01
Thrombectomy	29.3	19.6	0.04
Stroke mechanism (%)			
Large artery atherosclerosis	11.8	46.0	<0.01
Small vessel disease	9.2	8.8	0.90
Cardioembolic	22.7	6.1	<0.01
Cryptogenic	39.3	17.6	<0.01
>1 mechanism	7.0	10.1	0.28
Other	10.0	11.5	0.66
Length of stay, median (IQR)	5 (3–10)	5 (3–9.5)	0.63
Disposition (%)			
Home	28.8	23.0	0.21
Acute rehab	56.8	71.0	<0.01
Skilled nursing facility	9.2	3.4	0.03

SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; tPA, tissue plasminogen activator.

Abbreviations: DAPT, Dual antiplatelet therapy; SAPT, Single antiplatelet therapy; sICH, Symptomatic intracranial hemorrhage.

TABLE 2 | Bleeding rates by antiplatelet therapy at the time of event.

	Not DAPT ($N = 236$)	DAPT ($N = 141$)	*P*-value
Any systemic bleeding	3.8%	5.0%	0.59
Gastrointestinal	1.3%	0.7%	1.00
Genitourinary	0.8%	2.1%	0.37
Other	1.7%	2.1%	0.72
Serious systemic bleeding	1.3%	1.4%	1.00
Major bleeding	7.6%	2.1%	0.03
Asymptomatic ICH	11.0%	1.4%	<0.01
Symptomatic ICH (NIHSS any change)	6.4%	0.7%	<0.01
Symptomatic ICH (NIHSS change >/=4)	1.3%	0.7%	1.00
ICH classification			
HI1	5.1%	0.7%	0.04
HI2	3.4%	0%	0.03
PH1	2.1%	0%	0.16
PH2	4.2%	0.7%	0.06
Other (Any SAH, IVH, SDH)	8.9%	1.4%	<0.01

DAPT, dual antiplatelet therapy; ICH, intracranial hemorrhage; NIHSS, National Institute of Health stroke scale; HI1, hemorrhagic transformation type 1 (defined as small petechiae without mass effect); HI2, hemorrhagic transformation type 2 (defined as more confluent petechiae without mass effect); PH1, parenchymal hematoma type 1 (defined as hematoma <30% of infarct bed with some mild mass effect); PH2, parenchymal hematoma type 2 (defined as hematoma >30% of infarct bed with significant mass effect); SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; SDH: subdural hemorrhage.

Patients who received at least one dose of any form of therapeutic anticoagulation during their hospitalization were excluded.

We collected demographic characteristics, vascular risk factors, NIHSS, stroke mechanism, antiplatelet treatments throughout admission, and bleeding outcomes. Given the retrospective nature of this analysis, there was no pre-specified criteria for the use of DAPT. The primary outcome was symptomatic intracranial hemorrhage (sICH) with any change in NIHSS. Secondary outcomes included asymptomatic ICH, sICH with a change in NIHSS of 4 or more points, ICH classified according to the Heidelberg criteria (8), any systemic bleeding, and major bleeding (sICH or systemic bleeding that required transfusion, pressors, escalation of care, or causing death) (9). For each bleeding event it was determined if the bleeding occurred before or after initiation of DAPT. Only bleeding that occurred after initiation of DAPT was attributed to DAPT.

Variables were summarized by means and standard deviations or medians and interquartile range for continuous variables and frequencies/proportions for categorical variables. Differences between groups were evaluated using chi-squared tests for categorical variables and parametric (t-test) or non-parametric tests (Kruskal Wallis, Wilcoxon rank sum) as appropriate. We evaluated for differences in bleeding outcomes among patients on DAPT and those not on DAPT. We also performed secondary analysis stratified by NIHSS (4–7 vs. 8+) and based on whether patients received tPA and/or thrombectomy. Finally, multivariate logistic regression was used to determine if DAPT was independently associated with bleeding. Age, NIHSS, and variables significant in univariate analysis with $p < 0.10$ were included. Analysis was performed using Stata 15.0 (StataCorp LP. College Station, TX, 2017).

TABLE 3 | Bleeding rates among lower vs. higher NIHSS groups subcategorized by antiplatelet therapy groups.

NIHSS	**4–7 ($n = 160$)**			**≥8 ($n = 217$)**		
	Not DAPT ($n = 85$)	**DAPT ($n = 75$)**	***P*-value**	**Not DAPT ($n = 151$)**	**DAPT ($n = 66$)**	***P*-value**
Major bleeding	5.9%	0%	0.06	8.6%	4.6%	0.40
Asymptomatic ICH	5.9%	2.7%	0.45	13.9%	0%	<0.01
Symptomatic ICH (NIHSS any change)	5.9%	0%	0.06	6.6%	1.5%	0.18
Symptomatic ICH (NIHSS change >/=4)	1.2%	0%	1.00	1.3%	1.5%	1.00
ICH classification						
HI1	3.5%	1.3%	0.62	6.0%	0%	0.06
HI2	3.5%	0%	0.25	3.3%	0%	0.33
PH1	0%	0%	1.00	3.3%	0%	0.33
PH2	2.4%	0%	0.50	5.3%	1.5%	0.28
Other (Any SAH, IVH or SDH)	4.7%	1.3%	0.37	11.3%	1.5%	0.02

DAPT, dual antiplatelet therapy; ICH, intracranial hemorrhage; NIHSS, National Institute of Health stroke scale; HI1, hemorrhagic transformation type 1 (defined as small petechiae without mass effect); HI2, hemorrhagic transformation type 2 (defined as more confluent petechiae without mass effect); PH1, parenchymal hematoma type 1 (defined as hematoma <30% of infarct bed with some mild mass effect); PH2, parenchymal hematoma type 2 (defined as hematoma >30% of infarct bed with significant mass effect); SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; SDH, subdural hemorrhage.

TABLE 4 | Bleeding rates among those who received tPA or thrombectomy and those who didn't subcategorized by antiplatelet therapy groups.

Received tPA or Thrombectomy	**Yes ($n = 171$)**			**No ($n = 206$)**		
	Not DAPT ($n = 132$)	**DAPT ($n = 39$)**	***P*-value**	**Not DAPT ($n = 104$)**	**DAPT ($n = 102$)**	***P*-value**
Major bleeding	10.6%	2.6%	0.20	3.9%	2%	0.68
Asymptomatic ICH	15.2%	2.6%	0.05	5.8%	1.0%	0.12
Symptomatic ICH (NIHSS any change)	9.1%	2.6%	0.30	2.9%	0%	0.25
Symptomatic ICH (NIHSS change >/=4)	2.3%	2.6%	1.00	0%	0%	1.00
ICH classification						
HI1	3.8%	2.6%	1.00	6.7%	0%	0.01
HI2	5.3%	0%	0.35	1.0%	0%	1.00
PH1	3.8%	0%	0.59	0%	0%	1.00
PH2	6.8%	2.6%	0.46	1.0%	0%	1.00
Other (Any SAH, IVH or SDH)	13.6%	2.6%	0.08	2.9%	1.0%	0.62

tPA, tissue plasminogen activator; DAPT, dual antiplatelet therapy; ICH, intracranial hemorrhage; NIHSS, National Institute of Health stroke scale; HI1, hemorrhagic transformation type 1 (defined as small petechiae without mass effect); HI2, hemorrhagic transformation type 2 (defined as more confluent petechiae without mass effect); PH1, parenchymal hematoma type 1 (defined as hematoma <30% of infarct bed with some mild mass effect); PH2, parenchymal hematoma type 2 (defined as hematoma >30% of infarct bed with significant mass effect); SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; SDH, subdural hemorrhage.

TABLE 5 | Univariate analysis.

Variable	OR	95% CI	*P*-value
Age			
<60	Ref		
60–79	1.70	0.53–5.48	0.37
80+	2.30	0.63–8.45	0.21
Male gender	0.59	0.24–1.47	0.26
Stroke etiology			
Large vessel disease	Ref		
Small vessel disease	No bleeding events		
Cardioembolic	2.72		0.09
Other	0.46	0.85–8.73	0.49
More than 1 mechanism	1.24	0.05–4.08	0.80
Cryptogenic	0.81	0.23–2.89	0.745
Cardioembolic etiology	3.52	1.39–8.90	<0.01
NIHSS			
4–7	Ref		
8+	2.47	0.88–6.88	0.08
Past medical history			
Hypertension	1.68	0.48–5.86	0.413
Hyperlipidemia	1.65	0.65–4.19	0.29
Diabetes mellitus	1.04	0.42–2.59	0.93
Coronary artery disease	1.25	0.44–3.54	0.67
Chronic kidney disease	1.87	0.66–5.32	0.24
Congestive heart failure	1.35	0.38–4.81	0.64
Atrial fibrillation	6.62	2.45–17.89	<0.01
End stage liver disease	7.39	1.35–40.59	0.02
Prior GI Bleeding	1.75	0.49–6.26	0.39
Prior GU Bleeding	1.57	0.19–12.76	0.67
Prior hemorrhagic transformation	9.09	3.09–26.74	<0.01
Current smoking	1.39	0.55–3.56	0.49
tPA or thrombectomy	3.21	1.22–8.45	0.02

Ref, Reference; tPA, tissue plasminogen activator; GI, gastrointestinal; GU, genitourinary.

TABLE 6 | Multivariate analysis for variables associated with Major Bleeding.

Variable	OR	95% CI	*P*-value
Age			
<60	Ref		
60–79	1.42	0.41–4.89	0.58
80+	1.44	0.31–6.71	0.64
Male gender	0.73	0.26–2.04	0.55
Cardioembolic etiology	1.36	0.36–5.09	0.65
NIHSS			
4–7	Ref		
8+	1.84	0.59–5.76	0.30
Past medical history			
Atrial fibrillation	1.99	0.41–9.62	0.39
End stage liver disease	6.73	0.63–71.78	0.12
Prior hemorrhagic transformation	2.95	0.76–11.50	0.12
tPA or thrombectomy	1.63	0.56–4.72	0.37
DAPT at time of bleed	0.34	0.08–1.50	0.15

Ref, Reference; tPA, tissue plasminogen activator; DAPT, dual antiplatelet therapy.

RESULTS

A total of 377 patients met our inclusion criteria. Patients were divided into two groups based on the antiplatelet treatment they received throughout their admission. There were 148 patients who were treated with DAPT at any time during the hospitalization and 229 who were not (single antiplatelet therapy). All the DAPT subjects were treated with the combination of aspirin and clopidogrel. Of these 148 patients, 28.4% were loaded with 600 mg of clopidogrel and then maintained on 75 mg daily, 20.3% were loaded with 300 mg and then maintained on 75 mg daily, and 50.7% were started on 75 mg of clopidogrel daily without receiving a loading dose. Baseline demographics are summarized in **Table 1**. Patients in the DAPT group were more likely to have traditional vascular risk factors and large artery atherosclerosis as the mechanism of stroke. The median admission duration was 5 days and the median time from admission to start of DAPT was 1 day (IQR 0–2). About half (49%) of the patients in the DAPT group were loaded with clopidogrel (either 300 mg or 600 mg).

Bleeding outcomes are shown in **Table 2**. Of the 148 patients that received DAPT during their hospitalization, 7 had ICH before DAPT was initiated. For this analysis these 7 subjects are included in the "Not DAPT" group, as their bleeding event occurred while on single or no antiplatelet therapy. Asymptomatic, sICH with any change in NIHSS, and sICH with NIHSS change $\geq$4 were all less common in the DAPT group. Only 1 of 141 subjects in the DAPT group had a sICH with NIHSS change $\geq$4. This patient had a PH2 hemorrhagic transformation which occurred on the same day that the patient was loaded with 600 mg of clopidogrel. There were 15 subjects in the Not DAPT group with symptomatic ICH, of which 12 (80%) occurred within 1 day of hospital admission. The composite outcome of major bleeding was seen in 2.1% of subjects on DAPT and 7.6% of patients not on DAPT ($p = 0.03$).

In the stratified analysis (**Tables 3**, **4**), sICH was numerically less common in the DAPT group, but the differences were not significant (NIHSS 4–7: 0 vs. 5.9%, $p = 0.06$; NIHSS 8+: 1.5 vs. 6.6%, $p = 0.18$). Similarly, when stratified by treatment with tPA and/or thrombectomy, sICH was less frequent in the DAPT group but the differences were not significant (Yes: 2.6 vs. 9.1%, $p = 0.30$; No: 0 vs. 2.9%, $p = 0.25$). Of the 13 sICH that occurred in patients treated with tPA or thrombectomy 10 (77%) occurred within 1 day of admission.

DAPT was not associated with major bleeding in either the univariate (**Table 5**) or the multivariate regression analysis (**Table 6**).

DISCUSSION

Early treatment with DAPT has been shown to be beneficial in high-risk TIA and minor ischemic stroke, although the benefit

in moderate to severe stroke is uncertain. In this single center retrospective study, we found that patients with non-minor stroke defined by NIHSS ≥4 who were treated with DAPT did not have higher rates of major bleeding during their hospitalization than those who were not treated with DAPT.

Both asymptomatic and sICH were less common in the DAPT group than the group not on DAPT. We observed relatively high rates of ICH in the single antiplatelet therapy group. This outcome was biologically unexpected and we believe it reflects, in part, careful screening for asymptomatic ICH at our institution. It is probable that clinicians were less likely to use dual antiplatelet therapy in patients with asymptomatic ICH and this selection bias may have contributed to the observed difference in asymptomatic ICH between groups. Importantly, **Table 4** shows that 77% of asymptomatic ICH and 80% of sICH in the single antiplatelet group occurred in patients treated with tPA and/or thrombectomy. These hemorrhages likely reflect complications of those treatments and further biased the results toward a higher overall ICH rate in the single antiplatelet therapy group. While this bias impacts the comparison between groups in this study, it is still reassuring that ICH in the DAPT group was very low. Only 1 of the subjects had sICH after initiation of DAPT, and there was with no signal of increased ICH risk in the DAPT group in the stratified analyses. A prospective, randomized trial is needed to determine if DAPT is effective in moderate and severe stroke. Such a trial would likely exclude patients treated with tPA and/or thrombectomy, particularly if those treatments were complicated by ICH, and our data suggests that in such a population treatment with DAPT is associated with very low rates of sICH.

Major bleeding was seen in 2.1% of patients treated with DAPT. This is numerically higher than the major bleeding rates reported in the CHANCE (0.2%), POINT (0.9%), and THALES (0.5%) trials (1–3), but similar to the major bleeding rate reported in the medical arm of the SAMMPRIS Trial (2.2%) (10). It may be that the overall higher rates of bleeding in our study reflect a higher risk in this population, compared to a TIA and minor stroke population, rather than an effect specific to DAPT.

As a retrospective cohort, this study has limitations. The most important is the potential for selection bias. As discussed above, clinicians likely selected patients for DAPT who they felt were at a lower, or at least acceptable, risk of ICH, biasing the results toward a higher overall hemorrhage rate in the single antiplatelet group. We did not record the rationale for using DAPT. Additionally, only about half of the patients in this study were loaded with clopidogrel, which may also have contributed to lower bleeding rates in the DAPT group. We defined non-minor stroke using NIHSS, rather than infarct volume. This definition is consistent with published randomized trials which used NIHSS to define minor stroke. NIHSS is correlated with infarct volume (11) but nonetheless, direct volume measurements would have a stronger correlation with bleeding risk (12). Outcomes were defined as bleeding during hospitalization. Median time from admission to start of DAPT was 1 day, with an average length of stay of 5 days. Hemorrhagic transformation risk is likely highest early after ischemic stroke, but it is possible that there were bleeding events after discharge that were missed. Finally, the relatively small number of outcome events limited the statistical power.

CONCLUSION

In this single center retrospective study, we found that DAPT was associated with a very low rate of sICH in patients with moderate and severe ischemic stroke defined by NIHSS ≥4. A randomized trial is needed to confirm this finding and to determine if DAPT is effective at preventing recurrent stroke in this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Penn IRB. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

OK contributed to the writing of the paper. AR, MH, MB, DC, SR-E, FK, CF, SM, and MM contributed to data collection and review of written portion. MM contributed to the statistical analysis and writing of the paper as well as being the senior author. All authors contributed to the article and approved the submitted version.

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Statin Use and Outcomes of Patients With Acute Ischemic Stroke Treated With Intravenous Thrombolysis: A Systematic Review and Meta-Analysis

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Background: The data on the relationship between statin use and clinical outcomes after intravenous thrombolysis (IVT) for acute ischemic stroke (AIS) are in controversy.

Objective: This systematic review and meta-analysis aimed to evaluate the safety and efficacy of statins administered prior to onset and during hospitalization in patients with AIS treated with IVT.

Methods: We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from inception until June 8, 2021. Comparative studies investigating statin effect on intracranial hemorrhage (ICH), functional outcomes, and mortality in adults with AIS treated with IVT were screened. Random-effect meta-analyses of odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were performed. The protocol was registered in PROSPERO (CRD42021254919).

Results: Twenty-two observational studies were included, which involved 17,554 patients. The pooled estimates showed that pre-stroke statin use was associated with a higher likelihood of symptomatic ICH (OR 1.31; 95% CI 1.07–1.59; $p = 0.008$) and any ICH (OR 1.21; 95% CI 1.03–1.43; $p = 0.02$). However, the pre-stroke statin use was not significantly associated with the 3-month mortality, 3-month favorable functional outcome (FFO, modified Rankin Scale [mRS] score 0–1), and 3-month functional independence (FI; mRS score 0–2). However, in-hospital statin use was associated with a reduced risk of symptomatic ICH (OR 0.46; 95% CI 0.21–1.00; $p = 0.045$), any ICH (OR 0.51; 95% CI 0.27–0.98; $p = 0.04$), and 3-month mortality (OR 0.42; 95% CI 0.29–0.62; $p < 0.001$) and an increased probability of 3-month FFO (OR 1.33; 95% CI 1.02–1.744; $p = 0.04$) and 3-month FI (OR 1.41; 95% C, 1.11–1.80; $p = 0.005$).

Conclusions: The present systematic review and meta-analysis suggests that in-hospital statin use after IVT may be safe and may have a favorable impact on clinical outcomes, a finding not observed in studies restricted to patients with pre-stroke statin use.

Keywords: stroke, thrombolysis, statin, intracranial hemorrhage, functional outcomes, mortality, meta-analysis

HIGHLIGHTS

- Twenty-two observational articles with more than 15,000 patients were enrolled.
- Pre-stroke statin use probably increase the risk of intracranial hemorrhage, but has no effect on functional outcome or mortality.
- In-hospital statin use probably decrease the risk of intracranial hemorrhage and mortality and increase the odds of a good functional outcome.

INTRODUCTION

Stroke is a common devastating neurological condition and one of the top causes of disability and mortality worldwide (1, 2). There are two major types: ischemic stroke and hemorrhagic stroke. Of note, acute ischemic stroke (AIS) accounts for ∼80% of total strokes (3). In terms of treatment strategy of AIS, timely reperfusion of ischemic tissue to save the ischemic penumbra is the key to avoid severe disability and premature death (4). Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator, which is the only thrombolytic drug approved by the US Food and Drug Administration for AIS (5, 6), is considered to be most effective when administered within the first few hours of stroke onset (7).

For many years, researchers and medical doctors have been looking for a combination therapy to reduce the risk of mortality and improve functional outcomes for AIS patients treated with IVT. Statins, one of the most commonly prescribed medications for treatment of dyslipidemia, have gained attention recently as promising therapeutic agents for neurological conditions (8). Studies in animal models have shown that statins have pleiotropic effects on neuronal survival, angiogenesis, neurogenesis, and brain remodeling in ischemic stroke brain injury (9–12). Thereby, statins have potential neuroprotective and neurorestorative effects for AIS. Previous meta-analyses driven mostly by observational studies showed that statin use in AIS patients may be associated with improved functional outcome and short-term survival (13, 14). Accordingly, a recent guideline from the American Heart Association/American Stroke Association (15) recommends that AIS patients qualified for statin treatment should receive statin therapy as soon as possible. However, this recommendation is mainly based on observational studies of AIS patients with heterogeneous treatments. The existing observational studies on whether the use of statin is associated with any clinical benefit in AIS patients after IVT have reported fragmentary and conflicting results. Thus, a relatively homogeneous set of participants (AIS patients receiving IVT) was enrolled in this meta-analysis.

Abbreviations: AIS, acute ischemic stroke; CI, confidence interval; FFO, favorable functional outcome; FI, functional independence; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOS, Newcastle-Ottawa scale; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; RCT, randomized clinical trial.

We hypothesize that statin use is likely to be associated with improved mortality and functional outcomes in AIS patients treated with IVT. Given that there is no randomized clinical trial (RCT) to date evaluating the safety and efficacy of statin therapy in patients with AIS treated with IVT, we performed a comprehensive systematic review and meta-analysis of *post-hoc* analyses of RCTs and observational studies to investigate its comparative safety and efficacy.

METHODS

This meta-analysis was conducted strictly in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (16). It was prospectively registered in the PROSPERO (International Prospective Register of Systematic Reviews) registry, with registration number of CRD42021254919. The PRISMA checklist is available in **Supplementary Table 1**.

Search Strategy

One investigator (QB) performed a comprehensive literature search in multiple electronic databases (PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials) until June 8, 2021, without any restrictions. MeSH (in PubMed) and Emtree (in EMBASE) terms were used, as well as text words. Search terms included those related to stroke, thrombolysis, statins, and their variants. The detailed search strategy is available in **Supplementary Table 2**. Two investigators (YG and JY) manually searched all the references from relevant reviews and meta-analyses for additional studies.

Inclusion and Exclusion Criteria

Inclusion criteria included the following: (1) types of studies: *post-hoc* analyses of RCT, prospective or retrospective cohort study; (2) characteristics of participants: adult patients (≥18 years) with AIS treated with IVT (with recombinant tissue plasminogen activator); (3) types of interventions: statin therapy regardless of type and dose; and (4) types of outcome measures: at least one outcome of interest, including symptomatic intracranial hemorrhage (ICH), any ICH, 3-month mortality, 3-month favorable functional outcome (FFO), and 3-month functional independence (FI), with odds ratio (OR) or clinical data to calculate OR.

Exclusion criteria included the following: (1) abstract with insufficient data; (2) studies that included fewer than 50 patients; (3) statin use only as a covariate in the statistical model; (4) studies providing only overlapping data with previous publication.

Study Selection

The following study selection processes were performed. Step 1: the records obtained from initial search were imported into the Zotero citation management software (www.zotero.org) and duplicates were removed. Step 2: two investigators (YG and JY) screened the titles and abstracts of remaining articles and excluded the non-relevant articles. Step 3: the full texts of the relevant articles were retrieved for further assessment

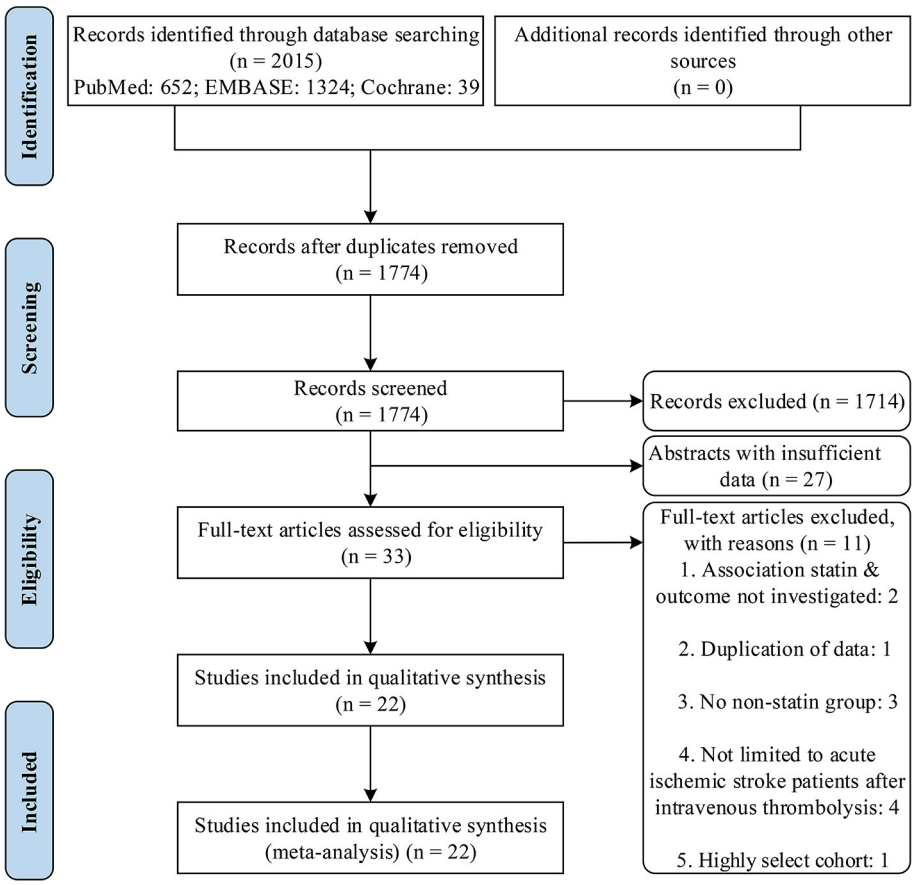

FIGURE 1 | PRISMA flow diagram.

of eligibility. Disagreements were resolved through group discussion with another investigator.

Data Extraction

Two investigators (YG and XG) independently extracted data from each included study using a standardized form. The following information was extracted: (1) study characteristics: name of first author, year of publication, country of origin, type of design, and total number of patients; (2) patient characteristics: age, sex, and baseline National Institutes of Health Stroke Scale (NIHSS) score; (3) intervention characteristics: use of statins; and (4) data on outcomes of interest, etc. Disagreements were resolved through group discussion with another investigator.

Risk of Bias Assessment

The Newcastle–Ottawa scale (NOS) (17) was used to evaluate the methodological quality of *post-hoc* analyses of RCTs and cohort studies included in this meta-analysis. The quality control and bias assessment were performed independently by two investigators (YG and XG). NOS score >7, 7 ≥ NOS score > 5, and NOS score ≤5 indicated good quality, fair quality, and poor quality, respectively. Disagreements were resolved through group discussion with another investigator.

Statistical Analysis

We investigated the association between statin use and clinical outcomes using pooled ORs and their corresponding 95% confidence intervals (CIs). To stabilize the variance and normalize the distribution, ORs with corresponding 95% CIs were extracted from each study and transformed into log OR and standard error (18). For studies that did not report risk estimates for the comparison of user vs. non-user of statins, we calculated ORs based on the available published data (19). Meta-analyses were performed using a random-effect model accounting for clinical heterogeneity (20). The effects of pre-stroke and in-hospital statin use were considered separately. $p < 0.05$ was considered statistically significant.

Statistical heterogeneity across studies was assessed by the Cochran Q test and quantified by the I^2 statistic. For the qualitative interpretation of heterogeneity, $I^2 > 50\%$ was considered significant (21). Potential publication bias across studies was graphically evaluated using a funnel plot and estimated through Egger's test (with $p < 0.1$ indicating significance) (22).

Meta-analyses were performed using RevMan 5.3 software (Nordic Cochrane Centre, Cochrane Collaboration,

TABLE 1 | Baseline characteristics of included studies.

References	Country	Study design	Total-n	Age-y	Male-%	Baseline NIHSS	Exposure	Statin-%	Follow up-m	Outcomes
Alvarez-Sabín et al. (23)	Spain	RC	145	72	52	17	Statin①	17.9	3	Ⓔ
Bruning et al. (24)	Germany	PC	542	72	51	11	Statin①②	26.4①, 35.7②	3	ⒶⒸ
Cappellari et al. (25)	Italy	RC	178	NR	58	NR	Statin④	35.4	3	ⒶⒺ
Cappellari et al. (26)	Italy	RC	2,072	67	58	13	Statin⑥	40.5	3	ⒶⒸⒹⒺ
Cui et al. (27)	China	PC	215	71	53	9	Statin②	83.7	3	ⒷⒺ
Engelter et al. (28)	Europe	PC	4,012	68	56	12	Statin①	22.9	3	ⒶⒷⒸⒹⒺ
Faivre et al. (29)	France	PC	101	63	59	15	Statin①	25.0	3	ⒶⒺ
Geng et al. (30)	China	RC	119	62	71	NR	Statin③	59.7	3	ⒶⒷⒸⒹ
Kang et al. (31)	Korea	PC	86	NR	NR	NR	Statin⑤	17.4	3	ⒶⒹⒺ
Makihara et al. (32)	Japan	RC	489	71	65	12	Statin①	31.7	3	ⒷⒹ
Martinez-Ramirez et al. (33)	Spain	PC	182	68	54	14	Statin①	16.3	3	ⒶⒷⒸⒺ
Miedema et al. (34)	Netherlands	PC	476	69	54	13	Statin①	20.6	3	ⒶⒺ
Montaner et al. (35)	Spain	*Post-hoc* RCT	55	NR	NR	7	Simvastatin③	49.1	3	ⒶⒷⒸⒺ
Mowla et al. (36)	USA	RC	834	71	51	12	Statin①	33.8	3	ⒶⒺ
Rocco et al. (37)	Germay	PC	1,066	73	53	12	Statin①	20.5	3	ⒶⒷⒸⒹ
Scheitz et al. (38)	Germany	PC	481	74	50	11	Statin②	17.2	3	ⒸⒺ
Scheitz et al. (39)	Germany, Switzerland	PC	1,446	75	54	11	Statin①	21.9	3	ⒶⒺ
Scheitz et al. (40)	International	*Post-hoc* RCT	2,583	68	57	14	Statin①	15.3	3	Ⓐ
Tong et al. (41)	China	RC	367	69	55	9	Statin⑥	51.2	3	ⒶⒺ
Tsivgoulis et al. (42)	International	PC	1,660	67	59	11	Statin①	22.5	3	ⒶⒸⒹⒺ
Uyttenboogaart et al. (43)	Netherlands	PC	252	68	54	12	Statin①	12.3	3	ⒶⒸⒹⒺ
Zhao et al. (44)	China	PC	193	65	64	9	Statin①	24.4	3	ⒶⒸⒹⒺ

NR, not report; PC, prospective cohort; RC, retrospective cohort; RCT, randomized clinical trial.
① pre-stroke statin use; ② post-stroke statin use; ③ started statin within 12 h of stroke onset; ④ started statin within 24 h of stroke onset; ⑤ started statin within 48 h of stroke onset; ⑥ started statin within 72 h of stroke onset; Ⓐ symptomatic intracranial hemorrhage; Ⓑ any intracranial hemorrhage; Ⓒ 3 month-mortality; Ⓓ 3 month-favorable functional outcome; Ⓔ 3 month-functional independence.

Copenhagen, Denmark). Egger's test was conducted with Stata 15.0 software (Stata Corporation, College Station, TX, USA).

RESULTS

Literature Search and Study Selection

Our literature searches in the PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials databases yielded 652, 1,324, and 39 records, respectively. After review of titles and abstracts, and exclusion of duplicate records, 33 potentially eligible studies were retrieved. After careful evaluation of full texts, 11 studies were excluded (data available from **Supplemental Table 3**), and 22 studies (23–44) were included. The study selection process is illustrated in **Figure 1**.

Study Characteristics

Among the included 22 studies (23–44), there were 2 *post-hoc* analyses of RCTs (35, 40), 13 prospective cohort studies (24, 27–29, 31, 33, 34, 37–39, 42–44), and 7 retrospective cohort studies (23, 25, 26, 30, 32, 36, 40). The 22 included studies were published from 2007 to 2021, with sample sizes ranging from 55 to 4,012 participants and a total of 17,554 participants. The mean age of participants ranged from 50 to 71 years, and most of them were male. The baseline NIHSS score varied from 7 to 17. The main outcomes were ICH, functional outcomes, and mortality after at least 3 months of follow-up. Statin therapy was classified into two major types: pre-stroke statin use and in-hospital statin use. Characteristics of included studies are summarized in **Table 1**.

Study Quality

Risk of bias among the *post-hoc* analyses of RCTs and cohort studies was assessed with NOS. The results showed that 15 studies were graded as good quality (25–28, 30, 32, 34–39, 41–43) and the remaining 7 studies were graded as fair quality. The overall score of the NOS was 173 of 198 (87%), which is considered to represent an overall high quality. Details of the quality assessment are shown in **Table 2**.

TABLE 2 | Risk of bias assessment.

References	Selection				Comparability	Outcome			Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis *	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Alvarez-Sabín et al. (23)		☆	☆	☆	☆☆	☆	☆		7
Bruning et al. (24)	☆	☆	☆	☆		☆	☆	☆	7
Cappellari et al. (25)		☆	☆	☆	☆☆	☆	☆	☆	8
Cappellari et al. (26)		☆	☆	☆	☆☆	☆	☆	☆	8
Cui et al. (27)	☆	☆	☆	☆	☆☆	☆	☆		8
Engelter et al. (28)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Faivre et al. (29)	☆	☆	☆	☆		☆	☆	☆	7
Geng et al. (30)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Kang et al. (31)		☆	☆	☆		☆	☆	☆	6
Makihara et al. (32)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Martinez-Ramirez et al. (33)	☆	☆	☆	☆		☆	☆		6
Miedema et al. (34)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Montaner et al. (35)		☆	☆	☆	☆☆	☆	☆	☆	8
Mowla et al. (36)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Rocco et al. (37)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Scheitz et al. (38)		☆	☆	☆	☆☆	☆	☆	☆	8
Scheitz et al. (39)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Scheitz et al. (40)		☆	☆	☆		☆	☆	☆	6
Tong et al. (41)		☆	☆	☆	☆☆	☆	☆	☆	8
Tsivgoulis et al. (42)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Uyttenboogaart et al. (43)	☆	☆	☆	☆	☆☆	☆	☆		8
Zhao et al. (44)		☆	☆	☆		☆	☆	☆	6
Total	13/22	22/22	22/22	22/22	32/44	22/22	22/22	18/22	173/198

**A maximum of 2 stars can be allotted in this category; one for age, and the other for other controlled factors.*

TABLE 3 | Overview of the safety and efficacy analyses on different endpoints.

Outcome	Pre-stroke statin use				In-hospital statin use			
	Studies, *n*	OR (95% CI)	*p*-value	Heterogeneity (I^2, *p* for Cochran Q)	Studies, *n*	OR (95% CI)	*p*-value	Heterogeneity (I^2, *p* for Cochran Q)
sICH	12	1.31 (1.07–1.59)	0.008	$I^2 = 20\%$, $p = 0.25$	5	0.46 (0.21–1.00)	0.05*	$I^2 = 0\%$, $p = 0.88$
Any ICH	4	1.21 (1.03–1.43)	0.02	$I^2 = 0\%$, $p = 0.91$	3	0.51 (0.27–0.98)	0.04	$I^2 = 0\%$, $p = 0.53$
Mortality (3 mo)	7	1.06 (0.74–1.51)	0.76	$I^2 = 64\%$, $p = 0.01$	5	0.42 (0.29–0.62)	< 0.001	$I^2 = 0\%$, $p = 0.44$
FFO (3 mo)	6	0.93 (0.81–1.07)	0.33	$I^2 = 0\%$, $p = 0.67$	3	1.33 (1.02–1.74)	0.04	$I^2 = 0\%$, $p = 0.72$
FI (3 mo)	10	1.14 (0.86–1.52)	0.37	$I^2 = 66\%$, $p = 0.002$	7	1.41 (1.11–1.80)	0.005	$I^2 = 6\%$, $p = 0.38$

CI, confidence interval; FFO, favorable functional outcome; FI, functional independence; ICH, intracranial hemorrhage; OR, odds ratio; sICH, symptomatic intracranial hemorrhage.
**The p-value was 0.045, approximately equal to 0.05.*

Association Between Statin Use and Outcomes

Table 3 provides a comprehensive overview of the association between pre-stroke or in-hospital statin use and various clinical outcomes.

Pre-stroke Statin Use and Outcomes

We identified 14 studies (23, 24, 28, 29, 32–34, 36, 37, 39, 40, 42–44) involving 13,990 participants that explored the effect of pre-stroke statin use on ICH, mortality, and functional outcome in patients with AIS treated with IVT. The pooled estimates showed

that pre-stroke statin use was associated with an increased odds of symptomatic ICH (12 studies, OR 1.31; 95% CI 1.07–1.59; $p = 0.008$; p for Cochran Q statistic = 0.25, $I^2 = 20\%$; **Figure 2A**; **Table 3**) and any ICH (four studies, OR 1.21; 95% CI 1.03–1.43; $p = 0.02$; p for Cochran Q statistic = 0.91, $I^2 = 0\%$; **Figure 2B**; **Table 3**). However, pre-stroke statin use was not significantly related to 3-month mortality (seven studies, OR 1.06; 95% CI 0.74–1.51; $p = 0.76$; p for Cochran Q statistic = 0.01, $I^2 = 64\%$; **Figure 2C**; **Table 3**), 3-month FFO (six studies, OR 0.93; 95% CI 0.81–1.07; $p = 0.33$; p for Cochran Q statistic = 0.67, $I^2 = 0\%$; **Figure 2D**; **Table 3**), and 3-month FI (10 studies, OR 1.14; 95% CI 0.86–1.52; $p = 0.37$; p for Cochran Q statistic = 0.002, $I^2 = 66\%$; **Figure 2E**; **Table 3**).

In-hospital Statin Use and Outcomes

Nine studies (24–27, 30, 31, 35, 38, 41) involving 4,115 patients reported outcomes according to in-hospital statin use. The pooled estimates showed that in-hospital statin use was associated with a lower likelihood of symptomatic ICH (five studies, OR 0.46; 95% CI 0.21–1.00; $p = 0.045$; p for Cochran Q statistic = 0.88, $I^2 = 0\%$; **Figure 3A**; **Table 3**), any ICH (three studies, OR 0.51; 95% CI 0.27–0.98; $p = 0.04$; p for Cochran Q statistic = 0.53, $I^2 = 0\%$; **Figure 3B**; **Table 3**), and 3-month mortality (five studies, OR 0.42; 95% CI 0.29–0.62; $p < 0.001$; p for Cochran Q statistic = 0.44, $I^2 = 0\%$; **Figure 3C**; **Table 3**). The pooled estimates also showed that in-hospital statin use was associated with 3-month FFO (three studies, OR 1.33; 95% CI 1.02–1.74; $p = 0.04$; p for Cochran Q statistic = 0.72, $I^2 = 0\%$; **Figure 3D**; **Table 3**) and 3-month FI (seven studies, OR 1.41; 95% CI 1.11–1.80; $p = 0.005$; p for Cochran Q statistic = 0.38, $I^2 = 6\%$; **Figure 3E**; **Table 3**).

Publication Bias

For the safety and efficacy analyses on different endpoints, visual inspection of the funnel plot and the Egger statistical test revealed no evidence of asymmetry, indicating no potential publication bias (data available from **Supplemental Figures 1, 2**).

DISCUSSION

There were two major findings in this comprehensive systematic review and meta-analysis with 22 studies involving more than 15,000 participants. The primary finding was that pre-stroke statin use was associated with a potentially higher risk of systematic ICH in AIS patients treated with IVT whereas in-hospital statin use was related with a lower likelihood of symptomatic ICH. The secondary finding was that in-hospital statin use was associated with improved outcome in AIS patients treated with IVT, a finding not observed in patients using statin prior to hospital admission.

According to the American Heart Association/American Stroke Association guidelines updated in 2019 (15), it is reasonable to initiate statin therapy in eligible AIS patients. This is supported by previously published meta-analyses (13, 14), which have shown that the use of statins was associated with improved outcome. However, conflicting data were observed in a subgroup restricted to thrombolysis-treated patients (13, 14, 45). The heterogeneity in the previous studies may be due to several reasons. Firstly, a heterogeneous population undergoing different treatment modalities, including mechanical recanalization, IVT, and intra-arterial thrombolysis, was included. Secondly, the starting time of statin administration, including pre-stroke statin use and in-hospital statin use, was not considered separately. A large multicenter RCT should be the best way to address the question whether the use of statin is associated with any clinical benefit in AIS patients after IVT. Such a trial may be challenging in determining the duration and frequency of statin. However, to date, there is only one small RCT with 310 patients that has investigated the safety and efficacy of intensive statin in the acute phase of ischemic stroke after IVT therapy (46). In this trial, because of the recommendation from the American Heart Association/American Stroke Association guidelines (15), the ethics committee did not approve the no-statin group based on the principles of non-maleficence and beneficence. Therefore, we performed a comprehensive systematic review and meta-analysis of observational studies and *post-hoc* RCT analyses. Our findings may provide a good basis for determining the use of statin in combination with IVT for patients with AIS.

Our findings have important implications for both policymakers and clinicians. Firstly, previously published systematic reviews have raised concerns that statin therapy could increase the risk of ICH (47, 48). We found that in-hospital statin use probably decreased the risk of systematic ICH. Our findings provide evidence against the theoretical concerns of increased ICH risk with statin treatment. Additionally, previously published systematic reviews found that statin therapy at stroke onset was associated with improved outcome; however, inconclusive results were observed in studies restricted to thrombolysis-treated patients (13, 14, 33, 45). Our meta-analysis found that, in AIS patients receiving IVT, statin use during hospitalization was associated with improved outcome. We consider that our findings further support current international recommendations that AIS patients qualified for statin treatment should receive statin therapy as soon as possible (class of recommendation = II, level of evidence = C) (15). In addition, we believe that pretreatment with statins is not recommended as it does not improve outcomes of AIS patient treated with IVT but increases the risk of ICH.

Our findings might be attributed to the cholesterol-independent (pleiotropic) protective effects of statins. Among these, the pleiotropic effects can inhibit the differentiation of microglia to M1 cells and the release of inflammatory factors after tissue plasminogen activator treatment, thereby protecting neurovascular function. Reducing blood–brain barrier destruction may explain the positive effect of in-hospital statin treatment on the incidence of hemorrhagic transformation and clinical outcomes (49, 50). In a rat model of embolic stroke, combination treatment with atorvastatin and tissue plasminogen activator at 4 h after stroke significantly reduced the infarct volume, improved the neurologic function, and decreased the incidence of hemorrhagic transformation by decreasing neutrophil infiltration and metalloproteinase-9 expression (49). In addition, Lu et al. also found that rosuvastatin combined with tissue plasminogen activator after stroke onset prevented

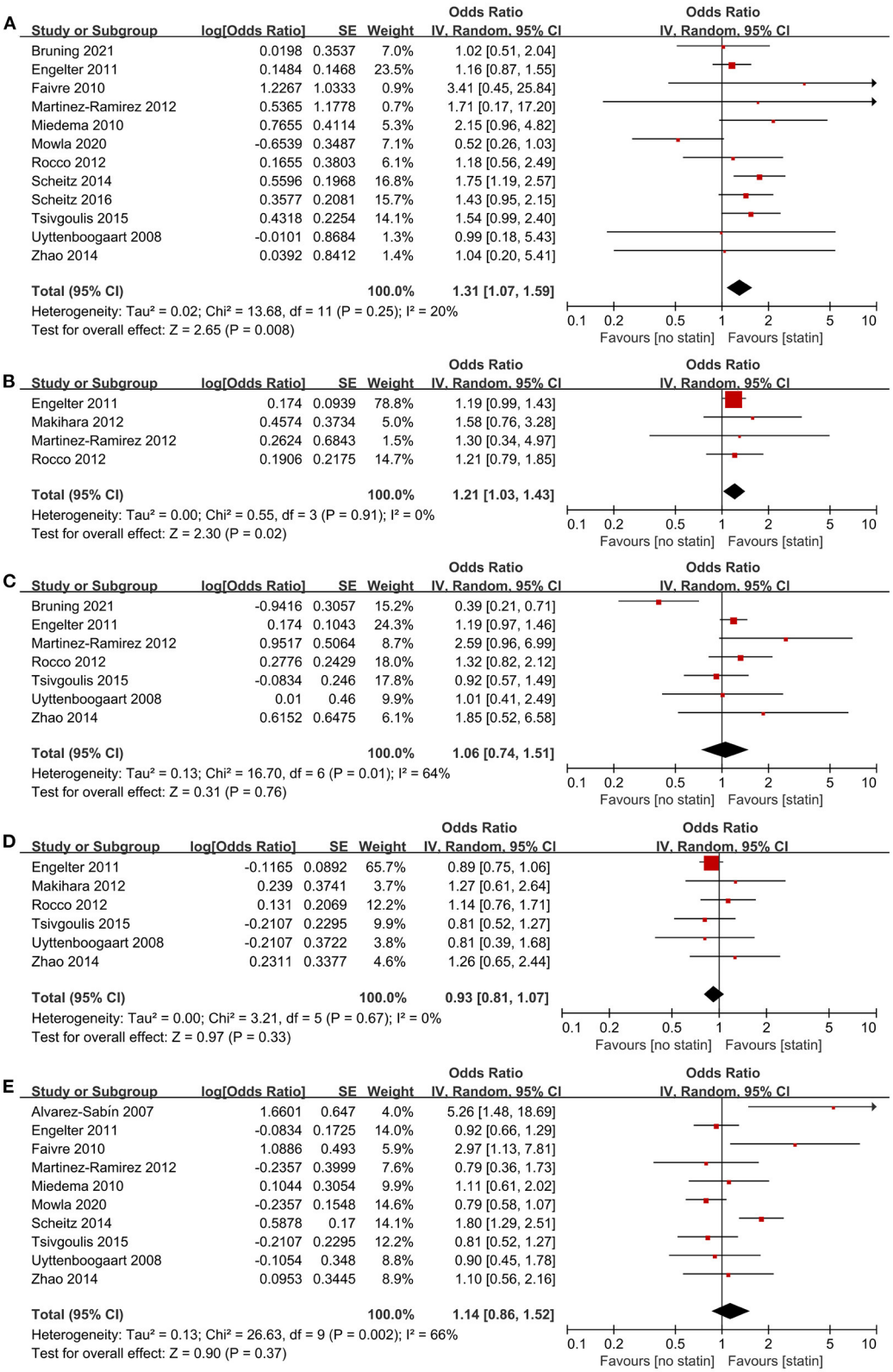

FIGURE 2 | Association of pre-stroke statin use with **(A)** symptomatic intracranial hemorrhage, **(B)** any intracranial hemorrhage, **(C)** 3-month mortality, **(D)** 3-month favorable functional outcome, and **(E)** 3-month functional independence.

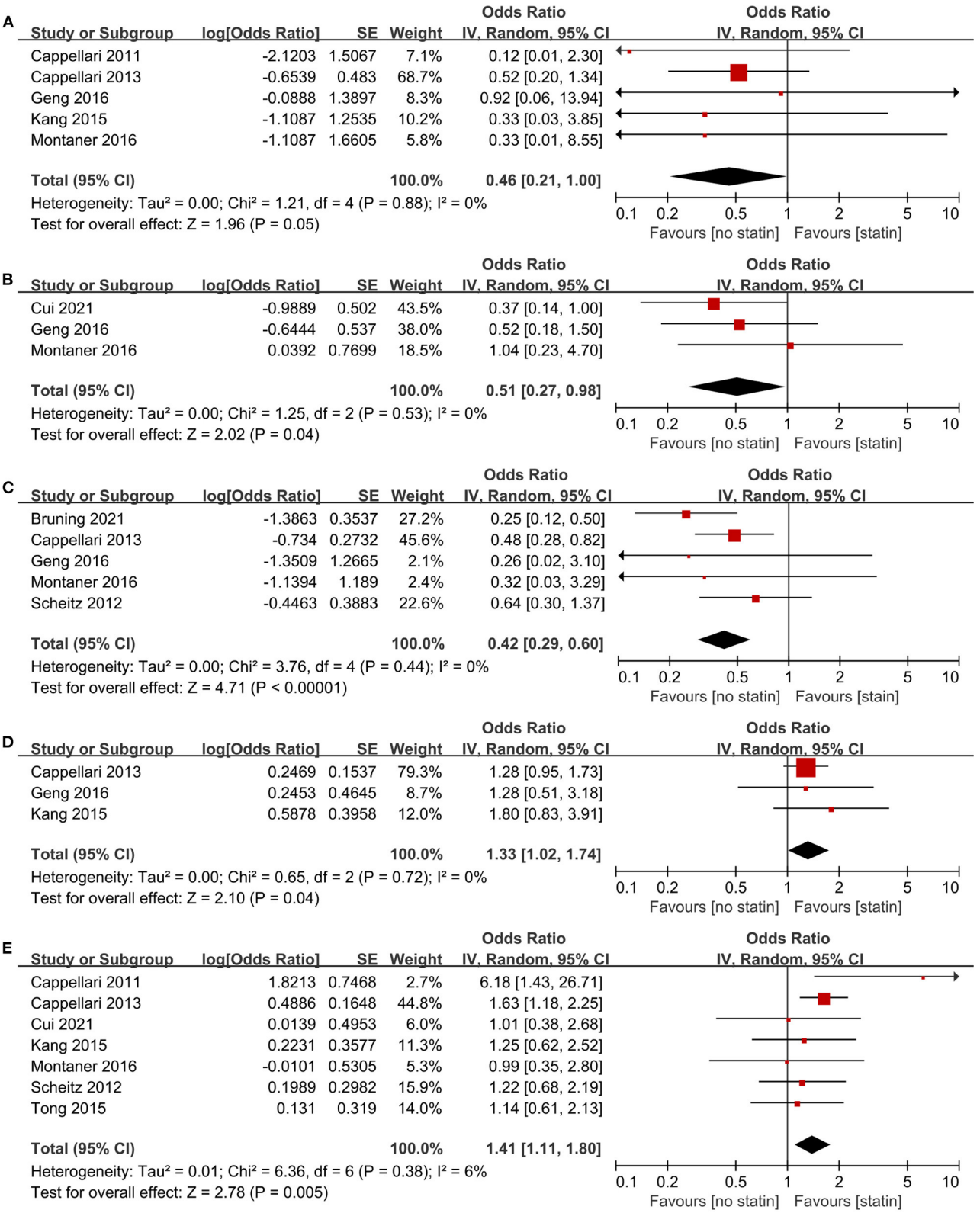

FIGURE 3 | Association of in-hospital statin use with **(A)** symptomatic intracranial hemorrhage, **(B)** any intracranial hemorrhage, **(C)** 3-month mortality, **(D)** 3-month favorable functional outcome, and **(E)** 3-month functional independence.

the activation of astrocytes and microglia and reduced the release of inflammatory factors, thereby alleviating blood–brain barrier disruption and hemorrhagic transformation severity (50). However, in stroke patients receiving IVT, the beneficial effects have not been observed consistently in prior statin users, because the beneficial effects of statins may diminish after withdrawal (51, 52), which is in agreement with one previous study (44). In addition, compared with statin treatment after thrombolysis, statin use before stroke significantly increased the fibrinolytic effect and disrupted homeostasis between coagulation and fibrinolysis (25). Hence, it might be possible that pre-stroke statin use associates with a potential higher risk of systematic ICH in AIS patients treated with IVT.

Certain limitations of the present study warrant further consideration. Firstly, this is a meta-analysis of observational studies. Our findings were exclusively based on data of observational studies that predispose to inherent biases, especially selection bias. Secondly, despite the use of adjusted ORs whenever applicable, unmeasured confounders cannot be eliminated due to a lack of individual study patient data. It is possible that differences in cardiovascular risk factors might account for observed associations, while the confounding role of pharmacologic differences in statins cannot be excluded. Thirdly, specific data for statin, including dosage, duration, compliance, pharmacokinetics, and statin type, were not assessed. These parameters could have introduced unmeasured biases in our analysis.

Our study also has several strengths. Firstly, to our knowledge, this is the first systematic review and meta-analysis to explore the effects of starting time of statin administration (pre-stroke or in-hospital) in patients with AIS treated with IVT. Secondly, the majority of the included studies were prospective cohort studies or *post-hoc* analysis of RCTs with high quality and had adequately adjusted for confounders. This might reduce the influences of other cardiovascular risk factors on the association of pre-stroke statin use with clinical outcomes. Thirdly, the number of available studies and the sample size were large, which allowed us to explore the association of pre-stroke and in-hospital statin administration with clinical outcomes.

CONCLUSION

In AIS patients treated with IVT, pre-stroke statin use was probably associated with increased risk of ICH, but had no effect on good functional outcome or mortality at 3 months. On the contrary, in-hospital statin use probably decreased the risk of ICH and 3-month mortality and was associated with good functional outcome at 3 months.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YG: study concept and design, acquisition of data, analysis and interpretation, and critical revision of the manuscript for important intellectual content. XG: acquisition of data, analysis and interpretation, and critical revision of the manuscript for important intellectual content. KZ: critical revision of the manuscript for important intellectual content. QB and JY: acquisition of data. MY: study supervision and critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.734927/full#supplementary-material

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CASE REPORT
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Successful Intravenous Thrombolysis in Ischemic Stroke Caused by Tuberculous Meningitis: A Case Report

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Tuberculous meningitis (TBM) has a variety of clinical manifestations and complications, and ischemic stroke is a common complication of TBM. However, there is no established prevention or treatment for stroke associated with TBM, and the safety and efficiency of thrombolysis in acute stroke caused by TBM remain unknown. Herein, we present a case of successful intravenous thrombolysis in ischemic stroke caused by TBM. A 50-year-old male patient with cerebral infarction had substantially improved neurological function after intravenous thrombolysis, and he was subsequently found to have TBM. Our findings suggest that intravenous thrombolysis might be an effective acute treatment method for infectious stroke.

Keywords: stroke, tuberculous meningitis, thrombolysis (tPA), neurological deficits, vasculitis

INTRODUCTION

Tuberculous meningitis (TBM), an important cause of infectious stroke, is the most devastating form of extrapulmonary tuberculosis (1, 2). Intravenous thrombolysis is the recommended therapy for acute ischemic stroke in adults within 4.5 h of the onset of symptoms. However, there are few clinical reports regarding the safety and outcomes of thrombolysis treatment for TBM. This case report describes a patient with cerebral infarction who had substantially improved neurological function after intravenous thrombolysis. The patient was subsequently diagnosed with TBM during the evaluation process to determine the mechanism of his stroke.

CASE REPORT

A 50-year-old man was admitted to our emergency department with sudden-onset right-sided weakness and aphasia that occurred 3 h ago. In the past month, the patient had headaches, manifested by paroxysmal pain in both temples and the base of the neck. He had a history of fever and chills and vomited 3 days ago. His initial National Institutes of Health Stroke Scale (NIHSS) score was 10 based on analyses of drowsiness, global aphasia, dysarthria, right-sided hypoesthesia, and facial nerve paralysis.

Initial laboratory examinations showed a white blood cell (WBC) count of 12.56 × 109/L (neutrophils, 88.2%), blood sodium level of 124.2 mmol/L, and chlorine level of 88.2 mmol/L. Initial non-enhanced head computed tomography (CT) revealed no hemorrhage but showed hypodensity throughout the left frontal lobe and left insular lobe, indicating acute ischemia (**Figure 1**). Transthoracic echocardiography showed no obvious neoplasms, and cerebral infarction caused by infective endocarditis was thus not considered. After excluding absolute contraindications for intravenous thrombolysis, the patient was treated with an intravenous recombinant tissue plasminogen activator (rt-PA). His neurological defects improved substantially after thrombolytic therapy. Twenty-four hours after rt-PA administration, he had only mild facial paralysis on the right side, and his reevaluated NIHSS score was only 1. Post-rt-PA magnetic resonance imaging (MRI) found multiple cerebral infarctions (**Figure 2**), and contrast-enhanced MRI revealed that the hypodense area in the left insula and frontal lobe was edema adjacent to a tuberculoma but not ischemia (**Figure 3**). The patient did not complete brain CT angiography (CTA) and CT perfusion (CTP). The initial hypodensity on the non-contrast CT scan, which had been misinterpreted as ischemic changes, did not match the patient's clinical symptoms. Chest CT showed a slight exudation of the double lower lungs and a few fibrous foci in the upper right and lower left lungs. The patient received empirical administration of piperacillin and tazobactam; however, his symptoms did not improve, and he continued to be intermittently febrile.

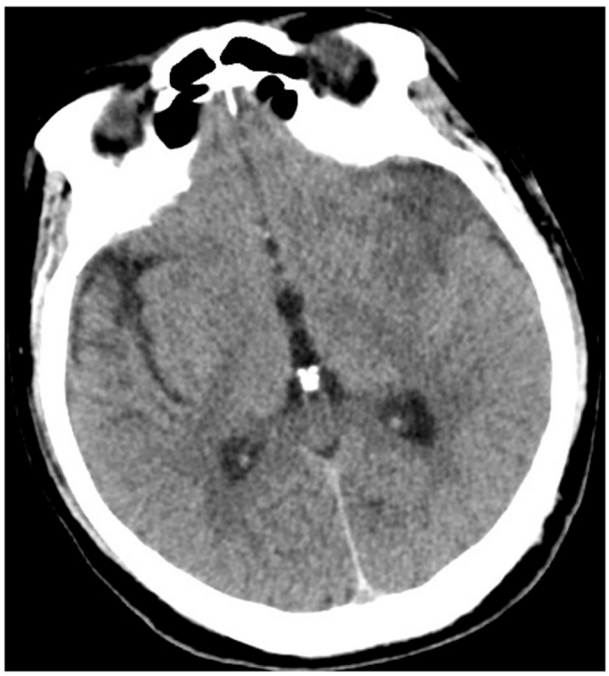

FIGURE 1 | Initial head CT revealed left frontal lobe and left insular lobe hypodensities.

On the third day of admission, the patient developed lethargy. Considering his persistent fever and refractory hyponatremia since admission, the patient underwent a lumbar puncture with pressure > 40 cmH20. The cerebrospinal fluid (CSF) analysis revealed a WBC count of 66 × 106/L, lymphocyte count of 70%, protein level of 925.1 mg/L, glucose level of 3.0 mmol/L, and chloride level of 103.5 mmol/L. Findings of CSF

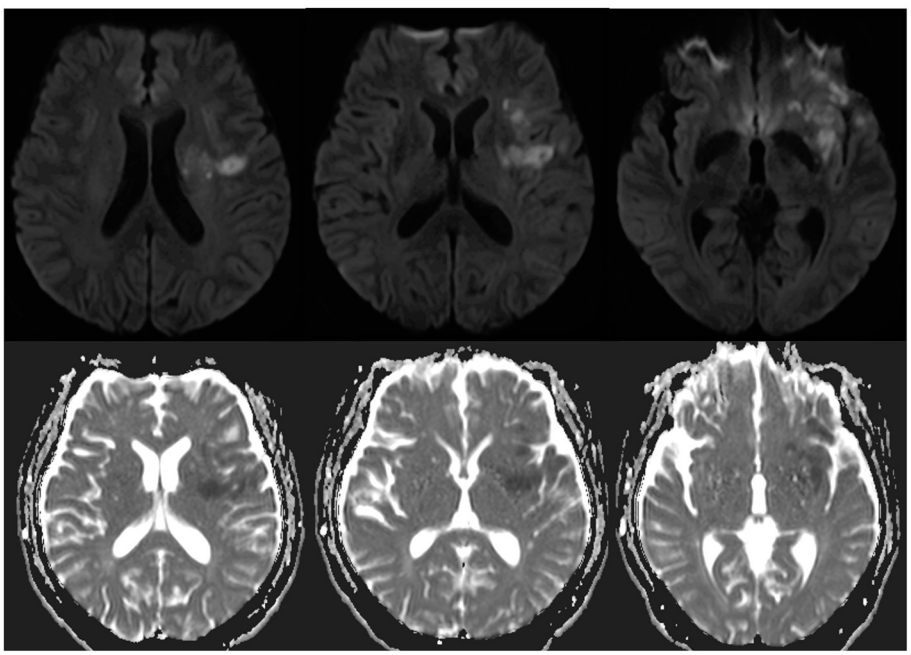

FIGURE 2 | Axial diffusion-weighted image and apparent diffusion coefficient showed acute infarction in the left temporal lobe, left insular lobe, left basal ganglia, and left radial crown 24 h after admission.

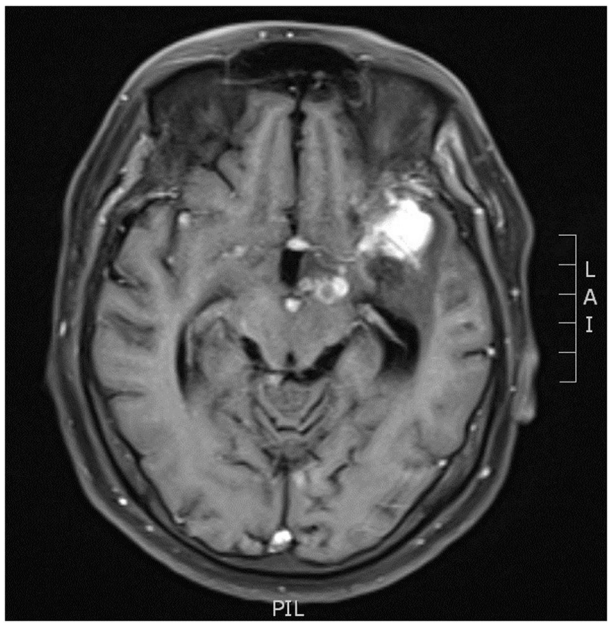

FIGURE 3 | MRI revealed nodular enhancement in the left pontine cistern.

cryptococcal antigen and bacterial and fungal cultures, as well as results of the purified protein derivation test and sputum cultures, were all negative. High-throughput sequencing of the CSF detected *Mycobacterium tuberculosis* with high confidence. Re-examination of head MRI enhancement revealed that the left pontine cistern showed nodular enhancement (**Figure 3**), and multiple cerebral infarctions with complicated TBM were diagnosed. The patient was thus started on a five-drug treatment for tuberculosis comprising isoniazid, ethambutol, pyrazinamide, rifampicin, and levofloxacin. Intrathecal administration of dexamethasone (4 mg/time) and isoniazid (100 mg/time) were given three times per week. Further CSF examinations showed improved tendencies (**Table 1**). The patient had only right facial paralysis when discharged, and he continued anti-tuberculosis treatment at a local hospital.

TABLE 1 | Results of serial cerebrospinal fluid analyses.

	4th day	9th day	29th day	41st day	51st day
Pressure (cmH20)	>40	22.5	16	21	18
WBC ($\times 10^6$/L)	66	140	62	33	0
Lymphocyte count (%)	30	60	10	10	0
Protein (mg/L)	925.1	476.6	598.0	982.1	497.2
Glucose (mmol/L)	3.0	2.4	3.6	3.3	3.0
Chloride (mmol/L)	103.5	115.8	113.7	117.3	117.6

DISCUSSION

TBM is the most life-threatening extrapulmonary tuberculosis due to its high mortality rate, and stroke may occur in 15−57% of TBM cases (1). Cerebral infarction is a predictor of poor outcomes (3), and the mortality rate of TBM patients with stroke may be three times that of patients without infarction (4). The extension of the inflammatory exudate along the perforating blood vessels into the brain substance causes vascular damage, which may lead to spasm or thrombosis of the vessels, with resulting ischemia or infarction (5). Most cerebral infarctions associated with TBM are multiple, and up to 75% of them are located in the basal ganglia, anteromedial thalamus, anterior limb, and genu of the internal capsule (6–8). Perforating arteries are most involved in cerebral infarctions caused by tuberculous cerebral arteritis; therefore, basal ganglia and internal capsule infarctions are the most common (9). Consistently, the patient in this study had multiple-site infarctions, further verifying that TBM is prone to cooccur with cerebral infarction. However, this patient had no history of tuberculosis before the onset of symptoms, which is usually uncommon.

Aspirin is the most commonly used treatment for ischemic stroke secondary to TBM because it can prevent stroke and modulate the host immune response in TBM patients (7, 8). However, aspirin is only used as a secondary prevention drug and cannot improve the symptoms of neurological deficits in stroke patients with intravenous thrombolysis. To date, no clear clinical guidelines recommend thrombolytic therapy for acute cerebral infarction secondary to TBM (7). According to the European Stroke Organization (ESO) guidelines on intravenous thrombolysis for acute ischemic stroke, infectious strokes, including infective endocarditis, are generally considered a relative contraindication to thrombolytic therapy (10). However, recently, Sloane et al. (11) analyzed 26 cases of infective endocarditis with endovascular recanalization treatment, and they found that only one case did not improve after successful removal of the thrombus. At the time of thrombolytic infusion, we were unaware that our patient had TBM. However, we noticed that the patient continued to have fever and headache, and we thus ruled out infective endocarditis in a limited time. Fortunately, this patient showed a good therapeutic effect after intravenous thrombolysis. We believe that our patient might have benefited from thrombolysis.

One limitation should be mentioned in this study. This study only analyzed one clinical case; thus, it is difficult to draw a firm conclusion, and further studies with a larger sample size are needed to confirm our present findings. Our findings suggest that in patients with acute cerebral infarction accompanied by headache and fever, the possibility of an infectious stroke should be considered, and intravenous thrombolysis might be an effective acute treatment method for patients with infectious stroke.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XW and YZ are the guarantor of integrity of the entire study. LL and QX performed data acquisition. XP was responsible for manuscript preparation and editing. CW and HZ performed manuscript review. All authors read and approved the final manuscript.

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STUDY PROTOCOL
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Endovascular Recanalization and Standard Medical Management for Symptomatic Non-acute Intracranial Artery Occlusion: Study Protocol for a Non-randomized, 24-Month, Multicenter Study

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Background: The management of patients with symptomatic non-acute intracranial artery occlusion (sNA-ICAO), which is a special subset with high morbidity and a high probability of recurrent serious ischemic events despite standard medical therapy (SMT), has been clinically challenging. A number of small-sample clinical studies have also discussed endovascular recanalization (ER) for sNA-ICAO; however, there is currently a lack of evidence from multicenter, prospective, large-sample cohort trials. The purpose of our present study was to evaluate the technical feasibility and safety of ER for sNA-ICAO.

Methods: Our group is currently undertaking a multisite, non-randomized cohort, prospective registry study enrolling consecutive patients presenting with sNA-ICAO at 15 centers in China between January 1, 2020 and December 31, 2022. A cohort of patients who received SMT and a cohort of similar patients who received ER plus SMT were constructed and followed up for 2 years. The primary outcome is any stroke from enrollment to 2 years of follow-up. The secondary outcomes are all-cause mortality, mRS score, NIHSS score and cognitive function from enrollment to 30 days, 3 months, 8 months, 12 months, 18 months, and 2 years of follow-up. Descriptive statistics and linear/logistic multiple regression models will be generated. Clinical relevance will be measured as relative risk reduction, absolute risk reduction and the number needed to treat.

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Discussion: The management of patients with sNA-ICAO has been clinically challenging. The current protocol aims to evaluate the technical feasibility and safety of ER for sNA-ICAO.

Trial Registration Number: www.ClinicalTrials.gov, identifier: NCT04864691.

Keywords: symptomatic non-acute intracranial artery occlusion, standard medical therapy, endovascular recanalization, major and mild stroke, primary and secondary outcomes

BACKGROUND

Large intracranial artery occlusion is a major cause of stroke and is associated with a high risk of stroke recurrence and poor stroke outcome, especially in China (1, 2). For symptomatic non-acute intracranial artery occlusion (sNA-ICAO) (within 24 h to 6 months), some patients continue to be symptomatic despite standard medical therapy (SMT) (3–5). Extracranial-intracranial (EC-IC) artery bypass surgery fails to show benefits in preventing ischemic attacks or ischemic stroke when performed for sNA-ICAO (6, 7). The optimal treatment for patients with sNA-ICAO disease remains undefined. Currently, SMT, including an antiplatelet regimen and risk factor management, has been used to treat patients with sNA-ICAO disease. Unfortunately, the natural course of this condition shows that these patients often experience recurrent symptoms despite SMT. Recently, a series of small-sample clinical studies have reported that endovascular recanalization (ER) is feasible for sNA-ICAO (8–13). However, most of the previous studies are based on small-sample, single-center retrospective analyses, and there is no high-level evidence from large multicenter samples or prospective studies to indicate the effectiveness and safety of ER for sNA-ICAO.

Therefore, we launched a prospective registry study of patients with sNA-ICAO from 15 centers in China to test whether ER combined with SMT is superior to SMT alone in the primary prevention of stroke in patients with symptomatic non-acute cerebral artery occlusion.

METHODS AND DESIGN

Study Design and Setting

The trial was retrospectively registered on ClinicalTrials.gov on April 25, 2021, with reference number NCT(04864691). The study is a multicenter, prospective registry, non-randomized cohort study sponsored by professor Feng Gao of Beijing Tiantan hospital to assess patients affected by sNA-ICAO undergoing ER and SMT. This protocol was developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement. Fifteen centers across China will participate in the study and provide data. All centers have a similar perioperative pathway and use enhanced recovery after surgery (ERAS) protocols. The participating centers are as follows: Department of Interventional Neuroradiology, Beijing Tiantan Hospital; Department of Neurology, Tong Ren Hospital Shanghai Jiaotong University School of Medicine; Department of Interventional Neurology, Beijing You 'anmen Hospital; Department of Neurology, Beijing Anzhen Hospital; Department of Neurology, Hebei General Hospital; Department of Neurology, Shanxi General Hospital; Department of Neurology, Taiyuan Central Hospital; Department of Neurology, Liangxiang Hospital; Department of Neurology, ORDOS Central Hospital; Department of Neurology, TongLiao City Hospital; Department of Neurology, Tai'an Hospital of Traditional Chinese Medicine; Department of Neurology, Handan Central Hospital; Department of Neurology, Dalian Municipal Central Hospital; Department of Neurology, Jingjiang people's Hospital; Department of Neurology, Taizhou first people's Hospital.

Participants

We will include patients with imaging (MRA/CTA/DSA) and clinical diagnosis of sNA-ICAO (**Figure 1**) between January 1, 2020 and December 31, 2022 in the participating centers. Eligibility screening will be performed by the principal investigator in accordance with the inclusion/exclusion criteria (**Tables 1**, **2**). Based on the patient's previous history, imaging features of the lesion and the attitudes of the patient and family members, the local investigative team in each center will determine whether to give SMT plus SMZ or SMT alone. Both groups of patients share general inclusion/exclusion criteria and primary and secondary endpoints.

Ethical Issues

Data collection will be performed according to the World Medical Association Declaration of Helsinki. All the patients gave written informed consent to participate. Ethical permission was received from Beijing Tiantan Hospital, the Capital Medical University Medical Ethics Committee (number: KY2020-114-02), and the institutional review boards of all partner sites. The standard of care for patients participating in this study will remain the same.

SMT

Sites implemented SMT for all patients with guidance from the Medical Management Core. Patients in SMT group will take aspirin (100 mg/day) and clopidogrel (75 mg/day) for 90 days followed by lifelong aspirin or clopidogrel monotherapy

Abbreviations: sNA-ICAO, symptomatic non-acute intracranial artery occlusion; SMT, standard medical therapy; ER, endovascular recanalization; EC-IC, Extracranial-intracranial; SPIRIT, Recommendations for Interventional Trials; ERAS, enhanced recovery after surgery; IRB, institutional review board; MEC, medical ethics committee; RAPID, Rapid Processing of Perfusion and Diffusion; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale.

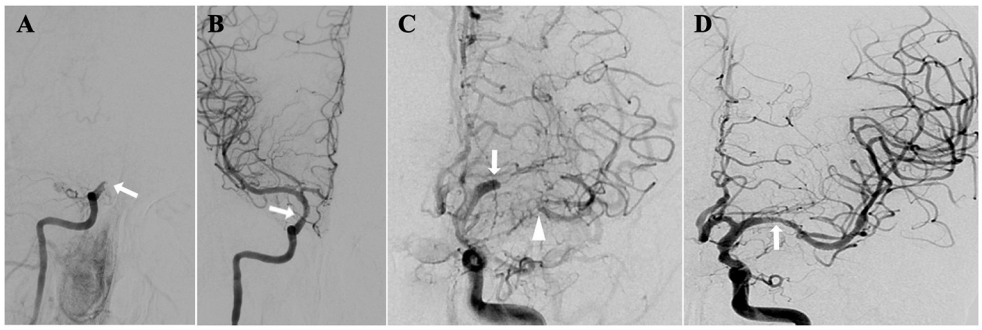

FIGURE 1 | sNA-ICAO diagnosed by DSA. **(A)** Illustrations of non-acute occlusion of intracranial segment of internal carotid artery; **(B)** recanalization after endovascular treatment; **(C)** illustrations of non-acute occlusion of middle cerebral artery; **(D)** recanalization after endovascular treatment.

TABLE 1 | Primary inclusion criteria for participants in the trial.

1. Patient age ≥ 18 years old.
2. Symptomatic sNA-ICAO defined as:
   - Diagnosed by CTA or MRA and confirmed by angiography;
   - Vascular occlusion time more than 24 h;
   - TIA or ischemic stroke (confirmed by CT or MRI) related to the LCAO despite SMT < 90 days prior to enrollment.
3. Modified Rankin scale score of 0 or 1 at the time of informed consent.
4. More than one risk factor for atherosclerosis.
5. For patients with ICA or MCA M1 segment occlusion, ipsilateral hypoperfusion confirmed by CTP or MRI perfusion imaging prior to enrollment and analysis by the RAPID system.
6. For patients with intracranial segment occlusion of the vertebral artery, severe stenosis or occlusion of the contralateral vertebral artery.
7. Among women, no childbearing potential; or if a woman with childbearing potential, a negative pregnancy test result prior to admission.
8. Agreement of the patient to comply with all protocol-specified follow-up appointments.
9. All enrolled patients refused bypass surgery.
10. Signature by a patient of a consent form that has been approved by the local governing institutional review board (IRB)/medical ethics committee (MEC) of the respective clinical site.

thereafter. The primary risk factors of cerebrovascular disease including systolic blood pressure and LDL cholesterol, will be controlled in line with protocols. Systolic blood pressure will be controlled below 140 mmHg or 130 mmHg in patients with diabetes and LDL will be controlled below 70 mg/dl with Atorvastatin (14). At each follow-up visit, blood pressure and LDL will be tested, and if the standard is not met, the medication will be adjusted based on the measurements. Management of secondary risk factors such as diabetes, non-HDL cholesterol, smoking, weight and physical activity will be coordinated with the patient's primary physician or other consultant as needed. A lifestyle modification program, INTERVENT, will be provided to each patient.

ER Protocol

A dual antiplatelet regimen with acetylsalicylic acid (100 mg) and clopidogrel (75 mg) is started at least 3 days before the procedure. All procedures are performed under general anesthesia by an experienced interventional neuroradiologist. After placement of sheath introducers, heparin is given intravenously to maintain the coagulation time between 200 and 300 s. The 6- or 8-French guiding catheter is located distal to the occluded artery as much as possible. Under the route map, the micro guidewire in combination with a microcatheter and the microcatheter are used to carefully pass through the occluded segment. Angiography with the microcatheter should confirm that the guidewire is in the true lumen. The exchange micro guidewire is then sent into the micro catheter, and the microcatheter is exchanged out. The balloon catheter is advanced smoothly into the occluded segment along the exchange micro guidewire. After the occluded segment is dilated with the balloon, angiography with a guiding catheter is performed. Stents are deployed in cases of residual severe stenosis, vascular dissection and failure to maintain forward flow (according to the judgment of the neuroradiologist to select the stent). If one stent cannot completely cover the lesion, multiple stents can be implanted. Successful revascularization is defined as a modified TICI grade 2b or 3 and residual stenosis <50%.

For patients with ICA or MCA M1 segment occlusion, ipsilateral hypoperfusion should be confirmed by CTP or MRI perfusion imaging prior to enrollment according to a previous study (15). Moreover, the non-contrast and perfusion scans are additionally transferred to the Rapid Processing of Perfusion and Diffusion (RAPID) system, providing analysis of perfusion source images with respect to the DEFUSE 3 criteria (16).

Periprocedural drug therapy is shown in **Table 3**. After the procedure, if there are no hemorrhagic complications on the head CT scan, intravenous anticoagulation or antiplatelet therapy is continued for at least 24-48 h. Then, dual antiplatelet therapy is maintained for 3-6 months followed by lifelong aspirin or clopidogrel monotherapy thereafter.

Data Design and Management

Data design and management is the responsibility of the Scientific Committee of Capital Medical University experts. They will keep watch on the database and propose amendments at any time to achieve the purpose of the study. We will collect patient information in a confidential manner in line with China

TABLE 2 | Primary exclusion criteria for participants in the trial.

1. Intolerance or allergic reaction to a study medication without a suitable management alternative.
2. No atherosclerotic intracranial vasculopathies, such as dissection, moyamoya disease and vasculitis.
3. Concomitant intracranial aneurysms or any bleeding disorder.
4. Life expectancy < 1 year due to other medical conditions.
5. Large infarction core, defined as an ASPECTS < 6 in anterior circulation and pc-ASPECTS < 6 points in posterior circulation.
6. For patients with MCA M1 segment occlusion, concomitant ≥50% stenosis of the proximal internal carotid artery or other intracranial arteries.
7. For patients with intracranial segment occlusion of the vertebral artery, continuance of the occluded vertebral artery to the posterior inferior cerebellar artery with no stump.
8. Incomplete clinical and imaging data.
9. Coexistent cardioembolic source (e.g., atrial fibrillation, mitral stenosis, prosthetic valve, MI within six weeks, intracardiac clot, ventricular aneurysm and bacterial endocarditis).
10. Occlusive lesions with severe calcification.
11. Platelet count < 100,000/ml or history of heparin-induced thrombocytopenia.
12. Left ventricular ejection fraction < 30% or admission for heart failure in the prior 6 months.
13. Extreme morbid obesity that would compromise patient safety during the procedure or the periprocedural period.
14. Coronary artery disease with two or more proximal or major diseased coronary arteries with 70% stenosis that have not or cannot be revascularized.
15. Anticoagulation with Marcumar, warfarin or direct thrombin inhibitors or anti-XA drugs.
16. Chronic atrial fibrillation.
17. Any history of atrial fibrillation or paroxysmal atrial fibrillation in the past 6 months that is considered to require long-term anticoagulant therapy.
18. Other high-risk cardiogenic embolisms, including left ventricular aneurysm, severe cardiomyopathy, aortic or mitral mechanical heart valve, severe calcified aortic stenosis (valve area < 1.0 cm2), endocarditis, moderate to severe mitral stenosis, left atrial thrombus or any intracardiac mass or known paradoxical embolism of unrepaired PFO.
19. Unstable angina defined as rest angina with ECG changes that is not amenable to revascularization (patients should undergo planned coronary revascularization at least 30 days before randomization).
20. Any major surgery, major trauma, revascularization procedure or acute coronary syndrome within the past 1 month.
21. serum creatinine > 2.5 mg/dl or estimated GFR < 30 cc/min.
22. Major surgery planned within 3 months after enrollment.
23. Currently listed or being evaluated for major organ transplantation (i.e., heart, lung, liver and kidney).
24. Participation in other trials and may affect the results of this study.
25. Inability to understand and cooperate with research procedures or provide informed consent.
26. Endarterectomy, bypass or stent implantation performed on the proximal end of the occlusion vessel.

TABLE 3 | Periprocedural drug therapy.

Medication	Preprocedure	Intraprocedure	Postprocedure	Postdischarge
Heparin	None	Maintain ACT 250–300 s	None	None
Aspirin	300 mg p.o. q.d. (Begin 72 h before)	None	100 mg p.o. q.d. (Begin 24 h later)	100 mg p.o. q.d. for 360 days
Clopidogrel	300 mg p.o. q.d. (Begin 72 h before)	None	75 mg p.o. q.d. (Begin 24 h later)	75 mg p.o. q.d. for 360 days
Cilostazol (Clopidogrel resistance)	100 mg p.o. b.i.d. (begin 72 h before)	None	100 mg p.o. b.i.d. (Begin 24 h later)	100 mg p.o. b.i.d. for 360 days
Tirofiban	None	PRN	0.15 μg/kg/min for 24 h	None
Atorvastatin (or dose equivalent of another statin)	Total of 40/80 mg	None	40/80 mg p.o. q.d	40/80 mg p.o. q.d

privacy laws. Each center will be in charge of the personal data collected related to the study. Then each patient will be assigned an anonymous identification code. In each center, a responsible physician will registered the information of every enrolled patients on the internet-based data storage file. Each center has its own account and password, and each center can only see patient information uploaded by their own center when they access the web database; if a center research investigator wants to see information on all patients enrolled in their study, they need to request it from the Scientific Committee. All the data will be analyzed anonymously by a statistician.

Information of baseline including demographics, vascular risk factors (such as diabetes mellitus, arterial blood pressure, hyperlipidemia, cardiac disease, and smoking) and stroke symptoms [with the Questionnaire for Verifying Stroke-free Status (QVSS) (17), the modified Rankin Scale (mRS) (18)

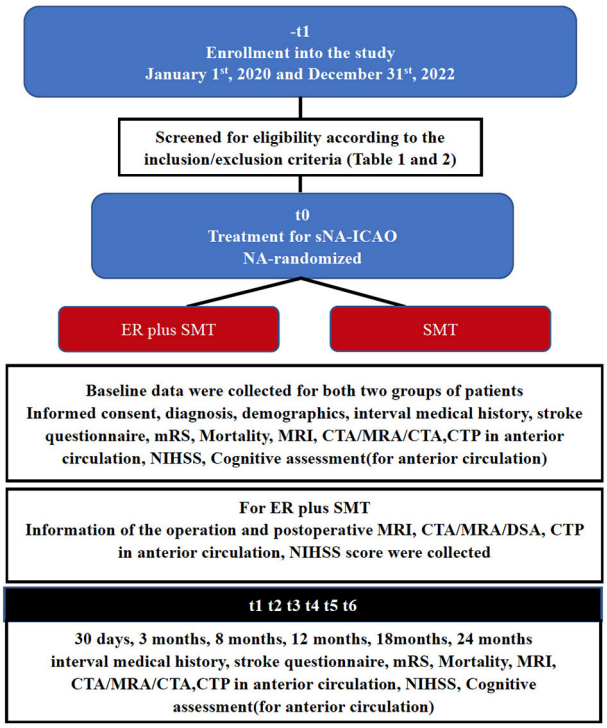

FIGURE 2 | Flowchart of the trial design.

and the National Institutes of Health Stroke Scale (NIHSS) (19)], including morphology occlusion stump, occlusion to recanalization, last symptom to recanalization and cognitive testing (in anterior circulation) were collected (**Figure 2**).

For patients with ICA or MCA M1 segment occlusion, Cognitive function assessment related to vascular cognitive status, is performed at baseline, 30 days, 3 months, 8 months, 12 months, 18 months, and 24 months. The assessment consists of five tests covering the following four domains of cognitive function: the word list learning test and the delayed recall test from the Chinese version of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) (20), executive function/processing speed (animal naming and letter fluency), and attention/working memory (digit span) (**Figure 2**).

Figure 2 illustrates the follow-up schedule. If the patient is unable to come to the hospital for a face-to-face follow-up visit, a telephone follow-up visit will be conducted if possible and will include a brief medication history, any ischemic events, daily functioning and changes in cognitive function.

Primary and Secondary Outcomes

In this trial, the primary outcome is any stroke from enrollment to 2 years of follow-up. The secondary outcomes are all-cause mortality, mRS score, NIHSS score and cognitive function from enrollment to 30 days, 3 months, 8 months, 12 months, 18months, and 2 years of follow-up. Stroke will be defined as rapidly developing clinical signs of focal disturbance of cerebral function lasting more than 24 h with no apparent cause other than that of vascular origin according to the World Health Organization (21). Outcome will be determined by an adjudication committee that is unaware of the trial design and grouping.

Major stroke is defined as the NIHSS score is $\geq$6 at least 30 days after the date of stroke onset, mild stroke is defined as deterioration in the NIHSS score is $\leq$4 points and bright spots appear on the brain DWI or as determined by the Stroke Adjudication Committee according to clinical data.

Statistical Analysis

Based on data from previous studies (6, 9), the 2-year incidence rates of ipsilateral ischemic stroke in ER plus SMT and SMT alone are approximately 10 and 20%, respectively. Assuming a two-sided significance level of 5%, a power of 80%, non-participating rate of 20% and dropout rate of 20%, the requirement for the ER plus SMT and SMT alone group was calculated to be 160 and 320 patients, respectively (1:2 allocation). Reviewing previous studies (8–13), we took the preoperative complication (arterial dissection, arterial perforation, thrombus translocation, subacute stent thrombosis, hemorrhage, and died) rate >15% as the termination criteria.

Prior to statistical analysis, the statistician will collate the data. If he finds any missing data, he will contact the responsible doctor and ask him to check the medical records of the patient visits and follow-up visits to clarify whether the missing information is in the data sheet. If the missing data cannot be obtained, we will conduct multiple imputation under a multivariate normal distribution to impute missing outcome data in the primary analysis of all outcomes, with a sensitivity analysis on complete cases only. Continuous variables are expressed as medians and interquartile ranges (IQRs) and as absolute numbers and percentages, while categorical variables are expressed as the means and standard deviations (SDs). Shapiro–Wilk test, histogram, and QQ chart were used to confirm normal distribution of data. We use chi-squared test, *t*-tests and Mann–Whitney *U*-test to compare categorical variables, continuous variables and scores, respectively. Using cox proportional regression models with 95% confidence intervals to test the risk of mortality or Ischemic events. Adjusted estimates of outcome (common odds ratio, odds ratio, and β) will be calculated by taking the following variables into account: age, baseline NIHSS and mRS score, baseline cognitive function, sex, medical history, ischemic stroke, duration from last neurologic event and occlusion site. For propensity score matching analysis, we will perform 1:1 matching based on the nearest-neighbor matching algorithm with a caliper width of 0.2 of the propensity score with age, baseline NIHSS and mRS score, baseline cognitive function, location of occlusion and medical history questionnaire. All statistical analyses will be performed with SPASS 25.0, and $P < 0.05$ will be considered significant.

The Responsibilities of the Scientific and Steering Committees

The responsibilities of the Scientific Committee is to supervise the publication and presentation of the final research results on the academic symposium, in consultation with the Steering

Committee. The Committee will make sure that all publications adhere to authorship guidelines. Members are Xuan Sun, and Miao Zhongrong.

The Steering Committee will be responsible for the planning and implementation of the registry. Specifically, they: approve the participating centers and the corresponding doctors in each center; perform quality control of the data; direct and propose amendments at any time to achieve the purpose of the study; analyze and revise the final results for submission to the congress and publication in a scientific papers. Members are Feng Gao; Xu Guo; Chao Wen; Hui-Jun Zhang.

DISCUSSION

Summary

The management of patients with sNA-ICAO, which is a unique subset with high morbidity and a high probability of recurrent serious ischemic events despite maximal medical therapy, has been clinically challenging. Some small-sample clinical studies have also discussed endovascular recanalization for sNA-ICAO; however, there is no evidence from multicenter large-sample trials. The aim of our present study is to evaluate the technical feasibility and safety of non-acute intracranial artery occlusion. We will perform subgroup analysis according to the angiographic classification of sNA-ICAO proposed by our previous studies (9, 13), stump morphology, duration from occlusion confirmed by imaging and clot characteristics evaluated by High Resolution MRI (optional examine).

Limitations

Non-randomized of the treatment arms is the main limitation of the present research. Clinical reasoning behind treatment choice may affect conclusions, but the extensive data collection of numerous potentially relevant factors will allow us to adjust for potential confounders. Comparative effectiveness trials such as this are valuable because both physicians and patients have a complex range of factors and decisions that affect their treatment options, which cannot be assessed in RCTs. Another limitation of the study design is that our present study population is limited to the Chinese patients which restrains generalizability of the results to other populations/ethnicities. For this limitation, we will perform our further studies which will include patients from other countries.

Strengths and Relevance

Our present study have several advantages except for non-randomization. Current studies on endovascular treatment of ICAS are mainly from a number of single-center, small-sample, single-arm retrospective analyses. First, our study is prospectively designed and will contain the largest sample size to date. Second, our study is a multicenter design across 15 provinces of the country, thus minimizing selection bias; finally, we will also compare the results of ER combined with SMT and SMT alone for sNA-ICAO. Importantly, we planned a long-term follow-up of 24 months, which will allow us to examine both short-term and long-term outcomes of patients.

ETHICS STATEMENT

We will follow the World Medical Association Declaration of Helsinki to collect data and all potential participants will be required to sign an informed consent form. Ethical permission was received from the Institutional Review Board of Beijing Tiantan Hospital (number: KY2020-114-02).

AUTHOR CONTRIBUTIONS

FG, XG, CWe, and HZ are on the Scientific Committee for the current project. XS and ZM are on the steering committee for the current project. HZ, XS, FG, XG, GX, YS, CWe, CWa, YW, YX, YJ, SZ, CL, DL, YL, and CX will provide patient information for the multicenter trial. HZ, XS, and FG wrote the draft. All authors were involved in the design of the protocol, revised the draft, and approved the final manuscript.

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Stress Hyperglycemia in Patients With Acute Ischemic Stroke Due to Large Vessel Occlusion Undergoing Mechanical Thrombectomy

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Stress hyperglycemia may impair outcomes in patients with acute ischemic stroke (AIS) undergoing mechanical thrombectomy (MT). The glucose-to-glycated hemoglobin ratio (GAR) was used to measure stress hyperglycemia. Data from our database of consecutive patients admitted to the Udine University Hospital with AIS who were treated with MT between January 2015 and December 2020 were retrospectively analyzed. We included 204 patients in the study and stratified them into four groups according to the quartiles of GAR (Q1–Q4). The higher the GAR index, the more severe the stress hyperglycemia was considered. Patients with more severe stress hyperglycemia showed a higher prevalence of 3-month poor outcome (Q1, 53.1%; Q2, 40.4%; Q3, 63.5%; Q4, 82.4%; $p = 0.001$), 3-month mortality (Q1, 14.3%; Q2, 11.5%; Q3, 15.4%; Q4, 31.4%; $p = 0.001$), and symptomatic intracranial hemorrhage (Q1, 2%; Q2, 7.7%; Q3, 7.7%; Q4, 25.4%; $p = 0.001$). After controlling for several confounders, severe stress hyperglycemia remained a significant predictor of 3-month poor outcome (OR 4.52, 95% CI 1.4–14.62, $p = 0.012$), 3-month mortality (OR 3.55, 95% CI 1.02–12.29, $p = 0.046$), and symptomatic intracranial hemorrhage (OR 6.89, 95% CI 1.87–25.36, $p = 0.004$). In summary, stress hyperglycemia, as measured by the GAR index, is associated with a detrimental effect in patients with AIS undergoing MT.

Keywords: stress hyperglycemia, GAR index, acute ischemic stroke, outcome, mechanical thrombectomy

INTRODUCTION

Mechanical thrombectomy (MT) is the "gold standard treatment" for patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO) (1). In contrast to randomized controlled trials that reported a prevalence of 3-month good outcomes after MT as high as 71% (2–6), lower rates of patients with functional independence, ranging between 34 and 39%, were reported by observational registries (7–9).

Glycemic status should be considered one of the most important modifiable predictors of poor outcomes in patients undergoing MT. Several mechanisms, such as alteration of the blood barrier permeability (10), exacerbation of the thromboinflammatory cascade (11), acidosis (12), and increased oxidative stress response (13), explain the poor outcome in AIS patients with

hyperglycemia. Hyperglycemia at admission has been associated with a decreased likelihood of good outcomes in patients with AIS undergoing MT (14–17). However, we recently demonstrated that persistent hyperglycemia—that is, hyperglycemia at admission and at 24 h post-admission—was a better predictor of poor outcome than baseline hyperglycemia in AIS subjects affected by LVO and treated with MT (18). Persistent hyperglycemia might impair outcomes as a marker of either diabetes mellitus or activation of the hypothalamic–pituitary–adrenal axis, that is, stress hyperglycemia. Although diabetes is a widely recognized predictor of stroke (19), little data are available on the possible detrimental effects of stress hyperglycemia in AIS patients undergoing recanalization therapy (20–22). In particular, only two recent Chinese studies reported that stress hyperglycemia was a strong predictor of poor clinical outcomes and mortality after MT (21, 22). To date, similar data in Caucasian patients are lacking.

Recently, the glucose-to-glycated hemoglobin (HbA1c) ratio (GAR) has been developed to assess stress hyperglycemia (23). In particular, Su et al. (23) performed a retrospective observational study to investigate if the acute elevation of plasma glucose among patients visiting the emergency department was associated with poor clinical outcomes. In order to distinguish between the stress-related hyperglycemia, due to acute illness, and the patient's premorbid glycemic condition, the authors introduced a new index, the GAR. The GAR index was calculated as the plasma glucose concentration divided by HbA1c (23). In contrast to HbA1c, which identifies the baseline average glucose status over the past 3 months, the GAR index measures the presence of acute elevation in plasma glucose, that is, stress hyperglycemia, in comparison with background plasma glucose levels.

In the present study, we investigated the role of stress hyperglycemia, measured by the GAR index, as a predictor of poor outcome in AIS patients treated with MT.

MATERIALS AND METHODS

Study Participants

Data from our database of consecutive patients admitted to the Udine University Hospital with AIS due to LVO who were treated with MT between January 2015 and December 2020 were analyzed. The patients were followed up for 3 months. The eligibility criteria for MT were as follows: (i) presence of LVO in the anterior or posterior circulation as revealed by CT angiography (CTA), (ii) onset of symptoms within 6 h, and (iii) Alberta Stroke Program Early CT Score (ASPECTS) >6 on a direct CT scan (24). In contrast, patients with a life expectancy of <6 months, severe medical conditions with signs of organ failure, and platelet count <55,000/mmc are not treated with MT at our center. According to the international guidelines, alteplase was used to treat AIS patients showing onset of symptoms within 4.5 h (1). A follow-up CT scan was performed approximately 24 h after recanalization therapy or sooner if clinical deterioration was observed. Written informed consent was obtained from all patients or their representatives. The study conformed to the Declaration of Helsinki of the World Medical Association and was approved by the local ethics committee, *Comitato Etico Unico Regionale* (Ref. No. CEUR-2020-Os-173).

Data Collection

We collected the following information: age, sex, laboratory findings, systolic blood pressure at admission, previous pharmacological treatment, and vascular risk factors, including previous transient ischemic attack or stroke, cardiovascular disease, atrial fibrillation, hypertension, diabetes mellitus, hypercholesterolemia, and active tobacco use. A history of diabetes mellitus that had been confirmed in medical records and/or the use of insulin/oral hypoglycemic agents were considered for defining diabetes. The ASPECTS score was used for grading early ischemic changes within the middle cerebral artery (MCA) territory on a native CT scan (24).

Clinical Assessment

According to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria, ischemic strokes are classified into different subtypes based on etiology (25). Stroke severity was quantified at admission and discharge using the National Institutes of Health Stroke Scale (NIHSS) score. Major neurological improvement was defined as an improvement of ≥8 points on the NIHSS score from baseline or an NIHSS score of 0 or 1 at discharge. The degree of previous functional disability was calculated at admission, based on pre-stroke disability, and 3 months after stroke using the modified Rankin Scale (mRS). The mRS score after discharge was recorded during the patients' routine clinical visits or through telephone interviews with patients or their immediate caregivers. We dichotomized mRS into favorable outcomes (0–2) and poor outcomes (3–6). The European Cooperative Acute Stroke Study (ECASS) definition of parenchymal hematoma types 1 and 2 was adopted to identify intracranial hemorrhage (ICH) (26), whereas the presence of symptomatic intracranial hemorrhage (SICH) was based on the ECASS III protocol (27).

Thrombectomy Procedure

The following information was collected: site of the cerebral artery occlusion, type of device used for MT procedure, presence or absence of secondary embolization, time from onset of symptoms to MT, time from hospital arrival to groin puncture (door-to-groin time), procedure duration, and successful recanalization rate, defined as thrombolysis in cerebral infarction (TICI) score of 2b−3. In addition, if patients received alteplase; we collected information on the time from onset of symptoms and hospital arrival to alteplase administration (door-to-needle time).

Assessment of Stress Hyperglycemia

For laboratory tests, including fasting plasma glucose and HbA1c, venous blood samples were drawn within 24 h after hospitalization, during the morning hours (range: 06:00–08:00) after an overnight fast (at least 12 h). Stress hyperglycemia was estimated using the GAR index. The GAR index was calculated as fasting plasma glucose (mg/dl)/HbA1c (%). We stratified patients into four groups according to quartiles of GAR (Q1–Q4) for

further comparisons. The higher the GAR index, the more severe the stress hyperglycemia was considered.

Outcome Measures

The following endpoints were analyzed: 3-month poor outcome, no major neurological improvement at discharge, 3-month all-cause mortality, in-hospital all-cause mortality, presence of SICH, and presence of ICH. All outcome measures were collected as part of routine clinical practice in patients affected by cerebrovascular events.

Statistical Analysis

Data are displayed in tables as mean and standard deviation unless otherwise specified.

Statistical comparisons were performed using the chi-square test or Fisher's exact test, when appropriate, for categorical variables. One-way analysis of variance for normally distributed continuous variables and the Kruskal–Wallis test for non-normally distributed continuous variables and ordinal variables were used. The Bonferroni–Dunn *post-hoc* test was used for *post-hoc* analysis. The Kolmogorov–Smirnov test with Lilliefors significant correction was performed to test the normality of the variables.

Multivariable logistic regression was performed to confirm the role of stress hyperglycemia, represented by GAR quartiles, as independent predictors of outcome in AIS patients undergoing MT. We used the lowest GAR quartile as the reference category. The regression model was adjusted for age, history of diabetes, ASPECTS score, baseline NIHSS score, pre-stroke mRS, time from symptom onset to MT, door-to-groin time, and procedure duration. We decided to add systolic blood pressure to other confounders in the analysis to evaluate the association between stress hyperglycemia and hemorrhagic transformation (i.e., SICH, ICH).

All probability values were two-tailed. Statistical significance was set at $p < 0.05$. Statistical analysis was carried out using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline Characteristics

During the study period, 240 patients were treated with MT for AIS due to LVO. Of these, 36 patients were excluded because

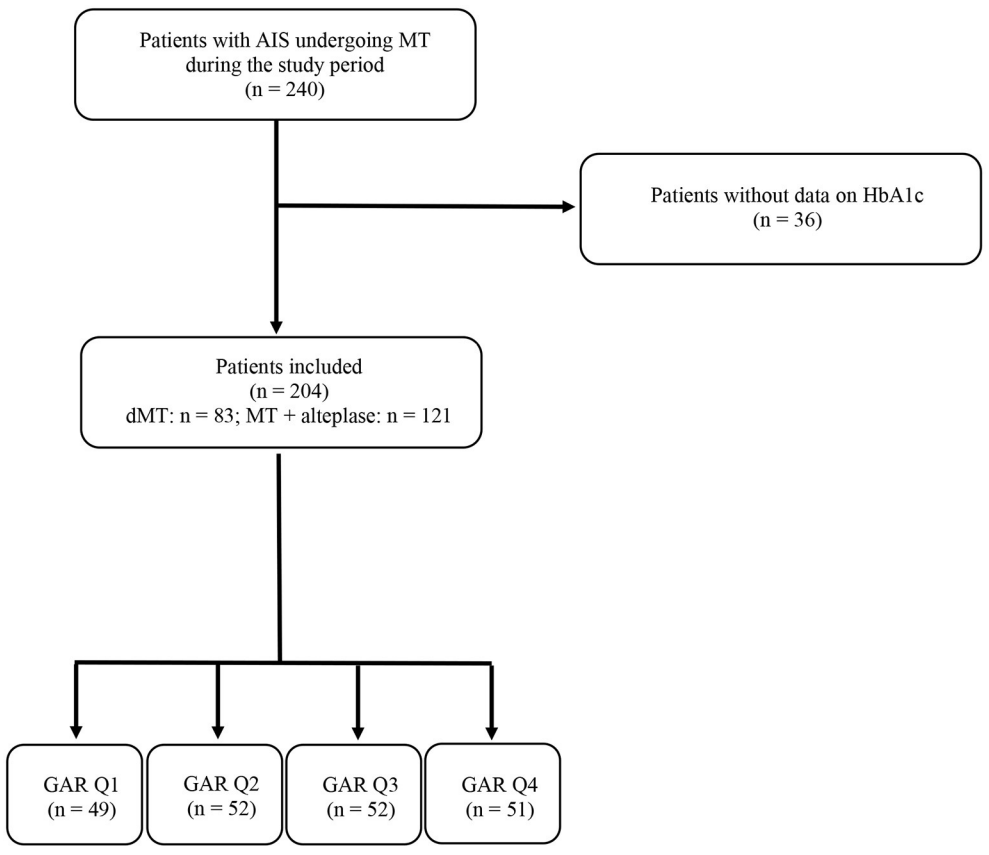

FIGURE 1 | Flow diagram of the study. AIS, acute ischemic stroke; MT, mechanical thrombectomy; HbA1c, glycated hemoglobin; dMT, direct mechanical thrombectomy; GAR Q1, first glucose-to-glycated hemoglobin ratio quartile; GAR Q2, second glucose-to-glycated hemoglobin ratio quartile; GAR Q3, third glucose-to-glycated hemoglobin ratio quartile; GAR Q4, fourth glucose-to-glycated hemoglobin ratio quartile.

TABLE 1 | General characteristics of the subjects according to the GAR quartiles.

	GAR Q1 (*n* = 49)	GAR Q2 (*n* = 52)	GAR Q3 (*n* = 52)	GAR Q4 (*n* = 51)	*p*
Demographic data					
Age, years*	74 (67.5–81.5)	73.5 (64–81.5)	75 (67.2–80.7)	75 (69–81)	0.953
Males, *n* (%)	24 (49)	23 (44.2)	29 (55.8)	24 (47.1)	0.681
Laboratory findings					
Hb, g/dl	12.4 ± 1.5	12.4 ± 1.5	12.8 ± 1.9	12.9 ± 1.8	0.268
Platelets, 10^3/mmc*	204 (160.5–255.5)	191 (151.1–233.2)	175 (141.1–225)	189 (151–238)	0.190
aPTT ratio*	0.97 (0.89–1.09)	0.95 (0.87–1.02)	0.94 (0.85–1.04)	0.92 (0.84–1.02)	0.309
INR*	1.1 (1.03–1.17)	1.1 (1.02–1.2)	1.09 (1.03–1.2)	1.1 (1.02–1.22)	0.872
Creatinine, mg/dl*	0.84 (0.74–1.04)	0.85 (0.77–1.04)	0.92 (0.75–1.08)	0.99 (0.78–1.14)	0.321
C-reactive protein, mg/l*	4.83 (2.39–14.49)	8.25 (3.49–14.42)	6.56 (2.78–15.25)	7.41 (3.12–14.39)	0.816
Protein, g/dl*	5.9 (5.5–6.4)	6 (5.7–6.5)	6 (5.6–6.6)	6.1 (5.7–6.6)	0.727
Fasting plasma glucose, mg/dl*	86 (82–90.5)	98.5 (91.5–106)	110.5 (106–121)	156 (138–187)	0.001
HbA1c values, %*	5.8 (5.6–6.1)	5.6 (5.4–5.9)	5.7 (5.2–6.1)	5.9 (5.6–6.5)	0.001
GAR index*	15.1 (13.6–15.7)	17.6 (16.9–18.1)	19.8 (18.9–20.8)	25.4 (23.1–28.4)	0.001
Total cholesterol, mg/dl*	155 (134–180.5)	167 (147–193)	175 (149–191)	162 (139–187.5)	0.210
HDL cholesterol, mg/dl*	47 (38.5–62)	51 (41–61)	51 (45–61)	51 (39–59)	0.379
LDL cholesterol, mg/dl	90.6 ± 30.8	96 ± 29	93.9 ± 34.2	96.4 ± 39.2	0.774
Triglycerides, mg/dl*	87 (63.5–130.5)	85 (64–105)	93 (78.5–131.5)	84 (62.2–143.7)	0.282
Blood pressure					
Systolic blood pressure, mmHg	143.2 ± 25.7	150.8 ± 20.8	156.4 ± 20	155.4 ± 20.6	0.031
Antithrombotic treatment at admission					
Antiplatelets, *n* (%)	18 (36.7)	10 (19.2)	12 (23.1)	14 (27.5)	0.223
Anticoagulants, *n* (%)	6 (12.2)	10 (19.2)	10 (19.2)	11 (21.6)	0.652
Antidiabetic drugs at admission					
Oral hypoglycemics, *n* (%)	3 (6.1)	2 (3.8)	6 (11.5)	5 (9.8)	0.457
Insulin, *n* (%)	0 (0)	0 (0)	0 (0)	1 (2)	0.389
Vascular risk factors					
Previous transient ischemic attack/stroke, *n* (%)	7 (14.3)	4 (7.7)	1 (1.9)	8 (15.7)	0.071
Cardiovascular disease, *n* (%)	11 (22.4)	6 (11.5)	6 (11.5)	8 (15.7)	0.378
Atrial fibrillation, *n* (%)	16 (32.7)	14 (26.9)	12 (23.1)	14 (27.5)	0.760
Hypertension, *n* (%)	33 (67.3)	35 (67.3)	33 (63.5)	44 (86.3)	0.048
Diabetes mellitus, *n* (%)	4 (8.2)	2 (3.8)	7 (13.5)	8 (15.7)	0.191
Hypercholesterolemia, *n* (%)	12 (24.5)	12 (23.1)	15 (28.8)	12 (23.5)	0.901
Current smoking, *n* (%)	6 (12.2)	6 (11.5)	9 (17.3)	8 (15.7)	0.811
Median baseline ASPECTS score (range)	10 (8–10)	10 (7–10)	10 (7–10)	10 (7–10)	0.280
Stroke subtypes based on TOAST classification					0.691
Large arterial atherosclerosis, *n* (%)	4 (8.2)	9 (17.3)	6 (11.5)	5 (9.8)	
Cardioembolism, *n* (%)	28 (57.1)	27 (51.9)	28 (53.8)	27 (52.9)	
Other determined etiology, *n* (%)	0 (0)	3 (5.8)	2 (3.8)	1 (2)	
Undetermined etiology, *n* (%)	17 (34.7)	13 (25)	16 (30.8)	18 (35.3)	
Baseline clinical characteristics					
Median NIHSS score at admission (IQR)	15 (11.5–20)	17 (12–19)	17 (16–20)	17 (14–21)	0.176
Median NIHSS score at discharge (IQR)	2 (0–9)	2 (0.5–11.5)	5 (1–10)	12.5 (3–17)	0.001
Pre-stroke mRS 0–2, *n* (%)	43 (87.8)	50 (96.2)	49 (94.2)	48 (94.1)	0.371

GAR Q1, first glucose-to-glycated hemoglobin ratio quartile; GAR Q2, second glucose-to-glycated hemoglobin ratio quartile; GAR Q3, third glucose-to-glycated hemoglobin ratio quartile; GAR Q4, fourth glucose-to-glycated hemoglobin ratio quartile; Hb, hemoglobin; aPTT, activated partial thromboplastin time; INR, international normalized ratio; HbA1c, glycated hemoglobin; GAR, glucose-to-glycated hemoglobin ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ASPECTS, Alberta Stroke Program Early CT Score; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

Data are presented as mean and standard deviation for normally distributed continuous variables. Non-normally distributed continuous variables are displayed as median and interquartile range and are identified by an asterisk (*).

there were no data on HbA1c. The remaining 204 patients with AIS were included in the study. Direct MT was performed in 83 patients (40.3%), while 121 patients (59.3%) received alteplase before MT. The number of patients included in each GAR quartile was as follows: 49 patients (24%) in the first quartile, 52 patients (25.5%) in the second and third quartiles, and 51 patients (25%) in the fourth quartile. These data are summarized in the flow diagram of the study (**Figure 1**).

The general characteristics of the enrolled subjects, distinguished by GAR quartiles, are presented in **Table 1**. We did not observe any differences in age or sex between the four groups. Hypertension was the only vascular risk factor that was significantly more common among patients in the highest quartile. In addition, patients in the fourth quartile had higher fasting glucose levels and HbA1c values than those in the other three quartiles. For patients in the first quartile, baseline systolic blood pressure values were significantly higher among subjects in the third quartile. Stroke etiology and neurological impairment at admission did not differ between the four quartiles. At discharge, patients in the fourth quartile showed significantly higher NIHSS scores than those in the other three quartiles. Almost all patients treated with MT in our center had a pre-stroke mRS score of $\leq$2.

Table 2 summarizes the information on the thrombectomy procedure in the four quartiles. As expected, MCA was the most common site of LVO in all four quartiles. We did not detect any difference in the type of device used for MT and the number of patients receiving alteplase before MT. Similarly, the median time from onset of symptoms and hospital arrival to MT was not significantly different among the four quartiles. A trend toward a decreased prevalence of successful recanalization was observed in patients with more severe stress hyperglycemia.

Association of Stress Hyperglycemia With Clinical Outcomes in Univariate Analysis

Figures 2–4 report the rates of 3-month poor outcome, 3-month mortality, and SICH according to GAR quartiles. The prevalence of no major neurological improvement (Q1, 23.4%; Q2, 26.5%; Q3, 19.1%; Q4 69.2%; $p = 0.001$), in-hospital mortality (Q1, 4.1%; Q2, 5.8%; Q3, 9.6%; Q4, 21.6%; $p = 0.02$), and ICH (Q1, 8.2%; Q2, 17.3%; Q3, 32.7%; Q4, 45.1%; $p = 0.001$) were significantly different among the four quartiles.

