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Mechanical thrombectomy and development of thrombectomy devices

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Mechanical thrombectomy and development of thrombectomy devices

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Editorial: Mechanical thrombectomy and development of new devices: emerging trends in rescue strategies for failed mechanical thrombectomy

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mechanical thrombectomy (MT), acute ischemic stroke (AIS), intracranial atherosclerotic disease (ICAD), failed thrombectomy, endovascular treatment (EVT)

Editorial on the Research Topic
Mechanical thrombectomy and development of thrombectomy devices

In 2015, a series of randomized trials led to the widespread acceptance of mechanical thrombectomy (MT) as a treatment for patients with acute ischemic stroke. Particularly, MT for large vessel occlusion (LVO) under specific pre-treatment conditions is now considered the standard of care (1).

Meanwhile, clinical investigations have shifted their focus toward expanding treatment indications by exploring the effectiveness of MT in cases with longer treatment time windows, lower pre-treatment ASPECT scores, distal branch occlusions, and posterior circulations. LVO associated with intracranial atherosclerotic disease (ICAD) is one of the actively discussed conditions. Reports indicate that ICAD accounts for 6% (2) to 29.6% (3) of ischemic strokes, with varying prevalence among ethnic backgrounds, being more common in Asian, African-American, and Hispanic populations.

The challenges in treating ICAD-related LVO are 2-fold. Firstly, diagnosing ICAD based on the initial imaging is often technically impossible due to the lack of contrast filling in the target lesion. As a result, interventionalists need to make a decision once partial recanalization of the target lesion is achieved although differentiating between ICAD-related occlusion and occlusion caused by hard clot or arterial dissection can also be challenging. Secondly, ICAD-related occlusions are known to be associated with a higher rate of post-treatment re-occlusion (4). Therefore, the selection of rescue therapies such as Percutaneous Transluminal Angioplasty (PTA), PTA with stenting (PTAS), and/or antiplatelet therapy (Glycoprotein IIB/IIIA inhibitor) plays a crucial role in maximizing treatment efficacy while minimizing post-procedure complications such as symptomatic intracerebral hemorrhage (sICH).

Numerous non-controlled studies have been conducted to address these issues; however, the optimal timing to shift from MT to PTA/PTAS during the procedure remains unclear. The number of thrombectomy attempts made can provide more convincing evidence of unsuccessful reperfusion/underlying ICAD, but it also raises concerns about intimal damage due to endothelial denudation, vessel perforations or stretching/torsions.

In this Research Topic of Frontiers of Neurology, Deng et al. conducted a retrospective subgroup analysis of the Angel-ACT registry to evaluate the efficacy and safety of PTAS for ICAD-related acute LVO. Of the 1,793 patients enrolled in the Angel-ACT group, 475 patients who met the inclusion criteria were included in the study. The patients were divided into three groups based on treatment methods: (1) Early Rescue Therapy Group: Patients underwent PTA/PTAS after one or no MT attempt, (2) No Rescue Therapy Group: Patients treated only with MT, and (3) Late Rescue Therapy Group: Patients underwent PTA/PTAS after two or more MT attempts.

After propensity score matching, the Early Rescue Therapy group showed better functional outcomes (mRS 0–1) at 90 days compared to the No Rescue Therapy group [adjusted odds ratio (aOR), 0.55, $p = 0.01$] or Late Rescue Therapy group (aOR 0.39, $p = 0.01$). There was no difference in the risk of symptomatic intracranial hemorrhage between the groups.

The authors concluded that once ICAD-related LVO is suspected, early decision-making to perform rescue therapy improves the efficacy of treatment without increasing the risk of post-procedural complications. The relatively poor clinical outcome in the Late Rescue Therapy group, which underwent MT attempts of twice or greater before transitioning to PTA/PTAS, was accounted for by (1) the lower reperfusion rate that can lead to prolonged procedure time and (2) more intimal damage causing vasospasm and intraluminal thrombosis.

This article provides a valuable contribution to the field of neuro-interventional practice by addressing another predicament that interventionalists have to face from time to time. The study provided another evidence that early decision making of shifting the procedure from simple MT to the rescue therapy improves the treatment outcomes of patient with ICAD-related-LVO.

The results above is also consistent with a recently performed large-scale study, the SAINT (Stenting and Angioplasty in Neurothrombectomy) study, which is a multicenter retrospective study evaluating the efficacy of rescue intracranial stenting for failed thrombectomy (2).

In our Research Topic, there is another article that delves into the same subject. Authored by Cai et al., the article is titled "*Rescue intracranial stenting for acute ischemic stroke after mechanical thrombectomy failure: a systematic review, meta-analysis, and trial sequential analysis*." The authors conducted a meta-analysis and trial sequential analysis of 15 clinical studies (1,595 patients) evaluating the efficacy and safety of rescue stenting for the failed MT. Compared to non-stenting approaches, rescue stenting was associated with better modified Rankin Scale (mRS) scores (0–2), a lower 90-day mortality rate, without increasing the risk of symptomatic intracranial hemorrhage. The trial sequential analysis also confirmed sufficient sample size and statistical power of the meta-analysis concerning mRS scores. Authors concluded that the study supported the use of rescue stenting as an effective and safe treatment for patients with acute ischemic stroke after a failed MT.

As we witness the growing body of positive clinical data regarding the effectiveness of rescue therapy for IACD-related-LVO, it is logical to consider a randomized clinical trial (RCT) as the subsequent phase to gain more clarity on the treatment's clinical advantages. Nevertheless, it is important to exercise caution due to the historical track record of PTA/PTAS for "symptomatic ICAD", which has been discouraging (5, 6). Recently, another RCT, the CASSIS trial, also failed to show the benefit of PTAS for the treatment of symptomatic severe ICAD (7). Needless to say the "ICAD-related-LVO" and "symptomatic ICAD" are totally different condition. Nevertheless, the occurrence of post-treatment stroke events or deaths within a 1-year timeframe, which range from 8.5 to 19.7% (5, 8), cannot be ignored, and it emphasizes the urgent requirement for new technological advancements or peri-procedural therapies to enhance the safety of the procedure.

The overall efficacy of rescue therapy for failed thrombectomy cases has been improving over the past several years, partially due to the improvement of the peri-procedural antiplatelet therapy. For instance, an increasing number of studies have reported the benefits of utilizing intra-arterial (IA) injection of short-acting IIb/IIIa inhibitors, such as Tirofiban, as a rescue treatment for failed thrombectomy (9). Furthermore, post treatment protocols of antiplatelet therapy have been changing. Interventionalists are now screening patients more frequently using CYP2C19 genetic testing or platelet aggregometry to rule out potential clopidogrel non-responders and proactively using the new-generation antiplatelet agents, such as ticagrelor or prasugrel, which are fast-acting agents with more consistent efficacy compared to the first-generation thienopyridine, clopidogrel. Given that the majority of RCTs in the past were designed to use clopidogrel for post-dual antiplatelet therapy, there is hope that future RCTs may be expected to have better efficacy and safety in the treated arm.

Currently, there are ongoing developments for the ICAD treatment with the introduction of new-generation endovascular stents specifically designed for this condition, including drug-eluting stent systems. Encouraging results have emerged from several clinical studies conducted in China (10). On the other hand, the lack of an appropriate animal model that accurately simulates ICAD poses challenges in conducting preclinical evaluations for these innovative devices. Therefore, there is a pressing need to establish ICAD animal models that effectively replicate post-treatment thromboembolism and in-stent stenosis. By doing so, we can expedite the progress of new device development aimed at treating patients with treatment resistant LVO.

Author contributions

IY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—original draft, Writing—review and editing. JC: Conceptualization, Investigation, Methodology, Supervision, Validation, Writing—review and editing.

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.

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References

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. American Heart Association Stroke, 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2018) 49:e46–110. doi: 10.1161/STR.0000000000000158

2. Mohammaden MH, Haussen DC, Al-Bayati AR, Hassan A, Tekle W, Fifi J, et al. Stenting and angioplasty in neurothrombectomy: matched analysis of rescue intracranial stenting versus failed thrombectomy. *Stroke.* (2022) 53:2779–88. doi: 10.1161/STROKEAHA.121.038248

3. Kim YD, Cha MJ, Kim J, Lee DH, Lee HS, Nam CM, et al. Increases in cerebral atherosclerosis according to CHADS2 scores in patients with stroke with nonvalvular atrial fibrillation. *Stroke.* (2011) 42:930–4. doi: 10.1161/STROKEAHA.110.602987

4. Kang DH, Kim YW, Hwang YH, Park SP, Kim YS, Baik SK. Instant reocclusion following mechanical thrombectomy of in situ thromboocclusion and the role of low-dose intra-arterial tirofiban. *Cerebrovasc Dis.* (2014) 37:350–5. doi: 10.1159/000362435

5. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. Aggressive medical management for preventing recurrent stroke in intracranial stenosis trial, aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet.* (2014) 383:333–41. doi: 10.1016/S0140-6736(13)62038-3

6. Zaidat OO, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA.* (2015) 313:1240–8. doi: 10.1001/jama.2015.1693

7. Gao P, Wang T, Wang D, Liebeskind DS, Shi H, Li T, et al. Effect of stenting plus medical therapy vs medical therapy alone on risk of stroke and death in patients with symptomatic intracranial stenosis: the CASSISS randomized clinical trial. *JAMA.* (2022) 328:534–42. doi: 10.1001/jama.2022.18921

8. Alexander MJ, Zauner A, Gupta R, Alshekhlee A, Fraser JF, Toth G, et al. The WOVEN trial: wingspan one-year vascular events and neurologic outcomes. *J Neurointerv Surg.* (2021) 13:307–10. doi: 10.1136/neurintsurg-2020-016208

9. Huo X, Raynald, Wang A, Mo D, Gao F, Ma N, et al. Safety and efficacy of tirofiban for acute ischemic stroke patients with large artery atherosclerosis stroke etiology undergoing endovascular therapy. *Front Neurol.* (2021) 12:630301. doi: 10.3389/fneur.2021.630301

10. Jia B, Zhang X, Ma N, Mo D, Gao F, Sun X, et al. Comparison of drug-eluting stent with bare-metal stent in patients with symptomatic high-grade intracranial atherosclerotic stenosis: a randomized clinical trial. *JAMA Neurol.* (2022) 79:176–84. doi: 10.1001/jamaneurol.2021.4804

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The human placenta as a model for training and research in mechanical thrombectomy: Clarifications and use of the chorionic plate veins

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Indications for mechanical thrombectomy in acute ischemic stroke are increasing, resulting in the continuous development of new devices and techniques. Therefore, there is a need for a realistic testing and training environment that offers the opportunity to practice different procedures and test the latest devices. Some authors have described the use of the human placenta as a model for neurointerventional surgery, with striking similarities to real-life conditions. This model has many advantages, including its relatively low cost and minimal infrastructure requirements, with fewer ethical concerns compared to animal models. So far, some preparation and set-up details were missing, and only arteries from the chorionic plate were used. This article provides the necessary clarifications and a mapping of the chorionic plate veins, so that the use of this model, which is particularly well suited for mechanical thrombectomy, can be as easy and wide as possible. A video explaining how to prepare the model is provided.

KEYWORDS

stroke, mechanical thrombectomy, placenta, vascular model, interventional neuroradiology

Introduction

Randomized controlled trials on acute ischemic stroke due to large vessel occlusion established the superiority of mechanical thrombectomy (MT) in addition to the best medical management, including intravenous thrombolysis, over the best medical management alone within 6 h from symptom onset (1–6). More recent trials demonstrated that the time window for MT can be extended up to 16 (7) or 24 h (8) from the last time the patient was known to be well, when the selection is based on neuroimaging evaluation showing a salvageable penumbra (7) or a mismatch

between clinical deficit and infarct size (8). Different techniques are currently used to perform these procedures, including stent retriever alone, contact aspiration alone, and combined techniques (using in different fashions stent retriever and aspiration catheter at the same time). However, there is no consensus on the optimal method for thrombectomy. Moreover, due to all these successes, there is a continuous development of novel therapeutic approaches. Hence, there is the need for a realistic testing and training environment with the possibility of practicing different procedures and improving neurointerventional skills. Available training setups include computer-based simulations, in *vitro* training using generalized or patient-specific vascular models, and animal-based training, such as swine or rabbit models (9, 10). While each model has certain advantages and drawbacks, it is difficult to reproduce all the haptic qualities necessary for these procedures using virtual simulators or animal model (11). It is therefore necessary to further improve existing models and to develop new models for research and training.

The human placenta (HP) is used as a vascular model for interventional neuroradiology. The HP model has many advantages, including its relatively low cost, minimal infrastructure requirements, ease of preparation and set-up, with fewer ethical concerns compared to animal models. Kwok et al. (9) conducted in 2014 some experimental studies, including a simulation of intra-arterial thrombolysis and a simulation of MT, with a comparison of different devices. However, the sample sizes were too small to perform statistical analyses. They reported that this model has striking similarities to real-life conditions. Nevertheless, some improvements are needed to better match real patient situations and to expand its use in research. Indeed, articles about the HP in neurointerventional surgery all report the use of CPAs to simulate intracranial arteries (9, 11, 12), whereas the chorionic plate arteries (CPAs) cross the chorionic plate veins (CPVs) above, unlike the intracranial arteries with the veins; and the umbilical arteries are much more difficult to catheterize than the veins. This article therefore explores the possibility of using the CPVs to simulate intracranial arteries and conduct research on MT.

Anatomy, histology and preparation method

Obtaining placentas

Fresh HP is relatively easy to obtain from hospitals with obstetric services. Written consent for donation of placenta for research and training in neurointerventional surgery is obtained from the mother before the baby is delivered. These placentas can be kept under refrigeration for approximately 2 weeks. However, it should be noted that the fresher the placenta is, the more faithful it will be to the actual practice conditions, and the tighter the artery-vein circuit will be.

Ethical statement

In most countries, including France, the placenta is considered as a human waste (like hair or nails). To avoid any confusion, all the women signed an informed consent form clearly stipulating that the placenta will be used only for training and research purposes and that no genetic research would be performed on the specimen.

Anatomy

A normal full-term HP is a circular discoidal organ with a diameter of about 22 cm, a central thickness of 2.5 cm, and an average weight of 470 g (13). The umbilical cord contains one vein (the umbilical vein) and two arteries (the umbilical arteries) surrounded by Wharton's jelly (see Figure 1). The umbilical vein carries oxygenated, nutrient-rich blood from the placenta to the fetus, and the umbilical arteries carry deoxygenated, nutrient-depleted blood from the fetus to the placenta (14). The umbilical arteries spiral around the umbilical vein. The umbilical cord most often inserts slightly eccentrically into the chorionic plate. The Hyrtl anastomosis is a common connection between the umbilical arteries near the cord insertion in most HPs. It has two main roles: safety valve (shunt), in case of partial compression of the placenta during uterine contractions or occlusion of one umbilical artery; pressure stabilizer between the umbilical arteries, when one of the arteries conducts a smaller blood flow into the placenta and a relatively smaller pressure gradient is developed, rebuilding the pressure gradients in the affected artery, and redistributing blood flow from the unaffected artery to the affected one to improve placental perfusion (15). Hyrtl anastomosis can be either a single connecting vessel or a fusion between the umbilical arteries. Most of the anastomoses (up to 90%) are of a single connecting tube, which may be transverse or oblique to the arteries (16).

The chorionic plate represents the fetal surface of the placenta, which is covered by the amnion. The amnion is only weakly attached to the chorion and can easily be removed from the delivered placenta. The chorion contains the chorionic vessels which are in continuity with the umbilical cord vessels. The chorionic plate arteries (CPAs) branches derive from the two umbilical arteries and form a disperse pattern where each artery divide in two or more branches, with gradually diminishing diameter, until their final branches, which supply the villous trees. The CPVs are direct extensions

Abbreviations: MT, Mechanical Thrombectomy; HP, Human Placenta; CPA, Chorionic Plate Artery; CPV, Chorionic Plate Vein; M1 segment, First segment of Middle cerebral artery; ICA, Internal Carotid Artery; PICA, Posterior Inferior Cerebellar Artery; DSA, Digital Subtraction Angiography.

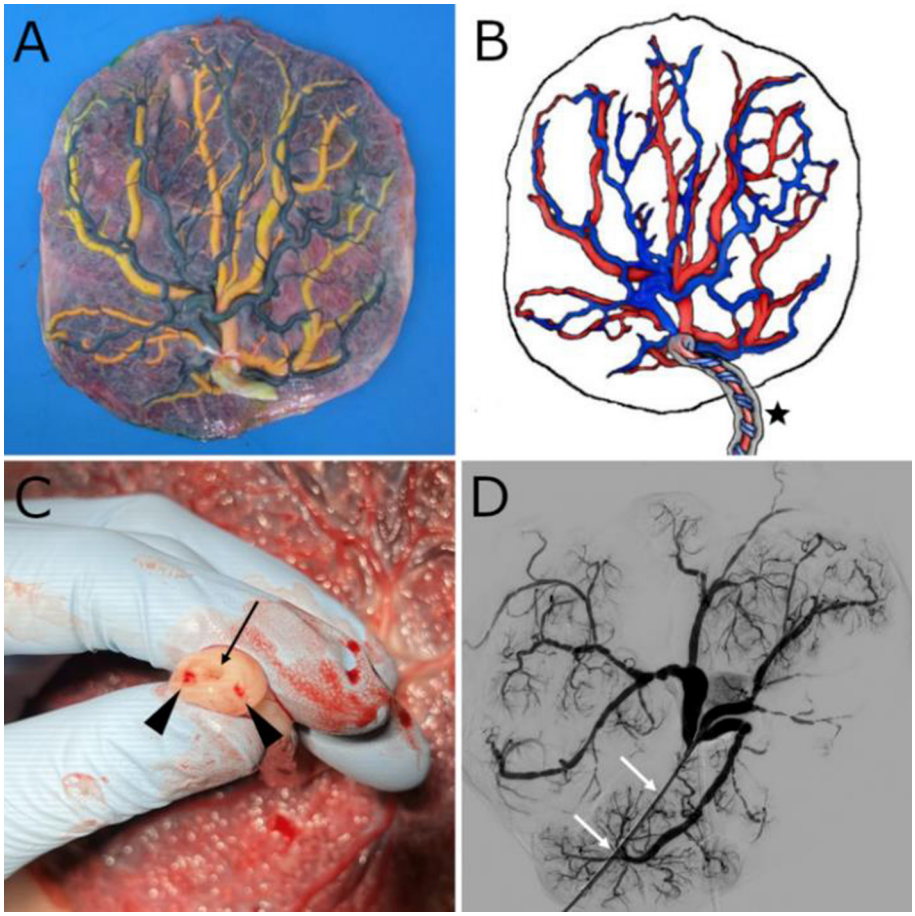

FIGURE 1
(A) Fresh placenta after removal of the amniotic sac and injection of color-dye into the chorionic plate vessels. Yellow vessels correspond to veins and dark green ones to arteries. **(B)** Schematic representation of a human placenta. The umbilical cord (black star) contains a vein and two arteries that spiral around it, buried within Wharton's jelly. The veins, which carry oxygenated blood, are shown in red, and the arteries in blue. **(C)** Umbilical cord cross-section with two umbilical arteries (black arrowheads) and a single umbilical vein (black arrow). **(D)** 2D-Angiographic appearance of the chorionic plate vein network after injection of contrast medium through an introducer sheath placed at the junction between the umbilical vein and the chorionic plate veins. The white arrows show the introducer sheath.

of the veins of the villous trees and usually cross the CPAs below. The CPVs give rise to the single umbilical vein (13).

Regarding CPAs, Bekov (17) defined the first-order segments as those diverging from the umbilical cord. The third-order segments are the end segments on the fetal surface that dive into the chorion to provide circulation into distinct cotyledons. The second-order segments are located between the first and third segments. Belykh et al. (18) provided data regarding CPAs lengths and diameters and a comparison with intracranial arteries. The first-order segments have a mean length of 28.8 ± 9.9 mm and a mean diameter of 6.5 ± 1.4 mm. The second division has a mean length of 35.9 ± 15.3 mm and a mean diameter of 3.4 ± 0.7 mm; these diameters are comparable to that of the first segment of a middle cerebral artery (M1 segment), an intracranial internal carotid artery (ICA) or a vertebral artery. The third-order segments have a mean length of 29.9 ± 10 mm and a mean diameter of 1.7 ± 0.4 mm; these diameters are comparable to that of an anterior cerebral artery, a posterior inferior cerebellar artery (PICA) or M2 to M4 segments. To the best of our knowledge, there is no study that maps the average lengths and diameters of the different segments of CPVs.

The basal plate represents the maternal surface of the placenta. It is an artificial surface, which emerged from the separation of the placenta from the uterine wall during delivery. A system of flat grooves or deeper clefts subdivides the basal plate into 10–40 slightly elevated regions called cotyledons, each of which consists of a main stem villus and all its branches (13). Because the basal plate is not used in

neurointerventional training or research, its description will not be further detailed.

Preparation

A strict transmissible disease protection protocol must be observed in all procedures. The first step is to remove the peripheral membranes with scissors and to peel off the portion of the amnion that adheres to the chorionic plate from the periphery to the umbilical cord, exposing the chorionic plate. Next, the blood adhering to both sides of the placenta should be removed with water or saline. The umbilical cord should be shortened by a clean cut with a scalpel to a length of 3–5 cm in order to facilitate future catheterization of the umbilical vessels, especially the arteries, which spiral around the vein. The two umbilical arteries and the umbilical vein can now be easily identified at the umbilical cord cross-section (Figure 1C).

The placenta is placed in a tray, which will be slightly inclined after preparation, to facilitate the emptying of fluid and contrast medium that extravasates out of the delicate capillary system, thus keeping the radiological field clear. The guide wire provided with a 6F introducer sheath is placed in the umbilical vein up to the CPVs, allowing then to position the introducer sheath with its dilator on this guide wire. The same strategy is used to catheterize each of the umbilical arteries up to the chorionic plate, with two particularities: the primary use of size 4–5F material may be useful to facilitate catheterization in these smaller vessels; rotating the cord around the venous introducer sheath is often useful to decrease the tortuosity of the umbilical arteries. The 4–5F introducers can be exchanged for 6–7F introducers for arteries and an exchange with 7–8F material can be done for the vein, to allow the introduction of larger caliber catheters depending on the context of use. A suture should now be placed around each umbilical vessel to avoid fluid reflux into them, another method being the use of clamps. At this stage, a 100- to 140-mmHg pressure bag is used to deliver a heparinized saline solution *via* an IV line into each arterial introducer (or in the venous introducer if the vessels used later for research or training will be the veins), dilating the vessels and removing the intraluminal clots. Note that digital pressures can help remove clots. Another IV line is connected to the venous introducer (or to each arterial introducer, if the anti-physiological direction is used), and its other end is placed in a tray, as the end of the circuit (placing a few gauze sponges in the bottom of this tray allows to mop up the liquid). Digital subtraction angiography (DSA) can now be practiced being as close as possible to the real conditions of intervention.

Note that one of the advantages of the HP model is the semi-transparent nature of the chorionic plate, which allows direct observation of changes within the blood vessels, the behavior of catheters, devices, clots, etc.

Histopathology and immunohistochemistry

For histopathological assessment, areas of the placenta that include CPAs and CPVs can be obtained to allow routine processing in cassettes. Samples are routinely fixed for at least 48–72 h in neutral buffered formalin before processing and embedding into paraffin blocks, from which histological sections of 3–5 μm can be obtained. Once in blocks, samples may be stored indefinitely at room temperature (19).

Unlike cerebral arteries, CPAs do not have an internal elastic lamina or elastic fibers in the media (18); therefore, these elements cannot be used for research purposes. However, because the endothelium of CPAs is positive for CD31 staining (9), the change in endothelium lining can be studied easily. The endothelial response to different devices or drugs can then be examined, which opens the door to many studies, such as the comparison between different MT devices or the comparison between different MT techniques.

Using CPVs as intracranial arteries

An improvement to the HP model could be its anti-physiological use, i.e., using CPVs as intracranial arteries. Indeed, CPAs are most often used to simulate intracranial arteries in neurointerventional surgery (9, 11, 12), whereas umbilical arteries are more difficult to catheterize than the vein, which is more straight and has a greater diameter. Furthermore, unlike intracranial vessels which have markedly different properties, histology, and vessel wall thickness between arteries and veins, due to different pressure requirements, chorionic plate vessels show far fewer disparities. Finally, this larger diameter, which allows the placement of larger introducers, will make it possible to use other catheters, capable for example of simultaneously accommodating two microcatheters. It is therefore necessary to map the lengths and diameters of the CPVs, and to verify that the endothelium of the placental veins is correctly labeled by CD31 (or CD34).

Methods

After written consent from the mothers, 6 placentas were prepared with the above-mentioned method (Supplementary Video 1), allowing the acquisition of standard anteroposterior 2D-projections and 3D-rotational angiography, after injection of iodinated contrast medium (6 mL with a velocity of 3 mL/s for 2D-projections and 15 mL with a velocity of 3 mL/s for 3D-rotational angiography), with a monoplane angiographic system (Azurion; Philips Healthcare, Best, the Netherlands). The lengths and diameters of the chorionic plate venous segments were measured, allowing

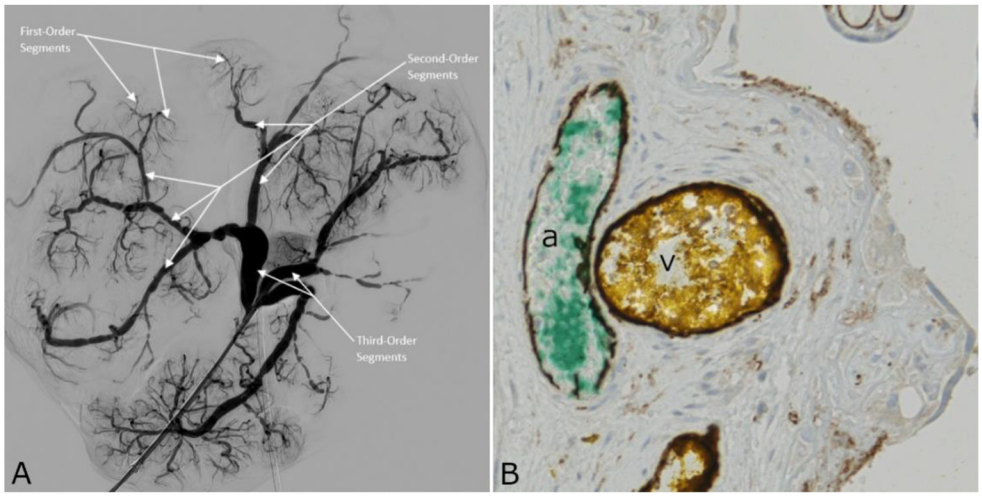

FIGURE 2
(A) 2D-Angiography of the chorionic plate veins with white arrows indicating first-, second-, and third-order segments. **(B)** Cross sectional image of the placenta shown in Figure 1A, obtained by light microscopy. The tissue sample was stained with CD31 for endothelium. Both CPA (a) and CPV (v) endothelia are CD31 positive, and appear in dark brown.

calculation of the mean measurements, with standard deviation. Measurements were made by one interventional neuroradiologist on the 3D-angiograms, on all segments well opacified by the contrast medium.

On another placenta, in which color-dye was injected (the one shown in Figure 1), immunohistochemical analyses were performed to verify that the venous endothelium is labeled by CD31. The placenta was fixed for 7 days in neutral buffered formalin before processing and embedding into paraffin blocks, from which histological sections were obtained, and immunostainings with CD31 were performed. Immunohistochemical analyses were performed by one perinatal pathologist.

Results

By analogy with Bekov's classification for CPAs (17), it can be defined (Figure 2): the first-order segments of the CPVs, those directly following the veins of the villous trees; the second-order segments, between the first and third segments; the third-order segments, joining the umbilical vein. Table 1 shows the average diameters and lengths of the first-, second-, and third-order venous segments. Figure 2B shows the immunohistochemical positivity of the arterial and venous vascular endothelium to CD31.

TABLE 1 **Average diameters (mm) and lengths (mm) of the first-, second-, and third-order venous segments.**

Segments	Mean Diameter ± SD (range)	Mean Length ± SD (range)
Third-order	11.6 ± 3.6 (7.4–17.9)	33.6 ± 8.8 (21.8–46)
Second-order	3.7 ± 1.1 (2.3–5.7)	28.3 ± 10.7 (15.1–49.7)
First-Order	1.3 ± 0.5 (0.7–2.1)	8.2 ± 2.3 (3.5–13.9)

Discussion

The HP is a useful vascular model for training and research in MT. One of its advantages is the ease of implementation in any hospital with a maternity ward and an angiographic system, at a very low cost. Unlike computer-based and silicone models, it can be used to study the endothelial response to drugs and devices used in MT. Another advantage is that a single HP has several vessels that can all be used for simulation and reproduce various endovascular anatomical situations. Furthermore, there are fewer ethical issues compared to animal models, and the equipment and personnel requirements are much lower. Ultimately, a single placenta can be used for several training sessions, as it keeps very well for up to 2 weeks.

Although the HP model cannot be used in longitudinal follow-up studies like animal models (10), it could be used to study immediate hemodynamic changes induced by different devices, such as stents for "intracranial" stenosis. This could be done in all imaging modalities and more easily than with silicone models. The absence of great vessels and supra-aortic trunks analogs in the HP model can be compensated by the combined use of HP and other vascular models, such as silicone models.

So far, papers referring to the use of placenta in neurointerventional surgery all reported the use of CPAs to simulate intracranial arteries (9, 11, 12). This study demonstrates

that CPVs can also be used thanks to their anatomy and histology, which are very similar to those of arteries. The following advantages have been observed: CPVs cross the CPAs below, just as intracranial arteries do with respect to veins; and the umbilical vein is much easier to catheterize initially (including with larger catheters), and can be the only vessel catheterized in case of difficulties in catheterizing arteries that are too tortuous (it would, however, implies higher fluid losses). However, it is preferable, if possible, to catheterize both the umbilical arteries and the umbilical vein, thus obtaining a closed vascular model and a larger number of vessels to use for research or training. Indeed, it is possible to change the direction of fluid flow during experiments, as both CPAs and CPVs can simulate intracranial vessels. Second-order venous segments of the chorionic plate, with a mean diameter of 3.7 ± 1.1 mm (range = 2.3–5.7 mm), are ideally suited for training and research in MT, because these values correspond to those of the large arterial trunks for which MT is performed. In addition, third-order venous segments, with an average diameter of 11.6 ± 3.6 mm (range = 7.4–17.9 mm), can sometimes be used to train for cervical carotid stenting when the length is sufficient [33.6 ± 8.8 mm (range = 21.8–46 mm)].

Currently, interventional neuroradiologists who perform procedures on *ex vivo* vascular models, including HP, use water or saline solution to represent blood. Unlike these fluids, blood is a shear-thinning fluid. As a consequence, it makes the simulation less realistic because it lacks tactile feedback. The best blood mimicking fluid must reproduce the physical properties and rheology of blood. This would allow tactile sensations similar to those of real patients, and the behavior of devices and drugs would be more accurate. In addition, if the fluid can be studied realistically in Doppler, it would be a significant improvement. Blood itself might seem like the best fluid to use. However, there are several limitations in using blood and its components. It is a potential biohazard and precautions must be taken to minimize this risk. In addition, the shelf life of blood is limited, and *in vitro* erythrocytes are easily damaged. Moreover, the rheological properties of blood are likely to be different at room temperature than at 37°C (20). A 60/40 (by volume) water–glycerol mixture is one of the most widely used blood-analog solutions for use with vascular flow models (21). It has a viscosity of $3.8 \pm 0.08 \times 10^{-6}$ m^2/s and a density of 1090 ± 15 kg/m^3 (22), which is comparable to human blood. This water-glycerol solution is an inexpensive option that can be used with the HP model to improve tactile feedback.

Vessel pulsatility in the HP model can be simulated by using a programmable pulsatile perfusion pump, generating varying pressures and flow volumes at predetermined intervals. Many pumps of this type already exist and are commercially available, the pumps used with silicone models being compatible with the HP model. For preclinical evaluation and development of MT devices, and for training in interventional techniques with these devices, clot analogs that are as close as possible to the clots that cause stroke in humans should be used. Such clots with different fibrin and red blood cells compositions have been developed as part of the Neuro Thromboembolic Initiative of Neuravi (Cerenovus, Galway, Ireland) (23).

To conclude, HP may provide a low-cost training and research model for MT. The use of the CPVs seems to facilitate model preparation and may open new insights. The immunohistochemical positivity of the arterial and venous endothelium to CD31 opens the door to fundamental research projects. Further studies are however warranted to validate this model.

Data availability statement

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

Ethics statement

Written consent for donation of placenta from the mothers was obtained. An explanation of what interventional neuroradiology is and how the placenta would be used was given to the mothers in a printed format.

Author contributions

JB, JC, SP, and FC: conception and design. JB, MG, AG, EG, CP, NS, ES, KP, CL, and FC: acquisition of data. JB, MG, SP, AG, EG, CP, NS, ES, KP, CL, and FC: analysis and interpretation of data. JB, JC, and FC: draft of the manuscript. JB, JC, MG, SP, AG, EG, CP, NS, ES, KP, CL, and FC: revision and final approval. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author NS reports a conflict of interest with Medtronic, Balt Extrusion, Microvention (consultant), and Stock/Stock Options: Medina. Author FC reports a conflict of interest with Medtronic, Guerbet, Balt Extrusion (payment for readings), and Codman Neurovascular (core lab).

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.925763/full#supplementary-material

References

1. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* (2015) 372:11–20. doi: 10.1056/NEJMoa1411587

2. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* (2015) 372:1009–18. doi: 10.1056/NEJMoa1414792

3. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* (2015) 372:1019–30. doi: 10.1056/NEJMoa1414905

4. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 h after symptom onset in ischemic stroke. *N Engl J Med.* (2015) 372:2296–306. doi: 10.1056/NEJMoa1503780

5. Saver JL, Goyal M, Bonafe A, Diener H-C, Levy EI, Pereira VM, et al. Stent-Retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med.* (2015) 372:2285–95. doi: 10.1056/NEJMoa1415061

6. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol.* (2016) 15:1138–47. doi: 10.1016/S1474-4422(16)30177-6

7. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* (2018) 378:708–18. doi: 10.1056/NEJMoa1713973

8. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 h after stroke with a mismatch between deficit and infarct. *N Engl J Med.* (2018) 378:11–21. doi: 10.1056/NEJMoa1706442

9. Kwok JCK, Huang W, Leung W-C, Chan S-K, Chan K-Y, Leung K-M, et al. Human placenta as an ex vivo vascular model for neurointerventional research. *J NeuroIntervent Surg.* (2014) 6:394–9. doi: 10.1136/neurintsurg-2013-010813

10. Herrmann AM, Meckel S, Gounis MJ, Kringe L, Motschall E, Mülling C, et al. Large animals in neurointerventional research: a systematic review on models, techniques and their application in endovascular procedures for stroke, aneurysms and vascular malformations. *J Cereb Blood Flow Metab.* (2019) 39:375–94. doi: 10.1177/0271678X19827446

11. Ribeiro de. Oliveira MM, Nicolato A, Santos M, Godinho JV, Brito R, Alvarenga A, et al. Face, content, and construct validity of human placenta as a haptic training tool in neurointerventional surgery. *JNS.* (2016) 124:1238–44. doi: 10.3171/2015.1.JNS141583

12. Okada H, Chung J, Heiferman DM, Lopes DK. Assessment of human placenta as an ex-vivo vascular model for testing of liquid embolic agent injections with adjunctive techniques. *J NeuroIntervent Surg.* (2018) 10:892–5. doi: 10.1136/neurintsurg-2017-013474

13. Huppertz B. The anatomy of the normal placenta. *J Clin Pathol.* (2008) 61:1296–302. doi: 10.1136/jcp.2008.055277

14. Wang Y. Vascular biology of the placenta, second edition. colloquium series on integrated systems physiology. *From Molecule Function.* (2017) 9:113. doi: 10.4199/C00153ED1V01Y201704ISP075

15. Gordon Z, Eytan O, Jaffa AJ, Elad D. Hemodynamic analysis of Hyrtl anastomosis in human placenta. *Am J Physiol. Regul.* (2007) 292:R977–82. doi: 10.1152/ajpregu.00410.2006

16. Ullberg U, Sandstedt B, Lingman G. Hyrtl's anastomosis, the only connection between the two umbilical arteries. A study in full term placentas from AGA infants with normal umbilical artery blood flow: hyrtl's anastomosis. Acta Obstet Gynecol Scand. (2001) 80:1–6. doi: 10.1034/j.1600-0412.2001.800101.x

17. Bekov DB. [Nomenclature of blood vessels of the chorion of mature human placenta]. *Arkh Anat Gistol Embriol.* (1991) 100:96–102.

18. Belykh E, Lei T, Safavi-Abbasi S, Yagmurlu K, Almefty RO, Sun H, et al. Low-flow and high-flow neurosurgical bypass and anastomosis training models using human and bovine placental vessels: a histological analysis and validation study. *JNS.* (2016) 125:915–28. doi: 10.3171/2015.8.JNS151346

19. Burton GJ, Sebire NJ, Myatt L, Tannetta D, Wang Y-L, Sadovsky Y, et al. Optimising sample collection for placental research. *Placenta.* (2014) 35:9–22. doi: 10.1016/j.placenta.2013.11.005

20. Samavat H, Evans J. An ideal blood mimicking fluid for doppler ultrasound phantoms. *J Med Phys.* (2006) 31:275. doi: 10.4103/0971-6203.29198

21. Brindise MC, Busse MM, Vlachos PP. Density- and viscosity-matched Newtonian and non-Newtonian blood-analog solutions with PDMS refractive index. *Exp Fluids.* (2018) 59:173. doi: 10.1007/s00348-018-2629-6

22. Najjari MR, Hinke JA, Bulusu KV, Plesniak MW. On the rheology of refractive-index-matched, non-Newtonian blood-analog fluids for PIV experiments. *Exp Fluids.* (2016) 57:96. doi: 10.1007/s00348-016-2185-x

23. Duffy S, Farrell M, McArdle K, Thornton J, Vale D, Rainsford E, et al. Novel methodology to replicate clot analogs with diverse composition in acute ischemic stroke. *J NeuroIntervent Surg.* (2017) 9:486–91. doi: 10.1136/neurintsurg-2016-012308

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Comparison of vacuum pressures and suction forces generated by different pump systems for aspiration thrombectomy

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Objective: Aspiration thrombectomy is used to treat endovascular stroke treatment by clot removal through vacuum and suction forces. We aimed to investigate the pressures and suction forces generated by different pump systems for aspiration.

Methods: Vacuum pressure was measured using a vacuum gauge with a closed tip for a 60cc syringe and aspiration pumps. Using an artificial thrombus made from polyvinyl alcohol hydrogel and latex membrane, we assessed the catheter tip force generated on an artificial thrombus using 5Fr Sofia and 6Fr Sofia PLUS intermediate catheters combined with Penumbra Jet Engine or Stryker Medela AXS Universal Aspiration Set. Subsequently, we calculated the catheter tip forces based on the pressure [catheter tip size (force = area × pressure)], and compared with the measured catheter tip force.

