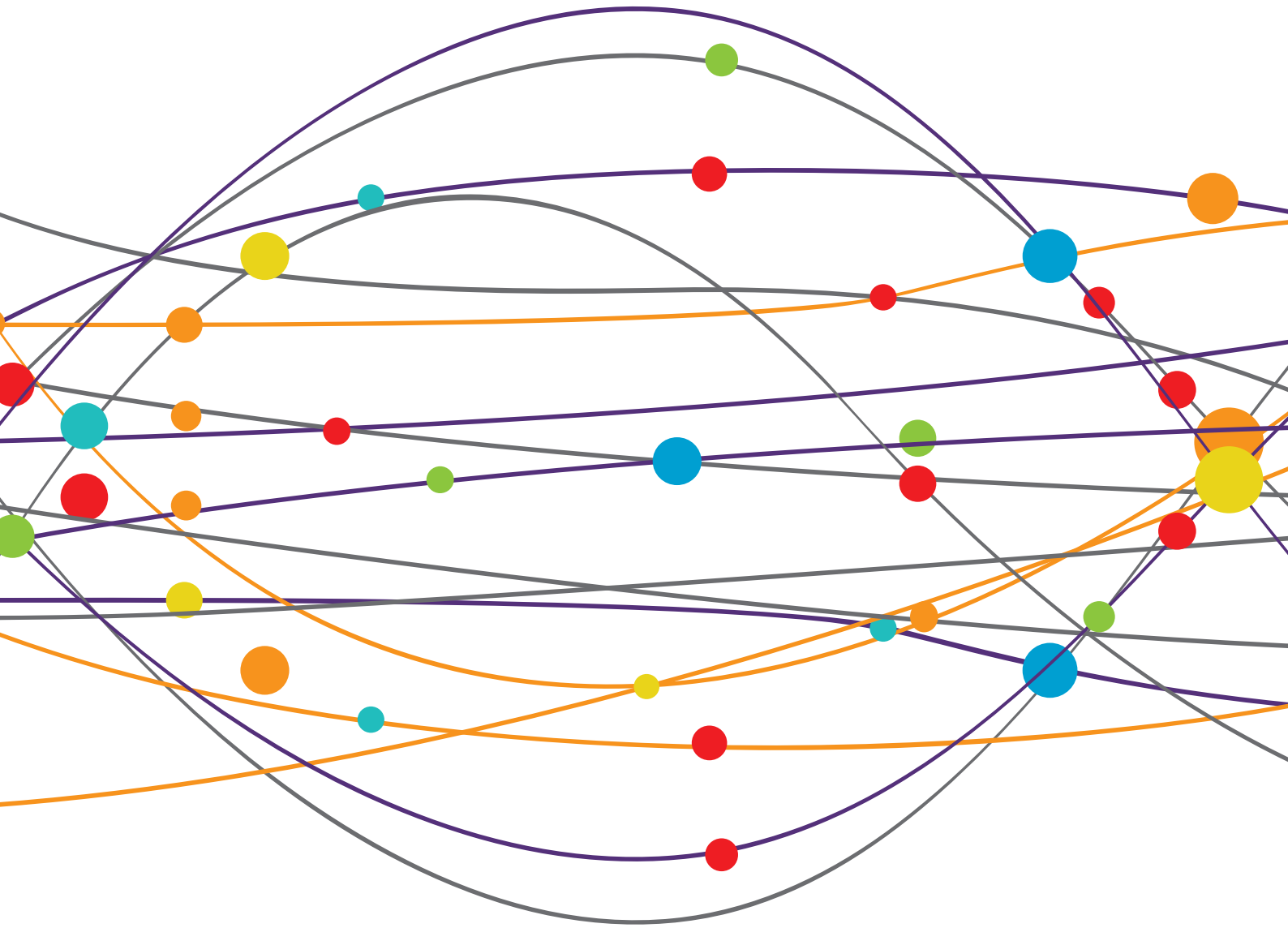
PRECISE DIAGNOSIS AND TREATMENT OF INTRACRANIAL STENOSIS OR OCCLUSION

EDITED BY: Liqun Jiao, Adam A. Dmytriw, Byung Moon Kim and QinJian Sun

PUBLISHED IN: Frontiers in Neurology



frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88974-834-1
DOI 10.3389/978-2-88974-834-1

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

PRECISE DIAGNOSIS AND TREATMENT OF INTRACRANIAL STENOSIS OR OCCLUSION

Topic Editors:
Liqun Jiao, Capital Medical University, China
Adam A. Dmytriw, Massachusetts General Hospital, Harvard Medical School, United States
Byung Moon Kim, Yonsei University, South Korea
QinJian Sun, Shandong University, China

Citation: Jiao, L., Dmytriw, A. A., Kim, B. M., Sun, Q. J., eds. (2022). Precise Diagnosis and Treatment of Intracranial Stenosis or Occlusion. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88974-834-1

Table of Contents

frontiers in Neurology

ORIGINAL RESEARCH
published: 02 March 2021
doi: 10.3389/fneur.2021.643633

Endovascular Management of Intracranial Atherosclerosis-Related Large Vessel Occlusion With the A Direct Aspiration First-Pass Thrombectomy Compared With Solumbra Technique

Zhao-Shuo Li, Teng-Fei Zhou, Qiang Li, Min Guan, Huan Liu, Liang-Fu Zhu, Zi-Liang Wang, Tian-Xiao Li and Bu-Lang Gao*

Henan Provincial People's Hospital, Henan University, Zhengzhou, China

OPEN ACCESS

Edited by:
Liqun Jiao,
Capital Medical University, China

Reviewed by:
Ning Ma,
Capital Medical University, China
Seong-Joon Lee,
Ajou University, South Korea

****Correspondence:***
Tian-Xiao Li
litianxiaod@163.com

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *18 December 2020*
Accepted: *26 January 2021*
Published: *02 March 2021*

Citation:
Li Z-S, Zhou T-F, Li Q, Guan M, Liu H, Zhu L-F, Wang Z-L, Li T-X and Gao B-L (2021) Endovascular Management of Intracranial Atherosclerosis-Related Large Vessel Occlusion With the A Direct Aspiration First-Pass Thrombectomy Compared With Solumbra Technique. Front. Neurol. 12:643633. doi: 10.3389/fneur.2021.643633

Background: To investigate the effect of the A Direct Aspiration First-Pass Thrombectomy (ADAPT) vs. Solumbra technique in the treatment of acute intracranial atherosclerosis-related large vessel occlusion (LVO).

Methods: Patients with acute atherosclerosis-related LVO who had undergone endovascular treatment were retrospectively enrolled into two groups: The Solumbra and ADAPT groups. The clinical data were analyzed.

Results: Patients (104) were enrolled with 48 in the Solumbra and 56 in the ADAPT group. The mean time from femoral access to recanalization was significantly ($P < 0.05$) shorter in the ADAPT than in the Solumbra group. The recanalization time at the first line was significantly shorter in the ADAPT group than in the Solumbra group (17 ± 10.21 vs. 26 ± 15.55 min, $P = 0.02$). However, the rate of switching to the alternative was significantly higher in the ADAPT group than that in the Solumbra group (46.42 vs. 33.33%, $P = 0.01$). Eighty-two patients had eventual recanalization, resulting in a final recanalization rate of 78.85%. At 3-month clinical follow-up for all patients, the good prognosis rate reached 51.92% with good prognosis in 24 patients (50%) in the Solumbra and 30 (53.57%) in the ADAPT group. The rate of symptomatic intracranial hemorrhage was 18.75% ($n = 9$) in the Solumbra and 19.64% ($n = 11$) in the ADAPT group. The mortality rate was 21.15% (22/104). Among 80 (76.92%) patients who had angiographic follow-up (3–30 months), five (6.25%) patients experienced in-stent stenosis, and two (2.5%) experienced asymptomatic stent occlusion.

Conclusion: In patients with acute intracranial atherosclerosis-related LVO, clinical outcomes treated using the ADAPT technique are comparable with those using the Solumbra technique, and more patients need additional remedial measures if treated with the ADAPT technique.

Keywords: intracranial atherosclerosis-related, large vessel occlusion, ADAPT, Solumbra, endovascular treatment

BACKGROUND

As a significant health burden worldwide, acute ischemic stroke is a leading cause of morbidity and mortality; however, early revascularization and reperfusion are correlated with improved clinical outcomes (1, 2). For acute intracranial large vessel occlusion (LVO), mechanical thrombectomy has become a standard approach of treatment because of the high efficacy and good prognoses (3–6). However, the etiology of LVO is different in different ethnics, with intracranial atherosclerosis as the most common cause of ischemic stroke and more common in Asian, Spanish, and Afro-American populations (7, 8). The clinical presentation, risk factors, and demographic features are different between patients with acute intracranial atherosclerosis-related LVO (ICAS-LVO) and those with thromboembolism-related LVO (8). Mechanical thrombectomy with a stent retriever has become the mainstay of modern endovascular therapy for LVO caused by thromboembolism, but the stent retriever is less efficient for atherosclerosis-related LVO (9–11). Moreover, reocclusion and residual stenosis are often encountered in the endovascular management of atherosclerosis-related LVO, and rescue treatment with balloon angioplasty is frequently required for complete recanalization (9, 12, 13). Since fast recanalization is the most important factor in determining the clinical outcomes, multiple endovascular management techniques are needed to recanalize intracranial atherosclerosis-related LVO compared with thromboembolism-related LVO. Two currently principal techniques for mechanical thrombectomy are (1) application of a stent retriever like the Solitaire FR stent (Medtronic Neurovascular, Irvine, CA, USA) and (2) direct aspiration of the thrombus with the technique of A Direct Aspiration First-Pass Thrombectomy (ADAPT) using a large-bore aspiration catheter like the ACE 64 or 5 Max ACE catheter (Penumbra, Alameda, CA, USA) (14, 15). Moreover, a stent retriever can be used together with direct aspiration at the proximal end of a thrombus at the time of mechanical thrombectomy (16–18). The Solumbra technique uses the Solitaire FR stent retriever for mechanical thrombectomy in combination with proximal thrombus aspiration using the Penumbra aspiration catheter (16–18). The Solumbra technique seems better in complete removal of the thrombus because it combines both the mechanical thrombectomy with a stent retriever and thrombus aspiration, while the ADAPT seems quicker in removing the thrombus. Studies have shown that the ADAPT technique can achieve the same clinical and imaging effects as those achieved by the Solumbra technique in mechanical thrombectomy of LVO (19, 20). However, no studies had compared these two techniques in endovascular management of intracranial atherosclerosis-related LVO. This study was consequently performed to compare the effect and clinical outcomes of the two techniques in recanalization of intracranial atherosclerosis-related LVO in a Chinese cohort.

Abbreviations: LVO, large vessel occlusion; ADAPT, A Direct Aspiration First-Pass Thrombectomy; CTA, computed tomography angiography; MRA, r magnetic resonance angiography; ICA, intracranial segment of the internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin scale score; NIHSS, National Institutes of Health Stroke Scale.

METHODS

Subjects

This study was approved by the ethics committee of our hospital, and all patients had given their signed informed consent to participate. Between March 2018 and August 2019, patients with LVO treated with either the Solumbra or ADAPT technique were enrolled. The residual stenosis >70% of a cerebral artery after the first-pass thrombectomy is usually used as a golden criterion to diagnose ICAS-LVO (21–23). If the residual stenosis is below 70%, but its distal blood flow is impaired, or it tends to re-occlude, it is also considered ICAS-LVO. Other indicators of ICAS-LVO may also be required to assist the definitive diagnosis, including truncal-type occlusions or the sign called the "microcatheter first-pass effect," which can be used to diagnose an ICAS-LVO. The inclusion criteria were patients with LVO, age ≥18 years, the time from disease onset to femoral artery puncture ≤8 h or between 8 and 24 h but consistent with the inclusion criteria of the DAWN experiment or DEFUSE-3 experiment (24), LVO confirmed by computed tomography angiography (CTA) or magnetic resonance angiography (MRA) including occlusion of the intracranial segment of the internal carotid artery (ICA), M1 segment of the middle cerebral artery (MCA), intracranial segments of the vertebral artery and basilar artery, atherosclerotic stenosis-related LVO, the modified Rankin scale score (mRS) ≤2, and baseline score of the National Institutes of Health Stroke Scale (NIHSS) ≥6. The exclusion criteria were intracranial hemorrhage confirmed by CT or MRI and LVO caused by arterial dissection, Moyamoya disease, or arteritic occlusion.

Treatment Approaches

Before endovascular treatment, patients who were within the time window for intravenous thrombolysis had rt-PA (recombinant tissue plasminogen activator) at a dose of 0.9 mg/kg. After digital subtraction angiography revealed the location and length of LVO, arterial stenosis, and collateral circulation, appropriate endovascular approaches were chosen for treatment. In both the Solumbra and ADAPT techniques, a 300-mm micro-guidewire was used to assist the microcatheter through the occlusion lesion so that a stent or suction catheter could be navigated in place.

Solumbra Technique

With the Solumbra technique, a long sheath was sent to the distal cervical segment of the ICA or the vertebral artery using an exchange technique under general or local anesthesia, and a 0.025-inch microcatheter (Rebar27, Medtronic Neurovascular, Irvine, CA, USA) harboring a 0.016-inch micro-guidewire was introduced into a large-bore aspiration catheter (ACE, Penumbra, Oakland, CA, USA; or the SOFIA, MicroVention Terumo, Tustin, CA, USA), which were all navigated into the long sheath as a unit. After the 0.025-inch microcatheter was navigated through the thrombus along the micro-guidewire, the large-bore aspiration catheter was sent to the proximal end of the

thrombus as close as possible before deployment of the Solitaire FR stent-retriever (Medtronic Neurovascular, Irvine, CA, USA) across the thrombus through the 0.025-inch microcatheter. The microcatheter was then completely removed. Three to five minutes later, the large aspiration catheter was connected for continuous aspiration while advancing the aspiration catheter to the proximal end of the thrombus as close as possible. If recanalization was not successful after aspiration for three times, the DAPT technique would be tried for recanalization.

DAPT Technique

The establishment of the access road to the thrombus was the same as that in the Solumbra technique. After the aspiration catheter (ACE60, Penumbra, Oakland, CA, USA; or the SOFIA PLUS, MicroVention Terumo, Tustin, CA, USA; REACT68, Medtronic Neurovascular, Irvine, CA, USA) was navigated to the proximal end of the thrombus as close as possible through a 0.021-inch microcatheter (Rebar27, Medtronic Neurovascular, Irvine, CA, USA) harboring a 0.014-inch 300-mm micro-guidewire, it was connected to a negative pressure suction pump for continuous aspiration for 60–90 s. Then, the aspiration catheter was slowly withdrawn until the blood flow velocity returned to normal in the connecting pipe of the negative pressure pump. If the flow velocity did not resume normal, the aspiration catheter was gradually removed under continuous negative pressure. This process was repeated three times until successful reperfusion. If the path is extremely tortuous and the suction catheter cannot be in place, a 300-mm micro-guidewire was used to help the microcatheter through the thrombus-occluded segment. If reperfusion could not be achieved after trying three times, the Solumbra technique was considered.

Remedial Measures for Treatment

If reperfusion was not successful after the Solumbra or the ADAPT technique had been tried three times, the LVO was thought to be an intractable vessel occlusion, and remedial measures would be taken. If the aspiration catheter could not be navigated through the occlusion segment, a 1.5- or 2-mm diameter rapid-exchanging balloon would be sent to expand the occluded segment while advancing the aspiration catheter, which was connected to the negative pressure pump for thrombus aspiration. The balloon was deflated and withdrawn after the aspiration catheter was in place. This was the so-called balloon-assisted aspiration technique. If recanalization was successful, but the blood flow was obviously limited due to severe vascular stenosis, or there was a tendency of vascular occlusion, remedial measures would be taken including mechanical thrombectomy, percutaneous balloon angioplasty, intracranial stent implantation, and intra-arterial injection of tirofiban (0.5–2.0 mg). For patients with intracranial stent implantation, intravenous tirofiban maintenance therapy was given after the treatment procedure. If the patient did not have intracranial hemorrhage or other hemorrhagic complications, double anticoagulation therapy with aspirin (100 mg/day) and clopidogrel (75 mg/day) was administered the second day after the procedure.

Effect Evaluation and Follow-Up

The modified Thrombolysis in Cerebral Infarction (mTICI) score was used to evaluate the recanalization of the large vessels during the procedure, and successful recanalization was defined as mTICI 2b-3. Post-procedure CT or MRI was performed to check if intracranial hemorrhage was present, and the intracranial hemorrhage was defined as any intracranial hemorrhage with increased NIHSS score $\geq$4.

Three months after the procedure, all patients were followed up either through outpatient clinics or *via* telephone contact. The prognosis was assessed with a good prognosis of mRS score between 0 and 2. Three to six months after the procedure, digital subtraction angiography was performed for patients with deployment of intracranial stents for possible in-stent restenosis.

Statistical Analysis

The statistical analysis was performed with the SPSS 19.0 software (IBM, Chicago, IL, USA). Measurement data in normal distribution were presented as mean ± standard deviation (normal distribution) or median with interquartile range (skewed distribution) and tested with the paired *t*-test or Mann–Whitney *U*-test as indicated between groups. Enumeration data were presented as percentage (*n* and %) with their corresponding 95% confidence intervals (CIs) and tested with the Chi square test. The significant *P* was set at <0.05.

RESULTS

Subjects

One hundred and four patients met the inclusion criteria and were enrolled including 77 (74.0%) male and 27 female (26.0%) patients with an age range of 36–88 years (mean 64.05 ± 12.10). Seventy-nine (76.0%) patients had hypertension, 23 (22.1%) had diabetes mellitus, 62 (59.6%) had hyperlipidemia, four (3.8%) had atrial fibrillation, and 24 (23.1%) had smoking. Twenty-six (25%) patients had ICA occlusion, 27 (26.0%) had M1 segment occlusion, 23 (22.1%) had occlusion of ICA-L (involving carotid terminus and MCA), 19 (18.3%) had basilar artery occlusion, and 9 (8.7%) had occlusion of both the basilar and vertebral arteries. The baseline NIHSS score was 16.05 ± 4.61. Forty-eight patients were treated with the Solumbra technique, while 56 with the ADAPT (**Figures 1**, **2**), and no significant ($P > 0.05$) differences were found in the age, sex distribution, and risk factors for atherosclerosis, or baseline NIHSS score between the two groups (**Table 1**). The proportion of patients with ICA-L serial occlusion was significantly ($P < 0.05$) higher in the ADAPT than in the Solumbra group. Among 104 patients, 10 patients (20.83%) in the Solumbra and nine (16.07%) in the ADAPT group had rt-PA intravenous thrombolysis, with no significant ($P > 0.05$) difference in the proportion between the two groups.

Clinical Effect and Follow-Up

The mean time from femoral access to recanalization was 76.57 ± 27.23 min for all patients, with a significantly ($P < 0.05$) shorter time for the ADAPT technique than that for the Solumbra (73.61 ± 24.66 vs. 78.05 ± 30.55 min) (**Table 2**). Twenty-one (43.75%) patients had recanalization at the first pass in the Solumbra

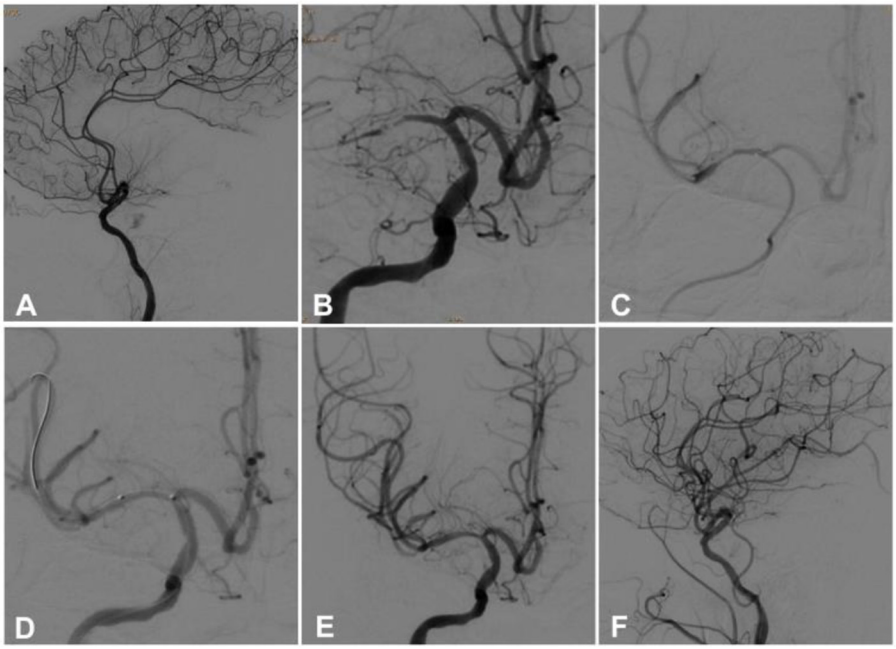


FIGURE 1 | A 36-year-old man had sudden onset of left limb weakness 17 h ago, and the symptom was relieved after intravenous thrombolysis. However, the symptom was aggravated 4 h later, and he was transferred to our hospital with the NIHSS score of 11. Magnetic resonance imaging demonstrated acute infarction in the right basal ganglia. **(A,B)** Before aspiration, cerebral angiography revealed occlusion of the right middle cerebral artery. **(C)** After the thrombus was removed by the aspiration catheter connected to the negative pressure pump, the blood flow forward was resumed. **(D)** During the procedure, a 2 mm × 12 mm balloon was used to expand the stenotic segment. **(E,F)** An Enterprise stent (4.5 mm × 22 mm) was deployed at the stenotic location, and the blood flow was restored to the modified Thrombolysis in Cerebral Infarction (mTICI) grade 3.

group, which was not significantly ($P > 0.05$) different from that in the ADAPT group ($n = 26$, 46.2%). The recanalization time at the first pass was significantly shorter in the ADAPT group than in the Solumbra group (17 ± 10.21 vs. 26 ± 15.55 min, $P = 0.02$). However, the rate of switching to the alternative was significantly higher in the ADAPT group than in the Solumbra group (46.42 vs. 33.33%, $P = 0.01$) (**Table 2**). Eighty-two patients had eventual recanalization, resulting in a final recanalization rate of 78.85%, with the final recanalization rate of 83.33% ($n = 40$) in the Solumbra group, which was not significantly ($P > 0.05$) different from that in the ADAPT group (75%, $n = 42$).

At 3-month clinical follow-up for all patients (**Table 3**), the good prognosis rate reached 51.92% with good prognosis in 24 patients (50%) in the Solumbra and 30 (53.57%) in the ADAPT group (**Figure 2**). The rate of symptomatic intracranial hemorrhage was 14.58% ($n = 9$) in the Solumbra and five 19.64% ($n = 11$) in the ADAPT group. The mortality rate was 21.15% (22/104). No significant ($P > 0.05$) difference existed in the rate of hemorrhagic transformation, parenchymal hemorrhage, subarachnoid hemorrhage, symptomatic intracranial hemorrhage, good prognosis, independent functions, or death (**Table 3**). Among 80 (76.92%) patients who had angiographic follow-up between 3 and 30 months following endovascular thrombectomy, five (6.25%) patients had in-stent stenosis, one of whom was recanalized with balloon expansion. The other four patients with in-stent stenosis were asymptomatic. Two (2.5%) patients had asymptomatic stent occlusion, which was not managed.

DISCUSSION

This study investigated the effect and clinical outcomes of the Solumbra and ADAPT technique in treating patients with intracranial atherosclerosis-related LVO, and it was found that the ADAPT technique is significantly quicker to obtain recanalization than the Solumbra technique (73.61 ± 24.66 vs. 78.05 ± 30.55 min), but no significant differences existed in the other aspects including the first-pass recanalization rate, final recanalization rate, periprocedural complication rate, good prognosis rate, and mortality at 3-month follow-up.

After comparing the effect and adverse events of the direct contact aspiration technique vs. the standard stent retriever technique as a first-line endovascular therapy for successful revascularization of acute ischemic stroke and LVO in the anterior circulation, Lapergue et al. (19) found no significant ($P > 0.05$) difference in the recanalization rate in the contact aspiration group vs. the stent retriever group [85.4 vs. 83.1%, odds ratio or OR: 1.20 (95% CI, 0.68–2.10); $P = 0.53$; difference, 2.4% (95% CI, −5.4 to 9.7%)]. No significant difference existed in the clinical efficacy outcomes at 90 days and adverse events. They drew a conclusion that first-line thrombectomy with contact aspiration did not have an increased recanalization rate compared with

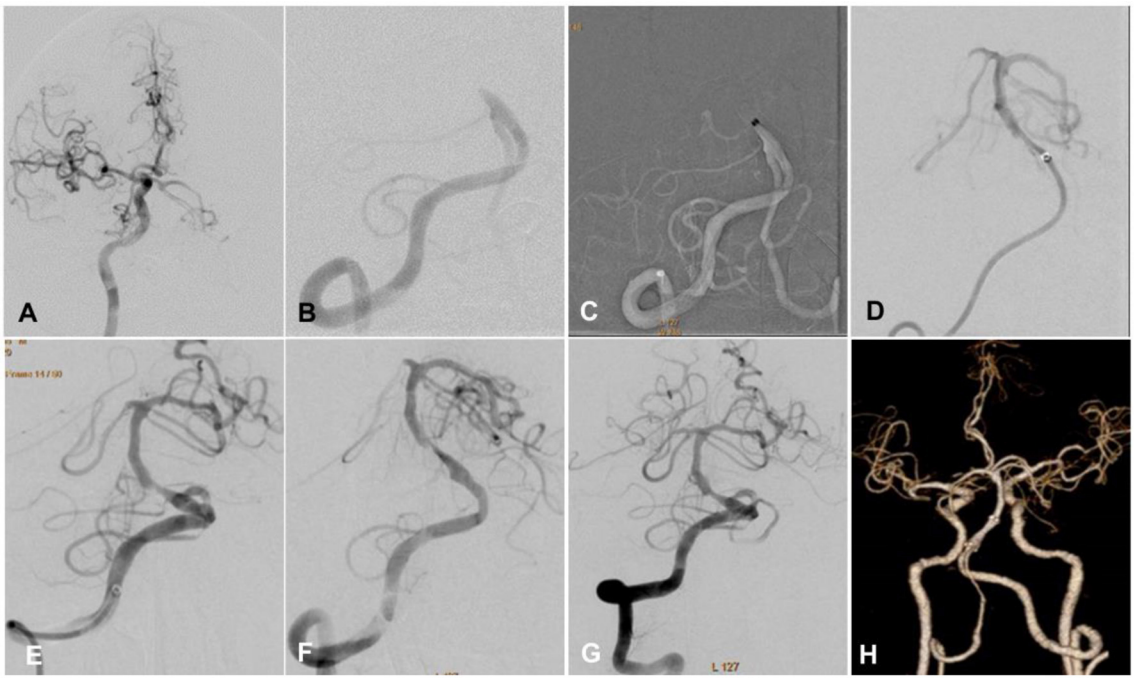


FIGURE 2 | A male patient in his 60s had paroxysmal dysphasia, left limb weakness for 1 h, and coma for 30 min. The NHISS score was 19. **(A)** Cerebral digital subtraction angiography showed lateral circulation and basilar artery tip, suggesting intracranial atherosclerotic stenosis-related large vessel occlusion (ICAS-LVO). **(B)** The right vertebral artery angiography demonstrated occlusion of the initial segment of the basilar artery. **(C)** A REACT68 suction catheter was navigated to the basilar artery proximal to the occlusion, and after 30 s of negative pressure suction *in situ*, the retrograde blood flow in the catheter suddenly recovered. **(D)** Angiography confirmed that the anterior blood flow of the basilar artery returned to normal. **(E)** The aspiration catheter was withdrawn, and angiography revealed severe stenosis at the middle segment of the basilar artery as ICAS-LVO. **(F)** After 10 min of observation, the stenosis degree was increased, and the forward blood flow gradually became worse. **(G)** A stent was implanted after balloon pre-dilation, with the blood flow reaching mTICI grade 3. **(H)** Computed tomography angiography of the head and neck was performed 3 days after operation, which indicated that the stent was unobstructed, and the basilar artery forward blood flow was stable. Seven days after operation, the patient was discharged, with the NIHSS score of 1.

the stent retriever technique. After studying reperfusion, adverse events, neurological recovery, and functional outcomes of patients with isolated M2 occlusions in 79 patients treated with the contact aspiration or the stent retriever technique, Gory et al. (25) found no significant difference in the reperfusion rate, in the 90-day mRS score ($\leq$ 2) rate (54.4 vs. 50.0%; $P = 0.84$), 24-h change in NIHSS score, or the Alberta Stroke Program Early Computed Tomography score, with the conclusion being that first-line mechanical thrombectomy with contact aspiration vs. stent retriever did not result in an increased successful revascularization rate in patients with acute stroke caused by isolated M2 occlusion. Zhu et al. (26) also found no significant increase in the successful reperfusion rate in acute ischemic stroke patients with LVO of the anterior circulation in the contact aspiration group compared with the stent retriever group. However, in a PRISMA-compliant systematic review and meta-analysis investigating the efficacy and safety of the direct aspiration approach of thrombectomy for recanalization in patients with acute ischemic stroke compared with the stent-retriever approach, Qin et al. (27) found better functional outcomes at 3 months defined as an mRS score of 0 to 2 (OR, 0.77; 95% CI, 0.66–0.97; $P = 0.03$), fewer adverse events especially in symptomatic intracerebral hemorrhage (OR, 0.56; 95% CI, 0.33–0.98; $P = 0.04$) and embolization to a new territory (OR, 0.49; 95% CI, 0.28–0.84; $P = 0.01$) in the direct aspiration group than in the stent retriever group even though no significant differences existed in the rate of successful recanalization between the two groups.

The above studies indicated that the direct contact aspiration technique is as good as or better than the stent retriever technique in achieving the recanalization rate or clinical outcomes in treating patients with LVO. These studies were conducted with only thrombus-related occlusion of LVO without the concomitant factor of atherosclerosis. Thus, the effect of direct contact aspiration with the ADAPT technique vs. the Solumbra technique with combined stent retriever and aspiration is not clear for patients with intracranial atherosclerosis-related LVO. These two entities of disease are different in the clinical presentation, risk factors, and demographic features (8), and the clinical outcomes treated with mechanical thrombectomy may also be different. Baek et al. (7) studied the outcomes of mechanical thrombectomy for acute intracranial LVO and found that recanalization with a stent retriever is significantly ($P < 0.001$) less successful in patients with intracranial atherosclerosis-related LVO, and more patients with intracranial atherosclerosis-related LVO need specific rescue

TABLE 1 | Demography and clinical data.

Variables	Solumbra ($n = 48$)	ADAPT ($n = 56$)	t/χ^2	P
Age (years)	64.27 ± 12.17	63.60 ± 11.73	2.613	0.213
Male	37 (77.08%)	40 (71.43%)	0.333	0.576
Hypertension	36 (75.00%)	43 (76.79%)	0.154	0.776
Diabetes mellitus	11 (22.92%)	12 (21.43%)	0.040	1.000
Hyperlipidemia	28 (58.33%)	34 (60.71%)	1.926	0.200
Atrial fibrillation	2 (4.17%)	2 (3.57%)	0.000	1.000
Smoking	12 (25.00%)	12 (21.43%)	0.154	0.776
Baseline NIHSS score	15.83 ± 4.63	16.49 ± 4.60	3.332	0.122
ASPECTS score	8 (7–10)	7 (6–10)	1.691	0.352
Medications prior to admission				
Antiplatelets	27 (56.25)	31 (55.35)	0.976	0.451
Anticoagulants	7 (41.3)	10 (41.3)	0.573	0.642
Favorable collaterals	(41.3)	(44.8)	0.663	0.570
Occluded artery				
ICA	12 (25.0%)	14 (25.0%)	1.579	0.452
MCA	12 (25.0%)	15 (26.79%)		
ICA-L type	11 (22.92%)	16 (28.57%)		
Basilar artery	9 (18.75%)	10 (17.86%)		
Vertebral terminus	4 (8.33%)	5 (8.93%)		
Intravenous thrombolysis	10 (20.83%)	9 (16.07%)	1.777	0.761

ICA-L type does not mean a tandem occlusion but occlusion involving carotid terminus and MCA. Vertebral terminus does not mean a tandem occlusion but occlusion involving two anatomical locations of the vertebral terminus and basilar arteries.

TABLE 2 | Radiologic outcomes of endovascular treatment.

Variables	Solumbra ($n = 48$)	ADAPT ($n = 56$)	χ^2/t	P
LKW to puncture time, min	367 (69–721)	302 (74–675)	1.568	0.691
Recanalization by first-pass thrombectomy	12 (25.00%)	9 (16.07%)	0.643	0.553
Recanalization by first-line thrombectomy	21 (43.75%)	26 (46.42%)	0.643	0.553
Time of puncture to recanalization by first-line thrombectomy, min	26 ± 15.55	17 ± 10.21	5.843	0.02
Rescue treatments after first-line thrombectomy Switching to the alternative	16 (33.33%)	26 (46.42%)	2.295	0.01
Tirofiban infusion	39 (81.25%)	49 (87.50%)	0.442	0.863
Balloon angioplasty only	10 (20.83%)	15 (26.78%)	0.651	0.270
Balloon and stenting angioplasty	27 (62.50%)	32 (58.13%)	0.484	0.11
Final successful recanalization	40 (83.33%)	42 (75%)	0.709	0.529
Puncture to final recanalization time, min	78.05 ± 30.55	73.61 ± 24.66	1.121	0.01

LKW, last known well.

TABLE 3 | Clinical outcomes at 3-month follow-up.

Variables	Solumbra ($n = 48$)	ADAPT ($n = 56$)	χ^2/t	P
Hemorrhagic complication				
HT	12 (25.00%)	16 (28.57%)	0.111	0.806
PH 2	6 (12.50%)	5 (8.93%)	0.571	0.108
SAH	3 (6.25%)	4 (7.1%)	0.177	0.761
sICH	9 (18.75)	11 (19.64)	0.812	0.358
Good functions (mRS 0–2)	24 (50.00%)	30 (53.57%)	0.111	0.806
Independent functions (mRS 0–1)	16 (33.33%)	21 (37.50%)	0.561	0.426
Mortality	10 (20.83)	12 (21.42)	0.623	0.437

HT, hemorrhagic transformation; PH2, parenchymal hemorrhage, type 2; SAH, subarachnoid hemorrhage; sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin scale score.

measures including balloon angioplasty, stenting, and intra-arterial glycoprotein IIb/IIIa inhibitor infusion, even though the rates for favorable outcomes, mortality, and symptomatic intracranial hemorrhage were not significantly different between the two groups. In investigating endovascular and clinical outcomes of vertebrobasilar intracranial atherosclerosis-related LVO, Baek et al. (28) also found a similar recanalization rate in patients of LVO with or without concurrent intracranial atherosclerosis, but the recanalization using conventional endovascular modalities such as stent retriever thrombectomy, contact aspiration, or intra-arterial urokinase infusion was less successful in patients with atherosclerosis-related LVO. In our study using the Solumbra technique with the stent retriever combined with aspiration vs. the ADAPT technique of contact aspiration, similar effects and clinical outcomes had been achieved. However, the ADAPT technique was quicker to achieve recanalization than the Solumbra technique, especially when a larger suction catheter is applied, which had been confirmed by some authors (19, 20). The mechanism of suction in the ADAPT technique is to aspirate the whole thrombus without further advancing the catheter once the catheter is in place (29), whereas the Solumbra technique is to send a stent to capture the thrombus and pull it out. The ADAPT technique is thus much quicker than the Solumbra technique in resuming blood flow. Being quicker, cheaper, and comparable in the clinical outcomes and safety, the ADAPT technique has thus become a comparable technique to the standard Solumbra technique in recanalizing intracranial atherosclerosis-related LVO. However, compared with the Solumbra technique, the ADAPT technique has a significantly ($P < 0.05$) greater rate (33.33 vs. 46.42%) of switching to the alternative because atherosclerosis-caused arterial stenosis and local arterial course may readily affect the efficiency of the ADAPT technique compared with the Solumbra technique. Moreover, when the suction catheter is parallel to the long axis of the thrombus in the ADAPT technique, the suction efficiency is the greatest; however, when the suction catheter forms an angle with the long axis of the thrombus (or the artery), the suction efficiency is decreased, and the thrombi may not all be aspirated (30). In the actual situation of suction, it may not always be easy to set the suction catheter parallel to the long axis of thrombus, especially in cases of ICAS-LVO, and it thus needs more remedial measures.

Recently, a study by Yoo et al. investigated the immediate effect of first-line thrombectomy devices for intracranial atherosclerosis-related occlusion using stent retrievers vs. contact aspiration (31). Successful reperfusion was more frequently achieved after first-line thrombectomy in the stent retriever group than in the contact aspiration group (77.6 vs. 43.5%, $P = 0.001$), with significantly fewer remedial measures (12.2 vs. 59.7%, $P < 0.001$) or lower iatrogenic dissection rate (8.2 vs. 29.0%, $P = 0.012$) in the stent retriever group. After remedial measures, the final successful reperfusion rate was similar in both groups (87.8 vs. 77.4%, $P = 0.247$), with no significant difference in the 3-month good outcomes (modified Rankin Scale, $P = 0.524$). However, this study was performed between 2011 and 2016 when the first-generation aspiration devices were used, while no aspiration-assisted techniques were applied in the stent retriever group. Currently, the second-generation aspiration devices with larger-diameter suction catheters had been applied and had achieved a better reperfusion rate and good prognosis rate. Moreover, the Solumbra technique had been standardized. In our study, the latest devices were used, and to compare the efficacy of these two mainstream techniques in ICAS-LVO cases may have more clinical significance.

Acute intracranial atherosclerosis-related LVO may be caused by thrombi at the stenotic location, at the segment proximal or distal to the stenosis, or covering a longer segment both proximal and distal to the stenosis. When the thrombus is only at the stenotic location, the thrombus load is small or soft with high permeability. In this situation, application of the ADAPT technique can easily remove the thrombus without damaging the intima at the stenosis caused by use of the Solumbra technique. Some authors suggested the use of balloon angioplasty for thrombus at the stenotic location (32). However, direct balloon angioplasty may cause distal embolization by escaped thrombi, injury to perforating arteries, and possible escape of the balloon or stent. For thrombi that are located at the segment only proximal to the stenosis or both proximal and distal to the stenosis, the current focus is on the management of the thrombus at the segment distal to the stenosis using the ADAPT technique. Because the aspiration catheter, if located proximal to the stenosis, has a low efficiency for aspirating thrombi distal to the stenosis, it is thus necessary to dilate the stenotic segment before navigating the aspiration catheter beyond the stenosis for aspiration. However, in doing this, the risk of thrombus escape is increased. Previous studies have demonstrated that stent pulling at the stenotic segment will damage the intima and that the stenosis will also increase the power of the stent to cut the thrombus, leading to the distal escape of more thrombi (33, 34). In our study using the ADAPT technique, we used an assisted aspiration technique as a rescue treatment in a small number of cases. A small-diameter balloon (1.5 or 2 mm) was used to predilate the stenotic segment while applying negative pressure for continuous aspiration, which effectively prevented thrombus escape distally. This is primarily based on the fact that the tip of the aspiration catheter has a 2-mm external diameter, and that after predilation with a 2-mm balloon, the passage of the aspiration catheter through the stenotic segment can limit forward flow, facilitating negative pressure aspiration of distal thrombus. Moreover, the ADAPT technique is the commonly used technique in clinics, and it has been confirmed that the aspiration catheter will not increase the risk of distal thrombus escape when passing through the stenotic segment (35). Third, a 2-mm rapid exchange balloon along a 300-mm intracranial support wire can be quickly navigated to the required location or withdrawn without increasing the operation time. Of course, if the occlusion is located in an arterial segment rich in perforating vessels, the risk of perforator occlusion will be increased if balloon dilation is performed before removal of the high-load thrombus.

Recently, the ADAPT technique has gradually gained clinical acceptance primarily because of the invention of large-caliber catheters suitable for thrombus aspiration and improvement of direct aspiration technology. The latest generation of large-diameter aspiration catheter can ensure enough local negative pressure for suction of thrombus and has excellent flexibility for passing through tortuous blood vessels to reach the required location, being more effective especially for cardiogenic or arterial emboli with large load. However, the key to the ADAPT technique is to ensure sufficient local negative pressure for aspiration. For intracranial atherosclerosis-related LVO with tortuous vessels or long segment stenosis, the effect of aspiration and efficiency will be affected even with balloon predilation because the large caliber catheter still has the risk of cutting plaques, causing vasospasm or even arterial dissection when passing through the stenosis. Tortuous vessels and long-segment stenosis may direct the negative pressure toward the vascular wall, affecting the treatment effect and efficiency.

Some limitations existed in this study including the retrospective nature, single center study, a small cohort of patients, and the enrolled Chinese patients only. Moreover, some patients had intravenous thrombolysis before enrollment, which may affect the effect of mechanical thrombectomy. All these factors may affect the generalization of the outcome of this study. Future studies will have to resolve these issues for better clinical outcomes.

CONCLUSION

In conclusion, in patients with acute intracranial atherosclerosis-related LVO, clinical outcomes and safety treated with the ADAPT technique are comparable with those achieved with the Solumbra technique even though additional remedial measures are required for both groups for complete recanalization.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of Henan Provincial People's

Hospital, Henan university. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Z-SL, T-FZ, QL, L-FZ, and Z-LW collected the data. Z-SL, T-XL, and B-LG designed the study. Z-SL and B-LG analyzed the data. L-FZ supervised the study. Z-SL wrote the original article. B-LG revised the article. All authors have read and approved the manuscript.

FUNDING

This study was funded by the Scientific and Technological Project (Nos. SGBJ2018063 and SGBJ202002001) of Henan Provincial Health Commission.

REFERENCES

1. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke*. (2007) 38:967–73. doi: 10.1161/01.STR.0000258112.14918.24
2. 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*. (2018) 10:i20–5. doi: 10.1136/neurintsurg-2013-010713.rep
3. 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
4. Hong KS, Ko SB, Yu KH, Jung C, Park SQ, Kim BM, et al. Update of the Korean clinical practice guidelines for endovascular recanalization therapy in patients with acute ischemic stroke. *J Stroke*. (2016) 18:102–13. doi: 10.5853/jos.2015.01655
5. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al. 2015 American heart association/American stroke association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2015) 46:3020–35. doi: 10.1161/STR.0000000000000074
6. 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.0000000000000172
7. Kang DH, Jung C, Yoon W, Kim SK, Baek BH, Kim JT, et al. Endovascular thrombectomy for acute basilar artery occlusion: a multicenter retrospective observational study. *J Am Heart Assoc*. (2018) 7:e009419. doi: 10.1161/JAHA.118.009419
8. 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*. (2020). doi: 10.1007/s00062-020-00899-x. [Epub ahead of print].
9. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Song D, et al. Importance of truncal-type occlusion in stentriever-based thrombectomy for acute stroke. *Neurology*. (2016) 87:1542–50. doi: 10.1212/WNL.0000000000003202
10. Lee JS, Hong JM, Lee KS, Suh HI, Choi JW, Kim SY. Primary stent retrieval for acute intracranial large artery occlusion due to atherosclerotic disease. *J Stroke*. (2016) 18:96–101. doi: 10.5853/jos.2015.01347
11. Matias-Guiu JA, Serna-Candel C, Matias-Guiu J. Stroke etiology determines effectiveness of retrievable stents. *J Neurointerv Surg*. (2014) 6:e11. doi: 10.1136/neurintsurg-2012-010395
12. Al Kasab S, 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
13. 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
14. Delgado Almandoz JE, Kayan Y, Young ML, Fease JL, Scholz JM, Milner AM, et al. Comparison of clinical outcomes in patients with acute ischemic strokes treated with mechanical thrombectomy using either solumbra or adapt techniques. *J Neurointerv Surg*. (2016) 8:1123–8. doi: 10.1136/neurintsurg-2015-012122
15. Prochazka V, Jonszta T, Czerny D, Krajca J, Roubec M, Hurtikova E, et al. Comparison of mechanical thrombectomy with contact aspiration, stent retriever, and combined procedures in patients with large-vessel occlusion in acute ischemic stroke. *Med Sci Monit*. (2018) 24:9342–53. doi: 10.12659/MSM.913458
16. Deshaies EM. Tri-axial system using the solitaire-fr and penumbra aspiration microcatheter for acute mechanical thrombectomy. *J Clin Neurosci*. (2013) 20:1303–5. doi: 10.1016/j.jocn.2012.10.037
17. Humphries W, Hoit D, Doss VT, Elijovich L, Frei D, Loy D, et al. Distal aspiration with retrievable stent assisted thrombectomy for the treatment of acute ischemic stroke. *J Neurointerv Surg*. (2015) 7:90–4. doi: 10.1136/neurintsurg-2013-010986
18. Lee JS, Hong JM, Lee SJ, Joo IS, Lim YC, Kim SY. The combined use of mechanical thrombectomy devices is feasible for treating acute carotid terminus occlusion. *Acta Neurochir (Wien)*. (2013) 155:635–41. doi: 10.1007/s00701-013-1649-5
19. Lapergue B, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, et al. Effect of endovascular contact aspiration vs. stent retriever on revascularization in patients with acute ischemic stroke and large vessel occlusion: the aster randomized clinical trial. *JAMA*. (2017) 318:443–52. doi: 10.1001/jama.2017.9644
20. 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
21. Lee JS, Lee S-J, Yoo JS, Hong JH, Kim CH, Kim YW, et al. Prognosis of acute intracranial atherosclerosis-related occlusion after endovascular treatment. *J Stroke*. (2018) 20:394–403. doi: 10.5853/jos.2018.01627
22. Qureshi AI, Caplan LR. Intracranial atherosclerosis. *Lancet*. (2014) 383:984–98. doi: 10.1016/S0140-6736(13)61088-0
23. Tsang ACO, Lau KK, Tsang FCP, Tse MMY, Lee R, Lui WM. Severity of intracranial carotid artery calcification in intracranial atherosclerosis-related occlusion treated with endovascular thrombectomy. *Clin Neurol Neurosurg*. (2018) 174:214–6. doi: 10.1016/j.clineuro.2018.09.030
24. Ragoschke-Schumm A, Walter S. Dawn and defuse-3 trials: is time still important? *Radiologe*. (2018) 58:20–3. doi: 10.1007/s00117-018-0406-4
25. Gory B, Lapergue B, Blanc R, Labreuche J, Ben Machaa M, Duhamel A, et al. Contact aspiration versus stent retriever in patients with acute ischemic stroke with m2 occlusion in the aster randomized trial (contact aspiration versus stent retriever for successful revascularization). *Stroke*. (2018) 49:461–4. doi: 10.1161/STROKEAHA.117.019598
26. Zhu F, Lapergue B, Kyheng M, Blanc R, Labreuche J, Ben Machaa M, et al. Similar outcomes for contact aspiration and stent retriever use according to the admission clot burden score in aster. *Stroke*. (2018) 49:1669–77. doi: 10.1161/STROKEAHA.118.021120
27. Qin C, Shang K, Xu SB, Wang W, Zhang Q, Tian DS. Efficacy and safety of direct aspiration versus stent-retriever for recanalization in acute cerebral infarction: a prisma-compliant systematic review and meta-analysis. *Medicine (Baltimore)*. (2018) 97:e12770. doi: 10.1097/MD.0000000000012770

28. Baek JH, Kim BM, Heo JH, Kim DJ, Nam HS, Kim YD. Endovascular and clinical outcomes of vertebrobasilar intracranial atherosclerosis-related large vessel occlusion. *Front Neurol*. (2019) 10:215. doi: 10.3389/fneur.2019.00215
29. Alawieh A, Chatterjee AR, Vargas J, Chaudry MI, Lena J, Turner R, et al. Lessons learned over more than 500 stroke thrombectomies using adapt with increasing aspiration catheter size. *Neurosurgery*. (2020) 86:61–70. doi: 10.1093/neuros/nyy444
30. Bernava G, Rosi A, Boto J, Brina O, Kulcsar Z, Czarnetzki C, et al. Direct thromboaspiration efficacy for mechanical thrombectomy is related to the angle of interaction between the aspiration catheter and the clot. *J Neurointerv Surg*. (2020) 12:396–400. doi: 10.1136/neurintsurg-2019-015113
31. Yoo J, Lee S-J, Hong J-H, Kim Y-W, Hong JM, Kim C-H, et al. Immediate effects of first-line thrombectomy devices for intracranial atherosclerosis-related occlusion: stent retriever versus contact aspiration. *BMC Neurol*. (2020) 20:283. doi: 10.1186/s12883-020-01862-6
32. 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
33. Kim SK, Yoon W, Heo TW, Park MS, Kang HK. Negative susceptibility vessel sign and underlying intracranial atherosclerotic stenosis in acute middle cerebral artery occlusion. *AJNR Am J Neuroradiol*. (2015) 36:1266–71. doi: 10.3174/ajnr.A4280
34. Lee JS, Hong JM, Kim JS. Diagnostic and therapeutic strategies for acute intracranial atherosclerosis-related occlusions. *J Stroke*. (2017) 19:143–51. doi: 10.5853/jos.2017.00626
35. Gurkas E, Akpinar CK, Aytac E. Advance: an effective and feasible technique in acute stroke treatment. *Interv Neuroradiol*. (2017) 23:166–72. doi: 10.1177/1591019916682358

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 07 April 2021
doi: 10.3389/fneur.2021.648081

OPEN ACCESS

Edited by:
Liqun Jiao,
Capital Medical University, China

Reviewed by:
Israr Ul Haq,
St. Vincent Mercy Medical Center, United States
Woong Yoon,
Chonnam National University Medical School, South Korea

***Correspondence:**
Xinfeng Liu
xfliu2@vip.163.com
Rui Liu
liurui8616@163.com

†ORCID:
Mingming Zha
orcid.org/0000-0001-7208-1514
Min Wu
orcid.org/0000-0003-4485-975X
Xianjun Huang
orcid.org/0000-0003-2646-982X
Kangmo Huang
orcid.org/0000-0003-1354-5459
Qingwen Yang
orcid.org/0000-0002-9746-8317
Dong Yang
orcid.org/0000-0002-2695-0499
Rui Liu
orcid.org/0000-0002-3504-368X
Xinfeng Liu
orcid.org/0000-0002-8182-9632

‡*These authors have contributed equally to this work*

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *31 December 2020*
Accepted: *25 February 2021*
Published: *07 April 2021*

Citation:
Zha M, Wu M, Huang X, Zhang X, Huang K, Yang Q, Cai H, Ji Y, Lv Q, Yang D, Dai Q, Liu R and Liu X (2021) A Pre-Interventional Scale to Predict in situ Atherosclerotic Thrombosis in Acute Vertebrobasilar Artery Occlusion Patients. Front. Neurol. 12:648081. doi: 10.3389/fneur.2021.648081

A Pre-Interventional Scale to Predict *in situ* Atherosclerotic Thrombosis in Acute Vertebrobasilar Artery Occlusion Patients

Mingming Zha[1†‡], Min Wu[2†‡], Xianjun Huang[3†], Xiaohao Zhang[4], Kangmo Huang[4†], Qingwen Yang[1†], Haodi Cai[1], Yachen Ji[3], Qiushi Lv[4], Dong Yang[4†], Qiliang Dai[4], Rui Liu[4*†] and Xinfeng Liu[1,2,4*†]

[1] Department of Neurology, Jinling Hospital, Medical School of Southeast University, Nanjing, China, [2] Department of Neurology, Jinling Hospital, The First School of Clinical Medicine, Southern Medical University, Nanjing, China, [3] Department of Neurology, The First Affiliated Hospital of Wannan Medical College, Wuhu, China, [4] Department of Neurology, Jinling Hospital, Affiliated Medical School of Nanjing University, Nanjing, China

Background and Purpose: Determining the occlusion mechanism before endovascular treatment (EVT) is of great significance for acute large vessel occlusion patients. We aimed to develop and validate a simple pre-EVT scale with readily available variables for predicting *in situ* atherosclerotic thrombosis (ISAT) in acute vertebrobasilar artery occlusion (VBAO) patients.

Materials and Methods: Consecutive patients were retrieved from Nanjing Stroke Registry Program between January 2014 and December 2019 as a derivation cohort. Anonymous data of consecutive patients between January 2014 and December 2019 were collected from another comprehensive stroke center as an external validation cohort. Demographics, medical histories, and clinical characteristics were collected. ISAT was defined according to the following criteria: (a) detection of moderate to severe (≥50%) stenosis or stenosis with significant distal flow impairment at the occluded segment when successful reperfusion was achieved; (b) transient visualization of eccentric plaque contour or a recurrent re-occlusion tendency when reperfusion was unsuccessful. Logistic regression was taken to develop a predictive scale. The performance of the scale was assessed by area under the receiver operating characteristic curve (AUC) and Hosmer–Lemeshow test.

Results: ISAT was observed in 41 of 95 (43.2%) patients included in the derivation cohort. The ISAT predictive scale consisted of three pre-interventional predictors, including the history of hypertension, atrial fibrillation rhythm, and baseline serum glucose level ≥7.55 mmol/L. The model depicted acceptable calibration (Hosmer–Lemeshow test, $P = 0.554$) and good discrimination (AUC, 0.853; 95% confidence interval, 0.775–0.930). The optimal cutoff value of the ISAT scale was 1 point with 95.1% sensitivity, 64.8% specificity, and 77.9% accuracy. In the validation cohort, the discrimination ability was still promising with an AUC value of 0.800 (0.682–0.918).

Conclusion: The three-item scale comprised of the history of hypertension, atrial fibrillation rhythm, and dichotomous serum glucose level had a promising predictive value for ISAT before EVT in acute VBAO patients.

Keywords: endovascular treatment, vertebrobasilar artery occlusion, *in situ* atherosclerotic thrombosis, acute ischemic stroke, predictive model

INTRODUCTION

Acute vertebrobasilar artery occlusion (VBAO) is one of the most devastating types of acute ischemic stroke with a high disability and mortality rate (1). The best treatment choice for VBAO is still under debate (2), but evidence on the effectiveness of endovascular treatment (EVT) in treating VBAO is accumulating (3–5).

Considering the heterogenicity in occlusion mechanisms, VBAO patients can be categorized into different subtypes (6, 7). Different occlusion mechanisms exert influences on device selections, reperfusion procedures, and clinical prognosis (8–10). One of the most frequent causes of VBAO is atherosclerotic occlusion resulting from local thrombosis due to severe stenosis (1). Previous studies indicate that intracranial atherosclerosis-related occlusion has a higher intraprocedural re-occlusion rate, need for rescue therapies, and longer puncture-to-reperfusion time (11). Figuring out the exact occlusion mechanism of VBAO is beneficial for EVT procedures.

Analyses and predictions of occlusion types have been investigated in previous studies (12, 13). However, these studies usually rely heavily on digital subtraction angiography (DSA) characteristics, which seems lagging in predicting models. Simple predictive scales with readily available parameters before EVT are needed.

Thus, we performed a retrospective analysis on consecutive patients from a prospectively enrolled stroke database to develop a pre-EVT predictive scale for ISAT in VBAO patients and tested its performance in a cohort enrolled from another comprehensive stroke center.

METHODS

Patient Selection

De-identified data collected from the Nanjing Stroke Registry Program were taken as the derivation cohort. Nanjing Stroke Registry Program is a prospectively maintained database based on Jinling Hospital. Detailed introductions on this registry have been published previously (14). The validation cohort was established based on de-identified data from the Neurology Department of the Yijishan Hospital.

Between January 2014 and December 2019, angiographically proved acute VBAO patients who underwent EVT (e.g., intra-arterial thrombolysis/glycoprotein IIb/IIIa inhibitor, mechanical thrombectomy, angioplasty, or various combinations of these) were included. Patients who had non-occlusion, sub-occlusion, and estimated occlusion time to puncture >24 h were excluded. Patients were also excluded if EVT procedures were aborted owing to an inability to advance the guidewire, catheter, or other EVT devices to the occlusion site and without endovascular rescue therapies. Analyses on the Nanjing Stroke Registry Program were approved by the ethical committee of Jinling Hospital. Informed consent was waived due to its retrospective design.

Data Collection

Demographic characteristics, medical histories, results of electrocardiogram examination on admission, imaging scale score, and lab results were collected and double-checked by two neurologists (MZ and MW). Severe stroke at the onset was defined when coma, quadriplegia, and locked-in syndrome were presenting symptoms (15). Prodrome was defined as stroke-associated symptoms before index events (coma, quadriplegia, and locked-in syndrome) of VBAO (16). Occlusion mechanisms were diagnosed according to established criteria (7), and ISAT was defined according to the following criteria: (a) detection of moderate to severe (≥50%) stenosis or stenosis with significant distal flow impairment at the occluded segment when successful reperfusion was achieved; (b) transient visualization of eccentric plaque contour or a recurrent re-occlusion tendency when reperfusion was unsuccessful. The embolism mechanism was diagnosed when there was no evidence of ISAT, including (a) complete recanalization without residual stenosis in occluded segments and (b) have established source of embolism with or without reperfusion (8).

Diagnoses of ISAT were independently finished by two experienced neurologists (MZ and MW) following the flowchart in the published reference (7), and disparities were solved by an experienced neuro-interventionalist (RL). Interobserver agreement for ISAT was assessed using Cohen's kappa coefficient (Cohen κ). Scores of the baseline National Institute of Health Stroke Scale (NIHSS) (17), the Glasgow Coma Scale (GCS) (18), and the modified Rankin Scale (mRS) (19) were collected. posterior circulation Acute Stroke Prognosis Early Computed Tomography Score (pc-ASPECTS) (20) was used to analyze brain ischemia before EVT.

Statistical Analyses

Multiple imputations with chain equations were performed to account for missing values (≤10%). Patients were categorized into the ISAT group and the embolism group. Continuous data were expressed as mean (standard deviation, SD) if normally distributed or median (interquartile range, IQR) if not. Categorical data were expressed as number (percentage). Clinical parameters between the ISAT group and the embolism group were compared with *t*-test, Mann–Whitney U test, Chi-square test, and Fisher exact test as appropriate.

Candidate variables with P-value < 0.1 on univariate analysis were included in multivariable regression. Continuous variables were transformed into dichotomous variables to facilitate application before enrolling in the regression model, and the cutoff values were calculated with the receiver operating characteristic (ROC) curve by maximizing the Youden index (sensitivity + specificity − 1). Colinearity diagnosis was performed by using the variance inflation factor (VIF). Binary logistic regression (forward, likelihood ratio) was taken to generate the regression model. The discrimination and calibration of the model were assessed by the area under the ROC curve (AUC) and the Hosmer–Lemeshow test, respectively. β-coefficients obtained from the regression model were rounded to the closest integer and used to generate the scoring system of the ISAT scale (21). ROC curve analysis was used to calculate the optimal cutoff value of the ISAT scale.

Two-sided P-values < 0.05 were considered statistically significant. Analyses were performed using the SPSS software package, version 25 (IBM-Armonk, NY) and R statistical software, version 3.6.3 (22).

RESULTS

Overview

Between January 2014 and December 2019, 95 patients in the derivation cohort fulfilled the criteria and were enrolled in the final analyses (**Figure 1**). The mean age was 62.2 years old, and men accounted for 75.8% (72/95). Median (IQR) baseline NIHSS and GCS score were 26.0 (17.5, 29.5) and 6.0 (6.0, 11.0), respectively. The median mRS score on admission was 5.0 (4.0, 5.0). Ten (10.5%) patients had a history of coronary heart disease. Thirty-five (36.8%) patients had a smoking history, and the prevalence of hypertension history was 69.5%. Sixteen (16.8%) patients were diagnosed with atrial fibrillation (AF) previously, and electrocardiograms (ECGs) on admission indicated that 24 (25.3%) patients had AF rhythm. Twenty-seven (28.4%) patients had severe stroke at the onset. According to the appearances of DSA documents, 41 (43.2%) patients were categorized into the ISAT group and 54 (56.8%) into the embolism group. There was a good agreement on the presence of ISAT (Cohen κ: 0.782 in the derivation cohort and 0.783 in the validation cohort) between two independent neurologists.

Predictors of *in situ* Atherosclerotic Thrombosis

Table 1 illustrates the comparisons of clinical parameters between the ISAT group and the embolism group. The average age in the ISAT group was significantly lower than that in the embolism group (59.5 vs. 64.3 years old, $P = 0.039$). The ISAT group had a lower percentage of AF history (2.4% vs. 27.8%, $P = 0.001$) and a higher proportion of hypertension history (85.4% vs. 57.4%, $P = 0.003$) when compared with the embolism group. Evaluations of stroke severity according to medical histories illustrated that fewer patients in the ISAT

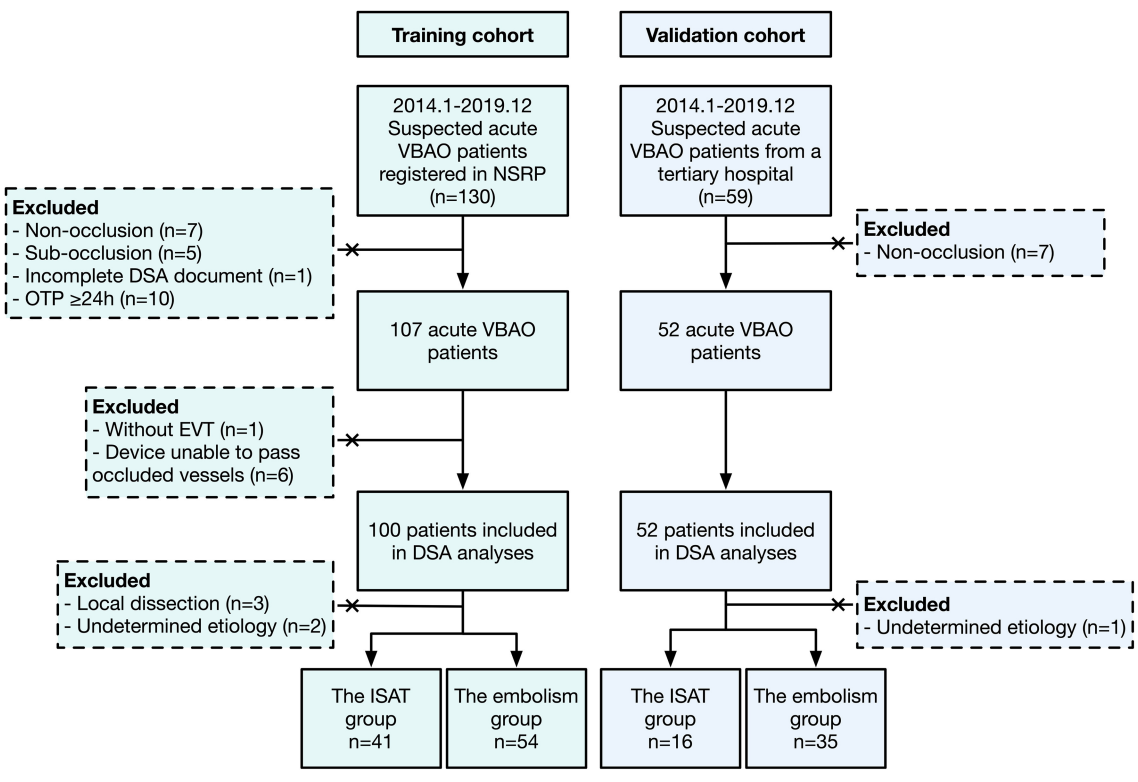


FIGURE 1 | The flowchart of this study. VBAO, vertebrobasilar artery occlusion; NSRP, Nanjing Stroke Registry Program; DSA, digital subtraction angiography; OTP, onset to puncture; EVT, endovascular treatment; ISAT, *in situ* atherosclerotic thrombosis.

TABLE 1 | Demographics and clinical characteristics between the *in situ* atherosclerotic thrombosis group and the embolism group.

Variable	The embolism group ($n = 54$)	The ISAT group ($n = 41$)	*P-value*
Age, year, mean (SD)	64.3 (11.4)	59.5 (10.9)	0.039
Male, *n* (%)	37 (68.5)	35 (85.4)	0.058
SBP, mmHg, median [IQR]	145.0 [129.2, 158.0]	149.0 [133.0, 170.0]	0.245
DBP, mmHg, median [IQR]	80.0 [73.2, 89.8]	86.0 [78.0, 97.0]	0.021
Medical history			
Coronary heart disease, *n* (%)	7 (13.0)	3 (7.3)	0.507
AF, *n* (%)	15 (27.8)	1 (2.4)	0.001
Hypertension, *n* (%)	31 (57.4)	35 (85.4)	0.003
Hyperlipidemia, *n* (%)	1 (1.9)	4 (9.8)	0.162
Diabetes mellitus, *n* (%)	9 (16.7)	10 (24.4)	0.351
Acute ischemic stroke, *n* (%)	8 (14.8)	10 (24.4)	0.238
Intracranial hemorrhage, *n* (%)	2 (3.7)	1 (2.4)	1.000
Smoking, *n* (%)	19 (35.2)	15 (36.6)	0.888
Prodrome, *n* (%)	19 (35.2)	18 (43.9)	0.388
Severe stroke at the onset, *n* (%)	22 (40.7)	5 (12.2)	0.002
AF rhythm, *n* (%)	23 (42.6)	1 (2.4)	<0.001
Admission NIHSS score, median [IQR]	27.0 [18.2, 30.0]	25.0 [12.0, 27.0]	0.044
Admission GCS score, median [IQR]	6.0 [4.5, 8.8]	6.0 [6.0, 13.0]	0.113
Admission mRS score, median [IQR]	5.0 [4.0, 5.0]	5.0 [4.0, 5.0]	0.094
pc-ASPECTS, median [IQR]	8.0 [8.0, 9.0]	8.0 [7.0, 9.5]	0.639

ISAT, in situ atherosclerotic thrombosis; SD, standard deviation; SBP, systolic blood pressure; IQR, interquartile range; DBP, diastolic blood pressure; AF, atrial fibrillation; NIHSS, National Institute of Health Stroke Scale; GCS, Glasgow Coma Scale; mRS, modified Rankin Scale; pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early Computed Tomography Score.

TABLE 2 | Comparisons of laboratory tests between the *in situ* atherosclerotic thrombosis group and the embolism group.

Variable	The embolism group ($n = 54$)	The ISAT group ($n = 41$)	*P-value*
White blood cell, *10^9/L, median [IQR]	8.6 [7.1, 12.3]	10.2 [7.9, 12.0]	0.286
Neutrophil-lymphocyte ratio, median [IQR]	6.17 [3.96, 11.38]	5.98 [3.66, 8.86]	0.578
Platelet count, *10^9/L, mean (SD)	203.1 (69.3)	212.0 (66.4)	0.533
Glucose level, mmol/L, median [IQR]	6.8 [5.8, 8.0]	7.7 [6.3, 10.4]	0.018
Glycosylated hemoglobin, %, median [IQR]	6.1 [5.6, 6.6]	6.0 [5.6, 7.1]	0.850
C-reactive protein, mg/L, median [IQR]	4.0 [1.9, 10.5]	4.5 [1.4, 7.6]	0.693
ALT, U/L, median [IQR]	28.5 [21.0, 35.8]	25.0 [19.0, 39.0]	0.545
AST, U/L, median [IQR]	26.0 [21.2, 31.0]	22.0 [19.0, 29.0]	0.117
Blood urea nitrogen, mmol/L, median [IQR]	4.8 [4.1, 5.9]	5.6 [4.8, 6.4]	0.047
Creatinine, μmol/L, median [IQR]	63.5 [55.0, 77.0]	70.0 [58.0, 78.0]	0.166
Total cholesterol, mmol/L, mean (SD)	4.39 (1.02)	4.92 (1.40)	0.036
Triglyceride, mmol/L, median [IQR]	1.16 [0.90, 1.48]	1.30 [1.00, 1.82]	0.130
Blood urine acid, μmol/L, mean (SD)	333.1 (120.4)	312.9 (97.8)	0.382
Thrombin time, s, median [IQR]	17.6 [16.4, 19.4]	17.7 [16.1, 19.4]	0.952
Prothrombin Time, s, median [IQR]	11.9 [11.2, 12.6]	11.7 [11.3, 12.4]	0.676
APTT, s, median [IQR]	24.4 [22.8, 27.3]	24.3 [22.0, 28.6]	0.795
Fibrinogen, g/L, median [IQR]	2.96 [2.54, 3.46]	3.22 [2.74, 4.03]	0.129
D-dimer, mg/L, median [IQR]	1.05 [0.60, 2.98]	0.84 [0.36, 2.03]	0.293
International normalized ratio, median [IQR]	1.03 [0.97, 1.10]	1.02 [0.98, 1.06]	0.599

ISAT, in situ atherosclerotic thrombosis; IQR, interquartile range; SD, standard deviation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APTT, activated partial thromboplastin time.

group had severe stroke at the onset (12.2 vs. 40.7%, $P = 0.002$). Median baseline NIHSS score of the patients in the ISAT group was statistically lower than that in the embolism group (25.0 vs. 27.0, $P = 0.044$), while the GCS score was comparable between the two groups (6.0 vs. 6.0, $P = 0.113$). **Table 2** shows the comparisons of admission laboratory tests between the two groups. Median glucose level (7.7 vs. 6.8 mmol/L, $P = 0.018$), median blood urea nitrogen level (5.6 vs. 4.8 mmol/L, $P = 0.047$), and average total cholesterol level (4.92 vs. 4.39 mmol/L, $P = 0.036$) before EVT were significantly higher in the ISAT group.

Formation and Assessment of the Predictive Scale

After excluding colinearity and enrolling all potential predictors into a logistic regression, three variables left in the predictive model: the history of hypertension, AF rhythm, and dichotomous serum glucose level (cutoff value, 7.55 mmol/L, **Table 3**). The model depicted acceptable calibration (Hosmer–Lemeshow test, $P = 0.554$) and good discrimination (AUC, 0.853; 95% confidence interval, 0.775–0.930). The β-coefficients of the three predictors are listed in **Table 3**, and the illustration of the ISAT scale is shown in **Figure 2**. The optimal cutoff value of the predictive scale was 1 point with 95.1% sensitivity, 64.8% specificity, and 77.9% accuracy. The distributions and percentages of ISAT patients according to the predictive scale risk categories are illustrated in **Figure 3**. The percentage of ISAT increased with the rising ISAT score. ROC curves of the consecutive and dichotomous predictive scale are depicted in **Figure 4**.

External Validation

In the validation cohort (**Table 4**), the performance of the ISAT score was still promising, with an AUC value of 0.800

(0.682–0.918). When using 1 point as the optimal cutoff value, the diagnostic efficacy of the ISAT scale was 100% sensitivity, 54.3% specificity, and 68.6% accuracy. Performances of the ISAT scale in the validation cohort are depicted in **Figures 3**, **4**.

DISCUSSIONS

The ISAT predictive scale consisted of dichotomous baseline serum glucose level, history of hypertension, and AF rhythm. This scale was convenient to use and had a promising predictive value for ISAT before EVT in acute VBAO patients.

As one of the most devastating subtypes of large vessel occlusion, the mortality rate of VBAO could be as high as 90% (23). No high-quality evidence favoring EVT has been established in VBAO (2, 24). Nevertheless, the superiority of EVT toward the best medical treatment is accumulating in studies worldwide (4, 5, 25), which shed light on this research area of uncertainty. ISAT is associated with a low recanalization rate and a high ratio of rescue therapy when compared with embolism-related occlusion (6, 26). The relationship between ISAT and poor prognosis is still debated (6, 8, 27, 28). Moreover, opinions on best treatment devices in ISAT populations are still controversial. Mechanical thrombectomy alone might not be sufficient enough to deal with ISAT and is associated with re-occlusion after EVT in ISAT patients (29).

TABLE 3 | Predictors of *in situ* atherosclerotic thrombosis in the final multivariable regression model.

Variable	ß-coefficient	Standard error	Wald	OR (95% CI)	*P-value*
History of hypertension	1.649	0.611	7.283	5.203 (1.571–17.233)	0.007
Serum glucose level ≥7.55 mmol/L	1.564	0.566	7.646	4.778 (1.577–14.480)	0.006
Atrial fibrillation rhythm	−3.930	1.119	12.326	0.020 (0.002–0.176)	<0.001

OR, odds ratio; CI, confidence interval.

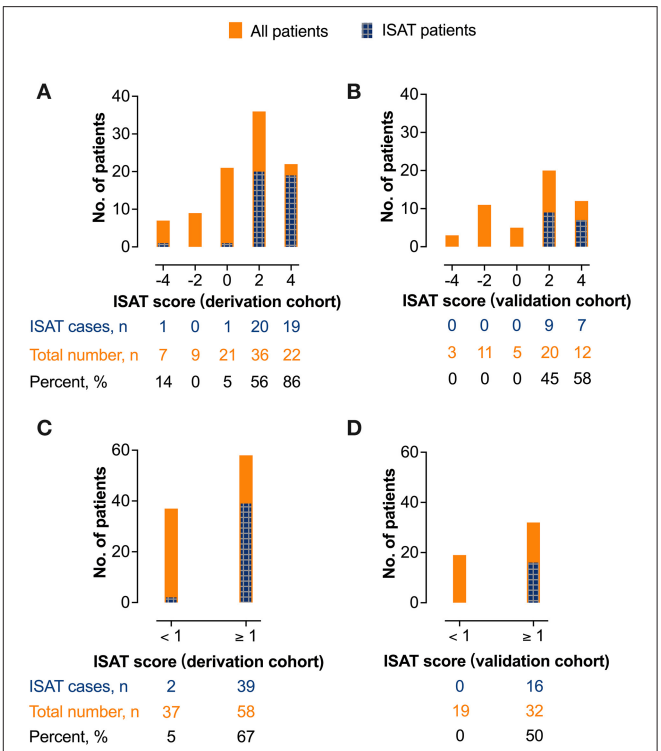


FIGURE 3 | The distributions and percentages of *in situ* atherosclerotic thrombosis patients in different predictive scale risk categories. **(A)** The derivation cohort (consecutive). **(B)** the validation cohort (consecutive). **(C)** the derivation cohort (dichotomous). **(D)** the validation cohort (dichotomous). ISAT, *in situ* atherosclerotic thrombosis.