Association of Stress Hyperglycemia With Clinical Outcomes in Multivariate Analysis

All outcome measures were significantly associated with severe stress hyperglycemia, even after controlling for confounders (**Table 3**). Independent predictors, other than the highest GAR quartile, were the following: ASPECTS score (OR 0.46, 95% CI 0.24–0.88, $p = 0.02$), NIHSS score at admission (OR 1.18, 95% CI 1.08–1.28, $p = 0.001$), pre-stroke mRS (OR 3.29, 95% CI 1.34–8.07, $p = 0.009$), door-to-groin time (OR 1.01, 95% CI 1.00–1.02, $p = 0.048$), and procedure duration (OR 1.01, 95% CI 1.00–1.02, $p = 0.035$) for 3-month poor outcome;

TABLE 2 | Information on thrombectomy procedure according to the GAR quartiles.

	GAR Q1 ($n = 49$)	GAR Q2 ($n = 52$)	GAR Q3 ($n = 52$)	GAR Q4 ($n = 51$)	*p*
Site of LVO					0.425
MCA, *n* (%)	39 (79.6)	43 (82.7)	40 (76.9)	39 (76.5)	
Tandem, *n* (%)	4 (8.2)	8 (15.4)	9 (17.3)	8 (15.7)	
Vertebrobasilar, *n* (%)	6 (12.2)	1 (1.9)	3 (5.8)	4 (7.8)	
Type of device use for MT					0.444
Thromboaspiration, *n* (%)	26 (53.1)	23 (44.2)	22 (42.3)	22 (43.1)	
Stent retriever, *n* (%)	2 (4.1)	1 (1.9)	2 (3.8)	5 (9.8)	
Thromboaspiration plus stent retriever, *n* (%)	15 (30.6)	19 (36.5)	24 (46.2)	20 (39.2)	
Permanent stenting, *n* (%)	6 (12.2)	9 (17.3)	4 (7.7)	4 (7.8)	
Other information on recanalization therapy					
Alteplase use prior to MT, *n* (%)	31 (63.3)	28 (53.8)	33 (63.5)	29 (56.9)	0.692
Time from onset of symptoms to alteplase, min*	127.5 (97–166.2)	125 (107.5–180)	152.5 (110.2–180)	151.5 (100–166.2)	0.604
Door-to-needle time, min*	53.5 (42–69.7)	50 (40–67.5)	54 (35–73.7)	64 (42.5–86.5)	0.462
Time from onset of symptoms to MT, min*	205 (165–290)	212.5 (186.2–251.2)	210 (146.2–255)	210 (165–265)	0.844
Door-to-groin time, min*	116 (103–165)	118 (86.2–152.7)	112 (75–143.7)	122 (85–155)	0.489
Procedure length, min*	70 (40–94)	62.5 (46.2–95)	60 (46.2–93.7)	70 (45–100)	0.734
Secondary embolization, *n* (%)	1 (2)	5 (9.6)	4 (7.7)	2 (3.9)	0.351
TICI 2b−3 after MT, n (%)	41 (85.4)	43 (91.5)	40 (88.9)	39 (79.6)	0.360

GAR Q1, first glucose-to-glycated hemoglobin ratio quartile; GAR Q2, second glucose-to-glycated hemoglobin ratio quartile; GAR Q3, third glucose-to-glycated hemoglobin ratio quartile; GAR Q4, fourth glucose-to-glycated hemoglobin ratio quartile; LVO, large vessel occlusion; MCA, middle cerebral artery; MT, mechanical thrombectomy; TICI, Thrombolysis in Cerebral Infarction.

Data are presented as mean and standard deviation for normally distributed continuous variables. Non-normally distributed continuous variables are displayed as median and interquartile range and are identified by an asterisk (*).

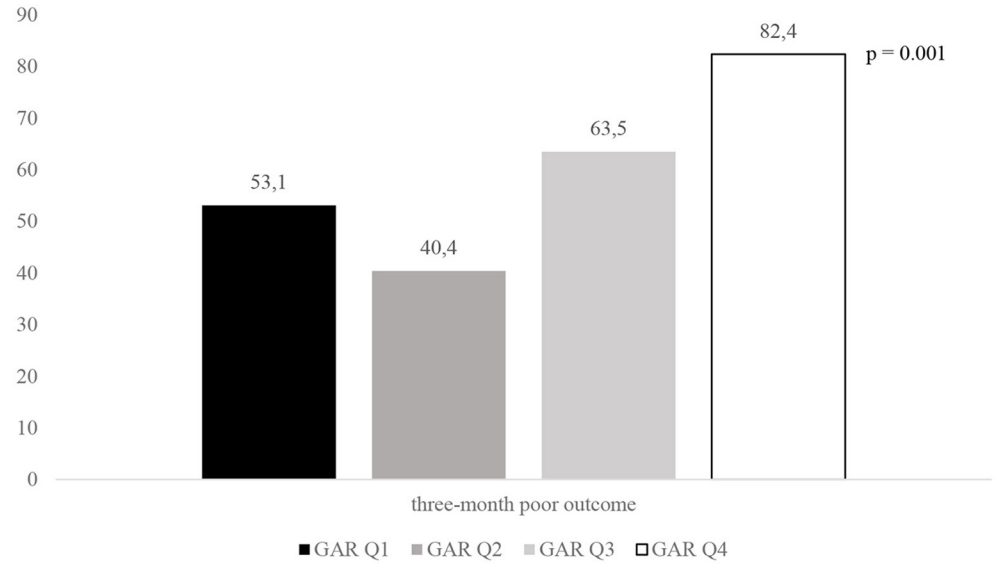

FIGURE 2 | Rates of 3-month poor outcome according to GAR quartile. GAR Q1, first glucose-to-glycated hemoglobin ratio quartile; GAR Q2, second glucose-to-glycated hemoglobin ratio quartile; GAR Q3, third glucose-to-glycated hemoglobin ratio quartile; GAR Q4, fourth glucose-to-glycated hemoglobin ratio quartile.

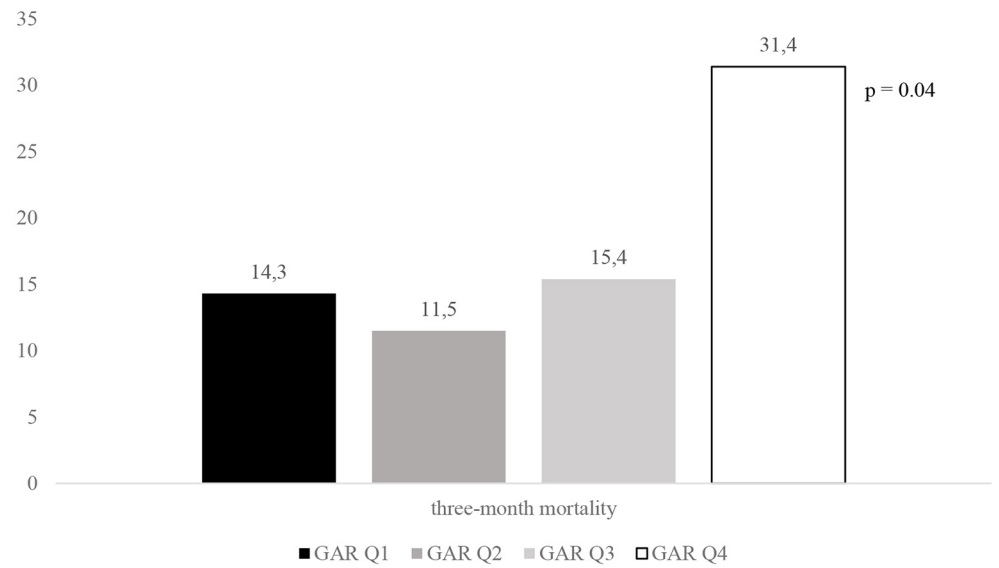

FIGURE 3 | Rates of 3-month mortality according to GAR quartile. GAR Q1, first glucose-to-glycated hemoglobin ratio quartile; GAR Q2, second glucose-to-glycated hemoglobin ratio quartile; GAR Q3, third glucose-to-glycated hemoglobin ratio quartile; GAR Q4, fourth glucose-to-glycated hemoglobin ratio quartile.

procedure duration (OR 1.02, 95% CI 1.01–1.03, $p = 0.002$) for no major neurological improvement; ASPECTS score (OR 0.56, 95% CI 0.31–0.98, $p = 0.045$) and pre-stroke mRS (OR 1.71, 95% CI 1.19–2.44, $p = 0.003$) for 3-month mortality; NIHSS score at admission (OR 1.1, 95% CI 1.01–1.2, $p = 0.024$) and systolic blood pressure (OR 1.03, 95% CI 1.01–1.05, $p = 0.01$) for ICH. In contrast, in-hospital mortality and SICH were not associated with variables other than the fourth quartile.

DISCUSSION

We demonstrated that independently of ethnicity, stress hyperglycemia is an independent predictor of worse outcomes not only in Chinese patients but also in Caucasian patients with AIS undergoing MT (21, 22).

The association between glucose level at admission and worse outcomes after MT in AIS patients is well known (14–17). In 2016, Kim et al. (14) reported that patients with

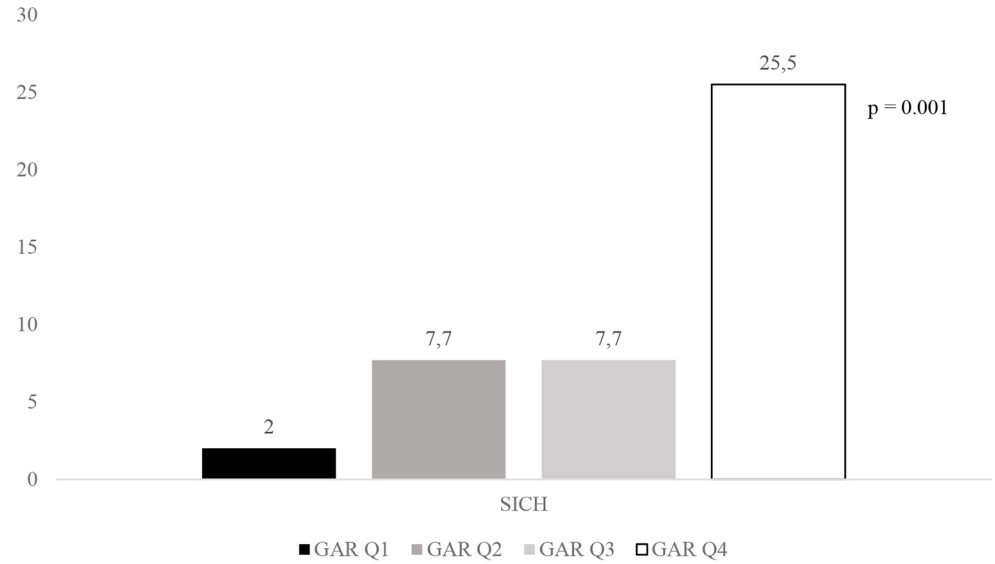

FIGURE 4 | Rates of SICH according to GAR quartile. SICH, symptomatic intracranial hemorrhage; GAR Q1, first glucose-to-glycated hemoglobin ratio quartile; GAR Q2, second glucose-to-glycated hemoglobin ratio quartile; GAR Q3, third glucose-to-glycated hemoglobin ratio quartile; GAR Q4, fourth glucose-to-glycated hemoglobin ratio quartile.

TABLE 3 | Logistic regression model: adjusted ORs (95% CIs) of the GAR quartiles in relation to the respective outcomes.

	GAR Q1	GAR Q2	GAR Q3	GAR Q4
Three-month poor outcome†	1	0.43 (0.15–1.22) $p = 0.114$	1.32 (0.47–3.71) $p = 0.6$	4.52 (1.4–14.62) $p = 0.012$
No major neurological improvement at discharge†	1	1.46 (0.51–4.23) $p = 0.481$	0.76 (0.24–2.37) $p = 0.635$	9.11 (2.94–28.23) $p = 0.001$
Three-month mortality†	1	1.05 (0.27–4.16) $p = 0.942$	1.59 (0.43–5.94) $p = 0.488$	3.55 (1.02–12.29) $p = 0.046$
In-hospital mortality†	1	1.52 (0.24–9.67) $p = 0.658$	2.79 (0.49–15.69) $p = 0.245$	6.79 (1.38–33.37) $p = 0.018$
Presence of SICH‡	1	3.74 (0.34–40.73) $p = 0.278$	3.86 (0.4–37.2) $p = 0.242$	11.22 (1.27–99.24) $p = 0.03$
Presence of ICH‡	1	1.95 (0.46–8.35) $p = 0.366$	2.89 (0.76–11.02) $p = 0.119$	6.89 (1.87–25.36) $p = 0.004$

GAR Q1, first glucose-to-glycated hemoglobin ratio quartile; GAR Q2, second glucose-to-glycated hemoglobin ratio quartile; GAR Q3, third glucose-to-glycated hemoglobin ratio quartile; GAR Q4, fourth glucose-to-glycated hemoglobin ratio quartile; SICH, symptomatic intracranial hemorrhage; ICH, intracranial hemorrhage; ASPECTS, Alberta Stroke Program Early CT Score; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; OR, odds ratio. †Adjusted for age, history of diabetes, ASPECTS, baseline NIHSS score, pre-stroke mRS, time from symptom onset to MT, door-to-groin time, and procedure duration. ‡Adjusted for age, history of diabetes, ASPECTS, baseline NIHSS score, pre-stroke mRS, time from symptom onset to MT, door-to-groin time, procedure duration, and systolic blood pressure.

hyperglycemia (>140 g/dl) exhibited an impaired outcome more frequently at 3 months than patients without hyperglycemia. These data were later reported by other authors (15–17). Since hyperglycemia in AIS represents a dynamic condition, some studies have investigated the contribution of the dynamic patterns of hyperglycemia to stroke outcomes among patients receiving alteplase. These trials revealed that, in addition to a single glucose measurement, the relative blood glucose changes should be considered in the prediction of stroke outcomes (28–30). This is true not only for AIS patients receiving alteplase but also for those subjects with LVO undergoing MT. Indeed, we previously reported that poor functional outcome, mortality, and hemorrhagic transformation after endovascular treatment were significantly associated with the presence of persistent hyperglycemia—that is, hyperglycemia at baseline *plus* at 24 h (18). Although our study provided new insights into the role of impaired glucose metabolism as a predictor of outcome in AIS patients undergoing MT, we were not able to discern between the detrimental effects due to the presence of underlying diabetes and those associated with stress hyperglycemia.

While diabetes is a recognized risk factor for cerebrovascular diseases (19), the consequences of stress hyperglycemia are not well-established. The latter is usually defined as spontaneously resolving hyperglycemia after acute illness dissipation (31). Stress hyperglycemia is mediated by the hypothalamic–pituitary–adrenal axis, the sympatho-adrenal system, and pro-inflammatory cytokines that cause a stress response with excessive gluconeogenesis, glycogenolysis, and insulin resistance (32). Although several studies have reported that stress hyperglycemia increases the risk of poor outcomes in AIS patients (33–36), very few studies have investigated the

impact of stress hyperglycemia in stroke patients treated with recanalization therapy (20–22).

The GAR index has been used to quantify stress hyperglycemia. A study by Su et al. (23), which enrolled patients with plasma glucose concentrations >500 mg/dl, reported that GAR independently predicted 90-day mortality, intensive care unit (ICU) admission, and use of mechanical ventilation. Another study showed that the odds of stroke recurrence and all-cause death were significantly increased in non-diabetic patients affected by stress hyperglycemia, as estimated by the GAR index (37). Recently, we demonstrated an independent association between stress hyperglycemia and impaired clinical outcomes in AIS patients undergoing alteplase (20).

To date, only two Chinese studies have investigated the role of stress hyperglycemia as a predictor of poor outcomes in AIS patients with LVO undergoing MT (21, 22). In particular, Wang et al. (21) included 321 patients with ischemic stroke who were treated with MT. They reported that the incidence of 3-month mortality was significantly higher in patients affected by stress hyperglycemia than in those with normoglycemia (21). In a smaller study by Chen et al. (22), which included 160 consecutive AIS patients treated with MT, increased values of stress hyperglycemia represented an independent predictor of poor outcome, defined as a 3-month mRS score of 3–6, also after controlling for multiple potential confounders. In our sample of Caucasian patients, the presence of stress hyperglycemia was independently associated with all outcome measures. In particular, despite the endovascular treatment, a very large proportion of patients with more severe stress hyperglycemia, that is, more than 80% of them, were functionally dependent/dead 3 months after the stroke, and they showed a mortality rate as high as 31.4% at follow-up, and more than a quarter of them were affected by symptomatic hemorrhagic transformation. The detrimental effect of stress hyperglycemia was also confirmed after controlling for all the other variables that could impair outcomes in AIS patients treated with recanalization therapy.

The mechanisms underlying the association between stress hyperglycemia and poor clinical outcomes in stroke patients undergoing MT are incompletely understood. Several hypotheses have been proposed: (1) hyperglycemia might directly cause toxic damage to the ischemic brain due to accumulation of lactate and intracellular acidosis (38); (2) stress-induced inflammatory response may increase circulating free fatty acids in patients with acute illness, thus impairing endothelium-dependent vasodilation (39) and promoting intracellular calcium overload (40); and (3) stress hyperglycemia may lead to reperfusion injury due to increased oxidative stress and inflammation (41).

Our results suggest that stress hyperglycemia should be promptly diagnosed and carefully treated in AIS patients with LVO undergoing MT. However, there is no universally accepted insulin regimen for glycemic control in critically ill patients. In these subjects, the aim of the treatment should be to limit fluctuations in blood glucose levels. The ideal protocol should quickly achieve and maintain the target blood glucose levels to prevent hyperglycemia but also lead to a minimal incidence of hypoglycemia. The SHINE trial, randomizing AIS patients to receive continuous intravenous insulin (intensive treatment group) or subcutaneous insulin on a sliding scale (standard treatment group), reported similar rates of favorable outcomes between the two groups. However, severe hypoglycemic events occurred more frequently in the intensive treatment group (42). The reason why the effects of stress hyperglycemia on the outcome are not influenced by the type of treatment, whether aggressive or standard insulin treatment, remains a puzzle. It is possible that, in the aggressive treatment, the greater benefit of damage produced by hyperglycemia is counterbalanced by the presence of more episodes of hypoglycemia. On the contrary, the standard insulin treatment, although obtaining the correction of hyperglycemia in a longer time interval, is likely less capable of causing hypoglycemic peaks.

Our patients undergoing MT were significantly older than the ones enrolled in previous randomized trials on MT for AIS (43). It probably reflects the fact that the population of Italy is getting older every year, becoming the oldest population in the world. This is particularly true for the Friuli Venezia Giulia, where the city of Udine is located, that represents one of the *oldest* regions in Italy. Although old age is associated with higher mortality and increased disability after AIS (44), we are confident that this risk factor did not affect our results on stress hyperglycemia and poor outcome. In fact, the median age did not differ between the four groups and, moreover, the multivariate analysis was controlled including age as a possible confounding factor.

Our study had several limitations. Since this was a retrospective observational study, the cause–effect relationship between stress hyperglycemia and outcome should be considered speculative. The retrospective nature of the study and the quartile-based analysis might have affected the adequate control for confounding variables. Finally, the relatively small sample size may have limited the statistical power; thus, differences between patients with mild-to-moderate hyperglycemia and those normoglycemic could not be detected.

In conclusion, stress hyperglycemia, as measured by the GAR index, seems to be associated with worse outcomes in AIS patients undergoing MT. In particular, the odds of disability, mortality, and hemorrhagic complications were significantly increased in patients with more severe stress hyperglycemia than in those with normoglycemia. Further studies with larger sample sizes are needed to confirm these preliminary results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Unico Regionale (Ref. No. CEUR-2020-Os-173). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GM and SP contributed to conceptualization and methodology. SP and SL contributed software. SL, GG, and MV contributed to validation. SP, SL, MS, CS, and AS contributed to the investigation. SP, SL, CS, and AS contributed resources. GM contributed to formal analysis and data curation, writing—original draft preparation, and writing—review and editing. GG contributed to visualization. MV contributed to supervision.

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BRIEF RESEARCH REPORT
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Endovascular Treatment for Acute Stroke Patients With a Pre-stroke Disability: An International Survey

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Background: It is unclear what factors clinicians consider when deciding about endovascular thrombectomy (EVT) in acute ischemic stroke patients with a pre-existing disability. We aimed to explore international practice patterns and preferences for EVT in patients with a pre-stroke disability, defined as a modified Rankin score (mRS) $\geq$ 2.

Methods: Electronic survey link was sent to principal investigators of five major EVT trials and members of a professional interventional neurology society.

Results: Of the 81 survey-responding clinicians, 57% were neuro-interventionalists and 33% were non-interventional stroke clinicians. Overall, 64.2% would never or almost never consider EVT for a patient with pre-stroke mRS of 4-5, and 49.3% would always or almost always offer EVT for a patient with pre-stroke mRS 2-3. Perceived benefit of EVT (89%) and severity of baseline disability (83.5%) were identified as the most important clinician-level and patient-level factors that influence EVT decisions in these patients.

Conclusion: In this survey of 80 respondents, we found that EVT practice for patients with pre-stroke disability across the world is heterogenous and depends upon patient characteristics. Individual clinician opinions substantially alter EVT decisions in pre-stroke disabled patients.

Keywords: ischemic stroke, endovascular treatment, acute stroke, treatment, survey, disability

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INTRODUCTION

The American Heart Association/American Stroke Association national practice guidelines for management of acute ischemic stroke only recommend offering endovascular thrombectomy (EVT) to patients with an acute ischemic stroke involving a large anterior cerebral vessel occlusion without a pre-stroke disability, defined as pre-stroke modified Rankin Score (mRS) of 0 or 1 (1). However, about a third of acute ischemic stroke patients are disabled at pre-stroke baseline (2, 3). Small, observational studies have shown that: (1) almost one in three patients undergoing EVT in routine clinical practice has a baseline pre-stroke disability, and (2) when treated with EVT, patients with pre-stroke disability have similar odds of retaining their baseline function as do patients without pre-stroke disability (4–6).

To better understand current EVT care approaches for pre-stroke disabled patients without guideline recommendations, it is important to study individual clinician and institutional level practice and preferences regarding EVT in patients with pre-stroke disability. We conducted a survey of international experts in EVT and practitioners of interventional neurology to understand how EVT decisions are made in routine clinical practice for patients with pre-stroke disability. Here, we describe factors influencing physician decisions when considering EVT for patients with pre-existing disability, including the impact of level and type of disability, additional patient characteristics, and institutional protocols informing EVT treatment decisions.

MATERIALS AND METHODS

Survey Design

A 20-item survey was developed by the authors based on factors most frequently cited in prior literature as influential in the EVT decision-making process. A pilot version was completed by 24 physicians at two institutions. Feedback from respondents was used to improve survey readability and accuracy. The final survey questionnaire in its entirety is provided in the **Supplementary Material**. The survey had inbuilt logic where participants could proceed with answering follow-up questions relevant to and dependent on their answers to a prior question. Participants were first asked if they would ever consider EVT in patients with pre-stroke mRS 2 and pre-stroke mRS 3. If they answered no, their responses for pre-stroke mRS 4-5 were automatically also handled as no. If they answered yes to either, they were asked to further rate the degree of their likelihood, on a 6-level Likert scale, of offering EVT to patients with pre-stroke mRS of 2-3 and patients with pre-stroke mRS of 4-5. Similarly, specifics of institutional patient selection protocols were only asked if a participant responded yes to having an institutional protocol on EVT practice. In addition, respondents were asked to identify among 14 general, patient-specific, and stroke-specific features those that were most important to their decision-making regarding offering EVT to individual patients with pre-stroke disability. As both benefits or harms of EVT are yet unknown for patients with a pre-stroke disability, we refer to each as "perceived" by the treating clinician.

Survey Distribution

Invitations to complete the final survey were emailed to all author-investigators of the first five international pivotal EVT trials of stent retrievers and to members of the Society of Vascular and Interventional Neurology (SVIN) (7–11). For the authors of the international trials, two follow-up emails were sent if initial emails did not elicit a response. For SVIN members, no follow-up emails were sent as per Society policy. Study data were collected from January 8, 2020 to January 9, 2020 and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Vanderbilt University Medical Center (12, 13). Survey responses were de-identified and analyzed across three major domains- current perspectives on how pre-stroke disability level and type, patient characteristics, and institutional factors impact decision to treat.

TABLE 1 | Demographics of survey respondents.

***n* = 81 (%)**	
Male	71 (87.7)
Years in practice	
<5 years	12 (14.8)
>10 years	47 (58.0)
5-10 years	22 (27.2)
Primary specialty	
Emergency medicine	1 (1.2)
General neurology	1 (1.2)
Interventional neuro-radiology	10 (12.3)
Interventional vascular neurology	36 (44.4)
Neuro hospitalist	3 (3.7)
Neurocritical care	1 (1.2)
Non-interventional vascular neurology	27 (33.3)
Other	1 (1.2)
Vascular neurosurgery	1 (1.2)
Academic rank	
Assistant Professor	15 (18.5)
Associate Professor	22 (27.2)
Fellow	10 (12.3)
Instructor	1 (1.2)
Other	10 (12.3)
Professor	23 (28.4)
Proportion of time dedicated to caring for stroke patients	
0-10%	2 (2.5)
11-50%	21 (25.9)
51-99%	46 (56.8)
100%	12 (14.8)

Analysis

Survey responses were de-identified. Survey respondent characteristics were characterized using frequencies (numerator/denominator) for each response option. Ordinal three-level frequency distributions of physician likelihood of pursuing EVT [(1) always/almost always, (2) often/sometimes, (3) almost never, never of pursuing EVT] were calculated separately for the two scenarios of patients with pre-stroke disability of mRS 2-3 and patients with pre-stroke disability of 4-5 and separately for non-interventionalists and interventionalists. Frequencies of physician selection of multiple-choices among 14 response options for general, patient-specific, and stroke-specific features most important to EVT decision-making in patients with pre-stroke disability were calculated and reported in rank order from most to least frequent.

RESULTS

Respondent Characteristics

Completed survey responses were received from a total of 81 physician-experts, including 33 from among the international EVT trial authors and 48 from among the SVIN society members. The response rate among the international EVT trial

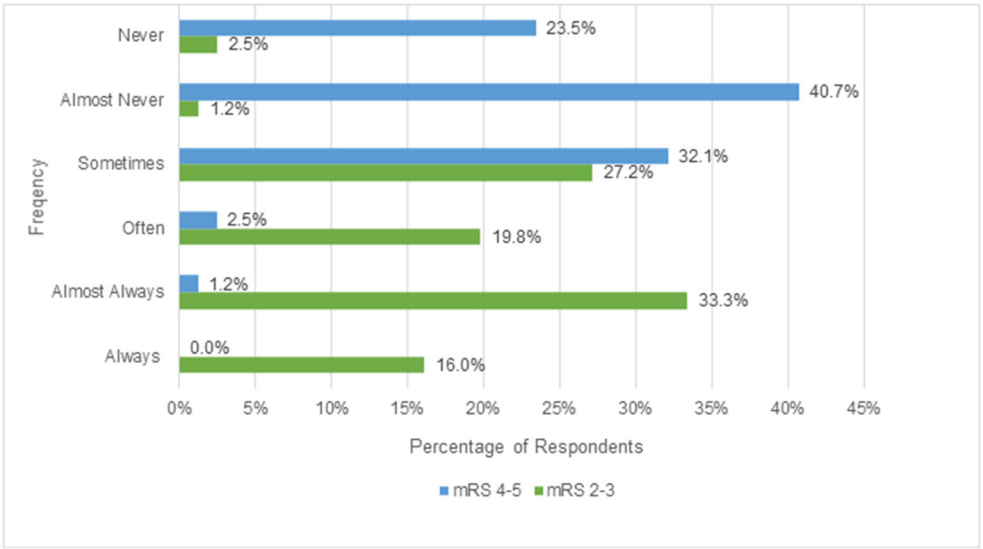

FIGURE 1 | Physician likelihood of considering EVT for patients with pre-stroke disability of mRS 2-3 vs. 4-5.

authors total was 33/119 (28%). The denominator for the SVIN survey recipients was unavailable due to use of email listserv technical constraints.

The characteristics of survey physician respondents is shown in **Table 1**. Among the 81 respondents, the majority identified as male (71/81, 87.7%). The most common specialties were interventional vascular neurology and non-interventional vascular neurology, followed by interventional neuroradiologists, with smaller proportions of neurohospitalists, vascular neurosurgeons, general neurologists, and emergency medicine physicians. The majority of respondents had practice experience of more than 10 years duration, and a little over a quarter between 5 and 10 years, with one-sixth having <5 years. The most common academic ranks were Full Professor and Associate Professor, followed by Assistant Professor, with Fellows accounting for just over 1 in 10. Overall, proportion of clinical time dedicated to stroke care was over half in 71.6% and between 10 and 50% in another 25.9%. No two respondents were from the same institution. There were no missing data for this analysis.

Perspectives on Pre-stroke Disability and Treatment

The frequency with which physicians indicated they would ever consider EVT for an otherwise eligible patient was: 97.5% for pre-stroke mRS 2; 79% for mRS 3; and 74% for mRS 4-5.

The degrees of physician likelihood of considering, performing, or offering EVT for patients with pre-stroke disability of mRS 2-3 and patients with pre-stroke disability of 4-5 are shown in **Figure 1.** For patients with mRS 2-3, a total of 49.3% (40/81) would always or almost always offer EVT; 47.0% (38/81) would often or sometimes offer EVT; and 3.8% (3/81) would almost never or never offer EVT. In contrast, for patients with pre-stroke mRS of 4 or 5, a total of 1.2% (1/81) would always or almost always offer EVT; 34.6% (28/81) would often or sometimes offer EVT; and 64.2% (52/81) would almost never or never offer EVT. **Table 2** shows the degree of physician likelihood of offering EVT separately for neurointerventionalists and non-interventionalists. Overall, neurointerventionalists were mildly more likely than non-interventionalists to offer EVT to both patients with pre-stroke disability of mRS 2-3 and patients with pre-stroke disability of mRS 4-5. **Supplementary Table 1** provides a detailed breakdown by subspecialty of the likelihood with which respondents indicated they would consider EVT for mRS 2-3 and EVT for mRS 4-5.

TABLE 2 | Frequency of EVT for mRS 2-3 and mRS 4-5 by subspecialty.

Frequency of EVT	Neuro-interventionalists ($n = 47$)	Non-interventionalists ($n = 34$)
Pre-stroke mRS 2-3		
Always	19%	12%
Almost always	32%	36%
Often	23%	15%
Sometimes	26%	29%
Almost never	0%	0%
Never	0%	3%
Pre-stroke mRS 4-5		
Always	0%	0%
Almost always	0%	3%
Often	0%	0%
Sometimes	38%	24%
Almost never	43%	39%
Never	19%	32%

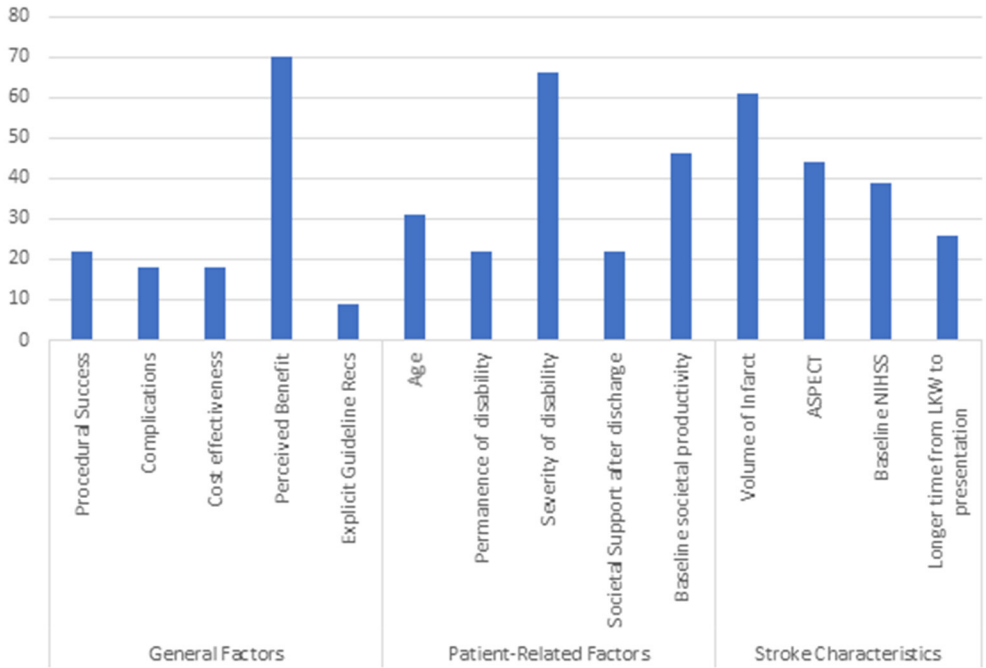

FIGURE 2 | Factors affecting EVT decision-making.

Most respondents considered the complication risk (60/79, 76%) and the likelihood of recanalization (73/79, 92%) to be the same between patients with vs. without pre-stroke disability. However, most physicians thought patients with pre-existing disability had a lower rate of return to baseline disability (53/79, 67%).

Respondents were asked to identify among 14 general, patient-specific, and stroke-specific features those that were most important to their decision-making regarding offering EVT to individual patients with pre-stroke disability. Among the 79 respondents who indicated they would ever offer EVT to a patient with pre-stroke mRS 2-5, **Figure 2** shows the frequency with which they identified 14 general, patient-specific, and stroke specific features as most important to their decision-making regarding offering EVT to individual patients with pre-stroke disability. Perceived benefit was the factor that physicians took into consideration most often when deciding whether to offer an EVT to a patient with pre-existing disability (70/79, 89%). Among patient-related factors that influenced decision making, 66 physicians chose severity of disability (83.5%), 46 chose baseline societal productivity (58.2%), and 31 chose age (39%) as important factors. Only 22 (28%) physicians chose either societal support and 22 (28%) permanence of disability as important factors. Among stroke-specific characteristics, volume of infarct was the factor that physicians most often cited as influential (61/79, 77%).

Institutional Practices

A substantial majority of physicians (65/81, 80%) responded that their institution had general guidance on how to select patients for EVT. Of those reporting institutional guidance, most indicated that protocols did not take a stand on how to treat patients with pre-existing disability and left the decision up to individual physicians (36/65, 55%). Only five institutions had explicit guidance on how to treat patients with pre-existing disability with three recommending to never treat and two recommending to always treat patients with pre-existing disability. The remaining 24 organizations providing any direction advised that patients with pre-stroke disability were sometimes candidates for EVT.

DISCUSSION

We observed considerable individual clinician and institutional-level heterogeneity in EVT practice among acute ischemic stroke patients with a pre-existing disability in this survey of 80 respondents. Disposition to pursue treatment was strongly influenced by the level of patients' pre-existing disability. While nearly half of the survey respondents noted that they would always or almost always treat patients with mild-to-moderate pre-existing disability, a preponderance of respondents noted they would almost never or never do so for patients with severe disability. In addition to the wide variation in overall propensity to treat, physicians varied substantially when identifying which general, patient-specific, and stroke-specific characteristics were important to them when making treatment decisions in individual patients with pre-stroke disability.

The current AHA/ASA guidelines only recommend offering EVT to acute ischemic stroke patients who do not have a pre-existing disability (1). This guideline is based on the completed randomized trials assessing EVT efficacy, which excluded patients with a pre-stroke mRS 2-5 (7–11). Patients

who are disabled at pre-stroke baseline are typically excluded from initial pivotal acute stroke clinical trials because the trials measure success of acute stroke therapies by the extent to which they reduce all-cause disability after stroke. Pre-stroke disabled patients are less informative for this outcome as their pre-stroke disability constrains the degree to which the acute stroke treatment can affect final all-cause disability. However, because a sizeable proportion of acute ischemic stroke patients are disabled prior to their index stroke, a detailed understanding of pre-stroke disability sources, pre-stroke disability functional profiles, ideal outcome measures, and presence and magnitude of treatment effects of acute stroke treatments such as EVT are urgently needed to ensure inclusive design of future acute stroke research and rapid translation of therapeutic advances into care of disabled patients. A detailed understanding of the current landscape of the EVT practice in this population could significantly aid such future, large, multicenter, prospective studies.

The present study not only highlights heterogeneity in EVT practice among patients with pre-stroke disability, but offers some insights into factors influencing individual clinician reasoning in this practice. While most of the survey respondents believed that the complication risks and success of recanalization were the same for patients with pre-stroke disability as those without pre-stroke disability, the majority also believed that patients with pre-stroke disability would be less likely to return to their baseline disability. Almost 90% of physicians considered their own valuation, or perception, of benefit to patient as a major factor in deciding whether to offer EVT to patients with disability. It is important to note that, in the absence of comparative data on benefits and risks of EVT compared with medical management, clinician perception is based on physiologic reasoning (as noted by majority of the physicians choosing baseline volume of infarct and Alberta Stroke Program Early CT, ASPECT, score as the most important stroke characteristic for offering EVT) and personal experience, rather than definitive randomized clinical trial evidence. Accordingly, the findings of this study reflect the current range of opinion and intuition among individual clinicians making EVT decisions for pre-stroke disabled patients and underscore the need for more reliable, formal evidence.

Importantly, large variation in institutional guidance for EVT in patients with pre-existing disability is highlighted in our study. The majority of institutional protocols remain silent on EVT specifically pertaining to pre-stroke disable patients and leave clinical decision making up to individual clinicians. Of the 6% of institutions with strict guidance on offering EVT to patients with existing disability, half recommended to always offer and half recommended to never offer EVT to pre-stroke disabled patients, highlighting inter-institutional heterogeneity in practice.

Our study has several limitations. First, respondents of our survey were drawn from lead investigators in international EVT trials and members of a US professional society largely populated by interventional neurologists. Therefore, our results may not be generalizable to the entire population of physicians that perform endovascular interventions for acute ischemic stroke. Second, the response rate to survey invitations was moderate and it is possible that the views of non-respondents would have differed from those of respondents. The strengths of our study include responses from physicians in nine different subspecialties with a good mix of practice experience, academic rank, and geographic diversity.

CONCLUSIONS

In this International survey of 80 respondents, we found considerable individual clinician and institutional-level heterogeneity in EVT practice among acute ischemic stroke patients with a pre-existing disability. Likelihood to offer EVT differed according to baseline disability as well as patient and stroke characteristics. Further research into effects of EVT among patients with a pre-stroke disability is warranted. Such research should utilize novel study methodologies and outcome measures to overcome challenges of studying this patient population.

DATA AVAILABILITY STATEMENT

The raw data supporting the results of this study will be made available upon a reasonable request.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SS contributed to data collection, analysis, and drafting of the manuscript. JN contributed to data collection. AH contributed to data collection and critical revision of the manuscript. CL, PK, JM, and JS contributed to conceptualization and critical revision of the manuscript. EM contributed to data collection, drafting of manuscript, and conceptualization. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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ORIGINAL RESEARCH
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Impact of Intravenous Alteplase Door-to-Needle Times on 2-Year Mortality in Patients With Acute Ischemic Stroke

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Objective: We sought to determine whether administration of Intravenous Thrombolysis (IVT) to patients with Acute Ischemic Stroke (AIS) within 60 min from hospital arrival is associated with lower 2-year mortality.

Methods: This retrospective study was conducted among patients receiving IVT in hospitals participating in the Georgia Coverdell Acute Stroke Registry (GCASR) from January 1, 2008 through June 30, 2018. Two-year mortality data was obtained by linking the 2008–2018 Georgia Discharge Data System data and the 2008–2020 Georgia death records. We analyzed the study population in two groups based on the time from hospital arrival to initiation of IVT expressed as Door to Needle time (DTN) in a dichotomized (DTN $\leq$ 60 vs. $>$ 60 min) fashion.

Results: The median age of patients was 68 years, 49.4% were females, and the median NIHSS was 9. DTN $\leq$60 min was associated with lower 30-day [odds ratio (OR), 0.62; 95% CI, 0.52–0.73; $P < 0.0001$], 1-year (OR, 0.71; 95% CI, 0.61–0.83; $P < 0.0001$) and 2-year (OR, 0.76; 95% CI, 0.65–0.88; $P = 0.001$) mortality as well as lower rates of sICH at 36 h (OR, 0.57; 95% CI, 0.43–0.75; $P = 0.0001$), higher rates of ambulation at discharge (OR, 1.38; 95% CI, 1.25–1.53; $P < 0.0001$) and discharge to home (OR, 1.36; 95% CI, 1.23–1.52; $P < 0.0001$).

Conclusion: Faster DTN in patients with AIS was associated with lower 2-year mortality across all age, gender and race subgroups. These findings reinforce the need for intensifying quality improvement measures to reduce DTN in AIS patients.

Keywords: acute stroke care, tissue plasminogen activator, mortality, door to needle time, thrombolytic therapy

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INTRODUCTION

Stroke is the fifth leading cause of death in the United States (US) (1, 2). The south-eastern states have the unenviable distinction of being the "Stroke-belt," accounting for higher stroke mortality as compared to rest of the US (3). Even worse, regions within the "Stroke-belt" states, including parts of Georgia along with North and South Carolina, form what is known as the "Stroke-buckle" where

Stroke mortality is ∼40% higher than rest of the states in the US (4). Although randomized clinical trials of IVT in patients with AIS have shown a time-sensitive beneficial reduction in long-term disability, there was no reduction in mortality at 3 months or at 1 year, possibly due to a small but clinically relevant increased risk of fatal intracranial hemorrhage (5–7). Although an analysis of the Get With The Guidelines-Stroke (GWTG) database provided clarity on the beneficial relationship between earlier IVT and short-term mortality, leading to further refinements of the consensus guidelines emphasizing the importance of time to IVT, the durability of this time-sensitive benefit on longer-term mortality remains to be determined (8). A more recent GWTG based study of Medicare patients showed beneficial effects of faster IVT administration and 1-year mortality (9). However, limitations of the study included under-representation of racial minorities and only including older, Medicare population. Thus, a better understanding of longer-term outcome across broader age and racial groups is needed. Our study aims to investigate the effect of faster treatment with IVT on long-term mortality among AIS patients in the GCASR.

METHODS

Study Design

We conducted a retrospective cohort study on AIS patients treated with IVT at hospitals participating in the GCASR. As part of the Centers for Disease Control and Prevention (CDC) National Paul Coverdell Acute Stroke Program initiative (10), GCASR aims to improve the quality of stroke care across the state of Georgia. The Emory University institutional review board approved the study and as it met the exceptions for informed consent requirements, the need for informed consent was waived. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Data Sources

We used three data sources: GCASR data, the Georgia Discharge Data System (GDDS), and Georgia death data. The GCASR and GDDS data were linked using a hierarchical deterministic linkage procedure (sensitivity 87%, positive predictive value 96%) (11); the output was then linked with the death data applying a probabilistic linkage approach (sensitivity 92%, specificity 100%) (12). The probabilistic linkage procedure and its yield have been described previously (13).

Study Population

A total of 9,524 records of adult AIS patients treated with IVT were captured by the registry over the period from January 1, 2008–June 30, 2018. Among these, 8,603 had valid linkage information. As the intent of this analysis was to focus on determining the relationship between time and outcome in patients who were treated with standard IVT in the emergency department, we excluded 1,492 due to in-hospital stroke, those receiving IVT as part of a clinical trial or outside the 4.5 h treatment window, or those who were either not admitted or received IVT more than once (**Figure 1**).

Outcome Measures and Predictors

The primary outcome was death from any cause at 30, 365, and 730 days after admission. We considered patients to be alive if neither the hospital discharge data reported them as having "Expired" under final discharge disposition nor were captured in the Georgia state death record. For secondary outcomes, we analyzed patients' ambulatory status at discharge (among those who were ambulating independently prior to admission), patients' discharge destination, and whether they developed symptomatic intracranial hemorrhage (sICH) within 36 h of IVT treatment.

Door-to-needle time (DTN), the primary predictor, was defined as the time difference between patient arrival at a hospital and the initiation of IVT. Based on a previous publication on predictors of in-hospital death (8) and clinical experience, we considered the following variables as covariates: socio-demographic characteristics (age, sex, and race), hospital bed-size, event-related characteristics (last known well to hospital arrival time, mode of transport to hospital, and calendar year), National Institutes of Health Stroke Scale (NIHSS) score, and patient medical history (atrial fibrillation/flutter, coronary artery disease/prior myocardial infarction, diabetes mellitus, dyslipidemia, heart failure, hypertension, smoking, previous stroke or transient ischemic attack).

Statistical Analysis

DTN was categorized into $\leq$60 and $>$60 min categories based on commonly held clinical intervals of significance and promoted by the quality improvement activities of the GCASR. Descriptive statistics were used to compare patient characteristics by DTN time. We assessed the association between DTN and the primary (30-day, 1-year, and 2-year mortality) and secondary outcomes using generalized estimating equations (GLIMMIX procedure) controlling for confounders and in-hospital correlation and considering hospital as a random variable. To assess effect modification by age, gender and race, we included interaction terms between DTN time and socio-demographic characteristics in the regression model. To evaluate the role of Intra-arterial (IA) Alteplase or mechanical thrombectomy as potential confounders, we conducted a separate analysis excluding the patients receiving IA alteplase/ MER and assessed the association between DTN and primary outcome. Age and last known well to hospital arrival time were centered around their mean values. To maintain stable estimates, patients from hospitals with $<$10 cases were excluded. About 7.8% of the observations had at least one missing value, mainly the NIHSS, and they were excluded from the multivariable regressions assuming a general missing pattern and values were missing at random. All Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Data Availability Policy

The data that support the findings of this study are available from the corresponding author upon reasonable request.

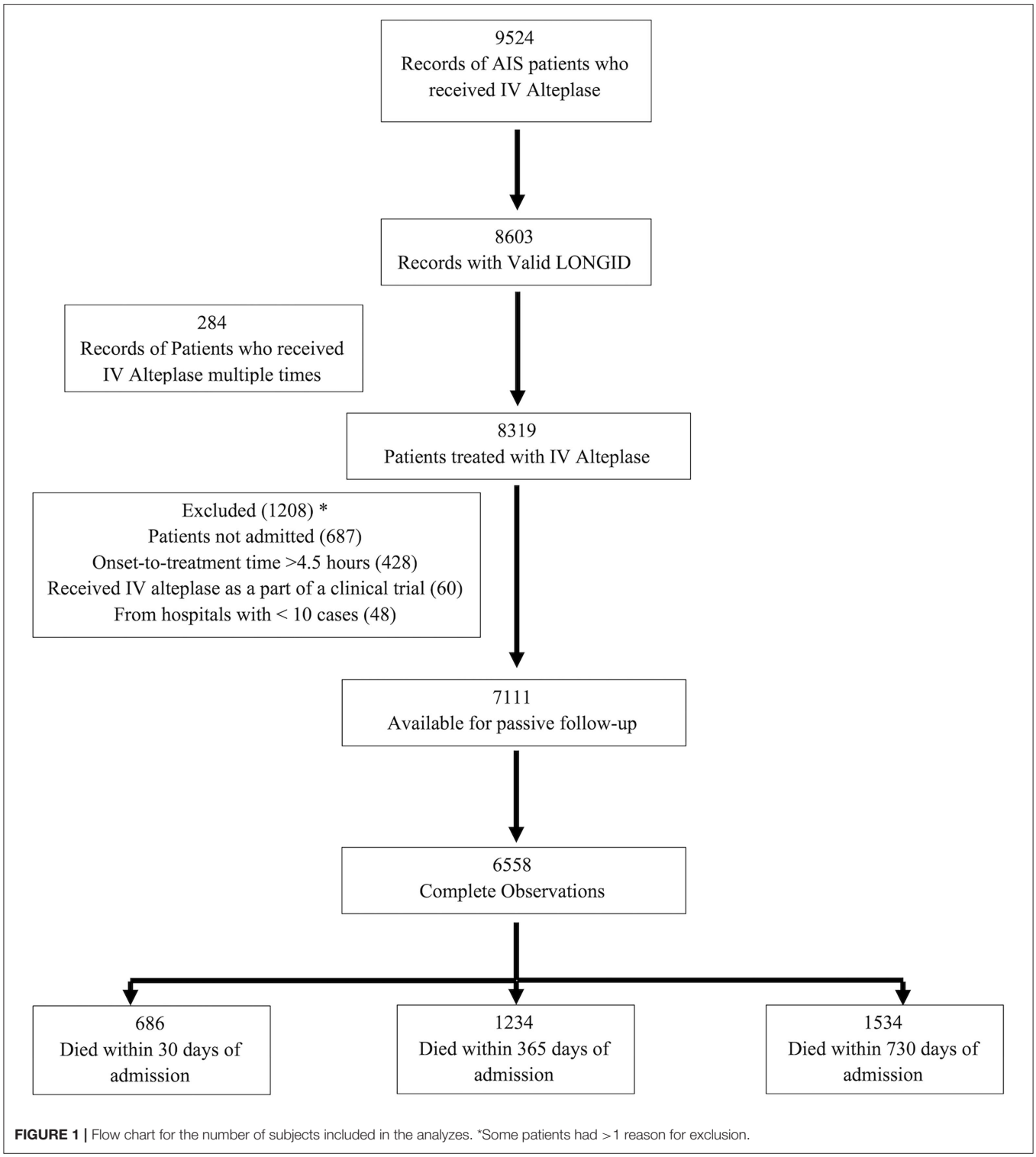

FIGURE 1 | Flow chart for the number of subjects included in the analyzes. *Some patients had >1 reason for exclusion.

RESULTS

A total of 6,558 patients with ischemic stroke received IVT and had complete information available for passive follow-up of mortality. Of these, 686 patients died at 30 days, 1,234 by 365 days and 1,534 by 730 days (**Figure 1**). Age ranged between 18 and 103 with a median of 68 years, 49.4% were female, and 35.5% were black. Median time from last known well to hospital arrival was higher in the $\leq$ 60 min DTN group [68 (IQR, 45–106) min] as compared to the $>$ 60 min DTN group [60 (IQR,

41–91) min]. The median NIHSS was 9 for both groups. There were fewer patients with history of atrial fibrillation and prior stroke or TIA in the ≤ 60 min group as compared to the > 60 min group (**Table 1**).

Patients who received IVT ≤60 min from hospital arrival had a 38% [OR 0.62 (95% CI, 0.52–0.73)], 29% [OR 0.71 (95% CI, 0.61–0.83)] and 24% [OR 0.76 (95% CI, 0.65–0.88)] risk reduction in 30-day, 1-year, and 2-year mortality, respectively, compared to those who were treated after 60 min of hospital arrival (**Table 3**). As age and NIHSS increased, the relative risk of mortality at 30 days, 1 year, and 2 year increased (**Table 2**). History of atrial fibrillation and diabetes mellitus were also associated with higher 30-day, 1-year, and 2-year mortality. The interaction terms between DTN and socio-demographic characteristics—age, gender and race group—were not statistically significant and were not included in the models.

The frequency and adjusted risk for sICH was lower in the group receiving IVT < 60 min compared to those receiving IVT after 60 min [2.7 vs. 5.0%; OR, 0.5 (95% CI, 0.43–0.75)]. Similarly, patients with IVT ≤ 60 min were more likely to be ambulatory at discharge [OR, 1.38 (95% CI, 1.25–1.53)] and more likely to be discharged to home [OR, 1.36 (95% CI, 1.23–1.52)] (**Table 3**). In stratified analysis, patients with DTN time ≤ 60 min had significantly lower 30-day, 1-year, and 2-year mortality across all age, race and gender subgroups, with the exception of 56–65 year old patients, in whom a trend toward lower 2-year mortality was seen (**Table 4**).

Similarly, when patients receiving intra-arterial Alteplase or mechanical thrombectomy were excluded, those with DTN time ≤ 60 min had lower 30-day, 1-year, and 2-year mortality as compared to those receiving IVT after 60 min (**Table 5**).

DISCUSSION

In this large, multi-center statewide registry of stroke patients treated with IVT, we found a strong and consistent association of DTN time with short- and long-term mortality. A DTN time 60 min or less was associated with 38% lower 30-day mortality, 29% lower 1-year mortality and 24% lower 2-year mortality. In addition, the risk of sICH, the most feared complication of IVT, was significantly lower in patients who were treated with IVT within 60 min of hospital arrival, and well-below published rates at 6.8% (6). Patients treated with IVT within 60 min of hospital arrival were also more likely to be ambulatory at the time of hospital discharge and more likely to be discharged home.

Despite an increased risk of sICH in patients treated with IVT, the landmark NINDS tPA trial showed no difference in 1-year mortality in AIS patients as compared to the patients who did not receive this treatment (14). Pooled analysis of individual trial data showed a modest association of earlier onset to treatment time (OTT) in reducing 90-day mortality as a continuous variable but failed to show any statistically significant mortality benefit at individual time epochs (0–90 min, 91–180 min, 181–270 min) (15). Furthermore, long-term mortality benefit with the use of IVT has been debated in several prospective observational studies (16–19). Concerns about the risk of IVT contribute to the reluctance of many clinicians to use alteplase in eligible patients despite consensus recommendations indicating Level 1A evidence.

A recent study of medicare beneficiaries showed that a shorter DTN was associated with lower 1-year mortality and reduced rates of readmission among patients 65 years and older (9). Besides the age of the population, one of the limitations of this study was related to missing Medicare claims data excluding a substantial proportion of patients leading to relative under-representation of racial minorities. Our study included all age-groups in a diverse and mostly bi-racial cohort (>30% black) that not only confirms the impact of faster treatment with IVT on reducing mortality but does so across a broader range of stroke patients while also highlighting for the first time the durability of benefit at 2 years after stroke.

Previous studies have highlighted the underutilization of IVT among black patients with AIS (20–22). However, after adjusting for IVT contraindications, the treatment rates among blacks were found to be comparable to whites, citing a delay in hospital arrival as one of the main reasons accounting for lower rates of IVT administration among blacks (22). Delays in recognition of stroke signs and underutilization of EMS among blacks have been shown to contribute to these delays (23, 24). In a GWTG-based study, although the onset-to-arrival times were similar between the blacks and whites, there was a slight delay in IVT administration among the blacks (25). While our study did not capture the reasons for delay in IVT administration, we did not find any racial disparities among the groups of patients receiving IVT within 60 min compared to those receiving IVT after 60 min of hospital arrival.

Furthermore, in our study, 30-day mortality was significantly lower in blacks as compared to whites. Similar findings have been reported for in-hospital mortality among blacks as compared to whites in previous studies (20, 25), and while the exact reasons for these differences remain unclear, varying approaches toward end-of-life and hospice care could have contributed to lower short-term mortality seen among blacks (26). Moreover, there was no statistically significant interaction between DTN and sociodemographic characteristics on the 30-day, 1-year, or 2-year mortality, indicating that all socio-demographic groups benefited equally from faster DTN times. The findings of our study further reinforce the need to implement specific interventions to reduce racial/ethnic disparities, improve stroke awareness and access to stroke healthcare among racial minorities (27).

This study reveals several other patient-related factors that affected the DTN times. Although women benefited from earlier treatment as much as men, fewer women received IVT within 60 min. This gender disparity has been shown in multiple other studies of IVT utilization (28, 29). A meta-analysis of 16 studies showed that women are less likely to receive IVT as compared to men. Although several sociocultural factors affecting women leading to delays in hospital arrival have been cited, these haven't been substantiated (30). Next, patients who received IVT within 60 min had a longer time from onset of symptoms to hospital arrival. A similar trend was shown in a large GWTG based study and it has been speculated that perhaps this may be related to a tendency of hospitals to take a more relaxed approach in patients

TABLE 1 | Characteristics and outcomes of ischemic stroke patients treated with intravenous alteplase, GCASR, January 2008–June 2018.

Characteristic/outcomes	Total	Door-to-IV alteplase time		*P*-value[a]
		≤60 min (*n* = 3,722)	>60 min (*n* = 2,836)	
Age, years, median (IQR)	68 (56, 79)	68 (57, 78)	68 (56, 79)	0.91
Female, *n* (%)	3,241 (49.4)	1,722 (46.3)	1,519 (53.6)	<0.0001
Race, *n* (%)				
Whites	4,125 (62.9)	2,363 (63.5)	1,762 (62.1)	0.53
Blacks	2,327 (35.5)	1,300 (34.9)	1,027 (36.2)	
Others	106 (1.6)	59 (1.6)	47 (1.7)	
NIH Stroke scale score, unit, median (IQR)	9 (5, 16)	9 (5, 15)	9 (5, 16)	0.05
Previous medical history of, *n* (%)				
Atrial fibrillation or flutter	1,115 (17.0)	595 (16.0)	520 (18.3)	0.01
Dyslipidemia	2,640 (40.3)	1,527 (41.0)	1,113 (39.2)	0.15
Diabetes mellitus	1,838 (28.0)	1,029 (27.6)	809 (28.5)	0.43
History of heart failure	724 (11.0)	411 (11.0)	313 (11.0)	0.99
Hypertension	5,027 (76.7)	2,854 (76.7)	2,173 (76.6)	0.96
Coronary artery disease/prior MI	1,496 (22.8)	834 (22.4)	662 (23.3)	0.37
Smoking in the past 1 year	1,506 (23.0)	856 (23.0)	650 (22.9)	0.94
Stroke or transient ischemic attack	1,694 (25.8)	916 (24.6)	778 (27.4)	0.01
Last known well to hospital arrival time, minutes, median (IQR)	64 (43, 100)	68 (45, 106)	60 (41, 91)	<0.0001
Brought to hospital				
Emergency medical service	5,267 (80.3)	3,076 (82.6)	2,191 (77.3)	<0.0001
Private transport	1,200 (18.3)	584 (15.7)	616 (21.7)	
Transferred from other hospital	91 (1.4)	62 (1.7)	29 (1.0)	
Hospital bed size, *n* (%)				
<500 beds	3,496 (53.3)	1,836 (49.3)	1,660 (58.5)	<0.0001
500+ beds	3,062 (46.7)	1,886 (50.7)	1,176 (41.5)	
Death, *n* (%)				
Death in 30 days	686 (10.5)	319 (8.6)	367 (12.9)	<0.0001
Death in 1-year	1,234 (18.8)	622 (16.7)	612 (21.6)	<0.0001
Death in 2-year	1,534 (23.4)	795 (21.4)	739 (26.1)	<0.0001
Ambulate independently at discharge,[b] *n* (%)	3,223 (53.2)	1,964 (56.3)	1,259 (49.1)	<0.0001
Intracranial hemorrhage within 36 h, *n* (%)	230 (3.7)	97 (2.7)	133 (5.0)	<0.0001
Discharged disposition, *n* (%)				
Home	3,453 (53.0)	2,052 (55.6)	1,401 (49.7)	<0.0001
Healthcare facilities but not hospice	2,359 (36.2)	1,305 (35.4)	1,054 (37.4)	
Hospice or died	697 (10.7)	333 (9.0)	364 (12.9)	

IQR, Interquartile range.

[a] *χ^2 and Wilcoxon tests were applied for nominal and quantitative variables, respectively.*

[b] *Able to ambulate independently with or without a device but no assistance from another person among patients who were ambulating on admission.*

who had a shorter onset of symptoms (31). Similarly, patients with atrial fibrillation were less likely to receive IVT within 60 min. One of the reasons for this may have been the additional time taken to obtain collateral clinical or laboratory information to establish IVT eligibility in these patients as many of these patients are expected to be on therapeutic anticoagulation.

The mechanisms by which IVT improves long-term mortality are not well-understood but better neurological function allowing increased physical activities, reduction in life-threatening pneumonia and increased independence leading to fewer medical complications have been cited among other reasons (32–35). In our study, the reduced rates of sICH in the patients with DTN ≤60 min may have contributed to reduced mortality in these patients as compared to the patients with DTN > 60 min.

Early reperfusion remains the cornerstone of success in AIS treatment which starts from early recognition of symptoms in the field. Delays in (1) recognition of symptoms, (2) access to medical care, and (3) initiation of treatment can ultimately negatively influence the final outcome of these patients. Moreover, transport *via* EMS with pre-hospital notification and single call stroke team activation has been shown to accelerate treatment times and promote favorable outcomes (36). This has been highlighted in our study with a higher proportion of patients transported

TABLE 2 | Relative risk of mortality among acute ischemic stroke patients treated with intravenous alteplase.

Predictors	30-day[a] mortality		1-yr[a] mortality		2-yr[a] mortality	
	Odds ratio[b] (95% CL)	*P*-value	Odds ratio[b] (95% CL)	*P*-value	Odds ratio[b] (95% CL)	*P*-value
Age groups						
>80 years	6.22 (4.34, 8.92)	<0.0001	11.27 (8.78, 14.47)	<0.0001	12.06 (9.80, 14.84)	<0.0001
66–80 years	2.16 (1.51, 3.10)		3.89 (3.05, 4.95)		3.86 (3.18, 4.68)	
56–65 years	1.61 (1.06, 2.44)		2.01 (1.50, 2.68)		1.98 (1.53, 2.55)	
≤55 years	Referent		Referent		Referent	
Gender						
Female	0.92 (0.79, 1.06)	0.24	0.95 (0.80, 1.12)	0.51	0.92 (0.80, 1.06)	0.24
Male	Referent		Referent		Referent	
Race						
Others	1.11 (0.43, 2.82)	0.01	0.96 (0.48, 1.91)	0.94	0.88 (0.49, 1.59)	0.43
Blacks	0.75 (0.63, 0.90)		1.02 (0.90, 1.16)		1.07 (0.94, 1.22)	
Whites	Referent		Referent		Referent	
NIH stroke scale score (unit)						
>15	9.24 (6.21, 13.75)	<0.0001	5.37 (4.24, 6.80)	<0.0001	4.49 (3.35, 6.03)	<0.0001
11–15	4.28 (2.93, 6.25)		2.69 (2.19, 3.30)		2.55 (2.05, 3.17)	
6–10	2.24 (1.47, 3.43)		1.53 (1.20, 1.94)		1.49 (1.17, 1.88)	
≤5	Referent		Referent		Referent	
Previous medical history of						
Atrial fibrillation or flutter	1.79 (1.46, 2.19)	<0.0001	1.62 (1.38, 1.89)	<0.0001	1.58 (1.35, 1.86)	<0.0001
Dyslipidemia	0.91 (0.75, 1.10)	0.31	0.77 (0.66, 0.90)	0.002	0.76 (0.67, 0.87)	0.0001
Diabetes mellitus	1.37 (1.09, 1.72)	0.01	1.39 (1.13, 1.70)	0.002	1.36 (1.13, 1.63)	0.002
History of heart failure	1.09 (0.83, 1.43)	0.55	1.51 (1.24, 1.84)	0.0001	1.70 (1.38, 2.10)	<0.0001
Hypertension	1.31 (0.98, 1.75)	0.07	1.27 (1.07, 1.52)	0.01	1.41 (1.17, 1.71)	0.001
Coronary artery disease/prior MI	1.15 (0.94, 1.42)	0.18	1.21 (1.06, 1.38)	0.01	1.27 (1.09, 1.48)	0.003
Smoking in the past 1 year	1.26 (1.00, 1.57)	0.05	1.22 (1.01, 1.46)	0.04	1.13 (0.95, 1.34)	0.16
Stroke or transient ischemic attack	0.86 (0.71, 1.04)	0.12	1.02 (0.83, 1.26)	0.84	1.14 (0.95, 1.37)	0.15
Brought to hospital by						
Transferred from other hospital	0.88 (0.42, 1.83)	0.002	0.78 (0.47, 1.32)	0.003	0.73 (0.42, 1.29)	0.002
Private transport	0.51 (0.35, 0.74)		0.59 (0.43, 0.79)		0.61 (0.46, 0.80)	
Emergency medical service	Referent		Referent		Referent	
Bed size						
500+ beds	0.79 (0.63, 0.99)	0.04	0.83 (0.69, 0.99)	0.04	0.87 (0.73, 1.04)	0.11
<500 beds	Referent		Referent		Referent	

95%CL, 95% confidence limit.

[a]*Days are counted from admission date.*

[b]*Estimates are adjusted for calendar year and last known well to hospital arrival time.*

via EMS having shorter DTN times. AIS treatment remains a complex process which requires close coordination and effective communication between various disciplines in the pre-hospital setting (EMS) as well as within the hospital (ED, Radiology, Nursing, Neurology, Laboratory, etc.). DTN time remains one of the most important modifiable variables in the treatment of AIS as the other variables are often influenced by several regional, socioeconomic and cultural characteristics of a community. This has led to DTN time being an important focus of several nationwide quality improvement initiatives in treatment of AIS (37).

The findings of our study are in keeping with previously published studies that showed faster treatment with IVT in larger hospitals as compared to small hospitals with lower annual IVT volume. Hospital-related reasons were previously shown to contribute to about 11% of patients getting delayed care leading to a substantial increase in DTN of more than 30 min in these patients (38). A recent study showed that with structural reorganization, critical training and well-defined protocol spearheaded by Emergency Physicians led to a significant reduction in DTN times (39). For hospitals with limited access to Vascular Neurology expertise, participation in Telestroke programs has also shown to reduce DTN times (40, 41). Thus, our study further emphasizes the need for each individual hospital to focus on continuous quality improvement to achieve safe and rapid reperfusion for eligible AIS patients.

TABLE 3 | Relative risk of mortality among ischemic stroke patients treated with intravenous alteplase and secondary outcomes by DTN.

Primary outcomes						
Door-to-needle time	**30-day[a] mortality**		**1-yr[a] mortality**		**2-yr[a] mortality**	
	Odds ratio[b] (95% CL)	***P*-value**	**Odds ratio[b] (95% CL)**	***P*-value**	**Odds ratio[b] (95% CL)**	***P*-value**
≤60 min	0.62 (0.52, 0.73)	<0.0001	0.71 (0.61, 0.83)	<0.0001	0.76 (0.65, 0.88)	0.001
>60 min	Referent		Referent		Referent	
Secondary outcomes						
Door-to-needle time	**Intracranial hemorrhage <36 h[c]**		**Ambulate[d] at discharge**		**Discharge home**	
	Odds ratio[b] (95% CL)	***P*-value**	**Odds ratio[b] (95% CL)**	***P*-value**	**Odds ratio[b] (95% CL)**	***P*-value**
≤60 min	0.57 (0.43, 0.75)	0.0001	1.38 (1.25, 1.53)	<0.0001	1.36 (1.23, 1.52)	<0.0001
>60 min	Referent		Referent		Referent	

95%CL, 95% confidence limit.

[a]Days are counted from admission date.

[b]Estimates are adjusted for age, sex, race, National Institute of Health stroke scale score, previous medical illness, duration of last known well to hospital arrival time, year of admission, and hospital number of beds.

[c]Patients whose clinical condition deteriorated due to a CT detected intracranial hemorrhage within 36 h of IV alteplase administration.

[d]Ambulate independently with or without a device but no assistance from another person among patients who were ambulating on admission.

TABLE 4 | Results from stratified analyses of adjusted odds ratio.

Category	**30-day mortality[a]**		**1-year mortality[a]**		**2-year mortality[a]**	
	Odds ratio[b] (95% CL)	***P*-value**	**Odds ratio[b] (95% CL)**	***P*-value**	**Odds ratio[b] (95% CL)**	***P*-value**
Age group						
≤55 years	0.46 (0.22, 0.97)	0.04	0.52 (0.30, 0.91)	0.02	0.57 (0.38, 0.86)	0.01
56–65 years	0.53 (0.36, 0.77)	0.002	0.70 (0.50, 0.98)	0.04	0.78 (0.58, 1.04)	0.09
66–80 years	0.71 (0.47, 1.08)	0.10	0.74 (0.58, 0.95)	0.02	0.77 (0.59, 0.99)	0.04
>80 years	0.57 (0.44, 0.75)	0.0001	0.71 (0.56, 0.90)	0.01	0.76 (0.60, 0.97)	0.03
Gender						
Male	0.55 (0.41, 0.75)	0.0003	0.71 (0.57, 0.89)	0.004	0.75 (0.61, 0.91)	0.01
Female	0.66 (0.52, 0.84)	0.001	0.71 (0.59, 0.86)	0.001	0.76 (0.62, 0.94)	0.01
Race group						
Black	0.61 (0.42, 0.89)	0.01	0.70 (0.52, 0.95)	0.02	0.70 (0.53, 0.93)	0.02
White	0.66 (0.52, 0.83)	0.001	0.72 (0.59, 0.87)	0.001	0.78 (0.65, 0.93)	0.01
All subjects	0.62 (0.52, 0.73)	<0.0001	0.71 (0.61, 0.83)	<0.0001	0.76 (0.65, 0.88)	0.001

95%CL, 95% confidence limit.

[a]Days are counted from admission date.

[b]Estimates are adjusted for age, sex, race, National Institute of Health stroke scale score, previous medical illness, duration of last known well to hospital arrival time, year of admission, and hospital number of beds.

AHA/ASA recognizes this unmet need and suggests several strategies that hospitals can implement to improve their DTN for AIS patients (42). Despite strong recommendations, the rate of adoption of these strategies among different hospitals remains suboptimal (37). Furthermore, this study reinforces the compelling need to establish regional stroke systems of care focused on reducing pre-hospital and in-hospital delays in IVT.

The strengths of our study include the fact that it represents a large and diverse state-wide cohort of AIS patients treated with IV Alteplase in a real-world situation. A substantial proportion of our cohort included black patients who are often under-represented in population-based studies. There are currently no large registries that report data on longer-term outcomes of AIS after IVT, but with the unique ability to crosslink de-identified data from multiple resources, we have been able to provide reliable estimates of 30-day, 1-year, and 2-year mortality rates.

LIMITATIONS

Our study has several limitations inherent to a retrospective analysis, such as unavailability of follow-up information on the patients with missing data leading to exclusion of such patients in the final analysis. As only GA state-based databases were

TABLE 5 | Relative risk of mortality among ischemic stroke patients treated with intravenous alteplase, GCASR January 2008–June 2018.

Predictors	30-day[a] mortality		1-yr[a] mortality		2-yr[a] mortality	
	Odds ratio[b] (95% CL)	*P*-value	Odds ratio[b] (95% CL)	*P*-value	Odds ratio[b] (95% CL)	*P*-value
Patients who received IA alteplase/MER are included						
Door-to-needle time						
≤60 min	0.62 (0.52, 0.73)	<0.0001	0.71 (0.61, 0.83)	<0.0001	0.76 (0.65, 0.88)	0.001
>60 min	Referent		Referent		Referent	
Patients who received IA alteplase/MER are excluded						
Door-to-needle time						
≤60 min	0.62 (0.52, 0.74)	<0.0001	0.72 (0.61, 0.85)	0.0002	0.77 (0.65, 0.90)	0.002
>60 min	Referent		Referent		Referent	

95%CL, 95% confidence limit.

[a]*Days are counted from admission date.*

[b]*Estimates are adjusted for age, sex, race, National Institute of Health stroke scale score, previous medical illness, duration of last known well to hospital arrival time, year of admission, and hospital number of beds.*

used, patients who died out of state would not be captured in the analyses, potentially underestimating the rate of mortality. However, it is unlikely this would have any relation to DTN time and outcome. In addition, the mortality rates in our study are similar to previously published data suggesting the vast majority of death events occurred in GA and were captured in the state death records (11, 12). Our study only includes patients from the state of Georgia which suffers a high burden of stroke, so generalizability to other populations may be limited. Our study did not capture the cause of death or other confounding factors which can influence long-term mortality such as certain terminal diseases (cancer), previous alcohol consumption, or social characteristics such as marital status which could limit our ability to attribute reduction in mortality directly to faster DTN time. Lastly, there were some imbalances across the groups including higher rates of atrial fibrillation in the >60 min DTN patients which is known to be associated with worse functional outcomes and higher chances of SICH and mortality (43, 44). However, multivariable analyses adjusted for several potential confounders, including atrial fibrillation, and the relationship between DTN times and outcomes remained significant.

CONCLUSIONS

This study of AIS patients across the state of Georgia provides robust evidence of 30-day, 1-year, and 2-year mortality benefit with faster IVT treatment. There was a consistent benefit of shorter DTN on mortality across all age, gender and race subgroups. It reinforces the critical need to expand and enhance quality improvement efforts at all stages of AIS treatment and for regions to establish systems of care to accelerate DTN times to reduce longer term mortality in these patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Emory University. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

NB, AB, and MF conceived the study. MI and RB provided statistical advice on study design and analyzed the data. NB and AB drafted the manuscript. MF takes responsibility for the paper as a whole. All authors contributed substantially to its revision.

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Predictors of Functional Outcome and Mortality in Endovascular Treatment for Acute Basilar Artery Occlusion: A Single-Centre Experience

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Background and Purpose: The objective of this study was to identify prognostic factors of endovascular treatment in patients with acute basilar artery occlusion and add evidence about the efficacy and safety of endovascular treatment for acute basilar artery occlusion.

Materials and Methods: We reviewed the data of 101 patients with acute basilar artery occlusion receiving endovascular treatment from January 2013 to September 2019. Baseline characteristics and outcomes were evaluated. A favourable functional outcome was defined as a mRS of 0 to 2 assessed at the 3 month follow-up. The association of clinical and procedural characteristics with the functional outcome and mortality was assessed.

Results: The study population consisted of 101 patients: 83 males and 18 females. Successful recanalization was achieved in 99 patients (97.1%). A favourable clinical outcome was observed in 50 patients (49.5%), and the overall mortality rate was 26.7%. A favourable outcome was significantly associated with NIHSS score at admission and lung infection. Mortality was associated with NIHSS score at admission, the number of thrombectomy device passes, the postoperative pons-midbrain index, and diabetes mellitus.

Conclusions: This study suggested that NIHSS score at admission, the number of thrombectomy device passes, the postoperative pons-midbrain index, diabetes mellitus, and lung infection can predict the functional outcome and mortality. These initial results add evidence about the efficacy and safety of endovascular treatment for acute basilar artery occlusion and need to be confirmed by further prospective studies.

Keywords: acute basilar artery occlusion, endovascular treatment, functional outcome, mortality, thrombectomy

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INTRODUCTION

Acute basilar artery occlusion (ABAO) is an uncommon but potentially devastating neurological condition, accounting for ∼20% of posterior circulation strokes (1) and approximately 1% of all ischaemic strokes (2), and is associated with a very poor outcome (3). With variable presentations and a broad differential diagnosis (4), BAO is associated with high rates of critical disability and mortality due to injury to the brainstem. Without active intervention or treatment, the patient mortality rate in BAO can exceed 90% (5, 6).

Compared with either intravenous or intraarterial thrombolysis, systematic meta-analyses of case series and registry data have indicated that mechanical thrombectomy provides the optimal potential for improved recanalization rates and more favourable clinical outcomes in patients with BAO, but well-conducted randomised controlled trials are needed (7–13). To date, the only large randomised controlled trial (the BASICS Study) has not shown obvious advantages of endovascular therapy over medical therapy, but too long time span, recruitment without achieving anticipated and partial presence of cross-group cases weaken the objectivity of the results (14). Further evidence in the use of endovascular treatment (EVT) in posterior-circulation strokes is required.

This study is based on data from a single-centre registry with 101 patients who received EVT. endovascular treatment in patients with acute basilar artery occlusion and. The purpose of the present study was to analyse prognostic factors of clinical outcomes of endovascular treatment for acute basilar artery occlusion and add evidence about the efficacy and safety of endovascular treatment for acute basilar artery occlusion.

METHODS

Selection of Patients

This was a retrospective study from one stroke centre in Changzhou, China. The time interval of this study ranged from January 2013 to December 2019. The clinical data of patients with ABAO confirmed by digital subtraction angiography treated with mechanical thrombectomy within 24 h from symptom onset were collected and statistically analysed.

Patients were enrolled if they met the following criteria: (a) age ≥18 years old; (b) diagnosis of BAO by CTA or MRA before EVT; (c) EVT performed within 24 h after symptom onset; and (d) mRS ≤ 2 before stroke. The exclusion criteria were as follows: (a) history of surgery or trauma within 2 months; (b) intracranial haemorrhage (ICH) or history of subarachnoid haemorrhage, tumour, ICH, or arteriovenous malformation; (c) large infarct core (exceeding two-thirds of the midbrain, pons, or either side of the cerebellum); (d) dysfunction of important organs; (e) definite bleeding tendency; and (f) voluntary abandonment of treatment or failure to follow doctor's instructions due to non-iatrogenic reasons.

All patients (or relatives) signed informed consent forms before treatment. This study was approved by the Ethics Committee of the Hospital.

Intervention Procedure

During mechanical thrombectomy, patients were under local or general anaesthesia depending on the clinical circumstances. Each patient treated under general anaesthesia underwent tracheal intubation before anaesthesia. Oxygenation and strict blood pressure control were maintained during the procedure in all cases. All interventions were performed by senior neurointerventionalists under general or local anaesthesia. Successful recanalization after mechanical thrombectomy was defined by TICI 2b-3 (15). A 24-h follow-up non-enhanced CT was always performed to rule out complications of ICH.

In this study, the whole treatment process of mechanical thrombectomy was almost consistent with that in our previous study (16). Together with the extensive surgical experience and the progress of neurointerventional materials, the stent-retriever thrombectomy technique combined with an intermediate catheter or a direct aspiration first-pass technique (ADAPT) (17) was applied in our centre for appropriate patients.

Once atherosclerosis or dissection was considered the stroke aetiology, 10 μg/kg tirofiban was immediately administered by an intravenous bolus and continued at 0.15 μg/kg/min. Balloon angioplasty and/or stent placement was considered if there was obvious stenosis, while stent placement was used for the dissected artery.

One hundred milligrammes of aspirin and 75 mg of clopidogrel were administered at 24 h postprocedure. Tirofiban was stopped after overlapping medicine treatment for at least 6 h. Aspirin and clopidogrel were administered daily for 3 months.

Neuroimaging Assessment

The time window was 24 h. Collected data included clinical data, such as age, sex, and vertebral artery lesions in the posterior circulation (occlusion or stenosis), cardiovascular risk factors, such as hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, history of ischaemic stroke or TIA, and smoking, stroke aetiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (18), and baseline NIHSS and Glasgow coma scale (GCS) scores at admission.

The baseline posterior circulation Acute Stroke Prognosis Early CT Score (Pc-ASPECTS) (19) and pons-midbrain index (PMI) (20) both at admission and within 24 h after surgery were evaluated based on preoperative and postoperative neuroimaging and CTA source images. The location of BA occlusion was also classified as proximal (from the vertebrobasilar junction to the origin of the anterior inferior cerebellar artery), middle (from the origin of the anterior inferior cerebellar artery to the origin of the superior cerebellar artery), or distal (distal to the origin of the superior cerebellar artery) according to previously published criteria (21). The OTT was defined as the time between symptom onset and the beginning of femoral artery puncture. Additionally, the puncture-to-recanalization time (PTR) was collected for reference.

The presence of hydrocephalus or evident ischaemic changes in the posterior circulation territory or ICH was reassessed via craniocerebral CT within 36 h after EVT. Symptomatic ICH was defined according to the definition of the safe thrombolysis in the stroke surveillance study (SITS-MOST): local

or remote intraparenchymal haemorrhage type 2 in the 22- to 36-h follow-up imaging scans, combined with a neurological deterioration of ≥4 points on the NIHSS from baseline, from the lowest NIHSS score between baseline and 24 h, or leading to death (22). Lung infection during the perioperative period and complications related to surgical instruments and operations (new vascular occlusion, reocclusion after successful opening, ICH, arterial dissection, vasospasm, haematoma or haemorrhage at the femoral artery puncture point, hypotension requiring medication, bradycardia requiring medication, etc.), considered a potential prognostic factors, were also documented.

Clinical Outcome Measures

The severity of stroke at the time of EVT was dichotomized as severe or mild to moderate, in conformity to the definition used in the Basilar Artery International Cooperation Study (BASICS) registry (6). Patients in a coma, with tetraplegia, or in a locked-in state were classified as having a severe stroke, whereas mild-to-moderate stroke was defined as any deficit that was less than severe. The functional outcome at 3 months was assessed with the mRS score obtained during a follow-up outpatient visit or via a semi-standardised telephone interview. A favourable outcome was defined as an mRS score of 0–2, in accordance with the definition used in the BASICS registry. Moreover, the patients were divided into two groups according to mortality to investigate the difference in the mortality rate between the two groups by risk factor stratification.

Statistical Analysis

All statistical analyses were performed using the software package SPSS 22.0. The chi-square test or Fisher's exact test was used to compare categorical variables, and Student's *t*-test or the Mann–Whitney U test was used to compare continuous variables. A logistic regression model was used for multivariate analysis to determine whether the potential risk factors on univariate analysis remained independently associated with a favourable functional outcome and mortality at 90 days. All tests were 2-sided, and *p*-values of 0.05 or less were considered statistically significant.

RESULTS

Baseline Characteristics

A total of 101 patients who underwent EVT for ABAO between January 2013 and September 2019 were included in this analysis, including 20 patients in the mild-to-moderate group and 81 patients in the severe group. Baseline clinical and neuroimaging characteristics are presented in **Table 1**. There were 83 males and 18 females, with a mean age of 62.2 ± 12.91 (mean ± SD) years. Eight patients (7.8%) underwent IVT prior to EVT in this series. The median baseline NIHSS score was 30 (interquartile

TABLE 1 | Baseline characteristics and functional outcome (mRS ≤2 vs. mRS >2).

Characteristics	Overall (*n* = 101)	Outcome		
		mRS ≤2 (*n* = 50)	mRS >2 (*n* = 51)	*P*-value
Age (years), mean (SD)	62.2 (12.91)	62.5 (12.85)	62 (13.09)	0.853
Male sex, No. (%)	83 (81.4)	42 (84)	41 (80.4)	0.636
Hypertension, No. (%)	81 (79.4)	38 (76)	43 (84.3)	0.295
Diabetes mellitus, No. (%)	20 (19.6)	7 (14)	13 (25.5)	0.147
Baseline glycaemia (mmol/L), mean (SD)	8.3 (2.98)	7.84 (2.83)	8.76 (3.08)	0.065
Atrial fibrillation, No. (%)	30 (29.4)	16 (32)	14 (27.5)	0.617
Coronary heart disease, No. (%)	8 (7.8)	4 (8)	4 (7.8)	0.999
Antithrombotic treatment, No. (%)	15 (14.7)	6 (12)	9 (17.6)	0.425
History of ischaemic stroke or TIA, No. (%)	20 (19.6)	9 (18)	11 (21.6)	0.653
Smoking, No. (%)	38 (37.3)	17 (34)	21 (41.2)	0.457
GCS score at admission, median (IQR)	5 (4–7)	6 (4–9)	5 (4–6)	0.008
NIHSS score at admission, median (IQR)	30 (22.5–36.5)	26 (20–32)	35 (28–38)	<0.001
Preoperative Pc-ASPECTS, median (IQR)	9 (9–10)	9 (9–10)	9 (9–10)	0.234
Preoperative PMI, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0.615
IVT, No. (%)	8 (7.8)	4 (8)	4 (7.8)	0.999
Stroke aetiology, No. (%)				0.435
Atherosclerosis	49 (48.0)	21 (42)	28 (54.9)	
Cardioembolic	30 (29.4)	15 (30)	15 (29.4)	
Other	7 (29.4)	4 (8)	3 (5.9)	
Unknown	15 (14.7)	10 (20)	5 (9.8)	

SD, standard deviation; GCS, Glasgow Coma Scale; IQR, interquartile range; Pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early CT Score; PMI, pons-midbrain index; IVT, intravenous thrombolysis.

TABLE 2 | Baseline characteristics and mortality.

Characteristics	Mortality		
	Yes ($n = 27$)	No ($n = 74$)	*P*-value
Age (years), mean (SD)	63.9 (12.78)	61.6 (12.99)	0.451
Male sex, No. (%)	20 (74.1)	63 (85.1)	0.321
Hypertension, No. (%)	22 (81.5)	59 (79.7)	0.845
Diabetes mellitus, No. (%)	9 (33.3)	11 (14.9)	0.039
Baseline glycaemia (mmol/L), mean (SD)	9.2 (3.40)	7.97 (2.76)	0.049
Atrial fibrillation, No. (%)	10 (37)	20 (27)	0.33
Coronary heart disease, No. (%)	2 (7.4)	6 (8.1)	0.999
Antithrombotic treatment, No. (%)	4 (14.8)	11 (14.9)	0.999
History of ischaemic stroke or TIA, No. (%)	5 (18.5)	15 (20.3)	0.845
Smoking, No. (%)	13 (48.1)	25 (33.8)	0.187
GCS score at admission, median (IQR)	4 (3–6)	5.5 (4–8)	<0.001
NIHSS score at admission, median (IQR)	37 (31–39)	28 (21–35)	<0.001
Preoperative Pc-ASPECTS, median (IQR)	10 (9–10)	9 (9–9)	0.333
Preoperative PMI, median (IQR)	0 (0–0)	0 (0–0)	0.209
IVT, No. (%)	3 (11.1)	5 (6.8)	0.764
Stroke aetiology, No. (%)			0.713
Atherosclerosis	11 (40.7)	38 (51.4)	
Cardioembolic	10 (37)	20 (27)	
Other	2 (7.4)	5 (6.8)	
Unknown	4 (14.8)	11 (14.9)	

SD, standard deviation; GCS, Glasgow Coma Scale; IQR, interquartile range; Pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early CT Score; PMI, pons-midbrain index; IVT, intravenous thrombolysis.

range [IQR], 22.5–36.5), and the median total GCS score was 5 (IQR, 4–7). Among the stroke risk factors, hypertension was most prevalent (81 of 101 patients [79.4%]). In this research, atherosclerosis, accounting for 48%, remained the most common cause of ABAO.

As shown in **Tables 1**, **2**, a favourable outcome was significantly associated with both the total GCS score at admission ($p = 0.008$) and the NIHSS score at admission ($p < 0.001$), which were also statistically associated with mortality (GCS score, $p < 0.001$; NIHSS score, $p < 0.001$), similar to diabetes mellitus ($p = 0.039$) and baseline glycaemia (mmol/L) ($p = 0.049$) (**Table 2**).

Periprocedural Characteristics and Clinical Outcomes

Tables 3, **4** show the periprocedural characteristics and outcomes. The median OTT was 240 min (IQR, 180–340), and the median PTR was 65 min (IQR, 50–115). Seventy-six patients (74.5%) were treated under general anaesthesia. Compared with the pour outcome group, the PTR was significantly lower ($p = 0.006$) in the favourable outcome group, while a longer PTR seemed to be associated with a higher mortality rate ($p = 0.002$). The distal BA was the most common site of ABAO (49/101, 48%).

During the progression of mechanical thrombectomy, 17 patients (16.7%) were treated with mechanical thrombectomy in combination with IA thrombolysis, and 47 patients (46.1%) received an intraarterial infusion of tirofiban. Direct balloon angioplasty combined with stenting without mechanical thrombectomy was performed in eight (11.8%) patients. Angioplasty with or without stenting after mechanical thrombectomy was performed in 46 (46.1%) patients: balloon angioplasty alone in 11 patients, stent placement alone in 11 patients, and balloon angioplasty combined with stenting in 24 patients. Among all 101 patients treated with angioplasty, TICI 2b−3 recanalization was achieved in 99 patients (97.1%). No significant effect of EVT on prognosis was found.

With regard to the postoperative neuroimaging evaluation based on the Pc-ASPECTS and PMI, the median Pc-ASPECTS was 6 (IQR, 5–8), and the median PMI was 2 (IQR, 1–3). It seemed that a higher postoperative Pc-ASPECTS was statistically related to a better functional outcome ($p = 0.001$), and a lower postoperative PMI was associated with both a better functional outcome ($p = 0.001$) and a lower mortality rate ($p = 0.008$). Overall, as shown in **Table 1**, a favourable functional outcome (mRS score 0–2) was reached by 50 (49.5%) patients, including 13 of 20 patients (65%) in the mild-moderate group and 37 of 81 patients (45.7%) in the severe group. Mortality occurred in 25 of 27 (92.6%) patients in the severe group ($p = 0.048$). Symptomatic ICH occurred in five patients (4.9%), all of whom experienced mortality ($p = 0.001$). Other complications included complications related to surgical instruments and operations in 11 patients, hydrocephalus in two patients, and perioperative

TABLE 3 | Periprocedural characteristics and functional outcome (mRS ≤2 vs. mRS score >2).

Characteristics	Overall ($n = 101$)	Outcome		
		mRS ≤ 2 ($n = 50$)	mRS > 2 ($n = 51$)	*P*-value
Symptom-onset-to-treatment time (OTT), median (IQR), min	240 (180–340)	240.5 (158.75–322.5)	240 (180–380)	0.541
OTT ≤ 360 min, No. (%)	79 (78.2)	44 (88)	35 (68.6)	0.018
Puncture-to-recanalization time (PTR), median (IQR), min	65 (50–115)	60 (45–83.25)	90 (52–120)	0.006
General anaesthesia, No. (%)	76 (74.5)	35 (70)	41 (80.4)	0.226
Number of thrombectomy device passes, median (IQR), min	1 (1–2)	1 (1–2)	2 (10–2)	0.133
BA occlusion site, No. (%)				0.807
Proximal BA	30 (29.7)	15 (30)	15 (29.4)	
Mid BA	22 (21.7)	10 (20)	12 (23.5)	
Distal BA	49 (48.6)	26 (52)	23 (45.1)	
Endovascular treatment				
IA thrombolysis, No. (%)	17 (16.7)	9 (18)	8 (15.7)	0.756
IA infusion of tirofiban, No. (%)	47 (46.1)	23 (46)	24 (47.1)	0.915
Emergency angioplasty, No. (%)				0.41
Simple stenting	11 (10.8)	5 (10)	6 (11.8)	
Simple balloon angioplasty	11 (10.8)	8 (16)	3 (5.9)	
Both stenting and balloon angioplasty	24 (23.5)	10 (20)	14 (27.5)	
None	55 (53.9)	27 (54)	28 (54.9)	
Postoperative Pc-ASPECTS, median (IQR)	6 (5–8)	7 (6–8)	6 (5–7)	0.001
Postoperative PMI, median (IQR)	2 (1–3)	1 (1–2)	3 (1–4)	0.001
Complications, No. (%)				
Complications related to surgical instruments and operations	11 (10.8)	4 (8)	7 (13.7)	0.356
Symptomatic ICH	5 (4.9)	0 (0)	5 (9.8)	0.07
Hydrocephalus	2 (2)	0 (0)	2 (3.9)	0.484
Lung infection	50 (49)	14 (28)	36 (70.6)	<0.001
TICI 2b-3, No. (%)	99 (98.0)	50 (100)	49 (96.1)	0.157

IQR, interquartile range; Pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early CT Score; BA, basilar artery; IA, intraarterial; PMI, pons-midbrain index; ICH, intracranial haemorrhage.

lung infection in fifty patients. Lung infection was significantly associated with a poor outcome ($p < 0.001$).

Risk Factors for Clinical Outcomes

On multivariate logistic analysis, three clinical factors were identified as predicting good clinical outcomes, including the NIHSS score at admission (OR 0.852; 95%CI, 0.748–0.970; $p = 0.016$) and lung infection (OR 0.135; 95%CI, 0.042–0.433; $p = 0.001$). Mortality was significantly associated with the NIHSS score at admission (OR 1.186; 95%CI, 1.005–1.399; $p = 0.044$), the number of thrombectomy device passes (OR 2.612; 95%CI, 1.190–5.731; $p = 0.017$), the postoperative PMI (OR 3.222; 95%CI, 1.544–6.726; $p = 0.002$), and diabetes mellitus (OR 25.037; 95% CI, 3.449–181.750; $p = 0.001$) (**Table 5**).

DISCUSSION

In this study, we analysed our single-centre outcomes of EVT in patients with ABAO in the past 7 years and found that the rate of a favourable functional outcome, defined as an mRS score of 0–2 at 3 months, was 49.5%, with an overall mortality rate of 26.7%. We obtained a high recanalization rate (97.1%) in patients with BAO treated with mechanical thrombectomy.

These results are comparable to those of other series published to date of patients with BAO treated with mechanical thrombectomy in terms of the rate of successful recanalization, a favourable outcome and mortality. According to previous studies, the recanalization rate of mechanical thrombectomy, including the last generation of mechanical devices in patients with ABAO, ranged from 75 to 94.8%, with higher rates in some studies performed with accepted EVT strategies with either stent retrievers, aspiration or a combination of both. Regarding the rate of a good functional outcome (mRS 0–2) and mortality, the results ranged from 29.4 to 46.1% and 21 to 40.9%, respectively (8, 10, 12, 13, 23). Based on two separate meta-analyses, the results from our study together with those of previous reports, showing higher recanalization rates and a better prognosis for patients with ABAO managed with endovascular thrombectomy when compared with drug therapy alone (either intravenous and/or intraarterial thrombolysis), suggest that our EVT strategy (mechanical thrombectomy combined with intracranial angioplasty or

TABLE 4 | Periprocedural characteristics and mortality.

Characteristics	Overall ($n = 101$)	Mortality		
		Yes ($n = 27$)	No ($n = 74$)	*P*-value
Severe group, No. (%)	81 (79.4)	25 (92.6)	56 (75.7)	0.048
Symptom-onset-to-treatment time (OTT), median (IQR), min	240 (180–340)	250 (200–386)	240 (153.75–330)	0.182
OTT ≤360 min, No. (%)	79 (78.2)	17 (63)	62 (83.8)	0.025
Puncture-to-recanalization time (PTR), median (IQR), min	65 (50–115)	93 (64–134)	60 (45–90)	0.002
General anaesthesia, No. (%)	76 (74.5)	20 (74.1)	56 (75.7)	0.869
Number of thrombectomy device passes, median (IQR), min	1 (1–2)	2 (1–3)	1 (1–2)	0.085
BA occlusion site, No. (%)				0.186
Proximal BA	30 (29.7)	7 (25.9)	23 (31.1)	
Mid BA	22 (21.8)	9 (33.3)	13 (17.6)	
Distal BA	49 (48)	11 (40.7)	38 (51.4)	
Endovascular treatment				
IA thrombolysis, No. (%)	17 (16.7)	4 (14.8)	13 (17.6)	0.979
IA infusion of tirofiban, No. (%)	47 (46.1)	11 (40.7)	36 (48.6)	0.481
Emergency angioplasty, No. (%)				0.558
Simple stenting	11 (10.8)	3 (11.1)	8 (10.8)	
Simple balloon angioplasty	11 (10.8)	1 (3.7)	10 (13.5)	
Both stenting and balloon angioplasty	24 (23.5)	8 (29.6)	16 (21.6)	
None	55 (53.9)	15 (55.6)	40 (54.1)	
Postoperative Pc-ASPECTS, median (IQR)	6 (5–8)	6 (3–8)	6 (5–8)	0.069
Postoperative PMI, median (IQR)	2 (1–3)	4 (0–6)	2 (1–3)	0.008
Complications, No. (%)				
Complications related to operations	11 (10.8)	5 (18.5)	6 (8.1)	0.26
Symptomatic ICH	5 (4.9)	5 (18.5)	0	0.001
Hydrocephalus	2 (2)	1 (3.7)	1 (1.4)	0.465
Lung infection	50 (49)	16 (59.3)	34 (45.9)	0.236
TICI 2b-3, No. (%)	99 (97.1)	25 (92.6)	74 (100)	0.119

IQR, interquartile range; Pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early CT Score; BA, basilar artery; IA, intraarterial; PMI, pons-midbrain index; ICH, intracranial haemorrhage.

TABLE 5 | Multifactor logistic regression for functional outcome and mortality.

Characteristics	Favourable outcome		Mortality	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Diabetes mellitus			25.037 (3.449–181.750)	0.001
GCS score at admission	0.898 (0.620–1.299)	0.567	0.730 (0.431–1.237)	0.242
NIHSS score at admission	0.852 (0.748–0.970)	0.016	1.186 (1.005–1.399)	0.044
OTT ≤360 min	2.509 (0.589–10.689)	0.214	0.243 (0.049–1.195)	0.082
Puncture-to-recanalization time (PTR)	0.985 (0.969–1.001)	0.059	1.016 (0.998–1.035)	0.081
Number of thrombectomy device passes			2.612 (1.190–5.731)	0.017
Postoperative Pc-ASPECTS	1.427 (0.894–2.277)	0.136	1.545 (0.841–2.837)	0.161
Postoperative PMI	0.628 (0.382–1.034)	0.067	3.222 (1.544–6.726)	0.002
Lung infection	0.135 (0.042–0.433)	0.001		

GCS, Glasgow Coma Scale; Pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early CT Score; PMI, pons-midbrain index; IVT, intravenous thrombolysis.

IA thrombolysis or IA infusion of tirofiban) has promise in patients with ABAO (24), despite the lack of good randomised controlled trials.

In fact, whether EVT is the best treatment for ABAO is controversial in some existing retrospective studies. In a multicentre clinical registry study (the EVT for Acute Basilar

Artery Occlusion Study, BASILAR), intravascular treatment within 24 h of ABAO improved the functional outcome and reduced mortality, supporting the superiority of EVT compared to drug therapy alone (25). However, according to the first randomised controlled trial to assess the effect of contemporary EVT, including stent retriever-based mechanical thrombectomy, in the treatment of acute vertebrobasilar occlusion (Endovascular treatment vs. standard medical treatment for vertebrobasilar artery occlusion (BEST): an open-label, randomised controlled trial), the difference in the occurrence of a favourable outcome between patients receiving EVT and those receiving standard medical therapy alone statistically did not make sense (26). In addition, the BASICS Study also has not shown superiority of EVT over medical therapy. All of these studies have their own limitations. BASILAR study could not balance the systematic differences between the two treatment groups. BEST study had too many cross-group individuals, leading to an insufficient study quality. The limitation of BASICS Study has been mentioned in the previous part. In our study, factors associated with EVT, such as the high recanalization rate, the course of treatment and treatment-related complications, did not affect the prognosis of BAO patients; the number of thrombectomy device passes also did not affect the prognosis and seemed to be more related to the complex vascular structure and the pathophysiology of the embolism (27). A limitation of our work is the small sample size of patients with unsuccessful reperfusion. If we can obtain more samples of unsuccessful recanalization (TICI 1-2a), the results would be more convincing. Based on the fact that a substantial proportion (∼50.5%) of our patients had poor clinical outcomes (mRS score 3–6) despite TICI 2b−3 recanalization, we support that successful recanalization by EVT could be essential but not sufficient to obtain good clinical outcomes in patients with ABAO.

There is conflicting evidence on the importance of timing in treating ABAO. The current American Heart Association guidelines suggest applying mechanical thrombectomy in patients with causative occlusion of the BA by a groin puncture time within 6 h of symptom onset (class IIb; level of evidence C) (28), which is supported by several previous reports (23, 29, 30). A retrospective study of 215 patients from two endovascular centres by Bouslama et al. (31) suggests that the time to recanalization does not predict the outcome, which is in line with some other studies (13, 32). In our study, we found that a time to treatment of more than 6 h was predictive of a poor outcome, and a shorter PTR could be associated with a favourable functional outcome and a lower mortality rate, based on a single-factor analysis. However, this correlation disappeared on multivariate analysis. In addition, we found that fewer thrombectomy device passes was associated with a lower mortality rate on multivariate logistic analysis. We tentatively propose that a delay from symptom onset, which is potentially related to a poorer functional outcome, should not discourage the application of reperfusion therapy in BAO patients; in addition, factors affecting the efficiency of mechanical thrombectomy, such as a complex cerebrovascular configuration or combination with other cerebrovascular lesions and a highly viscous thrombus, may be associated with a poor functional outcome.

Several prior studies have noted the importance of clinical severity at admission and found an association between higher admission NIHSS scores and poorer clinical outcomes (23, 33). Our study confirms this finding. In addition, in contrast to a published single-centre registry (8) of 28 patients with BAO undergoing EVT, we did not find a statistically significant association between the clinical outcome and the GCS score at admission.

In the current literature, the Pc-ASPECT for the posterior circulation is the subject of discussion. Some existing studies prefer to use diffusion-weighted imaging (DWI) rather than CT for evaluation of the Pc-ASPECT (34, 35). Unfortunately, we failed to collect DWI data from most patients to test this view. As in our study, in the vast majority of patients who received both a pre-interventional and post-interventional Pc-ASPECT via CT, these scores were not predictive of the functional outcome. Although on the PMI requires CT for evaluation, the post-interventional PMI was highly predictive of mortality, as suggested by the multifactor analysis in our study. This trend is in line with other findings reported in the literature (20, 36).

In our study, diabetes mellitus was a predictor of mortality on multivariate logistic analysis, which is supported by a large single-centre report on 231 patients by Ravindren et al. (23). Most reports on this topic are not in line with this observation (11, 13, 30–33). Furthermore, we found that perioperative lung infection was predictive of an unfavourable functional outcome, despite the lack of supporting findings in the literature. In fact, lung infection is not uncommon, and most ABAO patients undergoing EVT still need prolonged bed rest, which accounts for the high probability of sputum excretion disorder and pulmonary infection. This finding could be helpful to enhance the importance of the prevention and control of perioperative lung infection.

Our study has some limitations that stem primarily from its retrospective design, small sample size, long duration, lack of randomisation and comparison with patients treated with medical management only, and heterogeneity of the centre-specific study population. Additionally, some data, including the ASITN/SIR grade, which could be important to the assessment of prognostic factors, were missing. In the future, more results from large randomised controlled trials may provide more evidence about the safety and efficacy of mechanical thrombectomy in ABAO.

CONCLUSION

This study suggested that NIHSS score at admission, the number of thrombectomy device passes, the postoperative pons-midbrain index, diabetes mellitus, and lung infection can predict the functional outcome and mortality. These initial results add evidence about the efficacy and safety of endovascular treatment for acute basilar artery occlusion and need to be confirmed by further prospective studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YP and XZ conceived and designed the study, including quality assurance and control. JC and YM collected the data and wrote the paper. RC and JX designed the study's analytic strategy. HS reviewed and edited the manuscript. All authors read and approved the manuscript.

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CASE REPORT
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Cerebral Large Vessel Occlusion Caused by Fat Embolism—A Case Series and Review of the Literature

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The diagnosis of fat embolism syndrome typically involves neurological, respiratory and dermatological manifestations of microvascular occlusion 24–72 h after a precipitating event. However, fat embolism causing cerebral large vessel occlusion strokes and their sequelae have rarely been reported in the literature. This case series reports three patients with fat emboli post operatively causing cerebral large vessel occlusions, as well as a review of the literature to identify differences in clinical presentations and outcomes in stroke secondary to fat emboli causing large vessel occlusions compared to those with fat embolism syndrome.

Keywords: ischaemic stroke, large vessel occlusion (LVO), fat embolism, surgical complication, endovascular clot retrieval

CASE 1

A 71-year-old man with a history of hypertension, hypercholesterolaemia and osteoarthritis, underwent an elective left knee replacement lasting 150 min under general and spinal anaesthetic, using a limb tourniquet. Post-operatively, he was found unresponsive with a Glasgow Coma Score (GCS) of 6 (E1V2M3) and had a global aphasia and right hemiparesis with an initial National Institutes of Health Stroke Score (NIHSS) of 24. CT brain (**Figure 1A**) demonstrated a "hypodense artery sign" with Hounsfield units (HU) of −75 in the left M1 segment of the middle cerebral artery (MCA) suggestive of fat embolism, and tandem occlusions in the left internal carotid artery (ICA) and M1 MCA were seen on CT angiogram (CT-A).

He underwent endovascular clot retrieval (ECR) and reperfusion was achieved with large volume clot aspirated from the left M1 and M2 segments. Histopathology of the aspirated clot revealed adipose tissue and bone marrow with red blood cells, white cells and platelets, and fibrin fragments containing red blood cells with an admixture of eosinophils and neutrophils (**Figure 1B**). Magnetic resonance imaging (MRI) of the brain performed at day 3 (**Figure 1C**) showed extensive left MCA territory infarct with haemorrhagic transformation within the left basal ganglia. Transoesophageal echocardiogram revealed a large patent foramen ovale (PFO). At day 60, he had ongoing global aphasia, left sided gaze preference and dense right hemiparesis.

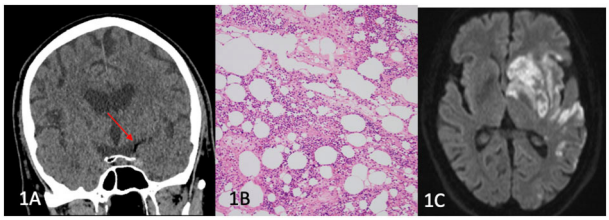

FIGURE 1 | (A) Left hypodense M1 artery (red arrow), **(B)** histopathology showing bone marrow constituents and adipose tissue consistent with fat embolism, **(C)** Diffusion weighted imaging (DWI) showing left MCA territory infarction.

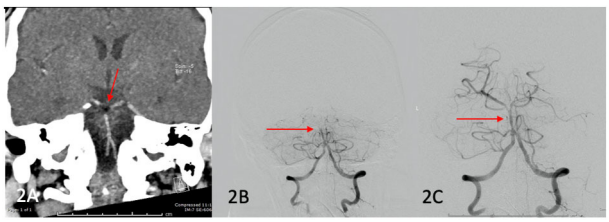

FIGURE 2 | (A) (Red arrow) fat embolism demonstrated in the basilar artery, **(B)** pre recanalization ECR images confirming occlusive thrombus in basilar artery (red arrow), **(C)** post recanalization images showing reperfusion of mid and distal basilar artery (red arrow).

CASE 2

A 47-year-old male with a background of valvular atrial fibrillation on warfarin, type 2 diabetes mellitus, chronic obstructive pulmonary disease, stage 3 chronic kidney disease and obesity was admitted for a mechanical mitral valve replacement for rheumatic mitral valve disease. Intraoperative cross-clamping time and bypass time was 66 and 90 min, respectively. Forty-eight hours post operatively, he developed evolving right sided hemiparesis and facial weakness, right gaze preference and right homonymous inferior hemianopia. CT-B initially did not demonstrate any acute changes although a hypodense basilar was noted retrospectively. At day 5 post-sternotomy, he had a deterioration in conscious state from GCS 15 to GCS 10 (E3V1M6). CT-A demonstrated a hypodense basilar artery (HU of−44) extending into the posterior cerebral arteries bilaterally (**Figure 2A**). He proceeded to ECR with successful recanalisation and stenting of the mid-basilar artery (see **Figures 2A–C**). Repeat CT-B showed established bilateral occipital and cerebellar strokes. The patient was managed with 48 h of heparin infusion post thrombectomy after which warfarin was reinstated. PFO was not demonstrated on post-operative TTE. He made a steady recovery and at 12 months post stroke was able to ambulate 50 metres without a gait aid.

CASE 3

A 69-year-old female with a past medical history of mastocytosis, asthma, and previous provoked deep venous thrombosis

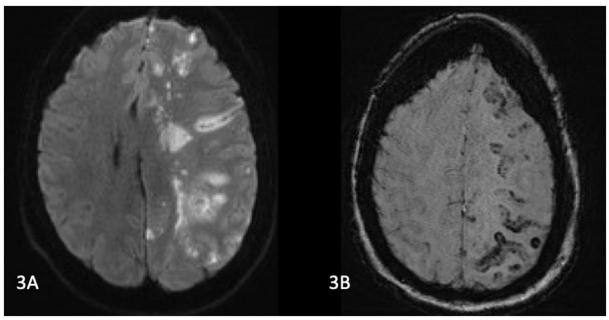

FIGURE 3 | (A) MRI Brain on day 1 post operatively. Diffusion weighted images show left MCA territory infarction with a similar distribution of abnormalities on suspectibility weighted imaging) **(B)**. MCA, middle cerebral artery; DWI, diffusion weight imaging; ECR, endovascular clot retrieval.

presented after a mechanical fall, sustaining a comminuted left intertrochanteric femoral fracture. She underwent insertion of a left intramedullary nail the next day, positioned in the right lateral position. Intraoperatively, concerns about fat embolism were raised after a transient period of hypoxia and hypotension that occurred 5 min after completion of the intramedullary nailing.

Whilst in recovery, the patient was noted to have a GCS of 8 (E3V1M4). She had a severe right sided hemiparesis, left gaze deviation, with a NIHSS of 23. CT brain, angiogram of the brain/neck, and perfusion imaging revealed loss of grey-white differentiation in the left frontal and parietal lobes. There was no large vessel occlusion or significant perfusion lesion. Diffusion weighted MRI the next day revealed a left MCA territory infarction, with cortical, basal ganglia, and thalamic involvement, and associated susceptibility weighted imaging (SWI) changes (**Figure 3**). She was treated with a trial of hyperbaric oxygen (100% for 60 min) and dexamethasone. Transthoracic echocardiogram (TTE) revealed a PFO. The following day, the patient clinically deteriorated and was found to have significant cerebral oedema and midline shift, and an emergency decompressive hemicraniectomy was performed. After a period of monitoring without meaningful clinical improvement, she was palliatively managed and died in hospital.