Results: The 60cc syringe generated the highest vacuum pressure. Among the automatic pumps, the Penumbra jet engine generated the highest vacuum pressure. The catheter tip forces on the artificial thrombus and latex membrane were 18.5 ± 1.70 and 8.0 ± 1.23 gf, respectively, and 13.9 ± 1.37 and 5.6 ± 0.83 gf, respectively using the 5 Fr Sofia with the Penumbra Jet Engine and the Stryker Medela AXS Universal Aspiration Set, respectively. The corresponding values for the 6 Fr Sofia PLUS with the Penumbra Jet Engine and Stryker Medela AXS Universal Aspiration Set were 39.7 ± 3.88 and 20.7 ± 0.92 gf and 25.4 ± 4.96 and 18.0 ± 0.84 gf. For a constant catheter diameter and the automatic pump, the catheter tip force was significantly larger in the artificial thrombus than latex membrane ($p < 0.001$, ANOVA).

Conclusion: The catheter diameter, vacuum pressure, and clot softness are positively correlated with the catheter tip force.

KEYWORDS

aspiration thrombectomy, vacuum pressure, suction force, endovascular stroke treatment, pump systems

Introduction

Since the introduction of intracranial thromboaspiration in 2002, there has been considerable progress in manual aspiration thrombectomy for treating acute ischemic stroke (1–5). Following the success of initial trials on mechanical thrombectomy using stent retrievers to achieve recanalization of occluded large vessels, randomized control trials have shown that frontline aspiration thrombectomy using a direct aspiration at first pass technique is a non-inferior, fast, and effective alternative (6, 7). Accordingly, there has been considerable evolution in aspiration catheter technology. Compared with smaller catheters, larger caliber catheters with greater aspiration forces are associated with shorter procedure times, increased rates of first-pass success, and improved clinical outcomes. Further, aspiration power can be enhanced using automatic aspiration pumps with high aspiration forces, which have started being used by neurointerventional physicians. The 60cc syringe was used before the introduction of automatic pumps (1). There have been inconsistent findings regarding the vacuum pressures generated by a 60cc syringe and automatic pumps according to the study designs (8–10). Additionally, no studies have compared the suction power at the catheter tip when the thrombus is engaged with the catheter. This study aimed to compare the vacuum pressures generated by a 60cc syringe and commercially available automatic pumps as well as the catheter tip forces generated by various combinations of suction catheters and automatic pumps.

Materials and methods

We evaluated the vacuum pressure generated by different pumps, including the Penumbra Jet Engine (Penumbra, Inc., CA, USA), Penumbra MAX pump, and Stryker Medela AXS Universal Aspiration Set (Stryker, MI, USA). We performed pressure testing of the 60cc syringe to ensure it was comparable to that of the automatic pumps for control. Additionally, we assessed the catheter tip force using 5F Sofia and 6F Sofia Plus catheters (MicroVention, Inc., Tustin, CA, USA) combined with the Penumbra Jet Engine and Stryker Medela AXS Universal Aspiration Set.

Vacuum pressure

We performed *in vitro* analysis of vacuum pressure using a calibrated pressure gauge (Fluke, 700G-10, Everett, WA, USA). The gauge was connected to the pump or 60cc syringe using a three-way pressure gauge inline adapter (Luer lock, ISO 594-2); additionally, a flow stopcock was positioned at the other side of this adapter (Figure 1A). A flow stopcock was completely closed to allow no flow and measure the pure negative pressure generated by the pumps or 60cc syringe at the pre-catheter level. After confirming that the pressure gauge was zero, we turned the pump on and started the timer. To evaluate the trend of the pump-generated negative pressure, we measured the pressure immediately after the pump was turned on, with the pressure trend being observed until the pump was turned off. Subsequently, the pump was turned on and the pressure was measured after 20 min to mimic the actual clinical environment. The flow rate of the Stryker Medela AXS Universal Aspiration Set can be adjusted; moreover, the pressure can be compared by setting the maximum and minimum flow rates. For syringe aspiration, we immediately applied maximal initial pressure, and the plunger was locked into place (Figure 1B). Pressure was recorded in kilopascals (kPa) at a rate of 1 pressure measurement per second.

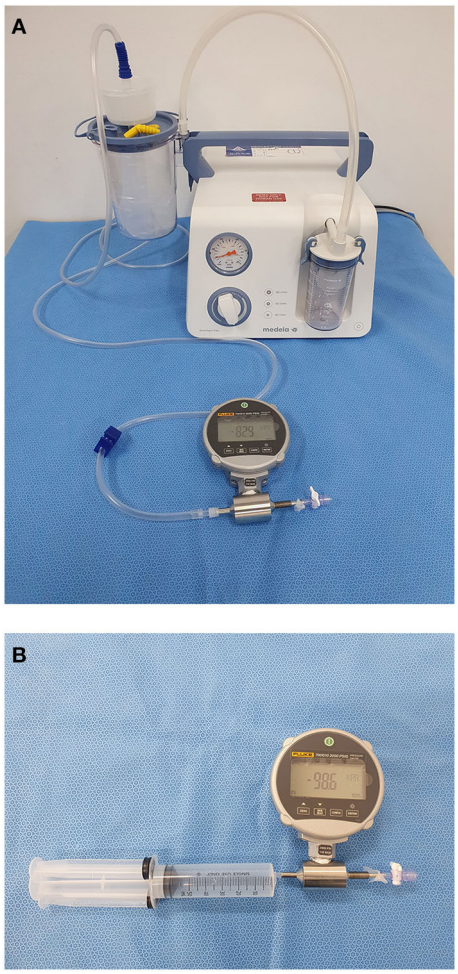

FIGURE 1
In vitro measurement of vacuum pressure. **(A)** The pump was connected to a pressure gauge using a three-way pressure gauge inline adapter (luer lock, ISO 594-2); additionally, the system was completely closed by stopcock, which is attached at the end of the three-way adapter. **(B)** A 60cc syringe was connected to a pressure gauge, and a plunge was locked into place.

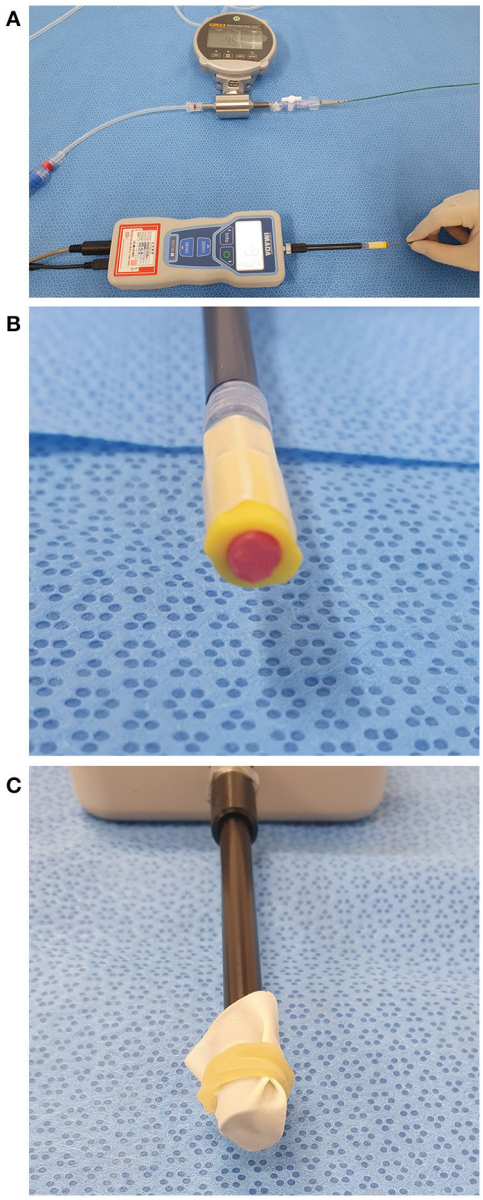

FIGURE 2
In vitro measurement of the catheter tip force. **(A)** A digital force gauge (ZTA-5N, IMADA Co., Toyohashi, Japan) was used to measure the catheter tip force. **(B)** The artificial thrombus was loaded into a 8 mm-sized polypropylene tube and attached at the end of a load cell attached to a digital force gauge. **(C)** A latex membrane was attached at the end of the load cell to simulate hard clots such as white clots.

Catheter tip force

The catheter tip force was measured using an artificial thrombus made using a polyvinyl alcohol (PVA) polymer and latex membrane. Here, a 10% PVA solution was mixed with sodium tetraborate and sodium bicarbonate. Before experimental use, the artificial thrombus was aged at room temperature for 1 day, loaded into an 8 mm-sized polypropylene tube, and attached at the end of the load cell attached to a digital force gauge (ZTA-5N, IMADA Co., Toyohashi, Japan) (Figures 2A,B). Additionally, to simulate a hard clot, including a white clot, a latex membrane was attached at the end of the load cell instead of the artificial thrombus (Figure 2C). After connecting the Sofia catheters combined with the Penumbra Jet Engine or Stryker Medela AXS Universal Aspiration Set, the pump was turned on and allowed to achieve a steady-state vacuum pressure by remaining on for >10 min. Subsequently, the catheter tip was directly placed onto an artificial thrombus or latex membrane. After confirming good apposition of the catheter tip with the artificial thrombus or latex membrane, the catheter was detached. This procedure was repeated manually 10 times, with continuous measurement of the catheter tip force [gram-force (gf)] throughout the entire procedure. The catheter tip force was defined as the maximum force, which was averaged by selecting the highest values recorded in each session. We compared the measured and calculated catheter tip forces. The catheter tip force was calculated as follows:

$$F_{aspiration} = A_{catheter} \times \Delta P_{catheter}\ (F = AP)$$

where $F_{\text{aspiration}}$ is the suction force at the aspiration catheter tip, A_{catheter} is the area at the tip, and $\Delta P_{\text{catheter}}$ is the vacuum pressure inside the aspiration catheter. For $A_{catheter}$, the catheter area was used, while for $\Delta P_{catheter}$, the average value of the measured maximum pressure for each pump was used, as aforementioned.

Statistics

A one-way analysis of variance (ANOVA) was used to compare the effect of automatic pumps and the 60cc syringe on vacuum pressures and catheter tip forces. Student's *t*-test was used to analyze differences in the vacuum pressures generated by the Stryker Medela AXS Universal Aspiration Set with two different flow rates. All statistical analyses were performed using SPSS 23 software (IBM, Armonk, NY, USA).

Results

Figure 3A shows the results for vacuum pressure. Compared with the other automatic pumps, the 60cc syringe reached the highest vacuum pressure (average maximum pressure: 98.24 ± 0.16 kPa). The maximum pressures of the Penumbra Jet Engine, Penumbra MAX pump, and Stryker Medela AXS Universal Aspiration Set were 96.01 ± 0.24, 94.31 ± 0.82, and 79.53 ± 1.40 kPa, respectively. There were significant differences in maximum vacuum pressures between the 60cc syringe and the other automatic pumps ($p < 0.0001$). The Stryker Medela

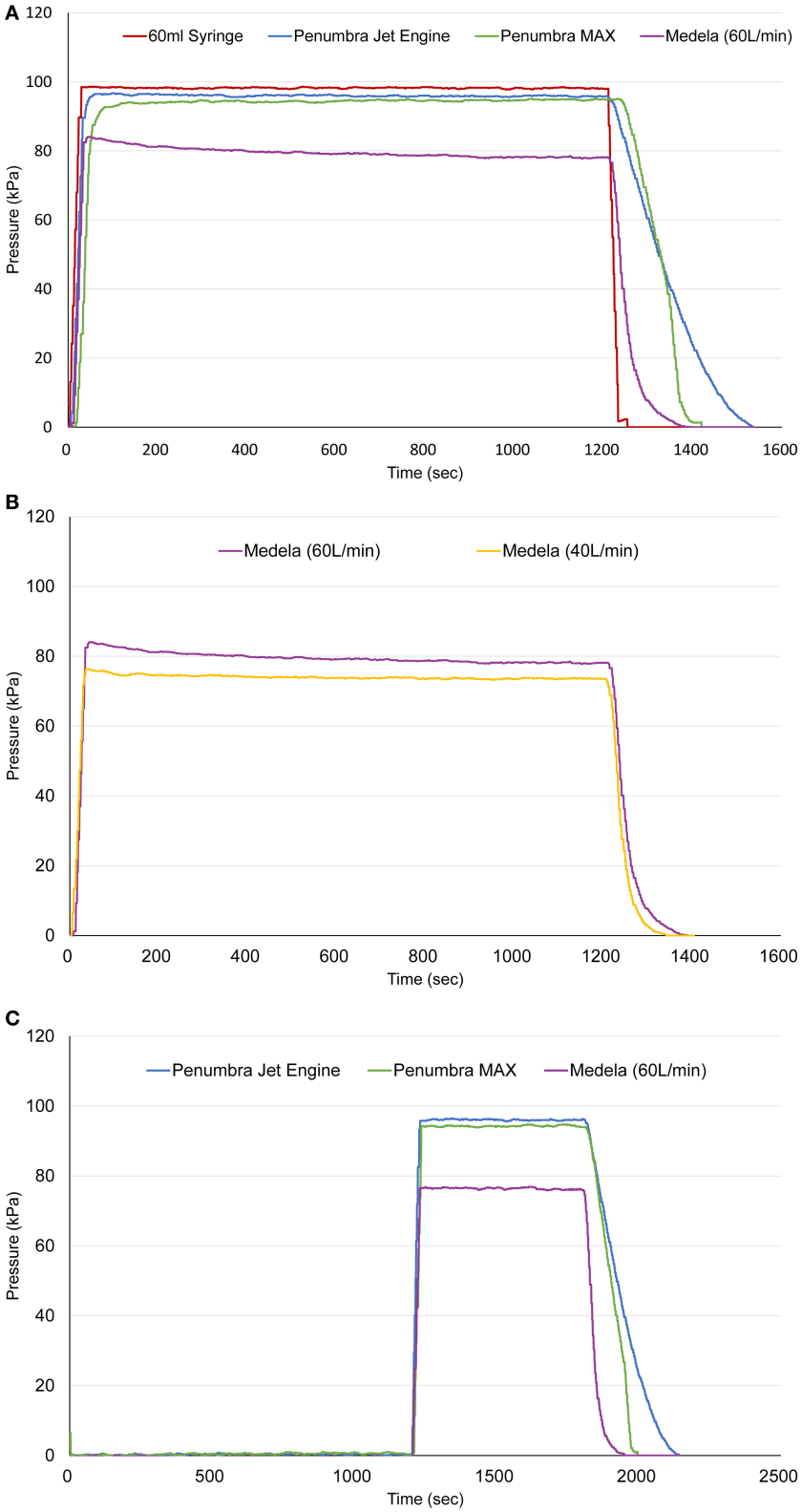

FIGURE 3
(A) Comparison of vacuum pressure between the 60cc syringe and other automatic pumps. **(B)** Vacuum pressure according to flow rate in the Stryker Medela AXS Universal Aspiration Set. **(C)** Vacuum pressures of automatic pumps at 20 min after turning on the pump.

AXS Universal Aspiration Set with the maximum flow rate (60 ml/min) reached the maximum pressure (82.91 ± 0.65 kPa) after 35 s. However, the pressure gradually decreased over time and plateaued at 78.77 ± 0.58 kPa after 400 s. After the pump was turned off, when using the 60cc syringe, the pressure reached 0 the fastest, followed by the Stryker Medela AXS Universal Aspiration Set, Penumbra MAX pump, and Penumbra Jet Engine. There was a significant difference in the vacuum pressures of the Stryker Medela AXS Universal Aspiration Set with the two flow rates (Figure 3B). The average maximum pressures with a flow rate of 60 ml/min and 40 ml/min were 79.53 ± 1.40 kPa and 74.06 ± 0.59 kPa, respectively ($p = 0.001$). Under 40 ml/min, the pump reached the maximum pressure (76.23 ± 0.12 kPa) after 35 s, followed by a gradual decrease over time and a plateau at 73.70 ± 0.46 kPa after 400 s. Further, there were significant differences in the maximum pressures of the three automatic pumps at 20 min after turning on the pump (Figure 3C).

In the PVA clot, the catheter tip force was measured to be 18.5 ± 1.70 gf and 39.7 ± 3.88 gf in the 5 Fr Sofia and 6 Fr Sofia PLUS combined with the Penumbra Jet Engine, respectively, as well as 13.9 ± 1.37 and 25.4 ± 4.96 gf in the 5 Fr Sofia and 6 Fr Sofia PLUS combined with the Stryker Medela AXS Universal Aspiration Set, respectively. In the latex membrane, the catheter tip force was measured to be 8.0 ± 1.23 and 20.7 ± 0.92 gf in the 5 Fr Sofia and 6 Fr Sofia PLUS combined with the Penumbra Jet Engine as well as 5.6 ± 0.83 and 18.0 ± 0.84 gf in the 5 Fr Sofia and 6 Fr Sofia PLUS combined with the Stryker Medela AXS Universal Aspiration Set, respectively (Figure 4). Regardless of the mechanical properties of the clot analog, the catheter diameter showed a significant positive correlation with the catheter tip force ($p < 0.001$). For a constant catheter diameter, the catheter tip force was significantly larger in the soft clot (PVA clot analog) than in the hard clot (latex membrane) ($p < 0.001$, ANOVA). The calculated catheter tip force was 12.6 and 22.2 gf in the 5 Fr Sofia and 6 Fr Sofia PLUS combined with the Penumbra Jet Engine, respectively, as well as 10.4 and 18.4 gf in the 5 Fr and 6 Fr Sofia PLUS combined with the Stryker Medela AXS Universal Aspiration Set, respectively. In the PVA clot analog, the measured catheter-tip force was greater than the calculated catheter-tip force. Contrastingly, in the latex membrane, the calculated catheter tip force was greater than the measured catheter tip force.

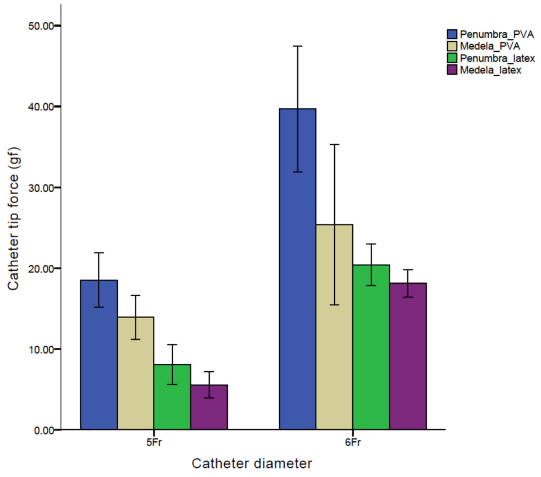

FIGURE 4
Comparison of catheter tip forces of the 5Fr Sofia and 6Fr Sofia Plus catheters combined with the Penumbra Jet Engine and Stryker Medela AXS Universal Aspiration Set.

Discussion

Mechanical suction thrombectomy involves engaging a thrombus with a large-bore catheter and establishing constant adherence between the thrombus and catheter with suction force. Classically, vacuum forces within a catheter are governed by Poiseuilli's law. Accordingly, studies have used various experimental models to investigate the vacuum flow rate (10, 11). For direct aspiration thrombectomy, the catheter should completely adhere to the thrombus, which causes flow arrest (12). Here, the suction force is directly affected by the applied vacuum pressure and cross-sectional area of the catheter ($F = PA$), as well as the diameter and resistance of the vessel wall, the size and mechanical properties of the thrombus, and the blood pressure behind the thrombus (13). However, we could only control the vacuum pressure and catheter diameter during the procedure. Therefore, we compared the vacuum pressure generated by the 60cc syringe and different automatic pumps at the pre-catheter level under a closed system, with the assumption of complete engagement of the thrombus at the aspiration catheter. We found that the 60cc syringe reached the highest vacuum pressure compared with the other automatic pumps. The 60cc syringe achieved a slightly higher vacuum pressure than the Penumbra Jet Engine and Penumbra MAX pumps, which could be because the syringe directly delivers vacuum pressure to the catheter. Conversely, Penumbra pumps deliver vacuum pressure through a silicon tubing set and canister, with a relatively large volumetric space where some pressure might be lost. Further, for the Stryker Medela AXS Universal Aspiration Set, there were differences between the measured and manufacturer-provided maximum pressures, which also significantly differed from the measured maximum pressure of the syringe. Additionally, for the Stryker Medela AXS Universal Aspiration Set, the maximum pressure was rapidly reached, followed by a gradual decrease in the pressure, which eventually plateaued. In addition to the tubing system, we observed a leaking point in ClotFinder^{TM}, where the body and lid were not completely sealed. This could have attributed to the drop in pressure and difference in the maximum pressure.

The catheter tip force was measured as the average value of the maximum pressure in different trials, where the catheter was engaged with the clot and pulled until it was removed from the clot. Because the negative pressure could not be continuously maintained using the 60cc syringe, the catheter tip force was compared using automatic pumps. Under the same vacuum pressure, the catheter diameter is positively correlated with the tip force. In addition, when the catheter diameter is constant, a difference in the tip force was confirmed by the difference in the vacuum pressure generated by the automatic pump. Our findings suggest that to successfully perform suction thrombectomy, it is important to use a catheter with a diameter as large as possible in consideration of the target vessel. The vacuum pressure is positively correlated with the tip force; however, it is difficult to suggest an appropriate vacuum pressure since the effective tip force for suction thrombectomy remains unclear. In the first published thromboaspiration, thrombectomy was performed using a 60cc syringe; subsequently, a 60cc syringe was mainly used for suction thrombectomy before the automatic pumps were commercially available (1, 14–16). Additionally, several studies have demonstrated that the 60cc syringe produces the highest maximum pressure and is both safe and cost-effective (14, 17). Therefore, when using an autonomic pump, it is important to use a pump that produces a vacuum pressure similar to that of a 60cc syringe for large vessel occlusions.

The clot softness was positively correlated with the catheter tip force. Since the suctioned material was sucked into the catheter, it changed to a convex shape in the proximal direction of the catheter. The softer the suction material, the more convex it is. Accordingly, soft material is thought to generate a large catheter tip force since the effective cross-sectional area to which the pressure is applied becomes larger than that in the hard material. In the PVA analog, the measured catheter tip force was larger than the calculated one, which could be attributed to the aforementioned phenomenon. Our findings suggest that the success rate of suction thrombectomy might be higher for soft clots than for hard clots. Future *in vitro* and clinical studies are warranted to confirm these findings.

This study had several limitations. First, we used PVA to fabricate a clot analog. Although it served as a good thrombus analog and effectively occluded the catheter tip, it does not fully reflect the mechanical properties of actual clots. Second, we investigated a small number of catheters. However, each catheter, for example, 5F Sofia and 6F Sofia Plus catheters, has a diameter that can represent 5Fr and 6Fr series catheters. Moreover, there is no significant difference in the diameter of catheters with the same series across companies. Since the study objective was comparing suction devices and catheters, absolute force measurement is less important than the between-device differences in values. Additionally, we compared two clot analogs with different mechanical properties and confirmed differences in the catheter tip force according to the mechanical properties of the clot. Human trials are warranted to confirm these findings.

Conclusion

Compared with other autonomic pumps, the 60cc syringe provides the highest vacuum pressure. Among the autonomic pumps, the Penumbra jet engine provides the highest vacuum pressure and catheter tip force. The vacuum pressure, inner catheter diameter, and clot softness are positively correlated with the catheter tip force on aspiration.

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

JL contributed to the conception and design of the study. SK and JL conducted experimental study, data 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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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

References

1. Chapot R, Houdart E, Rogopoulos A, Mounayer C, Saint-Maurice JP, Merland JJ. Thromboaspiration in the basilar artery: report of two cases. *AJNR Am J Neuroradiol.* (2002) 23:282–4.

2. Turk AS, Frei D, Fiorella D, Mocco J, Baxter B, Siddiqui A, et al. study: a direct aspiration first pass technique for acute stroke thrombectomy. *J Neurointerv Surg.* (2014) 6:260–4. doi: 10.1136/neurintsurg-2014-011125

3. Turk AS, Spiotta A, Frei D, Mocco J, Baxter B, Fiorella D, et al. Initial clinical experience with the ADAPT technique: a direct aspiration first pass technique for stroke thrombectomy. *J Neurointerv Surg.* (2014) 6:231–7. doi: 10.1136/neurintsurg-2013-010713

4. Frei D, Gerber J, Turk A, McPherson M, Heck D, Hui F, et al. The SPEED study: initial clinical evaluation of the Penumbra novel 054 Reperfusion Catheter. *J Neurointerv Surg.* (2013) 5(Suppl 1):i74–6. doi: 10.1136/neurintsurg-2012-010585

5. Tarr R, Hsu D, Kulcsar Z, Bonvin C, Rufenacht D, Alfke K, et al. The POST trial: initial post-market experience of the Penumbra system: revascularization of large vessel occlusion in acute ischemic stroke in the United States and Europe. *J Neurointerv Surg.* (2010) 2:341–4. doi: 10.1136/jnis.2010.002600

6. Turk AS 3rd, Siddiqui A, Fifi JT, De Leacy RA, Fiorella DJ, Gu E, et al. Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion (COMPASS): a multicentre, randomised, open label, blinded outcome, non-inferiority trial. *Lancet.* (2019) 393:998–1008. doi: 10.1016/S0140-6736(19)30297-1

7. Phan K, Dmytriw AA, Teng I, Moore JM, Griessenauer C, Ogilvy C, et al. Direct aspiration first pass technique vs standard endovascular therapy for acute stroke: a systematic review and meta-analysis. *Neurosurgery.* (2018) 83:19–28. doi: 10.1093/neuros/nyx386

8. Froehler MT. Comparison of vacuum pressures and forces generated by different catheters and pumps for aspiration thrombectomy in acute ischemic stroke. *Interv Neurol.* (2017) 6:199–206. doi: 10.1159/000475478

9. Yaeger K, Iserson A, Singh P, Wolf J, Vidal E, Oxley T, et al. A technical comparison of thrombectomy vacuum aspiration systems. *J Neurointerv Surg.* (2020) 12:72–6. doi: 10.1136/neurintsurg-2019-014929

10. Nikoubashman O, Wischer D, Hennemann HM, Busen M, Brockmann C, Wiesmann M. Under pressure: comparison of aspiration techniques for endovascular mechanical thrombectomy. *AJNR Am J Neuroradiol.* (2018) 39:905–9. doi: 10.3174/ajnr.A5605

11. Simon SD, Grey CP. Hydrodynamic comparison of the Penumbra system and commonly available syringes in forced-suction thrombectomy. *J Neurointerv Surg.* (2014) 6:205–11. doi: 10.1136/neurintsurg-2012-010638

12. Lally F, Soorani M, Woo T, Nayak S, Jadun C, Yang Y, et al. In vitro experiments of cerebral blood flow during aspiration thrombectomy: potential effects on cerebral perfusion pressure and collateral flow. *J Neurointerv Surg.* (2016) 8:969–72. doi: 10.1136/neurintsurg-2015-011909

13. Nikoubashman O, Nikoubashman A, Busen M, Wiesmann M. Necessary catheter diameters for mechanical thrombectomy with ADAPT. *AJNR Am J Neuroradiol.* (2017) 38:2277–81. doi: 10.3174/ajnr.A5401

14. Kang DH, Hwang YH, Kim YS, Park J, Kwon O, Jung C. Direct thrombus retrieval using the reperfusion catheter of the penumbra system: forced-suction thrombectomy in acute ischemic stroke. *AJNR Am J Neuroradiol.* (2011) 32:283–7. doi: 10.3174/ajnr.A2299

15. Eesa M, Almekhlafi MA, Mitha AP, Wong JH, Goyal M. Manual aspiration thrombectomy through balloon-tipped guide catheter for rapid clot burden reduction in endovascular therapy for ICA L/T occlusion. *Neuroradiology.* (2012) 54:1261–5. doi: 10.1007/s00234-012-1039-3

16. Pereira VM, Yilmaz H, Pellaton A, Slater LA, Krings T, Lovblad KO. Current status of mechanical thrombectomy for acute stroke treatment. *J Neuroradiol.* (2015) 42:12–20. doi: 10.1016/j.neurad.2014.11.002

17. Gross BA, Jadhav AP, Jovin TG, Jankowitz BT. Dump the pump: manual aspiration thrombectomy (MAT) with a syringe is technically effective, expeditious, and cost-efficient. *J Neurointerv Surg.* (2018) 10:354–7. doi: 10.1136/neurintsurg-2017-013520

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Application of Balloon AngioplaSty with the dIstal protection of Stent Retriever (BASIS) technique for acute intracranial artery atherosclerosis-related occlusion

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Background: Endovascular therapy (EVT) is complex in the context of intracranial atherosclerosis (ICAS)-related large vessel occlusion (LVO) and the re-occlusion rates are high due to residual stenosis, the procedure time is long and the optimal EVT technique is unclear. The Balloon AngioplaSty with the dIstal protection of Stent Retriever (BASIS) technique is a novel thrombectomy technique that allows emergent balloon angioplasty to be performed *via* the wire of the retrieval stent. Our study presents our initial experience with the BASIS technique in ICAS-related LVO and assesses its feasibility.

Method: In patients with ICAS-related LVO treated with BASIS, clinical and angiographic data were retrospectively analyzed. Angiographic data included first-pass reperfusion (PFR), the rate of residual stenosis, distal emboli, and re-occlusion post-procedure. The Extended Thrombolysis in Cerebral Infarction (eTICI) scale was used to assess reperfusion extent, and an eTICI score $\geq$2b was defined as successful perfusion. Clinical outcome was evaluated at 3 months (modified Rankin score [mRS]), and an mRS $\leq$2 was defined as a good clinical outcome.

Results: A total of seven patients with ICAS-related LVO were included, and the median age of the patients was 76 years. All patients achieved eTICI 3 reperfusion and FPR. The residual stenosis rate ranged from 5 to 10%. None of the patients had re-occlusion post-procedure. The median puncture-to-reperfusion time was 51 min. None of the patients had a symptomatic cerebral hemorrhage, re-occlusion, distal embolism, and

dissection. Good clinical outcomes were observed in four patients (4/7, 57.1%), and 1 patient (1/7, 14.3%) died.

Conclusion: The BASIS technique is feasible and safe for treating acute ICAS-related LVO.

KEYWORDS

intracranial atherosclerosis, large vessel occlusion, BASIS, endovascular therapy, first pass effect

Introduction

Endovascular thrombectomy (EVT) is the standard and effective treatment for ischemic stroke patients with large vessel occlusion (LVO) (1–8). The main strategy of EVT for LVO includes stentriever thrombectomy, aspiration thrombectomy, and emergent angioplasty. The optimal EVT therapy for LVO caused by intracranial atherosclerosis (ICAS)-related LVO is unclear. In contrast to embolic lesions, ICAS responds less to stentriever thrombectomy (9) and requires a more complex, technically demanding recanalization strategy and longer procedure time (10). The EVT strategy is complex in ICAS lesions due to the multiformity of plaque, angioarchitecture, and thrombus composition in such cases. The dilemma in treating ICAS-related LVO is listed as follows: (1) If stentriever thrombectomy is chosen as the first-line strategy, a thrombus located distal to the stenotic site is hard to retrieve by the retrieval stent for tight stenosis at the proximal segment, and artery dissection may also occur following repeated stentriever thrombectomy; (2) If emergent angioplasty is chosen as the first-line strategy, a thrombus located distal to the stenotic site will migrate distal to the stenotic site when the proximal stenotic site is opened, which will increase the difficulty and risk in treating it *via* EVT. On the other hand, the perforating artery may be occluded by thrombi caused by emergent angioplasty. Furthermore, the procedure-related complication rate might increase with additional endovascular operations (11, 12).

The dilemma may be resolved if angioplasty can be performed *via* balloon advancement through the wire of the retrieval stent. Therefore, we propose the novel EVT technique, which is called the BASIS technique (Balloon AngioplaSty with the dIstal protection of Stent Retriever), in treating ICAS-related LVO and assessed the feasibility of the BASIS technique in treating such types of lesions.

Materials and methods

Patients

Informed consent for treatment was obtained from all of the patients or their relatives. The study was approved by and conducted in accordance with the guidelines of our institutional review board (ID 2021 LWB227), and informed consent was not obtained for the study because of its retrospective nature. Patients with ICAS-related LVO who received the BASIS technique were included. Patients were selected based on the following criteria: (1) digital subtraction angiography (DSA) documentation of LVO; (2) ICAS was suspected by clinical presentation and the appearance of a tapered sign observed on CT angiography (CTA)/DSA (13) and the phenomenon of the "microcatheter first pass effect" (14) or culprit intracranial artery stenosis was diagnosed before stroke onset; and (3) the BASIS technique was adopted.

Endovascular treatment (BASIS)

An endovascular procedure was performed under conscious sedation. An 8F sheath was retrogradely inserted into the femoral artery, and diagnostic angiography was performed to confirm LVO suspected to be caused by ICAS. The novel technique referred to as BASIS is first described in this study. In brief, after deployment of the guiding catheter into the ICA or vertebral artery (VA), the microcatheter and a microwire are navigated through the area of total occlusion to the distal patent artery, and the microcatheter is then retrieved on the proximal side of the thrombus. Angiography is performed with a guiding catheter to determine whether blood flows through the vessel at the site of occlusion. When such flow is observed, a microcatheter "first-pass effect" is verified, which indicates a high probability of ICAS-related LVO. If thrombi located distal to the stenotic site are observed during the microcatheter "first pass effect" test, the BASIS technique is strongly recommended.

A microcatheter was re-navigated through the area of total occlusion to the distal patent artery, microwire retrieved, and a retrieval stent of which the diameter of the wire was 0.014 inch, was deployed at the occlusion site, fully covering the lesion and thrombus (Figure 1A); the microcatheter was withdrawn while the stent was in place (Figure 1B); a suitable balloon was advanced into the stenotic site through the wire of the retrieval stent, the stent was partially retrieved, and the balloon inflated (Figure 1C); the aspiration catheter was inserted through the stenotic site while the balloon was deflated (Figure 1D); the stent retriever was withdrawn under continuous manual negative

pressure formed with a 50-ml locked syringe without changing the position of the aspiration catheter (Figure 1E); continuous aspiration was performed *via* 50-ml locked syringe while totally withdrawing the stent retriever until there was blood flow from the aspiration catheter (Figure 1F); the retrieval stent was redeployed at the lesion site, then the aspiration catheter retrieved to the proximal site under continuous aspiration *via* 50-ml locked syringe (Figure 1G). Angiography was performed to determine the stenosis grade and reperfusion grade. If the successful reperfusion grade could be maintained, then the stent was retrieved *via* a microcatheter and withdrawn. If successful reperfusion could not be achieved and/or residual stenosis was high, angioplasty *via* balloon could be reperformed, in some clinical scenarios of stent implantation (Figure 1H).

This procedure was performed as per the following steps: (1) retrieval stent placement; (2) balloon angioplasty *via* wire of retrieval stent; (3) passage of aspiration catheter following after balloon deflated; (4) negative aspiration; (5) retrieval stent re-placement; (6) withdraw the retrieval stent; and (6) revascularization. The core novelty of this technique is summarized as Balloon AngioplaSty with the dIstal protection of a Stent Retriever; therefore, this technique, as adopted by us, is named the BASIS technique.

Clinical and outcomes assessment and measures

The National Institutes of Health Stroke Scale (NIHSS) was used to assess patients' neurological function, and 90-day mRS was used to assess the clinical outcome. The primary clinical efficacy outcome was the rate of good prognosis at 90 days postprocedure, as defined by an mRS score of 0–2. Safety was evaluated by the incidence of symptomatic intracranial hemorrhage (sICH) and the occurrence of re-occlusion post-procedure, which was assessed by CTA performed 24–72 h post-procedure. High-resolution MR was performed in high-cooperation patients, sICH was defined according to the Heidelberg criteria (15).

Angiographic and procedural outcomes

Brain tissue reperfusion was assessed radiologically immediately after the operation by the Extended Thrombolysis in Cerebral Infarction (eTICI) scale, with successful reperfusion defined as an eTICI score ≥2b (16). Achievement of complete reperfusion (eTICI 3) after a single operation of EVT was called first-pass reperfusion, which is the first-pass effect (FPE) (17). The primary angiographic outcomes were the rate of successful reperfusion, the FPE rate, and the residual stenosis rate. Secondary outcome measures included the incidence of distal emboli, arterial dissection, and procedure-related complications.

Data availability

Access to patient records for data collection and analysis was approved by our local medical ethics committee, and informed consent was not obtained because of the retrospective nature of the study. We will share the identified data of participants in our study upon request.

Statistical analysis

The data for categorical variables are described in absolute and relative frequencies. The data for continuous variables are given as the median and range or the mean and standard deviation. All statistical analyses were performed with IBM SPSS Statistics 22.0 (IBM, Inc., Armonk, NY).

Results

A total of seven patients (four men and three women) with acute ICAS-related LVO who received the BASIS technique (illustrated case is shown in Figure 2) were identified from our prospective acute ischemic stroke database of patients who received EVT. The patients' baseline characteristics and clinical outcomes are shown in Table 1. Six patients had hypertension, one had hyperlipidemia, one had diabetes mellitus, one had an ischemic stroke, two were smokers, two had hyperlipidemia, and none had atrial fibrillation. The median admission NIHSS score was 15 (ranging from 3 to 35), and the median baseline ASPECT score was 9 (ranging from 3 to 10). The premorbid mRS was 0 in all except 1 (mRS 2) patient. None of the patients had sICH or re-occlusion post-procedure. Two patients underwent the high-resolution MR, and irregular arteriosclerotic plaques of various thicknesses were observed on volume isotropic turbo spin echo acquisition images in these two cases. A good prognosis was observed in three patients and a poor prognosis in three patients, and one patient died because of a large infraction due to poor collateral.

Radiological assessment, endovascular treatment, and outcomes are shown in Table 1. Occlusions detected were as follows: M1 segment of the middle cerebral artery (MCA) in four patients, M2-MCA in one patient, an intracranial segment of vertebral artery (VA) in one patient, and basilar artery (BA) in one patient. The median puncture-to-reperfusion time (PRT) was 51 (ranging from 35 to 57). A 0.060-inch Catalyst (Boston, USA) aspiration catheter, Maverick balloon (Boston, USA), and Syphonet (Achieva, China) retrieval stent were adopted in all patients. All patients achieved eTICI grade 3 reperfusion and FPE, none had distal emboli during the procedure, and the residual stenosis rate ranged from 5 to 10%.