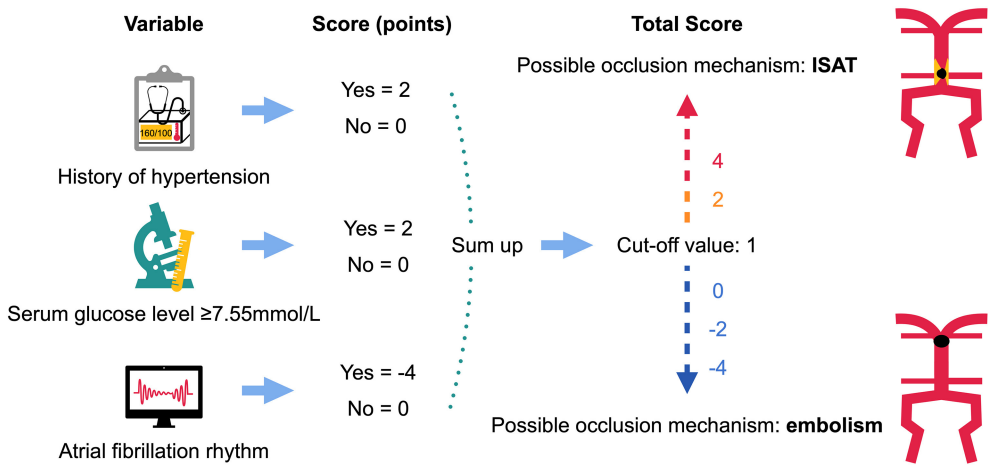


FIGURE 2 | The illustration of the predictive scale on *in situ* atherosclerotic thrombosis. ISAT, *in situ* atherosclerotic thrombosis.

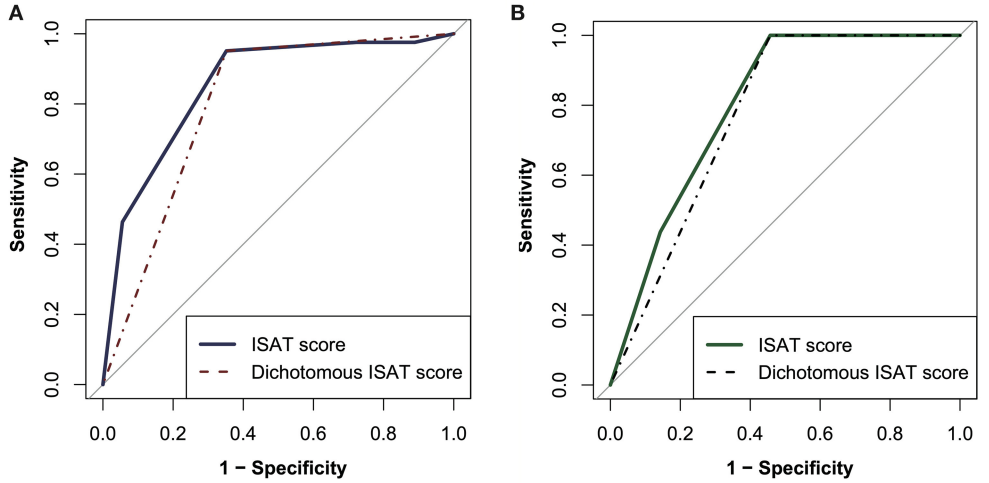


FIGURE 4 | The receiver operating characteristic curves of the consecutive and dichotomous predictive scale. **(A)** The derivation cohort. **(B)** the validation cohort. ISAT, *in situ* atherosclerotic thrombosis.

TABLE 4 | The characteristics of the validation cohort.

Variable	Overall (*n* = 51)	The embolism group (*n* = 35)	The ISAT group (*n* = 16)	*P-value*
Age, year, mean (SD)	63.6 (13.3)	65.0 (14.2)	60.6 (10.9)	0.281
Male, *n* (%)	36 (70.6)	21 (60.0)	15 (93.8)	0.014
Baseline SBP, mmHg, median [IQR]	156.0 [135.5, 170.0]	154.0 [135.0, 164.5]	164.5 [150.8, 179.0]	0.056
Baseline DBP, mmHg, median [IQR]	84.0 [76.5, 97.5]	83.0 [76.0, 90.0]	93.0 [81.5, 100.0]	0.066
Medical history				
Hypertension, *n* (%)	36 (70.6)	22 (62.9)	14 (87.5)	0.102
Diabetes mellitus, *n* (%)	12 (23.5)	8 (22.9)	4 (25.0)	1.000
Atrial fibrillation, *n* (%)	12 (23.5)	12 (34.3)	0 (0.0)	0.010
CHD, *n* (%)	7 (13.7)	5 (14.3)	2 (12.5)	1.000
Hyperlipidemia, *n* (%)	1 (2.0)	1 (2.9)	0 (0.0)	1.000
Smoking, *n* (%)	16 (31.4)	7 (20.0)	9 (56.2)	0.010
Baseline NIHSS score, median [IQR]	25.0 [17.0, 32.0]	25.0 [12.5, 32.0]	28.0 [20.0, 32.8]	0.304
Atrial fibrillation rhythm *n* (%)	15 (29.4)	15 (42.9)	0 (0.0)	0.002
Serum glucose level, mmol/L, median [IQR]	7.13 [5.58, 8.90]	7.11 [5.36, 7.80]	8.23 [6.53, 11.06]	0.025
Serum glucose level ≥7.55 mmol/L, *n* (%)	21 (41.2)	12 (34.3)	9 (56.2)	0.139
Intravenous thrombolysis, *n* (%)	2 (3.9)	2 (5.7)	0 (0.0)	1.000
OTP, min, mean (SD)	345.6 (211.1)	274.7 (127.1)	500.6 (273.1)	0.005

ISAT, in situ atherosclerotic thrombolysis; SD, standard deviation; SBP, systolic blood pressure; IQR, interquartile range; DBP, diastolic blood pressure; CHD, coronary heart disease; NIHSS, National Institute of Health Stroke Scale; OTP, onset to puncture.

Some researchers emphasize the importance of angioplasty and stenting in treating intracranial atherosclerosis-related occlusion (30, 31). Disparities between ISAT and embolism-caused large vessel occlusion (LVO) urge neuro-interventionalists to judge the exact type of occlusion and choose the optimal treatment device. Furthermore, the basilar artery is one of the most common sites of atherosclerotic lesions (32). How to predict this subtype of VBAO before EVT is a crucial clinical question waiting for clinical researchers to answer.

So far, various hypotheses on discriminations of ISAT have been put forward. Truncal type occlusion (10), tapered occlusion (33), and occluded segment (34) were all proved to be indicators of intracranial atherosclerosis-related occlusion. Baseline DSA appearance was useful to distinguish underlying etiology, but the significance of predicting ISAT by using pre-EVT variables is much higher. Early prediction could help neuro-interventionalists and nurses get ready for following EVT, choose the best treatment devices, prepare additional therapies (e.g., glycoprotein IIb/IIIa inhibitor) in advance, and face the potential challenge with mental preparations.

In previous studies, ISAT patients are much prevalent in males, hypercholesterolemia, and posterior circulation involvement (9). The percentage of AF is significantly lower in the ISAT population (8). In our research, elevated glucose level, history of hypertension, and AF rhythm were independent indicators of ISAT. History of hypertension was prevalent in the ISAT group in our study, which was correlated with previous discovery: hypertension is a kind of risk factor of intracranial artery atherosclerosis (32). AF is a well-known risk factor for ischemic stroke and systemic embolism (35). In our model, active AF status was more efficient than the history of AF in distinguishing ISAT patients, which emphasized the importance of ECG examination on admission in identifying occlusion mechanisms. High glucose levels witnessed in the

ISAT group correlated with previous research, as elevated blood glucose/hyperglycemia [fasting glucose ≥110 mg/dl (6.1 mmol/l)] is proved to be significantly associated with intracranial atherosclerosis (36), whereas the history of diabetes mellitus and glycosylated hemoglobin level were comparable between the ISAT group and the embolism group. This phenomenon might be attributed to the relatively small sample of this study. The deeper mechanism between ISAT and elevated glucose level still awaits further studies to answer.

Apart from variables left in the final model, other indicators might also be useful in distinguishing ISAT patients. ISAT is based on localized intracranial artery atherosclerosis. This long-lasting process might give additional time for collateral formation (28), and this might explain the reason why there is a lower percentage of severe stroke at the onset in the ISAT group.

Compared with previous studies, the most important strengths of our scale were convenient application, high sensitivity, and readily available parameters. It could be assessed within several minutes, and the accuracy was relatively high. The strengths of this study also included detailed data collection and credible assessments. External validation increased our persuasiveness.

However, it was worthwhile to mention the weaknesses of this study. First, potential recall and information bias were unavoidable in retrospective analyses, although various attempts (e.g., double-check the data collection process and independent evaluations) had been made. Second, a limited sample restricted the persuasiveness of our conclusion and the generalizability of the results. Third, relatively low specificity meant that some patients might be misclassified into the ISAT group and caused additional workloads for interventional doctors and nurses. Although the effectiveness of the ISAT scale was proved in the validation cohort with a lower ISAT percentage, it would be more practical to have the tools and medicines handy in the angio-suite regardless of the outcome of the scale, especially in a population where nearly half the cases were diagnosed as ISAT.

CONCLUSION

The three-item predictive scale comprised of the history of hypertension, atrial fibrillation rhythm, and dichotomous baseline serum glucose level had a promising predictive value for ISAT before EVT in acute VBAO patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethical committee of Jinling Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MZ, MW, RL, and XL designed the study. MZ, MW, XH, YJ, KH, and QY collected the data. MZ, MW, XH, YJ, XZ, RL, and XL analyzed and interpreted the data. MZ, MW, XH, XZ, KH, QY, HC, YJ, QL, DY, QD, RL, and XL drafted and modified the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

The project was partly supported by the National Natural Science Foundation of China (Grant Nos. 81901218, 81870946, 81530038, and 81701299).

REFERENCES

1. Mattle HP, Arnold M, Lindsberg PJ, Schonewille WJ, Schroth G. Basilar artery occlusion. *Lancet Neurol.* (2011) 10:1002–14. doi: 10.1016/S1474-4422(11)70229-0
2. 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.* (2020) 19:115–22. doi: 10.1016/S1474-4422(19)30395-3
3. van Houwelingen RC, Luijckx GJ, Uyttenboogaart M. Intra-arterial treatment for basilar artery occlusion-reply. *JAMA Neurol.* (2017) 74:130–1. doi: 10.1001/jamaneurol.2016.4870
4. Kang DH, Jung C, Yoon W, Kim SK, Baek BH, Kim JT, et al. Endovascular thrombectomy for acute basilar artery occlusion: A multicenter retrospective observational study. *J Am Heart Assoc.* (2018) 7:e009419. doi: 10.1161/JAHA.118.009419
5. Writing Group for the BG, Zi W, Qiu Z, Wu D, Li F, Liu H, et al. Assessment of endovascular treatment for acute basilar artery occlusion via a nationwide prospective registry. *JAMA Neurol.* (2020) 77:561–73. doi: 10.1001/jamaneurol.2020.0156
6. Baik SH, Park HJ, Kim JH, Jang CK, Kim BM, Kim DJ. Mechanical thrombectomy in subtypes of basilar artery occlusion: Relationship to recanalization rate and clinical outcome. *Radiology.* (2019) 291:730–7. doi: 10.1148/radiol.2019181924
7. Lee WJ, Jung KH, Ryu YJ, Kim JM, Lee ST, Chu K, et al. Impact of stroke mechanism in acute basilar occlusion with reperfusion therapy. *Ann Clin Transl Neurol.* (2018) 5:357–68. doi: 10.1002/acn3.536
8. Kim YW, Hong JM, Park DG, Choi JW, Kang DH, Kim YS, et al. Effect of intracranial atherosclerotic disease on endovascular treatment for patients with acute vertebrobasilar occlusion. *AJNR Am J Neuroradiol.* (2016) 37:2072–8. doi: 10.3174/ajnr.A4844
9. Lee JS, Hong JM, Lee KS, Suh HI, Demchuk AM, Hwang YH, et al. Endovascular therapy of cerebral arterial occlusions: Intracranial atherosclerosis versus embolism. *J Stroke Cerebrovasc Dis.* (2015) 24:2074–80. doi: 10.1016/j.jstrokecerebrovasdis.2015.05.003
10. 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

11. Tsang ACO, Orru E, Klostranec JM, Yang IH, Lau KK, Tsang FCP, et al. Thrombectomy outcomes of intracranial atherosclerosis-related occlusions. *Stroke.* (2019) 50:1460–6. doi: 10.1161/STROKEAHA.119.024889
12. Jin X, Shi F, Chen Y, Zheng X, Zhang J. Jet-like appearance in angiography as a predictive image marker for the occlusion of intracranial atherosclerotic stenosis. *Front Neurol.* (2020) 11:575567. doi: 10.3389/fneur.2020.575567
13. Chuming H, Yifan H, Ke X, Chukai X, Weijie Z, Hui L, et al. Association between occlusion type and etiology of acute intracranial large artery occlusion. *Front Neurol.* (2020) 11:582388. doi: 10.3389/fneur.2020.582388
14. Liu X, Xu G, Wu W, Zhang R, Yin Q, Zhu W. Subtypes and one-year survival of first-ever stroke in chinese patients: The nanjing stroke registry. *Cerebrovasc Dis.* (2006) 22:130–6. doi: 10.1159/000093241
15. Schonewille WJ, Wijman CA, 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
16. Conforto AB, de Freitas GR, Schonewille WJ, Kappelle LJ, Algra A, Group BS. Prodromal transient ischemic attack or minor stroke and outcome in basilar artery occlusion. *J Stroke Cerebrovasc Dis.* (2015) 24:2117–21. doi: 10.1016/j.jstrokecerebrovasdis.2015.05.020
17. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, et al. Measurements of acute cerebral infarction: A clinical examination scale. *Stroke.* (1989) 20:864–70. doi: 10.1161/01.STR.20.7.864
18. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet.* (1974) 2:81–4. doi: 10.1016/S0140-6736(74)91639-0
19. 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
20. Puetz V, Sylaja PN, Coutts SB, Hill MD, Dzialowski I, Mueller P, et al. Extent of hypoattenuation on ct angiography source images predicts functional outcome in patients with basilar artery occlusion. *Stroke.* (2008) 39:2485–90. doi: 10.1161/STROKEAHA.107.511162
21. Tong X, An J, Sun X, Gao F, Wang Y, Wang W, et al. A pre-intervention 4-item scale for predicting poor outcome despite successful recanalization in basilar artery occlusion. *Transl Stroke Res.* (2020) 11:1306–13. doi: 10.1007/s12975-020-00813-0
22. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing (2020). Available online at: https://www.R-project.org/
23. Hornig CR, Lammers C, Büttner T, Hoffmann O, Dorndorf W. Long-term prognosis of infratentorial transient ischemic attacks and minor strokes. *Stroke.* (1992) 23:199–204. doi: 10.1161/01.STR.23.2.199
24. van der Hoeven EJ, Schonewille WJ, Vos JA, Algra A, Audebert HJ, Berge E, et al. The basilar artery international cooperation study (basics): Study protocol for a randomised controlled trial. *Trials.* (2013) 14:200. doi: 10.1186/1745-6215-14-200
25. van Houwelingen RC, Luijckx GJ, Mazuri A, Bokkers RP, Eshghi OS, Uyttenboogaart M. Safety and outcome of intra-arterial treatment for basilar artery occlusion. *JAMA Neurol.* (2016) 73:1225–30. doi: 10.1001/jamaneurol.2016.1408
26. Mordasini P, Brekenfeld C, Byrne JV, Fischer U, Arnold M, Heldner MR, et al. Technical feasibility and application of mechanical thrombectomy with the solitaire fr revascularization device in acute basilar artery occlusion. *AJNR Am J Neuroradiol.* (2013) 34:159–63. doi: 10.3174/ajnr.A3168
27. Lee YY, Yoon W, Kim SK, Baek BH, Kim GS, Kim JT, et al. Acute basilar artery occlusion: Differences in characteristics and outcomes after endovascular therapy between patients with and without underlying severe atherosclerotic stenosis. *AJNR Am J Neuroradiol.* (2017) 38:1600–4. doi: 10.3174/ajnr.A5233
28. 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
29. Lee JS, Hong JM, Lee KS, Suh HI, Choi JW, Kim SY. Primary stent retrieval for acute intracranial large artery occlusion due to atherosclerotic disease. *J Stroke.* (2016) 18:96–101. doi: 10.5853/jos.2015.01347
30. 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. *Interv Neuroradiol.* (2018) 24:412–20. doi: 10.1177/1591019918763380
31. 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
32. Qureshi AI, Caplan LR. Intracranial atherosclerosis. *Lancet.* (2014) 383:984–98. doi: 10.1016/S0140-6736(13)61088-0
33. Garcia-Bermejo P, Patro SN, Ahmed AZ, Al Rumaihi G, Akhtar N, Kamran S, et al. Baseline occlusion angiographic appearance on mechanical thrombectomy suggests underlying etiology and outcome. *Front Neurol.* (2019) 10:499. doi: 10.3389/fneur.2019.00499
34. Zhang X, Luo G, Jia B, Mo D, Ma N, Gao F, et al. Differences in characteristics and outcomes after endovascular therapy: a single-center analysis of patients with vertebrobasilar occlusion due to underlying intracranial atherosclerosis disease and embolism. *Interv Neuroradiol.* (2019) 25:254–60. doi: 10.1177/1591019918811800
35. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke.* (1991) 22:983–8. doi: 10.1161/01.STR.22.8.983
36. Park JH, Kwon HM, Roh JK. Metabolic syndrome is more associated with intracranial atherosclerosis than extracranial atherosclerosis. *Eur J Neurol.* (2007) 14:379–86. doi: 10.1111/j.1468-1331.2007.01682.x

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.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 09 April 2021
doi: 10.3389/fneur.2021.628523

Factors Influencing Recanalization After Mechanical Thrombectomy With First-Pass Effect for Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

Xuesong Bai[1,2†], Xiao Zhang[1,2†], Jie Wang[1,2†], Yinhang Zhang[1,2], Adam A. Dmytriw[3], Tao Wang[1,2], Ran Xu[1,2], Yan Ma[1,2], Long Li[1,2], Yao Feng[1,2], Carolina Severiche Mena[4], Kun Yang[5], Xue Wang[6], Haiqing Song[7], Qingfeng Ma[7] and Liqun Jiao[1,2,8]*

[1] China International Neuroscience Institute, Beijing, China, [2] Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China, [3] Neuroradiology & Neurointervention Service, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States, [4] Pontifical Bolivarian University, Medellín, Colombia, [5] Department of Evidence-Based Medicine, Xuanwu Hospital, Capital Medical University, Beijing, China, [6] Medical Library, Xuanwu Hospital, Capital Medical University, Beijing, China, [7] Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China, [8] Department of Interventional Neuroradiology, Xuanwu Hospital, Capital Medical University, Beijing, China

OPEN ACCESS

Edited by:
Jin Soo Lee,
Ajou University, South Korea

Reviewed by:
Yong-Won Kim,
Kyungpook National University Hospital, South Korea
Tareq Kass-Hout,
Rush University Medical Center, United States

***Correspondence:**
Liqun Jiao
liqunjiao@sina.cn

[†]These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: 12 November 2020
Accepted: 08 March 2021
Published: 09 April 2021

Citation:
Bai X, Zhang X, Wang J, Zhang Y, Dmytriw AA, Wang T, Xu R, Ma Y, Li L, Feng Y, Mena CS, Yang K, Wang X, Song H, Ma Q and Jiao L (2021) Factors Influencing Recanalization After Mechanical Thrombectomy With First-Pass Effect for Acute Ischemic Stroke: A Systematic Review and Meta-Analysis. Front. Neurol. 12:628523. doi: 10.3389/fneur.2021.628523

Background: First-pass effect (FPE) is increasingly recognized as a predictor of good outcome in large vessel occlusion (LVO). This systematic review and meta-analysis aimed to elucidate the factors influencing recanalization after mechanical thrombectomy (MT) with FPE in treating acute ischemic stroke (AIS).

Methods: Main databases were searched for relevant randomized controlled trials (RCTs) and observational studies reporting influencing factors of MT with FPE in AIS. Recanalization was assessed by the modified thrombolysis in cerebral ischemia (mTICI) score. Both successful (mTICI 2b-3) and complete recanalization (mTICI 2c-3) were observed. Risk of bias was assessed through different scales according to study design. The I^2 statistic was used to evaluate the heterogeneity, while subgroup analysis, meta-regression, and sensitivity analysis were performed to investigate the source of heterogeneity. Visual measurement of funnel plots was used to evaluate publication bias.

Results: A total of 17 studies and 6,186 patients were included. Among them, 2,068 patients achieved recanalization with FPE. The results of meta-analyses showed that age [mean deviation (MD):1.21,95% confidence interval (CI): 0.26–2.16; $p = 0.012$], female gender [odds ratio (OR):1.12,95% CI: 1.00–1.26; $p = 0.046$], diabetes mellitus (DM) (OR:1.17,95% CI: 1.01–1.35; $p = 0.032$), occlusion of internal carotid artery (ICA) (OR:0.71,95% CI: 0.52–0.97; $p = 0.033$), occlusion of M2 segment of middle cerebral artery (OR:1.36,95% CI: 1.05–1.77; $p = 0.019$), duration of intervention (MD: −27.85, 95% CI: −42.11–13.58; $p < 0.001$), time of onset to recanalization (MD: −34.63, 95% CI: −58.45–10.81; $p = 0.004$), general anesthesia (OR: 0.63,95% CI: 0.52–0.77; $p < 0.001$), and use of balloon guide catheter (BGC) (OR:1.60,95% CI: 1.17–2.18; $p = 0.003$) were significantly associated with successful recanalization with FPE. At the same time, age, female gender, duration of intervention, general anesthesia, use of BGC, and occlusion

of ICA were associated with complete reperfusion with FPE, but M2 occlusion and DM were not.

Conclusion: Age, gender, occlusion site, anesthesia type, and use of BGC were influencing factors for both successful and complete recanalization after first-pass thrombectomy. Further studies with more comprehensive observations indexes are need in the future.

Keywords: acute ischemic stroke, mechanical thrombectomy, first pass effect, influencing factors, systematic review, meta-analysis

INTRODUCTION

Stroke is the second-leading cause of global morbidity and mortality (1, 2). Mechanical thrombectomy (MT) has been widely used to treat acute ischemic stroke (AIS) patients and has proved superior over intravenous tissue-type plasminogen activator (tPA) by several landmark randomized trials (RCTs) (3–6). Thus, the American Heart and American Stroke Association recommends MT as the first-line therapy for selected AIS patients with proximal artery large vessel occlusions (LVO) (2).

However, some trials showed that functional independence in AIS patients is only around 50% even with a high recanalization rate of over 70% (3, 6). Thrombectomy with first pass effect (FPE), an emerging new metric, is strongly correlated with improved functional outcomes (7–10). Thrombectomy with FPE may have many advantages such as less vessel wall injury, lower risk of clot fragments, and decreased time to reperfusion (8, 11). Also, FPE is associated with better outcomes than MPE after achieving successful or complete recanalization (12). Thus, identifying factors influencing FPE could help clinicians and interventionalists maximize the benefit of MT through suitable patient selection and pre-interventional risk modification. There are many studies seeking to explore this phenomenon, but with inconsistent results (7, 8, 11, 13–20). For example, balloon guide catheters (BGC) and non-internal carotid artery (ICA) terminus occlusion were correlated with FPE in the study of Zaidat et al. (7), but factors such as older age, a lower systolic blood pressure, and conscious sedation were not (17).

Thus, this systematic review and meta-analysis seeks to summarize the current literature investigating influencing factors of thrombectomy with first pass and elucidate associations with it.

METHODS

This study was reported in conformity to the criterion of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (21).

Search Strategy

Eligible studies were independently searched by two reviewers from the following databases: MEDLINE, EMBASE, Web of Science, and the Cochrane Library. Clinical trial registers were also searched as potential sources. The included studies were restricted to the publication time before October 31, 2020, and the English language. The following key words were used: "acute ischemic stroke," "mechanical thrombectomy," "endovascular thrombectomy," "first pass effect," "first attempt," "recanalization." A search strategy Table is presented in detail in the online supplementary material (online **Supplementary Table 1**).

Study Selection

Patient Selection Criteria

Inclusion criteria included age ≥18 years with AIS due to large vessel occlusion, including the anterior or posterior circulation. Arterial occlusion was confirmed by computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography (DSA). Exclusion criteria included patients with baseline pre-stroke mRS score ≥3 and artery occlusion of non-atherosclerotic etiology such as dissection, moyamoya disease, vasospasm, or vasculitis. Patients with ICH, significant cerebellar mass effect, and acute hydrocephalus on CT or MRI before the onset of stroke were also excluded.

Definitions

FPE was defined as achieving successful or complete recanalization by MT after first pass regardless of thrombectomy device, such as contact aspiration and stent retriever. By contrast, non-FPE was defined as failure to achieve successful or complete recanalization by MT after first pass using different thrombectomy devices, such as contact aspiration and stent retriever.

Outcome

The primary outcome was successful recanalization with FPE, and secondary outcome was complete recanalization with FPE. The definitions of successful recanalization and complete recanalization were up to modified thrombolysis in cerebral ischemia (mTICI) score of 2b-3 and 2c-3 respectively after MT by post-interventional DSA as per usual convention (22, 23).

Studies

RCTs and observational studies including cohort studies, case-controlled studies, and case series where the number of patients exceeded 10 were included to avoid type II errors from low power (24, 25). Case reports, conference abstracts, or case series reports with the number of included patients <10 were excluded.

Selection of Studies and Data Extraction

Studies which qualified were extracted by two independent reviewers (YZ and RX). In the initial stage of screening, titles, keywords, and abstracts were screened, and irrelevant studies were then excluded. Subsequently, reviewers obtained the full articles of all the remaining studies and checked the full texts to ascertain the included variables. In addition, the reasons for inclusion or exclusion of studies after full-text check were recorded. Disagreement in study selection between two reviewers was resolved by a third reviewer (TW).

Two reviewers independently (LL and XW) extracted the data according to a standardized data extraction form. The extracted information of included studies was as follows: (1) Authors, publication time, country, number of patients in FPE and non-FPE groups, inclusion and exclusion criteria; (2) Mean age, gender, medical history, site of occlusion by angiography, admission NIHSS score, baseline ASPECTS, MT strategy, use of tPA, and procedural times. The resolution of disagreement regarding data extraction was achieved through assistance of a third reviewer (TW). For missing or unclear data in included

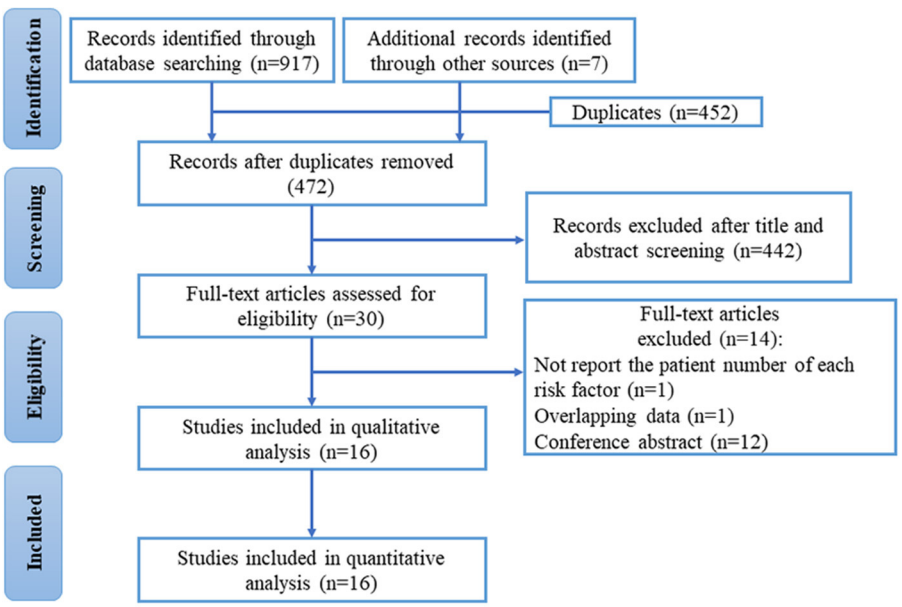


FIGURE 1 | Flow diagram for systematic review and meta-analysis.

TABLE 1 | Main characteristics of included studies.

Reference	Publication time	Included patients (*n*)	FPE (*n*, %)	Recruit period	Recanalization	Location	Center
Velasco Gonzalez et al. (20)	2020	200	102, 51.0	2016.1–2018.12	Complete	Europe	Single
Srivatsa et al. (19)	2020	76	35, 46.1	2016–2018	Complete	North America	Single
Mokin M et al. (18)	2020	609	140, 23.0	2013.3–2015.8	Complete	North America	Multiple
Mohammaden et al. (11)	2020	436	254, 58.3	2012.1–2019.5	Complete	North America	Single
Kang DH et al. (9)	2020	344	66, 19.2	2011.1–2015.12	Complete	Asia	Multiple
Ducroux et al. (28)	2020	336	97, 28.9	2015.10–2016.10	Complete	Europe	Multiple
Di Maria et al. (17)	2020	1832	417, 22.8	2013.10–2018.4	Complete	Europe	Multiple
García-Tornel et al. (10)	2020	459	213, 46.4	2012–2019	Successful	Europe	Single
Yi et al. (16)	2019	61	25, 41.0	2015.1–2016.10	Successful	Asia	Single
Tomasello et al. (15)	2019	193	97, 50.3	2017.2–2017.6	Successful	Europe	Multiple
Nikoubashman et al. (29)	2019	164	62, 37.8	2010.5–2018.1	Complete	Europe	Single
Anadani et al. (8)	2019	524	178, 34.0	2013.11–2018.1	Complete	North America	Multiple
Zaidat et al. (7)	2018	345	89, 25.8	2012.3–2013.2	Complete	North America	Multiple
Imahori et al. (30)	2018	50	21, 42.0	2015.7–2017.6	Successful	Asia	Single
Flottmann et al. (31)	2018	330	151, 46	2019–2017	Successful	Europe	Single
Baek et al. (13)	2017	136	68, 50.0	2010.9–2015,8	Successful	Asia	Single

FPE, first-pass effect.

studies, effort was made to contact the corresponding authors by e-mail in order to best guarantee the accuracy of data.

Assessment Risk Bias and Heterogeneity

Two reviewers (YF and CSM) independently assessed the risk of bias of each included study. The Cochrane Collaboration criteria were applied for RCTs, and the Newcastle–Ottawa scale was used for observational studies, including cohort studies and case–control studies (26). For case series, the method described in Methodological Quality and Synthesis of Case Series and Case Reports was applied (27). The heterogeneity of pooled outcomes was evaluated by the I^2 statistic. The I^2 statistic that was >60% demonstrated high heterogeneity, and the DerSimonian and Laird method for random-effect estimation was performed for pooling outcomes. If heterogeneity was mild or moderate, the Mantel–Haenszel method for fixed-effect estimation was applied. In instances where heterogeneity of outcomes and sufficient studies were high, we conducted subgroup analysis by site of occlusion, such as anterior circulation or posterior circulation. The meta-regression and sensitivity

TABLE 2 | Summary of meta-analysis of influencing factors for achieving successful recanalization with FPE.

	WMD/OR	95%CI		I^2 (%)	*P*-value
Age	1.21	0.26	2.16	20.1	**0.012**
Gender, female	1.12	1.00	1.26	22.2	**0.046**
Hypertension	1.10	0.97	1.26	43.1	0.134
Diabetes mellitus	1.17	1.01	1.35	0.0	**0.032**
CAD	0.88	0.69	1.13	0.0	0.320
Smoke	0.93	0.80	1.09	7.4	0.364
Atrial fibrillation	0.96	0.67	1.38	77.2	0.836
Previous anticoagulation therapy	1.16	0.93	1.45	20.6	0.197
Dyslipidemia	1.08	0.95	1.23	0.0	0.227
Initial NIHSS score	−0.65	−1.34	0.05	0.0	0.067
Systolic blood pressure	−1.31	−3.41	0.80	17.0	0.223
Diastolic blood pressure	−0.66	−2.12	0.79	42.0	0.374
Suspected stroke etiology					
Large artery atherosclerosis	1.07	0.76	1.51	0.0	0.710
Cardioembolic	1.01	0.60	1.70	72.3	0.973
Other	1.13	0.92	1.38	51.8	0.240
IV thrombolysis	1.015	0.904	1.141	0.0	0.798
Stroke demographics					
Laterality					
Right	0.56	0.14	2.15	93.4	0.398
Left	1.24	0.21	7.27	90.2	0.812
Location of occlusion					
ICA	0.71	0.52	0.97	70.6	**0.033**
M1	1.25	0.88	1.77	81.5	0.206
M2	1.36	1.05	1.77	37.5	**0.019**
Tandem occlusion	0.86	0.34	2.13	0.0	0.737
Ipsilateral AComA and PComA	0.73	0.42	1.24	34.7	0.243
Intervention characteristics					
Time of onset to puncture	20.42	0.00	40.83	0.0	0.050
Duration of intervention	−27.85	−42.11	−13.58	94.1	**<0.001**
Time of onset to recanalization	−34.63	−58.45	−10.81	0.0	**0.004**
General anesthesia	0.63	0.52	0.77	4.7	**<0.001**
Aspiration only	1.31	0.62	2.76	81.9	0.481
Stent retriever only	1.07	0.58	1.96	78.3	0.839
Aspiration and stent retriever both	0.59	0.20	1.72	90.3	0.334
Use of BGC	1.60	1.17	2.18	71.6	**0.003**
Migration to new territory	0.55	0.25	1.22	0.0	0.142

FPE, first-pass effect; WMD, weighted mean difference; OR, odds ratio; CI, confidence interval; I^2, the variation attributable to heterogeneity, CAD, coronary artery disease; NIHSS, National Institutes of Health Stroke Scale; IV, intravenous; ICA, internal carotid artery; M1, M1 segment of middle cerebral artery; M2, M2 segment of middle cerebral artery; AComA, anterior communicating artery; PComA, posterior communicating artery; BGC, balloon-guided catheter. Bold values mean P-value with significant difference.

analysis were also used to explore the potential sources of heterogeneity.

Statistical Analysis

The STATA statistical software package (version 15.0, Stata Corp, College station, Texas, USA) was used for all data analysis and heterogeneity assessments. For dichotomous data, we adopted odds ratios (OR) with 95% confidential interval (CI), and the mean difference (MD) with 95% CI was used for continuous data. The standard of p-value <0.05 was regarded as statistically significant. If the number of included studies was more than 10, publication bias was assessed by visualization of a funnel plot.

RESULTS

Study Selection and Study Characteristics

There were 924 records identified through the main database and clinical trials registers, and 16 studies were finally eligible for inclusion in the qualitative and quantitative analysis. The flow diagram of study selection is demonstrated in **Figure 1**.

Table 1 depicts the characteristics of included studies. A total of 16 studies and 6,095 patients were eligible according to inclusion criteria. Among them, 2015 (33.1%) patients achieved recanalization with FPE. All studies were published after 2016, seven conducted in Europe, five conducted in North America, and four in Asia. There were seven multicenter studies, and the remaining were single-center investigations. The number of patients in each study ranged from 50 to 1,832, and the numbers of male and female patients were essentially equal [2,929 (50.05%) vs. 2,923 (49.95%)]. Mean NIHSS scores ranged from 2 to 28. The location of occlusion by angiography was mostly within the anterior circulation, such as ICA and middle cerebral artery (MCA), particularly the M1 and M2 segments (Online **Supplementary Table 2**).

Influencing Factors

The following factors were assessed: age, gender, hypertension, DM, coronary artery disease, smoking history, atrial fibrillation, dyslipidemia, previous anticoagulation therapy, initial NIHSS score, systolic blood pressure, diastolic blood pressure, suspected stroke etiology, IV thrombolysis, stroke laterality, location

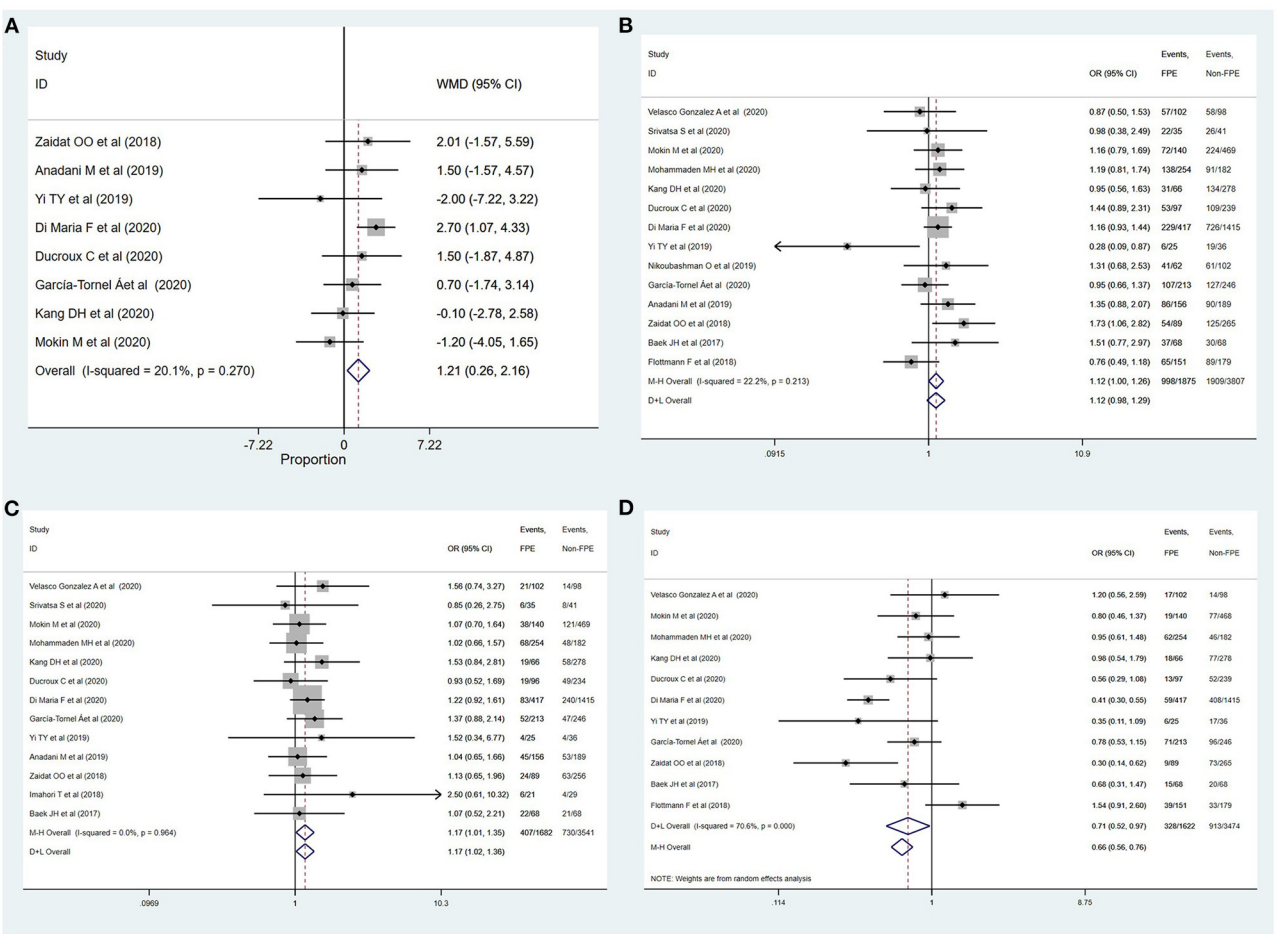


FIGURE 2 | Determinants of achieving successful recanalization with FPE. **(A)** Age; **(B)** female; **(C)** diabetes mellitus; **(D)** ICA.

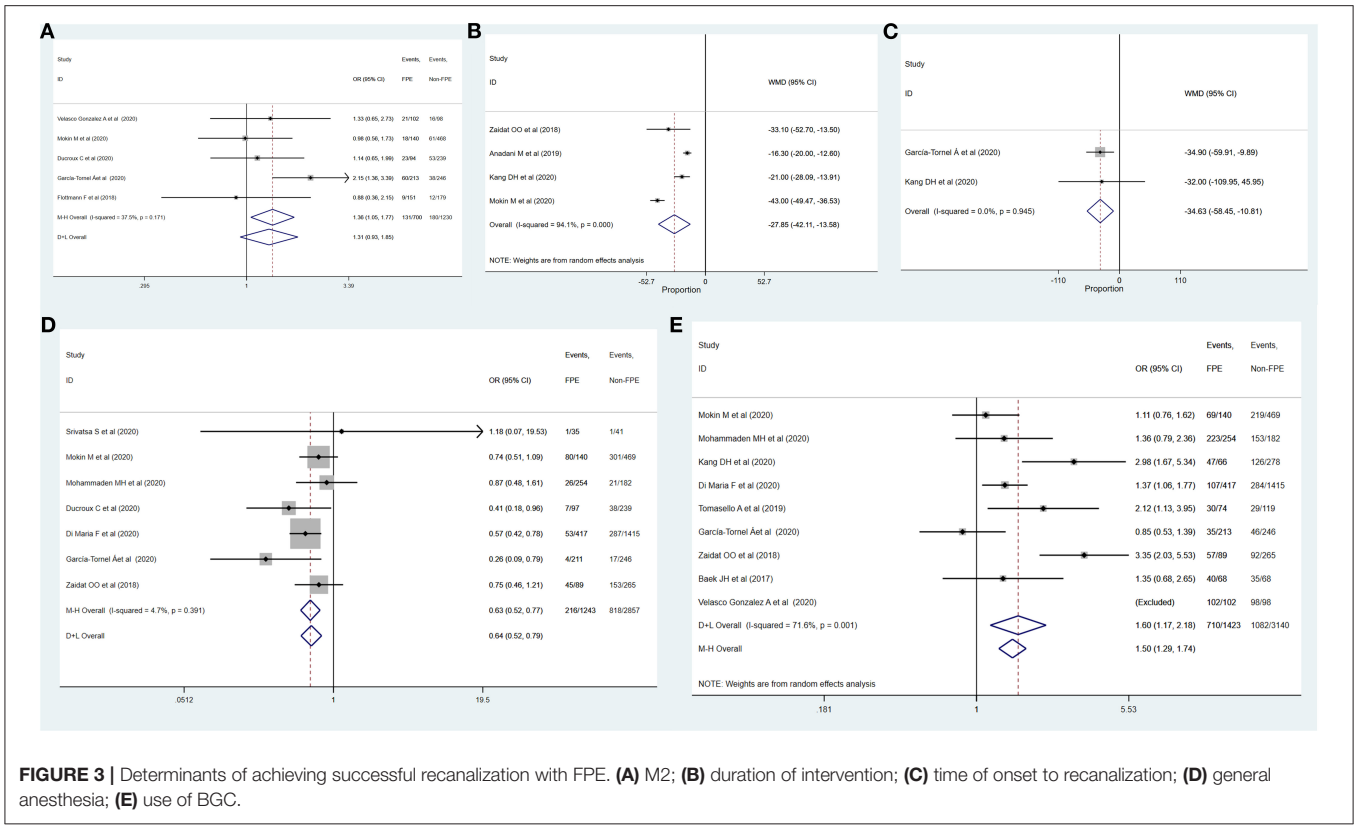


FIGURE 3 | Determinants of achieving successful recanalization with FPE. **(A)** M2; **(B)** duration of intervention; **(C)** time of onset to recanalization; **(D)** general anesthesia; **(E)** use of BGC.

of occlusion, anterior communicating artery (AComA) and posterior communicating artery (PComA) presence, and intervention characteristics.

Determinants for Achieving Successful Recanalization With FPE

The outcomes of meta-analysis showed that age (MD: 1.21, 95% CI: 0.26–2.16; $p = 0.012$), female gender (OR: 1.12, 95% CI: 1.00–1.26; $p = 0.046$), DM (OR: 1.17, 95% CI: 1.01–1.35; $p = 0.032$), ICA location (OR: 0.71, 95% CI: 0.52–0.97; $p = 0.033$), M2 segment (OR: 1.36, 95% CI: 1.05–1.77; $p = 0.019$), duration of intervention (MD: −27.85, 95% CI: −42.11–13.58; $p < 0.001$), time of onset to recanalization (MD: −34.63, 95% CI: −58.45–10.81; $p = 0.004$), general anesthesia (OR: 0.63, 95% CI: 0.52–0.77; $p < 0.001$), and use of BGC (OR: 1.60, 95% CI: 1.17–2.18; $p = 0.003$) were significantly associated with successful recanalization with FPE (**Table 2** and **Figures 2**, **3**). The remainder were not significantly correlated with achieving successful recanalization with FPE (online **Supplementary Figures 1**, **2**).

Determinants for Achieving Complete Recanalization With FPE

Table 3 summarizes the results of meta-analysis of factors influencing complete recanalization with FPE. Age (MD: 1.43, 95% CI: 0.39–2.48; $p = 0.007$), female gender (OR: 1.20, 95% CI: 1.06–1.37; $p = 0.006$), ICA (OR: 0.66, 95% CI: 0.45–0.97; $p = 0.035$), duration of intervention (MD: −27.85, 95% CI: −42.11–13.58; $p < 0.001$), general anesthesia (OR: 0.65, 95% CI: 0.54–0.80; $p < 0.001$), and use of BGC (OR: 1.81, 95% CI: 1.27–2.59; $p = 0.001$) were significantly associated with the complete recanalization with FPE (**Figures 4**, **5**). The remainder were not significantly correlated with achieving successful recanalization with FPE (Online **Supplementary Figures 3**, **4**).

Risk of Bias in Studies Included

The Newcastle–Ottawa scale was used to assess the bias risk of observational studies, such as case–control studies, with the majority of included studies being low risk bias (online **Supplementary Table 3**). Both meta-regression and sensitive analysis were conducted to explore the potential heterogeneity. We also used funnel plots to explore the publication bias, with the results demonstrating no evident reporting bias (**Supplementary Figures 5**–**16**).

DISCUSSION

In this systematic review and meta-analysis, the proportion of FPE ranged from 19 to 58% in the endovascular treatment of LVO inclusive of M2 occlusions. Factors contributing to successful recanalization with FPE included age, female gender, DM, general anesthesia, use of BGC, and occlusion of ICA and M2 segment. Among those, age, female gender, general anesthesia, use of BGC, and occlusion of ICA also increased the chance of complete reperfusion after first-pass thrombectomy.

TABLE 3 | Summary of meta-analysis of influencing factors for achieving complete recanalization with FPE.

	WMD/OR	95% CI		I^2 (%)	*P*-value
Age	1.43	0.39	2.48	28.2%	**0.007**
Gender, female	1.20	1.06	1.37	0.0%	**0.006**
Hypertension	1.06	0.92	1.22	37.1%	0.423
Diabetes mellitus	1.14	0.97	1.34	0.0%	0.106
CAD	0.81	0.61	1.07	0.0%	0.131
Smoke	0.96	0.80	1.14	0.0%	0.605
Atrial fibrillation	0.97	0.81	1.17	61.8%	0.747
Previous anticoagulation therapy	1.16	0.93	1.45	20.6%	0.197
Dyslipidemia	1.08	0.94	1.24	0.0%	0.286
Initial NIHSS score	−0.54	−1.26	0.17	0.0%	0.135
Systolic blood pressure	−1.91	−4.25	0.43	11.2%	0.109
Diastolic blood pressure	−1.53	−3.26	0.19	0.0%	0.081
Suspected stroke etiology					
Large artery atherosclerosis	1.09	0.77	1.56	0.0%	0.617
Cardioembolic	1.01	0.60	1.70	72.3%	0.973
Other	1.12	0.92	1.38	67.6%	0.261
IV thrombolysis	0.99	0.87	1.13	0.0%	0.940
Stroke demographics					
Laterality					
Right	0.81	0.14	4.73	90.2%	0.812
Left	1.24	0.21	7.27	90.2%	0.812
Location of occlusion					
ICA	0.66	0.45	0.97	71.7%	**0.035**
M1	1.44	0.97	2.15	80.4%	0.072
M2	1.12	0.79	1.58	0.0%	0.534
Tandem occlusion	0.86	0.34	2.13	0.0%	0.737
Ipsilateral AComA and PComA	0.73	0.42	1.24	34.7%	0.243
Intervention characteristics					
Time of onset to puncture	11.36	−23.38	46.09	9.0	0.522
Duration of intervention	−27.85	−42.11	−13.58	94.1	**<0.001**
General anesthesia	0.65	0.54	0.80	0.0%	**<0.001**
Aspiration only	1.48	0.69	3.16	85.2%	0.312
Stent retriever only	0.90	0.55	1.48	71.7%	0.689
Aspiration and stent retriever both	0.67	0.22	2.04	93.1%	0.479
Use of BGC	1.81	1.27	2.59	73.4%	**0.001**
Migration to new territory	0.55	0.25	1.22	0.0%	0.142

FPE, first-pass effect; WMD, weighted mean difference; OR, odds ratio; CI, confidence interval; I^2, the variation attributable to heterogeneity; CAD, coronary artery disease; NIHSS, National Institutes of Health Stroke Scale; IV, intravenous; ICA, internal carotid artery; M1, M1 segment of middle cerebral artery; M2, M2 segment of middle cerebral artery; AComA, anterior communicating artery; PComA, posterior communicating artery; BGC, balloon-guided catheter. Bold values mean P-value with significant difference.

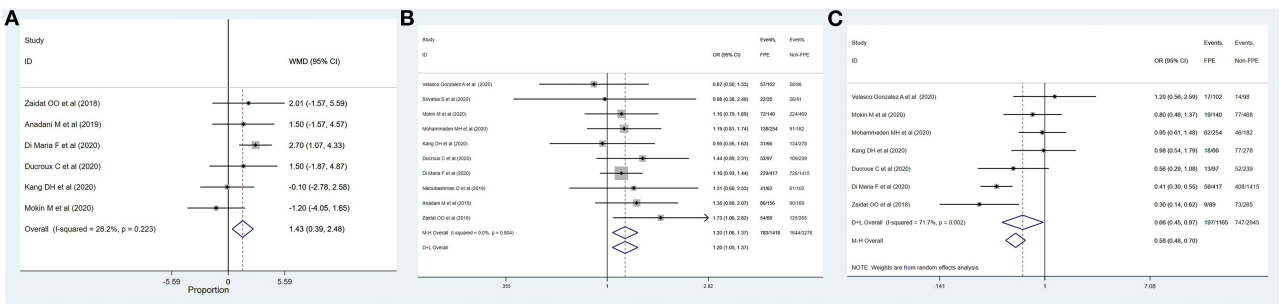


FIGURE 4 | Determinants of achieving complete recanalization with FPE. **(A)** Age; **(B)** female; **(C)** ICA.

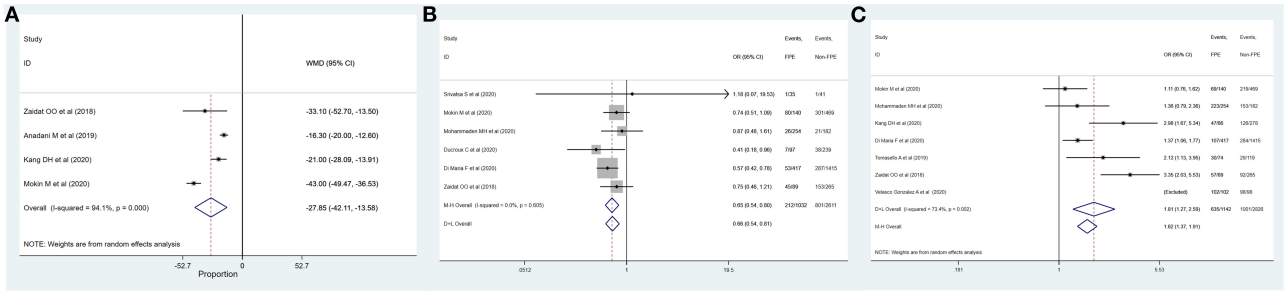


FIGURE 5 | Determinants of achieving complete recanalization with FPE. **(A)** Duration of intervention; **(B)** general anesthesia; **(C)** use of BGC.

BGC use has been widely accepted contributing to FPE during thrombectomy procedure (7, 9, 13, 15). One of the reasons may be decreased distal embolization and more importantly increased flow reversal. According to Kang et al. (9), additional positive effects of BGC use were suggested. One is the force needed for clot retrieving, including impaction force and combined force of friction and adhesion between the thrombus and vessel wall. The other is that inflating the BGC can markedly reduce systemic blood pressure on the proximal clot surface and decrease the pressure gradient across the clot.

It is difficult to explain why increased age was found a contributor to successful and complete recanalization after first-pass thrombectomy. One possible reason may be stroke etiology, as elderly patients are more likely to have cardioembolic cause (32). Clots from cardioembolic causes are more likely to be rich in red blood cells whereas thromboembolism due to preexisting atherosclerosis may be rich in fibrin and platelets. Clots composed predominantly of RBCs are considered fresh and less compact, and this may lead to easier recanalization through thrombectomy with first pass (33–37). Also, increased fibrin percentage could decrease the possibility of clot complete retrieval (38, 39). However, heterogeneous results exist among studies and we could not detect a relationship between FPE and stroke etiology, which may be due to limited data.

This study showed that females are more likely to achieve FPE than males. This phenomenon has been described by Zaidat et al. (7). Anatomical, pathophysiological, and biochemical factors may potentially account for observed difference in response to recanalization therapy between sexes (40). In addition, there was a difference of endogenous fibrinolytic activity between males and females (35, 41). Further studies are needed to explore the underlying biochemical interactions which are further felt to change with age/menopause (42).

Conscious sedation has been associated with better outcomes of MT than general anesthesia in previous researches (43). In this study, we further extended this preference of local anesthesia considering FPE, but the mechanisms remain unknown (17). One hypothesis is a shorter time to reperfusion by conscious sedation (44), as dynamic changes of clot composition found in previous studies, such as fibrin deposition, may increase the risk of re-occlusion (34, 36). However, some studies have mentioned that GA is associated with better outcome than conscious sedation. So, comparison of different anesthesia modalities needs further research (45). At the same time, difference in clot length may be a principal reason for the association between clot location and FPE. It was found that clots in ICA were with longer length and those in M2 segment were with relatively shorter length (7, 17).

There are some limitations of this study. Recruited studies were mostly retrospective with small sample size, and variables observed were not uniform. Some potentially important factors, such as clot volume (13), were only investigated occasionally and thus could not be reliably meta-analyzed. Potential differences may exist between anterior and posterior circulation stroke, and separate analysis may be more valuable. Also, device development could also influence the recanalization outcome, and comparison among different thrombectomy techniques may also be very important. However, it is unable to be analyzed due to high heterogeneity among studies. It remains elusive why DM was a contributor to successful recanalization with FPE (46). Maybe this is caused by bias from limited studies and should be further studied.

CONCLUSION

Age, gender, occlusion site, conscious sedation, and use of BGC were factors influencing both successful and complete recanalization after first-pass thrombectomy. Further studies with more comprehensive observational indices are needed to confirm these observations.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

XB, XZ, and LJ developed the initial idea for this study and formulated the study design. YZ, AD, TW, RX, YF, XW, and KY developed and revised the search strategy. LJ, YM, HS, and QM were consulted about clinical issues. XB, XZ, and JW contributed to the original draft. XB, XZ, AD, JW, YZ, TW, LL, KY, YM, HS, QM, and LJ were responsible for the revision of the draft. All authors approved the final version of the manuscript before submission.

FUNDING

This work was supported by the National Key Research and Development Project (Grant number 2016YFC1301703) and the Beijing Scientific and Technologic Project (Z201100005520019).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.628523/full#supplementary-material

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics-−2012 update: a report from the American Heart Association. *Circulation.* (2012) 125:e2–e220. doi: 10.1161/CIR.0b013e31823ac046
2. 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–e110. doi: 10.1161/STR.0000000000000158
3. 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.* (2018) 378:11–21. doi: 10.1056/NEJMoa1706442
4. 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
5. 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
6. 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. *New England J Med.* (2015) 372:2296–306. doi: 10.1056/NEJMoa1503780
7. 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
8. Anadani M, Alawieh A, Vargas J, Chatterjee AR, Turk A, Spiotta A. First attempt recanalization with ADAPT: rate, predictors, and outcome. *J Neurointerv Surg.* (2019) 11:641–5. doi: 10.1136/neurintsurg-2018-014294
9. Kang DH, Kim BM, Heo JH, Nam HS, Kim YD, Hwang YH, et al. Effects of first pass recanalization on outcomes of contact aspiration thrombectomy. *J Neurointerv Surg.* (2020) 12:466–70. doi: 10.1136/neurintsurg-2019-015221
10. Garcia-Tornel A, Requena M, Rubiera M, Muchada M, Pagola J, Rodriguez-Luna D, et al. When to stop. *Stroke.* (2019) 50:1781–8. doi: 10.1161/STROKEAHA.119.025088
11. Mohammaden MH, Haussen DC, Pisani L, Al-Bayati AR, Perry da Camara C, Bhatt N, et al. Baseline ASPECTS and hypoperfusion intensity ratio influence the impact of first pass reperfusion on functional outcomes. *J Neurointerv Surg.* (2020). doi: 10.1136/neurintsurg-2020-015953
12. 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.* (2020). doi: 10.1007/s00234-020-02586-7. [Epub ahead of print].
13. Baek JH, Yoo J, Song D, Kim YD, Nam HS, Kim BM, et al. Predictive value of thrombus volume for recanalization in stent retriever thrombectomy. *Sci Rep.* (2017) 7:15938. doi: 10.1038/s41598-017-16274-9
14. Jindal G, Carvalho HP, Wessell A, Le E, Naragum V, Miller TR, et al. Beyond the first pass: revascularization remains critical in stroke thrombectomy. *J Neurointerv Surg.* (2019) 11:1095–9. doi: 10.1136/neurintsurg-2019-014773
15. Tomasello A, Ribo 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) 25:491–6. doi: 10.1177/1591019919847623
16. 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
17. Di Maria F, Kyheng M, Consoli A, Desilles JP, Gory B, Richard S, et al. Identifying the predictors of first-pass effect and its influence on clinical outcome in the setting of endovascular thrombectomy for acute ischemic stroke: results from a multicentric prospective registry. *Int J Stroke.* (2020) 16:20–8. doi: 10.1177/1747493020923051
18. Mokin M, Primiani CT, Castonguay AC, Nogueira RG, Haussen DC, English JD, et al. First pass effect in patients treated with the trevo stent-retriever: a TRACK registry study analysis. *Front Neurol.* (2020) 11:83. doi: 10.3389/fneur.2020.00083
19. Srivatsa S, Duan Y, Sheppard JP, Pahwa S, Pace J, Zhou X, et al. Cerebral vessel anatomy as a predictor of first-pass effect in mechanical thrombectomy for emergent large-vessel occlusion. *J Neurosurg.* (2020):1–9. doi: 10.3171/2019.11.Jns192673
20. Velasco Gonzalez A, Görlich D, Buerke B, Münnich N, Sauerland C, Rusche T, et al. Predictors of successful first-pass thrombectomy with a balloon guide catheter: results of a decision tree analysis. *Transl Stroke Res.* (2020) 11:900–9. doi: 10.1007/s12975-020-00784-2
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* (2010) 8:336–41. doi: 10.1016/j.ijsu.2010.02.007
22. Dargazanli C, Fahed R, Blanc R, Gory B, Labreuche J, Duhamel A, et al. Modified thrombolysis in cerebral infarction 2C/thrombolysis in cerebral infarction 3 reperfusion should be the aim of mechanical thrombectomy: insights from the ASTER trial (contact aspiration versus stent retriever for successful revascularization). *Stroke.* (2018) 49:1189–96. doi: 10.1161/strokeaha.118.020700
23. Almekhlafi MA, Mishra S, Desai JA, Nambiar V, Volny O, Goel A, et al. Not all "successful" angiographic reperfusion patients are an equal validation of a modified TICI scoring system. *Interv Neuroradiol.* (2014) 20:21–7. doi: 10.15274/inr-2014-10004
24. Bai X, Feng Y, Yang K, Wang T, Luo J, Wang X, et al. Extracranial-intracranial bypass surgery for occlusive atherosclerotic disease of the anterior cerebral circulation: protocol for a systematic review and meta-analysis. *Syst Rev.* (2020) 9:70. doi: 10.1186/s13643-020-01325-6
25. Feng Y, Li L, Bai X, Wang T, Chen Y, Zhang X, et al. Risk factors for new ischaemic cerebral lesions after carotid artery stenting: protocol for a systematic review and meta-analysis. *BMJ Open.* (2019) 9:e030025. doi: 10.1136/bmjopen-2019-030025
26. Lo CK, Mertz D, Loeb M. Newcastle-ottawa scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol.* (2014) 14:45. doi: 10.1186/1471-2288-14-45
27. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med.* (2018) 23:60–3. doi: 10.1136/bmjebm-2017-110853
28. Ducroux C, Piotin M, Gory B, Labreuche J, Blanc R, Ben Maacha M, et al. First pass effect with contact aspiration and stent retrievers in the Aspiration versus Stent Retriever (ASTER) trial. *J Neurointerv Surg.* (2020) 12:386–91. doi: 10.1136/neurintsurg-2019-015215
29. 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
30. Imahori T, Okamura Y, Sakata J, Shose H, Yokote A, Matsushima K, et al. Stent expansion and in-stent thrombus sign in the trevo stent retriever predict recanalization and possible etiology during mechanical thrombectomy: a case series of 50 patients with acute middle cerebral artery occlusion. *World Neurosurg.* (2018). doi: 10.1016/j.wneu.2018.12.087. [Epub Ahead of Print].
31. Flottmann F, Leischner H, Broocks G, Nawabi J, Bernhardt M, Faizy TD, et al. Recanalization rate per retrieval attempt in mechanical

thrombectomy for acute ischemic stroke. *Stroke.* (2018) 49:2523–2525. doi: 10.1161/STROKEAHA.118.022737
32. Grifoni E, Giglio D, Guazzini G, Cosentino E, Latini E, Dei A, et al. Age-related burden and characteristics of embolic stroke of undetermined source in the real world clinical practice. *J Thromb Thrombolysis.* (2020) 49:75–85. doi: 10.1007/s11239-019-01951-5
33. Zivin JA, Fisher M, DeGirolami U, Hemenway CC, Stashak JA. Tissue plasminogen activator reduces neurological damage after cerebral embolism. *Science.* (1985) 230:1289–92. doi: 10.1126/science.3934754
34. Niessen F, Hilger T, Hoehn M, Hossmann KA. Differences in clot preparation determine outcome of recombinant tissue plasminogen activator treatment in experimental thromboembolic stroke. *Stroke.* (2003) 34:2019–24. doi: 10.1161/01.STR.0000080941.73934.30
35. Forster A, Gass A, Kern R, Wolf ME, Ottomeyer C, Zohsel K, et al. Gender differences in acute ischemic stroke: etiology, stroke patterns and response to thrombolysis. *Stroke.* (2009) 40:2428–32. doi: 10.1161/STROKEAHA.109.548750
36. Pikija S, Magdic J, Trkulja V, Unterkreuter P, Mutzenbach JS, Novak HF, et al. Intracranial thrombus morphology and composition undergoes time-dependent changes in acute ischemic stroke: a CT densitometry study. *Int J Mol Sci.* (2016) 17:1959. doi: 10.3390/ijms17111959
37. Goldmakher GV, Camargo EC, Furie KL, Singhal AB, Roccatagliata L, Halpern EF, et al. Hyperdense basilar artery sign on unenhanced CT predicts thrombus and outcome in acute posterior circulation stroke. *Stroke.* (2009) 40:134–9. doi: 10.1161/STROKEAHA.108.516690
38. Duffy S, McCarthy R, Farrell M, Thomas S, Brennan P, Power S, et al. Per-pass analysis of thrombus composition in patients with acute ischemic stroke undergoing mechanical thrombectomy. *Stroke.* (2019) 50:1156–63. doi: 10.1161/STROKEAHA.118.023419
39. Gunning GM, McArdle K, Mirza M, Duffy S, Gilvarry M, Brouwer PA. Clot friction variation with fibrin content; implications for resistance to thrombectomy. *J Neurointerv Surg.* (2018) 10:34–8. doi: 10.1136/neurintsurg-2016-012721
40. Savitz SI, Schlaug G, Caplan L, Selim M. Arterial occlusive lesions recanalize more frequently in women than in men after intravenous tissue plasminogen activator administration for acute stroke. *Stroke.* (2005) 36:1447–51. doi: 10.1161/01.STR.0000170647.42126.a8
41. Hill MD, Kent DM, Hinchey J, Rowley H, Buchan AM, Wechsler LR, et al. Sex-based differences in the effect of intra-arterial treatment of stroke: analysis of the PROACT-2 study. *Stroke.* (2006) 37:2322–5. doi: 10.1161/01.STR.0000237060.21472.47
42. Towfighi A, Saver JL, Engelhardt R, Ovbiagele B. A midlife stroke surge among women in the United States. *Neurology.* (2007) 69:1898–904. doi: 10.1212/01.wnl.0000268491.89956.c2
43. Campbell BCV, van Zwam WH, Goyal M, Menon BK, Dippel DWJ, Demchuk AM, et al. Effect of general anaesthesia on functional outcome in patients with anterior circulation ischaemic stroke having endovascular thrombectomy versus standard care: a meta-analysis of individual patient data. *Lancet Neurol.* (2018) 17:47–53. doi: 10.1016/s1474-4422(17)30407-6
44. Powers CJ, Dornbos D, 3rd, Mlynash M, Gulati D, Torbey M, Nimjee SM, et al. Thrombectomy with conscious sedation compared with general anesthesia: a DEFUSE 3 analysis. *AJNR Am J Neuroradiol.* (2019) 40:1001–5. doi: 10.3174/ajnr.A6059
45. Bai X, Zhang X, Wang T, Feng Y, Wang Y, Lyu X, et al. General anesthesia versus conscious sedation for endovascular therapy in acute ischemic stroke: a systematic review and meta-analysis. *J Clin Neurosci.* (2021) 86:10–7. doi: 10.1016/j.jocn.2021.01.012
46. Ye G, Gao Q, Qi P, Wang J, Hu S, Chen K, et al. The role of diabetes mellitus on the thrombus composition in patients with acute ischemic stroke. *Interv Neuroradiol.* (2020) 26:329–36. doi: 10.1177/1591019919896940

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 07 May 2021
doi: 10.3389/fneur.2021.653752

Cerebral Circulation Time Is a Potential Predictor of Disabling Ischemic Cerebrovascular Events in Patients With Non-disabling Middle Cerebral Artery Stenosis

Zhenze Chen[1†], Mingchun Li[1†], Zhihuan Wu[2†], Min Zhang[3], Guomei Weng[2], Minzi Li[1], Rongxin Liao[4], Peng Zhao[4], Jianming Wu[4], Shuzhen Zhu[1], Qing Wang[1], Chunguang Li[1*] and Xiaobo Wei[1*]*

[1] Department of Neurology, Zhujiang Hospital, Southern Medical University, Guangzhou, China, [2] Department of Neurology, 1st People Hospital of Zhaoqing, Zhaoqing, China, [3] Department of Neurology, Jiangmen Centrol Hospital, Jiangmen, China, [4] Department of Gerontology, Integrated Hospital of Traditional Chinese Medicine, Southern Medical University, Guangzhou, China

OPEN ACCESS

Edited by:
QinJian Sun,
Shandong University, China

Reviewed by:
Ahmed Mohamed Elhfnawy,
University Hospital Essen, Germany
Nabil Kitchener,
Cairo University, Egypt

***Correspondence:**
Xiaobo Wei
xiaobosswei@foxmail.com
Chunguang Li
lichunguang2005@126.com
Qing Wang
denniswq@yahoo.com

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: 15 January 2021
Accepted: 14 April 2021
Published: 07 May 2021

Citation:
Chen Z, Li M, Wu Z, Zhang M, Weng G, Li M, Liao R, Zhao P, Wu J, Zhu S, Wang Q, Li C and Wei X (2021) Cerebral Circulation Time Is a Potential Predictor of Disabling Ischemic Cerebrovascular Events in Patients With Non-disabling Middle Cerebral Artery Stenosis. Front. Neurol. 12:653752. doi: 10.3389/fneur.2021.653752

Patients with non-disabling middle cerebral artery (MCA) stenosis (ND-MCAS) are at risk for disabling ischemic cerebrovascular events (DICE) despite aggressive medical therapy. In this study, we aimed to verify whether cerebral circulation time (CCT) was a potential predictor of DICE in patients with ND-MCAS. From January 2015 to January 2020, 46 patients with ND-MCAS treated with aggressive medical therapy were enrolled for digital subtraction angiography (DSA) in this convenience sampling study. They were divided into the DICE (–) and DICE (+) groups based on the occurrence of DICE within 3 months after DSA. The CCT was defined as the time from the appearance of the MCA to the peak intensity of the Trolard vein during DSA. The rCCT (relative CCT) was defined as the ratio of the CCT of the stenotic side (sCCT) to the CCT of the healthy side (hCCT). The differences in sCCT, hCCT, and rCCT between the two groups were analyzed with Mann-Whitney U tests. Logistic regression analysis was performed to evaluate the association between the risk factors and DICE. Receiver operating characteristic (ROC) curves were constructed to assess the predictive value of rCCT in identifying DICE in ND-MCAS patients. The results showed that DICE appeared in 5 of the 46 patients within 3 months. rCCT were significantly increased in the DICE (+) group compared with the DICE (–) group [1.08 (1.05, 1.14) vs. 1.30 (1.22, 1.54), $p < 0.001$]. Logistic regression analysis found that prolonged rCCT was an independent positive prognostic factor for DICE (odds ratio = 1.273, $p = 0.019$) after adjustment for potential confounders (age, diabetes, antithrombotic use, and stenosis degree). ROC analysis showed that rCCT provided satisfactory accuracy in distinguishing the DICE (+) group from the DICE (–) group among ND-MCAS patients (area under the curve = 0.985, $p < 0.001$), with an optimal cutoff point of 1.20 (100% sensitivity, 97.6% specificity). In conclusion, prolonged rCCT is independently associated with the occurrence of DICE in ND-MCAS patients and may be used to identify individuals at risk of DICE.

Keywords: non-disabling middle cerebral artery stenosis, cerebral circulation time, digital subtraction angiography, disabling ischemic cerebrovascular events, prognosis

INTRODUCTION

Stenting, angioplasty and aggressive medical management are established procedures for the prevention of further ischemic events following middle cerebral artery (MCA) stenosis (1–6). In recent years, an increasing proportion of patients with non-disabling MCA stenosis (ND-MCAS) have been treated with dual antiplatelet agents (7). The evidence to support their use comes mainly from the results of the two randomized clinical trials Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) and Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT), which showed that pharmacologic management is safer and has a lower incidence of ischemic events than stenting (8, 9). However, SAMMPRIS and VISSIT showed a 5.8 and 9.4% risk of stroke and death, respectively, at 30 days during the treatment with dual antiplatelet agents (2, 8, 9). Therefore, early identification and subsequent stenting or angioplasty should be carried out for patients who are at high risk of disabling ischemic cerebrovascular events (DICE) or death.

Impaired cerebrovascular reserve is an important predictor of stroke and transient ischemic attack (TIA) in patients with cerebral artery stenosis or occlusion (10–12). At present, the clinical evaluation of the cerebrovascular reserve mainly relies on acetazolamide-challenged single-photon emission computed tomography (ACZ-challenged SPECT), computed tomography perfusion imaging (CTP) and magnetic resonance (MR) perfusion-weighted imaging (PWI), which are expensive and expose the patients to radiation and contrast medium (13–15). The cerebral circulation time (CCT) derived from digital subtraction angiography (DSA) has been reported to be well-correlated with cerebrovascular reserve (12, 16–21). It can help surgeons observe the patient's cerebrovascular reserve during surgery without the need for SPECT, CTP, and PWI.

In this study, we carried out a retrospective analysis of all prospectively collected data from patients with ND-MCAS treated with aggressive medical therapy, and aimed to verify whether CCT could be used as a potential predictor of DICE for patients with ND-MCAS.

MATERIALS AND METHODS

Patients and Study Design

The clinical and radiological data from 273 patients with MCA stenosis treated at Zhujiang Hospital of Southern Medical University, Guangzhou, China between January 2015 and January 2020 were reviewed in this convenience sampling study. After excluding 227 patients with disability or multiple vascular stenosis, we enrolled 46 patients with non-disabling unilateral MCA stenosis in the final analysis. Their demographic characteristics, stroke risk factors, clinical symptoms, medications and relevant scale scores [National Institutes of National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS)] were reviewed by two neurologists. According to the trial A Pooled Analysis of Clopidogrel in High-Risk Patients with Acute Non-Disabling Cerebrovascular Events (CHANCE), non-disabling ischemic stroke was defined as: 1. Transient ischemic attack (TIA); 2. Minor ischemic stroke (22, 23). Transient ischemic attack was defined as a transient episode of neurological symptoms caused by focal cerebral or retinal ischemia without radiographic evidence of acute infarction (24). Minor ischemic stroke was defined as a stroke with a NIHSS score ≤ 3 or mRS score ≤ 3 (25). Patients with ND-MCAS were allocated to the DICE (+) group if they suffered from disabling ischemic cerebrovascular events (NIHSS score > 3 or mRS score > 3) in 90 days after the onset of the stroke. Otherwise, patients were allocated to the DICE (–) group. This study was approved by the Ethics Committee of Zhujiang Hospital of Southern Medical University and conducted in accordance with the ethical standards of the 1975 Declaration of Helsinki and the 1999 National Institutes of Health Human Subjects Policies and Guidance.