DISCUSSION

Fat embolism syndrome (FES) is a clinical syndrome manifest by fat particles embolising into the systemic circulation and microcirculation. These emboli then cause damage within the microcapillaries, and may trigger a systemic immune response (1). Multiple different theories exist regarding the underlying pathophysiology of FES. The "mechanical theory" suggests that trauma causes the release of fat particles into the venous system, and then may enter the arterial system via cardiopulmonary shunts, or due to high pulmonary artery pressure (1, 2). The "biochemical theory" suggests that a stressed state within the body leads to systemic catecholamine release, and subsequently releases fat into the blood. Free fatty acids and activation of other

inflammatory markers then lead to a systemic inflammatory response (1, 2). Overall, an inflammatory response causing an acute respiratory distress syndrome, diffuse petechial rash, and diffuse encephalopathy with associated MRI changes have been reported (3, 4). Patients typically develop symptoms within 24–72 h of the triggering event, presumed related to the inflammatory reaction (1). Neurological features often occur concurrently with respiratory distress (2).

Not all patients with fat embolism develop FES. FES is most commonly reported after orthopaedic trauma, due to the increased intramedullary pressure in the long bones in this setting (5). The incidence and prevalence of fat emboli in the context of orthopaedic procedures has been reported variably. One prospective review of patients undergoing long bone and pelvic fractures found that 4–10% of patients developed FES. An earlier review suggested a higher prevalence of 19% in patients presenting after orthopaedic trauma, and some reviews suggest a much lower incidence of <1% (4, 6). There are likely multiple reasons for this heterogeneity in identified incidence, including the possibility that FES may be under-recognised with concurrent significant traumatic injuries, and patients may variably fulfil diagnostic criteria. A review of 100 cases secondary to trauma, with or without orthopaedic injuries, described respiratory symptoms occurring in 75% of patients, and that approximately a third presented first with either neurological or dermatological or respiratory involvement. Any one of respiratory, neurological and dermatological involvement met their major criteria for the diagnosis of FES but they did not describe the incidence of all three triad components occurring (7).

Neuroimaging features in FES typically show diffuse and bilateral abnormalities. Diffuse cytotoxic oedema, often referred to as the "starfield pattern" on MRI, is the most commonly associated finding (8). A systematic review by Kuo et al. identified 5 primary patterns of MRI abnormalities, all of which correlate to FES being a primarily immunologic and microcirculation pathology (9). They found that patients most commonly have scattered embolic ischaemic features in the acute FES phase, which progresses to features of cytotoxic and vasogenic oedema in the subacute phases. Petechial haemorrhage may be seen in both the acute and chronic phases, and chronic sequelae, including cerebral atrophy, and features of demyelination, have been described. Radiodensity measurement of hypodensities within the brain parenchyma to correlate with the density of fat (variably reported between −30 and −100 HU), is not commonly reported, although the finding of a "hypodense artery," has been more commonly reported in fat embolism associated LVO, and will be discussed further below (10–12).

In comparison to the well-established features of FES described above, all patients in our case series had features of LVO, warranting treatment with ECR and decompressive hemicraniectomy, which are not reported in FES patients. We performed a literature review to identify similar cases of fat embolism and LVO. Searches of Pubmed were independently performed by the first two authors. Medical search headings (MeSH) including "brain ischemia," "stroke," "ischemia," "arterial occlusive diseases," "ischemic stroke" were combined with "embolism, fat." Six hundred ninety results were identified on Pubmed. On Embase, MeSH terms included "brain ischemia," "cerebrovascular accident," "ischemia," combined with "fat embolism" identified 136 results. Where relevant publications were in other languages, attempts were made for English translations. Animal studies were excluded. All case reports and case series of patients who had identified large vessel occlusions on imaging, or who had a distribution of stroke in keeping with a large vessel occlusion were included where there was evidence of fat embolism. References of relevant articles were screened for additional cases.

Patients were excluded from our review where they underwent a recent procedure involving injection or removal of fat, including autologous fat filler procedures, and liposuction. The entity of filler induced cerebral embolism (FICE) has been well-reported and has been recently reviewed by Wang et al. FICE generally involves areas of extensive arterial supply and are known "danger zones" for intracranial emboli (13).

We identified 18 patients, in addition to the 3 reported in this series for the first time, and their characteristics are summarised in **Supplementary Table 1**. They ranged in ages from 25 to 91 years old. Nine patients were female, seven were male, and two did not have gender reported. Eight of the reported patients had undergone cardiac surgery, most commonly mitral valve replacement (6 patients) (11, 14–20). Six patients had orthopaedic procedures or preceding trauma, and three patients were deemed spontaneous (2, 10, 21–27). Of the spontaneous cases, one patient had a history of liposuction and gluteal augmentation 2 months prior, but this was presumed unrelated (2). One patient had LVO 9 days after Caesarean section, with multiple other embolic complications (28). Eleven of the 15 patients who did not have spontaneous LVO had onset of symptoms within 6 h of the presumed mechanism of injury (10, 11, 14, 15, 19–21, 23–25, 27). Four of the five patients who underwent PFO assessment were found to have a PFO (23–25, 27, 28). None of the patients had reported dermatologic manifestations, and only two patients had respiratory features (10, 28). With regards to treatment where it was available, one patient was treated with intravenous thrombolysis, eight patients underwent ECR or attempted ECR and three patients underwent decompressive hemicraniectomy. One patient also underwent (superficial temporal artery to middle cerebral artery) STA-MCA bypass in an attempt to bypass a right internal carotid artery occlusion (14). Of the patients with reported outcomes, 7 patients died within 3 months, 3 had mild persistent symptoms, and 3 had significant functional disability.

Our case series and literature review highlight key clinical, radiological and management considerations in LVO from fat embolism, in contrast to fat embolism syndrome (FES), which are summarised in **Table 1**. As highlighted above, the clinical presentation of the LVO cohort of patients was different, with most patients presenting within 6 h of the triggering event, in comparison to 24–72 h in FES patients. This might relate to some differences in the underlying pathophysiology. It is conceivable that in the context of PFO permitting intra-cardiac shunting, as was the case in patient 1 and 3 of our series, a sufficiently large fat vacuole could occlude a main branch in the Circle of Willis, with severe clinical symptoms occurring earlier due to mechanical

TABLE 1 | Difference in features between fat embolism syndrome and fat embolism related large vessel occlusion.

	Fat embolism syndrome	Fat embolism related large vessel occlusion
Precipitants	Most commonly orthopaedic trauma/procedures	Most commonly orthopaedic trauma/procedures, also seen post cardiac surgery (most commonly mitral valve replacement)
Symptom onset	Typically within 24–72 h	Most cases occurred within the first 6 h of the precipitant
Associated respiratory/dermatological manifestations	Typically present	Typically absent
Treatments	Conservative management	Thrombolysis, endovascular clot retrieval and decompressive hemicraniectomy may be considered depending on clinical and neuroimaging features
Prognosis	Typically good	High mortality and/or permanent disability

occlusion. This is in contrast to FES, whereby the inflammatory cascade begins with free fatty acid release which causes a diverse range of systemic and central nervous system symptoms, with the pulmonary circulation possibly acting as a "buffer," rather than the clinical expression of cerebral LVO (1).

Other features of fat embolism related LVO also support the "mechanical theory" hypothesis. Changes to intramedullary pressure, tourniquet release and limb reperfusion are postulated to cause right atrial pressure to increase. This may in turn precipitate intracardiac shunting *via* a PFO of released fat emboli (29) in the context of orthopaedic instrumentation of the medullary canal and increase risk of stroke. Four of the five patients in our literature review and two patients in our series were noted to have PFO, compared to the population prevalence of PFO from autopsy studies of 27.4%. A retrospective cohort study showed that peri-operative ischaemic stroke in patients with PFO is 3.2% compared to 0.5% in patients without PFO, and whilst fat embolism is often mentioned as a cause of perioperative stroke, the risk is not quantifiable (30). The findings of fat embolism related LVO post cardiac surgery may be related to the sternal bone marrow being a source of lipid emboli, or the cardiopulmonary bypass apparatus, which may also reintroduce scavenged pericardial blood containing fat emboli (31).

Given the common mechanism of fat emboli underpinning both FES and LVO, it is likely that LVO strokes lie on the spectrum of clinical phenomena that can be seen with fat emboli regardless of source. Illustrative of this is patient 3 in our case series, whom had more typical findings of FES with intraoperative transient hypoxia and hypotension, but was found to have a single territory LVO infarction. Respiratory and dermatological features that are typically seen in FES are also not seen as frequently in fat embolism LVO patients. In our literature review and our cases, no patients had dermatological features, and only 2 had respiratory features. The presumed mechanism for respiratory and dermatological features relates to progressive venous congestion after the inflammatory response is triggered – we speculate that this phenomenon does not occur as frequently in LVO patients, and there may be less inflammatory response in these patients (32). This is also supported by their earlier presentations, and also by MRI findings. The finding of the hypodense artery sign has been consistently reported in the literature, with Hounsfield units (HU) of −30 to −100 reflecting intraarterial fat, and was used to assist in the diagnosis in our case series (11, 12). In FES, the end product of the inflammatory response is the typical diffuse "starfield pattern," reflecting cytotoxic oedema (2). This was not seen in our case series, or commented on in the cases in the literature. The lack of respiratory or dermatological features is of relevance, as it may pose an additional challenge for the diagnosis of fat embolism associated LVO in the intraoperative or immediate post-operative state, where patients are also under the effects of anaesthesia and neurological assessment may be more challenging.

In FES, the overall mortality is 10%, and most patients return to baseline function (8, 33). In contrast, cases of LVO from fat emboli appear more neurologically severe compared to FES, with previous patient reports requiring decompressive hemicraniectomy for diffuse cerebral oedema (10, 15, 28, 34). Endovascular clot retrieval is also emerging as a treatment option for these cases (2, 14, 22–26, 28, 35). Successful endovascular clot retrieval has also been performed in large vessel occlusions due to fat embolism during liposuction (35). Techniques of endovascular clot retrieval vary in the devices used and include stent-retrievers, distal aspiration catheters, and proximal balloon occlusion catheters used alone or in combination. Selection of technique reflect site of occlusion, anatomical access, operator preference, and with clot composition one additional factor influencing first pass effect or final reperfusion success. Prospective assessment of clot composition can be based on density on NCCT, perviousness on post contrast studies, length, and MRI identification of red blood cell rich clot. Currently there is no consensus on procedural choice based on these findings, other than to suggest that thrombolysis may be less effective in the less common calcified, tumour or fat containing emboli, hence a lower threshold for proceeding with mechanical thrombectomy. Distal contact aspiration alone (ADAPT) OR used in combination with stent retrievers would be a favoured first line approach. Of the 7 reported patients who underwent reperfusion therapy (ECR or STA-MCA bypass, excluding the patient who had unsuccessful ECR), 5 survived with reasonable function (modified Rankin

scale 3 or better from case descriptions), one patient died due lack of clinical improvement, and another died due to intracranial haemorrhage shortly after ECR (2, 14, 22–26). In comparison, of the patients who did not receive reperfusion therapy or received unsuccessful reperfusion therapy, five patients died, and two were functionally disabled (mRS 4) (10, 15, 17, 18, 21, 27, 28). The outcomes of 4 patients are unknown.

CONCLUSION

To our knowledge, this is the largest case series of stroke from large vessel occlusion caused by fat embolism. We illustrate two cases of stroke from large vessel occlusions as a complication from orthopaedic surgery due to paradoxical cerebral fat embolism from PFO, and one case from cardiac sternotomy. In our first case, we were able to obtain histological confirmation by demonstrating the combination of adipocytes, bone marrow constituents and thrombus.

Fat emboli causing large vessel occlusion can be an important cause of acute neurological deterioration in the immediate post-operative period. In keeping with previous case reports, our case series highlights the importance of recognising large vessel stroke due to fat emboli post orthopaedic and cardiac surgery, and that patient outcomes appear poorer in comparison to fat embolism syndrome. It is likely that there is a clinical spectrum of FES which includes the patients presenting with LVO. Clinicians should be aware of this entity, and prompt neuroimaging should be performed when the diagnosis is suspected, as recanalisation treatments may improve clinical outcomes.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

PATIENT CONSENT

Informed consent was obtained from all patients described in this case series. In circumstances where the patients could not express consent, informed consent was obtained from their legally appointed medical decision maker(s).

AUTHOR CONTRIBUTIONS

SO and SR contributed equally to writing the manuscript. PM contributed to writing the manuscript. BC, EH, GC, and PM curated the cases, imaging, and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.746099/full#supplementary-material

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Distribution of Diagnoses and Clinical and Imaging Characteristics in 1,322 Consecutive Suspected Stroke Patients

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Background: Endovascular thrombectomy (EVT) has become the standard of care for large-vessel occlusion strokes, but several barriers for implementing an optimal organization of stroke management remain. Major issues include the lack of reliable data on the percentage of stroke patients potentially eligible for EVT especially in times of expanding indications for EVT. Our aim was therefore to study the frequencies of possible EVT-eligible patients such as patients with medium-vessel occlusions, patients with low Alberta Stroke Program Early Computed Tomography Scores (ASPECTS), patients presenting in an extended time window after onset of symptoms, and patients with mild symptoms at presentation (National Institutes of Health Stroke Scale, NIHSS $\leq$ 5). We also give detailed imaging and clinical information about the patients presenting with intracranial hemorrhage and other ischemic stroke mimics stratified by symptoms at presentation.

Methods: Cohort study of all consecutive patients with suspected acute stroke presenting to a tertiary care center in Germany between September 1, 2016, and August 31, 2017. Baseline and follow-up clinical and imaging characteristics were collected from patients' medical charts.

Results: Of 1,322 patients with a suspected acute stroke, 592 (44.8%) had ischemic strokes, 221 (16.7%) had hemorrhagic strokes, 190 (10.9%) had transient ischemic attacks (TIAs), and 319 (24.1%) were classified as stroke mimics. Stroke severity was mild (NIHSS $\leq$ 5) in 866 (65.5%) patients; 15.7% of the patients with an occlusion of the anterior circulation had an ASPECTS $\leq$ 5, 17.4% of the patients with an ischemic stroke had distal vessel occlusions, and 49% of the patients presented later than 6 h after onset of symptoms.

Conclusion: Our results help to plan resources in thrombectomy-capable centers in times of expanding indications for EVT where resources will have to be adjusted to

patients with low-NIHSS, low-ASPECTS, and distal occlusions, and patients presenting in the extended time window, which may altogether account for an additional 20% of all ischemic stroke patients.

Keywords: stroke, endovascular treatment, resources, intravenous thrombolysis, mechanical thrombectomy

INTRODUCTION

Endovascular thrombectomy (EVT) has become the standard of care for large-vessel occlusion strokes, and acute management of ischemic stroke has dramatically changed since the demonstration of the efficacy of EVT (1). However, several barriers for implementing an optimal organization of stroke management remain. A major issue among them is the lack of reliable data on the percentage of stroke patients eligible for EVT and their characteristics. Even though the number of patients with large-vessel occlusions and occlusions of the M2 segment of the middle cerebral artery has been estimated (2–5), detailed information about further characteristics such as frequency of stroke mimics and intracranial hemorrhages is lacking. Moreover, the available information is mostly confined to large-vessel occlusion strokes, but in times of expanding indications for EVT (6), the frequency of more medium-vessel occlusions, the distribution of Alberta Stroke Program Early Computed Tomography Score (ASPECTS), the time window of presentation, and the National Institutes of Health Stroke Scale (NIHSS) of those patients are also of crucial importance for planning thrombectomy resources. We therefore conducted a cohort study of consecutive patients admitted with suspected stroke to a tertiary care hospital and describe all these strategically important variables. We also give detailed imaging and clinical information about the patients presenting with intracranial hemorrhage and other ischemic stroke mimics and stratify the results by NIHSS at presentation.

METHODS

The authors declare that the underlying data will be made available upon reasonable request by the corresponding author.

Study Population

This study includes a prospectively collected cohort of all consecutive patients with suspected acute stroke presenting to a tertiary care center in Germany between September 1, 2016, and August 31, 2017. Acute stroke was suspected if patients (1) were transported to the hospital from an ambulance under the "stroke code (high probability of stroke according to the emergency doctor or paramedic)," (2) presented independently to the hospital and were triaged as suspected acute stroke after the first contact, or (3) were transferred from another hospital either with a confirmed stroke or suspected stroke. Patients were identified by screening reports of all head CTs performed in the study period and were validated by checking neurological clinical reports. All acute patients with suspected acute stroke undergo emergent CT at our center. Demographic information and risk factors were collected from the hospital information system. The National Institute of Health Stroke Scale (NIHSS) is routinely collected by a certified stroke neurologist on admission and discharge. The final diagnosis and modified Rankin Scale Score at discharge (mRS) were obtained from the final clinical report. Imaging findings were obtained through reviewing all scans—occlusion location was rated on baseline CT angiography (CTA) and validated on the Digital Subtraction Angiography (DSA) images if available. The Alberta Stroke Program Early CT Score (ASPECTS) was only evaluated in ischemic stroke patients with an occlusion of the anterior circulation. Additionally, the ABCD2 score estimating the risk of stroke after transient ischemic attack and minor stroke was calculated (7). Medium-vessel occlusions were defined as an occlusion visible on the CTA other than the M1, ICA, or BA. Small vessel occlusions were defined as an acute ischemic stroke (as determined by the non-contrast CT or perfusion CT) with no visible occlusion on the CTA. The local ethics committee waived the need for a formal application or a separate consent concerning the inclusion in our observational database.

Hospital Setting

The hospital has 1,563 beds and has 55,159 inpatient and 222,303 outpatient cases per year. The Department of Neurology has 4,791 inpatient cases per year (as per 2017). It serves as the primary tertiary hospital for eight German districts and has a catchment area of roughly 1,100,000 persons and 6,500 km^2. The largest city within its catchment area has 118,911 inhabitants, and the region has a below average population density. It is part of a stroke network with an integrated imaging service and serves as a referral center for 17 primary hospitals.

Statistical Analyses

Statistical analysis was performed using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA, https://www.graphpad.com/, 2021). Parametric variables are stated as mean ± standard deviation (SD). Non-parametric or ordinary variables are presented as median and interquartile range (IQR). No interference statistics were performed. All data are presented for the whole collective, patients with a mild stroke (NIHSS $\leq$ 5), a moderate stroke (NIHSS 6–12) and for patients with a severe stroke (NIHSS $>$ 12).

RESULTS

In the 1-year study period, 1,322 patients presented with a suspected acute stroke, of whom 592 (44.8%) had ischemic strokes, 110 (8.3%) had intraparenchymal hemorrhages (ICHs), 90 (6.8%) had subarachnoid hemorrhages (SAHs), 21 (1.6%) had subdural hematomas (SDHs), 190 (14.4%) had transient ischemic attacks (TIAs), and 319 (24.1%) were classified as

TABLE 1 | Baseline characteristics.

Variable	All patients (n = 1,322)	NIHSS ≤ 5 (n = 866, 65.5%)	NIHSS 6–12 (n = 282, 21.3%)	NIHSS ≥ 13 (n = 174, 13.2%)
Female, *n* (%)	605 (45.8%)	378 (43.6%)	136 (48.2%)	91 (52%)
Age, Mean (SD)	70.8 (±14.9)	69.1 (±15.3)	73.5 (±13.8)	74.8 (±12.7)
Over 80 years old	385 (29.1%)	222 (25.6%)	99 (35.1%)	64 (36.8%)
NIHSS, median (IQR)	4 (2-8)	2 (2-4)	9 (8-11)	17 (4-21)
Transfer patients	240 (18.2%)	110 (12.7%)	62 (22.0%)	68 (39.1%)
First diagnostic step				
Native CT	485 (36.7%)	384 (44.3%)	76 (27.0%)	25 (14.4%)
CT + CTA	519 (39.3%)	387 (44.7%)	89 (31.6%)	43 (24.7%)
CT + CTA + CTP	296 (22.4%)	83 (9.6%)	110 (39.0%)	103 (59.2%)
Polytrauma CT	22 (1.6%)	12 (1.4%)	7 (2.4%)	3 (1.7%)
Diagnosis				
Ischemic Stroke, *n* (%)	592 (44.5%)	300 (34.6%)	163 (57.8%)	129 (74.1%)
Acute Stroke	424 (71.6%)	193 (64.3%)	119 (73%)	112 (86.8%)
Media Ischemia	393 (66.4%)	168 (56.0%)	124 (76.1%)	101 (78.3%)
SVO	321 (54.2%)	228 (76%)	84 (51.5%)	9 (7%)
ICA	53 (9%)	12 (4%)	10 (6.1%)	31 (24%)
M1	88 (14.9%)	5 (1.7%)	27 (16.6%)	56 (43.4%)
M2	57 (9.6%)	19 (6.3%)	23 (14.1%)	15 (11.6%)
M3	17 (2.9%)	9 (3%)	4 (2.4%)	4 (3.1%)
VA	18 (3%)	11 (3.7%)	5 (3.1%)	2 (1.6%)
BA	9 (1.5%)	2 (0.7%)	1 (0.6%)	6 (4.7%)
P1	13 (2.2%)	8 (2.6%)	4 (2.5%)	1 (0.8%)
P2	6 (1%)	3 (1%)	3 (1.8%)	0 (0%)
A1	1 (0.2%)	0 (0%)	0 (0%	1 (0.8%)
A2	9 (1.5%)	3 (1.0%)	2 (1.2%)	4 (3.1%)
ICH, *n* (%)	110 (8.3%)	33 (3.8%)	49 (17.4%)	28 (16.1%)
Loco typico	52 (47.3%)	23 (69.7%%)	21 (42.8%)	8 (28.6%)
Atypical	58 (52.7%)	10 (30.3%)	28 (57.2%)	20 (71.4%)
SAH, *n* (%)	90 (6.8%)	65 (7.5%)	18 (6.4%)	7 (4%)
Conservative Treatment	50 (55.5%)	44 (67.7%)	4 (22.2%)	2 (28.6%)
Clipping	16 (17.8%)	9 (13.8%)	5 (27.8%)	2 (28.6%)
Coiling	24 (26.7%)	12 (18.5%)	9 (50%)	3 (42.8%)
TIA, *n* (%)	190 (14.4%)	169 (19.5%)	20 (7.1%)	1 (0.6%)
ABCD2 0–3	70 (36.8%)	67 (39.8%)	3 (15%)	0 (0%)
ABCD2 4–5	90 (47.4%)	78 (46.5%)	12 (60%)	0 (0%)
ABCD2 6–7	30 (15.8%)	23 (13.7%)	5 (25%)	1 (100%)
Mimic, *n* (%)	319 (24.1%)	289 (33.4%)	23 (8.2%)	7 (4%)
SDH, *n* (%)	21 (1.6%)	10 (1.2%)	9 (3.2%)	2 (1.1%)
Thrombectomy, *n* (%)	135 (10.2%)	15 (1.7%)	41 (14.5%)	79 (45.4%)
i.v. tPA	167 (12.6%)	48 (5.5%)	62 (22%)	57 (32.8%)
ASPECTS				
0–3, *n* (%)	8 (3.6%)	1 (2.1%)	1 (1.5%)	6 (5.5%)
4–5, *n* (%)	27 (12.1%)	2 (4.2%)	4 (6.1%)	21 (19.1%)
6–8, *n* (%)	61 (27.2%)	10 (20.8%)	15 (22.7%)	36 (32.7%)
9–10, *n* (%)	128 (57.1%)	35 (72.9%)	46 (69.7%)	47 (42.7%)
Previous stroke, *n* (%)	255 (19.3%)	141 (16.3%)	73 (25.9%)	41 (23.6%)
Previous TIA, *n* (%)	85 (6.4%)	61 (7.0%)	14 (5%)	10 (5.7%)
Coronary heart disease, *n* (%)	253 (19.3%)	153 (17.7%)	65 (23%)	35 (20.1%)
Peripheral artery disease, *n* (%)	71 (5.4%)	50 (5.8%)	13 (4.6%)	8 (4.6%)
Heart failure, *n* (%)	105 (7.9%)	56 (6.5%)	31 (11%)	18 (10.3%)
Smoking, *n* (%)	220 (16.6%)	151 (17.4%)	49 (17.4%)	20 (11.5%)
Alcohol, *n* (%)	83 (6.2%)	46 (5.3%)	17 (6%)	20 (11.5%)
Hypertension, *n* (%)	897 (67.9%)	562 (64.9%)	207 (73.4%)	128 (73.6%)
Hyperlipidemia, *n* (%)	507 (38.4%)	325 (37.5%)	118 (41.8%)	64 (36.8%)
Diabetes mellitus, *n* (%)	310 (23.4%)	183 (21.1%)	78 (27.7%)	49 (28.2%)
Atrial fibrillation, *n* (%)	250 (18.9%)	111 (12.8%)	67 (23.8%)	72 (41.4%)
Persistent foramen ovale, *n* (%)	359 (27.2%)	234 (27%)	84 (29.8%)	41 (23.6%)
Oral anticoagulation, *n* (%)	241 (18.2%)	138 (16.1%)	62 (22%)	41 (23.6%)
Onset (last seen well) to door (h)				
<4.5, *n* (%)	609 (46.1%)	337 (39%)	161 (57.1%)	111 (63.8%)
4.5–6, *n* (%)	66 (5.0%)	40 (4.6%)	16 (5.7%)	10 (5.7%)
6–12, *n* (%)	172 (13%)	113 (13%)	37 (13.1%)	22 (12.7%)
12–24, *n* (%)	278 (21%)	213 (24.6%)	42 (14.9%)	23 (13.2%)
>24, *n* (%)	197 (14.9%)	163 (18.8%)	26 (9.2%)	8 (4.6%)

ASPECTS, Alberta Stroke Program Early CT Score; BA, basilar artery; CTA, CT angiography; CTP, CT perfusion; ICA, internal carotid artery; ICH, intraparenchymal hemorrhage; IQR, interquartile range; i.v. tPA, intravenous tissue plasminogen activator; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; SAH, subarachnoid hemorrhage; SD, standard deviation; SDH, subdural hemorrhage; SVO, small vessel occlusion; TIA, transient ischemic attack; VA, vertebral artery.

stroke mimics. Mean age at admission was 70.8 years [standard deviation (SD) ±14.9 years], 385 (29.1%) were more than 80 years old, and 605 (45.8%) were female. Stroke severity was mild (NIHSS ≤ 5) in 866 (65.5%), moderate (NIHSS 6–12) in 282 (21.3%), and severe (NIHSS ≥ 13) in 174 (13.2%) patients. Arterial imaging was performed in 837 patients (63.3%), and of

those 296 (22.4%) patients who received additional CT perfusion (CTP). Overall, 135 (10.2%) patients underwent EVT and 167 (12.6%) of the patients were treated with intravenous tissue plasminogen activator (i.v.-tPA). In total, 675 patients (51.1%) presented within 6 h of symptom onset, 172 patients (13%) between 6 and 12 h of onset, 278 patients (21%) between 12 and 24 h of onset, and 197 patients (14.9%) even later than 24 h after onset of symptoms. Detailed information on baseline and imaging characteristics is presented in **Table 1**.

Suspected Stroke Patients With Mild Symptoms (NIHSS ≤ 5)

Most patients presented with mild symptoms (866 patients; 65.5%), and among those, ischemic stroke (300 patients; 34.6%), stroke mimics (289; 33.4%), and TIA (169; 19.5%) were the most common diagnoses. Additionally, 65 patients had SAHs (7.5%), 33 (3.8%) had ICHs, and 10 (1.2%) had SDHs. Median NIHSS was 2 (IQR 2–4) and mean age was 69.1 years (SD ± 15.3); 44.3% underwent native CT only, while arterial imaging was performed in the remaining 55.7%. Eighty-three patients (9.6%) underwent additional CTP.

Out of the 300 ischemic strokes, 168 (56%) were deemed acute and a causative occlusion was found in 72 (24%) patients. Out of the 72 occlusions, 19 (26.4%) were large-vessel occlusions (defined as ICA, M1 and BA) and the remaining 53 (73.6%) were medium-vessel occlusions; for a detailed overview of the occlusion locations, please refer to **Table 1**.

EVT was performed in 15 patients (5%) and i.v.-tPA was administered in 48 (16%) of the ischemic strokes. ASPECTS was very low (0–3) in 1 patient (2.1%), low (4, 5) in 2 patients (4.2%), medium (6–8) in 10 patients (20.8%), and high (9, 10) in 35 patients (72.9%) with an occlusion in the anterior circulation.

Although only mildly affected, excellent functional outcome (defined as mRS ≤ 1) was only achieved in 47.1% of the patients and 70.2% were functionally independent (mRS ≤ 2) at discharge (**Table 2**).

Suspected Stroke Patients With Moderate Symptoms (NIHSS 6–12)

In this group (n = 282 patients; 21.3%), 163 (57.8%) patients were diagnosed as ischemic stroke, 49 (17.4%) as ICH, 18 (6.4%) as SAH, 9 (3.2%) as SDH, 20 (7.7%) as TIA, and 23 (8.2%) patients had stroke mimics. Median NIHSS was 9 (IQR 8–11) and mean age was 73.5 years (SD ± 13.8). Within this group, 27% underwent native CT only, while arterial imaging was performed in the remaining 73%. One hundred and ten patients (39%) underwent additional CTP.

Out of the 163 ischemic strokes, 124 (76.1%) were deemed acute and a causative occlusion was found in 79 (48.5%) patients. Out of the 79 occlusions, 28 (35.4%) were large-vessel occlusions and the remaining 51 (64.6%) were medium-vessel occlusions. EVT was performed in 41 patients (25.2%) and i.v.-tPA was administered in 62 (38%) of the ischemic stroke patients. ASPECTS was very low in 1 (1.5%) patient, low in 4 patients (6.1%), medium in 15 patients (22.7%),

TABLE 2 | Overview of outcome variables stratified by severity.

Variable	All patients (n = 1,322)	NIHSS ≤ 5 (n = 866)	NIHSS 6–12 (n = 282)	NIHSS ≥ 13 (n = 174)
Length of stay (days), Median (IQR)	4 (1-9)	4 (1-7)	6 (1-12)	8 (3-15)
Discharge location				
Previous environment, *n* (%)	566 (42.8%)	498 (57.5%)	52 (18.4%)	16 (9.2%)
Nursing home, *n* (%)	210 (15.9%)	112 (12.9%)	62 (22.0%)	36 (21,1%)
Rehabilitation, *n* (%)	436 (33%)	225 (26%)	130 (46.1%)	81 (46.3%)
In-hospital dead, *n* (%)	112 (8.5%)	31 (3.6%)	39 (13.8%)	42 (24.1%)
NIHSS at discharge, Median (IQR)	1 (0–5)	0 (0–2)	5 (2-10)	12 (5-22)
mRS at discharge, Median (IQR)	2 (1-4)	1 (0–3)	2 (3-5)	5 (4-5)
mRS 0, *n* (%; cumulative within group %)	286 (21.6%; 21.6%)	256 (29.6%; 29.6%)	22 (7.8%; 7.8%)	8 (4.6%; 4.6%)
mRS 1, *n* (%; cumulative within group %)	271 (20.5%; 42.1%)	216 (24.9%; 54.5%)	46 (16.3%; 24.1%)	9 (5.1%; 9.7%)
mRS 2, *n* (%; cumulative within group %)	196 (14.8%; 56.9%)	144 (16.6%; 71,1%)	43 (15.2%; 39.3%)	9 (5.1%; 14.9%)
mRS 3, *n* (%; cumulative within group %)	166 (12.6%; 69.6%)	105 (12.1%; 83.2%)	44 (15.6%; 54.9%)	17 (9.7%; 24.6%)
mRS 4, *n* (%,: cumulative within group %)	159 (12%; 81.6%)	71 (8.2%; 91.4%)	54 (19.1%; 74%)	34 (19.4%; 44%)
mRS 5, *n* (%; cumulative within group %)	104 (7.9%; 89.5%)	16 (1.8%; 93.2%)	33 (11.7%; 85.7%)	55 (32%; 76%)
mRS 6, *n* (%; cumulative within group %)	112 (8.4%; 97.9%)	31 (3.6%; 96.8%)	39 (13.9%; 95.6%)	42 (24%; 100%)
mRS unknown (%; cumulative within group %)	28 (2.1%; 100%	27 (3.2%; 100%)	1 (0.4%; 100%)	0 (0%; 100%)
Hemicranectomy, *n* (%)	41 (3.1%)	16 (1.8%)	16 (5.7%)	9 (5.1%)

IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale.

and high in 46 (69.7%) of the patients with an occlusion in the anterior circulation. Excellent outcome was achieved in 25.8%, while 39.9% were functionally independent at discharge. In-hospital mortality was 9.2%. ICHs were far more common in this group with a frequency of 17.4% (**Table 2**).

Suspected Stroke Patients With Severe Symptoms (NIHSS ≥ 13)

In this group, ischemic stroke was the most common diagnosis (129 patients, 74.1%), followed by ICH (28 patients, 16.1%), SAH and stroke mimics (each 7 patients, 4%), SDH (2 patients, 1.1%), and TIA (1 patient, 0.6%). Median NIHSS was 17 (IQR 14–21) and mean age was 74.8 years (SD ± 12.7). Within this group, 14.4% underwent native CT only, while arterial imaging was performed in the remaining 85.6%. One hundred and three patients (59.2%) underwent additional CTP. Out of the 129 ischemic strokes, 101 (78.3%) were deemed acute and a causative occlusion was found in 119 (92.2%) patients. Out of the 119 occlusions, 93 (78.2%) were large-vessel occlusions and the remaining 26 (21.8%) were medium-vessel occlusions. EVT was performed in 79 (61.2%) and i.v.-tPA was administered in 57 patients (44.2%) with ischemic stroke. ASPECTS was very low in 6 (5.5%), low in 21 (19.1%), medium in 36 (32.7%), and high in 47 (42.7%) patients with an occlusion of the anterior circulation. Excellent outcome was achieved in 9.3%, while 16.3% of the patients were functionally independent at discharge. In-hospital mortality was 21.8% (**Table 2**).

DISCUSSION

Our study has several major findings: (1) it shows that a substantial proportion of patients with suspected stroke present with medium-vessel occlusions, which are potentially eligible for EVT; (2) it provides evidence that most suspected stroke patients present with mild symptoms to the emergency department (65.5% had an NIHSS ≤ 5); (3) it shows that a substantial proportion of stroke patients with an occlusion of the anterior circulation presents with an ASPECTS of ≤5 (15.7%); and (4) a large proportion of patients present in an extended time window of 6–24 h after onset of symptoms (34.0%) or even later than 24 h (14.9%).

These results demonstrate that it is important to plan resources in thrombectomy-capable centers not only for patients with LVO and selection criteria in randomized trials but also for patients with low NIHSS, low-ASPECTS patients, patients with distal occlusions, and patients presenting in extended time windows. Recent guidelines of the American Heart Association/American Stroke Association (AHA/ASA) and the European Stroke Organization (ESO)/European Society of Minimally Invasive Neurological Therapy (ESMINT) (8, 9) already partially account for these upcoming changes, and a recent review on expanding indication for EVT gives a foresight on the direction in which EVT will move with the help of advanced imaging and better endovascular devices (6). In this context, our study shows that an additional percentage of up to 20% of all patients with ischemic strokes might be candidates for EVT. This estimate is in line with an analysis for late-window patients by Jadhav et al. based on DAWN and DEFUSE-3 inclusion criteria (10). As we were not able to evaluate the impact of pre-stroke disability, this group might even be larger, as these patients get recognized as candidates for EVT as well (11). Therefore, resource planning in the future should address these developments since substantially higher numbers of EVT patients will lead to higher workloads for neurointerventionalists and other subspecialties such as anesthesiologists. Since the training of such specialists takes years, hospitals should act now and invest in better training capabilities (12). Moreover, our study gives detailed information about the distribution of stroke mimics such as different types of intracranial hemorrhages. It shows the overall frequency of all types of intracranial hemorrhages combined was 14.9% in our cohort which is in line with larger epidemiological studies (13, 14). It further suggests that the occurrence of ICH increases whereas SAH gets less common with increasing NIHSS.

Compared to previous studies, the frequency of LVOs was comparable with ∼25% having LVOs in total, and of those, ∼15% have M1, 9% have distal ICA, and 1.5% have basilar artery occlusions (5). This demonstrates the external validity of our results. The frequency of medium-vessel occlusions was with 17.4% lower compared to other studies who reported frequencies between 24 and 43% (15, 16). One possible explanation may be that only 22.4% of the patients in our study underwent perfusion imaging and medium-vessel occlusions might get frequently missed on CT angiography alone (17).

Another finding is the high morbidity and mortality in patients with mild to moderate symptoms (NIHSS ≤ 5) at presentation, with only 70% of the stroke patients being functionally independent (mRS ≤ 2) at discharge. This further underlines the potential importance of performing EVT in patients with low NIHSS. Last, our study is the first to describe the distribution of ASPECTS values in a consecutive cohort of patients with suspected stroke. This adds further information to the general understanding of the distribution of ischemic stroke patients at initial presentation and adds information on how many patients can be expected to be included when low-ASPECTS trials will present positive results for performing EVT (18, 19).

Limitations

Our study has limitations partly attributed to its single-center, retrospective design. Moreover, more patients may have been classified as ischemic stroke and less as TIA if the admission imaging modality would have been MRI instead of CT. The definition of the upper NIHSS bound of the moderate stroke group was made based on our best judgment as there is no clear consensus on this definition and it can be argued that other values in a range from 10 to 15 would have been a better fit. However, we present a comparably

large consecutive cohort with detailed clinical and imaging information that partially was not available before and that is urgently needed to adjust resources in thrombectomy-capable centers.

CONCLUSION

Our results predict an increase of EVT eligible patients of up to another 20% of all ischemic stroke patients. In this context, this study helps to plan resources in thrombectomy-capable centers in times of expanding indications for EVT where resources will have to be adjusted to patients with low-NIHSS, low-ASPECTS, distal occlusions, and patients presenting in the extended time window.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

AB, NN, IT, and CH designed the data collection sheets, collected the data, and performed the analysis. PS, AB, and MP wrote the manuscript. All authors gave final approval of the submitted version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and critically reviewed the manuscript.

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Rescue Endovascular Treatment for Emergent Large Vessel Occlusion With Underlying Intracranial Atherosclerosis: Current State and Future Directions

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Intracranial atherosclerosis (ICAS) is one of the most common causes of stroke worldwide and is associated with high risk of stroke recurrence. While the most common clinical presentation is acute–subacute transient ischemic attack or ischemic stroke, occasionally, patients with underlying ICAS present with acute occlusion of the affected vessel. Diagnosis and endovascular management of ICAS-related emergent large vessel occlusion (ELVO) can be challenging. Herein, we review the current evidence supporting endovascular management of ICAS-related ELVO and discuss future directions.

Keywords: stroke, thrombectomy, intracranial atherosclerosis, stenting, rescue

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INTRODUCTION

Endovascular treatment is the standard of care for acute ischemic stroke patients with emergent large vessel occlusion (ELVO) (1). The benefit from mechanical thrombectomy (MT) is largely driven by achieving successful revascularization (2). However, a subgroup of patients undergoing MT may have refractory occlusions due to underlying intracranial atherosclerosis (ICAS) with resultant residual severe stenosis or unstable plaque and *in situ* thrombosis/re-occlusion (3). Management of this group of patients can be challenging and commonly requires rescue therapy with intra-arterial antiplatelet, thrombolytics, anticoagulation, angioplasty, stenting, or combination of treatment modalities. The safety and efficacy of such rescue treatments have not yet been established, and current evidence is largely driven from small retrospective case series (4–6). In addition, the current literature on the prevalence and endovascular treatment of ICAS-related ELVO mostly comprised Asian studies. It is known that ICAS is more prevalent in Asian population; studies evaluating outcomes of angioplasty and/or stenting in Asian population showed promising results; on the other hand, strong evidence form randomized controlled trials in North America and Europe showed clear advantage of medical management over angioplasty/stenting (7–9). In this review, we discuss the prevalence, pathophysiology, and the available evidence supporting management of ICAS-related ELVO and provide insights on future directions.

PREVALENCE, PATHOPHYSIOLOGY, AND DIAGNOSIS

The prevalence of ICAS-related ELVO ranges from 1.9 to 30% depending on few factors including definition used, the study population included, and the involved vascular territory in the published literature (10–12). ICAS is much less common in Western population compared with Asian

population (12, 13). In Asian population, ICAS-related ELVO is estimated to be responsible for approximately one-third of ELVOs (9, 13); conversely, ICAS-related ELVO is much less common in Western population and is responsible for <10% of all ELVOs (14). This likely reflects the fact that ICAS is more common in Asian than Western population (15). Previous studies evaluating risk factors for ICAS-related ELVO showed that compared with embolic ELVO, ICAS-related ELVO patients are younger and more likely to be men. In addition, patients with ICAS-related ELVO have higher incidence of hypertension, hyperlipidemia, and diabetes mellitus and lower incidence of atrial fibrillation (4). While the abovementioned risk factors are suggestive of ICAS, diagnosis of ICAS-related ELVO poses a major challenge.

The mechanism of acute/subacute strokes with ICAS had been extensively studied before (16–19). The main mechanisms responsible for TIA/stroke with ICAS are as follows: (a) *in situ* thrombosis, (b) branch atheromatous disease, (c) hemodynamic compromise, (d) artery-to-artery embolism, or (e) combination of the mechanisms (20, 21). However, for ICAS-related ELVO, the main proposed mechanism is ruptured, unstable plaque with subsequent *in situ* thrombosis and resultant occlusion and re-occlusion (22, 23).

Evaluating pre-thrombectomy imaging can be helpful in identifying patients with ICAS. Findings such as calcification of the internal carotid artery on computed tomography, clot burden on computed tomography angiography (CTA), and magnetic resonance imaging could be suggestive of ICAS as the underlying mechanism of ELVO given that ICAS patients have lower clot burden (24, 25). The finding of calcifications on baseline CT imaging particularly in the posterior circulation is indicative of ICAS (26). Previous studies have also suggested the use of baseline infarct core volume to predict ICAS. Due to better collateral circulation in patients with ICAS-related ELVO compared with embolic ELVO (13), patients with ICAS are expected to have lower infarct volume. Baseline infarct volume was assessed in one study of patients with embolic ELVO and ICAS ELVO. Patients with ICAS ELVO had significantly lower baseline infarct volume (14 vs. 54 ml in ICAS vs. embolic ELVO, respectively, $p \leq 0.001$) (24).

The importance of collateral status in (a) aiding with the diagnosis of ICAS and (b) determining infarct volume has been studied before. A study by Lee et al. assessed leptomeningeal collateral status using the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral grading scale (27) in patients with middle cerebral artery (MCA) M1 segment occlusion. In this study, 8/10 (80%) patients with ICAS-related ELVO had excellent collateral grade compared with 19/43 (44.2%) of patients with embolic ELVO ($p = 0.032$) (13). A recent study by Baek et al. investigated the utility of pre-procedural leptomeningeal collateral status in predicting ICAS-related ELVO (28). The authors used CTA to assess collateral status utilizing Tan's collateral grading system (29). In brief, Tan's system has four grades, from A indicating absent collateral supply to D indicating complete collateral supply of 100% of the MCA territory (29). In the study by Baek et al. 40 patients with ICAS-related ELVO and 186 with embolic ELVO were included. Complete (100%) collateral status was significantly higher among patients with ICAS-related ELVO (52.5% vs. 20.4%) (28).

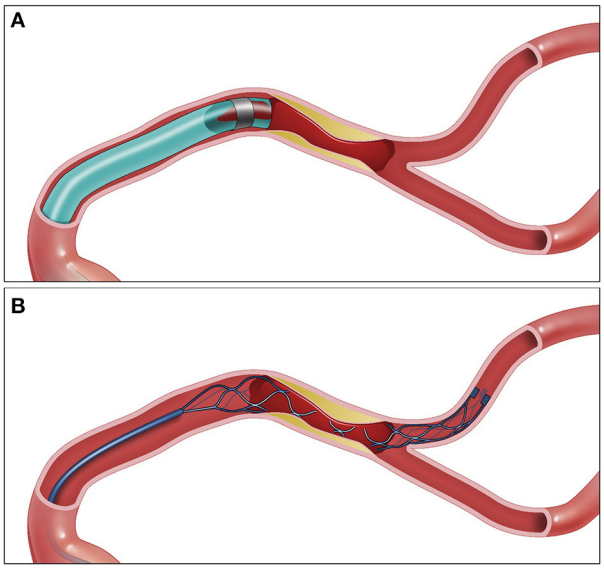

FIGURE 1 | ADAPT vs. SR for EVT in ICAS ELVO. **(A)** Aspiration catheter engulfing the proximal end of the thrombus. **(B)** Stent retriever engulfing the thrombus—the stent retriever shape is changed at the location of the plaque. SR, stent retriever; ADAPT, a direct aspiration first pass technique; MT, mechanical thrombectomy; ICAS, intracranial atherosclerosis; ELVO, emergent large vessel occlusion.

Intra-procedurally, diagnosis of ICAS as the underlying mechanism of ELVO is challenging and often times is made only following initial revascularization attempt. Occasionally, the use of stent retriever (SR) could help establish the diagnosis given that SRs often show full proximal and distal deployments but partial deployment across the stenotic area (truncal deployment) (**Figure 1**). In addition, the presence of robust leptomeningeal collateral on initial angiography is more likely to be found with ICAS compared with embolic ELVO (13). Nevertheless, there are currently no universally accepted diagnostic criteria; however, one study evaluated the inter-rater reliability of using the presence of any of the following: (a) residual fixed stenosis following MT that measures >50% or (b) mild–moderate stenosis with re-occlusion on follow-up angiography or (c) evidence of distal hypoperfusion and ruling out of other pathologies such as dissection (**Figure 2**). These criteria were validated in a previous study showing acceptable inter-rater reliability (9). While the presence of residual fixed severe stenosis following MT is the most straightforward diagnosis of ICAS, the presence of re-occlusion without associated significant stenosis can arguably be secondary to an organized partially removed thrombus. The presence of re-occlusion, however, is much less common in embolic ELVO compared with ICAS-related ELVO. A number of studies evaluated the rate of intra-procedural re-occlusion in ICAS-related ELVO compared with embolic ELVO. The rate of intraprocedural re-occlusion had been shown to

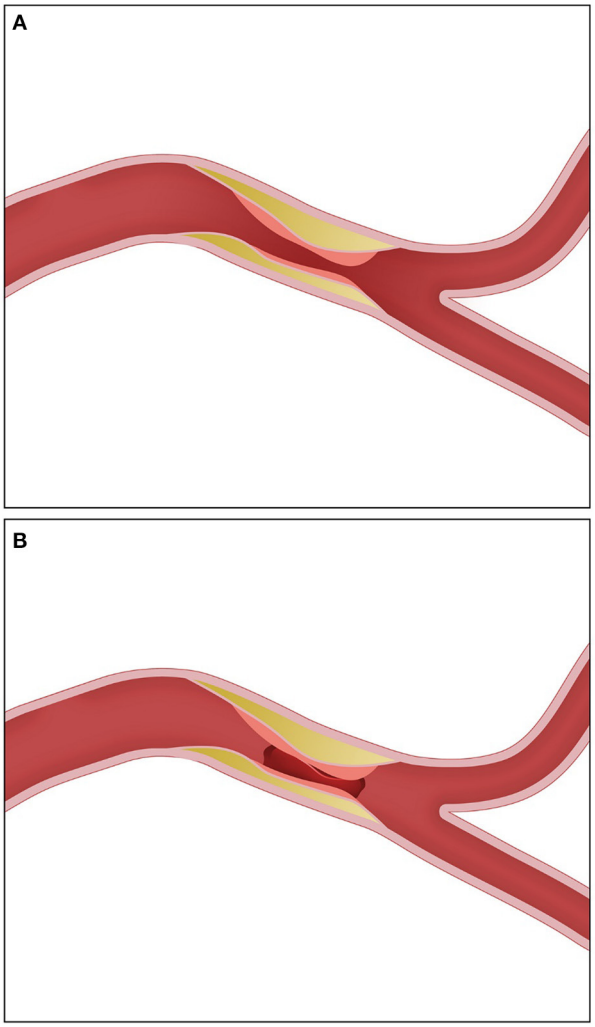

FIGURE 2 | Post-thrombectomy angiographic appearance in ICAS-related ELVO requiring rescue therapy. **(A)** Severe residual stenosis. **(B)** Re-occlusion. ICAS, intracranial atherosclerosis; ELVO, emergent large vessel occlusion.

be significantly higher in ICAS-related ELVO; most studies have reported a rate of 30% for ICAS-related ELVO compared with <3% for embolic ELVO (4, 30). A study by Kang et al. evaluated the rate of instant re-occlusion during MT; in their study, 40/132 (30%) had *in situ* thrombosis with re-occlusion; and all of those patients had underlying ICAS on follow-up imaging (31). The underlying mechanism of re-occlusion is not well studied. It is postulated that an underlying unstable plaque resulting in platelet activation followed by *in situ* thrombosis could result in re-occlusion. A postmortem study suggested underlying fibrous cap disruption and sub-intimal dissections as possible explanation of *in situ* thrombosis and resultant re-occlusion (30–32). Some interventionists repeat angiography 5–10 min after successful revascularization but with residual mild–moderate stenosis. Repeat angiography helps in evaluating for re-occlusion and ruling out other etiologies such as vasospasm.

DISCUSSION

ICAS-related ELVO poses a major therapeutic challenge; the main challenge is the tendency of re-occlusion of the affected vessel, or residual stable fixed severe stenosis impairing distal flow. The optimal treatment strategy for such cases is unclear; however, it often involves the use of angioplasty and/or stenting to achieve successful revascularization. When assessing the safety and efficacy of angioplasty and stenting for ICAS, it is important to distinguish this group of patients from patients with ICAS presenting with transient ischemic attack or subacute stroke. In the latter, there is strong evidence that medical management is superior to endovascular treatment with angioplasty and/or stenting; this is derived from the peri-procedural complications related to angioplasty and advancement in medical management (33, 34). In the ICAS-related ELVO group, however, patients are at risk of suffering from a large, often disabling stroke if left with unsuccessful revascularization. Treatment options depend on the clinical scenario, mainly related to the angiographic appearance following recanalization and whether there is re-occlusion of the vessel vs. residual severe flow-limiting stenosis. Treatment options could include intra-arterial treatment with thrombolytics, antiplatelets, angioplasty, and/or stenting. The evidence of the abovementioned treatment options and approaches is not strong and derived largely from small retrospective case series. Importantly, the vast majority of these studies were carried out in Asia with only few studies coming from the United States and Europe. Aside from ICAS being more common in Asian patient population, similar to ICAS in the non-emergent setting, studies coming from the United States and Europe have shown different results as compared with those coming from Asia (5, 6, 35). While it remains unclear why there are such stark differences in treatment effects between Asian and Western patient populations with ICAS, studies have suggested genetic, socioeconomic, and dietary differences as contributing factors (14, 20). A study by Yoon et al. evaluated the safety of emergent angioplasty with or without stenting in patients with ICAS-related ELVO; the authors reported more favorable outcomes in the ICAS group compared with the control group, with no difference in symptomatic intracranial hemorrhage or mortality (36). Conversely, a study from Spain by Matias-Guiu reported longer procedural times; higher mortality and lower rates of good functional outcomes in ICAS-related ELVO require rescue therapy with angioplasty with or without stenting (37). This study, however, only had 15 patients with ICAS (10, 11). Other studies reporting on comparably small sample sizes carried out in the United States and Europe have reported conflicting results with regard to rates of successful revascularization, complication rates, and long-term outcomes (4). The small sample size in those studies is likely due to the fact that ICAS is less prevalent in Western compared with Asian population (38).

In addition, the thrombectomy approach and whether an SR vs. a direct aspiration first pass technique (ADAPT) is used initially may influence the final rescue therapy treatment decision. There are advantages to each treatment approach. Although current evidence supports similar efficacy and safety

profile for SR and ADAPT as frontline MT techniques, the vast majority of patients included in these trials were embolic ELVOs (39, 40). Therefore, it remains unclear what the best firstline MT treatment for ICAS-related ELVO. Advantages of SR frontline thrombectomy approach include the following: (A) Early diagnosis. Given that SR takes the shape of the stenotic area (truncal occlusion), SR could help identify the lesion following the deployment of SR (**Figure 1**) and therefore earlier treatment planning. (B) With SR deployment, there is partial flow restoration, which could in theory reduce clot burden. (C) Some interventionists advocate for SR as frontline approach for ICAS-related lesions due to its ability to completely engulf the clot, whereas with aspiration, the aspiration catheter tip could be against the plaque; however, with newer larger caliber aspiration catheters where there is full engagement of the lesions, this argument is unlikely to be valid (**Figure 1B**). The main advantages of using ADAPT as firstline treatment for ICAS-related ELVO include (a) less interaction with the plaque as opposed to SR, which could lead to further endothelial damage, plaque inflammation, and clot propagation (41, 42). Furthermore, in perforator-rich segments such as M1 segment of the MCA, and midsegment of the basilar artery, the use of SR could lead to perforator occlusion "snow plowing," which is less likely to happen with ADAPT (43). Nevertheless, to our knowledge, there is no study to date that compared SR vs. ADAPT as frontline approach for patients with ICAS-related ELVO.

The approach to rescue therapy used depends on underlying lesion visualized following first successful thrombectomy pass, baseline core infarct, and involved segment. Once ICAS is identified, our practice is to repeat after waiting for 5–10 min and re-evaluate with follow-up angiography. In cases of residual severe stenosis without evidence of re-occlusion, angioplasty is performed first if lesion is not involving perforator-rich segment; if residual flow-limiting stenosis persists, stenting is then performed. In perforator-rich segments, we typically stent without balloon angioplasty (**Figure 3**). We avoid angioplasty in perforator-rich segments such as M1 and midbasilar segments, given associated risk of perforator occlusion. Angioplasty is typically performed using non-compliant balloon sized to the diameter of the normal intracranial segment proximal to the affected segment. Our practice has been to perform sub-maximal angioplasty to avoid perforator occlusion and reduce the amount of plaque disruption. A meta-analysis by Seyedaadat et al. evaluated 19 studies with 777 patients who underwent submaximal angioplasty for ICAS. The authors found 93% success rate with 3% stroke rate at 1 month (44), significantly lower rates than what were reported in SAMMPRIS (33) and VISSIT (5). In cases of re-occlusion, our practice has been to repeat MT and give a weight-based intra-arterial dose of tirofiban followed by stenting. Pre-stenting balloon angioplasty is performed in cases of associated severe flow-limiting stenosis (**Figure 4**).

The type of stent used in ICAS-related ELVO is also controversial. The ideal stent is one that is easy to deliver and has excellent radial force and low metal–vessel ratio. The Neuro-Form atlas stent is a self-expanding nitinol stent with hybrid cell structure. The stent has 6–12% vessel coverage and has a moderate radial force that is higher than flow diverters but lower than Wingspan stent (Stryker Neurovascular, Fremont, CA, USA). In our practice, we use Neuro-Form Atlas for ICAS-related ELVO with good success rate (45). In addition, balloon-mounted stents have recently emerged as potential effective stents in this population. The advantage of balloon-mounted stents is the added radial force as compared in Neuro-Form atlas (Stryker Neurovascular) and the pre-balloon angioplasty associated with deployment; however, due to their stiffness, navigating such stents could be challenging, particularly in tortuous anatomy. Mohammaden et al. recently evaluated the use of balloon-mounted stent in the treatment of symptomatic ICAS (46). Among 232 patients with symptomatic ICAS patients who failed medical management and were treated with balloon-mounted stents, 5.6% had strokes within 72 h, 3.9% were ischemic, and 1.7% were hemorrhagic. Recurrent strokes were reported in 3.7% at follow-up. While this patient population is different than ICAS-related ELVO patients, the safety profile of balloon-mounted stents in ICAS patients provides helpful data that could be used for future studies.

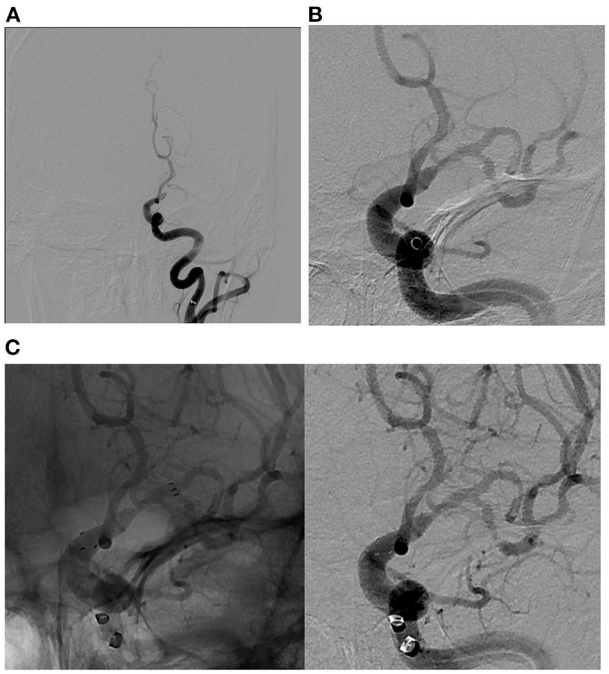

FIGURE 3 | Illustrative case of ICAS-related LVO in the M1 segment of the left middle cerebral artery. **(A)** Pre-MT angiographic image demonstrating complete occlusion of M1 segment of the left middle cerebral artery. **(B)** Post-MT angiographic image demonstrating partial recanalization of M1 segment of the left middle cerebral artery with persistent severe flow-limiting stenosis. Of note, ADAPT technique was used in this case. **(C)** Native (left) and digitally subtracted (right) angiographic images demonstrating successful intracranial stenting with Neuro-Form atlas stent as a rescue therapy with a goal of maintaining cerebral flow through the stenotic portion of M1 segment of the left middle cerebral artery. ADAPT, direct aspiration first pass technique; MT, mechanical thrombectomy; ICAS, intracranial atherosclerosis; ELVO, Emergent large vessel occlusion.

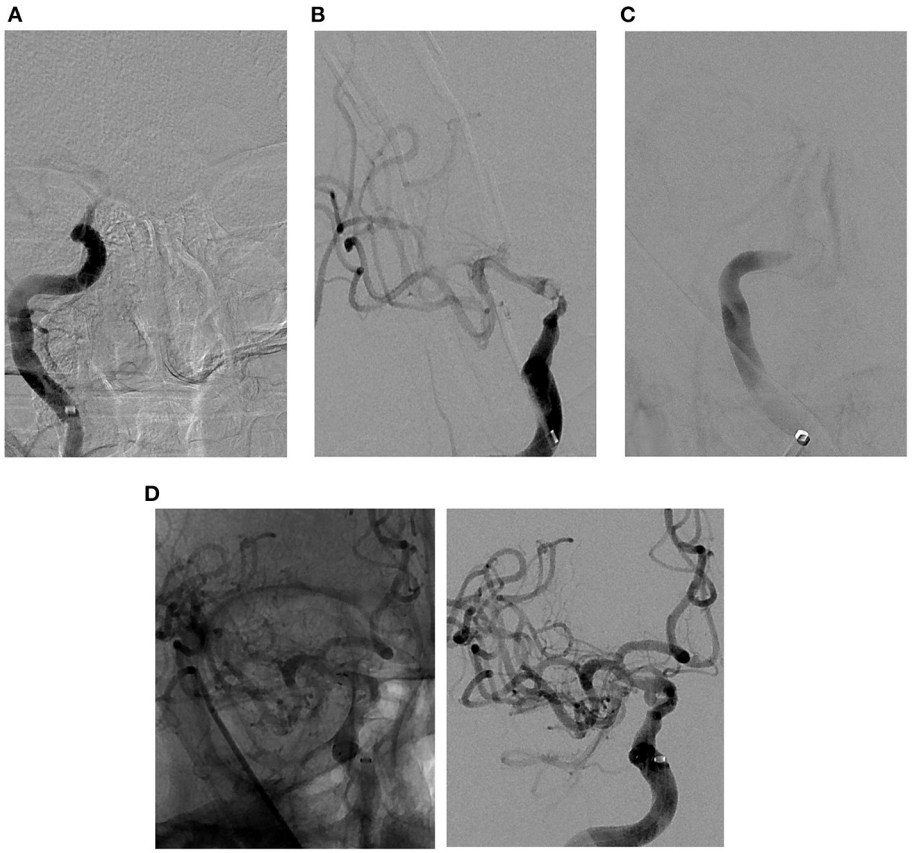

FIGURE 4 | Illustrative case of ICAS-related LVO in the cavernous segment of the right internal carotid artery. **(A)** Pre-MT angiographic image demonstrating complete occlusion of cavernous segment of the right internal carotid artery. **(B)** Post-MT angiographic image demonstrating partial recanalization of cavernous segment of the right internal carotid artery with persistent severe stenosis. **(C)** Delayed angiographic image 5 min post-MT demonstrating re-occlusion of the intracranial internal carotid artery. **(D)** Native (left) and digitally subtracted (right) angiographic images demonstrating successful angioplasty and stenting as a rescue therapy, with a significant improvement in the severe stenosis and near complete recanalization of the right internal carotid artery. ADAPT, a direct aspiration first pass technique; MT, mechanical thrombectomy; ICAS, intracranial atherosclerosis; ELVO, emergent large vessel occlusion.

The use of intra-arterial thrombolytics such as alteplase (tPA) or urokinase has been suggested. However, given prior evidence of increased risk for hemorrhage, prior failure of intra-arterial tPA trials' use of intra-arterial thrombolytics is generally avoided (1, 47). One study evaluated clot composition in 37 patients with large vessel occlusion undergoing MT. In this study, patients with large artery atherosclerosis were found to have higher proportion of platelets and fibrin and lower proportion of red blood cells as compared with those with cardio-embolic occlusion (23). Given the platelet/fibrin-rich component of ICAS-related clots, the use of antiplatelet as first-line rescue therapy has been evaluated. Tirofiban is a short-acting glycoprotein IIb/IIIa inhibitor and competitively inhibits platelet aggregation mediated by fibrinogen. The use of low-dose tirofiban was evaluated on patients undergoing MT with second-generation SR evaluated in a prospective observational study in China. In this study, the use of low-dose tirofiban was not associated with increased risk of hemorrhage or long-term mortality (48). A recent study carried out in Korea compared the outcomes of using intra-arterial glycoprotein IIb/IIIa inhibitor infusion with those emergent angioplasty and found that both techniques resulted in a successful revascularization rate of about 95% with similar rates of symptomatic hemorrhage, 3-month functional independence, and mortality (49). However, one major disadvantage of intra-arterial tirofiban is late re-occlusion as reported in prior studies (31). Finally, the mechanism of stroke and location of lesion should take into account the approach to treatment, and response to intra-arterial antiplatelets, angioplasty, and/or stenting should be taken into account when attempting to identify the ideal treatment approach for ICAS-related ELVO (50).

FUTURE DIRECTIONS

ICAS-related ELVO remains a challenging and poorly understood entity. Current evidence shows good safety and efficacy outcomes of rescue treatments with balloon angioplasty and/or stenting; however, evidence is limited to retrospective studies. Future direction should focus on attempting to identify this group of patients pre-procedurally utilizing calcium burden, collateral status, location of occlusion, and stroke severity on

arrival. In addition, while there is good evidence to support the use of balloon angioplasty and/or stenting, the ideal balloon and stent used are unknown and often dependent on the interventionist preference.

Furthermore, the amount of balloon angioplasty to be performed should also be better studied. Similar to refractory ICAS in the subacute setting, submaximal angioplasty could offer similar results to maximal angioplasty with lower complication rates. Finally, the long-term impact of angioplasty and/or stenting as well as intra-arterial treatment should be studied. Future studies should focus on assessing vessel patency on follow-up imaging.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Time-Based Decision Making for Reperfusion in Acute Ischemic Stroke

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Decision making in the extended time windows for acute ischemic stroke can be a complex and time-consuming process. The process of making the clinical decision to treat has been compounded by the availability of different imaging modalities. In the setting of acute ischemic stroke, time is of the essence and chances of a good outcome diminish by each passing minute. Navigating the plethora of advanced imaging modalities means that treatment in some cases can be inefficaciously delayed. Time delays and individually based non-programmed decision making can prove challenging for clinicians. Visual aids can assist such decision making aimed at simplifying the use of advanced imaging. Flow charts are one such visual tool that can expedite treatment in this setting. A systematic review of existing literature around imaging modalities based on site of occlusion and time from onset can be used to aid decision making; a more program-based thought process. The use of an acute reperfusion flow chart helping navigate the myriad of imaging modalities can aid the effective treatment of patients.

Keywords: stroke, thrombolysis, thrombectomy, acute ischaemia, magnetic resonance imaging (MRI), computer tomography (CT)

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INTRODUCTION

Reperfusion therapy using intravenous thrombolysis (IVT) or endovascular treatment (EVT) is the gold standard of treatment for acute ischemic stroke (AIS) (1). Treatment effect with both modalities is not only highly time dependent but also has lower complication rates if expedited early (2–5).

Whether and how fast a patient with AIS receives treatment depends on several factors including system-level and physician-level factors (6). System-level factors include the availability of ambulances, local geography, advanced imaging, and staffing resources at nearby hospitals. At the physician level, there are two conceptual ways of making treatment decisions: programmed (automated: routine and can be made using a systematic approach) or non-programmed (unique: individual and requiring thought-based analysis) (7). The latter is time consuming and especially precarious in a setting where every minute counts (8). This is further compounded in stroke care where adherence to guidelines is variable (9). The decision making process is further complicated

by access to advanced imaging. Where access to advanced imaging is a limiting factor transfer to the nearest comprehensive stroke center (CSC) should be considered. The decision to transfer a patient to the nearest CSC should be made in a timely fashion and made in the appropriate setting (10). Decision making now is therefore more complicated than ever and more time consuming.

The first EVT trials did not specify their imaging protocols in much detail; in fact, some did not even require vascular imaging (11–13). This heterogeneity in imaging, and subsequent variability in patient selection, was probably one of the reasons for their failure to show the benefit of EVT. Thus, subsequent randomized controlled trials (RCTs) for EVT had stricter, more homogeneous, yet relatively simple inclusion criteria that allowed for fast programmed decisions (14). These programmed decisions revolved around patient age, time from onset, and plain computed tomography (CT) findings. The same decision making pattern applied to patient selection for the early IVT trials. These trials only included patients based on age and time from symptom onset (15, 16). Using strict criteria and simple processes, decision making was more programmed but resulted in many patients being potentially excluded from treatment.

Recent data suggest that a greater number of patients can benefit from reperfusion treatment using a more individualized approach, by selecting patients using advanced imaging both for IVT and EVT (17–20). This has resulted in an update in guidelines, which now recommend the use of alteplase up to 9 h after the onset of stroke symptoms, given hypoperfusion-core mismatch on advanced imaging (21). EVT is reasonable in patients up to 24 h after symptom onset if advanced imaging criteria are met (1, 22). Some studies even indicate that selected patients meeting certain advanced imaging criteria might benefit from EVT more than 24 h after symptom onset (23). The selection process for reperfusion treatment in the late time window involves more and more non-programmed decision making based on a variety of relative variables instead of absolute cut-offs, and while this allows us to treat more patients, it also represents a challenge and can be confusing at times, particularly for less experienced physicians (7).

Herein, we review the available imaging modalities in AIS as relevant to reperfusion therapy and describe EVT and IVT decision making using different imaging modalities. We also provide a visual aid in the form of a flow chart to aid AIS decision making for acute reperfusion in clinical practice.

ACUTE ISCHEMIC STROKE AND IMAGING

Ischemic stroke symptoms are caused by a focal reduction in cerebral blood flow due to a vessel occlusion. Initially, the reduction of blood flow results in oligemia but upon worsening leads to ischemia followed by infarction if normal blood flow cannot be restored (24). Vessel occlusions in the setting of AIS can be broadly divided into large vessel occlusions (LVO), medium vessel occlusions (MeVO), and small vessel occlusions. An LVO is defined as an occlusion of the terminal intracranial carotid artery (ICA) and/or M1 segment of the middle cerebral artery (MCA) (14). A MeVO is defined as an occlusion of the M2 or M3 segment of the MCA, A2, or A3 segment of the anterior cerebral artery (ACA) and P2 or P3 segment of the posterior cerebral artery (PCA) (25).

LVO is currently the only vessel occlusion for which level 1A evidence exists demonstrating a clear benefit of EVT (1). These occlusions are unlikely to recanalize with intravenous thrombolysis alone, although current guidelines recommend IVT in addition to EVT where possible (26). Observational data suggest a beneficial effect of EVT for MeVO; however, data from RCTs are lacking (27).

In the early time window, defined as 4.5 h for IVT and 6 h for EVT, decision making is more programmed and treatment can be initiated on simplified imaging (plain CT and CT angiography). Outside the early time window, LVO and MeVO patients can be selected for both IVT and EVT based on advanced imaging ("tissue-window"). The goal of these advanced imaging methods is to classify tissue as irreversibly damaged (infarct core) or salvageable tissue (penumbra). Theoretically, patients with no salvageable tissue would not benefit from treatment and thus should not be unnecessarily exposed to treatment risks.

However, current advanced imaging methods do not allow us to accurately estimate infarct core and penumbra. This has casted doubt upon the validity of the term "infarct core" and led some authors to suggest the use of a more descriptive term, "severely ischemic tissue with unknown viability [SIT-uV]" (28). The limitations of imaging are important to bear in mind when relying on these methods for infarct core and penumbra estimation and treatment decision making.

COMPUTED TOMOGRAPHY

Ruling Out Intracranial Hemorrhage and Identifying Early Ischemic Changes

Non-contrast head CT (NCCT) or plain CT is the most basic type of CT imaging and the first part of any CT-based AIS imaging protocol. Plain CT allows us to rule out intracranial hemorrhage, which constitutes a contraindication for IVT and EVT. Acute hemorrhagic stroke typically presents with hyperdense intraparenchymal foci of blood. NCCT also allows for a rough estimate of ischemia, which manifests as early ischemic changes: loss of gray-white matter differentiation, parenchymal swelling, and subtle parenchymal hypodensity. The Alberta Stroke Program Early CT Score (ASPECTS; aspectsinstroke.com) is a 10-point binary NCCT score that can be used to assess early ischemic changes in the middle cerebral artery territory. It divides the middle cerebral artery territory in 10 regions—seven at the ganglionic level and three at the supra-ganglionic level. A region is either scored as "affected" if early ischemic changes are present or "not affected" if no early ischemic changes are present in the region. For each affected region, one point is subtracted from an initial value of 10 points. Thus, 10 is the highest ASPECT score, indicating no ischemic changes in any of the territories, and 0 is the lowest possible score, indicating ischemic changes in all middle cerebral artery territories. A modified ASPECTS score for posterior

circulation strokes (pcASPECTS) has also been described (29). If no intracranial hemorrhage and no extensive early ischemic changes are present, IVT can be administered, even before vascular imaging is performed. Although hyperdensity of an arterial vessel on NCCT, so-called "hyperdense vessel sign," can indicate a vessel occlusion, definitive identification of the occluded blood vessel requires vascular imaging.

Identifying Vessel Occlusion

CT angiography (CTA), either single-phase or multiphase, is used to identify the presence of an LVO or a MeVO. In a single-phase CTA, a single arch-to-vertex angiography is obtained after contrast injection to depict the pre- and intra- cerebral vessels. In multiphase CTA (mCTA), two additional scans, following a single-phase examination, are obtained during the peak-venous and the late-venous phase (30). These last two scans image only the intracranial vessels (skull base to vertex) and are obtained using the same bolus contrast dose. Single-phase CTA has good sensitivity and specificity for LVO detection, with high inter-rater reliability (31). However, accuracy for MeVO detection is much lower, with up to a third of MeVOs being missed on single-phase CTA (32). Multiphase CTA can increase accuracy for MeVO detection by visualizing delayed filling and washout of pial arterial collaterals in the ischemic tissue (**Figure 1**) (33).

Estimating the Infarct Core and Viable Penumbra

mCTA can be used to assess the infarct core both qualitatively and quantitatively. The time-resolved depiction of the collaterals allows for semiquantitative grading (30). Collateral circulation determined by such semiquantitative grading is an independent predictor of outcome following treatment with alteplase (34), and patients with good collaterals on baseline mCTA are more likely to benefit from EVT (35). Collateral grading on mCTA has a good interrater reliability, covers the whole brain, is robust against patient motion, and requires no post-processing. The use of machine-learning algorithms allows for derivation of tissue-level perfusion maps from mCTA that can be used to generate perfusion color maps and estimate core and penumbra volumes (**Figure 2**). Extracranial stenoses and poor cardiac output, however, could lead to underestimation of collaterals both in the qualitative and quantitative analysis.

In some ways, CT perfusion (CTP) can be seen as an extension of mCTA: the principle is the same, but time resolution is higher since 30–90 additional phases (as opposed to only two additional phases in mCTA) are obtained. After injection of an iodinated contrast bolus, a slab of 8–16 cm (depending on the scanner's detector width) is continuously imaged for 45–90 s. Several perfusion parameters, including cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time to peak enhancement (TTP) are then calculated using a deconvolution algorithm and displayed using axial color maps, similar to mCTA tissue level perfusion maps (**Figure 2**). Decreased CBV is commonly used as a surrogate for ischemic core, whereas in penumbra, CBV is thought to be preserved. CTP was used for patient selection in some EVT trials in the early time window (37), and the DAWN and DEFUSE-3 trials have proven the benefit of EVT in patients with small CTP core and

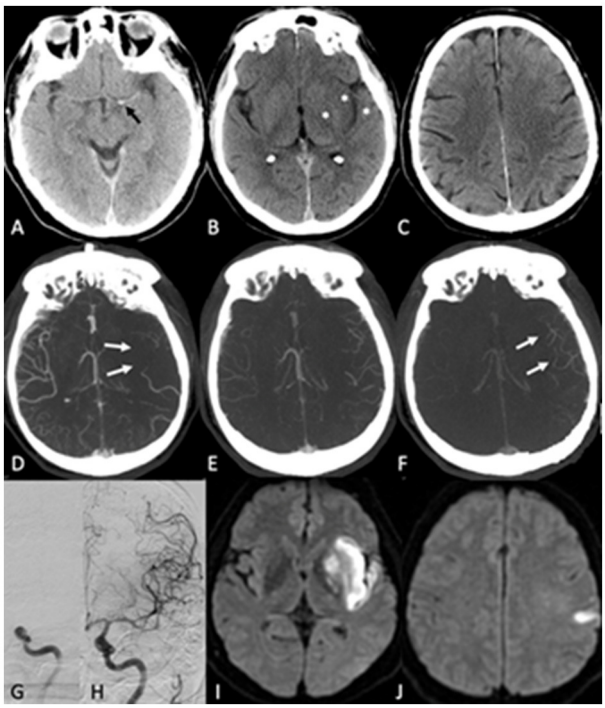

FIGURE 1 | Acute ischemic stroke due to a terminal internal carotid artery occlusion. **(A,B)** show the initial Plain CT. A hyperdense vessel sign [black arrow in **(A)**] is seen, and there is loss of gray-white matter differentiation in the left insula, lentiform nucleus and M2 region [asterisks in **(B)**], corresponding to an ASPECTS score of 7. No ischemic changes are seen at the supraganglionic level **(C)**. Multiphase CTA shows lack of collateral filling in the first (arterial) phase [white arrows in **(D)**]. However, the pial arterial collaterals fill eventually in the second (peak-venous) phase **(E)**. There is a slight delay in washout in the third phase **(F)**. Intravenous thrombolysis was administered between Plain CT and mCTA, and the patient was treated with EVT after mCTA has been completed. **(G)** shows the initial digital subtraction angiography run with the occlusion. **(H)** shows the last intracranial angiography run with complete recanalization [modified thrombolysis in cerebral infarction (mTICI 3)]. On follow-up diffusion-weighted MRI at 24 h, an infarct of moderate size in the left insula, lentiform nucleus, and M2 region was seen **(I)**, corresponding to the areas with early ischemic changes in the initial plain CT. There was also a small infarct in the left M5 region **(J)** that was not noted on the baseline plain CT.

core-penumbra mismatch presenting between 6 and 24 h from symptom onset (17, 18). There is some evidence to suggest that patients fulfilling these CTP criteria can benefit from EVT even if they present beyond 24 h (23). The color-coded format of CTP and quantitative mCTA maps is easy to interpret for readers with little experience and can help to identify the occlusion location. However, one has to bear in mind that CTP is subject to technical failures in up to as many as one-third of patients (38). A recent publication highlights the fact that CTP often overestimates infarct core volumes (39). Furthermore, some studies suggest that CTP does not actually improve treatment decision making beyond mere occlusion detection (38).

Posterior Circulation Stroke

NCCT is less sensitive for detecting ischemic stroke in the posterior fossa (sensitivity 41.8% CI 30.1–54.4) (40). The low sensitivity can be explained by several factors including the

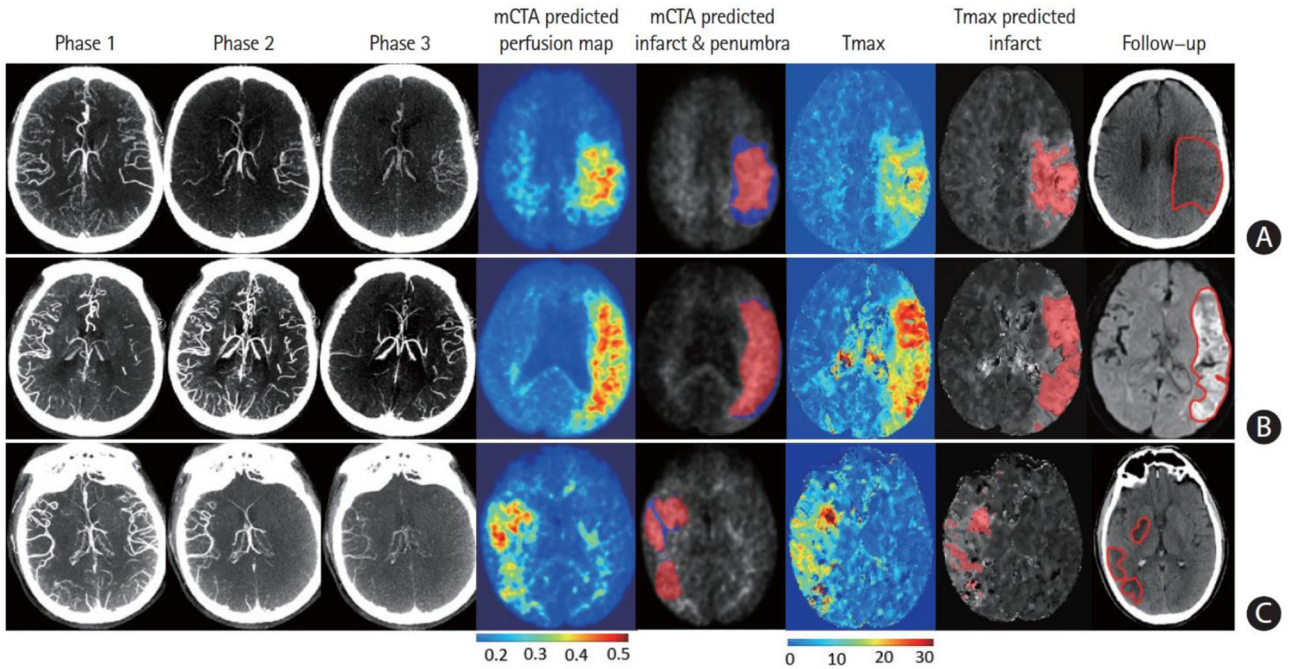

FIGURE 2 | Multiphase computed tomographic angiography (mCTA) predicted an infarct map compared to a computed tomographic perfusion (CTP) time-dependent Tmax threshold map when compared to a follow-up infarct. **(A)** Patient who achieved reperfusion (mTICI 2b); **(B)** patient who did not achieve reperfusion; and **(C)** patient who achieved complete reperfusion with EVT. Columns: mCTA phase 1–3, mCTA predicted perfusion maps, mCTA predicted core (red in column 5) and penumbra (blue in column 5) overlaid on the mCTA predicted perfusion map, CTP Tmax maps, CTP time-dependent Tmax threshold predicted infarct, infarct contoured in follow-up imaging, respectively. The penumbra is shown as affected tissue from the penumbra model minus affected tissue from the core model. [Reprinted with permission from Journal of Stroke, 2021 (36)].

extensive beam-hardening bony artifacts in the posterior fossa, as well as the relative delay for strokes to appear on imaging in the white matter relative to the gray matter (41, 42).

MAGNETIC RESONANCE IMAGING

Identifying Vessel Occlusion

Magnetic resonance imaging (MRI) sequences that are used to assess the vessels of the head and neck can be divided into non-contrast techniques [time of flight (TOF) MRA] and contrast-enhanced (CE) techniques (CE-MRA) (43). CE-MRA relies on injection of intra-arterial gadolinium-based contrast agents to depict the cervical and intracranial blood vessels, in a fashion similar to CTA. TOF-MRA, on the other hand, is a gradient echo sequence showing flow in vessels without the use of gadolinium contrast and can be acquired as 2D slabs or 3D volumes (44).

CE-MRA offers better diagnostic accuracy than TOF-MRA in acute ischemic stroke, being more accurate for identifying occlusion location (45, 46). However, CE-MRA has a lower diagnostic accuracy as compared to CTA: with a sensitivity of 80–92% and a specificity of 85–98% (47–49). Additionally, the time to achieve optimal arterial enhancement and acquisition times are longer as opposed to CTA, and the examination cannot be repeated with good quality until the intravascular gadolinium contrast is cleared (44).

TOF-MRA offers an alternative way to image intracerebral vessels in patients with contraindications to contrast agents. Furthermore, imaging can be repeated instantly as contrast wash out is not an issue (50). The sequence is however time-consuming and cannot accurately depict the extracranial vessels (51, 52). It is also more susceptible to motion artifacts because the signal is generated by directional blood flow (53).

Estimating the Infarct Core and Viable Penumbra

Diffusion-weighted Imaging (DWI) detects hyperacute and acute ischemic lesions with a high sensitivity and specificity, with sensitivities ranging from 88 to 100% and specificities ranging from 86 to 100% (54–57). Acute cerebral ischemia causes cytotoxic edema mediated by a decrease in extracellular space and restricted diffusion of water molecules, which is reflected by an immediate decline in the applied diffusion coefficient (ADC). Typically, an ADC threshold of <620 μm/s is used by automated software to identify tissue with severely restricted movement of water (58). This correlates with tissue that is at risk of being irreversibly injured (59). Areas with reduced ADC appear hyperintense on DWI. DWI lesions are, in many cases, seen just minutes after the onset of symptoms (60, 61). The initial DWI lesion is thought to represent tissue at risk and correlates well with end infarct volume if no intervention is performed (44, 62, 63). Although DWI is far superior to plain CT at detecting

hyperacute and acute ischemic change (47, 57), around 6% of AIS patients do not have any visible DWI lesions (64). Furthermore, DWI-reversible lesions have also been reported, particularly in the posterior circulation (31).

Subacute infarctions are characterized by the subsequent development of vasogenic edema, which is visualized as a hyperintense signal on T2-weighted fluid attenuated inversion recovery (FLAIR) MRI (65). FLAIR hyperintensity usually develops between 3 and 6 h after the onset of symptoms (60, 66–68). On rare occasions, however, the hyperintensity does not develop until up to 12 h after the onset of symptoms (69). The intensity of the signal can be used to temporally quantify symptom onset (70, 71). In one study, the positive predictive value of FLAIR hyperintensity increased from 0.87 to 1.00 when minor strokes, lacunar infarctions, and infratentorial strokes were excluded (66). Studies published as early as 1997 have shown that FLAIR hyperintensity is more clearly visible in cases of cortical supra-tentorial stroke (72).

Patients with a DWI-FLAIR mismatch, an acute ischemic lesion that is hyperintense on DWI but without any visible FLAIR correlation, are likely to be within a 3-h time window from symptom onset (19, 60). This has been implemented in clinical practice to assess the feasibility of IVT in patients where symptom onset is unknown, or the patient has awoken with stroke symptoms.

Perfusion weighted imaging (PWI) is used to map regional CBF, depicting hemodynamic conditions at the microvascular level, identical to CTP depiction. PWI can be obtained using either exogenous gadolinium contrast or endogenous contrast labeling [arterial spin labeling (ASL)]. For the most part, PWI in AIS is performed using an exogenous contrast agent (DSC—dynamic susceptibility contrast) (44). Following the intravenous administration of contrast, CBF, CBV, and MTT are calculated. These changes are depicted as color-coded maps as with CTP and mCTA tissue level perfusion maps (47). Using these parameters various thresholds for tissue viability for have been hypothesized. Most definitions of infarct core use a Tmax >6 s as threshold (73), while tissue with a Tmax <6 s is defined as oligemic tissue that is potentially salvageable. However, PWI alone cannot accurately distinguish between oligemia, penumbra, and core (47). The PWI-DWI mismatch, conceptually the same as the DWI-FLAIR mismatch, has been used to identify viable penumbra in the setting of reperfusion therapy (74–76).

CT vs. MRI-Based Imaging in AIS

The biggest advantage of MRI-based imaging is that DWI shows hyperacute and acute infarcts with higher sensitivity and very early on (minutes after symptom onset) as compared to plain CT.

With respect to vascular imaging, CTA has a much higher sensitivity and specificity for the detection of vessel occlusions when compared to MRA (both CE-MRA and TOF-MRA). Additional advantages of CTA are its shorter acquisition time, tolerability of patient motion artifacts, and the option to acquire two additional phases for collateral assessment (mCTA). Furthermore, as opposed to TOF-MRA, the extracranial and intracranial arterial vasculature can be imaged simultaneously. The risk of contrast-induced renal damage and allergic reactions exist for both CE-MRA and CTA, but these complications more often associated with the use of iodinated contrast in CTA.

As for perfusion imaging, both PWI and CTP are subject to a significant technical failure rate and are associated with contrast related complications. Furthermore, some studies suggest that perfusion imaging does not actually improve treatment decision making beyond mere occlusion detection (38).

In general, most centers use a CT-based imaging protocol due to the fewer contraindications, faster acquisition times, greater availability, and lower costs compared to MRI.

Posterior Circulation Strokes

DWI is the preferred imaging modality to exclude ischemia in the posterior circulation (40, 42). It is however important to recognize that DWI can be normal in posterior circulation strokes, especially in the hyperacute phase. Posterior circulation strokes had a five times greater chance of being so-called DWI-negative up to 72 h after symptom onset (64). FLAIR has a low sensitivity and specificity when it comes to identifying stroke in the posterior circulation (66). Therefore, it is difficult to rely on DWI-FLAIR mismatch as a form of tissue-based imaging in posterior circulation strokes. Applying the Posterior Circulation Alberta Stroke Program Early Computed Tomography Score (pc-ASPECTS) to pre-intervention DWI has been proven to be a sensitive and specific tool for predicting clinical functional outcome (77).

DISCUSSION

Recent advancements in reperfusion treatment, especially in the late time window, have diluted the hard and fast time-based exclusion criteria from the early reperfusion trials. The decision making was of a programmed type and based on strict time cutoffs. The ever-expanding indications for reperfusion therapies in AIS have led to the introduction of advanced imaging and "tissue windows" replacing time windows. Reperfusion decision making has thus evolved into non-programmed decision making. Decision making is ultimately complicated by two opposing factors: the time sensitive nature of treatment effect and the need to gather tissue information through neuroimaging (18, 59, 78).

Advanced imaging (CTP, PWI, DWI-FLAIR mismatch imaging) complements the more basic CT and MRI modalities. The sole purpose of advanced modalities is to establish the existence of viable penumbra. It is however important to note that the penumbra is fading by the minute, and attempting to interpret advanced imaging in a non-programmed fashion often leads to further confusion (79), as it requires interpretation of several relative variables rather than relying on absolute time cut-offs. Prolonged treatment windows and increased availability of advanced imaging also means that physicians should be well-informed about the limitations of the various imaging modalities used in acute ischemic stroke.

A simplification of imaging strategies is warranted, a program-based solution. The most pivotal piece of information for clinicians in this setting is time of onset. Establishing probable onset time through available information from the patient or a stroke witness is key. It is also important to note that imaging is

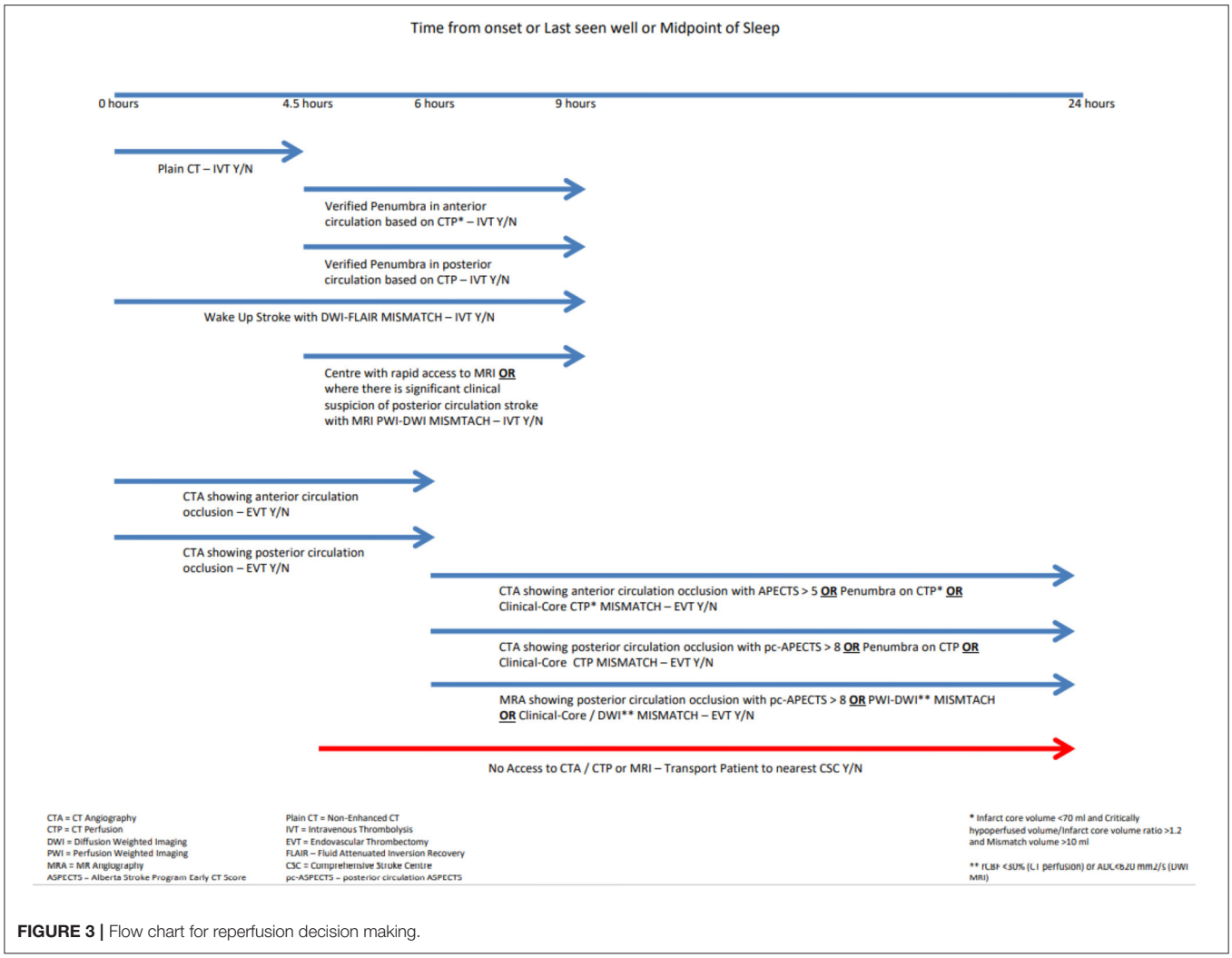

FIGURE 3 | Flow chart for reperfusion decision making.

only of limited value to establish time of onset, since the DWI-FLAIR mismatch has some variability and can falsely preclude treatment (78, 80). Therefore, clinical assessment of symptom onset is crucial to assist in the program-based decision making process. Once onset time or time since the patient was last seen well has been established, tissue-based imaging can be utilized to visualize penumbra (**Figure 3**).

In the early time window (0–6 h), less is more as far as imaging is concerned. Using plain CT to verify the lack of extensive early ischemic changes and CTA to verify an LVO or MeVO before going directly to the angiography suite is the most efficient strategy. In the late time window (6–24 h from last known well) the plethora of tissue-based imaging modalities comes into play. Selecting patients in the late time window is tissue-based rather than time-based (81). Of note, the 6-h cutoff is based on the inclusion criteria of early EVT RCTs and does not in any way reflect the underlying physiological variability neuronal loss (8).

Imaging modalities for tissue-based patient selection include CT-based (CTP) and or MRI based strategies (PWI), as well as the DWI-FLAIR mismatch. The type of tissue-based imaging used should be chosen based upon site of occlusion in the late window. In anterior circulation strokes, both CT- and MRI-based perfusion strategies have been successfully used to identify penumbra (59). A preference for use of these modalities ultimately comes down to traditions of practice and availability at individual centers. This has been well-reflected in the late window EVT RCTs in the anterior circulation, in which both CT-based and MRI-based protocols were successfully used (18, 82). It is worth bearing in mind that MRI tissue-based imaging is more time consuming, more susceptible to motion artifacts, and has a greater number of contraindications than CT imaging. The use of CT imaging is therefore more congruent with program-based decision making (83).

In the setting of posterior circulation strokes, PWI-DWI mismatch seems to be a more reliable marker of viable penumbra than CTP findings (83). Thus, to aid program-based decision making in the late window, in posterior circulation strokes MRI PWI-DWI mismatch should be preferred where available.

Figure 3 provides a visual aid to increase accuracy and timeliness of reperfusion decision making based on tissue imaging and up-to-date guidelines (84, 85). Focusing on onset time and site of occlusion helps decision making and simplifies the acute treatment setting. The figure also maintains focus

on imaging where transporting the patient to a CSC should not be forgotten.

Recent ESO recommendations regarding the use of IVT in late window thrombolysis also highlight the importance of tissue-based imaging. IVT has been traditionally administered within 4.5 h of symptom onset, but there is now a strong recommendation that alteplase should be considered between 4.5 and 9 h of symptom onset where viable penumbra is detected on advanced imaging (21). The updated ESO guidelines recommend the use of advanced imaging to establish a penumbra core mismatch ratio >1.2 with an infarct core of <70 ml. The recommendations do not favor the use of MRI over CT-based perfusion imaging, and each center should build on the use of the modality already previously established in treatment routines. In program-based decision making, however, simplifying algorithms reduces treatment times and expedites correct treatment (4). Thus, adhering to CTP only in anterior circulation strokes and MRI PWI-DWI mismatch in posterior circulation strokes is more congruent with program-based decision making leading to improved efficacy.

With the updated guidelines reinforcing the need for advanced imaging, it is crucial to consider the availability of advanced imaging at each treatment center. Transport of patients from a primary stroke center (PSC) to a comprehensive stroke center (CSC) is warranted where there is limited or no access to advanced imaging in cases where treatment can be initiated.

Extended reperfusion time windows and the growing availability of advanced imaging can become a labyrinth of pitfalls and missed opportunities for many stroke physicians, and patients, for that matter. A robust understanding of the imaging modalities and their limitations is paramount if timely decision making is to be expedited. The use of visual aids in the acute treatment setting can help revert back to a program-based decision making strategy for acute ischemic stroke patients, thus securing efficacious treatment for many more patients.

AUTHOR CONTRIBUTIONS

MG, RA, SA, MK, and JO contributed to the writing of the manuscript. MS, ES, and MK contributed to the editing of the manuscript. MS, ES, and RA contributed to the conceptualization of the manuscript. All authors contributed to the article and approved the submitted version.

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Multimodal CT Imaging Characteristics in Predicting Prognosis of Wake-Up Stroke

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Background: Multimodal CT imaging can evaluate cerebral hemodynamics and stroke etiology, playing an important role in predicting prognosis. This study aimed to summarize the comprehensive image characteristics of wake-up stroke (WUS), and to explore its value in prognostication.

Methods: WUS patients with anterior circulation large vessel occlusion were recruited into this prospective study. According to the 90-day modified Rankin Scale (mRS), all patients were divided into good outcome (mRS 0–2) or bad (mRS 3–6). Baseline clinical information, multimodal CT imaging characteristics including NECT ASPECTS, clot burden score (CBS), collateral score, volume of penumbra and ischemic core on perfusion were compared. Multivariate logistic regression analysis was further used to analyze predictive factors for good prognosis. Area under curve (AUC) was calculated from the receiver operating characteristic (ROC) curve to assess prognostic value.

Results: Forty WUS were analyzed in this study, with 20 (50%) achieving good outcome. Upon univariable analysis, the good outcome group demonstrated higher ASPECTS, higher CBS, higher rate of good collateral filling and lower penumbra volume when compared with the poor outcome group. Upon logistic regression analysis, poor outcome significantly correlated with penumbra volume (OR: 1.023, 95% CI = 1.003–1.043) and collateral score (OR: 0.140, 95% CI = 0.030–0.664). AUC was 0.715 for penumbra volume (95% CI, 0.550–0.846) and 0.825 for good collaterals (95% CI, 0.672–0.927) in predicting outcome.

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Conclusions: Penumbra volume and collateral score are the most relevant baseline imaging characters in predicting outcome of WUS patients. These imaging characteristics might be instructive to treatment selection. As the small sample size of current study, further studies with larger sample size are needed to confirm these observations.

Keywords: wake-up stroke, ischemic penumbra, collateral circulation, prognostic value, CT perfusion (CTP)

INTRODUCTION

Stroke is the second-leading cause of global morbidity and mortality. The incidence rate of stroke reaches to up 13.7 million per year worldwide (1). The disability rate is as high as 70–80%, which seriously endangers the life and health of the general population, causing great burden to families and society (2). Wake-up stroke (WUS) accounts for 14–28% of all cases (3, 4). As WUS occurs during sleep and patients may only recognize stroke symptoms when they awaken in the morning, the duration from last time seen well to symptom recognition for WUS ranges from up to almost 7 to 14 h (5). Thus, WUS is traditionally classified into the late-time window, and patients need commonly to be evaluated by CT perfusion (CTP) in order to assess the volume of ischemic core on perfusion and penumbra according to the latest guidelines (6). Furthermore, the recent published meta-analysis by EXTEND, ECASS-4 and EPITHET investigators also highlights the value for perfusion imaging in wake up stroke patients (7).

However, only minor differences in clinical and imaging characteristics were shown between WUS patients and early-time window stroke patients (8–10). For early-time window stroke patients, NECT and CT angiography (CTA) are essential for quick evaluation of early ischemic changes and early detection of large vessel occlusion, while CTP is not necessarily recommended (6). Considering the particularity of WUS, it arguably should not be simply classified into neither late nor early time window stroke. It is both possible and necessary to put forward tailored imaging evaluation criteria for WUS.

Recently published studies proposed different imaging evaluation criteria for WUS (11–14). One study (11) suggested that WUS should be evaluated by using the ratio of ischemic penumbra to hypo-perfusion area >50% on CTP. While another study (12) used the ratio of infarct core to ischemic penumbra <50% on CTP as the imaging standard to evaluate WUS. However, it is still difficult to evaluate WUS as both studies used totally different imaging standards and did not analyze the relationship between imaging and prognosis. The other two studies analyzed the correlation of CTP and CTA with prognosis of WUS, respectively. One study (13) used CTP for WUS evaluation and showed that CTP core volume ($\beta = 0.403$, $p = 0.000$) could predict NIHSS at 7 days in a multivariate analysis. While another study (14) used CTA for WUS evaluation and found that collateral circulation condition graded by the ASITN/SIR was an independent influencing factor for prognosis of wake-up ischemic stroke patients at 3 months. Although other studies attempt to predict the prognosis of WUS by using ischemic core on perfusion volume and collateral circulation, a major weakness of both studies was using separate indexes from just a single modality of CTP or CTA instead of multimodality assessment. Multimodal CT imaging can provide comprehensive image characteristics which are important for predicting prognosis. Thus, it may be advantageous to explore the predictive value of multimodality CT for WUS prognosis.

This prospective study aims to describe the relationship between multimodal CT imaging characteristics and outcome of WUS, and explore the quantitative and qualitative imaging criteria for distinguishing WUS patients with different outcomes.

Abbreviations: WUS, wake-up stroke; CTP, CT perfusion; CTA, CT angiography; mRS, modified Rankin Scale; NIHSS, national institute of health stroke scale; EVT, endovascular thrombectomy; mTICI, modified Thrombolysis In Cerebral Infarction; MIP, maximum intensity projection; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean time to transit; TTP, time to peak; Tmax, time to maximum of the residue function; CBS, clot burden score; AUC, Area under curve; ROC, receiver operating characteristic.

METHODS

Patient Selection Criteria

All patients were prospectively and consecutively admitted at a single quaternary comprehensive stroke center from September 2018 to September 2019. NECT, CTP, and CTA were performed for acute ischemic stroke patients suspected to have large vessel occlusion. The inclusion criteria were: (i) patients with ischemic stroke awaken with neurological deficits and last time seen well over 6 h; (ii) patient pre-morbid functional independence as determined by modified Rankin Scale (mRS) 0–2; (iii) CTA showing large vessel occlusion in the anterior circulation from the intracranial internal carotid artery to the M2-branch of the middle cerebral artery. Patients with intracranial hemorrhage or stroke mimics on NECT, known renal dysfunction, contrast allergy, poor imaging quality and loss of clinical data were excluded. Baseline clinical characteristics such as age, sex, last time seen well, national institute of health stroke scale (NIHSS) scores at admission and comorbidities were collected. The decision to offer treatment to this subset of patients was determined following discussion between the stroke physicians and the interventional neuroradiologists. Factors taken into consideration were: (i) the Alberta Stroke Program Early CT Score (ASPECTS) on NECT 6–10; (ii) perfusion image demonstrating a CBF/CBV mismatch pattern; (iii) no other contraindications. For patients who underwent endovascular thrombectomy (EVT), modified Thrombolysis In

TABLE 1 | Patient characteristics ($n = 40$).

	Study group $N = 40$	mRS 0–2 $N = 20$	mRS 3–6 $N = 20$	*p*-value
Baseline parameters				
Age, mean ± SD, y	60.12 ± 11.84	57.64 ± 10.65	65.50 ± 12.41	0.110
Male sex, *n* (%)	27 (67.5%)	13 (65.0%)	14 (70.0%)	0.741
NIHSS score, mean ± SD	11.00 ± 3.22	11.64 ± 2.65	16.00 ± 4.92	0.010
Comorbidities, *n* (%)				
Hypertension	19 (47.5%)	8 (40.0%)	11 (55.0%)	0.567
Atrial fibrillation	12 (30.0%)	6 (30.0%)	6 (30.0%)	0.941
Diabetes mellitus	15 (37.5%)	7 (35.0%)	8 (40.0%)	0.774
Last time seen well, mean ± SD, h	10.44 ± 4.15	9.16 ± 3.04	12.22 ± 4.96	0.074
EVT, *n* (%)	24 (60.0%)	14 (70.0%)	10 (50.0%)	0.523
Reperfusion, *n* (%)				0.200
unsuccessful reperfusion	17 (42.5%)	6 (30.0%)	11 (55.0%)	
Successful reperfusion	23 (57.5%)	14 (70.0%)	9 (45.0%)	

EVT, endovascular thrombectomy; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale, an acute ischemic stroke severity score ranging from 0 to 42: mild stroke = 1–4; moderate stroke = 5–15; moderate-severe stroke = 16–20; and severe stroke = 21–42; mTICI, modified Thrombolysis In Cerebral Infarction ranging from 0 to 3: 0/1/2a = unsuccessful reperfusion; 2b/2c/3 = successful reperfusion.

TABLE 2 | Imaging characteristics ($n = 40$).

	Study group $N = 40$	mRS 0–2 $N = 20$	mRS 3–6 $N = 20$	*p*-value
Baseline parameters				
ASPECTS 0–10, median (IQR)	9 (7–10)	9 (8–10)	8 (6–9)	0.017
Occlusion site, *n* (%) ICA	11 (27.5%)	3 (15%)	8 (40%)	0.077
MCA	29 (72.5%)	17 (85%)	12 (60%)	
CBS, mean ± SD	5.75 ± 3.13	7.35 ± 1.57	4.00 ± 3.56	0.003
Good collateral, *n* (%)	21 (52.5%)	17 (85%)	4 (20%)	<0.001
Ischemic core on perfusion,	29.68	24.64	36.32	0.094
Median (IQR), ml	(10.63–54.84)	(10.28–35.37)	(20.66–114.28)	
Penumbra, mean ± SD, mL	117.99 ± 73.15	85.21 ± 48.35	119.81 ± 69.13	0.020
Ischemic tissue to infarct core,	4.65	4.55	4.80	0.850
Median (IQR)	(2.47–6.74)	(2.99–6.13)	(2.53–8.45)	
rCBF, mean ± SD	29.19 ± 11.82	30.32 ± 13.85	29.10 ± 9.51	0.555
rCBV, mean ± SD	40.12 ± 17.23	43.64 ± 17.89	38.41 ± 16.10	0.200
rMTT, mean ± SD	143.06 ± 56.76	152.28 ± 67.12	135.85 ± 44.55	0.310
rTTP, mean ± SD	151.77 ± 24.64	152.06 ± 28.20	151.99 ± 21.82	0.941
rTmax, mean ± SD	448.12 ± 285.03	503.57 ± 372.93	386.41 ± 150.30	0.223

ASPECTS, Alberta Stroke Program Early CT Score; CT, computerized tomography; CBS, Clot Burden Score; rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; rMTT, relative mean transit time; rTTP, relative time to peak; rTmax, time to maximum of the residue function; Good collateral = 2–3 score.

Cerebral Infarction (mTICI) were collected as the end of the treatment. For patients who underwent conservative treatment, no reperfusion (mTICI 0) was recorded. For 90-day clinical outcome, this was assessed with mRS by the neurologist and interventional neuroradiologist in clinical follow up or by phone call. Good outcome was defined as mRS 0–2 and poor outcome as mRS 3–6.

All procedures performed in the studies involving human participants were following the ethical standards of the institutional and/or national research committee (LYS[2020]132).

Imaging Protocol

NECT, CTP and CTA of the cervical and cerebral arteries were performed with a third-generation dual-source CT scanner (Siemens SOMATOM Force, Siemens Healthcare, Forchheim, Germany). NECT was acquired with 120 kV, 300–375 mAs at a slice thickness of 0.625 mm, and reconstructed at 5 mm. CTP was acquired with 70 kVp, 100 mAs, gantry rotation time of 0.5 s, collimation of 192 × 0.6 mm, and coverage in the z-axis of 114 mm. Forty ml of iodinated contrast material (ioversol 370 mg/ml) was injected at a rate of 6 ml/s *via* the antecubital vein, followed by flushing with 40 ml of saline at 6 ml/s, and scanning

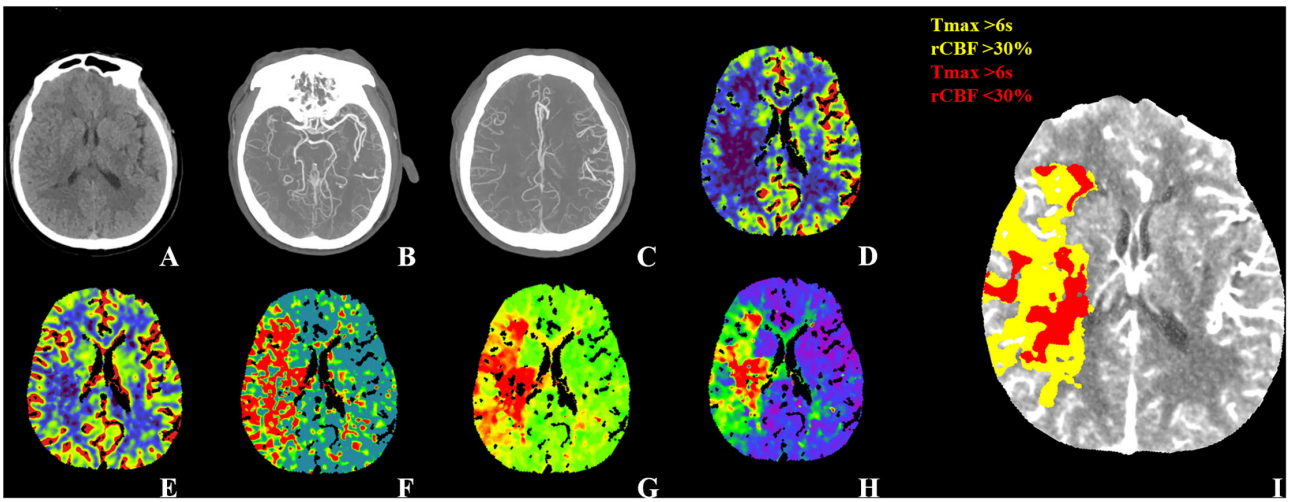

FIGURE 1 | WUS with good outcome. Fifty-four-year-old male patient WUS patient last seen well 6.4 h before imaging. **(A)** The NECT didn't show any hypodensity with ASPECTS 10. **(B)** CTA-MIP showed right distal M1 segment occlusion with CBS 8. **(C)** CTA-MIP showed collateral filling nearly 100% of the MCA flow territory with collateral score three. The CTP showed **(D)** a large area with decreased CBF, **(E)** a smaller area with decreased CBV and **(F–H)** a large area with increased MTT, TTP, and Tmax. The CTP summary map **(I)** showed 76 ml of Tmax >6 s (yellow) and 34.93 ml of <30% rCBF decrease (red). The patient was treated EVT and showed good recovery with a 90-day mRS of one. WUS, wake-up stroke; ASPECTS, Alberta Stroke Program Early CT Score; MIP, maximum intensity projection; CBS, clot burden score; MCA, middle cerebral artery; EVT, endovascular thrombectomy; mTICI, modified Thrombolysis In Cerebral Infarction; mRS, modified Rankin Scale.