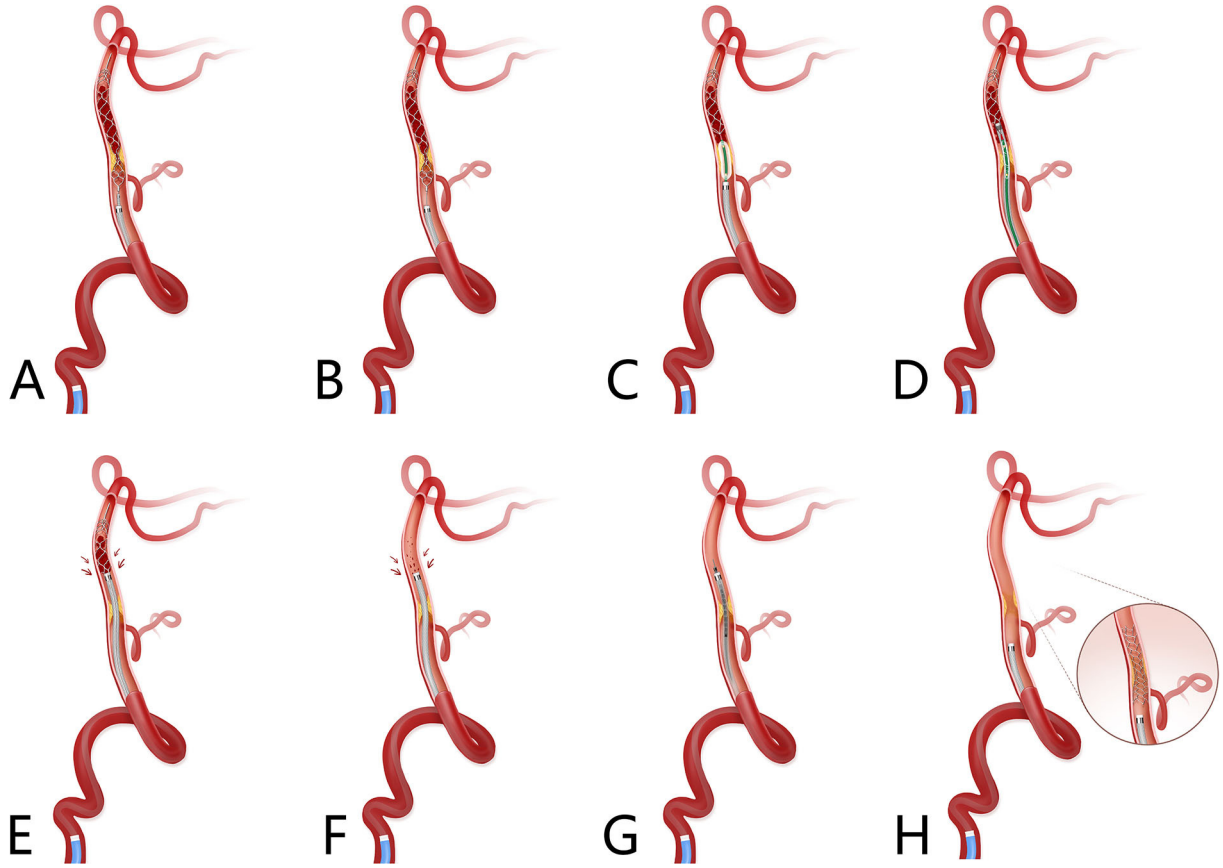

FIGURE 1
Schematic diagram of the Balloon AngioplaSty with the dIstal protection of Stent retriever (BASIS) technique. Basilar artery ICAS-related occlusion with thrombus formed distal to the stenotic site. **(A)** A microcatheter was navigated through the area of total occlusion to the distal patent artery, microcatheter first pass effect was performed to ascertain ICAS-related occlusion; microwire was retrieved while microcatheter stay at distal of occlusion site and retrieval stent, of which the diameter of wire was 0.014 inch, was deployed at the occlusion site, which fully covered the lesion and thrombus. **(B)** Microcatheter was withdrawn while stent was in place. **(C)** A suitable balloon was advanced into the stenotic site through wire of retrieval stent, and the stent was partially retrieved; then the balloon was inflated. **(D)** Aspiration catheter was inserted through the stenotic site when the balloon was deflated. **(E)** The stent retriever was withdrawn under continuous manual negative pressure exerted with a 50-ml locked syringe without changing the position of the aspiration catheter. **(F)** Continuous aspiration was performed while totally withdrawing the stent retriever and there was blood flow from the aspiration catheter. **(G)** Stent retriever was redeployed at the lesion site; then aspiration catheter was retrieved to the proximal site under continuous aspiration *via* 50-ml locked syringe. **(H)** Angiography was performed to determine the stenosis grade and reperfusion grade. If a successful reperfusion grade could be maintained, the stent was retrieved *via* a microcatheter and withdrawn, if successful reperfusion could not be achieved and/or residual stenosis was high, angioplasty *via* balloon could be reperformed, in some clinical scenarios of stent implantation. ICAS, indicates intracranial atherosclerosis.

Discussion

Intracranial atherosclerosis is common in Asian countries (18), so ICAS-related acute occlusion is also high in Asia. Due to different stenosis grades, plaque characteristics, thrombus compositions, and complex angioarchitectures, the pathogenesis of stroke caused by ICAS is diverse, and EVT for ICAS is complex. Thus far, the optimal EVT strategy is uncertain. Recently, the "Stent-Pass-Aspiration-resCuE-Micowire-Angioplasty (SPACEMAN)" technique was proposed by the China Stroke Team for ICAS-related LVO (19). However, neuro-interventionists may encounter some difficulties when they adapt this technique. First, the aspiration catheter may not totally penetrate the occlusion site because of the stenotic site. Second, if the thrombus located at the distal end is not completely cleared away, the thrombus may migrate into the distal artery when the aspiration is retrieved.

The BASIS technique we propose can overcome the difficulties encountered with SPACEMAN. First, the possibility of aspiration catheters going through the occlusion site increases after balloon angioplasty at the stenotic site. Second, the retrieval stent is repositioned in the culprit artery, and the possibility of migration of the thrombus at the lesion site decreases. Third, this technique increases the safety of EVT for ICAS-related LVO.

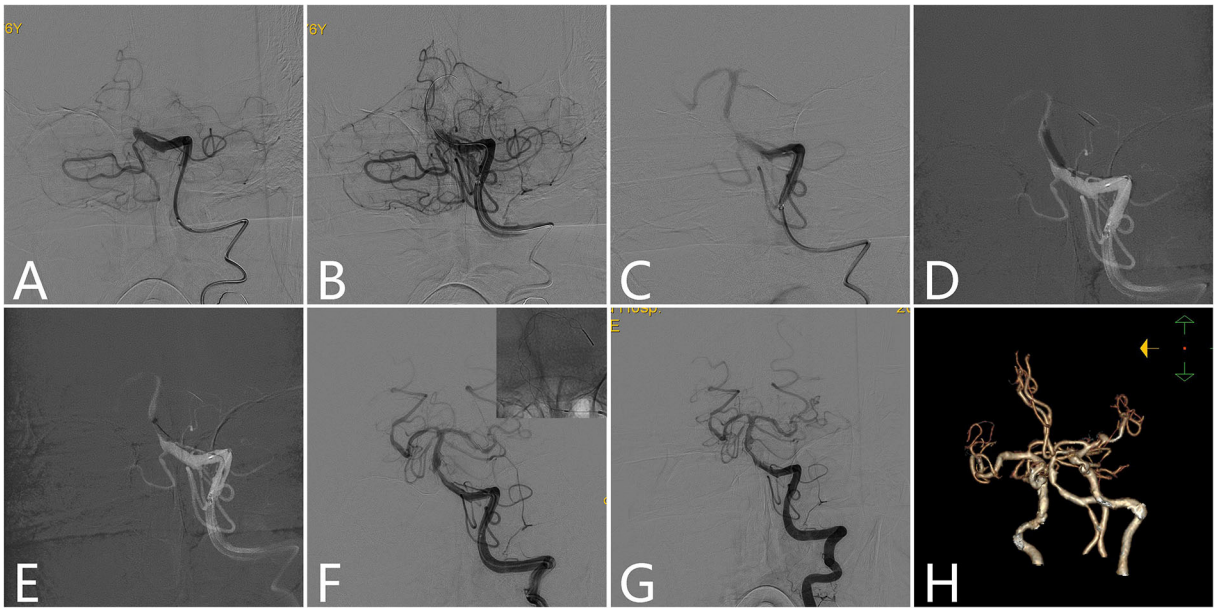

FIGURE 2
Illustrative case of BASIS technique. A 76-year-old male patient presented with dizziness for 5 h and sudden onset of unconsciousness and quadriplegia for 3 h. The admission NIHSS score was 35, and the GCS score was 5. **(A)** Left vertebral angiogram showed proximal BA occlusion. **(B)** Microcatheters and microwires completely passed through the occlusion site. Microcatheters were retrieved to the proximal segment of the occlusion site while microwires were kept in place, and angiograms showed slow blood flow through the occlusion site, that is there is a microcatheter first-pass effect phenomenon. **(C)** A Syphonet 4–30 mm stent was unsheathed at the occlusion site while the distal stent was placed at the SCA. **(D)** A Maverick 2.5/15 mm balloon was advanced over the wire of the retrieval stent into the stenotic site and partially retrieve the stent, then balloon angioplasty was performed. **(E)** The aspiration catheter was passed although the stenotic site after balloon angioplasty, and then the stent was retrieved by manual operation with a 50-ml locked syringe. **(F)** The retrieval stent was redeployed at the lesion site while the distal stent was placed at the posterior cerebarl artery (PCA). Then, the aspiration catheter was retrieved to the proximal stenotic site. An angiogram showed moderate stenosis at the proximal site of the BA, and successful reperfusion was achieved. **(G)** Sheathing and withdrawal of the retrieval stent and microwire were put through the lesion site. Twenty minutes later, a left vertebral angiogram showed that the stenosis was stable, and successful reperfusion was maintained. **(H)** Postprocedure CTA showed moderate stenosis located proximal to the BA. NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow coma scale; SCA, superior cerebellar artery; BA, basilar artery; CTA, CT angiography.

The whole EVT routine system will be more stable if the balloon advances through the wire of the retrieval stent than if the system involves the balloon advancing through a single microwire. The possibility of vessel perforation caused by microwires may increase (20).

There are some advantages of the BASIS technique in treating ICAS-related LVO. First, emergent balloon angioplasty and clot retrieval were performed simultaneously to decrease procedure-related complications (11, 12) and time-saving. Second, due to the special pathology of ICAS-related LVO, emergent angioplasty *via* balloon and/or stent was needed (21, 22). Therefore, the BASIS technique may increase the rate of successful reperfusion. Third, the possibility of vessel injury was reduced. Retrieval stent thrombectomy may cause vessel injury, especially in ICAS cases (23–25). In the BASIS technique, retrieval stent thrombectomy performed following aspiration catheter totally penetrates the stenotic lesion after balloon angioplasty. Such a procedure would minimize the touch area of the stent and vessel, especially if they did not touch the stenotic lesion, so it would minimize the possibility of vessel injury. Fourth, it is time-saving. This technique would minimize exchange passes, for example, if emergent angioplasty *via* balloon or/and the stent is needed after one pass of stent thrombectomy.

Some details should be noted in the BASIS technique. First, the most suitable case is a large clot located distal to the stenotic site, and the microcatheter first-pass effect could help neuro-interventionists recognize such lesions (14). Second, some specific characteristics of the device used in this technique are needed. The intrinsic appeal of the device is the compatibility between the stent and the balloon. The inner diameter of most balloons used in neuro-disease is 0.0165 inch or 0.017 inch (26), and the inner lumen of the balloon can allow partially retrieve of the stent. Therefore, the maximum diameter of the wire of the retrieval stent is 0.015 inch, indicating, as best we know, a retrieval stent such as Trevo XP (27) (StryKer), Syphonet (Achieva). Third, balloon angioplasty should be done with caution if the stenotic lesion covers the perforators of the penetrating artery, such as the lenticulostriate artery or pontine perforating arteries. Emergent angioplasty may

TABLE 1 Summary of patient characteristics and clinical and radiological outcomes.

Item	
Sex ratio (male/female)	4/3
Age (year), median (range)	76 (46–90)
Admission NIHSS, median (range)	15 (3–35)
Baseline ASPECT, median (range)	9 (5–10)
Risk factors, *n* (%)	
HT	6 (85.7%)
DM	1 (14.3%)
IS	1 (14.3%)
AF	0 (0%)
Smoker	2 (28.6%)
Hyperlipidemia	2 (28.6%)
90 days mRS, *n* (%)	
0–2	4 (57.1%)
3–5	2 (28.6%)
6	1 (14.3%)
sICH, *n* (%)	0
Culprit Artery, *n* (%)	
M1-MCA	4 (57.1%)
M2-MCA	1 (14.3%)
BA	1 (14.3%)
VA intracranial	1 (14.3%)
PRT, min, median(range)	51 (35–57)
eTICI, *n* (%)	
Grade 3	7 (100%)
Device used in procedure	
Maverick Balloon	7 (100%)
Syphonet 4–30 Retrieval stent	7 (100%)
FPE, *n* (%)	7(100%)
RSR median (range)	5% (5–10%)
Procedure related complication, *n* (%)	
Distal emboli, *n* (%)	0 (0%)
Arterial dissection, *n* (%)	0 (0%)
Reocclusion, *n* (%)	0

NIHSS, National Institutes of Health Stroke Scale; ASPECT, Alberta Stroke Program Early CT Score; HT, hypertension; DM, diabetes mellitus; AF, arterial fibrillation; IS, ischemic stroke; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage; MCA, middle cerebral artery; BA, basilar artery; VA, vertebral artery; eTICI, extended thrombolysis in cerebral infarction; PRT, puncture-to-recanalization time; FPE, first-pass effect; RSR, residual stenosis rate.

cause perforating artery occlusion due to plaque or thrombus. Fourth, hyperperfusion may occur once stenosis of the culprit artery is resolved (28). Therefore, we should give attention to the phenomena that might suggest disruption of cerebral autoregulation, such as the increased diameter of arterial branches, prominent capillary blush and early draining veins of the treated territories. If such angiographic characteristics are detected, we should control blood pressure according to middle cerebral artery mean flow velocity measurements by transcranial Doppler (TCD) (29). Re-occlusion occurrence is not rare in ICAS cases that achieve successful recanalization after endovascular therapy, especially in cases with high residual stenosis (30). Therefore, it would be better to face the risk of hyperperfusion which clinicians may control by post-procedure management than the risk of re-occlusion that may need another EVT.

This study had some limitations. First, it was a single-center study with relatively few study samples. However, our study focuses on innovative endovascular strategies for treating ICAS-related LVO. Also, due to few study samples and a 100% technique success rate, we cannot find out the satiation that the BASIS technique fails which needs a large and multi-center study sample to test and modify this technique. Second, the diagnosis of ICAS was not totally confirmed because it was in an emergent setting. However, our study was performed in a high-volume stroke center and had more than 500 thrombectomy cases per year. The neuro-interventionists had enough clinical experience to distinguish ICAS from embolic cases on the basis of clinical presentation, the morphology of CTA and DSA, and the microcatheter first-pass effect, and could ensure the diagnostic accuracy of ICAS to the greatest extent. Retrieval stents and balloons are highly selected in the BASIS technique, and this may influence the generalization of this technique; however, the situation may change as the neuro-intervention device becomes highly developed, the manufacturer can produce low-profile retrieval stent which is comparable to more delicate microcatheter and which also allow balloon fully withdraw, also we can produce balloon with a large inner core which can withdraw now available retrieval stent or so on.

Conclusion

Our case series suggests that the BASIS technique for treating acute ICAS-related LVO is technically feasible and safe and may be associated with decreasing procedure-related complications and time savings. This technique should be considered in cases of acute ICAS-related LVO, especially in cases with thrombi distal to the stenotic site. However, our findings should be confirmed by future multicenter, large-sample studies.

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 Zhangzhou Municipal Hospital Ethics Committee.

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

Author contributions

T-yY: conception and design, drafting the article, and revising it critically for important intellectual content. W-hC: conception and design, revising it critically for important intellectual content, final approval of the version to be published, 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. Y-mW: conception and design, analysis and interpretation of data, 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. D-lL, Z-nP, X-fZ, JG, and M-hW: analysis and interpretation of data, 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. X-hL, R-cC, and L-sZ: acquisition of data, analysis and interpretation of data, 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. All authors contributed to the article and approved the submitted version.

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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.

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References

1. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* (2015) 372:11–20. doi: 10.1056/NEJMoa1411587

2. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* (2015) 372:1019–30. doi: 10.1056/NEJMoa1414905

3. Saver JL, Goyal M, Bonafe A, Diener H-C, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med.* (2015) 372:2285–95. doi: 10.1056/NEJMoa1415061

4. Campbell BC V, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* (2015) 372:1009–18. doi: 10.1056/NEJMoa1414792

5. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet (London, England).* (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X

6. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N. Engl. J. Med.* (2017) NEJMoa1706442. doi: 10.1056/NEJMoa1706442

7. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* (2018) 378:708–18. doi: 10.1056/NEJMoa1713973

8. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018. Guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke. *Stroke.* (2019) 50:e344-e418. doi: 10.1161/STR.0000000000000211

9. Baek JH, Kim BM, Heo JH, Kim DJ, Nam HS, Kim YD. Outcomes of endovascular treatment for acute intracranial atherosclerosis-related large vessel occlusion. *Stroke.* (2018) 49:2699–705. doi: 10.1161/STROKEAHA.118.022327

10. Kasab S, Al Almadidy Z, Spiotta AM, Turk AS, Chaudry MI, Hungerford JP, et al. Endovascular treatment for AIS with underlying ICAD. *J Neurointerv Surg.* (2017) 9:948–51. doi: 10.1136/neurintsurg-2016-012529

11. Alexander MJ, Zauner A, Chaloupka JC, Baxter B, Callison RC, Gupta R, et al. WEAVE trial. *Stroke.* (2019) 50:889–94. doi: 10.1161/STROKEAHA.118.023996

12. Dumont TM, Kan P, Snyder KV, Hopkins LN, Siddiqui AH, Levy EI. Revisiting angioplasty without stenting for symptomatic intracranial atherosclerotic stenosis after the stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) study. *Neurosurgery.* (2012) 71:1103–10. doi: 10.1227/NEU.0b013e318271bcb8

13. Liang W, Wang Y, Du Z, Mang J, Wang J. Intraprocedural angiographic signs observed during endovascular thrombectomy in patients with acute ischemic stroke: a systematic review. *Neurology.* (2021) 96:1080–90. doi: 10.1212/WNL.0000000000012069

14. Chen W, Wu Y, Zhang M, Zhan A, Chen Y, Wu Z, et al. Microcatheter "first-pass effect" predicts acute intracranial artery atherosclerotic disease-related occlusion. *Neurosurgery.* (2018) 84:1296–305. doi: 10.1093/neuros/nyy183

15. Von Kummer R, Broderick JP, Campbell BCV, Demchuk A, Goyal M, Hill MD, et al. The heidelberg bleeding classification: Classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke.* (2015) 46:10. doi: 10.1161/STROKEAHA.115.010049

16. Liebeskind DS, Bracard S, Guillemin F, Jahan R, Jovin TG, Majoie CBLM, et al. ETICI reperfusion: defining success in endovascular stroke therapy. *J Neurointerv Surg.* (2019) 11:433–8. doi: 10.1136/neurintsurg-2018-014127

17. Bai X, Zhang X, Yang W, Zhang Y, Wang T, Xu R, et al. Influence of first-pass effect on recanalization outcomes in the era of mechanical thrombectomy: a systemic review and meta-analysis. *Neuroradiology*. (2021) 63:795–807. doi: 10.1007/s00234-020-02586-7

18. Wang Y, Zhao X, Liu L, Soo YOY, Pu Y, Pan Y, et al. Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in china: the chinese intracranial atherosclerosis (CICAS) study. *Stroke*. (2014) 45:663–9. doi: 10.1161/STROKEAHA.113.003508

19. Wu Y, Wang J, Sun R, Feng G, Li W, Gui Y, et al. A novel endovascular therapy strategy for acute ischemic stroke due to intracranial atherosclerosis-related large vessel occlusion: stent-pass-aspiration-resCuE-Micowire-angioplasty (SPACEMAN) technique. *Front Neurol*. (2022) 13:1–8. doi: 10.3389/fneur.2022.798542

20. Yi T, Chen W, Wu Y, Pan Z, Lin X, Lin D, et al. Intra-arterial injection of thrombin as rescue therapy of vessel perforation during mechanical thrombectomy for acute ischemic stroke. *Brain Sci*. (2022) 12:760. doi: 10.3390/brainsci12060760

21. Tsang ACO, Orru E, Klostranec JM, Yang IH, Lau KK, Tsang FCP, et al. Thrombectomy outcomes of intracranial atherosclerosis-related occlusions: a systematic review and meta-analysis. *Stroke*. (2019) 50:1460–6. doi: 10.1161/STROKEAHA.119.024889

22. Jia B, Feng L, Liebeskind DS, Huo X, Gao F, Ma N, et al. Mechanical thrombectomy and rescue therapy for intracranial large artery occlusion with underlying atherosclerosis. *J Neurointerv Surg*. (2017) 10:746–50.

23. Abraham P, Scott Pannell J, Santiago-Dieppa DR, Cheung V, Steinberg J, Wali A, et al. Vessel wall signal enhancement on 3-T MRI in acute stroke patients after stent retriever thrombectomy. *Neurosurg Focus*. (2017) 42:E20. doi: 10.3171/2017.1.FOCUS16492

24. Teng D, Pannell JS, Rennert RC Li J, Li YS, Wong VW, et al. endothelial trauma from mechanical thrombectomy in acute stroke: in vitro live-cell platform with animal validation. *Stroke*. (2015) 46:1099–106. doi: 10.1161/STROKEAHA.114.007494

25. Park H, Baek JH, Kim BM. Endovascular treatment of acute stroke due to intracranial atherosclerotic stenosis–related large vessel occlusion. *Front. Neurol*. (2019) 10:308. doi: 10.3389/fneur.2019.00308

26. Takayanagi A, Cheng PK, Feng L, A. novel technique for stenting of intracranial stenosis using the Neuroform Atlas stent and Gateway balloon catheter. *Interv Neuroradiol*. (2021) 27:770–3. doi: 10.1177/15910199211007295

27. Kühn AL, Wakhloo AK, Lozano JD, Massari F, Rodrigues KDM, Marosfoi MG, et al. Two-year single-center experience with the "Baby Trevo" stent retriever for mechanical thrombectomy in acute ischemic stroke. *J Neurointerv Surg*. (2017) 9:541–6. doi: 10.1136/neurintsurg-2016-012454

28. Diana F, Frauenfelder G, Botto A, Saponiero R, Romano DG. Cerebral hyperperfusion syndrome after intracranial stenting: Case report and systematic review. *Interv Neuroradiol*. (2021) 27:843–9. doi: 10.1177/15910199211011860

29. Karapanayiotides T, Meuli R, Devuyst G, Piechowski-Jozwiak B, Dewarrat A, Ruchat P, et al. Postcarotid endarterectomy hyperperfusion or reperfusion syndrome. *Stroke*. (2005) 36:21–6. doi: 10.1161/01.STR.0000149946.86087.e5

30. Hwang YH, Kim YW, Kang DH, Kim YS, Liebeskind DS. Impact of target arterial residual stenosis on outcome after endovascular revascularization. *Stroke*. (2016) 47:1850–7. doi: 10.1161/STROKEAHA.116.013046

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Mild and moderate cardioembolic stroke patients may benefit more from direct mechanical thrombectomy than bridging therapy: A subgroup analysis of a randomized clinical trial (DIRECT-MT)

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Background: The benefit of intravenous alteplase before endovascular thrombectomy is unclear in patients with acute cardioembolic stroke.

Methods: We collected cardioembolic (CE) stroke patient data from the multicentre randomized clinical trial of Direct Intra-arterial Thrombectomy to Revascularize Acute Ischaemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals (DIRECT-MT). The primary outcome was the 90-day modified Rankin Scale (mRS) score. Five subgroups of cardioembolic stroke patients were analyzed. A multivariable ordinal logistic regression analysis analyzed the difference in the primary outcome between the direct mechanical thrombectomy (MT) and bridging therapy groups. An interaction term was entered into the model to test for subgroup interaction. The DIRECT-MT trial is registered with clinicaltrials.gov Identifier: NCT03469206.

Results: A total of 290 CE stroke patients from the DIRECT-MT trial were enrolled in this study: 146 patients in the direct MT group and 144 patients in the bridging therapy group. No difference between the two treatment groups in the primary outcome was found (adjusted common odds ratio, 1.218; 95% confidence interval, 0.806 to 1.841; $P = 0.34$). In the subgroup analysis, CE stroke patients with an NIHSS $\leq$ 15 in the direct MT group were associated with better outcomes

(47 vs. 53, acOR, 3.14 [1.497, 6.585]) and lower mortality (47 vs. 53, aOR, 0.16 [0.026, 0.986]) than those in the bridging therapy group, while there were no significant differences between the two treatment groups in the outcome and mortality of CE stroke patients with an NIHSS >15.

Conclusion: Mild and moderate cardioembolic stroke patients may benefit more from direct mechanical thrombectomy than bridging therapy. This need to be confirmed by further prospective studies in a larger number of patients.

KEYWORDS

cardioembolic stroke, direct mechanical thrombectomy, bridging therapy, mild and moderate stroke, DIRECT-MT

Introduction

Mechanical thrombectomy (MT) combined with intravenous thrombolysis (IVT) was confirmed to be superior to IVT alone for acute ischaemic stroke (AIS) caused by large vessel occlusion (LVO) in the anterior circulation in five randomized trials in 2015 (1). Direct Intra-arterial Thrombectomy to Revascularize Acute Ischaemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicentre Randomized Clinical Trial (DIRECT-MT) pointed out that the effect and safety of direct MT was noninferior to bridging therapy for acute LVO patients eligible for IVT (2).

Cardioembolic (CE) stroke accounts for almost 30% of all ischaemic strokes (3), and the incidence is increasing (4). Cardioembolic stroke is usually more destructive than the nonembolic mechanisms of stroke, especially when considering that CE LVO is more likely to cause greater cerebral ischaemia (5). Approximately 50% of LVOs are caused by thrombi from cardioembolic (CE) sources such as atrial fibrillation (6), and the histopathologic composition of CE thrombi is different from that of noncardioembolic (N-CE) thrombi (7). The efficacy of endovascular treatment in CE LVO is higher than that in N-CE LVO (6). Alteplase is more effective in CE than in N-CE patients due to the clot composition and its dimensions (8). Our previous subgroup analysis indicated that there were no obvious differences in the modified Rankin Scale (mRS) score at 90 days and safety between the direct MT and bridging therapy groups in the different stroke etiology (9). However, we have not analyzed the effect of intravenous thrombolysis prior to endovascular treatment in the different subgroups of CE LVO in our main study.

In the DIRECT-MT trial, 44.2% of all enrolled patients were identified as having cardioembolic LVO (44.6% in the direct mechanical thrombectomy group and 43.8% in the bridging therapy). This study provided an opportunity to explore the benefit of intravenous alteplase before thrombectomy for the different subgroups of cardioembolic stroke.

Methods

Study design and population

We performed a *post hoc* analysis of the DIRECT-MT study. The data of patients with CE stroke were extracted and analyzed in this study. Five subgroups were designed according to the original DIRECT-MT study to estimate the effect of treatment on CE stroke: age, the baseline NIHSS, the time from onset of symptoms to randomization, the occlusion location and the collateral grades (10). NIHSS $\leq$ 15 was defined as the mild to moderate AIS based on Cincinnati Prehospital Stroke Severity Scale (CPSSS) study while a severe stroke was defined as NIHSS > 15 (11).

Outcome

The primary outcome was the modified Rankin scale score at 90 days (within a window of $\pm$14 days) (12).

The secondary outcomes were the following: the percentage of patients with functional independence (mRS $\leq$ 2) and a favorable outcome (mRS $\leq$ 3) at 90 days; the NIHSS score at 24 h and at 5 to 7 days (or at discharge); death within 90 days; the percentage of patients with successful reperfusion before thrombectomy as assessed using the extended thrombolysis in Cerebral Infarction (eTICI) score on the first intracranial angiogram (13), an eTICI score $\geq$ 2b on the final angiogram and recanalization at 24–72 h as assessed by CTA; and the final lesion volume on CT.

The safety outcomes included the mortality at 90 days, the percentage of patients with symptomatic and asymptomatic intracranial hemorrhage according to the Heidelberg criteria (14) and large or malignant MCA infarction, and the incidence of dissection, embolization in new cerebrovascular territory and contrast extravasation.

Statistical analysis

The baseline data are presented with descriptive statistics as appropriate. We used a multivariable ordinal logistic regression analysis to calculate the adjusted common odds ratio (acOR) for a shift in direction toward a better functional outcome on the mRS for direct MT than for bridging therapy. This method was also used for the subgroup analysis for the relationship between the baseline variables and the primary outcome. The interaction terms were entered into the models to test for interactions between treatment and the baseline NIHSS subgroups (NIHSS $\leq$ 15 vs. NIHSS $>$ 15 in primary, secondary and safety outcomes).

For the relationship between the baseline NIHSS and secondary or safety outcomes, linear or logistic-regression analyses were used, as appropriate, with the same adjustments that were used for the primary outcome. We adjusted the acOR and all secondary effect parameters for potential imbalances in the major prespecified prognostic variables adapted from the original DIRECT-MT trial protocol statistical analysis plan, and these variables included age, the modified Rankin scale score before stroke onset, cerebral collateral blood-flow status, and the time from stroke onset to randomization. Analysis of variance or the corresponding nonparametric test was used for between-treatment allocation comparisons by each subgroup. We analyzed the independent effect of the baseline NIHSS on the functional outcome and mortality with multivariable ordinal logistic regression analysis adjusted for the same prespecified variables and treatment allocation.

The acORs with 95% CIs are reported. The binary outcomes were analyzed with logistic regression and are presented as the adjusted ORs with 95% CIs. The continuous outcomes were analyzed with linear regression and are presented as the adjusted β with 95% CIs.

All analyses were conducted using SAS version 9.2 (SAS Institute). All *p*-values were two-sided, with a significance defined as $<$0.05.

Role of the funding source

The trial was funded by the Stroke Prevention Project of the National Health Commission of the People's Republic of China and the Wu Jieping Medical Foundation. This work was partly supported by the Basic Research Project of the Changzhou Science and Technology Bureau (No. CJ20200111).

Results

Patients and outcome of CE-LVOs

A total of 290 patients from the DIRECT-MT trial were regarded as cardioembolic LVOs, 146 received direct endovascular thrombectomy alone (direct MT group), and 144 underwent combination therapy with intravenous alteplase and endovascular thrombectomy (bridging therapy group). The baseline characteristics of the patients were similar in the two groups (Supplementary Table S1). The distribution of mRS at 90 days in the two groups is shown in Figure 1. For CE-LVOs, there was no obvious shift in the mRS distribution in the two treatment groups (Supplementary Table S2). The outcomes (Supplementary Table S2) between the two treatment groups for CE-LVOs have been described in our previous subgroup analysis.

Subgroup analyses for CE-LVOs

Five subgroups for CE-LVOs were created according to the original DIRECT-MT study to explore the benefit of intravenous alteplase before thrombectomy for the treatment of CE stroke. The subgroup analyses are shown in Table 1. It was found that the adjusted common odds ratio (acOR) in the baseline NIHSS 2–15 group for functional independence at 90 days was 2.609 (95% CI, 1.074 to 6.341; $p = 0.034$). There was no heterogeneity of the treatment effect in the other subgroups, and age, the time from onset of symptoms to randomization, the occlusion location and the collateral grades were similar between the groups.

The baseline NIHSS modifies the benefit of direct mechanical thrombectomy treatment in CE-LVO patients

In this subgroup analysis, the baseline characteristics of the patients are shown in Supplementary Table S3. 100(34.5%) of 290 CE-LVOs patients had an NIHSS $\leq$ 15 (47[47.0%] in the Direct MT group vs. 53[53.0%] in the Bridging Therapy group), 190 (65.5%) patients had an NIHSS $>$ 15 (99[52.1%] in the Direct MT group vs. 91[47.9%] in the Bridging Therapy group). Patients with an NIHSS $\leq$ 15 had a higher median age, higher rates of occlusion of the intracranial ICA and left hemisphere, and higher levels of serum glucose. In the analysis of the NIHSS $\leq$ 15 group, no significant difference was found in the baseline characteristics of the patients between the treatment groups (Table 2).

The outcomes of the patients of the two NIHSS subgroups of CE stroke are listed in Supplementary Table S4. For the primary outcome, there was a significant shift in the mRS distribution in the NIHSS $\leq$ 15 group between the two groups (acOR, 3.14 [1.497, 6.585]), while the mRS distribution was similar in the NIHSS $>$ 15 group (acOR, 0.765 [0.459 to 1.275]). The interaction of the treatment-by-baseline NIHSS with the ordinal mRS distribution was obvious ($p = 0.003$) (Table 3).

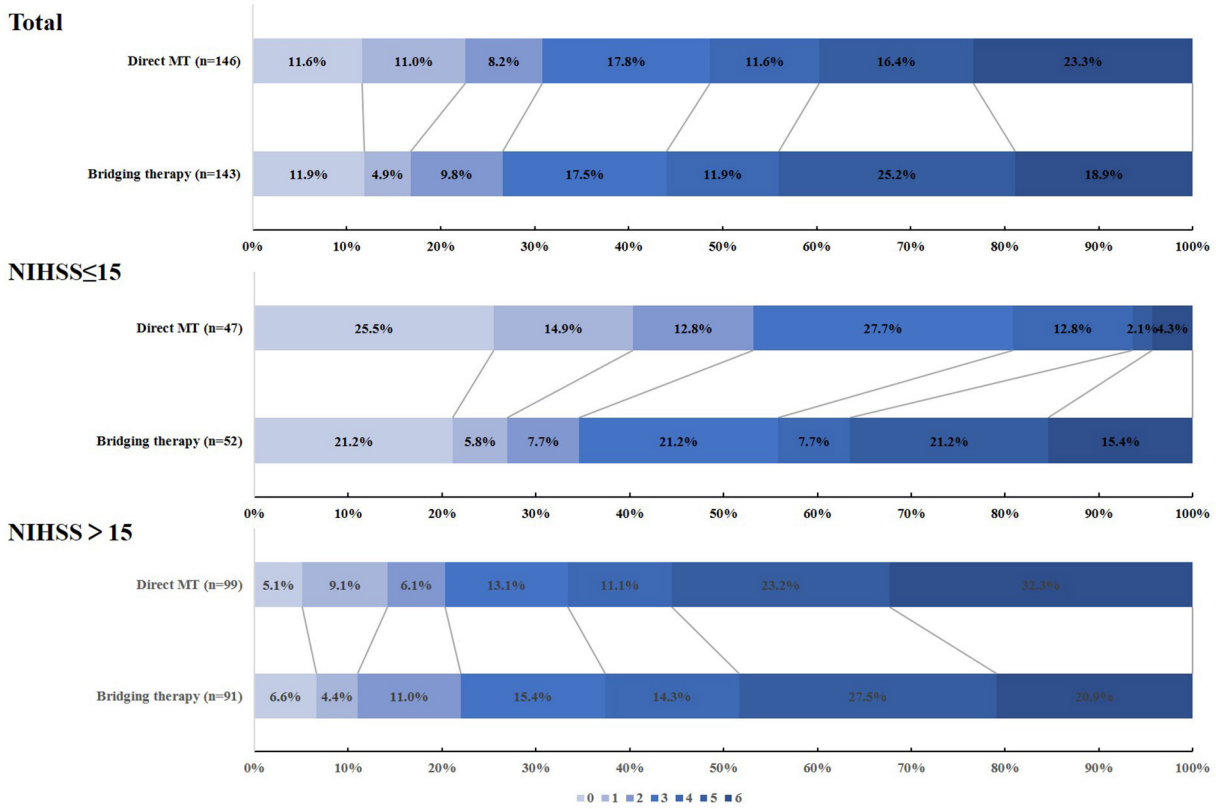

FIGURE 1
The distribution of mRS at 90 days in the direct MT and bridging therapy groups when evaluating cardioembolic stroke patients.

For the secondary outcomes, the OR in the NIHSS ≤ 15 CE-LVO group for functional independence (mRS 0–2) at 90 days was 2.609 (95% CI, 1.074–6.341), while the aOR in the NIHSS > 15 group was 1.045 (95% CI, 0.486–2.248), and no significant treatment-by-baseline NIHSS interaction for functional independence was observed ($p = 0.074$). There was an obvious interaction between the treatment and the baseline NIHSS for mRS 0–3 at 90 days ($p = 0.008$). The aOR was 5.495(95% CI, 1.855 to 16.274) in the NIHSS ≤ 15 patients, and the aOR was 0.923 (95% CI, 0.49 to 1.738) in the NIHSS > 15 group. No significant differences were found in the other secondary outcomes in the NIHSS subgroup between the two treatment groups (Table 3).

For the safety outcomes, the differences in mortality between the Direct MT and bridging therapy groups was significant in the NIHSS ≤ 15 CE-LVOs patients (aOR, 0.16 [0.026, 0.986]), while the mortality of the two groups with NIHSS > 15 was similar (aOR, 1.706[0.861, 3.377]). The interaction between the treatment and the baseline NIHSS with the mortality was obvious ($p = 0.022$). There were no obvious differences in symptomatic intracranial hemorrhage, asymptomatic intracranial hemorrhage, large or malignant MCA infarction or procedural complications in the NIHSS ≤ 15 and NIHSS > 15 CE-LVO patients between the two treatment groups (Table 3).

Moreover, we extracted some surgical data and found that the first pass rate was higher in the direct MT group in the NIHSS ≤ 15 CE-LVO patients (aOR, 3.465[1.419, 8.462]), while the first pass rate was similar between the two treatment groups with NIHSS > 15 (aOR, 0.741[0.407, 1.349]). The treatment-by-baseline NIHSS interaction for the first pass rate was significant ($p = 0.005$). There were no significant differences in the time from groin puncture to revascularization or the total passes of thrombectomy between the two treatment groups in the NIHSS ≤ 15 and NIHSS > 15 subgroups (Table 3).

Discussion

This subgroup analysis within the DIRECT-MT cohort evaluated the effectiveness and safety of intravenous alteplase before endovascular thrombectomy in acute cardioembolic stroke patients. No statistically significant benefit was found in the treatment of bridging therapy for CE-LVO stroke patients. In

TABLE 1 Subgroup analysis of the two treatment groups for CE stroke.

Subgroups	Direct MT	Bridging therapy	acOR (95% CI)
Age			
18–60 years	15	14	2.003 (0.358,11.197)
60–80 years	102	101	1.519 (0.761,3.031)
≥80 years	29	29	3.591 (0.283,45.501)
Baseline NIHSS			
≤15	47	53	2.609 (1.074,6.341)
>15	99	91	1.045 (0.486,2.248)
Time from onset of symptoms to randomization			
≤171	76	72	1.633 (0.705,3.781)
>171	70	72	1.716 (0.745,3.952)
Occlusion location			
ICA	59	46	1.414 (0.434,4.607)
M1	65	78	1.408 (0.660,3.002)
M2	19	18	2.754 (0.329,23.030)
Collateral grades			
Grade 0–1	116	114	1.370 (0.697,2.692)
Grade 2–3	30	30	1.796 (0.572,5.639)

the treatment-by-subgroup analysis for CE-LVO stroke patients, we found that age, the time from onset of symptoms to randomization, the occlusion location and the collateral grades did not affect the functional outcomes and safety of bridging therapy. However, in the treatment-by-baseline NIHSS analysis, it was found that patients with an NIHSS ≤ 15 in the direct MT group had better outcomes and lower mortality rates, while the efficacy and safety remained similar in the NIHSS > 15 CE-LVO stroke patients. This finding was different from previous studies, which indicated that LVO patients who underwent bridging therapy had better functional outcomes and lower mortality than patients who underwent direct MT treatment (15, 16).