DSA Protocol and Data Analysis

All patients were enrolled for DSA with a uniform and standard protocol in Zhujiang Hospital of Southern Medical University, Guangzhou, Guangdong, China. During the DSA procedures, a 5F angio-catheter was placed in the carotid artery at the C3 vertebral body level. All of the subjects were examined by a single-plane angiographic machine (GE IGS 330, America) with a power injector (5 ml ioversol injection with 3 ml/s speed, 150 psi/kg pressure). The stenotic degree was measured according to the NASCET criteria from DSA image (26). Neuroimaging and analysis were performed independently by two trained neurologists who were blinded to the clinical conditions and were responsible for assessing all of the neuroimaging variables used in this study.

Cerebral Circulation Time Measurement

During the angiography procedure, the CCT was defined as the time from the appearance of the MCA to the peak intensity of the Trolard vein (**Figure 1**). In order to reduce the data errors, the CCT of same patient was measured for three times, and then the average of these three measurements was used in the following analysis. The main research indicator of the present study was rCCT (relative CCT), which was calculated with the following formula: rCCT = the CCT of the stenotic side (sCCT)/the CCT of the healthy side (hCCT).

Treatment Options

All patients received aggressive medical therapy for at least 3 months after the DSA examination. Four of the 5 patients in the DICE (+) group and 27 of the 41 patients in the DICE (–) group received dual antiplatelet therapy (100 mg aspirin and 75 mg clopidogrel per day). The remaining patients all received single antiplatelet therapy. Patients suffering from hypertension, diabetes, or dyslipidemia all received standard drug treatment.

Statistical Analysis

All statistical analyses were conducted using SPSS 23 for Windows. All continuous variables were tested for normality and expressed as median (interquartile range). Categorical variables were expressed as numbers (%). The differences in demographic and clinical variables between the DICE (–) and DICE (+)

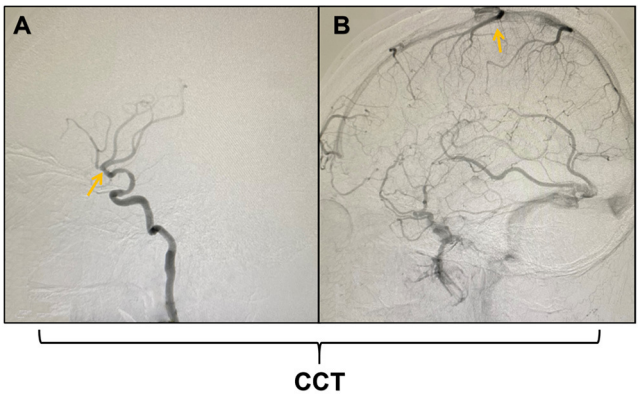


FIGURE 1 | Schematic diagram of the measurement of cerebral circulation time (CCT). **(A)** shows the appearance of the middle cerebral artery (MCA); **(B)** shows the peak intensity of the Trolard vein. The CCT was defined as the time from the appearance of the MCA to the peak intensity of the Trolard vein during digital subtraction angiography (DSA).

groups were analyzed by Mann-Whitney U-tests for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables. Logistic regression analysis was performed to estimate the odds ratio (OR) for DICE with rCCT and other risk factors as independent variables. $P < 0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curve analysis of rCCT was performed to evaluate the predictive accuracy of DICE in the ND-MCAS patients.

RESULTS

Between January 2015 and January 2020, 46 patients with ND-MCAS were confirmed by DSA in our hospital, including 30 males (65.2%), with an average age of 55 (48.7, 63) (range 25–87 years), hypertension (45.6%), diabetes (26.1%), dyslipidemia (45.6%) and smoking (26.1%). Eighteen of the patients presented with TIA, and 28 presented with minor ischemic stroke. Among all of the included patients, 5 patients suffered from DICE within 3 months after DSA and were allocated to the DICE (+) group, and the remaining patients without disability were allocated to the DICE (–) group. The demographic and clinical data of the patients is shown in **Table 1**.

No significant differences were observed in sex, stroke risk factors, baseline clinical manifestation or usage of drugs between the DICE (–) and DICE (+) groups. The rCCT in the DICE (+) group were prolonged compared with those in the DICE (–) group [1.08 (1.05, 1.14) vs. 1.30 (1.22, 1.54), $p < 0.001$; **Table 1**, **Figure 2**]. There was no significant difference in sCCT and hCCT between the two groups [6.83 (6.50, 7.75) vs. 7.67 (6.50, 10.67), $p = 0.258$; 6.33 (5.92, 7.00) vs. 6.25 (4.96, 7.25), $p = 0.480$; **Table 1**, **Figure 2**].

Logistic regression analysis showed that after adjustment for possible confounders, namely, age, diabetes, stenosis degree and antithrombotic use, a longer rCCT was independently associated with a higher risk of DICE (OR = 1.273, $p = 0.019$, **Table 2**). The ROC curves of CCT and the other risk factors for the prediction of DICE are shown in **Figure 3**. The optimal cutoff point of rCCT (1.20) predicted DICE with 100% sensitivity and 97.6% specificity (**Table 3**, **Figure 3**). In contrast, the optimal cutoff point of sCCT (9.5 s) predicted DICE with 40% sensitivity and 100% specificity; the optimal cutoff point of stenosis degree (65%) predicted DICE with 100% sensitivity and 43.9% specificity (**Table 3**, **Figure 3**).

TABLE 1 | The demographic and clinical data for patients with and without DICE.

Characteristics	DICE (–) ($N = 41$)	DICE (+) ($N = 5$)	p-value
Age (years)	54 (47.5, 61)	69 (57.5, 77)*	0.026
Male	28 (68.3)	2 (40)	0.449
Hypertension	19 (46.3)	2 (40)	1
Diabetes	9 (22.5)	3 (60)	0.197
Dyslipidemia	18 (43.9)	3 (60)	0.836
Cigarette smoking	11 (26.8)	1 (20)	1
Usage of drugs within 3 months			
Dual antiplatelet agents	27 (65.9)	4 (80)	0.895
Intensive lipid-lowering	13 (31.7)	2 (40)	1
Clinical manifestation and score			
Transient ischemic attack	15 (36.5)	3 (60)	0.598
minor ischemic stroke	26 (63.5)	2 (40)	
NIHSS (baseline)	0 (0, 1)	0 (0, 1)	0.587
NIHSS (3 month)	0 (0, 1)	6 (4.5, 8.5)***	< 0.001
mRs (baseline)	1 (0, 1)	0 (0, 1)	0.233
mRs (3 month)	1 (0, 1)	3 (2.5, 4)***	< 0.001
Image data			
Stenosis degree (%)	70 (30, 80)	80 (60, 85)	0.391
sCCT (s)	6.83 (6.50, 7.75)	7.67 (6.50, 10.67)	0.258
hCCT (s)	6.33 (5.92, 7.00)	6.25 (4.96, 7.25)	0.480
rCCT	1.08 (1.05, 1.14)	1.30 (1.22, 1.54)***	< 0.001

*$p < 0.05$ vs. DICE (–) group. ***$p < 0.001$ vs. DICE (–) group.
All continuous variables are expressed as median (interquartile range) and categorical variables are expressed as numbers (%). The statistically significant differences between the DICE (–) and DICE (+) groups were assessed by χ^2-test or Mann-Whitney U-tests. DICE, disabling ischemic cerebrovascular events; NIHSS, National Institutes of National Institutes of Health Stroke Scale; mRs, The Modified Rankin Scale; CCT, cerebral circulation time; sCCT, CCT of stenotic side; hCCT, CCT of healthy side; rCCT, relative CCT = sCCT/hCCT.

DISCUSSION

Non-disabling ischemic stroke, which indicates a patient is at risk of an early recurrent stroke, can lead to severe disabling events and even death, seriously affecting their quality of life (27–30). Therefore, early identification of such patients is particularly important (31–33). In this study, we provided novel observations by evaluating the usefulness of CCT for the prediction of DICE in ND-MCAS patients.

Compared with other previous studies, we specifically demonstrated the presence of prolonged rCCT in arterial stenosis. Yamamoto et al. detected prolonged CCT measured through visual observation in patients with unilateral occlusive lesions in the ICA or MCA (21). Lin et al. investigated multiple segments of CCT in 25 patients with carotid stenosis and 34

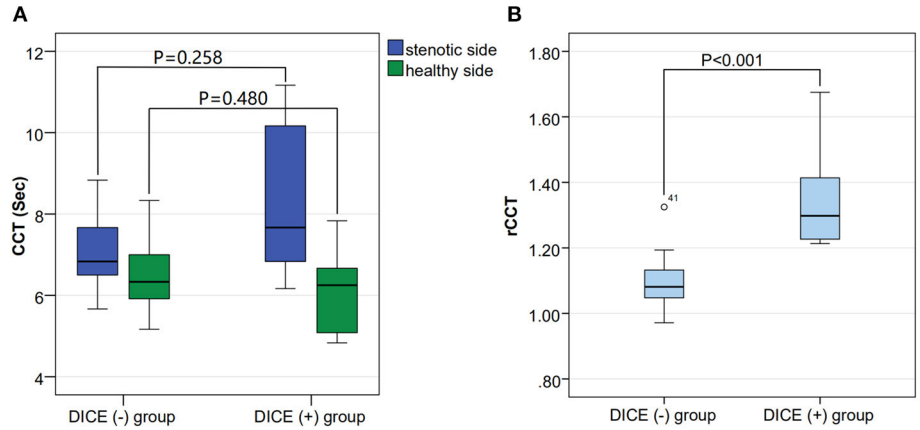


FIGURE 2 | Comparison of the stenotic side CCT (sCCT), the healthy side CCT (hCCT) and the relative CCT (rCCT) among the DICE (–) and DICE (+) groups. **(A)** shows no difference in hCCT [6.33 (5.92, 7.00) vs. 6.25 (4.96, 7.25), $p = 0.480$] and sCCT [6.83 (6.50, 7.75) vs. 7.67 (6.50, 10.67), $p = 0.258$] between the DICE (–) and DICE (+) groups. **(B)** shows a significant difference in rCCT (1.37 ± 0.19 vs. 1.09 ± 0.07, $p < 0.001$) between the DICE (–) and DICE (+) groups.

TABLE 2 | Multivariable logistic regression analysis to evaluate the association between DICE and risk factors, including rCCT.

Variables	Univariate			Multivariate model		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
rCCT	1.295	1.053–1.592	0.014	1.273*	1.041–1.556	0.019
Age (years) (mean ± SD)	1.093	1.004–1.190	0.040	1.063	0.865–1.306	0.564
Dual antiplatelet therapy	0.482	0.049–4.735	0.531	1.646	0.006–455.233	0.862
Stenosis degree	1.025	0.978–1.075	0.297	1.052	0.857–1.292	0.626
Diabetes	5.333	0.769–36.965	0.090	0.127	0.002–8.309	0.333

*$p < 0.05$.

DICE, disabling ischemic cerebrovascular events; CCT, cerebral circulation time; rCCT, relative CCT = sCCT/hCCT; OR, odds ratio; CI, confidence interval.

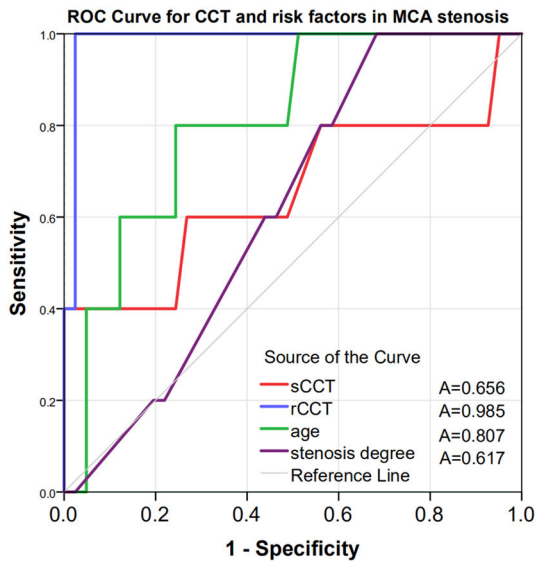


FIGURE 3 | Receiver operating characteristic curves to evaluate the utility of CCT and traditional risk factors in predicting DICE in patients with ND-MCAS. The AUC was 0.985 for rCCT (blue curve), 0.656 for sCCT (red curve), 0.807 for age (green curve) and 0.617 for stenosis degree (purple curve). CCT, cerebral circulation time; sCCT, CCT of the stenotic side; hCCT, CCT of the healthy side; rCCT, relative CCT = CCT of the stenotic side/CCT of the healthy side; A, area under the curve; ROC, receiver operating characteristic; DICE, disabling ischemic cerebrovascular events; ND-MCAS, non-disabling middle cerebral artery stenosis.

normal control subjects and found that some of the segments of CCT were longer in patients with carotid stenosis than in control subjects (34). In our study, we found that rCCT was a more sensitive marker than sCCT for predicting DICE in ND-MCAS.

Impaired cerebrovascular reserve is the main cause of cerebral infarction. Lin et al. showed that CBF, MTT and Tmax were found to correlate with CCT. Prolonged CCT may reflect the impairment of cerebrovascular reserve (20). This conclusion is in line with our findings, in which 5 of the 46 patients showed significant prolongation of rCCT and subsequently suffered DICE. The rCCT in these 5 patients were significantly increased compared with the patients without DICE. We could conclude that rCCT may reflect the cerebrovascular reserve and predict the occurrence of DICE. At the same time, possibly because rCCT excluded the difference in CCT among individuals, rCCT was found to be more effective than sCCT in predicting DICE (AUC of rCCT = 0.985, $p < 0.001$, AUC of sCCT = 0.656, $p < 0.259$).

Our results also suggested that rCCT (OR = 1.273, p = 0.019) was a more sensitive predictor of DICE than the degree of stenosis (OR = 1.025, p = 0.626) after adjustment for age, diabetes, usage of dual antiplatelet therapy and stenosis degree. Yong's study showed that prolonged CCT was more closely associated with symptomatic carotid stenosis than stenosis degree or collateral circulation (34). This theory also seems to be applicable in our study for intracranial vascular stenosis.

TABLE 3 | ROC curves for traditional risk factors and CCT in the prediction of disabling ischemic cerebrovascular events.

Variable	Traditional risk factors		CCT	
	Age	Stenosis degree	sCCT	rCCT
AUC	0.807*	0.617	0.656	0.985***
Cutoff value	0.556	0.439	0.4	0.976
p-value	0.026	0.397	0.259	<0.001
95% CI	0.636–0.979	0.417–0.817	0.338–0.974	0.953–1.000
Sensitivity	80%	100%	40%	100%
Specificity	75.6	43.9%	100%	97.6%

*$p < 0.05$, ***$p < 0.001$.
ROC, receiver operating characteristic; CCT, cerebral circulation time; rCCT, relative CCT = sCCT/hCCT; AUC, area under the curve; CI, confidence interval.

Scientific statements from the American Heart Association have shown that angioplasty or placement of a Wingspan stent may be warranted for patients with severe stenosis (70–99%) of a major intracranial artery who have progressing symptoms, recurrent TIA or stroke (2). In this study, the risk of DICE occurring in patients with MCA stenosis was assessed in real-time by intraoperative measurement of rCCT. For patients with severe rCCT prolongation, traditional drug therapy may not prevent the occurrence of severe DICE. Thus, with the help of rCCT in the prediction of DICE, the surgeons may prefer immediate intravascular treatment after calculating rCCT, avoiding the additional radiation, contrast agent and economic burden from SPECT, CTP, PWI, and secondary surgery.

The limitations of this study include the small number of cases and the imbalance in the number of cases between the DICE (–) and DICE (+) groups. The patients in the present study were followed up for only 3 months. Longitudinal studies of large cohorts and longer follow-up periods are needed to confirm our results. In addition, collateral circulation may influence the prognosis of the patients (35). The relationship between CCT and collateral circulation was not included in the analysis of this study, and it may need further investigation in the future.

CONCLUSIONS

Prolonged rCCT is an independent positive prognostic factor for the occurrence of DICE in patients with ND-MCAS treated with drugs, and it could be used by surgeons to identify individuals at high risk of DICE during surgery. In patients with a significantly prolonged CCT, angioplasty or placement of a balloon expandable and self-expanding vascular stents may be warranted even when their degree of stenosis is <70%. Future studies with larger sample sizes are required to further verify the sensitivity and accuracy of CCT in the clinical management of stroke.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Zhujiang Hospital of Southern Medical University and conducted in accordance with the ethical standards of the 1975 Declaration of Helsinki and the 1999 National Institutes of Health Human Subjects Policies and Guidance. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZC, XW, CL, and QW: conceived and designed the clinical study. ZC, MingL, ZW, MZ, MinzL, GW, SZ, CL, XW, and QW: performed the clinical study. ZC, CL, XW, and QW: analyzed the data. CL, XW, and QW: revised the paper for intellectual content. ZC, CL, XW, and QW: wrote the paper. All authors read and approved the final manuscript.

FUNDING

This work was supported by the Natural Science Foundations of Guangdong of China (Grant No: 2019A1515010281), Guangdong Provincial Key Laboratory of Shock and Microcirculation, Initiated Foundation of Zhujiang Hospital (Grant No: 02020318005), Science and Technology Program of Guangdong of China (No: 2020A0505100037), and Leading Talent in Talents Project Guangdong High-level Personnel of Special Support Program to QW; and National Natural Science Foundation of China (Grant No: 81801252) to XW.

ACKNOWLEDGMENTS

We thank all of the participants for their valuable contribution to this research and managing the data for this project.

REFERENCES

1. Chimowitz M, Lynn M, Howlett-Smith H, Stern B, Hertzberg V, Frankel M, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* (2005) 352:1305–16. doi: 10.1056/NEJMoa043033

2. Eskey C, Meyers P, Nguyen T, Ansari S, Jayaraman M, McDougall C, et al. Indications for the performance of intracranial endovascular neurointerventional procedures: a scientific statement from the American Heart Association. *Circulation.* (2018) 137:e661–89. doi: 10.1161/CIR.0000000000000567

3. Kernan W, Ovbiagele B, Black H, Bravata D, Chimowitz M, Ezekowitz M, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2014) 45:2160–236. doi: 10.1161/STR.0000000000000024
4. Liu S, Zheng H, Yu W, Ramakrishnan V, Shah S, Gonzalez L, et al. Investigation of S-Nitrosoglutathione in stroke: a systematic review and meta-analysis of literature in pre-clinical and clinical research. *Exp Neurol.* (2020) 328:113–262. doi: 10.1016/j.expneurol.2020.113262
5. Ni L, Zhou F, Qing Z, Zhang X, Li M, Zhu B, et al. The asymmetry of white matter hyperintensity burden between hemispheres is associated with intracranial atherosclerotic plaque enhancement grade. *Front Aging Neurosci.* (2020) 12:163. doi: 10.3389/fnagi.2020.00163
6. Shetty A, Upadhya R, Madhu L, Kodali M. Novel insights on systemic and brain aging, stroke, amyotrophic lateral sclerosis, and Alzheimer's disease. *Aging Dis*. (2019) 10: 470–82. doi: 10.14336/AD.2019.0330
7. Turan T, Cotsonis G, Lynn M, Wooley R, Swanson S, Williams J, et al. Intracranial stenosis: impact of randomized trials on treatment preferences of US neurologists and neurointerventionists. *Cerebrovasc Dis.* (2014) 37:203–11. doi: 10.1159/000358120
8. Chimowitz M, Lynn M, Derdeyn C, Turan T, Fiorella D, Lane B, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med.* (2011) 365:993–1003. doi: 10.1056/NEJMoa1105335
9. Zaidat O, Fitzsimmons B, Woodward B, 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
10. Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. *Brain*. (2001) 124:457–67. doi: 10.1093/brain/124.3.457
11. McKetton L, Cohn M, Tang-Wai D, Sobczyk O, Duffin J, Holmes K, et al. Cerebrovascular resistance in healthy aging and mild cognitive impairment. *Front Aging Neurosci.* (2019) 11:79. doi: 10.3389/fnagi.2019.00079
12. Riou-Comte N, Guillemin F, Gory B, Lapergue B, Zhu F, Soudant M, et al. Predictive factors of functional independence after optimal reperfusion in anterior circulation ischaemic stroke with indication for intravenous thrombolysis plus mechanical thrombectomy. *Eur J Neurol.* (2021) 28:141–51. doi: 10.1111/ene.14509
13. Doerfler A, Eckstein H, Eichbaum M, Heiland S, Benner T, Allenberg J, et al. Perfusion-weighted magnetic resonance imaging in patients with carotid artery disease before and after carotid endarterectomy. *J Vasc Surg.* (2001) 34:587–93. doi: 10.1067/mva.2001.118588
14. Leinsinger G, Piepgras A, Einhäupl K, Schmiedek P, Kirsch C. Normal values of cerebrovascular reserve capacity after stimulation with acetazolamide measured by xenon 133 single-photon emission CT. *AJNR Am J Neuroradiol.* (1994) 15:1327–32.
15. Wintermark M, Fischbein N, Smith W, Ko N, Quist M, Dillon W. Accuracy of dynamic perfusion CT with deconvolution in detecting acute hemispheric stroke. *AJNR Am J Neuroradiol.* (2005) 26:104–12.
16. Bashir A, Abebe Z, McInnes K, Button E, Tatarnikov I, Cheng W, et al. Increased severity of the CHIMERA model induces acute vascular injury, sub-acute deficits in memory recall, and chronic white matter gliosis. *Exp Neurol.* (2020) 324:113–6. doi: 10.1016/j.expneurol.2019.113116
17. Cramer N, Korotcov A, Bosomtwi A, Xu X, Holman D, Whiting K, et al. Neuronal and vascular deficits following chronic adaptation to high altitude. *Exp Neurol.* (2019) 311:293–304. doi: 10.1016/j.expneurol.2018.10.007
18. Guenego A, Fahed R, Albers G, Kuraitis G, Sussman E, Martin B, et al. Hypoperfusion intensity ratio correlates with angiographic collaterals in acute ischaemic stroke with M1 occlusion. *Eur J Neurol.* (2020) 27:864–70. doi: 10.1111/ene.14181
19. Aikawa H, Kazekawa K, Tsutsumi M, Onizuka M, Iko M, Kodama T, et al. Intraprocedural changes in angiographic cerebral circulation time predict cerebral blood flow after carotid artery stenting. *Neurol Med Chir.* (2010) 50:269–74. doi: 10.2176/nmc.50.269
20. Lin C, Hung S, Chang F, Guo W, Luo C, Kowarschik M, et al. Finding the optimal deconvolution algorithm for MR perfusion in carotid stenosis: correlations with angiographic cerebral circulation time. *J Neuroradiol.* (2016) 43:290–6. doi: 10.1016/j.neurad.2016.02.002
21. Yamamoto S, Watanabe M, Uematsu T, Takasawa K, Nukata M, Kinoshita N. Correlation of angiographic circulation time cerebrovascular reserve by acetazolamide-challenged single photon emission CT. *AJNR Am J Neuroradiol.* (2004) 25:242–7.
22. Pan Y, Elm J, Li H, Easton J, Wang Y, Farrant M, et al. Outcomes associated with clopidogrel-aspirin use in minor stroke or transient ischemic attack: a pooled analysis of clopidogrel in high-risk patients with acute non-disabling cerebrovascular events (CHANCE) and platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trials. *JAMA Neurol.* (2019) 76:1466–73. doi: 10.1001/jamaneurol.2019.2531
23. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med.* (2013) 369:11–9. doi: 10.1056/NEJMoa1215340
24. Easton J, Saver J, Albers G, Alberts M, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke.* (2009) 40:2276–93. doi: 10.1161/STROKEAHA.108.192218
25. Johnston S, Elm J, Easton J, Farrant M, Barsan W, Kim A, et al. Time course for benefit and risk of clopidogrel and aspirin after acute transient ischemic attack and minor ischemic stroke. *Circulation.* (2019) 140:658–64. doi: 10.1161/CIRCULATIONAHA.119.040713
26. Saba L, Mallarini G. A comparison between NASCET and ECST methods in the study of carotids: evaluation using multi-detector-row CT angiography. *Eur J Radiol*. (2010) 76:42–7. doi: 10.1016/j.ejrad.2009.04.064
27. Cheng Z, Geng X, Gao J, Hussain M, Moon S, Du H, et al. Intravenous administration of standard dose tirofiban after mechanical arterial recanalization is safe and relatively effective in acute ischemic stroke. *Aging Dis.* (2019) 10:1049–57. doi: 10.14336/AD.2018.0922
28. Wang Z, Wang C, Zhang P, Qu Y, Guo Z, Yang Y, et al. Effects of early changes in blood pressure during intravenous thrombolysis on the prognosis of acute ischemic stroke patients. *Front Aging Neurosci.* (2020) 12:601471. doi: 10.3389/fnagi.2020.601471
29. Wu L, Huber M, Wu D, Chen J, Li M, Ding Y, et al. Intra-arterial cold saline infusion in stroke: historical evolution and future prospects. *Aging Dis.* (2020) 11:1527–36. doi: 10.14336/AD.2020.0325
30. Zhu S, Wei X, Yang X, Huang Z, Chang Z, Xie F, et al. Plasma lipoprotein-associated phospholipase A2 and superoxide dismutase are independent predicators of cognitive impairment in cerebral small vessel disease patients: diagnosis and assessment. *Aging Dis.* (2019) 10:834–46. doi: 10.14336/AD.2019.0304
31. Li W, Qi Z, Kang H, Qin X, Song H, Sui X, et al. Serum occludin as a biomarker to predict the severity of acute ischemic stroke, hemorrhagic transformation, and patient prognosis. *Aging Dis.* (2020) 11:1395–406. doi: 10.14336/AD.2020.0119
32. Viderman D, Issanov A, Temirov T, Goligher E, la Fleur P. Outcome predictors of stroke mortality in the neurocritical care unit. *Front Neurol.* (2020) 11:579733. doi: 10.3389/fneur.2020.579733
33. Zhang S, Cho J, Nguyen T, Spincemaille P, Gupta A, Zhu W, et al. Initial experience of challenge-free MRI-based oxygen extraction fraction mapping of ischemic stroke at various stages: comparison with perfusion and diffusion mapping. *Front Neurosci.* (2020) 14:535441. doi: 10.3389/fnins.2020.535441
34. Lin CJ, Hung SC, Guo WY, Chang FC, Luo CB, Beilner J, et al. Monitoring peri-therapeutic cerebral circulation time: a feasibility study using color-coded quantitative DSA in patients with steno-occlusive arterial disease. *AJNR Am J Neuroradiol.* (2012) 33:1685–90. doi: 10.3174/ajnr.A3049
35. Hu YS, Guo WY, Lee IH, Chang FC, Lin CJ, Luo CB, et al. Prolonged cerebral circulation time is more associated with symptomatic

carotid stenosis than stenosis degree or collateral circulation. *J Neurointervent Surg.* (2018) 10:476–80. doi: 10.1136/neurintsurg-2017-013293

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 12 May 2021
doi: 10.3389/fneur.2021.644963

Association Between Metabolic Syndrome and Asymptomatic Cerebral Arterial Stenosis: A Cross-Sectional Study in Shandong, China

Shan Li[1†], *Xiao Sun*[1†], *Yuanyuan Zhao*[1,2], *Xiang Wang*[1,2], *Xiaokang Ji*[3], *Shaowei Sang*[4], *Sai Shao*[5], *Yuanyuan Xiang*[1,2], *Guangbin Wang*[5], *Ming Lv*[4], *Fuzhong Xue*[3], *Qinjian Sun*[1,2*] *and Yifeng Du*[1,2*]

[1] Department of Neurology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China, [2] Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China, [3] Department of Biostatistics, School of Public Health, Shandong University, Jinan, China, [4] Department of Clinical Epidemiology, Cheeloo College of Medicine, Qilu Hospital, Shandong University, Jinan, China, [5] Department of Radiology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China

OPEN ACCESS

Edited by:
Osama O. Zaidat,
Northeast Ohio Medical University,
United States

Reviewed by:
Mohamed Osman,
St. Vincent Mercy Medical Center,
United States
Philipp Gruber,
Aarau Cantonal Hospital, Switzerland

***Correspondence:**
Qinjian Sun
sqj1210@163.com
Yifeng Du
duyifeng2013@163.com

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: 22 December 2020
Accepted: 08 April 2021
Published: 12 May 2021

Citation:
Li S, Sun X, Zhao Y, Wang X, Ji X, Sang S, Shao S, Xiang Y, Wang G, Lv M, Xue F, Sun Q and Du Y (2021) Association Between Metabolic Syndrome and Asymptomatic Cerebral Arterial Stenosis: A Cross-Sectional Study in Shandong, China. Front. Neurol. 12:644963. doi: 10.3389/fneur.2021.644963

Metabolic syndrome (MetS) can worsen cerebral arterial atherosclerosis stenosis in patients with stroke; however, its effect on patients without stroke remains ambiguous. This study explored the association of MetS and its individual components with asymptomatic intracranial arterial stenosis (aICAS) and asymptomatic extracranial arterial stenosis (aECAS) among older Chinese adults. A total of 1988 participants from the Kongcun Town study aged ≥40 years and without a history of stroke were enrolled. The baseline data were obtained via face-to-face interviews. MetS was defined according to International Diabetes Federation criteria. Detection of aICAS was conducted using transcranial Doppler ultrasound, followed by diagnosis via magnetic resonance angiography. The evaluation of aECAS was performed using bilateral carotid ultrasonography. The aICAS and aECAS groups were 1:1 matched separately to the non-stenosis group by age and sex. The association between MetS and aICAS or aECAS was analyzed using multivariate logistic regression. Among the 1988 participants, 909 were diagnosed with MetS. The prevalence of MetS was higher in the aICAS group than in the non-stenosis group (P <0.001), but did not differ significantly between the aECAS and non-stenosis groups. The prevalence of aICAS increased with the number of MetS components from 3.4% in the ≤1 component group to 12.7% in the ≥4 components group (P for trend <0.001). After adjusting for confounding factors, MetS components associated with aICAS included central obesity, elevated triglyceride levels, and elevated blood pressure. None of the MetS components was associated with aECAS. MetS was positively associated with aICAS, but not with aECAS. Further, different components play different roles in the pathological process leading to aICAS.

Keywords: asymptomatic intracranial arterial stenosis, asymptomatic extracranial arterial stenosis, metabolic syndrome, asymptomatic cerebral arterial stenosis, stroke primary prevention

INTRODUCTION

Ischemic stroke caused by cerebral arterial atherosclerotic stenosis is a serious health and social issue worldwide, often leading to disability and mortality (1, 2). Some traditional vascular risk factors are involved in cerebral arterial atherogenesis, and they play different roles in the pathogenesis of intracranial and extracranial atherosclerosis (3). For instance, hyperlipidemia is more closely associated with extracranial arterial stenosis (ECAS), while diabetes mellitus (DM) and hypertension are associated with intracranial arterial stenosis (ICAS) (3, 4). Identifying different risk factors for ICAS and ECAS is helpful for efficient stroke prevention.

Metabolic syndrome (MetS) is a constellation of several metabolic risk factors, including central obesity, hypertension, elevated fasting blood glucose, and hyperlipidemia. The prevalence of MetS is gradually increasing with the aging population and changing lifestyle (5). In recent years, there has been a widespread concern regarding MetS as a novel risk factor for atherosclerosis (6).

MetS and its individual components are closely associated with ICAS or ECAS in patients with stroke, and this relationship is more significant with respect to ICAS than to ECAS (7–11). Some retrospective studies have evaluated the association of MetS with different locations (extracranial vs. intracranial) of asymptomatic cerebral arterial stenosis. A study in an asymptomatic Caucasians population found that MetS was an independent risk factor for moderate to severe (defined as ≥50% stenosis) intracranial atherosclerotic disease, but not for moderate to severe extracranial atherosclerotic disease (12). Another study involving a racially and ethnically diverse population found that the impact of MetS on the distribution of intracranial and extracranial atherosclerosis varied by race and ethnicity (13). Two community-based studies from China have separately reported a significant association between MetS and asymptomatic ICAS (aICAS) or asymptomatic ECAS (aECAS) (14, 15). However, no study has compared the association between MetS, including its individual components, and aICAS or aECAS in the Chinese population.

This study aimed to explore whether there is a differential profile in the association of MetS and its individual components with aICAS and aECAS among middle-aged and older adults living in rural communities in China.

MATERIALS AND METHODS

Study Design and Population

This study was based on the Kongcun Town study (16), a population-based study targeting 2,311 rural residents aged ≥40 years with no history of clinical stroke. Data on demographics, medical history, and physical examinations were obtained through face-to-face interviews. aICAS was detected using a two-phase procedure: screening using transcranial Doppler and diagnosis via magnetic resonance angiography. aECAS was evaluated using bilateral carotid ultrasonography. Among the 2,311 participants, 305 were excluded owning to incomplete information, two because of abnormal waist circumference, and 16 with combined aICAS/aECAS were excluded owning to the small number of cases. Finally, data from the 1988 eligible participants were analyzed. Participants were categorized into the following three groups according to the site of stenosis: (1) non-stenosis ($n = 1813$) (2) isolated aICAS ($n = 132$); and (3) isolated aECAS ($n = 43$).

The study protocol was approved by the Ethical Standards Committee on Human Experimentation at Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University. This study was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided a written informed consent.

Definitions of Vascular Risk Factors

Baseline data on demographics and risk factors were collected via interviews, clinical examinations, and laboratory tests in a similar manner as reported in our previous study (16). Hypertension was defined as a systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, use of antihypertensive drugs, or self-reported hypertension. DM was defined as a fasting plasma glucose level of ≥7.0 mmol/L (126.0 mg/dL), use of blood glucose-lowering drugs, receipt of insulin injection, or a self-reported history of diabetes. Based on smoking habits, participants were classified into current smokers (smoked at least one cigarette per day for more than 1 year) and former smokers (quit smoking <6 months earlier). Based on their drinking habits, participants were classified into current drinkers (consumed alcohol at least once a week for at least 6 months) and former drinkers (quit <6 months earlier).

Definition of MetS

MetS was defined using the criteria previously published by the International Diabetes Federation (17). The definition included the presence of central obesity (waist circumference ≥90 cm for Chinese men and ≥80 cm for Chinese women), plus any two of the following: (1) triglyceride (TG) level ≥1.7 mmol/L (150 mg/dL) or receiving specific treatment for this lipid abnormality (2) high-density lipoprotein cholesterol (HDL-C) level <1.03 mmol/L (40 mg/dL) in men and <1.29 mmol/L (50 mg/dL) in women or receiving specific treatment for this lipid abnormality; (3) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or receiving treatment for previously diagnosed arterial hypertension; and (4) fasting plasma glucose level ≥5.6 mmol/L (100 mg/dL) or previously diagnosed DM.

Assessment of aICAS and aECAS

The protocol for the evaluation of aICAS and aECAS has been described in detail in our previous study (16). In brief, aICAS was detected through a two-phase procedure: a screen phase using transcranial Doppler and the diagnostic phase using magnetic resonance angiography. Transcranial Doppler was performed by two physicians using a portable machine (VIASYS Companion III). The bilateral middle cerebral artery, internal carotid artery, anterior cerebral artery, posterior cerebral artery, vertebral artery, and basilar artery were examined with a 2-MHz probe via temporal, occipital, and eye windows. Stenosis of participants with poor temporal windows in the bilateral vertebral artery,

TABLE 1 | Demographic and clinical characteristics of study participants.

Characteristics	Overall (n = 1,988)	NS (n = 1,813)	aICAS (n = 132)	aECAS (n = 43)	OverallP
Age (years), mean (SD)	57.6 (10.3)	57.2 (10.3)	60.3 (10.8)[a]	66.6 (8.1)[a]	<0.001
Male, *n* (%)	956 (48.0)	880 (48.5)	51 (38.6)	25 (58.1)	0.037
Hypertension, *n* (%)	1148 (57.7)	1004 (55.3)	110 (83.3)[a]	34 (79.0)[a]	<0.001
Diabetes mellitus, *n* (%)	304 (15.2)	250 (13.7)	30 (35.7)[a]	15 (34.8)[a]	<0.001
Total cholesterol (mmol/l), mean (SD)	5.4 (1.0)	5.4 (1.0)	5.4 (1.0)	5.6 (1.0)	0.265
Triglycerides (mmol/l), mean (SD)	1.4 (0.9)	1.3 (0.9)	1.7 (1.2)[a]	1.5 (1.1)	<0.001
HDL-C (mmol/l), mean (SD)	1.6 (0.4)	1.6 (0.4)	1.5 (0.3)[a]	1.7 (0.4)	<0.001
LDL-C (mmol/l), mean (SD)	3.0 (0.7)	3.0 (0.7)	3.2 (0.7)[a]	3.1 (0.7)	0.013
Smoking habits, *n* (%)	448 (22.5)	420 (23.1)	15(11.3)[a]	13 (30.2)	0.004
Drinking habits, *n* (%)	658 (33.0)	608 (33.5)	35 (26.5)	15 (34.8)	0.246
BMI (kg/m²), mean (SD)	25.1 (3.3)	25.1 (3.4)	26.2 (3.0)[a]	24.6 (3.3)	0.001
Waist circumference (cm), mean (SD)	91 (9)	91 (9)	95 (8)[a]	91 (10)	<0.001
MetS, *n* (%)	909 (45.7)	788 (43.4)	95 (71.9)[a]	26 (60.4)	<0.001
MetS components					
Central obesity, *n* (%)	1547 (77.8)	1389 (76.6)	126 (95.4)[a]	32 (74.4)	<0.001
Raised triglycerides, *n* (%)	448 (22.5)	392(21.6)	45 (34.0)[a]	11 (25.5)	0.004
Reduced HDL-C, n (%)	217 (10.9)	188 (10.3)	25 (18.9)[a]	4 (9.3)	0.009
Raised BP, *n* (%)	1578 (79.3)	1419 (78.2)	118 (89.3)[a]	41 (95.3)[a]	<0.001
Elevated fasting glucose, *n* (%)	1062 (53.4)	944 (52.0)	86(65.1)[a]	32 (74.4)[a]	<0.001
Number of MetS component	2 (1)	2 (1)	3 (1)[a]	3 (1)	<0.001

NS, non-stenosis; aICAS, asymptomatic intracranial arterial stenosis; aECAS, asymptomatic extracranial arterial stenosis; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; BP, blood pressure; MetS, metabolic syndrome; SD: standard deviation.

[a]Significantly different from NS group, P < 0.05/3 = 0.017 (the Bonferroni correction was applied).

Overall p-value is for the test of difference among the NS group, aICAS group and aECAS group.

posterior cerebral artery, and basilar artery was examined via the occipital window. In this study, aICAS was defined according to the previously published criteria for the identification of one or more stenotic lesions of any degree in any one of the analyzed intracranial vessels on magnetic resonance angiography (18). The diagnosis and grading of aICAS was performed by a stroke specialist and clinical neuroradiologist. The degree of stenosis in the evaluated arteries (bilateral middle cerebral artery, bilateral intracranial internal carotid artery, anterior cerebral artery, posterior cerebral artery, and basilar artery) was classified into five grades by consensus as normal, mild (signal reduction <50%), moderate (signal reduction ≥50% and <70%), severe (signal reduction ≥70%), or occlusion (focal signal loss with the presence of distal signal). aECAS was diagnosed via carotid ultrasonography examination, which has a high sensitivity and specificity (19, 20), and was performed by two experienced physicians. aECAS was defined according to established carotid ultrasonography criteria (21) as the identification of one or more stenotic lesions of any degree in any one of the analyzed vessels, including the carotid artery, internal carotid artery, and external carotid artery. The degree of aECAS was classified into four grades: mild (<50% stenosis), moderate (50–69% stenosis), severe (70–99% stenosis), and total occlusion.

Statistical Analyses

All analyses were conducted using IBM Statistical Package for the Social Sciences Statistics V22.0 for Windows (IBM Corp., released 2013, Armonk, NY, USA). Baseline population statistics and continuous laboratory-based variables are expressed as terms of mean and standard deviation, and categorical variables are expressed as frequencies and percentages. Continuous variables were compared using the *t*-test or analysis of variance with *post hoc* tests, while categorical variables were compared using the chi-square test. The Bonferroni adjustment was performed to assess the statistical significance of the intergroup differences. The aICAS and aECAS groups were 1:1 matched separately to the non-stenosis group by age and sex. The multivariate logistic regression was used to determine the association between MetS and its individual components with aICAS or aECAS. The variables with a *P*-value of <0.1 in the univariate analysis were included in the logistic regression models. The associations of different cerebral arterial stenosis were reported as odds ratio (OR) values and their 95% confidence intervals (CI). All statistical tests were two-tailed, and $P < 0.05$, indicated statistical significance.

RESULTS

Baseline Characteristics of the Study Population

The demographic and clinical characteristics of the study participants are shown in **Table 1**. Compared with the non-stenosis group, the aICAS group had significantly higher mean

TABLE 2 | Demographic and clinical characteristics of the participants after matching for age and sex.

Characteristics	Control 1 (n = 132)	aICAS (n = 132)	P[a]	Control 2 (n = 43)	aECAS (n = 43)	P[b]
Age (years), mean (SD)	58.4 (10.6)	60.3 (10.8)	0.157	64.7 (8.0)	66.6 (8.1)	0.276
Male, *n* (%)	51 (38.6)	51 (38.6)	1.000	25 (58.1)	25 (58.1)	1.000
Hypertension, *n* (%)	84 (63.6)	110 (83.3)	<0.001	30 (69.8)	34 (79.0)	0.323
Diabetes mellitus, *n* (%)	32 (24.2)	39 (29.5)	0.331	15 (34.9)	15 (34.9)	1.000
Total cholesterol (mmol/l), mean (SD)	6.9 (1.0)	5.4 (1.0)	<0.001	7.1 (0.9)	5.6 (1.0)	<0.001
Triglycerides (mmol/l), mean (SD)	1.8 (1.2)	1.7 (1.2)	0.419	1.8 (1.3)	1.5 (1.1)	0.312
HDL-C (mmol/l), mean (SD)	1.7 (0.4)	1.5 (0.3)	<0.001	1.9 (0.4)	1.7 (0.4)	0.003
LDL-C (mmol/l), mean (SD)	3.9 (0.7)	3.2 (0.7)	<0.001	3.9 (0.8)	3.1 (0.7)	<0.001
Smoking habits, *n* (%)	22 (16.7)	15(11.3)	0.215	17(39.5)	13 (30.2)	0.365
Drinking habits, *n* (%)	34 (25.8)	35 (26.5)	0.889	18 (41.9)	15 (34.8)	0.506
BMI (kg/m²), mean (SD)	24.9 (3.5)	26.2 (3.0)	0.002	23.2 (3.7)	24.6 (3.3)	0.059
Waist circumference (cm), mean (SD)	92 (10)	95 (8)	0.021	87 (10)	91 (10)	0.058
MetS, *n* (%)	78 (53.8)	95 (71.9)	0.002	19 (44.2)	26 (60.4)	0.131
Central obesity, *n* (%)	108 (81.8)	126 (95.4)	<0.001	24 (55.8)	32 (74.4)	0.070
Raised triglycerides, *n* (%)	55(41.7)	45 (34.0)	0.205	17(39.5)	11 (25.5)	0.167
Reduced HDL-C, *n* (%)	11 (8.3)	25 (18.9)	0.012	3(7.0)	4 (9.3)	0.693
Raised BP, *n* (%)	109 (82.6)	118 (89.3)	0.111	35(81.4)	41 (95.3)	0.044
Elevated fasting glucose, *n* (%)	89(67.4)	86(65.1)	0.696	32 (74.4)	32 (74.4)	1.000
Number of MetS component	3 (1)	3 (1)	0.105	3 (1)	3 (1)	0.389

aICAS, asymptomatic intracranial arterial stenosis; aECAS, asymptomatic extracranial arterial stenosis; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; BP, blood pressure; MetS, metabolic syndrome.

P^a value is for the test of difference between the control 1 group and aICAS group.

P^b value is for the test of difference between the control 2 group and aECAS group.

age, body mass index, waist circumference, and TG and low-density lipoprotein cholesterol levels and a significantly lower mean HDL-C level. The prevalence of hypertension, DM, and MetS was also higher in the aICAS group than in the non-stenosis group. The mean age and prevalence of hypertension and DM were also higher in the aECAS group than in the non-stenosis group. Of the 1988 participants, 909 (45.7%) were diagnosed with MetS. Compared with the non-stenosis group, the prevalence of MetS and all its individual components (all $P < 0.017$) was higher in the aICAS group and that of elevated blood pressure and elevated fasting glucose (all $P < 0.017$) was higher in the aECAS group.

Demographic and Clinical Characteristics of the Participants After Matching for Age and Sex

Table 2 shows the demographic and clinical characteristics of the participants after matching for age and sex. Age, sex, smoking habits, and drinking habits showed no significant difference between the aICAS/aECAS and control groups. Compared with the control 1 group, the aICAS group had significantly higher body mass index, waist circumference, and a significantly lower mean HDL-C level. The prevalence of hypertension and MetS was also higher in the aICAS group than in the control 1 group. The HDL-C level was lower in the aECAS group than in the control 2 group.

Associations of MetS and Its Components With aICAS or aECAS

In the multivariate logistic regression analysis (**Figure 1**), MetS was significantly associated with aICAS (OR: 4.01; 95% CI: 1.84, 8.75) after adjusting for total cholesterol level, body mass index, and low-density lipoprotein cholesterol level, which were significantly related to aICAS or ECAS in the univariate logistic regression analysis (**Table 3**, all $P < 0.1$). Participants with more severe MetS components were more likely to have aICAS (P for linear trend =0.011). The following MetS components were significantly associated with aICAS: central obesity, elevated TG levels, and elevated blood pressure. However, no significant association between aECAS, MetS and its components was observed.

Prevalence of aICAS and aECAS According to the Number of MetS Components

The prevalence of aICAS increased significantly in proportion to the number of MetS components from 3.4% in the ≤1 component group to 12.7% in the ≥4 components group (P for trend <0.001). However, the same association was not found for aECAS (**Figure 2**).

DISCUSSION

This study found that MetS was associated with aICAS, but not with aECAS, and different components play different roles in the pathological process leading to aICAS. Among MetS

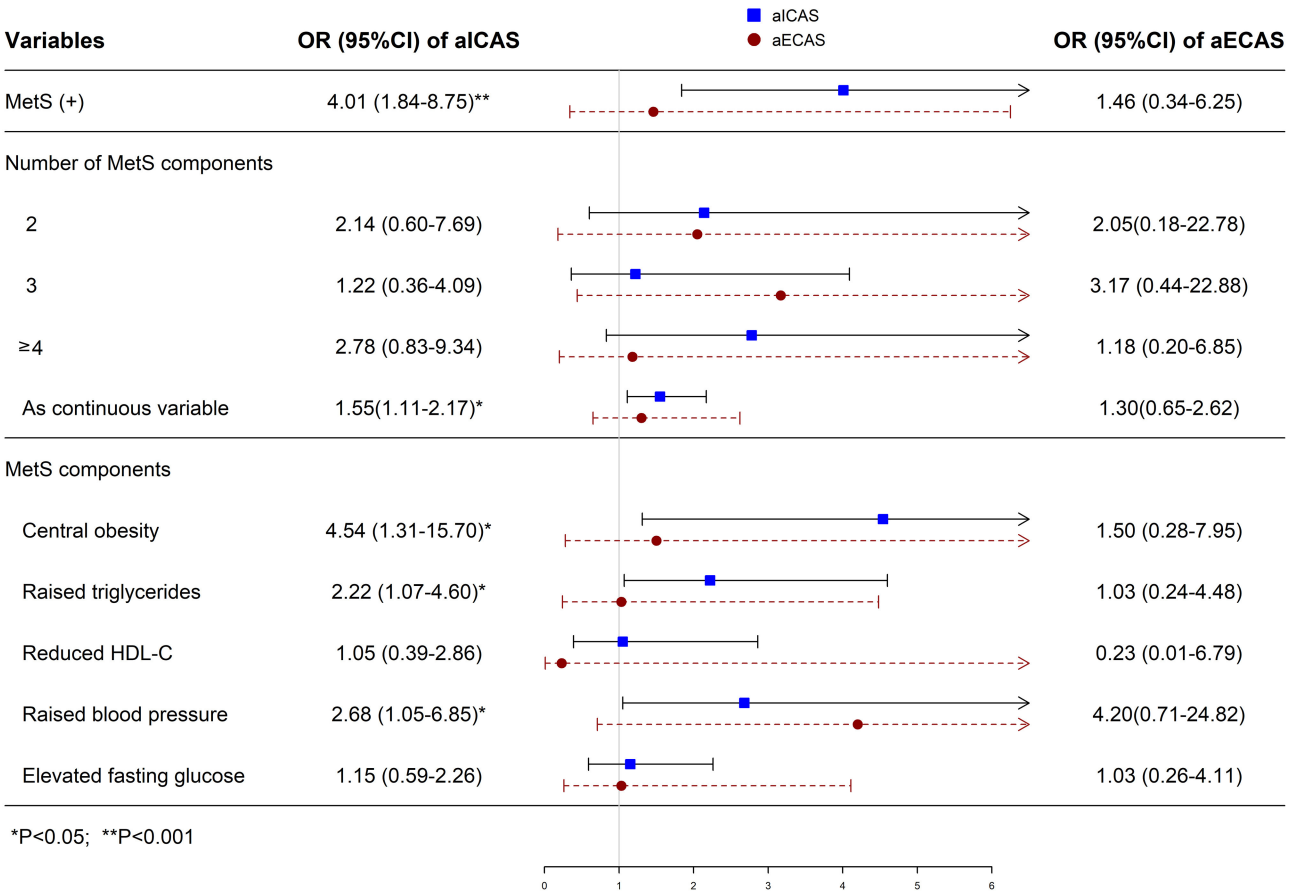


FIGURE 1 | Multivariate logistic regression analysis of the association of MetS with aICAS or aECAS. aICAS, asymptomatic intracranial arterial stenosis; aECAS, asymptomatic extracranial arterial stenosis; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; BP, blood pressure; MetS, metabolic syndrome; OR, odds ratio. ORs were calculated using logistic regression model after adjusting total cholesterol, BMI, and LDL-C.

components, central obesity, elevated TG levels, and elevated blood pressure were significantly associated with aICAS. To the best of our knowledge, this is the first study to investigate the association between MetS and aICAS or aECAS among middle-aged and older adults living in rural communities in China.

MetS is a proinflammatory and hypercoagulable state, which is mainly mediated by insulin resistance. It has been suggested that accelerated atherosclerosis in MetS is associated with defective insulin signaling pathways (22). In addition, oxidative stress is associated with MetS and plays a role in endothelial dysfunction and subsequent atherosclerosis (23). Previous hospital-based studies reported that MetS was an independent risk factor for stroke, and that patients with MetS were more likely to experience ICAS than ECAS (7–11). A prospective Korean study revealed that MetS was more prevalent in ICAS patients than in ECAS patients with posterior circulation stroke (3). These studies concluded that MetS could play an important role in promoting cerebral arterial stenosis and increasing the risk of subsequent stroke. Furthermore, several studies have focused on investigating the association between MetS and aICAS or aECAS in the stroke-free population. The Asymptomatic Polyvascular Abnormalities in Community study targeting employees and retirees of the Kailuan (Group) Co. Ltd (a large coal mine industry) reported significant associations between MetS and aICAS (14), which is consistent with our results. Another study involving asymptomatic Chinese people reported significant associations between MetS and aECAS in menopausal women (15). The reason for the inconsistent results may be that the participants investigated were different. Regarding severity, the Barcelona-Asymptomatic Intracranial Atherosclerosis study found that MetS was significantly associated with moderate to severe intracranial atherosclerotic disease and not with moderate to severe extracranial atherosclerotic disease (12). This finding was apparently corroborated by the finding that MetS may be independently associated with the early stage rather than the advanced stages of intracranial arterial atherosclerosis (24). To the best of our knowledge, some studies have reported that ECAS is common in Caucasian population, whereas ICAS is more frequent in Asian and African populations (25–27). A previous study involving a racially and ethnically diverse population found that the impact of MetS on the distribution of intracranial and extracranial atherosclerosis varied by race and ethnicity

TABLE 3 | Univariate logistic regression analysis of the association of MetS with aICAS or aECAS.

Variables	aICAS		aECAS	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Smoking habits	1.56 (0.77–3.16)	0.217	1.51 (0.62–3.69)	0.367
Drinking habits	1.04 (0.60–1.80)	0.889	1.34 (0.56–3.21)	0.506
BMI	1.13 (1.04–1.22)	0.003	1.13 (0.99–1.29)	0.064
Total cholesterol	3.89 (2.82–5.58)	<0.001	6.90 (3.02–15.87)	<0.001
LDL-C	4.13 (2.75–6.25)	<0.001	5.85 (2.53–13.51)	<0.001
MetS (+)	2.22 (1.32–3.68)	0.002	1.93 (0.81–4.56)	0.132
Number of MetS components				
≤1	Reference		Reference	
2	1.11 (0.44–2.80)	0.830	1.44 (0.34–6.05)	0.618
3	1.21 (0.49–3.00)	0.677	3.15 (0.86–11.60)	0.084
≥4	2.62 (1.01–6.80)	0.049	1.35 (0.34–5.44)	0.673
As continuous variables	1.21 (0.96–1.52)	0.105	1.19 (0.81–1.74)	0.385
MetS components				
Central obesity	4.67 (1.84–11.84)	0.001	2.30 (0.93–5.73)	0.073
Raised triglycerides	0.72 (0.44–1.19)	0.205	1.90 (0.76–4.76)	0.170
Reduced HDL-C	2.57 (1.21–5.47)	0.014	1.37 (0.29–6.51)	0.694
Raised BP	1.78 (0.87–3.63)	0.114	4.69 (0.93–23.53)	0.061
Elevated fasting glucose	0.90 (0.54–1.51)	0.696	1.00 (0.38–2.64)	1.000

aICAS, asymptomatic intracranial arterial stenosis; aECAS, asymptomatic extracranial arterial stenosis; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; BP, blood pressure; MetS, metabolic syndrome.

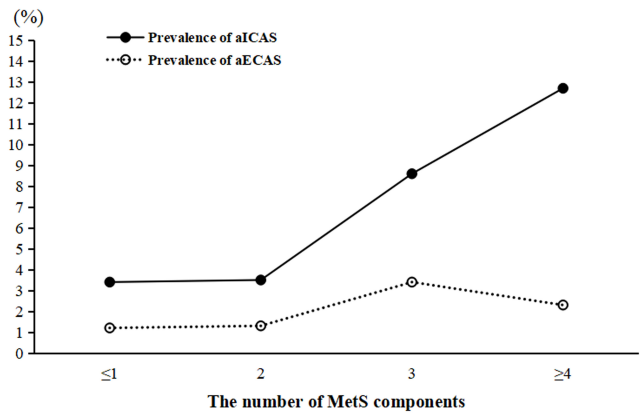


FIGURE 2 | Prevalence of aICAS and aECAS according to the number of MetS components. aICAS, asymptomatic intracranial arterial stenosis; aECAS, asymptomatic extracranial arterial stenosis; MetS, metabolic syndrome.

(13). The race-specific impact of MetS on the distribution of cerebral arterial atherosclerosis may be caused by racial-specific differences in the prevalence of MetS components and in the host response to the presence of specific components. This finding may partly explain the well-known differences in race-ethnic predilection to intracranial or extracranial atherosclerosis. Future studies with genotyping may be important to define the relationships between the biological race differences between ICAS and ECAS.

In this study, central obesity was associated with aICAS, but not with aECAS. Central obesity can lead to an increase in the free fatty acids, which play an important role in the pathogenesis of insulin resistance (28, 29). Furthermore, insulin resistance can damage intracranial vasodilatory function by increasing the stiffness of the vascular wall and reducing the buffering ability, which increases its susceptibility to arterial oxidative stress (30, 31). Therefore, early intervention for central obesity may delay the progression of cerebral arterial stenosis, especially aICAS.

In this study, elevated TG levels were significantly associated with aICAS. High TG levels can promote the formation of low-density lipoprotein particles (32); high levels of low-density lipoprotein cholesterol, especially its oxidized form, can facilitate endothelial dysfunction, which is the first step in atherosclerotic plaque formation (33).

The significant association between elevated blood pressure and aICAS detected in this study is consistent with previous studies (34, 35). Hypertension is a well-known risk factor for arteriosclerosis (36). Compared with the extracranial arteries, the thickness and elasticity of the tunica media is inferior in the intracranial arteries; therefore, it may be more vulnerable to the changes in vascular stress and blood flow caused by hypertension (36).

Among MetS components, the association between reduced HDL-C and elevated fasting glucose levels with MetS was not found. However, previous hospital-based studies found that the components (reduced HDL-C and elevated fasting glucose levels) constituting MetS were related to aICAS (9, 11). This suggests that MetS can affect intracranial arterial atherosclerosis

in different pathological states via different metabolic pathways. In addition, this finding may reveal that the association between aICAS and MetS may be derived from the specific components of MetS, such as central obesity, elevated TG levels, and elevated blood pressure, especially in the asymptomatic phase of intracranial arterial stenosis. More metabolism-related basic research is needed to confirm this inference in the future.

The reasons for the aforementioned differential effects of MetS on the distribution of cerebral arterial stenosis are not well-understood. The potential reasons for this are as follows: first, the differential responses of intracranial and extracranial arteries to oxidative stress may explain our finding that most components constituting MetS were associated with aICAS, since oxidative stress has been reported to be associated with MetS (23). Compared with the extracranial arteries, the intracranial arteries were found to be susceptible to oxidative stress with increasing age (37). Second, the histological differences between the intracranial and extracranial arteries should be considered. The extracranial arteries are elastic arteries whose tunica media are rich in elastin filaments. However, the intracranial arteries with a fewer elastic fibers may be more vulnerable to the circulatory abnormalities caused by MetS (36).

Some potential limitations of our study are worth mentioning. First, a cross-sectional study cannot prove the existence of a causal relationship between MetS and aICAS/aECAS; further studies using a prospective study are needed to confirm this relationship. Second, owning to the relatively small sample size, this study was unable to evaluate the association between MetS and distribution of stenosis in various strata of severity of stenosis. Finally, the findings of this study may not be generalizable to other populations since it included only Chinese adults living in rural areas. Nevertheless, to the best of our knowledge, this is the first study to investigate the differences in the associations between certain MetS components and the distribution of cerebral arterial stenosis.

In conclusion, the study findings indicate that MetS is associated with aICAS, but not with aECAS, and different components play different roles in the pathological process of aICAS. These differences may prompt the employment of individualized preventive measures during the asymptomatic stage of cerebral arterial stenosis; thereby, reducing the incidence of stroke.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QS, YD, and FX conceived and designed the research. SL, YZ, XW, XJ, SSa, SSh, and YX acquired the data. SL, XS, YZ, XW, XJ, SSa, SSh, YX, and GW analyzed and interpreted the data. SL and XS draft the manuscript. XW, ML, FX, QS, and YD made critical revisions of the manuscript. All authors approved the final manuscript.

FUNDING

This study was supported by the grants from Jinan Science and Technology Bureau [Grant Number 201704101], Department of Science and Technology of Shandong Province [Grant Numbers 2014GSF118106, 2016GSF201062, and ZR2017MH114], the National Nature Science Foundation of China [Grant Numbers 8171101298 and 81971128], the China Ministry of Sciences and Technology [Grant Numbers 2017YFC1310100 and 2017YFC0907003], and the International Science and Technology Cooperation Programme [Grant Number 2014DFA 32830].

ACKNOWLEDGMENTS

We would like to thank all the study participants, staff of the participating hospitals, and the Steering Committee Members of this study.

REFERENCES

1. Collaborators GN. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* (2019) 18:459–80. doi: 10.1016/s1474-4422(18)30499-x
2. Xu Y, Yuan C, Zhou Z, He L, Mi D, Li R, et al. Co-existing intracranial and extracranial carotid artery atherosclerotic plaques and recurrent stroke risk: a three-dimensional multicontrast cardiovascular magnetic resonance study. *J Cardiovasc Magnet Resonance.* (2016) 18:90. doi: 10.1186/s12968-016-0309-3
3. Kim JS, Nah HW, Park SM, Kim SK, Cho KH, Lee J, et al. Risk factors and stroke mechanisms in atherosclerotic stroke: intracranial compared with extracranial and anterior compared with posterior circulation disease. *Stroke.* (2012) 43:3313–8. doi: 10.1161/strokeaha.112.658500
4. Qureshi AI, Caplan LR. Intracranial atherosclerosis. *Lancet.* (2014) 383:984–98. doi: 10.1016/s0140-6736(13)61088-0
5. Li Y, Zhao L, Yu D, Wang Z, Ding G. Metabolic syndrome prevalence and its risk factors among adults in China: A nationally representative cross-sectional study. *PLoS ONE.* (2018) 13:e0199293. doi: 10.1371/journal.pone.0199293
6. Bang OY. Intracranial atherosclerotic stroke: specific focus on the metabolic syndrome and inflammation. *Curr Atherosc Rep.* (2006) 8:330–6. doi: 10.1007/s11883-006-0012-1
7. Bang OY, Kim JW, Lee JH, Lee MA, Lee PH, Joo IS, et al. Association of the metabolic syndrome with intracranial atherosclerotic stroke. *Neurology.* (2005) 65:296–8. doi: 10.1212/01.wnl.0000168862.09764.9f

8. Park JH, Kwon HM, Roh JK. Metabolic syndrome is more associated with intracranial atherosclerosis than extracranial atherosclerosis. *Eur J Neurol.* (2007) 14:379–86. doi: 10.1111/j.1468-1331.2007.01682.x
9. Park JH, Kwon HM. Association between metabolic syndrome and previous ischemic lesions in patients with intracranial atherosclerotic stroke. *Clin Neurol Neurosurg.* (2008) 110:215–21. doi: 10.1016/j.clineuro.2007.10.016
10. Rincon F, Sacco RL, Kranwinkel G, Xu Q, Paik MC, Boden-Albala B, et al. Incidence and risk factors of intracranial atherosclerotic stroke: the Northern Manhattan Stroke Study. *Cerebrovasc Dis.* (2009) 28:65–71. doi: 10.1159/000219299
11. Liu C, Yang X, Chen C. Correlation between Metabolic Syndrome and Intracranial versus Extracranial Arteriosclerosis among Chinese Patients with Stroke. *Iran J Public Health.* (2019) 48:1997–2006.
12. López-Cancio E, Galán A, Dorado L, Jiménez M, Hernández M, Millán M, et al. Biological signatures of asymptomatic extra- and intracranial atherosclerosis: the Barcelona-AsIA (Asymptomatic Intracranial Atherosclerosis) study. *Stroke.* (2012) 43:2712–9. doi: 10.1161/strokeaha.112.661702
13. Bang OY, Saver JL, Liebeskind DS, Pineda S, Yun SW, Ovbiagele B. Impact of metabolic syndrome on distribution of cervicocephalic atherosclerosis: data from a diverse race-ethnic group. *J Neurol Sci.* (2009) 284:40–5. doi: 10.1016/j.jns.2009.03.033
14. Wang A, Li Z, Luo Y, Liu X, Guo X, Wu S, et al. Asymptomatic intracranial arterial stenosis and metabolic syndrome: the APAC study. *PLoS ONE.* (2014) 9:e113205. doi: 10.1371/journal.pone.0113205
15. Zhu B, Zhang L, Cheng XP, Wang L, Tian Y, Li XX, et al. The association between metabolic syndrome and asymptomatic carotid artery stenosis in menopausal women: a cross-sectional study in a Chinese population. *Therap Clin Risk Manage.* (2018) 14:2183–8. doi: 10.2147/tcrm.S177265
16. Sun Q, Wang Q, Wang X, Ji X, Sang S, Shao S, et al. Prevalence and cardiovascular risk factors of asymptomatic intracranial arterial stenosis: the Kongcun Town Study in Shandong, China. *Eur J Neurol.* (2020) 27:729–35. doi: 10.1111/ene.14144
17. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome–a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med.* (2006) 23:469–80. doi: 10.1111/j.1464-5491.2006.01858.x
18. Samuels OB, Joseph GJ, Lynn MJ, Smith HA, Chimowitz MI. A standardized method for measuring intracranial arterial stenosis. *AJNR Am J Neuroradiol.* (2000) 21:643–6. doi: 10.1016/S0925-4927(99)00050-5
19. Honish C, Sadanand V, Fladeland D, Chow V, Pirouzmand F. The reliability of ultrasound measurements of carotid stenosis compared to MRA and DSA. *Can J Neurol Sci.* (2005) 32:465–71. doi: 10.1017/s0317167100004455
20. Mozzini C, Roscia G, Casadei A, Cominacini L. Searching the perfect ultrasonic classification in assessing carotid artery stenosis: comparison and remarks upon the existing ultrasound criteria. *J Ultrasound.* (2016) 19:83–90. doi: 10.1007/s40477-016-0193-6
21. Grant EG, Benson CB, Moneta GL, Alexandrov AV, Baker JD, Bluth EI, et al. Carotid artery stenosis: gray-scale and Doppler US diagnosis–Society of radiologists in ultrasound consensus conference. *Radiology.* (2003) 229:340–6. doi: 10.1148/radiol.2292030516
22. González-Navarro H, Vinué A, Vila-Caballer M, Fortuño A, Beloqui O, Zalba G, et al. Molecular mechanisms of atherosclerosis in metabolic syndrome: role of reduced IRS2-dependent signaling. *Arterioscl Thromb Vasc Biol.* (2008) 28:2187–94. doi: 10.1161/atvbaha.108.175299
23. Ahmadnezhad M, Arefhosseini SR, Parizadeh MR, Tavallaie S, Tayefi M, Darroudi S, et al. Association between serum uric acid, high sensitive C-reactive protein and pro-oxidant-antioxidant balance in patients with metabolic syndrome. *BioFactors.* (2018) 44:263–71. doi: 10.1002/biof.1424
24. Leng XY, Chen XY, Chook P, Xiong L, Lin WH, Liu JY, et al. Association between metabolic syndrome and carotid atherosclerosis: a community-based study in Hong Kong. *Metab Syndr Relat Disord.* (2013) 11:109–14. doi: 10.1089/met.2012.0099
25. Wityk RJ, Lehman D, Klag M, Coresh J, Ahn H, Litt B. Race and sex differences in the distribution of cerebral atherosclerosis. *Stroke.* (1996) 27:1974–80. doi: 10.1161/01.str.27.11.1974
26. Sacco RL, Roberts JK, Boden-Albala B, Gu Q, Lin IF, Kargman DE, et al. Race-ethnicity and determinants of carotid atherosclerosis in a multiethnic population. The Northern Manhattan Stroke Study. *Stroke.* (1997) 28:929–35. doi: 10.1161/01.str.28.5.929
27. Wong LK. Global burden of intracranial atherosclerosis. *Int J Stroke.* (2006) 1:158–9. doi: 10.1111/j.1747-4949.2006.00045.x
28. Arner P, Rydén M. Fatty Acids, Obesity and Insulin Resistance. *Obesity Facts.* (2015) 8:147–55. doi: 10.1159/000381224
29. Zhai W, Xu C, Ling Y, Liu S, Deng J, Qi Y, et al. Increased lipolysis in adipose tissues is associated with elevation of systemic free fatty acids and insulin resistance in perilipin null mice. *Hormone Metab Res.* (2010) 42:247–53. doi: 10.1055/s-0029-1243599
30. Menezes VP, Cohen C, Del-Rei J, Oigman W, Neves MF, Medeiros FJ. Evaluation of endothelial function and arterial stiffness in obese individuals with insulin resistance. *Nutr Health.* (2019) 25:85–92. doi: 10.1177/0260106018819374
31. Watt NT, Gage MC, Patel PA, Viswambharan H, Sukumar P, Galloway S, et al. Endothelial SHIP2 Suppresses Nox2 NADPH Oxidase-Dependent Vascular Oxidative Stress, Endothelial Dysfunction, and Systemic Insulin Resistance. *Diabetes.* (2017) 66:2808–21. doi: 10.2337/db17-0062
32. Lei C, Wu B, Liu M, Chen Y. Risk factors and clinical outcomes associated with intracranial and extracranial atherosclerotic stenosis acute ischemic stroke. *J Stroke Cerebrovasc Dis.* (2014) 23:1112–7. doi: 10.1016/j.jstrokecerebrovasdis.2013.09.024
33. Mitra S, Deshmukh A, Sachdeva R, Lu J, Mehta JL. Oxidized low-density lipoprotein and atherosclerosis implications in antioxidant therapy. *Am J Med Sci.* (2011) 342:135–42. doi: 10.1097/MAJ.0b013e318224a147
34. Zhang S, Zhou Y, Zhang Y, Gao X, Zhang Q, Wang A, et al. Prevalence and risk factors of asymptomatic intracranial arterial stenosis in a community-based population of Chinese adults. *Eur J Neurol.* (2013) 20:1479–85. doi: 10.1111/ene.12210
35. Jin H, Peng Q, Nan D, Lv P, Liu R, Sun W, et al. Prevalence and risk factors of intracranial and extracranial artery stenosis in asymptomatic rural residents of 13 villages in China. *BMC Neurol.* (2017) 17:136. doi: 10.1186/s12883-017-0924-0
36. Ritz K, Denswil NP, Stam OC, van Lieshout JJ, Daemen MJ. Cause and mechanisms of intracranial atherosclerosis. *Circulation.* (2014) 130:1407–14. doi: 10.1161/circulationaha.114.011147
37. D'Armiento FP, Bianchi A, de Nigris F, Capuzzi DM, D'Armiento MR, Crimi G, et al. Age-related effects on atherogenesis and scavenger enzymes of intracranial and extracranial arteries in men without classic risk factors for atherosclerosis. *Stroke.* (2001) 32:2472–9. doi: 10.1161/hs1101.098520

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 25 May 2021
doi: 10.3389/fneur.2021.668868

Thirty-Day and One-Year Outcomes of Endovascular Treatments for Severe Atherosclerotic Stenosis of Intracranial ICA: Results From a Single Center

Shengli Shen[1†], Yingjin Wang[1†], Xudong He[2†], Ning Ma[3], Feng Gao[3], Ligang Song[3], Xuan Sun[3], Lian Liu[3], Zhongrong Miao[3], Hongzhou Duan[1] and Dapeng Mo[3*]*

[1] Department of Neurosurgery, Peking University First Hospital, Beijing, China, [2] Department of Neurology, School of Medicine, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China, [3] Department of Interventional Neuroradiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

OPEN ACCESS

Edited by:
QinJian Sun,
Shandong University, China

Reviewed by:
Farhan Siddiq,
University of Missouri System, United States
Bu-Lang Gao,
Second Hospital of Hebei Medical University, China

***Correspondence:**
Dapeng Mo
bjttmodp@163.com
Hongzhou Duan
duanhongzhou@126.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: 17 February 2021
Accepted: 13 April 2021
Published: 25 May 2021

Citation:
Shen S, Wang Y, He X, Ma N, Gao F, Song L, Sun X, Liu L, Miao Z, Duan H and Mo D (2021) Thirty-Day and One-Year Outcomes of Endovascular Treatments for Severe Atherosclerotic Stenosis of Intracranial ICA: Results From a Single Center. Front. Neurol. 12:668868. doi: 10.3389/fneur.2021.668868

Background: Endovascular treatment for intracranial atherosclerotic stenosis (ICAS) has been developed. However, the intracranial internal carotid artery (ICA) presents a particular challenge due to the location and tortuous route, and the outcomes of endovascular treatment in patients with stenosis of the intracranial ICA still have not been reported. This article retrospectively investigated the 30-day and 1-year outcomes of tailored endovascular treatment for patients with severe intracranial ICA stenosis from a single center.

Methods: Between June 2014 and December 2017, 96 consecutive patients with severe atherosclerotic stenosis (70–99%) of the intracranial ICA were managed with endovascular treatment in Beijing Tiantan Hospital. Three different kinds of treatments [angioplasty with balloon dilatation alone (BD group), balloon-mounted stent (BMS group), and self-expanding stent (SES group)] were performed according to the characteristics of the lesions. The primary endpoints included any stroke or death within 30 days and ipsilateral ischemic stroke afterwards within 1 year. Secondary endpoints included the revascularization success rate (residual stenosis $<30\%$) and the restenosis rate (stenosis $\geq 50\%$) within 1 year.

Results: The 30-day death rate was 0, and the stroke rate of all patients was 7.3% (7/96). The stroke rate was higher in the BD group (15.8%) and SES group (9.8%) than in the BMS group (0%) ($p = 0.047$). Thirteen (13.5%) patients suffered at least one onset of ischemic stroke in the ipsilateral ICA territory within 1 year, and there was no significant difference among the three groups ($p = 0.165$). The overall revascularization success rate was 93.8%, and the revascularization success rate was significantly higher in the SES group (100%) than in the BD group (78.9%) ($p = 0.006$). The restenosis rate of all patients within 12 months was 20.8%, and there was no significant difference among the three groups. Patients with Mori type C target lesions were more likely to suffer stroke within 30 days (25%) and restenosis within 1 year (31.3%).