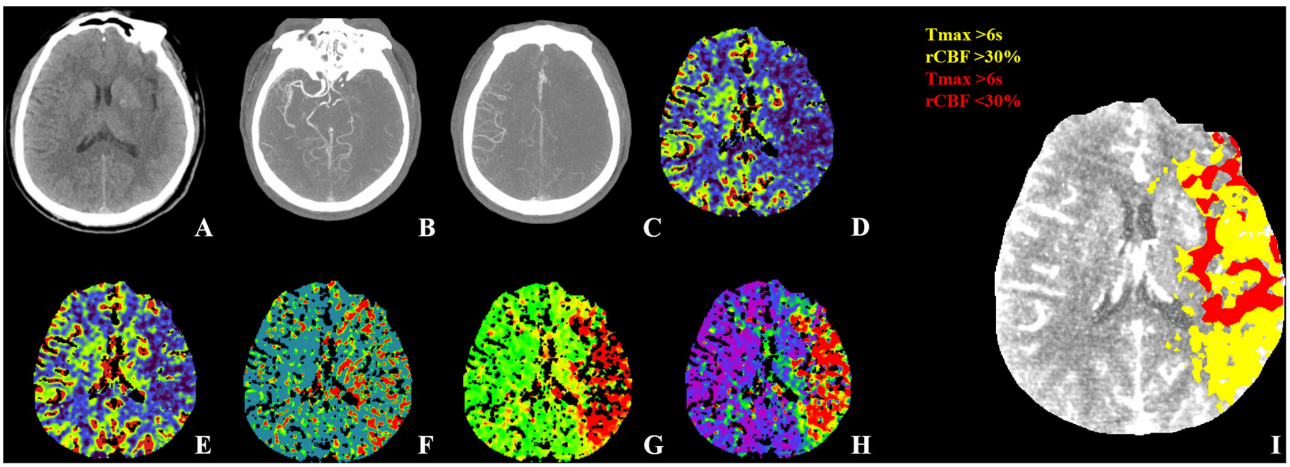

FIGURE 2 | WUS with poor outcome. Fifty-seven-year-old male patient WUS patient last seen well 6.7 h before imaging. **(A)** The NECT show hypodensity in left the insular, lenticular nucleus, M1 and M2 with ASPECTS 6. **(B)** The CTA-MIP showed left ICA, M1 and M2 occlusion with CBS 0. **(C)** CTA-MIP showed collateral filling nearly 0% of the MCA flow territory with collateral score one. The CTP showed **(D)** a large area with decreased CBF, **(E)** CBV and **(F–H)** a large area with increased MTT, TTP, and Tmax. The CTP summary map **(I)** showed 93.73 ml of Tmax >6 s (yellow) and 59.08 ml of <30% rCBF decrease (red). The patient was treated EVT (mTICI 2b) and showed poor recovery with a 90-day mRS of six. WUS, wake-up stroke; ASPECTS, Alberta Stroke Program Early CT Score; MIP, maximum intensity projection; CBS, clot burden score; MCA, middle cerebral artery; EVT, endovascular thrombectomy; mTICI, modified Thrombolysis In Cerebral Infarction; mRS, modified Rankin Scale.

commenced 5 s after the injection. The dynamic perfusion scan consisted of 22 slices of images, each with a thickness of 5 mm. CTA was acquired with 90 kVp, 100 mAs, a matrix of 512 × 512, from aorta arch to vertex. Intravascular bolus injections of 50 ml of contrast medium and 50 ml of saline then administered at a rate of 5 ml/s in all patients, and scanning commenced 2 s after the monitor region of aorta trigger the threshold of 100 HU. The CTA scan was at a slice thickness of 0.625 mm and reconstructed at 5 mm.

Imaging Evaluation

CTA and CTP raw data were transformed to the Syngo.via workstation (Siemens, version VB 2.0), then post-processed by "neuro vascular" and "neuro perfusion" software, respectively

in order to obtain the maximum intensity projection (MIP), cerebral blood flow (CBF), cerebral blood volume (CBV), mean time to transit (MTT), time to peak (TTP), time to maximum of the residue function (Tmax) imaging. All imaging data were evaluated by two neuroradiologists (with 5 years of experience in neuroimaging) and discussed to reach an agreement as needed.

Early ischemic change of the brain was assessed by ASPECTS (15) on NECT. To quantify the hemodynamic changes on CTP, region of interest was drawn manually at the most significant slice and mirrored to the contralateral hemisphere on syngo.via workstation, and relative perfusion index, such as relative CBF (rCBF), relative CBV (rCBV) was calculated. Then, ischemic core on perfusion and penumbra volume were automatically extracted by defining an ischemic core on perfusion threshold of rCBF <30% while penumbra for Tmax more than 6 s according to previous publication (16). The clot burden score (CBS), and collateral filling were graded on CTA-MIP followed the criteria proposed in the previous articles (17).

Statistical Analysis

Statistical analyses were performed using the SPSS software (Version 21 for Windows, SPSS, Armonk, NY, IBM Corp, USA). (i) The differences in categorical variables between the good outcome group and poor outcome group were analyzed separately by Chi-squared test or Fisher exact test. The differences in continuous variables were analyzed by independent-sample *t*-test or Mann-Whitney *U* test; (ii) After variables with significant differences were identified by above tests, Logistic regression analysis was used to explore predictive factors for good prognosis; (iii) Area under curve (AUC) was calculated from receiver operating characteristic (ROC) curve to check the efficiency of significant factors in (ii). In all tests, $p < 0.05$ was considered statistically significant.

RESULTS

One thousand six hundred ninety-nine patients came to the hospital with acute ischemic stroke symptom during study period. Among them, only 97 patients were wake-up stroke. Then, 77 wake-up stroke patients underwent multimodality CT imaging. Fifty-six wake-up stroke patients were found with occlusion of internal carotid artery or middle cerebral artery (M1 and M2 segment). Sixteen patients were excluded due to loss to follow-up ($n = 8$), poor imaging quality ($n = 7$) and loss of clinical data ($n = 1$). Ultimately, 40 patients were included in this study.

Good outcome defined as mRS 0–2 were seen in 20 (50%) patients. Severe disability (mRS 5) occurred in 3 (7.5%) patients and death (mRS 6) in 4 (10%) patients. No significant difference was observed in clinical parameters between good or poor outcome groups, except for NIHSS, (see **Table 1**).

On NECT, ASPECTS was significantly higher in the good outcome group compared with poor [9 (8–10) vs. 8 (6–9), $p = 0.017$]. For CTP, perfusion abnormalities were observed in all WUS patients with decreased CBF, CBV and prolonged MTT, TTP as well as Tmax. However, no significant difference was observed in preliminary quantitative measure of perfusion parameters. Further quantitative measure showed similar ischemic core on perfusion volume between groups [24.64 ml (10.28–35.37) vs. 36.32 ml (20.66–114.28), $p = 0.094$] while significant larger penumbra volume in poor outcome group compared with good (119.81 ± 69.13 vs. 85.21 ± 48.35 ml, p= 0.020). On CTA, 11 cases with intracranial internal carotid artery occlusion while 29 cases with middle cerebral artery occlusion were found among 40 wake-up stroke patients. There was no significant difference in occlusion site between group ($\chi^2 = 3.135$, $p = 0.077$). The mean CBS was significant lower in poor outcome group (4.00 ± 3.56 vs. 7.35 ± 1.57, $p = 0.003$) with a lower rate of good collateral filling (20 vs. 85%, $p < 0.001$), (see **Table 2**; **Figures 1**, **2**).

TABLE 3 | Predictors of patient outcome.

	Odds ratio (OR)	95% Confidence intervals (CI)	*p*-value
ASPECTS 0–10	0.482	0.140-1.662	0.248
CBS	0.728	0.466-1.139	0.165
Collateral score	0.140	0.030-0.664	0.013*
Penumbra volume	1.023	1.003-1.043	0.024*

ASPECTS, Alberta Stroke Program Early CT Score; CBS, Clot Burden Score.
**p-value of ≤0.05 was considered statistically significant.*

After subjecting all variables with significant differences identified by the above tests to logistic regression analysis, only penumbra volume (OR: 1.023, 95% CI = 1.003–1.043) and collateral score (OR: 0.140, 95% CI = 0.030–0.664) were found to be predictive for 90-day poor outcome, (see **Table 3**). AUC was 0.715 for penumbra volume (95% CI, 0.550–0.846) and 0.825 for good collaterals (95% CI, 0.672–0.927) in predicting outcome (**Figure 3**). At a cut-off value of 64.73, penumbra showed high sensitivity (0.95) and low specificity (0.45). At a cut-off value of one, collaterals showed high sensitivity (0.80) and high specificity (0.85).

DISCUSSION

In this prospective study, comprehensive image characteristics were summarized by using multimodality CT in WUS patients. Furthermore, the relationship between imaging and WUS patients' outcome was also analysis. We found that baseline NECT ASPECTS, clot burden score and collateral score were significantly higher in good outcome group compared with poor while penumbra volume was lower. Further analysis demonstrated that penumbra volume and collateral score are likely the most relevant baseline imaging characters in predicting outcome of WUS patients.

Compensating collateral flow is critical in maintaining blood flow to the benign oligemia and penumbra and restraining evolution of brain ischemia in patients with large vessel occlusion. Previous meta-analysis showed that patients with better collateral circulation could have a smaller ischemic core on perfusion and less severe neurological symptoms at baseline and have a better chance of achieving a favorable or excellent

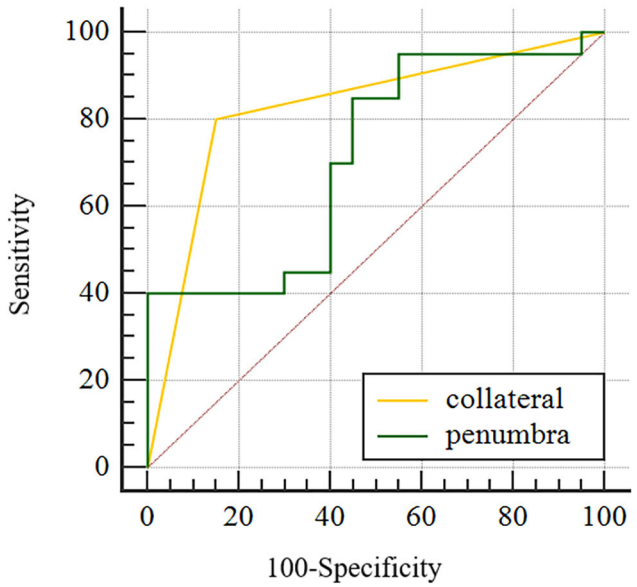

FIGURE 3 | Area under the curve for good collateral and penumbra volume in predicting functional independence (mRS 0–2) for WUS with large vessel occlusion in the anterior cerebral circulation.

functional outcome at 3 or 6 months after the index stroke (18). Another study (14) used CTA for WUS evaluation and found that collateral circulation condition graded by the ASITN/SIR was an independent risk factor for bad prognosis of wake-up ischemic stroke patients in 3 months. In this study, we found good collateral circulation (2–3 score) was a strong predictor for good outcome in WUS with relatively larger AUC than the penumbra volume. One multicenter study also showed that infarct growth was higher while penumbra salvage was lower among those with poor collaterals vs. those with good collaterals (19). If penumbra truly represents salvageable brain as is commonly maintained, collateral circulation appears to be a crucial the modulator of its fate.

Ischemic penumbra, indicating electrically non-functioning but metabolically viable brain tissue that is salvageable with rapid cerebral blood flow restoration, is the most common characteristic to measure ischemic range (20). CTP is the most common *in vivo* imaging to depict its "misery perfusion" in an emergent scenario. In this study, we found a larger penumbra volume and higher NIHSS score in poor outcome WUS patients. This finding seems contradictory to the commonly held concept that larger the salvable brain tissue volume, better the patient's outcome. However, we propose that this is explicable by the hypothesis that a larger penumbra represents a faster rate of progression from the hypo-perfused tissue to completed infarct. This characteristic will lead to larger final infarct volume as well as comparatively poor outcome. However, this hypothesis requires further confirmation, for instance by calculating the early infarct growth rate or analyzing the follow-up infarct volume on multisequence MRI. One another hand, if, for example, the penumbral tissue was located in a less eloquent part of the brain and the infarct core dominated the relationship to outcome, salvage of the penumbra would be less helpful. Supportive evidences include a meta-analysis by the HERMES collaborators (21) and a study which set up a model to predict outcome by collecting 1,476 ischemic patients (22). Both of them failed to find the associated between penumbra with either functional independence or functional improvement. The relationship between the penumbra and the infarct core may become more complex and is still under explosion.

For WUS patients, the good outcome group demonstrated higher NECT ASPECTS and higher CBS when compared with poor outcome group, which is largely consistent with previous studies focusing on onset clear stroke (23–25). However, NECT ASPECTS and CBS failed to be relevant with outcome upon logistic regression in this study. This could relate to the subjective evaluation method, lower specificity due to rater dependence, and lower sensitivity of NECT in detecting ischemic changes. In this study, we also evaluated relative perfusion parameters in predicting WUS patient outcome and failed to observe a significant difference. This result suggests in our view that it is the ischemic range, instead of the ischemic degree, which matters most for prognostication. However, this finding requires further confirmation.

There are some limitations of this study. Firstly, the sample size is moderate, and loss to follow-up rate is relatively high. Future studied with larger sample size are needed. Secondly, the post-processing software used for calculating penumbra and infarct core is not always consistent among studies. However, previous research has showed excellent agreement between RAPID software and syngo.via default settings (26). Thirdly, some other variables, such as sub-acute stroke complications, may also be valuable in predicting the prognosis of patients and are needed to be explored in future studies.

CONCLUSION

NECT ASPECTS, clot burden score, penumbra volume and collateral score differ between good and poor outcome patients following WUS. Penumbra volume and collateral compensation are the most relevant baseline imaging characters in predicting outcome of WUS patients. These imaging characteristics might be instructive to treatment selection. Further studies with larger sample size are needed to confirm these observations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Xuanwu Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FY, XB, LJ, QM, and JL contributed to conception and design of the study. FY organized the database and wrote the first draft of the manuscript. XB performed the statistical analysis. XB, YS, AD, and MZ wrote sections of the manuscript. AS and DG performed imaging examination for patients. All authors contributed to manuscript revision, read, and approved the submitted version.

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Cost-Consequence Analysis of Advanced Imaging in Acute Ischemic Stroke Care

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Introduction: The purpose of this study was to illustrate the potential costs and health consequences of implementing advanced CT angiography and perfusion (CTAP) as the initial imaging in patients presenting with acute ischemic stroke (AIS) symptoms at a comprehensive stroke center (CSC).

Methods: A decision-simulation model based on the American Heart Association's recommendations for AIS care pathways was developed to assess imaging strategies for a 5-year period from the institutional perspective. The following strategies were compared: (1) advanced CTAP imaging: NCCT + CTA + CT perfusion at the time of presentation; (2) standard-of-care: non-contrast CT (NCCT) at the time of presentation, with CT angiography (CTA) ± CT perfusion only in select patients (initial imaging to exclude hemorrhage and extensive ischemia) for mechanical thrombectomy (MT) evaluation. Model parameters were defined with evidence-based data. Cost-consequence and sensitivity analyses were performed. The modified Rankin Scale (mRS) at 90 days was used as the outcome measure.

Results: The decision-simulation modeling revealed that adoption of the advanced CTAP imaging increased per-patient imaging costs by 1.19% ($9.28/$779.72), increased per-patient treatment costs by 33.25% ($729.96/$2,195.24), and decreased other per-patient acute care costs by 0.7% (–$114.12/$16,285.85). The large increase in treatment costs was caused by higher proportion of patients being treated. However, improved outcomes lowered the other per-patient acute care costs. Over the five-year period, advanced CTAP imaging led to 1.63% (66/4,040) more patients with good outcomes (90-day mRS 0-2), 2.23% (66/2,960) fewer patients with poor outcomes (90-day mRS 3-5), and no change in mortality (90-day mRS 6). Our CT equipment utilization analysis showed that the demand for CT equipment in terms of scanner time (minutes) was 24% lower in the advanced CTAP imaging strategy compared to the standard-of-care strategy. The number of EVT procedures performed at the CSC may increase by 50%.

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Conclusions: Our study reveals that adoption of advanced CTAP imaging at presentation increases the demand for treatment of acute ischemic stroke patients as more patients are diagnosed within the treatment time window compared to standard-of-care imaging. Advanced imaging also leads to more patients with good functional outcomes and fewer patients with dependent functional status.

Keywords: cost-consequence analysis, acute ischemic stroke, computerized tomography (CT), angiography, perfusion

INTRODUCTION

Stroke is one of the leading causes of morbidity and mortality in the United States. Imaging has been reported as the second largest and the fastest growing component of stroke care costs (1). The increased utilization of advanced imaging, such as angiography and perfusion using CT (CTAP) or MRI (MRAP), has been implicated as a contributing factor in the rising trend in stroke imaging costs (1).

Current guidelines endorsed by the American Heart Association (AHA) (2) state that in most patients, non-contrast CT (NCCT) imaging may be enough to obtain the necessary information for immediate stroke triage decisions. The guidelines emphasize that utilization of advanced imaging with angiography and perfusion should not delay treatment. The current standard-of-care practice is to perform NCCT at the time of initial presentation to determine if the patient is eligible for intravenous-thrombolytic therapy (IV-tPA). Advanced imaging such as CTAP or MRAP are utilized in patients who are otherwise eligible for endovascular therapy (EVT) (3, 4). With additional information from angiography and perfusion imaging, particularly regarding large vessel occlusion and the extent of brain infarction vs. salvageable brain tissue, patients may be better triaged for treatment with IV-tPA (3–5) and/or EVT at the time of initial presentation (6–8). Numerous studies have demonstrated that faster time-to-treatment from the acute stroke onset is associated with better clinical outcomes and functional independence (9–15). However, this relationship is non-linear. Therefore, even small efficiency improvements in the pre-treatment pathway, like the immediate performance of advanced imaging upon patient arrival to the emergency department (ED), may have a significant impact on the clinical outcomes of acute stroke patients. This is especially true for those with large vessel occlusion, who without treatment, or with delayed treatment, have the highest morbidity and mortality (16). Thus, some healthcare institutions have started to perform CTAP as the initial imaging strategy in all patients suspected of acute ischemic stroke at presentation to prevent delays in treatment (8).

Advanced CTAP imaging in acute ischemic stroke patients was shown to be cost-effective in prior work (17). In that study, the cost-effectiveness analysis was performed from a health care perspective. Institutions considering whether to adopt advanced CTAP imaging need to understand the costs and health consequences of this decision for their institution. In this research we look at the adoption of the advanced CTAP imaging from the institutional perspective, while using the many of the input parameters, assumptions and conclusions from the prior cost-effectiveness analysis (17).

The purpose of this study was to investigate the potential cost and health consequences of implementing CTAP at the time of initial presentation in the workflow of suspected acute ischemic stroke (AIS) patients, excluding stroke mimics, presenting to a comprehensive stroke center (CSC) within 24 h from symptom onset time (SOT) with National Institutes of Health Stroke Scale (NIHSS) score higher than or equal to 6, compared to the standard-of-care imaging strategy using advanced imaging only in select patients who may be eligible for EVT and return to the scanner for the additional imaging.

METHODS

Institution review board (IRB) approval was not required because individual-level patient data was not utilized in this study. We developed a decision-simulation model of the acute stroke care pathways (17) from the perspective of a CSC using Microsoft Excel for Office 365 on Windows 10 operating system. The decision-simulation model algorithm for the patient work-up and clinical decision-making was based on the American Heart Association (AHA) Class-I recommendations for stroke management (2, 18). The structure of the patient workflow for the imaging strategies included: (1) Standard-of-care: all patients receive NCCT at the time of presentation; those patients who are eligible candidates for EVT within 0–6 h from SOT only receive CTA; those patients who are eligible candidates for Extended-EVT presenting at >6–24 h from SOT receive CTA+CTP; and (2) Advanced imaging: all patients receive CTAP (NCCT+CTA+CTP) at the time of presentation. In the advanced imaging strategy, we assume that perfusion imaging is performed on all patients within 24 h from SOT. **Figure 1** describes the primary logic employed at the key decision points in the workflow algorithm. In this study, we focused on the time period from patient arrival to the time of treatment in the analysis. When no treatment is indicated, the time period terminated at the last imaging test in the ED. Further details of the patient workflow after these time-points are beyond the scope of this study.

The inclusion and exclusion criteria for suspected AIS patients in the model are consistent with the American Heart Association guidelines (2019 Update) for patient selection (2). Patients presenting with hemorrhagic stroke, stroke mimics, initial NIHSS score <6, and SOT over 24 h were excluded from the analysis,

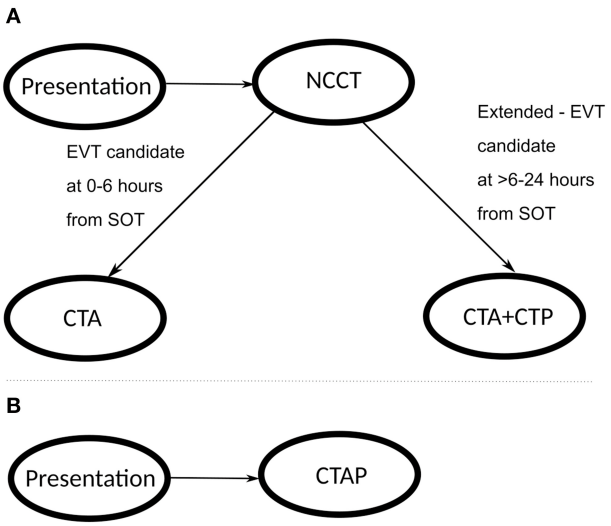

FIGURE 1 | Patient workflow through the stroke imaging pathway; **(A)** represents the standard-of-care pathway, and **(B)** represents the advanced CTAP imaging pathway.

TABLE 1 | Total number of AIS patients modeled in the study over the 5-year period.

Year	Number of patients
Historic year #−5	1,188
Historic year #−4	1,131
Historic year #−3	1,328
Historic year #−2	1,329
Historic year #−1	1,455
Future year #1	1,506
Future year #2	1,613
Future year #3	1,670
Future year #4	1,766
Future year #5	1,838

The volume of AIS patients in Future year #1 through Future year #5 was estimated as a linear projection of the trend based on the number of AIS patients admitted to our institution in the past 5 years using the method of least squares.

similar to the clinical trials (6, 8, 19–22). Detailed inclusion and exclusion criteria are listed in the **Supplementary Table 3**. We did not model all the potential scenarios in clinical practice in order to focus the analyses on the costs and health consequences of advanced CTAP imaging in acute ischemic stroke patients, which was shown to be cost-effective in prior work (17). The number of AIS patients admitted to our institution in prior years was utilized to extrapolate the trend in a linear model to estimate the number of stroke patients in the model in the next 5 years. **Table 1** describes the total AIS patients over the historic 5 years at our institution and future 5 years calculated as a linear trend using the method of least squares.

Because our model focused on the CSC perspective, we limited the analysis to the institutional acute care costs within first 90-days after stroke, including imaging and treatment costs associated with these patients. We explored the time horizon of 5 years in this analysis (23). We modeled the cost and health effects impact on the dynamic cohort of patients for the period of 5 years, where continuously new patients with stroke were added to the cohort, and after 90 days post discharge were removed from the cohort. The annual acute care costs were calculated for both strategies during the 5-year period. We also calculated the per-patient acute care costs of each strategy and reported the total annual costs for a CSC to implement advanced CTAP imaging by multiplying the per-patient costs by the total number of patients each year. In addition, we incorporated the 90-day (within the first 90 days of stroke onset) and lifetime (over the remaining lifetime of the patient) cohort quality-adjusted life-years (QALY) for each strategy, and the percentage of patients in different 90-day modified Rankin scale (mRS) groups, representing functional independence (90-day mRS 0-2), functional dependence (90-day mRS 3-5), and death (90-day mRS 6). We measured 90-day and lifetime health impact using QALYs, a commonly used metric that combines the length and quality of life into a single value (24). The model input parameters were based on published literature as shown in **Table 2**, representing the baseline scenario.

In this analysis, the initiation costs were set to $0 because we assumed that CSCs already had the necessary CT scanners and/or angiography equipment available for stroke patients both in standard-of-care and CTAP strategies. Thus, we focused this analysis on incremental costs associated with implementation of CTAP imaging for stroke care.

The ongoing operational and clinical acute care costs were derived from the published literature as shown in **Table 2**, which utilize Medicare CPT codes to estimate the costs. It is standard practice in health economics evaluations to use Medicare reimbursement as a substitute for actual costs (25, 33, 34) to minimize bias from practice variation. These costs include depreciation on all depreciable type assets that are used to provide covered services to beneficiaries (35). Total and per-patient costs were generated for the three main categories of interest: imaging, treatment, and other 90-day acute care costs. Other 90-day acute care costs consisted of the cost of hospital bed occupancy and the length of stay (28, 29). Sensitivity analyses were performed to calculate costs based on the variation of the input parameters in the model. By performing univariate sensitivity analyses, we determined the range from the least to the greatest per-patient costs. **Table 2** shows the baseline, minimum and maximum cost values used in the sensitivity analyses. The input parameters for sensitivity analyses were based on published literature.

In order to assess the impact of a new imaging strategy on the utilization of the CT equipment, we performed a thorough literature review and identified the scanner time required for NCCT, CTA, and CTP imaging, as well as the time interval between patients, shown in **Table 2**. Scanner time refers to the amount of time that a CT scanner is occupied for a certain procedure. The procedures for which the scanner time was calculated were: NCCT, CTA, CTA+CTP, CTAP, and the interval time between patients.

The costs and outcomes for each imaging strategy were calculated separately. Then the costs and outcomes of the

TABLE 2 | Cost data with minimum and maximum values adjusted for inflation to reflect values in 2019 U.S. dollars.

Model Parameter	Baseline value (minimum-maximum)	References
Costs		
IV-tPA	$7,518 ($7,217–$9,022)	(25, 26)
EVT	$15,714 ($15,085–$18,857)	(25, 26)
NCCT	$202 ($194–$242)	(1, 26, 27)
CTA ± CTP	$789 ($757–$947)	(1, 26, 27)
Acute-care cost		
Acute care costs within first 90 days after stroke (excluding imaging, IVT and EVT) mRS 0-2	$11,544 ($11,083–$13,853)	(26, 28, 29)
Acute care costs within first 90 days after stroke (excluding imaging, IVT and EVT) mRS 3-5	$26,818 ($25,745–$32,181)	(26, 28, 29)
Acute care costs within first 90 days after stroke (excluding imaging, IVT and EVT) mRS 6	$7,681 ($7,374–$9,217)	(26, 28, 29)
90-day utilities		
mRS 0-2	0.89	(30, 31)
mRS 3-5	0.33	(30, 31)
Lifetime discounted QALYs		
mRS 0-2	12.89	(32)
mRS 3-5	5.5	(32)
Time of diagnostic tests, minutes		
NCCT	5.00	(3)
CTA	15.00	(3)
CTA+CTP	25.00	(18)
CTAP (NCCT+CTA+CTP)	25.00	(18)
Interval between patients	10.00	(18)
Probabilities of transitioning to 90-day modified Rankin scale (mRS): standard-of-care imaging		
mRS 0-2	48.1340248%	(17)
mRS 3-5	35.2481406%	(17)
mRS 6	16.6178346%	(17)
Probabilities of transitioning to 90-day modified Rankin scale (mRS): advanced imaging		
mRS 0-2	48.9114442%	(17)
mRS 3-5	34.4948803%	(17)
mRS 6	16.5936755%	(17)

Utilities values are average utility values for the group of patients with the corresponding 90-day mRS scores. Lifetime discounted QALYs are the expected quality adjusted life years of people having respective 90-day mRS scores. Time to perform each of the imaging procedure, and interval time between patients in the CT scanner.

standard-of-care imaging scenario were separately subtracted from the costs and outcomes of the CTAP imaging scenario. The resulting differences in costs and outcomes represent the incremental differences reported in this analysis.

RESULTS

Adoption of the advanced CTAP imaging strategy increased per-patient imaging costs by 1.19% ($9.28/$779.72), increased per-patient treatment costs by 33.25% ($729.96/$2,195.24), and decreased per-patient other acute care costs by 0.7% (–$114.12/$16,285.85). The large increase in treatment costs was due to the higher proportion of patients being treated. Lower per-patient other acute care costs were mainly due to better health outcomes and shorter hospital stay.

The per-patient cost analysis for the two imaging strategies is shown in **Table 3**. While performing advanced CTAP imaging on the identical cohort of stroke patients, as in the standard-of-care strategy, the incremental imaging costs were higher by $9.28 per patient in the advanced CTAP imaging strategy. Since the costs were based on the Medicare CPT codes, the incremental costs of $9.28 in the advanced CTAP imaging strategy translates to the CSC receiving $9.28 more reimbursement revenue per patient. This higher cost was driven by greater utilization of the higher reimbursed CTAP imaging.

Our CT equipment utilization analysis showed that the demand for CT equipment in terms of scanner time (minutes) was 24% lower in the advanced CTAP imaging strategy compared to the standard-of-care strategy. Although executing the imaging protocols for NCCT, CTA and CTP in one session takes longer than performing only NCCT or CTA on an individual patient, 73.2% of the patients in the standard-of-care strategy return to the scanner for additional imaging with angiography (and some also with perfusion) if they are potentially eligible for EVT. Besides the penalty of the time spent on subsequent imaging for the same patient, additional burden is the time spent between imaging tests, as some time is needed for the first patient to leave the CT scanner, and the next one to arrive to the scanner.

Univariate sensitivity analyses revealed that the change for imaging costs in the 1st year ranged from –$46,264 to $77,676, the growth for treatment costs ranged from $1,060,335 to $1,293,210, the decline in other 90-day acute care costs ranged from –$232,672 to –$144,811. The largest variation was seen in the treatment costs; the imaging and other 90-day costs had a narrower variation between the lower and upper boundaries of the parameter values. Overall, the sensitivity analysis suggested that after implementation of advanced CTAP imaging, imaging costs would either grow or decline, treatment costs would definitely grow, and other 90-day acute care costs would definitely decline.

The average overall incremental care costs of the advanced CTAP imaging strategy for a CSC with 1,679 annual strokes were $1,049,322. Of the total incremental acute care costs in the 1st year, only 1.48% ($15,571/$1,049,322) was attributed to the growth in imaging costs, 116.77% ($1,225,314/$1,049,322) to the growth in treatment costs, and −8.26% (–$191,563/$1,049,322) to the decline in other 90-day acute care costs. The results of the costs analysis for 5 consecutive years after implementation, further details on the univariate sensitivity analysis, and CT equipment utilization analysis are included in **Supplementary Material**.

An analysis on the projected impact of the advanced CTAP imaging strategy on the number of EVT procedures performed at the CSC found that EVT procedures may increase by 50% and IV-tPA procedures may increase by 9% each year. **Table 4** details the

TABLE 3 | Per-patient costs projection for the 5-year period for the standard-of-care and advanced CTAP imaging strategies.

	Year 1	Year 2	Year 3	Year 4	Year 5	Average	Change
Annual per-patient costs							
Strategy 1: standard-of-care imaging							
CTA	$439.11	$439.11	$439.11	$439.11	$439.11	$439.11	
CTA+CTP	$138.61	$138.61	$138.61	$138.61	$138.61	$138.61	
NCCT	$202.00	$202.00	$202.00	$202.00	$202.00	$202.00	
IV-tPA	$906.69	$906.69	$906.69	$906.69	$906.69	$906.69	
EVT	$1,288.55	$1,288.55	$1,288.55	$1,288.55	$1,288.55	$1,288.55	
Imaging costs	$779.72	$779.72	$779.72	$779.72	$779.72	$779.72	
Treatment costs	$2,195.24	$2,195.24	$2,195.24	$2,195.24	$2,195.24	$2,195.24	
Other acute care costs within first 90 days after stroke (excluding imaging, IVT and EVT)	$16,285.85	$16,285.85	$16,285.85	$16,285.85	$16,285.85	$16,285.85	
Total costs	$19,260.82	$19,260.82	$19,260.82	$19,260.82	$19,260.82	$19,260.82	
Strategy 2: advanced imaging							
CTA	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	
NCCT+CTA+CTP	$789.00	$789.00	$789.00	$789.00	$789.00	$789.00	
NCCT	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	
IV-tPA	$992.38	$992.38	$992.38	$992.38	$992.38	$992.38	
EVT	$1,932.82	$1,932.82	$1,932.82	$1,932.82	$1,932.82	$1,932.82	
Imaging costs	$789.00	$789.00	$789.00	$789.00	$789.00	$789.00	
Treatment costs	$2,925.20	$2,925.20	$2,925.20	$2,925.20	$2,925.20	$2,925.20	
Other acute care costs within first 90 days after stroke (excluding imaging, IVT and EVT)	$16,171.73	$16,171.73	$16,171.73	$16,171.73	$16,171.73	$16,171.73	
Total costs	$19,885.93	$19,885.93	$19,885.93	$19,885.93	$19,885.93	$19,885.93	
Incremental costs							
Imaging incremental costs	$9.28	$9.28	$9.28	$9.28	$9.28	$9.28	1.19%
Treatment incremental costs	$729.96	$729.96	$729.96	$729.96	$729.96	$729.96	33.25%
Other acute care 90-days incremental costs	-$114.12	-$114.12	-$114.12	-$114.12	-$114.12	-$114.12	−0.70%
Total incremental costs	$625.11	$625.11	$625.11	$625.11	$625.11	$625.11	3.25%

Incremental costs section shows the per-patient difference between both strategies, where the corresponding value from the standard-of-care strategy is subtracted from the advanced CTAP imaging strategy.

projected increase in the number of EVT and IV-tPA procedures for both imaging strategies.

An additional important result of our analysis is that in the CTAP imaging strategy, health outcomes changed. The impact of CTAP imaging on health outcomes for the 5-year time period is shown in **Table 5**. We found that on average the lifetime quality-adjusted life years of a patient in the advanced CTAP imaging strategy improved by 0.03 QALYs, compared to the standard-of-care strategy. This corresponds to $20,837 per QALY gained. On average, the 90-day utility increased by 0.0044 QALYs because more patients were treated in the CTAP imaging strategy. In this acute stroke cohort, we found that the clinical outcomes in the CTAP imaging strategy improved, with 13 more patients having better functional outcomes, defined by the 90-day mRS 0-2, and 13 fewer patients having a dependent functional status (90-day mRS 3-5) compared to the standard-of-care strategy on average per year. This corresponds to $79,448 per functional dependence avoided in the 1st year. We found no change in mortality (90-day mRS 6).

Finally, the model projected that over 5 years in the advanced CTAP imaging strategy, out of 8,393 AIS patients, 66 more patients would have a good functional outcome (90-day mRS 0-2), and 66 fewer patients would have a dependent functional status (90-day mRS 3-5), with no change in mortality (90-day mRS 6).

DISCUSSION

The main finding from this analysis is that performing advanced imaging using CTAP for AIS patients at presentation increases overall costs for a CSC, with the greatest impact from treatment costs, over the 5-year period. Our analyses show that CTAP imaging in moderate-to-severe acute ischemic stroke care leads to more patients being eligible for treatment within the time

TABLE 4 | Estimated number of EVT and IV-tPA procedures in the advanced CTAP imaging and standard-of-care strategies for the 5-year period.

Year	Number of patients	Number of EVT procedures				Number of IV-tPA procedures			
		Number of EVTs in advanced imaging scenario	Number of EVTs in standard-of-care scenario	Increase in number of EVTs	Percentage increase in number of EVTs	Number of IV-tPAs in advanced imaging scenario	Number of IV-tPAs in standard-of-care scenario	Increase in number of IV-tPAs	Percentage increase in number of IV-tPAs
1	1,506	185	123	62	50%	199	182	17	9%
2	1,613	198	132	66	50%	213	195	18	9%
3	1,670	205	137	68	50%	220	201	19	9%
4	1,766	217	145	72	50%	233	213	20	9%
5	1,838	226	151	75	50%	243	222	21	9%
Total	8,393	1,031	688	343	50%	1,108	1,013	95	9%

window, and thus undergoing endovascular therapy, translating to improved health outcomes. To our knowledge, no studies have analyzed the incremental costs and benefits associated with implementing advanced CTAP imaging in the initial evaluation of patients presenting with moderate-to-severe acute ischemic stroke symptoms from the healthcare provider perspective.

While costs were higher, primarily due to more EVT performed, our study showed that the transition to advanced CTAP imaging strategy led to an increase in the number of patients with good functional clinical outcomes (90-day mRS 0-2), while the number of patients with moderate to severe disability decreased (90-day mRS 3-5). There was no change in mortality (90-day mRS 6). Importantly, this implies that the costs for long-term care will also be reduced. At $20,837/QALY, the advanced CTAP imaging strategy should be considered appropriate for adoption in clinical care when considering a threshold of $50,000/QALY, which is customarily used as a threshold in health policy (4, 5, 17, 25, 34).

Furthermore, our model results, based on Medicare CPT reimbursement, showed that for diagnostic imaging, the advanced CTAP imaging strategy is more costly than the standard-of-care strategy. However, the analysis of the scanner times showed that the advanced imaging strategy required less scanner time than the standard-of-care strategy, and therefore, the diagnostic imaging component could actually be less costly. We explain this discrepancy as the scanner time analysis represents opportunity costs for the hospital. With 24% less scanner utilization in the advanced CTAP imaging strategy, the remaining scanner time can potentially be used for other patients.

Although we showed that the demand for CT equipment in terms of minutes was lower in the advanced CTAP imaging strategy, the demand for angiography equipment to perform EVTs grew in the advanced imaging strategy. Having more stroke cases treated with EVT potentially indicates higher reimbursement revenue for the hospital. The potential effect of whether new angiography equipment needs to be purchased strongly depends on the case mix of the particular institution. Our analysis suggests that when contemplating shifting to the advanced CTAP imaging strategy in stroke care, an institution must consider the interventional neuroradiology capacity to handle the increased volume of EVT. If EVT capacity is insufficient, then implementation of the CTAP imaging strategy may lead to delayed treatment for EVT-eligible patients. This delay, in turn, could lead to worse outcome for AIS patients if treatment is not initiated in a timely manner.

The first limitation of this study is that we did not account for any initiation costs. Initiation costs depend on the availability of radiologists and/or CT scanners in a particular institution. At our institution ED CT scanners run 24/7 and they are currently not utilized at full capacity. We have hardware, software and personnel to accommodate peaks in the demand for radiology service and transition to advanced CTAP imaging. Therefore, we might not need any initiation costs going from the standard of care to advanced CTAP imaging. On the other hand, institutions currently running their CT scanners at full capacity might need an additional scanner for this transition to account for peaks in the demand. CSCs need to add our analysis to their baseline situation to determine if there are any relevant initiation costs for the transition at their institution.

Another limitation of our study is that we used Medicare CPT reimbursement as a surrogate for the costs to the institution. Although this approach may not accurately represent the actual costs at the specific institution level, it remains standard practice in health economics studies in radiology (25, 33, 34). Without more precise methodology available, we conformed to standard practice in this study with the potential for better generalizability to other institutions.

The next limitation of our study is that we did not measure discounted costs against an effectiveness outcome, as would be performed in a cost-effectiveness analysis from a broader societal perspective (17), which was out of the scope of this study. Healthcare institutions in the United States deciding on whether to implement advanced CTAP imaging for all incoming AIS patients might want or need to know the undiscounted costs and health impact of the proposed care pathway change in each of the next 1–5 years (23). Lifetime

TABLE 5 | Health impact projection of the number of people in each health outcome group for the advanced CTAP imaging and standard-of-care strategies for the 5 year period.

	Year 1	Year 2	Year 3	Year 4	Year 5	Total	Average
Annual health outcomes							
Strategy 1: standard-of-care imaging							
Lifetime QALYs of the cohort	8,839	9,467	9,803	10,369	10,790	49,267	9,853
Short term QALYs of the cohort	820	878	910	962	1,001	4,572	914
mRS 0-2	725	776	804	850	885	4,040	808
mRS 3-5	531	569	589	623	648	2,960	592
Deaths	250	268	277	293	305	1,393	279
Strategy 2: advanced imaging							
Lifetime QALYs of the cohort	8,884	9,515	9,853	10,422	10,845	49,519	9,904
90-day QALYs of the cohort	827	886	917	970	1,009	4,609	922
mRS 0-2	737	789	817	864	899	4,106	821
mRS 3-5	519	556	576	609	634	2,894	579
Deaths	250	268	277	293	305	1,393	279
Incremental health impact							
Lifetime QALYs of the cohort	45	48	50	53	55	252	50
Lifetime utility per person	0.0300	0.0300	0.0300	0.0300	0.0300		0.0300
90-day QALYs of the cohort	7	7	7	8	8	37	7
90-day utility per person	0.0045	0.0045	0.0044	0.0044	0.0043		0.0044
mRS 0-2	12	13	13	14	14	66	13
mRS 3-5	−12	−13	−13	−14	−14	−66	−13
Deaths	0	0	0	0	0	0	0
Relationship between costs and outcomes							
Cost per functional dependence avoided	$78,441	$77,550	$80,303	$78,872	$82,073		$79,448
Cost per QALY gained	$20,837	$20,837	$20,837	$20,837	$20,837		$20,837

The incremental health impact of switching from the standard-of-care to the advanced CTAP imaging strategy is also shown.

discounted costs and outcomes, which are the typical output of a cost-effectiveness analysis, are useful additional information, but shorter-term undiscounted costs and health impact information are often helpful complementary inputs for decision-making at the institutional level (23).

Furthermore, we do not have a reliable source of information how the costs used in our model will change, or how the treatment and care methods for AIS will change, in the next 5 years. We performed sensitivity analyses in our study in order to account for this uncertainty.

Besides, another limitation of our study is that we didn't have the reliable data to model MT outcomes of patients presenting in the LKWA >6–24-h time window. We used extrapolated data from our previously published population-based study (17) to model clinical outcomes of some stroke imaging subtypes because adequate data did not exist in the literature. Importantly, our model reflects stroke care pathways recommended by the AHA guidelines (2) with workflow from RCTs, which report arrival-to-treatment times between 74 and 148 min (9).

Finally, we excluded patients with NIHSS < 6 from our model, similar to the clinical trials (6, 8, 19–22). A separate study is required to analyze the cost-consequence of advanced CTAP imaging of suspected AIS in patients presenting with NIHSS < 6.

In this study we analyzed the incremental costs of advanced CTAP imaging for acute stroke care from the CSC perspective. Since actual costs are highly variable between different types of healthcare institutions, future research may analyze the adoption of advanced CTAP imaging strategy in practice settings other than a CSC.

CONCLUSIONS

Advanced CTAP imaging in acute ischemic stroke care increases diagnostic and treatment costs with more patients eligible for treatment in the time window undergoing endovascular therapy, thus leading to improved stroke health outcomes. Consequently, CTAP imaging leads to more patients with good functional outcomes (90-day mRS 0-2), fewer patients with dependent functional status (90-day mRS 3-5) and unchanged mortality (90-day mRS 6). The present study can be used as a resource-planning tool for CSCs considering adoption of advanced CTAP imaging protocols for acute ischemic stroke patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

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Predictive Factors for the Need of Tracheostomy in Patients With Large Vessel Occlusion Stroke Being Treated With Mechanical Thrombectomy

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Background: Patients with large vessel occlusion stroke (LVOS) eligible for mechanical thrombectomy (MT) are at risk for stroke- and non-stroke-related complications resulting in the need for tracheostomy (TS). Risk factors for TS have not yet been systematically investigated in this subgroup of stroke patients.

Methods: Prospectively derived data from patients with LVOS and MT being treated in a large, academic neurological ICU (neuro-ICU) between 2014 and 2019 were analyzed in this single-center study. Predictive value of peri- and post-interventional factors, stroke imaging, and pre-stroke medical history were investigated for their potential to predict tracheostomy during ICU stay using logistic regression models.

Results: From 635 LVOS-patients treated with MT, 40 (6.3%) underwent tracheostomy during their neuro-ICU stay. Patients receiving tracheostomy were younger [71 (62–75) vs. 77 (66–83), $p < 0.001$], had a higher National Institute of Health Stroke Scale (NIHSS) at baseline [18 (15–20) vs. 15 (10–19), $p = 0.009$] as well as higher rates of hospital acquired pneumonia (HAP) [39 (97.5%) vs. 224 (37.6%), $p < 0.001$], failed extubation [15 (37.5%) vs. 19 (3.2%), $p < 0.001$], sepsis [11 (27.5%) vs. 16 (2.7%), $p < 0.001$], symptomatic intracerebral hemorrhage [5 (12.5%) vs. 22 (3.9%), $p = 0.026$] and decompressive hemicraniectomy (DH) [19 (51.4%) vs. 21 (3.8%), $p < 0.001$]. In multivariate logistic regression analysis, HAP (OR 21.26 (CI 2.76–163.56), $p = 0.003$], Sepsis [OR 5.39 (1.71–16.91), $p = 0.004$], failed extubation [OR 8.41 (3.09–22.93), $p < 0.001$] and DH [OR 9.94 (3.92–25.21), $p < 0.001$] remained as strongest predictors for TS. Patients with longer periods from admission to TS had longer ICU length of stay ($r = 0.384$, $p = 0.03$). There was no association between the time from admission to TS and clinical outcome (NIHSS at discharge: $r = 0.125$, $p = 0.461$; mRS at 90 days: $r = -0.179$, $p = 0.403$).

Conclusions: Patients with LVOS undergoing MT are at high risk to require TS if extubation after the intervention fails, DH is needed, and severe infectious complications occur in the acute phase after ischemic stroke. These factors are likely to be useful for the indication and timing of TS to reduce overall sedation and shorten ICU length of stay.

Keywords: ischemic stroke, mechanical thrombectomy (MT), large vessel occlusion (LVO), intensive care medicine (ICM), tracheostomy (TS)

INTRODUCTION

Mechanical thrombectomy has been shown to be highly effective and is the standard of care for large vessel occlusion stroke (LVOS) (1). A large meta-analysis of randomized controlled trials, however, showed that >20% of patients with LVOS and mechanical thrombectomy (MT) had unfavorable outcomes with modified Rankin scores (mRS) of 4 or 5, likely requiring pronged in-patient stay with treatment on intensive care units (ICU) and increased risks for stroke and non-stroke related complications (1). Taking all ischemic stroke patients into account, it has been estimated that around 24% of this population needs ICU treatment (2).

Various complications in LVOS-patients are associated with ICU treatment and lead to unfavorable functional outcomes (3). These complications include neurological causes of decreased consciousness by large infarctions, cerebral edema, or symptomatic intracerebral hemorrhage (sICH), which also can lead to respiratory complications like pneumonia caused by stroke-associated dysphagia and again can result in hemodynamic instabilities caused by systemic inflammatory responses (4). In these scenarios, multiple factors influence the decision if-, and at which time point to perform a tracheostomy (TS) to achieve long term ventilatory support, drastically decrease sedatives and shorten prolonged orotracheal intubation, both in combination associated with increased rates of pneumonia and length of ICU stay (5). Failed extubation rates of around 17% in mixed neurological ICU (neuro-ICU) populations with acute brain injury have been reported, not only describing an association with quantitative and qualitative measurements of consciousness (e.g., a Glascow Coma Scale (GCS) of ≤8 points and the inability to obey commands), but also identifying multiple other factors like chronic obstructive pulmonary disease or congestive heart failure being associated with increased risk of reintubation, reflecting that conventional extubating criteria are not applicable in this patient group (6, 7). Therefore, the decision and timepoint of TS in major stroke patients should most likely be guided by clinical and functional status, emerging complications, and past medical history rather than only focusing on the state of consciousness and ventilatory function (5). If, in this context, an early TS translates into better clinical outcomes in major stroke patients is being investigated in a still unpublished randomized control trial (8), after Bösel et al. (9) showed feasibility and safety of early tracheostomy in major stroke patients in a pilot study.

Patients with LVOS, in contrast to a general population of major stroke patients, represent a well-characterized subgroup both at risk for intravenous thrombolysis (IVT)-/MT associated- as well as cardio-respiratory associated complications increasing the risk for ICU-treatment, as most patients receive general anesthesia with orotracheal intubation prior MT. In this subgroup of major stroke patients, a combination of factors increasing the risk for TS, to date, has not been systematically investigated. The aim of this study was to describe the proportion and characteristics of LVOS-patients receiving a TS after MT and to determine factors predicting the need for TS during their ICU stay.

MATERIALS AND METHODS

Patient Population and Clinical Characteristics

We used a prospectively derived, single-center database including all patients receiving MT for LVOS treatment between 2014 and 2019 in a large, academic stroke center and being treated on a neuro-ICU. This database includes information on time metrics, imaging, intervention, patient history, and stroke- as well as non-stroke associated complications after MT. Information on the timepoint of tracheostomy, blood gases, failed extubation and pulmonary diseases were obtained retrospectively through a chart review [IntelliSpace Critical Care and Anesthesia (ICCA) information system (Koninklijke Philips N.V., 2004–2017)]. Ethics approval was sought from the Ethics Committee of the University Medicine Göttingen (13/7/15) and all patients or next of kin gave informed written consent for the anonymized use of disease-related data on hospitalization. Patients were included in the analysis if a predefined dataset on pre-stroke history (comorbidities), periinterventional data (imaging, time metrics, scores), and clinical data on the post-stroke course (e.g., infectious complications) was complete and available, which was the case in 635 (88.7%) from 716 patients included in the databank in the mentioned time period.

In the case of complete datasets, we included all patients with LVOS receiving MT with or without prior IVT. As the success of the reperfusion therapy is a major predictor for clinical outcome, we only included patients with no- or minimal perfusion (complete or near-complete vessel occlusion) of the occluded vessel on the first angiogram prior to MT [defined as modified Thrombolysis in cerebral infarction (mTICI) ≤ 1]. Therefore, patients with spontaneous reperfusion or reperfusion through IVT were excluded. All patients were treated on the Neuro-ICU of the University Medical Center Göttingen, Germany. We included all types of LVO being treated at the

discretion of the neurointerventionalist performing the MT. The indication for IVT was according to the current German guidelines and all patients were treated from stroke experienced intensive care trained neurologists only. The decision for the need for a TS and its timepoint was made by ICU-trained senior consultant neurologists without the use of standard criteria or SOPs. All TSs were performed as surgical TSs by experienced Ears, Nose, and Throat (ENT) specialists. The indication for a decompressive hemicraniectomy was made in consensus with stroke experienced neurosurgeons.

Stroke and Non-stroke Associated Complications After MT

Following complications after MT were documented and investigated: failed extubation was defined as $\geq$ 1 complete removal of the orotracheal tube with the need of reintubation within a 48 h period. Hospital-acquired pneumonia (HAP) was diagnosed if an infiltrate/suspicion of an infiltrate was visualized on chest X-ray in presence of at least two clinical signs such as pyogenic secretion, fever (>38°C), leukocytosis, or leukopenia (>10,000 or <4,000/l) or the detection of a pneumonia-typical pathogen in the bronchial secretion or blood (10). For the diagnosis of sepsis, the sequential (sepsis-related) organ failure assessment (SOFA) score has been used and was $\geq$2 in combination with positive blood cultures (11).

Statistical Analysis

Statistical analysis was performed using SPSS 21 (IBM SPSS Statistics, Armonk, NY, USA). Characteristics of all patients are shown as $M \pm SD$ if normally distributed, and as median with interquartile range (IQR), if not. Category variables were given as absolute frequencies and percentages and examined by the Pearson Chi-Square test for statistically significant differences between the compared groups. The different groups were examined for significant differences by using independent samples *T*-test or Mann–Whitney U test, as appropriate. Uni- and multi-variate logistic regression analysis were performed for clinical and imaging factors as well as complications being unequally distributed between the TS and non-tracheostomy (nTS) group with $p < 0.1$ in a univariate pre-test. In multivariate logistic regression, the pre-identified factors for TS were included and the backward selection (Wald) was used. The clinical scores National Institute of Health Stroke Scale at discharge, mRS at discharge, and after 90 days were not included in the models and were only used to investigate an association between time from admission to TS and clinical outcome. In a final step, the model's regression coefficients of the identified predictors for TS were used to create a score, which again was analyzed using the Area Under the Receiver Operating Characteristic (AUROC) method. The cut-off score was defined as a score with maximal Youden-Index (Youdens J = sensitivity + specificity – 1). Pearson correlations have been used to investigate the strength and direction of associations between treatment times and functional outcome scores. In all procedures, a $p < 0.05$ was considered statistically significant.

RESULTS

From the 635 LVOS-patients included in this analysis, 40 (6.7%) required TS during their neuro-ICU stay after MT. Baseline characteristics are given in **Table 1**. Patients receiving TS were significantly younger [71 (62–75) vs. 77 (66–83), $p < 0.001$], had a higher NIHSS [18 (15–20) vs. 15 (10–19), $p = 0.009$], and a lower Alberta stroke program early CT score (ASPECTS) at baseline. Symptom-to-groin times were significantly longer in TS patients [268 (202–360) vs. 211 (154–284) min, $p = 0.005$], while rates of successful recanalization (mTICI$\geq$2b 72.5% vs. 79.8%, $p = 0.311$) and final mTICI scores ($p = 0.703$) did not differ between groups. Functional outcome was significantly worse in patients with TS compared with nTS [NIHSS discharge: 19 (14–23) vs. 5 (2–11), $p < 0.001$; mRS discharge: 5 (5) vs. 3 (1–5), $p < 0.001$] and patients with TS had a longer neuro-ICU length of stay [22 (14.25–29) vs. 9 (5–14), $p < 0.001$]. Mortality did not differ between groups (22.5 vs. 28.4%, $p = 0.470$). Significantly more patients in the nTS group received IVT (22.5 vs. 37.5%, $p = 0.019$); all other ischemic stroke treatment characteristics were comparable between the groups. With the exception of a history of pulmonary embolism, which was higher in the TS group (15 vs. 3.5%, $p = 0.005$), there was no difference in rates of pulmonary comorbidities between groups.

Concerning post stroke complications, almost all patients in the TS group developed a hospital acquired pneumonia (HAP) (97.5 vs. 37.6%, $p < 0.001$) and rates of failed extubation (37.5 vs. 3.2%, $p < 0.001$), sepsis (27.5 vs. 2.7%, $p < 0.001$), sICH (12.5 vs. 3.9%, $p = 0.026$) as well as decompressive hemicraniectomy (DH) (51.4 vs. 3.8%, $p < 0.001$) were significantly higher.

With exception for diabetes mellitus and symptom-onset-to-recanalization time, all factors described above were predictive for the need of TS in the univariate analysis. As shown in **Table 2**, HAP [OR 64.6 (8.81–473.41), $p < 0.001$], DH [OR 27.1 (12.44–59), $p < 0.001$], failed extubation [18.16 (8.27–39.9), $p < 0.001$], sepsis [18.16 (8.27–39.9), $p < 0.001$], a history of pulmonary embolism [4.82 (1.83–12.74), $p = 0.001$], no IVT treatment [0.32 (0.14–0.75), $p = 0.009$] and sICH [3.54 (1.26–9.91), $p = 0.016$] were among the strongest predictors for TS.

In multivariate logistic regression, all factors except ASPECTS and age were included. The latter were excluded because of a clear selection bias for age (younger patients are more likely to be selected for TS and older patients are more likely to receive limited therapy) and to avoid multicollinearity [as ASPECTS and NIHSS are highly correlated ($r = -0.248$, $p < 0.001$)]. Using the stepwise backward selection (Wald) function of the logistic regression model, HAP [OR 21.26 (2.76–163.56), $p = 0.003$], DH [OR 9.94 (3.92–25.21), $p < 0.001$], failed extubation [OR 8.41 (3.09–22.93), $p < 0.001$] and sepsis [OR 5.39 (1.71–16.91), $p = 0.004$] remained as strongest predictors for TS (**Table 3**).

The regression coefficients of the multivariate logistic regression model given in **Table 3** were used to create a score for the prediction of TS using the equation given in **Supplementary Figure 1**. This score, ranging from −7 to 4 points, showed an excellent predictive value for the need for TS (AUROC, 0.929, 95%CI, 0.884–0.974, $p < 0.001$). Patients with TS had a median score of −1 (IQR, −1 to 1), and patients without

TABLE 1 | Baseline characteristics of patients with- and without tracheostomy after mechanical thrombectomy ($n = 635$).

	Tracheostomy group ($n = 40$)	No tracheostomy group ($n = 595$)	*p*-value
Patient characteristics and past medical history			
Age (median, IQR)	71 (62–75)	77 (66–83)	<0.001
Sex (*n*, % male)	19 (47.5)	268 (45.0)	0.870
Arterial hypertension (*n*, %)	30 (78.9)	462 (80.8)	0.832
Hyperlipoproteinemia (*n*, %)	15 (40.5)	282 (49.7)	0.311
Diabetes Mellitus (*n*, %)	16 (43.2)	160 (28.2)	0.061
Atrial fibrillation (*n*, %)	20 (54.1)	257 (45.5)	0.395
Peripheral artery disease (*n*, %)	0 (0)	36 (6.4)	0.157
Obesity (*n*, %)	14 (38.9)	150 (26.8)	0.125
Smoking (*n*, %)	3 (8.3)	98 (17.5)	0.249
Coronary artery disease (*n*, %)	8 (21.6)	134 (23.8)	0.844
Chronic renal failure (*n*, %)	8 (22.9)	134 (23.9)	1.000
Congestive heart failure (*n*, %)	12 (30)	148 (25.3)	0.574
Pulmonary disease* (*n*, %)	15 (37.5)	134 (22.5)	0.106
COPD (*n*, %)	5 (12.5)	55 (9.2)	0.414
Bronchial asthma (*n*, %)	1 (2.5)	11 (1.8)	0.545
Lung cancer (*n*, %)	0 (0)	14 (2.4)	1.000
Pulmonary emphysema (*n*, %)	0 (0)	8 (1.3)	1.000
Pulmonary embolism (*n*, %)	6 (15)	21 (3.5)	0.005
Community acquired pneumonia (*n*, %)	1 (2.5)	7 (1.2)	0.408
Pulmonary fibrosis (*n*, %)	0 (0)	3 (0.5)	1.000
Pulmonary hypertension (*n*, %)	2 (5)	15 (2.5)	0.291
Clinical scores and imaging characteristics			
NIHSS baseline (median, IQR)	18 (15–20)	15 (10–19)	0.009
NIHSS discharge (median, IQR)	19 (14–23)	5 (2–11)	<0.001
mRS discharge (median, IQR)	5 (5)	3 (1–5)	<0.001
mRS 90 days (median, IQR)	5 (4–6)	4 (1–6)	0.062
Favorable functional outcome (mRS ≤ 3 at 90 days) (*n*, %)	5 (12.5)	286 (48.1)	<0.001
Mortality (mRS 6 at discharge) (*n*, %)	9 (22.5)	169 (28.4)	0.470
cCT ASPECTS at baseline (median, IQR)	7 (5–8)	8 (7–9)	<0.001
cCT ASPECTS 24-h follow-up (median, IQR)	4 (2–6)	7 (5–8)	<0.001
Symptom onset to recanalization time (median min, IQR)	268 (202–360)	211 (154–284)	0.005
Successful recanalization (*n*, %)	29 (72.5)	459 (79.8)	0.311
Final mTICI score			0.703
mTICI 0	3 (7.5)	49 (8.2)	
mTICI 1	3 (7.5)	21 (3.5)	
mTICI 2a	5 (12.5)	46 (7.7)	
mTICI 2b	13 (32.5)	201 (33.8)	
mTICI 2c	6 (15)	117 (19.7)	
mTICI 3	10 (25)	140 (23.5)	
Oxygenation index (median, IQR)	345 (195–472)	376 (292–508)	0.108
Ischemic stroke treatment characteristics			
Side of occluded vessel (*n*, % right)	18 (50)	243 (46.6)	0.960
Site of occluded vessel			0.232
M1 (*n*, %)	20 (50)	279 (48.2)	
M2 (*n*, %)	0 (0)	85 (14.7)	
ICA proximal (*n*, %)	2 (5)	19 (3.3)	
Intracranial carotid bifurcation (*n*, %)	14 (35)	117 (20.2)	
BA (*n*, %)	4 (10)	56 (9.7)	
Other (*n*, %)	0 (0)	23 (4)	
Missing (*n*, %)	0 (0)	16 (2.7)	
Stroke etiology (TOAST criteria)			0.752
Large vessel atherosclerosis	2 (5)	65 (10.9)	
Cardioembolism	21 (52.5)	272 (45.7)	
Stroke of other determined etiology	2 (5)	20 (3.4)	
Stroke of undetermined etiology	10 (25)	196 (32.9)	
Missing (*n*, %)	5 (12.5)	42 (7.1)	
Wake up stroke (*n*, %)	5 (12.5)	63 (10.6)	0.907
Intravenous thrombolysis (*n*, %)	9 (22.5)	223 (37.5)	0.019
Type of anesthesia for mechanical thrombectomy			0.070
General anesthesia (*n*, %)	29 (72.5)	277 (46.5)	
Conscious sedation (*n*, %)	4 (10)	126 (21.2)	
Switch from conscious sedation to general anesthesia (*n*, %)	4 (10)	46 (7.7)	
Length of in-hospital stay (median days, IQR)	22 (14.25–29)	9 (5–14)	<0.001
Length of mechanical ventilation (tube, median days, IQR)	14.22 (12.42–17.36)	0.04 (0–0.46)	<0.001
Length of mechanical ventilation (total, median days, IQR)	19.92 (16.38–24.94)	0.04 (0–0.46)	<0.001
Time from admission to tracheostomy (median days, IQR)	15.54 (12.95-18.85)	n.a.	n.a.
Postinterventional complications			
Failed extubation (*n*, %)	15 (37.5)	19 (3.2)	<0.001
Hospital acquired pneumonia (*n*, %)	39 (97.5)	224 (37.6)	<0.001
Sepsis (*n*, %)	11 (27.5)	16 (2.7)	<0.001
Any ICH (*n*, %)	15 (37.5)	83 (13.9)	<0.001
Symptomatic ICH# (*n*, %)	5 (12.5)	22 (3.9)	0.026
Subarachnoidal hemorrhage (*n*, %)	11 (27.5)	64 (10.8)	0.003
Decompressive hemicraniectomy (*n*, %)	19 (51.4)	21 (3.8)	<0.001

COPD, chronic obstructive pulmonary disease; NIHSS, National institute of health stroke scale; mRS, modified Rankin scale; ASPECTS, Alberta stroke program early CT score; mTICI, modified Thrombolysis in cerebral infarction scale; M1/2, medial cerebral artery in its M1 or M2 segment; ICA, internal carotid artery; BA, basilar artery, TOAST, Trial of Org 10172 in Acute Stroke Treatment; ICH, intracerebral hemorrhage.

**Pulmonary disease includes COPD, bronchial asthma, lung cancer, pulmonary emphysema, pulmonary fibrosis, pulmonary hypertension, and pulmonary embolism; Successful recanalization was defined as mTICI ≥ 2b.*

#Symptomatic intracerebral hemorrhage was defined as any intraparenchymal hemorrhage leading to a clinical deterioration of ≥4 points on the NIHSS.

TABLE 2 | Univariate logistic regression of predictive factors for the need of tracheostomy after mechanical thrombectomy.

	OR (95% CI)	*p*-value
Age	0.97 (0.95–0.99)	0.002
Diabetes mellitus	1.94 (0.99–3.82)	0.054
Pulmonary embolism	4.82 (1.83–12.74)	0.001
NIHSS at baseline	1.053 (1–1.11)	0.038
cCT ASPECTS	0.7 (0.57–0.86)	<0.001
cCT ASPECTS 24-h follow-up	0.73 (0.65–0.82)	<0.001
Symptom onset to recanalization time	1 (1–1)	0.070
Intravenous thrombolysis	0.32 (0.14–0.75)	0.009
General anesthesia	3.22 (1.12–9.27)	0.030
Any ICH	3.53 (1.79–6.99)	<0.001
sICH[#]	3.54 (1.26–9.91)	0.016
Subarachnoid hemorrhage	2.98 (1.42–6.26)	0.004
Decompressive hemicraniectomy	27.1 (12.44–59)	<0.001
Sepsis	13.7 (5.84–32.17)	<0.001
Hospital acquired pneumonia*	64.6 (8.81–473.41)	<0.001
Failed extubation	18.16 (8.27–39.9)	<0.001

NIHSS, National institute of health stroke scale; sICH, symptomatic intracerebral hemorrhage.

[#]Symptomatic intracerebral hemorrhage was defined as any intraparenchymal hemorrhage leading to a clinical deterioration of ≥ 4 points on the NIHSS.

** Any in-hospital pneumonia being diagnosed at least 48–72 h after admission.*

TABLE 3 | Multivariate logistic regression model including predictive factors for the need of tracheostomy after mechanical thrombectomy.

	OR (95% CI)	*p*-value
Decompressive hemicraniectomy	9.94 (3.92–25.21)	<0.001
Sepsis	5.39 (1.71–16.91)	0.004
Hospital acquired pneumonia*	21.26 (2.76–163.56)	0.003
Failed extubation	8.41 (3.09–22.93)	<0.001

**Any in-hospital pneumonia being diagnosed at least 48–72 h after admission; stepwise backward selection has been used to exclude predictors with p > 0.1.*

TS had a median score of −6 (IQR, −6 to −3; $p < 0.001$) points. A cut-off score of −2 points has been identified with a sensitivity of 81% and a specificity of 94%.

As it can be assumed that in a high proportion of LVOS-patients with severe neurological deficits and complications the therapy was limited and therefore no TS has been performed, we conducted a secondary analysis combining patients who died during their neuro-ICU stay (discharge mRS = 6) with TS patients in one group (TS plus severe cases group) and compared these patients to the nTS group. Baseline characteristics are given in **Supplementary Table 1**, which showed multiple differences, especially concerning clinical scores, imaging characteristics, and complication rates. All these different factors were included in a multivariate logistic regression model with stepwise backward selection, which again revealed HAP, failed extubation, sepsis, and DH as strongest predictors for a combined endpoint TS and death at discharge (**Supplementary Table 2**).

As shown in **Supplementary Table 3**, there was no difference in admission pH, paO_2, $paCO_2$, oxygenation index, or oxygen saturation. Patients with TS showed a trend towards higher lactate on admission (1.5 ± 1.2 vs. 1.3 ± 0.7, $p = 0.062$).

In patients with TS, the median time from admission to surgery was 16 days (IQR, 13–19). Patients with TS had a significant longer length of in-hospital stay [22 (14.25–29) vs. 9 (5–14) days, $p < 0.001$] and longer periods of orotracheal tube- [14.22 (12.42–17.36) vs.0.04 (0–0.46) days, $p < 0.001$] and total mechanical ventilation [19.92 (16.38–24.94) vs. 0.04 (0–0.46) days, $p < 0.001$]. The median period from admission to TS was 15.54 (12.95–18.85) days. Longer periods from admission to TS were significantly correlated with longer ICU length of stay ($r = 0.384$, $p = 0.03$), longer periods of orotracheal- ($r = 0.792$, $p < 0.001$) and total period of mechanical ventilation ($r = 0.445$, $p = 0.004$). Patients with TS and favorable clinical outcome (mRS ≤ 3) had no shorter periods from admission to TS [favorable outcome: 17 (IQR, 15–20) days vs. unfavorable outcome: 15 (IQR, 13–9), $p = 0.425$] and there was no significant correlation between the time period (days) from admission to tracheostomy and clinical outcome scores (NIHSS at discharge: $r = 0.125$, $p = 0.461$; mRS at 90 days: $r = -0.179$, $p = 0.403$).

Functional outcome scores were positively correlated with longer periods of orotracheal- (NIHSS at discharge: $r = 0.478$, $p < 0.001$; mRS at 90 days: $r = 0.256$, $p < 0.001$) and total period of mechanical ventilation (see **Supplementary Table 4**; NIHSS at discharge: $r = 0.448$, $p < 0.001$; mRS at 90 days: $r = 0.229$, $p < 0.001$).

DISCUSSION

In the present study, we identified HAP, failed extubation, the need for DH, and Sepsis as strong predictors for patients to undergo TS during their neuro-ICU stay after mechanical thrombectomy.

TS is believed to have distinct advantages to ease weaning in patients with severe dysphagia, reduced level of consciousness, and post-stroke complications. These advantages include a lower death space due to a shorter cannula with weaning facilitation, reduced sedatives, and therefore better mobilization and reduced complications like pneumonia and bedsores, and increases patient comfort (12, 13). However, reliable indications if- and when to perform a TS for patients with acute brain injury are not yet established (13). While studies on TS in mixed ICU populations showed conflicting results (14–16) a first prospective, randomized trial by Bösel et al. (9) (SETPOINT study) showed reduced mortality and sedatives associated with early TS in a population with ischemic and hemorrhagic strokes. A follow-up study (SETPOINT 2) in this respect is highly anticipated (8). In contrast to all possible advantages of TS in patients with acute brain injury, the procedural risks of TS (13) in its two forms as percutaneous tracheostomy and surgical tracheostomy in everyday clinical practice must be balanced against its benefits. Therefore, patient selection is key to being able to determine in which patients TS should be performed early and which patients

are more likely to benefit from prolonged orotracheal intubation and later extubation trials.

All previously published studies on the role of TS included either mixed ICU populations or mixed patient groups with acute brain injury or subtypes of stroke. Our study aimed to specifically address risk profiles for TS in patients with LVOS after mechanical thrombectomy, who became an important and intensively studied subgroup of stroke patients during the past years. Patients with LVOS with a short symptom to recanalization time, lower NIHSS, higher ASPECTS as well as no hemorrhagic transformation after MT are very likely to be early extubated in contrast to patients with MT/IVT associated early ICHs or large ischemic cerebral areas. Interestingly, we did not observe ischemic stroke-specific parameters or scores as strongest predictors for TS, but factors commonly complicating the clinical course of major ischemic stroke patients like HAP and (possible associated) sepsis. This reflects the finding, that—besides the reduced level of consciousness—in around 35% of cases cardio-respiratory complications lead to an ICU admission of stroke patients (17). In contrast, stroke severity is likely to be reflected by the high predictive value of DH and failed extubation. TS has been reported to be required in up to a third of patients requiring a DH (18) and is usually performed in patients with a reduced level of consciousness with high ICP associated space-occupying cerebral edema and it is highly variable if a patient requiring this surgery can be readily extubated in a short time period after the surgery (19). In addition, failed extubations are highly likely in patients with stroke-induced dysphagia and reduced level of consciousness, being both highly prevalent in LVOS patients (20, 21). Besides dysphagia and reduced level of consciousness also pneumonia contributes to the failure of extubations, prolonged ventilatory support, and TS (4). The risk for pneumonia itself is associated with stroke severity and stroke outcome and has been reported to be as high as 60% in multiple studies (4). In our study, almost all patients in the TS group had pneumonia compared with 37.6% in the nTS group, which is within the reported range of 4% to 56% of all stroke patients being treated in stroke units (4). This high prevalence of pneumonia increases the risk for sepsis again, which in most cases is caused by pneumonia (22).

Taking all thoughts on these contributing factors to indicate a TS into consideration, and overall patient type emerges known to neurointensivists, as all these factors are influencing each other. Patients with severe strokes are at high risk to develop HAP and are likely to require DH, both again leading to failed extubation and to severe systemic inflammatory responses caused by multiple infectious pathways and DH as major surgery itself. These major predicting factors for TS also were directly or indirectly represented in a previously published score to predict the need for TS in a mixed stroke population [Stroke-Related Early Tracheostomy Score (23)]. Our data suggest that especially these kinds of patients are likely to undergo TS and therefore can be scheduled early for this procedure if these risk factors are present. These patients also might represent the subgroup of ischemic stroke patients most likely to benefit from early TS, given the possible benefits mentioned above. In this respect, however, clinical outcome in our study was not correlated with time from admission to TS. This might be explained by the current practice in our hospital that TSs are performed late to give patients the chance to functionally improve and to perform weaning and extubation trials. Therefore, differences in timepoints of TS were small and no possible differences in outcome could have been detected. Another reason could be, that the TS group is too small, and therefore not enough statistical power is present to detect influences of earlier TS on clinical outcome. What we observed, however, was a significant positive correlation between the duration of mechanical ventilation and clinical outcome. Rather of being an epiphenomenon likely to be explained by the fact that patients with complications and more comorbidities are also more likely to require longer ventilatory support, detrimental effects of mechanical ventilation (e.g., barotrauma, immunotrauma triggering systemic inflammatory responses) and prolonged exposure to sedatives itself can contribute to unfavorable outcomes (24, 25). In this respect, as a correlation between mechanical ventilation periods and clinical outcome-, but not between the period from admission to TS and outcome was detected, from our data it can be speculated that not the modality of ventilatory support (TS vs. orotracheal tube) influences functional outcome, but the total time the patient is ventilator dependent. This again supports the notion and current recommendation that weaning should be initiated early and prolonged intubation should be avoided in stroke patients (5).

The strength of our study is the inclusion of a large number of LVOS patients with prospectively derived data, all undergoing MT and being solely treated in a specialized neuro-ICU. However, using this prospectively derived data does not change the retrospective design of this study, which represents one of its major limitations. Other limitations include a single-center study design, only reflecting local practices and procedures associated with the use of TS, the lack of information concerning extend and type of dysphagia as a major contributing factor for the decision to perform TS, and a relatively low number of TS patients in this ischemic stroke subgroup. Another major limitation of this study is represented by a selection bias applicable to age and limitation of medical and surgical therapy according to the presumed and the actual patient will. Therefore, our data must be interpreted with caution and the results only applied in patients wishing full treatment. In addition, the score created with our single-center data must be validated in other datasets and can only be used considering the aforementioned limitations.

In conclusion, the combination of HAP, failed extubation, DH, and sepsis after MT may be useful for patient selection to indicate TS. If, however, earlier TS—and not solely limitation of mechanical ventilation time—translate into better functional outcomes must be determined by prospective trials like the SETPPOINT 2 study.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because data can only be made accessible upon reasonable request. Requests to access the datasets should be directed to ilko.maier@med.uni-goettingen.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Commission of the University Medicine Göttingen, Germany. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

IM designed the study and was involved in the acquisition and statistical analysis of the data, drafted, finalized the manuscript, and approved the manuscript before submission. KS was involved in the acquisition and statistical analysis of the data and approved the manuscript before submission. MB and JL contributed to the manuscript and approved the manuscript before submission. DB and M-NP contributed to the manuscript, was involved in the acquisition of the data, and approved the manuscript before submission. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.728624/full#supplementary-material

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Sex Equitable Prehospital Stroke Triage Using Symptom Severity and Teleconsultation

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Objectives: We aimed to determine whether there are sex differences in prehospital accuracy of the Stockholm Stroke Triage System (SSTS) to predict large artery occlusion (LAO) stroke, and endovascular thrombectomy (EVT), and whether clinical characteristics differ between men and women undergoing "code stroke" ambulance transport.

Materials and Methods: This prospective observational study collected data between October 2017 and October 2018. We included 2,905 patients, transported as "code stroke," by nurse-staffed ground ambulance, to a Stockholm Region hospital. Exclusion criteria were private or helicopter transport, onset outside Stockholm, and in-hospital stroke. We compared overall accuracy, sensitivity, specificity, positive and negative predictive values, and clinical characteristics between sexes.

Results: No significant sex differences in SSTS predictive performance for LAO or EVT were found, overall accuracy for LAO 87.3% in women vs. 86.7% in men. Women were median 4 years older and more frequently had stroke mimics (46.2 vs. 41.8%). Women more commonly had decreased level of consciousness (14.0 vs. 10.2%) and moderate-to-severe motor symptoms (by 2.7–3.8 percentage points), and less commonly limb ataxia (7.2 vs. 9.7%).

Conclusions: The SSTS had equal predictive performance for LAO and EVT among men and women, despite minor sex differences in the clinical characteristics in patients undergoing ambulance transport for suspected stroke.

Keywords: acute ischemic stroke, thrombectomy, triage, telemedicine, sex characteristics

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INTRODUCTION

In 2015, clinical trials established the superiority of endovascular thrombectomy (EVT) over medical treatment in large artery occlusion (LAO) stroke (1). However, EVT is only available at certain hospitals and its benefits diminish rapidly with time, accentuating the need for an accurate prehospital triage.

The Stockholm Region in Sweden has a 2.3 million population, across 6,519 km^2. The region is served by one comprehensive stroke center (CSC), Karolinska University Hospital, and six primary stroke centers (PSC). Intravenous thrombolysis (IVT) and stroke unit care are provided at all stroke centers, while EVT is only available at the CSC.

Before October 10, 2017, guidelines in Stockholm-mandated code stroke, priority 1 ambulance transport for patients with positive modified face-arm-speech-time (FAST) test or other cause for stroke suspicion raised by the ambulance nurse, presented within 6 h of onset, to the most proximal stroke unit. Patients presenting beyond 6 h of onset, or with unknown time of onset, were also transported with code stroke if displaying critically affected vital signs. On hospital arrival, patients were examined using plain CT and, in eligible patients, IVT was administered. Thereafter, CT angiography (CTA) was performed, unless contraindicated by local hospital guidelines or on clinical grounds. Reasons to abstain from CTA included minor symptoms with >8 h since the last known well, demarcated CT infarct findings fully matching the clinical presentation, contraindications to EVT, such as modified Rankin Scale (mRS) four to five or prestroke life expectancy below 3 months, and contraindications to CTA, such as severe renal failure or contrast allergy. This routine remained unchanged after the Stockholm Stroke Triage System (SSTS) implementation in 2017. When anterior or posterior circulation LAO was found on CTA at the PSC, a CSC stroke physician, with access to electronically transferred images, was teleconsulted on the patient eligibility for transfer for EVT. Reasons for declining transfer were infarct changes > one-third of the middle cerebral artery or greater than one-half of another territory on plain CT, prestroke mRS score 4–5, prestroke life expectancy <3 months, or CTA results or medical history indicating severe catheter access difficulties. However, age and time since onset or last known well, did not alone affect transfer decisions. Regional quality registry data showed that onset-to-puncture time was 1–2 h longer in secondary transfers, which constituted 75% of the patients treated with EVT, compared with patients directly transported to the CSC when it was most geographically proximal to their place of symptom onset.

The SSTS combines a test for moderate-to-severe hemiparesis with ambulance-hospital teleconsultation, to identify patients with a high likelihood of LAO with EVT indication, for PSC bypass. The SSTS predicts LAO and EVT with high accuracy both within 6 and 6–24 h from onset or last known well, and has reduced regional median onset-to-puncture time in EVT by 69 min, without delaying IVT (2, 3). Studies on AIS have found that, unlike greater mortality, the lower poststroke functional level and quality of life in women remains significant after adjustment for prestroke mRS and age (4–6). To better understand these disparities, research has focused on sex differences in clinical characteristics in stroke. Among patients treated with IVT, women more often have anterior circulation LAO and strokes of greater severity, more frequently caused by cardioembolism because of the atrial fibrillation (7). Traditional stroke symptoms, including hemiparesis, are more common in men compared with women, and the opposite for non-traditional symptoms, such as mental status changes, loss of consciousness, and generalized weakness (7, 8). Presenting with non-traditional symptoms might be associated with a greater risk of misdiagnosis (9). Similarly, the greater frequency of stroke mimics in women could add to differences in diagnostic accuracy (7). It is unknown how any sex differences in the clinical characteristics might affect prehospital LAO triage accuracy.

We aimed to determine whether SSTS triage accuracy for LAO and EVT differs between sexes, and if there are sex differences in the clinical characteristics among patients undergoing code stroke ambulance transport.

MATERIALS AND METHODS

This observational study used data prospectively collected between October 2017 and October 2018, in patients undergoing code stroke ground ambulance transportation to a Stockholm Region hospital. Exclusion criteria were private or helicopter transportation, onset outside the Stockholm Region, and in-hospital stroke. Of 2,909 eligible patients, four opted out from the study participation, leaving 2,905 patients in the dataset.

Research Ethics Committee approval was obtained (approval 2017/374) with waived need for active consent. Patients were informed in writing of their right to decline study data collection.

On October 10, 2017, the novel SSTS, using a three-step algorithm, was implemented across the region. In step 1, stroke suspicion was raised by an ambulance nurse, due to positive modified FAST test or other clinical reasons. In step 2, stroke suspects were prehospitally assessed using an NIH Stroke Scale (NIHSS)-derived test for moderate-to-severe hemiparesis, defined as a score of ≥2 NIHSS points each in the ipsilateral arm and leg (the A2L2 test). Test status was classified as positive or negative. The test was inapplicable in the patients presenting with seizures, unconsciousness or bilateral paresis. In step 3, a CSC stroke physician was consulted by telephone on A2L2 positive cases, to discuss the diagnostic suspicion and assess EVT eligibility. This was followed by the destination decision, frequently directly to the CSC, bypassing any more proximal PSC(s). The region-wide electronic health record system allowed CSC physicians to assess prestroke mRS scores of the patients and comorbidities. In A2L2 negative or A2L2 inapplicable cases, a stroke physician at the most proximal hospital (most frequently a PSC) was prenotified of subsequent transportation of the patients there.

The SSTS guideline and protocol, including a patient flow chart (**Figure 1**), was published on the Stockholm Healthcare Region website, and programmed into ambulance portable tablet computers. All the regional ambulances have a crew of two: at least one specialist ambulance nurse (3-year university degree and 1 year of prehospital or anesthesia training) and an ambulance technician (nursing high school diploma and professional training). Prior to implementation, ambulance nurses had web-based training and live lectures, and hospital staff underwent group training.

Triage positive status was defined as suspected stroke with positive A2L2 test and acceptance for direct transport to the CSC following teleconsultation between an ambulance nurse and a hospital physician. Patients testing A2L2 negative or inapplicable, and those testing A2L2 positive but declined PSC bypass because of the EVT contraindications, were classified

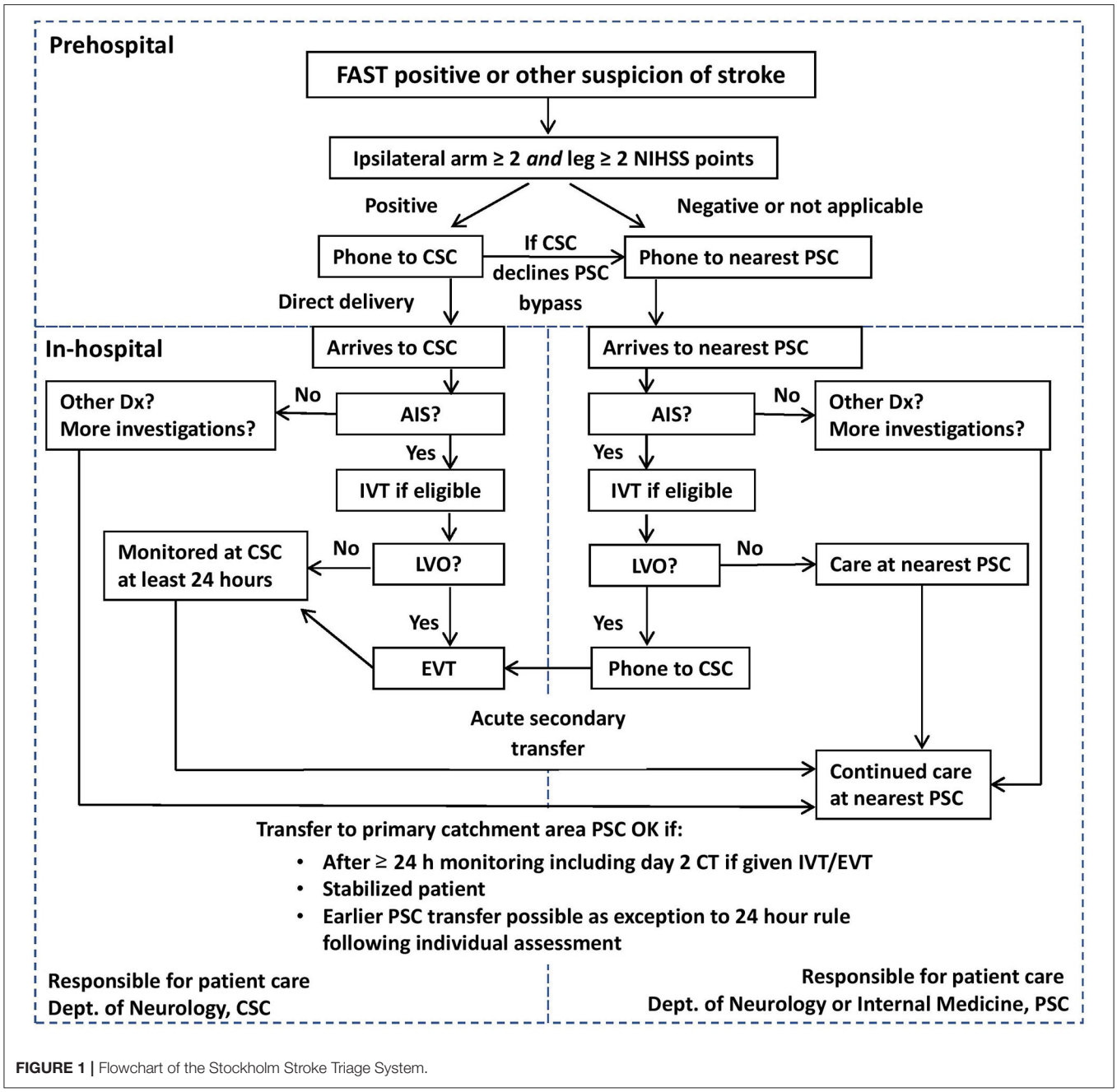

FIGURE 1 | Flowchart of the Stockholm Stroke Triage System.

as triage negative. Reasons for A2L2 positive patients to be declined PSC bypass were low suspicion of stroke, prestroke mRS 4–5, prestroke life expectancy <3 months and critically affected vital signs requiring stabilization at the nearest hospital. The same classification principles were applied when the CSC was the most proximal hospital, defining triage positivity as confirmed stroke suspicion, A2L2 positivity and absence of contraindications to EVT. LAO stroke was defined as acute ischemic stroke (AIS) with CTA-confirmed occlusion or subocclusion in the arterial segments routinely treated at the CSC: ICA, M1-2, A1-2, P1, BA, and intracranial VA. In the patients with contraindications to CTA, LAO stroke was defined as a dense cerebral artery on plain CT. For analyses of triage accuracy, patients with AIS not undergoing CTA were pooled with patients with CTA confirmed non-LAO AIS. Diagnostic imaging was routinely evaluated by two radiologists. EVT was defined as arterial puncture. Final diagnoses, including mimic diagnoses, as well as stroke and TIA diagnoses, were established during in-hospital care and were obtained from the final discharge notes signed by the senior consultant-level physician responsible for the in-hospital care period.

TABLE 1 | Clinical characteristics in men and women.

Characteristic	Men (n = 1,485)		Women (n = 1,420)		P
	No./total	Median (IQR) or %	No./total	Median (IQR) or %	
Age	1,485/1,485	74 (64–81)	1,420/1,420	78 (66–86)	<0.001
A2L2 positive	260/1,485	17.5	270/1,420	19.0	0.294
Triage positive	168/1,485	11.3	155/1,420	10.9	0.733
CTA performed	712/1,484	48.0	626/1,419	44.1	0.037
NIHSS total	1,298/1,485	4 (1–9)	1,221/1,420	4 (1–10.5)	0.007
NIHSS items (>0p[†])					
1a. LOC	123/1,207	10.2	158/1,127	14.0	0.005
1b. LOC questions	422/1,201	35.1	433/1,122	38.6	0.085
1c. LOC commands	180/1,194	15.1	220/1,116	19.7	0.003
2. Gaze	157/1,194	13.1	168/1,110	15.1	0.171
3. Visual	171/1,187	14.4	173/1,099	15.7	0.372
4. Facial palsy	420/1,196	35.1	410/1,116	36.7	0.417
5a. Arm, left, ≥2 p	165/1,202	13.7	196/1,120	17.5	0.012
5b. Arm, right, ≥2 p	144/1,201	12.0	164/1,119	14.7	0.059
6a. Leg, left, ≥2 p	177/1,200	14.8	207/1,124	18.4	0.017
6b. Leg, right, ≥2 p	160/1,200	13.3	188/1,118	16.8	0.019
7. Limb ataxia	114/1,179	9.7	79/1,093	7.2	0.037
8. Sensory	289/1,191	24.3	283/1,098	25.8	0.405
9. Best language	388/1,199	32.4	375/1,113	33.7	0.496
10. Dysarthria	447/1,195	37.4	399/1,110	35.9	0.467
11. Extinction or inattention	119/1,174	10.1	137/1,091	12.6	0.069
Diagnosis					
AIS with LAO	163/1,485	11.0	153/1,420	10.8	0.861
AIS without LAO	295/1,485	19.9	229/1,420	16.1	0.009
AIS, LAO unknown	226/1,485	15.2	231/1,420	16.3	0.438
Intracranial hemorrhage	181/1,485	12.2	151/1,420	10.6	0.188
Stroke mimic	620/1,485	41.8	656/1,420	46.2	0.016
Treatment					
EVT	64/1,485	4.3	55/1,420	3.9	0.553
IVT	179/1,485	12.1	158/1,420	11.1	0.435
OPT, min (EVT)	64/1,485	285 (121–373)	55/1,420	299 (134–325)	0.378
ONT, min (IVT)	176/1,485	122 (81–167)	156/1,420	124 (81–160)	0.847

A2L2 indicates ≥ 2 National Institutes of Health Stroke Scale points each in both the ipsilateral extremities; AIS, acute ischemic stroke; CTA, CT angiography; IQR, interquartile range; IVT, IV thrombolysis; LAO, large artery occlusion; LOC, level of consciousness; NIHSS, NIH Stroke Scale; No., number; ONT, Onset-to-Needle (thrombolysis) Time; OPT, Onset-to-arterial puncture time; p, points.

[†]All NIHSS items categorized as positive if scoring > 0 points, except motor items 5 and 6, which were categorized as ≥ 2 vs. 0–1 points.

Triage accuracy measures were sensitivity, specificity, positive and negative predictive values (PPV, NPV), and overall accuracy. Clinical characteristics included sex, age, A2L2 and triage status, use of CTA, site of occlusion or thrombosis, NIHSS total score and subitem scores, final diagnosis, onset-to-needle time (ONT) in IVT and onset-to-puncture time (OPT) in EVT. Pearson's chi-squared test and Mann-Whitney U-test were used for comparative analyses of categorical and continuous variables. Two-sided P values of < 0.05 were considered statistically significant. All the analyses were conducted using IBM SPSS version 27 (IBM Corp., Armonk, NY, USA).

RESULTS

Among 2,905 code stroke ambulance-transported patients, 1,420 (48.9%) were women. Clinical characteristics are presented in **Table 1**. Women were older than men, median 78 vs. 74 years. There were no significant sex differences in triage positive status (10.9 vs. 11.3%) or A2L2 positive test (19.0 vs. 17.5%). LAO stroke diagnosis was made in 10.8 and 11.0% in women and men, respectively. Women more frequently received a stroke mimic diagnosis, 46.2 vs. 41.8%. CTA was less frequently used in women, 44.1 vs. 48.0%. While the overall distribution of occlusion sites showed a statistically significant difference between the sexes

(**Table 2**), the absolute differences were modest, e.g., MCA M1 occlusion in 11.7% of women vs. 8.1% of men. **Table 3** shows nearly identical performance of the SSTS in both the sexes, regarding the prediction of LAO and EVT. Overall accuracy for LAO was 87.3 vs. 86.7%, and for EVT 90.7 vs. 90.4% in women and men respectively, with similar nonsignificant magnitudes of difference in sensitivity, specificity, NPVs, and PPVs.

Out of 2,905 cases, 2,519 (86.7%) cases with available hospital NIHSS scores, the median total was 4 points in both the sexes (**Table 1**). Regarding NIHSS subitems (**Table 1**), women somewhat more commonly had decreased level of consciousness (14.0 vs. 10.2%), affected ability to follow commands (19.7 vs. 15.1%), and more moderate-to-severe extremity motor deficits, reaching statistical significance in three out of four extremities (left arm 17.5 vs. 13.7%; left leg 18.4 vs. 14.8%; and right leg 16.8 vs. 13.3%). Conversely, women had a slightly lower frequency of limb ataxia, 7.2 vs. 9.7%.

TABLE 2 | Site of occlusion or thrombosis.

	Men (n = 1,485)		Women (n = 1,420)		P
	No./total	**%**	**No./total**	**%**	
Occlusion site‡					0.001
ICA, extradural only	12/718	1.7	5/640	0.8	0.141
ICA-T	11/718	1.5	17/640	2.7	0.146
ICA+MCA	11/718	1.5	5/640	0.8	0.201
M1	58/718	8.1	75/640	11.7	0.024
M2	47/718	6.5	43/640	6.7	0.898
M3 or more distal	5/718	0.7	5/640	0.8	0.855
ACA	2/718	0.3	4/640	0.6	0.337
PCA	8/718	1.1	13/640	2.0	0.172
Basilar	10/718	1.4	3/640	0.5	0.081
Vertebral	16/718	2.2	4/640	0.6	0.014
No occlusion or thrombosis	538/718	74.9	466/640	72.8	0.375

‡*On CTA, or, in patients with contraindications to CTA, corresponding to the dense vessel on CT.*

TABLE 3 | Triage accuracy for prediction of LAO and EVT.

Outcome	Men (n = 1,485)		Women (n = 1,420)		P
	No./total.	**% (95% CI)**	**No./total**	**% (95% CI)**	
LAO diagnosis					
Sensitivity	67/163	41.1 (33.6–48.7)	64/153	41.8 (34.0–49.6)	0.896
Specificity	1,221/1,322	92.4 (90.9–93.8)	1,176/1,267	92.8 (91.4–94.2)	0.657
PPV	67/168	39.9 (32.5–47.3)	64/155	41.3 (33.5–49.0)	0.797
NPV	1,221/1,317	92.7 (91.3–94.1)	1,176/1,265	93.0 (91.6–94.4)	0.803
Overall accuracy	1,288/1,485	86.7 (85.0–88.5)	1,240/1,420	87.3 (85.6–89.1)	0.636
EVT treatment					
Sensitivity	45/63	70.3 (59.1–81.5)	39/55	70.9 (58.9–82.9)	0.943
Specificity	1,298/1,421	91.3 (89.9–92.8)	1,249/1,365	91.5 (90.0–93.0)	0.882
PPV	45/168	26.8 (20.1–33.5)	39/155	25.2 (18.3–32.0)	0.740
NPV	1,298/1,317	98.6 (97.9–99.2)	1,249/1,265	98.7 (98.1–99.4)	0.696
Overall accuracy	1,343/1,485	90.4 (88.9–91.9)	1,288/1,420	90.7 (89.2–92.2)	0.806

CI indicates confidence interval; EVT, endovascular thrombectomy; LAO, large artery occlusion; NPV, negative predictive value; PPV, positive predictive value.

DISCUSSION

We found no sex differences in the prehospital accuracy of the SSTS to predict LAO stroke or EVT. While numerous prehospital LAO stroke triage algorithms have been published (10), we have found no publications on sex differences in this setting. Our results are consistent with a study of stroke triage in an urban, academic Emergency Department, and a study evaluating sex differences in a hub-and-spoke hospital telemedicine system (11, 12). Meanwhile, a study in the two US counties in 2005-07 showed somewhat lower sensitivity for prehospital stroke recognition in women (13).

The near-identical performance of our severity- and teleconsultation-based triage system in both the sexes is consistent with the similarity between men and women regarding hemiparalysis, a symptom strongly associated with the presence of LAO stroke (2, 14). Although statistically significant, sex differences in the clinical characteristics among prehospital code stroke patients were minor. We found a somewhat higher frequency of decreased level of consciousness in women upon hospital arrival. This could potentially have affected prehospital triage precision in women negatively, as loss of consciousness has been described as a non-traditional stroke symptom associated with risk of misdiagnosis (7, 9). Meanwhile, a minor such effect could have been offset by slightly more common moderate-to-severe extremity weakness in women, a traditional stroke symptom potentially facilitating correct stroke identification.

Our finding of more stroke mimics in women with suspected stroke is consistent with previous studies (7, 13, 15). This, however, did not apparently detract from the triage performance of the system for LAO stroke or EVT. Our finding of lower use of CTA in women deserves mention. Previous sex difference studies of imaging investigations in stroke have also shown a certain disadvantage for women in the crude analysis, which, however, was no longer evident after adjustment for the higher average age in women at stroke onset (7). The association between age and prestroke functional level could, in part, explain this, as premorbid mRS score 4–5 might in some cases have been considered a contraindication to CTA (since it may have been perceived by the managing physician as not leading to any change of care irrespective of findings) (16). Considering the association between age and comorbidity, and the greater frequency of hypertension among women with AIS, a lower CTA eligibility in women might be caused by a somewhat greater frequency of severe renal failure (17). Unfortunately, our data lack the desired granularity to pursue this question further. Furthermore, with a higher proportion of mimics in women, some of these mimicking conditions will have

been diagnosed immediately upon arrival at the Emergency Department, and in such cases, no CTA would have been ordered. Furthermore, some mimics would have been diagnosed on an initial plain CT (e.g., intracerebral tumors), with the radiologist actively choosing to abstain from an arterial-phase CTA, and instead do a non-arterial phase contrast-enhanced CT to better characterize the apparent mass lesion. We are presently conducting further analyses focused on stroke mimics in the SSTS aiming to present those findings in a subsequent publication. Regarding time from onset to thrombolysis and onset to thrombectomy, there were minor differences between the sexes, not reaching statistical significance. While detailed investigation of neuroimaging utilization and reperfusion treatments across sexes was outside the scope of this project, modern studies of sex differences in acute vessel imaging and thrombectomy are warranted, adjusting for prestroke functional level and comorbidity.

Limitations include risk of confounding by age and uncollected variables. The NIHSS was not performed in 386 patients, largely due to lack of perceived clinical indication in patients deemed on hospital arrival to have obvious mimics. It is possible that some of the 457 patients not undergoing CTA due to hospital guidelines, did have LAO stroke, and might have been eligible for EVT in healthcare systems employing other treatment criteria.

CONCLUSIONS

The SSTS had equal predictive performance for LAO stroke and EVT among men and women, despite minor sex differences in clinical characteristics in the patients undergoing ambulance transport for the suspected stroke.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Stockholm Ethics Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AB and MM contributed to the preparation of the dataset. MM, CS, and EE designed the study. MM supervised the project. EW performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Associations of Monocytes and the Monocyte/High-Density Lipoprotein Ratio With Extracranial and Intracranial Atherosclerotic Stenosis

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Background: Although the monocyte/high-density lipoprotein ratio (MHR) has been shown to be a potential marker of inflammatory of cardiovascular and cerebrovascular diseases, there are few studies on its relationships with the degree of intracranial and extracranial atherosclerotic stenosis and the stenosis distribution.

Methods: In total, 271 patients were admitted for digital subtraction angiography (DSA) examination and were classified into a non-stenosis group and a stenosis group. (1) The two groups were compared and the arteries were categorized according to the degree of intracranial or extracranial atherosclerotic stenosis (if ≥two branches were stenotic, the artery with the most severe stenosis was used). (2) Clinical baseline data and laboratory indexes of patients grouped according to stenosis location (intracranial vs. extracranial) were collected.

Results: (1) MHR × 10^2 [odds ratio (OR) = 1.119, $p < 0.001$], age (OR = 1.057, $p = 0.007$), and lymphocyte count (OR = 0.273, $p = 0.002$) significantly affected the presence of cerebral atherosclerotic stenosis, with an MHR area of 0.82 under the receiver operating characteristic (ROC) curve (AUC) and an optimal diagnostic value of 0.486. Analyses of the moderate, mild, and severe stenosis groups showed that MHR × 10^2 (OR = 1.07, $p < 0.001$) significantly affected the severity of stenosis in patients. (2) In the analysis of stenosis at different sites, the rate of extracranial artery stenosis in patients who smoked (OR = 3.86, $p = 0.023$) and had a reduced lymphocyte level (OR = 0.202, $p = 0.001$) was remarkably greater than that in patients who smoked (OR = 3.86, $p = 0.023$). With increasing age, the rate of extracranial artery stenosis raised sharply. With the increase in the MHR level, the stenosis rate of each group was highly greater than that of the non-stenosis group.

Conclusion: The MHR has a predictive value for the diagnosis of extracranial and intracranial atherosclerotic stenosis and is correlated with the degree and distribution of stenosis.

Trial Registration: Clinical Medical Research Center Project of Qinghai Province (2017-SF-L1). Qinghai Provincial Health Commission Project (Grant #2020-wjzdx-29).

Keywords: inflammation markers, atherosclerotic stenosis, DSA (digital subtraction angiogram), lipoprotein, cerebral arteries

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BACKGROUND

Atherosclerosis is a common chronic illness characterized by endovascular atheroma or fibrous plaque. Pathophysiological changes, namely, arterial wall hardening, decreased elasticity, and lumen stenosis or occlusion, are important risk factors for the occurrence and development of ischemic cerebrovascular diseases and mortality (1, 2). Inflammatory factors play an essential role in lipid metabolic disorders and their importance in thrombosis, plaque rupture, and stenosis in atherosclerosis is being increasingly reported (3). Studies on the correlations of the monocyte/high-density lipoprotein ratio (MHR) [determined *via* dividing the absolute monocyte count by the absolute high-density lipoprotein cholesterol (HDL-C) count] with coronary stenosis and myocardial infarction have shown that the MHR is a potential inflammatory marker of cerebrovascular and cardiovascular diseases (4, 5). Currently, there are few reports on cerebrovascular diseases and most are relevant to the occurrence and prognosis of ischemic stroke (6, 7). Digital subtraction angiography (DSA) is regarded as a perfect standard for diagnosing intracranial and extracranial arterial stenosis. However, studies using DSA to investigate the relationship between intracranial or extracranial arterial stenosis and the MHR are rarely reported. This study investigated the relationships between the MHR and intracranial and extracranial arterial stenosis and related risk factors, aiming to proposed a reliable theoretical foundation to guide the treatment and prevention of intracranial and extracranial arterial stenosis.

METHODS

Study Population

From May 2017 to May 2020, a total of 216 inpatients with intracranial and extracranial atherosclerotic stenosis confirmed by cerebrovascular DSA examination at the Qinghai Provincial People's Hospital were consecutively enrolled. There were 55 hospitalized patients without intracranial and extracranial atherosclerotic stenosis. DSA examination included the aortic arch, subclavian artery, vertebral artery, common carotid artery, and internal carotid artery. The common carotid artery, intracranial internal carotid artery (cervical segment, petrous segment, lacerum segment, and so on), V1–V3 segments of the vertebral artery, subclavian artery, and external carotid artery are classified as extracranial arteries. Intracranial arteries include the extracranial internal carotid artery (ophthalmic segment and communicating segment), A1–A2 segments of the anterior cerebral artery, basilar artery, M1–M2 segments of the middle cerebral artery, P1–P2 segments of the posterior cerebral artery, and V4 segment of the vertebral artery. The exclusion criteria were as follows: acute cardiovascular disease, signs of acute infection, immunosuppressive therapy, tumor, hematological system disorder, connective tissue disease, severe liver and kidney function impairment, moyamoya disease, and arteriovenous malformation. The Qinghai Provincial People's Hospital Ethics Committee approved this study.

Blood Analysis Methods

Basic clinical data, such as gender, age, ethnicity, hypertension, drinking, smoking, diabetes mellitus, and cerebral infarction, were collected from patients meeting the inclusion criteria. Additionally, laboratory measures of monocytes, HDL-C, and the MHR of patients were obtained within 24 h after admission (with monocytes and HDL-C measured from the same initial blood sample). (1) First, the stenosis and non-stenosis groups were compared. Then, the DSA examination results were assessed based on relevant diagnostic criteria developed for the Warfarin-Aspirin Symptomatic Intracranial Disease Study (8) to evaluate the content of intracranial and extracranial atherosclerotic stenosis, which was calculated as follows: Degree of stenosis (%) = (1-diameter at the narrowest point of a narrow segment/the diameter of the proximal normal vessel) × 100%. According to the degree of arterial stenosis, the patients were divided into a mild stenosis group (stenosis degree of 29% or less), a moderate stenosis group (stenosis degree of 30–69%), and a severe stenosis group (stenosis degree of 70–99%). The aim was to study the factors influencing the degree of atherosclerotic stenosis and to analyze the predictive value of the MHR for cerebral atherosclerotic stenosis. (2) Based on the location of extracranial and intracranial atherosclerotic stenosis, the patients were divided into four groups: a non-stenosis group, an intracranial atherosclerosis only group (ICAS group), an extracranial atherosclerosis only group (ECAS group), and an intracranial and extracranial atherosclerosis group (I-ECAS group). The non-stenosis group worked as a control group and was compared with the other three groups to analyze influencing factors.

Statistical Analyses

The SPSS software version 26.0 (Chicago, Illinois, USA) was employed for the analysis of the data. The chi-squared test was used for count data. The experimental data were examined for normality by the Shapiro–Wilk normality test; those with normal distributions were expressed as the mean ± SD and analyzed with the one-way ANOVA. The characteristics of baseline of the non-stenosis group and stenosis group were compared with the Mann–Whitney *U*-test. For data distributed non-normally, the data were expressed as medians (lower quartile-upper quartile) and analyzed with non-parametric tests. The predictive power of the MHR for the occurrence of cerebral atherosclerotic stenosis was analyzed using the subject working characteristic curve and the optimal threshold was determined. Finally, variables with statistical significance ($p < 0.05$) in the univariate analyses were involved within the logistic regression model.

RESULTS

Analysis of Logistic Regression and Receiver Operating Characteristic Curve for Cerebral Artery Stenosis

Age, neutrophil count, white blood cell (WBC) count, the MHR, C-reactive protein (CRP), proportion of males, smoking,

TABLE 1 | Comparison of factors between the non-stenosis group and the atherosclerotic stenosis group.

Variable	Univariate analysis		Z/c^2	*P*	Multifactor logistic regression		
	Non-stenosis group ($n = 55$)	Stenosis group ($n = 216$)			OR	95% CI	*P*
Age	53 (42–61)	62 (52–69)	−4.715	<0.001	1.057	1.016–1.1	0.007
Sex, male	19 (11.2%)	150 (88.8%)	22.747	<0.001	0.733	0.286–1.879	0.518
Smoking	12 (12.1%)	87 (87.9%)	6.443	0.011	1.129	0.425–2.998	0.807
Drinking	2 (4.3%)	45 (95.7%)	9.044	0.003	2.353	0.4–13.835	0.344
Hypertension	25 (14.3%)	150 (85.7%)	11.029	0.001	0.994	0.397–2.487	0.989
Diabetes mellitus	4 (6%)	63 (94%)	11.291	0.001	2.702	0.734–9.945	0.135
Acute stroke/TIA	10 (18.2%)	136 (63.0%)	40.305	<0.001	6.800	3.323–13.916	<0.001
WBC count	5.21 (4.43–6.62)	6.4 (5.47–7.63)	−3.949	<0.001	1	0.921–1.086	0.997
Neutrophil count	3.22 (2.24–3.83)	4.16 (3.24–5.28)	−4.916	<0.001	1.313	0.966–1.785	0.083
Lymphocyte count	1.83 (1.39–2.23)	1.62 (1.23–1.96)	−2.563	0.01	0.273	0.119–0.624	0.002
PLT	195 (160–253)	186.5 (144–227.5)	−1.92	0.055[a]	0.998	0.99–1.005	0.551
CRP	1.27 (0.56–2.45)	2.28 (1.07–5.63)	−3.872	<0.001[b]			
TC	4.27 (3.43–5.14)	4.21 (3.64–4.86)	−0.053	0.958			
TG	1.38 (1.08–1.92)	1.55 (1.09–2.24)	−1.095	0.274			
LDL	2.54 (1.95–3.3)	2.49 (2–3.08)	−0.233	0.816			
Apolipoprotein A	1.19 (1.1–1.47)	1.16 (1.05–1.31)	−1.741	0.082[a]	2.302	0.362 14.636	0.377
Apolipoprotein B	0.85 (0.66–1.05)	0.91 (0.75–1.04)	−1.215	0.224			
MHR×10^2	0.31 (0.25–0.43)	0.5 (0.39–0.58)	−7.366	<0.001	1.119	1.07–1.17	**<0.001**

[a]$p < 0.05$ as assessed by the univariate logistic regression; variable was subsequently included in the multivariate analysis. [b]$p > 0.05$ as assessed by the univariate logistic regression; variable was not included in the multivariate analysis.

WBC, white blood cell; PLT, blood platelets; CRP, C-reactive protein; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein.