Whether to initiate intravenous thrombolysis before mechanical thrombectomy for acute LVO is still controversial. It has been found that intravenous alteplase before MT can increase the early reperfusion rate and improve functional outcomes with the hypothesis that alteplase can reduce the hardness of the thrombi and can dissolve them (17, 18). On the other hand, intravenous alteplase was reported to cause thrombus fragmentation, thrombus migration and clot formation in new territories, which may lead to longer recanalization times and lower full reperfusion rates (19). In addition, intravenous alteplase may increase the incidence of symptomatic ICH (20). Our study found that higher percentages of sICH were more likely to occur in the patients treated with bridging therapy than in the patients with direct MT (aOR,

TABLE 2 Baseline characteristics of the patients of the two treatment groups of NIHSS ≤ 15 CE stroke.

Characteristic	Direct MT ($n = 47$)	Bridging therapy ($n = 53$)	p
Age, *y*, median (IQR)	73 (65, 76)	71 (66, 75)	0.361
Male sex, *n* (%)	24 (51.06)	24 (45.28)	0.564
NIHSS, median (IQR)	12 (10, 14)	13 (11, 14)	0.095
Systolic BP, mmHg, median (IQR)	142 (131, 158)	142 (134, 158)	0.774
Diastolic BP, mmHg, median (IQR)	84 (74, 101)	87 (78,98)	0.78
Serum glucose, mmol/liter, median (IQR)	6.7 (5.8, 8.1)	6.6 (5.7, 7.7)	0.689
Medical history, *n* (%)			
Previous ischemic stroke	9 (19.1)	4 (7.6)	0.085
Atrial fibrillation	47 (100)	52 (98.1)	1
Hypertension	28 (59.6)	35 (66.0)	0.504
Diabetes Mellitus	8 (17.0)	9 (17.0)	0.996
Location of intracranial artery occlusion, no./total no. (%)			
Intracranial ICA	12/46 (26.1)	12/52 (23.1)	0.422
M1	27/46 (58.7)	36/52 (69.2)	
M2	7/46 (15.2)	4/52 (7.7)	
Hemisphere CTA, *n* (%)			
Left	35 (74.5)	39(73.6)	0.92
Right	12 (25.5)	14(26.4)	
Reperfusion before intervention (eTICI) DSA, no./total no. (%)			
0	38/45 (86.4)	40/51 (78.4)	0.215
1	0 (0)	1/51 (2.0)	
2a	6/45 (13.6)	6/51 (11.8)	
2b	0 (0)	2/51 (3.9)	
2c/3	0 (0)	2/51 (3.9)	
ASPECTS, median (IQR)	9 (8, 10)	9 (7, 10)	0.206
Median duration (IQR), min			
Time from stroke onset to admission	106.5 (59, 155)	120 (83, 160)	0.377
Time from stroke onset to randomization	175 (118, 206)	175 (130, 211)	0.809
Time from stroke onset to IVT	NA	183.5 (139, 224)	NA
Time from stroke onset to groin puncture	202 (155, 260)	210 (172, 252)	0.759
From hospital admission to IVT	NA	64 (49, 79)	0.198
From hospital admission to groin puncture	87 (76, 108)	88 (74, 119)	0.811
From groin puncture to revascularization	61.5 (47.5, 100)	53.5 (42, 79.5)	0.169
From hospital admission to revascularization	152 (135, 203)	151 (122, 171)	0.191

TABLE 3 Treatment effect by NIHSS in CE stroke.

Outcome	Measure of effect	Adjusted value (95% CI)		P-interaction
		NIHSS≤ 15 ($n = 100$)	NIHSS > 15 ($n = 190$)	
Primary outcome				
mRS at 90 days	acOR	3.14 (1.497,6.585)	0.765 (0.459,1.275)	0.003
Secondary outcomes				
Functional independence (mRS 0–2)at 90 days	OR	2.609 (1.074,6.341)	1.045 (0.486,2.248)	0.074
mRS (mRS 0–3) at 90 days	OR	5.495 (1.855,16.274)	0.923 (0.49,1.738)	0.008
NIHSS after 24 h	β	−0.891 (−4.394, 2.613)	−0.61 (−3.735, 2.514)	0.910
NIHSS at 5–7 days or discharge	β	−2.904 (−6.865, 1.057)	−0.977 (−4.838, 2.884)	0.517
Imaging outcomes	OR			
Successful reperfusion before thrombectomy, as assessed on initial DSA	OR	NA	0.146 (0.009,2.253)	0.910
eTICI score of 2b, 2c, or 3, as assessed on final angiogram	OR	1.064 (0.32,3.533)	0.803 (0.374,1.721)	0.780
Recanalization at 24–72 h, as assessed on CTA	OR	0.892 (0.192,4.138)	0.384 (0.09,1.633)	0.379
Median lesion volume on CT	β	−12.618 (-36.746,11.51)	10.488 (-16.614,37.591)	0.173
Safety outcomes	OR	0.16 (0.026, 0.986)	1.706 (0.861,3.377)	0.022
Mortality at 90 days				
Serious adverse events				
Symptomatic intracranial hemorrhage	OR	NA	0.537 (0.167,1.726)	0.914
Asymptomatic intracranial hemorrhage	OR	0.559 (0.224,1.397)	0.745 (0.41,1.353)	0.608
Large or malignant MCA infarction	OR	0.614 (0.08,4.69)	1.456 (0.662,3.204)	0.450
Procedural complication(s)				
Dissection	OR	NA	0.979 (0.131,7.312)	0.900
Embolization in new territory	OR	1.196 (0.213,6.721)	1.198 (0.517,2.776)	0.837
Contrast extravasation	OR	NA	0.935 (0.18,4.847)	0.897
Operation data				
From groin puncture to revascularization	*β*	−12.618 (−36.746,11.51)	8.436(−6.771,23.643)	0.303
Total passes of thrombetomy	*β*	−12.618 (−36.746,11.51)	0.455 (−0.002, 0.912)	0.844
First pass rate	OR	3.465 (1.419,8.462)	0.741 (0.407,1.349)	0.005

0.37 [0.125, 1.089]; $p = 0.071$). However, no significant differences were found in the patient functional outcome, final recanalization rate or the development of an embolism in new territory between the direct MT and bridging groups.

In our study, a better functional outcome and a lower mortality rate were observed in the CE-LVO patients with an NIHSS $\leq$ 15 in the direct MT group, while no difference in the functional outcome and mortality was found in the CE-LVO patients with an NIHSS $>$ 15. Furthermore, a higher first-pass reperfusion rate was achieved in CE-LVO patients with an NIHSS $\leq$ 15 in the direct MT group, while there was no difference between the two treatment groups in the first-pass reperfusion rate in CE-LVO patients with an NIHSS $>$ 15. As Zaidat et al. (21) reported, first-pass reperfusion was associated with higher rates of a better functional outcome and a lower mortality rate. This interaction was also found in the ETIS (endovascular treatment in ischaemic stroke) study (22) and was identified by Nikoubashman et al. (23). Therefore, we boldly inferred that first-pass reperfusion was the main cause for the difference in the effectiveness and safety between the two treatment groups in CE-LVO patients with NIHSS $\leq$ 15, while there were no differences in the other factors. On the one hand, first-pass reperfusion can reduce the time from onset to recanalization and limit the expansion of the infarct core volume (24). On the other hand, repeated mechanical thrombectomy would cause more injury to the vascular endothelium, which potentially has a negative impact on the efficacy and safety (25, 26). In addition, Chueh et al. (27) reported that thousands of tiny thrombus fragments were caused by any mechanical thrombectomy, and these tiny thrombus fragments could escape to small arterioles and capillaries and occlude them. These tiny thrombus fragments cannot be seen on digital subtraction

angiography and magnetic resonance imaging, but they could lead to new small embolic infarctions and modify the clinical outcome (28). Moreover, as previous studies have described, the predictors of first-pass reperfusion included age, the occlusion sites, the combined first-line device strategy and so on. However, differences in these factors were not found in the two treatment groups in the CE-LVO patients with an NIHSS $\leq$ 15 in our study. A possible explanation could be that alteplase works better in medium vessel occlusions (29) or cardioembolic thrombi (8). In our study, more MCA occlusion occurred in the CE-LVO patients with an NIHSS $\leq$ 15 than in those with an NIHSS $>$ 15. However, a very low percentage of patients were infused with a full dose of alteplase before MT (2). We hypothesized that inadequate alteplase before MT would not only reduce the effect of intravenous thrombolysis but would also destroy the stability of the thrombus (30). The decrease in thrombus stability will increase the incidence of thrombus fragmentation and subsequent distal embolism (31, 32), further reducing the rate of successful reperfusion after the first pass and complete recanalization. A higher first-pass rate and complete recanalization were associated with better neurologic outcomes (21, 33). Although there was no difference in the final complete recanalization between the two treatments, thrombus fragmentation and small distal emboli may be important factors affecting the clinical outcome (28).

This study has some limitations. One limitation is the small sample size. In the DIRECT-MT study, approximately 45% of strokes were caused by cardioembolism, and patients with an NIHSS $<$ 15 accounted for only approximately one-third of the CE stroke patients, with ~50 patients per treatment group. And although the overall proportion of the site of the occlusion is not different, there were M2 patients of NIHSS $\leq$ 15 in the direct MT group which are more prone to be recanalized by IVT and associated with better prognosis. Second, almost all cardiogenic strokes (99%) are caused by atrial fibrillation, which is a relatively higher proportion than the real world. Previous studies have indicated that IVT for stroke patients with AF provided no benefit and potentially increased the risk of intracerebral hemorrhage and mortality (34). This may partially explain our results. In addition to atrial fibrillation, cardiogenic stroke can have many other causes, including foramen ovale, aortic arch atheroma, prosthetic heart valves and others (4). These patients were found to have an undetermined cause of stroke in the DIRECT-MT study through multimodal long-term vascular and cardiac examinations (35), although the thrombus composition could be similar to CE stroke (7). We might be able to generate more widely applicable theories when that data is available. In addition, the infusion of alteplase was completed before MT in only 4 of 53 patients of NIHSS $\leq$ 15 in the bridging group. DIRECT-MT study included no transit patients. The patients were all randomized at the main center. If the patient was randomly assigned to the bridging group, start using rt-PA and enter the operating room at the same time for thrombectomy. This may reduce the effect of alteplase and influence the results of this study.

In conclusion, thrombectomy alone might be a more reasonable choice for mild and moderate cardioembolic stroke patients. This need to be confirmed by further prospective studies in a larger number of 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 study was reviewed and approved by the ethics committees and research boards of the First People's Hospital of Changzhou and Naval Medical University Changhai hospital. Written informed consent was obtained before enrollment from all the patients or their legal representatives. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YP, ML, and JL conceived and designed the study and including quality assurance and control. JC and PX collected the data and wrote the paper. PY and YZ designed the study's analytic strategy. ZL, WC, TL, and SW analyzed the data. XZ, RC, HS, JX, and TJ reviewed and edited the manuscript. All authors read and approved the manuscript.

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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.

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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.2022.1013819/full#supplementary-material

References

1. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X

2. Yang P, Zhang Y, Zhang L, Zhang Y, Treurniet KM, Chen W, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med.* (2020) 382:1981–93. doi: 10.1056/NEJMoa2001123

3. Sacchetti D, Furie K, Yaghi S. Cardioembolic stroke: mechanisms and therapeutics. *Semin Neurol.* (2017) 37:326–38. doi: 10.1055/s-0037-1603465

4. Kamel H, Healey JS. Cardioembolic stroke. *Circ Res.* (2017) 120:514–26. doi: 10.1161/CIRCRESAHA.116.308407

5. Freeman WD, Aguilar MI. Prevention of cardioembolic stroke. *Neurotherapeutics.* (2011) 8:488–502. doi: 10.1007/s13311-011-0048-y

6. Tiedt S, Herzberg M, Kupper C, Feil K, Kellert L, Dorn F, et al. Stroke etiology modifies the effect of endovascular treatment in acute stroke. *Stroke.* (2020) 51:1014–6. doi: 10.1161/STROKEAHA.119.028383

7. Boeckh-Behrens T, Kleine JF, Zimmer C, Neff F, Scheipl F, Pelisek J, et al. Thrombus histology suggests cardioembolic cause in cryptogenic stroke. *Stroke.* (2016) 47:1864–71. doi: 10.1161/STROKEAHA.116.013105

8. Anticoli S, Bravi M, Perillo G, Siniscalchi A, Pozzessere C, Pezzella F, et al. Effect of cardioembolic etiology on intravenous thrombolysis efficacy for acute ischemic stroke. *Curr Neurovascular Res.* (2016) 13:193–8. doi: 10.2174/1567202613666160506125426

9. Xing P, Zhang X, Shen H, Shen F, Zhang L, Li Z, et al. Effect of stroke etiology on endovascular thrombectomy with or without intravenous alteplase: a subgroup analysis of DIRECT-MT. *J Neurointerv Surg.* (2022). doi: 10.1136/neurintsurg-2021-018275

10. Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke.* (2003) 34:e109–37. doi: 10.1161/01.STR.0000082721.62796.09

11. Katz BS, McMullan JT, Sucharew H, Adeoye O, Broderick JP. Design and validation of a prehospital scale to predict stroke severity: Cincinnati Prehospital Stroke Severity Scale. *Stroke.* (2015) 46:1508–12. doi: 10.1161/STROKEAHA.115.008804

12. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke.* (1988) 19:604–7. doi: 10.1161/01.STR.19.5.604

13. Goyal M, Fargen KM, Turk AS, Mocco J, Liebeskind DS, Frei D, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. *J Neurointerv Surg.* (2014) 6:83–6. doi: 10.1136/neurintsurg-2013-010665

14. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, et al. The heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke.* (2015) 46:2981–6. doi: 10.1161/STROKEAHA.115.010049

15. Katsanos AH, Malhotra K, Goyal N, Arthur A, Schellinger PD, Köhrmann M, et al. Intravenous thrombolysis prior to mechanical thrombectomy in large vessel occlusions. *Ann Neurol.* (2019) 86:395–406. doi: 10.1002/ana.25544

16. Mistry EA, Mistry AM, Nakawah MO, Chitale RV, James RF, Volpi JJ, et al. Mechanical thrombectomy outcomes with and without intravenous thrombolysis in stroke patients: a meta-analysis. *Stroke.* (2017) 48:2450–6. doi: 10.1161/STROKEAHA.117.017320

17. Alves HC, Treurniet KM, Jansen IGH, Yoo AJ, Dutra BG, Zhang G, et al. Thrombus migration paradox in patients with acute ischemic stroke. *Stroke.* (2019) 50:3156–63. doi: 10.1161/STROKEAHA.119.026107

18. Fischer U, Kaesmacher J, Pereira VM, Chapot R, Siddiqui AH, Froehler MT, et al. Direct mechanical thrombectomy versus combined intravenous and mechanical thrombectomy in large-artery anterior circulation stroke. *Stroke.* (2017) 48:2912–8. doi: 10.1161/STROKEAHA.117.017208

19. Kaesmacher J, Giarrusso M, Zibold F, Mosimann PJ, Dobrocky T, Piechowiak E, et al. Rates and quality of preinterventional reperfusion in patients with direct access to endovascular treatment. *Stroke.* (2018) 49:1924–32. doi: 10.1161/STROKEAHA.118.021579

20. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4. *5 hours after acute ischemic stroke N Engl J Med.* (2008) 359:1317–29. doi: 10.1056/NEJMoa0804656

21. Zaidat OO, Castonguay AC, Linfante I, Gupta R, Martin CO, Holloway WE, et al. First pass effect: a new measure for stroke thrombectomy devices. *Stroke.* (2018) 49:660–6. doi: 10.1161/STROKEAHA.117.020315

22. Drouard-de Rousiers E, Lucas L, Richard S, Consoli A, Mazighi M, Labreuche J, et al. Impact of reperfusion for nonagenarians treated by mechanical thrombectomy: Insights from the ETIS registry. *Stroke* 2019;50:3164–9. doi: 10.1161/STROKEAHA.119.026448

23. Nikoubashman O, Dekeyzer S, Riabikin A, Keulers A, Reich A, Mpotsaris A, et al. True first-pass effect. *Stroke.* (2019) 50:2140–6. doi: 10.1161/STROKEAHA.119.025148

24. Meretoja A, Keshtkaran M, Tatlisumak T, Donnan GA, Churilov L. Endovascular therapy for ischemic stroke: save a minute-save a week. *Neurology.* (2017) 88:2123–7. doi: 10.1212/WNL.0000000000003981

25. Broderick J, Palesch Y, Demchuk A, Yeatts S, Khatri P, Hill M, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med.* (2013) 368:893–903. doi: 10.1056/NEJMoa1214300

26. Mokin M, Fargen K, Primiani C, Ren Z, Dumont T, Brasiliense L, et al. Vessel perforation during stent retriever thrombectomy for acute ischemic stroke: technical details and clinical outcomes. *J Neurointerventional Surg.* (2017) 9:922–8. doi: 10.1136/neurintsurg-2016-012707

27. Chueh JY, Puri AS, Wakhloo AK, Gounis MJ. Risk of distal embolization with stent retriever thrombectomy and ADAPT. *J Neurointerventional Surg.* (2016) 8:197–202. doi: 10.1136/neurintsurg-2014-011491

28. Shih AY, Blinder P, Tsai PS, Friedman B, Stanley G, Lyden PD, et al. The smallest stroke: occlusion of one penetrating vessel leads to infarction and a cognitive deficit. *Nat Neurosci.* (2013) 16:55–63. doi: 10.1038/nn.3278

29. Menon BK, Al-Ajlan FS, Najm M, Puig J, Castellanos M, Dowlatshahi D, et al. Association of clinical, imaging, and thrombus characteristics with recanalization of visible intracranial occlusion in patients with acute ischemic stroke. *JAMA.* (2018) 320:1017–26. doi: 10.1001/jama.2018.12498

30. Kaesmacher J, Boeckh-Behrens T, Simon S, Maegerlein C, Kleine JF, Zimmer C, et al. Risk of thrombus fragmentation during endovascular stroke treatment. *AJNR Am J Neuroradiol.* (2017) 38:991–8. doi: 10.3174/ajnr.A5105

31. Gralla J, Schroth G, Remonda L, Nedeltchev K, Slotboom J, Brekenfeld C. Mechanical thrombectomy for acute ischemic stroke: thrombus-device interaction, efficiency, and complications in vivo. *Stroke.* (2006) 37:3019–24. doi: 10.1161/01.STR.0000248457.55493.85

32. Penumbra Pivotal Stroke Trial I. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke.* (2009) 40:2761–8. doi: 10.1161/STROKEAHA.108.544957

33. Kleine JF, Wunderlich S, Zimmer C, Kaesmacher J. Time to redefine success? TICI 3 versus TICI 2b recanalization in middle cerebral artery occlusion treated with thrombectomy. *J Neurointerv Surg.* (2017) 9:117–21. doi: 10.1136/neurintsurg-2015-012218

34. Saposnik G, Gladstone D, Raptis R, Zhou L, Hart RG, et al. Atrial fibrillation in ischemic stroke: predicting response to thrombolysis and clinical outcomes. *Stroke.* (2013) 44:99–104. doi: 10.1161/STROKEAHA.112.676551

35. Sposato L, Cipriano L, Saposnik G, Ruíz Vargas E, Riccio P, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet, Neurol.* (2015) 14:377–87. doi: 10.1016/S1474-4422(15)70027-X

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Endovascular treatment of acute ischemic stroke with a fully radiopaque retriever: A randomized controlled trial

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Objective: The Neurohawk retriever is a new fully radiopaque retriever. A randomized controlled non-inferiority trial was conducted to compare the Neurohawk and the Solitaire FR in terms of safety and efficacy. In order to evaluate the efficacy and safety of endovascular treatment in acute ischemic stroke (AIS) caused by intracranial atherosclerotic disease (ICAD) larger vessel occlusion (LVO), a sub-analysis was performed.

Methods: Acute ischemic stroke patients aged 18–80 years with LVO in the anterior circulation were randomly assigned to undergo thrombectomy with either the Neurohawk or the Solitaire FR. The primary efficacy endpoint was successful reperfusion (mTICI 2b-3) rate by the allocated retriever. A relevant non-inferiority margin was 12.5%. Safety outcomes were symptomatic intracranial hemorrhage (sICH) and all-cause mortality within 90 days. Secondary endpoints included first-pass effect (FPE), modified FPE, and

favorable outcomes at 90 days. In subgroup analysis, the patients were divided into the ICAD group and non-ICAD group according to etiology, and baseline characteristics, angiographic, and clinical outcomes were compared.

Results: A total of 232 patients were involved in this analysis (115 patients in the Neurohawk group and 117 in the Solitaire group). The rates of successful reperfusion with the allocated retriever were 88.70% in the Neurohawk group and 90.60% in the Solitaire group (95%CI of the difference, −9.74% to 5.94%; $p = 0.867$). There were similar results in FPE and mFPE in both groups. The rate of sICH seemed higher in the Solitaire group (13.16% vs. 7.02%, $p = 0.124$). All-cause mortality and favorable outcome rates were comparable as well. In subgroup analysis, 58 patients were assigned to the ICAD group and the remaining 174 to the non-ICAD group. The final successful reperfusion and favorable outcome rates showed no statistically significant differences in two groups. Mortality within 90 days was relatively lower in the ICAD group (6.90% vs. 17.24%; $p = 0.054$).

Conclusion: The Neurohawk retriever is non-inferior to the Solitaire FR in the mechanical thrombectomy of large vessel occlusion-acute ischemic stroke (LVO-AIS). The sub-analysis suggested that endovascular treatment including thrombectomy with the retriever and essential rescue angioplasty is effective and safe in AIS patients with intracranial atherosclerotic disease-larger vessel occlusion (ICAD-LVO).

Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT04995757, number: NCT04995757.

KEYWORDS

acute ischemic stroke, endovascular treatment, new fully radiopaque retriever, intracranial atherosclerotic disease, a randomized controlled trial

Introduction

Mechanical thrombectomy has become the standard of care for large vessel occlusion-acute ischemic stroke (LVO-AIS) since the five landmark trials were published (1–6). The high reperfusion rates and short procedure shown in these trials were driven by the use of stent-like retrievers. The Solitaire FR (Medtronic Inc., California, USA) has been one of the most frequently used retrievers (7, 8). However, various novel thrombectomy devices with improved visibility have been developed and tested. Although the physical properties of different novel thrombectomy devices have been investigated *in vitro*, the efficacy and safety of any device should also be demonstrated in clinical trials.

The Neurohawk (MicroPort NeuroTech Company, Shanghai, China) is a stent-like retriever with the closed-cell design. There are three radiopaque marks at the distal end of the retriever. In addition, three radiopaque wires twined around the entire struts of the retriever make it a fully radiopaque device, which allow the physician to visualize the overall placement of the retriever and the combination with thrombus. The useable section of the Neurohawk retriever is composed of large cells and small cells. The large cells is nearly twice as large as the small cells, which is dedicated to catching hard and large-sized thrombus, while the small cells is more conducive to embedding soft and small thrombus (Figure 1). This multi-center randomized controlled trial was designed and carried out

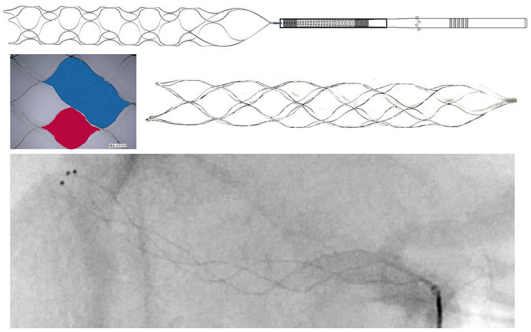

FIGURE 1
There are three radiopaque marks at the distal end of the Neurohawk retriever. And three radiopaque wires twined around the entire struts. The useable section of the Neurohawk retriever is composed of large cells (blue area) and small cells (red area).

to assess the efficacy and safety of this new device comparatively with the Solitaire FR.

As the etiologies of large vessel occlusion were different among ethnic groups, intracranial atherosclerotic disease-larger vessel occlusion (ICAD-LVO) account for a large proportion of patients with acute ischemic stroke (AIS) among Asians. It remains uncertain whether patients with acute ICAD-related occlusion can benefit from mechanical thrombectomy as those with embolism do. Prospective comparative data focusing on efficacy and safety of mechanical thrombectomy between patients with ICAD and those with non-ICAD are scarce. Therefore, a subgroup comparative analysis was conducted.

Methods

Study design and patients

This study was a prospective, multicenter, single-blind, randomized, controlled, non-inferiority clinical trial comparing the safety and effectiveness of patients with LVO-AIS treated with either the Neurohawk or the Solitaire FR. The clinical trial followed the principles of law and science, and was approved by the ethics committee at each participating site. This trial planned to enroll 238 patients in 21 tertiary care centers, which were each required to have performed at least 30 endovascular thrombectomy procedures during the previous year.

All patients or their legally authorized representatives provided written informed consent before enrollment. Inclusion criteria were: (1) 18–80 years of age; (2) AIS secondary to internal carotid artery (ICA) or middle cerebral artery (MCA) (M1 or M2) occlusion; (3) ability to undergo puncture within 6 h of symptom onset. Key exclusion criteria were: (1) a pre-stroke modified Rankin Scale (mRS) score (9) $\geq$2; (2) a baseline National Institutes of Health Stroke Scale (NIHSS) score $<$2 or $>$25; (3) massive cerebral infarction defined as an Alberta Stroke Program Early CT Score (ASPECTS) (10) $<$6 or $>$1/3 of blood supplying areas on CT/diffusion weighted imaging; (4) concomitant use of oral anticoagulation drugs and INR $>$3.0, or a platelet count $<30 * 10^9$ /L (11).

Procedures

According to guidelines, intravenous thrombolysis was administered before mechanical thrombectomy in all eligible patients (12). Depending on the patient's condition, procedures were performed with the patient under local anesthesia, conscious sedation or general anesthesia. The choice of the thrombectomy device was made according to random allocation, which was performed utilizing a 1:1 ratio. Randomization was accomplished by employing a Web-based system with stratification according to each participating site, occlusion segment of artery and the NIHSS. Treatment-group assignment was known to the operating physicians but blinded to the patients. The instructions of the Neurohawk were very similar to those of the Solitaire FR. Due to the presence of the fully radiopaque, the push-and-fluff technique (13), which may lead to better device opening with optimized wall apposition, could be used in the Neurohawk group. Stent retriever combined with aspiration catheter was allowed in both arms. Other retrievers, such as the Trevo (Stryker, Kalamazoo, MI, USA) or other techniques were allowed as salvage measures after unsuccessful recanalization with the Neurohawk or the Solitaire FR. The etiology of occlusion was assessed based on the medical history, risk factors, and angiographic characteristics. For patients with an underlying intracranial stenosis, repeated angiography was performed to exclude potential vasospasm or dissection after the first recanalization. Once atherosclerosis related occlusion was identified, salvage measures, including administration of tirofiban (glycoprotein IIb/IIIa inhibitor) or 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, United States) or an Apollo balloon mounted stent (MicroPort, Shanghai, China), were allowed (14). Daily oral dual antiplatelet therapy with 100 mg of aspirin and 75 mg of clopidogrel was started post-procedure and continued for 3 months, followed by life-long 100 mg aspirin.

Outcomes

The primary efficacy endpoint was successful reperfusion rate by the allocated retriever, defined as the percentage of patients achieving modified thrombolysis in cerebral infarction (mTICI) 2b or 3 (15). Secondary endpoints included first-pass effect (FPE, defined as achieving mTICI 3 with a single pass), modified FPE (defined as achieving mTICI 3/2b with a single pass) (16–18), the time from groin puncture to reperfusion, NIHSS at 30 $\pm$ 6 h, and favorable clinical outcome (defined as a mRS of 0–2 at 90 $\pm$ 14 days). The mRS at 90 days was determined by outpatient follow-up or telephone interview conducted by independent physicians unaware of treatment-group assignment in each center. Safety endpoint measurements were the rate of symptomatic intracranial hemorrhage (sICH) within 30 $\pm$ 6 h after intervention, all-cause mortality within 90 days, and all-cause adverse events within 90 days. The sICH was defined as any ICH identified by CT scan combined with a four-point increase in NIHSS or death. Images of the procedure were read by two independent neuroradiologists from the core lab, with consensus required in case of discrepancy. In subgroup analysis, the patients were divided into the ICAD and non-ICAD groups according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification (19). Baseline characteristics, treatments, and

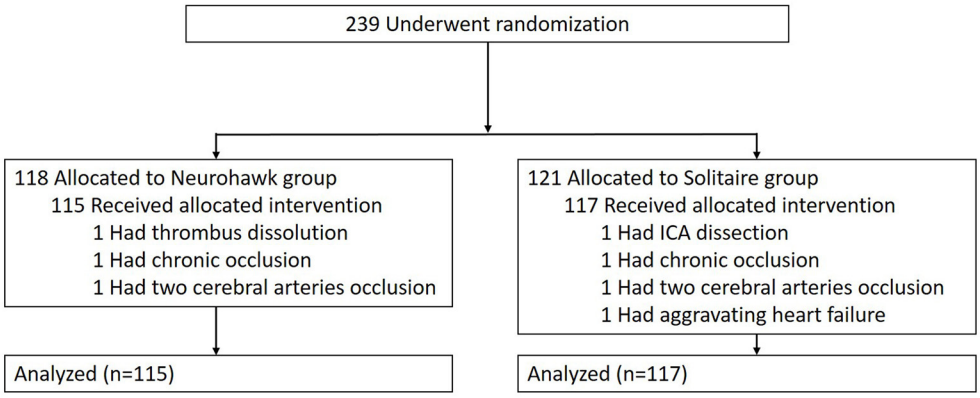

FIGURE 2
Randomization and treatment of the patients.

angiographic and clinical outcomes were also compared between the two groups.

Statistical analysis

The primary study hypothesis was that the successful reperfusion rate of the Neurohawk would be non-inferior to that of the Solitaire FR, with a relevant non-inferiority margin of 12.5%. The non-inferiority margin was calculated by using a two-step method based on the clinical practical significance according to the "Guidelines for the Design of Clinical Trials of Medical Devices" by National Medical Products Administration. All statistical analyses followed the intention-to-treat principle. Baseline data are presented as descriptive statistics according to treatment assignment. The non-inferiority test was based on the asymptotic Z-test. Two-sided 95% confidence intervals (CIs) of the differences in the rate of successful reperfusion between the groups were estimated by the Cochran–Mantel–Haenszel chi-squared test with adjusting centers. Statistical tests for continuous variables used Student's t-test or the Wilcoxon Mann-Whitney rank-sum test, and categorical variables were tested using the chi-squared test or Fisher's exact test. All statistical tests were two-tailed with a significance level of 0.05, using the SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

Results

A total of 239 patients were enrolled in this trial. A study flow diagram and protocol deviation details are shown in Figure 2. One patient had thrombus dissolution before the retriever reached the target vessel; two patients had chronic occlusion, and one showed aggravating heart failure after general anesthesia. One patient had ICA dissection and two cases had multiple cerebral artery occlusions, which did not align with the inclusion criteria. A total of 115 patients were treated with the Neurohawk, while 117 underwent thrombectomy with the Solitaire FR. Digital subtraction angiographic (DSA) imaging data were missing for one patient in each group. Five patients (two in the Neurohawk group and three in the Solitaire group) were lost to follow-up for mRS assessment at 90 days.

The patient baseline characteristics were similar in both treatment groups, and are detailed in Table 1. The median patient age was 66.6 years. A total of 95 patients had a history of atrial fibrillation and 149 patients had hypertension. Median NIHSS scores were 16 in the Neurohawk group and 17 in the Solitaire group. The median ASPECTS was 8. The most common target vessels were the MCA M1 (117 cases), the ICA (87 cases), and the MCA M2 (26 cases).

Procedural results and outcomes are shown in Table 2. In 92 patients, bridging intravenous fibrinolysis was administrated. General anesthesia was performed in 40.87% of the Neurohawk group and 33.33% of the Solitaire group. There were no differences in bridging therapy and anesthesia method between the two groups. In all 115 patients of the Neurohawk group, the Neurohawk was used as the single retriever with no rescuing needed using other retrievers. The use of a retriever combined with aspiration was similar between the two groups. However, more balloon guide catheters were used in the Solitaire group ($p = 0.038$).

The rates of successful reperfusion with the assigned retriever were 88.70% in the Neurohawk group and 90.60% in the Solitaire group (95%CI of difference, −9.74% to 5.94%; $p = 0.867$). And the median times of pass were two in both group. First-pass complete reperfusion (mTICI 3) was achieved in 61/232 (26.96% vs. 25.64%) and first-pass successful reperfusion (mTICI 3/2b) was achieved in 93/232 (42.61% vs. 37.61%). There were similar FPE and mFPE rates in both groups.

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TABLE 1 Baseline characteristics of the 232 patients.

Characteristic	Neurohawk group ($n = 115$)	Solitaire group ($n = 117$)	*P*
Age (year), median (IQR)	66.5 (57.3, 73.1)	66.6 (58.1, 70.9)	0.654
Male sex, no. (%)	73 (63.48%)	77 (65.81%)	0.710
BMI, mean ± sd	24.7 ± 3.7	24.5 ± 3.2	0.754
Medical history, no. (%)[a]			
Previous ischemic stroke	20 (18.20%)	19 (17.00%)	0.959
History of atrial fibrillation	47 (42.73%)	48 (42.86%)	1.000
History of diabetes mellitus	23 (20.91%)	19 (16.96%)	0.453
History of hypertension	77 (70.00%)	72 (64.29%)	0.365
Pre-stroke mRS 1, no. (%)	8 (6.96%)	13 (11.11%)	0.361
NIHSS, median (IQR)	16.0 (13.0, 21.0)	17.0 (13.0, 21.0)	0.853
ASPECTS, median (IQR)[b]	8.0 (7.0, 10.0)	8.0 (7.0, 10.0)	0.311
Time from stroke onset to groin puncture, min, median (IQR)	268.2 (202.2, 319.8)	255.0 (198.0, 315.0)	0.682
Cause of stroke, no. (%)			
Cardioembolism	56 (48.70%)	58 (49.57%)	0.335
ICAD	33 (28.70%)	25 (21.37%)	
Undetermined	26 (22.61%)	34 (29.06%)	
Cerebral arterial occlusion, no. (%)[c]			
ICA	40 (35.09%)	47 (40.52%)	0.684
MCA M1 segment	61 (53.51%)	56 (48.28%)	
MCA M2 segment	13 (11.40%)	13 (11.20%)	
Pre-procedure mTICI, no. (%)[c]			
0	96 (84.21%)	100 (86.21%)	0.678
1	14 (12.28%)	10 (8.62%)	
2a	3 (2.63%)	3 (2.59%)	
2b	1 (0.88%)	3 (2.59%)	
3	0 (0.00%)	0 (0.00%)	

[a]Data on the medical history were not available for five patients in each group.
[b]ASPECTS were not available for two patients in the Neurohawk group.
[c]Data on the arterial occlusion and pre-procedure mTICI were not available for one patient in each group duo to missing of DSA imaging.

TABLE 2 Procedural and outcomes data.

	Neurohawk group ($n = 115$)	Solitaire group ($n = 117$)	*P*
Bridging intravenous fibrinolysis, no. (%)	40 (34.78%)	52 (44.44%)	0.133
General anesthesia, no. (%)	47 (40.87%)	39 (33.33%)	0.477
Number of passes by retriever, median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.777
Use of balloon guide catheter	10 (8.70%)	21 (17.95%)	0.038
Retriever combined with aspiration, no. (%)	81 (70.43%)	82 (70.09%)	0.954
Balloon and/or stent angioplasty, no. (%)	27 (23.48%)	24 (20.51%)	0.586
Primary outcome:			
Successful reperfusion, no. (%)[a]	102 (88.70%)	106 (90.60%)	0.867
Major safety outcomes:			
Symptomatic Intracranial hemorrhage within 36 h, no. (%)[b]	8 (7.02%)	15 (13.16%)	0.124
Death within 90 days, no. (%)	14 (12.17%)	20 (17.09%)	0.289
Secondary outcomes:			
mTICI 3 with a first pass, no. (%)[a]	31 (26.96%)	30 (25.64%)	0.820
mTICI 2b/3 with a first pass, no. (%)[a]	49 (42.61%)	44 (37.61%)	0.437
Time from groin puncture to successful reperfusion, min, median (IQR)	58.8 (36.0, 85.2)	52.8 (39.0, 82.8)	0.772
NIHSS at 30 h, median (IQR)	11.0 (5.0, 20.0)	12.0 (5.0, 23.0)	0.316
mRS 0–2 at 90 days, no. (%)[c]	65 (57.52%)	67 (58.77%)	0.849
Final mTICI, no. (%)[a]			
0	7 (6.09%)	3 (2.56%)	0.401
1	0 (0.00%)	2 (1.71%)	
2a	4 (3.48%)	5 (4.27%)	
2b	38 (33.04%)	43 (36.75%)	
3	66 (57.39%)	64 (54.71%)	

[a]DSA imaging data were lost for one patient in each group, the core lab could not evaluate the procedural details, and the mTICI score of patient whose DSA imaging data lost was filled with the worst value—mTICI 0.
[b]Data on the symptomatic intracranial hemorrhage within 36 h were missing for four patients (one in the Neurohawk group and three in the Solitaire group).
[c]Data on mRS at 90 days were missing for five patients (two in the Neurohawk group and three in the Solitaire group).

Angioplasty with balloon and/or stent use was performed as a remedial measure to maintain a stable flow in 27 patients of the Neurohawk group and 24 of the Solitaire group ($p = 0.586$). Median time from groin puncture to successful reperfusion was similar in both treatment groups ($p = 0.772$). Finally, similar proportions of patients in the Neurohawk and Solitaire groups achieved successful reperfusion (90.43% vs. 91.45%, respectively).

Regarding the major safety outcomes, the rate of sICH within 36 h seemed higher in the Solitaire group (13.16% vs. 7.02%, respectively), but the difference was not statistically significant ($p = 0.124$). All-cause mortality rates within 90 days were 12.17% in the Neurohawk group and 17.09% in the Solitaire group, with no significant difference ($p = 0.289$). There were no significant differences between the two groups in terms of NIHSS at 30 h and favorable outcome (mRS 0–2) at 90 days.

According to the etiology of occlusion, 58 patients were assigned to the ICAD group and the remaining 174 patients to the non-ICAD group. In subgroup analysis, baseline,

TABLE 3 Baseline, clinical, and angiographic results in subgroup analysis.