Conclusions: Both the 30-day and 1-year outcomes of tailored endovascular treatments seemed to be acceptable in the treatment of symptomatic atherosclerotic stenosis of the intracranial ICA. However, this needs to be confirmed by further investigation, preferably in large multicenter randomized controlled clinical trials.

Keywords: endovascular treatment, atherosclerotic stenosis, intracranial internal carotid artery, outcome, complication

INTRODUCTION

Intracranial atherosclerotic stenosis (ICAS) is a common etiology of stroke worldwide, with the highest prevalence being in Asian, Hispanic, and African populations and ICAS accounting for approximately half of transient ischemic attacks (TIAs) and ischemic strokes in Asian populations (1, 2). The annual risk of recurrent stroke in patients with ICAS varies from 4 to 40% and is especially high in patients with severe stenosis (70–99%), for which the rate is ∼23% despite best medical therapy (BMT) (3, 4). Endovascular treatments, including percutaneous transluminal angioplasty (PTA) with balloon dilatation (BD) alone and PTA with stenting (PTAS) using either a balloon-mounted stent (BMS) or a self-expanding stent (SES) have been developed and widely used in some countries. These treatments initially appeared to be safe and effective (5). However, two randomized controlled trials [Stenting and Aggressive Medical Management Therapy for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) and Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT)] did not show superiority of stenting over aggressive medical management alone for ICAS, with a high incidence of periprocedural complications and recurrent stroke (6, 7). Restenosis is another major drawback with a rate of up to 34% (8).

One of the major concerns about the SAMMPRIS and VISSIT trials is that only one type of stent was used in each trial. However, different lesions are suitable for different treatments, and selecting either a BMS or SES based on the characterization of lesions might achieve a better clinical result (3, 9). In addition, the clinical outcome of endovascular treatment is also associated with the location of arteries (10). Symptomatic intracranial internal carotid artery (ICA) atherosclerotic stenosis plays an important role in ischemic stroke and responds poorly to anticoagulation therapy (11). Due to the location and tortuous route of the intracranial ICA, endovascular treatment for stenosis of intracranial ICA presents a particular challenge and is relatively underdeveloped, with more perioperative complications, higher long-term in-stent restenosis rates, and higher recurrent rates of ischemic stroke (12, 13). Currently, clinical trials with 30-day outcomes of tailored endovascular treatment for ICAS and endovascular treatments for intracranial ICA stenosis with small samples have been reported, while outcomes of individualized tailored endovascular treatments for intracranial ICA stenosis with large samples and a longer follow-up have not been reported (11, 14). This article aimed to investigate the 30-day and 1-year outcomes of tailored endovascular treatments for severe intracranial ICA stenosis.

MATERIALS AND METHODS

Patients and Study Design

This retrospective study was carried out at a tertiary stroke center and approved by the institutional ethics committee at Beijing Tiantan Hospital. Between June 2014 and December 2017, 96 consecutive patients with severe atherosclerotic stenosis of the intracranial ICA (70–99%), including the C5, C6, and C7 segments of the ICA were managed with endovascular treatment. The identification of segments of ICA was performed according to Bouthillier's classification system (15). Inclusion criteria were as follows: (1) Patients over 18 years old; (2) TIA or stroke attributable to the severe stenosis (≥70%) of intracranial ICA within the past 30 days; (3) stenosis was verified by digital subtraction angiography (DSA) and measured according to the warfarin-aspirin symptomatic intracranial disease (WASID) trial criteria with normal distal vessels as the reference; (4) ipsilateral hypoperfusion (≥40% decrease in cerebral blood flow in the territory distal to the target lesion) with poor collaterals by CT perfusion; and (5) atherosclerotic stenosis and having at least one atherosclerotic risk factor (hypertension, diabetes mellitus, hyperlipidemia, hyperhomocysteinemia, and smoking) (4, 14, 16). Exclusion criteria included (1) non-atherosclerotic causes of intracranial stenosis (arterial dissection, vasculitis, etc.), potential source of cardiac embolism, or concurrent intracranial pathology such as Moyamoya disease; (2) concurrent intracranial tumor, cerebral aneurysm, or arteriovenous malformation; (3) known contraindication to aspirin, clopidogrel, heparin, tirofiban, contrast media, metal, etc.; (4) life expectancy < 1 year because of other medical conditions such as cancer; and (5) other conditions not suitable for general anesthesia or endovascular treatment.

Strategy of Endovascular Treatment

DSA was performed for all patients, and the strategy of endovascular treatment was decided according to the site and characteristics of the target lesions and based on the operators' experience and preference (3, 9). In general, Apollo BMS (MicroPort Medical, Shanghai, China) was preferred in lesions with straightforward arterial access. SES (Wingspan, Boston Scientific; Enterprise, Codman Neurovascular; Solitaire, Covidien; Neuroform, Smart Therapeutics/Boston Scientific) with balloon pre-dilatation were selected in lesions with tortuous arterial access or lesions with a significant mismatch in the diameter between the proximal and distal segments. BD alone (Gateway, Stryker Neurovascular, USA) was performed in patients with more tortuous arterial access for which stenting was considered to be improper by operators (17).

Periprocedural Management

Aggressive medical management and intensive risk factor management were implemented pre-procedurally, including aspirin (100 mg/day), clopidogrel (75 mg/day), atorvastatin calcium (20 mg Qn), platelet function monitoring by thromboelastography, strict blood glucose control, and cigarette control.

Endovascular treatments were performed by experienced neurointerventionists. Either general anesthesia or local anesthesia was chosen based on the operator's experience and the patient's condition, and most of the procedures were performed under general anesthesia. An intravenous heparin regimen was administered to maintain an activated clotting time between 250 and 300 s during the procedure. Briefly, a 6F-guiding catheter was introduced through the common femoral artery and guided into the target ICA. After a microwire was first passed through the intracranial stenosis, one of the three kinds of interventional procedures (BD, BMS, SEM) was performed based on the operators' experience. The devices of endovascular treatment were as follows: BD alone with Gateway balloon, PTAS with the Apollo BMS, or balloon predilatation and subsequent deployment of a SES (Wingspan, Enterprise, Solitaire, or Neuroform).

Dual antiplatelet therapy was maintained for at least 6 months, and aspirin alone was continued daily afterwards. Rehabilitation treatment was recommended for patients with functional disability. Long-term management of individual medical risk factors such as blood pressure, cholesterol, and diabetes mellitus was implemented.

Patient Follow-Up and Outcome Measures

All patients were followed up regularly. CT angiography or CT perfusion was performed at the 30-day or 6-month follow-up. DSA was performed in the 6-month or 1-year follow-up. MRI was recommended if the patient had symptoms of ischemia. The primary endpoints were any stroke or death within 30 days and ipsilateral ischemic stroke beyond 30 days after angioplasty. Recurrent ischemic stroke was considered to be any focal neurological symptom of sudden onset that lasted for at least 24 h, was related to the corresponding vascular territory, was not associated with a hemorrhage on brain CT or MRI, and occurred within the follow-up period (8). Secondary endpoints included the revascularization success rate and the restenosis rate at the 1-year follow-up. The revascularization success of endovascular treatment was based on the following criteria: (1) the blood flow was unobstructed, reaching TICI grade 3; (2) the residual stenosis was <30% (measured according to WASID trial criteria); (3) the distal vessels were not embolized or missing; and (4) there was no leakage of contrast medium. Restenosis was defined as 50% or greater diameter stenosis at the follow-up angiography.

Statistical Analysis

The data were primarily analyzed by intention-to-treat analysis. Continuous variables were presented as the mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. The differences between groups were determined by one-way analysis of variance or Kruskal-Wallis test. Categorical variables were expressed as percentages, for which the chi-square test or Fisher's exact tests were used. Binary logistic regression analysis was used to relate the occurrence of the endpoints to multiple clinical factors, and factors were included as candidates for inclusion in the model if the probability value for the bivariate association with the endpoint was <0.2. A two-tailed p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS® software (SPSS Statistical Software 26).

RESULTS

Baseline Characteristics

Between June 2014 and December 2017, 124 consecutive patients with severe atherosclerotic stenosis (70–99%) of the C5-7 segments of the ICA were screened and managed with endovascular treatment in Beijing Tiantan Hospital, among which 96 patients (60.99 ± 8.00 years old) were followed up for at least 1 year. The 96 patients included 64 (66.7%) males and 32 (33.3%) females. According to the morphology and length of the stenosis lesions, different strategies of endovascular treatments were selected. Of the 96 patients, 19 (19.8%) were treated with BD alone (BD group), 36 (37.5%) were treated with BMS (BMS group), and 41 (42.7%) were treated with SES (SES group).

The baseline characteristics of the patients are presented in **Table 1**. The median mRS score of all enrolled patients was 0 (IQR 0–1), and the National Institutes of Health Stroke Scale (NIHSS) score was 0 (IQR 0–2). The most common risk factor was hypertension (75.0%), followed by diabetes mellitus (53.3%), and hyperlipidemia 35.4%. A total of 44.8% of patients had a past history of smoking or were still smoking. A total of 9.4 and 2.1% of patients had a past history of myocardial infarction and atrial fibrillation, respectively. There was no significant difference in functional scale, common risk factors, or relative disease history between the three groups.

For the characteristics of the target lesions in all patients, the mean rate of stenosis was 84.6 ± 7.4%, and the mean length of the lesions was 6.8 ± 2.6 mm. The mean length of the lesions in the SES group (7.9 ± 2.9 mm) was longer than that in the BMS group (5.9 ± 1.8 mm, $p = 0.003$) and the BD group (6.4 ± 2.8 mm, $p = 0.120$). The mean rate of stenosis in the BMS group (82.5 ± 7.7%) was slightly lower than that in the SES group (86.0 ± 6.2%, $p = 0.126$) and the BD group (85.7 ± 8.8%, $p = 1$); however, the difference was not significant. The BMS group tended to have more Mori type A lesions (27.8%) and fewer Mori type C lesions (8.3%) than the other two groups ($p = 0.126$), though the difference was not significant (**Table 1**).

Primary Endpoints

The 30-day stroke rate of all patients was 7.3% (7/96), and the death rate was 0. Among the seven patients who suffered stroke within 30 days, four suffered ischemic stroke, two suffered hemorrhagic stroke, and one suffered both. In detail, two patients suffered in-stent thrombosis, one patient suffered in-stent thrombosis and perforator occlusion, one patient suffered distant emboli, one patient suffered vascular perforation and distant emboli, and the other two patients suffered from

TABLE 1 | Baseline characteristics of patients receiving endovascular treatment in different groups.

	Balloon dilatation	Balloon-mounted stent	Self-expanding stent	Total	*p*-value
N (%)	19 (19.8)	36 (37.5)	41 (42.7)	96	
Sex: male (%)	12 (63.2)	31 (86.1)	21 (51.2)	64 (66.7)	0.005
Age in years [mean (SD)]	63.9 (8.4)	60.3 (8.0)	60.3 (7.8)	61.0 (8.0)	0.211
BMI [mean (SD), kg/m^2]	26.8 (7.31)	24.4 (1.76)	25.5 (2.9)	25.3 (3.8)	0.112
mRS [median (IQR)]	0 (0, 2)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.934
NIHSS [median (IQR)]	0 (0, 3)	0 (0, 2)	0 (0, 1)	0 (0, 2)	0.376
Hypertension (%)	14 (73.7)	27 (75.0)	31 (75.6)	72 (75.0)	0.979
Hyperlipidemia (%)	7 (36.8)	11 (30.6)	16 (39.0)	34 (35.4)	0.733
Diabetes mellitus (%)	11 (57.9)	12 (33.3)	26 (63.4)	49 (53.3)	0.046
Smoking (%)	11 (57.9)	22 (61.1)	10 (24.4)	43 (44.8)	0.018
Coronary disease (%)	2 (10.5)	5 (13.9)	2 (4.9)	9 (9.4)	0.389
Atrial fibrillation (%)	0 (0.0)	1 (2.8)	1 (2.4)	2 (2.1)	1.000
Stroke history (%)	0 (0.0)	1 (2.8)	2 (4.9)	3 (3.1)	1.000
Stenosis [%, mean (SD)]	85.7 (8.8)	82.5 (7.7)	86.0 (6.2)	84.6 (7.4)	0.096
Stenosis length [mean (SD), mm]	6.4 (2.8)	5.9 (1.8)	7.9 (2.9)	6.8 (2.6)	0.004
Mori type (%)					0.126
A	4 (21.1)	10 (27.8)	4 (9.8)	18 (18.8)	
B	10 (52.6)	23 (63.9)	29 (70.7)	62 (64.6)	
C	5 (26.3)	3 (8.3)	8 (19.5)	16 (16.7)	

BMI, body mass index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

TABLE 2 | Primary and secondary endpoints and other adverse events.

	Balloon dilatation	Balloon-mounted stent	Self-expanding stent	Total	*p*-value
n	19	36	41	96	
Primary endpoints					
Any stroke or death within 30 days (*n*, %)	3 (15.8)	0 (0.0)	4 (9.8)	7 (7.3)	0.047
Ipsilateral ischemic stroke within 12 months (*n*, %)	4 (21.1)	2 (5.6)	7 (17.1)	13 (13.5)	0.165
Secondary endpoints					
Revascularization success rate (*n*, %)	15 (78.9)	34 (94.4)	41 (100)	90 (93.8)	0.006
Restenosis rate within 12 months (*n*, %)	4 (21.1)	7 (19.4)	9 (22)	20 (20.8)	1.000
Other events					
Residual stenosis [%, mean (SD)]	27.4 (16.7)	15.7 (10.8)	13.5 (7.8)	17.1 (12.2)	0.000
Any ischemic stroke within 12 months (*n*, %)	4 (21.1)	2 (5.6)	8 (19.5)	14 (14.6)	0.142
Myocardial infarction within 12 months (*n*, %)	0 (0)	0 (0)	0 (0)	0 (0)	1.000

intraparenchymal hemorrhage (IPH). The 30-day stroke rate was higher in the BD group [15.8% (3/19)] and SES group [9.8% (4/41)] than in the BMS group (0%) ($p = 0.047$).

Of the 96 patients, 13 (13.5%) patients suffered at least one onset of ischemic stroke in the ipsilateral ICA territory within the 1-year follow-up. There were no significant differences among the three groups ($p = 0.165$), although the rate of recurrent ipsilateral ischemic stroke within 1 year in the BMS group tended to be lower (5.6%, 2/36) than that in the BD group (21.1%, 4/19) and the SES group (17.1%, 7/41). Detailed data are presented in **Table 2**.

Secondary Endpoints

The overall success rate of revascularization during surgery was 93.8% (90/96) and was significantly higher in the SES group (100%) than in the BD group (78.9%) ($p = 0.006$). The mean degree of residual stenosis was 17.1 ± 12.2%, which was significantly higher in the BD group (27.4 ± 16.7%) than in the BMS group (15.7 ± 10.8%, $p = 0.001$) and the SES group (13.5 ± 7.8%, $p = 0.000$). During follow-up, the restenosis rate of all patients within 1 year was 20.8% (20/96), and there were no significant differences among the three groups. Fourteen patients (14.6%) suffered ischemic stroke within 1 year, and no

TABLE 3 | Factors associated with primary and secondary endpoints.

Factor	*p*-value			
	Stroke/death within 30 days	Ipsilateral ischemic stroke within 12 months	Revascularization success rate	Restenosis rate within 12 months
Endovascular options (BD, BMS, SES)	0.047	0.165	0.006	1.000
Mori classification (Mori A, B, C)	0.020	0.303	0.309	0.138
Smoking	1	0.065	1	0.495
Stenosis rate	0.094	0.720	0.229	0.796
Stenosis length	0.844	0.635	0.406	0.365

BD, balloon dilatation; BMS, balloon-mounted stent; SES, self-expanding stent.

patient suffered myocardial infarction; there were no significant differences among the three groups.

Factors Associated With Primary and Secondary Endpoints

Univariate analyses showed that the strategy of endovascular treatments was associated with the stroke/death rate within 30 days ($p = 0.047$) and the revascularization success rate ($p = 0.006$). The patients with Mori type C target lesions were more likely to suffer stroke or death within 30 days (25%, 4/16) than patients with Mori type A lesions (0%, 0/18) and Mori type B lesions (4.8%, 3/62) ($p = 0.020$). Multivariate analyses showed that the restenosis rate within 1 year was also higher in Mori type C lesions (31.3%, 5/16) than in Mori type A lesions (5.6%, 1/18) ($p = 0.035$). Factors including the original stenosis rate, length of the target lesion, history of hypertension, diabetes mellitus, smoking, coronary disease, and atrial fibrillation were not significantly associated with the primary and secondary endpoints. Detailed data are presented in **Table 3**.

DISCUSSION

In this study, we retrospectively investigated the safety and efficacy of tailored endovascular treatments for severe atherosclerotic stenosis of intracranial ICA. This was the first study with a 1-year outcome of endovascular treatment specifically for severe intracranial ICA stenosis, and it had a larger sample than prior studies. Our study revealed that the 30-day stroke rate of patients with severe intracranial ICA atherosclerotic stenosis was 7.3 and 13.5% patients suffered at least one onset of ischemic stroke in the ipsilateral ICA territory within the 1-year follow-up.

Since the SAMMPRIS and VISSIT trials, the safety and efficacy of endovascular treatment for intracranial atherosclerotic stenosis has been questioned given the negative results. The SAMMPRIS trial showed a higher rate of 30-day stroke and death in the stenting arm with the Wingspan stent (14.7%) relative to aggressive medical management (5.8%) and a higher rate of 1-year stroke and death (19.7%) relative to the medical arm (12.6%) (7). The VISSIT trial demonstrated an even higher 30-day stroke/hard TIA rate in the stenting group with a BMS (24.1%) than in the medical group (9.4%) and a much higher 1-year stroke/hard TIA rate in the stenting group (36.2%) than in the medical group (15.1%) (5). However, owing to the limitations of the trials, researchers and clinicians still regard angioplasty as a promising measure for stroke prevention in patients with severe ICAS. Researchers have begun to study the outcomes of endovascular treatments for atherosclerotic stenosis in some specific sites of intracranial arteries (18, 19). In addition, several measures have been taken to modify the endovascular treatment strategies.

Endovascular treatment for stenosis of the intracranial ICA presents a particular challenge because of the artery's location and tortuous route. Compared with other sites of intracranial arteries, the intracranial ICA is more tortuous and thus it is difficult to transport endovascular devices in place (11). Studies in endovascular therapy specific for intracranial ICA remain particularly scarce. Detailed analysis of periprocedural strokes in patients undergoing intracranial stenting in SAMMPRIS showed that 15% of patients out of 40 patients with intracranial ICA stenosis had periprocedural strokes with Wingspan stents, including 3 (7.5%) hemorrhagic events and 3 (7.5%) ischemic events. Turk et al. disfavored interventional stenting with stenosis lesions in the ICA supraclinoid segment owing to high rates of in-stent restenosis and recurrent ischemic stroke (20). However, Wang's study showed that only one patient (1.7%) out of 36 patients with atherosclerotic stenosis in the intracranial ICA treated with Wingspan stents had ischemic stroke during the 30-day perioperative period, five patients (13.9%) had ipsilateral stroke and three patients (8.3%) had ipsilateral TIA during a 6–68-month follow-up (11). Wang's study also revealed that the outcomes of patients with intracranial ICA atherosclerotic stenosis treated with endovascular therapy were acceptable; however, this finding remains to be further verified owing to the limited number of patients enrolled. In our study, a larger number of patients with severe atherosclerotic stenosis of the intracranial ICA (70–99%) were managed with endovascular treatment and were followed up for at least 1 year, and both 30-day and 1-year outcomes were shown to be acceptable.

In addition, since the SAMMPRIS trial several measures have been proposed to modify the endovascular treatment strategy, these were utilized in our study. First, we restricted the inclusion criteria. The patients selected in our study had ipsilateral hypoperfusion and poor collateral circulations from

CT perfusion examination, as patients with hypoperfusion symptoms and poor collaterals were most likely to fail medical therapy and benefit from revascularization (14). Another measure taken in our study was variable device selection in cases of different lesions, as the devices exclusively used in prior studies (the Wingspan system for SAMMPRIS, the Vitesse intracranial stent for VISSIT) have not been shown to be well-suited for all ICAS lesions (17, 21). Miao used tailored angioplasty and/or stenting for ICAS, and the results showed that the complication rate within 30 days was 5.3% (14). However, longer-term outcomes of tailored endovascular treatment of ICAS have never been explored. The results of our study demonstrated that the overall 30-day stroke rate was 6.5%, the death rate was 0, and the overall 1-year ipsilateral ischemic stroke rate was 13.5%, which was much lower than that in the stenting arms of SAMMPRIS and VISSIT and comparable with that in the medical arm. Considering that the medical treatments in the trials above were too aggressive to be achieved in clinical practice, at least for a Chinese population, our study showed that outcomes of tailored endovascular treatment of intracranial ICA atherosclerotic stenosis were acceptable.

Intracranial segments of the ICA are more tortuous than other intracranial arteries, and the tailored endovascular treatment strategy used in this trial could mitigate this problem well, as different devices have inherent advantages and drawbacks and are thus suitable for different target lesions. BD alone has better flexibility but greater risk of elastic recoil and dissection. BMS has a high radial force but the flexibility is limited; it has a greater risk of injury to the vessel due to excessive straightening and is difficult to pass through tortuous vessels (22). SES has a certain degree of flexibility and conforms well to the vessel wall, but the radial force is limited; thus, it is less apt to achieve good revascularization in calcified lesions. Besides, as SES placement requires two steps (first balloon dilatation and then stenting angioplasty), a longer procedural time is required. Therefore, there was preference for BMSs for straight arterial access and Mori A lesions for better radial force and shorter procedural time, balloon pre-dilatation plus SES for tortuous arterial access and Mori B or C lesions for a certain degree of flexibility and radial force, and BD alone for more tortuous arterial access for safety.

In addition, we investigated the factors associated with the primary and secondary outcomes. Our results showed that the strategy of endovascular treatments had a significant effect on the results in patients with stenosis of the intracranial ICA. The 30-day stroke or death rate was significantly higher in the BD and SES groups than in the BMS group (0%), and the revascularization success rate was significantly higher in the SES group (100%) than in the BD group (78.9%). This was reasonable given the principle of stenting selection and the characteristics of the different endovascular strategies mentioned above. However, due to the high incidence of complications and stroke, and the low recanalization rate in BD group, it is suggested that patients with difficult lesions should be left alone, only be given medical therapy instead of intravascular therapy. Another notable and important factor was Mori type. In our study, patients with Mori type C target lesions were more likely to suffer stroke within 30 days and restenosis within 1 year. A number of papers have shown that lesions with different characteristics classified by Mori carry different risks during intracranial endovascular revascularization (17, 18). However, few studies have clearly demonstrated the incidence of primary and secondary endpoints. Mori's study showed that in type C lesions, the clinical success rate of angioplasty was 33%, the restenosis rate at 1 year was 100%, and the cumulative risk of ipsilateral ischemic stroke at 1 year was 56% (23). Our study showed that in type C lesions, the clinical success rate was 75%, the revascularization success rate was 87.5%, the restenosis rate at 1 year was 31.3%, and the annual ipsilateral ischemic rate was 25%; these results were all greatly improved when compared with Mori's. In addition to the development of techniques and richer experience with neurointerventionists, we believe modifications in our study such as tailored angioplasty also contribute much to this improvement. Even so, our study showed that both the safety and efficacy of endovascular treatments in type C lesions were still not satisfactory and more research should be performed on angioplasty for Mori type C lesions.

We also performed detailed analyses of periprocedural strokes in our study. Among the seven patients who suffered periprocedural strokes, there were six ischemic stroke events in five patients. Traditionally, ischemic strokes are categorized as perforator territory, distal embolic, or delayed in-stent thrombosis. Contrary with SAMMPRIS, in which most of the patients with ischemic stroke were perforator territories, only one patient suffered perforator occlusion in our study, while three suffered in-stent thrombosis and the other two were distal embolic strokes (24). This may be because the intracranial ICA has fewer tenuous perforators and thus fewer complications caused by perforator occlusion. Hemorrhagic strokes were categorized as subarachnoid or intraparenchymal. In our study, three patients suffered hemorrhagic stroke, among whom two suffered intraparenchymal hemorrhage and the other suffered vascular perforation. The mechanism of IPH post-stenting is uncertain, and hyperperfusion or autoregulatory dysfunction may be one possible mechanism (24). The ICA is much larger than other intracranial arteries, and hyperperfusion is thought to occur more frequently after carotid stenting, which may have contributed to IPH in our study (25).

Our study also has some limitations. First, the trial was performed in a single center and the patients enrolled were only Chinese people, which was not representative. Second, the pre-procedural NIHSS scores of patients in our study were relatively low, so there may be some extent of selection bias. In addition, this was a retrospective trial and was absent of a medical arm as the control group, therefore, the evidence-based level of this study is not so high. Also, a number of stents, such as Neuroform, Enterprise, and Solitaire, originally designed for neck remodeling in the treatment of intracranial aneurysms were used off label (21, 26, 27). Finally, the number of patients in our study was not large enough even though this is the largest study of tailored endovascular treatments for atherosclerotic stenosis of intracranial ICA.

CONCLUSIONS

Both the 30-day and 1-year outcomes of tailored angioplasty seemed to be acceptable in the treatment of symptomatic atherosclerotic stenosis of intracranial ICA. However, this needs to be confirmed by further investigation, preferably in large multicenter randomized controlled clinical trials.

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 Institutional ethics committee at Beijing Tiantan Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HD, DM, and ZM conceived the study and made critical revisions to the manuscript. SS and YW analyzed the data and drafted the manuscript. XH acquired most of the data. NM, FG, LS, XS, and LL participated in the data collection. All authors read and approved the submitted manuscript.

FUNDING

This work was supported by the National Key Research and Development Program of China (No. 2018YFC1312800 and 2018YFC1312801) and Youth Clinical Research Project of Peking University First Hospital (#2019CR02).

REFERENCES

1. Padalia A, Sambursky JA, Skinner C, Moureiden M. Percutaneous transluminal angioplasty with stent placement versus best medical therapy alone in symptomatic intracranial arterial stenosis: a best evidence review. *Cureus.* (2018) 10:e2988. doi: 10.7759/cureus.2988
2. Krasteva MP, Lau KK, Mordasini P, Tsang ACO, Heldner MR. Intracranial atherosclerotic stenoses: pathophysiology, epidemiology, risk factors and current therapy options. *Adv Ther.* (2020) 37:1829–65. doi: 10.1007/s12325-020-01291-4
3. Zhang Y, Sun Y, Li X, Liu T, Liu P, Wang H, et al. Early versus delayed stenting for intracranial atherosclerotic artery stenosis with ischemic stroke. *J Neurointerv Surg.* (2020) 12:274–8. doi: 10.1136/neurintsurg-2019-015035
4. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* (2005) 352:1305–16. doi: 10.1056/NEJMoa043033
5. 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
6. Hurford R, Wolters FJ, Li L, Lau KK, Kuker W, Rothwell PM, et al. Prevalence, predictors, and prognosis of symptomatic intracranial stenosis in patients with transient ischaemic attack or minor stroke: a population-based cohort study. *Lancet Neurol.* (2020) 19:413–21. doi: 10.1016/S1474-4422(20)30079-X
7. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. 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
8. Gruber P, Garcia-Esperon C, Berberat J, Kahles T, Hlavica M, Anon J, et al. Neuro Elutax SV drug-eluting balloon versus Wingspan stent system in symptomatic intracranial high-grade stenosis: a single-center experience. *J Neurointerv Surg.* (2018) 10:e32. doi: 10.1136/neurintsurg-2017-013699
9. Miao Z, Zhang Y, Shuai J, Jiang C, Zhu Q, Chen K, et al. Thirty-day outcome of a multicenter registry study of stenting for symptomatic intracranial artery stenosis in China. *Stroke.* (2015) 46:2822–9. doi: 10.1161/STROKEAHA.115.010549
10. Nordmeyer H, Chapot R, Aycil A, Stracke CP, Wallocha M, Hadisurya MJ, et al. Angioplasty and stenting of intracranial arterial stenosis in perforator-bearing segments: a comparison between the anterior and the posterior circulation. *Front Neurol.* (2018) 9:533. doi: 10.3389/fneur.2018.00533
11. Wang ZL, Gao BL, Li TX, Cai DY, Zhu LF, Xue JY, et al. Severe symptomatic intracranial internal carotid artery stenosis treated with intracranial stenting: a single center study with 58 patients. *Diagn Interv Radiol.* (2016) 22:178–83. doi: 10.5152/dir.2015.15191
12. Nakamura K, Sugimura K, Takahashi Y. Carotid artery stenting. *Masui.* (2012) 61:1205–15.
13. Fiorella DJ, Turk AS, Levy EI, Pride GL, Jr., Woo HH, et al. U.S. Wingspan Registry: 12-month follow-up results. *Stroke.* (2011) 42:1976–81. doi: 10.1161/STROKEAHA.111.613877
14. Miao Z, Song L, Liebeskind DS, Liu L, Ma N, Wang Y, et al. Outcomes of tailored angioplasty and/or stenting for symptomatic intracranial atherosclerosis: a prospective cohort study after SAMMPRIS. *J Neurointerv Surg.* (2015) 7:331–5. doi: 10.1136/neurintsurg-2014-011109
15. Bouthillier A, van Loveren HR, Keller JT. Segments of the internal carotid artery: a new classification. *Neurosurgery.* (1996) 38:425–32. Discussion 32–3. doi: 10.1227/00006123-199603000-00001
16. Yoon NK, Awad AW, Kalani MY, Taussky P, Park MS. Stent technology in ischemic stroke. *Neurosurg Focus.* (2017) 42:E11. doi: 10.3171/2017.1.FOCUS16507
17. Miao Z. Intracranial angioplasty and stenting before and after SAMMPRIS: "from simple to complex strategy - the chinese experience". *Front Neurol.* (2014) 5:129. doi: 10.3389/fneur.2014.00129
18. Al-Ali F, Cree T, Hall S, Louis S, Major K, Smoker S, et al. Predictors of unfavorable outcome in intracranial angioplasty and stenting in a single-center comparison: results from the Borgess Medical Center-Intracranial Revascularization Registry. *AJNR Am J Neuroradiol.* (2011) 32:1221–6. doi: 10.3174/ajnr.A2530
19. Liu P, Li G, Luo L, Sun Y, Liu T, Gong W, et al. Comparison of safety and mid-term effects between direct stenting and angioplasty before stenting in the basilar artery. *Clin Neurol Neurosurg.* (2020) 193:105773. doi: 10.1016/j.clineuro.2020.105773
20. Turk AS, Levy EI, Albuquerque FC, Pride GL, Jr., Woo H, et al. Influence of patient age and stenosis location on wingspan in-stent restenosis. *AJNR Am J Neuroradiol.* (2008) 29:23–7. doi: 10.3174/ajnr.A0869
21. Salik AE, Selcuk HH, Zalov H, Kilinc F, Cirak M, Kara B. Medium-term results of undersized angioplasty and stenting for symptomatic high-grade intracranial atherosclerotic stenosis with Enterprise. *Interv Neuroradiol.* (2019) 25:484–90. doi: 10.1177/1591019919832244
22. Henkes H, Miloslavski E, Lowens S, Reinartz J, Liebig T, Kühne D. Treatment of intracranial atherosclerotic stenoses with balloon dilatation and self-expanding stent deployment (WingSpan). *Neuroradiology.* (2005) 47:222–8. doi: 10.1007/s00234-005-1351-2

23. Mori T, Fukuoka M, Kazita K. Follow-up study after intracranial percutaneous transluminal cerebral balloon angioplasty. *Interv Neuroradiol.* (2000) 6 (Suppl. 1):243–9. doi: 10.1177/15910199000060S141
24. Derdeyn CP, Fiorella D, Lynn MJ, Rumboldt Z, Cloft HJ, Gibson D, et al. Mechanisms of stroke after intracranial angioplasty and stenting in the SAMMPRIS trial. *Neurosurgery.* (2013) 72:777–95. Discussion 95. doi: 10.1227/NEU.0b013e318286fdc8
25. Nagaraja N, Viamonte M, Yu J, Rohrbough SC, Jr., Khanna AY. Bilateral cerebral hyperperfusion syndrome following carotid artery stenting in stroke - a case report. *J Stroke Cerebrovasc Dis.* (2020) 30:105546. doi: 10.1016/j.jstrokecerebrovasdis.2020.105546
26. Jia ZC, Bian HJ, Li X, Luan JY, Wang CM, Liu QJ, et al. Application of Neuroform EZ stent in the treatment of severe intracranial arterial stenosis with complex symptomatic. *Beijing Da Xue Xue Bao Yi Xue Ban.* (2019) 51:835–9. doi: 10.19723/j.issn.1671-167X.2019.05.008
27. Duan G, Feng Z, Zhang L, Zhang P, Chen L, Hong B, et al. Solitaire stents for the treatment of complex symptomatic intracranial stenosis after antithrombotic failure: safety and efficacy evaluation. *J Neurointerv Surg.* (2016) 8:680–4. doi: 10.1136/neurintsurg-2015-011734

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 31 May 2021
doi: 10.3389/fneur.2021.629644

A Retrospective Study Comparison Between Stenting and Standardized Medical Treatment for Intracranial Vertebrobasilar Stenosis in a Real-World Chinese Cohort

Guanzeng Li[1,2†], *Peng Yan*[1,3†], *Yuanyuan Zhao*[1,3], *Shan Li*[1,3], *Yuan Xue*[1,3], *Yuanyuan Xiang*[1,3], *Xiaohui Liu*[1,3], *Jifeng Li*[1,3] *and Qinjian Sun*[1,3*]

[1] *Department of Neurology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China,* [2] *Department of Neurology, Liaocheng People's Hospital, Liaocheng, China,* [3] *Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China*

OPEN ACCESS

Edited by:
Osama O. Zaidat, Northeast Ohio Medical University, United States

Reviewed by:
Mikayel Grigoryan, Glendale Adventist Medical Center, United States
Lukas Meyer, University Medical Center Hamburg-Eppendorf, Germany

***Correspondence:**
Qinjian Sun
sqj1210@163.com

[†] *These authors have contributed equally to this work*

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *15 November 2020*
Accepted: *07 May 2021*
Published: *31 May 2021*

Citation:
Li G, Yan P, Zhao Y, Li S, Xue Y, Xiang Y, Liu X, Li J and Sun Q (2021) A Retrospective Study Comparison Between Stenting and Standardized Medical Treatment for Intracranial Vertebrobasilar Stenosis in a Real-World Chinese Cohort. Front. Neurol. 12:629644. doi: 10.3389/fneur.2021.629644

Background: To date, there has been no consensus regarding the benefits of percutaneous transluminal angioplasty and stenting (PTAS) vs. those of standardized medical treatment (SMT) for patients with symptomatic intracranial vertebrobasilar stenosis (IVBS). The purpose of this retrospective study was to compare the effects of PTAS or SMT on symptomatic IVBS in a real-world Chinese population.

Methods: We included 238 patients with ischemic stroke caused by IVBS stenosis who were admitted to Shandong Provincial Hospital Affiliated to Shandong University between September 2012 and May 2018; 62 of these patients were treated with SMT and 176 underwent PTAS. Ischemic stroke in the territory of the responsible artery, hemorrhage, and death within 1 year were recorded as primary endpoints. Secondary endpoints included assessment of stroke severity and the incidence of re-stenosis. The primary endpoint rates were compared between the PTAS and SMT groups at 7 days, 1, 6 months, and 1 year.

Results: In the PTAS group, the success rate of stent placement was 98.9%. During the entire trial, except for 7 days, the SMT group had a higher frequency of primary endpoint events than did the PTAS group. The primary endpoint was 17.7% (11/62) vs. 8.6% (15/174) at 1 month ($p = 0.049$), 29% (18/62) vs. 14.4% (25/174) at 6 months ($p = 0.01$), and 32.2% (20/62) vs. 17.2% (30/174) at 1 year ($p = 0.013$). The restenosis rate of the target lesion was 13.8%; 60% were symptomatic restenosis and 40% were asymptomatic restenosis. The rate of severe stroke at 1 year after PTAS was 0%, while that in the SMT group was 9.7%.

Conclusions: In a real-world Chinese cohort, PTAS for patients might be superior to SMT, and provide better long-term neurological function recovery and lower disability rate.

Keywords: real-world, standardized medical treatment, intracranial artery stenosis, stenting angioplasty, vertebrobasilar artery

INTRODUCTION

Intracranial atherosclerotic stenosis (ICAS) is an important cause of ischemic stroke worldwide. In Caucasians, 5–10% of strokes are caused by ICAS, while this ratio is 30–50% in Asian population (1). Approximately 20% of ischemic strokes are caused by vertebrobasilar artery stenosis (2). Compared with anterior circulation stenosis, intracranial vertebrobasilar artery stenosis (IVBS) leads to a higher risk of occurrence and recurrence of transient ischemic attack (TIA) or cerebral infarction (3–5). A study showed that patients with symptomatic IVBS had poor prognosis, high mortality, and high disability rate (4). It has been reported as high as 33% recurrence in the first month with the best medical therapy (5). Other studies, including patients with severe IVBS, have shown that despite aggressive medical treatment, the annual incidence of stroke remained between 10 and 28.7% (6–8).

Percutaneous transluminal angioplasty and stenting (PTAS) is another method of treating ICAS. The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) and the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) studies are the two prominent randomized clinical trials of intracranial stenting (9, 10). These studies showed no advantage of stenting over medical treatment for patients with ICAS, partly due to the high complication rate. However, a recent post-marketing surveillance trial (WEAVE trial) showed a 2.6% periprocedural stroke, bleeding, and death rate in patients with symptomatic ICAS lesions of 70–99% who underwent stenting angioplasty with the Wingspan stent (11). In the WOVEN trial, the natural extension of the WEAVE trial, stroke, or death rate was 8.5% at 1-year follow-up (12). A meta-analysis of symptomatic IVBS found that the annual stroke or death rate in the endovascular treatment group was approximately 8.9% (3). Therefore, it appears that the outcomes of endovascular procedures for symptomatic IVBS have been inconsistent. In addition, several studies in Asia showed inconsistent results of stenting vs. medical treatment for IVBS (13, 14). In the real world, the effect of PTAS on symptomatic IVBS remains elusive. Therefore, the purpose of this retrospective study was to compare the effects of PTAS and standardized medical treatment (SMT) in patients with IVBS in a real-world setting at a single center in China.

MATERIALS AND METHODS

Patient Selection

Detailed clinical information was obtained from the Department of Neurology at Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University between January 2012 and December 2018. All patients were from Shandong Province, China. This retrospective study was a single-center study. This study was reviewed and approved by the ethical standards committees on human experimentation at Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University.

The inclusion criteria were as follows: (1) age of 18–80 years; (2) digital subtraction angiography (DSA) revealing that the stenosis of the intracranial vertebrobasilar artery was $> 70\%$. The responsible arteries were the intracranial segment of the vertebral artery or the basilar artery. The degree of stenosis was measured using the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial method (5); and (3) TIA attack or cerebral infarction was related to posterior circulation. The typical symptoms of posterior circulation TIA include dizziness, numbness of limbs or face, weakness of limbs, vomiting, diplopia, hemianopia, gait disorder, temporary loss of consciousness, and falls. Cerebral infarction refers to magnetic resonance diffusion limitation in the cerebellum, brainstem, occipital lobe, and other posterior circulation areas.

Exclusion criteria were as follows: (1) severe systemic diseases or unsuitable or intolerable dual antiplatelet therapy; (2) non-atherosclerotic stenosis such as artery dissection, arteritis, or moyamoya disease, confirmed by DSA and high-resolution magnetic resonance; (3) international standardized ratio (INR) > 1.5, and uncorrectable bleeding tendency; (4) failure to follow up in time and life expectancy < 5 years.

SMT group was comprised of those who suffered first onset of posterior circulation TIA or cerebral infarction and those who had recurrent events without SMT but refused PTAS. The indication for PTAS was posterior circulation TIA or occurrence of cerebral infarction despite SMT, and despite the first attack of posterior circulation TIA or cerebral infarction, stenting was required.

Treatments

Standardized Medical Treatment

The medications in the SMT and PTAS groups were identical: aspirin 100 mg and clopidogrel 75 mg were given daily orally for 90 days in the SMT group and 180 days in the PTAS group after the onset of treatment. Thereafter, the administration of one antiplatelet agent was stopped. Statins (atorvastatin 20 mg or rosuvastatin 10 mg) were administered orally daily after the onset of treatment. All patients were treated with standard management of vascular risk factors, including systolic blood pressure < 140 mmHg (diabetic patients < 130 mmHg), and statins to lower low-density lipoprotein (LDL) levels < 1.80 mmol/L, and blood glucose < 7 mmol/L. We advised all patients to quit smoking, engage in sufficient exercise, and other lifestyle changes.

PTAS Procedure

PTAS was performed by a neurointerventionist, Qinjian Sun, who had been engaged in neurointerventional therapy for 10 years and had completed more than 500 cases of PTAS for ICAS. He had experience in more than 50 cases of intracranial artery stents before this study. He was credentialed to participate in this study based on a review of 20 consecutive intracranial angioplasty and stenting cases, at least five of which must have used the Wingspan system in order to reduce the occurrence of technical complications. The degree of stenosis before and after intervention was determined according to the WASID (5) criteria in DSA. Antiplatelet aggregation drugs were started 3–5 days before PTAS, along with clopidogrel 75 mg, and aspirin 100 mg orally. It was recommended to fast on the day of PTAS, but not to stop the administration of the antiplatelet drug.

TABLE 1 | Comparation between the Gateway-Wingspan system and the Apollo stent.

	Characteristics			Applicable patients
Gateway-Wingspan system	Self-expanding stent	Bare-metal	Better flexibility in traversing curvature	Tortuous arterial access, Mori C type of lesion, a lesion with a significant mismatch in the diameter between the proximal and distal segments.
Apollo stent	Balloon-mounted stent	Bare-metal	Rigid, does not require replacement, less surgical time	Smoother arterial access, Mori A type of lesion.

The interventional procedures were performed under general anesthesia. Using the modified Seldinger technique, a 6-French vascular sheath was placed in the right femoral artery. A bolus of 5,000 units of heparin was administered. The 6-French Mach 1 guiding catheter (Boston Scientific, US) was placed into the distal V2 segment of the vertebral artery to provide sufficient support. A guiding catheter was used to perform the responsible artery angiography. The degree of stenosis was calculated based on the adjacent distal normal blood vessel diameter (WASID standard). The guide catheter containing the contrast agent was used as a reference, and the blood vessel diameter was calibrated through the DSA workstation.

The choice of the type of stent (Gateway-Wingspan system, Stryker, US; or Apollo stent system, Microport, China) depended on the arterial pathway, lesion morphology, and operator discretion. Operator was instructed to choose the devices based on the need of a patient individually. This decision of tailored stenting would primarily take into consideration the ease of vascular access and lesion morphology. According to our experience, the Gateway-Wingspan system is more suitable for patients with tortuous vascular access because the system has better flexibility in traversing curvature. Compared with the Gateway-Wingspan system, the Apollo stent (a bare-metal balloon-expandable intracranial Stent) is more rigid; however, it is a good choice for patients with smoother access because the delivery of the balloon-expandable stent does not require replacement and requires less surgical time (**Table 1**). If the Gateway–Wingspan system was selected, the gateway balloon was used to pre-expand the stenosis before stent implantation. The recommended diameter of the gateway balloon was 80% of the diameter of the normal vessel at the distal end of the stenosis. The center has been using Gateway-Wingspan system or Apollo stents from beginning to end. We selected all cases with the same surgical methods and instruments to join the study. A prospective and observational registration study of multicenter symptomatic intracranial artery stenosis stent treatment in China showed that there was no difference in the probability of primary outcome between patients treated with balloon-mounted stent and patients treated with self-expanding stent (15).

According to the diameter and the length of the stenosis, the size of the Wingspan stent was selected (the stent extends at least 3 mm on both sides of the lesion). If the Apollo stent system was selected, the diameter of the Apollo stent was the same as that of the adjacent normal vessels (the smaller of the two sides of the stenosis) or slightly smaller (1:1 or 0.9:1), and the length of the stent was 1–2 mm longer than that of both sides of the target lesion. The guiding catheter was used for re-angiography.

All patients underwent computed tomography (CT) scans for bleeding or early cerebral infarction within 24 h after endovascular treatment. Dual antiplatelet therapy (clopidogrel 75 mg and aspirin 100 mg orally) and statins (atorvastatin 20 mg or rosuvastatin 10 mg orally) were generally continued for 6 months post-procedure, after which the intake of one antiplatelet agent was stopped. All medical management procedures were the same as that in the SMT group.

Follow Up

All patients were followed up by clinic visits or telephone interviews at 7 days, 1, 6 months, 1 year, and once a year after the start of medication or surgery. Neurologists perform detailed neurological assessments, including standardized assessment [National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Score (mRS), etc.] and recorded any intermittent occurrence of ischemic symptoms. Ischemic stroke in the territory of the qualifying artery, hemorrhage, or death within 1 year were recorded as primary endpoints. Stroke severity and incidence of restenosis were assessed during the follow-up period. The neurological disability at baseline was defined by mRS. The deterioration of the severity of a stroke event during follow-up was defined by NIHSS. Ischemic stroke is divided into mild (non-disabling) stroke, defined as NIHSS score worsening of 3 points or less, or severe (disabling) stroke, if the baseline NIHSS score deteriorated by more than 3 points. For patients with neurological symptoms, brain imaging examinations, including CT angiography and DSA were performed. We calculated the degree of restenosis relative to the adjacent distal normal blood vessel diameter (WASID standard). Restenosis was defined as $\geq$ 50%. If the patient was diagnosed with restenosis, we classified the patient as symptomatic or asymptomatic. Hemorrhagic stroke was defined as an intracerebral hemorrhage, including parenchymal, subarachnoid, or intraventricular hemorrhage, which was related to seizures, symptoms, or signs, and lasted for at least 24 h. The differences between the two groups at 7 days, 1, 6 months, and 1 year were analyzed. The stroke rates and severe stroke rates in 1–12 months between the two groups were analyzed.

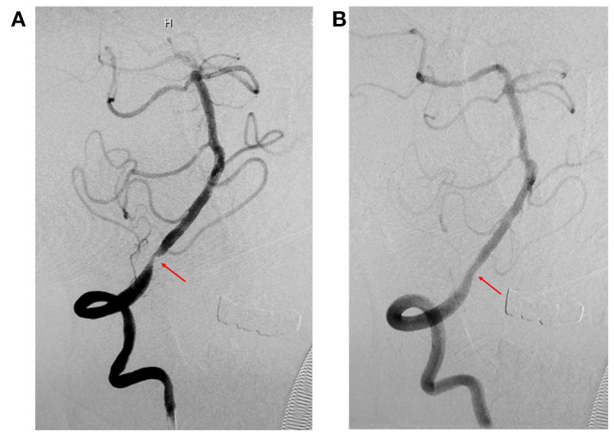


FIGURE 1 | Representative images of cases of V4 before and after stenting (Apollo stent). **(A)** Digital subtraction angiography (DSA) revealed severe stenosis of the right intracranial vertebral artery (V4) before stenting (red arrow). **(B)** DSA revealed significant improvement in stenosis of the right intracranial vertebral artery (V4) after stenting (red arrow).

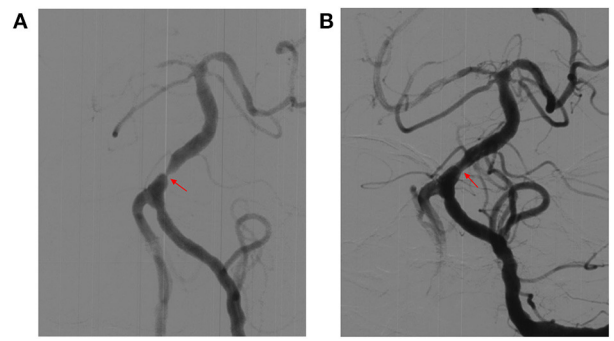


FIGURE 2 | Representative images of cases of basilar artery (BA) before and after stenting (Gateway-Wingspan system). **(A)** Digital subtraction angiography (DSA) revealed severe stenosis of BA before stenting (red arrow). **(B)** DSA revealed significant improvement in stenosis of BA after stenting (red arrow).

Statistical Methods

Using the SPSS 25.0 version statistical package (Armonk, NY: IBM Corp.), the measurement data were expressed as mean ± standard deviation ($\bar{x}\pm$ s). *The t*-test was used to compare the two samples (medical group and PTAS group). The chi-squared test or Fisher's exact probability method was used to compare the enumeration data. Patients from PTAS group were used as a reference group in the Cox proportional hazards model to determine hazard ratios (HRs) as effect size measures, with their 95% confidence intervals (CIs). Primary event rates were compared between the two groups using the Cox proportional hazards model adjusted by sex, age, hypertension, diabetes mellitus, coronary heart disease, smoking history, qualifying ischemic events, qualifying artery, high-density lipoprotein (HDL), LDL, and mRS. $P < 0.05$ was considered as statistically significant. HRs > 1 implied greater risk of SMT therapy and HRs < 1 implied greater risk of PTAS.

TABLE 2 | Baseline characteristics of the participants between PTAS and SMT group.

Characteristics	PTAS group ($n = 174$)	SMT group ($n = 62$)	*p*-value
Male, no. (%)	138 (79.3)	42 (67.7)	0.066
Age, y, mean (SD)	59.4 ± 8.7	61.0 ± 9.2	0.207
Risk factors			
Hypertension, no. (%)	150 (86.2)	55 (88.7)	0.616
Diabetes mellitus, no. (%)	62 (35.6)	27 (43.5)	0.269
Coronary heart disease, no. (%)	27 (15.5)	14 (22.6)	0.208
Smoking history			0.432
Current	56 (32.2)	15 (24.2)	
Former	28 (16.1)	13 (21)	
Never	90 (51.7)	34 (54.8)	
Cholesterol, mmol/L, mean (SD)			
High-density lipoprotein	1.0066 ± 0.216	1.0632 ± 0.243	0.088
Low-density lipoprotein	2.4474 ± 0.733	2.6195 ± 0.967	0.205
Qualifying ischemic events, no. (%)			
TIA	73 (42)	28 (45.2)	0.661
Cerebral infarction	99 (56.9)	32 (51.6)	0.472
Qualifying artery, no. (%)			0.998
BA	73 (42)	26 (41.9)	
Intracranial vertebral	101 (58)	36 (58.1)	
mRS, no. (%)			0.23
< 3	165 (94.8)	56 (90.3)	
≥ 3	9 (5.2)	6 (9.7)	

PTAS, percutaneous transluminal angioplasty and stenting; SMT, standardized medical treatment; BA, basilar artery; TIA, transient ischemic attack; mRS, modified Rankin Scale.

RESULTS

We included 238 patients with symptomatic severe IVBS; 62 patients were treated with SMT and 176 patients underwent PTAS for IVBS. In the PTAS group, stent angioplasty was successfully performed in 174 patients (**Figures 1**, **2**). The success rate was 98.9%. The reasons for the two patients not being able to complete surgery were tortuosity of the proximal vertebral artery, and the guide catheter could not reach the V2 segment. The mean time from the last event to stenting in the PTA cohort was 61 days.

Table 2 shows that there were no significant differences in sex, age, hypertension, diabetes mellitus, coronary heart disease, smoking history, cholesterol (HDL and LDL), or qualifying ischemic events (TIA or cerebral infarction) between the SMT and PTAS groups.

Except for the 7th day, the SMT group had a higher frequency of primary endpoint events than did the PTAS group (**Table 3**, **Figure 3**). **Figure 3** shows that the primary endpoint rates in the SMT and PTAS groups were 4.8% (3/62) and 5.2% (9/174) at the 7th day ($p = 1.000$), 17.7% (11/62) and 8.6% (15/174) at the 1st month ($p = 0.049$), 29% (18/62) and 14.4% (25/174) at the

TABLE 3 | Primary endpoints at 7 days, 1, 6 months, and 1 year.

Complications	7 days			1 month			6 months			1 year		
	PTAS group ($n = 174$)	SMT group ($n = 62$)	*p*-Value	PTAS group ($n = 174$)	SMT group ($n = 62$)	*p*-Value	PTAS group ($n = 174$)	SMT group ($n = 62$)	*p*-Value	PTAS group ($n = 174$)	SMT group ($n = 62$)	*p*-Value
Stroke, no. (%)	8 (4.6)	3 (4.8)		14 (8)	11 (17.7)		23 (13.2)	18 (29)		27 (15.5)	20 (32.3)	
Ischemic stroke	5 (2.9)	2 (3.2)		11 (6.3)	10 (16.1)		20 (11.5)	17 (27.4)		24 (13.8)	19 (30.6)	
TIA	0	2 (3.2)		1 (0.6)	5 (8.1)		7 (4)	7 (11.3)		10 (5.8)	7 (11.3)	
Cerebral infarction	5 (2.9)	0		10 (5.7)	5 (8.1)		13 (7.5)	10 (16.1)		14 (8)	12 (19.3)	
Cerebral hemorrhage	3 (1.7)	1 (1.6)		3 (1.7)	1 (1.6)		3 (1.7)	1 (1.6)		3 (1.7)	1 (1.6)	
Death, no. (%)	1 (0.6)	1 (1.6)		2 (1.1)	3 (4.8)		3 (1.7)	4 (6.5)		4 (2.3)	4 (6.5)	
Stroke-related death	0	1 (1.6)		1 (0.6)	3 (4.8)		1 (0.6)	4 (6.5)		1 (0.6)	4 (6.5)	
Heart-related death	1 (0.6)	0		1 (0.6)	0		2 (1.1)	0		3 (1.7)	0	
Primary endpoints, no. (%)	9 (5.2)	3 (4.8)	1.000	15 (8.6)	11 (17.7)	0.049	25 (14.4)	18 (29)	0.01	30 (17.2)	20 (32.3)	0.013
Restenosis				3/145 (2.1%)			12/145 (8.3%)			20/145 (13.8%)		
Symptomatic restenosis				2/145 (1.4%)			7/145 (4.8%)			12/145 (8.3%)		
Asymptomatic restenosis				1/145 (0.7%)			5/145 (3.5%)			8/145 (5.5%)		

PTAS, percutaneous transluminal angioplasty and stenting; SMT, standardized medical treatment; TIA, transient ischemic attack.

6th month ($p = 0.01$), and 32.2% (20/62) and 17.2% (30/174) at 1st year ($p = 0.013$), respectively. Although there was no significant difference in stroke rate from the 1st month to the 1st year between the SMT group (9/62, 14.5%) and the PTAS group (13/174, 7.5%), there was a significant difference in severe stroke rates between the SMT (6/62, 9.7%) and PTAS groups (0/174) (**Table 4**).

Table 3 shows the primary end points and other major adverse events during the follow-up period in each group. On the 7th day, there was one cardiogenic death, five ischemic strokes, and three cerebral hemorrhages in the PTAS group. All ischemic strokes were caused by the responsible artery. All cerebral hemorrhages were post-operative and symptomatic. There was one fatal hemorrhage stroke and two ischemic strokes due to the responsible artery in the SMT group. From the 7th day to the 1st month, there were six patients with ischemic strokes (one fatal stroke) due to the responsible artery in the PTAS group. In the SMT group, there were eight patients with ischemic strokes (two fatal strokes) due to the responsible artery. Between 1st and 6th month, one patient died of heart disease and nine patients suffered ischemic strokes caused by the responsible artery in the PTAS group. In the SMT group, ischemic stroke in seven patients was caused by the responsible artery, including one fatal stroke. Between 6th month and 1st year, one patient died of heart disease and four patients had ischemic strokes caused by the responsible artery in the PTAS group. In the medical treatment group, two patients had ischemic strokes caused by a responsible artery, and both survived.

The mortality rates at 7th day, 1st, 6th month, and 1st year were as follows (PTAS group vs. SMT group): 0.6 vs. 1.6%, 1.1 vs. 4.8%, 1.7 vs. 6.5%, and 2.3 vs. 6.5%. Among the four deaths in the PTAS group, one resulted from the responsible artery, and the other three were cardiogenic deaths. In the SMT group, four were stroke-related deaths.

Of the 174 patients in the PTAS group, 145 underwent neurovascular imaging in the 1st year. Of 145 patients, 20 patients (13.8%) showed restenosis of the surgical segment of 50% or more. Among these patients, 12 (60%) were symptomatic and eight (40%) were asymptomatic. In symptomatic patients, ten patients resumed dual antiplatelet therapy for 3 months, and two patients underwent angioplasty alone. In asymptomatic patients, all eight patients resumed dual antiplatelet therapy for 3 months. During the 1-year follow-up period, no further stroke or death occurred in the patients who underwent angioplasty or medical treatment again (**Table 3**).

Table 5 shows primary event rates which were compared between the PTAS group and SMT group using the Cox proportional hazards model adjusted for sex, age, hypertension, diabetes mellitus, coronary heart disease, smoke history, qualifying ischemic events, qualifying artery, HDL, LDL, and mRS. When no adjustment factors were added, PTAS group had a lower risk of primary endpoint compared with that of SMT group (HR, 2.04; 95% CI, 1.16, 3.59; $p = 0.014$). After adjusting for other factors, the difference was still significant (HR, 2.22; 95% CI, 1.22, 4.05; $p = 0.009$). The adjusted factors had no effect on the incidence of primary endpoint events.

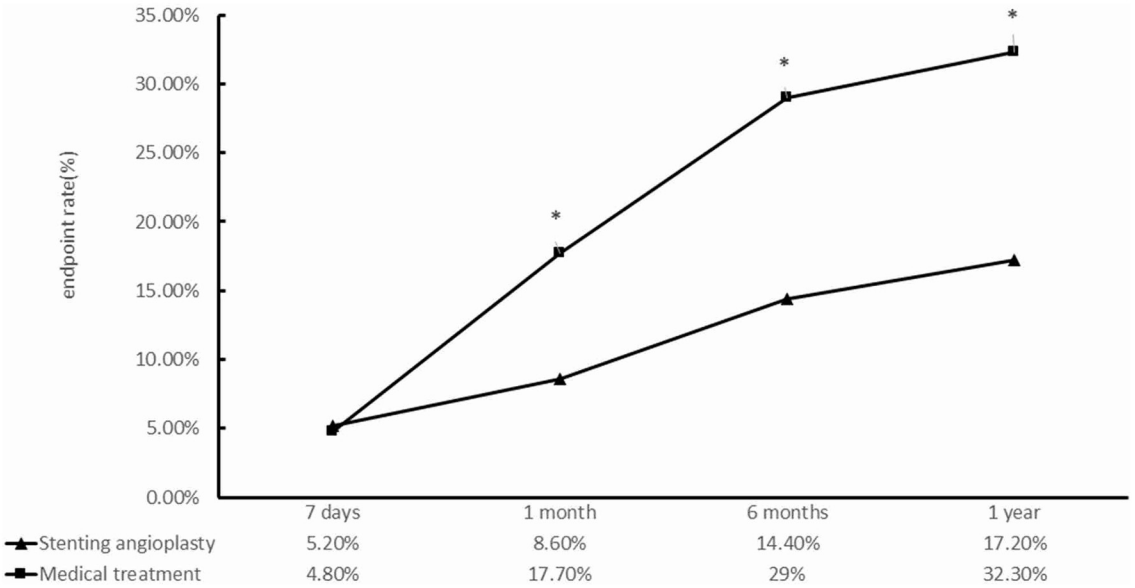


FIGURE 3 | Comparison between the standardized medical treatment group and the percutaneous transluminal angioplasty and stenting group for the primary endpoints at 7 days, 1, 6 months, and 1 year. *$p < 0.05$.

TABLE 4 | Comparison between early and delayed results in PTAS and SMT groups.

	1-month event rate	1–12-month stroke rate	1–12-month severe stroke*
PTAS group ($n = 174$)	14 (8%)	13 (7.5%)	0
SMT group ($n = 62$)	11 (17.7%)	9 (14.5%)	6 (9.7%)
p-Value	0.049	0.10	0

classified a stroke as a severe stroke if the baseline NIHSS score deteriorated by more than 3 points.
PTAS, percutaneous transluminal angioplasty and stenting; SMT, standardized medical treatment; NIHSS, National Institutes of Health Stroke Scale.

TABLE 5 | Comparison of the primary endpoints using the Cox proportional hazards model adjusted by various factors.

		HR (95% CI)	*p*-Value
Unadjusted*		2.04 (1.16, 3.59)	0.014
Adjusted by factors#	Male	1.94 (1.09, 3.43)	0.024
	Age	1.85 (1.04, 3.29)	0.036
	Hypertension	1.85 (1.04, 3.29)	0.036
	Diabetes mellitus	1.87 (1.05, 3.34)	0.034
	Coronary heart disease	1.85(1.03, 3.30)	0.039
	Smoke history	1.93 (1.07, 3.50)	0.029
	Qualifying ischemic events	1.87 (1.04, 3.39)	0.038
	High-density lipoprotein	1.95 (1.07, 3.53)	0.028
	Low-density lipoprotein	2.04 (1.12, 3.72)	0.019
	mRS	2.24 (1.23, 4.09)	0.008
	Qualifying artery	2.22 (1.22, 4.05)	0.009

regardless of other factors, patients in PTAS group were used as a reference group in the Cox proportional hazards model to determine hazard ratios (HRs) as effect size measures, with their 95% confidence intervals (CIs).
#*factors were sequentially added for adjusting. The comparison was adjusted by adding factors one by one; the last line was the adjusted result when all factors were added.*
HR, hazard ratio; CI, confidence interval; mRS, Modified Rankin Score.

DISCUSSION

In this study, we found significant differences in the primary endpoint event rates between PTAS and SMT in patients with symptomatic IVBS at 1, 6, and 12 months, which suggests that PTAS could be superior to SMT. On follow-up, the rate of severe stroke rate from the 1st to 12th month after stenting was very low at 0% in the PTAS group, while it was high to 9.7% in the SMT group. In addition, the restenosis rate of the surgical segment in the PTAS group was 13.8% in the first year, and among these patients, 60% were symptomatic restenosis, and 40% were asymptomatic restenosis.

PTAS showed an advantage in patients with symptomatic IVBS, which was inconsistent with the results of the SAMMPRIS and VISSIT trials. These studies showed that active medical treatment was superior to PTAS for patients with intracranial artery stenosis (9, 10). An analysis of the SAMMPRIS trial on the posterior artery subgroup showed that 2-year endpoint event rates were higher in the PTAS group than in the medical group (27% vs. 9.8%) (16). In the present study, the 1-year endpoint event rate was 32.2% for all patients in the medical group. The higher risk of end point event rate may be due to unsatisfactory implementation of SMT in this study. First,

all patients were treated with aspirin and clopidogrel double antiplatelet aggregation. However, some studies have shown that gene mutations in Chinese people (more than 50%) affect the antiplatelet efficacy of clopidogrel (17). In this study, only individual patients were performed platelet function testing, those patients were excluded from this study in order to avoid affecting the results. Second, the patients came from all parts of Shandong Province. During follow-up, the medication of some patients could not be completely unified because the drug manufacturers were different, which may lead to a reduction in drug efficacy, and was quite common in real-world China. Third, most patients were not treated by local hospitals due to complex conditions. In contrast, in the SAMMPRIS trial, a randomized controlled trial, the vast majority of patients were non-Asians, and great efforts have been made to control the interference factors (18). This type of aggressive medical treatment is difficult to carry out in the real world. This result suggests that medical treatment needs to be strengthened, so that patients can benefit from medical treatment in the real world.

In this study, the stroke recurrence or death rate for all patients in the PTAS group was 8.6% at 30 days after the procedure, and the annual rate was 17.2%, which was consistent with the results of previous studies on posterior circulation. A meta-analysis indicated that PTAS was associated with an 8% incidence of stroke recurrence or death in patients with IVBS within 30 days after the procedure (19). A study showed that stenting for symptomatic IVBS, the primary outcome of 30-day stroke, TIA, or death was 7.2% (13). Another meta-analysis of stroke recurrence rates in symptomatic IVBS patients showed that the risk of annual stroke recurrence or death was 14.8% (3). The WEAVE trial showed that in 152 patients with symptomatic ICAS (stenosis from 70 to 99%), there were 4 (2.6%) patients with stroke, bleeding, or death events within the 72 h after the procedure (11). In the WOVEN Trial, the natural extension of the WEAVE Trial, there were 11 strokes or deaths (8.5%) in 129 patients at 1-year follow-up (12). These studies suggest that through best practice and careful patient selection, the incidence of perioperative complications in symptomatic ICAS patients who receive stent implantation can be maintained at a low level, and the long-term effect of stent implantation may be comparable to or better than drug treatment alone. In this study, the mean time from the last event to stenting in the PTA cohort was 61 days. This may be one of the reasons for the lower rate of complications in the PTAS group. A study showed that patients with delayed ($>$ 14 days) ICAS stenting had a lower risk of long-term cerebral vascular events than those in whom the procedure was carried out $<$ 14 days of the qualifying event (20). Although there was no significant difference in stroke rates from the 1st to 12th month between the SMT (9/62, 14.5%) and PTAS groups (13/174, 7.5%), there was a significant difference in the rate of severe stroke between the PTAS (0%) and SMT groups (9.7%). The rate of severe stroke in the PTAS group showed a very low incidence of long time, as it was 0.8% in the WOVEN trial, and in the stenting arm of SAMMPRIS at 2.2% (12). This result suggests that symptomatic IVBS patients with stenting have a lower trend of delayed severe strokes than do patients with SMT. Patients with IVBS who receive stent therapy may have better long-term neurological function recovery and lower disability rates. Nevertheless, larger randomized trials are required to verify these findings.

All three cases of cerebral hemorrhage in the PTAS group occurred within 7 days after the surgery. In PTAS, the increased risk of rupture may be due to the following: (1) the thin wall of the intracranial arteries (21); (2) the intracranial arteries located in the cerebrospinal fluid of the subarachnoid cavity with no tissue around them; (3) the perforating arteries of the intracranial arteries and the possible damage of these arteries during stent placement (22); and (4) the experience of the operator is another important factor that affects the outcome of stent therapy. To reduce the risk of stroke recurrence or death, the technology needs to be improved based on the above characteristics in the future.

In the first year, the restenosis rate of the surgical segment in the PTAS group (13.8%) was similar to that in the WOVEN study (15.2%) (12). Among restenosis patients, 60% were symptomatic, which showed that in-stent restenosis was an important cause of recurrent stroke after PTAS in symptomatic IVBS patients. In future studies, the development of new technologies, new materials, or new drugs to reduce the rate of restenosis of stents may help reduce the incidence of stroke after stenting.

In this study, the duration of DAPT in the PTAS group was different from that in the SMT group. However, this discrepancy should not lead to misinterpretation of the results. A study showed that there was a tendency toward lower rate of any ischemic stroke in the patients who used DAPT beyond 90 days, but the difference was not statistically significant (23). Different from the high-dose applications of statins in Europe and America, the low doses of statins were used in this study. The results of the HPS2-THRIVE study showed that under the same dose of statin treatment, the incidence of liver adverse reactions in patients with cardiovascular disease in China was significantly higher than that in European patients, and the incidence of elevated liver enzymes was higher in European patients, and the risk of myopathy was 10 times higher than that in Europeans (24). The results of CHILLAS showed that high-intensity statins did not benefit Chinese patients more (25). Therefore, in China, moderate-intensity statins (atorvastatin 20 mg or rosuvastatin 10 mg) are used clinically.

This study was a retrospective real-world study for symptomatic IVBS in a Chinese population. It is a double-arm study with a medical group and a stent group, which has been less frequently used in previous studies. Nevertheless, this study has several limitations. First, this was a single-center retrospective study. The procedures of the medical treatment and PTAS were not random, which increased the possibility of bias. Second, the number of patients was small to be further divided into subgroups, which may have resulted in failure to investigate subgroups that benefit from medical treatment or PTAS. Although these limitations may compromise the conclusions, large multicenter randomized clinical trials may effectively confirm or refute these conclusions in the future.

In conclusion, in real-world China, PTAS for patients with symptomatic IVBS may be superior to SMT, have better long-term neurological function recovery, and lower disability rate.

In the real world, medical management needs to be strengthened to benefit more patients. These findings need to be confirmed or refuted by randomized controlled clinical trials.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethical standards committee on human experimentation at Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

QS, JL, and XL conceived and designed the research. GL, PY, YZ, SL, and YXu acquired the data. PY, SL, YXu, and YXi analyzed and interpreted the data. GL drafted the manuscript. QS made critical revisions of the manuscript. All authors approved the final manuscript.

FUNDING

This study was supported by the grants from Jinan Science and Technology Bureau (Grants no. 201704101) and Key Technology Research and Development Program of Shandong (Grants no. 2014GSF118106).

ACKNOWLEDGMENTS

We would like to thank all the study participants, staff of the participating hospitals, and the Steering Committee Members of this study.

REFERENCES

1. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. *Lancet Neurol.* (2013) 12:1106–14. doi: 10.1016/S1474-4422(13)70195-9
2. Markus HS, van der Worp HB, Rothwell PM. Posterior circulation ischaemic stroke and transient ischaemic attack: diagnosis, investigation, and secondary prevention. *Lancet Neurol.* (2013) 12:989–98. doi: 10.1016/S1474-4422(13)70211-4
3. Abuzinadah AR, Alanazy MH, Almekhlafi MA, Duan Y, Zhu H, Mazighi M, et al. Stroke recurrence rates among patients with symptomatic intracranial vertebrobasilar stenoses: systematic review and meta-analysis. *J Neurointerv Surg.* (2016) 8:112–6. doi: 10.1136/neurintsurg-2014-011458
4. Caplan LR, Wityk RJ, Glass TA, Tapia J, Pazdera L, Chang HM, et al. New England medical center posterior circulation registry. *Ann Neurol.* (2004) 56:389–98. doi: 10.1002/ana.20204
5. Gulli G, Khan S, Markus HS. Vertebrobasilar stenosis predicts high early recurrent stroke risk in posterior circulation stroke and TIA. *Stroke.* (2009) 40:2732–7. doi: 10.1161/STROKEAHA.109.553859
6. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* (2005) 352:1305–16. doi: 10.1056/NEJMoa043033
7. Qureshi AI, Suri MFK, Ziai WC, Yahia AM, Mohammad Y, Sen S, et al. Stroke-free survival and its determinants in patients with symptomatic vertebrobasilar stenosis: a multicenter study. *Neurosurgery.* (2003) 52:1033–40. doi: 10.1227/01.NEU.0000057744.96295.9F
8. Voetsch B, DeWitt LD, Pessin MS, Caplan LR. Basilar artery occlusive disease in the New England medical center posterior circulation registry. *Arch Neurol.* (2004) 61:496–504. doi: 10.1001/archneur.61.4.496
9. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. 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
10. Zaidat O, 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. *JAMA.* (2015) 313:1240–8. doi: 10.1001/jama.2015.1693
11. Alexander MJ, Zauner A, Chaloupka JC, Baxter B, Callison RC, Gupta R, et al. WEAVE trial: final results in 152 on-label patients. *Stroke.* (2019) 50:889–94. doi: 10.1161/STROKEAHA.118.023996
12. 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
13. Liu L, Zhao X, Mo D, Ma N, Gao F, Miao Z. Stenting for symptomatic intracranial vertebrobasilar artery stenosis: 30-day results in a high-volume stroke center. *Clin Neurol Neurosurg.* (2016) 143:132–8. doi: 10.1016/j.clineuro.2016.02.029
14. Jiang WJ, Du B, Hon SF, Jin M, Xu XT, Ma N, et al. Do patients with basilar or vertebral artery stenosis have a higher stroke incidence poststenting? *J Neurointerv Surg.* (2010) 2:50–4. doi: 10.1136/jnis.2009.000356
15. Ma N, Zhang Y, Shuai J, Jiang C, Zhu Q, Chen K, et al. Stenting for symptomatic intracranial arterial stenosis in China: 1-year outcome of a multicentre registry study. *Stroke Vasc Neurol.* (2018) 3:176–84. doi: 10.1136/svn-2017-000137
16. Lutsep HL, Lynn MJ, Cotsonis GA, Derdeyn CP, Turan TN, Fiorella D, et al. Does the stenting versus aggressive medical therapy trial support stenting for subgroups with intracranial stenosis? *Stroke.* (2015) 46:3282–4. doi: 10.1161/STROKEAHA.115.009846
17. Wang Y, Zhao X, Lin J, Li H, Johnston S C, Lin Y, et al. Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. *JAMA.* (2016) 316:70–8. doi: 10.1001/jama.2016.8662
18. Chimowitz MI, Lynn MJ, Turan TN, Fiorella D, Lane BF, Janis S, et al. Design of the stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis trial. *J Stroke Cerebrovasc Dis.* (2011) 20:357–68. doi: 10.1016/j.jstrokecerebrovasdis.2011.05.001
19. Mao Y, Nan G. Center volume and the outcomes of percutaneous transluminal angioplasty and stenting in patients with symptomatic intracranial vertebrobasilar stenoses: a meta-analysis. *PLoS ONE.* (2018) 13:e0200188. doi: 10.1371/journal.pone.0200188
20. Zhang Y, Sun Y, Li X, Liu T, Liu P, Wang H, et al. Early versus delayed stenting for intracranial atherosclerotic artery stenosis with ischemic stroke. *J Neurointerv Surg.* (2020) 12:274–8. doi: 10.1136/neurintsurg-2019-015035
21. Wilkinson IM. The vertebral artery extracranial and intracranial structure. *Arch Neurol.* (1972) 27:392–6. doi: 10.1001/archneur.1972.00490170024004
22. Markus HS, Harshfield EL, Compter A, Kuker W, Kappelle LJ, Clifton A, et al. Stenting for symptomatic vertebral artery stenosis: a preplanned

pooled individual patient data analysis. *Lancet Neurol.* (2019) 18:666–73. doi: 10.1016/S1474-4422(19)30149-8

23. Abdul Rahman L, Turan TN, Cotsonis G, Almallouhi E, Holmstedt CA, Chimowitz MI. Dual antiplatelet therapy beyond 90 days in symptomatic intracranial stenosis in the SAMMPRIS trial. *J Stroke Cerebrovasc Dis.* (2020) 29:105254. doi: 10.1016/j.jstrokecerebrovasdis.2020.105254
24. Group HTC. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J.* (2013) 34:1279–91. doi: 10.1093/eurheartj/eht055
25. Zhao SP, Yu BL, Peng DQ, Huo Y. The effect of moderate-dose versus double-dose statins on patients with acute coronary syndrome in China: results of the CHILLAS trial. *Atherosclerosis.* (2014) 233:707–12. doi: 10.1016/j.atherosclerosis.2013.12.003

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 16 June 2021
doi: 10.3389/fneur.2021.673367

Staged Endovascular Treatment for Symptomatic Occlusion Originating From the Intracranial Vertebral Arteries in the Early Non-acute Stage

Hongzhou Duan[1†], Li Chen[2†], Shengli Shen[1], Yang Zhang[1], Chunwei Li[1], Zhiqiang Yi[1], Yingjin Wang[1], Jiayong Zhang[1] and Liang Li[1]*

[1] Department of Neurosurgery, Peking University First Hospital, Beijing, China, [2] Department of Pediatric Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

OPEN ACCESS

Edited by:
Liqun Jiao,
Capital Medical University, China

Reviewed by:
Ju Han,
Shandong University, China
Luca Remonda,
Aarau Cantonal Hospital, Switzerland
Ahmed Mohamed Elhfnawy,
University Hospital Essen, Germany

***Correspondence:**
Hongzhou Duan
duanhongzhou@126.com

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *27 February 2021*
Accepted: *19 May 2021*
Published: *16 June 2021*

Citation:
Duan H, Chen L, Shen S, Zhang Y, Li C, Yi Z, Wang Y, Zhang J and Li L (2021) Staged Endovascular Treatment for Symptomatic Occlusion Originating From the Intracranial Vertebral Arteries in the Early Non-acute Stage. Front. Neurol. 12:673367. doi: 10.3389/fneur.2021.673367

Background: The ideal treatment for patients who survive from acute vertebrobasilar artery occlusion but develop aggressive ischemic events despite maximal medical therapy in the early non-acute stage is unknown. This paper reports the technical feasibility and outcome of staged endovascular treatment in a series of such patients with symptomatic intracranial vertebral artery occlusion.