Bold value indicates statistical analysis methods and groupings.

drinking, hypertension, and diabetes mellitus were greater within the stenosis group ($n = 216$) than in the non-stenosis group ($n = 55$) and lymphocyte count was lower in the non-stenosis group; these differences were remarkable ($p < 0.05$). In the univariate and multivariable logistic regression analyses, age was the independent variable found to be positively associated with the probability of narrow stenosis [$p = 0.007 < 0.05$, odds ratio (OR) $= 1.057 > 1$]. A higher MHR $\times 10^2$ value was associated with a greater probability of stenosis ($p < 0.001$, OR $= 1.119 > 1$) and a higher lymphocyte count was associated with a lower probability of stenosis ($p = 0.002 < 0.05$, OR $= 0.273 < 1$) as shown in **Table 1**. The ROC curve analysis of the MHR and cerebral atherosclerotic stenosis yielded an area under the ROC curve (AUC) of 0.82 and the optimal diagnostic value was 0.486; the results are plotted in **Figure 1**.

Patients with mild ($n = 72$), moderate ($n = 35$), and severe ($n = 60$) stenosis were selected for analysis and the group differences in WBC count, neutrophil count, CRP, apolipoprotein A, and the MHR were significant ($p < 0.05$). The variables found to be significant in the univariate ordered logistic regression analysis were included in the multivariate ordered logistic regression analysis, with the severity of stenosis as the dependent variable. The results showed that the MHR alone significantly influenced the severity of stenosis ($p < 0.001$, OR $= 1.07 > 1$), i.e., the greater the MHR value was, the greater the stenosis severity was, as shown in **Table 2**.

Analysis of the Factors Correlated With the Distribution of Atherosclerotic Stenosis in Intracranial and Extracranial Arteries

There were remarkable differences in sex, smoking, drinking, diabetes mellitus, hypertension, WBC count, neutrophil count, lymphocyte count, CRP, low-density lipoprotein (LDL), apolipoprotein A, and the MHR among the atherosclerosis-free, ICAS, ECAS, and I-ECAS groups ($p < 0.05$), as shown in **Table 3**.

Logistic Regression Analysis of Atherosclerotic Stenosis Distribution in Intracranial and Extracranial Arteries

Following the univariate ordered logistic regression analysis, the multivariate ordered logistic regression analysis was conducted, which excluded CRP and LDL, but included platelets. The results suggested that age was significantly and positively associated with the probability of simple extracranial stenosis ($p = 0.003 < 0.05$, OR $= 1.066 > 1$) and the probability of combined intracranial and extracranial atherosclerotic stenosis ($p < 0.001$, OR $= 1.102 > 1$). Smoking ($p = 0.023 < 0.05$, OR $= 3.86 > 1$) significantly increased the incidence of simple extracranial atherosclerotic stenosis. The higher the lymphocyte value was, the lower was the probability of developing simple extracranial atherosclerotic stenosis ($p = 0.001 < 0.05$, OR $= 0.202 < 1$). A higher MHR $\times 10^2$ value was associated with higher probabilities

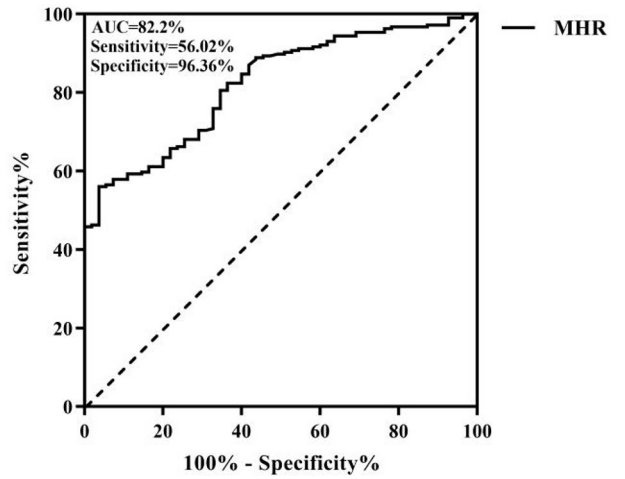

FIGURE 1 | Receiver operating characteristic (ROC) curve of the monocyte/high-density lipoprotein ratio (MHR) for intracranial and extracranial atherosclerotic stenosis.

of simple intracranial atherosclerotic stenosis ($p < 0.001$, OR = $1.12 > 1$), simple extracranial atherosclerotic stenosis ($p < 0.001$, OR = $1.121 > 1$), and combined intracranial and extracranial atherosclerotic stenosis ($p < 0.001$, OR = $1.147 > 1$), as shown in **Table 4**.

DISCUSSION

Atherosclerosis is a common chronic inflammatory disease. Inflammation is an important pathophysiological mechanism of atherosclerotic thrombosis, plaque rupture, and stenosis or occlusion. Monocytes are immune cells and when the vascular endothelium is damaged, the expression of adhesion molecules upon the surface of these cells increases. Upon stimulation by cytokines, these cells transform into macrophages. Phagocytosis of lipids occurs followed by the formation of foam cells under scavenger receptor mediation; these changes mark the initial phase of atherosclerosis and the transition from a stable to an unstable state. The lipid core of atherosclerotic lesions contains not only lipid deposits, but also a variety of immune cells derived from monocytes and macrophages that include T cells, mast cells, and dendritic cells, which act as major roles within the proliferation and progression of atherosclerosis (9, 10). Monocytes can aggravate inflammation and promote the development and instability of plaques, local thrombosis, and a series of responses, thus aggravating vascular stenosis. Dyslipidemia is another significant risk factor for atherosclerosis. The main function of HDL-C is the reverse transport of total cholesterol in the tissues toward the liver and out of the body. HDL-C can reduce thrombosis risk *via* platelet stabilization and decrease leukocyte adhesion to stable plaques. HDL-C can also prevent LDL oxidation and exhibit antithrombotic and anti-inflammatory properties, thereby playing a protective role (11, 12). Study has revealed great prospects of HDL-C infusion for the treatment of atherosclerosis (13, 14). Monocytes are closely related to HDL-C. Abnormal levels of blood lipids, especially elevated cholesterol, can stimulate the production of monocytes in the circulation. Furthermore, reduced HDL-C can reduce the monocyte inflammatory response (15). The ability of monocytes to phagocytose lipid particles is enhanced in atherosclerotic stenosis, making blood fat more likely to be deposited in the stenosis (16). Therefore, it is speculated that the MHR has more advantages than monocytes and HDL-C as an inflammatory marker. This study found that the MHR is an independent factor of risk for the occurrence of cerebral atherosclerosis. ROC curve analysis showed that the area under the ROC curve (AUC) of the MHR was 0.82 and the optimal diagnostic value was 0.486, showing that the MHR can be used as a good predictor of the occurrence of intracranial and extracranial atherosclerotic stenosis. In addition, age has been proven to be one of the most obvious independent factors of risk for the incidence of intracranial and extracranial atherosclerosis (17, 18), which is consistent with the results of this study.

The MHR is linked with cerebral atherosclerotic stenosis. However, there are few studies on the correlation between the MHR and the occurrence or degree of extracranial and intracranial atherosclerotic stenosis. From the analysis of the mild, moderate, and severe stenosis groups, this study concluded that the MHR significantly affects the degree of stenosis. Chen (16) found that monocytes are closely relevant to the degree of peripheral atherosclerosis stenosis. A population-level study of arterial atherosclerotic ischemic stroke in southern China found severe HDL with carotid artery stenosis in the brain [cervicocerebral atherosclerotic stenosis (CCAS)] (19). An elevated level reflects increased degrees of inflammation and oxidative stress and an increased severity of coronary artery stenosis (4, 20).

Domestic and international studies have found ethnic differences in the frequencies of extracranial and intracranial atherosclerotic stenosis. In Europe and the United States, extracranial artery stenosis is the dominant stenosis, while in Asia, intracranial arterial stenosis is more common (21, 22). However, in this study, the rate of extracranial artery stenosis was slightly greater than that of intracranial stenosis, which is consistent with the increasing prevalence of extracranial artery stenosis in Chinese people revealed by epidemiological surveys in the recent years (23). The higher rate of extracranial artery stenosis than of intracranial stenosis in this study may be due to the following factors: (1) Regional, dietary, and lifestyle differences. In high-altitude areas, the temperature difference between day and night due to the cold climate can limit the availability of fruits and vegetables. In addition, the dietary habits of the population include a high intake of meat, which can increase blood lipid levels and ATP (as measured by the plasma arteriosclerosis index). Moreover, long-term exposure to a hypoxic environment changes the blood microcirculation, anatomy, and physiology (24). (2) Aging with the proportion of stenosis cases involving intracranial arteries decreases, while the proportion of those involving extracranial

TABLE 2 | Associations of factors with the severity of intracranial atherosclerotic stenosis.

Variable	Univariate analysis			$F/c^2/Z$	*P*	Multifactor logistic regression		
	Mild stenosis ($n = 72$)	Moderate stenosis ($n = 35$)	Severe stenosis ($n = 60$)			OR	95% CI	*P*
Age	62.76 ± 12.48	60.49 ± 13.14	63.37 ± 10.67	0.666	0.515			
Sex, Male	46 (39.7%)	23 (19.8%)	47 (40.5%)	−1.747	0.081			
Smoking	22 (34.4%)	16 (25%)	26 (40.6%)	−1.565	0.118			
Drinking	12 (36.4%)	8 (24.2%)	13 (39.4%)	−1.565	0.118			
Hypertension	54 (45.4%)	24 (20.2%)	41 (34.5%)	−0.865	0.387			
Diabetes mellitus	16 (30.8%)	11 (21.2%)	25 (48.1%)	−2.392	0.017	1.74	0.882–3.435	0.11
Acute stroke/TIA	35 (48.6%)	12 (34.3%)	47 (78.3%)	12.274	0.002	2.57	1.428–4.609	0.002
WBC count	5.92±1.47	6.74±1.39	6.77±1.58	6.404	<0.001	1.063	0.588–1.919	0.84
Neutrophil count	3.56 (2.9–4.59)	4.23 (3.44–5.23)	4.15 (3.45–5.46)	8.431	0.015	1.052	0.591–1.876	0.862
Lymphocyte count	1.51±0.51	1.59±0.55	1.69±0.51	2.005	0.138			
PLT	171.17±52.47	182.83±43.45	186.48±58.51	1.472	0.232			
CRP	1.21 (0.74–2.29)	2.24 (1.23–4.42)	3.27 (2.1–8.07)	30.119	<0.001[a]			
TC	4.2 (3.66–4.85)	4.4 (3.56–5.2)	4.18 (3.7–4.79)	0.611	0.737			
TG	1.38 (0.97–1.84)	1.55 (1.16–2.32)	1.9 (1.18–2.57)	5.555	0.062			
LDL	2.48 (2.03–3.02)	2.69 (1.79–3.5)	2.55 (2.06–3.03)	0.665	0.717			
Apolipoprotein A	1.21 (1.11–1.39)	1.24 (1.1–1.39)	1.16 (1.01–1.25)	7.504	0.023[a]			
Apolipoprotein B	0.91 (0.77–0.99)	0.89 (0.7–1.1)	0.92 (0.78–1.05)	0.493	0.782			
MHR × 10^2	0.4 (0.28–0.51)	0.47 (0.38–0.55)	0.55 (0.45–0.68)	39.392	<0.001	1.07	1.043–1.1	**<0.001**

[a]*p > 0.05 as assessed by the univariate logistic regression; variable was not included in the multivariate analysis. p = 0.784 > 0.05 for the ordered logistic parallel line test.*
Bold value indicates statistical analysis methods and groupings.

arteries increases (25). China's Aging Society may exacerbate this phenomenon.

Conclusions vary with respect to the factors that influence the intracranial vs. extracranial distribution of atherosclerotic stenosis. This study concluded that male sex and smoking are independent risk factors for extracranial atherosclerosis alone, which is consistent with previous large-sample data studies (22, 26). Men are more prone to intracranial and extracranial atherosclerosis than women, which reflect the protective effects of estrogen on the cardiovascular and cerebrovascular systems such as its direct effect on the vascular wall and its beneficial effects on lipid composition. Estrogen resptor alpha 36 (ERa36) and estrogen receptor G protein-coupled receptor 30 (ERGPR30)/G protein coupled estrogen receptor (GPER1) signaling has been found to play an anti-inflammatory role in monocyte-/macrophage-related inflammatory processes (27). Recent studies have shown that estrogen can activate the GPER signaling pathway, which results in decreased SR-BI expression in endothelial cells and, thus, significantly reduces the transport of LDL-C (28). Furthermore, estrogen can inhibit liver esterase activity, improve the level of circulating HDL-C, reduce blood cholesterol and LDL-C, and directly interact with HDL-C to inhibit the oxidation of LDL-C, thus preventing atherosclerosis (29). However, diabetes mellitus was not found to be associated with extracranial or intracranial atherosclerotic stenosis, which is in contrast to previous results indicating that diabetes is a factor of risk for intracranial artery stenosis (24, 26, 30). The results may be due to the following: (1) Chronic hypoxic acclimatization at high altitude increases the dependence of the body on glucose and enhances glucose utilization, (2) With the improvement in standards of living of the residents, the incidence of diabetes mellitus has been rising rapidly. Diabetes mellitus has been shown to increase the incidence and burden of vascular risk factors and is common in both the intracranial and extracranial atherosclerotic stenosis (31, 32). This study concluded that age is an independent risk factor for intracranial and extracranial atherosclerosis and previous work has shown that the incidence of cerebral artery stenosis rises significantly with age (25). It is generally believed that the occurrence of extracranial artery stenosis is more strongly correlated with age than that of intracranial arterial stenosis (22, 30). However, a postmortem report (33) showed that the frequency of intracranial arterial stenosis increased with age. In addition, the results of this study suggest that lymphocytes might have protective effects against intracranial arterial stenosis. Recent studies have found that the number of circulating lymphocytes is significantly reduced in the progression of atherosclerotic lesions, which may be related to weakened adaptive immunity and healing effects in the atherosclerotic process (3, 34). The number of lymphocytes is highly related to the presence of extracranial artery stenosis. The lack of elastic fibers in intracranial vessels, the dense internal elastic layer, and increase in antioxidant enzyme activity with age provide good barrier effects. Intracranial atherosclerotic stenosis appears later than extracranial atherosclerotic stenosis and lymphocyte values are reduced in intracranial arterial stenosis (17). This study found that an elevated MHR value was related to significantly raised risks

TABLE 3 | Associations of factors with the distribution of intracranial atherosclerotic stenosis.

Variable	No stenosis (n = 55)	Intracranial atherosclerosis alone (n = 64)	Extracranial atherosclerosis alone (n = 115)	Combined intracranial and extracranial atherosclerosis (n = 37)	F/c^2	P
Age	50.91 ± 12.56	56.17 ± 11.6	61.59 ± 13.53	65.16 ± 8.5	13.752	<0.001
Sex, male	19 (11.2%)	39 (23.1%)	83 (49.1%)	28 (16.6%)	25.697	<0.001
Smoking	8 (8.1%)	29 (19.2%)	59 (59.6%)	13 (13.1%)	23.615	<0.001
Drinking	2 (4.3%)	14 (29.8%)	22 (46.8%)	9 (19.1%)	9.639	0.022
Hypertension	25 (14.3%)	43 (24.6%)	77 (44%)	30 (17.1%)	13.673	0.003
Diabetes mellitus	4 (6%)	19 (28.4%)	30 (44.8%)	14 (20.9%)	13.381	0.004
Acute stroke/TIA	10 (18.2%)	44 (68.8%)	73 (63.5%)	19 (51.4%)	38.259	<0.001
WBC count	5.21 (4.43–6.62)	6.73 (5.39–8.31)	6.25 (5.47–7.37)	6.54 (5.41–7.75)	17.34	0.001
Neutrophil count	3.22 (2.24–3.83)	4.24 (3.17–5.38)	4.13 (3.23–5.03)	4.09 (3.29–5.6)	24.742	<0.001
Lymphocyte count	1.83 (1.39–2.23)	1.71 (1.28–2.11)	1.57 (1.19–1.88)	1.65 (1.29–2.19)	11.11	0.011
PLT	195 (160–253)	194.5 (148–252)	172 (139–218)	191 (143.5–210.5)	7.503	0.057[a]
CRP	1.27 (0.56–2.45)	2.33 (1.27–6.54)	2.2 (0.99–5.63)	2.25 (1.23–5.24)	15.177	0.002[b]
TC	4.27 (3.43–5.14)	4.33 (3.66–4.92)	4.04 (3.53–4.66)	4.62 (3.88–5.22)	5.166	0.16
TG	1.38 (1.08–1.92)	1.55 (1.06–2.15)	1.51 (1.16–2.25)	1.6 (1.11–2.31)	1.818	0.611
LDL	2.54 (1.95–3.3)	2.56 (2.12–3.3)	2.37 (1.9–2.83)	2.81 (2.31–3.43)	8.604	0.035[b]
Apolipoprotein A	1.19 (1.1–1.47)	1.22 (1.11–1.43)	1.16 (1.04–1.28)	1.1 (1–1.3)	12.021	0.007
Apolipoprotein B	0.85 (0.66–1.05)	0.92 (0.75–1.06)	0.88 (0.74–1.01)	0.93 (0.8–1.11)	3.898	0.273
MHR × 10^2	0.31 (0.25–0.43)	0.46 (0.38–0.55)[c]	0.5 (0.38–0.58)[c]	0.55 (0.43–0.7)[c]	59.049	<0.001

[a] $p < 0.05$ as assessed by the univariate logistic regression; variable was subsequently included in the multivariate analysis. [b] $p > 0.05$ as assessed by the univariate logistic regression; variable was not included in the multivariate analysis. [c] There was a significant difference between the two groups ($p < 0.05$).

of simple intracranial arterial stenosis, combined extracranial and intracranial arterial stenosis, and simple extracranial arterial stenosis. The identification of the MHR as a common independent correlated factor in the ICAS, ECAS, and I-ECAS groups confirmed the MHR to be closely related to cerebral atherosclerotic stenosis.

Although the "gold standard" of cerebrovascular DSA examination was used in this study to diagnose intracranial and extracranial atherosclerotic stenosis, this method is traumatic, risky, and costly; thus, its use is mainly limited to the subset of patients with cerebral infarction who require surgery. For the patients in this study, DSA was found to be reliable for determining the stenosis rate and to have good precision and other advantages. However, patients with mild or no symptoms who did not opt for cerebrovascular DSA examination could not be included in this study. Thus, the total sample scale should be increased in future studies to verify the present results. Moreover, this study was limited to patients in plateau regions. In addition, data on the long-term (6 months or longer) clinical outcomes of patients are crucial to enhance the use of the MHR. Thus, follow-up clinical control studies should be conducted at multiple centers and regions to confirm the findings.

CONCLUSION

In conclusion, as a risk factor for extracranial and intracranial atherosclerotic stenosis, the MHR has predictive value and is highly related to the severity and location of stenosis. This study also expounds on the development of extracranial and intracranial atherosclerotic stenosis in the process of inflammation, providing a theoretical basis for targeted interventions. Such interventions would reduce the incidence of cerebral atherosclerotic stenosis caused by ischemic cerebrovascular disease and provide better health services to the residents of high-altitude areas.

TABLE 4 | The multivariate logistic regression analysis of the distribution of intracranial atherosclerotic stenosis.

Variable	ICAS		ECAS		I-ECAS	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.032 (0.987–1.078)	0.166	1.066 (1.022–1.113)	0.003	1.102 (1.045–1.162)	<0.001
Sex, Male	1.003 (0.336–2.994)	0.996	1.149 (0.409–3.229)	0.792	1.781 (0.469–6.759)	0.396
Smoking	1.347 (0.381–4.76)	0.644	3.86 (1.206–12.357)	0.023	1.119 (0.274–4.571)	0.875
Drinking	2.793 (0.417–18.706)	0.29	1.094 (0.172–6.964)	0.924	2.222 (0.292–16.937)	0.441
Hypertension	1.054 (0.376–2.958)	0.92	0.748 (0.28–1.996)	0.562	1.467 (0.408–5.269)	0.557
Diabetes mellitus	3.507 (0.877–14.023)	0.076	2.202 (0.563–8.608)	0.256	3.114 (0.7–13.856)	0.136
Acute stroke/TIA	9.900 (4.167–23.522)	<0.001	7.821 (3.573–17.119)	<0.001	4.750 (1.854–12.170)	0.001
WBC count	0.697 (0.094–5.195)	0.725	1 (0.906–1.103)	0.998	0.309 (0.018–5.317)	0.418
Neutrophil count	1.941 (0.245–15.35)	0.53	1.237 (0.89–1.719)	0.206	4.197 (0.228–77.345)	0.335
Lymphocyte count	0.467 (0.043–5.074)	0.531	0.202 (0.081–0.501)	0.001	1.243 (0.045–34.472)	0.898
PLT	0.999 (0.99–1.007)	0.8	0.997 (0.989–1.005)	0.483	0.998 (0.988–1.008)	0.664
MHR × 10^2	1.12 (1.067–1.176)	<0.001	1.121 (1.07–1.174)	<0.001	1.147 (1.087–1.21)	<0.001
Apolipoprotein A	4.903 (0.688–34.939)	0.113	1.085 (0.139–8.488)	0.938	2.202 (0.155–31.384)	0.56

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Qinghai Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZL, SW, and QF performed the study design, interpretation of the results, and statistical analyses. YL participated by analyzing and resolving difficulties of analytic strategies and the discussion. QF performed the final review and is the corresponding authors. All authors have approved the final manuscript after reading.

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Direct Endovascular Thrombectomy or With Prior Intravenous Thrombolysis for Acute Ischemic Stroke: A Meta-Analysis

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Background and purpose: It is unclear whether endovascular thrombectomy alone compared with intravenous thrombolysis combination with endovascular thrombectomy can achieve similar neurological outcomes in patients with acute large vessel occlusion stroke. We aimed to perform a systematic review and meta-analysis of randomized controlled trials to compare endovascular thrombectomy alone or intravenous thrombolysis plus endovascular thrombectomy in this population.

Methods: We systematically searched PubMed, Embase, and ClinicalTrials.gov. We restricted our search to randomized clinical trials that examined the clinical outcomes of endovascular thrombectomy alone vs. intravenous thrombolysis plus endovascular thrombectomy. The Cochrane risk of bias tool was used to assess study quality. Random-effects meta-analyses were used for evaluating all outcomes.

Results: Total three randomized controlled trials with 1,092 individuals enrolled were included in the meta-analysis, including 543 (49.7%) who received endovascular thrombectomy alone and 549 (50.3%) who received intravenous thrombolysis plus endovascular thrombectomy. The primary outcome of 90-day functional independence (modified Rankin scale (mRS) score $\leq$ 2) was 44.6% (242/543) in the endovascular thrombectomy alone group vs. 42.8% (235/549) in the alteplase with endovascular thrombectomy group (odds ratio (OR), 1.08 [95% CI, 0.85–1.38]; $P = 0.0539$). Among pre-specified secondary outcomes, no significant between-group differences were found in excellent outcome (mRS score $\leq$ 1) (OR, 1.12 [95% CI, 0.85–1.47]; $P = 0.418$), mortality at 90 days (OR, 0.93 [95% CI, 0.68–1.29]; $P = 0.673$), successful reperfusion (thrombolysis in cerebral infarction 2b-3) (OR, 0.75 [95% CI, 0.54–1.05]; $P = 0.099$), and symptomatic intracranial hemorrhage (OR, 0.72 [95% CI, 0.45–1.15]; $P = 0.171$).

Conclusions: Among patients with acute ischemic stroke in the anterior circulation within 4.5 h from the onset, endovascular thrombectomy alone was non-inferior to combined intravenous thrombolysis and endovascular thrombectomy.

Keywords: acute ischemic stroke, endovascular thrombectomy, intravenous thrombolysis, bridging thrombolysis, meta-analysis

BACKGROUND

Endovascular thrombectomy (EVT) has become a standard treatment for acute ischemic stroke patients caused by a large vessel occlusion in the anterior circulation (1–3). A subsequent analysis of individual patient data from five randomized trials showed that the effect of EVT was not influenced by prior intravenous thrombolysis (IVT), raising the question of whether treatment with IVT before EVT is still necessary (3). A *post hoc* analysis of the Solitaire With the Intention for Thrombectomy (SWIFT) and Solitaire Flow Restoration Thrombectomy for Acute Revascularization (STAR) studies indicates that EVT combined with standard alteplase treatment does not appear to provide a clinical benefit over EVT alone (4). In contrast, a meta-analysis of 13 studies suggested a better functional outcome, lower mortality, and higher rate of successful recanalization in patients treated with EVT and bridging IVT (5). However, in these 13 studies, a substantial number of patients with stroke received EVT alone who are not eligible for IVT due to unknown onset of stroke symptoms or contraindications to IVT. The eligibility for IVT may lead to group imbalances in stroke etiology, risk factors, and time to treatment. Thus, to eliminate the confusion about the eligibility for IVT between groups, the benefit and risk of direct EVT vs. EVT with prior IVT should be determined for patients with stroke who are eligible for IVT. To test the hypothesis that EVT alone was non-inferior to combined IVT and EVT in patients with a large vessel occlusion in the anterior circulation treated within 4.5 h of onset, three recent large randomized controlled trials were conducted (6–8). In this study, we intended to conduct a meta-analysis including complete results from recently published randomized controlled trials to compare effectiveness and safety between direct EVT and bridging therapy (EVT with prior IVT) for acute ischemic stroke with large vessel occlusions. Both included patients in direct EVT and bridging therapy groups who had no contraindications to IVT. Our results may provide more pieces of evidence to develop best practice guidelines for patients with acute ischemic stroke with large vessel occlusions.

METHODS

This systematic review and meta-analysis was conducted using a pre-specified protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (9).

Search Strategy and Inclusion Criteria

We searched PubMed, Embase, and the clinical trial registry maintained at ClinicalTrials.gov until April 16, 2021, using the terms "intravenous thrombolysis or intravenous alteplase" and "acute ischemic stroke or cerebrovascular ischemia" and "endovascular therapy or endovascular treatment or mechanical thrombectomy (MT) or stent-retriever." The references of published reviews and studies with potential met our pre-specified inclusion and exclusion criteria were manually screened to avoid missing any eligible studies that were not previously identified. We restricted studies published in the English language. Two investigators (LL and TFW) independently conducted the literature search. To facilitate higher quality evidence, we used strict inclusion and exclusion criteria for each study. Inclusion criteria were the following: (1) compared outcomes of IVT + EVT with EVT in acute ischemic stroke of large artery occlusion primarily in anterior circulation; (2) all the participants could be treated with IVT within 4.5 h after symptom onset; (3) reported functional outcome using the modified Rankin scale (mRS) as an endpoint; (4) reported the effect estimates of studies or calculating the effect estimates from the available data; and (5) a randomized clinical trial study design. We excluded case reports, reviews, *post hoc* analyses, observational studies, duplicate reports, commentaries, abstracts, animal studies, meeting proceedings, and studies with incomplete information. Moreover, studies included patients who are not eligible for IVT due to unknown onset of stroke symptoms or contraindications to IVT, which were also excluded.

Data Extraction and Outcomes

The study and patient characteristics, data on outcomes were abstracted by two authors (TFW and TCX) independently from article texts, tables, figures, supplementary appendixes, and protocols. Any disagreements were resolved by joint discussion. The study and patient characteristics were extracted including author name, publication year, study design type, study period, sources of data, inclusion and exclusion criteria, outcomes, and sample size in each group.

The primary outcome was three-month functional independence that was defined as a mRS score of 0–2. Secondary outcomes were the following: early recanalization and reperfusion thrombolysis in cerebral infarction (TICI) score 2b/3 after MT, symptomatic intracranial hemorrhage (sICH), asymptomatic intracranial hemorrhage (aICH), mortality at 90 days, 3-month favorable outcome (mRS 0–1).

Quality Assessment

Quality assessment of the studies was performed by two independent reviewers (LL and TFW). The risk of bias for each included RCT was assessed according to the Cochrane Collaboration's tool (10), which includes each of the following domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, reporting biases, and other potential sources of bias. The risk of bias was assigned as a score of low, unclear, or high, according to established criteria. The study with more than two high-risk components, was defined as having a moderate risk of bias. And the study with more than four high-risk components, was defined as having a high risk of bias. While the study with 0–2 high-risk components was defined as having a low risk of bias.

Statistics

From each study, we extracted a 2 × 2 table for binary outcomes. Meta-analysis results were expressed as odds ratios (ORs) for binary outcomes with respective 95% CIs. ORs with their 95% CIs were used as a measure of the association of EVT with each outcome of interest compared to IVT +

EVT. The random-effects meta-analysis model (DerSimonian–Laird method) or fixed-effects meta-analysis model (Mantel–Haenszel method) was used to pool count data across trials and the statistical significance of pooled ORs and 95% CIs were determined with an equivalent *Z*-test (11). Which model should be used for pooling count data across trials was following the heterogeneity among the included RCTs. The heterogeneity among the RCTs included in our meta-analysis was assessed by the *P*-value of chi-squared-based *Q*-tests and the *I*-squared (I^2) statistic. As the previous study reported, the I^2 value was <50% and the *P*-value of the *Q*-test was more than 0.1 among the RCTs included in the meta-analysis, which may suggest no obvious heterogeneity across studies. Then the fixed-effects model was used for pooling across studies. While the I^2 values of more than 50% and the *P*-value of the *Q*-test of <0.1 may indicate the studies included in the meta-analysis with obvious heterogeneity. Then the random-effects model was used (12). Statistical analyses were conducted using STATA software, version 12.0 (StataCorp, College Station, TX, USA). Statistical significance was set to $P < 0.05$.

RESULTS

Study Selection and Study Characteristics

A total of three trials met the inclusion criteria and were included in this meta-analysis (online-only **Data Supplement**): Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicenter Randomized Clinical Trial (DIRECT-MT), Direct Endovascular Thrombectomy vs. Combined IVT and Endovascular Thrombectomy for Patients With Acute Large Vessel Occlusion in the Anterior Circulation (DEVT), and Direct Mechanical Thrombectomy in Acute LVO Stroke (SKIP). The main characteristics of these included RCTs were summarized in **Tables 1**, **2**. All three trials were considered to have a low risk of bias (online-only **Data Supplement**), as assessed by the Cochrane Risk of Bias Tool. Among these three RCTs, a total of 1,092 individuals were enrolled, including 543 patients who were assigned to undergo MT alone (MT alone group) and 549 were assigned to receive combination therapy with intravenous alteplase and EVT (alteplase with EVT group). The distributions of the basic characteristics of the patients included in the analysis were similar across studies, including demographics and clinical characteristics (**Table 2**).

Primary Outcome

In the three trials and 1,092 patients with acute ischemic stroke that were included in the analysis of the primary outcome of 90-day functional independence (mRS score ≤ 2). The main analysis of the primary outcome showed no significantly different results in favor of the MT alone group (OR, 1.08 [95% CI, 0.85–1.38]; $P = 0.054$) (**Table 3**). The result of the score χ^2 test to assess the proportional assumption was not significant ($P = 0.573$), which indicates that the proportional odds assumption is acceptable. The I^2 value (variation in OR attributable to heterogeneity) was estimated as 0, which indicates no obvious heterogeneity was detected in the primary outcome. Moreover, **Figure 1** shows a graphical summary of the seven scores of the mRS between both MT alone and alteplase with EVT groups at 90 days for the individual trials and pooled results.

Secondary Outcomes

In the three trials and 1,092 patients that were included in the analysis of the excellent outcome (mRS score ≤ 1). An excellent outcome was observed in 144 of 543 patients (26.5%) in the MT alone group and 134 of 549 (24.4%) in the alteplase with EVT group (OR, 1.12 [95% CI, 0.85–1.47]; $P = 0.418$) (**Table 3**). Moreover, there was no significant difference in mortality rate at 90 days between MT and alteplase with EVT groups (OR, 0.93 [95% CI, 0.68–1.29]; $P = 0.673$) (**Table 3**). The percentage of patients with successful reperfusion (modified Thrombolysis in Cerebral InfarctionScore (mTICI) score, ≥2b) also showed no significant difference between two groups (OR, 0.75 [95% CI, 0.54–1.05]; $P = 0.099$) (**Table 3**). For safety outcome, the rate of symptomatic intracerebral hemorrhage in the two groups was 5.9% (32/542) vs. 8.0% (44/548) and did not differ significantly between the groups (OR, 0.72 [95% CI, 0.45–1.15]; $P = 0.171$) (**Table 3**).

DISCUSSION

In this meta-analysis, we comprehensively compared direct EVT vs. EVT with prior IVT for a large sample of acute ischemic stroke patients caused by a large vessel occlusion in the anterior circulation within 4.5 h from onset. We found that EVT with prior IVT does not appear to provide a functional outcome at 3 months over direct EVT for acute ischemic stroke patients who were eligible for treatment with both IVT and EVT. In addition, compared with direct EVT, the combination of IVT and EVT was non-inferior concerning early recanalization and reperfusion [TICI score 2b/3 after EVT or its equivalents], sICH, mortality at 90 days, 3-month excellent outcome (mRS 0–1).

Our findings are in contrast with the results of previous retrospective studies that reported worse functional outcomes in patients experiencing an acute ischemic stroke due to a large vessel occlusion who received general EVT alone compared with those who EVT with prior IVT (13–15). Previous meta-analysis studies also have examined differences between EVT with prior IVT vs. EVT alone, which have observed a trend toward higher rates of functional independence and successful recanalization among patients treated with IVT + EVT compared with patients treated only with EVT (5, 16, 17). In contrast to the aforementioned studies, a patient-level, pooled, *post hoc* analysis of the SWIFT and STAR studies revealed that treatment of patients experiencing an acute ischemic stroke due to a large vessel occlusion with IVT before EVT does not appear to provide a clinical benefit over EVT alone (4). However, there were important imbalances regarding inclusion criteria between groups in these studies, which make the data somewhat difficult to interpret. Most of the patients received EVT alone with contraindications for IVT treatment, including an extended period after known symptom onset, the unknown onset of stroke symptoms, or contraindications to IVT. Furthermore, to find

TABLE 1 | Characteristics of studies included in meta-analysis.

Trial characteristics	DIRECT-MT	DEVT	SKIP
Inclusion criteria	1. Age of 18 years or older; 2. A clinical diagnosis of acute ischemic stroke and eligible for IVT and MT (within 4.5 hours after symptom onset, NIHSS ≥ 2); 3. Caused by a large vessel occlusion of the anterior circulation (intracranial segment of internal carotid artery, M1 segment of the middle cerebral artery, proximal M2 segment of the middle cerebral artery) confirmed by CTA; 4. CT or MRI ruling out intracranial hemorrhage; 5. Written informed consent.	1. Aged 18 years or older; 2. Presenting with acute ischemic stroke symptom within 4.5 hours and eligible for intravenous alteplase; 3. Occlusion of the intracranial internal carotid artery or the first segment of the middle cerebral artery confirmed by CT or MR angiography; 4. Randomization no later than 4 hours 15 minutes after stroke symptom onset. Time of stroke onset was defined as time last known well; 5. Informed consent obtained from patients or their legal representatives.	1. Age ≥18 and <86 years at the time of informed consent; 2. Clinical diagnosis of acute ischemic stroke with clinical symptoms and initial NIHSS ≥6; Modified Rankin scale score ≤2; 3. ICA or M1 occlusion on MRA or CTA; ASPECTS on initial DWI ≥5 or on initial CT ≥6; 4. Onset to randomization within 4 h from onset; 5. Written informed consent by patient or next of kin.
Exclusion criteria	1. Pre-stroke disability which interferes with the assessment of functional outcome at 90 days, i.e., mRS >2; 2. Any contra-indication for IVT, according to guidelines of the AHA, i.e.: (1) blood pressure > 185/110 mmHg; (2) blood glucose < 2.7 or > 22.2 mmol/L; (3) cerebral infarction in the previous 6 weeks with residual neurological deficit or signs of recent infarction on neuro-imaging; (4) serious head trauma in the previous 3 months; (5) major surgery or serious trauma in the previous 2 weeks; (6) gastrointestinal or urinary tract hemorrhage in the previous 3 weeks; (7) previous intracerebral hemorrhage; (8) use of anticoagulant with INR exceeding 1.7; (9) known thrombocyte count <100 × 109/L; (10) treatment with direct thrombin or factor X inhibitors; (11) treatment with heparin (APTT exceeds the upper limit of normal value) in the previous 48 h.	1. CT or MR evidence of hemorrhage (the presence of micro-bleeds is allowed); 2. Contraindications of intravenous alteplase; 3. Premorbidity with a modified Rankin scale score of 0–2; 4. Currently in pregnant or lactating or serum beta HCG test is positive on admission; 5. Contraindication to radiographic contrast agents, nickel, titanium metals, or their alloys; 6. Arterial tortuosity and/or other arterial diseases that would prevent the device from reaching the target vessel; 7. Patients with a preexisting neurological or psychiatric disease that would confound the neurological functional evaluations; 8. Patients with occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation); 9. CT or MR evidence of mass effect or intracranial tumor (except small meningioma); 10. CT or MR evidence of cerebral vasculitis; 11. CT or MR angiography evidence of intracranial arteriovenous malformations or aneurysms; 12. Any terminal illness with a life expectancy of <6 months; 13. Unlikely to be available for 90-day follow-up; 14. Current participation in another clinical trial.	1. Contraindication for contrast agent or endovascular therapy; 2. Contraindication for IVT . Presence of severe renal disorder (patients undergoing dialysis can be included); 3. Pregnancy or possibility of pregnancy; 4. Unlikely to complete the study, such as due to progressive malignant tumor; 5. Judged incompatible with the study by the investigators.

CTA, computed tomography angiography; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; mRS: modified Rankin scale; HCG, human chorionic gonadotropin; ICA, internal carotid artery; DWI, diffusion weighted imaging.

randomized evidence to support or refute the role of IVT + EVT compared with EVT alone for patients with acute ischemic stroke, pooled analyses of randomized studies were conducted and attempted to resolve this issue, while the conclusions of these studies were also based on patients with contraindications to Tissue Plasminogen Activator (tPA), thus increasing the risk for bias and confounding. In consist with the results of our study, a meta-analysis conducted by Kaesmacher et al., which used only Recombinant Tissue Plasminogen Activator (rt-PA)–eligible patients did not find any benefit of EVT alone over EVT with prior intravenous alteplase (18). However, a common limitation of the aforementioned studies was that these meta-analyses pooled data mainly from retrospective cohort studies where the choice of EVT alone or EVT with prior intravenous alteplase for a given patient experiencing an acute ischemic stroke due to a large vessel occlusion was not randomized. Thus, the results of these meta-analyses may be confounded by indication and selection bias since all major guidelines recommend IVT in eligible patients before EVT (19).

Using IVT leading to favorable outcomes may associate with early recanalization for patients in the EVT with prior intravenous alteplase group. However, data from recent trials suggested that such early recanalization does not occur often. In the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) and Endovascular Treatment for Small Core and

TABLE 2 | Baseline patient characteristics among included randomized clinical trials.

Characteristics	DIRECT-MT		DEVT		SKIP	
	Mechanical thrombectomy alone (*n* = 327)	Alteplase with endovascular thrombectomy (*n* = 329)	Mechanical thrombectomy alone (*n* = 116)	Alteplase with endovascular thrombectomy (*n* = 118)	Mechanical thrombectomy alone (*n* = 101)	Alteplase with endovascular thrombectomy (*n* = 103)
Age, mean (SD) or median (IQR), y	69 (61–76)	69 (61–76)	70 (60-77)	70 (60-78)	74 (67-80)	76 (67-80)
Men, No. (%)	189 (57.8)	181 (55.0)	66 (56.9)	66 (55.9)	56 (55)	72 (70)
Medical history						
Hypertension, No. (%)	193 (59.0)	201 (61.1)	69 (59.5)	74 (62.7)	61 (60)	61 (59)
Atrial fibrillation, No. (%)	152 (46.5)	149 (45.3)	62 (53.5)	62 (52.5)	57 (56)	64 (62)
Diabetes, No. (%)	59 (18.0)	65 (19.8)	25 (21.6)	20 (17.0)	16 (16)	17 (17)
Ischemic stroke, No. (%)	43 (13.1)	47 (14.3)	14 (12.1)	19 (16.1)	12 (12)	14 (14)
TOAST classification						
Large artery (atherosclerosis), No. (%)	60 (18.3)	48 (14.6)	60 (51.7)	51 (43.2)	21 (21)	15 (15)
Cardioembolism, No. (%)	146 (44.6)	144 (43.8)	65 (56.0)	69 (58.5)	67 (66)	72 (70)
Other determined/undetermined etiology, No. (%)	121 (37.0)	137 (41.6)	19 (16.4)	21 (17.8)	13 (13)	16 (16)
NIHSS score, median (IQR)						
NIHSS score, median (IQR)	17 (12–21)	17 (14–22)	16 (12–20)	16 (13–20)	19 (13–23)	17 (12–22)
Baseline ASPECTS, median (IQR)	9 (7–10)	9 (7–10)	8 (7–9)	8 (7–9)	7 (6–9)	8 (6–9)
Systolic blood pressure, median (IQR), mm Hg	146 (130–163)	146 (131–161)	146 (129–165)	145 (128–168)	158 (132–172)	150 (134–171)
Glucose level, median (IQR), mmol/L or mean (SD), mg/dL	7.0 (5.8–8.6)	7.0 (5.9–8.8)	6.7 (5.7–8.1)	6.9 (5.9–8.9)	135 (48)	135 (52)
Occlusion site, *n* (%)						
Internal carotid artery	112/320 (35.0)	114/326 (35.0)	18/115 (15.5)	17/117 (14.4)	36 (36)	36 (35)
M1 MCA	161/320 (50.3)	178/326 (54.6)	95/115 (81.9)	99/117 (83.9)	54 (53)	47 (46)
M2 MCA	42/320 (13.1)	33/326 (10.1)	3/115 (2.6)	2/117 (1.7)	10 (10)	20 (19)

IQR, interquartile range; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; MCA, middle cerebral artery.

TABLE 3 | Distribution of 90-day modified Rankin scale scores.

Modified rankin scale score	No. (%)					
	DIRECT-MT		DEVT		SKIP	
	Mechanical thrombectomy alone (*n* = 326)	Alteplase with endovascular thrombectomy (*n* = 328)	Mechanical thrombectomy alone (*n* = 116)	Alteplase with endovascular thrombectomy (*n* = 118)	Mechanical thrombectomy alone (*n* = 101)	Alteplase with endovascular thrombectomy (*n* = 103)
0	43	45	15	18	20	23
1	37	29	29	19	21	23
2	39	47	19	18	19	13
3	63	48	15	20	14	14
4	36	38	10	14	11	13
5	50	59	8	8	8	8
6	58	62	20	21	8	9

Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trials, only eight of 216 patients (3.7%) and eight of 165 patients (4.8%) randomized to MT had TICI 2b or 3 on the first angiography run, respectively (1, 20). The chance of early recanalization in response to IVT is associated with the location of the occlusion, with M2 or M3 occlusions responding effectively compared with distal ICA occlusions. In the DEVT trial, the middle cerebral

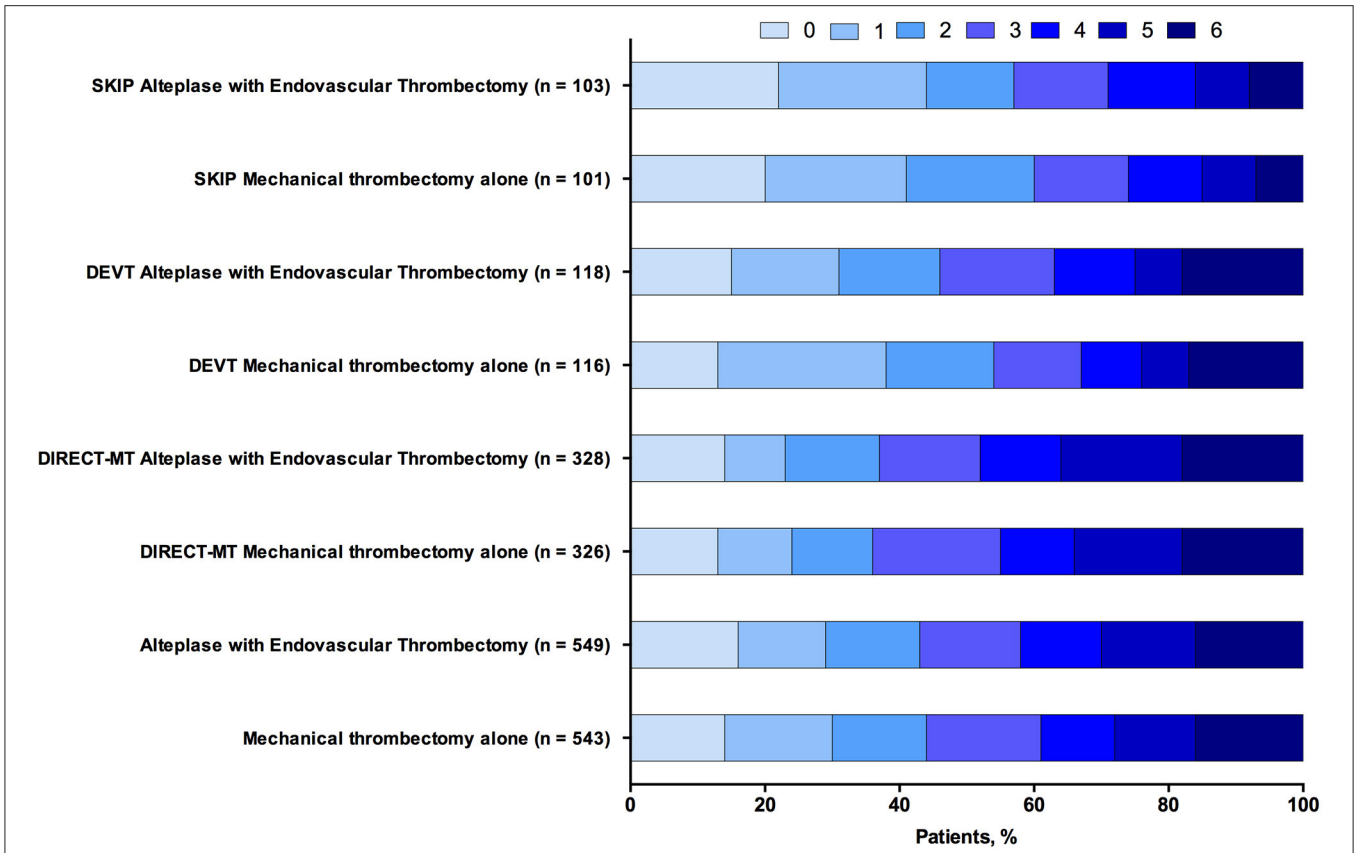

FIGURE 1 | Functional outcome at 90-day follow-up of endovascular thrombectomy alone vs. alteplase with endovascular thrombectomy. The modified Rankin scale measures functional outcome on a seven-point ordinal scale: 0, no symptoms at all; 1, no significant disability despite symptoms; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; 6, death.

TABLE 4 | Summary of pooled analyses for primary and secondary outcomes.

Outcomes	DIRECT-MT		DEVT		SKIP		Meta-analysis results	
	Mechanical thrombectomy alone (*n* = 327)	Alteplase with endovascular thrombectomy (*n* = 329)	Mechanical thrombectomy alone (*n* = 116)	Alteplase with endovascular thrombectomy (*n* = 118)	Mechanical thrombectomy alone (*n* = 101)	Alteplase with endovascular thrombectomy (*n* = 103)	OR (95% CI)	*P*-value
Primary outcome								
Functional independence	119 (36.4)	121 (36.8)	63 (54.3)	55 (46.6)	60 (59.4)	59 (57.3)	1.08 (0.85–1.38)	0.539
Secondary outcomes								
Excellent outcome	80 (24.5)	74 (22.5)	44 (37.9)	37 (31.4)	41 (40.6)	46 (44.7)	1.12 (0.85–1.47)	0.418
Successful reperfusion (TICI 2b-3), No. (%)	243/306 (79.4)	267/316 (84.5)	100 (88.5)	102 (87.2)	91 (90.1)	96 (93.2)	0.75 (0.54–1.05)	0.099
sICH, *n* (%)	14 (4.3)	20 (6.1)	10/115 (8.7)	12/115 (10.3)	8 (7.9)	12 (11.7)	0.72 (0.45–1.15)	0.171
Mortality at 90 days, *n* (%)	58 (17.7)	62 (18.8)	20 (17.2)	21 (17.8)	8 (7.9)	9 (8.7)	0.93 (0.68–1.29)	0.673

OR, odds ratio; TICI, thrombolysis in cerebral infarction; sICH, symptomatic intracranial hemorrhage.

artery M2 occlusions were excluded. Thereby, higher rates of successful reperfusion before thrombectomy were seen with combined intravenous alteplase and EVT in the DIRECT-MT and SKIP trials but not in the DEVT trial.

The benefit of recanalization after acute ischemic stroke is highly time-sensitive (21), thus the time delay due to the preparation of alteplase administration, which might be considered to be disadvantaged. A *post hoc* analysis of the MR

CLEAN trial revealed that the median door-to-groin-puncture time was 11 min longer in non-transferred patients in the IVT + EVT group, which indicates that administration of IVT might contribute to a small delay in the start of EVT (22). However, this meta-analysis showed either no significant or no clinically relevant differences in most pre-specified time intervals. Although several time intervals were shorter in the direct EVT group, no significant differences were found in randomization to puncture time or arrival to arterial puncture between the treatment groups, and the mean time delay due to the preparation of alteplase administration was only about 3 min in SKIP study (16 min [IQR, 11–24] vs. 19 min [13–27], $P = 0.38$).

The results of this study are not sufficient to support clinical practice and paradigm shift toward direct EVT for patients with acute ischemic stroke from large-vessel occlusion. However, they support the hypothesis that EVT alone was non-inferior to combined IVT and EVT in these patients. Moreover, the results of this study are probably a consequence of the standardized workflow instituted in all three randomized clinical trials, which may not have been present in individual centers participating in previous non-randomized studies. Furthermore, strengths of the present meta-analysis include the conduction and report of the analysis according to the PRISMA.

However, a common limitation of these studies was that all three trials were conducted in East Asia, limited racial/ethnic diversity, thus increasing the risk for bias and confounding. Second, additional three randomized clinical trials (MR CLEAN-NO IV [ISRCTN80619088], SWIFT DIRECT [NCT03192332], and DIRECT-SAFE [NCT03494920]) to examine whether MT alone is non-inferior to combined IVT plus MT are ongoing. An updated meta-analysis may be needed in the future. Third, we were only able to get part of the data among the included trials. Some of the baseline characteristics were unavailable. Thus, we could not conduct some subgroup analysis, such as by baseline NIHSS score, occluded artery, and time to treatment. Despite these limitations, our study represented the best available pieces of evidence regarding EVT alone was non-inferior to combined IVT and EVT on the outcomes of patients with acute ischemic stroke with large-vessel occlusion in the anterior circulation.

CONCLUSIONS

The pooled data from our meta-analysis of RCTs suggested that among patients with acute ischemic stroke in the anterior circulation within 4.5 h from the onset, EVT alone was non-inferior to combined IVT and EVT.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LL conceived the study. T-FW, G-CC, and JC collected the data and drafted the manuscript. H-SC, LL, and JC revised the manuscript and language. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.752698/full#supplementary-material

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Multimodality Characterization of the Clot in Acute Stroke

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Aim: Current treatment of occluded cerebral vessels can be done by a variety of endovascular techniques. Sometimes, the clot responds in varying degrees to the treatment chosen. The *Ex vivo* characterization of the clot occluding the arteries in acute ischemic stroke can help in understanding the underlying imaging features obtained from pre-treatment brain scans. For this reason, we explored the potential of microCT when combined with electron microscopy for clot characterization. Results were compared to the clinical CT findings.

Methods: 16 patients (9 males, 8 females, age range 54–93 years) who were referred to our institution for acute stroke underwent dual-source CT.

Results: Clinical CT clots were seen as either iso or hyperdense. This was corroborated with micro-CT, and electron microscopy can show the detailed composition.

Conclusion: MicroCT values can be used as an indicator for red blood cells-rich composition of clots. Meaningful information regarding the clot composition and modalities of embedding along the stent retrievers can be obtained through a combination of microCT and electron microscopy.

Keywords: stroke, clot, computed tomography, micro-CT, electron microscopy

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INTRODUCTION

Due to recent advances in clinical imaging in acute ischemic stroke (AIS), various imaging approaches are available for practitioners, as such that they can guide the reperfusion treatment (1–3).

Among the underlying imaging features related to the AIS (4, 5), visualization of the clot can be performed in a clinical setting using either magnetic resonance imaging (MRI) (4–6) or computed tomography (CT) scans (4, 6–8). Information such as clot extent (volume or length) (4, 9–11) and clot shape (12) is known to be linked to the treatment outcome. Red blood cell (RBC)-rich clots can be depicted and measured using the blooming artifact with susceptibility-weighted MRI imaging (4, 5), which is an important indicator for the clot amenability to endovascular treatment. In non-contrast enhanced CT (NCCT) images (4) the clot can be directly visualized when it appears as an area of relative high density within a blood vessel, referred to as a hyperdense artery sign (HAS) (4, 6, 7, 13, 14), and is a highly specific—albeit with low sensitivity—indicator of occlusive stroke

(4, 13, 15). In addition, the clot density in CT scan, as measured in Hounsfield Units (HU), can be an indication of the clot composition, in terms of red blood cells or fibrin content, with high density of the HAS being related to RBCs rich clots (16). In contrasting enhanced CT images, the clot can be indirectly visualized via the arterial filling defect. Clot permeability, represented by the residual flow grade (17), is associated with arterial recanalization after thrombolysis. The density of the clot could potentially be used to guide treatment choices and/or predict clinical outcome (18–20). For example, a higher density of the HAS is related to a better angiographic outcome after treatment, either by thrombolysis or thrombectomy (16, 18, 21). The advent of artificial intelligence and automated segmentation methods (22) brings to a new level the potential that clot visualization holds for indicating the underlying clot histological features (23), and for enabling the selection of treatment strategy (24, 25). To confirm the causality between the clot imaging features and the treatment outcome, the *ex vivo* characterization, in terms of clot composition, is necessary (26–28). Conventional histopathology is usually employed to gather information whether the clot is red blood cells-rich or fibrin/platelets-rich (29–31), or, more recently, to discover markers for resistance to treatment (32–34). Alternatively, electron microscopy can offer important information on clot organization, composition, and markers of intravital contraction (29). However, the compositional characteristics of the clot, as examined by histopathology or electron microscopy, are not straightforwardly linked to features observed in clinical imaging, since the blood pool around the clot can contribute, in addition to the clot itself, to the density observed in CT scans. Discriminating between the clot itself and the surrounding blood pool can lead to a more accurate interpretation of brain scans. For this reason, it is important to characterize the clot *ex vivo* with imaging techniques similar to those used in clinical setting. Recently, the preparation of analog clots series (35), spanning a wide range of red blood cells, fibrin, and platelets content, allowed the development of parametric studies which identified MRI sequences (36) and CT protocols (37) capable of differentiating different clot types *in vitro*.

However, clots extracted from patients differ in size, heterogeneity, and compactness from the *in vitro* clots. Characterizing the clots extracted from patients with acute ischemic stroke can be important for understanding how the clot bio-physical properties relate to clinical imaging features, and how such features can be relevant for the diagnosis and treatment of AIS (29). Such understanding will render clinical imaging useful for instituting personalized treatment. The aim of our study is to examine clots that were extracted from patients with acute stroke and examine, with high-resolution techniques, if more information could be obtained about the clot composition. We also aimed to compare, in a pilot experiment, the characterization of the clots in relation to clinical imaging data. Such understanding will, in perspective, render clinical imaging useful for designing personalized treatment.

METHODS

The study has been accepted by our local Ethics Committee (CCER number 2018-00476).

For clot characterization in relation to clinical CT imaging, we included in the study 16 patients (9 males, 8 females, age range 54–93 years) who were referred to our institution for acute stroke, and they underwent dual-source CT in the emergency department, and did not qualify for thrombolytic treatment prior to thrombectomy. Thrombectomy was performed according to the standard clinical practice. For the analysis of the clinical CT scans, the images were uploaded to a computer using OsiriX (Pixmeo, Geneva, Switzerland), and the mean Hounsfield units (HU) values were averaged from at least two regions of interest assigned to the clot occluding the arteries. In addition, with the purpose of examining the clots embedded onto the stents, we included 5 patients (3 males, 2 females, age range 49–87 years, 3 of them received thrombolytic treatment) from which the retrieved clots remained attached onto the stent retriever after thrombectomy.

MicroCT Imaging

Ex vivo experiments were carried out on a low dose X-Ray micro computed tomography scanner (Quantum GX, Perkin Elmer). The scanner uses a cone beam X-ray source and a flat panel X-ray detector to acquire high quality slice images, which are rendered for 3D visualization. CT scans of clots fixed in formalin were acquired on the micro-CT along the maximum intensity projections. The micro-CT can measure the Hounsfield Units (HU) of the analog clots along the x, y, and z axes. Calibration was performed by imaging a water-filled falcon tube, and the HU calibration values were adjusted for air (−1000) and water (0), which allowed measuring the attenuation value of the falcon tube. Then, each clot was rinsed with saline solution, drained on sterile pads, and subsequently placed in a sealed falcon tube to maintain moisture and prevent tissue degradation prior to imaging. The clots were imaged with the low noise imaging protocol (14 min), with 90kV X-ray energy, 88 μA, and 140 μm voxel size. Segmentation and quantification of clots attenuation *ex vivo* was performed in 3D Slicer[1] (38), using a linear fit, in which air and tube served as reference values.

Scanning Electron Microscopy (SEM) Imaging

After imaging with microCT, the clots, either self-standing or integrated onto the stent, were fixed in glutaraldehyde (2.5%) overnight at 4°C. Subsequently, samples were washed in phosphate buffer solution (PBS) 10X three times for 20 min each, were dehydrated in solutions of ascending concentrations of ethanol (50, 60, 70, 80, 90, and 100%) for 15 min each time, and were dried using critical point drying. The samples were mounted on scanning electron microscopy (SEM) stubs using carbon tape and carbon paint and sputtered with a 5 nm AuPd (80%/20%) coating. The microscopy observations were

[1] http://www.slicer.org

TABLE 1 | Baseline characteristics of patients with stroke included in this pilot study, and which did not receive thrombolytic therapy prior to mechanical thrombectomy.

	Antiplatelet *	Anticoagulant *	Antiplatelet and anticoagulant *	No antithrombotic medications
Patients, *n* **	1	9	1	5
Age (years), mean	80	82	71	67
Gender (male), *n*	0	6	1	2
Time thrombotic event onset -to-treatment >4.5 h, *n* (mean, h)	1 (7 h)	2 (8 h)	0	2 (12 h)
Conditions contraindicating the thrombolytic therapy, *n*				
Subcortical hemorrhage	0	0	0	1
Arterial hypertension	1	2	0	2
Intracranial aneurysm	0	0	0	1
Myocardial infarction	0	1	1	0
Occlusion location, *n*				
M1	1	7	0	4
M2	0	2	1	0
P3	0	0	0	1
Type of clot, *n*				
Fibrin-rich—white ***, *n*	0	2	0	1
Fibrin-rich—intermediate ****, *n*	0	0	1	3
RBCs rich *****, *n*	1	7	0	1
Endovascular technique, *n*				
Aspiration	0	2	1	0
Stent retriever	0	1	0	0
Combination	1	6	1	5
No. of passes, mean	2	1.7	4	3.6
Final TICI score, *n*				
0	0	0	0	2
2b	0	0	0	2
2c	0	1	1	0
3	1	8	0	1

* *Medication received prior to thrombotic event.*
** *n, number of patients.*
*** *Fibrin volumetric content > 95%.*
**** *Fibrin volumetric content >70% and <95%, RBCs volumetric content <30%.*
***** *RBCs volumetric content > 85%.*

performed with an ultra-high-resolution field emission Zeiss Merlin SEM, equipped with a Gemini II column, using the Everhart-Thornley secondary electron detector, 5 kV acceleration voltage and 500 pA probe current.

Clinical CT Scan Data Analysis

For the analysis of the clinical CT scans, the images were uploaded to a computer using the software OsiriX, and the mean HU values were averaged from at least two regions of interest assigned to the clot occluding the arteries. Analysis was performed by two blinded neuroradiologists who wrote down the numbers.

Statistical Methods

Hounsfield Units (HU) data is presented in mean ± standard deviation (SD). The normality of data was confirmed using the Shapiro-Wilk test. Two tailed Welch's *t*-test was used to find out if statistically significant differences occurred between the means of fibrin-rich clots and RBCs-rich clots. Receiver-operator characteristic curve (ROC) is used to determine the area under the curve (AUC). All the statistics were calculated using SPSS version 25 (SPSS Inc., Chicago, IL, USA).

RESULTS AND DISCUSSION

Baseline characteristics for patients included in this pilot study, and who did not qualify for thrombolytic therapy, are presented in **Table 1**. The table includes information on the antithrombotic medication prior to thrombotic event, time elapsed from the thrombotic event (when >4.5 h), conditions contraindicating the thrombolytic therapy, as well as extracted clot characteristics, and thrombectomy outcome.

Clinical Imaging

Typical CT brain scans, in which arterial occlusion sites can be seen as hyperdense or isodense, are illustrated in **Figures 1**, **2**.

Clots *ex vivo* Examination With Electron Microscopy

Based on our observations with electron microscopy, we categorized the clots as RBC-rich or fibrin-rich. RBC-rich clots are having red blood cells as main volumetric component (>85%), and core regions composed of compact polyhedrally-shaped RBCs (**Figures 3A,B**). Fibrin-rich clots can have the appearance of a white clot, usually without any red blood cells content (**Figures 3C,D**) or the appearance of a clot with intermediate composition, in which fibrin remains the main component, as volume fraction, although red blood cells are encapsulated in occasional pits and/or scattered on the outer clot surface (**Figures 3E,F**). The red clots extracted from patients included in this pilot study have a higher volume compared to the fibrin-rich clots, white or intermediate, and are associated with increased stroke severity, as expressed on the National Institutes of Health Stroke Scale (NIHSS), compared to fibrin-rich white clots, and with better recanalization outcomes compared to fibrin-rich clots (**Table 2**).

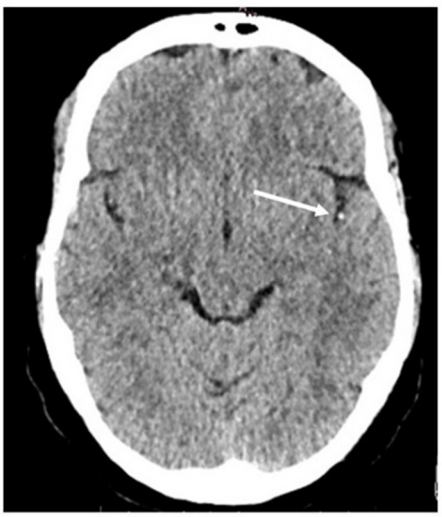

FIGURE 1 | Example of hyperdense artery sign (HAS) in M2 segment occlusion on the left (arrow), in non-contrast CT scan. The extracted clot was a RBCs-rich clot.

Clots *ex vivo* Examination With MicroCT

The mean HU values for the clots *ex vivo*, which are obtained from segmenting and quantifying the voxels values with Segment Statistics module in 3D Slicer, were in negative range. SD values are plotted along with the mean HU values in **Figure 4A**. Using two tailed Welch's *t*-test, a statistically significant difference was found between the means of fibrin-rich clots and RBCs-rich clots, where $t = -2.784059$, and $p = 0.0173484$. The receiver-operator characteristic curve (ROC) is plotted in **Figure 4B**. Based on these plotted values, the calculated area under the curve (AUC) is 0.84. The mean HU values measured *ex vivo* are plotted against the mean HU values measured in clinical imaging in **Figure 5**. Using the average value of the mean HU *ex vivo* as cut-off, we calculate a sensitivity of 30% and specificity of 100% for identifying with *ex vivo* microCT the clots that display HAS in clinical imaging. However, no statistically significant association was found between the clots *ex vivo* or those measured on the clinical CT.

Ex vivo Characterization of Clots Embedded on Stent Retrievers

We employed microCT along with electron microscopy to characterize the modality through which clots embed along the stent retrievers. A typical microCT depiction of a clot embedded along a stent retriever is illustrated in **Figure 6**. Both microCT and electron microscopy are useful at identifying the clot volume and the length of the stent covered by the clot. For each patient, we examined the various fragments of clots attached to the stent retriever, and we found that there is a linear correlation ($R^2 = 0.9236$) between the contact surface (calculated as clot volume-to-stent length covered by clot ratio) and the clot volume (**Figure 7A**). We found that RBC-rich clots tend to embed through sites at which the stent struts are protruding (**Figure 7B**). We also found that fibrin-rich clots are embedded along the stent

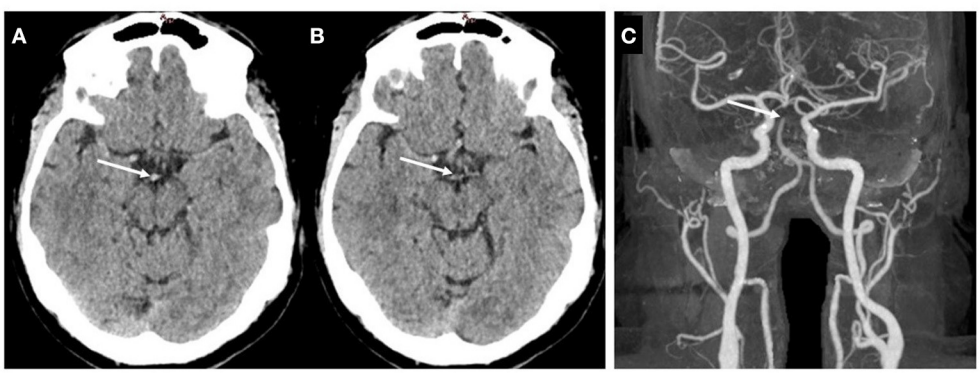

FIGURE 2 | Example of isodense clot. **(A,B)** Non-contrast CT. **(C)** contrast enhanced CT, illustrating the basilar artery tip occlusion. The extracted clot was a fibrin-rich clot.

through wrapping around the strut or by wetting the stent surface (**Figure 7C**). In general, the contact points with the stent are less compact than the core regions, situated between the stent struts.

DISCUSSION

Characterization of the clot, for example, volume, length (4, 9–11, 39, 40), shape (12), composition, and permeability, are known to be linked to the treatment outcome. More recently, antithrombotic therapy, which is used to prevent thrombus formation, was identified as an important variable in thrombus research (41). In our pilot study, red clots were extracted mainly from patients who received anticoagulant medications prior to the thrombotic event. However, studying the effect of antithrombotic medication onto the thrombus composition can encounter several limitations, and must be cautiously interpreted even when larger sample sizes are studied (41). Polyhedrocites, often found in core regions of red clots, are recognized as markers of intravital contraction (42–44), and potential contributors to stiffness (45). Polyhedrocites were previously found to be the prevailing cell type in red clots,

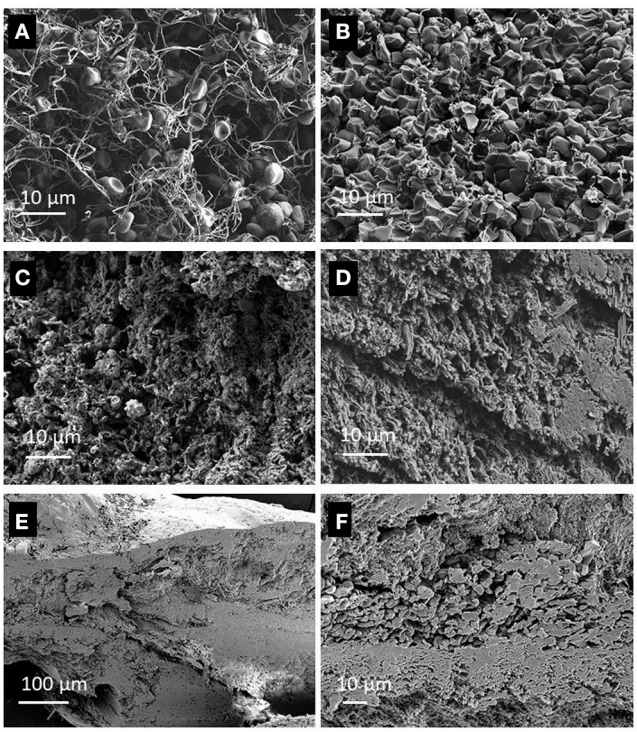

FIGURE 3 | Cross sectional view of clots, recorded with Scanning Electron Microscopy (SEM) showing: **(A)** Periphery of a red blood clot, with biconcave red blood cells in a loose fibrin mesh, **(B)**—The core of the same RBCs-rich clot as in **(A)**, with polyhedrocites as a marker of intravital contraction. **(C)**—A white clot, with fibrin mesh, platelets and white blood cells, **(D)**—Another section of the same white clot as in **(C)**, with dense fibrin and structures with crystalline appearance. **(E)**—A fibrin-rich clot, with scattered red blood cells on the outer surface, and inclusions of biconcave red blood cells, **(F)**—Higher magnification view of the red blood cells and fibrin walls.

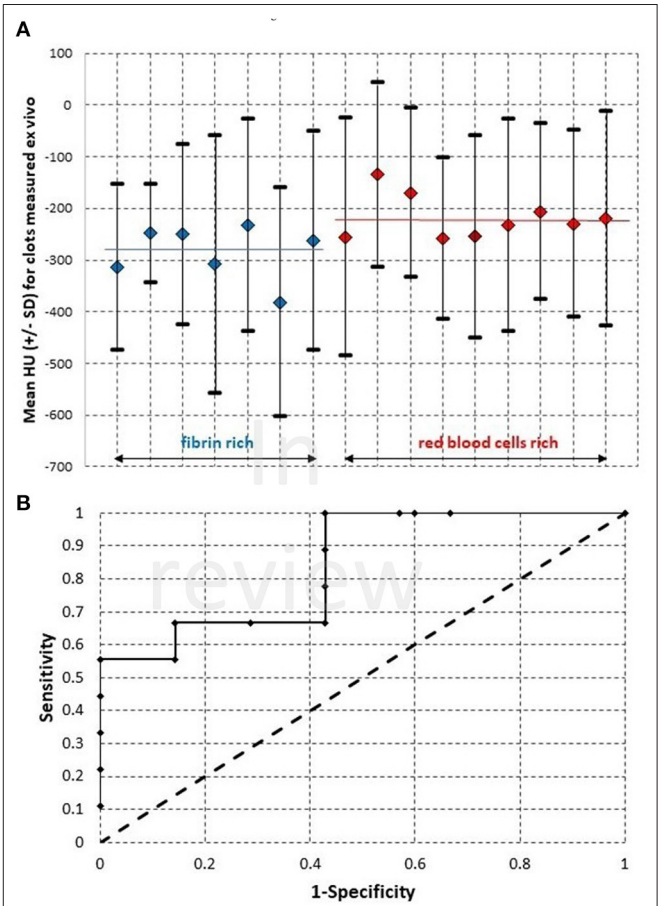

FIGURE 4 | (A)—Mean Hounsfield Unit (HU) values and the standard deviation (SD), as measured with microCT for clots extracted from patients by mechanical thrombectomy. The average values for the group of fibrin-rich clots and for the group of red blood cells rich clots are marked with blue bar, respectively red bar on the graph. **(B)**—The ROC curve plotted for the samples shown in **(A)**.

TABLE 2 | Extracted clots and clinical features.

	RBCs-rich clots	Fibrin-rich clots—intermediate	Fibrin-rich clots—white
Patients from which the clot was extracted, *n*	9	4	3
Volume of extracted clot (mm^3), mean (min, max)	48 (18, 110)	24 (12, 30)	8 (4, 15)
NIHSS at admission, mean (min, max)	19 (9, 27)	20 (17, 22)	4 (2,7)
Endovascular treatment, no. of passages, mean (min, max)	2.4 (1, 8)	3.2 (1, 6)	1 (1, 1)
Patients with final TICI score ≥ 2c, *n* (TICI min, TICI max)	9 (2c, 3)	2 (0, 3)	2 (2b, 3)

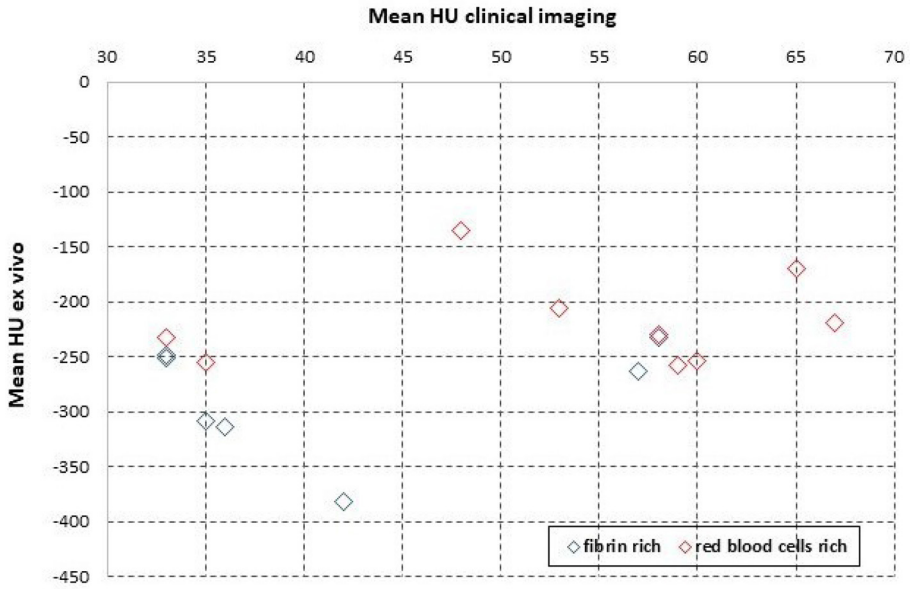

FIGURE 5 | The mean HU values measured *ex vivo* with microCT, for the same samples as in **Figure 4**, plotted against the values measured in patient, with clinical imaging.

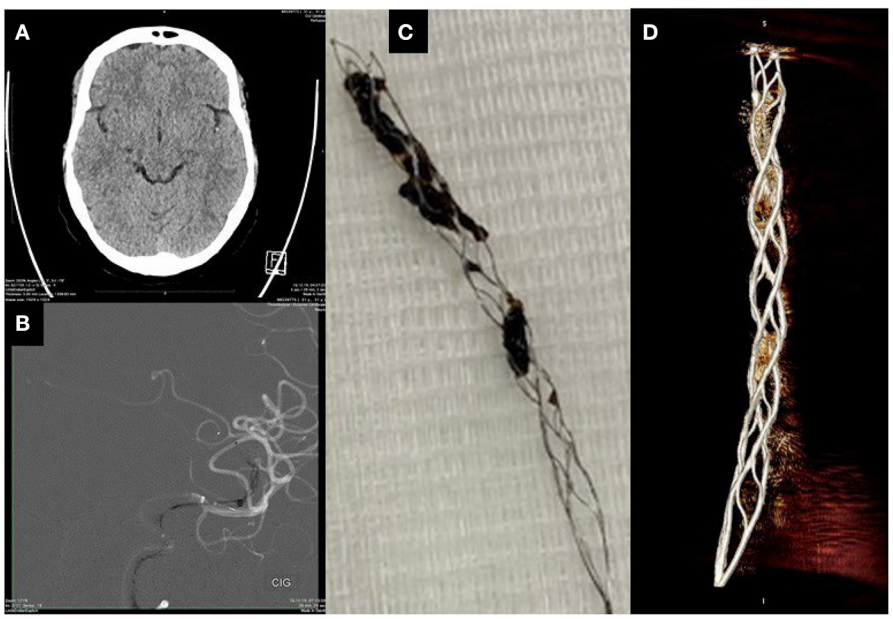

FIGURE 6 | Characterization of a clot on stent: **(A)**—Non-contrast clinical imaging showing HAS, **(B)**—Contrast enhanced CT showing the catheter and the stent deployed at the arterial occlusion site, **(C)**—Optical micrograph of the retrieved clot attached to the stent, **(D)**—MicroCT image of the retrieved clot attached to stent.

and can be related with clinical features such as stroke severity (44). The findings of our pilot study, mainly focused on patients who did not receive thrombolytic therapy prior to endovascular treatment, are in agreement with previous literature reports (44) and highlight that RBCs-rich clots are more amenable to endovascular treatment, compared to fibrin-rich clots.

Information obtained from clinical data is currently used to make treatment decisions. The composition of the clot, in particular, plays a role in its response to thrombolysis, thrombectomy, and, if recognized in clinical imaging, may even be helpful in deciding which kind of thrombectomy device should be used. It is important to find characterization techniques that better depict clot properties in relation to

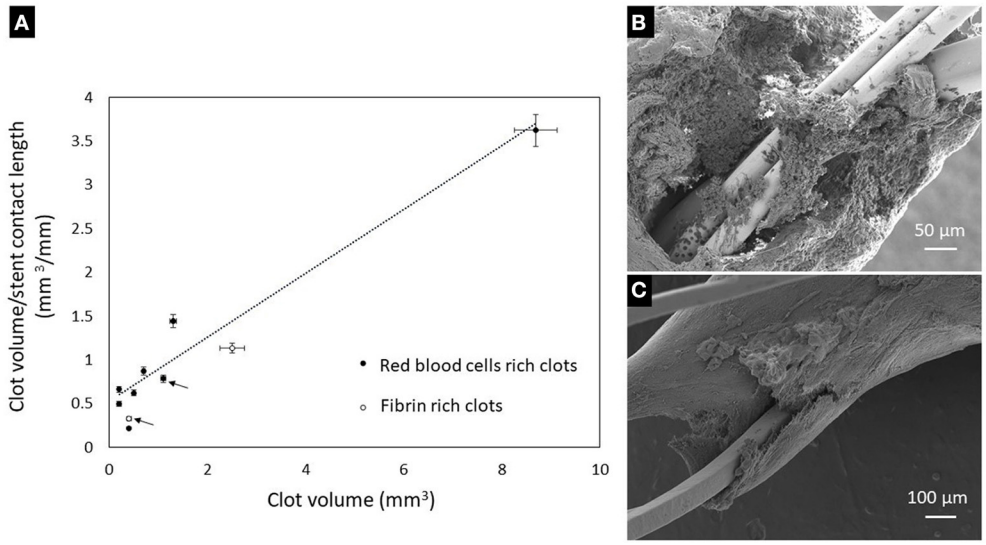

FIGURE 7 | (A)—Variation of clot-stent contact surface with the clot volume (the arrows indicate clots retrieved with Solitaire stent retriever, the non-marked clots being retrieved with Trevo stent retrievers). **(B)**—Attachment of a RBCs-rich clot to the stent: the stent struts are protruding through the non-compact region. **(C)**—Attachment of a fibrin-rich clot onto the stent by conforming to the stent strut surface.

clinical imaging. In this study, we examined the biophysical properties of the clots in relation to the clinical imaging data. We showed, in a pilot experiment, that clot density, as observed in microCT, is specific for clots with HAS. This finding can be used in designing experiments with larger sample sizes, in which segmentation methods can be used to delineate the clot appearance on clinical CT, and the significance of radiological signs of the clot can be better understood across the various scales. For example, statistically significant associations can be explored between various radiomic features extracted from clinical imaging and those features observed in terms of density (HU) in microCT, along with characteristics related to clot compactness, structure, and composition observed with sub-micron resolution with microscopy techniques. While not yet fully practical, further developments in CT imaging with the use of different scanning techniques, and eventually artificial intelligence, could help determine the clot composition before treatment has started, thereby helping the physician to optimize the choice of therapeutic tools.

CONCLUSION

Clots can be successfully imaged at various levels of resolution using microCT and electron microscopy as complementary techniques. Meaningful information regarding the clot composition and modalities of embedding along the stent retrievers can be obtained from these techniques. In perspective, exploration of clots structure and composition with high resolution microCT, using clots in dried state, will improve the sensitivity of this technique. The study of larger sample sizes with high resolution characterization techniques will allow correlative links with clinical imaging, which will be useful for harvesting the underlying information necessary for designing personalized treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Swissethics 2018-00476. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DDL, IW, and K-OL were responsible for initiating the project. DDL, JB, and K-OL wrote the manuscript. DDL, PM, DB, MV, and P-AP obtained funding. DDL, IW, PM, MV, JB, and P-AP edited the manuscript substantially. DDL, IW, GB, MM, AP, P-AP, and K-OL collected data. DDL and MM performed studies on samples. All authors contributed to the article and approved the submitted version.

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Real-World Cost-Effectiveness of Late Time Window Thrombectomy for Patients With Ischemic Stroke

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Background: To compare the cost-effectiveness of providing endovascular thrombectomy (EVT) for patients with ischemic stroke in the >4.5 h time window between patient groups who met and did not meet the perfusion imaging trial criteria.

Methods: A discrete event simulation (DES) model was developed to simulate the long-term outcome post EVT in patients meeting or not meeting the extended time window clinical trial perfusion imaging criteria at presentation, vs. medical treatment alone (including intravenous thrombolysis). The effectiveness of thrombectomy in patients meeting the landmark trial criteria (DEFUSE 3 and DAWN) was derived from a prospective cohort study of Australian patients who received EVT for ischemic stroke, between 2015 and 2019, in the extended time window (>4.5 h).

Results: Endovascular thrombectomy was shown to be a cost-effective treatment for patients satisfying the clinical trial criteria in our prospective cohort [incremental cost-effectiveness ratio (ICER) of $11,608/quality-adjusted life year (QALY) for DEFUSE 3-postive or $34,416/QALY for DAWN-positive]. However, offering EVT to patients outside of clinical trial criteria was associated with reduced benefit (−1.02 QALY for DEFUSE 3; −1.43 QALY for DAWN) and higher long-term patient costs ($8,955 for DEFUSE 3; $9,271 for DAWN), thereby making it unlikely to be cost-effective in Australia.

Conclusions: Treating patients not meeting the DAWN or DEFUSE 3 clinical trial criteria in the extended time window for EVT was associated with less gain in QALYs and higher cost. Caution should be exercised when considering this procedure for patients not satisfying the trial perfusion imaging criteria for EVT.

Keywords: stroke, large vessel occlusions, late time window thrombectomy, real-world, cost-effectiveness

INTRODUCTION

Seven large clinical trials have demonstrated that endovascular thrombectomy (EVT) is highly effective in increasing disability-free survival compared to the previous standard care, intravenous thrombolysis (IVT), in strokes due to a large vessel occlusion (LVO) (1–7). Based on these foundational trials, DAWN and DEFUSE 3 trials also extended the treatment time window for patients screened with perfusion imaging to identify treatment responders from 6 h out to 24 h (8, 9). These ground-breaking trials were highly selective but demonstrated considerable patient benefits. Since its introduction as routine care in Australia, providing EVT to patients with an LVO has seen a significant amount of "scope creep," where a large proportion of patients are now offered therapy outside of the trial criteria. Previous *post-hoc* analysis has shown that providing EVT to patients meeting the trial criteria is highly cost-effective within the normal and extended time window (10–16); however, it is not known if this cost-effectiveness is maintained when patients are treated outside of the trial criteria.

Patient outcomes after stroke and EVT are highly influenced by patient characteristics (17, 18), such as age, pre-morbid disability, co-morbidities, and imaging characteristics including the site of the vessel occlusion and the volume of core/penumbra (19). It is important to acknowledge that in clinical practice, which is distinct from controlled trials that are subject to strict selection criteria, the clinicians are more likely to treat patients who do not enroll into these trials, and not all these patients benefit from the treatment to the same extent, while some are even harmed due to hemorrhage, vessel perforation, or reperfusion injury. To investigate the effect of this scope creep on the likely cost of therapy, we undertook a discrete event simulation to assess the cost-effectiveness of EVT in the real world with respect to patients meeting/not meeting the clinical trial criteria, in comparison to the medical treatment alone.

MATERIALS AND METHODS

Study Population

Data from the International Stroke Perfusion Imaging Registry (INSPIRE) were used to source the baseline and 90-day clinical and imaging data over a 5-year period (2015–2019) (20, 21). Patients presenting with acute neurological deficit within 24 h of symptom onset underwent routine multimodal CT (non-contrast CT, perfusion CT, and CT angiography) and received thrombolysis and/or EVT if they were deemed eligible according to local clinical guidelines. Eligibility for EVT in routine clinical practice included the presence of an LVO [internal carotid artery (ICA) or M1 occlusion] that an interventionalist could potentially retrieve. Consent of the patients was obtained according to the Declaration of Helsinki. The Hunter New England Area Health Service Human Research Ethics Committee reviewed and approved the study protocol in 2012.

To assess the effect of late time window treatment, only patients presenting after 4.5 h from symptom onset were included from the INSPIRE database. In this study, the late window was defined as a patient presenting >4.5 h after stroke onset, so as to have a sufficient number of patients from INSPIRE registry to proceed with the analysis. All the other criteria from DAWN and DEFUSE 3 (as summarized in **Supplementary Table I**) were strictly applied to our study population. Medical treatment included non-EVT treatment with or without intravenous thrombolysis. Patients were split into groups of those who received and did not receive EVT. Patients were then matched (i.e., matching nearest neighbors) between EVT and non-EVT groups, based on age, sex, baseline National Institute of Health Stroke Scale (NIHSS), and computer tomography perfusion (CTP) ischemic core volume using the "psmatch2" command from Stata (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Premorbid modified ranking score (mRS) was insufficiently recorded in the INSPIRE, thus preventing it from being adopted as a matching variable. Next, all the patients that met and did not meet the DAWN and DEFUSE 3 criteria were, respectively, matched separately based on EVT and non-EVT following the same Stata command. Non-EVT patients with corresponding perfusion imaging criteria positive were employed as the comparator for EVT patients with positive selection criteria while those being criteria negative were adopted as a comparator for EVT patients being perfusion imaging criteria negative. Perfusion imaging selection criteria were as per the original DEFUSE 3 and DAWN trials and are summarized in **Supplementary Table I**. Distributions of propensity score were assessed after matching with EVT status and perfusion imaging selection criteria. The sociodemographic and clinical characteristics of the simulated cohort were defined by participants from the INSPIRE (summarized in **Table 1**).

Model Structure

The discrete event simulation (DES) model was initiated from Day 90 in one of seven health states as defined by the mRS score (0–6) on the basis of the INSPIRE registry data (**Table 1**) (22). The DES model was selected to avoid the use of fixed cycle lengths and improve the calculation efficiency. Both DES and Markov models produce results that are highly consistent and cost-effective and support the same resource allocation decisions (23–27). The resource constraints were not considered in the current DES model (e.g., EVT is always available to patients in need). In the long-term, myocardial infarction (MI) and recurrent stroke were simulated given the substantially increased risk of coronary heart disease (CHD) post stroke (i.e., the 5-year risk of MI or vascular death was 17.4%) (28). Following each event, the patient could die or survive from such events, or die from other non-cardiovascular disease (CVD) causes. TreeAge Pro was used for discrete event simulation (TreeAge Pro 2019, R2. TreeAge Software, USA). The model structure is presented in **Supplementary Figure I**. Detailed model description is provided in the **Supplementary Material**.

Model Inputs

Time-to-Event Distribution and Transition Probability

Given the 3-month follow-up of INSPIRE, the long-term event rates were sourced from published literature. Time to recurrent stroke was constructed using an exponential distribution (29),

TABLE 1 | Baseline characteristics of the cohort.

	Thrombectomy procedure (*N* = 131)		Medical treatment (*N* = 160)		Thrombectomy procedure (*N* = 111)		Medical treatment (*N* = 94)	
	DEFUSE 3_pos (*N* = 105)	DEFUSE 3_neg (*N* = 26)	DEFUSE 3_pos (*N* = 98)	DEFUSE 3_neg (*N* = 62)	DAWN_pos (*N* = 91)	DAWN_neg (*N* = 20)	DAWN_pos (*N* = 59)	DAWN_neg (*N* = 35)
Age (years, mean)	68.0 (15.27)	70.0 (14.16)	69.9 (13.40)	68.0 (13.62)	65.1 (15.17)	67.3 (17.41)	69.0 (13.99)	69.1 (14.79)
Gender (male, %)	38 (36.2%)	8 (30.8%)	43 (43.9%)	18 (29.0%)	39 (42.9%)	5 (25.0%)	24 (40.7%)	13 (37.1%)
Baseline NIHSS	16 (11–21)	16 (11–21)	15 (11–19)	14 (8–19)	17 (14–21)	18 (14–22)	17 (13–20)	18 (8–22)
Baseline core volume (ml, median)	19 (8–36)	91 (73–126)	21 (11–46)	15 (0.1–76)	21 (10–36)	92 (82–128)	23 (10–40)	76 (19–95)
Perfusion lesion volume (ml, median)	112 (76–149)	199 (162–229)	113 (81–160)	24 (7–151)	123 (86–150)	207 (191–234)	113 (75–137)	137 (104–196)
Penumbra volume (ml, median)	90 (62–117)	93 (63–123)	83 (51–124)	11 (3–73)	98 (62–120)	99 (88–125)	79 (58–113)	86 (44–109)
Treatment type (*n*, %)								
Both EVT and tPA	50 (47.6%)	16 (61.5%)	0	0	43 (47.2%)	12 (60.0%)	0	0
EVT only	55 (52.4%)	10 (38.5%)	0	0	48 (52.8%)	8 (40.0%)	0	0
tPA only	0	0	7 (7.1%)	5 (8.1%)	0	0	4 (6.8%)	3 (8.6%)
Symptom onset to CTP (mins, mean)	322 (86)	394 (72)	403 (79)	372 (83)	335 (94)	387 (92)	384 (73)	393 (81)
Target mismatch (n, %)	105 (100%)	0	98 (100%)	3 (4.8%)	86 (94.5%)	1 (5%)	56 (94.9%)	10 (28.6%)
Core volume>70ml (n, %)	0 (0)	20 (76.9%)	0 (0)	24 (38.7%)	0 (0)	19 (95.0%)	0 (0)	24 (68.6%)
Proportion receiving EVT 4.5–6 hours (n, %)	31 (29.5%)	9 (34.6%)	–	–	23 (25.3%)	6 (30.0%)	–	–
Occlusion location (*n*, %)								
ICA	35 (33.3%)	15 (57.7%)	28 (28.6%)	27 (43.6%)	37 (40.7%)	12 (60.0%)	24 (40.7%)	21 (60.0%)
M1	70 (66.7%)	11 (42.3%)	70 (71.4%)	35 (56.5%)	54 (59.3%)	8 (40.0%)	35 (59.3%)	14 (40.0%)
3 m mRS								
0	14 (13.33%)	2 (7.69%)	11 (11.22%)	12 (19.35%)	15 (16.48%)	2 (10.0%)	9 (15.25%)	4 (11.43%)
1	20 (19.05%)	3 (11.54%)	15 (15.31%)	13 (20.97%)	12 (13.19%)	1 (5.0%)	7 (11.86%)	4 (11.43%)
2	14 (13.33%)	3 (11.54%)	10 (10.2%)	2 (3.23%)	9 (9.89%)	2 (10.0%)	6 (10.17%)	1 (2.86%)
3	30 (28.57%)	5 (19.23%)	13 (13.27%)	9 (14.52%)	20 (21.98%)	4 (20.0%)	9 (15.25%)	3 (8.57%)
4	12 (11.43%)	3 (11.54%)	27 (27.55%)	8 (12.9%)	11 (12.09%)	3 (15.0%)	12 (20.34%)	4 (11.43%)
5	5 (4.76%)	1 (3.85%)	8 (8.16%)	7 (11.29%)	6 (6.59%)	0 (0%)	4 (6.78%)	9 (25.71%)
6	10 (9.52%)	9 (34.62%)	14 (14.29%)	11 (17.74%)	18 (19.78%)	8 (40.0%)	12 (20.34%)	10 (28.57%)

DEFUSE_neg/pos, patient not meeting/meeting the DEFUSE 3criteria; DAWN_neg/pos, patien not meeting/meeting the DAWN criteria; EVT, endovascular clot retrieval; tPA, tissue plasminogen activator; CTP, computer tomography perfusion; mRS, modified Rankin scale.

Unlike normal matching (in which single characteristics that distinguish two groups are matched, e.g., baseline infarct core volume), propensity score matching attempts to reduce the potential bias due to a range of confounding variables (e.g., age, sex, baseline NIHSS and baseline ischemic core volume). Subsequently, the comparability of one particular variable could be suboptimal than that from the normal matching approach.

The number of patients meeting the DEFUSE 3 or DAWN criterion in the thrombectomy/medical treatment groups overlaps.

while a Gompertz distribution following a previously published study was tested in the sensitivity analysis (30). Time to MI was constructed using an exponential distribution derived from a registry that prospectively recorded incidence of MI post stroke ($N = 9{,}840$) during the period of 2003–2016 (median follow-up: 4.7 years) (31).

For patients within or outside of clinical trial criteria for EVT and controls, the identical time-to-event distribution for all the possible events was applied, and this was considered conservative as there was insufficient evidence to support the carry-on effect of EVT. Parameters for the time-to-event distributions are provided in **Supplementary Table II**. Mortality rates (due to non-CVD and CVD causes) by age are summarized in **Supplementary Tables III, IV**.

Costs

The healthcare costs related to the index stroke (including the cost for EVT procedure), rehospitalization due to MI and stroke, and long-term management costs (including medications and GP/specialist consultations) were considered in the model-based simulation study (32, 33). For recurrent stroke, the costs of acute care (i.e., hospitalization) based on the severity of stroke (as defined by the mRS score) were extracted from national administrative databases (34). The long-term management costs for stroke (according to the functional status defined by mRS score) and MI were sourced from the published literature (32–34). All the costs (valued in Australian dollars in 2018, where 1 AUD = 0.75 USD was the average exchange rate in 2018) applied in the model are presented in **Supplementary Table II**.

Utility Weights

Utility weights are preference weights representing the strength of desirability toward different health states (i.e., more preferred health states will have greater weight). They are measured on a cardinal scale of 0–1, where 0 indicates death and 1 indicates perfect health (negative values represent a health state worse than death) (14). In the current study, utility weights associated with being in the post-stroke health states by mRS score were informed based on published literature. A utility decrement was applied immediately following a CVD event to account for the temporarily reduced quality of life after an event (35, 36). The utility weights are shown in **Supplementary Table II**.

Cost-Effectiveness Analysis

In the base case, 50,000 Australian patients with suspected LVO were modeled in the DES. The perspective of the Australian healthcare system was considered to measure the costs and benefits over a 25-year time horizon. Utility weights were utilized to estimate the quality-adjusted life years (QALYs) (14). In addition, the life years lived were estimated to measure the survival gains. The primary outcome for the cost-effectiveness analysis was the incremental cost-effectiveness ratio (ICER) per QALY gained, which is calculated as the ratio between incremental cost and incremental QALYs gained (intervention vs. control). Separate ICERs were estimated for patients undergoing EVT by satisfying the DAWN and DEFUSE 3 criteria. Costs and benefits were discounted at a rate of 3% per annum (37). The often quoted willingness-to-pay (WTP) per QALY threshold of AUD50,000 was adopted to assess the cost-effectiveness of EVT measured against medical treatment without EVT (38).

Sensitivity Analyses

One-way deterministic sensitivity analyses (i.e., varying one model parameter at a time within a plausible range) were undertaken to examine the robustness of base case results. The results of deterministic sensitivity analyses were presented in the form of a tornado diagram. In addition, probabilistic sensitivity analyses by constructing the distribution for the key uncertain parameters were run to further explore the results. A key assumption made in the probabilistic sensitivity analyses was that the distributions for each parameter were not correlated (i.e., the variation in one parameter is not associated with a change in another parameter). An incremental cost-effective plane and a cost-effectiveness acceptability curve were generated to illustrate the results of probabilistic sensitivity analyses.

Model Validation

The long-term data for patients post stroke were utilized to validate the outcomes from the simulation study. In particular, studies reporting the long-term survival and recurrence of stroke and MI were retrieved from a rapid literature review through key databases to examine the model outputs.

Expanded methods are shown in the **Supplementary Materials**.

Data Availability

INSPIRE data may be available following a reasonable request to the corresponding author in the anonymized form by any qualified investigator.

RESULTS

Study Population

In this study, a total of 372 patients were included from the INSPIRE registry. Of the 372 patients, 291 patients were positive for DEFUSE 3 and 205 were also positive for DAWN criteria. There were 124 patients (33.3% of the total study population) who were positive for both DEFUSE 3 and DAWN criteria (and were within 6- and 16-h time windows); 85 of this received EVT while 39 did not receive EVT.

Of the 372 patients, 161 were treated with EVT beyond 4.5 h. Among the EVT patients, 83 were also treated with thrombolysis, of which 11 were treated beyond 4.5 h. Of the 372 patients, 211 were not treated with EVT and presented to the hospital beyond 4.5 h. Of these, 16 (7.6%) were treated with thrombolysis beyond 4.5 h. Next, of the 161 patients in the EVT cohort, 133 met the DEFUSE 3 criteria (105 were matched and 28 were unmatched for the analysis) while 28 did not (26 were matched and 2 were unmatched). Among these 161 patients, 123 met the DAWN criteria (91 were matched and 32 were unmatched) while 38 did not (20 were matched and 18 were unmatched). Patients who were not matched for DAWN or DEFUSE 3 were not included in the long-term cost-effectiveness analysis by that criteria. The process of propensity matching is illustrated in **Figure 1**.

The patient details and cohort sizes are described in **Table 1**. The characteristics of patients unmatched based on EVT status and perfusion criteria are shown in **Supplementary Table V**. The distribution of propensity score after matching based on EVT and DAWN/DEFUSE 3 criteria is shown in **Supplementary Figure II**.

Additional results of population characteristics are supplied in the **Supplementary Materials**.

Cost-Effectiveness Analysis

Of the patients treated with EVT, the presence or absence of DEFUSE 3 mismatch was associated with different outcomes: $70,810 in costs and 8.81 QALYs for DEFUSE-positive patients, $59,302 and 6.03 QALY for DEFUSE-negative patients. Comparatively, the cost of best medical practice with/without thrombolysis was $50,347 and 7.05 QALYs for DEFUSE-positive and $48,767 and 7.61 QALY for DEFUSE-negative patients, respectively (**Table 2**). Therefore, compared with patients who did not undergo EVT regardless of their trial eligibility, offering EVT to patients satisfying the DEFUSE 3 criteria was cost-effective (ICER $11,608 vs. DEFUSE 3 positive without EVT or $18,303/QALY vs. DEFUSE 3 negative without EVT). However, using the same set of comparators, it was not cost-effective (more costly and less effective) to treat patients with EVT who did not meet the DEFUSE 3 criteria in the extended time window (**Table 2**).

The results according to DAWN criteria showed a similar trend: $66,096 and 7.56 QALYs for DAWN-positive patients,

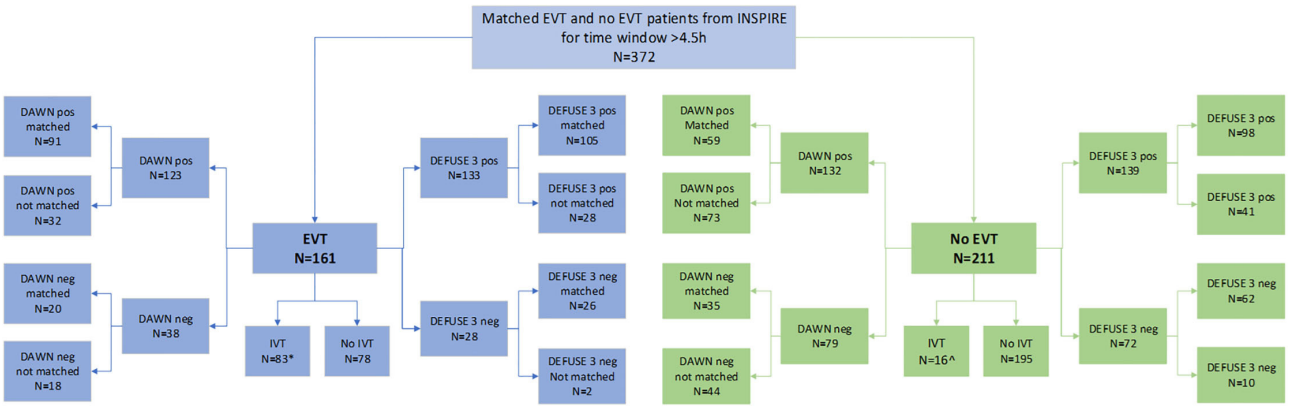

FIGURE 1 | Illustration of propensity score matching by treatment and perfusion criteria.

TABLE 2 | Base case results from the cost–effectiveness analysis.

	Thrombectomy procedure		Medical treatment		Thrombectomy procedure		Medical treatment	
	DEFUSE 3 positive	**DEFUSE 3 negative**	**DEFUSE 3 positive**	**DEFUSE 3 negative**	**DAWN positive**	**DAWN negative**	**DAWN positive**	**DAWN negative**
Total QALYs	8.81	6.03	7.05	7.61	7.56	5.59	7.02	4.64
Total LYs	12.77	9.19	12.09	11.60	11.30	8.45	11.22	10.05
Total costs	$70,810	$59,302	$50,347	$48,767	$66,096	$56,788	$47,517	$43,801
Average number of events*								
Deaths	0.626	0.730	0.645	0.660	0.669	0.752	0.671	0.705
MI	0.216	0.153	0.202	0.194	0.190	0.141	0.188	0.168
Stroke	0.822	0.594	0.779	0.747	0.728	0.544	0.723	0.649
Cost of hospitalization	$36,729	$34,622	$18,015	$17,720	$35,864	$34,161	$17,509	$16,826
Cost of management	$24,082	$24,680	$32,332	$31,047	$30,232	$22,627	$30,008	$26,974
ICER								
	$11,608	dominated^	–	–	$34,416	dominated^	–	–

QALY, quality–adjusted life year; LY, life year; ICER, incremental cost–effectiveness ratio.

**this is the average number of event per patient (not all patients experienced the CVD event). ^the dominance was based on higher number of death occurred even though the ICER was $13,588.*

Dominated refers to the results showing the intervention is more expensive whereas has less benefits than the comparator.

$56,788 and 5.59 QALY for DAWN-negative patients, in comparison to $47,517 and 7.02 QALYs in those who did not receive EVT but being DAWN-positive and $43,801 and 4.64 QALYs in those being DAWN-negative (**Table 2**). In summary, compared with the patients who did not undergo EVT, EVT was a cost-effective treatment for patients meeting the DAWN perfusion criterion (ICER $34,416 vs. DAWN positive without EVT or $7,611/QALY vs. DAWN negative without EVT). However, again, it was not cost-effective to treat patients with EVT when they did not fulfill the DAWN criteria. It was more costly and less effective when compared to DAWN-positive patients who did not undergo EVT. It was also more costly and incurred higher rates of death (detailed below) when compared to DAWN-negative patients who did not undergo EVT, even with an ICER of $13,588/QALY below the WTP/QALY threshold.

The results of cost-effectiveness analysis by 3-month mRS score from INSPIRE are summarized in **Supplementary Tables VI, VII**. Generally, patients who achieved better functional outcomes at 3-month follow-up incurred lower annual costs post the index stroke.

Over the modeled time horizon, more simulated deaths occurred among patients who received EVT but were outside of either of the criteria [N = 7,300 (DEFUSE 3-negative) or N = 7,520 (DAWN-negative) per 10,000 patients], compared to those treated without EVT [N = 6,450 (DEFUSE-positive) or N = 6,600 (DEFUSE-negative), N = 6,710 (DAWN-positive) or N = 7,050 (DAWN-negative) per 10,000 patients] (**Table 2**).

Sensitivity Analysis

In comparison with medical treatment, the cost-effectiveness of extended time window EVT in patients not meeting the DAWN or DEFUSE 3 criteria was very sensitive to the time horizon, discount rate, probability of recurrent stroke

being fatal, and cost of acute care for recurrent stroke (**Supplementary Figures III, IV**).

Compared to the medical treatment without EVT, probabilistic sensitivity analysis consistently showed that EVT was highly likely to be cost-effective in patients satisfying the clinical trial criteria for EVT, with a corresponding probability of 100% for DEFUSE 3 and DAWN criteria, respectively. On the other hand, it consistently showed that the patients receiving EVT, but not meeting the trial criteria, achieved inferior health outcomes in the long-term, rendering EVT not cost-effective (with 0% probability of being cost-effective for both criteria) when compared with medical treatment (**Supplementary Figures V, VI)**.

Results of using a 5-year time horizon and Gompertz distribution for the probability of recurrent stroke are provided in **Supplementary Tables VIII, IX**.

Model Validation

The 5-year survival predicted by the current model was around 51.8% for patients who received non-EVT treatment. In comparison, the Oxford Vascular Study reported a 5-year survival rate of over 50% (39), and a Swedish study found a 49.4% survival for ischemic stroke (40). Moreover, the predicted 5-year QALY gains from the non-EVT group were 2.07 in our study vs. 2.21 from the long-term observation (39).

In addition, our model also predicted the number of recurrent strokes and MI, which are highly comparable with the systematic review of long-term observational studies (29, 31, 41).

Additional results of model validation are provided in the **Supplementary Materials**.

DISCUSSION

In this study, we found that treating patients with EVT who did fulfill the DAWN and DEFUSE 3 trial criteria had significantly better outcomes compared to non-EVT patients, which was also highly cost-effective. However, for patients who did not fulfill the trial criteria, EVT was unlikely to be cost-effective based on the primary comparator (medical therapy patients being perfusion criteria positive), given the higher costs and number of deaths, and lower QALY gains based on the widely accepted threshold of $50,000/QALY. Importantly, this study reflects the practice in the real world and is not within a tightly controlled clinical trial, and so represents the implementation of the evidence rather than the evidence itself. The patients in the trial negative cohort were predominantly with a large established ischemic core. Important to note is that while the trial negative groups have been shown to have a reduced rate of cost-effective clinical benefit from EVT, there may be individual patients within these groups who do benefit, and this requires further investigation. Even though there are currently randomised controlled trials (RCTs) underway to ascertain the benefit of EVT in the large core at baseline (i.e., the SELECT 2; RESCUE Japan-LIMIT NCT03702413; TENSION NCT03094715) (42), the results from the current study including, largely, patients with baseline infarct core over 70 ml of imaging selection criteria negative could stress the importance of careful patient selection in offering EVT in real-world.

Evaluations of the cost-effectiveness of EVT were based on a decision tree combined with a Markov model, drawing efficacy data from clinical trials (i.e., 100% of the patients fulfilled the EVT criterion) and localized costs (10–13, 16, 32, 33, 36, 43–47). Most of the economic evaluations concluded that EVT was a dominant treatment option (i.e., higher QALYs and lower costs) for patients with ischemic stroke, while the rest reported its positive cost-effectiveness (i.e., ICER falls below the WTP/QALY threshold for various jurisdictions), including late window EVT (studies listed in **Supplementary Table X**). The gains in QALYs from these studies ranged from 0.54 (43) to 2.51 (46) over the lifetime horizon. However, positive cost-effectiveness outcomes that are built upon efficacy outcomes from clinical trials may misinform clinical and policy decision-making, thereby leading to inappropriate management of patients with ischemic stroke. This in turn may result in unnecessary use of health resources (high medical costs of EVT) and worsening health outcomes, representing significant inefficient allocation of resources.

Our data suggest that offering EVT based on the DEFUSE 3 criteria is associated with greater QALY gains than that by the DAWN criteria as a confirmatory result from a non-selected registry of routine care. In contrast, treating patients outside of the DAWN criteria leads to poorer outcomes in terms of survival gains. The difference is driven by the post-stroke outcome after 3 months, where more patients achieved functional independence (i.e., mRS $\leq$2). In terms of 3-month functional outcomes, there was no significant difference between the DAWN-positive and DAWN-negative patients (ordinal logit regression, $p = 0.055$). The long-term modeling enabled the translation from short-term temporary health status to the eventual health outcomes. The modeling suggested that neurologists/neuro-interventionists should exercise more caution when offering EVT to patients not satisfying the perfusion criteria.

It is important to highlight that EVT treatment for patients in the standard time window of up to 6 h of symptom onset is widely thought to be cost-effective no matter what the perfusion imaging characteristics are. However, in the early time window, there is still limited health economic assessment on a real-world dataset of comparable depth to that seen in the current extended time window (i.e., with CTP data available). The primary source of such patient outcome variation includes the differences in salvageable ischemic lesion volume identified by CTP (18, 48, 49).

The favorable cost-effectiveness of offering EVT to DAWN-negative patients compared to those receiving medical treatment being DAWN-negative should be interpreted with caution. It is worth noting that even though the resultant ICER in this scenario was cost-effective, treatment with EVT in this cohort led to a greater number of deaths ($N = 470$ per 10,000 patients treated) over the simulated time horizon, which rendered it inferior to medical treatment. The analysis based on all patients without EVT procedure regardless of DAWN criterion revealed consistent results as the analysis according to the primary comparator—offering EVT to DAWN-negative patients has zero probability of being cost-effective.