	ICAD group ($n = 58$)	Non-ICAD group ($n = 174$)	*P*
Age (year), median (IQR)	63.6 (53.3, 69.9)	67.4 (59.5, 72.5)	**0.021**
Male sex, no. (%)	43 (74.14%)	107 (61.49%)	0.081
NIHSS, median (IQR)	15.0 (11.0, 19.0)	18.0 (14.0, 21.0)	**0.002**
ASPECTS, median (IQR)	8.0 (8.0, 10.0)	8.0 (7.0, 10.0)	0.521
Time from stroke onset to groin puncture (min), median (IQR)	282.6 (214.8, 334.8)	255 (195, 310.2)	**0.024**
Bridging intravenous fibrinolysis, no. (%)	26 (44.83%)	66 (37.93%)	0.352
Cerebral arterial occlusion, no. (%)§			
ICA	19 (32.76%)	68 (39.54%)	**0.022**
MCA M1 segment	37 (63.79%)	80 (46.51%)	
MCA M2 segment	2 (3.45%)	24 (13.95%)	
Use of balloon guide catheter	1 (1.72%)	30 (17.24%)	**0.003**
Rescue measures, no. (%)			
Single balloon angioplasty	13 (22.41%)	0 (0.00%)	
Single stenting	11 (18.97%)	5 (2.87%)	**<0.001**
Balloon and stent angioplasty	22 (37.93%)	0 (0.00%)	
Final successful reperfusion, *n*. (%)[a]	55 (94.83%)	156 (90.70%)	0.476
Symptomatic Intracranial hemorrhage within 36 h, no. (%)[b]	4 (6.90%)	19 (11.18%)	0.350
Time from groin puncture to successful reperfusion, min, median (IQR)	67.2 (46.2, 90.0)	52.8 (35.4, 76.8)	**0.004**
mRS 0–2 at 90 days, no. (%)[c]	37 (64.91%)	95 (55.88%)	0.232
Death within 90 days, no. (%)	4 (6.90%)	30 (17.24%)	**0.054**

[a]DSA imaging data were lost for two patient in the non-ICAD group, and in sub-analysis, the lost mTICI score wasn't filled with the worst value.
[b]Data on the symptomatic intracranial hemorrhage within 36 h were missing for four patients in the Non-ICAD group.
[c]Data on mRS at 90 days were missing for one patient in the ICAD group and four patients in the non-ICAD group.
Bold values of *P* indicate a statistically significant difference.

clinical, and angiographic data between these two groups were compared, and are summarized in Table 3. Compared with the non-ICAD group, individuals with ICAD-LVO had younger age, lower initial NIHSS, and longer time from onset to puncture. Besides, MCA M1 occlusion was more frequent among the patients with ICAD. In terms of treatment method, the proportions of bridging intravenous fibrinolysis were similar in both groups. However, the use of a balloon guide catheter was more preferred in the non-ICAD group (1.72% vs. 17.24%, $p = 0.003$). To maintain a stable flow, 79.31% of patients with ICAD-LVO needed rescue measures. Time from groin puncture to successful reperfusion was longer in the ICAD-LVO group ($p = 0.004$). However, there was no statistically significant difference in successful reperfusion rate between the two groups. In the ICAD group, the successful reperfusion rates were 96.97% in Neurohawk group and 92.0% in Solitaire group ($p = 0.804$). The ICAD group seemed to have a lower frequency of sICH, but without statistical significance. Although mortality within 90 days was relatively lower in the ICAD group (6.90% vs. 17.24%; $p = 0.054$), the rates of favorable outcome at 90 days were comparable between the two groups.

Discussion

This randomized controlled trial demonstrated that the Neurohawk achieved comparable rates of successful reperfusion and PFE vs. the Solitaire FR for the treatment of patients with LVO-AIS. From a safety perspective, the rates of sICH were similar. These angiographic results translated to comparable proportions of patients with good clinical outcomes, with close to 60% of patients regaining functional independence at 90 days in each group. In subgroup analysis, almost 80% of individuals with ICAD-LVO needed rescue measures to maintain a favorable reperfusion, including balloon and/or stent angioplasty, which would prolong the time of the procedure. Even so, patients with ICAD-LVO AIS had similar successful reperfusion rate and favorable outcome rate at 90 days vs. those with non-ICAD-LVO AIS. In addition, patients with ICAD-LVO AIS had a relatively lower mortality rate within 90 days.

The Neurohawk retriever is a closed-cell designed retriever with full radiopaque visibility, which can be delivered through a 0.021-inch microcatheter. The available working lengths of the Neurohawk are 25 mm with diameter of 4 mm, and 30 mm with diameter of 6 mm. For a retriever with only several radiopaque marks, physicians could see the ends of the device but not the retrieval area, indicating that they often had to make assumptions regarding the positional relationship between the clot and opened cells. However, the radiopaque Neurohawk retriever allows the physician to visualize the placement of struts at the location of the clot. In addition, it allows a particular deployment maneuver, the push and fluff technique, which may lead to better device opening and optimized wall apposition (20, 21). After partially unsheathing the retriever by retracting the delivery microcatheter, the forward force is applied to the device delivery wire and the forward tension continues to push the device into maximal expansion. Therefore, the larger stent cell area may allow for incorporation of higher volumes of clot.

This study is one of the few randomized controlled trials that focus on the efficacy and safety of a new device for thrombectomy. Although new devices for thrombectomy are constantly emerging, most of them are validated for clinical effects in single-arm studies. Usually, the data from a single group are compared with previous studies of other devices.

However, direct comparison of prognoses between single-arm studies and previous registries could produce bias from inhomogeneous baselines and inconsistent operator experiences (22–27). In this study, the prospective randomization design generated a well-balanced baseline between the two groups. From the perspective of angiographic results and clinical outcomes, the Neurohawk was demonstrated to be non-inferior to the Solitaire FR in the treatment of LVO-AIS in the anterior circulation. Although the visibility of Neurohawk may improve the usage experience, the angiographic endpoint showed no difference. One reason might be the high rate of mTICI 2b-3 seen with the modern endovascular technology results in a ceiling effect, making the measurement insensitive. The subtle difference caused by minor improvements may require larger sample sizes and more sensitive measurements to confirm.

While embolism and extracranial atherosclerotic disease is the leading cause of AIS in Caucasian patients, ICAD-LVO cases are more prevalent among Asians (28, 29). In this study, one-fourth of cases resulted from ICAD-LVO. The characteristics of occlusions arising from ICAD and non-ICAD differed in terms of therapeutic responses. For instance, subsequent plaque irritation and platelet aggregation are persistent even after mechanical thrombectomy, which often leads to re-occlusion. Another concern for these patients is whether the use of antiplatelet drugs post-angioplasty would increase the risk of hemorrhagic complications. However, limited studies have so far assessed the efficacy and safety of mechanical thrombectomy in AIS due to ICD-LVO, and the only information available is based on single center, retrospective studies conducted on few samples (14, 30–32).

In this study, patients with ICAD-LVO had lower initial NIHSS, which might be attributed to ischemic preconditioning and better collateral compensation. This finding was in line with the EAST study in which admission NIHSS in the ICAD group was lower than that of the embolic group (33). Endovascular treatment of AIS underlying ICAD-LVO is technically more complex. About four-fifth of patients with ICAD-LVO received angioplasty, while only five patients in the non-ICAD group needed single stent implantation. The EAST study in China showed 63.8% (30/47) of patients were considered to be eligible for rescue treatment. In our previous meta-analysis of endovascular treatment of ICAD-LVO, the most common rescue therapy was stenting with or without balloon angioplasty (32.7%), followed by single balloon angioplasty (12.3%) (30). Besides, our data showed additional rescue therapy was indeed reflected by significantly longer procedure time, in concordance with the previous study. Finally, our findings corroborate studies that also demonstrated similar angiographic and clinical outcomes were obtained in the treatment of acute ICAD-LVO.

This study had several underlying limitations because of the restrictive nature of the randomized controlled non-inferiority trial design, including the limited sample size, and strict inclusion and exclusion criteria. In addition, the mRS was accessed by physicians in each center, which can lead to heterogenous judgments. The sub-analysis also had several limitations. Data for this sub-analysis were derived from the original trial, and therefore, selection bias was inevitable. There was heterogeneity in the intraoperative antiplatelet regimen among different centers.

Conclusion

This randomized clinical trial demonstrated that the Neurohawk retriever is non-inferior to the Solitaire FR in the mechanical thrombectomy of LVO-AIS. Meanwhile, the sub-analysis suggested that endovascular treatment including thrombectomy with the retriever and essential rescue angioplasty is effective and safe in patients with AIS underlying ICAD-LVO.

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.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee at each participating site (the full list is available as a Supplementary file). The patients/participants provided their written informed consent to participate in this study.

Author contributions

PY and JLiu: conceptualization, responsible for theoretical guidance and conceptual specification, methodology, funding acquisition, project research fund, data collection and collation, and supervision. PY, JLiu, YongxZ, PL, MS, and ML: responsible for the guidance of research methods, formal analysis, and investigation. YongxZ and PL: analyze the current research status and put forward the research direction, writing—original draft preparation, and writing—review and editing. YongxZ, PL, ZL, YP, WC, LiZ, JC, DK, ZC, WW, YXu, YongZ, BZ, YG, CY, JLi, MW, NZ, XP, ZJ, YXi, XZ, XC, LeZ, BH, PX, HS, and YongwZ: resources. All authors read and approved the final manuscript.

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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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.962987/full#supplementary-material

References

1. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* (2016) 387:1723–31. doi: 10.1016/s0140-6736(16)00163-x

2. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* (2015) 372:11–20. doi: 10.1056/NEJMoa1411587

3. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* (2015) 372:2296–306. doi: 10.1056/NEJMoa1503780

4. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* (2015) 372:1019–30. doi: 10.1056/NEJMoa1414905

5. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* (2015) 372:1009–18. doi: 10.1056/NEJMoa1414792

6. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med.* (2015) 372:2285–95. doi: 10.1056/NEJMoa1415061

7. Malisch TW, Zaidat OO, Castonguay AC, Marden FA, Gupta R, Sun CJ, et al. Clinical and angiographic outcomes with the combined local aspiration and retriever in the North American Solitaire Stent-Retriever Acute Stroke (NASA) Registry. *Interv Neurol.* (2018) 7:26–35. doi: 10.1159/000480353

8. Zaidat OO, Castonguay AC, Gupta R, Sun CH, Martin C, Holloway WE, et al. North American Solitaire Stent Retriever Acute Stroke registry: post-marketing revascularization and clinical outcome results. *J Neurointerv Surg.* (2014) 6:584–8. doi: 10.1136/neurintsurg-2013-010895

9. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke.* (1988) 19:604–7. doi: 10.1161/01.str.19.5.604

10. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet.* (2000) 355:1670–4. doi: 10.1016/s0140-6736(00)02237-6

11. Yang P, Zhang Y, Liu J. LAST(2) CH(2)ANCE: a summary of selection criteria for thrombectomy in acute ischemic stroke. *AJNR Am J Neuroradiol.* (2017) 38:E58–9. doi: 10.3174/ajnr.A5249

12. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2018) 49:e46–110. doi: 10.1161/str.0000000000000158

13. Haussen DC, Rebello LC, Nogueira RG. Optimizating clot retrieval in acute stroke: the push and fluff technique for closed-cell stentrievers. *Stroke.* (2015) 46:2838–42. doi: 10.1161/strokeaha.115.010044

14. Yang W, Zhang Y, Li Z, Zhang L, Li H, Hua W, et al. Differences in safety and efficacy of endovascular treatment for acute ischemic stroke: a propensity score analysis of intracranial atherosclerosis-related occlusion versus embolism. *Clin Neuroradiol.* (2021) 31:457–64. doi: 10.1007/s00062-020-00899-x

15. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke.* (2013) 44:2650–63. doi: 10.1161/strokeaha.113.001972

16. Yoo AJ, Soomro J, Andersson T, Saver JL, Ribo M, Bozorgchami H, et al. Benchmarking the extent and speed of reperfusion: first pass TICI 2c-3 is a preferred endovascular reperfusion endpoint. *Front Neurol.* (2021) 12:669934. doi: 10.3389/fneur.2021.669934

17. Abbasi M, Liu Y, Fitzgerald S, Mereuta OM, Arturo Larco JL, Rizvi A, et al. Systematic review and meta-analysis of current rates of first pass effect by thrombectomy technique and associations with clinical outcomes. *J Neurointerv Surg.* (2021) 13:212–16. doi: 10.1136/neurintsurg-2020-016869

18. Zaidat OO, Castonguay AC, Linfante I, Gupta R, Martin CO, Holloway WE, et al. First pass effect: a new measure for stroke thrombectomy devices. *Stroke.* (2018) 49:660–6. doi: 10.1161/strokeaha.117.020315

19. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke.* (2001) 32:2735–40. doi: 10.1161/hs1201.100209

20. Ohshima T, Kawaguchi R, Nagano Y, Miyachi S, Matsuo N, Takayasu M. Experimental direct measurement of clot-capturing ability of stent retrievers. *World Neurosurg.* (2019) 121:e358–63. doi: 10.1016/j.wneu.2018.09.106

21. Tomasello A, Ribò M, Gramegna LL, Melendez F, Rosati S, Moreu M, et al. Procedural approaches and angiographic signs predicting first-pass recanalization in patients treated with mechanical thrombectomy for acute ischaemic stroke. *Interv Neuroradiol.* (2019) 25:491–96. doi: 10.1177/1591019919847623

22. Mattle HP, Scarrott C, Claffey M, Thornton J, Macho J, Riedel C, et al. Analysis of revascularisation in ischaemic stroke with EmboTrap (ARISE I study) and meta-analysis of thrombectomy. *Interv Neuroradiol.* (2019) 25:261–70. doi: 10.1177/1591019918817406

23. Brouwer PA, Yeo LLL, Holmberg A, Andersson T, Kolloch J, KuntzeSöderqvist Å, et al. Thrombectomy using the EmboTrap device: core laboratory-assessed results in 201 consecutive patients in a real-world setting. *J Neurointerv Surg.* (2018) 10:964–68. doi: 10.1136/neurintsurg-2018-013765

24. Sakai N, Ota S, Matsumoto Y, Kondo R, Satow T, Kubo M, et al. Efficacy and safety of REVIVE SE thrombectomy device for acute ischemic stroke: river JAPAN (reperfuse ischemic vessels with endovascular recanalization device in Japan). *Neurol Med Chir (Tokyo).* (2018) 58:164–72. doi: 10.2176/nmc.oa.2017-0145

25. Siemonsen S, Forkert ND, Bernhardt M, Thomalla G, Bendszus M, Fiehler J. ERIC acute stroke recanalization: a study using predictive analytics to assess a new device for mechanical thrombectomy. *Int J Stroke.* (2017) 12:659–66. doi: 10.1177/1747493017700661

26. Kallenberg K, Solymosi L, Taschner CA, Berkefeld J, Schlamann M, Jansen O, et al. Endovascular stroke therapy with the aperio thrombectomy device. *J Neurointerv Surg.* (2016) 8:834–9. doi: 10.1136/neurintsurg-2015-011678

27. Kahles T, Garcia-Esperon C, Zeller S, Hlavica M, Añon J, Diepers M, et al. Mechanical thrombectomy using the new ERIC retrieval device is feasible, efficient, and safe in acute ischemic stroke: a swiss stroke center experience. *AJNR Am J Neuroradiol.* (2016) 37:114–9. doi: 10.3174/ajnr.A4463

28. Kim BJ, Kim JS. Ischemic stroke subtype classification: an asian viewpoint. *J Stroke.* (2014) 16:8–17. doi: 10.5853/jos.2014.16.1.8

29. Qureshi AI, Caplan LR. Intracranial atherosclerosis. *Lancet.* (2014) 383:984–98. doi: 10.1016/s0140-6736(13)61088-0

30. Li H, Zhang Y, Zhang L, Li Z, Xing P, Zhang Y, et al. Endovascular treatment of acute ischemic stroke due to intracranial atherosclerotic large vessel occlusion: a systematic review. *Clin Neuroradiol.* (2020) 30:777–87. doi: 10.1007/s00062-019-00839-4

31. Yang D, Hao Y, Zi W, Wang H, Zheng D, Li H, et al. Effect of retrievable stent size on endovascular treatment of acute ischemic stroke: a multicenter study. *AJNR Am J Neuroradiol.* (2017) 38:1586–93. doi: 10.3174/ajnr.A5232

32. Sun B, Shi Z, Pu J, Yang S, Wang H, Yang D, et al. Effects of mechanical thrombectomy for acute stroke patients with etiology of large artery atherosclerosis. *J Neurol Sci.* (2019) 396:178–83. doi: 10.1016/j.jns.2018.10.017

33. Jia B, Feng L, Liebeskind DS, Huo X, Gao F, Ma N, et al. Mechanical thrombectomy and rescue therapy for intracranial large artery occlusion with underlying atherosclerosis. *J Neurointerv Surg.* (2018) 10:746–50. doi: 10.1136/neurintsurg-2017-013489

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Association of baseline core volume and early midline shift in acute stroke patients with a large ischaemic core

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Background: Midline shift (MLS) is troublesome problem that may occur in patients with a large infarct core (LIC) and may be related to the baseline infarct core volume. The purpose of this study was to explore the relationship between baseline infarct core volume and early MLS presence.

Materials and methods: Patients with acute intracranial large artery occlusion and a pretreatment relative cerebral blood flow (rCBF) <30% volume ≥50 ml on CT perfusion (CTP) were included, clinical outcomes following endovascular treatment (EVT) were retrospectively analyzed. The primary endpoint was MLS within 48 h (early MLS presence). The association between baseline ICV and early MLS presence was evaluated with multivariable regression.

Results: Ultimately, 95 patients were included, and 29.5% (28/95) of the patients had early MLS. The number of patients with a baseline rCBF < 15% volume (median [interquartile range], 46 [32–60] vs. 29 [19–40]; $P < 0.001$) was significantly larger in the early severe MLS presence group. A baseline rCBF < 15% volume showed significantly better predictive accuracy for early MLS presence than an rCBF < 30% volume (area under the curve, 0.74 vs. 0.64, $P = 0.0023$). In addition, an rCBF < 15% volume ≥40 ml (odds ratio, 4.34 [95% CI, 1.571–11.996]) was associated with early MLS presence after adjustment for sex, age, baseline National Institutes of Health Stroke Scale score, onset-to-recanalization time.

Conclusion: In patients with an acute LIC following EVT, a pretreatment infarct core volume > 40 ml based on an rCBF < 15% showed good predictive value for early MLS occurrence.

KEYWORDS

midline shift, large ischaemic core, prognosis, acute ischemic stroke, thrombectomy

Introduction

Endovascular thrombectomy (EVT) is the standard treatment for ischaemic stroke patients with large vessel occlusion (LVO) (1–8). However, most clinical trials of EVT focused on patients with small ischaemic cores defined as a volume with a relative cerebral blood flow (rCBF) <30% of <50 or <70 cm^3 on computed tomographic perfusion (CTP) images or an Alberta Stroke Program Early CT Score [ASPECTS] ≥6 on non-contrast computed tomography (CT) imaging prior to thrombectomy (9). Recently, a meta-analysis showed that patients with a large ischaemic core (LIC) defined by an ASPECTS < 6, ischaemic core volume ≥ 50 ml or both can benefit from EVT (10). Moreover, a recent randomized clinical trial (RCT) performed in Japan showed that patients with an LIC had better functional outcomes with endovascular therapy than with medical care alone but had more intracranial hemorrhages (11).

However, one concern of patients with an LIC who receive EVT is cerebral oedema, which can lead to early cerebral midline shift (MLS) occurrence and poor prognosis. The causes of cerebral oedema remain unclear. Studies have shown that in patients with a core volume > 130 mL or CT-ASPECTS ≤ 3, EVT is not significantly associated with a clinical benefit and may be detrimental through the exacerbation of oedema. Therefore, we hypothesize that the baseline ischaemic core volume is associated with MLS occurrence.

Traditionally, the infarct core is defined as an rCBF < 30% (12); however, the chronological progression to infarction is different for different cell types (neurons are already severely damaged at a time and place where astrocytes are only minimally injured), and it is variable in both time and space (13). Currently, there is no optimal ischaemic core CTP parameter, and an rCBF < 30% ischaemic volume may also be reversible after reperfusion therapy, similar to the theory of diffusion MR reversibility (14, 15). Furthermore, we hypothesized that an rCBF < 15% ischaemic volume is extremely ischaemic tissue and is very difficult to save despite rapid reperfusion. In our study, we aimed to explore the relationship between an rCBF < 15% ischaemic volume and early MLS occurrence and determine the optimal ischaemic volume for predicting early MLS occurrence.

Methods

Patient population and data collection

The patient data analyzed in the present study were derived from our Prospective Registry database of Endovascular Treatment. For the present analysis, all patients enrolled between January 1, 2015, and July 1, 2021, were included. The inclusion criteria of this study were as follows: at least 18 years of age; acute occlusion of anterior intracranial large vessels and EVT; a baseline National Institutes of Health Stroke Scale (NIHSS) score ≥ 6; a baseline CTP and pretreatment ischaemic core volume ≥ 50 ml (autoassessed by CTP); a premorbid modified Rankin Scale (mRS) score ≤ 2; and an onset-to-presentation time within 24 h.

Ethics approval

The study was approved by the local hospital ethics committees (ID 2021 LWB251). Written informed consent for EVT was obtained from the patient or the proxy. Informed consent for this study was waived because it was a retrospective study.

Clinical variables and outcomes

The baseline data included sex, age, comorbidities (hypertension, diabetes, hyperlipidaemia, and atrial fibrillation), occlusion site, time from onset to treatment, neurologic deficits using the NIHSS score, and stroke subtype according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) categories (16).

The primary outcome was midline shift (MLS), Secondary outcomes were functional independence at 3 months, corresponding to a modified Rankin Scale (mRS) score of 0–2, death at 3 months and symptomatic intracranial hemorrhage (sICH) according to the definition of Heidelberg (17).

Radiological variables and outcomes

For the patients in our study, we used the following acquisition protocol and post-processing algorithms. CT perfusion was performed on a 320-slice scanner (GE Revolution). With each time point acquisition, a total of 320 slices with a thickness of 0.5 mm were obtained, which covered the whole brain (220 mm total coverage). Typically, 19 time points were obtained commencing 4 seconds after non-ionic iodinated contrast injection into an antecubital vein (50 mL, 5 mL/s; Bayer HealthCare). The acquisition parameters were 80 kilovolts (peak; kVp) and 200 mA. This acquisition also allowed the generation of intracranial angiographic data as well as perfusion maps. Whole-brain non-contrast CT (NCCT) was performed before CTP. After acquisition, CTP data were processed by the commercial software Mistar (Apollo Medical Imaging Technology). The mathematical model of delay-corrected singular value decomposition (dSVD) was chosen to generate perfusion parameters, which were presented as cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and delay time (DT). We further generated a penumbra/core map by setting thresholds for

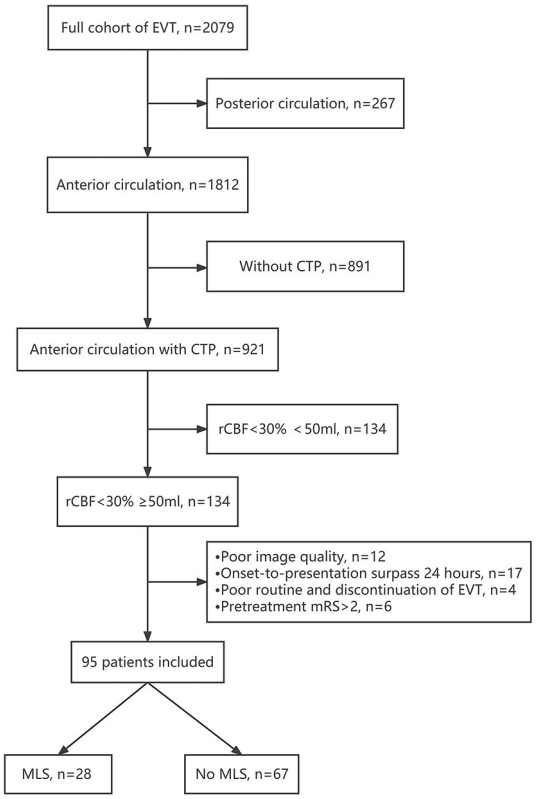

FIGURE 1
Study flow chart. CTP, CT perfusion; EVT, endovascular Therapy; MLS, midline shift.

parametric maps. A DT > 3 sec was defined as hypoperfusion of brain tissue, and the ischaemic core volume was defined as rCBF < 30% (18). The mismatch volume (volume of DT > 3 s minus volume of rCBF < 30%) and mismatch ratio (volume of DT > 3 s divided by volume of rCBF < 30%) were also calculated by Mistar software (12). We can also derive the value of rCBF < 15%. The reperfusion grade was assessed with the Extended Thrombolysis in Cerebral Infarction (eTICI) scale (19), and substantial reperfusion was defined as a score of 2b, 2c, or 3 (19).

Early severe MLS presence was defined as an MLS greater than 3 mm (20) within 48 h post-EVT. MLS measurements were performed by readers who were blinded to the clinical data (Dr P.Z.N), and MLS was assessed as dichotomous (present or absent). In patients who had >1 follow-up scan, the scan with the highest MLS was analyzed. MLS was measured in millimeters at the level of the septum pellucidum (21, 22). The quantitative assessment of MLS was performed on patients previously categorized as having MLS. MLS measurements were independently assessed in 30% of the study cohort (29 consecutive subjects) by a second neurologist (Dr L.X.H) and found to have excellent interrater agreement (K = 0.95). Then, the patients were divided into 2 groups: the early severe MLS presence group was defined by the presence of an MLS > 3 mm, and the no early severe MLS presence group was defined by the presence of an MLS < 3 mm or MLS absence.

Statistical analysis

Standard descriptive statistics are reported as medians and IQRs for continuous variables and as numbers and percentages for categorical variables. For between-group comparisons of categorical variables, the $\chi 2$-test or Fisher's exact test was used, as appropriate. The Mann–Whitney U test was employed for continuous variables. The areas under the curve from receiver operating characteristic (ROC) analyses were used to assess the predictive value of the baseline ischaemic core calculated by different levels of rCBF for early MLS presence. The Youden index was used to calculate the optimal cut-off predictive value of different rCBF threshold values. A bootstrap test was used to compare the areas under the curve (AUCs) between rCBF < 15% volume and rCBF < 30% volume. Multivariable logistic regression analyses were performed to determine the associations between early MLS presence and some important baseline factors, including core volume calculated by rCBF < 15%. Statistical analyses were performed using SPSS 18.0 (IBM SPSS, Chicago, IL) and R software version 4.13. A 2-sided P value < 0.05 was considered indicative of statistical significance.

Results

The study flow chart is shown in Figure 1. Of the 2,079 patients enrolled in our registry database, 44.3% (921/2,078) of anterior circulation infarction patients had baseline CTP data, and 134 patients had a baseline core infarct volume ≥50 ml. Ultimately, 95 patients were included after the exclusion of 39 patients for the following reasons: (1) poor image quality (12 patients); (2) onset-to-presentation time surpassing 24 h (17 patients); (3) poor routine and discontinuation of endovascular therapy (4 patients); and (4) a pretreatment mRS > 2 (6 patients). A total of 29.5% (28/95) of patients had early severe MLS.

Baseline characteristics and clinical outcomes of the whole cohort

Of the 95 included patients (Table 1), 58.9% (56/95) were males, and the median age was 72 (IQR, 63–79) years. The median baseline NIHSS score of this cohort was 19 (IQR, 16–22). A total of 49.5% (47/95) of the occlusion sites were intracranial carotid artery. Overall, successful revascularization (eTICI 2b,2c,3) was achieved in 98.9% (94/95) patients, and

TABLE 1 Comparison of baseline characteristics between patients with early severe MLS presence and without early severe MLS presence.

Parameter	All patients $N = 95$	No MLS $N = 67$	MLS $N = 28$	*P* value
Sex (male, *n*)	56 (58.9%)	44 (65.7%)	12 (42.9%)	0.039
Age, y, median (IQR)	72 (63–79)	72 (63–79)	74 (64–80)	0.358
Risk factors, *n* (%)				
Smoking	15 (15.8%)	13 (19.4%)	2 (7.1%)	0.236
Hypertension	70 (73.7%)	48 (71.6%)	22 (78.6%)	0.484
Diabetes mellitus	27 (28.4%)	18 (26.9%)	9 (32.1%)	0.603
Atrial fibrillation	23 (24.2%)	15 (22.4%)	8 (28.6%)	0.521
Baseline NIHSS score (median, IQR)	19 (16–22)	19 (15–22)	19 (18–23)	0.180
Intravenous thrombolysis, n (%)	25 (26.3%)	18 (26.9%)	7 (25.0%)	0.851
Onset-to-recanalization time, median (IQR)	349 (266–445)	323 (253–438)	385 (307–446)	0.194
ASPECT	3 (1–5)	3 (2–6)	3 (0–5)	0.158
Occlusion site, *n* (%)				
ICA	47 (49.5%)	32 (47.8%)	15 (56.6%)	0.606
M1 segment	39 (41.1%)	26 (38.8%)	13 (46.4%)	0.491
M2 segment	9 (9.5%)	9 (13.4%)	0 (0%)	0.098
Endovascular therapy detail				
Mechanical thrombectomy	93 (97.9%)	66 (98.5%)	27 (96.4%)	0.505
Angioplasty	15 (15.8%)	11 (16.4%)	4 (14.3%)	1.000
Intravenous tirofiban	29 (30.5%)	25 (37.3%)	4 (14.3%)	0.026
Intraarterial rt-PA	2 (2.1%)	1 (1.5%)	1 (3.6%)	0.505
TOAST subtype, *n* (%)				
CE	64 (67.4%)	40 (59.7%)	24 (85.7%)	0.014
LAA	29 (30.5%)	25 (37.3%)	4 (14.3%)	0.026
Other	2 (2.1%)	2 (3.0%)	0 (0%)	0.888
eTICI $\geq$ 2b, *n* (%)	94 (98.9%)	66 (98.5%)	28 (100%)	1.000
Clinical outcome, *n* (%)				
sICH	9 (9.5%)	3 (4.5%)	6 (21.4%)	0.029
mRS 0–2	21 (22.1%)	21 (31.3%)	0 (0%)	0.001
Mortality	32 (33.7%)	17 (25.4%)	15 (53.6%)	0.008

IQR, interquartile range; ASPECT, Alberta Stroke Program Early CT Score; TOAST, Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale; ICA, intracranial carotid artery; LAA, large-artery atherosclerosis; CE, cardio embolism; sICH, symptomatic intracranial hemorrhage.

functional independence was achieved in 22.1% (21/95) of patients; 33.7% (31/95) of patients died.

Comparison between the early severe MLS presence and no early severe MLS presence groups

Table 1 shows that the TOAST subtype was different between the 2 groups. Compared with the no early severe MLS presence group, the early severe MLS presence group included more patients with the cardiac embolic type (85.7 vs. 59.7%, $P = 0.014$) and fewer with large artery atherosclerosis (LAA) (14.3 vs. 37.3%, $P = 0.026$).

The clinical outcome was poorer in the early severe MLS presence group: there were more patients with sICH (21.4 vs. 4.5%, $P = 0.029$) and fewer patients with functional independence (0 vs. 31.3%, $P = 0.001$). Furthermore, more patients died (53.6 vs. 25.4%, $P = 0.008$) in the early severe MLS presence group.

TABLE 2 Comparison of baseline infarct core between patients with early severe MLS presence and without early severe MLS presence.

Parameter	All patients $N = 95$	No MLS $N = 67$	MLS $N = 28$	*P* value
rCBF < 30%, median (IQR)	75 (64–96)	71 (61–93)	91 (71–113)	0.010
rCBF < 15%, median (IQR)	35 (23–46)	29 (19–40)	46 (32–60)	<0.001
CBF < 15% ≥40 ml, n (%)	34 (35.8%)	17 (25.4%)	17 (60.7%)	0.001

MLS, midline shift; IQR, interquartile range; ml, milliliter; rCBF, relative cerebral blood flow.

No significant differences were found between the 2 outcome groups in age (74 year in the early severe MLS presence group vs. 72 yrs. in the no early severe MLS presence group, $P = 0.358$), baseline NIHSS (19 vs. 19, $P = 0.180$), risk factors including smoking (7.1 vs. 19.4%, $P = 0.236$), hypertension (78.6 vs. 71.6%, $P = 0.484$), diabetes mellitus (32.1 vs. 26.9%, $P = 0.603$), or atrial fibrillation (28.6 vs. 22.4%, $P = 0.521$), except there were fewer male patients in the early severe MLS presence group (42.9 vs. 65.7%, $P = 0.039$). The occlusion site was similar in the 2 groups, including intracranial internal carotid artery occlusion (56.6% in the early severe MLS presence group vs. 47.8% in the no early severe MLS presence group, $P = 0.606$) and the M1 segment of the MCA (46.4 vs. 38.8%, $P = 0.491$).

No significant differences were found between the 2 outcome groups in endovascular therapy detail except more patients received intravenous tirofiban in no MLS group than that in MLS group (37.3 vs. 14.3%, $P = 0.026$).

Baseline infarct core volume calculated by different thresholds of rCBF between the 2 groups

As Table 2 shows, compared with the no early severe MLS presence group, patients in the early severe MLS presence group showed a larger infarct core volume of rCBF < 30% (median [IQR], 91 [71–113] vs. 71 [61–93]; $P = 0.01$) and rCBF < 15% (median [IQR], 46 [32–60] vs. 29 [32–60]; $P < 0.001$). There were 29 patients with rCBF < 15% volumes > 40 ml and rCBF < 30% volumes < 130 ml, and 14 of these patients (48.3%) had early severe MLS occurrence.

ROC analyses and logistic regression analyses

Figure 2 shows that an rCBF < 15% ischaemic volume showed significantly better predictive accuracy than an ischaemic volume of rCBF < 30% (area under the curve, 0.74 vs. 0.64, $P = 0.002$). The optimal threshold points from the ROC analyses to differentiate patients likely to have a higher likelihood of MLS were core volume calculated by rCBF < 15% of ≥40 ml (sensitivity 0.61, specificity 0.76) and an rCBF < 30% core volume of ≥86 ml (sensitivity 0.61, specificity 0.70), as showed in Table 3.

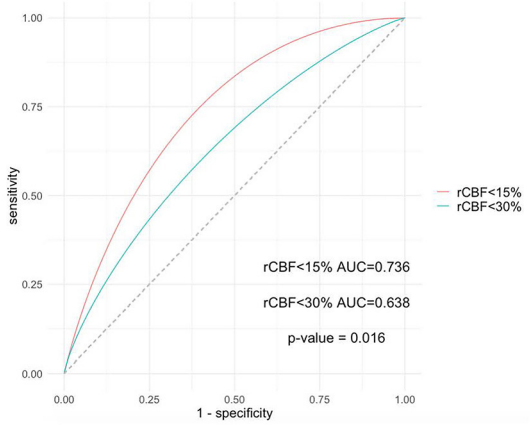

FIGURE 2
Receiver operating characteristic analyses of the rCBF < 15% volume and rCBF < 30% volume. An rCBF < 15% volume showed a better predictive value of MLS than an rCBF < 30% volume (AUC, 0.735 vs. 0.646, $P = 0.023$). rCBF indicates relative cerebral blood flow; AUC indicates the area under the curve.

Table 2 indicates that there were more patients with rCBF≥40 ml in the early severe MLS presence group (60.7 vs. 25.4%, $P = 0.001$). Based on the results of multivariate logistic regression, an rCBF < 15% core volume ≥ 40 ml was an independent predictor of early severe MLS presence (odds ratio [OR], 4.34 [95% CI, 1.571–11.996, $P = 0.005$]) after adjustment for sex, age, baseline NIHSS score, onset-to-recanalization time and TOAST subtype, as showed in Table 4.

Discussion

Our study showed that an rCBF < 15% core volume is a better tool for predicting early severe MLS presence than an rCBF < 30% core volume and an rCBF < 15% core volume ≥ 40 ml was a strong predictor of early MLS presence in patients with an LIC treated by EVT.

MLS is the gold standard imaging marker of cerebral oedema (23). MLS occurrence is one clinical scenario that patients with an LIC treated with reperfusion therapy may face and is of

TABLE 3 ROC analysis of the cut-off value of MLS.

	AUC	Sensitivity	Specificity	Cut-off value	*P* value
rCBF <30%	0.64 (0.52–0.75)	0.61	0.70	86	0.01
rCBF <15%	0.74 (0.62–0.84)	0.61	0.76	40	<0.001

rCBF indicates relative cerebral blood flow.

TABLE 4 Multivariate logistic regression analyses of variables associated with the occurrence of MLS.

Parameter	Odds ratio	95%CI	*P* value
CE	2.67	0.743–9.618	0.132
Male sex	0.40	0.137–1.160	0.091
Age, one-year increase	1.00	0.958–1.040	0.923
Onset-to-recanalization time	1.00	0.999–1.004	0.260
Baseline NIHSS score	1.00	0.923–1.154	0.579
rCBF < 15% volume ≥40 ml	4.34	1.571–11.996	0.005

CE, cardioembolism; NIHSS, National Institutes of Health Stroke Scale; rCBF, relative cerebral blood flow.

great concern to clinicians. MLS occurrence may be due to cerebral oedema caused by the infarction volume itself. Cerebral blood flow is the optimal CT perfusion parameter for assessing the infarct core (24), and an rCBF < 30% is traditionally defined as the infarct core (12). The chronological progression to infarction is different among different cell types and different individuals, and accurate core assessment is challenging (13). A case–control study indicated that the optimal threshold to define the ischaemic core in thrombectomy patients was an rCBF <20%, whereas in alteplase controls, the optimal ischaemic core threshold remained at an rCBF <30% (25), and the reason may be due to earlier reperfusion. Therefore, the traditional biomarker of an rCBF < 30% ischaemic volume may also be reversible. An rCBF < 15% ischaemic volume indicates extremely ischaemic tissue, which is very difficult to reverse and save. Our study showed that compared with an rCBF < 30%, an rCBF < 15% is a better tool for predicting MLS occurrence.

In animal models, reperfusion can exacerbate cerebral oedema because severely ischaemic tissue is unlikely to survive even with reperfusion, and oedema increases after reperfusion, which supplies blood flow and water content to already infarcted tissue (21). However, clinical studies have shown that reperfusion can reduce cerebral oedema (21, 22, 26, 27). Nevertheless, reperfusion may be harmful and exacerbate cerebral oedema in patients with a very large infarct core >130 ml (21). Our study showed that an rCBF < 15% was more accurate in predicting early MLS occurrence than an rCBF < 30% and that an rCBF < 15% volume ≥ 40 ml was a strong predictor of early MLS severe occurrence, which indicated that reperfusion therapy should be used with caution in patients with an rCBF < 15% volume > 40 ml. Furthermore, our study showed that half of the patients with an rCBF < 15% volume ≥ 40 ml and an rCBF < 30% volume < 130 ml had early severe MLS occurrence. To some extent, the predictive value of rCBF < 15% volume ≥ 40 ml for the presence of MLS is better than that of rCBF < 30% volume > 130 ml.