Methods: Ten consecutive patients who presented with aggressive ischemic events in the early non-acute stage of intracranial vertebral artery occlusion from Jan 2015 to Nov 2020 were retrospectively reviewed. Among them, eight male and two female patients with a mean age of 66.7 years developed aggressive ischemic events, and the NIHSS score was elevated by a median of 7 points despite medical therapy. All patients received staged endovascular treatment 4–21 days from onset, at an average of 11 days. The strategy of staged treatment was as follows: first, a microwire was passed through the portion of the occlusion, which was then dilated with balloon inflation to maintain the perfusion above TICI grade 2b. Then, with the use of antiplatelet drugs, the residual intravascular thrombus was gradually eliminated by the continuous perfusion and an activated fibrinolytic system, leaving the residual stenosis. A second stage of angioplasty with stent implantation was subsequently performed if residual stenosis was ≥50%. The NIHSS scores and mRS scores were compared between pre- and post-endovascular treatment groups and in the follow-up period.

Results: Technical success was achieved in 9 patients who received staged endovascular treatment (perforation occurred in one patient during the first stage). The NIHSS scores were significantly improved, with a median score 7 points lower on discharge compared with the scores for the most severe status. Favorable outcomes with mRS score≤2 were achieved in 7 and 9 patients at the 3-month follow-up and the latest follow-up, respectively, which was better than the preoperative status.

Conclusion: Staged endovascular treatment might be a safe, efficient, and viable option in carefully selected patients with symptomatic intracranial vertebral artery occlusion in the early non-acute stage. However, this needs to be confirmed by further investigation, preferably in a large, controlled setting.

Keywords: occlusion, endovascular treatment, recanalization, vertebral artery, staged

INTRODUCTION

Acute vertebrobasilar artery occlusion is a serious condition with high mortality rates that range from 80 to 95% (1). Thrombolysis and/or mechanical thrombectomy has historically achieved rates of recanalization of 45–78%, which provides the patients with favorable functional outcomes (2). However, effective therapies for acute treatment of ischemic stroke rely on timely restoration of the blood supply to salvageable brain tissue. Currently, only 10–20% of stroke patients in China reach the hospital within 3 h of the stroke onset (3). In addition, fewer than 3% of patients receive intravenous thrombolysis, a proportion much lower than that in high-income countries (4). A subset of patients with vertebrobasilar artery occlusion survive the acute events without endovascular recanalization due to the leptomeningeal collaterals; however, as the collaterals usually fail to provide sufficient perfusion during periods of increased oxygen demand, the patients may develop recurrent or aggressive ischemic events and progressive disability in the early non-acute stage (>24 h) despite intensive medical therapy. These patients miss the optimal period for endovascular recanalization, and extracranial-intracranial bypass treatment is not recommended in such cases because of technical challenges and a high risk of morbidity and mortality (5, 6). Herein, we report our experience with staged endovascular treatment in such patients.

METHODS

Patient Enrollment

We retrospectively reviewed our maintained neurointerventional database for cases from January 2015 to November 2020 at Peking University First Hospital, Beijing. We identified consecutive cases of the intracranial vertebral artery occlusion in the early non-acute stage in our database. According to the results of the DAWN clinical trials, the time window of thrombectomy can be extended to 24 h (7), and the thrombosis is almost organized about 1 month after the occlusion (8), therefore, we defined the "early non-acute stage" as the time from 24 h to 1 month after the onset of ischemic stroke. Ten patients receiving endovascular treatment in this stage were enrolled in this study, including 8 males and 2 females with a mean age of 66.7 years (range: 52–78 years) (**Table 1**). All patients had high-risk factors for stroke (**Table 1**), and they all suffered typical ischemic symptoms of posterior circulation, such as vertigo, ataxia, dysarthria, blurred vision, facial paralysis, dysphagia and weakness. The National Institute of Health stroke scale (NIHSS) score at onset ranged from 3 to 11, with a median of 6. None of these patients had undergone intravenous thrombolysis or mechanical thrombectomy in the acute phase of infarction. Magnetic resonance imaging (MRI) or computed tomography (CT) examinations showed new or recent infarctions in the territory of the vertebrobasilar artery. All patients received CT angiography (CTA) or magnetic resonance angiography (MRA) examination, which confirmed that the dominant intracranial vertebral artery was occluded and that the contralateral vertebral artery was occluded, hypoplastic, or severely stenotic. Although intensive medical therapy and strict control of risk factors were used, these patients experienced elevated NIHSS scores and severe neurological manifestations such as disturbance of consciousness and hemiplegia. The NIHSS scores were 4–10 points higher in the most severe stage than at onset, with a median increase of 7 points. Because of the aggravation of symptoms despite extensive medical treatment, these patients ultimately received neuroendovascular treatment. The time between symptom onset and endovascular recanalization ranged from 4 to 21 days, with an average of 11 days (**Table 1**). Each patient himself or his or her family members were authorized to sign an informed consent form, and the protocol for this recanalization study was approved by our institutional ethics committee (No. G202037).

Strategy of Endovascular Treatment

Inclusion and Exclusion Criteria

The inclusion criteria for recanalization treatment were as follows: (1) patient age >18 years and <80 years; (2) the patient had evidence of infarctions related to intracranial vertebral artery distribution on MRI; (3) the patient was in an early non-acute stage of intracranial vertebral artery occlusion; (4) the unilateral or dominant intracranial vertebral artery was completely occluded together with total occlusion, hypoplasia, absence, or severe (≥70%) stenosis of the contralateral vertebral artery; (5) the patient had severe neurological manifestations refractory to maximal medical therapy, including double antiplatelet therapy plus a statin use and management of risk factors (e.g., smoking, drinking, diabetes, hyperlipidemia and hyperhomocysteinemia); (6) the patient had at least one atherosclerotic risk factor; and (7) the grade of collateral flow was ≤3 (according to the modified grading system of the American Society of Interventional and Therapeutic Neuroradiology) (9).

The exclusion criteria were as follows: (1) non-atherosclerotic occlusion, e.g., arterial dissection or vasculitis; (2) intracranial hemorrhage on CT or MRI; (3) known allergies or contraindication to aspirin, clopidogrel, heparin, tirofiban, contrast medium, metal, etc.; (4) life expectancy <1 year due to other diseases, such as malignant tumors; and (5)

TABLE 1 | Baseline characteristics of the enrolled patients.

Case no.	Age(yrs)/Sex	Clinical presentation	Lesion location	NIHSS 1	Risk factors	Time 1, days	NIHSS 2	Findings of MRI after onset
1	64/M	Vertigo, tinnitus, dysarthria, weakness	Lt VA	6	Hypertension, diabetes, myocardial infarction, hyperlipemia, smoking	21	10	Infarction in pons and bilateral cerebellum
2	72/M	Vertigo, dysphasia, facial paralysis	Rt VA	3	Diabetes	16	8	Fresh infarction in right cerebellum and medulla
3	52/F	Vertigo, ataxia, dysphasia, facial paralysis	Rt VA	4	Hypertension, diabetes	17	11	Infarction in right cerebellum
4	66/M	Vertigo, tinnitus, ataxia, weakness	Rt VA	8	Hypertension, hyperlipemia	9	18	Infarction in right cerebellum and pons
5	59/F	Vertigo, weakness, ataxia	Lt VA	10	Hypertension, diabetes, obesity	8	14	Infarction in bilateral cerebellum and pons
6	64/M	Vertigo, ataxia, facial paralysis	Rt VA	5	Hypertension, smoking	9	9	Fresh infarction in right cerebellum
7	70/M	Vertigo, ataxia, weakness, dysphasia	Rt VA	11	Hypertension, smoking, drinking, hyperhomocysteinemia	10	16	Fresh infarction in pons and bilateral cerebellum
8	73/M	Vertigo, ataxia, facial paralysis	Lt VA	4	Hypertension, diabetes	6	11	Fresh infarction in left cerebellum and pons
9	78/M	Dizziness, blurred vision, weakness	Rt VA	3	Smoking, drinking	10	13	Fresh infarction in right occipital lobe and cerebellum
10	69/M	Vertigo, weakness	Lt VA	7	Obesity, drinking, hyperlipemia	4	16	Fresh infarction in bilateral cerebellum and pons

NIHSS 1, NIHSS score of onset; NIHSS 2, Worst NIHSS score in aggravation; Time 1, Time between symptom onset and recanalization; F, female; Lt, left; M, male; MRI, magnetic resonance imaging; Rt, right; VA, vertebral artery.

other conditions that were unconducive to general anesthesia or surgery.

Neurointerventional Procedure

All patients were scheduled to receive two stages of endovascular treatment. In the first stage, the procedure was performed under local anesthesia. Heparin was given as an anticoagulant throughout the procedure in all cases to maintain an activated clotting time between 250 and 300 s. Cerebral angiography was first performed to evaluate the condition of all cerebral arteries and collateral perfusion. After confirmation of the occlusive lesion, which usually included the V3 and V4 segments of the vertebral artery, a 6F guiding catheter (Envoy, Cordis, USA) was placed in the distal V2 segment. Then, an Echelon-10 microcatheter (Medtronic, USA) or an Excelsior SL-10 microcatheter (Stryker Neurovascular, USA) with the support of a Pilot-50 microwire (Abbott, USA) or a Synchro 14 microwire (Stryker Neurovascular, USA) was advanced through the occlusive lesion. Once injection confirmed that the microcatheter was in the true lumen of the distal part, a 300-cm-long Transend 300 Floppy microwire (Stryker Neurovascular, USA) was advanced to replace the microcatheter. Then, a Gateway angioplasty balloon (Stryker Neurovascular, USA) was placed at the site of the occlusion and inflated from the distal part to the proximal portions. Anterograde flow through the occluded portion was graded using the Thrombolysis in Cerebral Ischemia (TICI) grading system (10). Technical success in this stage was determined by recanalization with a TICI grade of $\geq$2b. If the TICI grade was <2b or the perfusion did not remain stable for over 30 min during the observation, one or more additional balloons could be used and inflated in the same way until the TICI grade was $\geq$2b; meanwhile, a bolus dose of tirofiban was injected through the guiding catheter, and then additional tirofiban was continuously infused intravenously for 48 h. Throughout the treatment process, we communicated with the patients to monitor their discomfort and conducted timely physical examinations if necessary.

After the first stage of endovascular treatment, a head CT scan was performed in the first 24 h after intervention. Intravenous injection of tirofiban was routinely used for 48 h, and preoperative drugs were maintained. Blood pressure was controlled below 140/90 mmHg. Follow-up CTA, MRA or transcranial Doppler (TCD) was performed once a week after the recanalization procedure. If the thrombus in the intracranial vertebral artery was eliminated and the residual stenosis was more than 50% or if there was a dissection in the portion with stenosis, a second stage of the neurointerventional procedure was performed. Nine patients with residual stenosis <50% received a second stage of endovascular treatment, and one patient had complication of dissection. The average interval between the two endovascular treatments was 15.6 d (11–25 d) (**Table 2**).

In the second stage of endovascular treatment, the procedure was performed under general anesthesia. A 6F guiding catheter was placed in the V2 segment of the vertebral artery, and then a microwire was advanced through the stenotic lesion. A Gateway balloon was placed in the lesion and inflated, and then a

TABLE 2 | Clinical summary of 9 patients undergoing staged neuro-endovascular recanalization.

Case No.	mRS 1	First stage of neuro-endovascular recanalization					Time3, days	Second stage of treatment				mRS 2	NIHSS 3	mRS 3	ISR	mRS 4
		Angiographic findings	Collateral blood flow	Technical success	TICI grade	Intraoperative complication		Preoperative residual stenosis	Stent used (mm)	Technical success	Complications					
1	4	V3 and V4 of Lt VA occlusion	Rt PCOM supplied PCA with retrograde flow to the top of the BA	Yes	2b	NA	15	80%	Apollo 3.5*18	Yes	NA	3	4	1	0	0
2	4	V4 of Rt VA occlusion	Lt PCOM supplied PCA with retrograde flow to the top of the BA	Yes	2b	NA	14	60%	Apollo 3.5*18	Yes	NA	3	3	1	-	1
3	4	V4 of Rt VA occlusion	Occluded Lt VA with leptomeningeal collaterals to BA	Yes	2b	VA dissection	25	75% (dissection)	Winspan 3.0*20	Yes	NA	2	2	0	50%	0
4	5	V3 and V4 of Rt VA occlusion	Lt PCOM supplied PCA with retrograde flow to the top of the BA	No	0	Microguidewire-perforated out of the VA						5	14	6		
5	4	V3 and V4 of Lt VA occlusion	Rt thin VA with severe stenosis in V4 segment	Yes	2b	NA	19	70%	Winspan 3.0*20	Yes	NA	3	4	1	-	1
6	4	V4 of Rt VA occlusion	Anastomosis between left ACA and distal VA	Yes	2b	NA	16	80%	Apollo 2.5*13	Yes	SAH	4	8	3	20%	2
7	5	Distal V2 to V4 segment of Rt VA occlusion	PCOMs supplied PCAs with retrograde flow to the top of the BA	Yes	2b	NA	15	60%	Apollo 2.5*13	Yes	NA	4	7	2	0	1
8	4	V4 of Lt VA occlusion	Rt hypoplasia VA with severe stenosis in V4 segment	Yes	2b	NA	11	70%	Winspan 3.5*20	Yes	NA	3	4	2	20%	1
9	4	V3 and V4 of Rt VA occlusion	Lt PCOM supplied PCA with retrograde flow to the top of the BA	Yes	2b	NA	13	60%	Apollo 3.5*13	Yes	NA	3	5	2	0	1
10	5	V3 and V4 of Lt VA occlusion	Rt hypoplasia VA with severe stenosis in V4 segment	Yes	2b	NA	12	70%	Appollo 3.5*18	Yes	NA	4	5	3	10%	2

mRS 1, mRS score before the first stage of neuro-endovascular treatment; mRS 2, mRS score at discharge; mRS 3, mRS score at 3 months follow-up; mRS 4, mRS score at the latest follow-up; NIHSS 3, NIHSS score at discharge; Time3, The time between the first and the second stage of neuro-endovascular treatment; ACA, ascending cervical artery; BA, basilar artery; FU, follow-up; ISR, in-stent restenosis; Lt, left; mRS, modified Rankin Scale, NA, No complication; PCOM, posterior communication artery; PCA, posterior cerebral artery; Rt, right; SAH, subarachnoid hemorrhage; VA, vertebral artery.

balloon expanding Apollo stent (MicroPort Medical, Shanghai, China) or a self expanding nitinol Wingspan stent (Stryker Neurovascular, USA) was released across the stenotic lesion. Post-balloon inflation was performed if there was more than 40% residual stenosis. After the second stage of neurointerventional therapy, dual antiplatelet drugs were maintained for at least 6 months, and aspirin alone was given every day thereafter. Rehabilitation treatment was recommended for patients with functional disability (Illustrative case in **Figure 1**).

Follow-Up Study and Statistical Analysis

All patients were followed up regularly. The modified Rankin Scale (mRS) and NIHSS scores were applied before endovascular treatment, at discharge and at follow-up. CTA, MRA or cerebral catheter angiography was performed at the 6-month or 1-year follow-up.

SPSS 16.0 statistical software was used for analysis. The Wilcoxon signed rank test was used to compare the NIHSS and mRS scores before the operation, at discharge and during the follow-up. The difference was statistically significant if $P < 0.05$.

RESULTS

Cerebral catheter angiography showed that all the 10 patients suffered occlusion of the intracranial vertebral artery on the dominant side. The occlusion sites included the V4 segment of the vertebral artery in 4 patients, originating at the V4 segment and extending to the V3 segment in 5 patients, and originating at the V4 segment and extending to the V2 segment in one patient. Collateral perfusion of the posterior circulation commonly came from the posterior communicating arteries (PCOMs) (5/10) and hypoplastic or stenotic contralateral vertebral arteries (3/10). Technical success of recanalization during the first stage was achieved in 9 cases, in whom the final perfusion was achieved at least on TICI 2b. The procedure failed in 1 patient (case 4) due to microwire perforation of the vertebral artery. Although the patient didn't suffer a symptomatic deterioration after the operation, he died of pneumonia and respiratory failure 3 months after discharge. Another patient (case 3) experienced asymptomatic dissection of the intracranial vertebral artery after the first stage of endovascular treatment (Illustrative case in **Figure 2**). The mean interval time between the two stages of neuroendovascular treatment was 15.6 d (11–25 d), and during which there were no hemorrhagic complications. Angiographic examination revealed that the residual thrombi in the vertebral arteries were all eliminated, leaving severe stenosis (>50%) in all patients. Then, the patients underwent angioplasty with stent implantation, during which nine stents were implanted, including 6 balloon-expanded Apollo stents and 3 self-expanding Wingspan stents. One patient (case 6) experienced aggressive headaches and disturbed consciousness after stent implantation, and a CT scan showed subarachnoid hemorrhage (SAH) around the pons and medulla associated with moderate hydrocephalus. The patient recovered well with ventricular drainage and rehabilitation. Among the 10 patients, symptoms and NIHSS and mRS scores had improved in 9 at the time of discharge. The NIHSS scores were significantly improved by a median of 7 points on discharge compared with the scores for the most severe status ($P < 0.05$). The patients were followed up for a mean of 12.8 months (range: 5–36). Excluding the patient who died (case 4), the median mRS scores were 2 (range: 0–3) at the 90-day follow-up and 1 (range: 0–2) at the latest follow-up, both of which were much better than the median score before the first stage of endovascular treatment (range: 4–5; median: 4) ($P < 0.05$). Angiographic follow-up was available for 7 patients, most of whom had no or mild in-stent stenosis (**Table 2**).

DISCUSSION

Acute vertebrobasilar artery occlusion is a life-threatening condition and requires immediate treatment. Despite recent advances in stroke care, the rate of poor outcomes for those with vertebrobasilar artery occlusion remains high (11). In 2016, a meta-analysis of 5 recent landmark endovascular therapy trials confirmed the superiority and better outcomes of mechanical thrombectomy in large-vessel occlusion for acute anterior circulation strokes (12). Several subsequent trials showed that high rates (ranging from 79 to 96.86%) of successful reperfusion and favorable outcomes could also be achieved in acute vertebrobasilar artery occlusion patients (13–15). Subsequent studies also showed that the window for thrombectomy in cases of acute ischemic stroke could be carefully extended to 24 or 16 h (7, 16, 17). However, there are still limited studies reporting on the ideal treatment strategy in patients presenting more than 24 h from stroke symptom onset. Some patients survived the acute stage of vertebrobasilar artery occlusion because of the collateral flow but developed aggressive ischemic events and progressive disability in the following stage despite receiving maximal medical therapy. A prior study by our group has reported carotid-vertebral artery bypass with saphenous vein grafts for symptomatic V1 segment occlusion (18). However, for patients with intracranial vertebral artery occlusion, bypass surgery is risky and technically challenging (5). Although it has been reported that multiple stenoses or occlusions in the posterior circulation might hide an underlying inflammatory vascular disease, which might increase the interventional risk (19), some researchers have attempted to recanalize the occluded intracranial vertebral artery with endovascular therapy in the non-acute stage.

There is limited literature reporting on interventional therapy for large occluded intracranial vessels beyond the acute phase (1, 2, 20, 21). In a recent study, Gao et al. summarized six previous studies on endovascular recanalization for non-acute occlusions after 2009 (21). In the seven reported studies, including the cases reported by Gao et al. there were 72 patients with early non-acute (6) or chronic (66) occlusion of the intracranial vertebral artery or basilar artery who received endovascular treatment, and the success rate of the technique was 93% (67 in 72 cases), with a mortality rate of 1.39% (1 in 72 cases). In our case series, the technical success rate was 90%, and the mortality was 0% at discharge. Complications occurred in 2 patients: asymptomatic intracranial vertebral artery dissection in one patient and subarachnoid hemorrhage in the other patient

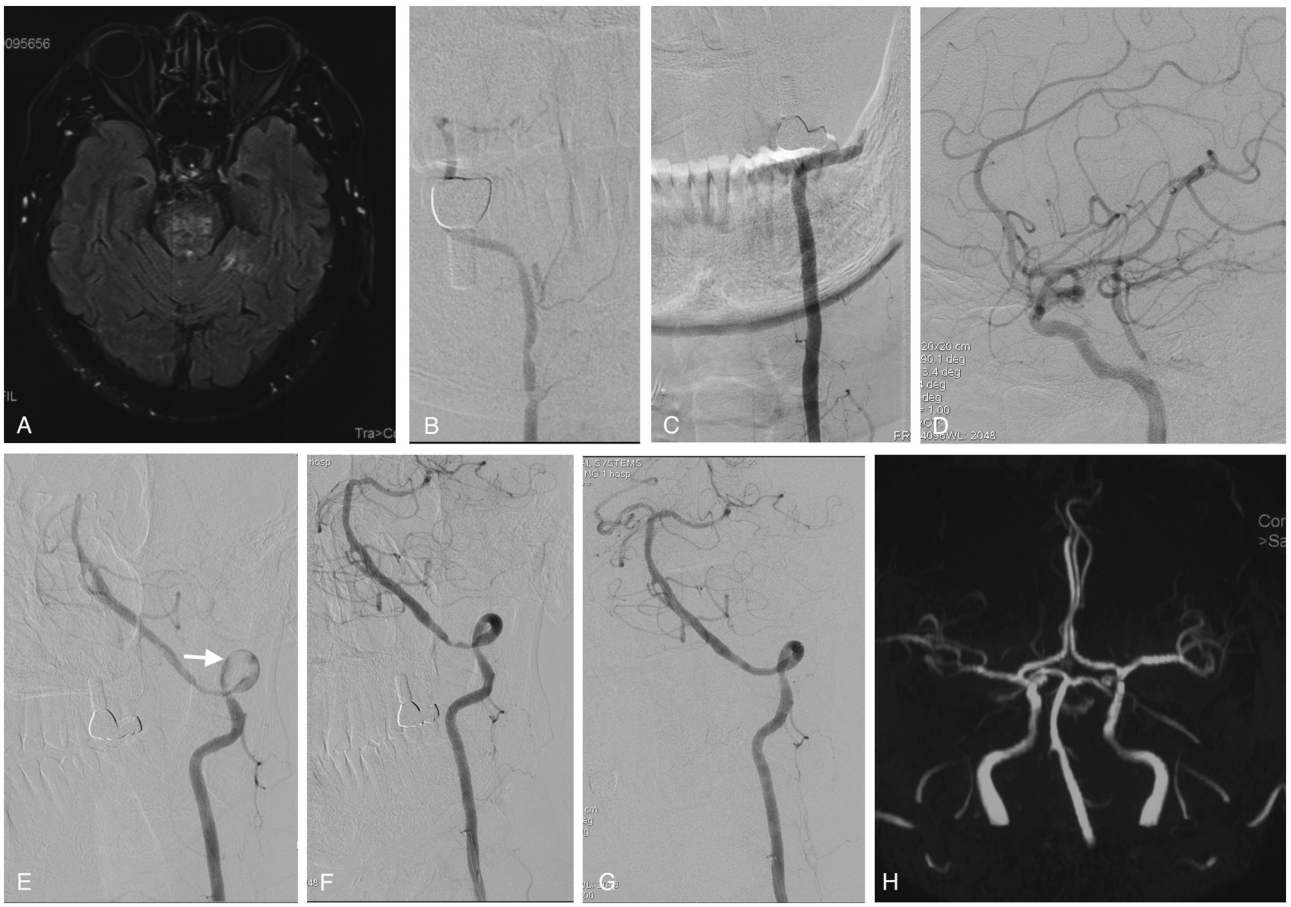


FIGURE 1 | Imaging studies of case 1. Axial FLAIR MRI sequences showed ischemic infarctions in the pons **(A)** and bilateral cerebellum (not shown here). The right vertebral artery was hypoplastic **(B)**, and the left vertebral artery was occluded from the V3 segment onward **(C)**. The right PCOM supplied the PCA with retrograde flow to the top of the BA **(D)**. In the first stage of endovascular treatment, the left intracranial vertebral artery was recanalized by passing a microwire through and dilating a balloon in the stenotic region; some thrombus material remained on the vessel wall (white arrow) **(E)**. In the second stage of endovascular treatment, vertebral angiography showed that the thrombus had disappeared, leaving only the primary stenosis **(F)**, which was fully resolved by angioplasty with stenting **(G)**. Follow-up MRA performed 6 months later showed that the perfusion of the left intracranial vertebral artery and BA was unobstructed **(H)**. MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; PCOM, posterior communicating artery; PCA, posterior cerebral artery; BA, basilar artery; MRA, magnetic resonance angiography.

(case 6), which might be associated with heavy calcification in the intracranial vertebral artery because a recent study showed that larger vertebrobasilar artery calcification volumes were a significant predictor of reduced technical success and functional independence and increased mortality (22). Although our results seemed encouraging, it should be emphasized that revascularization of intracranial vertebral artery occlusion in the early non-acute stage is a high-risk procedure.

The major technical challenge during the first stage of endovascular recanalization is traversing the occlusion site with a microwire. Gao et al. indicated that preoperative high-resolution MRI (HRMRI) and simultaneous two-vessel injection during the recanalization procedure might be helpful in guiding the wire to the distal cavity (21). HRMRI is helpful in the diagnosis of intracranial vertebral artery occlusion and luminal thrombosis and can help to identify the subset of patients with high embolism risk before the procedure (23). Simultaneous two-vessel injection is a good technique for helping the surgeon advance the microwire to the true lumen of the distal vessel. In our case series, this technique was not conducted because the procedure of recanalization procedure was performed under local anesthesia, as slight movements make the road map images unclear. It is critical to communicate with the patient frequently during the procedure. If the patient complains of pain, sweating, nausea, or vomiting, it usually indicates that the microwire has penetrated the blood vessel wall. In our case series, there were two patients (case 3 with dissection and case 4 with perforation) with intraoperative complications. Both of these patients complained of pain as the microwire was being advanced through the occlusion, and sweating and vomiting occurred in case 4. We suspect that patients' self-reports might be more accurate and occur earlier than indications from angiography in reflecting whether the microwire is in the true lumen.

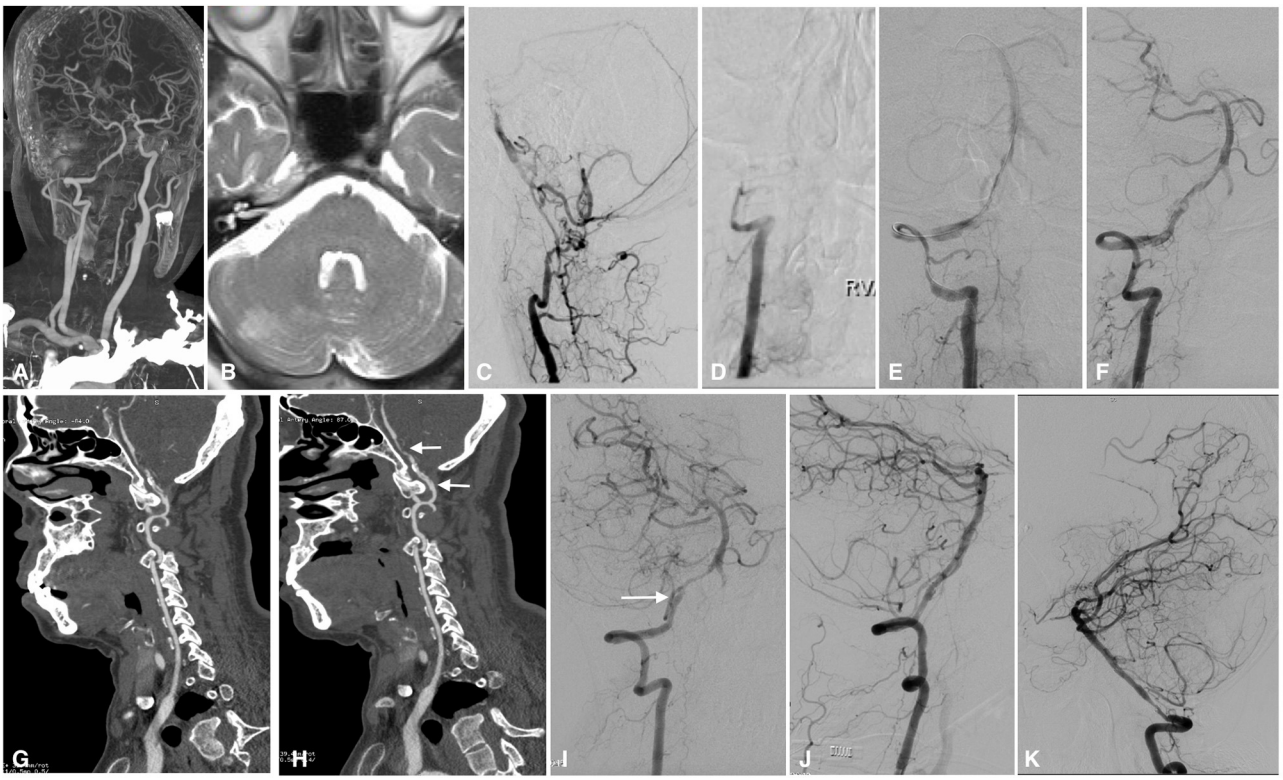


FIGURE 2 | Imaging studies of case 3. CTA in a local hospital showed severe stenosis of the right intracranial vertebral artery 6 months before admission **(A)**. Axial T2-weighted MRI showed ischemic infarction in the right cerebellum **(B)**. The left intracranial vertebral artery was occluded, and the BA was supplied by the anastomotic branches and leptomeningeal collaterals **(C)**. The right intracranial vertebral artery was occluded from the V3 segment onward **(D)**. In the first stage of endovascular treatment, the right intracranial vertebral artery was recanalized by balloon inflation **(E)**, and stable perfusion was achieved after sufficient dilation with 3 balloons; however, some thrombus remained on the vessel wall **(F)**. CTA performed 1 week later showed intraluminal thrombus and a dissection in the right intracranial vertebral artery **(G)**. Two weeks later, CTA showed that the thrombus had decreased significantly, leaving a dissection and residual stenosis **(H)**. Angiography performed in the second stage confirmed that the thrombus had disappeared and that there was a dissection (white arrow) and residual stenosis in the V4 segment of the intracranial vertebral artery **(I)**; the dissection and stenosis were resolved by a Winspan stent **(J)**. Follow-up angiography performed 12 months later showed moderate stenosis in the proximal part of the stent **(K)**. CTA, computed tomography angiography; MRI, magnetic resonance imaging; BA, basilar artery.

Treatment of early non-acute thrombi is the key to recanalization. In the acute stage, it is advisable to use recombinant tissue plasminogen activator for thrombolysis or mechanical thrombectomy because the thrombus is not firm. In the chronic stage, as the thrombus is well-organized and strongly adhered to the vessel wall, the key point of recanalization is to pass the microwire through the occluded lesion, and there is no need to deal with the organized thrombus except for performing balloon inflation. There are no reports in the literature regarding how to deal with an intravascular thrombus in the early non-acute stage of occlusion, as recanalization treatment is a relatively contraindicated in this stage, and there is a considerable risk of hemorrhagic conversion with early revascularization. In our previous cases involving anterior circulation, we attempted thrombectomy with aspiration and a stent retriever, which failed because the thrombus had a gum-like consistency. New-generation aspiration devices with larger bores and stronger suction force might be useful in clearing the thrombus from the proximal part of the original stenosis (24); however, we speculate that there could be many thrombi in the distal part of the stenoses due to the absence of continuous perfusion, and the aspiration catheter should not be placed over the original stenotic part to aspirate the distal thrombus as this would be dangerous and might result in dissection or thrombus translocation. In our research, we found that the thrombus in the early non-acute stage could be inflated by a balloon without translocation, and the anterograde flow could be achieved stably. Furthermore, these thrombi could be slowly eliminated through sustained blood flow, an activated human fibrinolytic system, and antiplatelet drugs. Among the 9 patients undergoing staged treatment, thromboembolisms did not occur during our observation, suggesting that thrombus elimination with drugs and the patient's own fibrinolytic system is safe. CTA or MRA can clearly show the intraluminal structure, including the dissection and thrombolysis (25–27). Through weekly CTA or MRA examination, we observed that the time to complete thrombus elimination was ∼2 weeks, depending on the length of the thrombus, the time from occlusion, the degree of perfusion recovery and the response of patients to antiplatelet drugs. After thrombus elimination,

angioplasty with stenting in the severe residual stenotic area becomes straightforward.

Although staged treatment increases the length of hospitalization, our strategy still has some advantages. First, after the initial intervention treatment, there is usually moderate to severe residual stenosis due to the residual thrombus, which limits the perfusion to the basilar artery and reduces the risk of hemorrhagic conversion. Second, in the later stage, the stent does not need to be implanted if the residual stenosis is not severe or only one stent needs to be deployed in the residual severely stenotic portion; thus, it is not necessary to use multiple stents to cover the thrombus, as it would be if only one stage of treatment were performed. Third, our strategy avoids the deployment of stents in the atlantoaxial segments of the vertebral artery, where stents may be develop fractures or in-stent occlusion in the long term as a result of cervical movement. Finally, our study showed good outcomes with an acceptable rate of technical success and a low rate of severe complications.

There are also many limitations in our study. First, the number of subjects was small ($n = 10$). Future studies with a greater number of included subjects could provide more persuasive evidence. Second, this is a retrospective study and lacks a control group, and therefore, it does not definitively show that staged intervention is more beneficial than other treatment strategies. Third, after revascularization in the first stage, we injected a loading dose of tirofiban into the blood vessel and maintained it for 48 h. Although recent research conducted by Quan et al. showed that low-dose tirofiban did not increase the risk of symptomatic intracranial hemorrhage or 90-day mortality in endovascular treatment of acute intracranial vertebrobasilar artery occlusion (15), its safety, effectiveness and necessity in the early non-acute stage of occlusion recanalization need to be further confirmed. Forth, some recent studies have shown that simultaneous endovascular recanalization and stent implantation may be safe and effective for such patients (23). However, how to select these patients and avoid the risks of hemorrhagic transformation needs further research. Fifth, in this study, we used TICI grading as a measure of technical success for posterior circulation, which is mostly commonly used for anterior circulation. Although some other authors have also used this grading system, AOL might be better in evaluating the posterior circulation (23, 28). Sixth, NIHSS is not ideal to assess stroke in the posterior circulation, because several manifestations of stroke in the posterior circulation, such as vertigo, vomiting, gait instability, and truncal ataxia, are not represented on the NIHSS scale (29). Furthermore, the several angiographic examinations of CTA or catheter angiography increase the risk of renal injury in patients. Finally, as there was variability in the types of stents used (balloon-mounted and self-expanding stents), the durability of stents in this context is also unclear and needs to be further studied. However, our results are encouraging, with a high recanalization rate and a low rate of significant intracranial hemorrhage. Our strategy may be considered an option in a highly select group of patients who have aggressive ischemic events or symptoms despite maximal medical therapy. The effectiveness of this approach in the prevention of progressive strokes and in the improvement of long-term outcomes should be evaluated prospectively in the future.

CONCLUSIONS

Our report based on a small case series suggests that staged neuroendovascular treatment of intracranial vertebral artery occlusion in the early non-acute stage is feasible, with an acceptable rate of technical success and a low rate of complications. However, its efficacy and safety need further investigation, preferably in a randomized controlled setting.

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 Peking University First Hospital ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HD: conception and design. CL, ZY, and YZ: acquisition of data. HD and LC: drafting the article. JZ: critically revising the article. SS, YW, and LL: technical support. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Youth Clinical Research Project of Peking University First Hospital (2019CR02).

REFERENCES

1. He Y, Bai W, Li T, Xue J, Wang Z, Zhu L, et al. Perioperative complications of recanalization and stenting for symptomatic nonacute vertebrobasilar artery occlusion. *Ann Vasc Surg.* (2014) 28:386–93. doi: 10.1016/j.avsg.2013.03.014
2. Lin R, Aleu A, Jankowitz B, Kostov D, Kanaan H, Horowitz M, et al. Endovascular revascularization of chronic symptomatic vertebrobasilar occlusion. *J Neuroimaging.* (2012) 22:74–9. doi: 10.1111/j.1552-6569.2010.00554.x
3. Jiang B, Ru X, Sun H, Liu H, Sun D, Liu Y, et al. Pre-hospital delay and its associated factors in first-ever stroke registered in communities from three cities in China. *Sci Rep.* (2016) 6:29795. doi: 10.1038/srep 29795
4. Wang Y, Li Z, Zhao X, Wang C, Wang X, Wang D, et al. Effect of a multifaceted quality improvement intervention on hospital personnel adherence to performance measures in patients with acute ischemic stroke in China: a randomized clinical trial. *JAMA.* (2018) 320:245–54. doi: 10.1001/jama.2018.8802

5. Rennert RC, Steinberg JA, Strickland BA, Ravina K, Bakhsheshian J, Fredrickson V, et al. Extracranial-to-intracranial bypass for refractory vertebrobasilar insufficiency. *World Neurosurg.* (2019) 126:552–9. doi: 10.1016/j.wneu.2019.03.184
6. Britz GW, Agarwal V, Mihlon F, Ramanathan D, Agrawal A, Nimjee SM, et al. Radial artery bypass for intractable vertebrobasilar insufficiency: case series and review of the literature. *World Neurosurg.* (2016) 85:106–13. doi: 10.1016/j.wneu.2015.08.004
7. 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.* (2018) 378:11–21. doi: 10.1056/NEJMoa1706442
8. Ro A, Kageyama N, Mukai T. Pathophysiology of venous thromboembolism with respect to the anatomical features of the deep veins of lower limbs: a review. *Ann Vasc Dis.* (2017) 10:99–106. doi: 10.3400/avd.ra.17-00035
9. Lee WJ, Jung KH, Ryu YJ, Kim JM, Lee ST, Chu K, et al. Utility of digital subtraction angiography-based collateral evaluation in medically treated acute symptomatic basilar artery stenosis. *Eur J Neurol.* (2017) 24:1148–55. doi: 10.1111/ene.13351
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. Wajima D, Aketa S, Nakagawa I, Masui K, Yonezawa T, Enami T, et al. Effectiveness of intracranial percutaneous transluminal angioplasty or stenting for atherosclerotic vertebrobasilar artery occlusion in the acute phase of ischemic stroke. *World Neurosurg.* (2017) 97:253–60. doi: 10.1016/j.wneu.2016.09.106
12. 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
13. Bouslama M, Haussen DC, Aghaebrahim A, Grossberg JA, Walker G, Rangaraju S, et al. Predictors of good outcome after endovascular therapy for vertebrobasilar occlusion stroke. *Stroke.* (2017) 48:3252–7. doi: 10.1161/STROKEAHA.117.018270
14. Singer OC, Berkefeld J, Nolte CH, Bohner G, Haring HP, Trenkler J, et al. Mechanical recanalization in basilar artery occlusion: the ENDOSTROKE study. *Ann Neurol.* (2015) 77:415–24. doi: 10.1002/ana.24336
15. Quan T, Hou H, Xue W, Yu G, Ma H, Sun J, et al. Endovascular treatment of acute intracranial vertebrobasilar artery occlusion: a multicenter retrospective observational study. *Neuroradiology.* (2019) 61:1477–84. doi: 10.1007/s00234-019-02282-1
16. Feil K, Reidler P, Kunz WG, Küpper C, Heinrich J, Laub C, et al. Addressing a real-life problem: treatment with intravenous thrombolysis and mechanical thrombectomy in acute stroke patients with an extended time window beyond 4.5 h based on computed tomography perfusion imaging. *Eur J Neurol.* (2020) 27:168–74. doi: 10.1111/ene.14051
17. 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
18. Duan H, Mo D, Zhang Y, Zhang J, Li L. Carotid-vertebral artery bypass with saphenous vein graft for symptomatic vertebrobasilar insufficiency. *Neurosurg Focus.* (2019) 46:E8. doi: 10.3171/2018.11.FOCUS18360
19. Elhfnawy AM, Elsalamawy D, Abdelraouf M, Schliesser M, Volkmann J, Fluri F. Red flags for a concomitant giant cell arteritis in patients with vertebrobasilar stroke: a cross-sectional study and systematic review. *Acta Neurol Belg.* (2020) 120:1389–98. doi: 10.1007/s13760-020-01344-z
20. Aghaebrahim A, Jovin T, Jadhav AP, Noorian A, Gupta R, Nogueira RG. Endovascular recanalization of complete subacute to chronic atherosclerotic occlusions of intracranial arteries. *J Neurointerv Surg.* (2014) 6:645–8. doi: 10.1136/neurintsurg-2013-010842
21. Gao P, Wang Y, Ma Y, Yang Q, Song H, Chen Y, et al. Endovascular recanalization for chronic symptomatic intracranial vertebral artery total occlusion: experience of a single center and review of literature. *J Neuroradiol.* (2018) 45:295–304. doi: 10.1016/j.neurad.2017.12.023
22. Diprose WK, Diprose JP, Tarr GP, Sutcliffe J, McFetridge A, Brew S, et al. Vertebrobasilar artery calcification and outcomes in posterior circulation large vessel occlusion thrombectomy. *Stroke.* (2020) 51:1301–4. doi: 10.1161/STROKEAHA.119.027958
23. Zhao W, Zhang J, Meng Y, Zhang Y, Zhang J, Song Y, et al. Symptomatic atherosclerotic non-acute intracranial vertebral artery total occlusion: clinical features, imaging characteristics, endovascular recanalization, and follow-up outcomes. *Front Neurol.* (2020) 11:598795. doi: 10.3389/fneur.2020.598795
24. Tonetti DA, Desai SM, Casillo S, Zussman BM, Brown MW, Jadhav AP, et al. Large-bore aspiration catheter selection does not influence reperfusion or outcome after manual aspiration thrombectomy. *J Neurointerv Surg.* (2019) 11:637–40. doi: 10.1136/neurintsurg-2018-014633
25. Porelli S, Leonardi M, Stafa A, Barbara C, Procaccianti G, Simonetti L. CT angiography in an acute stroke protocol: correlation between occlusion site and outcome of intravenous thrombolysis. *Interv Neuroradiol.* (2013) 19:87–96. doi: 10.1177/159101991301900114
26. Covello BR, Chukus A. Vertebral artery dissection: a pain in the neck. *Cureus.* (2021) 13:e12985. doi: 10.7759/cureus.12985
27. Beutler BD, Rangaswamy R, King RD, Tabaac BJ. Delayed endovascular thrombectomy for ischemic stroke in a young woman with no known risk factors: a case report. *Am J Case Rep.* (2021) 22:e930291. doi: 10.12659/AJCR.930291
28. Pampana E, Fabiano S, De Rubeis G, Bertaccini L, Stasolla A, Pingi A, et al. Switch strategy from direct aspiration first pass technique to solumbra improves technical outcome in endovascularly treated stroke. *Int J Environ Res Public Health.* (2021) 18:2670. doi: 10.3390/ijerph18052670
29. Elhfnawy AM, Abd El-Raouf M, Volkmann J, Fluri F, Elsalamawy D. Relation of infarction location and volume to vertigo in vertebrobasilar stroke. *Brain Behav.* (2020) 10:e01564. doi: 10.1002/brb3.1564

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.

The Handling Editor declared a shared affiliation, though no other collaboration, with one of the authors LC.

frontiers in Neurology

ORIGINAL RESEARCH
published: 17 June 2021
doi: 10.3389/fneur.2021.678443

Frequency-Domain Optical Coherence Tomography for Intracranial Atherosclerotic Stenosis: Feasibility, Safety, and Preliminary Experience

*Bin Yang[1], Yiding Feng[1], Yan Ma[1], Yabing Wang[1], Jian Chen[1], Long Li[1], Jia Dong[2], Bairu Zhang[2], Peng Gao[1,2], Yanfei Chen[1], Adam A. Dmytriw[3] and Liqun Jiao[1,2]**

[1] Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China, [2] Department of Interventional Neuroradiology, Xuanwu Hospital, Capital Medical University, Beijing, China, [3] Neuroradiology & Neurointervention Service, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

OPEN ACCESS

Edited by:
Atilla Ozcan Ozdemir, Eskişehir Osmangazi University, Turkey

Reviewed by:
Sombat Muengtaweepongsa, Thammasat University, Thailand
Mikayel Grigoryan, Glendale Adventist Medical Center, United States

***Correspondence:**
Liqun Jiao
liqunjiao@sina.cn

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *09 March 2021*
Accepted: *14 May 2021*
Published: *17 June 2021*

Citation:
Yang B, Feng Y, Ma Y, Wang Y, Chen J, Li L, Dong J, Zhang B, Gao P, Chen Y, Dmytriw AA and Jiao L (2021) Frequency-Domain Optical Coherence Tomography for Intracranial Atherosclerotic Stenosis: Feasibility, Safety, and Preliminary Experience. Front. Neurol. 12:678443. doi: 10.3389/fneur.2021.678443

Background: Despite advances in non-invasive imaging, the characterization of atherosclerotic plaque remains superior with frequency-domain optical coherence tomography (FD-OCT) in the clinical coronary and experimental cerebrovascular literature. An assessment of the feasibility and safety of FD-OCT for intracranial atherosclerotic stenosis (ICAS) is desirable.

Methods: We analyzed a cohort of all consecutive FD-OCT evaluations for ICAS performed at our institution from April 2017 to August 2018 (16 months) in patients who suffered from transient ischemic attack (TIA) or non-disabling stroke despite optimal medical management within 90 days of admission attributable to angiographically verified 70–99% stenosis of an intracranial artery.

Results: Thirty-three patients harboring 36 lesions with an average age of (57.6 ± 7.1) years (male sex 27 cases) comprising nine cases of lesions located within the anterior circulation and 24 cases within the posterior circulation were identified. Of the 33 patients with 36 lesions, the FD-OCT imaging catheter detected 35/36 (97%) lesions except in one case in which the FD-OCT catheter failed to navigate excessively tortuous vessels, and FD-OCT images in 27 patients (81.8%) were finally obtained successful, where the target lesion was fully visible, and image quality under at least one pullback was graded 2 or 3. There were no symptomatic complications. Blood flow was the most common artifact encountered (51.9%).

Conclusion: FD-OCT is safe and feasible for the assessment of ICAS in the anterior and posterior circulation. The use of diagnostic interferometry will have to be weighed against its cost, and these preliminary findings should be verified by prospective large-scale studies.

Keywords: intracranial stenosis, ischemic stroke, optical coherence tomography, percutaneous intervention, vertebrobasilar insufficiency

INTRODUCTION

Intracranial atherosclerotic stenosis (ICAS) is a major worldwide cause of stroke, accounting for 30–50% and 8–9% ischemic events in Asians and Caucasians, respectively (1, 2). Its presence is accurately diagnosed by conventional imaging modalities including computed tomography angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). However, these methods are insufficient for the characterization of plaque composition. Novel non-invasive methods have achieved some success in this domain, such as high-resolution vessel wall magnetic resonance imaging (HR VW-MRI), which can depict morphology and determine the location of plaque relative to branch artery ostia. However, even its sub-millimeter resolution (typically <0.7 mm) does not always completely satisfy the clinical need for plaque characterization (3–6).

Frequency-domain optical coherence tomography (FD-OCT) is a relatively new intravascular imaging modality in the neuroendovascular armamentarium with ultra-high resolution (approximately 10 μm), which can offer expanded spatial detail of plaque characteristics. The scope of FD-OCT has extended from the coronary arteries to the peripheral and cerebrovascular circulation within the last 10 years (7–13). Of late, there have been several reports regarding its application within intracranial arteries in carefully selected patients (14–19). However, the data surrounding feasibility and safety in the context of ICAS assessment are still limited. In this study, we report our preliminary experience of FD-OCT in the largest cohort of ICAS patients of which we are aware of.

METHODS

Patient Selection and Study Design

We analyzed a prospective cohort of all consecutive FD-OCT evaluations for ICAS performed at our institution from April 2017 to August 2018 (16 months). These patients all suffered from transient ischemic attack (TIA) or non-disabling stroke despite optimal medical management within 90 days of admission. Ischemic events were attributable to angiographically verified 70–99% stenosis of an intracranial artery based on Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) criteria (20). Percutaneous transluminal angioplasty and stenting (PTAS) was performed with a balloon-mounted stent or self-expandable stent. Clinical data including patient age, gender, National Institutes of Health stroke scale (NIHSS), serum creatinine, Mori type, and operative time were recorded. The study protocol was approved by our ethics committee, and written informed consent was obtained from all patients. The study was approved our Research Ethics Board.

Frequency-Domain Optical Coherence Tomography Techniques in Intracranial Atherosclerotic Stenosis

FD-OCT images were obtained with the Ilumien Optis System (St. Jude Medical, St. Paul, MN, USA) employing a non-occlusive technique. The procedure was performed under general anesthesia. A 6F Navien distal intracranial catheter (Medtronic, Irvine, CA, USA) with an 8F ENVOY guiding catheter (Codman Neurovascular, Raynham, MA, USA) was advanced to the distal part of V2 segment of the vertebral artery or C1 of the carotid artery *via* transfemoral approach. Then, a 0.014-in. Transcend microwire (Stryker, Kalamazoo, MI, USA) was introduced into the vessel and passed through the site of stenosis with the guidance of an Echelon-10 microcatheter (Medtronic, Minneapolis, MN, USA). The tip of the microwire was navigated to either the P2 segment of posterior cerebral artery (PCA) for posterior circulation cases or M2 segment of middle cerebral artery (MCA) for anterior circulation cases. The Echelon microcatheter was exchanged for a 2.7F Dragonfly Duo OCT catheter (St. Jude Medical, St. Paul, MN, USA), and the imaging catheter was positioned distal to the index region of interest using a standard "monorail" approach. The catheter was used at two different scanning ranges, 75 and 54 mm. The 75-mm scanning length was employed for longer lesions, the higher-detail 54-mm range was chosen by default, and the pullback speed was set to 18 mm/s.

OCT acquisition was performed using the automatic injection system (Mark V ProVis; Medrad Interventional/Possis, Warrendale, PA, USA) in the first 20 patients. Nine milliliters of iso-osmolar Visipaque contrast medium (GE Healthcare, Cork, Ireland) was injected through an Navien catheter at a rate of 3 ml/s at 200 psi. Acquisition was achieved by hand injection of the same volume contrast medium in the last 13 patients. Pullback was trigged as soon as the blood was completely replaced by the contrast medium distal to the interested region. During image acquisition, continuous images were stored digitally for subsequent analysis.

Frequency-Domain Optical Coherence Tomography Image Analysis

The image quality of all FD-OCT pullbacks was assessed by two experienced investigators (LL and BY), graded on a predefined four-category scale as proposed in the coronary literature (21). If <10% of cross sections in a pullback were considered suitable to be analyzed, the image quality was defined as grade 0; if 10–50% of cross sections in a pullback were suitable, the image quality was defined as grade 1; if 51–90% of cross sections in a pullback were suitable, the image quality was defined as grade 2; and if >90% of cross sections in a pullback were suitable, the image quality was defined as grade 3.

Examination was considered successful when (1) image acquisition could be adequately performed, (2) the target lesion was fully visible, and (3) the image quality under at least one pullback was graded 2 or 3. Examination was considered unsuccessful if (1) image acquisition could not be performed due to technical or anatomical problems, or (2) the target lesion could not be reliably assessed, or (3) image quality in all pullbacks was graded 0. Examination was considered partially successful if image quality under at least one pullback was graded 1, and at least a part of the region of interest could be assessed.

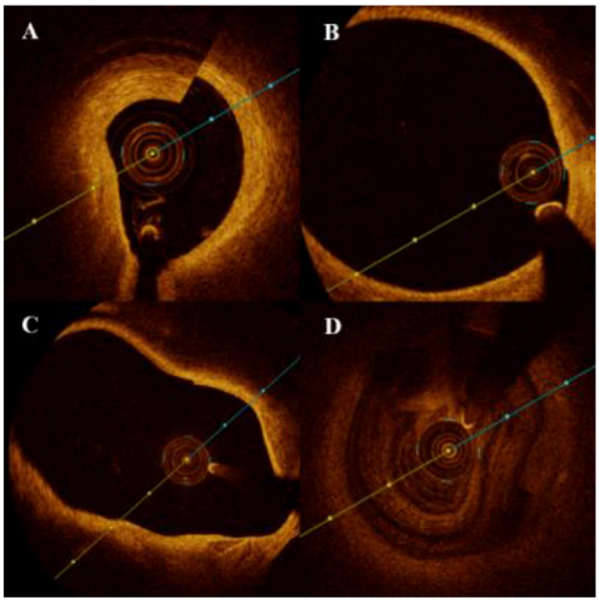


FIGURE 1 | Artifacts of optic coherence tomography for the detection of intracranial atherosclerotic stenosis (ICAS). **(A)** Rotational artifact appears as an apparent misalignment of the luminal border due to rapid axial rotation of the imaging catheter during pullback. **(B)** Decentration artifact appears as the distortion and/or invisible part of image because of the eccentric position of frequency-domain optical coherence tomography (FD-OCT) catheter. **(C)** Caliber artifact was defined as the integrity loss of the whole lumen due to the large diameter of the vessel, and **(D)** blood-flow artifact was defined as light dissipation caused by the residual blood due to inadequate replacement.

TABLE 1 | Baseline clinical and procedural data.

Variable	Total	Anterior circulation	Posterior circulation
Cases	33	9	24
Age (years)	57.6 ± 7.1	60.2 ± 8.6	56.7 ± 6.5
Male gender	27 (81.8)	9 (100)	18 (75)
Pullbacks	52	13	39
Pullbacks per examination	1.58 ± 0.75	1.44 ± 0.53	1.63 ± 0.82
Tortuous index*	0.74 ± 0.13	0.65 ± 0.12	0.78 ± 0.12
Stroke	28 (84.8)	7 (77.8)	21 (87.5)
Hypertension	20 (60.6)	7 (77.8)	13 (54.2)
DM	18 (54.5)	6 (66.7)	12 (50)
Hyperlipidemia	8 (24.2)	3 (33.3)	5 (20.8)
CHD	3 (9.1)	1 (11.1)	2 (8.3)
Smoking	17 (51.5)	4 (44.4)	13 (54.2)
Drinking	16 (48.5)	5 (55.6)	11 (45.8)
mRS ≤ 2	32 (96.9)	9 (100)	23 (95.8)
Mori type			
A	12 (36.4)	5 (55.6)	7 (29.2)
B	15 (45.5)	2 (22.2)	13 (54.2)
C	6 (18.2)	2 (22.2)	4 (16.7)
Stenosis (%)	78.1 ± 5.7	77.5 ± 5.4	78.3 ± 6.0
Preoperation Cr (μmol/L)	65.6 ± 13.9	68.1 ± 9.0	63.9 ± 15.5
Postoperation Cr (μmol/L)	70.2 ± 17.8	80 ± 14.6#	66.5 ± 17.7

Continuous variables are presented as mean ± SD, while categorical variables are presented as frequency (%). DM, diabetes mellitus; CHD, coronary heart disease; mRS, modified Rankin Scale; Cr, creatinine.
**Student's t-test, p = 0.01.*
#Student's t-test, p = 0.006.

Artifact Definition

OCT rotational artifact was defined as an apparent misalignment of the lumen border due to rapid axial rotation of the imaging catheter during pullback. Decentration artifact was defined as the distortion and/or invisible image section due to eccentric position of FD-OCT catheter. Caliber artifact was defined as integrity loss of the whole lumen due to the large diameter of the vessel, and lastly blood artifact was defined as light occlusion caused by residual blood due to inadequate replacement (**Figure 1**) per standard definitions.

Tortuosity Index

Tortuosity index was defined as the ratio of the linear length to the real length between the first and third markers of the FD-OCT image catheter. The linear length was measured by the DSA software (Siemens, Munich, Germany). All these data were measured by two independent and experienced neuroradiologists. The average of the two data was the final recorded linear length.

Safety Evaluation

NIHSS data were obtained before, immediately after, and 24 h after surgery by two independent and experienced neurologists. Blood creatinine was measured before surgery and 24 h after surgery. If postoperative NIHSS was higher than baseline, MRI was performed to confirm ischemic or hemorrhagic events. Acute kidney injury (AKI) was defined as an increase of ≥44.2 μmol/L and/or an increase of ≥30% of preoperative to postoperative blood creatinine levels within 48–72 h after the procedure.

RESULTS

A total of 33 patients were included in this study. Baseline data are shown in **Table 1**. Thirty-three cases of patients with an average age of (57.6 ± 7.1) years (male sex 27 cases) comprising nine cases of lesions located within the anterior circulation (**Figure 2**) and 24 cases within the posterior circulation (**Figure 3**) were identified. There were a total of 36 severe stenotic lesions, including 11 cases of Mori type A, 15 cases of type B, and seven cases of type C. The FD-OCT imaging catheter successfully detected 35/36 (97%) lesions except one case in which the FD-OCT catheter failed to navigate excessively tortuous vessels, related to an ophthalmic segment stenosis. All patients completed FD-OCT pullback 52/52 (100%) times in total, with an average of 1.58 ± 0.74 pullbacks per person. Pullback in the anterior circulation was performed 13 times, with an average of 1.44 times per person, among which the imaging quality was grade 2 six times and level 3 seven times. Pullback in the posterior circulation was performed 39 times, with an average

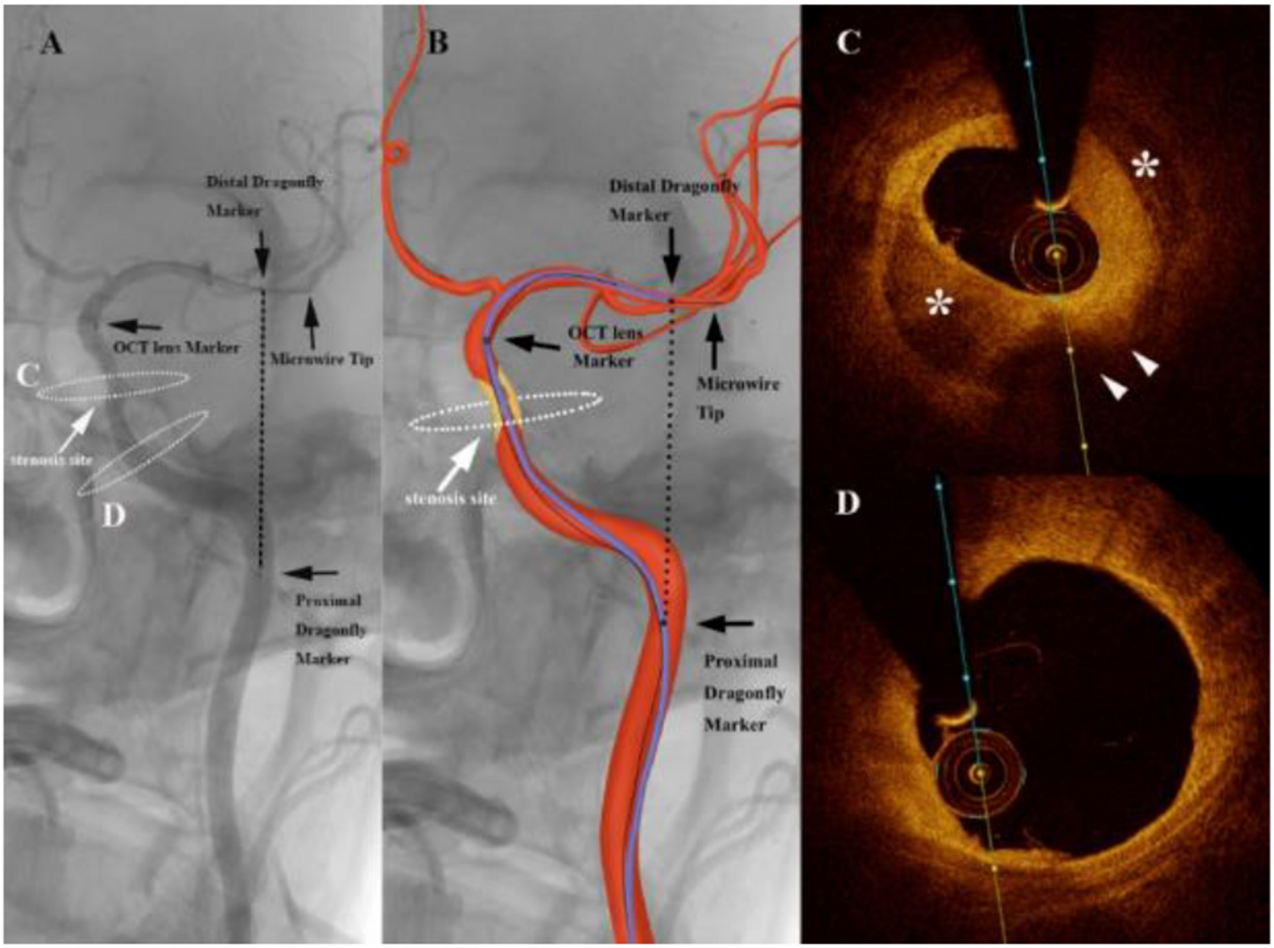


FIGURE 2 | Angiography of an intracranial atherosclerotic stenosis (ICAS) patient suffering from repeated weakness of the right upper limb with dual-antiplatelet therapy **(A)** showing a severe stenosis of the internal carotid artery (white arrows). The graphic of the imaging catheter and artery is overlaid in the middle panel **(B)**. The markers of the Dragonfly Duo imaging catheter and the optical coherence tomography (OCT) lens are noted in the left and middle panels (black arrows). The black dashed line represents the linear length between the first and third markers. White dashed ellipses on the left panel correspond to the cross section of the OCT acquisition. **(C)** Frequency-domain optical coherence tomography (FD-OCT) imaging demonstrated the atherosclerotic plaque (white arrowheads) with calcification (*), which imparted the severe stenosis. **(D)** 10 mm proximal to the cross section A, the artery wall was almost normal.

of 1.63 times per person, of which the imaging quality was grade 0 one time, grade 1 six times, grade 2 12 times, and grade 3 19 times. The tortuosity index was 0.74 ± 0.13 on average. The tortuosity index for the posterior circulation was significantly higher than that of anterior circulation (0.78 ± 0.12 vs. 0.65 ± 0.12, $p = 0.01$).

From femoral artery puncture to completion of OCT withdrawal, the average time was 36.7 ± 12.4 min. The average amount of contrast agent per patient was 57.8 ± 13.2 ml. NIHSS was consistent before and after procedure in all patients. The average serum creatinine before angiography and intervention was 65.6 ± 13.9 U/L, and the average serum creatinine afterward was 70.2 ± 17.8 U/L. The serum creatinine was significantly higher afterward in patients with a lesion in anterior circulation (**Table 2**; 80 ± 14.6 vs. 68.1 ± 9.0, $p = 0.006$), but no AKI was observed. Iatrogenic dissection occurred in two patients, but neither transcatheter nor medical intervention was needed in either patient. No death or other severe procedural complications were observed in 7 days post-procedure. All patients had the same post-procedural NIHSS compared with pre-procedure.

Image quality is shown in **Table 3**. In all 52 pullbacks, the image quality reached grade 3 26 times (50%), grade 2 18 times (34.6%), grade 1 six times (11.5%), and level 0 two times (3.8%). The grade 0 pullbacks occurred in the first two consecutive patients. Blood artifacts were observed in 27 pullbacks, which was the most common (51.9%), decentration artifacts in 13 pullbacks (25%), caliber artifacts in three pullbacks (5.8%), and rotational artifacts in 10 pullbacks (19.2%). Of the 33 patients, 27 underwent successful FD-OCT (81.8%), three were partially successful (9%), and three were unsuccessful (9%). For the intracranial internal carotid artery, eight cases were successful, and one case was a failure. For intracranial

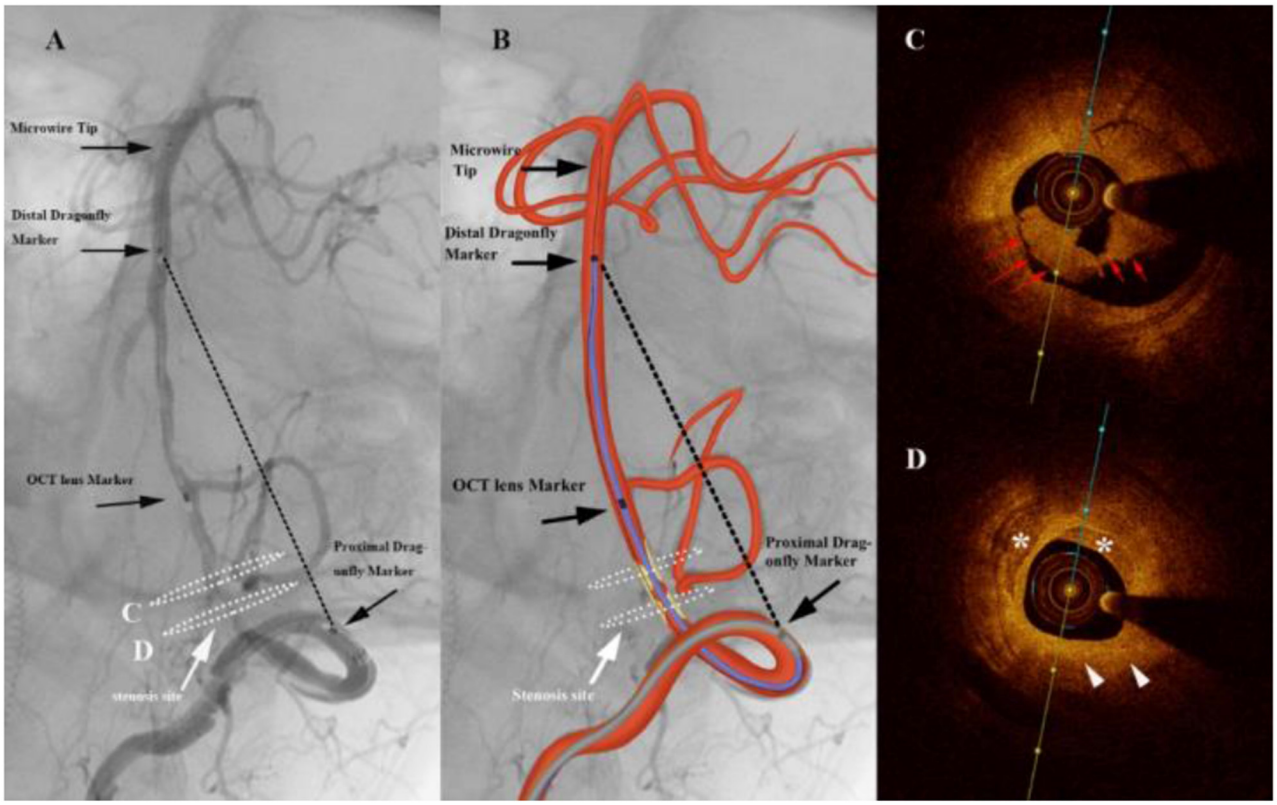


FIGURE 3 | Angiography of a patient complaining of dizziness and slurred speech for 5 months **(A)** shows a severe stenosis of the vertebral artery (white arrows). The graphic of the imaging catheter and artery is overlaid in the middle panel **(B)**. The markers of the Dragonfly Duo imaging catheter and the optical coherence tomography (OCT) lens are noted in the left and middle panels (black arrows). The black dashed line represents the linear length between the first and third markers. White dashed ellipses on the left panel correspond to the cross section of the OCT acquisition. **(C)** Frequency-domain optical coherence tomography (FD-OCT) imaging demonstrated intraluminal thrombosis (red arrows). **(D)** Atherosclerotic plaque (white arrowheads) with calcification (*) were found at the site of stenosis.

TABLE 2 | Procedural complications.

	ICA	V4	BA
Examination	9	19	5
Total complications	0	2 (10.5)	0
Death	0 (0.0)	0 (0.0)	0 (0.0)
Iatrogenic dissection	0 (0.0)	2 (10.5)	0 (0.0)
AKI	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)
Major stroke hemorrhages	0 (0.0)	0 (0.0)	0 (0.0)
Major non-stroke hemorrhages	0 (0.0)	0 (0.0)	0 (0.0)

Variables are presented as frequency (%). ICA, internal carotid artery; V4, intracranial vertebral artery; BA, basilar artery; AKI, acute kidney injury.

TABLE 3 | Image quality of optical coherence tomography.

Image quality	Total	ICA			V4 (%)	BA (%)
		C2~C3	C4	C6		
3	26 (50)	5 (62.5)	2 (66.7)	0 (0.0)	15 (51.7)	4 (40)
2	18 (34.6)	3 (37.5)	1 (33.7)	2 (100)	8 (27.6)	4 (40)
1	6 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (13.8)	2 (20)
0	2 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.9)	0 (0.0)

Variables are presented as frequency (%). ICA, internal carotid artery; C2, petrous segment; C3, lacerum segment; C4, cavernous segment; C6, ophthalmic segment; V4, vertebral artery V4 segment; BA, basilar artery.

vertebrobasilar artery (V4), 15 cases were successful, two cases were partially successful, and two cases were a failure per the established definitions. For the basilar artery (BA), four cases were successful, and one case was partially successful. No significant difference was found between the examination success rate of the posterior and anterior circulation (91.7 vs. 88.9%, $p =$ 1). The tortuosity indices of successful, partially successful, and unsuccessful groups were significantly different (**Table 4**; 0.715 ± 0.125 vs. 0.846 ± 0.067 vs. 0.890 ± 0.057, $p = 0.03$), but further multiple comparisons (Tukey's test) showed no significant difference between all three groups (i.e., successful, partially successful, and unsuccessful). No correlation was discovered with age, gender, underlying disease status, stenosis degree, or Mori classification.

TABLE 4 | Success and tortuosity index of OCT examination.

Variable	Successful	Partially successful	Failure
Lesion position			
ICA	8 (88.9)	0 (0.0)	1 (11.1)
V4	15 (78.9)	2 (10.5)	2 (10.5)
BA	4 (80)	1 (20)	0 (0.0)
Tortuosity index*#	0.715 ± 0.125	0.846 ± 0.067	0.889 ± 0.057

Tortuosity index is presented as mean ± SD, while categorical variables are presented as frequency (%). S, successful; PS, partially successful; F, failure.
**One-way ANOVA, p = 0.03.*
#Tukey's test for multiple comparisons: S–PS p = 0.185, F–S p = 0.056, and F–PS p = 0.893.

DISCUSSION

In this study, we performed FD-OCT in ICAS patients with standard non-occlusive technique in what is the largest reported cohort to date. The FD-OCT imaging catheter reached the distal end of the stenosis and completed at least one pullback in all cases. In 2014, Given et al. (15) reported FD-OCT images of Wingspan stent implantation for vertebrobasilar artery stenosis, and subsequently Gao et al. (14) employed FD-OCT to detect basilar artery dissection. Building on these case reports, we performed a safety study of FD-OCT evaluation for ICAS, suggesting feasibility for obtaining high-quality FD-OCT images.