There are limitations to this study. First, the severity of recurrent stroke was not modeled explicitly but was accounted for when assigning the costs and utility weights implicitly

(i.e., when a recurrent stroke occurred, the hospitalization and management costs and utility weights were determined by the severity of that stroke). Second, the effectiveness of EVT was based on prospectively collected cohort data; there might be some concerns regarding the comparability of the compared cohorts (e.g., EVT patients with perfusion criteria negatives had higher baseline core volume than that for the primary comparator). The non-significant between-group difference in other baseline characteristics may partly ease this concern. Third, INSPIRE recruited more non-EVT patients with mild stroke compared to the landmark RCTs, which may confound the comparison. However, participants were matched in terms of onset age, gender, baseline NIHSS, and infarct core volume with propensity score matching approach. Fourth, the time-to-event distributions for recurrent stroke and MI were sourced from non-Australian-based studies, but between-country differences are likely to be minimal given the similar socio-economic settings. Fifth, the subgroup cost-effectiveness analysis pertaining to the variations in onset time and age, NIHSS score, and clinical infarct mismatch ratio are not performed due to limited sample size (e.g., the smallest sample size in the EVT group of DAWN negative patients was 20). Last, the recurrence of stroke was slightly overestimated in the DES model; however, in the sensitivity analysis, lowering the probability of recurrent stroke did not alter the conclusion about the cost-effectiveness of EVT in patients outside of the clinical trial criteria.

CONCLUSIONS

Treating patients meeting the clinical trial perfusion imaging criteria in the extended time window with EVT is highly cost effective, while patients not meeting these criteria may not be cost effective, thereby highlighting the importance of the selection of patients. It is recommended that careful selection should be exercised when considering this procedure for patients not satisfying the perfusion imaging criteria for extended time window EVT. The real-world data analysis also confirmed that EVT is cost-effective for patients fulfilling the DEFUSE 3 or DAWN criteria in Australia.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this study can be requested from Associate Professor Andrew Bivard (abivard@unimelb.edu.au) by a qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Hunter New England Area Health Service Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LG, AB, MP, and MM conceived and designed the study. LG conducted data analysis and drafted the manuscript. AB, MP, NJS, CL, KB, TK, BY, QD, XC, ML, CY, CC, PW, LL, PC, and FM contributed to the data collection and provided important inputs to the manuscript. All authors provided consent to submit the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.780894/full#supplementary-material

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Mechanical Thrombectomy With and Without Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke: A Systematic Review and Meta-Analysis Using Nested Knowledge

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Background: Mechanical thrombectomy (MT) is now the standard-of-care treatment for acute ischemic stroke (AIS) of the anterior circulation and may be performed irrespective of intravenous tissue plasminogen activator (IV-tPA) eligibility prior to the procedure. This study aims to understand better if tPA leads to higher rates of reperfusion and improves functional outcomes in AIS patients after MT and to simultaneously evaluate the functionality and efficiency of a novel semi-automated systematic review platform.

Methods: The Nested Knowledge AutoLit semi-automated systematic review platform was utilized to identify randomized control trials published between 2010 and 2021 reporting the use of mechanical thrombectomy and IV-tPA (MT+tPA) vs. MT alone for AIS treatment. The primary outcome was the rate of successful recanalization, defined as thrombolysis in cerebral infarction (TICI) scores ≥2b. Secondary outcomes included 90-day modified Rankin Scale (mRS) 0–2, 90-day mortality, distal embolization to new territory, and symptomatic intracranial hemorrhage (sICH). A separate random effects model was fit for each outcome measure.

Results: We subjectively found Nested Knowledge to be highly streamlined and effective at sourcing the correct literature. Four studies with 1,633 patients, 816 in the MT+tPA arm and 817 in the MT arm, were included in the meta-analysis. In each study, patient populations consisted of only tPA-eligible patients and all imaging and clinical outcomes were adjudicated by an independent and blinded core laboratory. Compared to MT alone, patients treated with MT+tPA had higher odds of eTICI ≥2b (OR = 1.34 [95% CI: 1.10; 1.63]). However, there were no statistically significant differences in the rates of 90-day mRS 0-2 (OR = 0.98 [95% CI: 0.77; 1.24]), 90-day mortality (OR = 0.94 [95% CI: 0.67; 1.32]), distal emboli (OR = 0.94 [95% CI: 0.25; 3.60]), or sICH (OR = 1.17 [95% CI: 0.80; 1.72]).

Conclusions: Administering tPA prior to MT may improve the rates of recanalization compared to MT alone in tPA-eligible patients being treated for AIS, but a corresponding

improvement in functional and safety outcomes was not present in this review. Further studies looking at the role of tPA before mechanical thrombectomy in different cohorts of patients could better clarify the role of tPA in the treatment protocol for AIS.

Keywords: stroke, thrombectomy, tissue plasminogen activator, thrombolysis, meta-analysis, semi-automated analysis

INTRODUCTION

Acute ischemic stroke (AIS) is caused by embolic or thromboembolic occlusion of a cervical or cerebral artery. Until recently, AIS treatment focused on intravenous thrombolysis with tissue plasminogen activator (IV-tPA), and eligible patients could be treated within 3–4.5 h of symptom onset (1). More recently, multiple randomized clinical trials demonstrated that mechanical thrombectomy (MT) results in superior functional outcomes compared to standard medical therapy, which includes IV-tPA treatment (2–9). Moreover, MT may be offered to eligible patients up to 24 h after symptom onset, which has expanded treatment options for thousands of AIS patients.

Currently, patients who are eligible for both MT and IV-tPA are recommended to receive both treatments (10). However, the effectiveness of MT has raised the question of whether IV-tPA offers any additional benefit in the treatment of AIS patients who are eligible for both therapies.

The recently reported DIRECT-MT, SKIP, DEVT, and MR CLEAN NO IV trials randomized patients to either MT alone to MT+tPA, and each of these trials failed to identify a significant difference in functional outcomes between these two treatment strategies (11–14). In addition, it is not clear whether MT+tPA results in a higher frequency of vessel recanalization compared to MT alone (11–14). We hypothesized that these individual studies were underpowered to detect significant differences in recanalization rates and functional outcomes between MT+tPA and MT alone patients. Therefore, we performed a systematic review and meta-analysis to consolidate the findings of all eligible randomized controlled trials that address this comparison.

Traditional reviews and meta-analyses require researchers to manually identify relevant literature across multiple databases, a process which can be inefficient and unorganized. The data extraction process too requires manually standardizing the format of data, units, and time point definitions, which lends itself to errors and can often be tedious (15). We sought to investigate a more streamlined approach, and thus performed this study using a novel semi-automated software platform (AutoLit, Nested Knowledge, Saint Paul, MN) that allows for the rapid identification, collation, synthesis, and analysis of data. Assessing the performance of this software platform was a secondary aim of this study.

METHODS

Nested Knowledge Systemic Review Platform

A PRISMA and MOOSE-compliant systematic review of the literature was undertaken on the PubMed database through the Nested Knowledge (NK) platform (**Supplementary Video 1**) Prior to study selection and screening, two authors (G.A. and J.J.H.) established the framework for the study by writing up a protocol for the systematic review that included acceptable study designs, intervention arms, patient characteristics to collect as baseline and outcome variables, as depicted in the NK sunburst diagram in **Figure 1**. These authors, also non-affiliates of NK, were also responsible for evaluating the functionality and efficiency of the NK platform as a secondary aim of this study.

Literature Search and Study Selection

Initial search was completed on the PubMed database using the Application Program Interface (API) in the AutoLit platform; all study metadata and abstracts from the search results were also obtained *via* API. We included randomized control trials (RCTs) that reported a comparison of MT vs. MT+tPA in patients with anterior circulation AIS, and we captured these using the search strings:

1) "intravenous thrombolysis" AND (Trevo OR Solitaire)
2) ["without intravenous" AND (thrombectomy OR endovascular)] AND (clinical trial [Publication Type]).

Studies identified in the initial literature search were screened automatically by the AutoLit platform for two pre-configured automated exclusion criteria: (1) Published before 01/01/2010 and (2) Not published in English. Two independent raters (G.A. and K.H.) then used the AutoLit dual screening module to vet the remaining studies and included studies if they met the inclusion criteria: (1) RCTs of IV-tPA-eligible patients with treatment arms of patients treated with MT alone and patients treated with MT+tPA and (2) reported 90-day modified Rankin Scale score (mRS) 0–2, Expanded Thrombolysis in Cerebral Infarction (eTICI) $\geq$ 2b rate, 90-day mortality, distal emboli, and symptomatic intracranial hemorrhage (sICH) among the outcome variables. Studies that were not RCT by design or had IV-tPA-ineligible patients included in patient groups were excluded. Other manual exclusion criteria included:

- Includes pediatric patients
- Does not report an MT arm
- Does not report patient outcomes
- MERCI thrombectomy device used in MT arm.

After manual screening was completed, all disagreements between the two independent raters were independently adjudicated by another rater (N.H.). Detailed results of our study search, screening, and data extraction process are hosted on the Nested Knowledge website (https://nested-knowledge.com/).

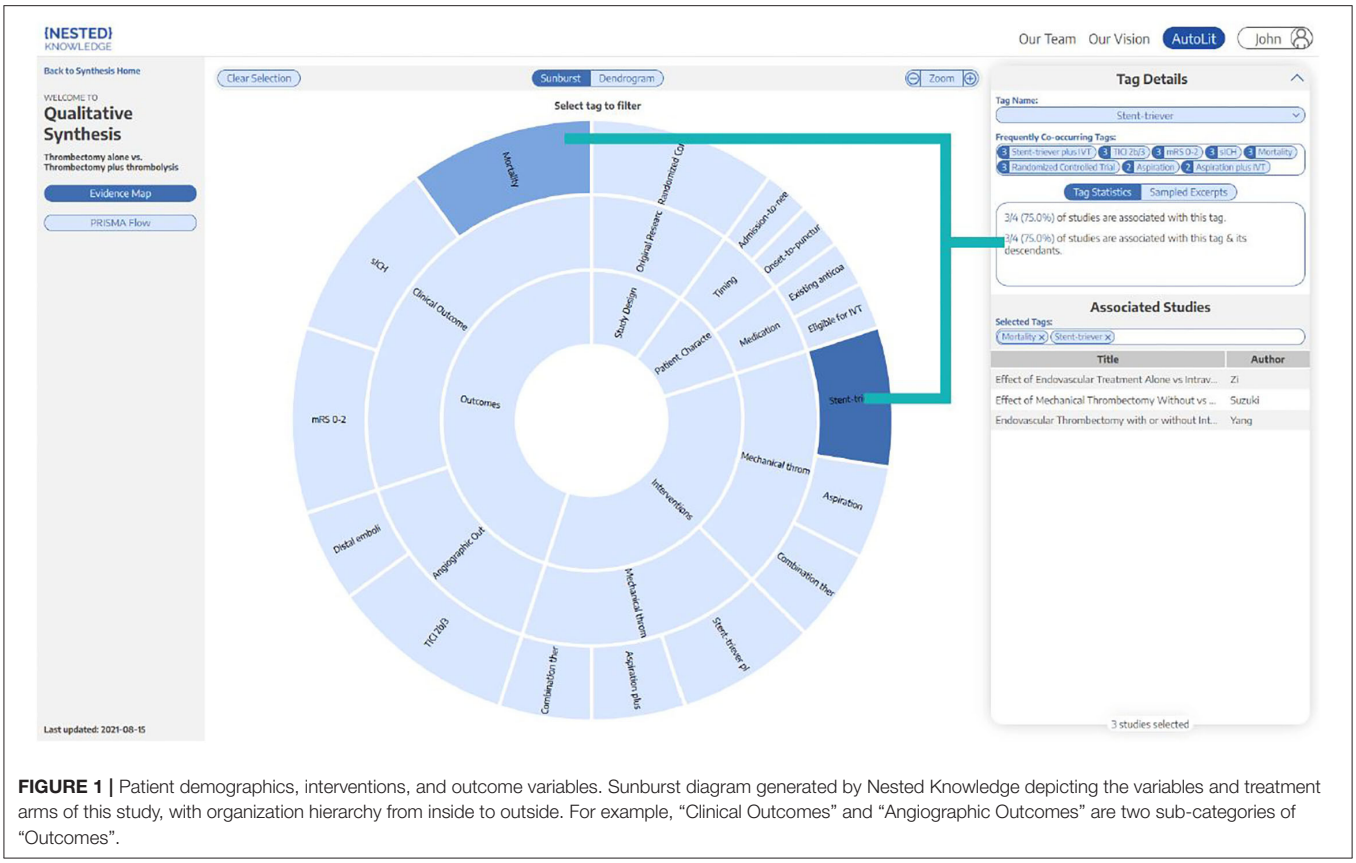

FIGURE 1 | Patient demographics, interventions, and outcome variables. Sunburst diagram generated by Nested Knowledge depicting the variables and treatment arms of this study, with organization hierarchy from inside to outside. For example, "Clinical Outcomes" and "Angiographic Outcomes" are two sub-categories of "Outcomes".

Extraction of Patient Characteristics and Outcome Variables

Extraction of the data from each selected study was completed by two authors (G.A. and K.H.) and confirmed for accuracy independently by two other authors (H.K. and D.M.H.). Patient characteristics collected included: age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score, onset-to-needle time, and onset-to-puncture time. Our primary outcome was rate of successful reperfusion, defined as eTICI $\geq$ 2b after MT. Secondary outcomes included functional independence (mRS score 0–2 at 90 days), 90-day mortality, sICH, and rate of distal emboli to new territories.

Risk of Bias Assessment

The risk of bias and levels of evidence of each study was scored using the Scottish Intercollegiate Guidelines Network (SIGN) checklists for controlled clinical trials and cohort studies (16). Within their separate checklists, non-randomized controlled trials were rated no higher than 1+. The risk of bias assessment was completed independently by 2 authors (H.K. and D.M.H.). Any disagreements were discussed and resolved by a third author (J.M.P.).

Statistical Analysis

Data was extracted within the Nested Knowledge interface, exported as a.csv file, and imported to RStudio (Version 1.3.959, RStudio, PBC, Boston, MA) running on R-4.0.2 for analysis. The "meta" (Version 4.18-0) and "metaphor" (Version 2.4-0) packages were used to perform meta-analyses (17, 18).

Effect sizes from each study were computed as logarithmically transformed odds ratios (ORs) with random-effects, Mantel-Haenszel weighting. Logarithmic transformations were used to correct for skewed marginal distributions and to shrink the influence of high leverage outliers. To aid in interpretation, logarithmically transformed pooled effect sizes were back-transformed to their original scale. The between-study variance component of random-effects models were estimated using restricted effects maximum likelihood (REML) with 95% CIs computed using the Q-profile method (19). Due to the small number of studies/patients included in the meta-analysis, 95% CIs around pooled effect sizes were calculated using Hartung-Knapp adjustment to provide a more conservative estimate of the true intervention effect and to reduce the risk of false positives (20). While significance tests of the pooled effect usually assume a standard normal distribution (typically using Wald-type tests), the Hartung-Knapp method is based on a *t*-distribution which typically produces larger CIs around the pooled effect size. 95% prediction intervals (PIs) around the pooled effect sizes were also

calculated for each outcome measure using methods described by Higgins et al. (21).

RESULTS

Nested Knowledge Platform Performance

We found the Nested Knowledge AutoLit platform to be expeditious, streamlined, and effective at sourcing the correct literature for our research question. No training was required to use this platform. Once appropriate search strings were identified, the process of running the search algorithm and excluding among 226 studies based on automated, pre-defined exclusion criteria took <1 min. The dual screening process for the remaining 185 studies took ∼2 h in total per screener, with most of the time being allocated to verifying studies that were not clearly excludable by the abstract. Finally, data extraction for the four studies eventually included took <30 min. Most notably, the AutoLit platform maintained a full audit record of our search, screening criteria and activities, organized our interventions and data of interest, and provided an extraction environment with straightforward export for analysis (**Supplementary Figure 1**).

Literature Search Results

Our initial search identified 221 studies, with 8 additional records identified through expert recommendation. After removing duplicates, a total of 226 articles were screened for inclusion. A total of 222 articles were excluded after screening based on title and abstract. A total of 3 full-text articles (DIRECT-MT, DEVT, SKIP) and 1 oral abstract presentation (MR CLEAN NO IV) were assessed for eligibility and included in the final quantitative meta-analysis (**Supplementary Figure 2**) (11–14). Among this study population, 817 patients were treated with MT alone, and 816 patients were treated with MT+tPA. The list of studies and patient characteristics are presented in **Table 1**, and study-specific patient outcomes are provided in **Table 2**.

Risk of Bias and Qualitative Appraisal of Evidence

According to the SIGN checklists for controlled clinical trials, our risk of bias assessment identified 3 studies of high quality and 1 study of low quality. Of note, the MR CLEAN NO IV study was primarily considered low quality due to limited available information and the absence of peer-reviewed results at this time (12). The results of our quality appraisal are summarized in **Supplementary Table I**. Outcome reporting was fairly homogenous among the included studies, with all studies reporting eTICI ≥2b, sICH, 90-day mRS 0–2, and 90-day mortality. However, only two of the included studies reported rates of distal embolization to a new vascular territory. All included studies analyzed 90-day mRS as the primary endpoint of interest, with 2 studies dichotomizing mRS score as 0–2 (good clinical outcome) vs. 3–6 (poor clinical outcome) and the remaining 2 studies analyzing mRS score on its full ordinal scale. Qualitatively, two RCTs failed to demonstrate non-inferiority for MT alone compared to MT+tPA, whereas the other two RCTs suggested non-inferiority of MT alone compared to MT+tPA. Of note, none of the included studies demonstrated inferiority or superiority of either MT alone or MT+tPA.

Successful Recanalization (eTICI ≥2b)

All included studies reported successful recanalization defined by the eTICI ≥2b criteria and all results were adjudicated by an independent core laboratory blinded to treatment groups. The overall rate of eTICI ≥2b for the MT+tPA group was 85.6% (95% CI: 82.0–88.6%) vs. 83.0% (95% CI: 76.9–87.8%) in the MT alone group. The odds of achieving eTICI ≥2b were significantly higher in the MT+tPA group compared to the MT alone group (OR = 1.34 [95% CI: 1.10; 1.63]), $p = 0.018$; **Figure 2**). The estimated between-study heterogeneity unrelated to sampling error was low ($I^2 = 0.0\%$ [95% CI: 0.0–27.3%]).

Functional Independence (mRS 0–2 at 90 Days)

The overall mRS 0–2 rate for the MT+tPA group was 47.4% (95% CI: 38.9–56.2%), and for the MT alone group was 49.2% (95% CI: 39.4–59.1%). There was no statistically significant difference in the odds of mRS 0–2 at 90 days between the MT+tPA group and the MT alone group (OR = 0.98 [95% CI: 0.77; 1.24], $p = 0.787$; **Figure 3**). The estimated between-study heterogeneity unrelated to sampling error ranged from low to high ($I^2 = 0.0\%$ [95% CI: 0.0–72.4%]).

Mortality at 90 Days

The overall mortality rate at 90 days for the MT+tPA group was 16.3% (95% CI: 13.2–19.9%), and for the MT alone group was 16.5% (95% CI: 12.3–21.8%). There was no statistically significant difference in the odds of mortality at 90 days between the MT+tPA group and the MT alone group (OR = 0.94 [95% CI: 0.67; 1.32], $p = 0.582$; **Figure 4**). The estimated between-study heterogeneity unrelated to sampling error ranged from low to high ($I^2 = 0.0\%$ [95% CI: 0.0–76.5%]).

Symptomatic Intracranial Hemorrhage (SICH)

Three studies reported sICH based on the Heidelberg Bleeding Classification criteria and one study reported sICH based on the SIT-MOST and NINDS criteria (22–24). Since the SKIP Randomized Clinical Trial reported sICH as both the SIT-MOST and NINDS criteria, we collected data based on the SIT-MOST criteria which more closely resembles the criteria defined by the Heidelberg Bleeding Classification, which was reported in the rest of the included studies. The overall rate of sICH for the MT+tPA group was 6.2% (95% CI: 4.7–8.1%), and for the MT alone group was 5.3% (95% CI: 4.0–7.1%). There was no statistically significant difference in the odds of sICH between the MT+tPA group and the MT alone group (OR = 1.17 [95% CI: 0.80; 1.72], $p = 0.275$; **Figure 5**). The estimated between-study heterogeneity unrelated to sampling error ranged from low to moderate ($I^2 = 0.0\%$ [95% CI: 0.0–50.6%]).

Distal Emboli to a New Territory Post-MT

The overall rate of distal emboli for the MT+tPA group was 12.9% (95% CI: 6.7–23.5%), and for the MT alone group was 13.1% (95% CI: 8.3–20.8%). There was no statistically significant difference in the odds of distal emboli between the MT+tPA group and the MT alone group (OR = 0.94 [95% CI: 0.25; 3.60],

TABLE 1 | Patient characteristics of the four studies included in the meta-analysis.

	Yang et al. (DIRECT-MT)		Zi et al. (DEVT)		Sukuzi et al. (SKIP)		Treurniet et al. (MR CLEAN NO IV)	
Treatment Arm	MT	MT±tPA	MT	MT±tPA	MT	MT±tPA	MT	MT±tPA
Number of patients	327	329	116	118	101	103	273	266
Age, years (median)	69	69	70	70	74	76	N/A	N/A
Sex	189 M, 138 F	181 M, 148 F	66 M, 50 F	66 M, 52 F	56 M, 45 F	72 M, 31 F	N/A	N/A
Baseline NIHSS (median)	17	17	16	16	19	17	N/A	N/A

TABLE 2 | Angiographic, functional, and safety outcomes of patients in the four studies included in the meta-analysis.

	Yang et al. (DIRECT-MT)		Zi et al. (DEVT)		Sukuzi et al. (SKIP)		Treurniet et al. (MR CLEAN NO IV)	
Treatment Arm	MT	MT±tPA	MT	MT±tPA	MT	MT±tPA	MT	MT±tPA
eTICI ≥ 2b	243/306 (79.4%)	267/316 (84.5%)	100/116 (86.2%)	102/118 (86.4%)	91/101 (90.0%)	96/103 (93.2%)	214/273 (78.4%)	221/266 (83.1%)
mRS 0–2	119/327 (36.4%)	121/329 (36.8%)	63/116 (54.3%)	55/118 (46.6%)	60/101 (59.4%)	59/103 (57.3%)	134/273 (49.1%)	136/266 (51.1%)
Mortality	58/327 (17.7%)	62/329 (18.8%)	20/116 (17.2%)	21/118 (17.8%	8/101 (7.9%)	9/103 (8.7%)	56/273 (20.5%)	42/266 (15.8%)
sICH	14/327 (4.3%)	16/329 (4.9%)	7/115 (6.1%)	8/117 (6.8%)	6/101 (5.9%)	8/103 (7.8%)	16/273 (5.9%)	14/266 (5.3%)
Distal Emboli	35/327 (10.7%)	31/329 (9.4%)	19/113 (16.8%)	21/117 (17.9%)	N/A	N/A	N/A	N/A

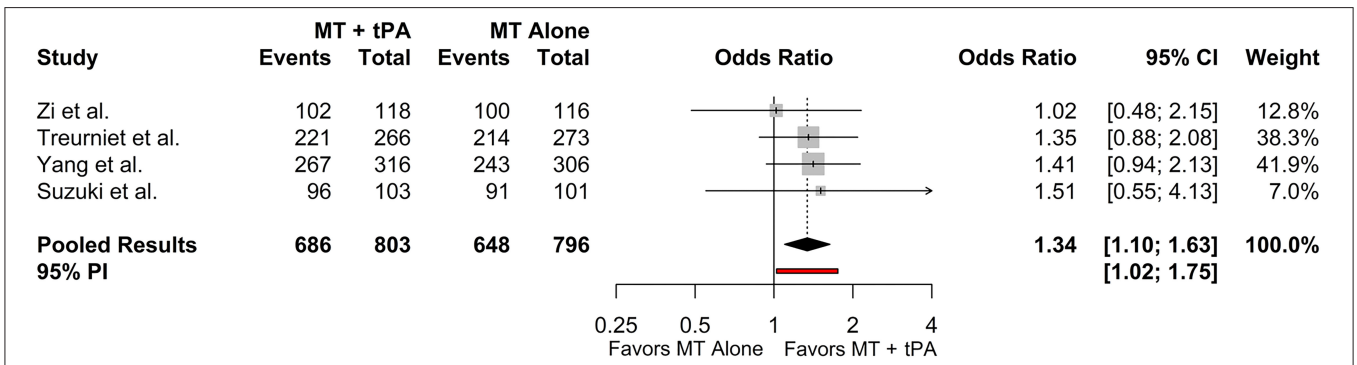

FIGURE 2 | Forest plot of comparisons of eTICI ≥2b. Pooled results were computed *via* the Mantel-Haenszel method, using restricted effects maximum likelihood for estimation of the between-study variance component and Hartung-Knapp adjustment to calculate a 95% confidence interval (CI) around the pooled effect size. A 95% prediction interval (PI) for the pooled results are also displayed as a red bar.

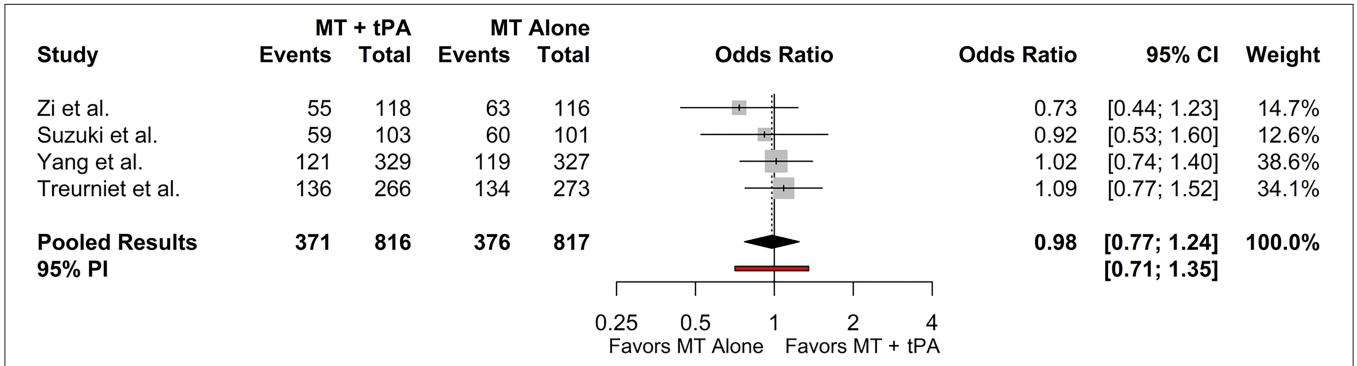

FIGURE 3 | Forest plot of comparisons of mRS 0–2 at 90 days. Pooled results were computed *via* the Mantel-Haenszel method, using restricted effects maximum likelihood for estimation of the between-study variance component and Hartung-Knapp adjustment to calculate a 95% confidence interval (CI) around the pooled effect size. A 95% prediction interval (PI) for the pooled results are also displayed as a red bar.

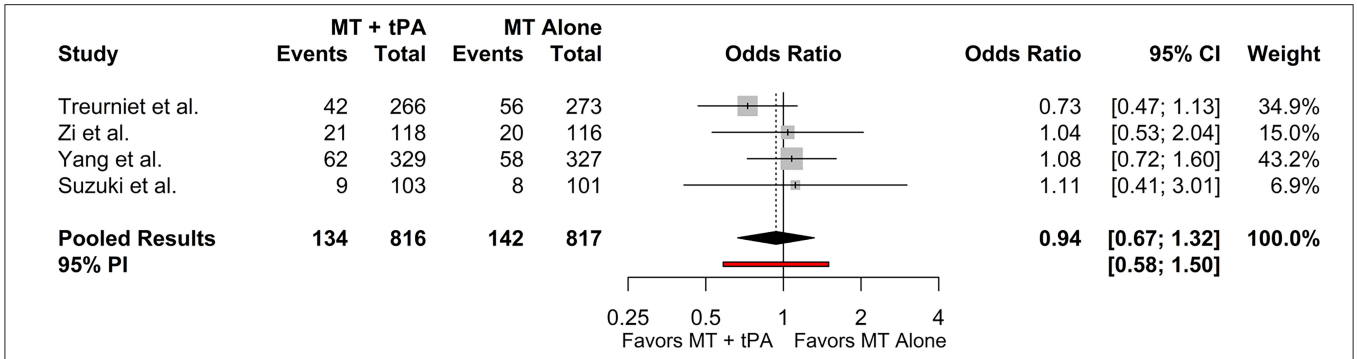

FIGURE 4 | Forest plot of comparisons of mortality at 90 days. Pooled results were computed *via* the Mantel-Haenszel method, using restricted effects maximum likelihood for estimation of the between-study variance component and Hartung-Knapp adjustment to calculate a 95% confidence interval (CI) around the pooled effect size. A 95% prediction interval (PI) for the pooled results are also displayed as a red bar.

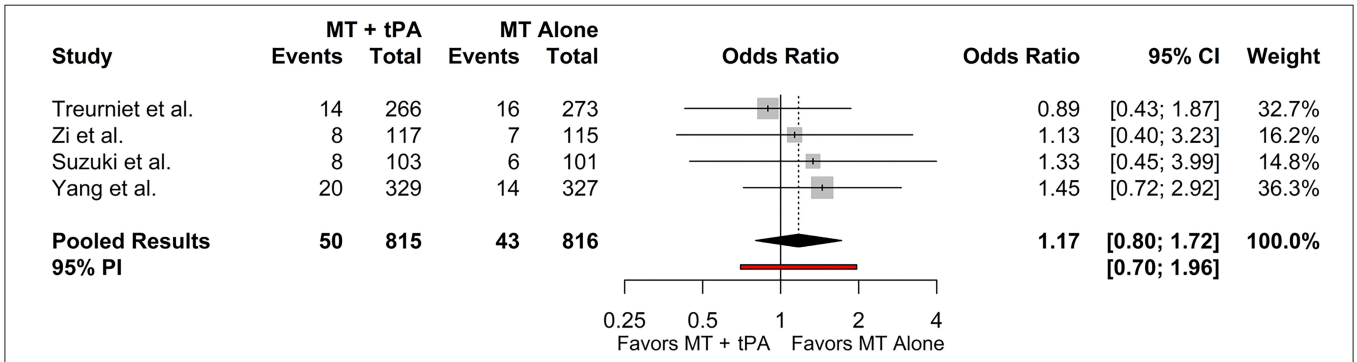

FIGURE 5 | Forest plot of comparisons of sICH. Pooled results were computed *via* the Mantel-Haenszel method, using restricted effects maximum likelihood for estimation of the between-study variance component and Hartung-Knapp adjustment to calculate a 95% confidence interval (CI) around the pooled effect size. A 95% prediction interval (PI) for the pooled results are also displayed as a red bar.

$p = 0.659$; **Figure 6**). While the point estimate of the I^2 statistic indicates low heterogeneity ($I^2 = 0.0\%$), the true heterogeneity unrelated to sampling error is likely underestimated and this result should be interpreted with caution since only two studies were included in the analysis and a 95% CI could not be produced.

DISCUSSION

Summary

In our meta-analysis of RCTs comparing outcomes of AIS patients treated with MT+tPA vs. MT alone, we found that patients treated with MT+tPA have higher odds of successful recanalization (eTICI ≥ 2b) (11–14) However, there were no detectable differences in rates of functional independence, 90-day mortality, sICH, or distal emboli between the MT+tPA and the MT alone groups. Overall, the results of this meta-analysis suggest that while angiographic outcomes after MT are superior with associated IV-tPA administration, it remains uncertain whether IV-tPA leads to improved functional outcomes or reduced complications.

Takeaways: MT+IV-TPA vs. MT Alone

MT has transformed AIS treatment and results in improved clinical outcomes compared to medical therapy alone (2–9). Adequate revascularization of the cerebral circulation (eTICI >2b) after MT is important for the preservation of brain tissue, and the degree of revascularization has been correlated with improved clinical outcomes (25, 26). Whether adjunctive treatment with IV-tPA leads to higher revascularization rates and improved functional outcomes after MT remains uncertain. IV-tPA inherently increases the risk of complications such as intracranial hemorrhage, systemic hemorrhage, and angioedema, and the invasive nature of MT may further compound these risks (27). Combined treatment may be justified if patients have significantly better angiographic and functional outcomes, but reported RCTs (DIRECT-MT, DEVT, SKIP, and MR CLEAN-NO IV) have failed to identify significant differences between MT alone and MT+tPA treatment (11–14).

Our findings in this meta-analysis are consistent with a recent meta-analysis on this topic (28). However, of note, we replicated the findings of a manual study with a semi-automated approach through Nested Knowledge. We found that combined MT+tPA treatment increases the odds of achieving eTICI ≥

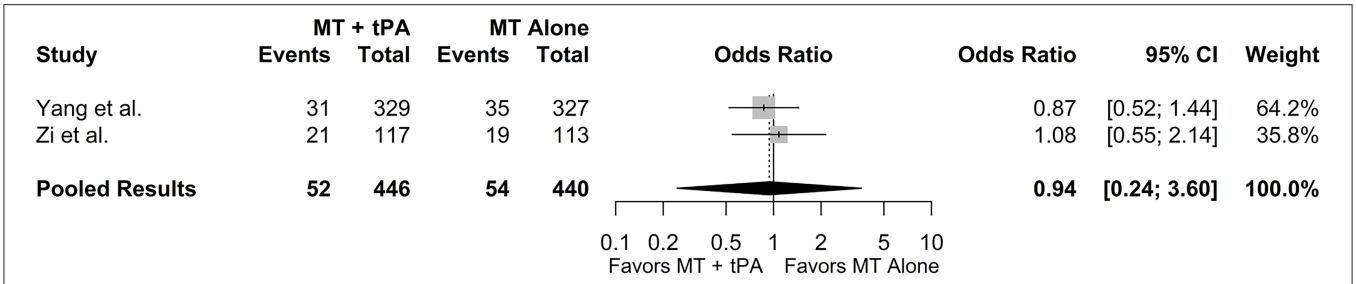

FIGURE 6 | Forest plot of comparisons of distal embolization to new territory. Pooled results were computed *via* the Mantel-Haenszel method, using restricted effects maximum likelihood for estimation of the between-study variance component and Hartung-Knapp adjustment to calculate a 95% confidence interval (CI) around the pooled effect size.

2b reperfusion by a factor of 1.34. While superior reperfusion is expected to result in superior clinical outcomes, we did not detect any difference in functional outcomes, mortality, or sICH between MT and MT+tPA groups. The reasons for the discrepancy between angiographic and functional outcomes requires further study and is likely multifactorial (29–32). We did find a consistent trend toward favorable outcomes in each of these variables in MT+tPA patients, which suggests that a continued benefit for intravenous thrombolysis exists despite the strong effectiveness of MT. We also note that our analysis and future analyses would be bolstered by a more uniform reporting of near perfect (eTICI 2c) and perfect (TICI 3) revascularization, which are more strongly correlated with favorable outcomes (25, 26). It is possible that future RCTs and meta-analyses with larger patient numbers may clarify some of these findings.

Nested Knowledge

In this study, we were able to test the process and functionality of the Nested Knowledge platform in performing efficient and focused systematic reviews. After a research protocol was written, search term selection for the automated scan of PubMed was intuitive and expeditious. Easy access to our inclusion and exclusion criteria, and a database of the reasons why each excluded study was removed was essential in preventing redundant work or a misguided review of literature. For each included study, the complete manuscript and recorded outcome variables were juxtaposed under the same function, which reduced the likelihood of error and served as a safety net to determine whether an included study truly fit our protocol. Finally, prior to formal statistical analyses, we utilized the Nested Knowledge automated data analysis feature to visually summarize potentially significant results that would warrant additional statistical analyses. We subjectively found the platform to be a streamlined, preferable alternative to standard practice in pooled research, and we appreciated the one-stop access to project details that it allowed.

Limitations

The major limitation of this meta-analysis is the limited number of studies and the heterogeneity of techniques and devices classified as MT within data groups. Though this meta-analysis is strictly comprised of RCTs with well-balanced baseline patient characteristics, access to patient-level data would allow for a more robust analysis with rigorous control over differences in thrombectomy techniques and various other patient and study characteristics. This approach would also further clarify our research question. Furthermore, though we included four RCTs in this analysis, our study was relatively underpowered and could not detect small but clinically important differences in rates of our outcome variables between groups.

Another limitation is that the MR CLEAN-NO IV study results have not yet been published as a full-text, peer-reviewed article; as such, this study was classified as a low quality RCT associated with a relatively high risk of bias. Quality of data reporting also varied across studies, with only two studies reporting rates of distal embolization to new territory. Another minor limitation is that definitions of sICH varied, with 3 studies reporting sICH based on the Heidelberg Bleeding Classification and 1 study reporting sICH based on the SIT-MOST and NINDS criteria. Since the SKIP Randomized Clinical Trial reported sICH as both the SIT-MOST and NINDS criteria, we collected data based on the SIT-MOST criteria which more closely resembles the criteria defined by the Heidelberg Bleeding Classification which was reported in the rest of the included studies.

A final limitation is that the evaluation of the Nested Knowledge platform was subject to bias by the very nature of several authors being affiliated with the organization. However, we sought to mitigate this bias by having two authors (G.A. and J.J.H) who were not affiliated with NK evaluate the platform independently and report on their subjective experience.

CONCLUSIONS

In this meta-analysis of the DIRECT-MT, DEVT, SKIP, and MR CLEAN-NO IV studies, we found superior revascularization after MT when IV-tPA was administered. However, these higher rates of revascularization in MT+tPA patients did not result in increased rates of functional independence or reduced complications compared to MT treatment alone. We also found the novel Nested Knowledge semi-automated systematic review platform to be an excellent and rapid tool for identifying and consolidating these studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All contributing authors of this work have: 1. Made a substantial contribution to the concept and design, acquisition of data or analysis and interpretation of data. 2. Drafted the article or revised it critically for important intellectual content. 3. Approved the version to be published.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.759759/full#supplementary-material

Supplementary Figure 1 | Step-by-step schematic of the systematic review process in Nested Knowledge. The first step is conceiving a study protocol and a nest with arms, baseline variables, and outcomes to guide the rest of the process. This is followed by an semi-automated literature search based on search strings, screening of studies for inclusion, tagging of included studies with relevant labels from the nest, extraction of data, and cursory review of the automated data synthesis prior to a full analysis. Each of these steps is sequentially included in this figure.

Supplementary Figure 2 | PRISMA diagram of search records and included studies automatically generated by the AutoLit platform.

Supplementary Table 1 | Risk of bias assessment per the Scottish Intercollegiate Guideines Network for the four studies included in this meta-analysis.

Supplementary Video 1 | Video walkthrough of the steps in the systematic review process on the Nested Knowledge living platform and other functionality features.

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Workflow Intervals and Outcomes of Endovascular Treatment for Acute Large-Vessel Occlusion During On-Vs. Off-hours in China: The ANGEL-ACT Registry

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Background: There may be a delay in or a poor outcome of endovascular treatment (EVT) among acute ischemic stroke (AIS) patients with large-vessel occlusion (LVO) during off-hours. By using a prospective, nationwide registry, we compared the workflow intervals and radiological/clinical outcomes between patients with acute LVO treated with EVT presenting during off- and on-hours.

Methods: We analyzed prospectively collected Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke (ANGEL-ACT) data. Patients presenting during off-hours were defined as those presenting to the emergency department from Monday to Friday between 17:30 and 08:00, on weekends (from 17:30 on Friday to 08:00 on Monday), and on national holidays. We used logistic regression models with adjustment for potential confounders to determine independent associations between the time of presentation and outcomes.

Results: Among 1,788 patients, 1,079 (60.3%) presented during off-hours. The median onset-to-door time and onset-to-reperfusion time were significantly longer during off-hours than during on-hours (165 vs. 125 min, $P = 0.002$ and 410 vs. 392 min, $P = 0.027$). The rates of successful reperfusion and symptomatic intracranial hemorrhage were similar in both groups. The adjusted odds ratio (OR) for the 90-day modified Rankin Scale score was 0.892 [95% confidence interval (CI), 0.748–1.064]. The adjusted OR for the occurrence of functional independence was 0.892 (95% CI, 0.724–1.098), and the adjusted OR for mortality was 1.214 (95% CI, 0.919–1.603).

Conclusions: Off-hours presentation in the nationwide real-world registry was associated with a delay in the visit and reperfusion time of EVT in patients with AIS.

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However, this delay was not associated with worse functional outcomes or higher mortality rates.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03370939.

Keywords: endovascular treatment, on-hours, off-hours, acute ischemic stroke, large vessel occlusion

INTRODUCTION

Stroke is the leading cause of death and disability in China (1). Ischemic stroke accounts for 65% (2) of stroke patients in China, of whom 35–40% have large-vessel occlusion (LVO) (1). LVO results in a large ischemic area and can cause severe brain damage (3, 4), leading to high mortality and disability rates (5–7). As a landmark in the treatment of acute ischemic stroke (AIS) with proximal intracranial LVO (8–12), endovascular treatment (EVT) has been widely used in real-world clinical practice. However, stroke causes 2 million neurons to undergo apoptosis every minute, and the brain ages 3.6 years per hour (13). Therefore, performing EVT as soon as possible in patients with LVO is the key to improving patient prognosis (14, 15).

Approximately half of patients present during so-called off-hours, i.e., evenings, nights, weekends, and holidays, and EVT needs to be performed jointly by emergency department staff, digital subtraction angiography (DSA) room nurses, technicians, anesthesiologists, and surgeons. Therefore, off-hour presentation may be associated with a delay in the start of EVT. The MR CLEAN trial found that presenting off-hours was associated with a slight delay of EVT but that this treatment delay did not translate into worse functional outcomes or an increased rate of complications (16). Data on off-hours delays in workflow intervals have shown delays in different workflow intervals and related performance, but these data are mostly based on single-center studies and are difficult to interpret given variations in acute stroke care (17–20). However, there have been no multicenter studies on the association of off-hour presentation and EVT workflow intervals in Chinese patients with LVO.

The Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke (ANGEL-ACT) registry was established to evaluate the utilization and subsequent outcomes of AIS patients who received EVT and has confirmed that favorable outcomes of EVT can be achieved in clinical practice in China (21). In this study, we analyzed prospectively collected ANGEL-ACT data to observe whether the workflow intervals and radiological/clinical outcomes were different between patients with acute LVO treated with EVT who presented during on-vs. off-hours.

METHODS

Study Participants

Data were derived from the ANGEL-ACT registry. ANGEL-ACT was a nationwide, prospective, observational study of 1,793 consecutive adult patients with acute LVO treated with EVT at 111 hospitals from 26 provinces in China between November 2017 and March 2019 (https://www.clinicaltrials.gov; unique identifier: NCT03370939). Detailed information about the ANGEL-ACT registry can be found in a previously published article (21). Ethics approval was granted by the ethics committees of Beijing Tiantan Hospital and all participating centers. Subjects or their representatives provided written informed consent.

For the present study, patients who adhered to the following criteria were included: (1) age $\geq$18 years; (2) diagnosis of AIS on computed tomography (CT) angiography confirming intracranial LVO; and (3) initiation of any type of EVT, including mechanical thrombectomy, intra-arterial thrombolysis, stenting and angioplasty. Patients were divided into the on-hours group and the off-hours group based on their presentation time.

Data Collection and Outcome Measures

Off-hours presentation was defined as presentation to the emergency department (participating centers) from Monday to Friday between 17:30 and 08:00, on weekends (from 17:30 on Friday to 08:00 on Monday), and on national holidays.

All variables, including demographic data, medical history, vital signs, laboratory and neurovascular imaging results, workflow intervals, and clinical outcomes, were prospectively collected.

The workflow intervals included the door-to-puncture time, onset-to-puncture time, onset-to-door time, door-to-imaging time, onset-to-needle time, puncture-to-reperfusion time and onset-to-reperfusion time. The radiological and clinical outcomes included the 90-day modified Rankin Scale (mRS) score as an ordinal variable, functional independence (defined as a 90-day mRS score from 0 to 2), mortality within 90 days, successful reperfusion [defined as the modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b or 3 (22)], and symptomatic intracranial hemorrhage (sICH) within 24 h according to the Heidelberg Bleeding Classification (23).

Statistical Analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC). All data are described as the median [interquartile range (IQR)] for continuous/ordinal variables and number (percentage) for categorical variables. The Wilcoxon test was used for continuous/ordinal variables, and Fisher's exact test or the chi-square test was used for categorical variables. A P-value of <0.05 was considered statistically significant. Multivariable logistic regression models were used to determine the independent associations between the time of presentation (on-vs. off-hours) and radiological/clinical outcomes with adjustment for age, pretreatment with intravenous thrombolysis

(IVT), baseline NIHSS score, occlusion site, prestroke mRS score, and onset-to-door time.

RESULTS

Baseline Characteristics

Among the 1,793 subjects included in the ANGEL-ACT registry, 5 were excluded because the admission time was missing; thus, 1,788 patients were eligible for analyses. In total, 1,079 patients (60.3%) presented to the emergency department during off-hours, and 709 (39.7%) presented during on-hours. The baseline characteristics were similar in both groups except for the proportion of transferred patients. More patients in the off-hours group than in the on-hours group were transferred from primary stroke centers (36.98 vs. 32.02%, $P = 0.033$) (**Table 1**).

Workflow Intervals

The median onset-to-door time during off-hours presentation was 165 (IQR: 70–295) minutes, which was significantly longer than that during on-hours presentation [125 (IQR: 60–260) min, $P = 0.002$]. The median onset-to-reperfusion time was also significantly longer during off-hours [410 (IQR: 310–561) min vs. 392 (IQR: 285–546) min, $P = 0.027$]. The door-to-puncture time, onset-to-puncture time, door-to-imaging time, onset-to-needle time and puncture-to-reperfusion time were similar between the two groups (**Table 2**).

Radiological and Clinical Outcomes

The rates of successful reperfusion and sICH were similar in both groups. The adjusted OR for the 90-day mRS score was 0.892 [95% confidence interval (CI), 0.748–1.064] (**Table 3**; **Figure 1**). The adjusted OR for the occurrence of functional independence was 0.892 (95% CI, 0.724–1.098), and the adjusted OR for mortality was 1.214 (95% CI, 0.919–1.603) (**Table 3**).

DISCUSSION

This large-scale multicenter study reported the relationship of on- and off-hour presentation with workflow intervals and radiological/clinical outcomes and included over 1,700 patients treated at 111 different comprehensive stroke centers in China. This study showed that the visit and reperfusion times of EVT were 40 and 18 min later, respectively, in AIS patients presenting off-hours than in those presenting on-hours. There was no difference in the rates of successful reperfusion, sICH, or functional independence at 90 days, the mRS score distribution or mortality.

Similar to previous multicenter studies (16, 24–27), this study did not reveal a difference in the prognosis or rate of complications between the two groups. Benali et al. observed a significantly increased rate of good functional outcomes among inpatients admitted at night (51 vs. 35%, $P = 0.05$) (28), but another study found a higher mortality rate among patients admitted at night for EVT (29), which may be due to heterogeneity in stroke center processes and sample sizes. Although this multicenter study did not observe a difference in the effect of on-vs. off-hours presentation on the prognosis, exploring OR trends and differences in the workflow intervals between the two groups may help to improve the efficiency of EVT implementation.

Off-hours patients have a longer onset-to-door time. The 40-min gap suggests more delays before the hospitalization of off-hours patients. Experiencing a stroke after waking up at night may be an important contributing factor. Another factor may be transfers, as a higher proportion of off-hours patients required transfer. We hypothesize that some hospitals may not have the capability to provide EVT over 24 h, so patients who are first diagnosed at these hospitals during off-hours may need to be transferred to a suitable stroke center. Previous research has also described this phenomenon (16). Notably, in the treatment of patients requiring EVT, interhospital transfer will increase the onset-to-first door time (30–32). Therefore, when establishing the EVT process, the delay caused by referral should be recognized, special attention should be given to the impact of off-hours referrals, and effective public information campaigns should be used to make patients aware of hospitals with 24-h EVT capabilities in advance to ensure that patients can be delivered directly after stroke onset.

The overall door-to-puncture time in this study was 124 min, which is considerably greater than the 85 min reported in a prospective, randomized, controlled study conducted in China (33) and exceeds the requirement of 90 min for advanced Chinese stroke centers, suggesting that the EVT process needs to be further optimized in the real world. Given that door-to-imaging and door-to-needle times were relatively short, a better understanding of the reasons for the long door-to-puncture times would be helpful. Possible factors include but are not limited to the frequency of using advanced imaging modalities [i.e., computed tomography (CT) perfusion or magnetic resonance imaging (MRI)], some centers waiting for IVT finished prior to taking patients for EVT, and the proportion of patients who presented in the late window (i.e., >6 h from onset).

Our research showed that the median onset-to-reperfusion time in off-hours patients was 410 min, which is 18 min longer than that in on-hours patients. This finding indicates a certain delay in the EVT process for patients presenting off-hours. However, the time difference of 40 min in the onset to door times between the off-hours vs. on-hours patients was reduced to only 18 min of a difference in the onset to reperfusion times, suggesting more efficient in-hospital workflow during off-hours. We hypothesize that the possible reasons are as follows: (1) There were fewer patients in general during off-hours, a high proportion of idle machines and a reduced waiting time for patients. (2) More patients were interhospital transfers, and these patients may have received some examinations and learned about relevant treatments, reducing the time for communication after admission.

We found that the reperfusion rate in the off-hours group was similar to that in the on-hours group, whereas the puncture-to-reperfusion time in the off-hours group was 8 min longer than that in the on-hours group. We hypothesize that such a time difference may be attributed to the availability of the off-hours intervention team. Based on experience at our center, for patients who require general intravenous anesthesia, the

TABLE 1 | Baseline Characteristics (median, IQR/*n*, %).

Items	On-hours (*n* = 709)	Off-hours (*n* = 1,079)	*P*
Age, y	65 (55–73)	66 (56–73)	0.496
Men	469 (66.2)	705 (65.3)	0.760
Baseline NIHSS (*n* = 1,780)	16 (12–22)	16 (12–21)	0.320
PremRS (*n* = 1,787)	0 (0–0)	0 (0–0)	0.539
Baseline ASPECTS (*n* = 1,773)	9 (7–10)	9 (7–10)	0.414
SBP (mmHg)	145 (130–160)	145 (131–162)	0.882
Medical history			
Hypertension	411 (58.0)	616 (57.1)	0.732
Diabetes	118 (16.6)	213 (19.7)	0.106
Hyperlipidemia	66 (9.3)	93 (8.6)	0.612
Coronary heart disease	111 (15.7)	162 (15.0)	0.737
Atrial fibrillation	217 (30.6)	344 (31.9)	0.602
Previous stroke	159 (22.4)	238 (22.1)	0.862
Smoking (recent or current)	292 (41.2)	424 (39.3)	0.430
IVT performed	491 (69.3)	774 (71.7)	0.265
Interhospital transfer	227 (32.0)	399 (37.0)	0.033
Anesthesia			0.384
Local anesthesia only	322 (45.4)	455 (42.2)	
General anesthesia	274 (38.7)	447 (41.4)	
Local anesthesia plus sedation	113 (15.9)	177 (16.4)	
Occlusion site			0.912
Internal carotid artery	185 (26.1)	269 (24.9)	
M1	298 (42.0)	471 (43.7)	
Basilar/vertebral artery	149 (21.0)	222 (20.6)	
Other	77 (10.9)	117 (10.8)	
Stroke classification			0.875
Large atherosclerotic stroke	344 (48.5)	533 (49.4)	
Cardiogenic cerebral embolism	229 (32.3)	346 (32.0)	
Other stroke with definite etiology	79 (11.1)	124 (11.5)	
Stroke of unknown etiology	57 (8.0)	76 (7.0)	

Total number is 1,788 unless otherwise indicated. NIHSS indicates National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ASPECTS, Alberta Stroke Program Early CT Score; SBP, systolic pressure; IVT, intravenous therapy; M1, first segment of the middle cerebral artery.

TABLE 2 | Workflow intervals (median, IQR).

Items	On-hours (*n* = 709)	Off-hours (*n* = 1,079)	*P*
Door-to-puncture time (*n* = 1,787)	124.5 (81.5–190)	123 (83–175)	0.164
Onset-to-puncture time (*n* = 1,774)	290 (200–431)	305 (218–445)	0.078
Onset-to-door time (*n* = 1,754)	125 (60–260)	165 (70–295)	0.002
Door-to-imaging time (*n* = 1,523)	15 (0–30)	14 (0–28)	0.345
Onset-to-needle time (*n* = 410)	160 (110–220)	159.5 (119.5–213)	0.843
Puncture-to-reperfusion time (*n* = 1,788)	80 (50–128)	88 (55–130)	0.078
Onset-to-reperfusion time (*n* = 1,774)	392 (285–546)	410 (310–561)	0.027

response of the anesthesiologist during off-hours may not be as good as that during on-hours. Furthermore, more junior doctors may be on duty during off-hours, the interventionalists available off-hours may not be as experienced as those available on-hours, and physician or staff fatigue during late-night procedures may cloud judgment or increase the risk of procedural complications (34, 35). In the future, attention needs to be given to optimizing the configuration of the

TABLE 3 | Clinical outcomes (median, IQR/*n*, %).

Items	On-hours (*n* = 709)	Off-hours (*n* = 1,079)	Unadjusted OR (95% CI)	Unadjusted *p*-value	Adjusted OR (95% CI)	Adjusted *p*-value
mRS at 90 d (*n* = 1,771)	3 (0–5)	3 (0–5)	0.942 (0.794–1.118)	0.493	0.892 (0.748–1.064)	0.204
mRS (0–2) at 90 d (*n* = 1,771)	306 (45.7)	466 (44.7)	0.960 (0.790–1.166)	0.691	0.892 (0.724–1.098)	0.280
Reperfusion rate (TICI 2b–3) (*n* = 1,788)	618 (87.2)	955 (88.5)	1.134 (0.850–1.514)	0.414	1.087 (0.809–1.462)	0.579
Mortality at 90 d (*n* = 1,771)	101 (14.3)	172 (15.9)	1.142 (0.875–1.490)	0.347	1.214 (0.919–1.603)	0.172
sICH within 24 h (*n* = 1,695)	56 (8.4)	74 (7.2)	0.842 (0.586–1.209)	0.352	0.878 (0.606–1.272)	0.492

mRS, modified Rankin Scale; TICI, Thrombolysis in Cerebral Infarction; sICH, symptomatic intracranial hemorrhage.

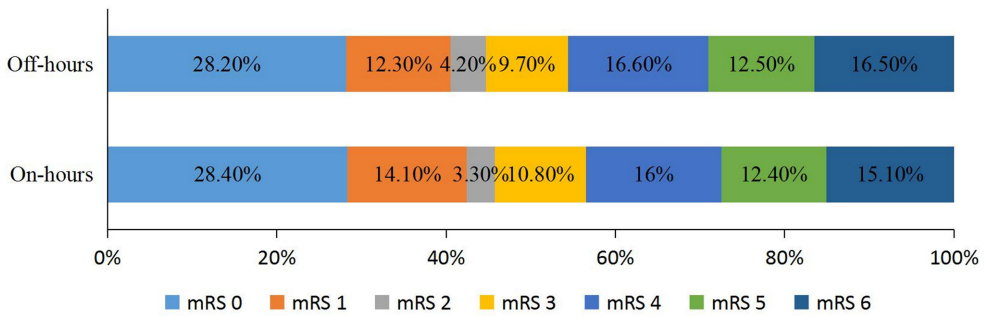

FIGURE 1 | Distribution of modified Rankin Scale (mRS) scores at 90 days.

intervention team during off-hours to reduce the puncture-to-reperfusion time.

The definition of off-hours was set according to statutory holidays and time points. The ANGEL-ACT registry contains data from 111 hospitals in 26 provinces in China (21). These hospitals operated under Beijing time in Dongba District, which is the standard time in China. Therefore, it is possible that when Dongba District has entered the evening, the Eastern Fifth District may still be in daytime hours. Thus, it is necessary to carefully define off-hours. We analyzed the locations of the 111 hospitals and found that 106 (95.4%) hospitals were located in the time zone of the East 8th District and East 7th District. These hospitals accounted for 1716 (95.9%) patients. Thus, the time zone difference for 95.9% patients was <1 h. We conducted a survey on the work and rest time of all hospitals in the group. In total, 98.2% of the hospitals' work hours were 7:30–18:30 with off-hours of 17:00–8:00 in both summer and winter. Therefore, it is reasonable to choose the hours between 08:00 and 17:30 when defining the time points of off-hours.

This study has some limitations. First, 17 of 1,788 patients did not have 3-month follow-up data available from phone interviews; thus, the rates of poor outcomes or serious events may have been underestimated. Second, Saad et al. found that the workflow interval had no effect on EVT in teaching hospitals but did have an effect on EVT in non-teaching hospitals (36). Our study included stroke centers with 24-h EVT capability, and most of these centers were associated with teaching hospitals. Therefore, whether the results can be extended to all stroke centers in China remains unclear. Finally, our definition of off-hours included statutory holidays. However, some hospitals included in the study follow a normal work schedule on statutory holidays, and some hospitals even have a 24-h neurointervention emergency team on duty.

CONCLUSION

In conclusion, according to the nationwide real-world registry, off-hour presentation was associated with a delay in the visit and reperfusion time of EVT in patients with AIS. However, this delay was not associated with worse functional outcomes or greater mortality. In future optimization of the EVT process during off-hours, the onset-to-door time and onset-to-reperfusion time should be key targets for improvement.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article are available upon reasonable request. Requests to access the datasets should be directed to Zhongrong Miao, Department of Interventional Neuroradiology, Beijing Tiantan Hospital, Capital Medical University, email: zhongrongm@163.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of Beijing Tiantan Hospital and all participating centers. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL, ZRM, JLN, YLD, FG, YJ, TTZ, XT, and BXJ conceived and designed the study. All authors assessed and diagnosed the patients. All authors were involved in the acquisition, analysis and interpretation of the data with JLN taking the primary role in statistical analysis. YL, JLN, YLD, FG, YJ, TTZ, XT, and BXJ drafted the manuscript. All authors were involved in revising the manuscript critically and gave final approval of the manuscript.

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SUPPLEMENTARY MATERIAL

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SYSTEMATIC REVIEW
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A Systematic Review and Meta-Analysis Comparing FAST and BEFAST in Acute Stroke Patients

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Objective: To evaluate and compare the predictive value of Face, Arm, Speech Test (FAST) and Balance, Eyes, Face, Arm, Speech, Time (BEFAST) scale in the acute ischemic stroke (AIS).

Methods: We searched Medline and Ovid databases for relevant literature in the English language. There were no limitations on the date. The sensitivity, specificity, likelihood ratio, and diagnostic odds ratio were pooled for meta-analysis. The symmetric receiver operator characteristic curve and Fagan's Nomogram were drawn, and meta-regression and subgroup analysis were used to explore the source of heterogeneity.

Results: A total of 9 studies, including 6,151 participants, were analyzed. The combined sensitivity of FAST was 0.77 [95% *CI* (0.64–0.86)], specificity was 0.60 [95% *CI* (0.38–0.78)], the area under the ROC curve was 0.76, and the diagnostic ratio was 1.57, while the sensitivity of BEFAST was 0.68 [95% *CI* (0.23–0.93)], specificity was 0.85 [95% *CI* (0.72–0.92)], the area under the ROC curve was 0.86, and the diagnostic odds ratio was 2.44. No publication bias was detected in Deeks' funnel plot. For FAST, meta-regression analysis showed that the prospective design, satisfactory description of the index test, and a broad spectrum of disease contributed to the heterogeneity in sensitivity, while no sources contributed to the heterogeneity in sensitivity. When the pretest probability was set as 20%, the posterior probability in Fagan's Nomogram was 32%; however, when the pretest probability was set as 20% in BEFAST, the posterior probability in Fagan's Nomogram was 52%.

Conclusions: Our findings indicated that FAST and BEFAST might be useful in the diagnosis of acute ischemic stroke. The diagnostic value of BEFAST in acute ischemic stroke was higher than in FAST; thus, it might have an important role in the fast recognition of acute ischemic stroke.

Keywords: stroke, acute stroke, FAST, BEFAST, meta-analysis, systematic review

INTRODUCTION

Stroke is one of the most common acute and severe diseases presented to an emergency department (ED). Stroke is a major global burden, with 10.3 million new strokes and 113 million disability-adjusted life years (DALYs) per year worldwide (1). It can be divided into transient ischemic attack (TIA), ischemic stroke (IS), hemorrhagic stroke (HS), and subarachnoid hemorrhage. Acute ischemic stroke (AIS) can have serious lifelong consequences. In contrast to HS, significantly improved survival in IS patients has been reported since the early 2000s (2). Therefore, early recognition of stroke is of utmost importance. Rapid recognition of stroke warning signs is a crucial factor in the acute treatment of stroke. Prehospital stroke scales are helpful to guide the prehospital selection of people suspected of having a stroke (3). The screening tools can develop to help the public recognize stroke early. Earlier and improved stroke detection by ED and ambulance may reduce treatment delays (4).

Insufficient knowledge on stroke among the general public may lead to serious consequences. Several screening tools, including the Cincinnati Prehospital Stroke Scale (CPSS), Face, Arm, Speech Test (FAST), Los Angeles Prehospital Stroke, Screen (LAPSS), Melbourne Ambulance Stroke Screen (MASS), Medic Prehospital Assessment for Code Stroke (Med PACS) and Recognition of Stroke in the Emergency Room score (ROSIER), which are characterized by simple, structured, and easy-to-use

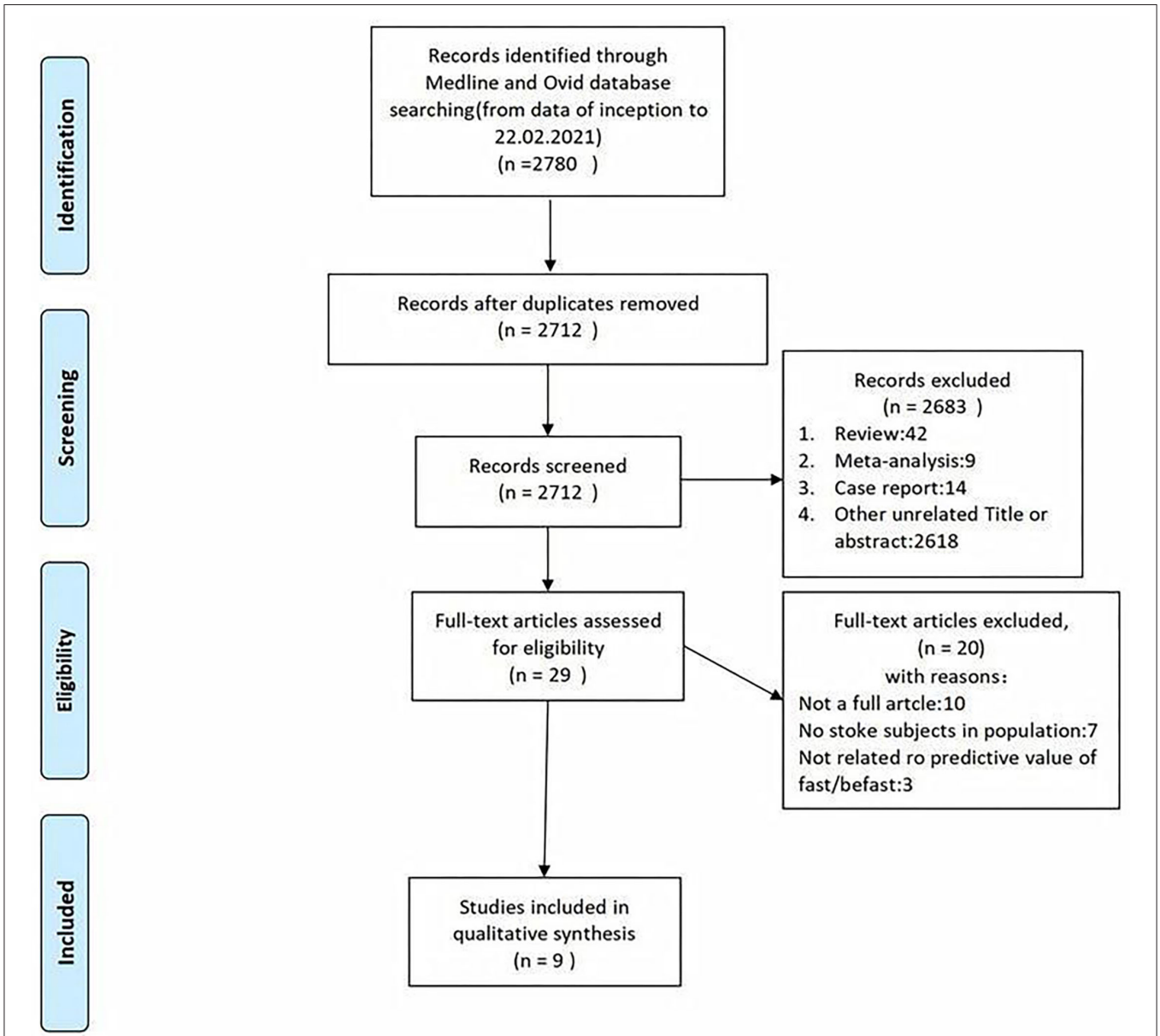

FIGURE 1 | The literature with Face Arm Speech Test (FAST) and Balance, Eyes, Face, Arm, Speech, Time (BEFAST) screening process of the meta-analysis.

TABLE 1 | Basic characteristics of enrolled studies.

Author	Study	Year	Region	number	Age (mean ± sd)	Sex (male%)	Scale used	Outcome
D. Václavík (10)	Prospective cohort	2018	Czech	435	74 ± 12	215 (51.0)	FAST-plus	The sensitivity, specificity, positive predictive value, negative predictive value of the FAST plus test in detecting LVO stroke.
S. Aroor (7)	Cross-sectional	2017	American	736	NA	NA	FAST/BEFAST	Missed diagnosis rate of the FAST or BEFAST in detecting stroke.
D. Pickham (4)	Prospective cohort	2018	American	359	NA	Stroke: 55 (34.6); Non-stroke: 46 (23.0)	FAST	The sensitivity, specificity of the diagnosis of stroke after using FAST or BEFAST.
H. Mao (11)	Prospective cohort	2016	China	416	Stroke ($n = 358$): 69.2 ± 13.8; non-stroke ($n = 58$): 70.6 ± 11.4	Stroke: 210 (58.7): non-stroke:37 (63.8)	FAST	The sensitivity, specificity of the diagnosis of stroke after using FAST.
RT. Fothergill (12)	Prospective cohort	2013	UK	295	65	156 (53.0)	FAST	The sensitivity, specificity, positive predictive value, negative predictive value of the FAST plus test in detecting stroke.
A. Berglund (13)	Prospective cohort	2014	Sweden	900	71	NA	FAST (EMCC) FAST (Ambulance)	The positive predictive values (PPV) for a stroke/TIA diagnosis at discharge after using FAST.
JC. Purrucker (5)	Prospective cohort	2015	Germany	689	Total ($n = 689$): 61.7 ± 20.9; Stroke ($n = 00$): 75.6 ± 13.4; non-stroke ($n = 489$): 56.0 ± 20.8	Total: 357 (51.8); Stroke: 80 (40.0); non-stroke: 277 (56.6)	FAST	The sensitivity, specificity, positive predictive value, negative predictive value of the FAST plus test in detecting stroke.
WN Whiteley (14)	Prospective cohort	2011	UK	356	NA	173 (48.6)	FAST	The sensitivity, specificity of the diagnosis of stroke or TIA after using FAST.
F. El Ammar (8)	Cross-sectional	2020	American	1965	Total: 63 ± 16.1; In-hospital stroke: 61.6 ± 17.3; Prehospital/ED stroke: 63.3 ± 15.6	Total: 844 (43); In-hospital stroke: 232 (47.4); Prehospital/ED stroke: 612 (41.5)	BEFAST (All patients); BEFAST (prehospital/ED)	The sensitivity, specificity of the diagnosis of stroke after using BEFAST.

NA, not available from original study paper or supplementary or registration information; ED, emergency department; LVO, large vessel occlusion. EMCC, Emergency Medical Communication Center.

stroke recognition scores, have been developed to help the public identify if a person is having an acute stroke so as to facilitate rapid access to medical care. Among these scales, the FAST provides the highest sensitivity with 85%. However, the available stroke recognition scores have a huge variety of length and complexity, which complicates choosing the optimal score in the emergency setting (5). Furthermore, it is truly difficult to compare the reported diagnostic accuracies of recognition scores. The FAST fails to detect 40% of those with posterior circulation events, especially those with ataxia and visual disturbances (6). A previous study showed that "FAST" failed in 14% of AIS patients (7).

BEFAST (Balance, Eyes, Face, Arm, Speech, Time), which was previously studied to determine whether adding gait or visual abnormalities to the FAST scale would improve stroke detection rates, revealed statistically lower Sensitivity for the detection of AIS in the inpatient population compared with the ED (8). However, a prospective study in 2018 has shown that BEFAST assessment does not improve stroke detection in the prehospital setting (4).

It is necessary to improve the accuracy of scales. This systematic review and meta-analysis aimed to explore the diagnostic value of the FAST and BEFAST for AIS patients; a quantitative reference for clinical practice was provided.

METHODS

Search Strategy

Two reviewers (CXJ and ZXX) independently searched the PubMed, Embase, and Cochrane libraries for all the relevant

TABLE 2 | Inclusion and exclusion criteria.

Author	Inclusion criteria	Exclusion criteria	Scale
D. Václavík (10)	(a) Suspected acute stroke patient admitted to one of the three-stroke centers; (b) FAST PLUS test evaluation by paramedics; and (c) CT and CTA evaluations.	The exclusion criterion was suspected stroke with more than 12 h from symptom onset.	FAST-plus
S. Aroor (7)	Patients with a discharge diagnosis of acute ischemic stroke (International Classification of Diseases, Ninth Revision, Clinical Modification codes) were reviewed.	Those misclassified, having missing NIHSS data, or were comatose or intubated were excluded. Presenting symptoms, demographics, and examination findings based on the NIHSS were abstracted.	FAST
D. Pickham (4)	NA	NA	FAST
H. Mao (11)	Suspected stroke patients ≥18 years old presenting to the ED with symptoms or signs within 7 days were recruited.	Patients were excluded if they were <18 years old, had a traumatic brain injury, subarachnoid hemorrhage, or unknown diagnosis.	FAST
RT. Fothergill (12)	Aged >18 years if they presented with symptoms of stroke, were assessed by participating ambulance clinicians using the ROSIER, and conveyed to the Royal London Hospital.	We did not include those who were <18 years, not assessed using the ROSIER, or transferred to another hospital.	FAST
A. Berglund (13)	The study population consisted of all calls to the EMCC concerning patients presenting at least one FAST symptom or a history/finding, making the EMCC or ambulance personnel suspect a stroke within 6 h.	NA	FAST (EMCC) FAST (Ambulance)
JC. Purrucker (5)	we selected consecutive cases allocated to the database category "suspected central nervous system disorder," that is, patients with potential stroke and stroke-mimics.	Excluding repeated and primary neurotrauma admissions and cases with missing discharge diagnosis.	FAST
WN Whiteley (14)	(a) whose symptoms began <24 h before admission, (b) who were still symptomatic at the time of assessment and (c) in whom a general practitioner, a paramedic or a member of the emergency-department staff had made a diagnosis of "suspected stroke."	NA	FAST
F. El Ammar (8)	(a) age 18 year or older; (b) PH stroke alert activation by emergency medical personnel enroute to the ED, stroke activation by ED staff members, or in-hospital stroke alert activation.	(a) age 17 years or younger; (b) cancellation of stroke alert activation by the primary team prior to arrival of the stroke response team; (c) conversion of stroke alert to cardiac arrest code at time of arrival of stroke response team, (d)missing data at time of chart review.	BEFAST (All patients); BEFAST (prehospital/ED)
S. Aroor (7)	Patients with a discharge diagnosis of acute ischemic stroke (International Classification of Diseases, Ninth Revision, Clinical Modification codes) were reviewed.	Those misclassified, having missing NIHSS data, or were comatose or intubated were excluded. Presenting symptoms, demographics, and examination findings based on the NIHSS were abstracted.	BEFAST
D. Pickham (4)	Patients with sudden onset of neurological symptoms <6 h from EMS arrival were assessed with BEFAST in the field.	NA	BEFAST

NA, not available from original study paper or supplementary or registration information; FAST, Face Arm Speech Test; BEFAST, Balance, Eyes, Face, Arm, Speech, Time; NIHSS, National Institutes of Health Stroke Scale; ED, emergency department; ROSIER, Recognition of Stroke in the Emergency Room score; EMCC, Emergency Medical Communication Center.

publications published thus far. We chose the keywords "stroke," "ischemic stroke," and "hemorrhagic stroke" as text words and MeSH terms to identify related studies, language, region, or publication type. The search was limited to published clinical studies. Search terms are listed as follows:

1) (FAST)[Title/Abstract]
2) *(BEFAT)[Title/Abstract]*
3) *1 OR 2*
4) *("stroke" or "ischemic stroke" or "hemorrhagic stroke") [Title/Abstract]*

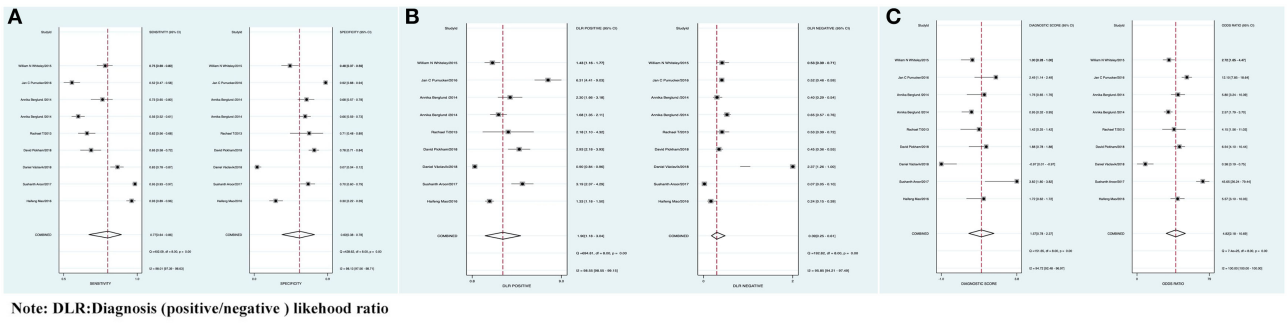

FIGURE 2 | (A) Forest plot of sensitivity (Se) and specificity (Sp) of FAST in the diagnosis of acute ischemic stroke (AIS). **(B)** Forest plot of diagnosis (positive/negative) likehood ratio (DLR) positive and negative of AIS. **(C)** Forest map of the diagnostic odds ratio (DOR) of FAST in the diagnosis of AIS.

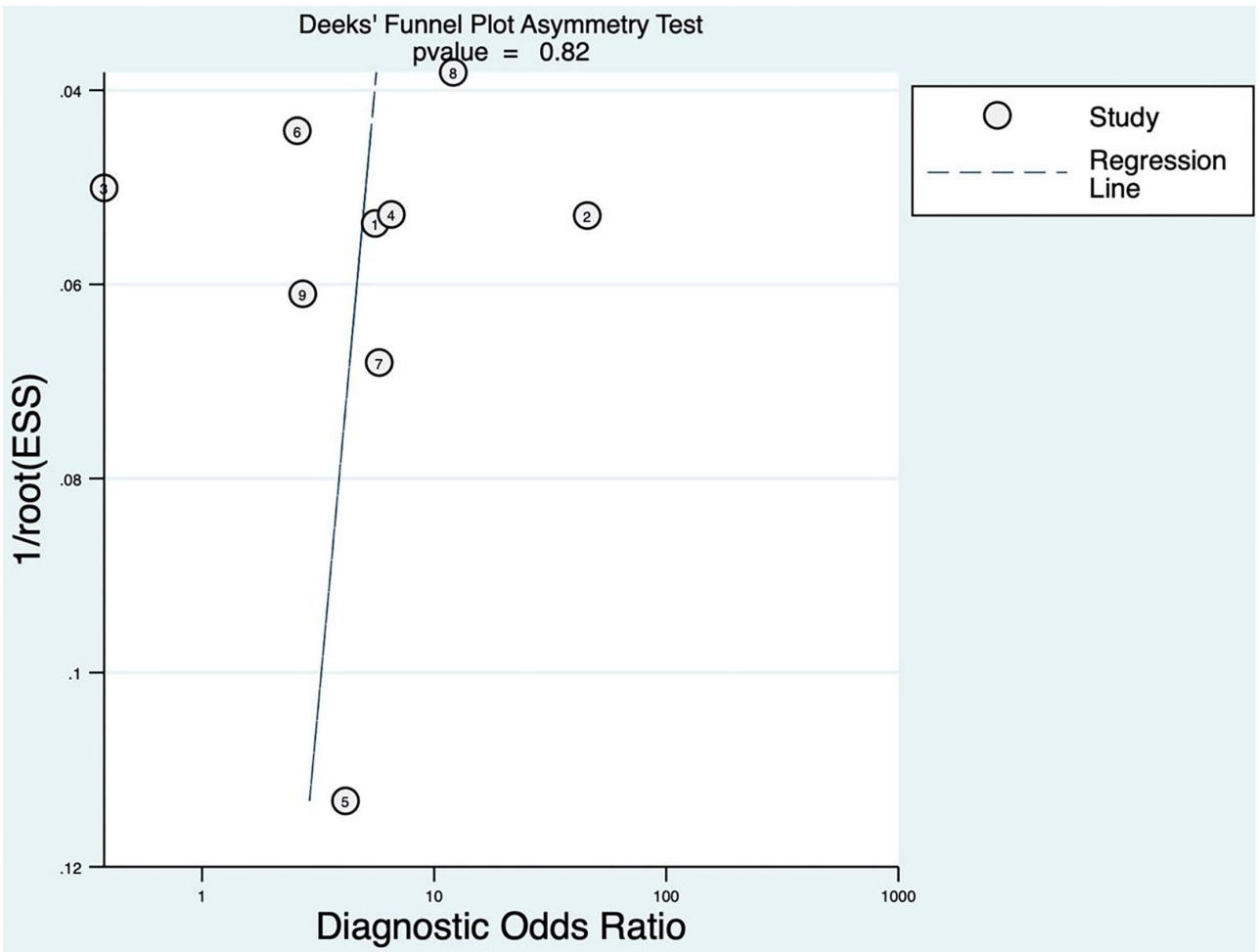

FIGURE 3 | Deeks' funnel plot asymmetry test for FAST.

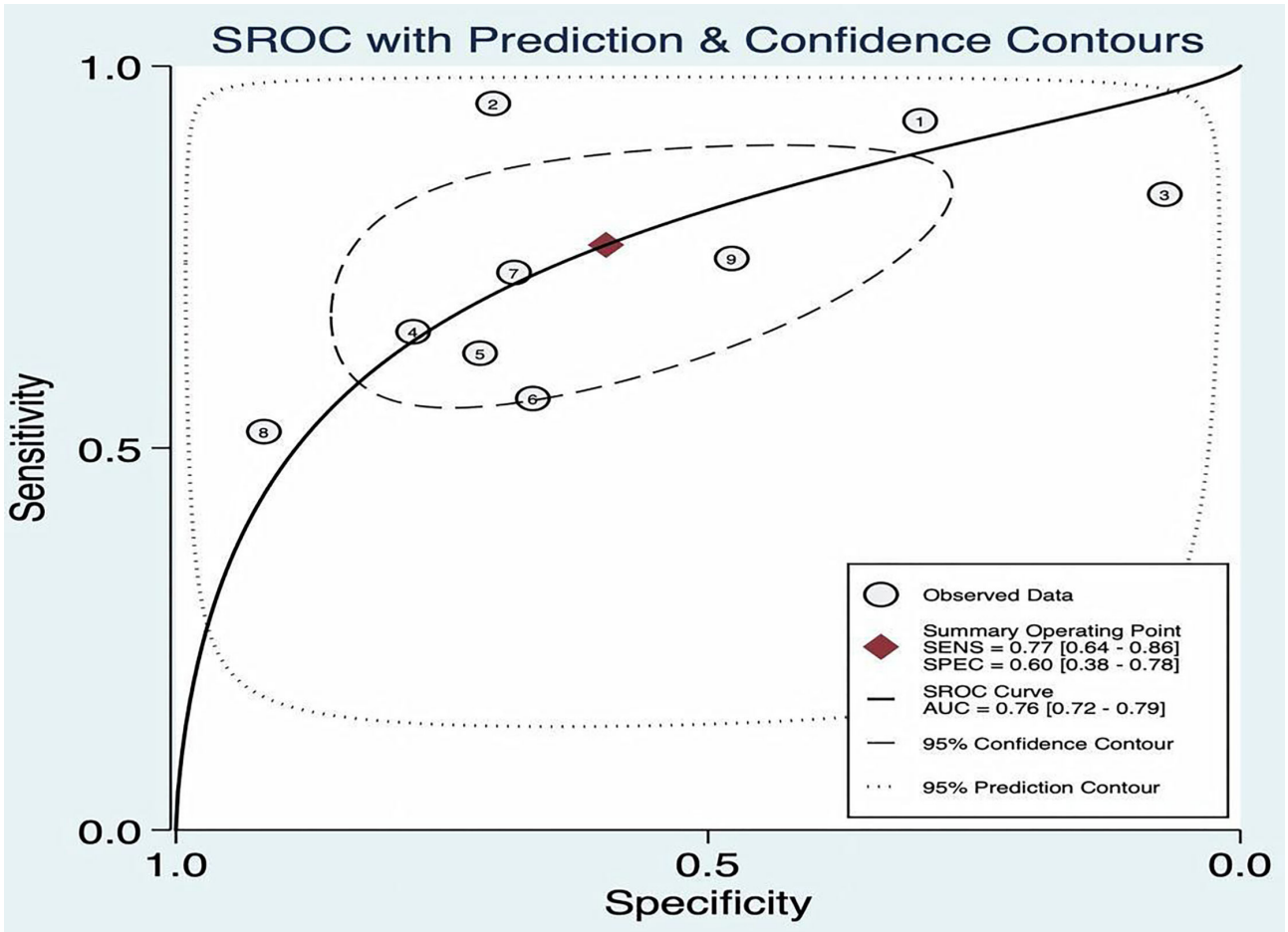

FIGURE 4 | Summary receiver operating characteristic (ROC) of FAST.

5) *3 AND 4*
6) *From 2011 to 2021*

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) all types of strokes; (2) included FAST or/and BEFAST; (3) clinical study; (4) published within past 10 years; and (5) published in the English language.

Exclusion criteria were: (1) no described outcomes; (2) no control groups; (3) impossible to find original paper; and (4) the sensitivity, specificity (Sp), positive predictive value, and negative predictive value cannot be extracted.

Data Extraction

Two authors (CXJ and ZXX) independently extracted the demographic data and treatment information, and if a disagreement occurred, a third author (XF) was involved. Baseline information extracted from 9 studies contained the first author name, year of publication, title, design type, study subjects (number, age, male/female ratio), disease degree, and length of the disease. Besides, the primary outcomes included True positives (Tp), False positives (Fp), False negatives (Fn), true negatives (Tn) with FAST and BEFAST.

Quality Assessment

The Agency for Healthcare Research and Quality (AHRQ) was used to rate the methodological quality of cross-sectional studies. An item was scored with "0" if it was answered "NO" or "UNCLEAR"; if it was answered "YES," then it was scored "1." Article quality was assessed as follows: low quality = 0–3; moderate-quality = 4–7; and high quality = 8–11. The quality of studies was assessed by using the Newcastle Ottawa scale (NOS), which generated a maximum of nine stars for each study, including four stars for the selection of participants, two stars for the comparability of participants, and three stars for the assessment of outcomes. Quality was assigned according to the final scores, where 7–9 stars indicated high quality, 4–6 stars for middle quality, and 0–3 stars for low quality (9).

Statistical Analysis

Stata 15.0 software (Stata Corp 4905 Lakeway Drive, College Station, TX, USA) was used to perform a meta-analysis. The bivariate model was used to calculate the combined Sensitivity (Se), Specificity (Sp), the positive likelihood ratio (PLR), the negative likelihood ratio (NLR), and diagnostic odds

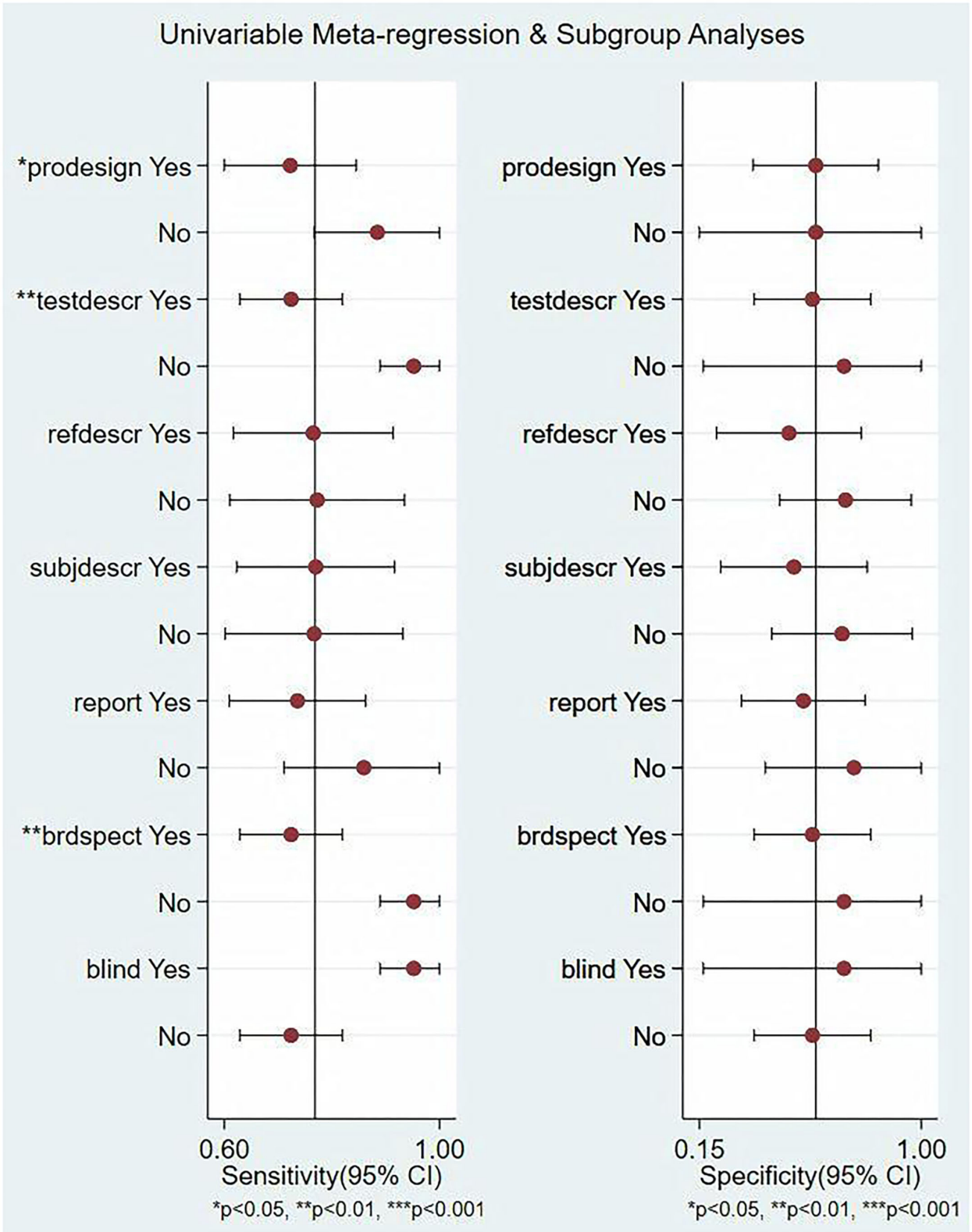

FIGURE 5 | Single-factor meta-regression and subgroup analysis. Prospective design: prodesign, testdescr: satisfactory description of the index test, subjdescr: adequate description of study subjects, refdescr: satisfactory description of ref test, and brdspect: broad spectrum of disease[1].

[1]The following variables used to adjust whether included studied met these criteria.

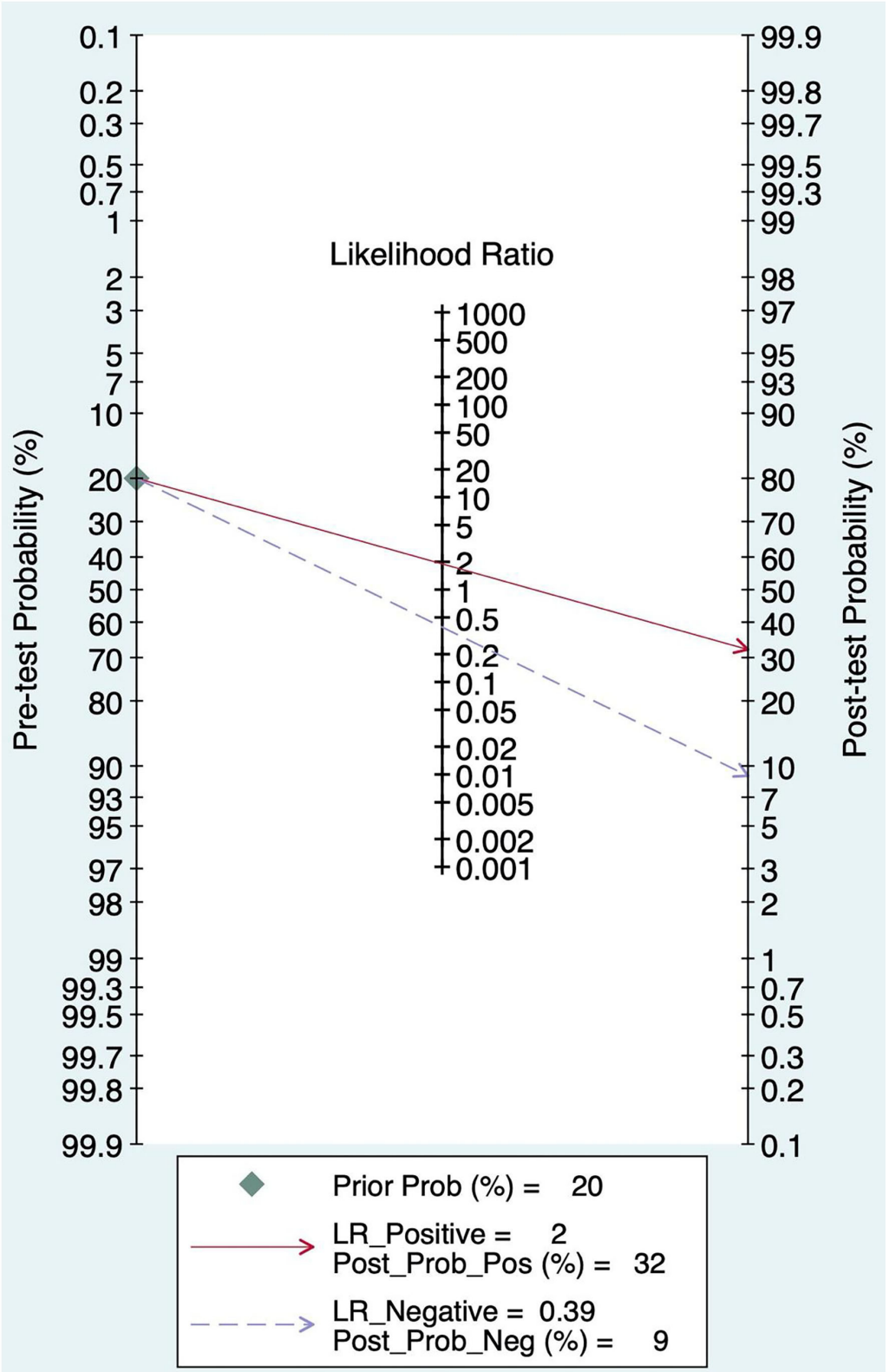

FIGURE 6 | Fagan diagram of FAST in the diagnosis of AIS.

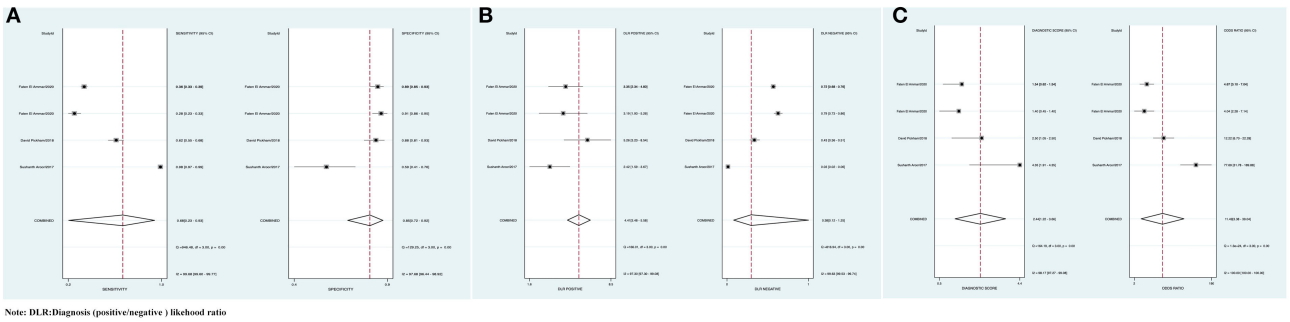

FIGURE 7 | (A) Forest plot of Se and Sp of BEFAST in the diagnosis of AIS. **(B)** Forest plot of diagnosis (positive/negative) likehood ratio (DLR) positive and negative of AIS. **(C)** Forest map of the DOR of BEFAST in the diagnosis of AIS.

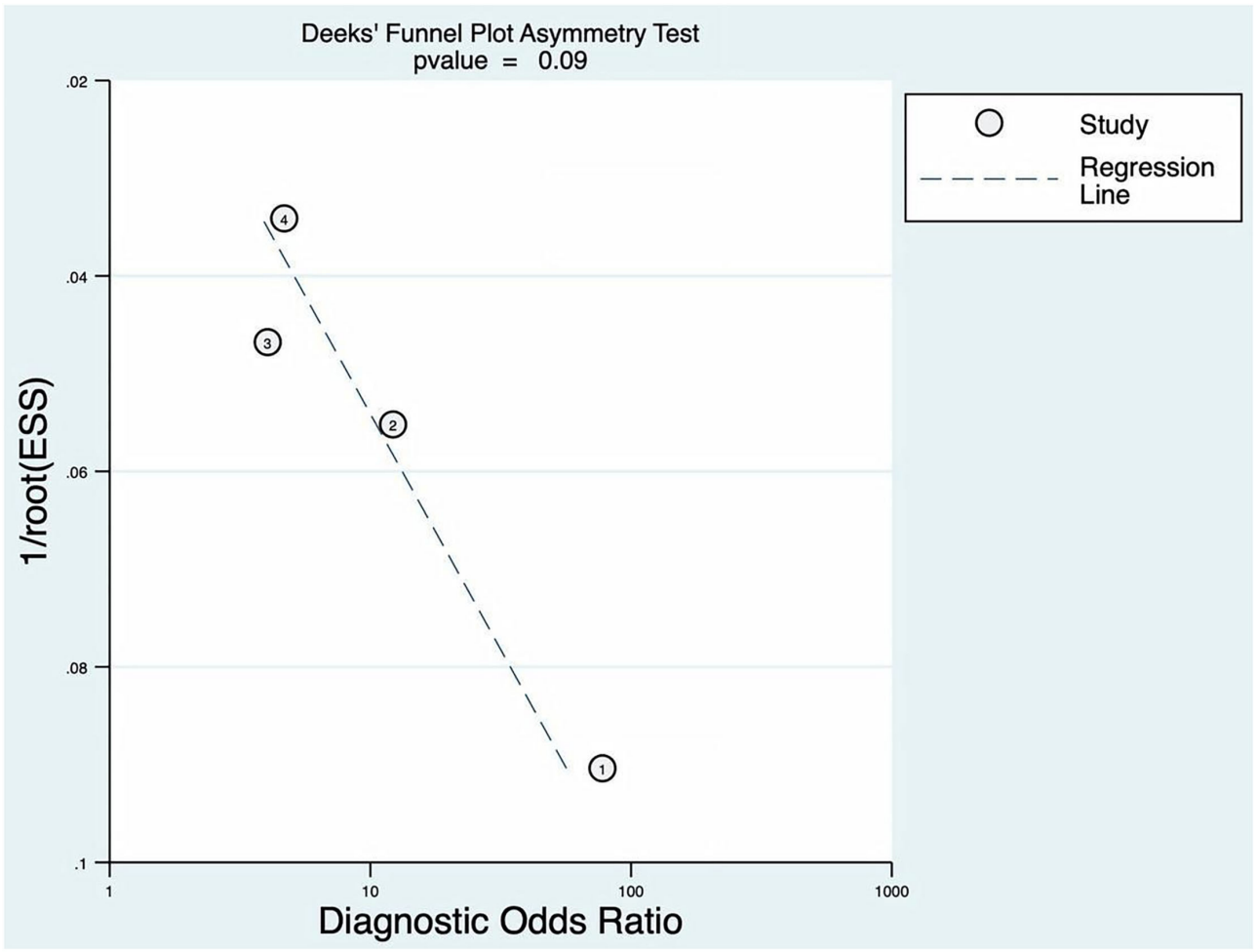

FIGURE 8 | Deeks' funnel plot asymmetry test for BEFAST.

ratio (DOR), and to draw the symmetric receiver operator characteristic curve (SROC) so as to estimate the total diagnostic accuracy. Pre-test probabilities may be estimated from routine data, practice data, or clinical judgment. Post-test probabilities are used to determine whether the probability of diagnosis has raised or fallen, compared with pre-test probabilities. The

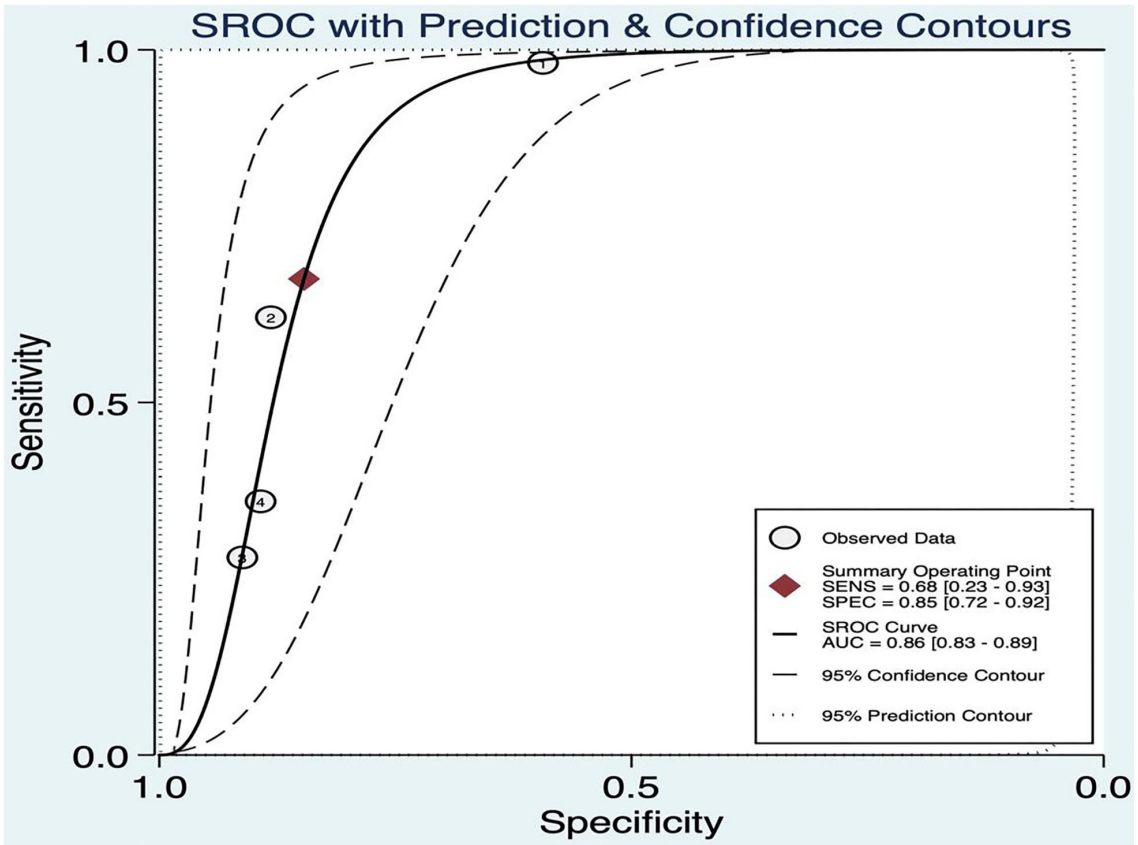

FIGURE 9 | Summary ROC of BEFAST.

heterogeneity was assessed by Cochrane's *Q* statistics (chi-square), or inverse variance (I^2). $I^2 < 50\%$ and $p > 0.1$ indicated that these studies could be considered as homogeneous by using a fixed-effect model; otherwise, $I^2 \geq 50\%$, $p < 0.10$, the random effect model, was used for meta-analysis. If heterogeneity among studies was recorded, the potential source of heterogeneity was investigated *via* meta-regression. A p value < 0.05 was considered statistically significant.

RESULTS

Flowchart and Study Quality

A total of 7,690 papers with FAST and BEFAST (including documents, reviews, animal experiments, case reports, and repeated studies) were retrieved from each database. After 1,825 duplicate records were removed, the full text of the remaining 5,865 studies was read. Among those studies, 201 were excluded because the articles were reviews, meta-analyses, or case reports, while 5,642 studies did not have related titles and abstracts. The full text of the remaining 21 studies was read, and 12 studies were removed due to incomplete data. The remaining 9 papers were extracted from the corresponding data according to the data extraction requirements. Seven studies used the FAST; one study used the BEFAST and one study used the FAST and BEFAST. The literature screening process is shown in **Figure 1**. The basic characteristics and inclusive and exclusive criteria of each included study are shown in **Tables 1**, **2**.

FAST Against AIS

The combined Se of FAST in AIS was 0.77 [95% *CI* (0.64, 0.86)], Sp was 0.60 [95% *CI* (0.38, 0.78)], PLR was 1.90 [95% *CI* (1.18, 3.04)], NLR was 0.39 [95% *CI* (0.25, 0.61)], area under ROC curve was 0.76, and DOR was 4.82, which indicated the FAST had a medium value in the screen of AIS. As all heterogeneity w*as* $I^2 > 50\%$, the random model was used. The details of the combined Se and Sp forest plot are shown in **Figure 2A**, the combined likelihood ratio forest plot in **Figure 2B**, and the combined diagnosis ratio forest plot in **Figure 2C**.

Publication Bias

The linear regression was used to test funnel asymmetry so as to evaluate publication bias. The results showed no asymmetry, while the linear regression test p was 0.82, which indicated no publication bias, as shown in **Figure 3**.

Threshold Effect

The SROC curve plane test was used to threshold effect. However, there was no typical "shoulder arm" found, indicating no

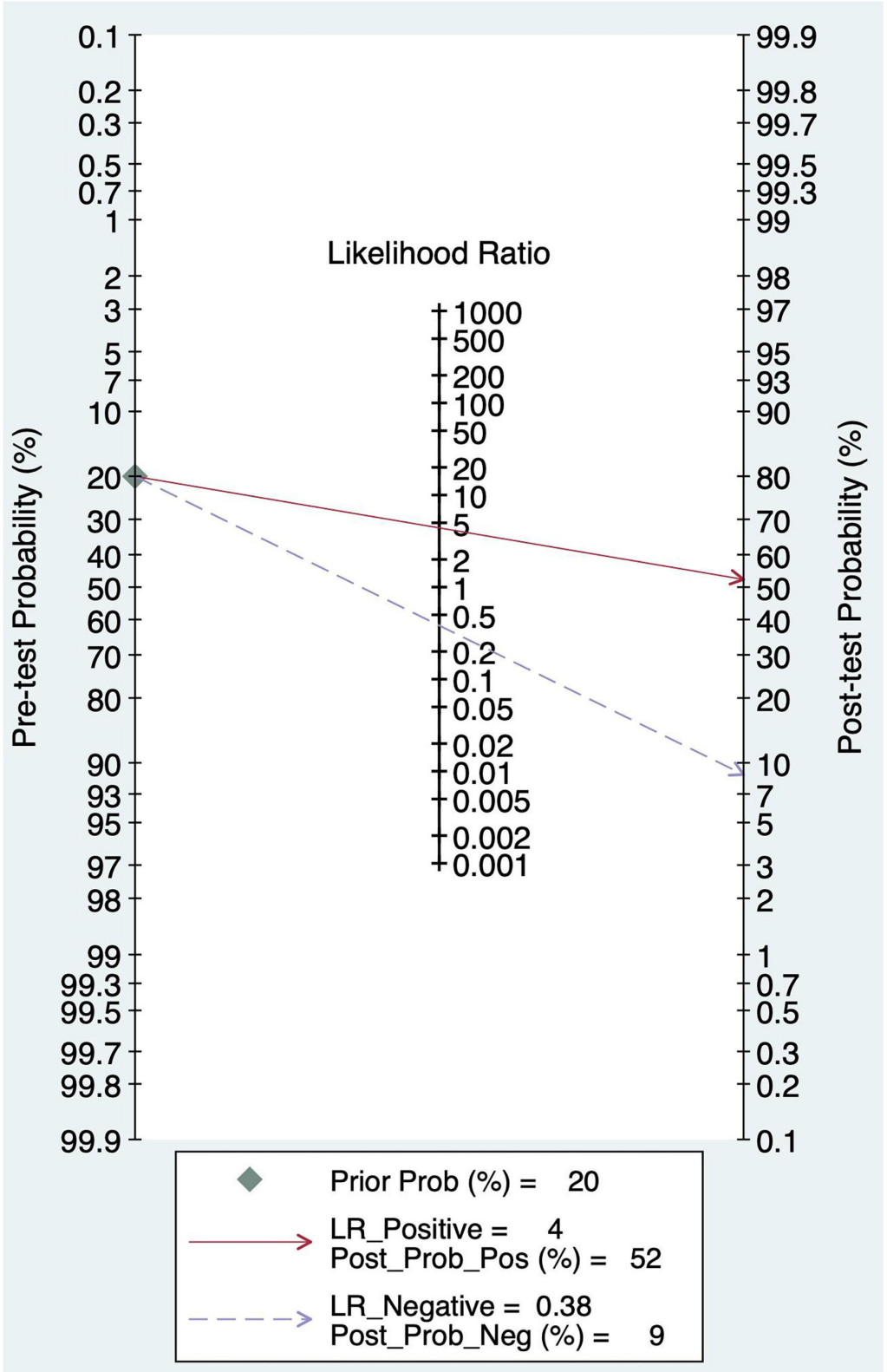

FIGURE 10 | Fagan diagram of BEFAST in the diagnosis of AIS.

threshold effect. Moreover, Cochran's Q value was 59.49, and the p was <0.05, which indicated that the heterogeneity was caused by the non-threshold effect. A moderate diagnostic value could be concluded by the value of the area under the SROC curve (AUC), which was 0.76 [95% *CI* (0.72–0.79)], as shown in **Figure 4**.

Meta-Regression and Subgroup Analysis

In this study, we evaluated the factors that may affect the heterogeneity, such as non-threshold effect, prospective design (prodesign), satisfactory description of index test (testdescr), an adequate description of study subjects (subjdescr), satisfactory description of ref test (refdescr), report, a broad spectrum of disease (brdspect), and whether the test results were evaluated by a blind method. The meta-regression analysis of the above factors revealed that although the sources of heterogeneity of Se were statistically related to the prodesign, testdescr, and brdspect, the sources of heterogeneity of Sp were not related to these factors, as shown in **Figure 5**.

Pre-test Probability, Likelihood Ratio, and Post-test Probability

The Fagan graph was plotted to show the relationship among the prior probability, the likelihood ratio, and the posterior probability. The pretest probability was 20%, and the post-test probability of AIS was 32%. In addition, the PLR was <10 (PLR = 1.90), and the NLR was >0.1(NLR = 0.39), indicating that the diagnosis can neither be confirmed nor excluded. Their diagnostic value of FAST in AIS was limited, as shown in **Figure 6**.

BEFAST Against AIS

The combined Se was 0.68 [95% *CI* (0.23, 0.93)], Sp was 0.85 [95% *CI* (0.72, 0.92)], PLR was 4.41 [95% *CI* (3.48, 5.58)], NLR was 0.38 [95% *CI* (0.12, 1.25)], AUC was 0.86, and DOR was 11.49, which indicated that the BEFAST had a medium value in the screening of AIS. All heterogeneity was I^2 > 50%; therefore, the random model was used in **Figure 7**.

Publication Bias

The p of Deeks' funnel plot asymmetry test was 0.09 (p > 0.05). There was no evidence of publication bias; the details are shown in **Figure 8**.