MLS presence, especially an MLS value > 3 mm, predicts poor outcome (20, 28). In concordance, our exploratory analysis suggests that none of the patients with early severe MLS presence achieved functional independence, and half of them died. sICH is another important factor that can exacerbate cerebral oedema and cause MLS. In our study, the sICH occurrence rate was as high as 21.4%.

Our analysis adds further evidence to support the safety and benefit of EVT in patients presenting with an LIC. Our study showed that functional independence was achieved in 22.1% of patients and that sICH occurred in 9.5%, which was consistent with previous studies. Previous studies have also shown that the functional independence rate ranges from 21.7% (29) to 36.5% (11, 30, 31), the mortality rate ranges from 22.5% (31), 30.8% (31) to 44.7% (29), and the sICH occurrence rate ranges from 3.7% (32) to 7.0% (31).

The strengths of this study are the use of data from a prospective registry database, a relatively large sample and the use of objective imaging criteria with automated core volume calculations for CTP, which is more accurate than core volumes assessed with CT-ASPCET. However, our study also had some limitations.

Because of the lack of a control group that received the best medical treatment alone, we cannot judge the treatment effect sizes. Additionally, our database does not track patients with LVO who did not undergo thrombectomy, and thus, data relating to a proportion of treated patients are not available. Third, individual treatment decisions were made by different interventionalists or/and patients/families' preferences rather than on a specific selection protocol. This may have led to a selection bias that could have confounded our results but at the same time allowed us to explore the paradigm of treating patients with LIC more pragmatically. Fourth, although post-procedural neurocritical care could have some effects on the outcome, the influence may be minimized since the critical care of all these included patients was performed by a designated team. Therefore, factors regarding post-procedural critical care were not considered in the analysis.

Conclusion

In summary, our data provide reassurance that iatrogenic exacerbation of space-occupying cerebral oedema following EVT in patients is unlikely in patients presenting with an LIC, particularly among patients with an rCBF < 15% core volume < 40 ml. However, reperfusion therapy should be used with caution in patients with an rCBF < 15% core volume ≥ 40 mL. Trials are needed to mitigate the adverse effects of cerebral oedema and offer an avenue to reduce the morbidity and mortality of patients with LIC.

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 Zhangzhou Municipal Hospital Ethics Committee. The Ethics Committee waived the requirement of written informed consent for participation.

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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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.

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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.2022.1077824/full#supplementary-material

References

1. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* (2015) 372:11–20. doi: 10.1056/NEJMoa1411587

2. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* (2015) 372:1019–30. doi: 10.1056/NEJMoa1414905

3. Saver JL, Goyal M, Bonafe A, Diener H-C, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. *t-PA alone in stroke N Engl J Med.* (2015) 372:2285–95. doi: 10.1056/NEJMoa1415061

4. Campbell BC V, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* (2015) 372:1009–18. doi: 10.1056/NEJMoa1414792

5. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X

6. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med.* (2017) 378:11–21. doi: 10.1056/NEJMoa1706442

7. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N Engl J Med.* (2018) 378:708–18. doi: 10.1056/NEJMoa1713973

8. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke. *Stroke.* (2019) 50:e344–418. doi: 10.1161/STR.0000000000000211

9. Sarraj A, Hassan AE, Savitz S, Sitton C, Grotta J, Chen P, et al. Outcomes of Endovascular Thrombectomy vs Medical Management Alone in Patients with Large Ischemic Cores: A Secondary Analysis of the Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT) Study. *JAMA Neurol.* (2019) 76:1147–56. doi: 10.1001/jamaneurol.2019.2109

10. Diestro JDB, Dmytriw AA, Broocks G, Chen K, Hirsch JA, Kemmling A, et al. Endovascular thrombectomy for low aspects large vessel occlusion ischemic stroke: a systematic review and meta-analysis. *Can J Neurol Sci.* (2020) 47:612–9. doi: 10.1017/cjn.2020.71

11. Yoshimura S, Sakai N, Yamagami H, Uchida K, Beppu M, Toyoda K, et al. Endovascular therapy for acute stroke with a large ischemic region. *N Engl J Med.* (2022) 386:1303–13. doi: 10.1056/NEJMoa2118191

12. Gunasekera L, Churilov L, Mitchell P, Bivard A, Sharma G, Parsons MW, et al. Automated estimation of ischemic core prior to thrombectomy: Comparison of two current algorithms. *Neuroradiology.* (2021) 63:1645–9. doi: 10.1007/s00234-021-02651-9

13. Goyal M, Ospel JM, Menon B, Almekhlafi M, Jayaraman M, Fiehler J, et al. Challenging the ischemic core concept in acute ischemic stroke imaging. *Stroke*. (2020) 51:3147–3155. doi: 10.1161/STROKEAHA.120.030620

14. Lakomkin N, Pan J, Stein L, Malkani B, Dhamoon M, Mocco J. Diffusion MRI reversibility in ischemic stroke following thrombolysis: a meta-analysis. *J Neuroimaging*. (2020) 30:471–6. doi: 10.1111/jon.12703

15. Yoo J, Choi JW, Lee SJ, Hong JM, Hong JH, Kim CH, et al. Ischemic diffusion lesion reversal after endovascular treatment: prevalence, prognosis, and predictors. *Stroke*. (2019) 50:1504–9. doi: 10.1161/STROKEAHA.118.024263

16. Adams H, Adams H, Bendixen B, Bendixen B, Kappelle L, Kappelle L, et al. Classification of subtype of acute ischemic stroke. *Stroke*. (1993) 23:35–41. doi: 10.1161/01.STR.24.1.35

17. Von Kummer R, Broderick JP, Campbell BCV, Demchuk A, Goyal M, Hill MD, et al. The heidelberg bleeding classification: Classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. (2015) 46:2981–6. doi: 10.1161/STROKEAHA.115.010049

18. Lin L, Bivard A, Parsons MW. Perfusion patterns of ischemic stroke on computed tomography perfusion. *J Stroke*. (2013) 15:164. doi: 10.5853/jos.2013.15.3.164

19. Liebeskind DS, Bracard S, Guillemin F, Jahan R, Jovin TG, Majoie CBLM, et al. ETICI reperfusion: Defining success in endovascular stroke therapy. *J Neurointerv Surg*. (2019) 11:433–8. doi: 10.1136/neurintsurg-2018-014127

20. McKeown ME, Prasad A, Kobsa J, Top I, Snider SB, Kidwell C, et al. Midline shift greater than 3 mm independently predicts outcome after ischemic stroke. *Neurocrit Care*. (2022) 36:46–51. doi: 10.1007/s12028-021-01341-x

21. Ng FC, Yassi N, Sharma G, Brown SB, Goyal M, Majoie CBLM, et al. Cerebral edema in patients with large hemispheric infarct undergoing reperfusion treatment: A hermes meta-analysis. *Stroke*. (2021) 52:3450–3458. doi: 10.1161/STROKEAHA.120.033246

22. Kimberly WT, Dutra BG, Boers AMM, Alves HCBR, Berkhemer OA, Van Den Berg L, et al. Association of reperfusion with brain edema in patients with acute ischemic stroke: A secondary analysis of the MR CLEAN Trial. *JAMA Neurol*. (2018) 75:453–61. doi: 10.1001/jamaneurol.2017.5162

23. Battey TWK, Karki M, Singhal AB, Wu O, Sadaghiani S, Campbell BCV, et al. Brain edema predicts outcome after nonlacunar ischemic stroke. *Stroke*. (2014) 45:3643–8. doi: 10.1161/STROKEAHA.114.006884

24. Campbell BCV, Christensen S, Levi CR, Desmond PM, Donnan GA, Davis SM, et al. Cerebral blood flow is the optimal CT perfusion parameter for assessing infarct core. *Stroke*. (2011) 42:3435–40. doi: 10.1161/STROKEAHA.111.618355

25. Bivard A, Kleinig T, Miteff F, Butcher K, Lin L, Levi C, et al. Ischemic core thresholds change with time to reperfusion: A case control study. *Ann Neurol*. (2017) 82:995–1003. doi: 10.1002/ana.25109

26. Thorén M, Dixit A, Escudero-Martínez I, Gdovinová Z, Klecka L, Rand VM, et al. Effect of recanalization on cerebral edema in ischemic stroke treated with thrombolysis and/or endovascular therapy. *Stroke*. (2020) 51:216–23. doi: 10.1161/STROKEAHA.119.026692

27. Jo KW, Bajgur SS, Kim H, Choi HA, Huh PW, Lee K, et al. simple prediction score system for malignant brain edema progression in large hemispheric infarction. *PLoS ONE*. (2017) 12:1–12. doi: 10.1371/journal.pone.0171425

28. Kim H, Tak S, Woo Y, Rim S, Seong I, Wook K. Predictors of malignant brain edema in middle cerebral artery infarction observed on CT angiography. *J Clin Neurosci*. (2014) 22:554–60. doi: 10.1016/j.jocn.2014.08.021

29. Deb-Chatterji M, Pinnschmidt H, Flottmann F, Leischner H, Broocks G, Alegiani A, et al. Predictors of independent outcome of thrombectomy in stroke patients with large baseline infarcts in clinical practice: A multicenter analysis. *J Neurointerv Surg*. (2020) 12:1064–8. doi: 10.1136/neurintsurg-2019-015641

30. Bouslama M, Barreira CM, Haussen DC, Rodrigues GM, Pisani L, Frankel MR, et al. Endovascular reperfusion outcomes in patients with a stroke and low ASPECTS is highly dependent on baseline infarct volumes. *J Neurointerv Surg*. (2021) 14:117–21. doi: 10.1136/neurintsurg-2020-017184

31. Zaidat OO, Liebeskind DS, Jadhav AP, Ortega-Gutierrez S, Nguyen TN, Haussen DC, et al. Impact of age and alberta stroke program early computed tomography score 0 to 5 on mechanical thrombectomy outcomes: analysis from the STRATIS registry. *Stroke*. (2021) 52:2220–8. doi: 10.1161/STROKEAHA.120.032430

32. Kakita H, Yoshimura S, Uchida K, Sakai N, Yamagami H, Morimoto T. Impact of endovascular therapy in patients with large ischemic core: subanalysis of recovery by endovascular salvage for cerebral ultra-acute embolism Japan registry 2. *Stroke*. (2019) 50:901–8. doi: 10.1136/neurintsurg-2018-SNIS.224

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Rescue intracranial stenting for acute ischemic stroke after the failure of mechanical thrombectomy: A systematic review, meta-analysis, and trial sequential analysis

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Background: Intracranial rescue stenting (RS) might be an option for acute ischemic stroke after the failure of mechanical thrombectomy (MT). However, the findings were not consistent in previous systematic reviews, and whether the conclusion was supported by sufficient statistical power is unknown.

Aim: To examine the effect of RS on acute ischemic stroke after the failure of MT with a systematic review, meta-analysis, and trial sequential analysis (TSA).

Methods: We searched Ovid Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 15 June 2022, without any language restriction. Studies assessing the effect of RS for acute ischemia stroke after MT failure were included. Two reviewers independently screened the retrieved articles, extracted data, and evaluated the quality of the included studies through the New Ottawa Scale (NOS). The primary outcome was the recanalization rate after RS. Secondary outcomes included modified Rankin Scale (mRS) at 3 months after stroke, symptomatic intracranial hemorrhage (sICH), and mortality rate. We synthesized the data through a random-effects model and performed a TSA analysis.

Results: We included 15 studies (containing 1,595 participants) after screening 3,934 records. The pooled recanalization rate for rescue stenting was 82% (95% CI 77–87%). Compared with non-stenting, rescue stenting was associated with a higher proportion of patients with 0–2 mRS score (OR 3.96, 95% CI 2.69–5.84, $p < 0.001$) and a lower 90-day mortality rate (OR 0.46, 95% CI 0.32–0.65, $p < 0.001$), and stenting did not increase sICH rate (OR 0.63, 95% CI 0.39–1.04, $p = 0.075$). The TSA analysis showed that the meta-analysis of the mRS score had a sufficient sample size and statistical power.

Conclusions: Our study showed that rescue stenting was effective and safe for patients with acute ischemia stroke who also had a failed MT, and this result was confirmed in a TSA analysis.

KEYWORDS

acute ischemic stroke, mechanical thrombectomy failure, rescue stenting, meta-analysis, trial sequential analysis

Introduction

The prevalence and incidence of ischemic stroke are increasing because the global population ages, the absolute number of incidence of ischemic stroke increases from 4,309,356 in the year 1990 to 6,892,857 in the year 2013 (1). Stroke is now the second leading cause of death and a major cause of disability worldwide. The extent of collateral circulation in patients with ischemic stroke was closely related to their clinical outcomes. A good collateral circulation normally correlates with a good clinical outcome, and good collateral circulation has also been associated with the greater benefit of intravenous thrombolysis and endovascular treatment (2).

Mechanical thrombectomy (MT) is now becoming the first-line treatment option for reperfusion in patients with acute ischemic stroke, especially for those with contraindications for intravenous thrombolysis (3). Although promising, MT therapy still has a high rate of failure, which is estimated to be around 30% (4). Several approaches were proposed for patients with failed MT attempts, and glycoprotein IIb/IIIa inhibitors, balloon angioplasty, and rescue stenting are the three most frequently selected (5). Rescue stenting is of great interest to neurologists since it is a non-pharmacological therapy that could avoid the contraindications of pharmacological treatments and has a high rate of recanalization which enables rapid reperfusion. Previous systematic reviews have examined the effectiveness of rescue stenting for patients with acute ischemic stroke after MT failed, and the results showed that rescue stenting had favorable rates of recanalization and led to a better functional outcome than non-stenting treatments (6–9). However, owing to small sample sizes and the observation nature of the included studies, these reviews could not reach firm conclusions.

In the recent 2 years, studies that focused on the effectiveness of rescue stenting for patients with failed MT treatment were emerging (10–12). Among them, one study published in 2022 recruited 499 participants—the largest sample size today (12), and the study adopted the design of propensity score matching, which balanced the baseline characteristics between the stenting and non-stenting group and therefore generated a more robust result than previous studies did. The addition of these studies in a new systematic review with meta-analysis might further clarify whether rescue stenting is effective and safe for patients with acute ischemia stroke who had at least one failed MT.

Insufficient sample size and repeated significance testing are the major threats to the generation of robust results in meta-analyses. Trial sequential analysis (TSA), a statistical analysis method analog to interim analyses in randomized controlled trials, is believed to have better control over type-I and type-II errors in a meta-analysis (13). In addition, the TSA analysis can estimate the needed sample size in a meta-analysis for a pre-specified effect size (14).

Based on the grounds, we performed a systematic review with meta-analysis and TSA, aiming to examine whether rescue stenting after the failure of MT improves the outcomes in patients with acute ischemic stroke.

Methods

A systematic review with meta-analysis was conducted to examine the effectiveness of rescue stenting after mechanical thrombectomy for acute ischemia stroke, which was conducted according to PRISMA (15). We acquired summary-level data from published literature, and ethical approvals were acquired in each original study.

Literature search

We searched Ovid Medline, Embase, and the Cochrane Controlled Register of Trials (CENTRAL) from inception to 15 June 2022, setting no language restriction during the literature search. We searched the databases with the search strategies combining the following keywords: stroke, middle cerebral artery, thrombectomy, endovascular, clot retrieval, rescue stenting, and angioplasty. We read the reference lists of the previously published systematic reviews and meta-analyses, to check whether studies were missing from the literature search. We searched the website of the American Academy of Neurological Surgery (https://americanacademyns.org/), the European Association of Neurosurgical Societies (https://www.eans.org), and the American Association of Neurological Surgeons (https://www.aans.org/) for meeting abstracts and conference posters that reported studies of interest.

Study screening

The inclusion criteria of this meta-analysis included: (1) participants with ischemia stroke who had at least one attempt of MT but failed [defined as modified Thrombolysis in Cerebral Infarction (mTICI) score $\leq$ 2b]; (2) participant's age $>$ 18 years; (3) participants received rescue stenting after failed MT, and the type of stents and stenting procedure were not limited; (4) observational studies (case series, cohort studies) and experimental design (randomized controlled trials) were all included; (5) the control group being no rescue stenting or normal medical care; (6) studies that reported any of the following outcomes: recanalization rate, Modified Rankin Scale (mRS), assessment of symptomatic intracranial hemorrhage (sICH), and mortality rate.

The exclusion criteria included: (1) studies that recruited $<$5 participants in the rescue stenting arm; (2) studies that reported the outcomes but with missing and insufficient data for analysis; (3) studies that were reported in the form of conference abstracts, research letters, or news reports.

The study screening was performed by one reviewer, and the results were checked and confirmed by another reviewer. The titles and abstracts of the retrieved articles were first screened, and the remained articles of interest were further searched for full-text copies. Disagreements in the study selection between the two reviewers were arbitrated by a third reviewer.

Outcome measurements

The outcome measurements included recanalization rate, mRS score, sICH rate, and 90-day mortality. The recanalization rate was normally reported for the rescue stenting arm but not for the non-stenting arm, so our primary outcome was an mRS score from 0 to 2, a score range that is conventionally recognized as achieving a good outcome following stroke (16). The mRS is an ordinal scale

that ranges from 0 (no symptoms at all) to 6 (death), and the score of 1 indicates no significant disability despite symptoms while the score of 2 indicates slight disability but able to look after own affairs without assistance (17). The sICH was considered the potentially harmful effect of stenting treatment, especially in the circumstance that antiplatelet medications should be used after the stenting procedure. We, therefore, assessed this outcome to evaluate the safety of rescue stenting. Previous studies demonstrated a decrease in 90-day mortality in patients receiving rescue stenting, so we assessed it as an efficacy outcome.

Data extraction

Standardized forms, designed and entered through Excel software (Excel 2016), were used to extract data from the included studies. Two reviewers independently extracted the following information: the name of the first author, year of publication, the country where the studies were conducted, the total number of participants, study design, the use of propensity score matching analysis (yes or no), the type of control group, mean age, the proportion of participants using intravenous tPA, the proportion of participants with middle cerebral artery (MCA) occlusion, the type of rescue stenting, and the assessed outcomes. The reviewers also extracted outcome parameters (i.e., means, standard deviations, events, number of participants in the stenting or non-stenting arm) from the included studies, and they tried to contact the authors when the data needed for meta-analysis were not reported in the articles. A third reviewer checked and validated the extracted data, and passed the cleared data to a statistician.

Assessment of study quality

The quality of the included studies was assessed by using the Newcastle-Ottawa Scale (NOS), which assesses the quality of study design in three domains: the selection of cohorts, the comparability between cohorts, and the assessed outcomes. Possible total points are four points for selection, two points for comparability, and three points for outcomes. A higher score on the NOS scale indicates a better study quality.

Statistical analysis

We reviewed and summarized the recanalization rate of rescue stenting after mechanical thrombectomy for acute stroke. Owing to the lack of controls for this outcome, we performed a single-proportions meta-analysis to pool the proportions of recanalization reported in the included studies. This meta-analysis was performed with the use of the inverse-variance weighted method (18), and the generalized linear mixed model was adopted for analysis to test the robustness of the findings.

For the outcome of 90-day mRS (0–2), sICH, and 90-day mortality, we first calculated the odds ratio (OR) of rescue stenting vs. non-stenting in these outcomes, and we secondly pooled the ORs using a fixed-effect model when the I^2 value was under 50%. The 95% confidence intervals (95% CIs) of the pooled effect sizes were estimated, and the p-values of the comparisons were also provided. The heterogeneity of the meta-analysis was estimated by using the Cochran Q-test, and the degree of the heterogeneity was estimated by using the I^2 value—with a cut-off point of 50% to determine whether there was significant heterogeneity. The meta-analysis was conducted in the R environment (R 4.0.1, meta package).

We performed a TSA analysis on the outcome of 90-day mRS, since it is the most commonly used measurement for the functional outcome of patients with stroke. The TSA analysis investigates the type-I error in the aggregated result of the meta-analysis—repeated significance testing increases the risk of type-I error. We re-adjusted the significance level by using the O'Brien-Flemming α-spending function, and the type-I error was controlled at the level of 0.05 while the type-II error was controlled at 0.2. We plotted the cumulative Z-curve of the meta-analysis to define sequential boundaries to infer the levels of type-I and type-II errors, calculate the required information size (RIS), and determine whether further trials in the field is needed—when the total sample size of recruited participants exceeds the RIS, further studies are not required. The TSA analysis was conducted by using the TSA software (V. 0.9.5.10).

Results

Study characteristics

We retrieved 3,934 records from the three databases: 1,587 from Medline, 1,988 from Embase, and 359 from CENTRAL. A total of 15 studies were finally included (10–12, 19–30). Before the full-text screening, we excluded 1,634 duplicates, 1,288 records because of reviews, abstracts only, or conference papers without detailed information, 527 records that reported the effect of mechanical thrombectomy, and 368 records that were not relevant to stenting treatment. One hundred and seventeen records were sought for retrieval, and 15 of them were unavailable for full-text copies. In the full-text assessment, 13 records were excluded for a sample size <5, 28 records for reviews, 36 records for mechanism studies, and 10 records for meta-analysis, with no available data or no intended outcomes. The process and flowchart of screening were shown in the Supplementary Figure 1.

The included 15 studies recruited 1,595 participants, and these studies were published from the year 2015–2022. Six of the studies were from South Korea, three from China, two from the USA, two from Italy, and the rest two from Spain and Sweden. The study with the largest sample size was from the USA, recruiting 499 participants. Five studies adopted a prospective design, and one of the five studies adopted a multicenter design; the rest 10 studies were with retrospective design. Seven studies had non-stenting arms as the control group. The mean age of the participants ranged from 61.4 to 70.1 years. All the studies assessed the mRS score and used the score of 0–2 as the indicator of a good outcome. The other information, the proportion of patients who used intravenous tPA, the proportion of patients with middle artery occlusion, and the assessed outcomes were shown in Table 1. Eight studies were rated six points by using the NOS scale, three were rated seven points, two were rated eight points, and the rest two were rated nine points.

TABLE 1 Characteristics of the included trials.

References	Country	Sample size	Study design	Propensity score matching	Control group	Mean age	IV tPA (%)	MCA occlusion	Rescue stenting type	Assessed outcomes	Nos score
Kasab et al. (19)	USA	36	Retrospective single-center cohort study	No	No	66.4 (14.1)	NA	NA	Wingspan, Precise, Enterprise	Recanalization rate (mTICI 2b-3); revascularization time; mean procedural time; mRS; postprocedural complications	6
Baek et al. (20)	South Korea	45	Retrospective single-center cohort study	No	Non-stenting	70.1 (11.1)	31.1	55.6	Solitaire AB/FR, Wingspan	Recanalization rate (mTICI 2b-3); mRS; cerebral herniation rate; sICH; mortality rate	7
Baracchini et al. (21)	Italy	109	Prospective single-center cohort study	No	Non-stenting	65 (15.3)	NA	80.4	Solitaire AB	Recanalization rate (mTICI 2b-3); mRS; sICH; mortality rate	7
Chang et al. (22)	South Korea	148	Retrospective multicener-center cohort study	No	Non-stenting	66.6 (13.7)	49.5	63.5	Solitaire AB, Wingspan, Enterprise, balloon expandable	Recanalization rate; mRS; sICH; mortality rate	8
Cornelissen et al. (23)	Sweden	26	Retrospective single-center cohort study	No	Non-stenting	67.3 (9.5)	34.6	NA	Enterprise, Solitaire	mRS; mortality rate	7
Delgado Acosta et al. (24)	Spain	42	Retrospective single-center cohort study	No	No	61 (53–72)	NA	NA	Enterprise	Recanalization rate; mRS; sICH; mortality rate	6
Kim et al. (25)	South Korea	46	Retrospective single-center cohort study	No	No	66 (58–75)	47.1	56.5	Wingspan	Recanalization rate; mRS; sICH; mortality rate	6
Nappini et al. (26)	Italy	17	Retrospective single-center cohort study	No	No	62 (37–80)	47	41.1	Solitaire AB	Recanalization rate; mRS; sICH; mortality rate	6
Peng et al. (10)	China	132	Retrospective multicenter case-control study	Yes	Non-stenting	66 (55–76)	31.8	NA	Solitaire, Stryker	Recanalization rate; mRS; sICH; mortality rate	9
Seo et al. (27)	South Korea	10	Prospective single-center cohort study	No	No	62.5 (11.3)	10	40	Wingspan	Recanalization rate; mRS	6
Woo et al. (28)	South Korea	27	Retrospective single-center cohort study	No	No	NA	NA	NA	Solitaire FR	Recanalization rate; mRS; sICH; mortality rate	6
Yoon et al. (29)	South Korea	172	Retrospective single-center cohort study	No	No	69.1 (9.5)	50.6	58.7	Wingspan	Recanalization rate; mRS; sICH; mortality rate	6
Zhou et al. (30)	China	193	Prospective single-center cohort study	No	No	63 (12.1)	23.3	NA	Solitaire, Apollo, Enterprise, Wingspan, Neuroform	Recanalization rate; time from groin puncture to recanalization; mRS; sICH; mortality rate	6
Luo et al. (11)	China	93	Prospective single-center cohort study	No	Non-stenting	61.4 (12)	17.2	NA	NA	Recanalization rate; mRS; sICH; mortality rate	8
Mohammaden et al. (12)	USA	499	Prospective multicenter case-control study	Yes	Non-stenting	65.2 (14.9)	29	67.3		mRS; sICH; mortality rate	9

mRS, modified Rankin Scale; NOS, Newcastle-Ottawa scale; sICH, symptomatic intracranial hemorrhage.

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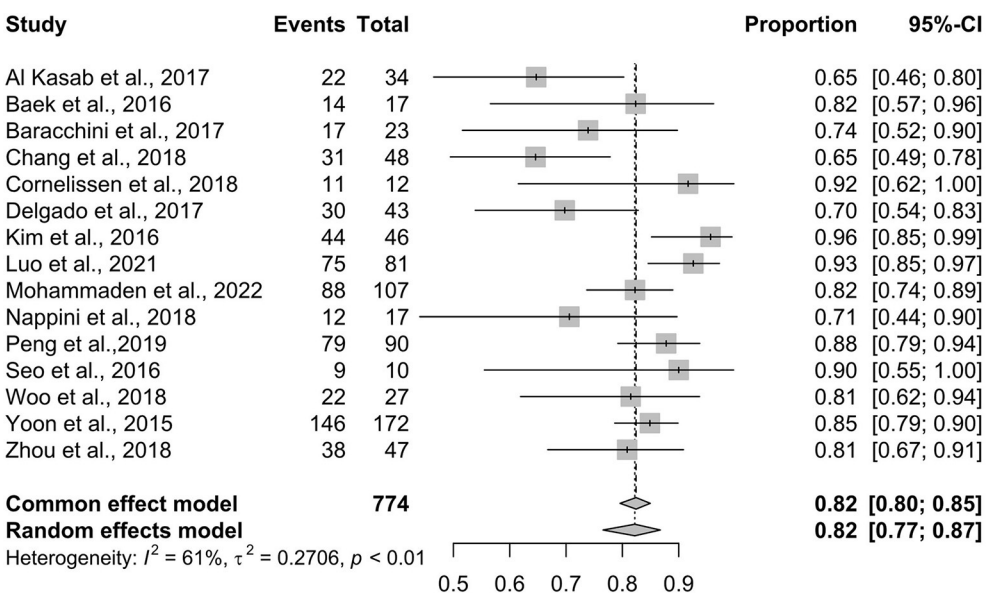


FIGURE 1
Recanalization rate.

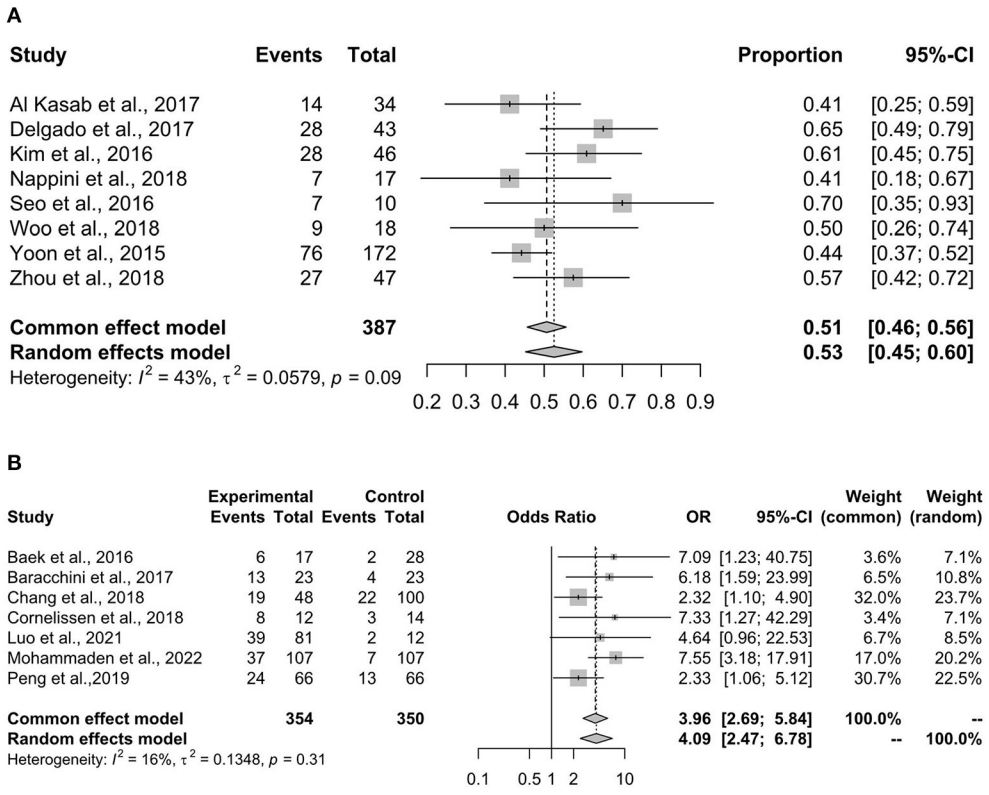


FIGURE 2
The mRS score assessment. The mRS score of 0–2 indicates a good outcome of patients with ischemia stroke. **(A)** Summarizes the proportion of patients with 0–2 mRS scores, using data from cohorts without control groups. **(B)** Shows the comparison of stenting vs. non-stenting in the proportion of patients with 0–2 mRS score, and a higher OR indicates a better result of the stenting arm. mRS, modified Rankin Scale; OR, odds ratio.

Recanalization rate

Figure 1 shows the pooled result of the recanalization rate. Fifteen studies recruiting 774 participants were included, and the results showed a recanalization rate of 82% (95% CI 77–87%). A large and significant heterogeneity was noticed in the analysis ($I^2 = 61\%$, $p < 0.01$); the lowest recanalization rate was 65% (19) while the highest rate was 96% (25).

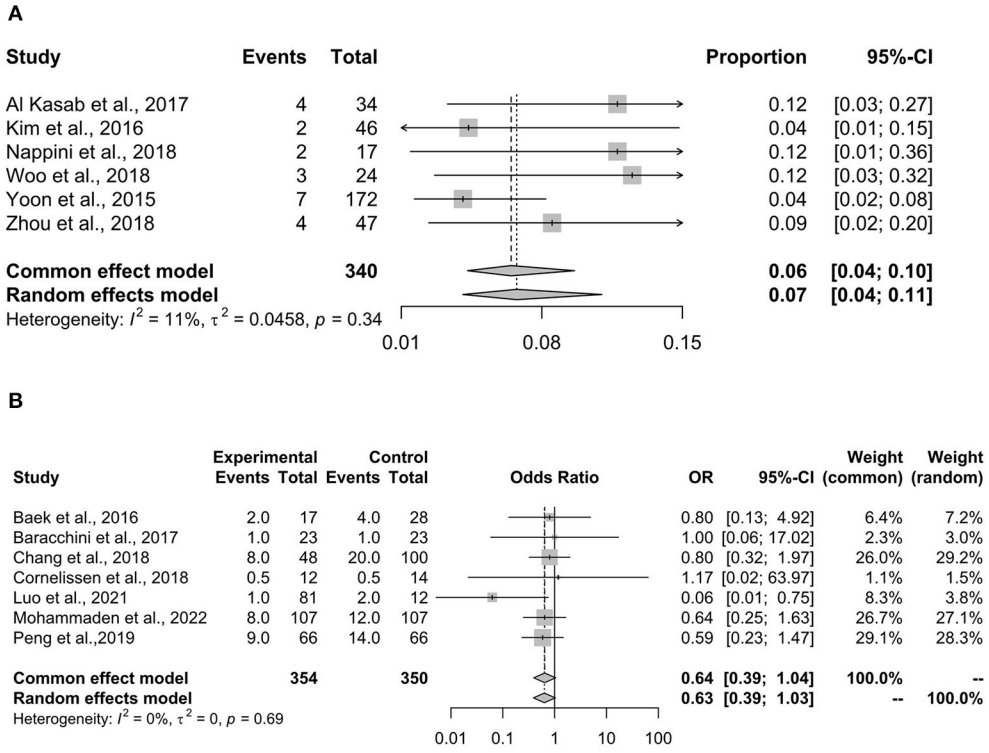


FIGURE 3
The proportion of patients with sICH. sICH, symptomatic intracranial hemorrhage. sICH is a negative outcome for patients receiving rescue stenting. **(A)** Summarizes the proportion of patients developing sICH after receiving stenting. **(B)** Shows the comparison of stenting with non-stenting in the proportion of patients developing sICH, and a lower OR indicates a better result for the stenting arm. OR, odds ratio.

90-days mRS

Figure 2A shows the pooled result of the proportion of patients with 0–2 mRS scores, which indicates a good outcome. The fixed-effects model estimated a proportion of 51% (95% CI 46–56%) of the participants with 0–2 mRS. The heterogeneity was small and insignificant in this analysis ($I^2 = 43\%$, $p = 0.09$).

Figure 2B shows the comparison of rescue stenting vs. non-stenting in achieving the outcome of 0–2 mRS. The results showed that stenting had a significantly higher success rate in achieving 0–2 mRS (OR 3.96, 95% CI 2.69–5.84, $p < 0.001$), and the fixed-effect model was consistent with the random-effect model. A small and insignificant heterogeneity was noted in the analysis ($I^2 = 16\%$, $p = 0.31$).

sICH

Figure 3A shows the synthesized result of the proportion of patients who developed sICH after rescue stenting. The result showed that the incidence of sICH was 6% (95% CI 4–11%). The results were consistent between the fixed-effects model and the random-effects model. The heterogeneity in this analysis was small ($I^2 = 11\%$) and insignificant ($p = 0.34$).

Figure 3B shows the comparison of stenting vs. non-stenting in the proportion of patients with sICH. The results showed that stenting had a lower but not statistically significant proportion of sICH compared with non-stenting (OR 0.63, 95% CI 0.39–1.04, $p = 0.075$). The fixed-effects and random-effects models showed consistent results. No heterogeneity was detected in this analysis ($I^2 = 0\%$, $p = 0.69$).

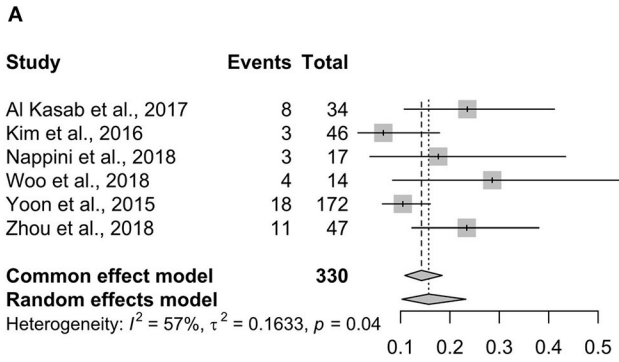
90-days mortality

Figure 4A shows the pooled result of the 90-day mortality rate, which showed a synthesized mortality rate of 16% (95% CI 10–23%). The heterogeneity was large and significant ($I^2 = 57\%$, $p = 0.04$), so the result of the random-effects model was adopted.

Figure 4B shows the comparison of stenting vs. non-stenting in the 90-day mortality rate, which showed that stenting was associated with a significantly lower mortality rate when compared with non-stenting (OR 0.46, 95% CI 0.32–0.65, $p < 0.001$). A small and insignificant heterogeneity was found in the analysis ($I^2 = 25\%$, $p = 0.24$).

TSA analysis

Figure 5 shows the result of TSA analysis on the comparison of stenting vs. non-stenting in the outcome of achieving a 0–2 mRS score. Considering a 50% rate of 0–2 mRS score in the stenting arm and a 35% rate in the non-stenting arm—resulting in a ratio difference of 15%, a type-I error of 0.05, and a type-II error of 0.2, the required information size would be 442 participants. The sample size of our meta-analysis was 704 participants, which exceeds the required



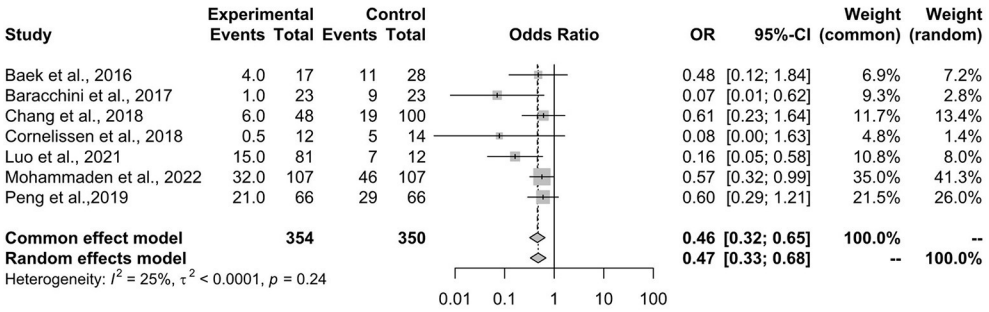


FIGURE 4
90-day mortality. 90-day mortality is a negative outcome for patients receiving rescue stenting. **(A)** Summarizes the proportion of 90-day mortality. **(B)** Shows the comparison of stenting with non-stenting in the proportion of 90-day mortality, and a lower OR indicates a better result for the stenting arm. OR, odds ratio.

information size. Figure 5 also shows that the difference between stenting and non-stenting in the proportion of 0–2 mRS score was evident since the cumulative *Z* curve had crossed conventional boundaries—the result was in favor of the stenting arm.

Discussion

Whether rescue stenting should be recommended for patients with acute stroke having a failed mechanical thrombectomy is still controversial. We performed a systematic review to evaluate current evidence and a meta-analysis incorporating TSA analysis to examine the benefit of rescue stenting and estimate whether the primary result has a sufficient sample size. First, we found that stenting had a high recanalization rate and was beneficial for patients after the failure of mechanical thrombectomy. The pooled recanalization rate of stenting was 82%; the proportion of patients with a 0–2 mRS score was 51% after receiving stenting, and patients receiving stenting had a significantly higher rate of achieving a 0–2 mRS score—indicating a good outcome of functional capability. The other outcomes—sICH rate and 90-day mortality rate—supported the use of stenting, which was associated with a significantly lower 90-day mortality but did not cause a higher rate of sICH. Second, we confirmed that current evidence is of sufficient power to detect a 15% difference in the proportion of patients achieving a 0–2 mRS score. This finding indicated that the advantage of stenting is confirmed when compared with non-stenting, since the ratio difference in achieving a 0–2 mRS score between stenting and non-stenting exceeded 15% (a pooled OR of 3.96 and an estimated ratio difference of 31% in our meta-analysis). To the best of knowledge, our study was the first to adopt the TSA analysis to confirm whether rescue intracranial stenting was effective for acute ischemic stroke after the failure of MT.