Feasibility of Frequency-Domain Optical Coherence Tomography for Intracranial Arteries

In 2011, Mathews et al. (22) performed OCT scanning in the cavernous sinus segment and the petrous segment of internal carotid artery for the first time in the literature, which used time-domain OCT assembled in a laboratory rather than a commercial product. Although, a small number of cases were enrolled, the result suggested that OCT examination of intracranial arteries was feasible. OCT was then applied to the field of the treatment of intracranial aneurysms using flow diverters (23–25). These authors considered that there were two difficulties in OCT examination for intracranial arteries. Firstly, blood was difficult to clear completely. Secondly, anatomical tortuosity limited the placement of the OCT catheter.

As red blood cells and near-infrared light interact poorly, circulating blood must be completely cleared to obtain a high-quality image *via* current transcatheter interferometric technology. Initially, OCT was applied in coronary arteries by using a detachable balloon to arrest flow and flushing saline in order to replace blood completely (26). However, with the progress of imaging techniques, non-occlusive methods by continuous injection of contrast media to clear blood can also obtain high-quality images. The new generation of Dragonfly Duo OCT imaging catheters can achieve faster pullback speed and longer pullback distances than previously methods, which helps to reduce contrast agent volumes and improves rotational artifacts (27). In this study, the first two patients presented with intracranial vertebral artery severe stenosis. The 6F guiding catheter was placed in the distal end of V2 segment per routine. Although, the OCT catheter could successfully reach the predetermined position and complete the pullback, severe blood artifacts were observed due to poor blood clearance. In subsequent cases, the Navien distal intracranial catheter was used. Due to its flexibility, the distance between the catheter tip and the target lesion was minimized to enhance blood clearance, and the image quality was significantly improved. Unmistakably, technique contributed to the first scores being low, and a learning curve for OCT implementation was at play.

There was one failed case of tandem severe stenosis of cavernous sinus segment and petrous segment of ICA because tortuosity made the OCT imaging catheter unable to reach a stenosis located at the distal end of the cavernous sinus segment. We investigated the tortuosity index of the artery and found that the tortuosity index of ICA was significantly lower than that of the V4 and BA. Furthermore, a significant difference was observed in the tortuosity indexes among successful, partially successful, and unsuccessful groups. Although, the multiple comparisons did not show a difference between each group, this is likely due to the small number of patients in the series for Tukey's calculation. The overall result suggests the tortuosity index may quantifiably assess the tortuosity of intracranial arteries and might be a potential predictor of success of OCT scanning. Although, there is a 20-mm rapid exchange tip in the front of Dragonfly Duo catheter, the tapered design allows the catheter to pass through arteries more easily in its current iteration. Nevertheless, its initial design for detection of coronary disease does not inherently consider the anatomical features of intracranial arteries.

Imaging Technology

Yoshimura et al. (28) reported two failed cases due to early withdrawal of the imaging OCT catheter during non-occlusive technique in the carotid artery. To avoid this phenomenon, our strategy was to begin withdrawal as soon as the distal blood clearance was apparent. For some cases, when contrast agent could not pass through a severe stenosis, pullback was initiated 1–2 s after injection. The withdrawal of the Dragonfly Duo OCT imaging catheter in high-resolution mode takes 3 s, so the injection parameters are set at 3 ml/s with a total volume of 9 ml. In particularly, filling the Navien catheter with contrast media before injection could reduce blood interference and improve image quality significantly. The microwire and imaging catheter are appropriately retracted to release tension and maintain coaxial positioning after the OCT imaging catheter passes through the stenotic lesion, which can reduce the decentration artifacts and rotational artifacts.

Safety of Frequency-Domain Optical Coherence Tomography for Intracranial Artery

Most of the early OCT detection data for intracranial arteries were case reports, and no safety reports have been formally published. Reimers et al. (29) used a proximal balloon occlusion technique for OCT examination in seven patients undergoing

carotid artery stenting (CAS), and only one patient could not tolerate occlusion during the operation, although, they recovered completely after recanalization of blood flow. Yoshimura et al. (28) also applied proximal occlusion for OCT detection of 34 cases of carotid artery stenosis, with no perioperative complications reported.

In an OCT study before and after carotid artery stent implantation using non-occlusive technique by Setacci et al. (30), no complications were reported in all 25 patients. In our study, all patients were assessed under general anesthesia. A total of 52 OCT pullbacks were performed in 33 patients, with 9 ml of contrast agent used in each retraction. The serum creatinine level elevated mildly after operation, especially in the anterior circulation cases, but no AKI was observed. We adopted distal intracranial catheter as a carrier of the OCT imaging catheter to obtain better blood clearance. As the distance navigated by the catheter within the blood vessel increases, the likelihood of vascular injury increases. Two cases of V4 segment iatrogenic dissection were confirmed by DSA, and both were caused by the distal intracranial catheter. Fortunately, blood flow was not impeded.

FD-OCT has been a powerful tool in the treatment of atherosclerosis of coronary artery, assessing the plaque characterization and guiding the stent implantation (31, 32). With ultra-high resolution, it can also help to study the plaque morphology and composition in ICAS, such as vasa vasorum (33) and neovascularization (34), which have potential contribution to recurrent ischemic events beyond the mere degree of stenosis. Further, large prospective studies and cost–benefit analyses are needed.

Limitations

This study is based on a single-center retrospective data, and while the sample size is the largest to date, it is still modest. Regarding the complications of OCT examination, there is no established control group. Lastly, there were more posterior circulation than anterior circulation cases, which may reflect selection bias.

CONCLUSION

This study suggests the feasibility and safety of FD-OCT for ICAS using a non-occlusive technique. Diagnostic images are obtained in the majority of cases. Further, large prospective studies and cost–benefit analyses are needed.

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 Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BY initiated the study. YF has been involved in the study design and drafted this manuscript. YM, YW, JC, LL, PG, YC, AD, and LJ have been involved in the conception and study design. JD and BZ has made important statistical contributions. All authors provided feedback on drafts of this paper, read, and approved the final manuscript.

FUNDING

This work was supported by the National Key Research and Development Project (2016YFC1301703) and the National Scientific and Technologic Project (D161100003816002).

REFERENCES

1. Wong LK. Global burden of intracranial atherosclerosis. *Int J Stroke.* (2006) 1:158–9. doi: 10.1111/j.1747-4949.2006.00045.x
2. White H, Boden-Albala B, Wang C, Elkind MS, Rundek T, Wright CB, et al. Ischemic stroke subtype incidence among whites, blacks, and hispanics: the Northern Manhattan Study. *Circulation.* (2005) 111:1327–31. doi: 10.1161/01.CIR.0000157736.19739.D0
3. de Havenon A, Mossa-Basha M, Shah L, Kim SE, Park M, Parker D, et al. High-resolution vessel wall MRI for the evaluation of intracranial atherosclerotic disease. *Neuroradiology.* (2017) 59:1193–202. doi: 10.1007/s00234-017-1925-9
4. de Donato G, Pasqui E, Alba G, Giannace G, Panzano C, Cappelli A, et al. Clinical considerations and recommendations for OCT-guided carotid artery stenting. *Expert Rev Cardiovasc Ther.* (2020) 18:219–29. doi: 10.1080/14779072.2020.1756777
5. Ibrahimi P, Jashari F, Nicoll R, Bajraktari G, Wester P, Henein MY. Coronary and carotid atherosclerosis: how useful is the imaging? *Atherosclerosis.* (2013) 231:323–33. doi: 10.1016/j.atherosclerosis.2013.09.035
6. Prati F, Zimarino M, Stabile E, Pizzicannella G, Fouad T, Rabozzi R, et al. Does optical coherence tomography identify arterial healing after stenting? An *in vivo* comparison with histology, in a rabbit carotid model. *Heart.* (2008) 94:217–21. doi: 10.1136/hrt.2006.112482
7. Ali ZA, Karimi Galougahi K, Maehara A, Shlofmitz RA, Ben-Yehuda O, Mintz GS, et al. Intracoronary optical coherence tomography 2018: current status and future directions. *JACC Cardiovasc Interv.* (2017) 10:2473–87. doi: 10.1016/j.jcin.2017.09.042
8. Yoshimura S, Kawasaki M, Yamada K, Hattori A, Nishigaki K, Minatoguchi S, et al. OCT of human carotid arterial plaques. *JACC Cardiovasc Imaging.* (2011) 4:432–6. doi: 10.1016/j.jcmg.2011.01.013
9. Jones MR, Attizzani GF, Given CA II, Brooks WH, Costa MA, Bezerra HG. Intravascular frequency-domain optical coherence tomography assessment of atherosclerosis and stent-vessel interactions in human carotid arteries. *AJNR Am J Neuroradiol.* (2012) 33:1494–501. doi: 10.3174/ajnr.A3016
10. Dohad S, Zhu A, Krishnan S, Wang F, Wang S, Cox J, et al. Optical coherence tomography guided carotid artery stent procedure: technique and potential applications. *Catheter Cardiovasc Interv.* (2018) 91:521–30. doi: 10.1002/ccd.27344
11. Nerla R, Castriota F, Micari A, Sbarzaglia P, Secco GG, Ruffino MA, et al. Carotid artery stenting with a new-generation double-mesh stent in three high-volume Italian centres: clinical results of a multidisciplinary approach. *EuroIntervention.* (2016) 12:e677–83. doi: 10.4244/EIJV12I5A109

12. Wicks RT, Huang Y, Zhang K, Zhao M, Tyler BM, Suk I, et al. Extravascular optical coherence tomography: evaluation of carotid atherosclerosis and pravastatin therapy. *Stroke.* (2014) 45:1123–30. doi: 10.1161/STROKEAHA.113.002970
13. Alotaibi NM, Sarzetto F, Ramjist J, Yang VXD. Carotid artery stenting with optical coherence tomography. *Neurology.* (2018) 90:384–5. doi: 10.1212/WNL.0000000000005003
14. Gao P, Gui L, Yang B, Krings T, Jiao L. Optical coherence tomography of spontaneous basilar artery dissection in a patient with acute ischemic stroke. *Front Neurol.* (2018) 9:858. doi: 10.3389/fneur.2018.00858
15. Given CA II, Ramsey CN III, Attizzani GF, Jones MR, Brooks WH, Bezerra HG, et al. Optical coherence tomography of the intracranial vasculature and Wingspan stent in a patient. *BMJ Case Rep.* (2014) 2014:bcr2014011114. doi: 10.1136/bcr-2014-011114
16. Safian RD. Is optical coherence tomography a coherent strategy for carotid artery stenting? *Catheter Cardiovasc Interv.* (2018) 91:531–2. doi: 10.1002/ccd.27533
17. Harada K, Oshikata S, Kajihara M. Optical coherence tomography evaluation of tissue prolapse after carotid artery stenting using closed cell design stents for unstable plaque. *J Neurointerv Surg.* (2018) 10:229–34. doi: 10.1136/neurintsurg-2017-013004
18. Prabhudesai V, Phelan C, Yang Y, Wang RK, Cowling MG. The potential role of optical coherence tomography in the evaluation of vulnerable carotid atheromatous plaques: a pilot study. *Cardiovasc Intervent Radiol.* (2006) 29:1039–45. doi: 10.1007/s00270-005-0176-z
19. Blackham KA, Kim BS, Jung RS, Badve C, Manjila S, Sila CA, et al. *In vivo* characterization of carotid neointimal hyperplasia by use of optical coherence tomography: before and after cutting balloon angioplasty. *J Neuroimaging.* (2015) 25:1044–6. doi: 10.1111/jon.12223
20. Samuels OB, Joseph GJ, Lynn MJ, Smith HA, Chimowitz MI. A standardized method for measuring intracranial arterial stenosis. *AJNR Am J Neuroradiol.* (2000) 21:643–6.
21. Lehtinen T, Nammas W, Airaksinen JK, Karjalainen PP. Feasibility and safety of frequency-domain optical coherence tomography for coronary artery evaluation: a single-center study. *Int J Cardiovasc Imaging.* (2013) 29:997–1005. doi: 10.1007/s10554-013-0196-8
22. Mathews MS, Su J, Heidari E, Levy EI, Linskey ME, Chen Z. Neuroendovascular optical coherence tomography imaging and histological analysis. *Neurosurgery.* (2011) 69:430–9. doi: 10.1227/NEU.0b013e318212bcb4
23. Lopes DK, Johnson AK. Evaluation of cerebral artery perforators and the pipeline embolization device using optical coherence tomography. *J Neurointerv Surg.* (2012) 4:291–4. doi: 10.1136/neurintsurg-2011-010102
24. Matsuda Y, Chung J, Lopes DK. Analysis of neointima development in flow diverters using optical coherence tomography imaging. *J Neurointerv Surg.* (2018) 10:162–7. doi: 10.1136/neurintsurg-2016-012969
25. Umemoto T, Pacchioni A, Nikas D, Reimers B. Recent developments of imaging modalities of carotid artery stenting. *J Cardiovasc Surg.* (2017) 58:25–34. doi: 10.23736/S0021-9509.16.09813-X
26. Regar E, Schaar JA, Mont E, Virmani R, Serruys PW. Optical coherence tomography. *Cardiovasc Radiat Med.* (2003) 4:198–204. doi: 10.1016/j.carrad.2003.12.003
27. Bezerra HG, Tahara S, Parikh SA, Costa MA. "Old" problems revisited; imaging the coronary in high resolution. *EuroIntervention.* (2009) 5:523–5. doi: 10.4244/EIJV5I5A84
28. Yoshimura S, Kawasaki M, Yamada K, Enomoto Y, Egashira Y, Hattori A, et al. Visualization of internal carotid artery atherosclerotic plaques in symptomatic and asymptomatic patients: a comparison of optical coherence tomography and intravascular ultrasound. *AJNR Am J Neuroradiol.* (2012) 33:308–13. doi: 10.3174/ajnr.A2740
29. Reimers B, Nikas D, Stabile E, Favero L, Sacca S, Cremonesi A, et al. Preliminary experience with optical coherence tomography imaging to evaluate carotid artery stents: safety, feasibility and techniques. *EuroIntervention.* (2011) 7:98–105. doi: 10.4244/EIJV7I1A17
30. Setacci C, de Donato G, Setacci F, Galzerano G, Sirignano P, Cappelli A, et al. Safety and feasibility of intravascular optical coherence tomography using a nonocclusive technique to evaluate carotid plaques before and after stent deployment. *J Endovasc Ther.* (2012) 19:303–11. doi: 10.1583/12-3871R.1
31. Ali ZA, Maehara A, Genereux P, Shlofmitz RA, Fabbiocchi F, Nazif TM, et al. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. *Lancet.* (2016) 388:2618–28. doi: 10.1016/S0140-6736(16)31922-5
32. Ali ZA, Karimi Galougahi K, Maehara A, Shlofmitz RA, Fabbiocchi F, Guagliumi G, et al. Outcomes of optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation: one-year results from the ILUMIEN III: OPTIMIZE PCI trial. *EuroIntervention.* (2021) 16:1085–91. doi: 10.4244/EIJ-D-20-00498
33. Li L, Dmytriw AA, Krings T, Feng Y, Jiao L. Visualization of the human intracranial vasa vasorum *in vivo* using optical coherence tomography. *JAMA Neurol.* (2020) 77:903–5. doi: 10.1001/jamaneurol.2020.0546
34. Feng Y, Dmytriw AA, Yang B, Jiao L. Neovascularization in human intracranial atherosclerotic in-stent restenosis. *Diagnostics.* (2021) 11:322. doi: 10.3390/diagnostics11020322

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.

frontiers in Neurology

MINI REVIEW
published: 27 July 2021
doi: 10.3389/fneur.2021.692208

Drug-Coated Balloons for the Treatment of Symptomatic Intracranial High-Grade Stenosis: A Review of the Current Rationale

Philipp Gruber[1†], Samarth Singh[2†], Lukas Andereggen[3,4], Jatta Berberat[1] and Luca Remonda[1,4]*

[1] Department of Neuroradiology, Kantonsspital Aarau, Aarau, Switzerland, [2] Department of Neurology, Norvic International Hospital, Kathmandu, Nepal, [3] Department of Neurosurgery, Kantonsspital Aarau, Aarau, Switzerland, [4] Faculty of Medicine, University of Bern, Bern, Switzerland

Symptomatic intracranial atherosclerotic disease (sICAD) remains a challenging disorder in the neurovascular field. Despite best medical treatment, the recurrence rate for stroke remains high in patients with intracranial high-grade stenosis (>70–99%). Furthermore, two large randomized trials (SAMMPRIS and VISSIT) failed to prove the efficacy of percutaneous transluminal angioplasty and stenting in patients with sICAD. Drug-coated balloon percutaneous transluminal angioplasty (DCB-PTA) represents an alternative treatment modality with therapeutic benefits for interventional cardiology. However, there are very few articles in the existing literature that relate to the use of DCB-PTA in sICAD patients. Here, we aimed to review the rationale underlying the use of DCB-PTA in sICAD patients and summarize recent developments in the neurovascular field.

Keywords: stroke, intracranial stenosis, intracranial atherosclerotic disease, endovascular procedures, angioplasty, drug-coated balloon

OPEN ACCESS

Edited by:
Liqun Jiao,
Capital Medical University, China

Reviewed by:
Waldo Rigoberto Guerrero,
University of South Florida, United States
Adam Kobayashi,
Cardinal Stefan Wyszyński University, Poland

***Correspondence:**
Philipp Gruber
philipp.gruber@ksa.ch

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *07 April 2021*
Accepted: *21 June 2021*
Published: *27 July 2021*

Citation:
Gruber P, Singh S, Andereggen L, Berberat J and Remonda L (2021) Drug-Coated Balloons for the Treatment of Symptomatic Intracranial High-Grade Stenosis: A Review of the Current Rationale. Front. Neurol. 12:692208. doi: 10.3389/fneur.2021.692208

INTRODUCTION

Intracranial atherosclerotic disease (ICAD) is a common global disease. Symptomatic ICAD (sICAD) is known to cause 10% of all transient ischemic attacks and strokes worldwide (1, 2). The treatment of sICAD remains challenging given that the recurrence rate of strokes can reach up to 38.2% of patients despite best medical treatment (BMT) (3). The risk of stroke recurrence is particularly high in patients with hemodynamically relevant stenosis or unstable atherosclerotic plaques (3). Current guidelines recommend BMT, a combination of anti-platelet therapy and vascular risk factor control, as first-line therapy (4, 5), with endovascular therapies considered as rescue therapies (4, 5).

The "Warfarin-Aspirin Symptomatic Intracranial Disease" (WASID) trial demonstrated that oral anticoagulation (warfarin) was not superior to aspirin as a single therapy for ICAD patients (6). Subsequently, the findings of the "Clopidogrel plus aspirin vs. aspirin alone for reducing embolization in patients with acute symptomatic cerebral or carotid artery stenosis" (CLAIR) trial and the "Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis" (CARESS) trial provided the rationale behind the use of short-term dual antiplatelet therapy for patients with ICAD (7, 8).

The successful use of percutaneous transluminal angioplasty (PTA) to treat symptomatic, high-grade, basilar stenosis was first reported in 1980 (9). In the early 2000s, the publication

of numerous case series clearly demonstrated the feasibility of applying PTA as a single therapy, or in combination with stenting (PTAS), for patients with ICAD (10, 11). With regards to stroke and death rates, the outcomes of PTA tend to vary widely (4–40%) within 30 days of treatment; in addition, 24–50% of patients undergoing PTA developed restenosis (12). Furthermore, dissection and immediate re-coiling can occur during the PTA technique. The results published by the WASID trial were not encouraging (6); consequently, the use of PTAS was strongly encouraged. The single-arm "Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries" (SSYLVIA) trial subsequently provided convincing data to support the use of a stent system to treat symptomatic intra- and extracranial stenosis (13). In addition, two different cohort studies reported promising results for the use of a novel self-expanding Wingspan stent system (14, 15). Therefore, the "Stenting vs. Aggressive Medical Management for Intracranial Arterial Stenosis" (SAMMPRIS) trial was initiated to specifically compare aggressive medical treatment (AMM) with PTAS using the Gateway Balloon PTA system combined with the Wingspan stent (Stryker, Kalamazoo, USA) (16). The SAMMPRIS trial failed to demonstrate any superiority of the PTAS treatment in comparison with AMM due to the discovery of a significantly higher risk of early ischemia within 30 days in the PTAS group (14.7%) compared with an AMM only group (5.8%) (16). Furthermore, the PTAS group was dominated by peri-interventional complications. Shortly thereafter, the SAMMPRIS data were confirmed by the "Vitesse Intracranial Stent Study for Ischemic Stroke Therapy" (VISSIT) trial, which compared BMT with a balloon-expandable stent system and found that the two techniques were similar with regards to outcome (17). The long-term results provided by the SAMMPRIS trial highlighted the early benefit of AMM compared with PTAS in patients with high-grade ICAD; this effect persisted over an extended median follow-up period of 32.4 months (18). As a consequence, there was a significant decline in the use of endovascular treatment to treat patients with sICAD. Nevertheless, there is an ongoing debate relating to the use of endovascular treatment for patients with sICAD (19, 20).

Short-term results derived from a Chinese multicenter registry study ($n = 300$) revealed a stroke, bleeding, and death rate of only 4.5% of patients (21). The on-label, multicenter "Wingspan Stent System Post Market Surveillance" (WEAVE) trial demonstrated that the peri-interventional complication rate of PTAS in ICAD patients decreased to only 2.6% in centers with experienced interventionalists and rigorous patient selection protocol (22). Furthermore, the longer-term (1-year) "Wingspan One-year Vascular Events and Neurologic Outcomes" (WOVEN) trial reported sustained benefit for the PTAS group (23). The "China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis" (CASSISS) trial, involving the Wingspan stent system, presented their preliminary results at the 14th World Federation of Interventional Radiology and Therapy: stroke or death only occurred in 2% of patients (24, 25). In addition, other self-expanding stent systems such as the Enterprise (Codman, Raynham, USA) or Neuroform stents (Stryker Neurovascular, Fremont, USA) showed in several series promising results in the treatment of symptomatic ICAD patients (26, 27). The introduction of the first-balloon-then-stent technique with the novel self-expanding Credo stent (Acandis, Pforzheim, Germany) together with the NeuroSpeed balloon-catheter system (Acandis, Pforzheim, Germany) may further reduce the perinterventional complication rate (28). In a cohort of 76 ICAD patients treated with another new-generation, self-expanding stent system [Acclino stent/NeuroSpeed balloon catheter system (Acandis, Pforzheim, Germany)], feasibility and safety were promising with a periprocedural stroke rate of 6.5% (29). Thus, novel stent technologies as well as new procedural techniques may further reduce the overall morbidity and mortality in ICAD stenting in the future.

RESTENOSIS: A COMMON LONG-TERM SEQUELA IN ENDOVASCULAR THERAPY

In addition to peri-procedural complications, restenosis is frequently observed as a long-term sequela, both in PTA and PTAS. In PTA, restenosis rate within 6 months was reported in 5–30% of cases (30). A similar proportion of patients (25%) experienced in-stent-restenosis following PTAS (31). The precise mechanisms underlying these findings have yet to be elucidated; however, restenosis is mainly caused by neointimal hyperplasia (NIH), a condition that is induced by mechanical stress and endothelial lesions during PTA and PTAS (32). There are several risk factors for NIH, including age, diabetes mellitus, lesion location, and a history of active smoking (33). NIH is a frequent long-term problem associated with peripheral PTA and interventional cardiology. Consequently, drug-eluted stents (DES) and drug-coated balloons (DCB) were introduced to overcome this issue. In addition, a range of drugs are now available to prevent NIH. Mitotic inhibitors (e.g., paclitaxel) or immuno-modulators (e.g., sirolimus) are commonly used for DES and DCB-PTA coating. DES and DCB-PTA are frequently used in interventional cardiology and have been found to be both safe and effective (34).

Publications relating to the use of DCB-PTA and DES in patients with ICAD are scarce. With the introduction of stent-assisted intracranial stenosis treatment, the use of DES has been shown to be both safe and efficient (35, 36). Similarly, studies have shown that the use of coronary DES for sICAD is feasible and safe. However, a high rate of technical failure has been reported due to DES stiffness. An improved stent deployment rate was achieved using a more flexible DES (37). A study of sICAD patients treated by DCB and the deployment of a bare-metal stent revealed encouraging results with a low rate of restenosis rate (3%) (38).

DRUG-COATED BALLOONS IN THE TREATMENT OF SYMPTOMATIC ICAD

DCB-PTA may represent a promising alternative to PTA or PTAS for the treatment of patients with ICAD (39). DCB-PTA has the potential to minimize peri-interventional and long-term complication rates in the endovascular treatment. In the

TABLE 1 | An overview of existing drug-coated balloon percutaneous transluminal angioplasty (DCB-PTA) studies in patients with symptomatic high-grade intracranial stenosis.

Study group	No. of patients*	DCB type	Follow-up period in months	Degree of pretreatment stenosis (%)	DCB-PTA only*	Degree of post-treatment stenosis (%)	Complications No. (%)**	Restenosis No. (%)**	Symptomatic restenosis No. (%)**
Gruber et al. (42)	8†	Neuro Elutax SV	9.5	80	Yes	37.5%	0	1 (13%)	0
Han et al. (43)	30	Sequent Please	9.8	82%	No	20%	2 (3.2)	1 (3.2)	0
Gruber et al. (44)	10	Sequent Please NEO	3	78%	Yes	50%	0	0	0
Zhang et al. (45)	42††	Sequent Please	6	90%	No	10%	4	2 (4.8%)	1 (2.4%)
Wang et al. (46)	35	Sequent Please	20.9	76.6%	No	32.4%	4 (11.4%)	3 (8.3%)	0
Remonda et al. (47)	33	Neuro Elutax SV/Sequent Please NEO	9	80%	Yes	50%	3 (9%)	5 (15%)	4 (12%)

**without pre-dilation using another PTA balloon system (Gateway balloon); **No, number; † comparative study with a total number of 19 patients; †† comparative study with a total number of 115 patients.*

tortuous neurovascular anatomy, DCB-PTA is more flexible due to a softer distal PTA tip compared with DCS, thus enabling the operator to reach more distant lesions. Endovascular DCB-PTA procedures do not leave residual foreign bodies, thus exerting a positive impact on the possibility of subsequent adverse material-tissue reactions and local flow dynamics (40). In contrast to DES, DCB-PTA offers a uniform anti-proliferative drug coverage of the diseased vessel lumen. Furthermore, a shorter duration of recommended dual anti-platelet therapy (DAPT) might be reasonable for DCB-PTA given the lower risk of delayed endothelialization and subsequent thrombosis when compared with DES (41).

Since 2018, various retrospective and comparative cohort and single studies of DCB-PTA for the treatment of sICAD patients have been published (42–47) (**Table 1**). These studies featured a range of different DCB-PTA systems, including the Neuro Elutax SV (Aachen Resonance, Aachen, Germany), the Sequent Please (B Braun, Melsungen, Germany), and the Sequent Please NEO (B Braun). All of these DCBs were coated with paclitaxel, a highly lipophilic mitotic inhibitor. These studies also described a range of different DCB-PTA procedures. Three ($n = 6$) of these studies reported the use of only submaximal angioplasty using a DCB-PTA (42, 44, 47). The other three studies pre-dilated the target lesion using a non-coated PTA balloon (Gateway balloon) immediately followed by DCB-PTA (Sequent Please) (43, 45, 46). When comparing the final post-procedural degree of stenosis, the DCB-PTA only group revealed a higher degree of residual stenosis (37.5–50%) compared with the combined PTA/DCB-PTA group (10–32%). However, there is a lack of systematic data that could demonstrate which method is superior with regards to short- and longer-term outcome. One advantage of the DCB-PTA only approach over the combined approach is that the numbers of intracranial maneuvers can be reduced, whereas the combined approach affords at least one additional step (the exchange of PTA to a DCB-PTA).

Further analysis showed that the mean follow-up period was variable and ranged from 3 to 21 months, while follow-up was heterogeneously defined. Two factors that were common to all of these DCB-PTA studies were an overall low complication rate and promising results with regards to symptomatic and asymptomatic restenosis rates.

In their series of sICAD patients treated with either Sequent Please NEO alone ($n = 10$) or Neuro Elutax SV and Sequent Please NEO ($n = 33$), Gruber et al. reported promising short- (a median of 3 months) and mid-term results (a median of 9 months) with only few symptomatic cases of restenosis (12%) along with low rates of intracranial complications (6%) (44, 47). Another study of sICAD patients ($n = 30$), treated with routine PTA followed by additional DCB-PTA, reported similar results with regards to restenosis and complication rates (43). A recent Chinese study ($n = 35$), using the Sequent Please DCB-PTA procedure, reported low complications and a low recurrence rate (stenosis >50%) (45).

Two retrospective comparative studies of DCB-PTA and PTAS provided further support to the findings of the mono-cohort studies (45, 46). A small, single-center, retrospective study ($n = 19$) comparing DCB-PTA and PTAS using the Wingspan Stent system demonstrated a lower asymptomatic and symptomatic restenosis rate compared with the PTAS group (41) although there was no difference between the two techniques with regards to complication rates. In a recently published Chinese study ($n = 115$), the restenosis rate was significantly lower in the DCB-PTA group than in a PTAS group (45). However, there were no differences between the two groups with regards to safety and the recurrence of stroke (45). Overall, the technical success rate was reported to be high, although in

one study, DCB-PTA could not be advanced over the lesion due to difficult local anatomy (42); two other studies reported few bail-out maneuvers with PTAS (43, 46). The most common periprocedural complication was ischemic events.

In summary, all of these studies demonstrated promising results for symptomatic intracranial high-grade stenosis. However, there is a lack of prospective data with regards to long-term results.

FUTURE DIRECTION AND CONCLUDING REMARKS

It is clear that DCB-PTA offers an alternative treatment option for patients with sICAD compared with BMT and the other endovascular procedures that are used at present. Recent studies have demonstrated encouraging results regarding the use of DCB-PTA, with low complication and restenosis rates. However, future studies should address several key questions. For example, is submaximal DCB-PTA alone superior to the combination of PTA followed by DCB-PTA? Is paclitaxel the appropriate choice for drug coating or are other coating strategies more beneficial for neurovascular applications? Furthermore, we need to be able to identify the ICAD patients for whom DCB-PTA would be the most suitable treatment option. Randomized trials may shed light on whether DCB-PTA is superior to BMT or PTAS in patients with sICAD.

In conclusion, DCB-PTA is a feasible procedure for the treatment of patients with sICAD and represents a promising treatment modality for the future treatment of ICAD. However, further prospective data are now needed to validate the precise role of DCB-PTA in sICAD.

AUTHOR CONTRIBUTIONS

PG helped to conceive and design this research, acquired, analyzed, interpreted the data, and wrote the article. SS helped to conceive and design the research and revised the article for important intellectual content. JB and LA revised the article for important intellectual content. LR helped to conceive and design this research, revised the article for important intellectual content, and approved the final version of the article for publication. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Wong LK. Global burden of intracranial atherosclerosis. *Int J Stroke.* (2006) 1:158–9. doi: 10.1111/j.1747-4949.2006.00045.x
2. Arenillas JF. Intracranial atherosclerosis: current concepts. *Stroke.* (2011) 42:20–3. doi: 10.1161/STROKEAHA.110.597278
3. Mazighi M, Tanasescu R, Ducrocq X, Vicaut E, Bracard S, Houdart E, et al. Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. *Neurology.* (2006) 66:1187–91. doi: 10.1212/01.wnl.0000208404.94585.b2
4. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K. 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.* (2010) 49:e46–e110. doi: 10.1161/STR.0000000000000158
5. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2014) 45:2160–236. doi: 10.1161/STR.0000000000000024
6. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* (2005) 352:1305–16. doi: 10.1056/NEJMoa043033
7. Wong KS, Chen C, Fu J, Chang HM, Suwanwela NC, Huang YN, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. *Lancet Neurol.* (2010) 9:489–97. doi: 10.1016/S1474-4422(10)70060-0
8. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation.* (2005) 111:2233–40. doi: 10.1161/01.CIR.0000163561.90680.1C
9. Sundt TM, Smith HC, Campbell JK, Vlietstra RE, Cucchiara RF, Stanson AW. Transluminal angioplasty for basilar artery stenosis. *Mayo Clin Proc.* (1980) 55:673–80.
10. Mazighi M, Yadav JS, Abou-Chebl A. Durability of endovascular therapy for symptomatic intracranial atherosclerosis. *Stroke.* (2008) 39:1766–9. doi: 10.1161/STROKEAHA.107.500587
11. Qureshi AI, Hussein HM, El-Gengaihy A, Abdelmoula M, K Suri MF. Concurrent comparison of outcomes of primary angioplasty and of stent placement in high-risk patients with symptomatic intracranial stenosis. *Neurosurgery.* (2008) 62:1053–60. doi: 10.1227/01.neu.0000325867.06764.3a
12. Marks MP, Wojak JC, Al-Ali F, Jayaraman M, Marcellus ML, Connors JJ, et al. Angioplasty for symptomatic intracranial stenosis: clinical outcome. *Stroke.* (2006) 37:1016–20. doi: 10.1161/01.STR.0000206142.03677.c2
13. SSYLVIA Study Investigators. Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA): study results. *Stroke.* (2004) 35:1388–92. doi: 10.1161/01.STR.0000128708.86762.d6
14. Bose A, Hartmann M, Henkes H, Liu HM, Teng MM, Szikora I, et al. A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses: the Wingspan study. *Stroke.* (2007) 38:1531–7. doi: 10.1161/STROKEAHA.106.477711
15. Fiorella D, Levy EI, Turk AS, Albuquerque FC, Niemann DB, Aagaard-Kienitz B, et al. US multicenter experience with the wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. *Stroke.* (2007) 38:881–7. doi: 10.1161/01.STR.0000257963.65728.e8
16. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med.* (2011) 365:993–1003. doi: 10.1056/NEJMoa1105335
17. 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
18. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. 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
19. Zaidat OO, Castonguay AC, Nguyen TN, Becker KJ, Derdeyn CP, Nelson PK, et al. Impact of SAMMPRIS on the future of intracranial atherosclerotic disease management: polling results from the ICAD symposium at the

International Stroke Conference. *J Neurointerv Surg.* (2014) 6:225–30. doi: 10.1136/neurintsurg-2013-010667
20. Turan TN, Cotsonis G, Lynn MJ, Wooley RH, Swanson S, Williams JE, et al. Intracranial stenosis: impact of randomized trials on treatment preferences of US neurologists and neurointerventionists. *Cerebrovasc Dis.* (2014) 37:203–11. doi: 10.1159/000358120
21. Miao Z, Zhang Y, Shuai J, Jiang C, Zhu Q, Chen K, et al. Thirty-day outcome of a multicenter registry study of stenting for symptomatic intracranial artery stenosis in China. *Stroke.* (2015) 46:2822–9. doi: 10.1161/STROKEAHA.115.010549
22. Alexander MJ, Zauner A, Chaloupka JC, Baxter B, Callison RC, Gupta R, et al. WAEVE trial: final results in 152 on-label patients. *Stroke.* (2019) 50:889–94. doi: 10.1161/STROKEAHA.118.023996
23. Alexander MJ, Zauner A, Gupta R, Alshekhlee A, Fraser JF, Toth G, et al. The WOVEN trail: Wingspan one-year vascular events and neurologic outcomes. *J Neurointerv Surg.* (2021) 13:307–10. doi: 10.1136/neurintsurg-2020-016208
24. Gao P, Zhao Z, Wang D, Wu J, Cai Y, Li T, et al. China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): a new, prospective, multicenter, randomized controlled trial in China. *Interv Neuroradiol.* (2015) 21:196–204. doi: 10.1177/1591019915581778
25. Wang Y, Meng R, Liu G, Cao C, Chen F, Jin K, et al. Intracranial atherosclerotic disease. *Neurobiol Dis.* (2019) 124:118–32. doi: 10.1016/j.nbd.2018.11.008
26. Sun B, Xu C, Wu P, Li M, Xu S, Wang C, et al. Intracranial angioplasty with Enterprise stent for intracranial atherosclerotic stenosis: a single-center experience and a systematic review. *Biomed Res Int.* (2021) 2021:6645500. doi: 10.1155/2021/6645500
27. Zhou K, Cao Y, He X-H, Qiu Z-M, Liu S, Gong Z-L, et al. A comparison of safety and effectiveness between Wingspan and Neuroform stents in patients with middle cerebral artery stenosis. *Front Neurol.* (2021) 12:527541. doi: 10.3389/fneur.2021.527541
28. Möhlenbruch MA, Pfaff J, Herweh J, Bösel J, Rizos T, Nagel S, et al. One-pass endovascular treatment of intracranial atherosclerotic stenosis with a novel PTA balloon and self-expanding microstent. *Neuroradiology.* (2016) 58:893–9. doi: 10.1007/s00234-016-1716-8
29. Meyer L, Leischner H, Thomalla G, Krause LU, Lowens S, Rothaupt J, et al. Stenting with Acclino (flex) for symptomatic intracranial stenosis as secondary stroke prevention. *J Neurointerv Surg.* (2020) 12:1127–31. doi: 10.1136/neurintsurg-2019-015744
30. Wojak JC, Dunlap DC, Hargrave KR, DeAlvare LA, Culbertson HS, Connors JJ. Intracranial angioplasty and stenting: long-term results from a single center. *AJNR Am J Neuroradiol.* (2006) 27:1882–292.
31. Jin M, Fu X, Wei Y, Du B, Xu XT, Jiang WJ. Higher risk of recurrent ischemic events in patients with intracranial in-stent restenosis. *Stroke.* (2013) 44:2900–4. doi: 10.1161/STROKEAHA.113.001824
32. Papafaklis MI, Chatzizisis YS, Naka KK, Giannoglou GD, Michalis LK. Drug-eluting stent restenosis: effect of drug type, release kinetics, hemodynamics and coating strategy. *Pharmacol Ther.* (2012) 134:43–53. doi: 10.1016/j.pharmthera.2011.12.006
33. Xiong Y, Zhou Z, Lin H, Lin M, Liu J, Niu G, et al. The safety and long-term outcomes of angioplasty and stenting in symptomatic intracranial atherosclerotic stenosis. *Int J Cardiol.* (2015) 179:24. doi: 10.1016/j.ijcard.2014.10.081
34. Jackson D, Tong D, Layland J. A review of the coronary applications of the drug coated balloon. *Int J Cardiol.* (2017) 226:77–86. doi: 10.1016/j.ijcard.2016.09.045
35. Gupta R, Al-Ali F, Thomas AJ, Horowitz MB, Barrow T, Vora NA, et al. Safety, feasibility, and short-term follow-up of drug-eluting stent placement in the intracranial and extracranial circulation. *Stroke.* (2006) 37:2562–6. doi: 10.1161/01.STR.0000242481.38262.7b
36. Abou-Chebl A, Bashir Q, Yadav JS. Drug-eluting stents for the treatment of intracranial atherosclerosis: initial experience and midterm angiographic follow-up. *Stroke.* (2005) 36:165–8. doi: 10.1161/01.STR.0000190893.74268.fd
37. Kurre W, Aguilar-Perez M, Fischer S, Arnold G, Schmid E, Bazner H, et al. Solving the issue of restenosis after stenting of intracranial stenoses: experience with two thin-strut drug-eluting stents (des)-taxus element and resolute integrity. *Cardiovasc Intervent Radiol.* (2015) 38:583–91. doi: 10.1007/s00270-014-1001-3
38. Vajda Z, Guthe T, Perez MA, Kurre W, Schmid E, Bazner H, et al. Prevention of intracranial in-stent restenoses: predilatation with a drug eluting balloon, followed by the deployment of a self-expanding stent. *Cardiovasc Intervent Radiol.* (2013) 36:346–52. doi: 10.1007/s00270-012-0450-9
39. Gruber P, Remonda L. Device profile of different paclitaxel-coated balloons: Neuro Elutax SV, Elutax '3'Neuro and Sequent Please NEO for the treatment of symptomatic intracranial high-grade stenosis: overview of their feasibility and safety. *Expert Rev Med Devices.* (2020) 17:87–92. doi: 10.1080/17434440.2020.1719829
40. Tesfamariam B. Local arterial wall drug delivery using balloon catheter system. *J Control Release.* (2016) 238:149–56. doi: 10.1016/j.jconrel.2016.07.041
41. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol.* (2006) 48:2584–91. doi: 10.1016/j.jacc.2006.10.026
42. Gruber P, Garcia-Esperon C, Berberat J, Kahles T, Hlavica M, Anon J, et al. Neuro Elutax Sv drug-eluting balloon versus Wingspan stent system in symptomatic intracranial high-grade stenosis: a single-center experience. *J Neurointerv Surg.* (2018) 10:e32. doi: 10.1136/neurintsurg-2017-013699
43. Han J, Zhang J, Zhang X, Zhang J, Song Y, Zhao W, et al. Drug-coated balloons for the treatment of symptomatic intracranial atherosclerosis: initial experience and follow-up outcome. *J Neurointerv Surg.* (2019) 11:569–73. doi: 10.1136/neurintsurg-2018-014237
44. Gruber P, Braun C, Kahles T, Hlavica M, Anon J, Diepers M, et al. Percutaneous transluminal angioplasty using novel drug-coated balloon catheter Sequent Please NEO for the treatment of symptomatic intracranial severe stenosis: feasibility and safety study. *J Neurointerv Surg.* (2019) 11:719–22. doi: 10.1136/neurintsurg-2018-014378
45. Zhang J, Zhang X, Zhang J, Song Y, Zheng M, Sun L, et al. Drug-coated balloon dilation compared with conventional stenting angioplasty for intracranial atherosclerotic disease. *Neurosurgery.* (2020) 87:992–8. doi: 10.1093/neuros/nyaa191
46. Wang AY, Chang CH, Chen CC, Wu YM, Lin CM, Chen CT, et al. Leave nothing behind: treatment of intracranial atherosclerotic disease with drug coated balloon angioplasty. *Clin Neuroradiol.* (2021) 31:35–44. doi: 10.1007/s00062-020-00935-w
47. Remonda L, Diepers M, Berberat J, Kahles T, Anon J, Nedeltchev K, et al. Drug-coated balloon treatment in symptomatic intracranial high-grade stenosis: a retrospective study of 33 patients. *Clin Neuroradiol.* (2021) 31:45–9. doi: 10.1007/s00062-020-00936-9

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 29 July 2021
doi: 10.3389/fneur.2021.705949

Neutrophil-to-Lymphocyte Ratio as a Predictive Biomarker for Stroke Severity and Short-Term Prognosis in Acute Ischemic Stroke With Intracranial Atherosclerotic Stenosis

Yuanlin Ying[1†], Fang Yu[1†], Yunfang Luo[1], Xianjing Feng[1], Di Liao[1], Minping Wei[1], Xi Li[1], Qin Huang[1], Zeyu Liu[1], Lin Zhang[1], Tingting Zhao[1], Ruxin Tu[1] and Jian Xia[1,2,3]*

[1] Department of Neurology, Xiangya Hospital, Central South University, Changsha, China, [2] Clinical Research Center for Cerebrovascular Disease of Hunan Province, Central South University, Changsha, China, [3] National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, China

OPEN ACCESS

Edited by:
QinJian Sun,
Shandong University, China

Reviewed by:
P. N. Sylaja,
Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), India
Lung Chan,
Taipei Medical University, Taiwan

***Correspondence:**
Jian Xia
xjian1216@csu.edu.cn

[†] These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *06 May 2021*
Accepted: *05 July 2021*
Published: *29 July 2021*

Citation:
Ying Y, Yu F, Luo Y, Feng X, Liao D, Wei M, Li X, Huang Q, Liu Z, Zhang L, Zhao T, Tu R and Xia J (2021) Neutrophil-to-Lymphocyte Ratio as a Predictive Biomarker for Stroke Severity and Short-Term Prognosis in Acute Ischemic Stroke With Intracranial Atherosclerotic Stenosis. Front. Neurol. 12:705949. doi: 10.3389/fneur.2021.705949

Background: Neutrophil-to-lymphocyte ratio (NLR) is an indicator of poor prognosis in acute ischemic stroke (AIS), but associations between NLR with stroke severity and prognosis of intracranial atherosclerotic stenosis (ICAS)-related ischemic events have not been well-elucidated; therefore, we aimed to evaluate whether admission NLR levels correlate with the early stroke severity and short-term functional prognosis in patients with symptomatic intracranial atherosclerotic stenosis (sICAS).

Methods: This retrospective study enrolled 899 consecutive patients with AIS attributed to ICAS at Xiangya Hospital stroke center between May 2016 and September 2020. The initial stroke severity was rated by the admission National Institutes of Health Stroke Scale (NIHSS) scores, and the short-term prognosis was evaluated using the 14-day modified Rankin Scale (mRS) scores after stroke onset. A severe stroke was defined as NIHSS >8; an unfavorable functional outcome was defined as mRS scores of 3–6. Admission NLR was determined based on circulating neutrophil and lymphocyte counts.

Results: The median admission NLR of all patients was 2.80 [interquartile range (IQR), 2.00–4.00]. In univariate analysis, admission NLR was significantly elevated in patients with severe stroke and poor short-term prognosis. After multivariate adjustment, admission NLR levels were significantly correlated with severe stroke [odds ratio (OR), 1.132; 95% confidence interval (95% CI), 1.038–1.234; $P = 0.005$] and unfavorable short-term prognosis (OR, 1.102; 95% CI, 1.017–1.195; $P = 0.018$) in Model 1. In Model 2, the highest NLR tertile (≥3.533) remained an independent predictor of severe stroke (OR, 2.736; 95% CI, 1.590–4.708; $P < 0.001$) and unfavorable functional outcome (OR, 2.165; 95% CI, 1.416–3.311; $P < 0.001$) compared with the lowest NLR tertile (<2.231). The receiver operating characteristic (ROC) curves showed the predictability of NLR regarding the stroke severity [area under the curve (AUC), 0.659; 95% CI, 0.615–0.703; $P < 0.001$] and short-term prognosis (AUC, 0.613; 95% CI, 0.575–0.650; $P < 0.001$). The nomograms were constructed to create the predictive models of the severity and short-term outcome of sICAS.

Conclusions: Elevated admission NLR levels were independently associated with the initial stroke severity and could be an early predictor of severity and poor short-term prognosis in AIS patients with ICAS, which might help us identify a target group timely for preventive therapies.

Keywords: ischemic stroke, intracranial atherosclerotic stenosis, neutrophil-to-lymphocyte ratio, stroke severity, short-term prognosis

INTRODUCTION

Stroke is a growing public health concern and remains a leading cause of mortality and disability worldwide (1). Of all different stroke subtypes, ischemic stroke is the most common subtype, accounting for about 80% of all strokes and mainly caused by large artery atherosclerosis (LAA), especially intracranial atherosclerotic stenosis (ICAS), which has a higher prevalence in Asians, Africans, and Hispanics compared with Caucasians (1–3). Accumulating evidence suggests that ICAS was associated with increased risks of cognitive impairment, dementia, stroke recurrence, and death (4–6). However, the pathogenesis of ICAS has not been well-investigated. Previous studies have established that atherosclerosis is an inflammatory disorder mediated by activation of inflammatory markers and infiltration of various inflammatory cells, especially activated macrophages and T cells, which could release metalloproteinases, thus leading to atherosclerotic plaque instability or rupture, ischemia, and infarction (7, 8). Since ICAS is on the spectrum of atherosclerosis, inflammation might also be a pathophysiological mechanism for the development and progression of ICAS.

Neutrophil-to-lymphocyte ratio (NLR) is emerging as an objective and easily accessible indicator of systemic inflammatory status, reflecting the balance between neutrophils and lymphocytes in peripheral blood (9). An increase in NLR levels has been reported to be associated with atherosclerotic events, serving as a prognostic predictor in coronary artery disease (CAD), peripheral arterial occlusive disease (PAOD), and ischemic stroke (10–12). Specifically, it has previously been observed that high NLR levels were correlated with stroke severity, poor functional outcomes, and recurrent ischemic events in stroke patients (12, 13). Furthermore, large vessel occlusion patients with high admission NLR values had increased risks of symptomatic intracranial hemorrhage (sICH) and 3-month mortality after mechanical thrombectomy (14). Even in a healthy population, an elevated NLR has been proved to be linked to the prevalence and burdens of ICAS (15). However, few studies have examined the association between NLR and symptomatic intracranial atherosclerotic stenosis (sICAS). Although a recent study has explored the relationships between NLR with ICAS and ischemic stroke and demonstrated that the association between NLR and ischemic stroke was partially mediated by ICAS (16), there is a relative paucity of studies investigating the underlying relationships between admission NLR with the initial severity and prognosis of sICAS.

In this study, we aimed to determine the potential predictive capacity of admission NLR levels for stroke severity and short-term prognosis of patients with acute ischemic stroke (AIS) attributed to ICAS to help identify a promising therapeutic strategy.

MATERIALS AND METHODS

Patients and Population

This study retrospectively enrolled and analyzed 899 consecutive patients with AIS attributed to ICAS, who were admitted to Xiangya Hospital stroke center between May 2016 and September 2020, satisfying the following inclusion criteria: (1) age $\geq$18 years; (2) time interval from symptom onset to admission $\leq$72 h; and (3) blood sampling performed within 24 h after hospital admission. Those patients, who had cardioembolic stroke or evidence of cardioembolic propensity, severe stenosis of extracranial carotid artery, malignant tumors, severe renal or hepatic diseases, hematological diseases, inflammatory or infectious diseases, or history of immunosuppressant medications within the past 3 months, were excluded from the current study. The criteria for diagnosing AIS have been described in detail previously (17). Each participant in this study has provided the informed consent form. The study was approved by the Medical Ethics Committee of Xiangya Hospital, Central South University, China.

Stroke Severity and Outcome Assessment

The National Institutes of Health Stroke Scale (NIHSS) scores have been collected on admission for the assessment of initial stroke severity, stratifying patients into two groups: mild stroke (NIHSS score $\leq$8) and severe stroke (NIHSS score >8). The 14-day modified Rankin Scale (mRS) scores after stroke onset have been used to evaluate the short-term prognosis after stroke, and patients were therefore categorized into two groups: favorable functional outcome group with mRS scores of 0–2 and unfavorable functional outcome group with mRS scores of 3–6.

Clinical and Laboratory Data Collection

Baseline characteristics including demographics, cardiovascular risk factors, clinical data, and laboratory data were collected and recorded on admission. Histories of hypertension, diabetes mellitus, dyslipidemia, and coronary artery disease (CAD), as well as cigarette smoking and alcohol intake, have been considered cardiovascular risk factors. Besides, systolic and diastolic blood pressure levels were measured on admission. Admission NIHSS scores and 14-day mRS scores were collected as previously mentioned. The treatments including intravenous thrombolysis (IVT), endovascular treatment (EVT), and

antiplatelet therapy were collected during hospitalization. Blood samples were collected within 24 h after admission for the examination of laboratory parameters, including white blood cell (WBC), platelet (Plt), neutrophil, lymphocyte, NLR, fasting blood glucose (FBG), uric acid (UA), homocysteine (Hcy), fibrinogen (Fib), and a lipid profile which consists of total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL). The diagnostic criteria and parameters have been described in detail in our prior work (17, 18). Admission NLR was calculated based on neutrophil and lymphocyte counts in the peripheral blood.

Radiological Assessment

Standard magnetic resonance imaging (MRI) of the brain was performed in all participants on 1.5 or 3.0 T scanners, including sequences of T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). The lesions of stenosis or occlusion were measured using three-dimensional time-of-flight (3D TOF) magnetic resonance angiography (MRA), computerized tomography angiography (CTA), or digital subtraction angiography (DSA). The presence of ICAS was defined as stenosis or occlusion of intracranial atherosclerotic arteries rated by two experienced radiologists, and the percentage of luminal stenosis was calculated according to the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) criteria, classifying the severity of stenosis into mild (<50%), moderate (50–69%), severe (70–99%), and occlusion (100%) (19). Moreover, hemorrhagic transformations (HT) and cerebral edema (CED) were defined using the computed tomography (CT) or MRI and classified according to the European Cooperative Acute Stroke Study-2 (ECASS-II) criteria by at least two experienced radiologists (20, 21). In this study, we stratified HT into hemorrhagic infarction (HI) 1, HI2, parenchymal hemorrhage (PH) 1, and PH2; and we dichotomized CED into none or mild (grades 0–1) and moderate-to-severe (grades 2–3) (20, 22).

Statistical Analysis

Continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (IQR) for data with normal and non-normal distributions, respectively, whereas categorical variables were described as number and percentage. For continuous variables, Student *t*-test and Mann-Whitney *U*-test were used for intergroup comparisons, while for categorical variables, Pearson χ^2-test was used to assess the intergroup difference. Multivariate binary logistic regression analysis was conducted to evaluate associations between NLR with early severity and short-term prognosis after adjustment for age, sex, and other possible confounders, involving all variates with a $P < 0.05$ in initial univariate analysis, with results exhibited as odds ratios (OR) and 95% confidence interval (CI). Model 1 (the laboratory parameters as continuous variables) and Model 2 (the laboratory parameters as dichotomous or trichotomous variables) were used in multivariate binary logistic regression analysis, and NLR levels were categorized into tertiles: the first tertile, <2.231; the second tertile, 2.231–3.533; and the third tertile, ≥3.533 in Model 2. To evaluate the predictive capacity of NLR to discriminate early severity and short-term prognosis, we illustrated receiver operating characteristic (ROC) curves, measured the area under the curve (AUC), and determined the CIs. The nomograms were plotted using the independent significant variables based on the results of multivariate logistic regression analysis. All statistical analyses were conducted with Empower Stats (http://www.empowerstats.com) and R software (http://www.R-project.org/). $P < 0.05$ was considered statistically significant.

RESULTS

Patient Baseline Characteristics

From May 2016 to September 2020, totally 899 consecutive AIS patients with ICAS were enrolled in the study analysis. The median age of all participants was 61 years (IQR, 53–68 years) and 64.3% ($n = 578$) were male (as shown in **Table 1**). Cardiovascular risk factors included histories of hypertension ($n = 699$, 77.8%), diabetes mellitus ($n = 310$, 34.5%), dyslipidemia ($n = 412$, 45.8%), CAD ($n = 130$, 14.5%), smoking ($n = 390$, 43.4%), and drinking ($n = 302$, 33.6%) (as shown in **Table 1**). During hospitalization, almost all patients were on antiplatelet therapy, in which 48.9% ($n = 440$) were using mono-antiplatelet drugs, and 48.2% ($n = 433$) were using dual antiplatelet drugs (as shown in **Table 1**). The rates of participants treated with IVT and EVT were 2.3% ($n = 21$) and 2.8% ($n = 25$), respectively (**Table 1**). Additionally, patients were stratified as having mild stenosis ($n = 148$, 16.5%), moderate stenosis ($n = 212$, 23.6%), severe stenosis ($n = 188$, 20.9%), and occlusion ($n = 351$, 39.0%) (**Table 1**). The median admission NLR of all included patients was 2.80 (IQR, 2.00–4.00) (**Table 1**). Patients with intracranial atherosclerotic artery occlusion had statistically higher admission NLR levels compared to patients with mild stenosis ($P = 0.024$) and moderate stenosis ($P = 0.013$) (as shown in **Figure 1A**). Regarding the number of stenosis, higher admission NLR levels were documented in patients with multiple intracranial artery stenosis (the number of stenosis ≥3) ($n = 467$, 51.9%) compared to patients with single stenosis ($n = 242$, 26.9%; $P = 0.007$) (as shown in **Table 1** and **Figure 1B**). Besides, patients with HT ($n = 52$, 5.8%) had statistically higher admission NLR levels compared to patients without HT ($P = 0.014$), and patients with moderate-severe CED ($n = 87$, 9.7%) had statistically elevated admission NLR levels compared to patients with none-mild CED ($P = 0.001$) (as shown in **Table 1** and **Figure 2**). The median admission NIHSS score of the participants was 5 (IQR, 2–8), and the initial stroke severity was stratified according to admission NIHSS scores as follows: mild stroke, NIHSS score ≤8 ($n = 698$, 77.6%); severe stroke, NIHSS score >8 ($n = 201$, 22.4%) (as shown in **Table 1**). The median mRS score on the 14th day after stroke onset of the participants was 2 (IQR, 1–3), and the short-term prognosis was stratified by 14-day mRS scores as follows: a favorable outcome, mRS scores ≤2 ($n = 521$, 58.0%); an unfavorable outcome, mRS scores >2 ($n = 378$, 42.0%) (as shown in **Table 1**). Baseline clinical characteristics, as well as the admission laboratory data of the participants, were summarized in **Table 1**.

TABLE 1 | Baseline characteristics of the study population.

Variables	Patients ($n = 899$)
Age (years)	61 (53–68)
Sex, male, *N* (%)	578 (64.3%)
Hypertension, *N* (%)	699 (77.8%)
Diabetes, *N* (%)	310 (34.5%)
Dyslipidemia, *N* (%)	412 (45.8%)
CAD, *N* (%)	130 (14.5%)
Smoking, *N* (%)	390 (43.4%)
Drinking, *N* (%)	302 (33.6%)
IVT, *N* (%)	21 (2.3%)
EVT, *N* (%)	25 (2.8%)
Antiplatelet drugs, *N* (%)	
Mono-antiplatelet	440 (48.9%)
Dual antiplatelets	433 (48.2%)
None	26 (2.9%)
Severity of stenosis, *N* (%)	
Mild	148 (16.5%)
Moderate	212 (23.6%)
Severe	188 (20.9%)
Occlusion	351 (39.0%)
Number of stenosis, *N* (%)	
1	242 (26.9%)
2	190 (21.1%)
≥3	467 (51.9%)
HT, *N* (%)	52 (5.8%)
ECASS II classification, *N* (%)	
HI1	12 (1.3%)
HI2	19 (2.1%)
PH1	10 (1.1%)
PH2	11 (1.2%)
Moderate–severe CED, *N* (%)	87 (9.7%)
NIHSS score	5 (2–8)
NIHSS ≤ 8, *N* (%)	698 (77.6%)
NIHSS > 8, *N* (%)	201 (22.4%)
mRS score	2 (1–3)
mRS 0–2, *N* (%)	521 (58.0%)
mRS 3–6, *N* (%)	378 (42.0%)
SBP (mmHg)	144.00 (132.00–158.00)
DBP (mmHg)	84.00 (76.00–93.00)
WBC ($\times 10^9$/L)	6.90 (5.60–8.50)
Plt ($\times 10^9$/L)	207.00 (169.00–251.00)
Neutrophil ($\times 10^9$/L)	4.40 (3.40–5.90)
Lymphocyte ($\times 10^9$/L)	1.60 (1.20–2.00)
NLR	2.80 (2.00–4.00)
TC (mmol/L)	4.37 (3.58–5.18)
TG (mmol/L)	1.56 (1.18–2.12)
HDL (mmol/L)	1.00 (0.86–1.20)
LDL (mmol/L)	2.70 (2.12–3.32)
FBG (mmol/L)	5.69 (4.96–7.29)
UA (μmol/L)	311.20 (253.10–378.20)
Hcy (μmol/L)	13.36 (11.06–16.42)
Fib (g/L)	3.28 (2.76–4.03)

CAD, coronary artery disease; IVT, intravenous thrombolysis; EVT, endovascular therapy; HT, hemorrhagic transformation; ECASS II, European Cooperative Acute Stroke Study II; HI, hemorrhagic infarction; PH, parenchymal hematoma; CED, cerebral edema; NIHSS, the National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; Plt, platelet; NLR, neutrophil-to-lymphocyte ratio; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBG, fasting blood glucose; UA, uric acid; Hcy, homocysteine; Fib, fibrinogen.

Association Between NLR and Initial Stroke Severity in sICAS Patients

Of all participants, 698 (77.6%) were classified as having a mild stroke, and 201 (22.4%) had a severe stroke as mentioned before. In univariate analysis, sex, dual antiplatelet therapy, stenosis severity, moderate-severe CED, WBC, neutrophils, lymphocytes, NLR, FBG, UA, and Fib were significantly related to stroke severity at admission with a $P < 0.05$ (as shown in **Table 2**). Patients with severe stroke had statistically elevated admission NLR levels (median, 3.53; IQR, 2.43–5.25) compared to patients with mild stroke (median, 2.63; IQR, 1.93–3.64; $P < 0.001$) (as shown in **Table 2** and **Figure 3A**). Moreover, the proportions of female gender, occlusion, and moderate-severe CED, and levels of WBC, neutrophil, FBG, and Fib in the severe stroke group were higher than those in the mild stroke group, whereas the proportion of dual antiplatelet therapy and the levels of lymphocyte and UA were lower in the severe stroke group (as shown in **Table 2**). Multivariate logistic regression analysis indicated that admission NLR levels were significantly correlated with severe stroke (OR, 1.132; 95% CI, 1.038–1.234; $P = 0.005$) in Model 1 and both the middle and the highest NLR tertiles were significantly correlated with severe stroke (tertile 2: OR, 1.851; 95% CI, 1.089–3.145; $P = 0.023$; and tertile 3: OR, 2.736; 95% CI, 1.590–4.708; $P < 0.001$) compared with the lowest NLR tertile in Model 2 after adjustment for age, sex, dual antiplatelet therapy, stenosis severity, moderate-severe CED, WBC, FBG, UA, and Fib (as shown in **Table 3**).

Association Between NLR and Short-Term Prognosis in sICAS Patients

Among all participants, 521 (58.0%) had a favorable short-term functional outcome, and 378 (42.0%) had an unfavorable short-term functional outcome as mentioned before. In univariate analysis, age, sex, histories of CAD, smoking, and drinking, dual antiplatelet therapy, stenosis severity, moderate-severe CED, and levels of WBC, Plt, neutrophils, lymphocytes, NLR, HDL, FBG, UA, and Fib were significantly correlated with short-term prognosis in sICAS patients (as shown in **Table 2**). NLR levels were statistically elevated in patients with unfavorable outcomes (median, 3.18; IQR, 2.25–4.53) compared with those with favorable outcomes (median, 2.60; IQR, 1.88–3.54; $P < 0.001$) (as shown in **Table 2** and **Figure 3B**). Moreover, age, the proportions

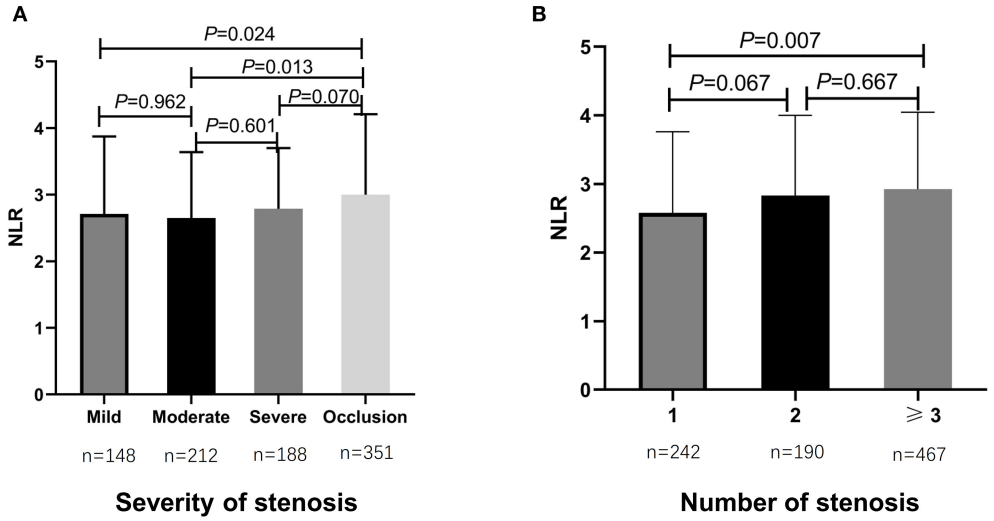


FIGURE 1 | Comparisons of admission NLR levels according to the severity and number of intracranial atherosclerotic stenosis in sICAS patients. **(A)** Comparison of admission NLR levels according to the severity of intracranial atherosclerotic stenosis. **(B)** Comparison of admission NLR levels according to the number of intracranial atherosclerotic stenosis. $P < 0.05$ was considered statistically significant. NLR, neutrophil-to-lymphocyte ratio; sICAS, symptomatic intracranial atherosclerotic stenosis.

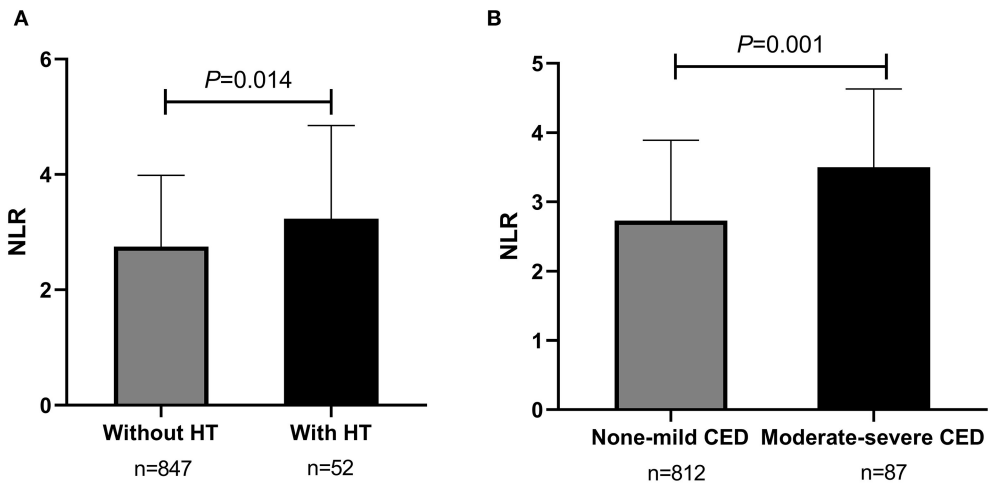


FIGURE 2 | Comparisons of admission NLR levels according to HT and CED in sICAS patients. **(A)** Comparison of admission NLR levels according to HT (without HT vs. with HT). **(B)** Comparison of admission NLR levels according to CED (none-mild CED vs. moderate-severe CED). $P < 0.05$ was considered statistically significant. NLR, neutrophil-to-lymphocyte ratio; sICAS, symptomatic intracranial atherosclerotic stenosis; HT, hemorrhagic transformation; CED, cerebral edema.

of female gender, occlusion, and moderate-severe CED, the prevalence of CAD, and levels of WBC, Plt, neutrophil, HDL, FBG, and Fib in the unfavorable outcome group were higher than those in the favorable outcome group, whereas the proportion of dual antiplatelet therapy, the frequencies of smoking and drinking, and the levels of lymphocyte and UA were lower in the unfavorable outcome group (as shown in **Table 2**). Multivariate logistic regression analysis showed that admission NLR levels were significantly correlated with unfavorable short-term prognosis (OR, 1.102; 95% CI, 1.017–1.195; $P = 0.018$) in Model 1 and the highest NLR tertile was positively associated with unfavorable short-term prognosis (OR, 2.165; 95% CI, 1.416–3.311; $P < 0.001$) compared with the lowest NLR tertile in Model 2 after adjusting for age, sex, CAD, smoking, drinking, dual antiplatelet therapy, severity of stenosis, moderate-severe CED, WBC, Plt, HDL, FBG, UA, and Fib (as shown in **Table 4**).

Predictive Values of NLR for the Severity and Short-Term Prognosis of sICAS

Receiver operating characteristic curve analysis was conducted to determine the predictability of NLR with the results illustrated in **Figure 4**. Area under the curve values for discriminating

TABLE 2 | Clinical characteristics of sICAS patients according to the initial stroke severity and short-term prognosis.

Variables	Mild ($n = 698$) (NIHSS ≤ 8)	Severe ($n = 201$) (NIHSS >8)	*P*-value	Favorable ($n = 521$) (mRS 0–2)	Unfavorable ($n = 378$) (mRS 3–6)	*P*-value
Age (years)	61 (52–68)	63 (54–69)	0.080	60 (52–68)	63 (53–69)	**0.015**
Sex, male, *N* (%)	464 (66.5%)	114 (56.7%)	**0.011**	360 (69.1%)	218 (57.7%)	**<0.001**
Hypertension, *N* (%)	542 (77.7%)	157 (78.1%)	0.890	399 (76.6%)	300 (79.4%)	0.322
Diabetes, *N* (%)	237 (34.0%)	73 (36.3%)	0.534	166 (31.9%)	144 (38.1%)	0.052
Dyslipidemia, *N* (%)	313 (44.8%)	99 (49.3%)	0.269	231 (44.3%)	181 (47.9%)	0.292
CAD, *N* (%)	96 (13.8%)	34 (16.9%)	0.261	60 (11.5%)	70 (18.5%)	**0.003**
Smoking, *N* (%)	304 (43.6%)	86 (42.8%)	0.847	241 (46.3%)	149 (39.4%)	**0.041**
Drinking, *N* (%)	228 (32.7%)	74 (36.8%)	0.272	189 (36.3%)	113 (29.9%)	**0.046**
IVT, *N* (%)	15 (2.1%)	6 (3.0%)	0.439	10 (1.9%)	11 (2.9%)	0.375
EVT, *N* (%)	22 (3.2%)	3 (1.5%)	0.328	17 (3.3%)	8 (2.1%)	0.412
Dual antiplatelets, *N* (%)	349 (50.0%)	84 (41.8%)	**0.045**	281 (53.9%)	152 (40.2%)	**<0.001**
Severity of stenosis, *N* (%)			**<0.001**			**<0.001**
Mild	128 (18.3%)	20 (10.0%)		98 (18.8%)	50 (13.2%)	
Moderate	170 (24.4%)	42 (20.9%)		118 (22.6%)	94 (24.9%)	
Severe	154 (22.1%)	34 (16.9%)		127 (24.4%)	61 (16.1%)	
Occlusion	246 (35.2%)	105 (52.2%)		178 (34.2%)	173 (45.8%)	
Number of stenosis, *N* (%)			0.821			0.610
1	191 (27.4%)	51 (25.4%)		137 (26.3%)	105 (27.8%)	
2	148 (21.2%)	42 (20.9%)		116 (22.3%)	74 (19.6%)	
≥ 3	359 (51.4%)	108 (53.7%)		268 (51.4%)	199 (52.6%)	
HT, *N* (%)	37 (5.3%)	15 (7.5%)	0.235	26 (5.0%)	26 (6.9%)	0.249
ECASS II classification, *N* (%)			0.320			0.161
HI1, *N* (%)	9 (1.3%)	3 (1.5%)		6 (1.2%)	6 (1.6%)	
HI2, *N* (%)	15 (2.1%)	4 (2.0%)		13 (2.5%)	6 (1.6%)	
PH1, *N* (%)	5 (0.7%)	5 (2.5%)		3 (0.6%)	7 (1.9%)	
PH2, *N* (%)	8 (1.1%)	3 (1.5%)		4 (0.8%)	7 (1.9%)	
Moderate–severe CED, *N* (%)	43 (6.2%)	44 (21.9%)	**<0.001**	39 (7.5%)	48 (12.7%)	**0.012**
SBP (mmHg)	144 (132–158)	147 (134–160)	0.208	143 (132–156)	146 (134–160)	0.102
DBP (mmHg)	84 (76–93)	85 (76–92)	0.861	84 (76–93)	85 (76–92)	0.986
WBC ($\times 10^9$/L)	6.70 (5.50–8.10)	7.70 (6.30–9.75)	**<0.001**	6.70 (5.47–8.10)	7.20 (5.90–8.70)	**<0.001**
Plt ($\times 10^9$/L)	205.00 (169.00–246.00)	218.00 (171.75–259.50)	0.06	204.00 (164.50–244.00)	211.50 (176.00–256.25)	**0.021**
Neutrophil ($\times 10^9$/L)	4.30 (3.30–5.40)	5.30 (4.00–7.00)	**<0.001**	4.20 (3.20–5.30)	4.80 (3.80–6.40)	**<0.001**
Lymphocyte ($\times 10^9$/L)	1.60 (1.20–2.00)	1.40 (1.10–1.90)	**0.003**	1.60 (1.20–2.00)	1.50 (1.20–1.90)	**0.010**
NLR	2.63 (1.93–3.64)	3.53 (2.43–5.25)	**<0.001**	2.60 (1.88–3.54)	3.18 (2.25–4.53)	**<0.001**
TC (mmol/L)	4.37 (3.54–5.16)	4.42 (3.74–5.25)	0.157	4.34 (3.54–5.14)	4.45 (3.63–5.20)	0.168
TG (mmol/L)	1.57 (1.18–2.11)	1.54 (1.19–2.20)	0.991	1.58 (1.18–2.11)	1.54 (1.20–2.17)	0.924
HDL (mmol/L)	1.00 (0.85–1.18)	1.02 (0.89–1.23)	0.131	0.99 (0.84–1.17)	1.02 (0.88–1.24)	**0.045**
LDL (mmol/L)	2.66 (2.10–3.29)	2.75 (2.16–3.35)	0.143	2.63 (2.10–3.27)	2.76 (2.13–3.38)	0.133
FBG (mmol/L)	5.56 (4.91–7.17)	6.15 (5.19–7.96)	**<0.001**	5.54 (4.91–6.99)	5.95 (5.07–7.82)	**0.002**
UA (μmol/L)	315.70 (261.45–381.72)	290.60 (230.95–365.00)	**0.002**	318.50 (271.10–383.19)	300.39 (234.57–370.55)	**0.003**
Hcy (μmol/L)	13.45 (11.04–16.41)	12.59 (11.11–16.51)	0.578	13.43 (11.12–16.48)	13.27 (11.01–16.36)	0.445
Fib (g/L)	3.20 (2.74–3.89)	3.69 (2.96–4.39)	**<0.001**	3.15 (2.71–3.86)	3.45 (2.90–4.25)	**<0.001**

Bold values denote statistical significance at the P < 0.05 level. NIHSS, the National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; sICAS, symptomatic intracranial atherosclerotic stenosis; CAD, coronary artery disease; IVT, intravenous thrombolysis; EVT, endovascular therapy; HT, hemorrhagic transformation; ECASS II, European Cooperative Acute Stroke Study II; HI, hemorrhagic infarction; PH, parenchymal hematoma; CED, cerebral edema; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; Plt, platelet; NLR, neutrophil-to-lymphocyte ratio; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBG, fasting blood glucose; UA, uric acid; Hcy, homocysteine; Fib, fibrinogen.

stroke severity and short-term prognosis were 0.659 (95% CI, 0.615–0.703; $P < 0.001$) and 0.613 (95% CI, 0.575–0.650; $P < 0.001$), respectively, and the optimal cut-off values of NLR were 3.33 (specificity, 69.49%; sensitivity, 54.87%) for stroke severity and 3.31 (specificity, 70.45%; sensitivity, 47.43%) for short-term prognosis (as shown in **Figure 4**).