Threshold Effect

The threshold effect was assessed by the SROC curve plane test. As no typical "shoulder arm" was found, there was no threshold effect. A moderate diagnostic value was concluded by the value of the AUC, which was 0.86 [95% *CI* (0.83–0.89)]; details are shown in **Figure 9**.

Pre-test Probability, Likelihood Ratio, and Post-test Probability

The pretest probability was 20%, and the probability of AIS was 52%. In addition, the PLR was <10 (PLR = 4.41), and the NLR was >0.1(NLR = 0.38), which indicated that the diagnosis could be neither confirmed nor excluded. Their diagnostic value of BEFAST in AIS was also limited; details are shown in **Figure 10**.

Comparison of FAST, BEFAST, and FAST in Combination With BEFAST

Comparison of FAST, BEFAST, and FAST in combination with BEFAST was performed using ROC, Se, and Sp analysis. Among

TABLE 3 | Diagnostic performance of FAST, BEFAST, and FAST in combination with BEFAST.

Scale	Sensitivity	Specificity	AUC	Sensitivity combined	Specificity combined	Prior P	PLR (%)	NLR(%)
FAST	0.77	0.60	0.76	0.74	0.69	20	32	9
BEFAST	0.68	0.85	0.86	0.68	0.85	20	52	9
FAST+BEFAST	0.74	0.69	0.78	0.74	0.69	20	37	9

FAST, Face Arm Speech Test; BEFAST, Balance, Eyes, Face, Arm, Speech, Time; PLR, the positive likelihood ratio; NLR, the negative likelihood ratio.

TABLE 4A | Methodological quality assessments of included observational studies by Newcastle Ottawa scale (NOS).

Study	Study design	NEWCASTLE - OTTAWA SCALE		
		Selection	Comparability	Exposure
RT. Fothergill et al. (12)	Prospective cohort study	★★★★	★★	★☆☆
A. Berglund et al. (13)	Prospective cohort study	★★★★	★★	★☆☆
JC. Purrucker et al. (5)	Prospective cohort study	★★★★	★★	★☆☆
H. Mao et al. (11)	Prospective cohort study	★★★☆	★★	★☆☆
D. Pickham et al. (4)	Prospective cohort study	★★★★	★★	★☆☆
D. Václavík et al. (10)	Prospective cohort study	★★★★	★★	★☆☆

them, the BEFAST had the best diagnostic value; details are shown in **Table 3**.

Quality of All Studies

For prospective studies, the NOS scores varied from 6 to7 stars (**Table 4A**). For cross-sectional studies, the AHRQ scores varied from 4 to 6 (**Table 4B**).

DISCUSSION

The phrase "time is brain" highlights that human nervous tissue is rapidly and permanently lost as stroke progress and that therapeutic intervention should be emergently pursued. Nonetheless, <10% of patients with stroke in hospitals undergo emergency treatment within the thrombolytic time window (15). Currently, stroke is a major cause of death and disability. The mean lifetime cost of ischemic stroke per person, which includes inpatient care, rehabilitation, and follow-up care, is expensive and unaffordable (16). Meanwhile, it affects the quality of life of patients and their families. Therefore, early recognition and accurate diagnosis are of essential importance for a positive outcome. In 1998, the FAST included a rapid ambulance protocol to improve the rapid triage of patients suspected of an acute stroke at our acute stroke unit (ASU) (17). Recently, it has been recorded that the ambulance services most commonly use the FAST to assess patients suspected of stroke (12).

Over recent years, the prehospital stroke scales have become increasingly used to assess acute stroke. Among them, FAST has the highest diagnostic value, with 88.9% of identified stroke/TIA patients within our population. However, the FAST failed to detect 38% of posterior cerebral circulation strokes (18, 19). Posterior circulation stroke, which represents 20∼25% of patients with IS, is associated with a greater risk of disability and death compared with anterior circulation strokes (4). The FAST showed the ability to identify 69–90% of strokes, but it missed up to 40% of those with posterior circulation events. Missed diagnosis rates improved with the addition of visual symptoms and limb ataxia. Therefore, "B" was added for balance and an "E" for eyes (7). In 2020, Ammar et al. performed a retrospective analysis of inpatients screened with the stroke alert system and a final diagnosis of AIS, who were candidates for reperfusion therapy, revealing the Se of BEFAST to be 83% (20).

There has been an increasing number of Systematic reviews and meta-analyses assessing the diagnostic performance of clinical assessment over recent years. The previous systemic review and meta-analysis have evaluated the diagnostic value of the current common stroke identification scales worldwide. In 2014, a Systematic review showed that prehospital stroke scales varied in their accuracy, missing up to 30% of acute strokes in the field through the evaluation of FAST, CPSS, MASS, LAPSS Ontario Prehospital Stroke Screening Tool (OPSS), and Med PACS for diagnostic value with stroke in urban environment (21). In 2019, the assessment of both cortical and motor function using the Rapid Arterial Occlusion Evaluation Scale (RACE), Field Assessment Stroke Triage for Emergency Destination (FAST-ED) and National Institute of Health stroke scale (NIHSS) showed the best diagnostic accuracy values for selecting subjects with large

TABLE 4B | Methodological quality assessments of included cross-sectional studies by the Agency for Healthcare Research and Quality (AHRQ).

Question	Define the source of information	List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Indicate time period used for identifying patients	Indicate whether or not subjects were consecutive if not population-based	Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Describe any assessments undertaken for quality assurance purposes	Explain any patient exclusions from analysis	Describe how confounding was assessed and/or controlled.	If applicable, explain how missing data were handled in the analysis	Summarize patient response rates and completeness of data collection	Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	Score
Answer	Yes (+) or no/unclear (–)	Yes (+) or no/unclear (–)	Yes (+) or no/unclear (–)	Yes (+) or no/unclear (–)	Yes (+) or no/unclear (–)	Yes (+) or no/unclear (–)	Yes (+) or no/unclear (–)	Yes (+) or no/unclear (–)	Yes (+) or no/unclear (–)	Yes (+) or no/unclear (–)	Yes (+) or no/unclear (–)	
WN Whiteley et al. (14)	+	+	–	+	–	+	–	–	–	–	–	4
S. Aroor et al. (7)	+	+	+	+	+	–	–	–	–	–	–	5
F. El Ammar et al. (8)	+	+	+	+	+	–	+	–	–	–	–	6

vessel occlusion (LVO) (22). In 2020, a systematic review and meta-analysis revealed that ROSIER was a valid scale with high clinical applicability (23). Even though numerous scales have emerged for assessing the stroke, only a few studies compared the Se and Sp between FAST and BEFAST.

Our results showed that the FAST had higher Se than BEFAST in detecting AIS. By contrast, BEFAST had a higher Sp than FAST. In general, BEFAST had the highest diagnostic value; however, FAST, as well as BEFAST, may be useful in the diagnosis of AIS. Previous studies found that 14% of patients with AIS would be missed using FAST alone, and this proportion was reduced to 4.4% with the addition of a history of gait and visual symptoms (BEFAST). Our results were consistent with previous reports (7).

CONCLUSION

Our findings indicated that FAST, as well as BEFAST, might be useful in the diagnosis of AIS; however, AIS could neither be confirmed nor excluded by the sole use of FAST or BEFAST. The diagnostic value of BEFAST in AIS was higher than FAST; thus, it might have an important role in the fast recognition of AIS. Nonetheless, it still remains unclear whether it could be applied for screening of all patients with stroke in the prehospital setting or in hospital, or whether the test characteristics of the FAST and BEFAST scales could be separately assessed for posterior and anterior circulation. Future prospective studies are needed to explore the diagnostic value of FAST and BEFAST in the anterior and posterior circulation, respectively, so as to improve the recognition rate of stroke, promote timely intervention, and reduce the burden on families and society.

Study Limitation

First, there was moderate heterogeneity across studies, meta-regression, and subgroup analysis fail output due to the limited BEFAST data. Second, few included studies did not explicitly exclude participants. Both shortcomings should be further investigated and addressed by future studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

XC: perform the literature screening, data extraction, data analysis, results representation, and drafting the manuscript for intellectual content. XL: statistical analysis, interpreted the data, and contributed to and revised the manuscript for intellectual content. XW: study initiate and contribute to and revised the manuscript for intellectual content. LZ and YY: revised the manuscript. MG: electronic search and articles election. FX: instruct the detail steps for groups and draft the manuscript. XZ: perform the literature screening, data extraction, data analysis, and results representation. All authors contributed to the article and approved the submitted version.

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Clinical Outcomes of Endovascular Treatment for Carotid Artery Dissection Without Intracranial Large Vessel Occlusion in Patients With Cerebral Ischemia Presentation

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Background and Purpose: We describe the clinical characteristics and outcomes (including the long-term patency of endovascular treatment [EVT]) of patients with acute ischemic strokes (AISs) featuring carotid artery dissection (CAD) but not intracranial large vessel occlusion.

Methods: We retrospectively reviewed patients who underwent EVT for spontaneous or post-traumatic AISs with CAD over a 13 year period from September 2005 to November 2018. The indications for EVT in patients with AIS-related CAD were a pretreatment diffusion-weighted imaging-Alberta Stroke Program early computed tomography (ASPECT) score > 6 and, clinical-diffusion mismatch. But, if the patients showed fluctuated ischemic symptoms, the joint decision by a stroke neurologist and neurointerventionist was done according to the onset-to-door time, symptoms, patient data, and the initial neuroimaging findings whether indicated that EVT was appropriate.

Results: Twenty-two dissected carotid arteries underwent balloon angioplasty and/or stent placement. The patients were 6 women and 16 men of median age 46 years. Twelve lacked any trauma history. Recombinant tissue plasminogen activator was prescribed for two (9.1%) patients. Four developed symptomatic intracranial hemorrhages (18.2%) but 86.4% exhibited modified Rankin scores ≤ 2.

Conclusions: Although attention to the hemorrhagic complication is required, EVT for selective patients with cerebral ischemia associated with CAD may be safe and acceptable treatment strategy for reconstruction of luminal patency, with good clinical outcomes. Prospective large-scale randomized studies are required to optimize EVT for CAD patients.

Keywords: carotid artery, internal, dissection, ischemic stroke, stents, angioplasty, balloon

INTRODUCTION

Recent trials of endovascular treatment (EVT) have proven its effectiveness in patients with acute ischemic stroke (AIS) and intracranial large-vessel occlusion (ILVO) compromising anterior cerebral circulation (1). Carotid artery dissection is a rare cause of ischemic stroke, but is responsible for 20–25% of strokes in young patients (2). The cerebral ischemia associated with CAD reflects embolisms of dissected vessels, and triggers hemodynamic insufficiency (3). CAD with concomitant ILVO is usually associated with very poor clinical outcomes; emergency EVT is required (4). However, conservative treatment is an option if the ischemic symptoms associated with CAD (without ILVO) are mild and do not progress significantly (5). However, CAD patients without ILVO may develop hemodynamic insufficiency or a recurrent embolism raising a strong suspicion of ischemic symptom fluctuation (6). Although most patients with this AIS subtype undergo EVT, the clinical outcomes have been but rarely studied. As EVT timing depends on the symptoms, identification of the available time window for patients with CAD without ILVO remains challenging. Here, we share our clinical experience with, and the results of, management of AIS related to CAD, and explore EVT safety and efficacy in patients with CAD without ILVO.

METHODS

Study Population

We reviewed the data on consecutive patients with CAD evaluated in our comprehensive stroke center between January 1 September 2005 and November 31, 2018. All were retrospectively selected from a prospective neurointerventional database and a stroke registry. Clinical and radiological data were reviewed. We collected information on patient demographics, vascular risk factors, imaging findings, time from symptom onset to the procedure, baseline National Institutes of Health Stroke Scale (NIHSS) scores, the modified Rankin Scale (mRS) scores at 3 months, and the length of hospital stay. Cerebral angiograms were reviewed in terms of the location of dissection and reperfusion status after EVT. The inclusion criteria of EVT were as follows: (1) Patients with AIS associated CAD which showed clinical-diffusion mismatch or symptom fluctuation [at least pretreatment Diffusion-Weighted Imaging–Alberta Stroke Program Early Computed Tomography Scores (DWI-ASPECT) $>$ 6] and (2) if patients who showed fluctuated ischemic symptoms were judged to be beneficial to performing EVT for CAD by a discussion between neurologist and neurointerventionist about onset-to-door time, symptoms, patient information, and initial neuro-imaging findings. We excluded patients when (1) incidentally identified CAD (thus lacking clinical symptoms), (2) those with onset to puncture time $>$1 week, (3) DWI-ASPECT $\leq$ 6, (4) those who underwent mechanical thrombectomy to treat ILVO, and (5) those with an intracerebral hemorrhage evident in initial CT or magnetic resonance imaging (MRI). The histories of all ischemic events were recorded, and the physical and neurological statuses of all patients were evaluated by our stroke neurologists. In line with our acute stroke management protocol, all patients underwent MRI with magnetic resonance angiography (MRA) or CT angiography (CTA) of the circle of Willis and the carotid vessels prior to EVT. Detailed EVT data were retrieved from our electronic medical records and our picture archive and communication system (PACS). This study was approved by our institutional review board, and the need for written, informed patient consent was waived because of the retrospective nature of the study.

Interventions

All procedures were performed via the percutaneous transfemoral route with patients under local anesthesia. All EVT procedures were performed by two of our neurointerventionalists who treat all patients with symptomatic

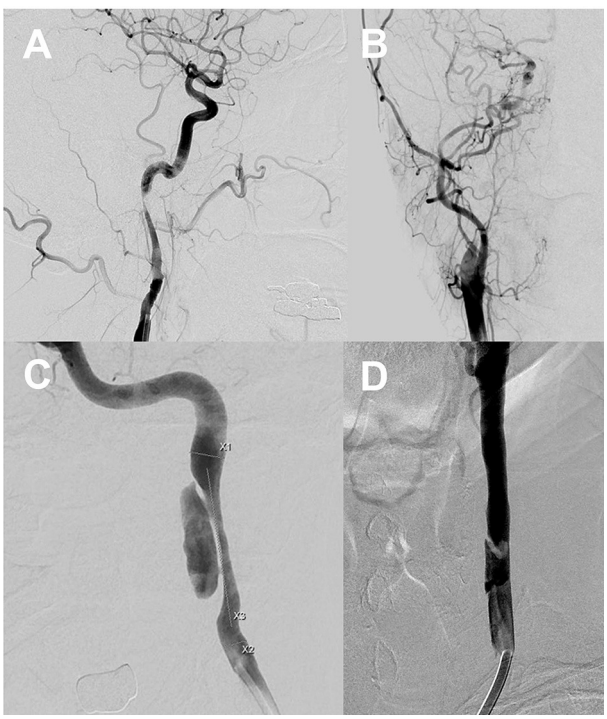

FIGURE 1 | Type I dissections with intact intima **(A,B)**. The Type IA dissection (left) exhibits sustained antegrade flow without complete occlusion. The Type IB dissection (right) is completely occluded. Type II dissections with intimal disruptions **(C,D)**. The Type IIA dissection **(C)** exhibits a small intimal disruption with a side-wall aneurysm. The Type IIB dissection **(D)** exhibits a clear intimal flap and an aneurysmal dilation. X1: Distal carotid luminal diameter, X2: Proximal carotid luminal diameter, X3: Length of a dissected segment of the carotid artery.

Abbreviations: AIS, Acute ischemic stroke; CAD, Carotid artery dissection; CI, Confidence interval; CNS, Central nervous system; CT, Computed tomography; DWI-ASPECT, Diffusion-weighted imaging–alberta stroke program early computed tomography; ECASS, European Co-operative acute stroke study; EVT, Endovascular therapy; FLAIR, Fluid-attenuated inversion recovery; HARM, Hyperintense acute reperfusion marker; ILVO, Intracranial large vessel occlusion; IQR, Interquartile range; MRI, Magnetic resonance imaging; mRS, Modified rankin scale; NIHSS, National institutes of health stroke scale.

CAD. After placement of a sheath introducer, unfractionated heparin was intravenously administered to maintain the activated clotting time at 2-fold the normal value. All patients were prescribed dual antiplatelet agents and a statin before the procedure (7). Typically, a long 6–8 Fr. sheath (Shuttle-SL; Cook Medical, Bloomington, IN, USA) was deployed. A microcatheter of internal diameter 0.021 or 0.027 inches was navigated distally to the point of dissection, over a 0.014-inch steerable microwire. When the microcatheter lay above the dissected carotid artery, angiography was performed to identify the arterial lumen. Then the microcatheter was replaced with a 300 cm microwire for delivery of a balloon or a stent catheter. Balloon angioplasty with stent placement allowed of reperfusion in selected patients. Balloon angioplasty was performed at the discretion of the neurointerventionist.

Imaging

All patients underwent MRI with magnetic resonance angiography (MRA) or CT angiography (CTA) of the circle of Willis and the carotid vessels. A final diagnosis of CAD was based on prolonged conventional angiography performed using an adequate contrast level. Imaging follow-up performed within 72 h after EVT comprised three-dimensional time-of-flight MRI and CTA, including T2*imaging, fluid-attenuated inversion recovery (FLAIR), and diffusion imaging.

Classification of CAD

We used the Borgess classification (8) of CAD that reflects the intimal tear status of the dissected vessel and its influence on blood flow assessed via digital subtraction imaging (**Figure 1**). Intimal injury was considered present if imaging revealed contrast filling outside the vascular lumen, a false lumen with an intimal flap, or fusiform vessel dilation. We explored whether blood attained the carotid artery beyond the dissecting segment. Type I dissections featured intact intimae, and type II dissections had injured intimae; both types were divided into two subtypes. Type IA dissections exhibited luminal stenosis caused by an intramural hematoma, but antegrade flow was preserved. Type IB dissections evidenced no antegrade flow. Type IIA dissections exhibited small, focal intimal tears; one intimal side became filled with contrast medium and stagnation was evident within the dissection. Type IIB dissections featured intimal flaps with false lumina distinct from the normal lumina, or aneurysmal dilation of the dissected vessels. The location of carotid dissection was recorded according to the initial DSA.

Outcomes

Neurological status after EVT was evaluated by dedicated neurologists; all patients were transferred to the neurological intensive care unit after EVT. Clinical outcomes were assessed immediate improvement of NIHSS after interventional therapy,

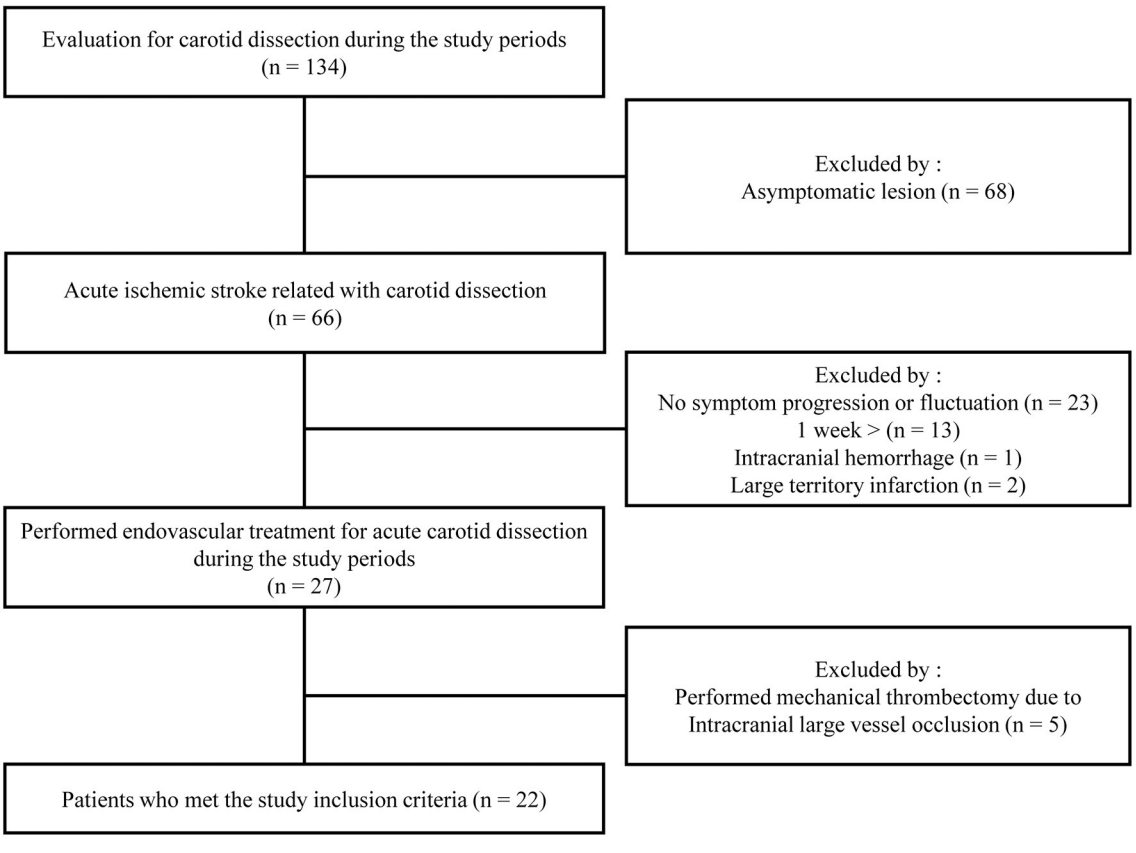

FIGURE 2 | Flowchart of the patient selection process.

TABLE 1 | Baseline patient characteristics.

	(*N* = 22)
Demographics	
Age, years	46.0 (42.0–60.0)
Sex, male	15 (68.2%)
Comorbidities and risk factors	
Hypertension	6 (27.3%)
Diabetes mellitus	1 (4.5%)
Hypercholesterolemia	3 (13.6%)
Atrial fibrillation	1 (4.5%)
Coronary artery disease	2 (9.1%)
Previous stroke	2 (9.1%)
Cancer	0 (0%)
Smoking	8 (36.4%)
Alcohol consumption	10 (45.5%)
Trauma	10 (45.5%)
Headache	5 (22.7%)
Borgess classification	
IA	8 (36.4%)
IB	7 (31.8%)
IIA	5 (22.7%)
IIB	2 (9.1%)
Tissue plasminogen activator	2 (9.1%)
Initial NIHSS	1.0 (0.0–6.0)

NIHSS, national institutes of health stroke scale.

TABLE 2 | Clinical and imaging outcomes.

	(*N* = 22)
Any hemorrhage evident on follow-up imaging	4 (18.2%)
HI-1	0 (0.0%)
HI-2	0 (0.0%)
PH-1	1 (4.5%)
PH-2	3 (13.6%)
Symptomatic hemorrhage	4 (18.2%)
NIHSS at discharge	1.0 (0.0–3.0)
mRS at 90 days	
0	10 (45.5%)
1	7 (31.8%)
2	2 (9.1%)
4	3 (13.6%)
Mortality at 90 days	0 (0.0%)
Infarct volume extension on follow-up imaging	6 (27.3%)
Clinical worsening within 24hr of the procedure	4 (18.2%)
Hospital stay, days	9.0 (8.0–11.0)
Craniectomy	2 (9.1%)
Periprocedural in-stent thrombosis	1 (4.5%)

HI, hemorrhagic infarction; PH, parenchymal hematoma; NIHSS, national institutes of health stroke scale; mRS„ modified rankin scale.

and via modified Rankin Scale (mRS) scoring at 90 days; scores $\leq$ 2 indicated functional independence and good clinical outcomes. Patients exhibiting increases >2 points on the NIHSS underwent CT or MRI, with the exception of those except for whom these procedures were contraindicated or whose cooperation was poor. We evaluated 3 month mortality, the length of hospital stay, cerebral hemorrhage status (any hemorrhagic transformation or subarachnoid hemorrhage evident on follow-up images), symptomatic intracranial hemorrhage status (any parenchymal hematoma, subarachnoid hemorrhage, or intraventricular hemorrhage associated with worsening of the NIHSS score by $\geq$4 points within 24 h of EVT) (9), postprocedural infarct extension, and any newly detected infarction. Stent patency was assessed via ultrasound, CTA, or MRA within the 3 days, at the discretion of the attending neurologist.

RESULTS

A patient flowchart is shown in **Figure 2**. Patient baseline characteristics are summarized in **Tables 1**, **2**. All patients exhibited small ischemic cores as indicated by ASPECT scores > 6 in initial non-contrast CT or evidence of an overt diffusion/perfusion mismatch. Twenty two patients met the inclusion criteria (**Figure 2**). The median age was 46 years (interquartile range [IQR] 42.0–60.0 years) and 15 (57.7%) were men. The median interval from symptom onset to a procedure was 53.7 h (IQR 18.3–72.0 h) (**Table 1**). Ten (45.5%) trauma patients had high-energy non-penetrating injuries, and five (22.7%) headaches associated with the initial ischemic symptoms. Two (9.1%) patients had experienced previous strokes, but all patients had baseline mRS scores of 0. Tissue plasminogen activator was administered to two (9.1%) patients. All stents were proved the patency at follow-up examination within the 3 days after EVT.

In terms of the Borgess classification, eight (36.4%) patients exhibited diffuse luminal narrowing without intimal disruption (Type IA), and seven (31.8%) had carotid occlusion without residual anterograde flow (Type IB). Five (22.7%) progressed to small intimal disruptions with side-wall aneurysms and two (9.1%) evidenced clear intimal flaps. The location of carotid dissection was described in **Table 3**. Multiple stents were placed (median of 1.2 per patient) in the distal intracranial lesions, including self-expanding carotid stents (15/22 patients), coronary balloon-expanding stents (3/22 patients), and self-expanding intracranial stents (5/15 patients). Long-segment, carotid stent reconstruction was technically successful in all patients with no significant (50%) residual stenosis/occlusion or flow limitation evident in post-procedural angiographic analyses.

Clinical Outcomes

Procedural complications developed in four (18.2%) patients (1, 13, 16, and 17); all developed symptomatic hemorrhage (parenchymal hematoma grades 1 or 2 using the European Cooperative Acute Stroke Study criteria) in the ipsilateral hemisphere secondary to reperfusion/hyperperfusion injury. Although no procedure-related mortality was noted to discharge or the 90 day follow-up, subsequent clinical deterioration and a poor clinical outcome at 90 days yielded an overall procedural morbidity of three (13.6%). Rapid post-procedural clinical improvement was observed; the median NIHSS score of 1.0 (0.0–6.0) at admission became 1.0 (0.0–3.0) at discharge. At follow-up during admission, 6 (27.3%) patients demonstrated the infarct volume increased at follow-up imaging and all of those

TABLE 3 | EVT for symptomatic patients with CAD.

ID	Age	Type	Side	Symptom	Trauma	Location	NIHSS	IVtPA	LSCW to procedure time	Infarct pattern	Hemodynamic insufficiency	Embolism	Infarct volume extension on follow-up imaging	Clinical worsening within 24 h of the procedure	Hemorrhage	Stent	mRS at 90 days
1	79	1	Left	Aphasia, Neck pain	No	C2-4	21	No	8 h	Cortical/border zone	Yes	Yes	Yes	No	No	PRECISE	4
2	48	2	Left	Dysarthria	No	Petrous-C2	1	No	72 h	Cortical/border zone	Yes	Yes	No	Yes	PH-2	PRECISE	1
3	42	2	Left	Aphasia	No	C3-C4	7	No	24 h	Cortical/border zone	Yes	Yes	Yes	Yes	No	Neuroform	4
4	47	1	Left	Right-side weakness	No	C3-C4	6	Yes	11 h	Cortical/border zone	Yes	Yes	No	No	No	PRECISE	1
5	45	2	Left	Aphasia, Right-side weakness	No	Petroug-C3	16	No	15 h	Deep/border zone	Yes	Yes	No	No	No	PRECISE	1
6	77	1	Left	Right-side weakness	Yes	C6-7	1	No	72 h	Cortical/border zone	Yes	No	No	No	No	PRECISE	0
7	40	2	Left	Visual disturbance	Yes	Cavernous-Petrous	4	No	72 h	Cortical/border zone	Yes	Yes	No	No	No	Driver	1
8	43	2	Left	Dysarthria	No	C2-C4	0	No	72 h	No lesion	Yes	Yes	No	No	No	Wallstent	0
9	70	2	Left	Aphasia	No	C2-C4	16	Yes	7 h	Cortical/border zone	Yes	Yes	Yes	No	No	Solitaire FR	1
10	41	2	Left	Right-side weakness	Yes	Petrous	0	No	1 week	Cortical/border zone	Yes	Yes	No	No	No	Neuroform	0
11	54	1	Left	Aphasia	Yes	Petrous-C1	4	No	53 h	Cortical/border zone	Yes	Yes	No	No	No	Neuroform	1
12	33	2	Left	Mono-ocular blindness	Yes	C2-C3	2	No	48 h	No lesion	Yes	No	No	No	No	Protégé	0
13	50	2	Left	Right-hand weakness	Yes	Petrous-C3	0	No	1 week	Cortical/border zone	Yes	Yes	No	No	No	Xpert	0
14	43	2	Right	Mono-ocular blindness, Right	Yes	C2-C4	0	No	1 week	No lesion	Yes	No	Yes	Yes	PH-2	PRECISE	2
15	45	1	Both	Visual disturbance, headache	Yes	C2-C3	0	No	1 week	No lesion	Yes	No	No	No	No	Acculink	0
16	85	2	Right	Confusion	Yes	C1-C2	1	No	19 h	Cortical/borderzone	Yes	Yes	No	No	No	Protégé	1
17	42	2	Right	Left-side weakness	No	C1-4	0	No	12 h	Cortical	Yes	Yes	No	No	No	Protégé	0
18	40	1	Right	Mono-ocular blindness	No	C2-C3	0	No	25 h	No lesion	Yes	No	No	No	No	Xpert	0
19	61	2	Left	Dysarthria	No	C1-C3	14	No	24 h	Deep/borderzone	Yes	Yes	No	Yes	PH-2	PRECISE	4
20	48	2	Left	Seizure	Yes	C1-3	0	No	24 h	No lesion	Yes	No	No	No	No	Protégé	0
21	45	2	Right	Visual disturbance	No	Petrous-C3	0	No	16 h	No lesion	Yes	No	Yes.	No	No	LVIS Blue	0
22	60	1	Left	Dysarthria, Visual disturbance	No	C2-C3	3	No	24h	Cortical/borderzone	Yes	Yes	Yes	No	PH-1	PRECISE	2

NIHSS, national institutes of health stroke scale; LCSW, last significant clinical worsening; mRS, modified rankin scale; PH, parenchymal hematoma.

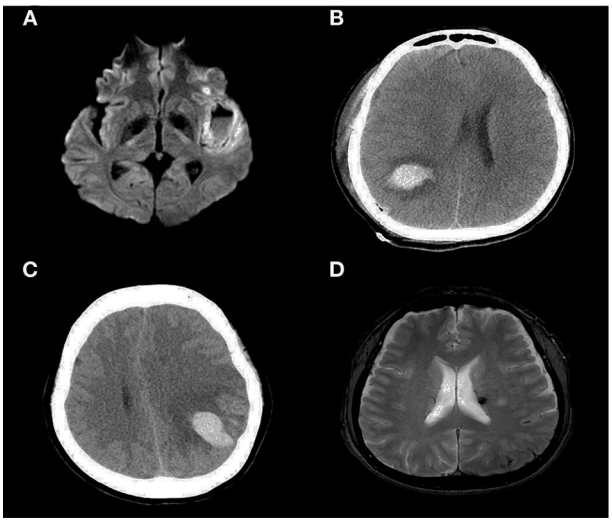

FIGURE 3 | Diffusion-weighted image showing a large, left-side, insular cortical hemorrhage with a distinct fluid level **(A)**. A CT scan showing a parenchymal hemorrhage in the right temporal-parietal area **(B)** and left parietal cortex **(C)**. A newly developed (small) subarachnoid hemorrhage in the left parietal convexity and microbleeds in the thalamus **(D)**.

with symptomatic hemorrhage worsened within 24 h (**Figure 3**). Two (9.1%) patients underwent decompressive hemicraniectomy after their procedures and one (4.5%) developed an in-stent thrombosis (**Table 2**). There were no recurrent ischemic symptoms or strokes during clinical follow-up. Follow-up carotid Doppler ultrasound and CTA/digital subtraction angiography data collected 3–6 months later were available for 21/22 patients, of whom 21 evidenced stent patency, complete restoration of the carotid artery caliber, and no evidence of in-stent thrombosis or significant re-stenosis, suggestive of successful stent-associated flow diversion and intimal flap reconstruction (**Table 3**).

DISCUSSION

We report the case series of flow-limiting CADs without ILVO, presenting as AIS requiring EVT. Most CAD patients who underwent EVT in our report exhibited favorable clinical outcomes and successful revascularization. The median discharge NIHSS score was 1.0 (0.0–3.0) and the 90 day mRS scores were good for 86.4% of those who were so scored. We wished to evaluate the outcomes of EVT in patients with ischemic symptoms caused by the hemodynamic deficit associated with CAD alone. EVT is not always necessary, as noted in an earlier studies (10), EVT can serve as a rescue therapy for CAD patients who lack adequate cerebral perfusion (4, 6). Restoration of antegrade flow to the brain parenchyma is critical when treating hemodynamically unstable CAD; this prevents recurrent thromboembolism and re-occlusion after successful recanalization (11). In addition, EVT for CAD patients not only restores anterograde flow but also inhibit the formation of new thrombi under the torn vessel wall because the flying intima becomes attached to the sidewall (12).

We graded patients using the Borgess classification (8), which is based on the presence or absence of a ruptured tunica intima in the dissected vessel, and the hemodynamic effects on blood flow, as revealed by conventional angiography. However, our patient number was small, and differences in prognosis by the Borgess classification could not be determined.

Angioplasty and stenting seek to improve perfusion by closing a false lumen and restoring the patency of the injured vessel. However, two major risk factors are in play: iatrogenic CAD expansion and reperfusion injury. The device must pass through the dissected carotid artery, and it is always possible that the wire or catheter may enter the false lumen. This can be very dangerous if anterograde flow is lacking, as in Borgess Type IB patients. We encountered no iatrogenic injuries. Reperfusion injury is caused by abrupt restoration of cerebral blood flow following revascularization (13), and may trigger the loss of flow autoregulation followed by damage to the blood–brain barrier (14). Of all patients, 18.2% developed symptomatic hemorrhages (reperfusion injury). Craniectomy was performed in 50% of these cases. All patients with reperfusion injuries had undergone the procedure more than 24 h after symptom onset. Re-perfusion has been reported deep associated with the provocation of hemorrhagic transformation through infarcted lesions. Previous reports based on MRI stated that blood-brain barrier disruption was an independent predictor of hemorrhagic transformation and reperfusion at the ischemic core was the most significant independent predictor of early blood-brain barrier disruption. Also, such injury may be related to the use of dual antiplatelet agents to prevent in-stent thrombosis.

No well-designed clinical trial has explored the optimal peri-procedural management of patients with CAD. Although we excluded patients with ILVOs, symptomatic hemorrhagic transformation or parenchymal hematoma (known complications of reperfusion injury) may develop peri-procedurally even after extracranial EVT (15). Prevention of reperfusion injury is most important; physicians must be aware that CAD patients are at risk for such injury during the entire admission period (13). All patients who undergo EVT require intensive hemodynamic monitoring; reperfusion injury requires prompt diagnosis and management (16). In our view, the optimal therapeutic approach is vigilant monitoring of vital signs and control of the systolic blood pressure (17). Although we do not have enough clinical evidence supporting such an approach, we believe that it greatly reduces the risk of potentially devastating reperfusion injury. In our four patients with reperfusion injuries (intracranial hemorrhages), we controlled the arterial pressures within hours; the several days without antiplatelet agents did not precipitate in-stent thrombosis.

Our EVT procedure differed from that employed to treat atherosclerotic stenosis. In our patients, the lesions were considerably higher and/or extended, and the dissected segment requiring treatment was longer than atherosclerosis (18). However, in most patients, if the entry zone of the dissected intima is fully covered, a 40 mm stent is sufficient. Stents were initially placed after balloon angioplasty, but in later cases,

angiography revealed luminal patency even after stenting alone. We did not employ an embolic protective device because of the risk that the dissection might expand; we encountered no distal embolization.

The limitations of this study include its retrospective cross-sectional nature. The number of patients was small and we lacked a control group. However, we provide preliminary data that may guide future prospective randomized studies seeking to confirm our results and to consolidate a therapeutic approach for the management of ischemic strokes related to CAD.

We found that EVT of ischemic strokes associated with CAD afforded an acceptable reperfusion rate and good outcomes. Further studies are necessary to validate our findings and to explore their clinical implications with regard to triggering additional and timely interventions in patients with CAD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Jeju National University Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

J-GK and DL conceptualized and designed the study. J-GK, YS, C-HK, JC, DS, and DL reviewed relevant articles, recruited patients, and collected data. J-GK, JC, and DL analyzed the data. All authors contributed to data interpretation, write-up, editing, revision of the final manuscript, and contributed to the production of the final version of this manuscript.

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Effectiveness of Standard-Dose vs. Low-Dose Alteplase for Acute Ischemic Stroke Within 3–4.5 h

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Background: The efficacy and safety of intravenous alteplase administered 3–4.5 h after acute ischemic stroke have been demonstrated. However, whether responses differ between low-dose and standard-dose alteplase during this time window and whether certain subgroups benefit more remain unknown.

Patients and Methods: The current analysis was based on a multicenter matched-cohort study conducted in Taiwan. The treatment group comprised 378 patients receiving intravenous alteplase 3–4.5 h after stroke onset, and the control group comprised 378 age- and sex-matched patients who did not receive alteplase treatment during the same period. Standard- and low-dose alteplase was administered to patients at the physician's discretion.

Results: Overall, patients receiving alteplase exhibited more favorable outcomes than did controls [34.0 vs. 22.7%; odds ratio (OR): 1.75, 95% confidence interval (CI): 1.27–1.42], and the effectiveness was consistent in all subgroups. Although patients in the standard-dose group (n = 182) were younger than those in the low-dose (n = 192) group, the proportions of patients with favorable outcomes (36.3 vs. 31.8%; OR: 1.22, 95% CI: 0.80–1.88) and symptomatic hemorrhage (2.8 vs 4.2%; OR: 0.65, 95% CI: 0.21–2.02) were consistently comparable in a covariate-adjusted model and an age-matched cohort. In the subgroup analysis, patients with cardioembolism, atrial fibrillation, and hypercholesterolemia were more likely to achieve favorable outcomes after receiving standard-dose than low-dose alteplase.

Conclusion: In the 3–4.5 h time window, the effectiveness and safety of standard-dose and low-dose alteplase may be comparable. A standard dose may be selected for patients with cardioembolism, atrial fibrillation, or hypercholesterolemia.

Keywords: thrombolysis, alteplase, rt-PA, atrial fibrillation, hypercholesterolemia

INTRODUCTION

The efficacy and safety of intravenous thrombolysis with 0.9 mg/kg alteplase at 3–4.5 h after acute ischemic stroke (AIS) were first demonstrated in the European Cooperative Acute Stroke Study III [ECASS III; (1)] and have been subsequently verified by a meta-analysis (2) and several real-world studies (3–5). Intravenous alteplase treatment for AIS within 4.5 h of symptom onset is currently recommended by various professional organizations (6–9). However, the Food and Drug Administrations in the United States and Taiwan have yet to approve the use of alteplase in the time window of 3–4.5 h.

Whether a low dose of alteplase reduces the risk of intracerebral hemorrhage (ICH) with similar effectiveness as that of a standard dose has long been debated. The ENhanced Control of Hypertension And Thrombolysis strokE stuDy (ENCHANTED) demonstrated that although low-dose alteplase was not non-inferior to standard-dose alteplase in reducing death and disability when used within 4.5 h of stroke onset, significantly fewer symptomatic ICH (sICH) events were reported in the low-dose group than in the standard-dose group (10). Currently, 0.6 mg/kg is the only approved low dose for alteplase in Japan; moreover, low-dose alteplase is commonly used in several other Asian countries, including Taiwan, for safety and cost reduction (11).

Most studies comparing standard-dose and low-dose alteplase have included patients treated within 3 or 4.5 h; however, few studies have specifically emphasized the time window of 3–4.5 h. Because the response to alteplase treatment may gradually decrease with time, whether a low dose can achieve similar effectiveness as that of a standard dose in the time window of 3–4.5 h remains unknown. Additionally, whether certain patient subgroups may benefit more from standard-dose or low-dose alteplase merits investigation. Therefore, in this study, we analyzed data of a published multicenter matched-cohort study in Taiwan that had demonstrated the real-world effectiveness of alteplase administered in the time window of 3–4.5 h after symptom onset (12).

METHODS

Study Design

This study involved the analysis of data from a multicenter, retrospective, matched-cohort study initiated by the Taiwan Stroke Society to evaluate the effectiveness and safety of intravenous alteplase at 3–4.5 h after symptom onset in patients with AIS. The detailed study protocol and results have been published, and the present study is a subgroup analysis of the primary study (12). Briefly, data were extracted from 16 hospitals participating in the Taiwan Stroke Registry, which contains prospectively collected data on patients' basic demographic characteristics and risk factors, clinical course and treatment, and etiology and outcomes of stroke. The study period was from January 2008 to December 2017. The use of data from the Taiwan Stroke Registry was approved by the Institutional Review Board of National Taiwan University Hospital (Research Ethical Committee No. 201801064RINC) and informed consent was waived because this was a retrospective analysis of the prospective stroke registry. All study methods were performed in accordance with the Declaration of Helsinki. The data used in the present study can be obtained from the corresponding author on reasonable request.

Study Population

Although this was not a randomized controlled trial, we enrolled patients at a 1:1 ratio according to whether they received intravenous alteplase (treatment group) or not (control group) within the specified time window. Patients ≥18 years old with a clinical diagnosis of AIS were included in the analysis. Patients in the treatment group received intravenous alteplase within a time window of 3–4.5 h after stroke onset; their treatment complied with the regulations of the Taiwan Food and Drug Administration and the reimbursement criteria of the National Health Insurance program in Taiwan (13). For each patient in the treatment group, one age- and sex-matched patient arriving at the emergency room in the same hospital within 2–4.5 h, but not receiving intravenous alteplase, was enrolled into the control group. The rationale behind selecting 2 h as a lower limit of onset-to-door time was that thrombolysis could not be administered to these patients within 3 h. In addition, patients were assigned to the control group only if they did not have any obvious contraindication to intravenous alteplase. Patients who received any other reperfusion therapy such as intra-arterial thrombolysis or endovascular thrombectomy were excluded from the current analysis.

The Taiwan Food and Drug Administration has approved the administration of 0.9 mg/kg intravenous alteplase for AIS as the standard dose in clinical practice. In addition, the Taiwan Food and Drug Administration has recommended that low-dose (0.6 mg/kg) intravenous alteplase may be associated with lower sICH risk on the basis of the results in the ENCHANTED and Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) trials (10, 14). In clinical practice, a standard or low dose is used according to the treating physicians' initial evaluation of the patient and professional discretion. Generally, physicians in Taiwan prefer using low-dose alteplase in patients >70 years old on the basis of the results of the TTT-AIS study (14).

Clinical Characteristics and Outcome Measures

The demographic profile, body weight, and vascular risk factors (namely hypertension, diabetes mellitus, hyperlipidemia, previous ischemic stroke, ischemic heart disease, atrial fibrillation, and ever or current smoking) of the study patients were documented. Furthermore, the initial National Institute of Health Stroke Scale (NIHSS) score, blood pressure, and laboratory data (including glucose, creatinine, platelets, and international normalized ratio) at the index stroke event were recorded. The NIHSS score was recorded at least once every day in the first 3 days and then recorded according to regional clinical practice. Hyperlipidemia was defined as receiving of lipid-lowering agents or having one of the following: fasting serum total cholesterol $\geq$ 200 mg/dl, fasting serum low-density lipoprotein cholesterol $\geq$ 130 mg/dl, fasting serum high-density lipoprotein $<$ 40 mg/dl, or fasting serum triglyceride $\geq$ 150 mg/dl. Hyperlipidemia was further classified as hypercholesterolemia (total cholesterol $\geq$ 200 mg/dl or low-density lipoprotein cholesterol $\geq$ 130 mg/dl) or hypertriglyceridemia (triglyceride $\geq$ 150 mg/dl). Ischemic stroke was classified into the subtypes large-artery atherosclerosis, small vessel occlusion, cardioembolism, and others on the basis of the Trial of Org 10172 in the Acute Stroke Treatment (TOAST) classification (15).

The primary effectiveness outcome was the percentage of patients with favorable functional outcomes as defined by modified Rankin Scale (mRS) scores of 01 at 90 days after index stroke event. The secondary effectiveness outcomes were the percentage of patients with mRS scores of 02 at 90 days and early neurological deterioration (END), which was defined as an increase in the NIHSS score by two or more points from the initial or the lowest NIHSS score between the time of admission and 72 h. The safety outcomes were any ICH event after thrombolysis and sICH occurrence as defined by the ECASS III criteria (1). To detect ICH, a brain computed tomography or magnetic resonance imaging scan was routinely performed at 24–36 h after thrombolysis.

Statistical Analysis

The original study consisted of 748 eligible patients (original cohort), of whom 374 received alteplase (alteplase cohort) and 374 did not receive alteplase (control cohort). In the original cohort, the baseline characteristics were comparable, as reported in the published article [**Supplemental Table 1**; (12)]. The demographic, clinical, and laboratory profiles were compared between the standard-dose and low-dose groups in the alteplase cohort by using the Mann–Whitney *U* test or chi-square test, as appropriate. An additional comparison was performed between patients treated with alteplase (standard and low doses) and controls. Because a considerable age gap existed between patients treated with standard and low doses of alteplase, the cohorts were age- and NIHSS score–matched by using the SAS PSMATCH procedure.

The effectiveness and safety outcomes (expressed in percentage) of the standard-dose and low-dose groups in

TABLE 1 | Baseline characteristics of patients who were given standard-dose and low-dose alteplase vs. controls.

Characteristics	Standard dose (n = 182)	Low dose (n = 192)	Control (n = 374)
Age (year)	63 (53–72)	72 (63–79)*	69 (60–77)†
Age≥70 y, *n* (%)	53 (29.1)	107 (55.7)*	183 (48.9)†
Age≥80 y, *n* (%)	16 (8.8)	40 (20.8)	70 (18.7)†
Male sex, *n* (%)	123 (67.6)	128 (66.7)	251 (67.1)
Body weight (Kg)	63 (56–75)	65 (56–71)	65 (56–73)
Stroke subtype			
LAA	40 (22.0)	47 (24.5)	97 (25.9)
SVO	32 (17.6)	22 (11.5)	75 (20.1)
CE	52 (28.6)	66 (34.4)	108 (28.9)
Others	58 (31.9)	57 (29.7)	94 (25.1)
NIHSS	11 (7–17)	10 (6–17)	9 (5–15)†,‡
Systolic BP (mmHg)	156 (136–181)	158 (141–182)	161 (138–182)
Diastolic BP (mmHg)	92 (81–106)	88 (77–100)*	90 (79–102)
Onset-to-needle (min)	195 (184–215)	205 (190–238)*	-
Door-to-needle (min)	67 (51–99)	64 (50–87)	-
Medical history			
Hypertension	136 (74.7)	146 (76.0)	291 (77.8)
Diabetes mellitus	62 (34.1)	75 (39.1)	160 (42.8)†
Previous stroke	32 (17.6)	43 (22.4)	97 (25.9)†
Diabetes mellitus with previous stroke	14 (7.7)	23 (12.0)	45 (12.0)
Ischemic heart disease	19 (10.4)	26 (13.5)	38 (10.2)
Atrial fibrillation	55 (30.2)	72 (37.5)	113 (30.2)
Hyperlipidemia	101 (55.5)	98 (51.0)	201 (53.7)
Hypercholesterolemia	82 (45.1)	92 (47.9)	175 (46.8)
Hypertriglyceridemia	40 (22.0)	27 (14.1)*	64 (17.1)
Ever smoking	57 (31.3)	71 (37.0)	137 (36.6)
Current smoker	51 (28.0)	52 (27.1)	98 (26.2)
Prior antiplatelet use	35 (19.2)	47 (24.5)	99 (26.5)
Prior anticoagulant use	5 (2.8)	5 (2.6)	16 (4.3)
Laboratory data			
Glucose (mg/dl)	132 (112–172)	133 (105–180)	130 (110–182)
INR	1.00 (0.96–1.07)	0.99 (0.94–1.05)	1.00 (0.95–1.06)
Creatinine (mg/dl)	1.01 (0.85–1.34)	1.00 (0.80–1.27)	1.00 (0.80–1.30)
Platelet count (10^5/mm^3)	221 (178–258)	201 (166–236)*	203 (168–251)†
Outcome			
mRS 0–1	66 (36.3)	61 (31.8)	85 (22.7)†,‡
mRS 0–2	92 (50.6)	87 (45.3)	150 (40.1)†
END	23 (12.6)	33 (17.2)	73 (19.5)†
Any ICH	29 (15.9)	36 (18.8)	32 (8.6)†,‡
Symptomatic ICH	5 (2.8)	8 (4.2)	9 (2.4)

*All variables were compared between patients receiving standard-dose and the low-dose alteplase first. Additional comparisons were performed between the controls and standard-dose or low-groups. *$P < 0.05$ between the standard-dose and the low-dose groups. †$P < 0.05$ between the standard-dose group and control; ‡$P < 0.05$ between the low-dose group and control.*

BP, blood pressure; CE, cardioembolism; END, early neurological deterioration; ICH, intracerebral hemorrhage; INR, international normalized ratio; mRS, modified Rankin Scale; LAA, large-artery atherosclerosis; NIHSS, national institute of health stroke scale; SVO, small vessel occlusion.

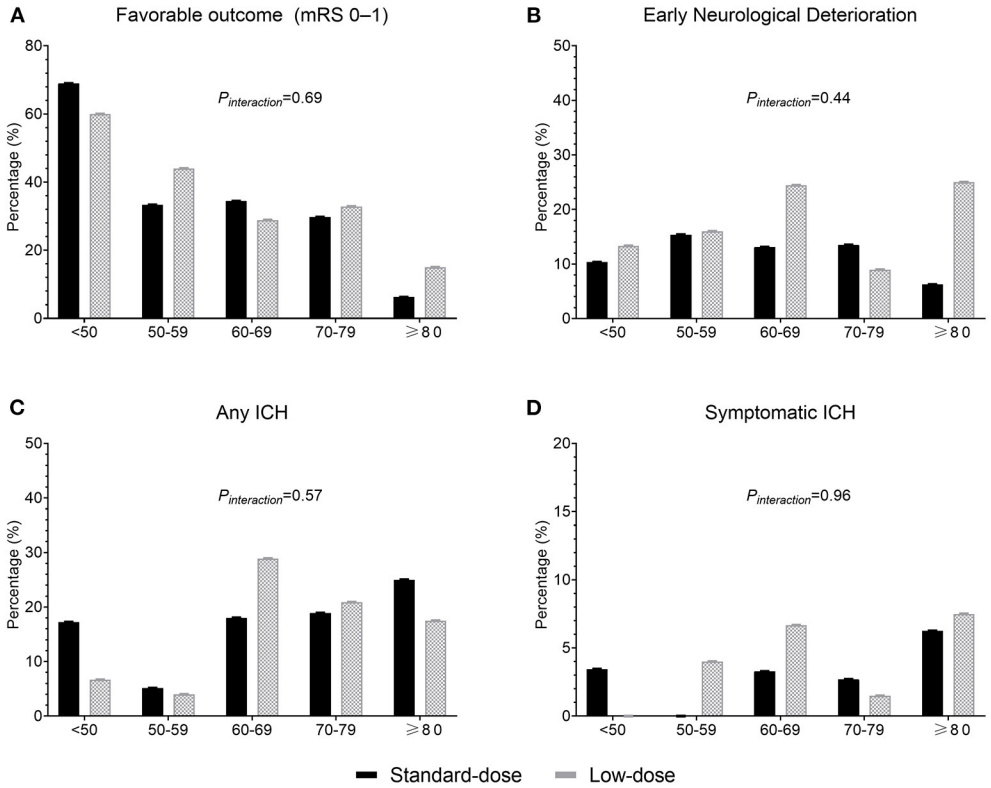

FIGURE 1 | Proportions of clinical outcomes between the standard-dose and low-dose groups according to age. **(A)** Favorable outcome (modified Rankin Scale score 01); **(B)** early neurological deterioration; **(C)** any intracerebral hemorrhage (ICH); and **(D)** symptomatic ICH.

the alteplase cohort were plotted by age at 10-year intervals (<50, 5059, 6069, 7079, and ≥80), and the trend between the age groups and alteplase dose was tested using the generalized linear mixed model. To compare clinical outcomes between the standard-dose and low-dose groups, logistic regression analyses were performed with effectiveness (mRS scores 01, mRS scores 02, and END) and safety outcomes (any ICH and sICH event) as dependent variables. First, an unadjusted analysis was performed, and the crude odds ratio (OR) was calculated. Subsequently, a multivariable analysis was performed and adjusted for covariates that were significantly associated with outcomes in the univariate analysis (**Supplemental Table 2**). The covariates were age, NIHSS score, diabetes mellitus, previous ischemic stroke, and atrial fibrillation for mRS score 01; NIHSS score, diabetes mellitus, and atrial fibrillation for END; and male sex, NIHSS score, diabetes mellitus, and atrial fibrillation for any ICH event. Symptomatic ICH was not adjusted for in the analysis owing to its rarity. Furthermore, unadjusted logistic regression analyses were performed between the matched patients of the standard-dose and low-dose groups.

To explore which subgroup may benefit more from the treatment (alteplase vs. control or standard dose vs. low dose), logistic regression analyses were performed with effectiveness outcomes as the dependent variable and clinical variables, treatment, and interaction terms between the clinical variables and treatment as the predictors. Statistically significant interaction terms in the subgroup analyses implied that treatment effects may differ in the subgroup. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA), and a P-value of <0.05 indicated significance.

RESULTS

Patient Characteristics

Baseline demographics, vascular risk factors, laboratory results, and stroke profiles of patients in the standard-dose alteplase (n = 182), low-dose alteplase (n = 192), and control (n = 374) groups are summarized in **Table 1**. Patients in the low-dose group were significantly older than those in the standard-dose group (69.5 ± 12.4 vs. 62.5 ± 13.1 years, P < 0.0001). The door-to-needle time was comparable between the two groups, whereas the onset-to-needle time was longer in the low-dose group. The age- and NIHSS score–matched cohorts comprised 65 patients each at a 1:1 ratio. The median age was 68 years in both the groups, and their demographic profiles were comparable (**Supplemental Table 3**).

Clinical Outcomes Between Patients Treated With Standard-Dose and Low-Dose Alteplase

Figure 1 presents the distribution of favorable functional outcomes (mRS scores 01), END, any ICH event, and sICH by age at the 10-year intervals between the standard-dose and

TABLE 2 | Outcomes of patients receiving standard-dose and low-dose alteplase.

Clinical outcome	Standard-dose	Low-dose	Crude OR (95% CI)	Covariate-adjusted OR (95% CI)	Matched cohort OR (95% CI)
mRS 0–1	66 (36.26)	61 (31.77)	1.22 (0.80–1.88)	0.96 (0.85–1.61)	0.87 (0.43–1.80)
mRS 0–2	92 (50.55)	87 (45.31)	1.23 (0.82–1.85)	1.08 (0.65–1.78)	0.94 (0.47–1.87)
END	23 (12.64)	33 (17.19)	0.70 (0.39–1.24)	0.75 (0.41–1.37)	0.89 (0.35–2.27)
Any ICH	29 (15.93)	36 (18.75)	0.82 (0.48–1.41)	0.86 (0.47–1.56)	0.88 (0.33–2.34)
Symptomatic ICH	5 (2.75)	8 (4.17)	0.65 (0.21–2.02)	0.65 (0.21–2.02)*	0.49 (0.04–5.57)

**Symptomatic ICH outcome was not further adjusted with covariates owing to its rarity.*
END, early neurological deterioration; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale.

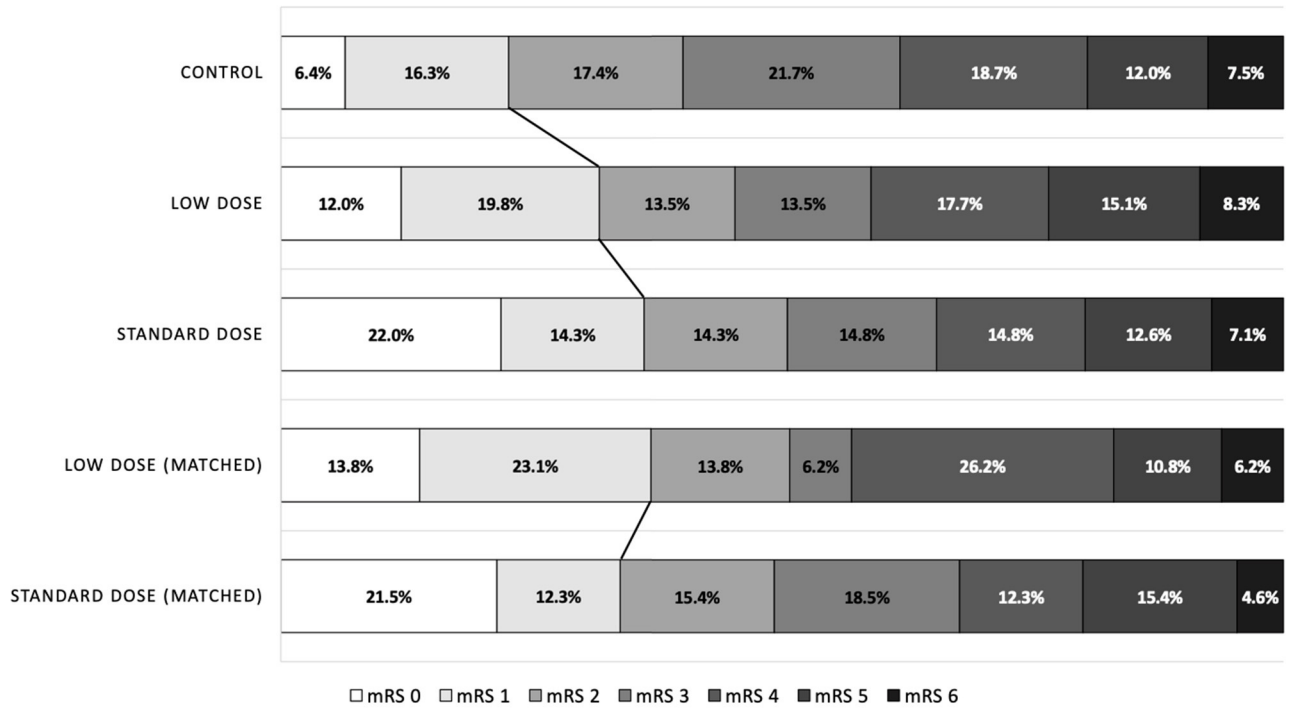

FIGURE 2 | Distribution of modified Rankin Scale scores at 90 days after stroke, according to the treatment groups.

low-dose groups. Despite the trend of fewer favorable outcomes (P_{trend} = 0.0002) and more ICH events (P_{trend} = 0.06) with increasing age, no significant age and dose interaction effect was observed for all clinical outcomes. For mRS scores 0–1, 36.3% and 31.8% of patients exhibited the primary effectiveness outcome in the standard-dose and low-dose groups, respectively (OR = 1.22, 95% confidence interval [CI] = 0.80–1.88, P = 0.36). For mRS scores 02, the corresponding proportions were 50.6% and 45.3% (OR = 1.23, 95% CI = 0.82–1.85). Compared with the low-dose group, fewer patients reported END, any ICH event, and sICH in the standard-dose group, although the results were nonsignificant (**Table 2**).

In the covariate-adjusted model, the results were overall comparable when the point estimates moved toward null as expected. However, in the matched cohort, the proportions of patients exhibiting favorable outcome were 33.9% and 36.9% in the standard-dose and low-dose groups, respectively (OR = 0.87, 95% CI = 0.43–1.80; **Figure 2**). The point estimates of other outcomes were similar to those of the alteplase cohort.

Subgroup Analysis of Effectiveness Outcomes

In the original cohort (alteplase vs. control), no clinical variable significantly influenced the primary outcome (all $P_{interaction}$ > 0.05; **Table 3** and **Figure 3A**), indicating that the effectiveness of alteplase was consistent in all patient subgroups. These included subgroups that would otherwise be excluded from the ECASS III trial, such as patients aged >80 years ($P_{interaction}$ = 0.89), those with concomitant diabetes mellitus and prior stroke ($P_{interaction}$ = 0.37), and those using oral anticoagulants ($P_{interaction}$ = 0.15).

In the alteplase cohort (standard dose vs. low dose), significant interactions were observed between the alteplase dose and the presence of atrial fibrillation ($P_{interaction}$ = 0.01) as well as between the alteplase dose and the presence of

TABLE 3 | Subgroup analysis of the effectiveness of alteplase in yielding favorable outcome.

Variables		*N*	OR	95% CI	$P_{interaction}$
Age	<70 y	405	1.571	1.040–2.373	0.558
	≥70 y	343	1.926	1.118–3.318	
	<80 y	622	1.697	1.205–2.389	0.888
	≥80 y	116	1.857	0.555–6.216	
Sex	Male	502	1.611	1.095–2.370	0.441
	Female	246	2.131	1.172–3.877	
Hypertension	Yes	573	1.636	1.124–2.379	0.530
	No	175	2.078	1.088–3.967	
Diabetes mellitus	Yes	297	1.437	0.813–2.538	0.483
	No	451	1.843	1.235–2.749	
Previous stroke	Yes	172	1.495	0.598–3.740	0.791
	No	576	1.707	1.199–2.430	
Diabetes mellitus with previous stroke	Yes	82	3.267	0.779–13.701	0.370
	No	666	1.666	1.191–2.329	
Ischemic heart disease	Yes	83	1.799	0.633–5.115	0.964
	No	665	1.754	1.247–2.466	
Atrial fibrillation	Yes	240	2.216	1.146–4.288	0.475
	No	508	1.680	1.152–2.451	
Hyperlipidemia	Yes	400	1.610	1.041–2.490	0.579
	No	348	1.936	1.194–3.139	
Hypercholesterolemia	Yes	349	1.444	0.909–2.296	0.262
	No	399	2.094	1.330–3.296	
Hypertriglyceridemia	Yes	131	1.444	0.909–2.296	0.952
	No	617	2.094	1.330–3.296	
Smoking habit	Yes	255	1.367	0.807–2.316	0.240
	No	483	2.042	1.351–3.085	
Current smoking	Yes	201	1.450	0.804–2.615	0.462
	No	547	1.889	1.281–2.787	
Prior antiplatelet use	Yes	181	1.111	0.542–2.278	0.181
	No	567	1.924	1.334–2.775	
Prior anticoagulant use	Yes	26	10.00	0.915–109.2	0.145
	No	722	1.665	1.200–2.310	
Initial NIHSS score	≤10	202	2.122	1.421–3.169	0.966
	>10	546	2.086	1.042–4.174	
Ischemic stroke types	LAA	184	1.147	0.561–2.346	0.614
	SVO	129	2.057	0.984–4.031	
	CE	226	1.892	1.022–3.504	
	Others	209	2.016	1.112–3.656	

Favorable outcome was defined as a modified Rankin Scale score of 0 or 1.
CE, cardioembolism; LAA, large-artery atherosclerosis; NIHSS, national institute of health stroke scale; SVO, small vessel occlusion.

hypercholesterolemia ($P_{interaction} = 0.01$; **Table 4** and **Figure 3B**). In patients with atrial fibrillation, administration of a standard dose resulted in higher odds of favorable outcomes than using a low dose (OR = 2.80, 95% CI = 1.24–6.32); in patients without atrial fibrillation, opposite results were obtained (OR = 0.82, 95% CI = 0.49–1.38). Furthermore, administration of a standard dose was associated with favorable outcome in patients with hypercholesterolemia (OR = 2.23, 95% CI = 1.17–4.26) but not in patients without hypercholesterolemia (OR = 0.73, 95% CI = 0.41–1.32). Regarding ischemic stroke type, administration of standard-dose alteplase was associated with favorable outcome only in patients with the cardioembolism subtype (OR = 2.49, 95% CI = 1.12–5.54). The interaction effect between the alteplase dose and atrial fibrillation remained significant even after adjustment for age and NIHSS score ($P_{interaction} = 0.03$) or in the matched cohort ($P_{interaction} = 0.04$). On the other hand, the interaction effect between the dose and hypercholesterolemia persisted in the age- and NIHSS score–adjusted model ($P_{interaction} = 0.04$) but not in the matched cohort ($P_{interaction} = 0.38$). No significant interaction was noted between the occurrence of any ICH event and clinical variables (all $P_{interaction} > 0.05$; **Table 5**).

DISCUSSION

The present study demonstrated that in the time window of 3–4.5 h after AIS onset, patients who received thrombolysis with intravenous alteplase exhibited functional improvement compared with controls, and the results were consistent across patient subgroups. Moreover, standard-dose and low-dose alteplase exhibited comparable effectiveness and safety in this time window, although the standard dose may be preferred in patients with atrial fibrillation or hypercholesterolemia.

The main novelty of our study is the comparison of the effectiveness of standard-dose and low-dose alteplase in the late time window, which has never been specifically investigated before. Japan proposed the use of low-dose alteplase at 0.6 mg/kg in 2006 on the basis of the results of an uncontrolled, open-label parallel study, in which the thrombolytic agent was administered within 3 h (16). This low-dose approach was soon adopted by neighboring Asian countries such as China, Korea, and Taiwan; however, several observational studies have reported contrary results regarding the benefit of the low-dose regimen (14, 17, 18). Notably, comparative studies using standard- or low-dose alteplase unquestionably extended the time limit to 4.5 h following the publication of the ECASS III trial in 2008, although the ECASS III trial only demonstrated the benefit of 0.9 mg/kg alteplase within 3–4.5 h (1).

To date, the strongest evidence of the effectiveness of low-dose alteplase administration within a window of 3–4.5 h was provided by the ENCHANTED trial published in 2016, which included patients who were given alteplase within 4.5 h of stroke onset (10). In the subgroup analysis of the ENCHANTED trial, no significant interaction was observed between the alteplase dose and time from onset to randomization (<3 vs. ≥3 h). In the ≥3-h subgroup (i.e., 3–4.5 h), the proportion of death and disability was 51.1% in the low-dose group and 50.1% in the standard-dose group (OR = 1.04, 95% CI = 0.84–1.30). In a study published in 2019 that included data of 6,250 patients from nine stroke registries in six Asian countries (the largest real-world data–based study to date) and compared the effectiveness of low-dose and standard-dose alteplase (11), the adjusted odds of death and disability or sICH were not significantly different between the low-dose and standard-dose groups. Although no

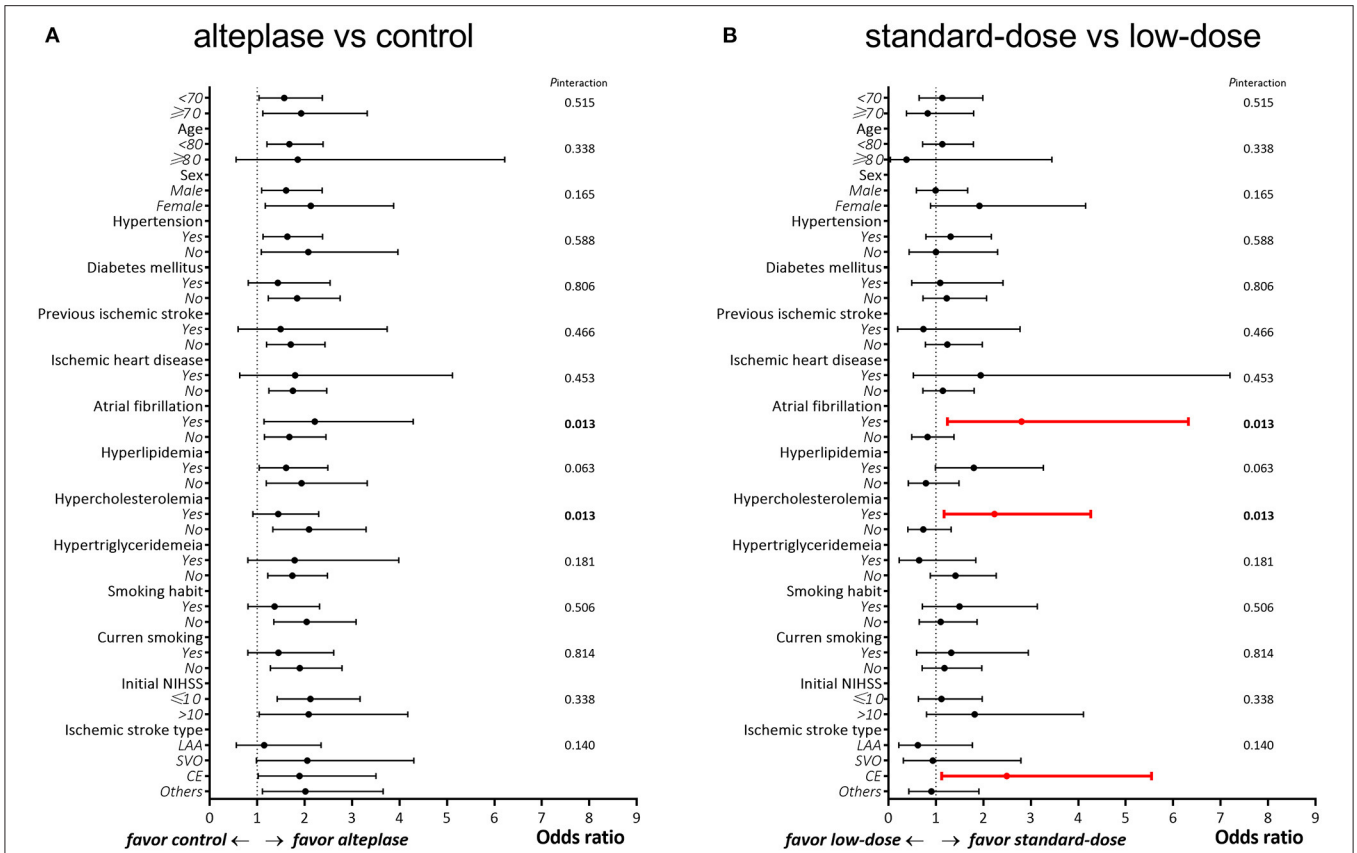

FIGURE 3 | Subgroup analysis between patients treated with **(A)** alteplase vs. control and **(B)** standard-dose vs. low-dose alteplase.

significant interaction was observed between the alteplase dose and time (<3 vs. ≥3 h; $P_{interaction} = 0.395$), a trend favoring low-dose alteplase was noted in the ≥3-h subgroup (OR = 0.75 for death and disability, 95% CI = 0.51–1.10) compared with the <3-h subgroup (OR = 1.13, 95% CI = 0.93–1.37).

In comparison, our study only enrolled patients treated within a window of 3–4.5 h; this study might be the first matched-cohort study in Asia with a quasi-randomized control design to specifically consider this indication. The original goal of this study was to demonstrate the benefit of alteplase administered within a window of 3–4.5 h in comparison with the control. Further subgroup analyses revealed that the effectiveness and safety outcome were numerically higher in patients who were given standard-dose alteplase than in those who were given low-dose alteplase. Because of the observational study design, confounding by indication is inevitable, and physicians tend to prescribe low-dose alteplase for older patients. This is partly attributed to a finding reported by a multicenter study in Taiwan that a low dose of 0.6 mg/kg is associated with improved functional outcomes in elderly patients [71–80 years; (14)]. In our study, the overall effectiveness diminished with increasing age, irrespective of the alteplase dose used. Thus, more favorable outcomes may be observed in the standard-dose group. To overcome this selection bias, an age- and severity-matched cohort was created, and the results revealed a slightly greater number of favorable outcomes in the low-dose group than in the standard-dose group (36.9 vs. 33.9%). However, the aforementioned results were nonsignificant. Nevertheless, the present results do not preclude the use of a standard dose in older patients within the 3–4.5-h time window, even in those of Asian ethnicity.

A low-dose regimen, however, was associated with significantly lower sICH occurrence rate (1.0 vs. 2.1%, $P = 0.01$) in the ENCHANTED trial (10). Furthermore, a multicenter study in Taiwan revealed that in elderly patients (7180 years), the rate of sICH occurrence increased significantly as the dose increased (14). Our study, however, found that the rates of any ICH event and sICH occurrence were nonsignificantly higher in the low-dose group than in the standard-dose group. This may be related to the higher age in the low-dose group. However, no obvious interaction effect between age and the alteplase dose on ICH was observed (**Figure 1**), and the result remained consistent in age-adjusted or age-matched analyses. Certain unobserved factors in the low-dose group may have contributed to a higher sICH rate, or it could have occurred by chance given the low event rates. Our study results indicate that standard-dose alteplase within 3–4.5 h of stroke onset can be administered without causing an absolute increase in the risk of hemorrhage.

TABLE 4 | Subgroup analysis of the effectiveness of standard-dose vs. low-dose alteplase.

Variables		*N*	OR	95% CI	$P_{interaction}$
Age strata	<70 y	214	1.14	0.65–1.99	0.52
	≥70 y	160	0.83	0.38–1.80	
	<80 y	318	1.14	0.72–1.79	0.34
	≥80 y	56	0.38	0.04–3.44	
Sex	Male	251	0.99	0.59–1.67	0.17
	Female	123	1.92	0.89–4.15	
Hypertension	Yes	282	1.31	0.79–2.17	0.59
	No	92	1.00	0.44–2.30	
Diabetes mellitus	Yes	137	1.09	0.49–2.41	0.81
	No	237	1.23	0.73–2.07	
Previous stroke	Yes	75	0.74	0.16–2.77	0.47
	No	299	1.24	0.78–1.98	
Diabetes mellitus with previous stroke	Yes	37	0.22	0.02–2.06	0.12
	No	337	1.31	0.84–2.05	
Ischemic heart disease	Yes	45	1.94	0.53–7.20	0.45
	No	329	1.15	0.73–1.81	
Atrial fibrillation	Yes	127	**2.80**	**1.24–6.32**	**0.01**
	No	247	0.82	0.49–1.38	
Hyperlipidemia	Yes	199	1.80	0.99–3.26	0.06
	No	175	0.79	0.42–1.49	
Hypercholesterolemia	Yes	174	**2.23**	**1.17–4.26**	**0.01**
	No	200	0.73	0.41–1.32	
Hypertriglyceridemia	Yes	67	0.65	0.23–1.84	0.18
	No	307	1.41	0.88–2.27	
Smoking habit	Yes	128	1.50	0.71–3.14	0.51
	No	246	1.10	0.65–1.87	
Current smoking	Yes	103	1.32	0.59–2.95	0.81
	No	271	1.18	0.71–1.97	
Prior antiplatelet use	Yes	82	1.10	0.38–3.16	0.88
	No	292	1.20	0.75–1.93	
Prior anticoagulant use	Yes	10	1.00	0.08–12.7	0.88
	No	364	1.23	0.79–1.90	
Initial NIHSS score	≥10	191	1.12	0.63–1.97	0.34
	>10	183	1.82	0.80–4.11	
Ischemic stroke types	LAA	87	0.62	0.22–1.77	0.14
	SVO	54	0.93	0.31–2.79	
	CE	118	**2.49**	**1.12–5.54**	
	Others	115	0.90	0.43–1.91	

Favorable outcome was defined as a modified Rankin Scale score of 0 or 1.
CE, cardioembolism; LAA, large-artery atherosclerosis; NIHSS, national institute of health stroke scale; SVO, small vessel occlusion.
Values in bold indicate statistical significance.

TABLE 5 | Subgroup analysis of the safety (all ICH) of standard-dose vs. low-dose alteplase.

Variables		*N*	OR	95% CI	$P_{interaction}$
Age	<70 y	214	0.757	0.357–1.602	0.538
	≥70 y	160	1.073	0.472–2.436	
	<80 y	318	0.752	0.417–1.355	0.341
	≥80 y	56	1.571	0.388–6.369	
Sex	Male	251	0.914	0.442–1.890	0.674
	Female	123	0.722	0.317–1.648	
Hypertension	Yes	282	0.745	0.406–1.373	0.485
	No	92	1.197	0.368–3.895	
Diabetes mellitus	Yes	137	0.941	0.430–2.058	0.731
	No	237	0.777	0.363–1.663	
Previous stroke	Yes	75	1.010	0.311–3.278	0.706
	No	299	0.783	0.426–1.436	
Diabetes mellitus with previous stroke	Yes	37	1.133	0.255–5.037	0.680
	No	337	0.810	0.453–1.449	
Ischemic heart disease	Yes	45	2.538	0.599–10.754	0.100
	No	329	0.688	0.382–1.238	
Atrial fibrillation	Yes	127	0.582	0.264–1.284	0.121
	No	247	1.428	0.633–3.225	
Hyperlipidemia	Yes	199	0.657	0.302–1.429	0.405
	No	175	1.039	0.490–2.207	
Hypercholesterolemia	Yes	174	0.507	0.213–1.205	0.156
	No	200	1.139	0.560–2.316	
Hypertriglyceridemia	Yes	67	0.629	0.162–2.434	0.655
	No	307	0.879	0.488–1.585	
Smoking habit	Yes	128	0.524	0.170–1.614	0.398
	No	246	0.912	0.487–1.710	
Current smoking	Yes	103	0.407	0.116–1.423	0.211
	No	271	0.987	0.538–1.811	
Prior antiplatelet use	Yes	82	0.775	0.280–2.146	0.830
	No	292	0.884	0.464–1.683	
Prior anticoagulant use	Yes	10	0.788	0.457–1.359	0.975
	No	364	N/A	N/A	
Initial NIHSS score	≥10	191	0.669	0.210–2.131	0.764
	>10	183	0.819	0.429–1.562	
Ischemic stroke types	LAA	87	1.219	0.410–3.623	0.061
	SVO	54	1.000	N/A	
	CE	118	**0.417**	**0.177–0.980**	
	Others	115	3.101	0.921–10.44	

CE, cardioembolism; LAA, large-artery atherosclerosis; NIHSS, national institute of health stroke scale; SVO, small vessel occlusion.
N/A, not accessible because of the absence of or insufficient data on number of events.
Values in bold indicate statistical significance.

In the ECASS III trial, no heterogeneity in the treatment effect within a time window of 3–4.5 h was observed across all patient subgroups (19). Our study demonstrated similar benefits in various patient groups, including those groups that were excluded from the ECASS III trials, such as elderly patients (age > 80 years), those with concomitant diabetes mellitus and prior stroke, or those using anticoagulants. These findings are consistent with the 2019 American Stroke Association guideline for the early management of AIS, which stated that "careful analysis of available published data…indicates that these exclusion criteria from the trial may not be justified in practice" (8).

In the ENCHANTED trial, low-dose alteplase may have exerted a net benefit in patients without atrial fibrillation (20). Consistent with this finding, our study showed that patients with atrial fibrillation or hypercholesterolemia benefited

more from standard-dose alteplase than from the low-dose option. In the histopathological composition of thrombi, atrial fibrillation–related cardioembolism is typically characterized by a higher percentage of fibrin with smaller fractions of red blood cells compared with noncardioembolic thrombi (21). Because alteplase specifically binds to fibrin and initiates fibrinolysis, patients with fibrin-rich thrombi may respond better to standard-dose than to low-dose alteplase. To rule out the age effect, age-adjusted or matched analyses were performed in the current study, which yielded findings similar to those of the aforementioned studies. The association between standard-dose alteplase and hypercholesterolemia is implicit and may also involve alteplase "resistance" in platelet-rich thrombi (22). Nevertheless, further studies are warranted to verify these results.

This is the first study to test the dose effect of alteplase given within the 3–4.5-h time window; this approach differs from that in subgroup analyses in previous larger studies (10, 11). Furthermore, we conducted sufficient subgroup evaluation to assess the heterogeneity of treatment effects. However, several limitations must be addressed. A major drawback of this study is the nonrandomized study design, due to which an imbalance in baseline characteristics may be observed between the treatment and control groups. However, we enrolled age- and sex-matched controls from the same hospital to minimize selection bias. Moreover, we adopted several statistical models to adjust the baseline imbalance. Second, the alteplase dose regimen was determined at the discretion of the physicians in charge, and this decision may be influenced by various clinical practices. Third, the sample size was relatively small and might limit the statistical power for detecting clinically meaningful differences. Fourth, the median door-to-needle time in our study was 65 min, which was longer than that in most clinical trials (23). However, our study started in 2008, at which time many hospitals in Taiwan had not implemented a dedicated code stroke yet (24). Physicians may also need to explain the off-label use of alteplase in the 3–4.5-h time window. These factors may significantly prolong the door-to-needle time. Nonetheless, our time metrics are comparable with the result of 65 min recorded in the participating hospitals of Get with the Guidelines—Stroke in the United States from 2006 to 2016 (25). Finally, patients treated with mechanical thrombectomy were excluded; thus, the results may not be extrapolated to patients with large vessel occlusion undergoing bridging reperfusion therapy. We did not collect information on the presence of intracranial large vessel occlusions. Therefore, we could not explore whether an interaction existed between the presence of large vessel occlusion and the efficacy of the standard-dose or low-dose alteplase, thus limiting the generalizability of our findings.

In summary, the present study demonstrated that the effectiveness of standard-dose alteplase may be comparable to that of low-dose alteplase in patients with AIS within a 3–4.5-h time window, without increasing the risk of hemorrhage. Additionally, standard-dose alteplase may be selected for patients with atrial fibrillation or hypercholesterolemia. In countries where the standard and low doses of alteplase are used in parallel, the current analysis may guide physicians in the selection of appropriate regimens.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article are available upon reasonable request to the corresponding author.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of National Taiwan University Hospital and informed consent was waived.

AUTHOR CONTRIBUTIONS

J-SJ contributed to the conception and design of the study. C-HaC and J-SJ analyzed the data. C-HaC contributed to the first draft of the manuscript. S-CT and J-SJ provided critical revision on the manuscript. All authors contributed to the acquisition of data and agreed with the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.763963/full#supplementary-material

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Triglyceride-Glucose Index and Intravenous Thrombolysis Outcomes for Acute Ischemic Stroke: A Multicenter Prospective–Cohort Study

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Background: The triglyceride-glucose (TyG) index has recently been proposed as a reliable marker of insulin resistance. There is insufficient evidence to verify that the TyG index is correlated with functional outcomes and hemorrhagic transformation and in patients with stroke treated with intravenous thrombolysis (IVT).

Methods: We designed a multicenter cohort study, which enrolled patients with acute ischemic stroke treated with IVT between December 2004 and December 2016. The TyG index was divided into tertiles and calculated on a continuous scale. Unfavorable functional outcomes were defined by the modified Rankin Scale of 3–6 at 90 days and the incident rates of symptomatic intracranial hemorrhage (SICH) within 36 h of IVT onset were surveyed. Stroke severity was defined as mild (4–8), moderate (9–15), or high (≥16) based on the National Institutes of Health Stroke Scale (NIHSS) scores.

Results: Among 914 enrolled patients, the tertiles of the TyG index were 8.48 for T1, 8.48–9.04 for T2, and 9.04 for T3. T3 showed an increased risk of unfavorable functional outcomes at 90 days [odds ratio (OR): 1.76; $P = 0.0132$]. The TyG index was significantly associated with unfavorable functional outcomes at 90 days (OR: 1.32; $P = 0.0431$ per unit increase). No association was found between the TyG index and SICH. These

findings were applicable for T3 with stroke of moderate (OR, 2.35; $P = 0.0465$) and high severity (OR: 2.57, $P = 0.0440$) patients with stroke.

Conclusion: This study supports the strong association between the increased TyG index and increased unfavorable functional outcomes at 90 days in patients with acute ischemic stroke treated with IVT. These findings were found to be robust in patients with moderate and high stroke severity.

Keywords: acute ischemic stroke, triglyceride, triglyceride-glucose index, intravenous thrombolysis, symptomatic intracranial hemorrhage

INTRODUCTION

Early detection of insulin resistance (IR) is crucial in preventing cardiovascular diseases (1, 2). Glucose clamp tests are performed in the two ways: (1) the hyperglycemic clamp technique for quantification of beta-cell sensitivity to glucose and (2) the euglycemic insulin clamp technique for quantification of peripheral cell sensitivity to insulin (3). These techniques are regarded as the gold standard for quantifying IR (4) and rely on constant insulin infusion and measurement of glucose disposal under steady-state conditions (3, 4). The limitations of the glucose clamp technique include labor-intensive and time-consuming procedures, which require experienced physicians to perform human studies. In 1985, a simple equation homeostasis model assessment-IR (HOMA-IR) (5) was developed to assess IR by calculating the product of fasting levels of insulin and glucose (6). Although widely used in the research field, the use of HOMA-IR is greatly limited in clinical practice because of the need for insulin measurement.

Recently, the triglyceride-glucose (TyG) index has been recognized as a reliable surrogate biomarker of IR (7) and has been proposed and validated to be highly correlated with HOMA-IR across all the ages and various ethnic groups (7–10). The TyG index was used for the first time in 2008 by Simental-Mendia et al. (11) to identify IR in an apparently healthy population and it was formally proposed by Guerrero-Romero et al. (12) in 2010. The rationale for the application of the TyG index is that IR is the most common cause of increased triglyceride (TG) and glucose levels in serum tests (13). Some studies showed high correlation between the TyG index and IR by glucose clamp tests (9, 14) and a study (9) showed that the TyG index exhibited higher diagnostic performance than HOMA-IR for IR in some studies. Furthermore, there has been increasing evidence supporting the correlation between the TyG index and acute adverse outcomes in patients with cardiovascular disease. Recent studies have suggested that the TyG index is highly associated with carotid atherosclerosis (15) and the outcomes and prevalence of coronary artery diseases (16, 17). By using HOMA-IR, previous studies have found that IR is associated with neurological worsening and functional status (18–20). In addition, a recent study (21) found that an increased TyG index was associated with a higher risk of stroke recurrence, functional worsening, and mortality. The above studies suggest that the TyG index is a marker for acute adverse effects in cardiovascular and cerebrovascular diseases.

Nonetheless, relevant investigations of the association between the TyG index and intravenous thrombolytic outcomes for stroke are lacking. The Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) registry contains a nationwide cohort of Taiwan and longitudinal follow-up data for patients with stroke treated with intravenous thrombolysis (IVT) (22, 23). The TTT-AIS registry comprehensively enrolls patients with acute ischemic stroke with all the levels of severity. The aim of this study was to investigate the relationship between the TyG index and outcomes of functional status and symptomatic intracranial hemorrhage among ethnic Chinese patients with acute ischemic stroke treated with IVT. The novelty and significance of this study are as follows: (1) evaluation of patients with acute ischemic stroke in different categories of the TyG index, (2) nationwide, multicenter cohort study design encompassing the representative population, and (3) evaluation of patients with acute ischemic stroke of all the levels of severity.

METHODS

Study Design

This study had a prospective cohort design and encompassed a multicenter study of 30 hospitals in Taiwan. Clinical data were collected prospectively and registered in the TTT-AIS registry. Baseline demographic information included age, sex, alcohol use, history of hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, blood pressure on arrival at the hospital, use of antiplatelet and anticoagulant medications, the National Institutes of Health Stroke Scale (NIHSS) score at baseline, and time from stroke onset to IVT was retrieved by the investigators. For patients with acute ischemic stroke arriving at the hospital within 3 h of stroke onset, IV alteplase was used for the thrombolytic regimen. Serum glucose levels and lipid profiles were obtained from each patient after an overnight fast $\geq$8 h within 24–48 h of stroke onset. A written informed consent was obtained from all the patients. This study was approved by the Institutional Review Board of the Kaohsiung Medical University Hospital (reference number: KMUH-IRB-20140305).

Participants

The TyG index was calculated by using the following formula: Ln [TG (mg/dl) $\times$ fasting glucose (mg/dl)/2]. According to the previous studies (24, 25), a simple cutoff of the TyG index $\geq$8.4 is sufficiently reliable to classify Asian individuals with

IR. The inclusion criteria for eligible patients were as follows: (1) treatment with IVT for acute ischemic stroke adhering to the National Institute of Neurological Disorders and Stroke (NINDS) criteria (26) and (2) measurement of fasting glucose and lipid profiles in a fasting state during 24–72 h following the administration of IV alteplase. The exclusion criteria for IVT were based on the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) study criteria (27). All the enrolled patients with stroke underwent brain CT on arrival to the hospital and another routine brain CT was performed within 24–36 h post-IVT.

Outcomes Measures

We evaluated the clinical outcomes of (1) unfavorable functional outcome status defined by the modified Rankin Scale (mRS) of 3–6 at 90 days; (2) mortality at 90 days; (3) symptomatic intracranial hemorrhage (SICH); (4) the NINDS standard as per which any intracranial hemorrhage deteriorated to the NIHSS score of ≥ 1 or led to death within 36 h (26); (5) the European Cooperative Acute Stroke Study (ECASS) II standard, as per which any intracranial hemorrhage deteriorated to the NIHSS score of ≥ 4 or led to death (28); and (6) the SITS-MOST standard for a type 2 parenchymal hemorrhage (a local or remote parenchymal intracranial hemorrhage exceeding 30% of the infarct) with clinical deterioration of the NIHSS score of ≥ 4 or death within 36 h (27). Patients who presented with the baseline NIHSS scores of 4–8, 9–15, and ≥ 16 were categorized into the mild, moderate, and high severity groups, respectively.

Statistical Analysis

To compare the groups with and without IR, the Student's *t*-test was used for continuous variables and the Pearson's chi-squared test was used for categorical variables. We evaluated the relationship between the TyG index and lipid profiles by using two methods: (1) partitioning of the TyG index to the territorial scale and (2) examination of the TyG index on a continuous scale. The multiple logistic regression models were employed to determine the odds ratios (ORs) and their 95% CIs, the study outcomes were used as dependent variables, and the TyG index (either in tertile or in continuous scale) and the unbalanced covariates between the groups with and without IR were independent variables. T1 was used as the reference group for the models analyzed on a tertile scale. As a sensitivity analysis, we performed a stratified analysis according to the stroke severity of each patient. Statistical significance was defined as $p < 0.05$. All the analyses were performed by using SAS software (version 9.4; North Carolina, USA) and Stata software (version 15; Texas, USA).

Sample Size Estimation

At the time of designing this study, there had been no published study investigating the relationship between the TyG index and clinical outcomes in patients with acute ischemic stroke treated with IVT. The required sample size was estimated in a previous study (29), which explored the relationship between HOMA-IR and clinical outcomes in patients with stroke treated with IVT. In this study (29), HOMA-IR in the upper tertile (OR, 8.54, 95% CI, 1.67–43.55; $P = 0.01$) was associated with unfavorable functional outcome when compared with the lower tertile and HOMA-IR in the middle tertile (OR, 2.96, 95% CI, 0.61–14.40; $P = 0.178$) was

TABLE 1 | Demographic characteristics of patients.

Variable	No Insulin Resistance (TyG < 8.4) (*N* = 262)	Insulin resistance (TyG ≥ 8.4) (*N* = 652)	*p*-value
Age (years)	69.8 ± 13.0	68.8 ± 11.9	0.2941
Age groups (years)			0.5287
20–39 years	2.3% (6/262)	1.2% (8/652)	
40–49 years	3.1% (8/262)	3.5% (23/652)	
50–59 years	16.0% (42/262)	17.9% (117/652)	
60–69 years	21.4% (56/262)	25.8% (168/652)	
70–79 years	33.2% (87/262)	31.8% (207/652)	
80–89 years	21.4% (56/262)	17.5% (114/652)	
≥ 90 years	2.7% (7/262)	2.3% (15/652)	
Female sex; *n* (%)	36.6% (96/262)	36.2% (236/652)	0.8994
Alcoholism; *n*/total *N* (%)	25/262 (9.5%)	61/652 (9.4%)	0.9305
Mean NIHSS on arrival	14.2 ± 6.6	13.6 ± 7.4	0.2809
Stroke Severity at baseline			0.1678
Mild (NIHSS of 4–8)	72/262 (27.5%)	178/652 (27.3%)	
Moderate (NIHSS of 9–15)	80/262 (30.5%)	238/652 (36.5%)	
High (NIHSS of ≥ 16)	110/262 (42.0%)	236/652 (36.2%)	
Alteplase dose (mg/kg)	0.78 ± 0.14	0.80 ± 0.14	0.0747
Groups of Alteplase dosage			0.9898
Standard dose (0.9 mg/kg)	67/262 (25.6%)	167/652 (25.6%)	
Low dose (<0.9 mg/kg)	195/262 (74.4%)	485/652 (74.4%)	
Blood pressure on arrival			
Systolic BP (mmHg)	154.1 ± 29.1	161.6 ± 29.6	0.0011*
Diastolic BP (mmHg)	87.6 ± 18.3	91.4 ± 19.7	0.0078*
Time to treatment (min)	131.3 ± 46.7	130.6 ± 46.4	0.8441
Medical history			
Hypertension	168/262 (64.1%)	508/652 (77.9%)	<0.0001*
Diabetes mellitus	37/262 (14.1%)	279/652 (42.8%)	<0.0001*
Coronary artery disease	35/262 (13.4%)	105/652 (16.1%)	0.2973
Atrial fibrillations	131/208 (63.0%)	268/501 (53.5%)	0.0204*
Antithrombotic use			
Aspirin	33/148 (22.3%)	85/365 (23.3%)	0.8092
Clopidogrel	4/148 (2.7%)	18/365 (4.9%)	0.2589
Ticlopidine	1/148 (0.7%)	1/365 (0.3%)	0.4942
Warfarin	8/148 (1.6%)	12/365 (3.3%)	0.3133
Metabolism markers			
Fasting glucose	103.5 ± 25.8	153.3 ± 115.2	<0.0001*
Lipids (mg/dL)			
Total cholesterol	160.9 ± 39.3	191.7 ± 46.9	<0.0001*
LDL-C	95.2 ± 33.4	115.7 ± 42.5	<0.0001*
HDL-C	49.6 ± 20.9	48.1 ± 25.4	0.3985
TG	64.7 ± 19.0	147.4 ± 82.9	<0.0001*

BP, blood pressure; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; NIHSS, National Institutes of Health Stroke Scale; TG, triglyceride; TyG, triglyceride-glucose index.

*Continuous variables are expressed as the mean ± SD. *Statistically significant at p < 0.0.*

not significantly associated with unfavorable functional outcome. Therefore, the required sample size should be 101; when we hypothesized that the parameters of effect size of OR were in a range from 2.96 to 8.54, the probability of exposure (the upper tertile) was 0.33 and significance level and power were 0.05 and 0.95, respectively.

RESULTS

Baseline Characteristics

From 1st December, 2004 to 31st December, 2016, a total of 914 patients with acute ischemic stroke who had completed IVT were enrolled and laboratory tests for glucose and lipid profile were performed in a fasting state following admission. Of these, 652 patients had IR (TyG index $\geq$ 8.4) and 262 patients did not had IR (TyG index $<$ 8.4). In the groups without and with IR (**Table 1**), the average age was 69.8 $\pm$ 13.0 and 68.8 $\pm$ 11.9 years ($P = 0.2941$), the proportion of female sex was 36.6 and 36.2% ($P = 0.8994$), the average dose of alteplase was 0.78 $\pm$ 0.14 and 0.80 $\pm$ 0.14 ($P = 0.0747$), and the mean NIHSS score at onset was 14.2 $\pm$ 6.6 and 13.6 $\pm$ 7.4 ($P = 0.2809$), respectively; there was no significant difference in the antithrombotic medication usage. The systolic (161.6 $\pm$ 29.6 vs. 154.1 $\pm$ 29.1 mm Hg, $P = 0.0011$) and diastolic (91.4 $\pm$ 19.7 vs. 87.6 $\pm$ 18.3 mm Hg, $P = 0.0078$) blood pressures were noted for the group with IR. Medical comorbidities of hypertension and diabetes mellitus were higher in the group with IR than in the group without IR, while the prevalence of atrial fibrillation was higher in the group without IR.

Functional Outcome Distribution by the TyG Index

The functional outcome distribution defined by the mRS at 90 days is shown in **Figure 1**. Patients with stroke in the group without IR showed higher proportions of favorable outcome (mRS, 0–2) at 90 days (47.9%) than those patients with stroke in the group with IR (41.7%). The cutoff value of the TyG index on the tertiles was T1 $<$ 8.48, T2 ranging between 8.48 and 9.04, and T3 $>$ 9.04, respectively. On classification by tertiles, the proportions of favorable functional outcomes at 90 days

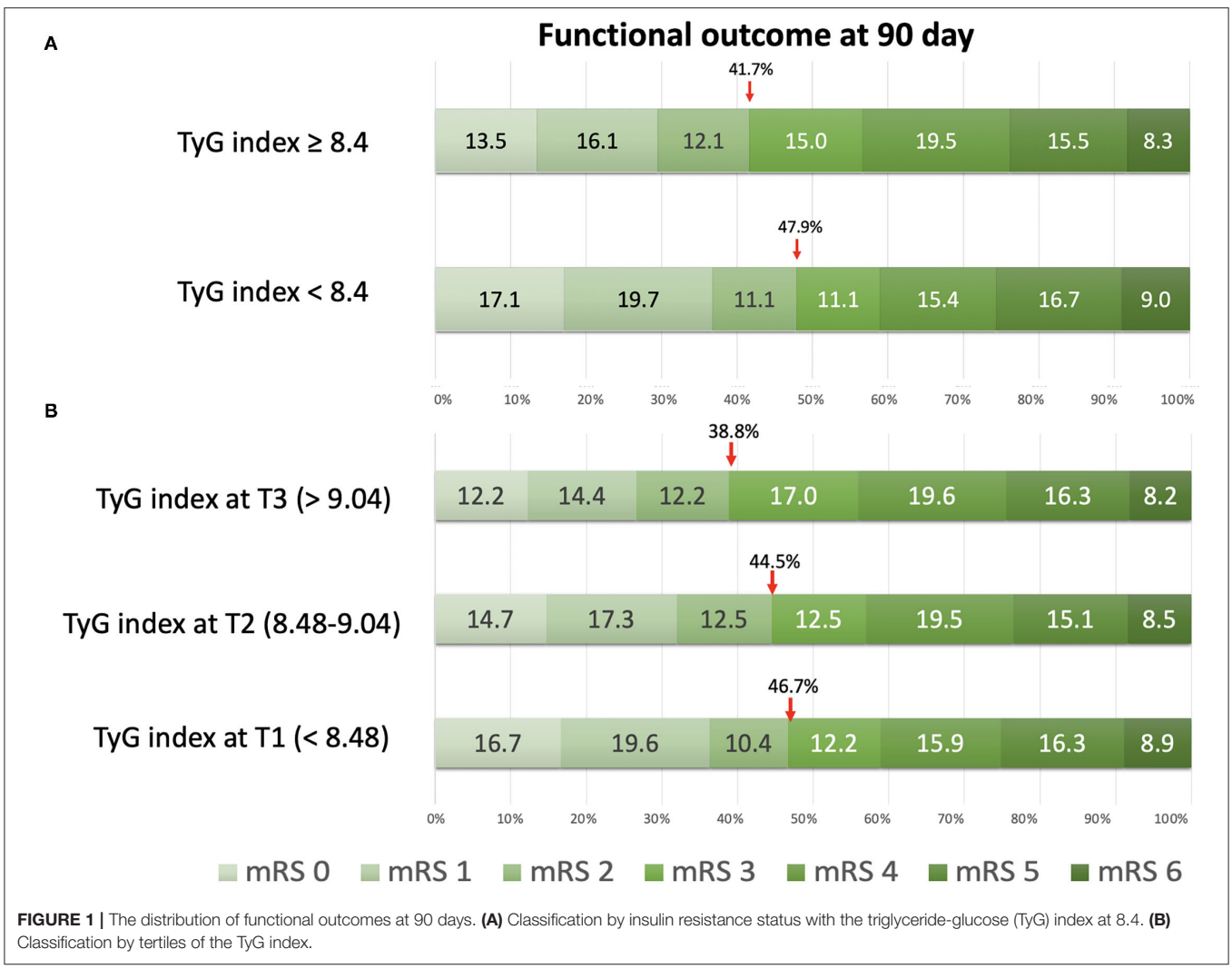

FIGURE 1 | The distribution of functional outcomes at 90 days. **(A)** Classification by insulin resistance status with the triglyceride-glucose (TyG) index at 8.4. **(B)** Classification by tertiles of the TyG index.

decreased with increasing tertiles (T1, 46.7%; T2, 44.5%; and T3, 38.8%).

Outcomes by the TyG Index on the Tertile Scale

Clinical outcomes that were investigated by categorizing patients with stroke into tertiles of the TyG index are shown in **Figure 2**. For unfavorable functional outcomes at 90 days, T3 had the highest event rate of 73.6%, compared to T1 (63.8%) and T2 (68.0%) (**Table 2**). After adjustment for age and sex, the logistic regression model showed a significant increase in unfavorable functional outcomes at 90 days for T3 (OR, 1.69; 95% CI, 1.16–2.46; $P = 0.0059$). In the multivariate-adjusted models, T3 showed a significantly increased risk of unfavorable functional outcomes at 90 days (OR, 1.76; 95% CI, 1.13–2.76; $P = 0.0132$). All the tertiles showed similar rates for mortality, ranging from 8.2 to 8.9%. Additionally, there was no significant difference in the rates of SICH according to the NINDS, the ECASS II, and the SITS-MOST criteria.

Outcomes by the TyG Index on Continuous Scale

The association between clinical outcomes and the TyG index was explored on a continuous scale (**Table 3**). The TyG index on a continuous scale showed a significantly increased risk of unfavorable functional outcomes at 90 days in the models of adjustment for age and sex (OR, 1.27, 95% CI, 1.02–1.58; $P = 0.0361$) and of multivariate adjustment (OR, 1.32, 95% CI, 1.01–1.73; $P = 0.0431$). Consistent with the results analyzed by using tertiles, the TyG index was not significantly associated with the outcomes of mortality and SICH within 36 h.

Sensitivity Analysis: Stratification by Stroke Severity

The stratification analysis according to stroke severity and tertiles of the TyG index are shown in **Table 4**. The analysis of unfavorable functional outcomes at 90 days after severe stroke is shown in **Figure 3**. For patients with mild stroke severity (NIHSS score of 4–8) treated with IVT, no significant association between the TyG index and unfavorable functional outcomes at 90 days

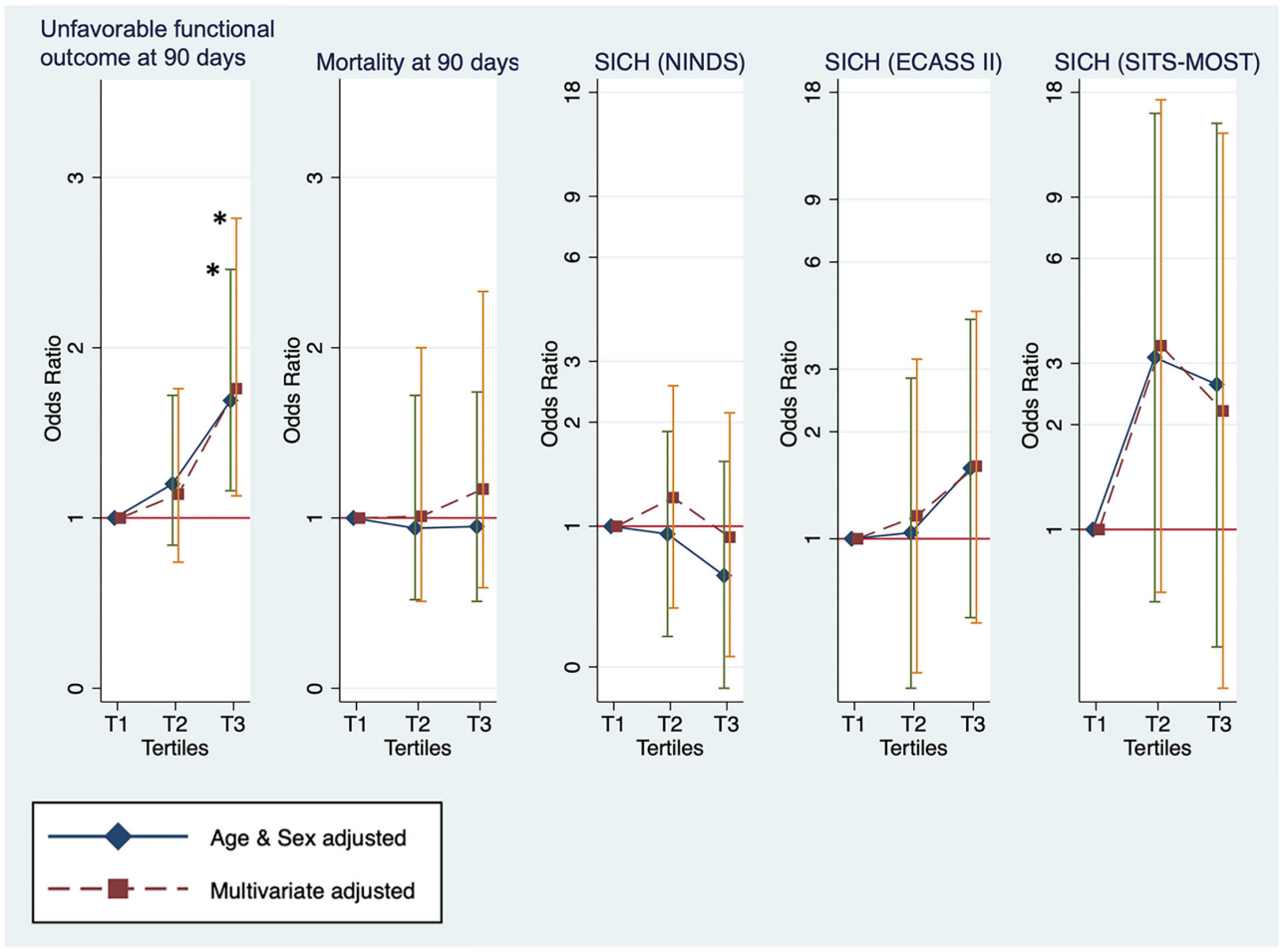

FIGURE 2 | The outcomes measures for unfavorable functional outcome status and mortality at 90 days and symptomatic intracranial hemorrhage (SICH) by tertiles of the TyG index. *Statistical significance ($p < 0.05$).

TABLE 2 | Functional outcomes and symptomatic intracranial hemorrhage (SICH) by tertiles of the triglyceride-glucose (TyG) index.

Models	TyG	*N*	Events (%)	Age, sex- adjusted of TyG index		Multivariable- adjusted† of TyG index	
Variable				OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Unfavorable functional outcome at 90 days	T1	271	63.8% (173/271)	1.00	–	1.00	–
	T2	272	68.0% (185/272)	1.20 (0.84–1.72)	0.3233	1.14 (0.74–1.76)	0.5455
	T3	269	73.6% (198/269)	1.69 (1.16–2.46)	0.0059*	1.76 (1.13–2.76)	0.0132*
Mortality at 90 days	T1	271	8.9% (24/271)	1.00	–	1.00	–
	T2	272	8.5% (23/272)	0.94 (0.52–1.72)	0.8491	1.01 (0.51–2.00)	0.9746
	T3	269	8.2% (22/269)	0.95 (0.51–1.74)	0.8542	1.17 (0.59–2.33)	0.6529
SICH at 24–36 h by NINDS	T1	305	5.9% (18/305)	1.00	–	1.00	–
	T2	303	5.6% (17/303)	0.95 (0.48–1.88)	0.8704	1.21 (0.58–2.55)	0.6091
	T3	305	3.9% (12/305)	0.72 (0.34–1.54)	0.4028	0.93 (0.41–2.13)	0.8715
SICH at 24–36 h by ECASS II	T1	305	2.6% (8/305)	1.00	–	1.00	–
	T2	303	2.6% (8/303)	1.04 (0.38–2.83)	0.9374	1.16 (0.42–3.20)	0.7719
	T3	305	3.3% (10/305)	1.58 (0.60–4.14)	0.3543	1.60 (0.58–4.36)	0.3619
SICH at 24–36 h by SITS-MOST	T1	305	0.7% (2/305)	1.00	–	1.00	–
	T2	303	2.0% (6/303)	3.12 (0.62–15.67)	0.1681	3.37 (0.66–17.14)	0.1442
	T3	305	1.3% (4/305)	2.61 (0.46–14.67)	0.2764	2.19 (0.35–13.74)	0.4033

NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.
**Statistically significant at $p < 0.05$. † The multivariate logistic regression analysis was adjusted for age, sex, hypertension, and atrial fibrillation.*

TABLE 3 | Functional outcomes and SICH by the TyG index on continuous scale (per unit).