The results of our meta-analysis were consistent with the previously published systematic reviews with meta-analysis (6–9). These systematic reviews concluded that rescue stenting might be an effective treatment for patients who had failed MT procedures. However, all these reviews mentioned the same limitations—the small sample sizes and the observational design of the included studies. After the publication of these reviews, two studies with larger sample size and with a matched-analysis design to balance the baseline characteristics were published (10, 12). One study published in 2022 had the largest sample size on this topic (12), and it adopted a propensity score matching analysis—leading to more balanced baseline parameters in the stenting and non-stenting arms, which provided more accurate estimates than previous studies. We therefore performed a TSA analysis, which had not been studied in previous systematic reviews, to clarify whether current evidence had a sufficient sample size and statistical power. The TSA model was developed to address statistical problems that arise with multiplicity due to repeated significance testing (31). One study reported that a cumulative chance of a type-I error became 8, 14, 25, and 37% when the statistical hypothesis was repeatedly tested for two, five, twenty, and 100, respectively (13). In that case, our meta-analysis would have the risk of type-I error increasing to at least 14% if we did not perform a TSA to confirm the main findings. Our TSA analysis showed that, for the proportion of patients achieving a 0–2 mRS score, the results of the meta-analysis had a sufficient sample size and statistical power

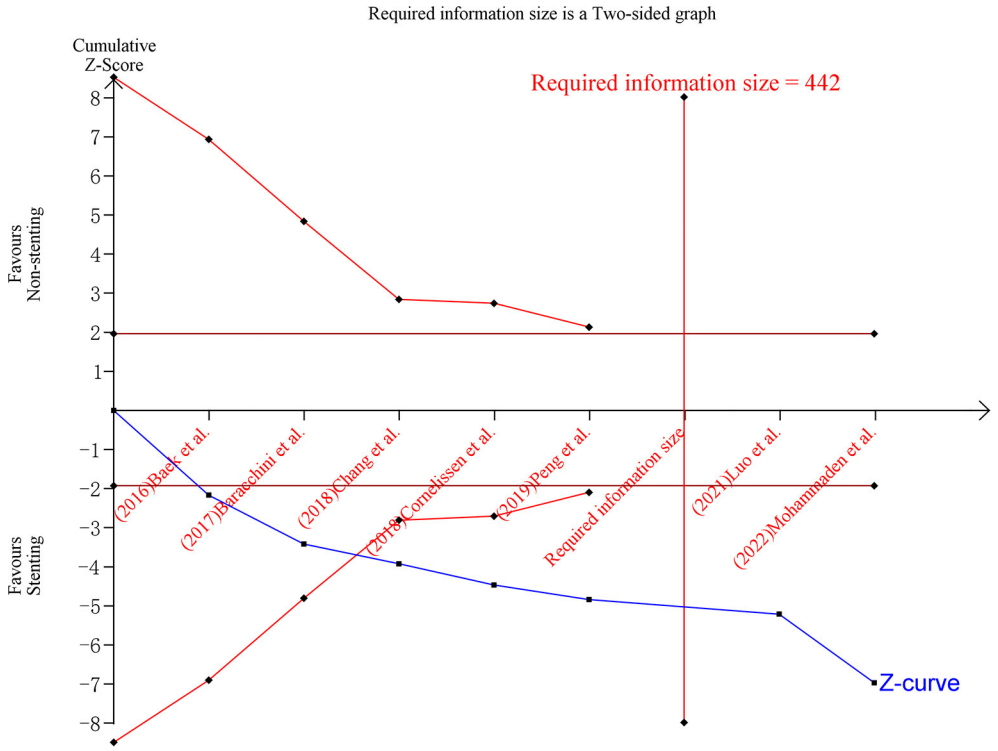


FIGURE 5
TSA analysis on the mRS score. mRS score of 0–2 is a positive outcome for patients receiving rescue stenting. The *x*-axis ticks refer to the studies added sequentially into the analysis. The blue curve was the adjusted *Z*-curve, and it crossed the dark-red horizontal line (conventional boundary for $\alpha = 0.05$). The vertical red line shows the required information size—the needed sample size for a robust result with sufficient statistical power. The analysis included 704 participants, which exceed the required information size ($n = 442$). mRS, modified Rankin Scale; TSA, trial sequential analysis.

(80%) to reject a null hypothesis at the level of 0.05, which confirmed the robustness of results.

Several adjunct options for failed MT were proposed, including antiplatelet glycoprotein IIb/IIIa inhibitors, intracranial angioplasty, and rescue stenting (5). Glycoprotein IIb/IIIa inhibitors were normally used as adjunctive salvage interventions for early vessel reocclusion. However, it was not recommended in the management of acute ischemia stroke, since it was associated with a significant risk of intracranial hemorrhage with no evidence of any reduction in death or disability in survivors (32). Intracranial angioplasty, performed with the expansion of a balloon, was normally followed by stenting to prevent vessel reocclusion after reperfusion was achieved. Intracranial angioplasty with stenting was more frequently selected than glycoprotein IIb/IIIa inhibitors alone, according to a north American cohort (5).

The rescue stenting requires antiplatelet medications to prevent in-stent thrombosis and vessel reocclusion. Antiplatelet medications may increase the probability of sICH, especially in patients with large infarct volumes. Our meta-analysis showed that stenting did not increase the risk of sICH when compared with non-stenting (OR 0.63, 95% CI 0.39–1.04). The finding was consistent with previous systematic reviews (7, 9) and a recent large-scale cohort (12). This finding should be further confirmed in randomized controlled trials, since participants who chose non-stenting treatments might be at higher risk of intracranial hemorrhage—for example, they might choose a higher dose of antiplatelet medication to manage reocclusion or deterioration of stenosis, which might lead to a higher risk of intracranial hemorrhage.

Our study had limitations. First, the observational design of the included studies would be affected by confounding factors. Although the recent large-scale matched analysis provided a more robust estimation of the effect of rescue stenting for this condition, the results were still under the risk of confounding bias. The matched analysis, normally propensity score matching analysis, could only adjust for known and measured factors. Randomized controlled trials are still the best solution for unmeasured factors that might cause bias in estimation. Second, the follow-up period is short. In most studies, the mRS score and mortality rate were only assessed for 90 days. In future studies, a follow-up period longer than 1 year might provide essential information for patients and clinicians in making their decision on whether permanent stenting should be preferred. Third, owing to the limited number of the includes studies and limited baseline information, we did not conduct subgroup analysis concerning region, study design or tPA factors.

In conclusion, our meta-analysis showed that rescue stenting was effective and safe for patients with ischemia stroke who also had a failed MT, and this result was confirmed in a TSA analysis—showing that the analysis had a sufficient sample size and statistical power for the mRS outcome.

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

LW and JD proposed the conception and designed the protocol and critically reviewed or revised the manuscript for important intellectual content. JC and HX managed the study, acquired data, interpreted the results, and drafted the manuscript. RX and LH managed the study and performed the statistical analyses. PX, XG, YX, MP, JT, QG, YL, and RS supervised the data analysis, provided the interpretation of results, and contributed to the drafting and critical review of the manuscript. All authors approved the final draft.

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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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1023089/full#supplementary-material

References

1. Katan M, Luft A. Global burden of stroke. *Semin Neurol.* (2018) 38:208–11. doi: 10.1055/s-0038-1649503

2. Uniken Venema SM, Dankbaar JW, van der Lugt A, Dippel DWJ, van der Worp HB. Cerebral collateral circulation in the era of reperfusion therapies for acute ischemic stroke. *Stroke.* (2022). doi: 10.1161/STROKEAHA.121.037869

3. Derex L, Cho TH. Mechanical thrombectomy in acute ischemic stroke. *Rev Neurol.* (2017) 173:106–13. doi: 10.1016/j.neurol.2016.06.008

4. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X

5. Abdalla RN, Cantrell DR, Shaibani A, Hurley MC, Jahromi BS, Potts MB, et al. Refractory stroke thrombectomy: prevalence, etiology, and adjunctive treatment in a north american cohort. *Am J Neuroradiol.* (2021) 42:1258–63. doi: 10.3174/ajnr.A7124

6. Wareham J, Flood R, Phan K, Crossley R, Mortimer A. A systematic review and meta-analysis of observational evidence for the use of bailout self-expandable stents following failed anterior circulation stroke thrombectomy. *J Neurointerv Surg.* (2019) 11:675–82. doi: 10.1136/neurintsurg-2018-014459

7. Maingard J, Phan K, Lamanna A, Kok HK, Barras CD, Russell J, et al. Rescue intracranial stenting after failed mechanical thrombectomy for acute ischemic stroke: a systematic review and meta-analysis. *World Neurosurg.* (2019) 132:e235–45. doi: 10.1016/j.wneu.2019.08.192

8. Zhang P, Xing Y, Li H, Yao Q, Shen J, Liu Y, et al. Efficacy and safety of rescue angioplasty and/or stenting for acute large artery occlusion with underlying intracranial atherosclerosis: a systematic review and meta-analysis. *Clin Neurol Neurosurg.* (2021) 203:106538. doi: 10.1016/j.clineuro.2021.106538

9. Premat K, Dechartres A, Lenck S, Shotar E, Bouc RL, Degos V, et al. Rescue stenting versus medical care alone in refractory large vessel occlusions: a systematic review and meta-analysis. *Neuroradiology.* (2020) 62:629–37. doi: 10.1007/s00234-020-02360-9

10. Peng F, Wan J, Liu W, Huang W, Wang L, Qiu T, et al. Efficacy and safety of rescue stenting following failed mechanical thrombectomy for anterior circulation large vessel occlusion: propensity score analysis. *J Neurointerv Surg.* (2020) 12:271–3. doi: 10.1136/neurintsurg-2019-015154

11. Luo G, Gao F, Zhang X, Jia B, Huo X, Liu R, et al. Intracranial stenting as rescue therapy after failure of mechanical thrombectomy for basilar artery occlusion: data from the ANGEL-ACT registry. *Front Neurol.* (2021) 12:739213. doi: 10.3389/fneur.2021.739213

12. Mohammaden MH, Haussen DC, Al-Bayati AR, Hassan A, Tekle W, Fifi J, et al. Stenting and angioplasty in neurothrombectomy: matched analysis of rescue intracranial stenting versus failed thrombectomy. *Stroke.* (2022). doi: 10.1161/STROKEAHA.121.038248

13. Wetterslev J, Jakobsen JC, Gluud C. Trial sequential analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol.* (2017) 17:39. doi: 10.1186/s12874-017-0315-7

14. Shah A, Smith AF. Trial sequential analysis: adding a new dimension to meta-analysis. *Anaesthesia.* (2020) 75:15–20. doi: 10.1111/anae.14705

15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71. doi: 10.1136/bmj.n71

16. Weisscher N, Vermeulen M, Roos YB, de Haan RJ. What should be defined as good outcome in stroke trials; a modified Rankin score of 0-1 or 0-2? *J Neurol.* (2008) 255:867–74. doi: 10.1007/s00415-008-0796-8

17. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke.* (2007) 38:1091–6. doi: 10.1161/01.STR.0000258355.23810.c6

18. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edn.* Chichester: John Wiley & Sons (2019).

19. Kasab SA, Almadidy Z, Spiotta AM, Turk AS, Chaudry MI, Hungerford JP, et al. Endovascular treatment for AIS with underlying ICAD. *J Neurointerv Surg.* (2017) 9:948–51. doi: 10.1136/neurintsurg-2016-012529

20. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Yoo J. Stenting as a rescue treatment after failure of mechanical thrombectomy for anterior circulation large artery occlusion. *Stroke.* (2016) 47:2360–3. doi: 10.1161/STROKEAHA.116.014073

21. Baracchini C, Farina F, Soso M, Viaro F, Favaretto S, Palmieri A, et al. Stentriever thrombectomy failure: a challenge in stroke management. *World Neurosurg.* (2017) 103:57–64. doi: 10.1016/j.wneu.2017.03.070

22. Chang Y, Kim BM, Bang OY, Baek J-H, Heo JH, Nam HS, et al. Rescue stenting for failed mechanical thrombectomy in acute ischemic stroke: a multicenter experience. *Stroke.* (2018) 49:958–64. doi: 10.1161/STROKEAHA.117.020072

23. Cornelissen SA, Andersson T, Holmberg A, Brouwer PA, Söderman M, Bhogal P, et al. Intracranial stenting after failure of thrombectomy with the emboTrap® device. *Clin Neuroradiol.* (2019) 29:677–83. doi: 10.1007/s00062-018-0697-x

24. Delgado Acosta F, Jiménez Gómez E, Bravo Rey I, Bravo Rodríguez FA, Ochoa Sepúlveda JJ, Oteros Fernández R. Intracranial stents in the endovascular treatment of acute ischemic stroke. *Radiologia.* (2017) 59:218–25. doi: 10.1016/j.rxeng.2017.01.001

25. Kim GE, Yoon W, Kim SK, Kim BC, Heo TW, Baek BH, et al. Incidence and clinical significance of acute reocclusion after emergent angioplasty or stenting for underlying intracranial stenosis in patients with acute stroke. *Am J Neuroradiol.* (2016) 37:1690–5. doi: 10.3174/ajnr.A4770

26. Nappini S, Limbucci N, Leone G, Rosi A, Renieri L, Consoli A, et al. Bail-out intracranial stenting with Solitaire AB device after unsuccessful thrombectomy in acute ischemic stroke of anterior circulation. *J Neuroradiol.* (2019) 46:141–7. doi: 10.1016/j.neurad.2018.05.004

27. Seo WK, Oh K, Suh SI, Seol HY. Intracranial stenting as a rescue therapy in patients with stroke-in-evolution. *J Stroke Cerebrovasc Dis.* (2016) 25:1411–6. doi: 10.1016/j.jstrokecerebrovasdis.2016.01.054

28. Woo HG, Sunwoo L, Jung C, Kim BJ, Han M-K, Bae H-J, et al. Feasibility of permanent stenting with solitaire FR as a rescue treatment for the reperfusion of acute intracranial artery occlusion. *Am J Neuroradiol.* (2018) 39:331–6. doi: 10.3174/ajnr.A5477

29. Yoon W, Kim SK, Park MS, Kim BC, Kang HK. Endovascular treatment and the outcomes of atherosclerotic intracranial stenosis in patients with hyperacute stroke. *Neurosurgery*. (2015) 76:680–6; discussion 686. doi: 10.1227/NEU.0000000000000694

30. Zhou T, Li T, Zhu L, Wang M, He Y, Shao Q, et al. Intracranial stenting as a rescue therapy for acute ischemic stroke after stentriever thrombectomy failure. *World Neurosurg.* (2018) 120:e181–7. doi: 10.1016/j.wneu.2018.08.002

31. Clephas PRD, Kranke P, Heesen M. How to perform and write a trial sequential analysis. *Anaesthesia.* (2022). doi: 10.1111/anae.15811. [Epub ahead of print].

32. Ciccone A, Motto C, Abraha I, Cozzolino F, Santilli I. Glycoprotein IIb-IIIa inhibitors for acute ischaemic stroke. *Cochr Database Syst Rev*. (2014) CD005208. doi: 10.1002/14651858.CD005208.pub3

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Selection of patients with acute vertebrobasilar artery occlusion for endovascular treatment by magnetic resonance imaging

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Background and purpose: The best method for selecting patients with acute vertebrobasilar artery occlusion (VBAO) who would benefit from endovascular treatment (EVT) is still the key question. This study aimed to assess the efficacy of magnetic resonance imaging (MRI) for selecting patients with acute VBAO for EVT.

Materials and methods: A total of 14 patients with suspected acute VBAO on MR angiography (MRA) in the EVT database (from April 2016 to August 2019) were enrolled. Acute Stroke Prognosis Early Computed Tomography Score (ASPECTS) and pons–midbrain index were assessed on diffusion-weighted imaging (DWI). EVT included a stent retriever and a rescue treatment (angioplasty and/or stenting). The proportion of successful reperfusion and favorable functional outcomes (modified Rankin Scale ≤3) at 90 days was documented.

Results: A total of 11 patients were included in the final analysis. The median DWI-ASPECTS and pons–midbrain index were 7 and 2, respectively. Underlying stenosis was detected in 10 of 11 (90.9%) patients. Balloon angioplasty and/or stenting were used as rescue therapy for five patients and two patients, respectively. A total of nine patients (81.8%) achieved successful reperfusion (mTICI, 2b, or 3). The 90-day mRS score of 0–3 was achieved in six (54.5%) patients. The mortality rate within 90 days was 18.2% (two of 11 patients).

Conclusion: DWI plus MRA could help select the patients with acute VBAO for EVT by assessing ASPECTS and the pons–midbrain index. Patients could achieve good reperfusion and favorable functional outcomes.

KEYWORDS

endovascular treatment, ischemic stroke, mechanical thrombectomy, diffusion-weighted imaging (DWI), acute vertebrobasilar artery occlusion

Introduction

Basilar artery occlusion accounts for 5%−10% of all proximal intracranial occlusions and is associated with severe disability and death in up to 80% of patients, despite recent advances in the treatment of acute stroke (1). Recently, multiple randomized trials have shown the benefit of early recanalization with mechanical thrombectomy for treating acute ischemic stroke (AIS) due to large-vessel occlusion in the proximal anterior circulation (2). The result of endovascular treatment (EVT) for vertebrobasilar artery occlusion (VBAO) is still controversial.

Two preceding randomized trials, the Basilar Artery Occlusion Endovascular Intervention vs. Standard Medical Treatment (BEST) trial (3) and Basilar Artery International Cooperation Study (BASICS) trial (4), for comparing EVT vs. best medical management did not demonstrate significant differences in favorable functional outcomes at 90 days between the two groups. However, two recent randomized trials from China, namely, the Basilar Artery Occlusion Chinese Endovascular trial (BAOCHE) (5) and Endovascular Treatment for Acute Basilar Artery Occlusion(ATTENTION) (6), were reported with better functional outcomes and reduced mortality for EVT over best medical therapy alone. The best method for selecting patients with acute VBAO who would benefit from EVT is still the key question.

Imaging with the Acute Stroke Prognosis Early Computed Tomography Score (ASPECTS) was often used to identify patients who were most likely to be benefited from EVT in most trials (7, 8). In addition to ASPECTS, ischemic regions were also related to functional outcomes (9). Patients with acute VBAO could present with various symptoms from dizziness to coma, depending on the degree of involvement of the brainstem (10), even with similar ASPECTS. The pons–midbrain index was used to assess the degree of involvement of the brainstem in some studies (11, 12). Diffusion-weighted imaging (DWI) was regarded as the diagnostic "gold standard" for patients with posterior circulation (pc) stroke (12). Better imaging of the brainstem by DWI could help select a suitable patient for EVT. The combined use of the pc-ASPECTS and pons–midbrain index might help selection for the treatment of acute VBAO for EVT. We report a case series of AIS due to acute VBAO diagnosis with DWI and treated with EVT.

Methods

Patient selection

We reviewed our endovascular treatment (EVT) database (from April 2016 to August 2019) for patients with AIS. All patients signed informed consent before the operation. We included data of consecutive patients with AIS if they fulfilled the following criteria: (1) age 18–85 years; (2) symptoms suggest acute posterior ischemic stroke $\leq$24 h; (3) pre-stroke modified Rankin Scale (mRS) score $\leq$2; (4) baseline NIHSS $\geq$6; (5) an ability to provide informed consent. Patients were excluded from the study in the case of (1) being allergic to iodized contrast medium and unable to complete DSA examination; (2) without MR examination before EVT; (3) having acute cerebral hemorrhage; and (4) pregnancy.

This observational study was approved by the local institutional ethics committees. Demographics, clinical findings, imaging data, and risk factors such as hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking, and atrial fibrillation were noted. After admission, the National Institutes of Health Stroke Scale (NIHSS) score of patients before thrombectomy was evaluated by stroke experts. The NIHSS score of patients with unconscious/coma was 38. The NIHSS score at admission and time information were documented.

Imaging evaluation

Brain computer tomography (CT) scans were acquired for all patients upon hospital admission to exclude intracranial parenchymal hemorrhage or subarachnoid hemorrhage. The MRI modalities included two sequences: DWI and MRA. The ischemic core was assessed on DWI, and the pc-ASPECTS and the pons-midbrain index was calculated on DWI by two independent stroke experts. The site of VBAO was evaluated on MRA and confirmed on digital subtraction angiography (DSA). The degree of VBAO recanalization of patients submitted to endovascular treatment was classified using the modified Thrombolysis in Cerebral Infarction (mTICI) by two experienced neuroradiologists who were blinded to clinical outcome.

Procedures

In this study, patients received intravenous alteplase within 4.5 h or intravenous urokinase within 6 h of stroke symptom onset. EVT was performed under either conscious sedation or general anesthesia according to the clinical condition of each patient.

A stent retriever was the preferred device for thrombectomy. Balloon angioplasty and/or stenting of the vertebral artery or basilar artery was allowed in the case of persistent occlusion or high-grade stenosis after thrombectomy. For patients without prior use of antiplatelet therapy, an antiplatelet loading dose (aspirin 300 mg + clopidogrel 300 mg) was given when the decision to proceed to stent placement was made. The successful reperfusion was defined as an mTICI 2b (50%—99% reperfusion) or 3 (complete reperfusion) at the end of all endovascular procedures. The maximum number of passes for devices was done according to the manufacturer's instructions.

Follow-up and outcome

The primary outcome was the proportion of patients achieving successful post-procedure reperfusion (mTICI 2b-3), and favorable outcomes were defined as mRS score of 0–3 (with 0 meaning no symptoms, 1 able to do all usual activities, 2 able to look after own affairs without assistance but unable to do all previous activities, and 3 requires some help but able to walk unassisted) at 90 days. The secondary endpoints included functional independence (mRS score 0–2) at 90 days, and symptomatic intracranial hemorrhage (defined as evidence of intracranial hemorrhage on brain CT and an increase of 4 or more points on the NIHSS within 24 h).

Statistical analysis

The intraclass correlation coefficient (ICC) with 95% confidence intervals (CIs) was used to assess the intraobserver or interobserver reliability for the evaluation of DWI-ASPECTS and pons–midbrain index. Cohen's k-statistic was computed to assess the observer reproducibility. Continuous variables were presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR). Categorical variables such as male sex, risk factors, and

degree of stenosis were presented as percentages. SPSS 11.5 (SPSS, Inc., Chicago, IL) was used as the statistical analysis software. All reported p-values were two-sided, and p-values < 0.05 were considered significant.

Results

The data of 14 patients with suspected acute VBAO on MRA were reviewed. One patient with suspicious acute VBAO on MRA was finally diagnosed with severe stenosis of the basilar artery by DSA and excluded from this study. In total, 13 patients were finally confirmed as acute VBAO by DSA. Among these patients, two patients without management with EVT were also excluded in the final analysis due to unavailable arterial access to the bilateral vertebral arteries including one patient with chronic occlusion in the bilateral vertebral artery and another patient with chronic occlusion in the right vertebral artery and left vertebral artery hypoplasia. Eleven patients were included in the present analysis. The mean age was 56.9 ± 5.7 years, and eight (72.7%) were male patients. The most common baseline risk factors for stroke included hypertension ($n = 10$, 90.9%), diabetes mellitus ($n = 6$, 54.5%), cigarette smoking ($n = 5$, 45.5%), and atrial fibrillation ($n = 0$). The median initial NIHSS score was 20 (IQR: 8–38). One of 11 (9.1%) patients received intravenous thrombolysis with tPA.

The median DWI-ASPECTS was 7.0 (IQR, 6.0–7.0) with high intraobserver (ICC:0.977, 95% CI: 0.916–0.994) and interobserver agreement (ICC: 0.936, 95% CI: 0.763–0.983). An ischemic stroke involving the brainstem was found in nine patients with the median pons–midbrain index 2 (IQR: 2–3) with high intraobserver (ICC:0.966, 95% CI: 0.875–0.911) and interobserver agreement (ICC: 0.958, 95% CI: 0.843–0.989; Table 1, Figure 1).

Among the 11 patients, the median time from stroke onset to reperfusion was 487.5 min (IQR: 316.3–898.5 min). The median time from a puncture to successful recanalization was 36.5 min (IQR: 18.0–71.8 min). The median procedure time for patients with rescue therapy was 71.0 min (IQR: 55.5–86.5 min), which is longer than the median procedure time for patients without rescue therapy [19.0 min (IQR: 14.5–24.0) min, $p = 0.009$].

A stent retriever (Solitaire AB device) was used for all 11 patients. Underlying intracranial atherosclerosis (ICAS) was detected in 10 of 11 (90.9%) patients, including moderate stenosis in two patients, and severe stenosis in eight patients. Balloon angioplasty and/or stenting were then used as rescue therapy for four patients and two patients, respectively. Among the 11 patients treated with EVT, seven (63.6%) used a stent retriever (Solitaire AB device) alone, two (18.2%) were treated with EVT plus basilar or vertebral artery balloon angioplasty, and two (18.2%) were treated with EVT plus balloon angioplasty and stent (Table 1).

A total of ten patients (90.9%) achieved successful reperfusion (mTICI, 2b or 3). One patient did not achieve successful reperfusion (mTICI, 0) after multiple thrombectomy. The 90-day mRS score of 0–2 and 0–3 was achieved in four (36.4%) patients and six (54.5%) patients, respectively. The mortality rate within 90 days was 18.2% (two of 11 patients). Intracranial parenchymal hemorrhage and subarachnoid hemorrhage were found in one patient (9.1%) and two patients (18.2%), respectively.

Discussion

This study showed that MRI with DWI and MRA could identify the occluded intracranial arteries and assess the ischemic size (ASPECTS) and regions (pons–midbrain index) for the patients with suspicious acute VBAO. Mechanical thrombectomy with a stent retriever plus rescue therapy (balloon angioplasty and/or stenting), when necessary, could quickly and effectively restore blood flow to the brain and improve the prognosis of patients with acute VBAO in the real world.

Previous studies showed ischemic core volume was independently associated with functional independence (13, 14). The optimal imaging methods for selecting patients who might benefit from EVT in acute ischemic stroke included CTP and DWI (15, 16). RAPID software could be used to assess the ischemic core in some large studies (7, 16) but might be unavailable in many hospitals due to its high price. ASPECTS was correlated with ischemic core volume and is often used for assessing the ischemic core in the real world (7, 15, 16). DWI was more sensitive than CT for detecting acute ischemic stroke (17). The pc-ASPECTS and pons–midbrain index could be evaluated on DWI with high intraobserver and interobserver agreement, which could help in the selection of suitable patients for EVT.

The stroke causative mechanism included ICAS, cardioembolism, and other or unknown reasons (17). ICAS-related occlusions were reported more frequently in the Asian population than in the Western population (3, 5, 6, 18), with unique risk factors. In the study, atherosclerotic risk factors were more frequently detected than atrial fibrillation ($n = 0$). The preoperative diagnosis of ICAS-related occlusion was still difficult with current imaging modalities. Residual stenosis of 50% or more after initial thrombectomy, or intraprocedural restenosis or reocclusion in the procedure was regarded as accepted diagnostic criteria of underlying ICAS-related occlusion (19, 20). Furthermore, the prevalence of ICAS-related vertebrobasilar occlusion was higher compared with anterior circulation, especially in Chinese patients (BEST, 52%; ANGEL-ACT Registry, 51%) (3, 18). In this study, underlying severe and moderate vertebrobasilar stenosis was found in eight (72.7%) and two (18.2%) of the 11 patients, respectively.

A stent retriever is recommended as the first-line device for mechanical thrombectomy. However, for the patients with IACS-related occlusion, good reperfusion might fail to be achieved by a stent retriever alone, possibly because of new thrombus formation induced by intimal injury from the passage of the stent retriever. The stent retriever could damage the plaque surface, resulting in increased platelet activation and thrombus formation, even reocclusion. Angioplasty and/or stenting have been considered as a rescue treatment for ICAS-related occlusions refractory to thrombectomy (18–21). In this study, four of eight patients with underlying severe stenosis could not achieve satisfactory reperfusion after initial stent retriever thrombectomy and received angioplasty and/or stenting.

In this study, the time from onset to reperfusion and the time from door to reperfusion were slightly longer than in the previous studies. The following reasons could help explain the findings. The procedure time would be longer for the patients with rescue therapy than for the patients without rescue therapy. A meta-analysis of studies of thrombectomy for ICAS-related occlusions showed

TABLE 1 Procedural-associated characteristics of the patients.

Patient no.	Occlusion site	Underlying site of stenosis	DWI-regions	DWI-aspects	Pons-midbrain-index	Pretreatment NIHSS	Onset-to-reperfusion time (min)	Treatment with IVT	Endovascular treatment	mTICI	mRS on 90-days
1	BA	50%	L-pon, R-cerebellum	7	2	8	363	No	Solitaire	2b	0
2	BA	78%	B-pon, R-cerebellum	7	2	7	1074	No	Solitaire + angioplasty + apollo stent	3	0
3	BA	—	B-pon, L-midbrain	6	4	8		No	Solitaire	0	6
4	BA	80%	R-pon, R-cerebellum	7	3	12	328	No	Solitaire	2b	1
5	BA	80%	B-pon, R-occipital lobe	7	4	38	1226	No	2Solitaire + angioplasty	2b	4
6	Left V + BA	70%	B-pon, B-cerebellum	6	2	38	840	No	Solitaire + angioplasty	2a	6
7	BA	70%	L-pon, R-PCA territory	7	2	11	218	No	Solitaire	2b	3
8	Left V4 + BA	70%	R-pon, L-ganglion, B-cerebellum, B-PCA territory	3	2	20	509	No	Solitaire	2b	3
9	BA	75%	B-pon, B-cerebellum, L-PCA territory	5	3	20	804	No	Solitaire + angioplasty + stent	2b	5
10	BA	80%	L-ganglion, R-cerebellum, R-PCA territory	7	0	38	281	No	Solitaire	3	5
11	Right V4	50%	L-ganglion, L-cerebellum, L-PCA territory	7	0	24	466	Yes	Solitaire	3	2

BA, basilar artery; DWI, diffusion-weighted imaging; ASPECTS, Acute Stroke Prognosis Early Computed Tomography Score; NIHSS, National Institutes of Health Stroke Scale; mTICI, modified Thrombolysis in Cerebral Infarction; mRS, modified Rankin Scale.

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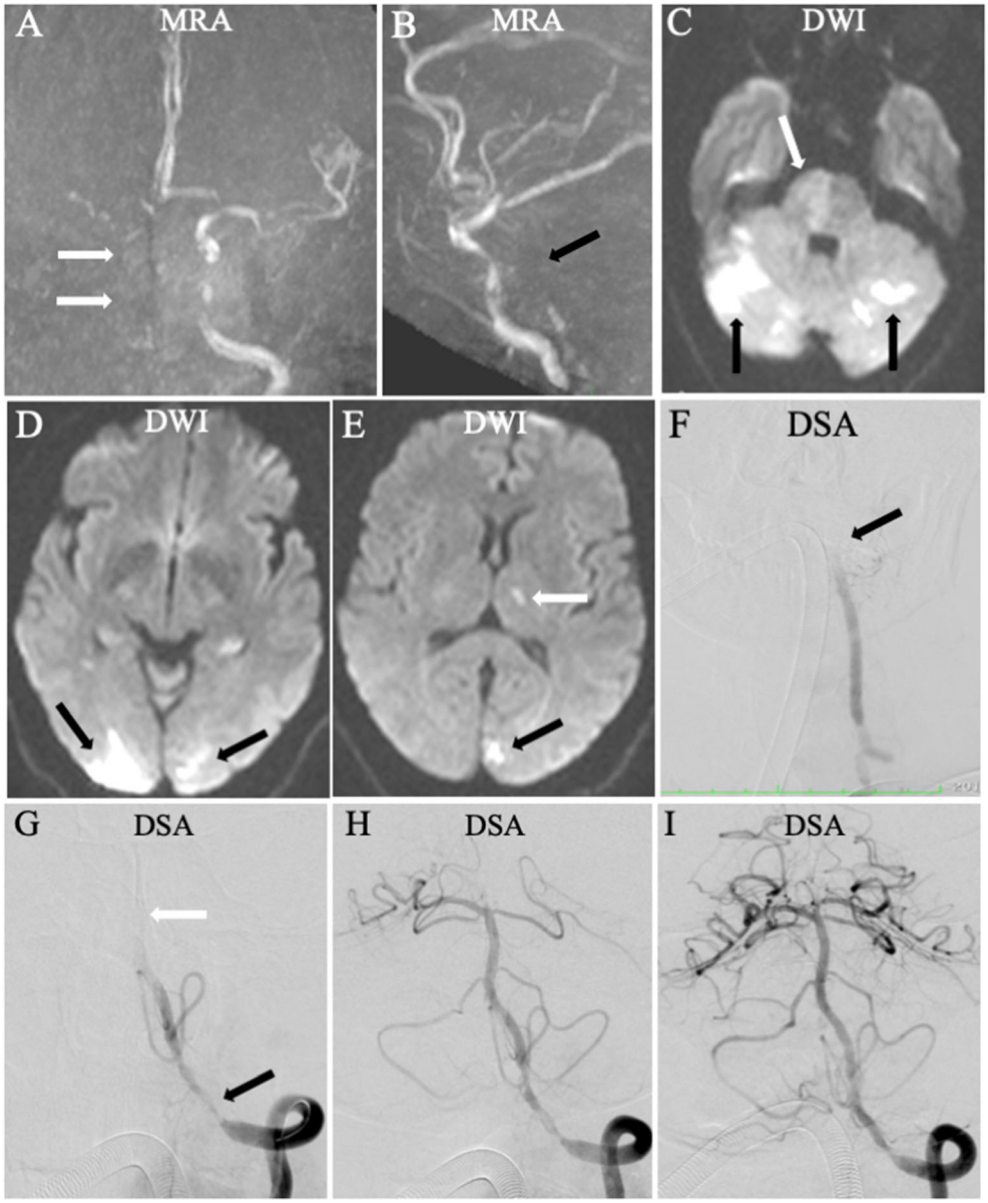

FIGURE 1
Endovascular treatment (EVT) for a patient with higher National Institutes of Health Stroke Scale (NIHSS) score: 20 and lower Acute Stroke Prognosis Early Computed Tomography Score (ASPECTS). Magnetic resonance angiography displayed the right internal carotid artery occlusion [**(A)**, arrow] and the vertebrobasilar artery occlusion [**(B)**, black arrow]. Diffusion-weighted imaging showed multiple acute ischemic stroke in posterior circulation involving the right pons [**(C)**, white arrow], bilateral cerebellum [**(C)**, black arrow], bilateral occipital lobe [**(D)**, black arrow], and left ganglion [**(E)**, white arrow]. The Acute Stroke Prognosis Early Computed Tomography Score (ASPECTS) and pons–midbrain index were 3 and 2, respectively. Based on the findings of DWI and MRA, the left vertebral and basilar artery was diagnosed as the "criminal" artery. Digital subtraction angiography (DSA) confirmed the artery occlusion for the left vertebral and basilar artery [**(F, G)**, white arrow). Endovascular treatment was performed with a stent retriever **(H)**, resulting in successful reperfusion with the modified thrombolysis in cerebral infarction 2b **(I)**. The modified Rankin Scale (mRS) score was 3 at 90 days.

atherosclerotic occlusions were associated with longer procedure times than non-atherosclerotic occlusion (20). In addition, diffusion MRI-selected patients for EVT were associated with a longer time than CTP-selected patients (15).

Our study has several limitations. First, this was a retrospective study with a small number of patients. A larger cohort study would be performed in the future. Second, there was no control group of patients for assessing the safety and efficacy of EVT.

Conclusion

MRI with DWI and MRA could identify the occluded intracranial arteries and assess the ischemic size (ASPECTS) and regions (pons–midbrain index) for the patients with suspicious acute VBAO. Mechanical thrombectomy with a stent retriever, combined with rescue treatment of angioplasty and/or stenting, could achieve good reperfusion and favorable functional outcome for patients with acute VBAO.

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.

Ethics statement

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

Author contributions

JC, JZ, and XZhu: conceived and designed the research and made critical revisions of the manuscript. JC, JZ, XZhu, and XZha: acquired the data. JC, JZ, XZhu, XZha, BJ, and QL: analyzed and interpreted the data. JC, JZ, XZhu, and ZW: draft the manuscript. JC, JZ, XZhu, XZha, ZW, BJ, and QL: approved the final manuscript.

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.

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References

1. Nguyen TN, Strbian D. Endovascular therapy for stroke due to basilar artery occlusion: a BASIC challenge at BEST. *Stroke.* (2021) 52:3410–3. doi: 10.1161/STROKEAHA.121.035948

2. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X

3. Liu X, Dai Q, Ye R, Zi W, Liu Y, Wang H, et al. Endovascular treatment versus standard medical treatment for vertebrobasilar artery occlusion (BEST): an open-label, randomised controlled trial. *Lancet Neurol.* (2019) 19:115–22. doi: 10.1016/S1474-4422(19)30395-3

4. Langezaal LCM, van der Hoeven EJRJ, Mont'Alverne FJA, de Carvalho JJF, Lima FO, Dippel DWJ, et al. Endovascular therapy for stroke due to basilar-artery occlusion. *N Engl J Med.* (2021) 384:1910–20. doi: 10.1056/NEJMoa2030297

5. Jovin TG Li C, Wu L, Wu C, Chen J, Jiang C, et al. Trial of thrombectomy 6 to 24 hours after stroke due to basilar-artery occlusion. *N Engl J Med.* (2022) 387:1373–984. doi: 10.1056/NEJMoa2207576

6. Tao C, Nogueira RG, Zhu Y, Sun J, Han H, Yuan G, et al. Trial of endovascular treatment of acute basilar-artery occlusion. *N Engl J Med.* (2022) 387:1361–972. doi: 10.1056/NEJMoa2206317

7. Campbell BCV, Majoie CBLM, Albers GW, Menon BK, Yassi N, Sharma G, et al. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. *Lancet Neurol.* (2019) 18:46–55.