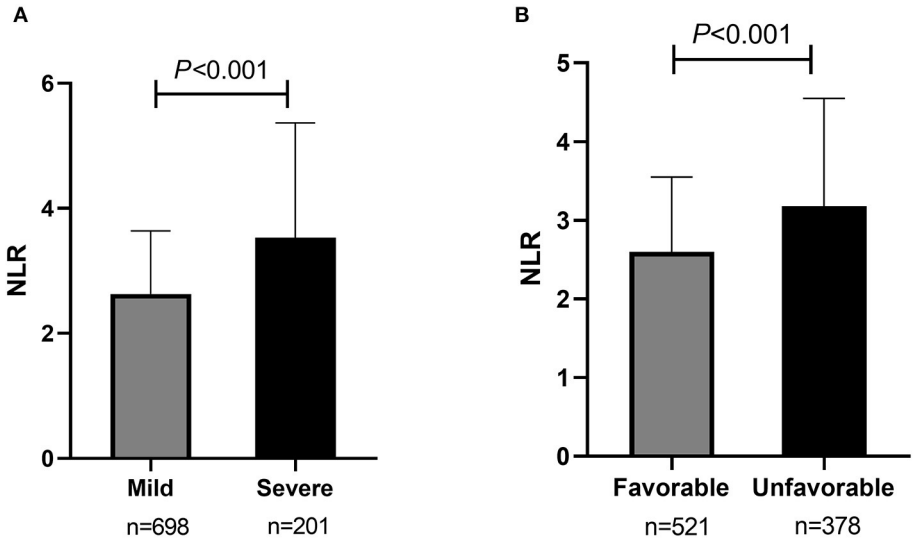


FIGURE 3 | Comparisons of admission NLR levels according to the initial stroke severity and short-term prognosis of sICAS. **(A)** Comparison of admission NLR levels according to the initial stroke severity (severe stroke vs. mild controls). **(B)** Comparison of admission NLR levels according to the short-term prognosis (unfavorable outcome vs. favorable outcome). NLR, neutrophil-to-lymphocyte ratio; sICAS, symptomatic intracranial atherosclerotic stenosis.

TABLE 3 | Multivariate logistic regression analysis of the relationship between NLR and the initial stroke severity of sICAS.

	Model 1				Model 2		
	***P*-value**	**OR**	**95% CI**		***P*-value**	**OR**	**95% CI**
Age (years)	0.227	1.011	0.993–1.030	Age (≥61 years)	0.063	1.461	0.980–2.177
Sex (male vs. female)	**0.028**	0.634	0.423–0.951	Sex (male vs. female)	0.073	0.689	0.459–1.035
NLR	**0.005**	1.132	1.038–1.234	**NLR tertiles**			
WBC ($\times 10^9$/L)	**0.020**	1.108	1.016–1.208	Tertile1 (<2.231)	Reference		
UA (μmol/L)	0.209	0.999	0.997–1.001	Tertile2 (2.231–3.533)	**0.023**	1.851	1.089–3.145
FBG (mmol/L)	0.269	1.040	0.970–1.115	Tertile3 (≥3.533)	**<0.001**	2.736	1.590–4.708
Fib (g/L)	0.101	1.082	0.985–1.190	WBC ($\geq 6.9\times 10^9$/L)	0.237	1.290	0.846–1.966
Dual antiplatelets	0.676	1.085	0.739–1.594	UA (≥311.2 μmol/L)	0.290	0.806	0.541–1.201
Severity of stenosis				FBG (≥5.69 mmol/L)	**0.008**	1.700	1.147–2.521
Mild	Reference			Fib (≥3.28 g/L)	**0.001**	2.048	1.357–3.091
Moderate	0.636	1.180	0.594–2.345	Dual antiplatelets	0.604	1.109	0.751–1.638
Severe	0.561	1.232	0.610–2.487	**Severity of stenosis**			
Occlusion	**0.013**	2.183	1.183–4.029	Mild	Reference		
Moderate–severe CED	**<0.001**	3.105	1.785–5.403	Moderate	0.723	1.136	0.561–2.301
				Severe	0.594	1.213	0.596–2.470
				Occlusion	**0.017**	2.140	1.143–4.006
				Moderate–severe CED	**<0.001**	3.095	1.765–5.426

Bold values denote statistical significance at the P < 0.05 level. NLR, neutrophil-to-lymphocyte ratio; sICAS, symptomatic intracranial atherosclerotic stenosis; WBC, white blood cell; FBG, fasting blood glucose; UA, uric acid; Fib, fibrinogen; CED, cerebral edema; OR, odds ratio; CI, confidence interval.

Predictive Models of the Severity and Short-Term Outcome of sICAS

To establish a more direct correlation of NLR with sICAS, we constructed nomograms using the variables identified by multivariate logistic regression analysis. We chose the independent risk factors identified in Model 1. The selected factors were shown by lines in the nomograms. Higher nomogram total scores indicated a higher risk of severe neurological deficit or unfavorable short-term outcome of sICAS patients. **Figures 5A**, **6A** showed the nomograms for predicting the severity and short-term prognosis of sICAS patients. **Figures 5B**, **6B** showed the performance of the nomograms. **Supplementary Figures 1A–D** showed the nomograms using the variables identified by multivariate logistic regression in Model 2 as well as their performances.

TABLE 4 | Multivariate logistic regression analysis of the relationship between NLR and the short-term prognosis of sICAS.

	Model 1				Model 2		
	***P*-value**	**OR**	**95% CI**		***P*-value**	**OR**	**95% CI**
Age (years)	0.286	1.008	0.993–1.024	Age (>61 years)	0.146	1.277	0.919–1.775
Sex (male vs. female)	0.107	0.704	0.459–1.079	Sex (male vs. female)	0.092	0.686	0.443–1.064
CAD	**0.007**	1.816	1.180–2.796	CAD	**0.007**	1.828	1.178–2.839
Smoking	0.376	1.214	0.790–1.864	Smoking	0.212	1.324	0.852–2.057
Drinking	0.229	0.772	0.507–1.177	Drinking	0.167	0.736	0.477–1.136
NLR	**0.018**	1.102	1.017–1.195	**NLR tertiles**			
WBC ($\times 10^9$/L)	0.257	1.050	0.965–1.143	Tertile1 (<2.231)	Reference		
Plt ($\times 10^9$/L)	0.842	1.000	0.998–1.003	Tertile2 (2.231–3.533)	0.111	1.374	0.929–2.033
HDL (mmol/L)	0.835	0.954	0.614–1.483	Tertile3 (≥3.533)	**<0.001**	2.165	1.416–3.311
UA (μmol/L)	**0.030**	0.998	0.997–1.000	WBC (≥6.9×10^9/L)	0.476	1.139	0.796–1.632
FBG (mmol/L)	0.054	1.062	0.999–1.128	Plt (≥207×10^9/L)	0.948	1.011	0.722–1.416
Fib (g/L)	0.520	1.030	0.942–1.127	HDL (≥1 mmol/L)	0.985	1.003	0.720–1.398
Dual antiplatelets	**0.037**	0.717	0.525–0.980	UA (≥311.2 μmol/L)	0.094	0.756	0.546–1.048
Severity of stenosis				FBG (≥5.685 mmol/L)	**0.044**	1.390	1.008–1.915
Mild	Reference			Fib (≥3.28 g/L)	**0.019**	1.482	1.067–2.059
Moderate	0.342	1.273	0.774–2.094	Dual antiplatelets	0.059	0.735	0.533–1.012
Severe	0.482	0.829	0.490–1.400	**Severity of stenosis**			
Occlusion	**0.020**	1.727	1.090–2.736	Mild	Reference		
Moderate–severe CED	0.856	1.051	0.615–1.797	Moderate	0.472	1.208	0.722–2.020
				Severe	0.352	0.776	0.454–1.325
				Occlusion	**0.032**	1.674	1.045–2.683
				Moderate–severe CED	0.968	1.011	0.585–1.746

Bold values denote statistical significance at the P < 0.05 level. NLR, neutrophil-to-lymphocyte ratio; sICAS, symptomatic intracranial atherosclerotic stenosis; CAD, coronary artery disease; WBC, white blood cell; Plt, platelet; HDL, high-density lipoprotein; FBG, fasting blood glucose; UA, uric acid; Fib, fibrinogen; CED, cerebral edema; OR, odds ratio; CI, confidence interval.

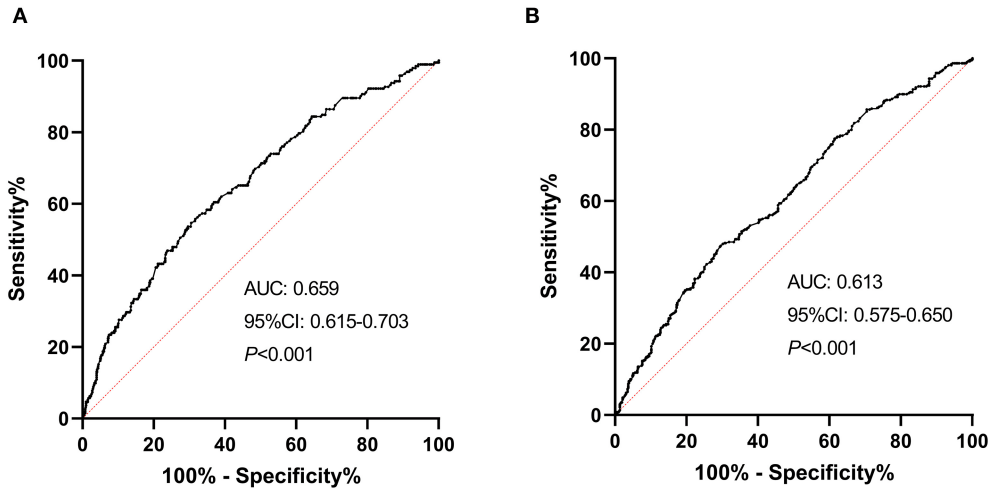


FIGURE 4 | ROC curves for the initial stroke severity and short-term prognosis of sICAS with NLR. **(A)** ROC curve for the initial stroke severity of sICAS with NLR (severe stroke vs. mild controls). **(B)** ROC curve for the short-term prognosis of sICAS with NLR (unfavorable outcome vs. favorable outcome). ROC, receiver operating characteristic; sICAS, symptomatic intracranial atherosclerotic stenosis; AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; CI, confidence interval.

DISCUSSION

In the present study, we demonstrated that elevated admission NLR was significantly correlated with initial stroke severity and poor short-term prognosis in sICAS patients. The statistical significance remained after adjustment for clinical and laboratory variables when NLR was 3.533 or more. Moreover, we demonstrated that NLR had good predictive

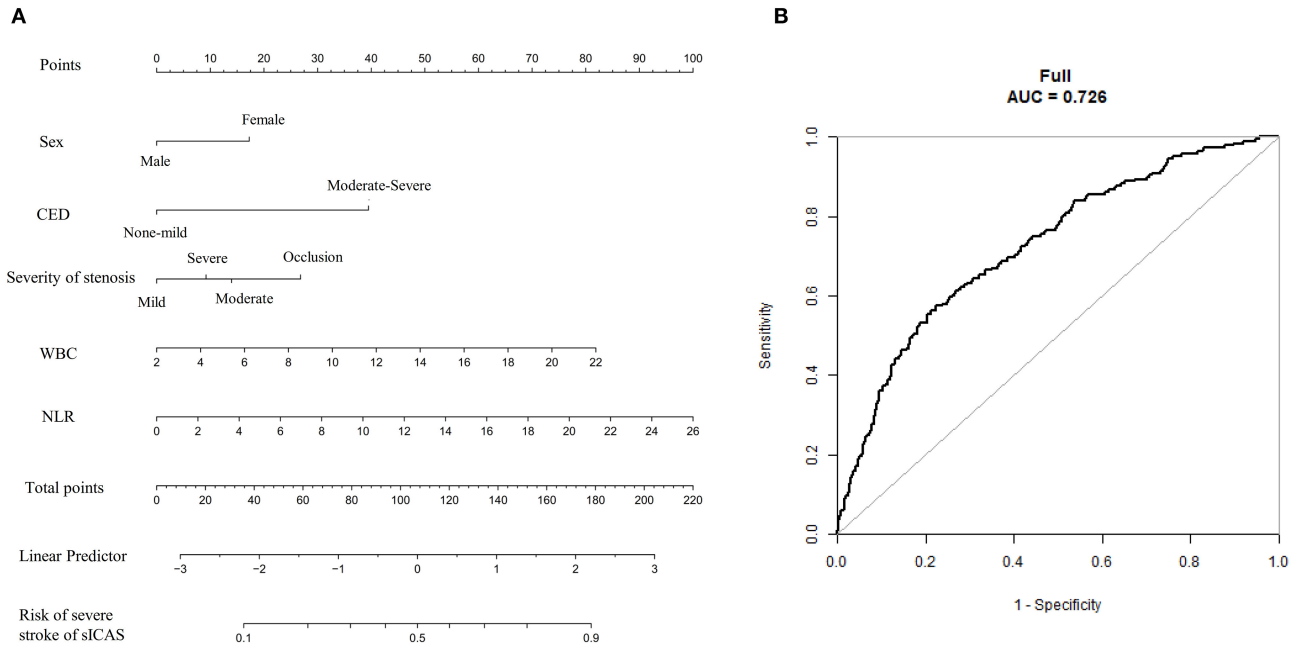


FIGURE 5 | The nomogram for predicting the severity of sICAS patients. **(A)** The nomogram for predicting the risk of severe neurological deficit of sICAS patients. **(B)** The ROC curve of the nomogram. The predictors were chosen based on the results of multivariate logistic regression in Model 1. Each selected factor was shown by a line in the nomograms. sICAS, symptomatic intracranial atherosclerotic stenosis; CED, cerebral edema; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristic; AUC, area under the curve.

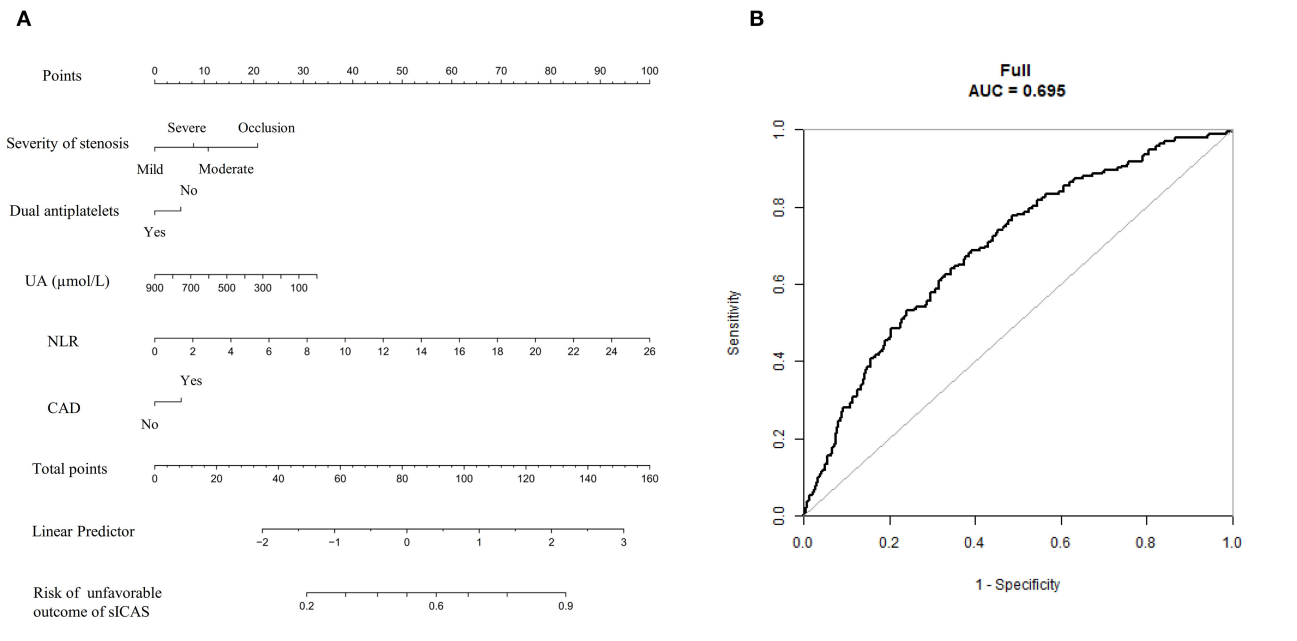


FIGURE 6 | The nomogram for predicting the short-term prognosis of sICAS patients. **(A)** The nomogram for predicting the risk of unfavorable short-term outcome of sICAS patients. **(B)** The ROC curve of the nomogram. The predictors were chosen based on the results of multivariate logistic regression in Model 1. Each selected factor was shown by a line in the nomograms. sICAS, symptomatic intracranial atherosclerotic stenosis; NLR, neutrophil-to-lymphocyte ratio; UA, uric acid; CAD, coronary artery disease; ROC, receiver operating characteristic; AUC, area under the curve.

power for the early severity and short-term prognosis of sICAS.

Our results are in accordance with prior studies relating to NLR and ischemic stroke. Researchers have reported that NLR was independently associated with stroke severity, hemorrhagic complications, poor short-term and long-term functional outcomes, high mortality rates, and stroke-associated pneumonia in acute cerebral ischemia (23–26). In patients with AIS attributable to LAA, high NLR was associated with increased risks for HT after LAA (27). In our study, we also observed that NLR values were higher in sICAS patients with HT, but HT was not a risk factor for the severity and prognosis of sICAS. More recently, a study in Portugal found that increased NLR was linked to the greater severity of CED, early neurological deterioration (END), and worse long-term prognosis in AIS patients undergoing reperfusion therapy (21). However, the predictive role of NLR in the prognosis of ischemic stroke due to ICAS has not been defined before. Our study revealed a similar role of NLR; that is, NLR was an early predictor of the early stroke severity and poor short-term outcome in patients with AIS attributed to ICAS, independent of other risk factors including CED, whereas the underlying mechanisms remain unclear.

Intracranial atherosclerotic stenosis is one of the most predominant causes of ischemic stroke, with a higher prevalence in Asians (3). Prior studies have demonstrated that traditional cardiovascular risk factors, metabolic syndrome, and unhealthy lifestyles are crucial risk factors associated with ICAS, accounting for endothelial dysfunction and increased permeability, thereby initiating a series of inflammatory reactions, which have been considered to be implicated in the pathogenesis of atherosclerosis and might play a critical role in the development of ICAS and plaque destabilization (8, 28). Although there are various risk factors and predictive models for ICAS, more convenient and easily accessible biomarkers are required to identify high-risk patients. Neutrophil-to-lymphocyte ratio, a biomarker indicating systemic inflammatory status, has been shown to be related to intracranial atherosclerosis. A study by Chung et al. (29) revealed that high NLR was correlated with intracranial atherosclerosis (OR= 1.87; 95% CI, 1.15–3.06; $P = 0.01$) in healthy individuals, consistent with another study by Nam et al. (15) indicating that NLR could be a predictor for the prevalence and burdens of ICAS. However, few studies revealed the independent predictive values of NLR in the prognosis of sICAS. Our prior study has determined the association between leukocyte levels and the prognosis of sICAS, whereas NLR might be a more accurate biomarker reflecting the balance of neutrophils and lymphocytes. Therefore, we examined whether NLR levels correlate with the early stroke severity and prognosis of sICAS and indicated that NLR could be employed as a good predictor with respect to the severity and short-term prognosis of sICAS.

Since NLR represents the ratio of neutrophils to lymphocytes, both neutrophilia and lymphopenia could be associated with increased NLR levels, providing clues to the possible underlying mechanisms. A growing body of evidence suggests that elevated circulating neutrophils were related to stroke severity, infarction volume, hemorrhagic complications, and poor outcomes in ischemic stroke (24, 30, 31). When stroke events occur, blood neutrophils could be rapidly recruited to areas of ischemic brain, release matrix metalloproteinases-9 (MMP-9), which could degrade tight junction proteins and basal lamina type IV collagen, increasing the blood-brain barrier (BBB) permeability, thereby resulting in BBB disruption and tissue damage, which is accompanied by edema and hemorrhage (32–35). Besides, an experimental study demonstrated that accumulated neutrophils could impair vascular remodeling during stroke recovery via producing neutrophil extracellular traps (NETs) (36). The expanded neutrophils after ischemic stroke might result from hematopoietic stem cell activation and a hematopoiesis bias mediated by increased sympathetic tone (37). Additionally, neutrophils are implicated in the development and progression of atherosclerosis. Neutrophils could be recruited and activated on the vascular wall, secreting granule proteins and limiting the use of nitric oxide, thus leading to endothelial dysfunction and subsequent atherosclerosis (38). Also, neutrophils could induce macrophages to release cytokines and activate T helper 17 (TH17) cells via releasing NETs, further amplifying pro-inflammatory responses and causing atherosclerotic plaque destabilization and rupture (39, 40).

However, the exact role of lymphocytes in atherosclerosis and ischemic stroke has not been fully elucidated. A study by Kim et al. (41) demonstrated the associations between reduced lymphocyte counts with END and unfavorable long-term prognosis in cerebral ischemia, implying that lymphocytes might be a protector for brain injury. It could be supported by another study, which reported that a lower admission lymphocyte-to-monocyte ratio (LMR) was an independent predictor for greater stroke severity and worse 3-month functional outcomes of acute cerebral infarction (42). Since the initial severity of stroke paralleled a more robust stress response, lymphopenia has been suspected to be mechanistically mediated by stress-induced cortisol production and sympathetic tone after stroke, which could further induce redistribution of lymphocytes and lymphocyte apoptosis (43, 44). Another possible mechanism lies in the protective role of regulatory lymphocytes in stroke via secreting interleukin-10 (IL-10), a critical anti-inflammatory and neuroprotective cytokine modulating post-stroke neuroinflammation (45, 46). Collectively, both inflammation and immune responses have considerable influence on the pathogenesis of ischemic stroke.

Early risk assessment is essential in determining the appropriate treatment and improving long-term life quality in patients with sICAS. Hence, it is critical to seek early predictors of sICAS to identify patients at high risk of severe stroke and unfavorable outcomes for early clinical intervention. Admission NLR, as an easy and straightforward biomarker, has the potential to help clinicians make decisions early and accurately. Our findings suggested that high NLR levels were correlated with severe stroke and poor prognosis in AIS patients due to ICAS, highlighting a promising potential therapeutic strategy for sICAS by reducing the ratio, which requires further investigations.

LIMITATIONS

There are several limitations in this study that should be noted. First, a selection bias might exist since it was a retrospective study with participants recruited from a single stroke center. Second, our data are descriptive, so associations do not necessarily imply causality. Further studies remain to be conducted to elucidate the causality between NLR with early severity and outcomes in AIS patients with ICAS. Third, NLR was only examined on admission, and longitudinal data were lacking. Otherwise, more precise and consistent information could be provided. Moreover, the functional outcomes were only assessed on the 14th day after stroke onset, limiting the predictive values of NLR for long-term prognosis in ICAS-related stroke. Forthcoming studies should be undertaken to examine whether NLR levels could estimate stroke recurrence or dementia after sICAS.

CONCLUSIONS

This study has demonstrated that elevated admission NLR was independently correlated with severe stroke and poor functional outcome of sICAS and served as a useful parameter for early prediction of severity and short-term prognosis of sICAS. Therefore, NLR might be an essential and practical prognostic marker in patients with sICAS, helping us identify a target group for preventive therapies.

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 Medical Ethics Committee of Xiangya Hospital, Central South University, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JX and FY conceptualized and designed the study. YY drafted the manuscript and interpreted the data. FY analyzed the data and revised the manuscript. YL, XF, DL, MW, XL, QH, ZL, LZ, TZ, and RT collected the data. All authors contributed to the article and approved the final version to be published.

FUNDING

This work was supported by the National Natural Science Foundation of China (grant number 81671166) and the Fundamental Research Funds for the Central Universities of Central South University (grant number 2019zzts902).

ACKNOWLEDGMENTS

The authors thank all patients for their participation in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.705949/full#supplementary-material

REFERENCES

1. Virani S, Alonso A, Benjamin E, Bittencourt M, Callaway C, Carson A, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation.* (2020) 141:e139–596. doi: 10.1161/CIR.0000000000000757
2. Ornello R, Degan D, Tiseo C, Di Carmine C, Perciballi L, Pistoia F, et al. Distribution and temporal trends from 1993 to 2015 of ischemic stroke subtypes: a systematic review and meta-analysis. *Stroke.* (2018) 49:814–9. doi: 10.1161/STROKEAHA.117.020031
3. Wong L. Global burden of intracranial atherosclerosis. *Int J Stroke Offic J Int Stroke Soc.* (2006) 1:158–9. doi: 10.1111/j.1747-4949.2006.00045.x
4. Wong K, Li H. Long-term mortality and recurrent stroke risk among Chinese stroke patients with predominant intracranial atherosclerosis. *Stroke.* (2003) 34:2361–6. doi: 10.1161/01.STR.0000089017.90037.7A
5. Dearborn J, Zhang Y, Qiao Y, Suri M, Liu L, Gottesman R, et al. Intracranial atherosclerosis and dementia: the Atherosclerosis Risk in Communities (ARIC) Study. *Neurology.* (2017) 88:1556–63. doi: 10.1212/WNL.0000000000003837
6. Suri M, Zhou J, Qiao Y, Chu H, Qureshi A, Mosley T, et al. Cognitive impairment and intracranial atherosclerotic stenosis in general population. *Neurology.* (2018) 90:e1240–e7. doi: 10.1212/WNL.0000000000005250
7. Ross R. Atherosclerosis–an inflammatory disease. *N Engl J Med.* (1999) 340:115–26. doi: 10.1056/NEJM199901143400207
8. Hansson G. Atherosclerosis–an immune disease: the Anitschkov Lecture 2007. *Atherosclerosis.* (2009) 202:2–10. doi: 10.1016/j.atherosclerosis.2008.08.039
9. Zahorec R. Ratio of neutrophil to lymphocyte counts–rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy.* (2001) 102:5–14.
10. Papa A, Emdin M, Passino C, Michelassi C, Battaglia D, Cocci F. Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. *Clin Chim Acta.* (2008) 395:27–31. doi: 10.1016/j.cca.2008.04.019
11. Erturk M, Cakmak HA, Surgit O, Celik O, Aksu HU, Akgul O, et al. Predictive value of elevated neutrophil to lymphocyte ratio for long-term cardiovascular mortality in peripheral arterial occlusive disease. *J Cardiol.* (2014) 64:371–6. doi: 10.1016/j.jjcc.2014.02.019
12. Wang L, Song Q, Wang C, Wu S, Deng L, Li Y, et al. Neutrophil to lymphocyte ratio predicts poor outcomes after acute ischemic stroke: a cohort study and systematic review. *J Neurol Sci.* (2019) 406:116445. doi: 10.1016/j.jns.2019.116445
13. Xue J, Huang W, Chen X, Li Q, Cai Z, Yu T, et al. Neutrophil-to-lymphocyte ratio is a prognostic marker in acute ischemic stroke. *J Stroke Cerebrovasc Dis.* (2017) 26:650–7. doi: 10.1016/j.jstrokecerebrovasdis.2016.11.010
14. Goyal N, Tsivgoulis G, Chang J, Malhotra K, Pandhi A, Ishfaq M, et al. Admission neutrophil-to-lymphocyte ratio as a prognostic biomarker of outcomes in large vessel occlusion strokes. *Stroke.* (2018) 49:1985–7. doi: 10.1161/STROKEAHA.118.021477

15. Nam K, Kwon H, Jeong H, Park J, Kim S, Jeong S. High neutrophil to lymphocyte ratios predict intracranial atherosclerosis in a healthy population. *Atherosclerosis.* (2018) 269:117–21. doi: 10.1016/j.atherosclerosis.2017.12.035
16. Huang L, Sun F, Yin J, Ma Y, Li H, Zhong X, et al. Associations of the neutrophil to lymphocyte ratio with intracranial artery stenosis and ischemic stroke. *BMC Neurol.* (2021) 21:56. doi: 10.1186/s12883-021-02073-3
17. Yu F, Lu J, Li Z, Zhou X, Zeng S, Zhan Q, et al. Correlation of plasma vascular endothelial growth factor and endostatin levels with symptomatic intra- and extracranial atherosclerotic stenosis in a Chinese Han population. *J Stroke Cerebrovasc Dis.* (2017) 26:1061–70. doi: 10.1016/j.jstrokecerebrovasdis.2016.12.021
18. Feng X, Zhou X, Yu F, Liu Z, Wang J, Li Z, et al. Low-normal free triiodothyronine and high leukocyte levels in relation to stroke severity and poor outcome in acute ischemic stroke with intracranial atherosclerotic stenosis. *Int J Neurosci.* (2019) 129:635–41. doi: 10.1080/00207454.2018.1503179
19. Samuels O, Joseph G, Lynn M, Smith H, Chimowitz M. A standardized method for measuring intracranial arterial stenosis. *Am J Neuroradiol.* (2000) 21:643–6.
20. Larrue V, von Kummer RR, Müller A, Bluhmki E. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). *Stroke.* (2001) 32:438–41. doi: 10.1161/01.STR.32.2.438
21. Ferro D, Matias M, Neto J, Dias R, Moreira G, Petersen N, et al. Neutrophil-to-lymphocyte ratio predicts cerebral edema and clinical worsening early after reperfusion therapy in stroke. *Stroke.* (2021) 2021:STROKEAHA120032130. doi: 10.1161/STROKEAHA.120.032130
22. Strbian D, Meretoja A, Putaala J, Kaste M, Tatlisumak T. Cerebral edema in acute ischemic stroke patients treated with intravenous thrombolysis. *Int J Stroke.* (2013) 8:529–34. doi: 10.1111/j.1747-4949.2012.00781.x
23. Maestrini I, Tagzirt M, Gautier S, Dupont A, Mendyk A, Susen S, et al. Analysis of the association of MPO and MMP-9 with stroke severity and outcome: Cohort study. *Neurology.* (2020) 95:e97–e108. doi: 10.1212/WNL.0000000000009179
24. Maestrini I, Strbian D, Gautier S, Haapaniemi E, Moulin S, Sairanen T, et al. Higher neutrophil counts before thrombolysis for cerebral ischemia predict worse outcomes. *Neurology.* (2015) 85:1408–16. doi: 10.1212/WNL.0000000000002029
25. Yu S, Arima H, Bertmar C, Clarke S, Herkes G, Krause M. Neutrophil to lymphocyte ratio and early clinical outcomes in patients with acute ischemic stroke. *J Neurol Sci.* (2018) 387:115–8. doi: 10.1016/j.jns.2018.02.002
26. Nam K, Kim T, Lee J, Kwon H, Lee Y, Ko S, et al. High Neutrophil-to-lymphocyte ratio predicts stroke-associated pneumonia. *Stroke.* (2018) 49:1886–92. doi: 10.1161/STROKEAHA.118.021228
27. Zhang WB, Zeng YY, Wang F, Cheng L, Tang WJ, Wang XQ, et al. high neutrophil-to-lymphocyte ratio predicts hemorrhagic transformation of large atherosclerotic infarction in patients with acute ischemic stroke. *Aging.* (2020) 12:2428–39. doi: 10.18632/aging.102752
28. Wang Y, Meng R, Liu G, Cao C, Chen F, Jin K, et al. Intracranial atherosclerotic disease. *Neurobiol Dis.* (2019) 124:118–32. doi: 10.1016/j.nbd.2018.11.008
29. Chung D, Lee K, Choi J, Kim N, Kim O, Kim S, et al. Blood neutrophil/lymphocyte ratio is associated with cerebral large-artery atherosclerosis but not with cerebral small-vessel disease. *Front Neurol.* (2020) 11:1022. doi: 10.3389/fneur.2020.01022
30. Buck B, Liebeskind D, Saver J, Bang O, Yun S, Starkman S, et al. Early neutrophilia is associated with volume of ischemic tissue in acute stroke. *Stroke.* (2008) 39:355–60. doi: 10.1161/STROKEAHA.107.490128
31. Semerano A, Laredo C, Zhao Y, Rudilosso S, Renú A, Llull L, et al. Leukocytes, collateral circulation, and reperfusion in ischemic stroke patients treated with mechanical thrombectomy. *Stroke.* (2019) 50:3456–64. doi: 10.1161/STROKEAHA.119.026743
32. Price C, Menon D, Peters A, Ballinger J, Barber R, Balan K, et al. Cerebral neutrophil recruitment, histology, and outcome in acute ischemic stroke: an imaging-based study. *Stroke.* (2004) 35:1659–64. doi: 10.1161/01.STR.0000130592.71028.92
33. Perez-de-Puig I, Miró-Mur F, Ferrer-Ferrer M, Gelpi E, Pedragosa J, Justicia C, et al. Neutrophil recruitment to the brain in mouse and human ischemic stroke. *Acta Neuropathol.* (2015) 129:239–57. doi: 10.1007/s00401-014-1381-0
34. Gidday J, Gasche Y, Copin J, Shah A, Perez R, Shapiro S, et al. Leukocyte-derived matrix metalloproteinase-9 mediates blood-brain barrier breakdown and is proinflammatory after transient focal cerebral ischemia. *Am J Physiol Heart Circ Physiol.* (2005) 289:H558–68. doi: 10.1152/ajpheart.01275.2004
35. Rosell A, Cuadrado E, Ortega-Aznar A, Hernández-Guillamon M, Lo E, Montaner J. MMP-9-positive neutrophil infiltration is associated to blood-brain barrier breakdown and basal lamina type IV collagen degradation during hemorrhagic transformation after human ischemic stroke. *Stroke.* (2008) 39:1121–6. doi: 10.1161/STROKEAHA.107.500868
36. Kang L, Yu H, Yang X, Zhu Y, Bai X, Wang R, et al. Neutrophil extracellular traps released by neutrophils impair revascularization and vascular remodeling after stroke. *Nat Commun.* (2020) 11:2488. doi: 10.1038/s41467-020-16191-y
37. Courties G, Herisson F, Sager H, Heidt T, Ye Y, Wei Y, et al. Ischemic stroke activates hematopoietic bone marrow stem cells. *Circ Res.* (2015) 116:407–17. doi: 10.1161/CIRCRESAHA.116.305207
38. Soehnlein O. Multiple roles for neutrophils in atherosclerosis. *Circ Res.* (2012) 110:875–88. doi: 10.1161/CIRCRESAHA.111.257535
39. Warnatsch A, Ioannou M, Wang Q, Papayannopoulos V. Inflammation. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis *Science (New York, NY).* (2015) 349:316–20. doi: 10.1126/science.aaa8064
40. Döring Y, Soehnlein O, Weber C. Neutrophil extracellular traps in atherosclerosis and atherothrombosis. *Circ Res.* (2017) 120:736–43. doi: 10.1161/CIRCRESAHA.116.309692
41. Kim J, Song T, Park J, Lee H, Nam C, Nam H, et al. Different prognostic value of white blood cell subtypes in patients with acute cerebral infarction. *Atherosclerosis.* (2012) 222:464–7. doi: 10.1016/j.atherosclerosis.2012.02.042
42. Ren H, Liu X, Wang L, Gao Y. Lymphocyte-to-monocyte ratio: a novel predictor of the prognosis of acute ischemic stroke. *J Stroke Cerebrovasc Dis.* (2017) 26:2595–602. doi: 10.1016/j.jstrokecerebrovasdis.2017.06.019
43. Urra X, Cervera A, Villamor N, Planas A, Chamorro A. Harms and benefits of lymphocyte subpopulations in patients with acute stroke. *Neuroscience.* (2009) 158:1174–83. doi: 10.1016/j.neuroscience.2008.06.014
44. Macrez R, Ali C, Toutirais O, Le Mauff B, Defer G, Dirnagl U, et al. Stroke and the immune system: from pathophysiology to new therapeutic strategies. *Lancet Neurol.* (2011) 10:471–80. doi: 10.1016/S1474-4422(11)70066-7
45. Liesz A, Hu X, Kleinschnitz C, Offner H. Functional role of regulatory lymphocytes in stroke: facts and controversies. *Stroke.* (2015) 46:1422–30. doi: 10.1161/STROKEAHA.114.008608
46. Liesz A, Suri-Payer E, Veltkamp C, Doerr H, Sommer C, Rivest S, et al. Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke. *Nat Med.* (2009) 15:192–9. doi: 10.1038/nm.1927

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 11 August 2021
doi: 10.3389/fneur.2021.671778

Hemodynamic Versus Anatomic Assessment of Symptomatic Atherosclerotic Middle Cerebral Artery Stenosis: the Relationship Between Pressure Wire Translesional Gradient and Angiographic Lesion Geometry

Long Li[1], Bin Yang[1], Adam A. Dmytriw[2], Tao Wang[1], Jichang Luo[1], Yanling Li[3], Yan Ma[1], Jian Chen[1], Yabing Wang[1], Peng Gao[4], Yao Feng[1], Xuesong Bai[1], Xiao Zhang[1], Jia Dong[4], Renjie Yang[1], Liqun Jiao[1,4†] and Feng Ling[1,4*†]*

[1] Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China, [2] Neuroradiology & Neurointervention Service, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States, [3] Department of Epidemiology and Biostatistics, School of Public Health, Capital Medical University, Beijing, China, [4] Department of Interventional Neuroradiology, Xuanwu Hospital, Capital Medical University, Beijing, China

Background: Intracranial cerebral atherosclerosis (ICAS) is a leading etiology of ischemic stroke. The diagnosis and assessment of intracranial stenosis are shifting from anatomic to hemodynamic for better risk stratification. However, the relationships between lesion geometry and translesional pressure gradient have not been clearly elucidated.

Methods: Patients with symptomatic unifocal M1 middle cerebral artery (M1-MCA) stenosis were consecutively recruited. The translesional pressure gradient was measured with a pressure wire and was recorded as both mean distal/proximal pressure ratios (Pd/Pa) and translesional pressure difference (Pa–Pd). Lesion geometry measured on angiography was recorded as diameter stenosis, minimal lumen diameter, and lesion length. The correlations between pressure-derived and angiography-derived indices were then analyzed.

Results: Forty-three patients were analyzed. A negative correlation was found between Pd/Pa and diameter stenosis ($r = -0.371$; $p = 0.014$) and between Pa – Pd and minimal lumen diameter ($r = -0.507$; $p = 0.001$). A positive correlation was found between Pd/Pa and minimal lumen diameter ($r = 0.411$; $p = 0.006$) and between Pa – Pd and diameter stenosis ($r = 0.466$; $p = 0.002$).

Conclusions: In a highly selected ICAS subgroup, geometric indices derived from angiography correlate significantly with translesional pressure gradient indices. However,

OPEN ACCESS

Edited by:
Hong-Qi Zhang,
Capital Medical University, China

Reviewed by:
Mehmet Akif Topçuoglu,
Hacettepe University, Turkey
Qazi Zeeshan,
University at Buffalo, United States

***Correspondence:**
Liqun Jiao
liqunjiao@sina.cn
Feng Ling
ling-feng@vip.163.com

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *24 February 2021*
Accepted: *25 June 2021*
Published: *11 August 2021*

Citation:
Li L, Yang B, Dmytriw AA, Wang T, Luo J, Li Y, Ma Y, Chen J, Wang Y, Gao P, Feng Y, Bai X, Zhang X, Dong J, Yang R, Jiao L and Ling F (2021) Hemodynamic Versus Anatomic Assessment of Symptomatic Atherosclerotic Middle Cerebral Artery Stenosis: the Relationship Between Pressure Wire Translesional Gradient and Angiographic Lesion Geometry. Front. Neurol. 12:671778. doi: 10.3389/fneur.2021.671778

the correlation strength is weak-to-moderate, which implies that anatomic assessment could only partly reflect hemodynamic status. Translesional pressure gradient measured by pressure wire may serve as a more predictive marker of ICAS severity. More factors need to be identified in further studies.

Keywords: intracranial cerebral atherosclerosis, stenosis, hemodynamics, translesional pressure gradient, Pd/Pa, Pa-Pd

INTRODUCTION

Intracranial cerebral atherosclerosis (ICAS) is the most common cause of ischemic events worldwide, particularly in Asian, Hispanics, and Africans, and may be underestimated in Caucasians (1–4). In the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, higher degrees of anatomic stenosis were identified as independent predictors of recurrent ischemic stroke (5, 6). This inspired investigators to adopt more aggressive treatments, including balloon angioplasty or stenting, toward improved outcomes in patients with >70% stenosis. However, failures of previous randomized controlled trials have raised the concern that there may be bias in identifying patients at high risk solely on anatomic assessment (7–9). Additional approaches are thus urgently needed.

In ICAS patients with ischemic stroke, identification of the underlying mechanism is critical for management. The current proposed mechanisms include artery-to-artery embolism, perforator occlusion, hemodynamic dysfunction, and mixed etiologies (10). Patients with symptomatic ICAS and hemodynamic insufficiency may benefit from angioplasty beyond optimal medical therapy alone, as the former could further improve distal perfusion (11–13). Thus, hemodynamic assessment may improve stratification of patients for such treatment strategies. Hemodynamic insufficiency may be inferred from infarct pattern (i.e., watershed infarction) or various models of cerebral perfusion imaging (e.g., asymmetry between bilateral hemispheres). However, these are ultimately evaluations of brain parenchyma, and focal or arterial lesion-related assessments of hemodynamics could have more important therapeutic implications.

Fractional flow reserve (FFR), defined as the ratio of maximum flow in the presence of a stenosis to normal maximum flow, has become the gold standard in assessing the hemodynamic insufficiency of epicardial coronary stenosis (14–16). Besides, translesional pressure gradient and its derivative indices, for instance, rest Pd/Pa and instantaneous wave-free ratio (iFR), have been widely used on guiding coronary revascularization therapy (17–20). Basically, they utilize a pressure wire to measure mean distal coronary (Pd) and arterial pressure (Pa) with or without pharmacological vasodilation and present as their radio (Pd/Pa). It has demonstrated that FFR and these lesion-related indices are superior on defining myocardial ischemia risk than the degree of coronary stenosis.

Despite that hemodynamic assessment by pressure wire has been well-established in coronary revascularization, the application of this invasive method in ICAS has rarely been explored. A few studies validated its feasibility (21–24); however, the difference and relationships between pressure-derived and angiography-derived indices have not been fully elucidated. In the current study, we preliminarily investigated the correlations in a selected group of ICAS patients.

MATERIALS AND METHODS

Patient Selection

From June 2019 to December 2020, patients that were scheduled for digital subtraction angiography (DSA) for symptomatic intracranial atherosclerosis stenosis were consecutively recruited to an observational study in our quaternary center. The study protocol was approved by the local Institutional Review Board, and all patients provided written informed consent.

Adult patients meeting the following criteria were enrolled for the current study: (1) presented with recurrent stroke or transient ischemic attack (TIA) within the past 6 months attributed to 50–99% unifocal M1 middle cerebral artery (M1-MCA) stenosis; (2) patients understood that the pressure measurements were part of a novel functional assessment of MCA stenosis for study purposes and give permission to the off-label use of a pressure wire; and (3) expected ability to traverse the lesion with a pressure wire. We excluded patients based on the following criteria: (1) non-atherosclerotic MCA stenosis (e.g., dissection, moyamoya disease, or vasculitis); (2) concurrent >50% stenosis or occlusion of intra- or extracranial arteries; (3) history of surgical and/or interventional procedures of intra- and extracranial arteries; (4) massive cerebral infarction (>1/2 MCA territory); or (5) known intracranial tumor, infection, hydrocephalus, aneurysm, or arteriovenous malformation.

Cerebrovascular Angiography and Intracranial Pressure Measurements

General anesthesia was employed in all cases. A 6F sheath was used to access the femoral artery, after which a 6F guiding catheter was positioned in the ipsilateral petrous or foraminal internal carotid artery (ICA) segment with a 0.035-inch guidewire. Three-dimensional DSA was obtained for selecting the optimal view to access lesion geometry, including minimal lumen diameter, lesion length, and diameter stenosis. The diameter stenosis grade was calculated by measuring the minimal lumen diameter at the most stenotic site compared with the normal proximal segment diameter (first choice) or the normal feeding artery diameter (second choice), as the modified WASID method recommended in 2009 (25).

A 0.014-inch pressure wire (C12008, Abbot St. Jude Medical, Minneapolis, MN, USA), designed for coronary systems, was used off-label for intracranial pressure measurements. For safety,

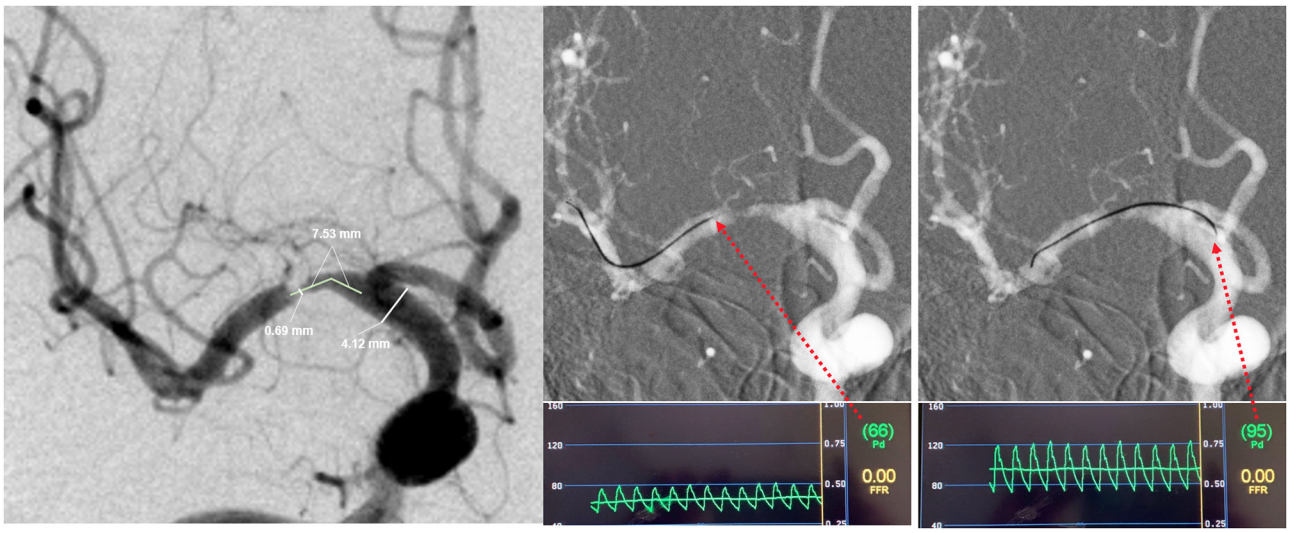


FIGURE 1 | Representative case of intracranial lesion geometry and translesional pressure measurements. In this patient, **(A)** the minimal lumen diameter was 0.69 mm, and the normal segment diameter was 4.12 mm, so the stenosis was calculated as 83.3%, and the lesion length was 7.53 mm; **(B)** the mean distal pressure (Pd) was 66 mmHg; **(C)** the mean proximal pressure (Pa) was 95 mmHg. The translesional pressure gradient radio (Pd/Pa) and translesional pressure gradient difference (Pa–Pd) were thus found to be 0.69 and 29 mmHg.

a microcatheter (Rebar18, eV3 Covidien, Irvine, CA, USA) was used by exchange technique in all procedures to aid the pressure wire crossing the stenosis under roadmap guidance. Mean distal pressure (defined as Pd in current study) and proximal pressure (defined as Pa) were measured successively under resting conditions. The translesional pressure gradient radio (Pd/Pa) and translesional pressure gradient difference (Pa–Pd) were calculated. A representative case is displayed in **Figure 1**.

In addition to direct correlation analysis, subgroup analysis based on stenosis severity classification and collateral circulation was also performed. Patients were divided into moderate (50–69%) and severe (70–99%) stenosis, as the SAMMPRIS did (12). And collateral circulation was evaluated using the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral flow grading system (26). Patients with grades 0–2 were grouped as poor collateral circulation, and grades 3–4 were deemed good ones.

Intra-Observer and Inter-Observer Variability

Two experienced neurointerventionalists (first observer [LL] and second observer [BY]), who were blinded to clinical data and pressure values, measured angiographic geometry of all lesions independently. To assess intra-observer variability, the first grader repeated the step 4 weeks after an initial measurement again.

Statistical Analyses

Intra- and inter-observer measurements of minimal lumen diameter, diameter stenosis, and lesion length were evaluated by absolute agreement model of intraclass correlation coefficient (ICC) analyses. Quantitative data were examined to determine presence of normal distribution. Continuous variables of normally distributed were expressed as mean ± standard deviation, or median [interquartile range (IQR)] in the presence of abnormal distribution, and qualitative data were described as percentages. The correlations between Pd/Pa or Pa–Pd and stenosis and lesion length were assessed by Pearson's test for normally distributed continuous variables while Spearman's test for non-normally distributed variables. All statistical analyses were carried out in SPSS version 23.0 and R studio. All reported p-values were two-sided, and $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Demographics

Proximal and distal pressure datasets were obtained in 43 consecutive patients after angiography. There were no complications related to translesional pressure measurement. Mean age was 54 ± 10 years, and 31 (72.1%) were male. The qualifying event was recurrent stroke in 30 patients (69.8%) and recurrent TIA in the other 13 patients (30.2%). The mean angiographic percentage of stenosis and minimal lumen diameter were 75.9 ± 7.8% and 0.59 ± 0.22 mm, respectively. The mean lesion length was 6.81 (median, 5.90; IQR, 4.78–8.62) mm. Patient characteristics and vascular risk factors are summarized in **Table 1**.

Correlation Between Pressure-Derived and Angiography-Derived Indices

Regarding *correlation between resting Pd/Pa and lesion geometry*, the median resting Pd/Pa was 0.69 (IQR 0.49–0.74). A weak but statistically significant correlation was found between resting Pd/Pa and diameter stenosis ($r = -0.371$; $p = 0.014$; **Figure 2A**).

TABLE 1 | Clinical characteristics and lesion profile.

Variables	*N* = 43
Age, mean (±SD), years	54 (±10)
Male, *n* (%)	31 (72.1)
BMI, mean (±SD)	25.7 (±2.7)
Hypertension, *n* (%)	31 (72.1)
Diabetes mellitus, *n* (%)	14 (32.6)
Hyperlipidemia, *n* (%)	16 (37.2)
Coronary heart disease, *n* (%)	3 (7.0)
Atrial fibrillation, *n* (%)	0
Tobacco use, *n* (%)	22 (51.2)
Alcohol use, *n* (%)	20 (46.5)
Qualifying event—stroke, *n* (%)	30 (69.8)
Qualifying event—TIA, *n* (%)	13 (30.2)
Diameter stenosis, mean (±SD), %	75.9 (±7.8)
Diameter stenosis-–50–69%, *n* (%)	6 (14.0)
Diameter stenosis-–70–99%, *n* (%)	37 (86.0)
Minimal lumen diameter, mean (±SD), mm	0.59 (±0.22)
Lesion length, median (IQR), mm	5.90 (4.78–8.62)
Resting Pd/Pa, median (IQR)	0.69 (0.49–0.74)
Pa – Pd, mean (±SD), mmHg	28 (±13)
Collateral grading (ASITN/SIR), *n* (%)	
Grade 0	1(2.3)
Grade 1	15 (34.9)
Grade 2	1 (2.3)
Grade 3	2 (4.7)
Grade 4	24 (55.8)

BMI, body mass index; TIA, transient ischemic attack; IQR, interquartile range; ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology collateral flow grading system.

The correlation was stronger between resting Pd/Pa and minimal lumen diameter ($r = 0.411$; $p = 0.006$; **Figure 2B**). No significant correlation was found between resting Pd/Pa and lesion length (**Figure 2C**).

Regarding *correlation between translesional pressure gradient and lesion geometry*, the translesional pressure gradient (Pa–Pd) ranges from 7 to 64 (mean 28 ± 13) mmHg. Compared with resting Pd/Pa, it presented further enhanced correlations with both diameter stenosis ($r = 0.466$; $p = 0.002$; **Figure 2D**) and minimal lumen diameter ($r = -0.507$; $p = 0.001$; **Figure 2E**). This was also uncorrelated with lesion length (**Figure 2F**).

Statistically, the strongest correlation was between Pa–Pd and minimal lumen diameter (correlation coefficients: 0.507).

Correlation Between Pressure-Derived and Angiography-Derived Indices Based on Stenosis Severity Classification and Collateral Circulation

Subgroup Analysis Based on Stenosis Severity Classification

Six patients (14%) were found to have moderate stenosis. There was no significant difference in patients with moderate and severe stenoses on neither Pd/Pa (0.69 ± 0.26 vs. 0.62 ± 0.17, $p = 0.107$) nor Pa – Pd (22.5 ± 20.1 vs. 29.2 ± 11.5 mmHg, $p = 0.248$).

In the moderate stenosis group, no significant correlation was found between pressure-derived and angiography-derived indices. In the severe stenosis group, statistically significant correlations were found between resting Pd/Pa and diameter stenosis ($r = -0.341$; $p = 0.039$), and between Pa–Pd and diameter stenosis ($r = 0.352$; $p = 0.033$) and minimal lumen diameter ($r = -0.343$; $p = 0.038$). The detailed results are presented in **Table 2**.

Subgroup Analysis Based on Collateral Circulation

Seventeen patients (39.5%) were grouped as poor collateral circulation status, and the other 26 (60.5%) were grouped as good. The correlation between pressure-derived and angiography-derived indices was still significant in patients with good collateral circulation. However, no significant correlation was found in patients with poor collateral circulation. The detailed results are presented in **Table 3**.

Intra-Observer and Inter-Observer Variability

Intra-observer measurements of lesion geometry revealed ICC values of 0.966, 0.976, and 0.955 for minimal lumen diameter, diameter stenosis, and lesion length, respectively, which indicate near-perfect agreement (**Table 4**). Meanwhile, inter-observer measurements revealed ICC values of 0.870, 0.842, and 0.902 for minimal lumen diameter, diameter stenosis, and lesion length respectively, which indicate good agreement (**Table 4**).

DISCUSSION

The present study demonstrated that in patients with symptomatic M1 stenosis, hemodynamic indices as assessed by pressure wire are significantly associated with anatomic indices on DSA. This was reflected by weak-to-moderate correlations between translesional pressure gradient measured by pressure wire (Pd/Pa and Pa–Pd) and lesion geometry measured by angiography (diameter stenosis and minimal lumen diameter). Our interpretation is that either luminal diameter or percentage stenosis only partly reflects hemodynamic status, and stenoses require greater assessment to evaluate the hemodynamic functional significance of intracranial atherosclerotic stenosis. Translesional pressure gradient may serve as a more predictive marker of ICAS severity.

A few studies have investigated the relationship between luminal narrowing and hemodynamic indices, measured by pressure wire in ICAS, without consensus reached as yet on its utility. Mario et al. reported that that neither luminal diameter nor percentage stenosis (visual or quantified) was correlated with distal/proximal pressure ratios or proximal-to-distal pressure gradients (23), which is contrary to our findings. The difference may be due to the small sample size and various lesion sites ($n =$ 9: 2 cavernous, three supraclinoid, and 4 M1) in their study.

Liu et al. demonstrated a weak-to-moderate correlation between anatomic stenosis and hemodynamic measurements across an atherosclerotic lesion (22), which is consistent with our

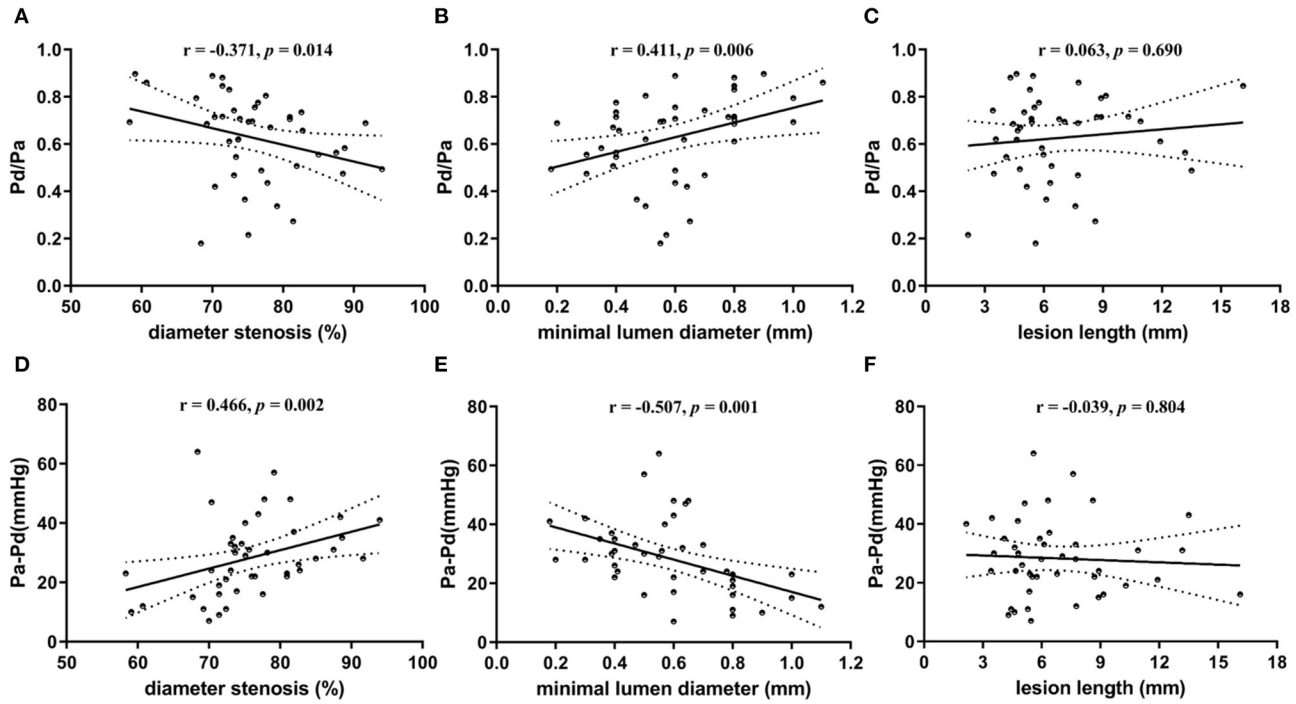


FIGURE 2 | Scatter plots showing correlation between translesional pressure gradient and lesion geometry. **(A)** Pd/Pa vs. diameter stenosis; **(B)** Pd/Pa vs. minimal lumen diameter; **(C)** Pd/Pa vs. lesion length; **(D)** Pa-Pd vs. diameter stenosis; **(E)** Pa-Pd vs. minimal lumen diameter; **(F)** Pa-Pd vs. lesion length. Pd indicates distal pressure of stenosis; and Pa indicates proximal pressure of stenosis. ※ indicates Spearman test for non-normally distributed variables; and † indicates Pearson test for normally distributed continuous variables.

TABLE 2 | Correlation between pressure-derived and angiography-derived indices based on stenosis severity classification.

	Moderate stenosis (50–69%)				Severe stenosis (70–99%)			
	Resting Pd/Pa		Pa–Pd (mmHg)		Resting Pd/Pa		Pa–Pd (mmHg)	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Minimal lumen diameter (mm)	0.638	0.173	−0.116	0.827	0.286	0.087	−0.343	0.038
Diameter stenosis (%)	−0.600	0.208	0.029	0.957	−0.341	0.039	0.352	0.033
Lesion length (mm)	0.143	0.787	0.486	0.329	0.051	0.764	−0.078	0.645

TABLE 3 | Correlation between pressure-derived and angiography-derived indices based on collateral circulation.

	Poor collateral (ASITN/SIR 0–2)				Good collateral (ASITN/SIR 3–4)			
	Resting Pd/Pa		Pa–Pd (mmHg)		Resting Pd/Pa		Pa–Pd (mmHg)	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Minimal lumen diameter (mm)	0.318	0.213	−0.591	0.012	0.462	0.018	−0.492	0.011
Diameter stenosis (%)	−0.129	0.622	0.327	0.200	−0.469	0.016	0.538	0.005
Lesion length (mm)	0.105	0.687	−0.115	0.659	−0.069	0.736	0.083	0.687

ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology collateral flow grading system.

study. However, the authors emphasized that this only reached statistical significance in patients with poor collateralization, which implies that collateral state may be another factor that affects translesional pressure gradient in ICAS, which was not shown in our study. There may be several reasons for the difference. First, the sample size of both Liu's ($n = 25$) and our

TABLE 4 | Intra-and inter-observer variability analyses of lesion geometry.

	Minimal lumen diameter (mm)		Diameter stenosis (%)		Lesion length (mm)	
	ICC (95% CI)	*p*	ICC (95% CI)	*p*	ICC (95% CI)	*p*
Intra-observer	0.966 (0.937, 0.981)	<0.001	0.976 (0.956, 0.987)	<0.001	0.955 (0.951, 0.957)	<0.001
Inter-observer	0.870 (0.774, 0.927)	<0.001	0.842 (0.726, 0.911)	<0.001	0.902 (0.831, 0.921)	<0.001

Intra-observer and inter-observer variability and agreement were evaluated using absolute agreement model of ICC analyses. CI, confidence interval; ICC, intraclass correlation coefficient.

study ($n = 43$) was limited. Therefore, the results of subgroup analysis were unreliable. Second, the current grading system, for instance, the ASITN/SIR grade (26), the Capillary Index Score (CIS) (27), or the MMD Collateral Grading System (28), may have inadequate accuracy to grade the hemodynamic status for this application. A novel composite grading system, such as the angiographic DILEMMA score for cardiovascular disease (29), which combines lesion geometry indices and dynamic changes in angiography, could be more powerful. In addition, this score requires the inclusion of less-selected patients.

It should be noted that an accurate and precise measurement of the lesion geometry is critical for meaningful assessment of ICAS or other hemodynamic analyses. For stenosis grading of the intracranial major cerebral arteries, the WASID Group established a reliable method in 1999 (30), which is now widely used in clinical practice (22). For the denominator, the normal proximal segment, distal segment, and feeding artery diameter are chosen as the first, second, and third options, respectively. However, to avoid the error caused by slight physiologic distal narrowing of some intracranial arteries, we always choose proximal diameter as the denominator (i.e., the normal proximal segment diameter and feeding artery diameter as the first and second choices, respectively) (25). Furthermore, for circumventing the limitation on choosing a denominator, we also compared the minimal luminal diameter as an independent index with accompanying pressure-derived indices. Our findings suggest that this method may be more accurate than grade of stenosis alone.

The relationship between pressure gradient and lesion geometry was also studied in interventional cardiology literature. The results appear to vary according to the population included. A curvilinear relation was found by Jozef et al. between myocardial FFR and both stenosis diameter ($r = 0.79$) and the smallest lumen diameter ($r = 0.82$) (31). Osman et al. found a significant linear correlation between FFR and lesion length ($r = -0.314$) and minimal lumen diameter ($r = 0.415$) (29). Antonio et al. demonstrated that FFR values were correlated to the smallest lumen diameter ($r = 0.34$) and stenosis diameter ($r = -0.28$) (32). Compared with the coronary arteries, intracranial arteries have more intricate collateral circulation (i.e., the circle of Willis and secondary collateral pathways) and cerebral blood flow autoregulation. In addition, blood pressure, lesion morphology, and characteristics, as well as the territory perfused, may also affect the hemodynamic state of cerebral arteries. In ICAS, the application of hemodynamic assessment is still in its naissance and requires further exploratory study and evidence.

Impediments to replicating the success of focal hemodynamic assessment in cardiovascular disease in the context of ICAS partly lie in the lack of well-recognized and reliable evaluation methods. For instance, there is no similar gold standard to exercise testing to indicate inducible ischemia in cerebrovascular field (33). Xenon computed tomography (Xe-CT), the gold standard method to quantitatively measure cerebral blood flow, is difficult to obtain and intolerant for a considerable proportion of patients (34). Nevertheless, an increasing number of stroke clinicians are beginning to shift their focus from intracranial stenosis grading to hemodynamic assessment.

Some researchers have attempted to establish the relations between hemodynamic indices and stroke risk by non-invasive approaches, with promising results. The modalities include signal intensity ratio (SIR) on time-of-flight magnetic resonance angiography, computational fluid dynamics (CFD) modeling, and quantitative magnetic resonance angiography (QMRA) (35–41). But all have their own limitations. We assume that direct translesional pressure gradient measurement could play a leading role. And large and prospective cohort studies have been started, which may provide stronger evidence.

Study Limitations

Limitations of the current study include the following: (1) the findings are based on a highly selected group. In patients with symptomatic unifocal M1 stenosis, the factors affecting hemodynamic status may be limited to blood pressure, secondary collateral circulation (i.e., anastomoses from ipsilateral anterior cerebral artery and posterior cerebral artery to MCA supply) and distal territory resistance. Thus, the correlation may alter as the lesion site changes. For instance, when lesions are in the terminal segment of ICA (distal to posterior communicating artery) or middle segment of ICA (proximal to posterior communicating artery), blood flow may vary through the circle of Willis. (2) Unlike the measurement of FFR in coronary stenosis, we measured the pressure without the use of vasodilatory agents, as previous studies have demonstrated that intracranial arteries are often already maximally dilated in symptomatic patients (42, 43). Based on this, we further simplified the process of pressure measurement as we equalized the pressure sensor to zero only once before introducing the pressure wire into the target vessel. Thereafter, we measured Pd and Pa successively by pullback of the pressure wire. We assumed the pressure

dataset was recorded under the same condition and that its accuracy was not affected even if there was a so-called "drift" of the pressure values. Further tests are needed to verify this approach.

CONCLUSIONS

This observational study preliminary indicates that in patients with unifocal M1 stenosis, geometry indices derived from angiography correlate significantly with translesional pressure gradient indices. However, the correlation strength is weak-to-moderate, which implies that anatomic assessment could only partly reflect the hemodynamic status. Translesional pressure gradients measured by pressure wire may serve as a more predictive marker of ICAS severity. More factors need to be identified in further studies.

DATA AVAILABILITY STATEMENT

The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Xuanwu Hospital (protocol code (20170613) and date of approval (20171011)). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FL and LJ: conceptualization, YM, BY, YL, and LL: methodology, YL: formal analysis, JL, YM, JC, YW, PG, YF, XB, XZ, JD, and RY: data curation, LL: writing—original draft preparation, TW and AD: writing—review and editing, FL: supervision, LJ: project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

FUNDING

This research was funded by the National Key Research and Development Project (2016YFC1301701) and the Beijing Municipal Administration of Hospitals Incubating Program (PX2020034).

REFERENCES

1. Wong KS, Huang YN, Gao S, Lam WW, Chan YL, Kay R. Intracranial stenosis in Chinese patients with acute stroke. *Neurology*. (1998) 50:812–3. doi: 10.1212/WNL.50.3.812
2. Kim JT, Yoo SH, Kwon JH, Kwon SU, Kim JS. Subtyping of ischemic stroke based on vascular imaging: analysis of 1,167 acute, consecutive patients. *J Clin Neurol*. (2006) 2:225–30. doi: 10.3988/jcn.2006.2.4.225
3. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The northern manhattan stroke study. *Stroke*. (1995) 26:14–20. doi: 10.1161/01.STR.26.1.14
4. Mazighi M, Labreuche J, Gongora-Rivera F, Duyckaerts C, Hauw JJ, Amarenco P. Autopsy prevalence of intracranial atherosclerosis in patients with fatal stroke. *Stroke*. (2008) 39:1142–7. doi: 10.1161/STROKEAHA.107.496513
5. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med*. (2005) 352:1305–16. doi: 10.1056/NEJMoa043033
6. Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. *Circulation*. (2006) 113:555–63. doi: 10.1161/CIRCULATIONAHA.105.578229
7. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*. (2011) 365:993–1003. doi: 10.1056/NEJMoa1105335
8. 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
9. Pu Y, Lan L, Leng X, Wong LK, Liu L. Intracranial atherosclerosis: From anatomy to pathophysiology. *Int J Stroke*. (2017) 12:236–45. doi: 10.1177/1747493016685716
10. Lopez-Cancio E, Matheus MG, Romano JG, Liebeskind DS, Prabhakaran S, Turan TN, et al. Infarct patterns, collaterals and likely causative mechanisms of stroke in symptomatic intracranial atherosclerosis. *Cerebrovasc Dis*. (2014) 37:417–22. doi: 10.1159/000362922
11. Izumi T, Imamura H, Sakai N, Miyachi S. Angioplasty and stenting for intracranial stenosis. *Neurol Med Chir*. (2014) 54:46–53. doi: 10.2176/nmc.oa.2013-0319
12. Qureshi AI, Al-Senani FM, Husain S, Janjua NA, Lanzino G, Lavados PM, et al. Intracranial angioplasty and stent placement after stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) trial: present state and future considerations. *J Neuroimag*. (2012) 22:1–13. doi: 10.1111/j.1552-6569.2011.00685.x
13. Yaghi S, Prabhakaran S, Khatri P, Liebeskind DS. Intracranial atherosclerotic disease. *Stroke*. (2019) 50:1286–93. doi: 10.1161/STROKEAHA.118.024147
14. Pijls NH, Bech GJ, De Bruyne B, van Straten A. Clinical assessment of functional stenosis severity: use of coronary pressure measurements for the decision to bypass a lesion. *Ann Thorac Surg*. (1997) 63:S6–11. doi: 10.1016/S0003-4975(97)00418-9
15. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol*. (2010) 56:177–84. doi: 10.1016/j.jacc.2010.04.012
16. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. (2012) 367:991–1001. doi: 10.1056/NEJMoa1205361
17. Jeremias A, Maehara A, Genereux P, Asrress KN, Berry C, De Bruyne B, et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *J Am Coll Cardiol*. (2014) 63:1253–61. doi: 10.1016/j.jacc.2013.09.060
18. Casadonte L, Verhoeff BJ, Piek JJ, VanBavel E, Spaan JAE, Siebes M. Influence of increased heart rate and aortic pressure on resting indices of functional coronary stenosis severity. *Basic Res Cardiol*. (2017) 112:61. doi: 10.1007/s00395-017-0651-0
19. Hennigan B, Oldroyd KG, Berry C, Johnson N, McClure J, McCartney P, et al. Discordance between resting and hyperemic indices of coronary stenosis severity: the VERIFY 2 study (a comparative study of resting coronary pressure gradient, instantaneous wave-free ratio and fractional flow reserve in an unselected population referred for invasive angiography). *Circ Cardiovasc Interv*. (2016) 9:e004016. doi: 10.1161/CIRCINTERVENTIONS.116.004016

20. Kobayashi Y, Johnson NP, Berry C, De Bruyne B, Gould KL, Jeremias A, et al. The influence of lesion location on the diagnostic accuracy of adenosine-free coronary pressure wire measurements. *JACC Cardiovasc Interv*. (2016) 9:2390–9. doi: 10.1016/j.jcin.2016.08.041
21. Han YF, Liu WH, Chen XL, Xiong YY, Yin Q, Xu GL, et al. Severity assessment of intracranial large artery stenosis by pressure gradient measurements: a feasibility study. *Catheter Cardiovasc Interv*. (2016) 88:255–61. doi: 10.1002/ccd.26414
22. Liu X, Dornbos D, 3rd, Pu Y, Leng X, Song L, Jia B, et al. Collateral circulation alters downstream hemodynamic stress caused by intracranial atherosclerotic stenosis. *Neurol Res*. (2017) 39:498–503. doi: 10.1080/01616412.2017.1315483
23. Zanaty M, Rossen JD, Roa JA, Nakagawa D, Hudson JS, Kasab SA, et al. Intracranial atherosclerosis: a disease of functional, not anatomic stenosis? How trans-stenotic pressure gradients can help guide treatment. *Oper Neurosurg*. (2020) 18:599–605. doi: 10.1093/ons/opz335
24. Liu J, Yan Z, Pu Y, Shiu WS, Wu J, Chen R, et al. Functional assessment of cerebral artery stenosis: a pilot study based on computational fluid dynamics. *J Cereb Blood Flow Metab*. (2017) 37:2567–76. doi: 10.1177/0271678X16671321
25. Schumacher HC, Meyers PM, Higashida RT, Derdeyn CP, Lavine SD, Nesbit GM, et al. Reporting standards for angioplasty and stent-assisted angioplasty for intracranial atherosclerosis. *J Neurointerventional Surg*. (2010) 2:324–40. doi: 10.1136/jnis.2010.002345
26. 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
27. Al-Ali F, Berkhemer OA, Yousman WP, Elias JJ, Bender EN, Lingsma HF, et al. The capillary index score as a marker of viable cerebral tissue: proof of concept-the capillary index score in the MR CLEAN (multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands) trial. *Stroke*. (2016) 47:2286–91. doi: 10.1161/STROKEAHA.116.013513
28. Liu ZW, Han C, Zhao F, Qiao PG, Wang H, Bao XY, et al. Collateral circulation in moyamoya disease: a new grading system. *Stroke*. (2019) 50:2708–15. doi: 10.1161/STROKEAHA.119.024487
29. Beton O, Kaya H, Turgut OO, Yilmaz MB. Prediction of fractional flow reserve with angiographic DILEMMA score. *Anatol J Cardiol*. (2017) 17:285–92. doi: 10.14744/AnatolJCardiol.2016.7379
30. Samuels OB, Joseph GJ, Lynn MJ, Smith HA, Chimowitz MI. A standardized method for measuring intracranial arterial stenosis. *AJNR Am J Neuroradiol*. (2000) 21:643–6.
31. Bartunek J, Sys SU, Heyndrickx GR, Pijls NH, De Bruyne B. Quantitative coronary angiography in predicting functional significance of stenoses in an unselected patient cohort. *J Am Coll Cardiol*. (1995) 26:328–34. doi: 10.1016/0735-1097(95)80003-Y
32. Leone AM, De Caterina AR, Basile E, Gardi A, Laezza D, Mazzari MA, et al. Influence of the amount of myocardium subtended by a stenosis on fractional flow reserve. *Circ Cardiovasc Interv*. (2013) 6:29–36. doi: 10.1161/CIRCINTERVENTIONS.112.971101
33. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation*. (1995) 92:3183–93. doi: 10.1161/01.CIR.92.11.3183
34. Pindzola RR, Yonas H. The xenon-enhanced computed tomography cerebral blood flow method. *Neurosurgery*. (1998) 43:1488–92. doi: 10.1227/00006123-199812000-00147
35. Liu H, Lan L, Leng X, Ip HL, Leung TWH, Wang D, et al. Impact of side branches on the computation of fractional flow in intracranial arterial stenosis using the computational fluid dynamics method. *J Stroke Cerebrovasc Dis*. (2018) 27:44–52. doi: 10.1016/j.jstrokecerebrovasdis.2017.02.032
36. Chen Z, Qin H, Liu J, Wu B, Cheng Z, Jiang Y, et al. Characteristics of wall shear stress and pressure of intracranial atherosclerosis analyzed by a computational fluid dynamics model: a pilot study. *Front Neurol*. (2019) 10:1372. doi: 10.3389/fneur.2019.01372
37. Leng X, Lan L, Ip HL, Abrigo J, Scalzo F, Liu H, et al. Hemodynamics and stroke risk in intracranial atherosclerotic disease. *Ann Neurol*. (2019) 85:752–64. doi: 10.1002/ana.25456
38. Fang H, Leng X, Pu Y, Zou X, Pan Y, Song B, et al. Hemodynamic significance of middle cerebral artery stenosis associated with the severity of ipsilateral white matter changes. *Front Neurol*. (2020) 11:214. doi: 10.3389/fneur.2020.00214
39. Feng X, Chan KL, Lan L, Abrigo J, Ip VHL, Soo YOY, et al. Translesional pressure gradient alters relationship between blood pressure and recurrent stroke in intracranial stenosis. *Stroke*. (2020) 51:1862–4. doi: 10.1161/STROKEAHA.119.028616
40. Lan L, Leng X, Ip V, Soo Y, Abrigo J, Liu H, et al. Sustaining cerebral perfusion in intracranial atherosclerotic stenosis: the roles of antegrade residual flow and leptomeningeal collateral flow. *J Cereb Blood Flow Metab*. (2020) 40:126–34. doi: 10.1177/0271678X18805209
41. Lan L, Liu H, Ip V, Soo Y, Abrigo J, Fan F, et al. Regional high wall shear stress associated with stenosis regression in symptomatic intracranial atherosclerotic disease. *Stroke*. (2020) 51:3064–73. doi: 10.1161/STROKEAHA.120.030615
42. Badruddin A, Taqi MA, Abraham MG, Dani D, Zaidat OO. Neurocritical care of a reperfused brain. *Curr Neurol Neurosci Rep*. (2011) 11:104–10. doi: 10.1007/s11910-010-0156-9
43. Tagawa T, Naritomi H, Mimaki T, Yabuuchi H, Sawada T. Regional cerebral blood flow, clinical manifestations, and age in children with moyamoya disease. *Stroke*. (1987) 18:906–10. doi: 10.1161/01.STR.18.5.906

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.