Models	*N*	Events (%)	Age, sex- adjusted of TyG index		Multivariable- adjusted† of TyG index	
Variable			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Unfavorable functional outcomes at 90 days	813	68.4% (556/813)	1.27 (1.02–1.58)	0.0361*	1.32 (1.01–1.73)	0.0431*
Mortality at 90 days	813	8.5% (69/813)	1.09 (0.76–1.56)	0.6573	1.16 (0.76–1.76)	0.4959
SICH at 24–36 h by NINDS	914	5.1% (47/914)	0.83 (0.53–1.30)	0.4217	1.00 (0.62–1.62)	0.9947
SICH at 24–36 h by ECASS II	914	2.8% (26/914)	1.24 (0.70–2.19)	0.4698	1.22 (0.67–2.21)	0.5255
SICH at 24–36 h by SITS-MOST	914	1.3% (12/914)	1.43 (0.62–3.29)	0.4065	1.27 (0.51–3.16)	0.6133

NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; UFO, unfavorable functional outcome.
**Statistically significant at $p < 0.05$. † The multivariate logistic regression analysis was adjusted for age, sex, hypertension, and atrial fibrillation.*

was found. In contrast, the T3 category of patients with stroke with moderate severity (NIHSS score of 9–15) showed a 2-fold increased risk of unfavorable functional outcomes at 90 days in both the age and sex-adjusted (OR: 2.47, 95% CI 1.25–4.90, $P = 0.0096$) and multivariate-adjusted regression models (OR, 2.35; 95% CI, 1.01–5.44; $P = 0.0465$). The T3 category of patients with stroke with high stroke severity (NIHSS score of $\geq$16) showed a two-fold increased risk of unfavorable functional outcomes at 90 days in age and sex-adjusted (OR: 2.31, 95% CI 1.06–5.02, $P = 0.0355$) and multivariate-adjusted regression models (OR: 2.57, 95% CI 1.03–6.44, $P = 0.0440$). Similar to the previous analysis, no significant association was found between the TyG index and outcome measures of mortality and SICH. Lastly, the TyG index on a continuous scale for moderate and severe stroke severity consistently showed an increased risk of unfavorable functional outcomes at 90 days (**Table 5**).

DISCUSSION

Our results showed that the TyG index was associated with unfavorable functional outcomes at 90 days in patients with acute ischemic stroke treated with IVT. This association was more robust in patients with stroke presenting with moderate to high baseline severity. In addition, there was no significant association between the TyG index and outcomes of mortality or SICH within 36 h.

Our analysis employing the TyG index corroborated the results of previous studies. In an earlier investigation, higher resistance to IVT therapy and poor clot dissolution were observed in patients with stroke with metabolic syndrome under transcranial Doppler examination (30, 31). An earlier study showed that HOMA-IR in the upper tertile was associated with eight-fold increased risk of unfavorable functional outcome when

TABLE 4 | Sensitivity analysis: functional outcomes and SICH by tertiles of the TyG index on different stroke severities.

Models	TyG	*N*	Events (%)	Age, sex- adjusted of TyG index		Multivariable-adjusted† of TyG index	
Variable				**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Mild severity (NIHSS of 4–8)							
Unfavorable functional outcomes at 90 days	T1	72	41.7% (30/72)	1.00	–	1.00	–
	T2	63	42.9% (27/63)	1.02 (0.51–2.06)	0.9510	0.83 (0.36–1.88)	0.6488
	T3	75	46.7% (35/75)	1.23 (0.64–2.39)	0.5324	1.26 (0.58–2.77)	0.5619
Mortality at 90 days	T1	72	6.9% (5/72)	1.00	–	1.00	–
	T2	63	1.6% (1/63)	0.23 (0.03–2.06)	0.1899	0.78 (0.06–9.72)	0.8463
	T3	75	1.3% (1/75)	0.17 (0.02–1.52)	0.1127	0.71 (0.06–9.26)	0.7962
SICH at 24–36 h by NINDS	T1	81	2.5% (2/81)	1.00	–	1.00	–
	T2	76	2.6% (2/76)	1.11 (0.15–8.16)	0.9196	0.58 (0.05–6.96)	0.6684
	T3	92	2.2% (2/92)	0.89 (0.12–6.56)	0.9100	1.08 (0.13–8.74)	0.9428
SICH at 24–36 h by ECASS II	T1	81	0% (0/81)	1.00	–	1.00	–
	T2	76	0% (0/76)	dispersion	–	dispersion	–
	T3	92	2.2% (2/92)	1.87 (0.24– ∞)[a]	0.3122	1.54 (0.19–∞)	0.3696
SICH at 24–36 h by SITS-MOST	T1	81	0% (0/81)	1.00	–	1.00	–
	T2	76	0% (0/76)	dispersion	–	dispersion	–
	T3	92	1.1% (1/92)	1.00 (0.05–∞) [a]	0.5000	1.00 (0.05–∞) [a]	0.5000
Moderate severity (NIHSS of 9–15)							
Unfavorable functional outcomes at 90 days	T1	84	63.1% (53/84)	1.00	–	1.00	–
	T2	105	66.7% (70/105)	1.23 (0.66–2.29)	0.5105	1.08 (0.50–2.35)	0.8483
	T3	97	78.4% (76/97)	2.47 (1.25–4.90)	0.0096*	2.35 (1.01–5.44)	0.0465*
Mortality at 90 days	T1	84	7.1% (6/84)	1.00	–	1.00	–
	T2	105	2.9% (3/105)	0.37 (0.09–1.55)	0.1711	0.36 (0.08–1.59)	0.1786
	T3	97	3.1% (3/97)	0.45 (0.11–1.92)	0.2815	0.55 (0.12–2.55)	0.4463
SICH at 24–36 h by NINDS	T1	96	7.3% (7/96)	1.00	–	1.00	–
	T2	114	1.8% (2/114)	0.23 (0.05–1.11)	0.0676	0.37 (0.07–2.02)	0.2489
	T3	108	2.8% (3/108)	0.37 (0.09–1.51)	0.1669	0.82 (0.17–3.86)	0.8018
SICH at 24–36 h by ECASS II	T1	96	5.2% (5/96)	1.00	–	1.00	–
	T2	114	0.9% (1/114)	0.16 (0.02–1.43)	0.1021	0.18 (0.02–1.63)	0.1272
	T3	108	2.8% (3/108)	0.61 (0.14–2.72)	0.5166	0.84 (0.17–4.04)	0.8259
SICH at 24–36 h by SITS-MOST	T1	96	1.0% (1/96)	1.00	–	1.00	–
	T2	114	0% (0/114)	0.77 (0.00–14.68)[a]	0.4359	0.50 (0.00–9.50)[a]	0.3333
	T3	108	0.9% (1/108)	0.85 (0.01–83.22)[a]	1.0000	1.50 (0.08–∞)[a]	0.4000
High severity (NIHSS ≥ 16)							
Unfavorable functional outcomes at 90 days	T1	114	78.1% (89/114)	1.00	–	1.00	–
	T2	104	84.6% (88/104)	1.57 (0.78–3.19)	0.2091	2.32 (0.94–5.73)	0.0679
	T3	98	88.8% (87/98)	2.31 (1.06–5.02)	0.0355*	2.57 (1.03–6.44)	0.0440*
Mortality at 90 days	T1	114	11.4% (13/114)	1.00	–	1.00	–
	T2	104	18.3% (19/104)	1.74 (0.81–3.74)	0.1530	1.65 (0.69–3.92)	0.2594
	T3	98	18.4% (18/98)	1.77 (0.81–3.83)	0.1502	1.71 (0.72–4.08)	0.2272
SICH at 24–36 h by NINDS	T1	127	7.1% (9/127)	1.00	–	1.00	–
	T2	113	11.5% (13/113)	1.77 (0.72–4.36)	0.2136	2.32 (0.88–6.13)	0.0890
	T3	106	6.6% (7/106)	1.03 (0.37–2.91)	0.9545	0.96 (0.61–3.03)	0.9502
SICH at 24–36 h by ECASS II	T1	127	2.4% (3/127)	1.00	–	1.00	–
	T2	113	6.2% (7/113)	3.00 (0.74–12.17)	0.1238	3.38 (0.81–14.20)	0.0959
	T3	106	4.7% (5/106)	2.72 (0.61–12.06)	0.1891	2.09 (0.43–10.24)	0.3652
SICH at 24–36 h by SITS-MOST	T1	127	0.8% (1/127)	1.00	–	1.00	–
	T2	113	5.3% (6/113)	7.51 (0.88–63.93)	0.0650	8.14 (0.94–70.65)	0.0573
	T3	106	1.9% (2/106)	2.89 (0.25–32.94)	0.3928	1.39 (0.08–23.37)	0.8200

NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.
**Statistically significant at $p < 0.05$. † The multivariate logistic regression analysis was adjusted for age, sex, hypertension, and atrial fibrillation.*
[a] Exact logistic regression model was used.

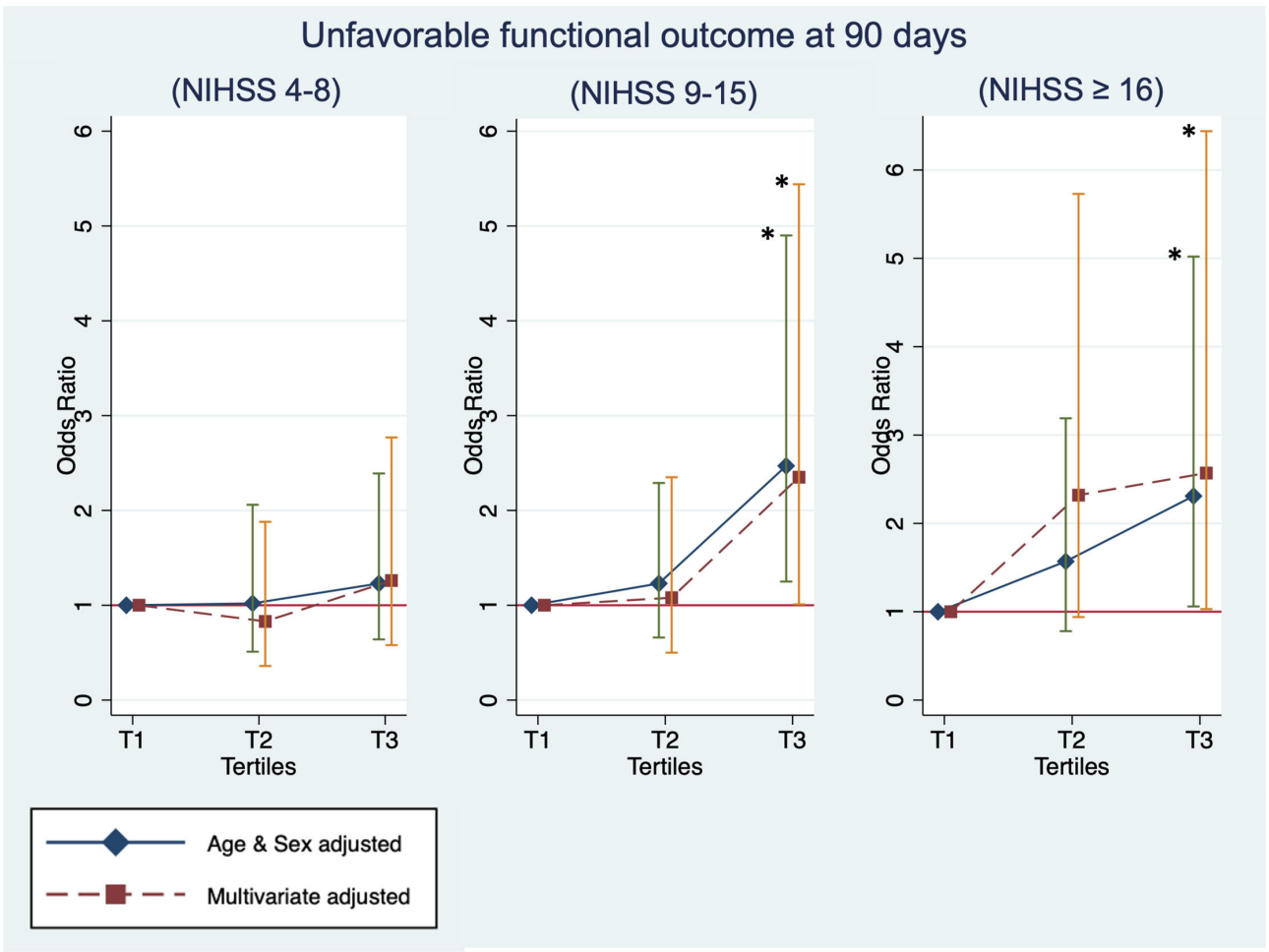

FIGURE 3 | Sensitivity analysis: The unfavorable outcome at 90 days by tertiles of the TyG index and the baseline stroke severity of mild [National Institutes of Health Stroke Scale (NIHSS) of 4–8], moderate (NIHSS of 9–15), and high (NIHSS of ≥16). *Statistical significance ($p < 0.05$).

compared with the lower tertile (29). In addition, a recent large-scale study that enrolled nondiabetic Chinese patients with stroke found that higher HOMA-IR was linked to poor stroke recovery and recurrence (19). These studies suggested that patients with stroke presenting with higher IR should be poor responders to IVT and more susceptible to unfavorable recovery. This study uncovers important implications that the TyG index, such as HOMA-IR, is an effective biomarker for selecting patients who benefit from aggressive strategies for vascular reperfusion. Unlike HOMA-IR, the TyG index is more practical for use in clinical conditions due to the lack of insulin measurement.

Recent studies have suggested that the TyG index is highly associated with carotid atherosclerosis (15), major adverse cardiovascular events in patients with non-ST-segment elevation acute coronary syndrome (ACS), and major adverse cardiovascular and cerebrovascular events in patients with ST-segment elevation ACS (16, 17). The above studies support that the TyG index is a marker for acute adverse effects in cardiovascular and cerebrovascular diseases. In terms of physiology, high values of the TyG index or IR should oppose IVT for ischemic stroke by several mechanisms. First, several studies reported that higher IR was associated with elevated levels of thrombin activatable fibrinolysis inhibitor and plasminogen activator inhibitor 1 (PAI-I) (32, 33), which attenuated fibrinolysis by IVT (33). Second, IR augments the density of blood clots and impairs the effect of IVT (34).

Our results showed no significant association between the TyG index and SICH outcomes and are compatible with our previous analysis of SICH outcomes on TG levels in the TTT-AIS study (35). This findings were consistent with an earlier study that used HOMA-IR for patients with stroke treated with IVT (29). Based on previous studies of TG, which did not show robust association with intracranial hemorrhage in patients with stroke treated without thrombolysis (36–40), we deduced that the TyG index was not a reliable biomarker for hemorrhagic transformation. Additionally, the TyG index showed no significant association with the outcome of mortality.

TABLE 5 | Sensitivity analysis: functional outcomes and SICH by the TyG index on continuous scale (per unit) and different stroke severities.

Models	*N*	Events (%)	Age, sex- adjusted of TyG index		Multivariable- adjusted[†] of TyG index	
Variable			**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Mild severity (NIHSS of 4–8)						
Unfavorable functional outcomes at 90 days	211	44.1% (93/211)	0.99 (0.62–1.59)	0.9709	1.04 (0.64–1.69)	0.8850
Mortality at 90 days	211	3.3% (7/211)	0.99 (0.23–4.30)	0.9912	1.35 (0.32–5.62)	0.6807
SICH at 24–36 h by NINDS	250	2.4% (6/250)	1.06 (0.32–3.55)	0.9290	1.23 (0.34–4.39)	0.7547
SICH at 24–36 h by ECASS II	250	0.8% (2/250)	2.54 (0.48–13.58)	0.2763	2.52 (0.42–15.19)	0.3144
SICH at 24–36 h by SITS-MOST	250	0.4% (1/250)	3.80 (0.19–76.59)	0.3838	1.00 (0.10–∞)[a]	0.5000
Moderate severity (NIHSS of 9–15)						
Unfavorable functional outcomes at 90 days	286	69.6% (199/286)	1.38 (0.85–2.25)	0.1983	1.43 (0.87–2.36)	0.1575
Mortality at 90 days	286	4.2% (12/286)	0.46 (0.17–1.25)	0.1285	0.50 (0.18–1.40)	0.1877
SICH at 24–36 h by NINDS	318	3.8% (12/318)	0.79 (0.28–2.19)	0.4217	0.96 (0.31–2.99)	0.9491
SICH at 24–36 h by ECASS II	318	2.8% (9/318)	0.79 (0.27–2.32)	0.6705	0.95 (0.28–3.18)	0.9280
SICH at 24–36 h by SITS-MOST	318	0.6% (2/318)	2.06 (0.24–17.59)	0.5091	8.99 (0.22–376.14)	0.2491
High severity (NIHSS of ≥ 16)						
Unfavorable functional outcomes at 90 days	316	83.5% (264/316)	1.77 (1.02–3.07)	0.0431*	1.88 (1.07–3.33)	0.0295*
Mortality at 90 days	316	15.8% (50/316)	1.42 (0.88–2.29)	0.1481	1.40 (0.86–2.29)	0.1713
SICH at 24–36 h by NINDS	346	8.4% (29/346)	0.99 (0.56–1.77)	0.9736	0.97 (0.54–1.74)	0.9041
SICH at 24–36 h by ECASS II	346	4.3% (15/346)	1.22 (0.56–2.65)	0.6120	1.19 (0.55–2.54)	0.6593
SICH at 24–36 h by SITS-MOST	346	2.6% (9/346)	0.95 (0.34–2.71)	0.9302	0.94 (0.33–2.62)	0.9006

NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.
**Statistically significant at $p < 0.05$. [†] The multivariate logistic regression analysis was adjusted for age, sex, hypertension, and atrial fibrillation.*
[a] Exact logistic regression model was used.

The most reasonable explanation was that two-thirds of patients with stroke presented with moderate and high severity and these patients were more susceptible to SICH with IVT when compared to those with low severity or with the low NIHSS score (41–44). In a separate analysis, the mortality in our cases was also strongly attributable to SICH (**Supplementary Table S1**).

Our cutoff values for tertiles of the TyG index at 8.48 and 9.04 should be used as a standard. A recent study investigating patients with type 2 diabetes mellitus found that the TyG index >9.5 significantly increased macrovascular complications, including cerebrovascular diseases and albuminuria (45). Another study that enrolled patients with minor cases (the median NIHSS score, 4; quartile deviation, 2.5) reported that the TyG index of >9.2 increased neurological worsening (21). A cross-sectional study exploring silent brain infarcts reported increased multiple silent infarcts in the group with the median TyG index >8.5 (46). To the best of our knowledge, patients with acute ischemic stroke with the TyG index >9 should be cautious of worsening clinical neurological function.

We confirmed that the TyG index was robust in predicting unfavorable functional outcomes at 90 days for moderate and severe stroke severity. This was also the first study to explore the TyG index for different stroke severities. In terms of physiology, we proposed that the harder and longer segments of clots in patients with stroke with high severity would be aggravated by attenuated fibrinolysis due to increased IR. In addition, the distinctive strengths of this study are as follows: (1) a longitudinal cohort study design with a large sample size of patients with stroke treated with IVT, (2) determination of the extent to which a higher level of the TyG index contributes to unfavorable functional outcomes at 90 days, and (3) estimation of outcomes using the TyG index on tertile and continuous scales, with robust results in sensitivity analysis.

Overall, our results are consistent to earlier studies investigating the effect of IR in patients with acute ischemic stroke. Due to the need of insulin measurement, use of HOMA-IR in the real-world practice is limited. For patients with stroke, the lipid profile and blood glucose are routine laboratory tests. Therefore, physicians can easily monitor the effect of IR in patients with stroke with the TyG index. However, further study is warranted to evaluate whether controlling the TyG index <9.0 would improve the functional outcomes and accelerate neurological recovery. More evidence is needed to generalize the results for clinical practice in Asians and other ethnic population.

Stress hyperglycemia and IR are reported as the adaptive response that increase the chance of the patient to survive (47). Chronic hyperglycemia is known harmful with numerous complications (48, 49). Recently, acute hyperglycemia has been considered protective, since patients could have greater cellular resistance to ischemic and hypoxic injury (47, 50). In terms of pathophysiology, stress hyperglycemia is caused predominantly by excessive gluconeogenesis, glycogenolysis, and IR. While epinephrine and norepinephrine augment hepatic gluconeogenesis and glycogenolysis, inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein, induce IR (51, 52). In addition, glucose is the primary energy source of the brain (53). Therefore, we consider that stress hyperglycemia should not be excluded, since

it represents the physiological response to improve survival in patients with stroke.

This study had some limitations. First, the TTT-AIS registry (22, 23) has no clinical data on insulin levels. Further, HOMA-IR was not used in this study. Second, the TTT-AIS registry was initiated in 2004 at a time when thrombectomy had not been introduced in Taiwan. Third, although we have conducted the subgroup analysis in diabetic and nondiabetic patients according to medical history, no significant association between functional outcomes and the TyG index was found (**Supplementary Table S2**). Two factors should explain this: (1) history of diabetes mellitus reported by patients was imprecise and underdiagnosed and (2) the smaller sample size in subgroup analysis. However, a recently published study (54) showed that the TyG index was associated with early neurological deterioration (an increase of the NIHSS $\geq$2 or the NIHSS $\geq$1 in the motor dysfunction within 72 h) in patients with untreated diabetes (adjusted OR: 3.94, 95% CI, 1.47–10.53, $P = 0.006$). Accordingly, the TyG index should be applicable in predicting functional outcome in patients with stroke with diabetes mellitus. Fourth, hemoglobin A1c was not measured in this study. The prevalence of diabetes mellitus was possibly underdiagnosed in this study.

CONCLUSION

In conclusion, this study supports a strong association between higher levels of the TyG index and increased unfavorable functional outcomes at 90 days in patients with acute ischemic stroke treated with IVT. This association was robust in patients with moderate (NIHSS of 9–15) and high stroke severity (NIHSS $\geq$ 16). While HOMA-IR is not readily available, the TyG index would be a surrogate marker of IR. This study determines a cutoff value of TyG index >9.0 that is useful for predicting unfavorable functional outcomes in patients with acute ischemic stroke treated with IVT in Asians, but further study is needed to validate this cutoff value in other ethnic population.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The datasets presented in this article are not readily available because the Institutional Review Board of Kaohsiung Medical University has restricted their distribution. Requests to access these datasets should be directed to A-Ching Chao, achch@cc.kmu.edu.tw.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kaohsiung Medical University Hospital (IRB: KMUH-IRB-20140305). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

S-FL wrote the first draft of the article. All authors contributed to the conception and design of the study, acquisition, analysis, and interpretation of data.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.737441/full#supplementary-material

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New Remote Cerebral Microbleeds on T2*-Weighted Echo Planar MRI After Intravenous Thrombolysis for Acute Ischemic Stroke

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Background: The main and well-defined complication of intravenous administration of recombinant tissue plasminogen activator (tPA) in patients with acute ischemic stroke (AIS) is symptomatic intracranial hemorrhage (sICH). However, rtPA might also be connected with the formation of cerebral microbleeds (CMBs), located remotely from the ischemic lesions, that may remain clinically silent. This association might be important because the load of CMBs has been associated with cognitive impairment. We investigated whether administration of rtPA in AIS results in the appearance of new CMBs and if the initial load of CMBs is associated with hemorrhagic transformation.

Methods: A total of fifty-nine consecutive patients with AIS treated with rtPA underwent MRI including T2*-weighted Echo Planar Imaging (T2*-EPI) shortly before and 7–9 days after rtPA administration. We calculated the load of new CMBs located outside the MR diffusion restriction area in the follow-up imaging and assessed hemorrhagic transformation with ECASS-II scoring.

Results: A total of forty-nine patients were included for the final analysis. On initial T2*-EPI-GRE, 37 baseline microbleeds (CMBs) were observed in 14 patients (28.6%). On follow-up T2*-EPI-GRE amount of CMBs increased to a total number of 103. New CMBs were found in 5 (14.3%) of 35 patients without and in 9 (64.3%) of 14 with any baseline CMBs. Multiple logistic regression analysis indicated that presence of baseline CMBs (risk ratio [RR] 5.95, 95% CI 2.69–13.20, $p < 0.001$) and lower platelets level (risk ratio [RR] 0.992, 95% CI 0.986–0.998, $p = 0.007$) were independently associated with new CMBs. The baseline load of CMBs was not associated with the risk of hemorrhagic transformation.

Conclusion: In this study, new CMBs were found in nearly 30% of patients with AIS on the 7–9 days after rtPA treatment. Baseline CMBs correlated with a higher risk of new CMBs appearing after the rtPA treatment, independently of other factors. At the same time, in our sample, baseline CMBs did not correlate with an increased

risk of hemorrhagic transformation. Since the associations between the CMBs load and cognitive impairment have already been proved, further studies are warranted to investigate possible associations between the thrombolytic treatment of patients with AIS, mainly those with baseline CMBs, and the risk of earlier cognitive decline.

Keywords: cerebral microbleeds, acute ischemic stroke, thrombolysis, hemorrhagic transformation, neuroimaging, MRI

INTRODUCTION

Intravenous thrombolysis with recombinant tissue plasminogen activator (tPA) is the mainstay therapeutic method of acute ischemic stroke (AIS) with proven clinical benefit (1) and is recommended up to 4.5 h after stroke onset (2). In addition, recent randomized controlled trials and meta-analyses enabled the extension of the time window in selected cases or administration of rtPA in some subjects with unknown onset of stroke (3–5).

The most common complication of rtPA treatment is the hemorrhagic transformation of the ischemic lesion. This transformation might be of various severity that has been classified with ECASS-II score (**Table 1**) (6). The severity of hemorrhagic transformation is strictly connected with clinical significance and the symptomatic intracerebral hemorrhage (sICH), which occurs in 3–7% of rtPA treated patients, is of the highest clinical interest since it is associated with poor functional outcomes. Symptomatic intracerebral hemorrhage has been well-characterized in the multiple studies (2, 7–9).

Administration of rtPA might also result in another hemorrhagic complication—cerebral microhemorrhages or microbleeds (CMBs). CMBs are small, rounded signal loss lesions surrounded by brain tissue with a diameter up to 5 mm. CMBs might appear remotely from the ischemic lesion in an isolated or diffuse pattern across the brain. The CMBs neuroimaging characteristics are listed in **Table 2** (10–13). The prevalence of CMBs is significantly higher in the elderly population with multiple comorbidities and high-total cardiovascular risk, especially hypertension with subsequent hypertensive arteriopathy (13, 14). Usually, CMBs are clinically silent in the terms of acute stroke care but might have a cumulative impact on patients in the following years, mainly because of the associations between the load of CMBs and cognitive impairment (15–20).

Cerebral microbleeds have also been under study because of their possible pathophysiological connection with hemorrhagic transformation as CMBs are commonly treated as markers of increased vascular vulnerability due to severe small vessel disease (21–23). This connection seems plausible also in light of the recent analyses that have revealed that CMBs burden might be a useful single marker of the risk of sICH in patients, after stroke or TIA, receiving oral anticoagulants (OACs) (24, 25). In these reports, CMBs burden was more predictive of sICH than other tools, including HAS-BLED (26).

The problem of rtPA-associated CMBs has already been addressed in a few studies (27–32). However, only four of them were planned to assess true baseline CMBs load with MRI preceding the rtPA administration (28–31). The problem to quantify and compare CMBs before and after the thrombolytic treatment is related to the fact that their proper assessment requires the use of MRI. The long duration of standard MRI testing interferes with the urge of administering the rtPA and thus precludes regular and easy use of this neuroimaging technique in thrombolysed patients.

In the presented study, we investigated whether administration of rtPA in AIS results in the appearance of new CMBs and whether the baseline CMBs load increases the risk of new CMBs and hemorrhagic transformation after the rtPA treatment. The assessment was performed using pre- and post-thrombolysis special MRI protocols.

TABLE 1 | The european cooperative acute stroke study classification of hemorrhagic transformation.

Hemorrhage classification	Radiographic appearance
Haemorrhagic infarction type 1 (HI1)	Small hyperdense petechiae.
Haemorrhagic infarction type 2 (HI2)	More confluent hyperdensity throughout the infarct zone; without mass effect.
Parenchymal hematoma type 1 (PH1)	Homogeneous hyperdensity occupying <30% of the infarct zone; some mass effect.
Parenchymal hematoma type 2 (PH2)	Homogeneous hyperdensity occupying >30% of the infarct zone; significant mass effect. Or, any homogenous hyperdensity located beyond the borders of the infarct zone.

METHODS

Patients and Study Protocol

A total of fifty-nine consecutive patients with AIS treated with intravenous thrombolysis between March 20, 2019 and October 19, 2020 were prospectively enrolled into the study. The study protocol included the following:

(1) head MRI that includes T2*-weighted Echo Planar Imaging (T2*-EPI-GRE) in the protocol before rtPA administration (to exclude ICH);
(2) intravenous thrombolysis, as the main therapy (without mechanical thrombectomy) with standard dosage of rtPA administered either within 4.5 h after stroke onset (the time when a patient was last known to be without symptoms), according to standard dosing protocol approved and recommended for thrombolysis in patients with AIS (33)

TABLE 2 | Cerebral microbleeds (CMBs)—neuroimaging characteristics.

Small, rounded signal loss lesions surrounded by brain tissue
Located outside the infarcted area
Diameter up to 5 mm
Detected on T2*-weighted and susceptibility-weighted imaging (SWI)
Blooming effect on T2*-weighted MRI
Generally not seen on computed tomography, FLAIR, T1-weighted MRI

or with unknown time of onset based on WAKE-UP trial protocol (3) with DWI-FLAIR MRI mismatch (five patients).

(3) Follow-up MRI that includes T2*-EPI-GRE in the protocol, performed on 7–9 days after stroke onset (for therapeutic reasons, in eight cases, follow-up MRI was performed out of the target time frame).

The aforementioned steps constituted the eligibility criteria—patients who could not follow one or more of the steps were not included in the assessments. In addition, the exclusion criterion was the poor quality of obtained neuroimaging data. Forty-nine patients (26 women and 23 men, mean age - 66 years) were included in the final analysis. Three of them had been treated with the non-vitamin K antagonist oral anticoagulant (NOAC) before stroke onset because of atrial fibrillation. However, their laboratory-assessed anticoagulant activity on admission was low (<20 ng/ml) and did not constitute a contraindication for thrombolysis. None of the patients involved in the analysis received any kind of anticoagulation before the follow-up MRI.

All the patients provided informed consent for the involvement in the study. The clinical characteristics of the study group are presented in **Table 3**.

MRI Protocol and Image Analysis

All MRI examinations were performed with a 1.5-T MRI scanner (Magnetom Aera, Siemens, Erlangen, Germany) with 20 channel head/neck coil in AutoCoil selection mode. Baseline MRI—the "Go-Brain" protocol—designed for the fast imaging in the acute phase of stroke (34), consisted of sagittal T1-weighted gradient recalled echo (GRE), axial T2-weighted turbo spin-echo (TSE), axial T2-weighted TSE fluid-attenuation inversion recovery (FLAIR), axial diffusion-weighted (DWI) single-shot echo-planar imaging (EPI), and axial T2*-weighted EPI-GRE. The high-diagnostic value of ultrafast sequences was presented by Prakkamakul et al. (35). The "Go-Brain" protocol included the "AutoAlign" mode, which uses anatomical landmarks for automated alignment for slice position and prevents erroneous double counting in the follow-up assessment.

The follow-up MRI protocol included axial T2*-weighted EPI-GRE sequences that were used to assess the number of CMBs. Next, where needed the susceptibility-weighted imaging (SWI) was used to confirm CMBs detected on the follow-up T2*-weighted EPI-GRE images. DWI sequence was also used to evaluate baseline (before rtPA administration) infarct volume. Axial T2 FLAIR sequence was used to assess the leukoaraiosis severity in the Fazekas scale (36). Detailed MRI parameters are listed in **Table 4**.

Cerebral microbleeds neuroimaging characteristics are listed in **Table 2** (10–13). CMBs observed in the region of the ischemic lesion were not included in the analysis. CMBs in T2*-weighted EPI-GRE sequences were manually assessed by three observers—a neurologist (BJ) and a radiologist working together with a physicist (ESz, DO). Discrepancies were resolved by consensus and by independent decisions of an experienced stroke neurologist (BK).

Hemorrhagic transformation was graded by the ECASS-II (European Cooperative Acute Stroke Study) classification (6) (**Table 1**). Symptomatic intracerebral hemorrhage was defined according to SITS-MOST (The Safe Implementation of Thrombolysis in Stroke- Monitoring Study) criteria (37): a type 2 parenchymal hemorrhage (PH2) with deterioration in the National Institutes of Health Stroke Scale (NIHSS) score of 4 points or more, or death.

Clinical Assessment

All the patients enrolled were clinically assessed by an experienced stroke neurologist and classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (38).

Statistics

Interrater agreement for the MRI reading was evaluated using the weighted Cohen's kappa with linear weights and interpreted in the following way: 0.01–0.20 as poor agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as substantial agreement, and above 0.80 as almost perfect agreement.

The characteristics of the patients were presented according to mean and standard deviation (SD) for normally distributed continuous data, whereas non-normally distributed variables were described as quartiles; categorical variables were reported as counts and percentages. The between-group differences were evaluated using *t*-test or Mann-Whitney test for continuous data and the chi-square test or Fisher's exact test for categorical variables. The two-tailed tests were carried out at a significance level of $p \leq 0.05$. A generalized linear model assuming Poisson distribution with a log-link function was used to identify risk factors for the incidence of new CMBs. A stepwise forward selection was applied to build up a model with the lowest score of the Akaike information criterion. The final model was recalculated taking into account a robust error variance. Regression coefficients were expressed as adjusted relative risk (aRR) with a 95% CI. All the statistical analyses were performed using the R statistical package (version 3.6.3.).

RESULTS

On initial T2*-EPI-GRE we identified 37 baselines CMBs in 14 patients (28.6%). A total of thirty-four (91.9%) of CMBs were localized in the cortical/subcortical area and only 3 (8.1%) in the deep brain structures. In all but one patient, the number of baseline CMBs did not exceed 3. Interobserver agreement

TABLE 3 | Characteristics of two groups – with ($N = 14$) and without ($N = 35$) new CMBs.

	1 ($N = 14$)	0 ($N = 35$)	Total ($N = 49$)	*p* value
Age, y, median (Q1, Q3)	72.5 (66.5, 84.0)	62.0 (46.0, 75.5)	66.0 (56.0, 80.0)	**0.026**
Time from onset to treatment, min, mean (SD)	177.4 (63.3)	170.9 (59.5)	172.8 (60.0)	0.734
Hypertension	13 (92.9%)	27 (77.1%)	40 (81.6%)	0.415[fe]
Diabetes	6 (42.9%)	11 (31.4%)	17 (34.7%)	0.448
Atrial fibrillation	4 (28.6%)	4 (11.4%)	8 (16.3%)	0.202[fe]
Antiplatelet drugs	5 (35.7%)	15 (42.9%)	20 (40.8%)	0.646
NOAC on admission	2 (14.3%)	1 (2.9%)	3 (6.1%)	0.193[fe]
Previous clinical stroke	3 (21.4%)	7 (20.0%)	10 (20.4%)	0.999[fe]
Systolic blood pressure admission, mmHg, mean (SD)	164.1 (21.6)	154.5 (26.1)	157.2 (25.1)	0.226
Diastolic blood pressure admission, mmHg, mean (SD)	86.5 (15.5)	84.6 (13.7)	85.2 (14.1)	0.679
Glucose, mg/dl, median (Q1, Q3)	126.0 (104.5, 141.2)	121.0 (105.0, 142.0)	121.0 (104.0, 143.0)	0.715[m−w]
Platelets, x10^9/l, median (Q1, Q3)	222.0 (182.5, 240.8)	234.0 (192.5, 296.5)	231.0 (182.0, 266.0)	0.250[m−w]
Creatinine, mg/dl, mean (SD)	1.0 (0.2)	0.9 (0.2)	0.9 (0.2)	**0.035**
INR, mean (SD)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	0.827
NIHSS score, admission, median (Q1, Q3)	5.0 (4.0, 5.8)	5.0 (3.0, 10.0)	5.0 (3.0, 7.0)	0.600[m−w]
NIHSS score, discharge, median (Q1, Q3)	0.5 (0.0, 1.8)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.698[m−w]
TOAST classification				0.624[fe]
LAA	2 (14.3%)	7 (20.0%)	9 (18.4%)	
CE	5 (35.7%)	6 (17.1%)	11 (22.4%)	
SVD	3 (21.4%)	9 (25.7%)	12 (24.5%)	
UE	4 (28.6%)	13 (37.1%)	17 (34.7%)	
Hemorrhagic transformation, ECASS				0.647[fe]
HI1	3 (21.4%)	3 (8.6%)	6 (12.2%)	
HI2	1 (7.1%)	1 (2.9%)	2 (4.1%)	
NH	10 (71.4%)	29 (82.9%)	39 (79.6%)	
PH1	0 (0.0%)	1 (2.9%)	1 (2.0%)	
PH2	0 (0.0%)	1 (2.9%)	1 (2.0%)	
Baseline DWI Volume, ml, median (Q1, Q3)	2.2 (0.0, 13.4)	3.9 (0.6, 19.5)	3.4 (0.0, 16.0)	0.584[m−w]
Periventricular and deep white matter hyperintensities [2–3 in Fazekas scale]	5 (35.7%)	8 (22.9%)	13 (26.5%)	0.357
Presence of baseline CMBs	9 (64.3%)	5 (14.3%)	14 (28.6%)	**< 0.001**

SD, standard deviation; Q1, the first quartile; Q3, the third quartile; fe, Fisher's exact test; m-w, Mann-Whitney test; ICH, intracerebral hemorrhage; TOAST, Trial of Org 10172 in Acute Stroke Treatment (classification); LAA, large-artery atherosclerosis; CE, cardioembolism, SVD, small-vessel disease; UE- stroke of undetermined etiology; ECASS, European Cooperative Acute Stroke Study (classification); NH, no hemorrhage; HI1, haemorrhagic infarction type 1; HI2, hemorrhagic infarction type 2; PH1, parenchymal hematoma type 1; PH2, parenchymal hematoma type 2; NOAC, novel oral anticoagulant; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; DWI, diffusion weighted imaging. Statistically significant differences between these two groups of patients are marked with bald fonts of the p-value.

TABLE 4 | MRI sequences and parameters used in the study.

Sequence	TR [ms]	TE [ms]	IT [ms]	Slices	Slice thickness [mm]	Gap [mm]	*b*-value
Sagital T1 (GRE)	595	11	-	27	5	1	-
Axial T2 (TSE)	4,700	101	-	25	5	1	-
Axial T2 FLAIR	5,500	78	1,930	25	5	1	-
Axial T2* (EPI-GRE)	6,120	75	-	25	5	1	-
Axial DWI (EPI)	4,500	89	-	31	5	0.6	0.800
3D SWI (GRE)	49	40	-	56	2	-	-

GRE, gradient recalled echo; TSE, turbo spin echo; FLAIR, fluid-attenuated inversion recovery; EPI, echo-planar imaging; DWI, diffusion-weighted imaging; SWI, susceptibility-weighted imaging.

was high and kappa values are presented in **Table 5**. On follow-up T2*-EPI-GRE, the total amount of CMBs increased up to an absolute number of 103 (all patients combined). New CMBs were found in 5 (14.3%) of 35 patients without baseline CMBs (**Figure 1**) and in 9 (64.3%) of 14 with CMBs detected in baseline MRI. Among a total of 66 new CMBs, 48 (72.7%) were localized in the cortical/subcortical area, 18 (27.3%) in deep brain structures, and 35 (53.0%) in the ipsilateral hemisphere. Hemorrhagic transformation (ECASS) was observed in 10 (20.4%) patients - 6 HI1, 2 HI2, 1 PH1, and 1 PH2. Baseline CMBs did not correlate significantly with hemorrhagic transformation ($p = 0.647$).

Patients with new CMBs were older (median 72.5, interquartile range (IQR) 66.5, 84.0 vs. 62.0, IQR 46.0, 75.5; $p = 0.026$), had higher creatinine level (median 1.0, IQR 0.9,1.1 vs. 0.8, IQR 0.7, 0.9; $p = 0.035$) and more often had higher counts of baseline CMBs: 9 (64.3%) vs. 5 (14.3%), $p < 0.001$. Other parameters were not statistically significantly different between the groups including pre-existing hypertension, the National Institutes of Health Stroke Scale (NIHSS) admission score, stroke subtype according to TOAST classification, the severity of leukoaraiosis, and baseline DWI lesion volume.

Multiple logistic regression analysis (**Table 6**) indicated that presence of baseline CMBs (risk ratio 5.95, 95% confidence interval CI 2.69–13.20, $p < 0.001$) and lower platelets level (risk ratio 0.992, 95% CI 0.986–0.998, $p = 0.007$) were independently associated with new CMBs.

DISCUSSION

In our patient sample, administration of rtPA resulted in the appearance of new CMBs in nearly 30% of the subjects with AIS, and the baseline CMBs were associated with the higher risk of the new ones appearing after the treatment. However, in this cohort, the baseline CMB load was not related to the increased risk of hemorrhagic transformation, unlike in many of the previous reports (21, 23, 32, 39). This finding seems not to be in line with the pathophysiological connections of CMBs and various vascular pathologies, notably small vessel disease, which in turn is related to increased vascular vulnerability and thus with hemorrhagic transformation—these correlations have been extensively discussed elsewhere (21–23). The reason for this discrepancy might be that these associations may be influenced by many confounding factors connected with the individual characteristics of a patient. CMBs are to be found in "healthy" populations, however, the insight in the available reports prove susceptibility of these populations for numerous future health risks that are additionally modulated by many coexisting factors such as hypertension, smoking, Apo E homozygosity, aspirin intake, white matter lesions or cerebral amyloid angiopathy (40). In addition, it has been reported that the correlation between CMBs and hemorrhagic transformation is not linear and that

TABLE 5 | Inter-observer agreement for the MRI assessment of CMBs.

CMBs on MRI	Baseline [kappa]*	Follow-up [kappa]*
Deep structures	0.64	0.78
Cortical/subcortical	0.58	0.74
All	0.63	0.77

** interobserver agreement was evaluated using the weighted Cohen's kappa with linear weights and interpreted in the following way: 0.01–0.20 as poor agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as substantial agreement, and above 0.80 as almost perfect agreement. The interobserver agreement was evaluated between the assessments of the neurologist (BJ) and the radiology team (ES and DO).*

TABLE 6 | Multiple logistic regression analysis for new CMBs in the follow-up T2*-EPI.

	New CMBs in the follow up T2*-EPI		
Risk factors	**Adjusted risk ratio**	**95% CI**	***p*-value**
Presence of baseline CMBs	5.95	2.69–13.20	<0.001
Hypertension	5.45	0.99–29.90	0.051
Platelets	0.992	0.986–0.998	0.007
Observations	49		

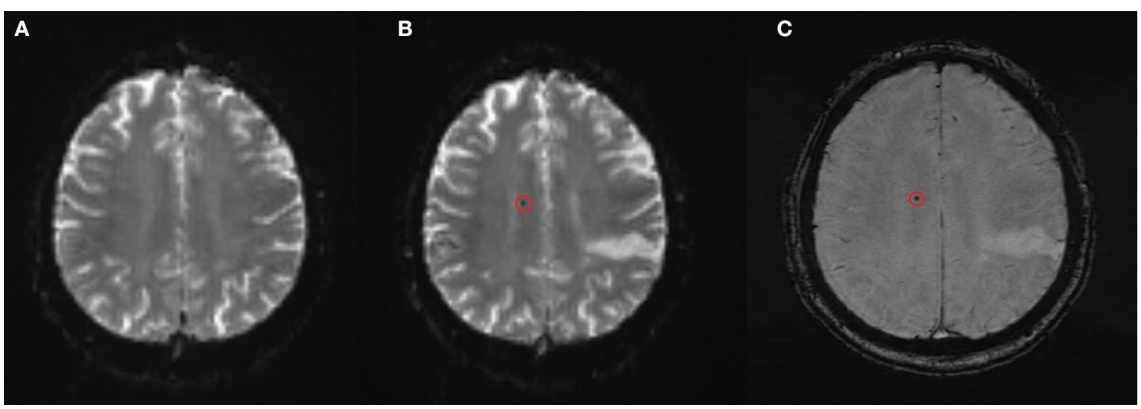

FIGURE 1 | New CMB found on the follow-up MRI on day 7–9 after rtPA treatment **(A)** baseline T2*-weighted EPI-GRE sequence, **(B)** follow-up T2*-weighted EPI-GRE, **(C)** susceptibility-weighted imaging confirmatory slice.

there is a threshold of baseline CMBs that, only when exceeded, results in higher risks for the transformation, especially for the sICH. The most commonly reported threshold is the > 10 CMBs (41) and the definite majority of our patients presented with not more than 3 baseline CMBs.

One of the future health issues of patients with CMBs is cognitive decline. The available studies suggest strong correlations between CMBs and cognitive impairment (15, 16). The substantial correlation between rtPA treatment and new CMBs found in our study, may have a major implication for the cognitive health of patients with AIS, and thus, longitudinal long-term studies in rt-PA treated patients with AIS are warranted for the need of powerful assessment of potential relations between thrombolytic treatment, CMBs, and cognitive function. This seems to be specifically important in patients with minor and/or lacunar stroke, where thrombolytic treatment does not have that much scientific data, as large vessel occlusion strokes, to prove favorable outcomes (42).

The study was not controlled with a placebo sample and therefore the direct correlation of new CMBs with rtPA treatment cannot be concluded. Additionally, the acute cerebral infarction itself is suggested to promote the development of CMBs (43). However, taking into account other studies on CMBs in acute stroke, and the known rate of the hemorrhagic infarction unrelated to rtPA administration, it is unlikely that this burden value would be as high as about 30% with no connection to rtPA. Furthermore, a strong indication of rtPA-CMBs correlation has been presented in the recent study by Miwa et al., where new CMBs were found only in patients who received rtPA (31). The high percentage of new CMBs in our study is much higher in comparison with other studies that revealed rates in the range of 4–13% (27–31). We believe that it is probably connected with a small sample size that resulted in incidental recruitment of more predisposed patients, as we discussed earlier.

This study has several methodological limitations. Importantly, as discussed earlier, we do not have a control group of non-thrombolysis patients to compare with. Another limitation of this study was the use of a 1.5-T field MR machine which is inferior to a 3-T in detecting CMBs, and the T2*EPI-GRE imaging sequence—much shorter but less sensitive than SWI for CMBs detection (44, 45). To support the lower sensitivity of T2*EPI-GRE sequences, SWI sequences were additionally used to confirm the CMB assessments. Finally, our study encompassed a relatively small sample of subjects, which is, however, similar to many of the reported cohorts. The main reason for the small number of patients is the conflict of interest between the optimal timing of rtPA treatment and the demanding circumstances of MRI testing that is necessary for proper CMBs assessment.

In conclusion, in this study, we present that baseline CMBs burden in patients with AIS is associated with a higher risk of new CMBs after rtPA treatment, but not with the risk of hemorrhagic transformation. New CMBs alone or combined with other selected characteristics (e.g., age, platelet count, or creatine level as indicated in this study) may become a useful predictor of long-term CMBs-related complications of thrombolytic treatment of stroke.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk, Poland (Approval No. NKBBN/76/19). The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

BJ co-conceptualization of the study, patient recruitment, data assessment and analysis, combined analysis of all data, and writing. AG-G patient recruitment, data assessment and analysis, writing, and editing. DO neuroimaging data collection and assessment and writing. ES neuroimaging data assessment. AW statistical analysis and writing. BR clinical data assessment. BK conceptualization and funding receipt (a major project), writing, review, editing, and coordination. All authors contributed to the article and approved the submitted version.

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Interactive Training of the Emergency Medical Services Improved Prehospital Stroke Recognition and Transport Time

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Background and Purpose: Acute stroke treatment outcomes are predicated on reperfusion timeliness which can be improved by better prehospital stroke identification. We aimed to assess the effect of interactive emergency medical services (EMS) training on stroke recognition and prehospital care performance in a very high-risk cardiovascular risk population in Lithuania.

Methods: We conducted a single-center interrupted time-series study between March 1, 2019 and March 15, 2020. Two-hour small-group interactive stroke training sessions were organized for 166 paramedics serving our stroke network. We evaluated positive predictive value (PPV) and sensitivity for stroke including transient ischemic attack identification, onset-to-door time, and hospital-based outcomes during 6-months prior and 3.5 months after the training. The study outcomes were compared between EMS providers in urban and suburban areas.

Results: In total, 677 suspected stroke cases and 239 stroke chameleons (median age 75 years, 54.8% women) were transported by EMS. After the training, we observed improved PPV for stroke recognition (79.8% *vs*. 71.8%, $p = 0.017$) and a trend of decreased in-hospital mortality (7.8% *vs*. 12.3, $p = 0.070$). Multivariable logistic regression models adjusted for age, gender, EMS location, and stroke subtype showed an association between EMS stroke training and improved odds of stroke identification (adjusted odds ratio [aOR] 1.6 [1.1–2.3]) and onset-to-door $\leq$ 90 min (aOR 1.6 [1.1–2.5]). The improvement of PPV was observed in urban EMS (84.9% *vs*. 71.2%, $p = 0.003$), but not in the suburban group (75.0% *vs*. 72.6%, $p = 0.621$).

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Conclusions: The interactive EMS training was associated with a robust improvement of stroke recognition, onset to hospital transport time, and a trend of decreased in-hospital mortality. Adapted training strategies may be needed for EMS providers in suburban areas. Future studies should evaluate the long-term effects of the EMS training and identify optimal retraining intervals.

Keywords: training, triage, emergency medical services (EMS), transient ischemic attack (TIA), prehospital/EMS, stroke

INTRODUCTION

Stroke is a life-threatening condition in which prompt and accurate diagnosis is essential for successfully implementing reperfusion therapies (1). Emergency medical services (EMS) play a crucial role in early recognition of stroke, as they are the first-line providers in about two-thirds of cases (2). Although EMS use by stroke patients is associated with earlier emergency department (ED) arrival, quicker evaluation, and more rapid treatment, how healthcare providers respond to stroke remains an essential factor in explaining prehospital delays (1). The process of clinically identifying a stroke is still the most significant challenge for EMS, as a percentage of stroke mimics reaches up to 50% (3, 4). Consequently, stroke mimics utilize the limited resources of acute stroke care pathways that might otherwise be directed toward the actual stroke patients who may benefit from acute time-sensitive revascularization therapies the most (5). Of concern, stroke mimic number in stroke care systems is expected to rise due to demographic changes in the coming decades (6). Therefore, it is crucial to improve the EMS performance in early stroke recognition. Fast and correct stroke diagnosis facilitates an early transfer to stroke-ready hospitals, reduces the volume of stroke mimics, and improves outcomes of acute stroke.

Intensive efforts are made to improve the quality of early stroke care. Training programs for EMS staff in simulated neurological environments increase knowledge on stroke recognition and awareness of time-sensitive medical emergencies (1, 7–12). The hospital prenotification has improved in-hospital timeliness metrics and increased intravenous thrombolysis (IVT) rates (13). In addition, prehospital stroke scales and screening methods for EMS staff have been introduced to allow for a more objective stroke identification (e.g., Face Arm Speech Time test, Los Angeles Motor Scale, Cincinnati Prehospital Stroke Scale) (14, 15). Moreover, specific scales for large vessel occlusion stroke were developed to facilitate the identification of candidates for endovascular therapy (EVT) (16). Given the changing landscape of prehospital stroke identification, a continuous educational effort is required to ensure optimal implementation of prehospital stroke protocols.

Stroke education interventions in prehospital care provided mixed results. A large multicenter randomized control trial in the United Kingdom did not show any benefit on the IVT rate. Surprisingly, the onsite care duration was prolonged in the EMS group that applied an enhanced stroke assessment protocol (17). On the other hand, several interventions increased the accuracy of stroke identification, the number of patients who underwent reperfusion therapy, and significantly reduced the time from the symptom onset to hospital arrival (7–9, 11, 18). Furthermore, the duration of the training effects remains unknown (19). Finally, the paucity of studies in very high cardiovascular risk populations, such as the Baltic countries, urged us to investigate prehospital stroke care intervention in Lithuania (20). Following the European (21) and North American guidelines (13), it is crucial to systematically assess the effectiveness of specific stroke education interventions and maintain the continuity of EMS education.

This study aimed to prospectively evaluate the effect of interactive EMS training on stroke recognition accuracy and the continuum of stroke care metrics. Second, we hypothesize that the EMS training effect might differ in the communities served and compare the training effect in urban and suburban locations.

METHODS

Study Design

We used an interrupted time-series design (22) to examine the impact of interactive EMS stroke training on EMS and hospital-based performance measures. We evaluated the positive predictive value (PPV) and sensitivity for identifying stroke patients, onset-to-door (OTD) $\leq$90 min rate, and hospital-based outcomes, including door-to-CT $\leq$30 min rate, reperfusion therapy, door-to-needle $\leq$30 min rate, and in-hospital mortality. We compared these variables between two periods—6 months before and 3.5 months after the interactive EMS training. The EMS personnel were blinded to the assessment.

The study was approved by the Vilnius Regional Biomedical Research Ethics Committee and conducted following the Declaration of Helsinki. The manuscript complies with STROBE guidelines for observational research.

Setting

This single-center study was conducted in Vilnius University Hospital (VUH) from 1 March 2019 to 16 March 2020, terminated earlier due to an unanticipated state-wide COVID-19 lockdown (23). VUH is one of the two comprehensive stroke centers (CSC) in Eastern Lithuania with a catchment population of 945,000[1], served by one EMS agency in urban and seven in suburban municipalities (24). The EMS response team consisted of a two-person team—paramedic and driver-paramedic. The

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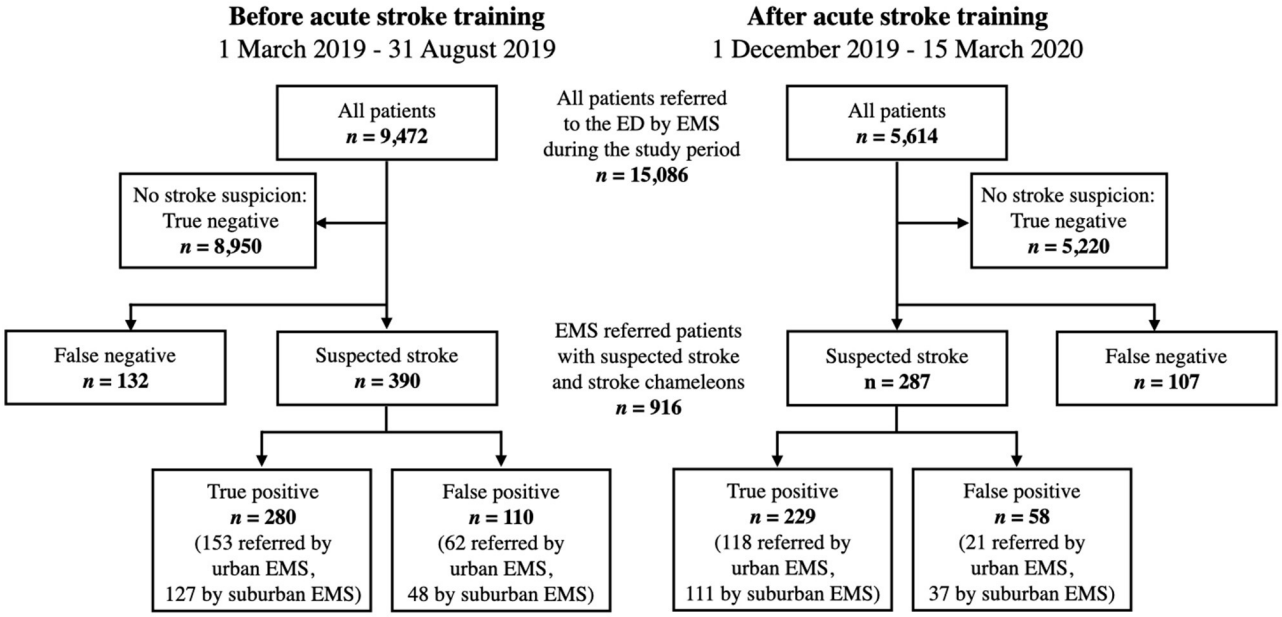

FIGURE 1 | Flowchart of the study population. Patients were referred to the emergency department (ED) of Vilnius University Hospital by emergency medical services (EMS) between March 1, 2019 and March 15, 2020.

EMS agencies were staffed by 331 specialists (217 in urban and 114 in suburban locations) and transported ≈20,400 patients.[2] The paramedics had prior training in nursing (307, 92.7%) or medicine (24, 7.3%).

The post-training period coincided with the change in national stroke triage guidelines, implemented on January 1, 2020. The new regulations affected the workflow of suburban EMS as it required direct transport of all suspected stroke cases to the stroke-ready hospitals with IVT or EVT capability, bypassing regional hospitals irrespective of the time from symptom onset.[3]

Study Population

We collected data of suspected stroke or transient ischemic attack (TIA) patients referred by the EMS to the VUH ED. Secondary transfers from other hospitals and in-hospital strokes were not included. We also collected data on false negatives, that is, stroke cases that were not identified by the EMS. EMS used the Face Arm Speech Time test (FAST) for the identification of suspected strokes (25). Overall, 15,086 patients were referred to the ED by the EMS, of whom 916 patients with EMS suspected or hospital confirmed strokes were included in the analysis (**Figure 1**). Stroke case ascertainment was done after arrival at the hospital by an attending neurologist after a complete stroke work-up. We did not include cases admitted during the 3-month training period.

Interactive EMS Training

Twelve 2-h interactive prehospital stroke recognition training sessions were held in the Neurology Department of VUH over 3 months (from September to November 2019). Interactive training sessions were given by stroke neurologists from the Lithuanian Stroke Association. Each training session was limited to 20 EMS staff members. In total, 166 out of 331 (50.2%) paramedics working in our stroke network participated in the training. The training curriculum was based on the publicly available ANGELS initiative's e-learning course for stroke education for emergency medical teams[4] adapted for local needs and in-person delivery (available online[5]). The EMS stroke training covered stroke epidemiology, pathophysiology, acute stroke treatment, and outcomes, emphasizing the time-sensitive aspects of acute stroke care. The EMS staff was trained to recognize stroke with the FAST test and identify the major stroke syndromes and stroke mimics. Additionally, participants received an update on prehospital acute stroke management. The presentation emphasized the importance of last known well (LKW) documentation, glucose check, minimizing the on-scene time, and hospital prenotification, followed by an interactive discussion.

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TABLE 1 | Baseline characteristics and outcomes of emergency medical services suspected stroke admissions.

	All patients (*n* = 916)	Admitted before training (*n* = 522)	Admitted after training (*n* = 394)	*P*-value	Referred by urban EMS (*n* = 500)	Referred by suburban EMS (*n* = 416)	*P*-value
Median age, years (IQR)	75 (66–82)	74 (65–82)	75 (66–82)	0.596	75 (66–82)	75 (65–82)	0.340
Female sex, *n* (%)	502 (54.8)	276 (52.9)	226 (57.4)	0.177	272 (54.4)	230 (55.3)	0.788
Confirmed strokes, *n* (%)	748 (81.7)	412 (78.9)	336 (85.3)		417 (83.4)	331 (79.6)	
Ischemic stroke	606 (66.2)	339 (64.9)	267 (67.8)	0.371	335 (67.0)	271 (65.1)	0.555
Hemorrhagic stroke	86 (9.4)	46 (8.8)	40 (10.2)	0.491	48 (9.6)	38 (9.1)	0.810
ICH	68 (7.4)	37 (7.1)	31 (7.9)	0.656	38 (7.6)	30 (7.2)	0.823
SAH	18 (2.0)	9 (1.7)	9 (2.3)	0.545	10 (2.0)	8 (1.9)	0.933
Transient ischemic attack	56 (6.1)	27 (5.2)	29 (7.4)	0.171	34 (6.8)	22 (5.3)	0.342
Stroke mimics, *n* (%)	168 (24.8)	110 (28.2)	58 (20.2)	0.017	83 (23.4)	85 (26.3)	0.388
Stroke chameleons, *n* (%)	239 (32.0)	132 (32.0)	107 (31.8)	0.955	146 (35.0)	93 (28.1)	0.044
Daily volume, median (IQR)							
Stroke alerts	2 (1-3)	2 (1-3)	3 (2-4)	0.002	1 (0-2)	1 (0-2)	0.275
Confirmed strokes	2 (1-4)	2 (1-3)	3 (2-4)	<0.001	1 (1-2)	1 (1-2)	0.005
Reperfusion of ischemic strokes, *n* (%)	203 (33.5)	126 (37.2)	77 (28.8)		110 (32.8)	93 (34.3)	
Not eligible	403 (66.5)	213 (62.8)	190 (71.2)	0.031	225 (67.2)	178 (65.7)	0.701
IVT	97 (16.0)	54 (15.9)	43 (16.1)	0.953	59 (17.6)	38 (14.0)	0.231
EVT	86 (14.2)	62 (18.3)	24 (9.0)	0.001	41 (12.2)	45 (16.6)	0.126
Combined treatment	20 (3.3)	10 (2.9)	10 (3.7)	0.586	10 (3.0)	10 (3.7)	0.629
Median timeliness metrics, min (IQR)							
Onset-to-door†	114 (75-198)	119 (78-205)	110 (74-196)	0.606	93 (67-159)	137 (89-269)	<0.001
Door-to-needle	41 (29-59)	41.5 (31-58)	41 (29-60)	0.850	46 (31-63)	37.5 (28-51)	0.078
Door-to-groin	81.5 (61-102)	73.5 (61-100)	90 (65-110)	0.206	88 (60-107)	78 (61-98)	0.517
Baseline NIHSS, median (IQR)‡	8 (4–15)	9 (5–15)	7 (4–15)	0.072	8 (4–15)	8 (5–15)	0.643
Discharge NIHSS, median (IQR)‡	3 (1–5)	3 (1–5)	3 (1–5)	0.962	3 (1–4)	3 (1–5)	0.360

IQR, interquartile range; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; IVT, intravenous thrombolysis; EVT, endovascular treatment; NIHSS, National Institutes of Health Stroke Scale.

†Only patients with established onset of symptoms are included (n = 433).

‡Baseline (n = 343) and discharge NIHSS (n = 172) are reported only for ischemic stroke patients who were considered for reperfusion therapy.

Data Collection

Demographic and clinical characteristics such as age, gender, stroke type, daily stroke volume, type of reperfusion therapy, acute stroke care timeliness metrics (onset-to-door, door-to-needle, door-to-groin), and the National Institutes of Health Stroke Scale (NIHSS) scores at admission and discharge were collected for all confirmed strokes and stroke alerts referred by EMS. True positives were defined as EMS-suspected strokes followed by in-hospital confirmation of stroke (ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage) or TIA after a complete neurologic evaluation, including neuroimaging by CT or MRI. False positives, or stroke mimics, were defined as stroke alerts given an alternative diagnosis after a full assessment. Furthermore, we collected information on false negative cases, termed stroke chameleons. The NIHSS score was documented only for patients who were considered for reperfusion therapy.

Statistical Analysis

We compared categorical variables using the χ^2 test and Fisher's exact test, as appropriate. Based on their Gaussian distribution, the quantitative variables were compared using the Student's *t*-test or Mann–Whitney *U* test. Baseline characteristics and outcome measures were compared before and after the training and based on EMS location strata (urban *vs*. suburban). The 95% confidence intervals (CI) were calculated, where applicable.

Before the training, baseline trends in monthly EMS performance and hospital-based outcomes were assessed using univariate linear regression and the χ^2 test for trend. We performed multivariable logistic regression models to assess the association between the training and EMS performance and in-hospital outcome measures. To account for potential confounding effects of age, gender, EMS location, and stroke subtype where appropriate, we used the hybrid backward/forward stepwise selection using the Akaike information criterion (26), removing variables with a nonsignificant ($p > 0.05$) association. Age was forced into all models as an *a priori* confounder. $P < 0.05$ (two-sided) was considered statistically significant. IBM SPSS Statistics 23.0 software (IBM Corp., Armonk, NY, United States) and R version 3.6.2 were used for statistical analyses.

RESULTS

We enrolled 916 patients with a median age of 75 (interquartile range: 66–82) years, of which 502 (54.8%) were female. In total, 677 suspected strokes (73.9%) were admitted to the ED, comprising 509 true positives (55.6%) and 168 false positives (18.3%). In contrast, EMS did not recognize 239 (26.1%) strokes, labeled false negatives or stroke chameleons. The study groups before and after the training were balanced in terms of demographics, stroke subtype, and baseline NIHSS (**Table 1**). Urban EMS providers transported 500 patients (54.6%), whereas suburban EMS transported 416 (45.4%).

Demographic and Clinical Characteristics Before and After the Training

More daily stroke alerts (3 [2–4] *vs.* 2 [1–3], $p = 0.002$) and confirmed strokes (3 [2–4] *vs.* 2 [1–3], $p < 0.001$) were observed in the post-training period. However, proportionally fewer patients were eligible for reperfusion therapy (28.8% post-training *vs.* 37.2% pre-training, $p = 0.031$) due to a decreased rate of endovascular therapy compared to the pre-training period (9.0% *vs.* 18.3%, $p = 0.001$). No significant differences in IVT and combined treatment groups were observed.

The median onset-to-door time (110 [74–196] min *vs.* 119 [78–205] min, $p = 0.606$) improved numerically after the training but did not reach statistical significance. The door-to-needle, door-to-groin times, and discharge NIHSS did not differ significantly before and after the stroke training.

We did not identify any trends in EMS performance or prehospital care metrics during the 6 months before the EMS training (**Table 2**); thus, next, we assessed the impact of EMS training on these metrics.

EMS Training Effect

In the pairwise comparison, the PPV for the identification of acute stroke patients was significantly higher in the post-training period (79.8% [75.1–84.4] *vs.* 71.8% [67.3–76.3], $p = 0.017$). Notably, however, the proportion of false negatives and the EMS recognized stroke patients (sensitivity) did not differ before and after the intervention (**Table 3**). Although there was a weak trend for improvement in door-to-needle times and in-hospital mortality, there was no statistically significant difference in other hospital-based outcomes before and after the EMS training.

Multivariable logistic regression showed improved odds of stroke identification (PPV) (**Table 4**), which remained significant after adjusting for age, gender, and EMS location (adjusted odds ratio (aOR) 1.6 [1.1–2.4]). Furthermore, we observed improved odds of patient arrival within 90 min of stroke onset (aOR 1.6 [1.1–2.5]), driven by an improvement in OTD $\leq$ 90 min time in urban EMS (56.8% [46.4–66.7] post-training *vs.* 41.1% [33.5–49.0] pre-, $p = 0.019$).

Urban vs. Suburban EMS

EMS-referred patients from urban and suburban areas did not differ in demographic characteristics, acute stroke types, baseline and discharge stroke severity, and eligibility for reperfusion therapy (**Table 1**). Although there were more overall daily confirmed strokes referred by urban EMS (1 [1–2] *vs.* 1 [0–2], $p = 0.005$), there was no difference in the proportion of suspected strokes *vs.* total patients transported by urban and suburban EMS; thus, indicating similar suspected stroke prevalence in both groups.

There was no significant baseline difference in PPV values between urban and suburban EMS (**Figure 2**). However, after the training, the PPV improved in the urban EMS group (84.9% [78.9–90.8] *vs.* 71.2% [65.1–77.2], $p = 0.003$), but not in the suburban EMS (75.0% [68.0–82.0] *vs.* 72.6% [66.0–79.2], $p = 0.621$). Marginally more stroke chameleons were referred by urban than suburban EMS (35.0% [30.6–39.7] *vs.* 28.1% [23.5–33.2], $p = 0.044$), indicating lower sensitivity in the urban EMS group. However, there was no significant difference in sensitivity before and after the training within each EMS group.

Shorter overall median onset-to-door time was observed in patients referred by urban EMS (93 [67–159] min *vs.* 137 [89–269] min, $p < 0.001$), and more urban patients reached the CSC within 90 min (46.9% [40.6–53.2] 25.3% [19.7–31.8], $p < 0.001$) compared to the suburban EMS. After the training, there was a weak trend for improvement of the absolute onset-to-door time (84.5 min *vs.* 108.0 min, $p = 0.074$) and a significant improvement in onset-to-door $\leq$ 90 min rate in the urban EMS (70.5% [60.2–79.0] *vs.* 41.1% [33.5–49.0], $p = 0.019$), but not in the suburban EMS group (28.0% [19.9–37.8] *vs.* 22.8% [15.7–31.9], $p = 0.406$) (**Figure 2**).

DISCUSSION

We have several main findings from this prospective interrupted time-series study evaluating the effect of interactive EMS training on prehospital stroke care. First, we found a sustained improvement of prehospital stroke recognition during at least four consecutive months after the training. Second, we found an improved rate of timely transfers of suspected strokes to the hospital, demonstrating the overall benefit of EMS training on the continuum of prehospital care. Third, we

TABLE 2 | Trends in emergency medical services performance and hospital-based outcomes during the 6 months before the training.

Performance	Regression coefficient†	*P*-value‡
EMS recognized stroke patients (sensitivity)	−0.0173	0.527
PPV for identification of stroke patients	−0.0027	0.692
Onset-to-door ≤90 min	−0.0131	0.924
Door-to-CT ≤30 min	−0.0035	0.848
IVT rate	−0.0054	0.425
Door-to-needle time ≤30 min	−0.0169	0.415
In-hospital mortality	0.0028	0.606

PPV, positive predictive value; CT, computed tomography; IVT, intravenous thrombolysis.
†Linear regression coefficient for the proportion of cases with each outcome during 1-month intervals.
‡$\chi 2$ or Fisher's Exact Test for trend, as appropriate.

found a trend of decreased in-hospital mortality that could be related to more timely stroke patient transport to the hospital. Finally, the training effect was more pronounced in the urban EMS group and, thus, we discuss the possible reasons and implications.

We found fewer stroke mimics in the post-training period without an increase in the false negative rate. Thus, increasing the PPV did not result in suboptimal triage of strokes, nor did it deprive stroke patients of time-sensitive revascularization treatment. The improvement of PPV was driven by a reduced rate of stroke mimics in the urban EMS group. One of the reasons for significantly improved PPV in the urban but not the suburban EMS group could be the implementation of new national regulation of prehospital stroke triage on January 1, 2020, that partially overlapped with the post-training period. According to the new law, suspected stroke patients were transferred directly to stroke-ready hubs bypassing primary evaluation in the regional hospitals irrespective of their LKW time. The new guidelines were designed to improve access to reperfusion therapy for stroke patients in the suburban regions. However, the stroke triage pathway change may have increased the false positive rate in the suburban EMS group as they transported more suspected stroke cases directly to the CSC instead of the regional hospitals. Thus, we speculate that the weak trend of PPV improvement in the suburban EMS group reflects the effect of EMS training offsetting the expected dip of PPV in the suburban EMS group. Another possible explanation could be differences in stroke knowledge between urban and suburban paramedics before the training or other variables, such as differing socioeconomic status, comorbidities, or secular trends, not evaluated in this study.

The increase in PPV after the training is clinically relevant because it can help reduce the false positive cases overflowing the acute stroke care pathways. Optimal utilization of the frontline stroke care and neuroimaging resources is particularly relevant during peak hours of stroke incidence, such as the morning hours (27) or public health emergencies, as was the case during the COVID-19 pandemic (23). Therefore, continuous efforts are crucial to ensure optimal prehospital stroke identification.

Previous studies have shown that a brief educational EMS intervention could substantially improve EMS knowledge of prehospital stroke scales, prenotification compliance, and field triage protocols (10, 28). Moreover, a recent prospective study by Oostema et al. assessed the real-world impact of EMS training on prehospital stroke recognition and found that an online EMS education module coupled with performance feedback was associated with improved stroke recognition sensitivity, increased hospital prenotification, and faster tPA delivery (9). In addition to these findings, our study demonstrates that in-person interactive EMS training improves prehospital stroke identification and timely transfer to the ED. We also note that the sensitivity in our study did not change after the training, which might be explained by a relatively high baseline performance. The baseline stroke recognition sensitivity in our study (68.0%) was comparable to the post-training sensitivity in the Oostema et al. study (69.5%), suggesting a ceiling effect of stroke sensitivity improvement. Consequently, the improvement in PPV did not

TABLE 4 | Logistic regression models showing the association between emergency medical services training and acute stroke care performance measure and hospital-based outcomes.

Outcome	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)
EMS recognized stroke patients (sensitivity)	1.0 (0.7–1.4)	1.0 (0.7–1.4)‡
PPV for identification of stroke patients	1.6 (1.1–2.2) *	1.6 (1.1–2.4) *
Onset-to-door time ≤90 min	1.4 (1.0–2.1)	1.6 (1.1–2.5)‡*
Door-to-CT time ≤30 min	1.0 (0.4–2.9)	0.8 (0.3–2.4)
IVT rate	1.1 (0.7–1.6)	1.1 (0.7–1.6)
Door-to-needle time ≤30 min	1.5 (0.7–3.5)	1.5 (0.6–3.5)
In-hospital mortality	0.6 (0.3–1.0)	0.6 (0.4–1.1)‡

OR, odds ratio; CI, confidence interval; PPV, positive predictive value; CT, computed tomography; IVT, intravenous thrombolysis.
†Adjusted for age, gender, and EMS location (urban vs. suburban).
‡Adjusted for age, gender, EMS location, and stroke type.
**P < 0.05.*

TABLE 3 | Emergency medical services performance and hospital-based outcomes among 916 suspected or confirmed strokes before and after the training.

Performance	All patients (95% CI)	Before training (95% CI)	After training (95% CI)	*P*-value
EMS recognized stroke patients (sensitivity)	68.0% (64.6–71.3)	68.0% (63.3–72.3)	68.2% (63.0–72.9)	0.955
PPV for identification of stroke patients	75.2% (71.9–78.4)	71.8% (67.3–76.3)	79.8% (75.1–84.4)	0.017
Onset-to-door ≤90 min	37.2% (32.8–41.8)	33.7% (28.2–39.8)	42.0% (35.0–49.3)	0.079
Door-to-CT ≤30 min†	84.2% (78.6–88.6)	84.1% (76.8–89.5)	84.4% (74.7–90.9)	0.956
IVT rate‡	19.3% (16.4–22.6)	18.9% (15.1–23.4)	19.9% (15.5–25.1)	0.764
Door-to-needle time ≤30 min	27.4% (20.1–36.1)	23.4% (14.8–35.1)	32.1% (21.1–45.5)	0.297
In-hospital mortality§	10.5% (8.4–13.2)	12.3% (9.4–16.0)	7.8% (5.1–11.8)	0.070

CI, confidence interval; PPV, positive predictive value; CT, computed tomography; IVT, intravenous thrombolysis.
†Included stroke patients, who underwent reperfusion treatment (n = 203).
‡Only ischemic stroke patients (n = 606).
§Only hospitalized stroke patients (n = 636).

result in a false negative rate (type II error) increase and, thus, did not deprive stroke patients of time-sensitive treatment. Similarly, our intervention did not affect the reperfusion therapy rate. Nevertheless, our baseline IVT rate was at least two times higher (15.9%) than in 10 out of 13 studies reported in a recent meta-analysis (19). Therefore, this suggests interventions had less effect in populations with high baseline performance.

A recent attempt to enhance prehospital stroke care was undertaken in the Paramedic Acute Stroke Treatment Assessment (PASTA), a multicenter randomized clinical trial in the UK. Surprisingly, the intervention resulted in 8.5 min longer onsite care time and did not show any tPA rate improvement (17). Arguably, sophisticated prehospital assessment protocols did not facilitate IVT decision-making. On the other hand, we find conflicting results from non-randomized intervention studies showing that prehospital intervention improved reperfusion therapy rates (11, 19) and in-hospital treatment times (9, 11). In addition to the previous studies, our study shows that interactive EMS training can improve stroke recognition and prehospital transfer times and, thus, improve the overall timeliness of acute stroke care. In contrast, we did not observe changes in hospital-based metrics. However, our study was not designed to evaluate the in-hospital performance since we did not collect data on hospital prenotification rate, and the EMS staff was not involved in the clinical care after the ED admission. Other in-hospital variables, such as imaging capacity, availability of rapid image interpretation, and ED workload influence the stroke care but are not accounted for in our study.

The training effect on timely prehospital transportation was more robust in the urban compared to the suburban EMS group. Since transport time from suburban regions is longer due to greater distances between the patient and the CSC, fewer patients could arrive within 90 min of symptom onset. Furthermore, due to the national regulatory changes during the study, all suspected stroke cases were to be transported to stroke-ready hospitals, irrespective of the time of symptom onset. Thus, the number of stroke alerts outside the acute treatment window increased in the suburban but not the urban EMS group. Hence, the actual training effect in the suburban EMS group was confounded by these regulatory changes.

The recent stroke triage changes in Lithuania were aimed to increase EVT access to patients in suburban areas by transporting suspected stroke cases directly to stroke-ready centers. However, the choice between drip and ship or mothership model is context-specific (29) and poses thorny clinical dilemmas (30). EVT has a remarkable treatment effect with the number needed to treat of 2.6 to reduce disability in the early hours after stroke onset (31). If large vessel occlusion (LVO) is suspected, direct transfer to a CSC with EVT capacity might be privileged, as a shorter time to reperfusion would improve the treatment effect (32). On the other hand, bypassing primary stroke centers with IVT capacity might cause unnecessary delays to IVT and an increase in false positive large vessel occlusion transfers due to suboptimal triage. To address these questions, the RACECAT study was conceived in Catalonia, Spain, a first randomized clinical trial in the field (ClinicalTrials.gov, identifier: NCT02795962). After randomizing 1,401 patients, the preliminary study results showed no difference in ischemic stroke outcomes between drip-and-ship and mothership models in a highly coordinated stroke network (33). Similarly, in our study, we did not observe any change in IVT rate, whereas surprisingly there was a decrease in EVT rate. However, the comparison of IVT and EVT rates before and after the training should be made with caution. The post-training period coincides with the increased transfer rate of suspected suburban stroke cases with elongated LKW, resulting in a higher number of strokes arriving at the CSC beyond the EVT window. Another explanation could be a cyclical variation in EVT eligible cases. Nevertheless, since all stroke alerts were analyzed, the regulation change was not expected to confound the comparison of EMS stroke recognition. Future studies should evaluate the impact of the triage regulation change on reperfusion therapy accessibility and stroke outcomes that was out of scope of the current study.

Although the direct transfer to the CSC could be most beneficial for LVO patients, the FAST scale used in our study

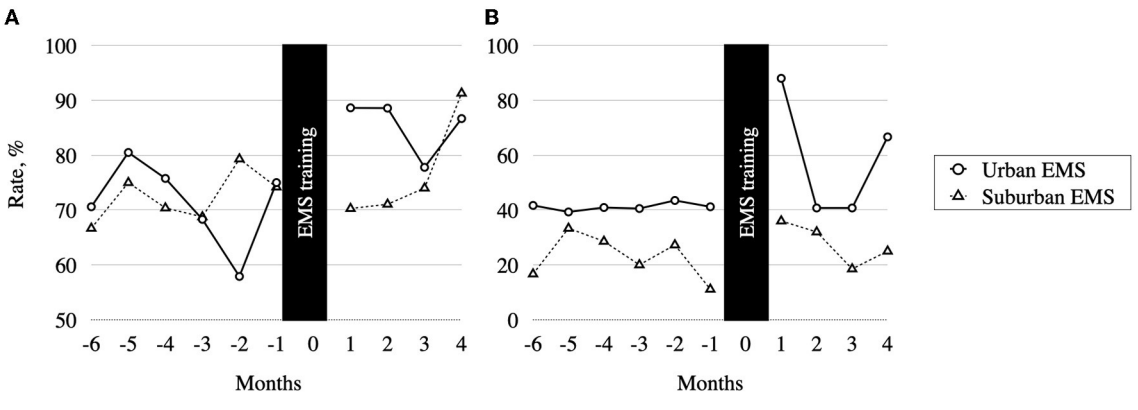

FIGURE 2 | Emergency medical services (EMS) performance before and after the EMS training. **(A)** Positive predictive value (PPV) for identification of stroke patients. **(B)** Onset-to-door time ≤90 min rate stratified by EMS location.

was not explicitly designed to detect LVO. In this context, a prospective study comparing eight prehospital scales for LVO identification showed that an adapted version of Gaze-Face-Arm-Speech-Time (G-FAST) had high LVO recognition accuracy similar or higher to other LVO scores (34). Moreover, improving the PPV of the stroke screening tools can increase the area where the mothership model provides the best stroke treatment outcome (29). More studies will be needed to explore the optimal LVO prediction methods to triage patients for different transfer pathways.

The main strength of our study is a prospective design and relatively large sample size. The blinding of EMS staff to the assessment allowed us to evaluate the training effect and avoid the apprehension bias, also known as the Hawthorne effect, when participants modify their behavior in response to their awareness of being observed (35). The main limitation of our study was the absence of a control group to fully evaluate the actual effect of the intervention. However, since there were no significant differences in demographic and clinical characteristics of suspected stroke cases before and after the training, the confounding by unmeasured factors was limited. Also, the overlap between the first month before and the last month after the training allowed us to compare similar calendar periods. Second, due to optional attendance, just over half of the EMS staff underwent the training. However, this rather introduces a bias toward the null, and we expect a stronger training effect with higher participation. Third, we found increased daily stroke rates in the post-training period, influenced by the change in the stroke triage regulations in suburban regions. However, the marginal increase in stroke prevalence during the post-training period could not fully explain the PPV improvement. We observed improved PPV with non-overlapping CI in the urban EMS and a weak trend in the suburban group favoring a consistent effect of EMS training across both groups. Fourth, our intervention did not target the dispatcher stroke recognition or hospital prenotification rate; thus, the inclusion of additional actors in the intervention might further improve the prehospital stroke care. Fifth, due to the emerging COVID-19 pandemic, we terminated our analysis before the national lockdown which significantly limited access to urgent and non-urgent healthcare (23). Had the study been continued and more cases were included in the post-training period, we could have expected a more significant effect on the in-hospital mortality. Also, we could not conclude on the long-term effects of the training beyond four months. Finally, our study was conducted in a very high cardiovascular risk population (20). These findings are generalizable to currently underrepresented populations with similar healthcare systems and EMS staffing patterns, including but not limited to Baltic states and Eastern European countries. Therefore, this study could inform prehospital clinical care and study design to improve prehospital stroke workflow using publicly available e-learning stroke education resources.

CONCLUSIONS

Interactive EMS training improved the prehospital stroke recognition that was maintained during at least four consecutive months. Consequently, we found a measurable improvement in prehospital stroke transfer metrics and a trend toward decreased in-hospital mortality providing evidence for EMS training's positive effect on overall acute stroke care. The EMS training effect was more robust in the urban than the suburban EMS group. Thus, context-tailored training programs should be considered for EMS providers in different locations. Future studies should evaluate the long-term effects of the EMS training on prehospital stroke care, hospital-related outcomes, and aim to determine optimal retraining intervals.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Vilnius Regional Bioethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LS, KM, DJ, AV, and RM: conception and design of the research. KM and RM: acquisition of the data. LS, KM, and RM: analysis and interpretation of the data and drafting the manuscript. LS, KM, AW, AV, KP, ES, KJ, AE, DJ, and RM: critical revision of the manuscript. All authors approved the final version to be published.

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Metric-Based Simulation Training to Proficiency for Endovascular Thrombectomy in Ischemic Stroke

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Ischemic stroke is one of the leading causes of death and long-term disability in the West. Mechanical revascularization techniques are considered the standard of care for large vessel occlusive stroke. Traditional apprenticeship models involve doctors training their skills on patients. Simulation platforms have long been recognized as an alternative to this. There has however been very little robust assessment of the training outcomes achieved on some of these platforms. At best, these simulations increase understanding of the procedural process and may help improve some technical skills; at worst they may instill bad habits and poor technique. The prerequisite of any simulation process must be to teach what to do, with which devices, in the correct sequence as well as what *not* to do. It should provide valid metric-based feedback to the trainee that is objective, transparent, and fair for formative and summative performance feedback. It should deliver a training program that measures the performance progress of trainees against expert benchmarks—benchmarks that represent an evidence-based peer-reviewed standard. In this paper, we present a perspective for PBP training for thrombectomy based on our experience with the process of procedure characterization, metric validation, and early experience of using this approach for proficiency training. Patient outcomes are not only determined by optimal performance in the Angio Suite but also by an efficient patient procedure pathway. There will be value in utilizing the PBP training standard not only for the procedure itself but also for the constituent elements of the stroke pathway to further improve treatment outcomes for ischemic stroke patients.

Keywords: proficiency-based progression, metric-based, endovascular thrombectomy (EVT), simulation training, virtual reality simulation

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BACKGROUND

Acute stroke is a common and devastating condition that causes the death of one-third of patients within 6 months and leaves another third permanently disabled. Prospective and randomized clinical trials on mechanical thrombectomy for large vessel occlusions have led to a revolution in treating ischemic stroke patients. Its efficacy is unmatched by any previous therapy in stroke

medicine. Despite the proven effectiveness of mechanical thrombectomy, access to this treatment is limited in many countries, in part due to the lack of specially trained doctors.

AGENTS OF CHANGE

Changing work practices and the evolution of more complex interventions in surgery, interventional radiology, cardiology, and medicine are forcing a paradigm shift in the way doctors are trained (1). Minimally invasive surgery (2), implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy (CRT) (3), transcatheter aortic valve implantation (TAVI) (4), and acute stroke intervention procedures (5, 6) are producing these changes at a faster pace than in other medical disciplines. Consequently, surgery, radiology, and cardiovascular medicine have had to develop a sophisticated understanding of precisely what is meant by "training" and "skill". This understanding is derived from psychological science, and the main findings have been generated from a quantitative applied experimental psychological approach (based on metrics) (7, 8). However, these need to be transferred into clinical practice requiring customized adaptation by the respective clinical disciplines themselves (translational science).

In the US, the 2014 report from the Institute of Medicine, Committee on the Governance and Financing of Graduate Medical Education that meets the nation's health needs came with a stark message: training in medicine must move to "outcome" rather than "process" driven graduate medical education (GME) (9). The settled conclusion is that deliberate practice (10) training on a (virtual reality) simulation presents the best current solution. These simulations should characterize the important performance characteristics of procedural skills which have been derived and operationally defined from, and then benchmarked by experienced surgeons (i.e., level of proficiency). Simulation training is optimal with metric-based feedback, particularly formative assessments on trainee procedural error enactment, proximate to their performance. In prospective, randomized studies (11–13), learners trained to a benchmarked proficiency level on the simulator performed significantly (i.e., 15–60%) (14) better than learners who were traditionally trained. Endovascular medicine has the most sophisticated virtual reality simulators available in medicine, and these have been used for the rollout of interventions such as carotid artery stenting in the US. The US Food and Drug Administration (FDA) has advocated the use of simulations as part of the approval of new devices (15, 16) and the American Board of Internal Medicine has adopted simulation as part of the maintenance of certification (17). Simulation is rapidly becoming a mainstay of surgery and endovascular education, training, certification, and the safe adoption of new technology.

A SCIENTIFIC APPROACH TO TRAINING

Although the methodologies to act on a more efficient and effective approach to learning skills exist, their implementation is not trivial. Simulation is useful, but without the proficiency-based progression (PBP) process, it is not as effective. PBP puts a clear measurable structure to simple simulation and gives clear feedback to the trainee. PBP (8) training on simulations outside the clinical environment can augment and quality-assure a work-based approach to skill acquisition. Considerable validation evidence already exists as to the effectiveness of this approach to training clinical skills (14, 18). However, PBP training programs require detailed, comprehensive, and validated metric-based characterization of the skills to be learned (19). Such metrics are also used to establish a quantitative benchmark that trainees must demonstrate before training progression or completion. Benchmarks are derived from, validated by, and benchmarked based on the objectively assessed performance of experienced clinicians. Trainees are fully cognizant of the metrics which are also used to implement a deliberate practice (10) rather than a repeated practice approach to training. Training is complete only on demonstration of the proficiency benchmark. When applied with scientific rigor, a PBP approach to learning skills is very effective, objective, transparent, and fair to the trainee and the training organization.

The PBP approach to training is based on solid research and has been validated in different healthcare settings for over a decade [e.g., laparoscopic (11–13), arthroscopic (20, 21), robotic (22), endovascular skills (23), anesthetic (24–26), mechanical thrombectomy for ischemic stroke (5), and communication skills (27)]. Results from the first multicenter randomized prospective trial of proficiency-based progression simulation training (for an arthroscopic shoulder procedure) showed that intra-operative errors were reduced by 56% when compared to the standard approach to training (21). The magnitude of the reduction in epidural analgesia failure during labor was similar (i.e., 53%) (28). Those randomized trial results demonstrate that requiring trainees (no matter how senior or experienced) to "train" and use a simulation or skills laboratory does not guarantee quality assurance and verified performance level at the completion of training. On the other hand, using the exact same resources with a PBP curriculum and the requirement to demonstrate quantitatively defined skills benchmarks does. The first step in using this approach is to develop and validate the performance metrics which characterize optimum (and sub-optimal) procedure performance. Once validated the metrics can then be used to guide the construction of a PBP training curriculum and the establishment of proficiency benchmarks that trainees must demonstrate before successful training completion and progression to the implementation of their skills in a clinical setting.

PBP METHODS

During preliminary meetings of the team (**Figure 1**) consensus was reached to comprehensively characterize a "reference approach" (i.e., straightforward, uncomplicated, commonly encountered, accepted, etc.) to the performance of the procedure e.g., mechanical thrombectomy (MT). The team then set about identifying the procedure-phases, steps, errors, and critical errors. This meant that the investigators identify and then operationally define these behavioral units, i.e.,

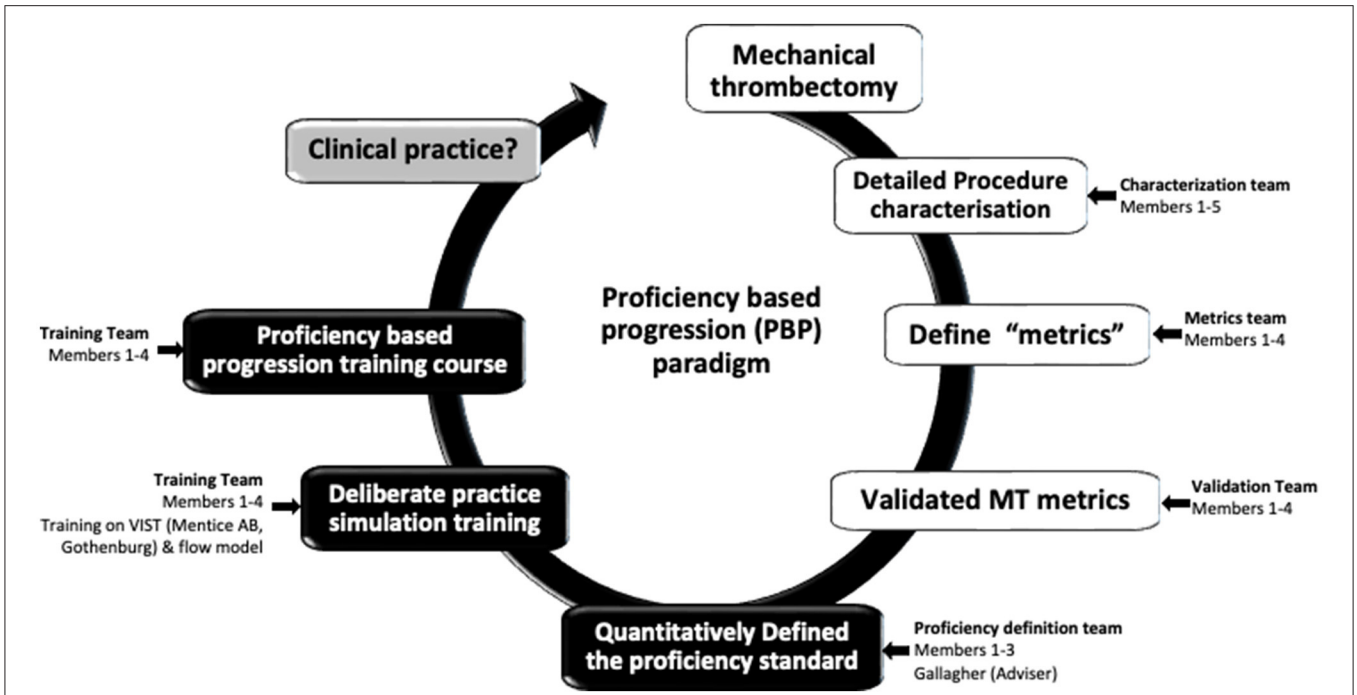

FIGURE 1 | The Proficiency based progression (PBP) metric development, validation and training paradigm (Crossley,[1] Holtmannspötter,[2] Liebig,[3] (Interventional Neuro Radiologists); Gallagher[4] (Behavioural Scientist); Lindkvist[5] (VR Sim engineer advisor)).

- the steps required to perform the procedure safely
- the performance characteristics that indicate deviations from optimal performance (or errors)
- fundamental performance errors (or critical errors) which expose the patient or operator to unnecessary risk

For the MT procedure, these goals are facilitated by viewing video recordings of the procedural performance (5, 20, 29). Viewing was initially done by the investigators in the same room with ongoing verbalized descriptions of performance and interaction between the investigators about what they were viewing, its meaning, and whether the performance was as per "instruction for use", optimal or sub-optimal.

METRICS STRESS TESTING AND DEFINITION VERIFICATION

When the team was satisfied that they had characterized a reference approach to the procedure in its entirety, they began the process of metric verification as operationally defined (8, 19, 30). This process involved the scoring of novel video recordings of the procedures. The team scored these video recordings initially all at the same time but latterly in discrete pairs. The function of these scoring exercises was to stress test the applied and practical usage of the metrics and their operational definitions. Problems with either of these aspects were usually indicated by low inter-rater reliability of scores. Metrics that are not scored reliably would need to be redefined or removed from the scoring matrix (see **Figure 2** as an example for some metrics).

FACE AND CONTENT VALIDITY ASSESSMENT—DELPHI MEETING

Once the metrics (that were demonstrated as being representative of the procedure to be characterized and could be reliably scored) were identified, they were presented to an independent group of peers during a ∼3-h face-to-face meeting (5, 20, 29, 31). This group of individuals was selected because they had very good knowledge of the endovascular thrombectomy procedures that had been characterized and they were also judged to be independent and fair-minded. Their task was to reach a consensus on whether the metrics and their operational definitions appropriately characterize the reference procedure in question. On the basis of consensus, metrics or groups of metrics were accepted, modified, or rejected. A very high level of consensus could be achieved (5).

ASSESSMENT OF CONSTRUCT VALIDITY

Metrics retained as part of the procedure characterization and agreed by the Delphi meeting were then used to establish the construct validity, i.e., the metrics distinguish between the objectively assessed performance of experienced and novice interventionalists when performing the procedure. After an initial period of assessor training to achieve inter-rater reliability >0.8 of metric identification between raters, objective assessment of novel videos by pairs of raters commenced. If valid, the metrics should demonstrate a significant difference in scores between experienced and novice operators (32, 33). In the mechanical

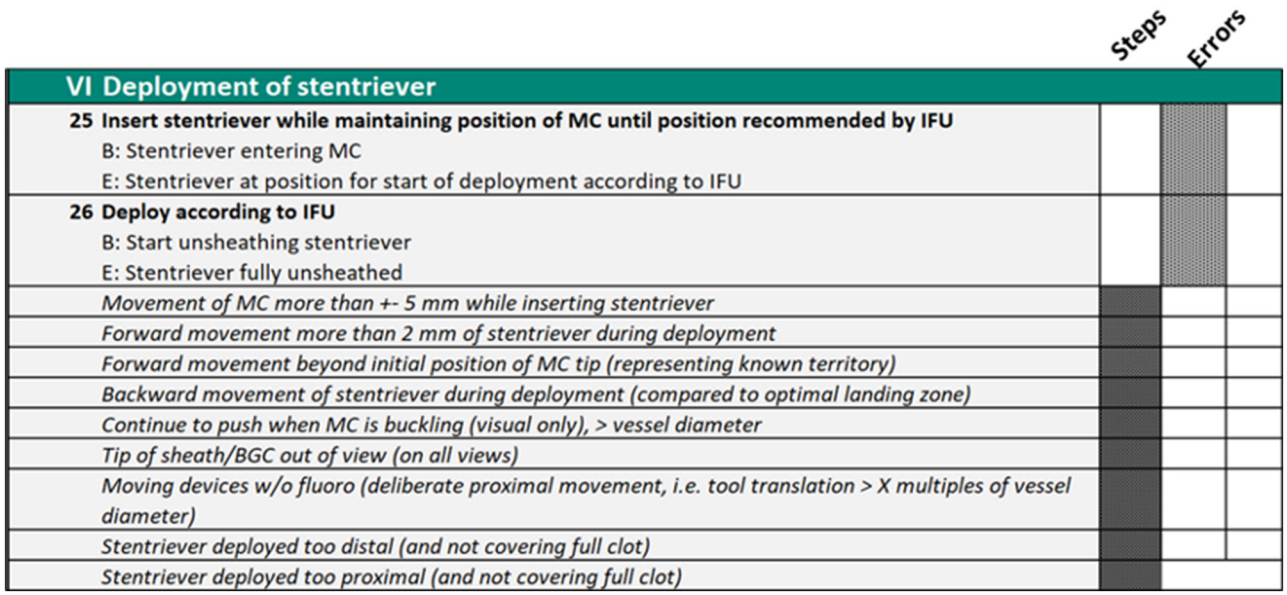

FIGURE 2 | Phase VI of the procedure metrics which explicitly define what the operator must do to complete the procedure and the errors they should avoid.

thrombectomy project the metrics demonstrated good construct validity (5).

PROFICIENCY DEFINITION

On demonstration of construct validity for the metrics, the team met to reach a consensus on which metrics or groups of metrics' proficiency should be defined. This involved the metrics which best or most reliably distinguished between experienced and novice operators. It also involved the identification of performance characteristics which were a compulsory part of proficiency demonstration. The proficiency benchmark was thus quantitatively defined (19, 21, 23).

PROFICIENCY VS. COMPETENCY

While some clinicians are concerned that perhaps the skill level for PBP training has been established at too high a benchmark for trainees, experience suggests that most trainees will reach this level. In a recent study, Angelo et al. demonstrated that >80% of trainees demonstrated the proficiency benchmark on a weekend course for learning two arthroscopic procedures (34). Furthermore, it has also been demonstrated that trainees, who had been allowed to train on the proficiency-based progression training program but had not reached the requisite level of proficiency, performed better than their traditionally trained peers, but markedly less well than those who did demonstrate proficiency at the termination of training (13). The advantage of a proficiency-based progression training program is that it is transparent, objective, and fair. Furthermore, it is flexible enough to deal with individuals who acquire their skills at a slower rate just as easily as those who acquire their skills more quickly. Also, this approach to training ensures a less variable graduating skill level. Contrary to popular belief, the developers of this approach to training do not assume that a trainee who has acquired the mean technical performance capability of practicing surgeons, has acquired the same level of wisdom. The goal has simply been to ensure a skill level of the trainee that indicates that their procedural performance has been automated to the point where they have the attentional capacity to hear and to follow instructions from the master surgeon/physician/radiologist during an intra-operative training procedure (8), an interpretation which has recently been validated (35). Proficiency-based progression training ensures that the learning experience in the operating room is more efficient and effective, thus operative procedures that the trainee is exposed to are used for maximal learning benefit. This approach to training does not presume some binary acquisition of technical skills or knowledge or decision making (36), rather skill acquisition is seen as a developmental process. All trainees using this approach are first taught anatomy and physiology, what to do and what not to do, *but* are not allowed to proceed to *in vivo* training before demonstrating the requisite knowledge (11). This ensures that training goals can be accomplished more effectively and efficiently, and quality assures the progression process.

PBP COURSE(S) FOR MECHANICAL THROMBECTOMY

Courses were delivered at the ASSERT center (UCC, Cork, Ireland), a bespoke simulation facility, over a 2-day period.

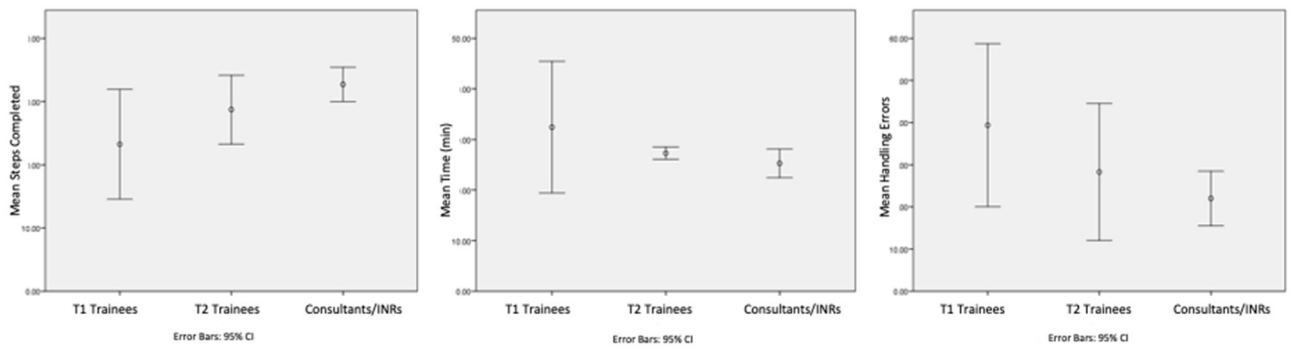

FIGURE 3 | T1 represents trainees at baseline, T2 represents trainees after the course and Consultants/INRs represent the proficiency benchmark. The performance of the trainees in terms of number of procedure steps completed, procedure time and handling errors all improved, but none of them reached the proficiency in the given time of the course.

Interventional Neuroradiology Fellows from the UK, Belgium, and the Netherlands of varying experience were invited to attend. The minimum skill set required was to be (as judged by their department) "competent in cerebral angiography."

The course introduction involved outlining the concepts of PBP and a description of the reference approach. A demonstration case was then performed by faculty members with commentary to demonstrate phases, steps, and errors in the procedure.

Delegates were then given time to familiarize themselves with the model before being asked to perform an unprompted case. Faculty assisted with the operation of the simulator but did not offer technical procedural assistance. This formed the baseline delegate performance assessment.

In a series of small group practical workshops, the delegates were given intensive training on the procedure with immediate proximate feedback on performance. At the end of the course, a further assessment case was performed in the same manner as the baseline case had been, with faculty providing technical simulator assistance but no procedural input. An overview of the results from these early courses is summarized in **Figure 3**.

Performance in terms of steps and time taken became more homogenous among the trainees; this increasing homogeneity of performance is an indicator but not a guarantor of increasing skill.

It is also important to note, that despite improvements being made none of the trainees achieved the performance benchmark. In essence, the platform was still able to discern the performance of those in training vs. experts. Fundamentally, a 2-day simulation course does not replace clinical training and experience.

TRAINING MT SKILLED PERFORMANCE

Mechanical thrombectomy is a life-changing procedure for patients but it is a high-risk procedure for the clinician to perform and requires considerable skill. Traditionally these skills have and still are widely acquired through the apprenticeship-style model on real patients over an extended period of training, like many other similar surgical and interventional skills. Without starting to train directly on patients, physics-based virtual reality simulation offers the potential solution to this considerable problem. Used properly, VR simulation ensures that the trainees, regardless of seniority, do not perform the procedure until they are skilled enough (i.e., proficiency-based progression). As demonstrated in other specialties in prospective, randomized, and blinded clinical trials, a proficiency-based progression approach to learning to perform the procedure utilizing VR simulation, is safer, more effective, and efficient. It ensures that the trainee knows what to do and what not to do before they attend the skills laboratory for training. Customizing this for mechanical thrombectomy, trainees are taught in the skill laboratory how to do the procedure on a physics-based VR simulation by intervention neuroradiologists, who are very experienced and good at performing the procedure and know the metrics. Faculty need specific training on the metrics as it is the VR simulation and their capability to deliver timely, explicit, constructive, and formative feedback to the trainee that determines training effectiveness. Trainees must know that they will not progress in their training until they demonstrate the requisite proficiency benchmarks.

PATIENT OUTCOMES

Though it has not yet been proven in mechanical thrombectomy, there is a growing body of evidence from other areas of medicine and surgery that demonstrates that skill of the surgeon is linked to patient outcomes (37) including e.g., cancer procedures (37). It has been demonstrated that a PBP training program significantly reduces failure rates e.g., in epidural anesthesia procedures (28). What is still not well-understood is the specifics of operator performance and how they impact patient outcomes. In mechanical thrombectomy, patient outcomes are not only determined by optimal performance in the Angio Suite but also

by an efficient and effective patient procedure pathway. Delays in the treatment pathway due to sub-optimal infrastructure or communications are known to contribute to some patients' poor outcomes. A 30 min delay in reperfusion, regardless of the means, reduces the chance for a neurological independent outcome by 10 %, Kathri et al. analyzed on basis of IMS III data (38).

The striking example of simulation training for thrombolysis treatment in Stavanger, Norway underlines that pathway time savings can be greatly enhanced by simulation training too. For instance, reducing the door-to-needle time from 30 min down to 13 min (39). We propose the value of utilizing proficiency-based training standards in the constituent elements of the stroke pathway before and after the Angio Suite to further improve treatment outcome results for ischemic stroke patients, thereby broadening the use of simulation with PBP not confined to the procedure alone. We foresee benefits in pre-hospital, imaging assessment, and transport/infrastructural aspects of regional pathways. It will not require every constituent step in the pathway to be reinvented but will likely lead to greater structured interconnectivity and parallel simultaneous decision making. Challenges remain to integrate different disciplines at regional and local levels. Different health systems will face different infrastructure, population, and geographical challenges, and it is likely that a system that works in Southern Germany may not be exactly the same as one that works in Southwest England. However, there will be themes and common principles that represent "exemplar" practice in any location.

Dave Brailsford attributed the phenomenal success of the British Olympic cycling team at the London 2012 Olympic Games to the "aggregation of marginal gains" (AMG). AMG, he explained, is "the 1% margin for improvement in everything you do". He described this process of multiple and seemingly minuscule improvements throughout the athlete's entire preparation process for competition, which, collectively achieved a far superior track performance from his athletes.

Procedural-based medicine has for over a decade engaged with a similar approach for the improvement of operative skills. This approach i.e., "proficiency-based progression" (PBP) (8, 19, 30), pays similar attention to the exacting level of detail as in the AMG approach used by Brailsford. The supposition underpinning PBP training is that individuals who are good at performing a procedure attend to small and apparently inconsequential aspects of performance that in isolation appear unimportant. However, when these small and detailed aspects of performance are effected and chained together, then that individual performs considerably better than an individual who is at best average at performing the same procedure. The PBP approach is however considerably more systematic and scientific than the AMG approach. In PBP, the performance skills to be taught and acquired are derived from a detailed and systematic procedure characterization. During this characterization process (described here), the specific attributes of optimal and suboptimal performance are identified and operationally defined rather than described (8, 19). Furthermore, rather than assuming, that these attributes accurately and comprehensively characterize the skills or procedure in question, the characterization is subjected to detailed and scientific validation, initially through a Delphi panel (20) with peers and then through quantitative construct validity testing that is objective, transparent and fair (32, 40).

We believe that is this attention to detail and quality assurance which will impact patient outcomes. It is the explicit identification, robust validation, and proficiency benchmarking of the performance metrics in a PBP training program that will ensure a more standardized approach to MT training leading to the production of more homogeneous skill levels of trainees that positively impacts patient outcomes.

The way doctors are trained to perform interventional procedures is evolving from an apprenticeship-type model to something that is more scientific, systematic, and evidence-based. A proficiency-based progression approach to training is based on performance metrics that are derived from, agreed upon by, and benchmarked by experienced and practicing clinicians who are "good" at performing the procedure. Physics-based virtual reality simulation training with the exact same procedure devices affords trainees the opportunity to acquire a very high level of procedure skill outside of the intervention suite and operating room, rather than training on real patients at the beginning of their learning curve in "apprentice-style training". Evidence from prospective, randomized, and blinded studies have shown that simulation training without detailed performance metrics for formative feedback to the trainee and proficiency benchmarks is no better than an interesting educational experience. These performance benefits of proficiency-based progression training are too substantial to ignore. The bottom line of PBP training is that the performance level of the trainee must be known at the end of training. Furthermore, the trainee should only be allowed to proceed to perform on real patients when they have demonstrated the necessary proficiency benchmarks based on the performance of experienced operators/interventionalist.

CONCLUSIONS

The PBP approach has been validated and proven beneficial across multiple medical disciplines. Mechanical thrombectomy can no doubt be a beneficiary too, with application across the multidisciplinary team including neurologists and anesthetists. We set the PBP approach in mechanical thrombectomy framed around the physics-based virtual reality simulation, as the successful and proficiently performed mechanical recanalization is the core of the treatment. Without recanalization, any additional improvements in the pre and post-angiography setting are rather pointless. But not only in the spirit of the Brailsford AMG approach, but PBP in thrombectomy also needs to incorporate the stroke treatment pathways before and after the Angio Suite to further reduce poor outcomes and improve the overall benefit of mechanical thrombectomy.

Another area that offers potential for additional study includes the use of this methodology for skill retention in procedures that

may be infrequently performed. Intuitively there may be benefits here not just for trainees or clinicians early in their careers but also for experts. Incorporating a PBP refresher approach for a procedure that may only be performed on a handful of occasions per year could potentially be of great value and interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MH, RC, TL, and AG contributed to conception and design of the study. AG, RC, and MH composed the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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