8. Sang H, Li F, Yuan J, Liu S, Luo W, Wen C, et al. Values of baseline posterior circulation acute stroke prognosis early computed tomography score for treatment decision of acute basilar artery occlusion. *Stroke.* (2021) 52:811–20. doi: 10.1161/STROKEAHA.120.031371

9. Seyedsaadat SM, Neuhaus AA, Nicholson PJ, Polley EC, Hilditch CA, Mihal DC, et al. Differential contribution of aspects regions to clinical outcome after thrombectomy for acute ischemic stroke. *AJNR Am J Neuroradiol.* (2021) 42:1104–8. doi: 10.3174/ajnr.A7096

10. Schonewille WJ, Wijman CAC, Michel P, Rueckert CM, Weimar C, Mattle HP, et al. Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study. *Lancet Neurol.* (2009) 8:724–30. doi: 10.1016/S1474-4422(09)70173-5

11. Li C, Wu C, Wu L, Zhao W, Chen J, Ren M, et al. Basilar artery occlusion Chinese endovascular trial: protocol for a prospective randomized controlled study. *Int J Stroke.* (2022) 17:694 L, Zhao W, Chen J, Ren M, et al.

12. Puetz V, Khomenko A, Hill MD, Dzialowski I, Michel P, Weimar C, et al. Extent of hypoattenuation on ct angiography source images in basilar artery occlusion. *Stroke.* (2011) 42:3454–9. doi: 10.1161/STROKEAHA.111.622175

13. Haussen DC, Dehkharghani S, Rangaraju S, Rebello LC, Bouslama M, Grossberg JA, et al. Automated CT perfusion ischemic core volume and noncontrast CT aspects (Alberta stroke program early CT score). *Stroke.* (2016) 47:2318–22. doi: 10.1161/STROKEAHA.116.014117

14. Yoon W, Kim SK, Heo TW, Baek BH, Lee YY, Kang HK. Predictors of good outcome after stent-retriever thrombectomy in acute basilar artery occlusion. *Stroke.* (2015) 46:2972–5. doi: 10.1161/STROKEAHA.115.010840

15. de Champfleur NM, Saver JL, Goyal M, Jahan R, Diener H-C, Bonafe A, et al. Efficacy of stent-retriever thrombectomy in magnetic resonance imaging versus computed tomographic perfusion–selected patients in SWIFT PRIME Trial (Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke). *Stroke.* (2017) 48:1560–6. doi: 10.1161/STROKEAHA.117.016669

16. Mokin M, Levy EI, Saver JL, Siddiqui AH, Goyal M, Bonafé A, et al. Predictive value of rapid assessed perfusion thresholds on final infarct volume in SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment). *Stroke.* (2017) 48:932–8. doi: 10.1161/STROKEAHA.116.015472

17. Hetts SW. Diving into a shallow pool: endovascular treatment for basilar artery occlusion. *Radiology.* (2019) 291:738–9. doi: 10.1148/radiol.2019190375

18. Jia B, Ren Z, Mokin M, Burgin WS, Bauer CT, Fiehler J, et al. Current status of endovascular treatment for acute large vessel occlusion in China: a Real-World Nationwide Registry. *Stroke.* (2021) 52:1203–12. doi: 10.1161/STROKEAHA.120.031869

19. Tsang ACO, Orru E, Klostranec JM, Yang I-H, Lau KK, Tsang FCP, et al. Thrombectomy outcomes of intracranial atherosclerosis-related occlusions. *Stroke.* (2019) 50:1460–6. doi: 10.1161/STROKEAHA.119.024889

20. Park H, Baek JH, Kim BM. Endovascular treatment of acute stroke due to intracranial atherosclerotic stenosis–related large vessel occlusion. *Front Neurol.* (2019) 10:308. doi: 10.3389/fneur.2019.00308

21. Gao F, Lo WT, Sun X, Mo DP, Ma N, Miao ZR. Combined use of mechanical thrombectomy with angioplasty and stenting for acute basilar occlusions with underlying severe intracranial vertebrobasilar stenosis: preliminary experience from a single Chinese center. *AJNR Am J Neuroradiol.* (2015) 36:1947–52. doi: 10.3174/ajnr.A4364

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Necessity and timing of angioplasty in acute large-vessel occlusion strokes due to intracranial atherosclerotic disease: A cohort analysis with data from the angel-ACT registry

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Background: The effects of angioplasty on intracranial atherosclerotic disease (ICAD)-related acute large-vessel occlusion stroke (LVOS) are unknown. We analyzed the efficacy and safety of angioplasty or stenting for ICAD-related LVOS and the optimal treatment duration.

Methods: Patients with ICAD-related LVOS from a prospective cohort of the Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemia Stroke registry were classified as follows: the early intraprocedural angioplasty and/or stenting (EAS) group was defined as the strategy using angioplasty or stenting without mechanical thrombectomy (MT) or one attempt of MT; the non-angioplasty and/or stenting (NAS) group, MT procedure without any angioplasty; and the late intraprocedural angioplasty and/or stenting (LAS) group, using same angioplasty techniques following two or more passes of MT. The primary endpoint was the modified Rankin Scale (mRS) score at 90 days. Other efficacy outcomes included mRS scores 0–1, mRS 0–2, and successful recanalization. Death within 90 days, and symptomatic ICH were safety endpoints. We use propensity score method to diminish the effect of treatment-selection bias. The odds ratio of recanalization rate and mRS score among EAS, NAS, and LAS groups were examined by unadjusted and adjusted logistic regression analysis among unweighted samples and inverse probability of treatment weighting (IPTW) samples.

Results: We divided 475 cases into three groups. Functional outcomes at 90 days were better in the EAS group than in the NAS and LAS groups. The proportion of mRS 0–1, mRS 0–2, and successful recanalization cases were the highest in the EAS group. However, after IPTW, mortality rate among the three groups were similar (EAS vs. NAS vs. LAS: 19.0 vs. 18.1 vs. 18.7%, $p = 0.98$) as well as

symptomatic intracranial hemorrhage within 24 h however, mortality rate and symptomatic intracranial hemorrhage among the three groups were similar. Logistic regression analysis in unweighted samples and IPTW samples both showed that EAS group had better outcomes. IPTW-adjusted logistic regression analysis demonstrated that the EAS group had better outcomes (mRS 0–1) than the NAS group (adjusted odds ratio [aOR], 0.55; 95% confidence interval [CI]: 0.34–0.88, $p = 0.01$) and LAS (aOR, 0.39; 95% CI: 0.22–0.68, $p = 0.001$).

Conclusions: Angioplasty and/or stenting should be performed at an early stage for ICAD-related acute LVOS.

Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03370939.

KEYWORDS

acute large-vessel occlusion strokes, intracranial atherosclerotic disease, efficacy, safety, angioplasty

Introduction

Mechanical thrombectomy (MT) is gaining popularity as the gold standard for the treatment of patients with acute large-vessel occlusion strokes (LVOS) owing to its efficacy in different stroke types (1–4). Compared with embolic etiologies, intracranial atherosclerotic disease (ICAD) remains a huge therapeutic challenge because MT alone does not effectively resolve the underlying atheromatous plaque, thus often requiring angioplasty or stenting as mechanical rescue treatment (5–7). Unfortunately, *in situ* atherothrombotic occlusions are more commonly encountered in non-white populations and patients with diabetes and hypertension (8, 9).

Previous studies have demonstrated the safety and efficacy of direct and emergency angioplasty, and/or stenting after thrombectomy in certain patients with ICAD-related LVOS (10–12). However, no conclusions have been attained regarding whether angioplasty should be used in ICAD-related LVOS. Here, we aimed to assess both the necessity and optimal timing of angioplasty or stenting for ICAD-related acute LVOS by describing the safety and efficacy of different endovascular strategies.

Methods

Study population

LVOS patients receiving MT were selected from the Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke (ANGEL-ACT) database (ClinicalTrials.gov Identifier: NCT 03370939), a prospective nationwide registry of 1,793 continuous patients in 111 hospitals from 26 provinces of China between November 2017 and March 2019 (13). Patients with ICAD-related LVOS were included in the registry. The exclusion criteria were as follows: (1) without EVT medical records; (2) without the TOAST classification appraisal; and (3) with small-vessel occlusion and/or cardioembolism without ICAD.

The study was approved by the Ethics Committees of the Beijing Tiantan Hospital and all participating centers. All procedures were conducted in accordance with the 1964 Declaration of Helsinki and subsequent amendments. Written informed consent from all patients or their legally authorized representatives was obtained.

Data collection

Data on the baseline demographic characteristics (age and sex), medical history (hypertension, atrial fibrillation, diabetes mellitus, current smoking, antiplatelet agents, and anticoagulants), clinical characteristics (onset-to-door time, systolic blood pressure, Alberta Stroke Program Early Computed Tomography Score, National Institutes of Health Stroke Scale and intravenous thrombolysis), site of intracranial occlusion location, presence of tandem occlusion, type of anesthesia, and premorbid Modified Rankin Scale (mRS) scores were recorded.

Endovascular treatment and classification of strategy

Either local anesthetic or general anesthetic was utilized for the procedure depending on the patient's cooperation and condition. If no contraindications were available, intravenous thrombolysis was performed before MT. After digital subtraction angiography, the neurointerventionist decided optimal strategy and materials for endovascular therapy.

The type of surgical strategy depends on the surgical situation and personal experience of neurointerventionists. Different strategies for *in situ* stenosis include balloon expansion angioplasty only (Gateway, Stryker, Kalamazoo, MI, USA; Neuro-RX SINOMED, Tianjin, China), balloon-mounted stents only (Apollo, MicroPort, Shanghai, China), balloon-mounted stents, or self-expanding stents (Wingspan or EZ, Stryker, Kalamazoo, MI, USA; Solitaire AB, Medtronic, Minneapolis, Minnesota, USA;

Enterprise, Codman & Shurtleff Inc., Miami, FL, USA) after balloon expansion.

ICAD-related LVOS was divided into three groups based on the different treatment strategies. The early intraprocedural angioplasty and/or stenting (EAS) group was defined as the strategy involving balloon angioplasty alone, balloon-mounted stenting, or self-expanding stent after either no or one single pass of MT. The non-angioplasty and/or stenting (NAS) group was defined as undergoing the MT procedure without any angioplasty (including multiple passes of MT). Moreover, the late intraprocedural angioplasty and/or stenting (LAS) group was defined as the strategy of balloon angioplasty alone, balloon-mounted stenting, or self-expanding stent after two or more passes of MT.

Outcome measures

Clinical outcomes included both efficacy and safety assessments, and all data were recorded by experienced investigators. We considered the functional outcome at 90-days post procedure (90-day mRS score) as the primary efficacy endpoint (Supplementary material). Meanwhile, mRS 0–1, mRS 0–2, and mRS 0–3, and successful recanalization—defined as the modified thrombolysis 2b/3 in cerebral infarction (14)—were considered as the secondary efficacy outcomes. Death within 90 days, symptomatic ICH were considered safety endpoints according to the Heidelberg Bleeding Classification (15). We also recorded procedure-related complications including intraprocedural embolization, arterial dissection, arterial perforation, and vasospasm requiring treatment.

Statistical analysis

Data were recorded in standard forms and double-keyed into the EpiData statistics document. For continuous and ordinal variables, data are presented as medians (interquartile ranges [IQRs]), and for categorical variables, data are expressed as numbers (percentages). The student *t*-test was used for parametric data, while the non-parametric test (Mann–Whitney *U*-test) was used to compare the mean or median, respectively; Fisher's exact test or Pearson's chi-square test was used to compare the proportions or frequencies, respectively.

We used propensity scores to account for potential confounding factors and derive IPTW. The propensity score was estimated using a logistic regression model in which treatment assignment (EAS, NAS, and LAS) was regressed on the following covariates: demographic characteristics, hypertension, systolic blood pressure, atrial fibrillation, baseline NIHSS score, baseline ASPECTS score, presence of tandem occlusion, and type of anesthesia. Standardized mean differences were used to assess between-group balance of baseline characteristics, and a standardized mean difference smaller than 10% was considered insignificant difference.

We performed univariable logistic regression analysis, multivariable logistic regression analysis as well as IPTW-adjusted multivariable logistic regression analysis. The adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CI) were determined using the multivariate logistic regression analysis to compare successful recanalization and clinical outcomes at 90 days between the three groups. We also evaluated the outcomes of EAS, NAS, and LAS groups with 1:1 propensity score matching using the nearest-neighbor method, however, the sample size was small and the results were inconclusive. The outcomes after propensity score matching differed significantly while *P*-value was still over 0.05 due to small sample size (Supplementary material). SAS Version 9.4 (SAS Institute, Cary, NC, USA) was used to perform statistical analysis.

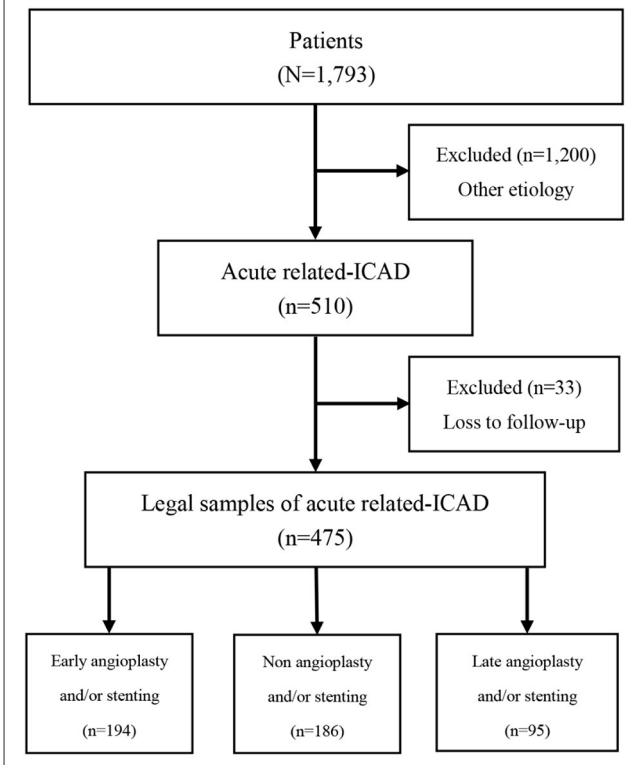

FIGURE 1
Flow diagram of recruitment of patients with acute intracranial atherosclerotic disease-related large-vessel occlusion stroke.

Results

Baseline and procedural characteristics

Table 1 showed unweighted and IPTW baseline characteristics of LVOS patients in EAS, NAS and LAS groups. Among the 1,793 participants in the Angel-ACT group, 475 cases met the inclusion criteria (27.9%) and were divided into three groups: 194 (40.1%) in the EAS group, 186 (40.3%) in the NAS group, and 95 (19.6%) in the LAS group. The process of patient selection is shown in Figure 1.

The three groups showed baseline differences in age, sex, preoperative systolic blood pressure, preoperative National Institutes of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT Score (ASPECTS), presence of tandem stenosis, and type of anesthesia (Table 1). Generally, patients in the EAS

TABLE 1 Baseline characteristics of EAS, NAS, and LAS groups before and after inverse probability of treatment weighting*.

Variables	Unweighted sample ($n = 475$)				IPTW sample ($n = 430.65$)			
	EAS ($n = 194$)	NAS ($n = 186$)	LAS ($n = 95$)	SMD	EAS ($n = 150.15$)	NAS ($n = 187.55$)	LAS ($n = 92.95$)	SMD
Demographic characteristics								
Median age, y, median (IQR)	61 (54–67)	65 (54–72)	60 (51–68)	0.198	63 (54–68)	61 (52–69)	60 (53–67)	0.098
Men	154 (79.4)	137 (73.7)	83 (87.4)	0.234	32 (21.0)	38 (20.1)	18 (18.8)	0.036
Medical history								
Hypertension	144 (74.2)	113 (60.8)	55 (57.9)	0.211	91 (60.5)	120 (63.8)	59 (62.9)	0.045
Diabetes	41 (21.1)	41 (22.0)	22 (23.2)	0.067	25 (16.4)	42 (22.6)	22 (23.8)	0.123
Atrial fibrillation	6 (3.1)	31 (16.7)	6 (6.3)	0.306	18 (12.0)	18 (9.6)	9 (9.4)	0.054
Smoking	99 (51.0)	91 (48.9)	46 (48.4)	0.080	73 (48.4)	97 (51.8)	38 (41.1)	0.145
Antiplatelet agents	40 (20.6)	30 (16.1)	14 (14.7)	0.029	24 (16.2)	32 (17.0)	12 (13.1)	0.073
Anticoagulants	5 (2.6)	3 (1.6)	1 (1.1)	0.108	6 (4.1)	4 (2.1)	1 (0.8)	0.145
Clinical characteristics								
Onset-to-door time, min, median (IQR)	178 (77–340)	180 (80–330)	180 (88–341)	0.005	170 (61–294)	180 (70–330)	148 (57–284)	0.073
SBP, mmHg, median (IQR)	150 (137–168)	145 (130–160)	150 (132–172)	0.208	146 (132–164)	149 (132–165)	149 (130–164)	0.032
Baseline NIHSS score, median (IQR)	14 (8–20)	16 (12–22)	16 (11–21)	0.084	17 (10–22)	16 (12–22)	15 (11–21)	0.090
ASPECTS, median (IQR)	8 (7–10)	9 (7–10)	8 (7–10)	0.109	8 (7–10)	8 (7–10)	8 (7–10)	0.033
IV thrombolysis before procedure	53 (27.3)	36 (19.4)	22 (23.2)	0.175	46 (30.6)	36 (19.1)	23 (24.4)	0.179
Intracranial occlusion location				0.280				0.296
ICA	42 (21.7)	39 (21.0)	16 (16.8)		25 (16.4)	39 (20.9)	13 (14.0)	
M1	81 (41.8)	84 (45.2)	39 (41.1)		68 (44.9)	85 (45.1)	44 (47.7)	
M2	7 (3.6)	13 (7.0)	2 (2.1)		9 (5.9)	12 (6.2)	1 (1.1)	
VA	63 (32.5)	45 (24.2)	36 (37.9)		48 (32.0)	47 (25.1)	33 (35.2)	
Other	1 (0.5)	5 (2.7)	2 (2.1)		1 (0.8)	5 (2.7)	2 (2.0)	
Presence of tandem occlusion	49 (25.3)	27 (14.5)	22 (23.2)	0.148	27 (18.3)	37 (19.8)	17 (18.5)	0.026
Type of anesthesia				0.314				0.086
Local anesthesia only	81 (41.8)	86 (46.2)	24 (25.3)		58 (38.3)	74 (39.3)	32 (33.9)	
Local anesthesia plus sedation	84 (43.3)	75 (40.3)	50 (52.6)		67 (44.5)	81 (43.3)	46 (49.5)	
General anesthesia	29 (15.0)	25 (13.4)	21 (22.1)		26 (17.2)	33 (17.5)	15 (16.6)	
Premorbid mRS score				0.149				0.151
0	160 (82.5)	163 (87.6)	79 (84.0)		128 (85.4)	163 (87.1)	78 (83.9)	
1	30 (15.5)	23 (12.4)	13 (13.8)		19 (12.7)	24 (12.9)	14 (14.9)	
2	4 (2.1)	0 (0.0)	2 (2.1)		3 (2.0)	0 (0.0)	1 (1.2)	

*The numbers of patients in IPTW samples are not necessarily integers due to inverse probability weighting.

EAS, early angioplasty and/or stenting (n = 201); LAS, late angioplasty and/or stenting (n = 98); NAS, non-angioplasty and/or stenting (n = 202); IPTW, inverse probability of treatment weighting; IQR, interquartile range; SMD, standardized mean difference; SBP, systolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke program Early CT score; ICA, internal carotid artery; M1, M1 segment of the middle cerebral artery; M2, M2 segment of the middle cerebral artery; VA, vertebral artery; mRS, modified Rankin Scale.

(mean age: 61 years) and LAS (mean age: 60 years) groups were younger than those in the NAS group (mean age: 65 years), overall $p = 0.010$; EAS group vs. NAS group: $p = 0.01$; EAS group vs. LAS group: $p = 0.65$; and NAS group vs. LAS group: $p = 0.02$ (p-value was shown in Supplementary material). The EAS (3.1%) and LAS (6.3%) groups had a lower proportion of atrial fibrillation than the NAS group (16.7%), overall $p < 0.0001$; EAS group vs. NAS group, $p < 0.0001$; EAS group *vs.* LAS group, $p = 0.20$; NAS group vs. LAS group, $p = 0.02$. The EAS group had lower NIHSS (EAS group: 14 vs. NAS group: 16 vs. LAS group: 16; overall $p = 0.02$; EAS group vs. NAS group: $p = 0.01$; EAS group vs. LAS group: $p = 0.05$; NAS group vs. LAS group: $p = 0.81$) and ASPETS (EAS group: 8 vs. NAS group: 9 vs. LAS group: 8; overall $p = 0.03$; EAS group vs. NAS group: $p = 0.01$; EAS group vs. LAS group: $p = 0.81$; NAS group vs. LAS group: $p = 0.08$) than NAS group and higher systolic blood pressure (EAS group: 150 mmHg vs. NAS group: 145 mmHg vs. NAS group: 150 mmHg; overall $p = 0.02$; EAS group vs. NAS group: $p = 0.01$; EAS group vs. LAS group: $p = 0.74$; NAS group vs. LAS group: $p = 0.07$) than NAS group. The EAS group also had a higher proportion of tandem occlusions than the NAS group (EAS group: 25.3% vs. NAS group: 14.5% vs. NAS group: 23.2%; overall $p = 0.03$; EAS group vs. NAS group: $p = 0.01$; EAS group vs. LAS group: $p = 0.70$; NAS group vs. LAS group: $p = 0.07$).

The standardized mean differences (SMD) of baseline characteristics of patients showed that the EAS, NAS, and LAS groups differed in terms of demographic characteristics, medical history, clinical characteristics, intracranial occlusion location, type of anesthesia, and premorbid mRS score before inverse probability of treatment weighting. We conducted IPTW to account for confounding factors, and the baseline variables are more balanced after IPTW. However, the SMD of diabetes, smoking, anticoagulants, IV thrombolysis before procedure, intracranial occlusion location and premorbid mRS score are still over 0.1.

Outcomes measures

Clinical outcome assessments, including efficacy and safety assessments, significantly differed among the three groups (Table 2).

The safety assessments were similar among EAS, NAS, and LAS groups. Mortality rate among the three groups were similar (EAS vs. NAS vs. LAS: 19.0 vs. 18.1 vs. 18.7%, $p = 0.98$) as well as symptomatic intracranial hemorrhage within 24 h (EAS vs. NAS vs. LAS: 9.7 vs. 2.3 vs. 9.7%, $p = 0.11$; Supplementary material).

After adjusting for age, sex, hypertension, atrial fibrillation, systolic blood pressure, baseline NIHSS score, baseline ASPECTS score as a continuous variable, presence of tandem occlusion, and type of anesthesia, logistic regression analyses revealed that the EAS group had better outcomes at 90 days than those of the NAS and LAS groups (mRS 0–1: EAS group vs. NAS group, aOR, 0.54, 95% CI: 0.34–0.86, $p = 0.009$; EAS group vs. LAS group, aOR, 0.41, 95% CI: 0.23–0.72, $p = 0.002$; mRS 0–2: EAS group vs. NAS group, aOR, 0.54, 95% CI: 0.34–0.85, $p = 0.01$; EAS group vs. LAS group, aOR, 0.46, 95% CI: 0.27–0.80, $p = 0.01$). The recanalization rate was higher in the EAS than in the LAS group (EAS group vs. LAS group, aOR, 0.28; 95% CI: 0.09–0.83, $p = 0.02$; Table 2). And IPTW-adjusted logistic regression model showed more distinguished outcome of EAS group which justified our conclusion (mRS 0–1: EAS group vs. NAS group, aOR, 0.55, 95% CI: 0.34–0.88, $p = 0.01$; EAS group vs. LAS group, aOR, 0.39, 95% CI: 0.22–0.68, $p = 0.001$; mRS 0–2: EAS group vs. NAS group, aOR, 0.54, 95% CI: 0.34–0.85, $p = 0.01$; EAS group vs. LAS group, aOR, 0.45, 95% CI: 0.25–0.78, $p = 0.004$). The recanalization rate was higher in the EAS than in the LAS group (EAS group vs. LAS group, aOR, 0.16; 95% CI: 0.04–0.53, $p = 0.02$; Table 2).

Discussion

To our knowledge, this is the first study to explore the association between different endovascular treatment strategies for angioplasty and functional prognosis in ICAD-related LVOS. This study revealed two main findings as follows: (1) performing angioplasty and/or stenting in patients with acute ICAD-related LVOS compared to patients without angioplasty is effective and safe; and (2) EAS is superior to LAS.

First, our results suggest that angioplasty yields greater benefits than does the choice to not undergo angioplasty. EAS had better revascularization rates than NAS groups on the final angiogram according to IPTW-adjusted logistic regression analysis. Even with a longer time for door to revascularization, the EAS group still exhibited better outcomes. However, the complication rate is low. Previous retrospective studies have identified better results with the performance of angioplasty (11, 16, 17). One retrospective study confirmed that angioplasty and/or stenting could be as the first-line treatment strategy for patients with acute anterior large-vessel occlusion caused by atherosclerosis (18). We considered urgent angioplasty and/or stenting to be feasible for the following reasons. Blood flow conditions can be maintained after angioplasty treatment (16). The possible causes of acute LVOS due to *in situ* stenosis include *in situ* thrombosis and proximal cardiogenic or arterial-to-arterial embolus incarceration in the stenosis (19). Thrombosis *in situ*, if the injured endothelium is not treated with angioplasty, may repeatedly lead to neovascularization and proximal embolus, if not relieved of the cause, will still be dislodged and lead to re-occlusion. Therefore, angioplasty can reduce re-occlusion in these patients. Second, angioplasty does not increase the risk of hyperperfusion bleeding (18). Finally, re-occlusion may occur immediately even in cases where thrombolysis is successful, as fibrinolytic agents may exacerbate the prothrombotic tendency of atherosclerotic lesions.

This study also elaborates on the optimal timing for first time angioplasty. Our results reveal that the outcomes for angioplasty treatment, either without MT or after one attempt pass of MT, is better than that after two or more MTs, with mortality reduced by half. This may be because

TABLE 2 Comparison of treatment effect of EAS, NAS, and LAS groups.

Parameter	mTICI 2b-3		(mRS 0–1) at 90 d		(mRS 0–2) at 90 d		Mortality at 90 d	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Unadjusted estimates								
NAS vs. EAS	0.39 (0.15–1.04)	0.06	0.56 (0.38–0.85)	0.006	0.54 (0.36–0.81)	0.003	1.84 (1.03–3.31)	0.04
LAS vs. EAS	0.31 (0.11–0.88)	0.03	0.40 (0.24–0.67)	0.001	0.44 (0.26–0.72)	0.001	2.06 (1.05–4.05)	0.04
Adjusted estimates*								
NAS vs. EAS	0.40 (0.14–1.12)	0.08	0.54 (0.34–0.86)	0.009	0.54 (0.34–0.85)	0.01	1.60 (0.84–3.05)	0.15
LAS vs. EAS	0.28 (0.09–0.83)	0.02	0.41 (0.23–0.72)	0.002	0.46 (0.27–0.80)	0.01	1.90 (0.93–3.89)	0.08
IPTW adjusted estimates*†								
NAS vs. EAS	0.25 (0.06–0.78)	0.03	0.55 (0.34–0.88)	0.01	0.54 (0.34–0.85)	0.01	1.08 (0.60–1.99)	0.79
LAS vs. EAS	0.16 (0.04–0.53)	0.01	0.39 (0.22–0.68)	0.001	0.45 (0.25–0.78)	0.004	1.25 (0.61–2.55)	0.54

mTICI, modified thrombolysis in cerebral infarction; OR, odds ratio; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale. Early angioplasty and/or stenting group was used as the reference category.

*Adjusted for age, sex, hypertension, systolic blood pressure, atrial fibrillation, baseline NIHSS score, baseline ASPECTS score as a continuous variable, presence of tandem occlusion, and type of anesthesia.

†IPTW obtained after adjustment.

multiple MTs may lead to more severe vascular endothelial injury, increasingly poorer outcomes, and significantly lower recanalization rates. After multiple thrombectomies, the operative time was significantly delayed, and prognosis worsened. Simultaneously, more attempts at MT may lead to vascular injury and significantly increased bleeding rates—resulting in poor prognosis and increased mortality. Therefore, early angioplasty can achieve more significant clinical outcomes than late angioplasty. A study showed that in ICAD populations, angioplasty and stenting had better efficacy than stent-retriever (18). Unfortunately, no studies reported satisfactory results when performing thrombectomy. After a single thrombectomy, the embolus was clearly identified as an *in-situ* stenosis. However, multiple thrombectomy passes causes negative effects such as vascular plaque exposure, intimal damage, and vasospasm.

Although MT has become the standard treatment for acute intracranial arterial occlusion (20, 21), the treatment for patients with ICAD is different from that for embolization. Therefore, it is important to identify ICAD early. Although ICAD is consistently associated with advanced age, the risk of ICAD in young people should not be ignored (22). Vascular risk factors for ICAD—including hypertension (23), hypercholesterolemia, diabetes, and smoking—Gutierrez et al. (24) can increase the patient's risk. Thus, timely detection and treatment of vascular risk factors is necessary to prevent further disease development. ICAD diagnostic methods include routine cerebral angiography, CT angiography (CTA), magnetic resonance angiography, high-resolution MRI, and transcranial Doppler ultrasound. Notably, MRI-based high-resolution imaging can directly show state of the intracranial arterial wall. Using these diagnostic imaging techniques can help identify high-risk populations. However, CTA has higher specificity and sensitivity for detecting ICAD and is now the method of choice for diagnosing ICAD in the United States (8). Briefly, ICAD should be identified, and angioplasty should be administered as early as possible.

In summary, angioplasty should be performed as early as possible in ICAD-related LOVS. It is essential to identify ICAD lesions before or after one MT pass. Current methods include the first-pass effect (25) and artificial intelligence (AI) technology (26). Once an ICAD lesion has been identified, thrombectomy should be performed according to the specific situation. MT should be performed first to remove the thrombus surrounding the *in-situ* stenosis. We also confirmed the presence and morphology of the stenosis based on the shape of the stent. This study used the STROBE cohortreporting guidelines.

This study had some limitations. Firstly, it was not a randomized study and thus can only partly illustrate the issue. Secondly, owing to the small, homogenous sample size and the prevalence of ICAD in China, our results may not be generalizable. Thus, future studies conducted on a wider scale with more data are required to confirm our results. Finally, although our results are controversial, angioplasty undeniably holds promise in select patients.

In conclusion, angioplasty and/or stenting is effective and safe and should be performed at an early stage of ICAD-related acute LVOS. However, randomized controlled trials are required to confirm this hypothesis.

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 IRB of Beijing Tiantan Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YD and YYa participated in the research design, model computations, data analysis, and drafted the manuscript. XT, YYi, AW, and YZ carried out the data collection and computation. GL, NM, and FG participated in model computations. DM, LS, and XS participated in table and figure design. BJ and XH participated in data analysis. DC and FG supervised this work, carried out the research design, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1087816/full#supplementary-material

References

1. Yang P, Zhang Y, Zhang L, Zhang Y, Treurniet KM, Chen W, et al. Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke. *N Engl J Med*. (2020) 382:1981–93. doi: 10.1056/NEJMoa2001123

2. Tiedt S, Herzberg M, Küpper C, Feil K, Kellert L, Dorn F, et al. Stroke etiology modifies the effect of endovascular treatment in acute stroke. *Stroke*. (2020) 51:1014–6. doi: 10.1161/strokeaha.119.028383

3. Huo X, Sun D, Raynald, Jia B, Tong X, Wang A, et al. Endovascular treatment in acute ischemic stroke with large vessel occlusion according to different stroke subtypes: data from ANGEL-ACT registry. *Neurol Ther*. (2022) 11:151–65. doi: 10.1007/s40120-021-00301-z

4. Baek JH, Kim BM, Heo JH, Kim DJ, Nam HS, Kim YD. Outcomes of endovascular treatment for acute intracranial atherosclerosis-related large vessel occlusion. *Stroke*. (2018) 49:2699–705. doi: 10.1161/strokeaha.118.022327

5. Kang DH, Yoon W, Kim SK, Baek BH, Lee YY , Kim YW, et al. Endovascular treatment for emergent large vessel occlusion due to severe intracranial atherosclerotic stenosis. *J Neurosurg*. (2008) 130:1949–56. doi: 10.3171/2018.1.jns172350

6. Jia B, Feng L, Liebeskind DS, Huo X, Gao F, Ma N, et al. Mechanical thrombectomy and rescue therapy for intracranial large artery occlusion with underlying atherosclerosis. *J Neurointervent Surg*. (2018) 10:746–50. doi: 10.1136/neurintsurg-2017-013489

7. Dobrocky T, Kaesmacher J, Bellwald S, Piechowiak E, Mosimann PJ, Zibold F, et al. Stent-retriever thrombectomy and rescue treatment of M1 occlusions due to underlying intracranial atherosclerotic stenosis: cohort analysis and review of the literature. *Cardiovasc Intervent Radiol*. (2019) 42:863–72. doi: 10.1007/s00270-019-02187-9

8. Gutierrez J, Turan TN, Hoh BL, Chimowitz MI. Intracranial atherosclerotic stenosis: risk factors, diagnosis, and treatment. *Lancet Neurol*. (2022) 21:355–68. doi: 10.1016/s1474-4422(21)00376-8

9. Banerjee C, Chimowitz MI. Stroke caused by atherosclerosis of the major intracranial arteries. *Circul Res*. (2017) 120:502–13. doi: 10.1161/circresaha.116.308441

10. Gross BA, Desai SM, Walker G, Jankowitz BT, Jadhav A, Jovin TG. Balloon-mounted stents for acute intracranial large vessel occlusion secondary to presumed atherosclerotic disease: evolution in an era of supple intermediate catheters. *J Neurointervent Surg*. (2019) 11:975–8. doi: 10.1136/neurintsurg-2019-014877

11. Wu C, Chang W, Wu D, Wen C, Zhang J, Xu R, et al. Angioplasty and/or stenting after thrombectomy in patients with underlying intracranial atherosclerotic stenosis. *Neuroradiology*. (2019) 61:1073–81. doi: 10.1007/s00234-019-02262-5

12. Ma G, Sun X, Tong X, Jia B, Huo X, Luo G, et al. Safety and efficacy of direct angioplasty in acute basilar artery occlusion due to atherosclerosis. *Front Neurol*. (2021) 12:651653. doi: 10.3389/fneur.2021.651653

13. Jia B, Ren Z, Mokin M, Burgin WS, Bauer CT, Fiehler J, et al. Current Status of Endovascular treatment for acute large vessel occlusion in China: a real-world nationwide registry. *Stroke*. (2021) 52:1203–12. doi: 10.1161/strokeaha.120.031869

14. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke*. (2013) 44:2650–63. doi: 10.1161/strokeaha.113.001972

15. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, et al. The heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. (2015) 46:2981–6. doi: 10.1161/strokeaha.115.010049

16. Yoon W, Kim SK, Park MS, Kim BC, Kang HK. Endovascular treatment and the outcomes of atherosclerotic intracranial stenosis in patients with hyperacute stroke. *Neurosurgery*. (2015) 76:680–6; discussion: 686. doi: 10.1227/neu.0000000000000694

17. Kim JG, Suh DC, Song Y, Choi JC, Lee DH. Direct stenting of intracranial atherosclerosis-related acute large vessel occlusion. *Clin Neuroradiol*. (2021) 31:833–41. doi: 10.1007/s00062-020-00934-x

18. Yang D, Lin M, Wang S, Wang H, Hao Y, Zi W, et al. Primary angioplasty and stenting may be superior to thrombectomy for acute atherosclerotic large-artery occlusion. *Intervent Neuroradiol*. (2018) 24:412–20. doi: 10.1177/1591019918763380

19. Prabhakaran S, Liebeskind DS, Cotsonis G, Nizam A, Feldmann E, Sangha RS, et al. Predictors of early infarct recurrence in patients with symptomatic intracranial atherosclerotic disease. *Stroke*. (2021) 52:1961–6. doi: 10.1161/strokeaha.120.032676

20. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. (2015) 372:1009–18. doi: 10.1056/NEJMoa1414792

21. Chen WH, Yi TY, Zhan AL, Wu YM, Lu YY, Li YM, et al. Stent-unsheathed effect predicts acute distal middle cerebral artery atherosclerotic disease-related occlusion. *J Neurol Sci*. (2020) 416:116957. doi: 10.1016/j.jns.2020.116957

22. von Sarnowski B, Schminke U, Tatlisumak T, Putaala J, Grittner U, Kaps M, et al. Prevalence of stenoses and occlusions of brain-supplying arteries in young stroke patients. *Neurology*. (2013) 80:1287–94. doi: 10.1212/WNL.0b013e31828ab2ed

23. Suri MF, Qiao Y, Ma X, Guallar E, Zhou J, Zhang Y, et al. Prevalence of intracranial atherosclerotic stenosis using high-resolution magnetic resonance angiography in the general population: the atherosclerosis risk in communities study. *Stroke*. (2016) 47:1187–93. doi: 10.1161/strokeaha.115.011292

24. Gutierrez J, Khasiyev F, Liu M, DeRosa JT, Tom SE, Rundek T, et al. Determinants and outcomes of asymptomatic intracranial atherosclerotic stenosis. *J Am Coll Cardiol*. (2021) 78:562–71. doi: 10.1016/j.jacc.2021.05.041

25. Yi TY, Chen WH, Wu YM, Zhang MF, Zhan AL, Chen YH, et al. Microcatheter "first-pass effect" predicts acute intracranial artery atherosclerotic disease-related occlusion. *Neurosurgery*. (2019) 84:1296–305. doi: 10.1093/neuros/nyy183

26. Soun JE, Chow DS, Nagamine M, Takhtawala RS, Filippi CG, Yu W, et al. Artificial intelligence and acute stroke imaging. *Am J Neuroradiol*. (2021) 42:2–11. doi: 10.3174/ajnr.A6883

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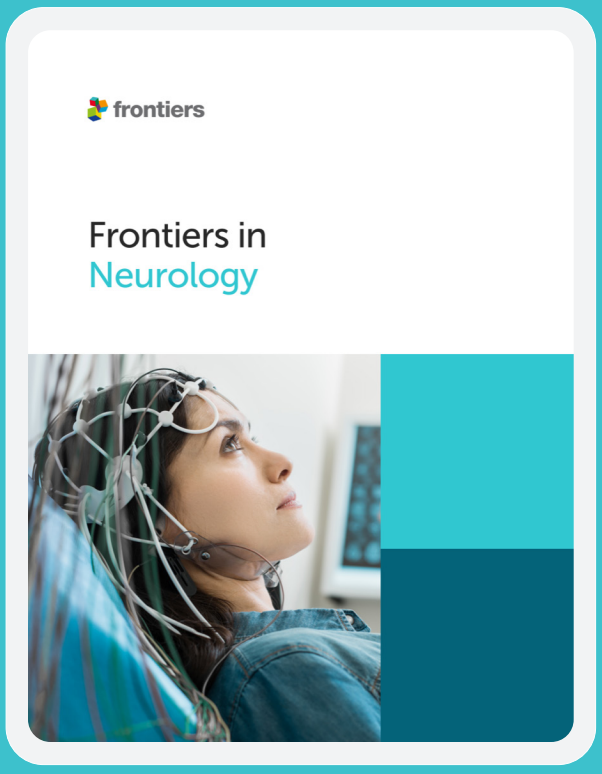

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