The handling editor HQZ declared a shared affiliation, though no other collaboration, with one or more authors LL, BY, TW, JL, YL, YM, JC, YW, PG, YF, XB, XZ, JD, RY, LJ, FL at the time of the review.

frontiers in Neurology

ORIGINAL RESEARCH
published: 26 August 2021
doi: 10.3389/fneur.2021.700732

Effects of Anterior Borderzone Angle Grading on Predicting the 90-Day Prognosis After Recanalization of Acute Middle Cerebral Artery Occlusion

Ying Chen[1†], Quanlong Hong[2†], Junpeng Liu[1], Zhen Zheng[1], Yingchao He[1], Shuheng Chen[1], Canxiong Wang[1], Mengjuan Cai[1], Qiong Cheng[1], Yinzhou Wang[1,3] and Yongkun Li[1,4*]*

[1] Department of Neurology, Fujian Provincial Hospital, Shengli Clinical College of Fujian Medical University, Fuzhou, China, [2] Department of Neurology, The First Hospital of Quanzhou Affiliated to Fujian Medical University, Quanzhou, China, [3] Fujian Academy of Medical Sciences, Fujian Key Laboratory of Medical Measurement, Fuzhou, China, [4] Department of Neurology, Xiamen Key Laboratory of Brain Center, The First Affiliated Hospital of Xiamen University, Xiamen, China

OPEN ACCESS

Edited by:
Liqun Jiao,
Capital Medical University, China

Reviewed by:
Yohei Tateishi,
Nagasaki University Hospital, Japan
Simon Fandler-Höfler,
Medical University of Graz, Austria

***Correspondence:**
Yinzhou Wang
wphd@163.com
Yongkun Li
liyongkun721@139.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: 26 April 2021
Accepted: 17 June 2021
Published: 26 August 2021

Citation:
Chen Y, Hong Q, Liu J, Zheng Z, He Y, Chen S, Wang C, Cai M, Cheng Q, Wang Y and Li Y (2021) Effects of Anterior Borderzone Angle Grading on Predicting the 90-Day Prognosis After Recanalization of Acute Middle Cerebral Artery Occlusion. Front. Neurol. 12:700732. doi: 10.3389/fneur.2021.700732

Objective: This work explores collateral circulation metrics, such as the anterior borderzone angle grading (ABZA-grading), as a predictor of the prognosis in patients with acute middle cerebral artery occlusion (MCAO) following endovascular treatment (EVT).

Methods: Clinical data from 108 patients with acute MCAO, treated by EVT, were retrospectively analyzed. In patients with MCAO, ABZA is the angle between the median line of the sagittal sinus and the borderzone of the pial arterioles of ACA and MCA, and the ABZA/23.0° was rounded to obtain the corresponding collateral circulation score (ABZA-grading). In parallel, the primary outcome was defined as the 90-day clinical outcome by modified ranking scale score (mRS). Univariate analysis and logistic regression were used to analyze the independent predictors of the 90-day clinical outcome (mRS). Receiver operating characteristic curve (ROC) analysis was used to judge the predictive value of ABZA.

Results: Univariate analysis and logistic regression analysis showed that ABZA-grading $>$ 2 and age were independent predictors of the 90-day clinical outcome after EVT in patients with acute MCAO. The ROC analysis showed that ABZA alone could predict a favorable 90-day clinical outcome with an area under the curve (AUC) of 0.868. Using an ABZA of $>$57.8° (the corresponding ABZA-grading of $>$2) as the cut-off value, the predictive sensitivity and specificity were 75.7 and 88.7%, respectively. Contingency table analysis showed a statistical difference in mRS score between ABZA-grading subgroups, and ABZA-grading between stroke caused by large artery atherosclerosis (LAA) and cardiogenic embolism (CE).

Conclusion: The ABZA-grading is an easy and objective assessment of collateral circulation that is independently associated with short-time clinical outcome after EVT in patients with acute MCAO. Therefore, it may guide selection of patients with acute ischemic stroke (AIS) suitable for EVT. The ABZA-grading of collateral circulation can be a supplemental metric to help differentiate stroke by LAA and CE.

Keywords: anterior borderzone angle grading, collateral circulation, endovascular treatment, acute ischemic stroke, prognosis

INTRODUCTION

Numerous studies have shown that good collateral circulation is essential to maintain ischemic penumbra, and is associated with smaller infarct cores and improved clinical outcomes after intravenous and intrarterial thrombolysis. Contrastingly, poor collateralization increases mortality in patients with large vessel occlusion acute ischemic stroke (LVO-AIS) (1–4). Preserving ischemic penumbra, where collateral circulation plays an important role, is key to successful treatment. Therefore, it becomes important to evaluate collateral circulation before endovascular therapy (EVT).

Angiography is considered the gold standard for the assessment of collateral blood flow, providing complete and reliable information on the circle of willis and the leptomeningeal collateral circulation. At present, the scoring methods based on digital subtraction angiography (DSA) for assessing collateral state include: the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) and the Capillary Index Score (CIS). Of these two, ASITN/SIR-grading is most widely used because of its simplicity and operability. However, most of the collateral circulation scoring methods are subjective, and some studies show that the reproducibility between observers and repeatability by the same observer are weak (5). The middle cerebral artery (MCA) is the most frequently involved site of LVO-AIS, while the anterior cerebral artery (ACA) is the main compensatory source of pial collateral in MCA stenosis and occlusion. Our previous study introduced a new quantitative parameter of anterior borderzone angle (ABZA), to study changes of ACA-MCA boundary area; and exposed its relationship to hemodynamic changes during MCA stenosis and occlusion. Together these could be used as a quantitative index to evaluate the compensation of ACA pial collateral (6). Therefore, we tested the predictive value of this measurement ABZA (ABZA-grading), on the prognosis of patients with acute middle cerebral artery occlusion (MCAO) treated by EVT.

MATERIALS AND METHODS

Data were collected from 69 patients attending the Department of Neurology at Fujian Provincial Hospital from June 2016 to November 2020 and 39 patients attending the First Hospital of Quanzhou City from April 2019 to November 2020, a total of 108 AIS patients from both hospitals receiving EVT who met the inclusion criteria. The Block diagram of enrollment was showed in **Figure 1**. Inclusion criteria were as follows: (1) All patients met the diagnostic criteria for AIS established by the American Heart Association/American Stroke Association (AHA/ASA) in 2018; (2) Age $\geq$ 18 years; (3) Treatment started within 6 h after symptoms onset; (4) M1 segment occlusion of the MCA was confirmed by computed tomography angiography (CTA) or DSA, and there was no forward blood flow; (5) Pre-onset mRS $\leq$ 2 points; NIHSS score $\geq$ 6 points on admission; (6) Early CT ischemic changes of Albert Stroke Program early CT score (ASPECTS) $\geq$ 6 or infarct volume $<$ 1/3 MCA blood supply area; (7) No contraindications to EVT and signed informed consent for EVT; (8) Patients whose symptoms did not resolve after intravenous thrombolysis and who met the above criteria could also be enrolled.

Exclusion criteria included: (1) Patients with severe stenosis or occlusion of other intracranial and extracranial vessels, including in the contralateral internal carotid or MCA or external carotid, anterior cerebral or posterior cerebral artery; (2) Tandem lesions exist in the common carotid artery and internal carotid artery on the symptomatic side; (3) Stenosis after bifurcation of M1 segment without involvement of trunk; (4) The image quality does not meet the analysis requirements; (5) All patients with the contraindications of EVT.

This study was approved by the Ethics Committee of Fujian Provincial Hospital and Quanzhou first Hospital and was conducted with the informed consent of patients or their legal representatives. Patients' information was analyzed retrospectively, including demographic characteristics (age, sex), stroke risk factors (hypertension, diabetes, hyperlipidemia, smoking, stroke, coronary heart disease), baseline clinical features (NIHSS score, systolic blood pressure, blood glucose, TOAST etiological classification), and imaging characteristics (baseline ASPECTS, collateral circulation score). The definition of TOAST etiological classification is based on the previous published study (7). Patients with large artery atherosclerosis (LAA) will meet the flowing criteria: (1) clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis. (2) Clinical findings include those of cerebral cortical impairment or brain stem or cerebellar dysfunction. (3) Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts $>$ 1.5 cm in diameter on CT or MRI. (4) Supportive evidence by duplex imaging or arteriography of a stenosis of >50% of an appropriate intracranial or extracranial artery is needed. (5) Excluding potential sources of cardiogenic embolism. And the patients with cardioembolism

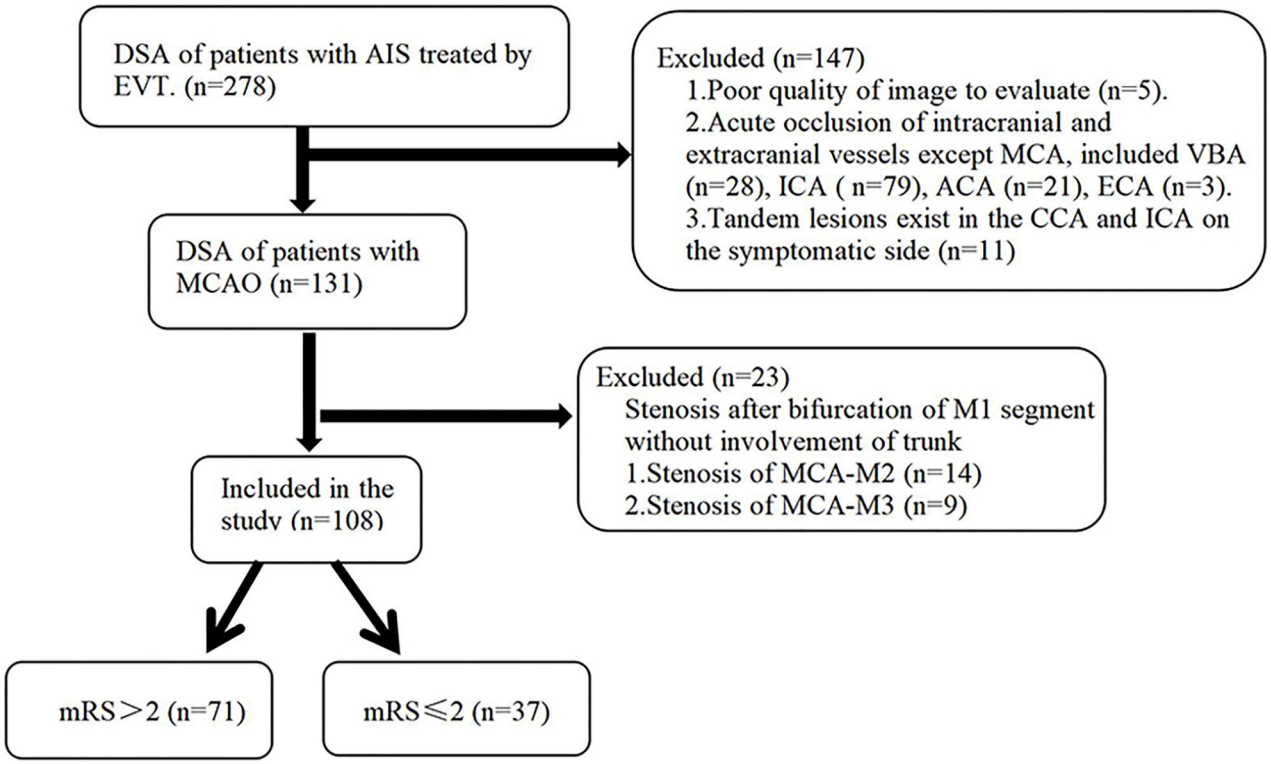


FIGURE 1 | Block diagram of enrollment into this study. MCAO, middle cerebral artery occlusion; ABZA, anterior borderzone angle grading; mRS, modified Rankin score; PCA, posterior cerebral artery; ACA, anterior cerebral artery; CCA, common carotid artery; ECA, external carotid artery.

(CE) will meet the following criteria: (1) patients with at least one cardiac source of emboli. (2) Evidence of a previous TIA or stroke in more than one vascular territory or systemic embolism. (3) Eliminating the potential LAA sources of thrombosis or embolism. (4) A stroke in a patient with a medium-risk cardiac source of embolism and no other cause of stroke is classified as a possible cardioembolic stroke.

Treatment Method

EVT was routinely performed according to the guidelines for EVT of acute ischemic cerebrovascular disease (8), and alteplase was given within the therapeutic time window when patients meet the criteria for intravenous thrombolysis. If there was a suspicion of excess embolus load, possible inefficacy of intravenous thrombolytic therapy or contraindication of intravenous thrombolytic therapy, the Neurointerventional Specialist could directly administer EVT with the informed consent of the patient.

Surgical Method

Patient was placed in supine position, and punctured 1.5 cm under the pulsation of the right inguinal femoral artery. Anesthesia was adjusted to patients cooperation; local anesthesia for cooperative patients, and general anesthesia for those who could not cooperate. Cerebral angiography was performed first, the MCAO confirmed and then thrombectomy was performed according to general medical procedures. Thrombectomy can be was performed by simple aspiration, simple stent, or stent combined with aspiration treatment. Stent (4 × 20 mm or 6 × 30 mm Solitair FR stent, EV3, CA, USA), was selected according to vessel diameter and thrombus length. When necessary, Tirofiban was slowly injected when embolus could not be removed during embolectomy, or residual embolus or thrombus formation was observed during stent removal. If embolectomy was followed by re-occlusion, remedial treatment was taken, such as balloon dilation, intra-arterial thrombolysis or stent implantation.

The Measurement of ABZA

The ABZA was measured as previously reported (6). Briefly, the projection of intracranial bifurcation of internal carotid artery on the median line of sagittal suture is defined as the vertex, and the median line of sagittal suture as the starting edge on the DSA image of Tang's position. The angle between the center and the vertices of the ACA-MCA cortical junction (the central point of the junction area was determined according to the points at which the pia mater arterioles of ACA and MCA first met) (**Figure 2A**). In patients with complete occlusion of MCA, the line between the farthest point of the retrograde collateral circulation and the vertex was selected as the terminal edge (**Figures 2B,C**). In patients with dysplasia or ACA-A1 deletion (diameter < 0.5 mm) but AcoA was not closed, ABZA was measured from contralateral carotid angiography

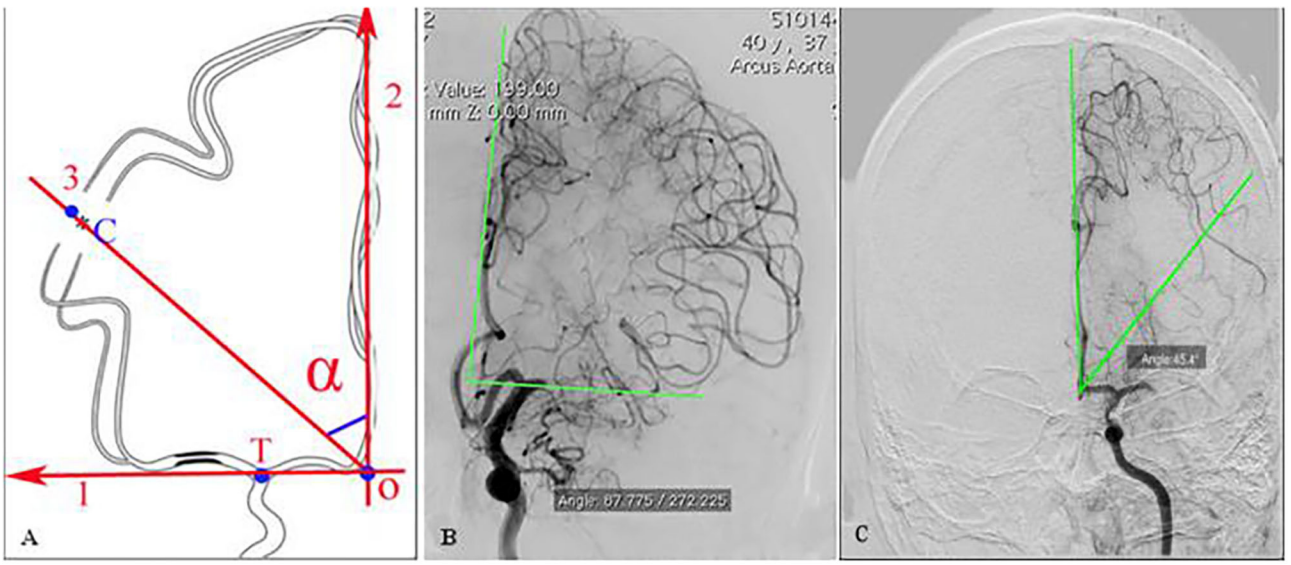


FIGURE 2 | Definition of ABZA on DSA image (with permission) (6). **(A)** determine point T at the intracranial bifurcation of ICA, find the midline 2, that is, the projection of sagittal sinus, the vertex O is obtained from the vertical projection of point T on midline 2, and determine the central point C of the boundary zone of ACA-MCA, with line 2 as the starting edge and OC as the ending edge, and the angle α formed is ABZA. **(B,C)** The central point C was determined by the several farthest points of ACA cortical meningeal arterioles retrograde flows, which was the terminal edge of ABZA in patients with MCAO. **(B)** Demonstrated excellent collaterals with ABZA near to 90°; **(C)** showed a moderate collaterals with ABZA of 45.4°.

images. ABZA was 0° when both AcoA and ipsilateral ACA-A1 were not visible (6). The assessment of angiographic images was performed by two experienced neurointerventionalists (Y. CH. and MJ. C) using the image processing software of the GE PACS system to measure ABZA, and any disputes were resolved after consultation. The inter-rater reliability (IRR) was evaluated.

Classification Method of ABZA-Grading

The classification method of ABZA-grading is shown in **Figure 3** (6). The ABZA/23.0° (the upper limit of 95% normal reference range of ABZA) was rounded to obtain the corresponding collateral circulation score. ABZA/23.0° is defined as $ABZA_{trans}$: ABZA-grading is 0 if $ABZA_{trans} \leq 1.0$; if $1 \leq ABZA_{trans} < 1.5$, ABZA-grading is 1; $1.5 \leq ABZA_{trans} < 2.5$, ABZA-grading is 2; $2.5 \leq ABZA_{trans} < 3.5$, ABZA -grading is 3; $3.5 \leq ABZA_{trans} < 4.0$, corresponding ABZA-grading is 4 (**Figure 3**).

Statistical Analysis

IBM SPSS Statistics 22 statistical software was used for statistical analysis. Quantitative data meeting normal distribution were described by mean ± standard deviation ($\bar{x} \pm s$), and quantitative data with non-normal distribution were described by median (M) and inter quartile range (IQR). Univariate analysis was used to compare the baseline data between two groups. Logistic regression analysis was used to analyze the independent predictors of the 90-day clinical outcome. The 90-day functional outcome (mRS) of ABZA-grading group and the ABZA-grading of different TOAST (*Trial of Org 10172 in acute stroke treatment*) types were analyzed by contingency table analysis. Receiver operating characteristic curve (ROC) analysis was used to judge the predictive value of ABZA and the prediction accuracy of each logistic regression analysis model. Previous studies confirmed a linear relationship between ABZA-grading and ASITN/SIR-grading (6). Considering such close interaction, either ASITN/SIR-grading or ABZA-grading was manually eliminated, while the other was retained as collateral circulation score when performing multivariate analysis. In addition, all variables with $P < 0.05$ in univariate analysis were included in logistic regression analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Analysis of Baseline Clinical Data

Patients with mRS ≤ 2 or mRS > 2 were stratified into good and poor prognosis groups, respectively (**Table 1**). A total of 108 patients with acute MCAO treated with EVT were included, including 69 cases (63.9%) in Fujian Provincial Hospital, 39 cases (36.1%) in Quanzhou First Hospital. Among which 63 cases (58.3%) were male. According to TOAST etiological classification and 59 cases (54.6%) were cardiogenic embolism (CE) and 44 cases (40.7%) with LAA. Finally, 37 cases (34.3%) had a good prognosis (mRS ≤ 2) and 71 cases (65.7%) had poor prognosis (mRS > 2). Compared with the poor prognosis group, the good prognosis group were younger [media 61 versus (vs.) 72 years, $P < 0.001$], Furthermore, the proportion of patients with LAA (59.5 vs. 31.0%, $P = 0.012$) was higher in the good prognosis group compared with the poor one. There were no significant differences in baseline ASPECTS, baseline NIHSS, other stroke risk factors (including hypertension, diabetes, hyperlipidemia, coronary atherosclerotic heart disease, stroke

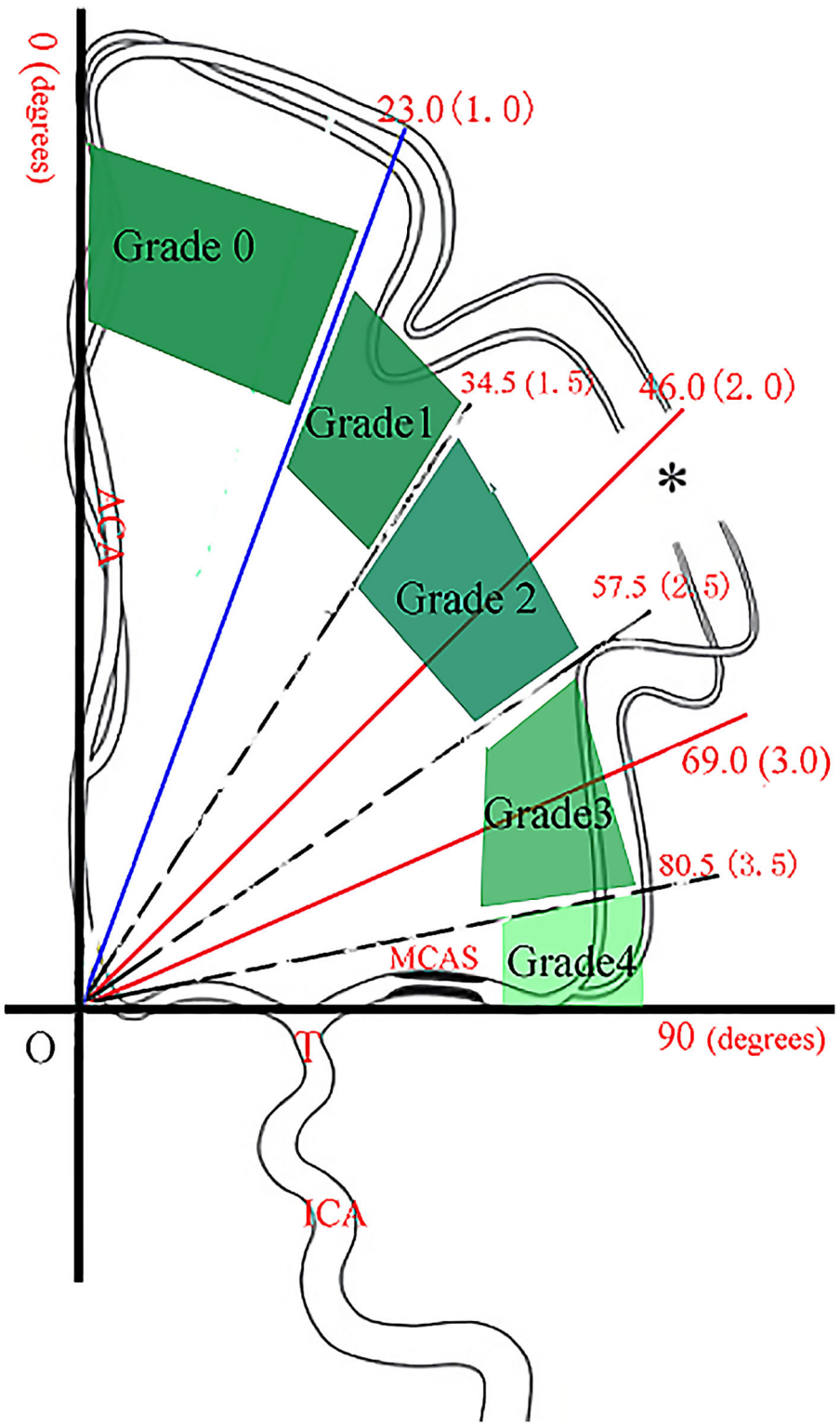


FIGURE 3 | The classification method of ABZA-grading (with permission) (6). On the coordinate graph, point T is the end bifurcation point of internal carotid artery, the vertical line is the middle line of the sagittal sinus, and OT is the vertical line of the middle line. * indicates the central point at which the pia mater arterioles of ACA and MCA first met. The vertical area is divided into four parts from three solid lines, corresponding to ABZA: 23.0°, 46.0°, and 69.0°. In addition, the three dashes correspond to ABZA: 34.5°, 57.5°, and 80.5°. The red number in each bracket indicates the corresponding ABZA-trans (ABZA/23.0°), and when rounded it up, the integer number is the corresponding collateral score (ABZA-grading).

TABLE 1 | The baseline clinical data of patients with and without a favorable outcome.

Variables	mRS > 2 (*n* = 71)	mRS ≤ 2 (*n* = 37)	*P*-value
Patients characteristics, *n* (%)			
Age, y (M, IQR)	72 (64–78)	61 (55–67)	<0.001**
Male	38 (53.5)	25 (67.6)	0.160
Hospital, *n* (%)			0.125
Fujian Provincial Hospital	49 (69.0)	20 (54.1)	
Quanzhou First Hospital	22 (31.0)	17 (45.9)	
Risk factors of stroke, *n* (%)			
Hypertension	50 (70.4)	24 (64.9)	0.555
Diabetes mellitus	22 (31.0)	7 (18.9)	0.179
Hyperlipidemia	15 (21.1)	11 (29.7)	0.321
CHD	9 (12.7)	4 (10.8)	1.000
History of stroke	15 (21.1)	5 (13.5)	0.334
Smoking	12 (16.9)	9 (24.3)	0.355
Drinking	7 (9.9)	6 (16.2)	0.335
Clinical characteristics			
SBP > 140 mmHg, *n* (%)	41 (57.7)	15 (40.5)	0.089
DBP > 90 mmHg, *n* (%)	20 (28.2)	6 (16.2)	0.168
Baseline glucose > 7 mmol/L, *n* (%)	43 (60.6)	17 (45.9)	0.147
Baseline NIHSS (SD)	18.0 ± 5.4	14.1 ± 5.6	0.761
Baseline ASPECTS (M, IQR)	9 (8, 10)	10 (9, 10)	0.053
TOAST types, *n* (%)			0.012*
LAA	22 (31.0)	22 (59.5)	
CE	46 (64.8)	13 (35.1)	
Other and unknown reasons	3 (4.2)	2 (5.4)	

*M, median; IQR, inter quartile range; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale; aspects, Alberta stroke program early CT Score; toast, acute stroke treatment Org 10172 trial standard; AF, atrial fibrillation; CDH, coronary atherosclerotic heart disease; LAA, large atherosclerosis; CE, cardiogenic embolism. *P < 0.05; **P < 0.001.*

history, smoking, and drinking history), hospital, and gender between the two groups.

Analysis of Related Variables of Endovascular Therapy

The Inter-rater reliability of ABZA was very good (IRR = 0.78). There was no significant difference in anesthesia mode, requirement for remedial measures (balloon angioplasty or stent implantation), passes of retriever or recanalization, bridging therapy and onset to recanalization time between the good and poor prognosis groups. Compared with poor prognosis group, patients in good prognosis group had higher proportion of good collateral circulation (ABZA-grading > 2) (75.7 vs. 11.3%, $P < 0.001$) and mTICI 2b/3 grade (94.6 vs. 76.1%, $P = 0.016$) (**Table 2**).

Logistic Regression Analysis of the Independent Predictors of the 90-Day Clinical Outcome

Univariate analysis of the factors with $P < 0.05$, including age, TOAST types, ASITN/SIR-grading (poor vs. good) and ABZA-grading (poor vs. good), mTICI (poor vs. good) were included in logistic regression analysis by enter method, and two models were established. ROC curve was used to analyze the prediction accuracy of each models. The results are shown in **Table 3**. Model 1 and model 2 were manually screened out either ASITN/SIR-grading or ABZA-grading, respectively. The AUC of Model 1 was 0.903 (95% CI: 0.844–0.961; $P < 0.001$) and Model 2 was 0.862 (95% CI: 0.794–0.929; $P < 0.001$). The above results suggest that ABZA-grading (OR 18.948; 95% CI: 5.728–62.680; $P < 0.001$), ASITN/SIR-grading (OR 8.529; 95% CI: 2.455–29.634; $P < 0.001$) and age (OR 0.939; 95% CI: 0.892–0.988; $P = 0.016$) are independent predictors of the 90-day clinical outcome, and the model with ABZA-grading had a higher predictive value than ASITN/SIR-grading. In contrast, there were no significant

TABLE 2 | The EVT related variables of patients with and without a favorable outcome.

Variables	mRS > 2 (*n* = 71)	mRS ≤ 2 (*n* = 37)	*P*-value
Type of anesthesia, *n* (%)			0.935
Local anesthesia	61 (85.9)	32 (86.5)	
General anesthesia	10 (14.1)	5 (13.5)	
Collateral circulation score, *n* (%)			<0.001**
ASITN/SIR-grading			<0.001**
ASITN/SIR-grading ≤ 2	65(91.5)	17 (45.9)	
ASITN/SIR-grading > 2	6 (8.5)	20 (54.1)	
ABZA-grading			<0.001**
ABZA-grading ≤ 2	63 (88.7)	9 (24.3)	
ABZA-grading = 0	4 (5.6)	0 (0)	
ABZA-grading = 1	28 (39.4)	2 (5.4)	
ABZA-grading = 2	31 (43.7)	7 (18.9)	
ABZA-grading > 2	8 (11.3)	28 (75.7)	
ABZA-grading = 3	6 (8.5)	25 (67.6)	
ABZA-grading = 4	2 (2.8)	3 (8.1)	
Bridging therapy, *n* (%)	29 (40.8)	14 (37.8)	0.762
Remedies, *n* (%)			0.227
Balloon angioplasty	4 (5.6)	4 (10.8)	
Stenting	0 (0)	1 (2.7)	
Onset to puncture, min (SD)	219.9 ± 103.5	221 ± 109.0	0.623
Puncture to recanalization, min (M, IQR)	100 (60–175)	95 (60–120)	0.264
Onset to recanalization, min (SD)	338.3 ± 104.2	323.9 ± 113.2	0.497
mTICI 2b/3, *n* (%)	54 (76.1)	35 (94.6)	0.016*
Passes of retriever, *n* (%)			0.157
1	32 (45.1)	20 (54.1)	
2	20 (28.2)	13 (35.1)	
≥3	19 (26.8)	4 (10.8)	
Passes of recanalization, *n* (%)			0.733
1	34 (47.9)	19 (51.4)	
≥2	37 (52.1)	18 (48.6)	

*SD, standard deviation; M, median; IQR, inter quartile range; mRS, modified Rankin Scale score; ABZA-grading, anterior borderzone angle grading; mTICI, modified thrombolytic grade of cerebral infarction. *P < 0.05; **P < 0.001.*

TABLE 3 | Logistic regression analysis of the 90-day-outcome predictors in MCAO patients after EVT.

Variables	Model 1	Model 2
Model description	ASITN/SIR-grading was manually eliminated: enter method	ABZA-grading was manually eliminated: enter method
Age	OR 0.939; 95% CI: 0.892–0.988; $P = 0.016$*	OR 0.938; 95% CI: 0.893–0.985; $P = 0.011$*
TOAST types (LAA, CE, other)	$P = 0.314$	$P = 0.215$
ASITN/SIR-grading (poor vs. good)	–	OR 8.529; 95% CI: 2.455–29.634; $P < 0.001$**
ABZA-grading (poor vs. good)	(OR 18.948; 95% CI: 5.728–62.680; $P < 0.001$**)	–
mTICI (poor vs. good)	OR 5.869; 95% CI: 0.837–41.128; $P = 0.075$	OR 5.712; 95% CI: 1.037–31.463; $P = 0.045$*
AUC	0.903 (0.844–0.961)	0.862 (0.794–0.929)

*mRS, modified Rankin Scale score; mTICI, modified thrombolytic grade of cerebral infarction; ABZA-grading, anterior borderzone angle grading; NIHSS, National Institutes of Health Stroke Scale; ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; AUC, The area under ROC curve; *P < 0.05; **P < 0.001.*

differences in TOAST types, final mTICI 2b/3 between the good and poor prognosis groups.

The Predictive Value of ABZA

Sensitivity and specificity of ABZA on disease prognosis was measured by ROC analysis (**Figure 4**). The area under ROC curve (AUC) of ABZA was 0.868 (95% CI: 0.798–0.938; $P < 0.001$), indicative of ABZA good predictive value for the 90-day prognosis of patients with acute MCAO after EVT. In addition, Youden index of ROC analysis was 0.644, with a best cut-off value of ABZA of 57.8° corresponding to an ABZA-grading of 2. The sensitivity and specificity for predicting favorable prognosis at 90 days were 75.7 and 88.7%, respectively, supporting the hypothesis of ABZA-grading > 2 as an excellent collateral circulation.

The Analysis of mRS Score According to the ABZA-Grading Subgroups

The change of mRS score at 90 days in ABZA-grading subgroups are shown in **Figure 5**. Among ABZA-grading ≤ 2 and ABZA-grading > 2, the cases of mRS ≤ 2 were 9 (13%) and 28 (78%), respectively, the ABZA-grading ≤ 2 group tended to have a higher mRS score. Contingency table analysis was used to analyze the mRS score between the ABZA-grading subgroups (ABZA-grading > 2 vs. ≤ 2). The results showed statistically significant differences in mRS scores between ABZA-grading subgroups ($P < 0.001$).

ABZA-Grading for Patients With Different TOAST Subtypes

The ABZA-grading distribution between CE and LAA is shown in **Figure 6**. Contingency table was used to analyze the difference of ABZA-grading between CE and LAA following TOAST classification. The results showed that the difference of ABZA-grading between the two subtypes was statistically significant ($P = 0.003$).

DISCUSSION

Collateral circulation is an alternate vascularization path that circumvents severely stenosed or occluded vessels and provides natural blood perfusion compensation for ischemic tissues. Collateral circulation is an important determinant of clinical prognosis in patients with AIS (9). Previous studies have shown the importance of collateral circulation. Good collateral circulation plays an important role in prolonging the maintenance time of ischemic penumbra, reducing core infarct volume, improving the recanalization rate, reducing the risk of bleeding transformation after recanalization, increasing the prognosis of good neurological function, and ultimately reducing the risk of death (10). In recent years, many related clinical studies, including MR CLEAN, EACAPE, EXTEND-IA, and SWIFT-PRIME, demonstrated the benefits of EVT in patients with LVO-AIS (11–15). However, many factors limit the effectiveness of EVT and affect the prognosis, such as onset time to treatment, collateral circulation and the equipment and technology of interventional embolectomy.

Nevertheless, animal studies have shown that collateral circulation is transient and gradually attenuates over time (16). Further studies found that elevated intracranial pressure, blood pressure fluctuations, venous steal and collateral thrombosis may attenuate collateral circulation (17, 18). Most collateral circulation can only be maintained for 6 h. For patients with LVO of anterior circulation, regardless of whether there is evaluation of magnetic resonance perfusion imaging, the infarct core volume increases over time (6–24 h). Therefore, the role of collateral circulation has a limited impact on EVT therapeutic window extension. However, patients who can maintain collateral circulation for more than 6 h may benefit from EVT through advanced imaging screening (19). Therefore, the assessment of collateral circulation during angiography can guide the treatment decision of LVO-AIS, screen potential patients and improve the prognosis. Therefore, we aimed to study whether ABZA-grading could act as an independent prognostic factor of a good 90-day clinical outcome in MCAO patients after EVT. Furthermore, we analyzed the predictive value of ABZA-grading for the prognosis of acute MCAO patients after intravascular recanalization.

This study demonstrated that ABZA-grading was an independent predictor of good functional prognosis in LVO-AIS patients after EVT, and that ABZA-grading > 2 has a significant predictive value for a good 90-day clinical outcome.

ASITN/SIR-grading is a classical DSA collateral evaluation method that subjectively reflects the compensation of actual ischemic area (20). In fact, there are few reports on internal consistency of observers. Some researchers also proposed the use of a 4-point system capillary index score (CIS) to evaluate

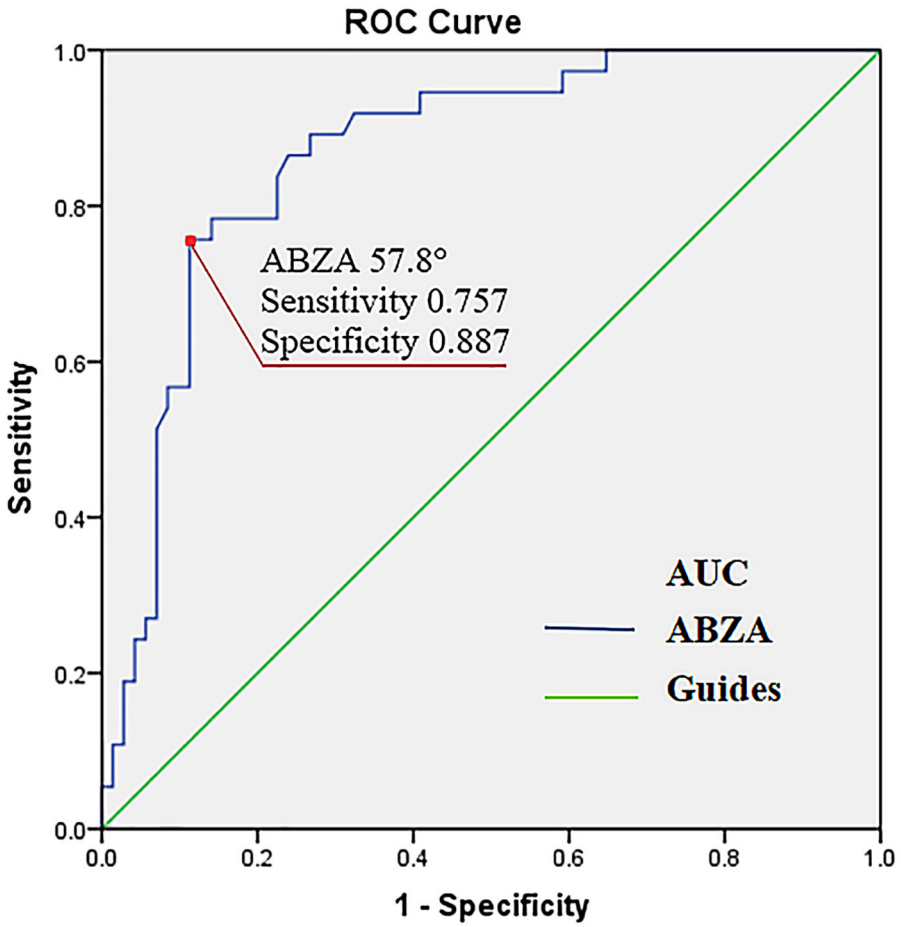


FIGURE 4 | Receiver operating characteristic curve (ROC) of ABZA predicting a favorable 90-day clinical outcome. The area under ROC curve (AUC) of ABZA was 0.868 (95% CI: 0.79–0.938; $P < 0.001$). For an ABZA of >57.8° (corresponding ABZA-grading of >2), the predictive sensitivity and specificity were 75.7 and 88.7%, respectively (the red point). ABZA, anterior borderzone angle.

collateral circulation and predict the prognosis of EVT (21). In this grading system, the MCA blood supply area is divided into three equal parts. During the capillary phase of DSA, if there is capillary staining in each part, one point will be recorded. The higher the score, the better the collateral circulation. This method can evaluate the collateral compensation of ACA and posterior cerebral artery (PCA) in patients with MCAO, but is again highly subjective.

From our study, we also found that ABZA-grading may be a slightly stronger predictor than ASITN/SIR-grading. As we know, ABZA is a quantitative index based on the clear boundary anatomical area of ACA and MCA, and in imaging, the terminal edge can be determined according to the initial meeting points of the pial arterioles of ACA and MCA, and the angle between them and the median line of the sagittal sinus is ABZA. In patients with MCAO, the farthest point of retrograde collateral circulation was selected to determine the terminal edge (6). Furthermore, we found that after data transformed (ABZA/95% normal upper limit), the quadrant was divided into four equal parts. According to the degree of retrograde blood flow, the collateral circulation score was very similar to ASITN/SIR-grading. For example, ASITN/SIR-grading 1 was defined as a small amount of collateral blood flow reaching the edge of ischemic area, which corresponded to ABZA slightly > 23° and an ABZA-grading of 1. In complete contrast, ASITN/SIR-grading 4 was defined as complete compensation with retrograde blood flow to M1 bifurcation, corresponded to an ABZA close to 90° and ABZA-grading of 4. Although ABZA-grading and ASITN/SIR-grading resemble each other, ABZA-grading is based on a relatively objective measurement, while the latter one is mainly based on subjective judgment. David Liebeskind et al. had reported an excellent inter-rater reliability (IRR = 0.87) in the International Stroke Conference 2017 (22), and in this study, it was also very good (IRR = 0.78). Therefore, ABZA-grading is more intuitive and objective for clinical application. Nonetheless, repeatability and feasibility across observers needs further clinical research.

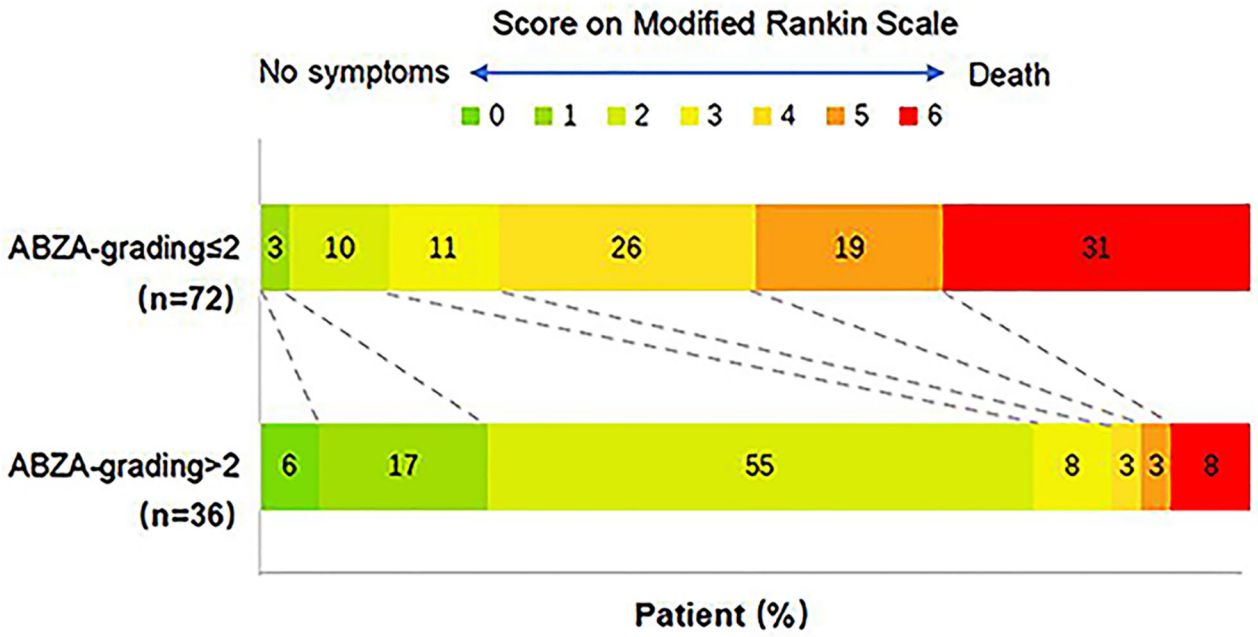


FIGURE 5 | Comparison of the 90-day functional outcomes stratified to ABZA-grading. ABZA-grading ≤ 2 was defined as poor colleral circulation, and ABZA-grading > 2 was defined as excellent collateral circulation. Among them, the cases of mRS ≤ 2 were 9 (13%) and 28 (78%), respectively. Contingency table analysis showed that there were significant differences in mRS score between ABZA-grading subgroups ($P < 0.001$). mRS scores ranged from 0 to 6, with 0 indicating asymptomatic, 1 non-clinically significant disability, 2 mild disability (patients can take care of their own affairs, but cannot carry out all previous activities), 3 moderate disability (patients need some help but can walk independently), 4 severe disability (patients cannot walk independently, cannot take care of their own physical needs), 5 Severe disability (patients need continuous care), 6 death.

However, we did not find the predictive value of time, including time from onset to recanalization, time from onset to puncture, time from puncture to recanalization, as an independent factor for the 90-day clinical outcome. The study of HERMES showed that (23), the favorable 90-day clinical outcome of EVT patients decreased with the extension of the time from onset to puncture. With the progress of stroke, any time delay from onset to treatment will bring significant brain cell damage and death. In addition, the correlation between EVT times, functional prognosis, and clinical outcome of LVO-AIS has been neglected in recent years. Several studies have shown that more than three occurrences of thrombectomy and remedial treatment are associated with delayed reperfusion and increasing the risk of complications (24–27). Meanwhile, repeated thrombectomy can cause vascular damage and damage to the blood-brain barrier, which increases the risk of postoperative intracranial hemorrhage transformation leading to poor prognosis. Recent studies have also found that patients with good collateral circulation have fewer embolectomies to achieve recanalization (28), possibly due to the beneficial impact of cross thrombus pressure gradient, generated by collateral circulation, on thrombus removal. Secondly, collateral circulation can remove micro emboli, thus reducing the distal embolism caused by thrombus escape during thrombectomy. It may be the indirect reason for patients with good collateral circulation to obtain a favorable prognosis. However, this study did not show the relationship between passes of retrieve and a good 90-day clinical outcome. Here, multivariate analysis showed no significant differences in clinical prognostic factors, such as baseline NIHSS, ASPECTS, mTICI between the good and poor prognosis groups. However, this might be a result of the small sample size of this retrospective study. We cannot exclude possible systematic and random errors in the study process, which can cause bias and affect the prognosis analysis results.

In addition, the results of this study show that ABZA-grading is different in different TOAST etiological types (CE and LAA). Compared with CE patients, the proportion of ABZA-grading > 2 in LAA patients is higher, indicating that CE patients may have worse collateral circulation than LAA patients. These results suggest that ABZA-grading may have a significant value to differentiate the etiology of cerebral infarction.

Some animal experimental studies have found that chronic cerebral hypoperfusion can promote the formation and recruitment of new collaterals. Meanwhile the vascular blockage of CE occurs suddenly without chronic cerebral hypoperfusion, by which time the formation of cortical pial collateral circulation is usually too late. In fact this might be the reason for the difference of collateral circulation between the two (29, 30).

In clinical practice, only a few CE patients had good collateral circulation, again suggesting that most LAA patients

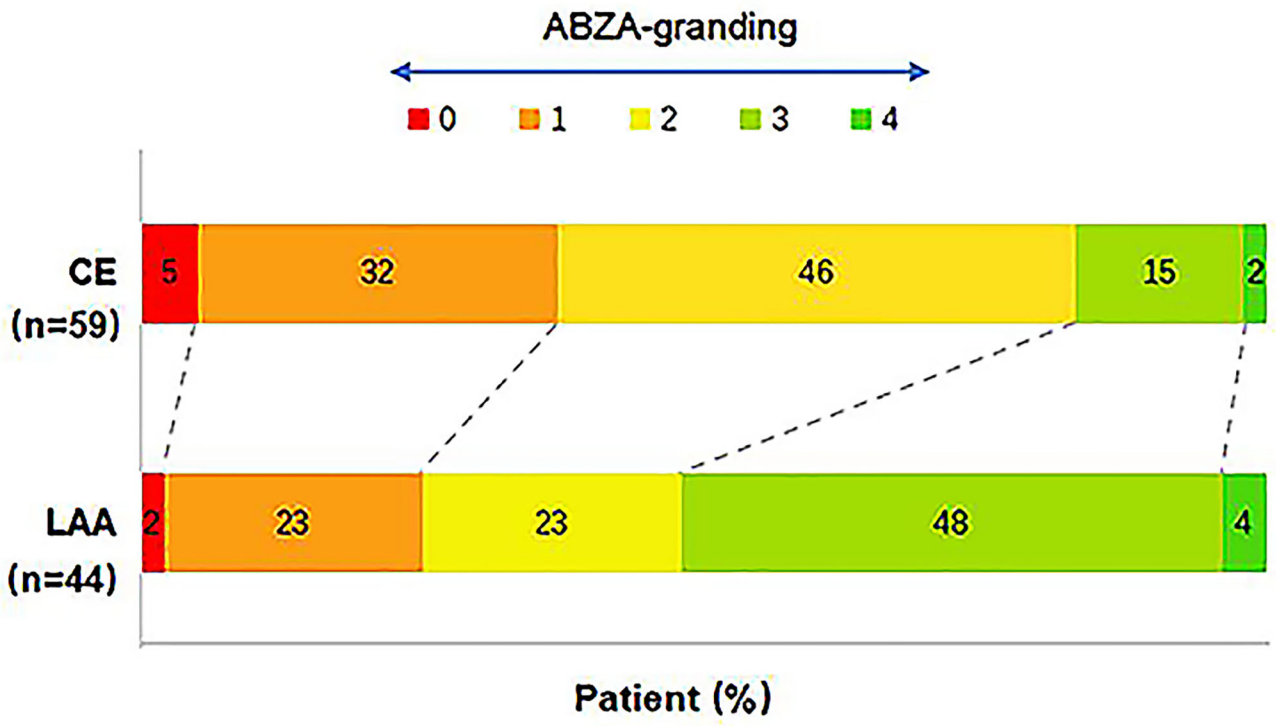


FIGURE 6 | Distribution comparison of ABZA-grading between CE and LAA subgroups. The ABZA-grading scores ranged from 0 to 4. The figure showed that there were 59 cases with CE and 44 cases with LAA. Among them, the cases of ABZA-grading > 2 were 10 (17%) and 23 (52%), respectively. The results of contingency table analysis indicated that the difference of ABZA-grading between the two subtypes of cerebral infarction etiology was statistically significant ($P = 0.003$).

may have good collateral circulation. Future studies should test this hypothesis by combining clinical data, imaging characteristics, and first pass effect of the microcatheter (31). Similarly, further studies are needed to verify the efficacy of ABZA-grading in predicting the prognosis of EVT and the etiological classification of cerebral infarction in patients with acute MCAO.

Our study has several limitations. First, the ABZA is a planar conception that cannot accurately reflect the real three-dimensional status of the blood supply of the brain. Moreover, it may not reflect the actual status of brain perfusion when some MCA leptomeningeal arteries have disappeared or a large cortical infarction is present (6). Second, all data here presented were extracted from two hospitals, but the neurointerventional physicians in two hospitals received common interventional treatment training. Therefore, EVT adopted a similar scheme, and there was no significant difference in patient characteristics between the two institutions, the reason why these comprehensive data could be used for further statistical analysis. Third, as far as we knew, ABZA is a quantitative index based on the clear boundary anatomical area of ACA and MCA. Therefore, it was not fit to be reliably used in the clinical setting of ICA or MCA-$M_{2/3}$ occlusions. Finally, this study is a retrospective study with a small sample size, which is prone to bias and affects the results. Therefore, we need to test our hypothesis through a multicenter prospective study with a large sample size.

CONCLUSION

The ABZA-grading can be an objective and easy assessment of collateral circulation, and is independently associated with short-time clinical outcome in patients with acute MCAO following EVT treatment. Therefore, ABZA-grading and other measurements of collateralisation may guide AIS patient selection for EVT. The ABZA-grading of collateral circulation can be a supplemental metric that helps differentiate stroke by LAA and CE.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Fujian Provincial Hospital and Quanzhou First Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL, YW, and JL conceived, designed, and supervised the study. YC and QH contributed to data analysis, data interpretation, and writing original draft. ZZ, YH, SC, CW, MC, and QC contributed to data collection and image analysis and interpretation. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported in part by grants from the Science and Technology Innovation Joint Foundation of Fujian Province (No. 2019Y9024), the Natural Science Foundation of Fujian province (No. 2020J011060), and the Medical Science Innovation Foundation of Fujian Provincial Health and Family Planning Commission (No. 2014-CX-1) to YL; and the Special Basic Scientific Fund for Fujian Provincial Public Welfare Research Institutes (2020R1011004) to YW.

ACKNOWLEDGMENTS

We thank Dr. Zhixing Huang, from the Second People Hospital of Guangdong Province, for his kind help in revising the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.700732/full#supplementary-material

REFERENCES

1. Bang OY, Saver JL, Kim SJ, Kim GM, Chung CS, Ovbiagele B, et al. Collateral flow predicts response to endovascular therapy for acute ischemic. *Stroke.* (2011) 42:693–9. doi: 10.1161/STROKEAHA.110.595256
2. Liebeskind DS, Jahan R, Nogueira RG, Zaidat OO, Saver JL, SWIFT investigators, et al. Impact of collaterals on successful revascularization in solitaire FR with the intention for thrombectomy. *Stroke.* (2014) 45:2036–40. doi: 10.1161/STROKEAHA.114.004781
3. Fanou EM, Knight J, Aviv RI, Hojjat SP, Symons SP, Zhang L, et al. Effect of collaterals on clinical presentation, baseline imaging, complications, and outcome in acute stroke. *AJNR Am J Neuroradiol.* (2015) 36:2285. doi: 10.3174/ajnr.A4453
4. Agarwal S, Bivard A, Warburton E, Parsons M, Levi C. Collateral response modulates the time–penumbra relationship in proximal arterial occlusions. *Neurology.* (2018) 90:e316–22. doi: 10.1212/WNL.0000000000004858
5. Ben Hassen W, Malley C, Boulouis G, Clarencon F, Bartolini B, Bourcier R, et al. Inter- and intraobserver reliability for angiographic leptomeningeal collateral flow assessment by the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scale. *J NeuroInterv Surg.* (2019) 11:338–41. doi: 10.1136/neurintsurg-2018-014185
6. Li Y, Xiong Y, Cai Q, Liu Q, Dai Q, Liu W, et al. Anterior Borderzone angle for hemodynamic collateral metric in patients with symptomatic middle cerebral artery stenosis. *Eur Neurol.* (2018) 79:45–53. doi: 10.1159/000484313
7. Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke.* (1993) 24:35–41. doi: 10.1161/01.STR.24.1.35
8. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, et al. European stroke organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischemic stroke. *J NeuroInterv Surg.* (2019) 2018:14569. doi: 10.1136/neurintsurg-2018-014568
9. Liebeskind DS. Collateral circulation. *Acta Psychiatrica Scandinavica.* (2003) 34:2279. doi: 10.1161/01.STR.0000086465.41263.06
10. Sheth SA, Sanossian N, Hao Q, Starkman S, Ali LK, Kim D, et al. Collateral flow as causative of good outcomes in endovascular stroke therapy. *J Neurointerv Surg.* (2016) 8:2–7. doi: 10.1136/neurintsurg-2014-011438
11. 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
12. 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
13. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HW, 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
14. 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
15. 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
16. Wang Z, Luo W, Zhou F, Li P, Luo Q. Dynamic change of collateral flow varying with distribution of regional blood flow in acute ischemic rat cortex. *J Biomed Opt.* (2012) 17:125001. doi: 10.1117/1.JBO.17.12.125001
17. Campbell BC, Christensen S, Tress BM, Churilov L, Desmond PM, Parsons MW, et al. Failure of collateral blood flow is associated with infarct growth in ischemic stroke. *J Cereb Blood Flow Metab.* (2013) 33:1168–72. doi: 10.1038/jcbfm.2013.77
18. Beard DJ, McLeod DD, Logan CL, Murtha LA, lmtiaz MS, van Helden DF, et al. Intracranial pressure elevation reduces flow through collateral vessels and the penetrating arterioles they supply. A possible explanation for 'collateral failure' and infarct expansion after ischemic stroke. *J Cereb Blood Flow Metab.* (2015) 35:861–72. doi: 10.1038/jcbfm.2015.2
19. 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
20. Higashida RT, Furlan A J, 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.0000082720.85129.0A
21. Al-Ali F, Berkhemer OA, Yousman WP, Elias JJ, Bender EN, Lingsma HF, et al. The capillary index score as a marker of viable cerebral tissue: proof of concept-the capillary index score in the MR CLEAN (multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the netherlands) trial. *Stroke.* (2016) 47:2286–91. doi: 10.1161/STROKEAHA.116.013513
22. Liebeskind DS, Li Y, Woolf GW, Scalzo F, Cotsonis GA, Zaidat OO, et al. *A Novel Collateral Metric of MCA Hemodynamics in SAMMPRIS*. Houston, TX: ISC (2017). Control/Tracking Number: 17-ISC-A-1649-AHA.
23. 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
24. Linfante I, Walker GR, Castonguay AC, Dabus G, Starosciak AK, Yoo AJ, et al. Predictors of mortality in acute ischemic stroke intervention: analysis of the North American solitaire acute stroke registry. *Stroke.* (2015) 46:2305–8. doi: 10.1161/STROKEAHA.115.009530

25. Loh Y, Jahan R, McArthur DL, Shi ZS, Gonzales NR, Duckwiler GR, et al. Recanalization rates decrease with increasing thrombectomy attempts. *AJNR Am Neuroradiol.* (2010) 31:935–9. doi: 10.3174/ajnr.A1958
26. Jindal G, Carvalho HP, Wessell A, Le E, Naragum V, Miller TR, et al. Beyond the first pass: revascularization remains critical in stroke thrombectomy. *J Neurointerv Surg.* (2019) 11:1095–9. doi: 10.1136/neurintsurg-2019-014773
27. Krueger M, Bechmann I, Immig K, Reichenbach A, Hartig W, Michalski D. Blood—brain barrier breakdown involves four distinct stages of vascular damage in various models of experimental focal cerebral ischemia. *J Cerebral Blood Flow Metab.* (2015) 35:292–303. doi: 10.1038/jcbfm.2014.199
28. García-Tornel Á, Ciolli L, Rubiera M, Reqena M, Muchada M, Pagola J, et al. Leptomeningeal collateral flow modifies endovascular treatment efficacy on large-vessel occlusion strokes. *Stroke.* (2021) 52:299–303. doi: 10.1161/STROKEAHA.120.031338
29. Jing Z, Shi C, Zhu L, Xiang Y, Chen P, Xiong Z, et al. Chronic cerebral hypoperfusion induces vascular plasticity and hemodynamics but also neuronal degeneration and cognitive impairment. *J Cereb Blood Flow Metab.* (2015) 35:1249–59. doi: 10.1038/jcbfm.2015.55
30. Guglielmi V, Lecouffe NE, Zinkstok SM, Compagne KCJ, Eker R, Treurniet KM, et al. Collateral circulation and outcome in atherosclerotic versus cardioembolic cerebral large vessel occlusion. *Stroke.* (2019) 50:3360–8. doi: 10.1161/STROKEAHA.119.026299
31. Ogata A, Ebashi R, Koguchi M, Suzuyama K, Liu X, Tanaka T, et al. Influence of microcatheter position on first-pass success of thrombectomy for acute ischemic stroke. *World Neurosurg.* (2021) 146:e708–13. doi: 10.1016/j.wneu.2020.10.173

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 27 August 2021
doi: 10.3389/fneur.2021.691430

Cortical Venous Changes on Susceptibility-Weighted Imaging Predict the Cerebral Collateral Circulation as Confirmed by Digital Subtraction Angiography

Yun-Hao Zhan[1], Yang-Kun Chen[1], Run-Xiong Li[1], Gen-Pei Luo[1], Zhi-Qiang Wu[1], Yong-Lin Liu[1], Wei-Min Xiao[1], Wei-Dong Hu[1] and Cai-Qin Xie[2]*

[1] Department of Neurology, Affiliated Dongguan Hospital, Southern Medical University (Dongguan People's Hospital), Dongguan, China, [2] Department of Radiology, Affiliated Dongguan Hospital, Southern Medical University (Dongguan People's Hospital), Dongguan, China

OPEN ACCESS

Edited by:
QinJian Sun,
Shandong University, China

Reviewed by:
Ian Winship,
University of Alberta, Canada
Jiachun Feng,
First Affiliated Hospital of Jilin University, China
Takashi Shimoyama,
Nippon Medical School, Japan

***Correspondence:**
Yang-Kun Chen
cykun78@163.com

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: 06 April 2021
Accepted: 16 July 2021
Published: 27 August 2021

Citation:
Zhan Y-H, Chen Y-K, Li R-X, Luo G-P, Wu Z-Q, Liu Y-L, Xiao W-M, Hu W-D and Xie C-Q (2021) Cortical Venous Changes on Susceptibility-Weighted Imaging Predict the Cerebral Collateral Circulation as Confirmed by Digital Subtraction Angiography. Front. Neurol. 12:691430. doi: 10.3389/fneur.2021.691430

Objective: Asymmetrical cortical vein sign (ACVS) shown on susceptibility-weighted imaging (SWI) can reflect regional hypoperfusion. We investigated if ACVS could predict the cerebral collateral circulation (CC) as assessed by digital subtraction angiography (DSA) in acute ischemic stroke patients with ipsilateral severe stenosis/occlusion of the anterior circulation.

Methods: Clinical data and imaging data of 62 acute ischemic stroke patients with ipsilateral severe stenosis or occlusion of the anterior circulation confirmed by DSA were collected retrospectively. Participants underwent magnetic resonance imaging, including an SWI sequence. ACVS was defined as more and/or larger venous signals in the cerebral cortex of one side of SWI than that in the contralateral side. ACVS was measured using the Alberta Stroke Program Early Computed Tomography score based on SWI. The grading of the cerebral CC was judged using DSA.

Results: Of the 62 patients, 30 patients (48.4%) had moderate-to-severe ACVS. According to DSA assessment, 19 patients (30.6%) had a good CC (grade 3–4), and 43 (69.4%) patients had a poor-to-moderate CC (grade 0–2). Among the 30 patients with moderate-to-severe ACVS, only three (10%) patients had a good CC, and 27 (90%) patients had a poor-to-moderate CC; among the 32 patients with none or mild ACVS, 16 (50%) of them had a good CC, and the other 50% had a moderate-to-severe CC. We constructed two logistic regression models with ACVS grading and none or mild ACVS entered into the models, respectively, together with age and large-artery occlusion. In model 1, no ACVS (compared with severe ACVS; OR = 40.329, 95%CI = 2.817–577.422, $P = 0.006$), mild ACVS (compared with severe ACVS; OR = 17.186, 1.735–170.224, 0.015) and large-artery occlusion (OR = 45.645, 4.603–452.592, 0.001) correlated with a good CC. In model 2, none or mild ACVS (OR = 36.848, 95%CI = 5.516–246.171, $P < 0.001$) was significantly associated with a good CC as judged by DSA, adjusted by age and large-artery occlusion.

Conclusions: Cortical venous changes in SWI may be a useful indicator for the cerebral CC as confirmed by DSA.

Keywords: acute ischemic stroke, susceptibility weighted imaging, asymmetrical cortical vessel sign, digital subtraction angiography, collateral circulation

INTRODUCTION

For patients who have suffered acute ischemic stroke (AIS) in the anterior circulation, the key to saving ischemic penumbra is to open the occluded vessels responsible as soon as possible (1). The cerebral collateral circulation (CC) is an essential factor for the early existence of ischemic penumbra (2).

The CC can be divided into three levels. The first level is the circle of Willis. The second level is ophthalmic collateral arteries, pia-mater anastomosis, and other relatively small collateral anastomoses. The third level is neovascularization, which is time-consuming and cannot be evaluated appropriately by digital subtraction angiography (DSA) (3, 4). Commonly used methods for detecting cerebral CC include DSA, multimodal computed tomography angiography (CTA), magnetic resonance perfusion (MRP), and arterial spin labeling (ASL). DSA is the "gold standard" for evaluating a grade-I and -II CC (5). However, it is a traumatic and expensive procedure that necessitates the support of a professional neurointerventional team. Multimodal CTA (6, 7) may be less sensitive for assessment of the leptomeningeal CC compared with that using DSA. DSA and CTA require injection of a contrast agent and carry the risk of contrast-related injuries. MRP (8) or ASL (9) can be used for perfusion assessment rather than direct evaluation for CC. Presence of good CC may enhance the success rate of reperfusion and recanalization in endovascular treatment for AIS (10). CC is a predictor of maintaining brain tissue and good clinical prognosis after AIS, and poorer CC may result in poorer perfusion.

Susceptibility-weighted imaging (SWI) is a magnetic resonance imaging (MRI) sequence. It has high spatial resolution and sensitivity to identify differences in magnetic susceptibility between tissues. Besides its capacity to detect cerebral microbleeds, SWI is considered to reflect oxygen saturation in brain tissues and cerebral vessels. Asymmetrical cortical vein sign (ACVS) denotes more and/or larger venous signals in the cerebral cortex of one side of SWI than that in the contralateral side (11, 12). Several studies show that ACVS is more common in patients with large-vessel occlusion or severe stenosis and reflects cerebral hypoperfusion. Park *et al.* (13) found that total mismatch of diffusion-weighted imaging (DWI)–SWI may be a predictor of good response to treatment in patients with AIS and is associated with cerebral perfusion. In patients with moyamoya disease, ACVS on SWI might be considered as a neuroimaging marker for the evaluation of hemodynamics (14). Moreover, ACVS was observed to be significantly lessened after revascularization (15). ACVS has also been studied in the outcome of AIS. Our recent study (16) found that ACVS might be a useful predictor of early neurological deficits in AIS patients with symptomatic large artery stenosis or occlusion after r-tPA treatment. As perfusion status was significantly affected by CC, it will be interesting to know the relationship between ACVS and CC. To date, very few studies have investigated the relationship between ACVS and CC. Xu *et al.* (17) found that ACVS was associated with good leptomeningeal collateral flow assessed by hyperintense vessel sign (HVS) on T2-FLAIR images rather than DSA. We wished to assess if ACVS could predict the cerebral CC assessed by DSA in AIS patients with ipsilateral severe stenosis/occlusion of the anterior circulation (ISSACS).

MATERIALS AND METHODS

Ethical Approval of the Study Protocol

The requirement for written informed consent was waived by the Ethics Committee of the Affiliated Dongguan Hospital, Southern Medical University (Dongguan, China) because this was a retrospective study.

Inclusion Criteria

The inclusion criteria were (i) age $\geq$18 years; (ii) AIS patients with acute infarction of the anterior circulation within 7 days; (iii) complete clinical and imaging data, including, as a minimum, a DWI sequence, SWI sequence, and DSA image: (iv) prestroke modified Rankin scale score $\leq$2.

Exclusion Criteria

The exclusion criteria were (i) a parenchymatous hemorrhage (PH) evident on CT, (ii) MRI-confirmed AIS of the posterior circulation, (iii) absence of complete clinical and imaging data, (iv) emergency or elective endovascular therapy before MRI completion.

Participants

We retrospectively recruited 62 patients with AIS in the Affiliated Dongguan Hospital between January 1, 2019, and December 31, 2020. During the study period, 534 patients received DSA, and 188 were diagnosed with AIS by DWI. Of these 188 patients, 126 were excluded because of lack of complete clinical and imaging data ($n = 65$); AIS of the posterior circulation ($n = 55$); diagnosed with Moyamoya disease ($n = 4$); or PH detection by CT ($n = 2$). Eventually, 62 patients formed the study cohort.

Collection of Clinical Data

We acquired demographic (age, sex) and clinical (National Institutes of Health Stroke Scale score, history of hypertension, previous stroke, diabetes mellitus, tobacco smoking, atrial fibrillation, homocysteine level, hyperlipidemia) data from each patient.

MRI Assessment

MRI (T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery, DWI, and SWI) of the brain was undertaken for each participant using a 3.0-T system (Skyra; Siemens Medical, Hamburg, Germany) within 7 days of hospital admission.

The MRI parameters for T1-weighted imaging were time of repetition [TR]/time of echo [TE]/excitation = 1,500/11/1, field of view [FOV] = 220 mm, slice thickness/gap = 4 mm/1.2 mm, matrix = 320 × 320, and time of acquisition = 1 min 26 s. The MRI parameters for T1-weighted imaging were TR/TE/excitation = 4,720/96/2, turbo factor = 15, FOV = 220 mm, slice thickness/gap = 4 mm/1.2 mm, matrix of 512 × 512, and time of acquisition = 1 min 50 s. The MRI parameters for DWI (echo planar imaging (EPI) were TR/TE/excitation = 4,640/67/1, matrix = 192 × 192, FOV = 230 mm, slice thickness/gap = 4 mm/1.2 mm, EPI factor = 91, and acquisition time = 1 min 44 s; three orthogonally applied gradients were applied with b values of 0 and 1000. The MRI parameters for SWI were TR/TE/excitation = 27/20/1, FOV = 220 mm, slice thickness/ gap = 3 mm/0.6 mm, matrix 256 × 256, and time of acquisition = 2 min 28s.

One experienced neuroradiologist (C.Q.X.) and one trained neurologist (Y.L.L.), blinded to patients' clinical data, assessed the ACVS grade on SWI independently based on the Alberta Stroke Program Early Computed Tomography (ASPECT) score ("Ins," "Deep," and "M1-6") (18). The SWI-ASPECT score ranged from 0 ("no ACVS") to 8 ["ACVS abutting all middle cerebral artery (MCA) cortical areas"]. The ACVS grade was classified as (1) "none" (no ACVS in any MCA cortical area), (2) "mild" (ACVS in 1–3 defined MCA cortical areas), (3) "moderate" (ACVS in 4–6 defined MCA cortical areas), or (4) "severe" (ACVS in 7–8 defined MCA cortical areas) (19) (**Figure 1**). Testing of inter-rater and intra-rater reliability of ACVS grade was done in 10 randomized cases. The intra-rater agreement of SWI measurements was good-to-excellent; kappa was 0.83; the kappa for inter-rater agreement was 0.76.

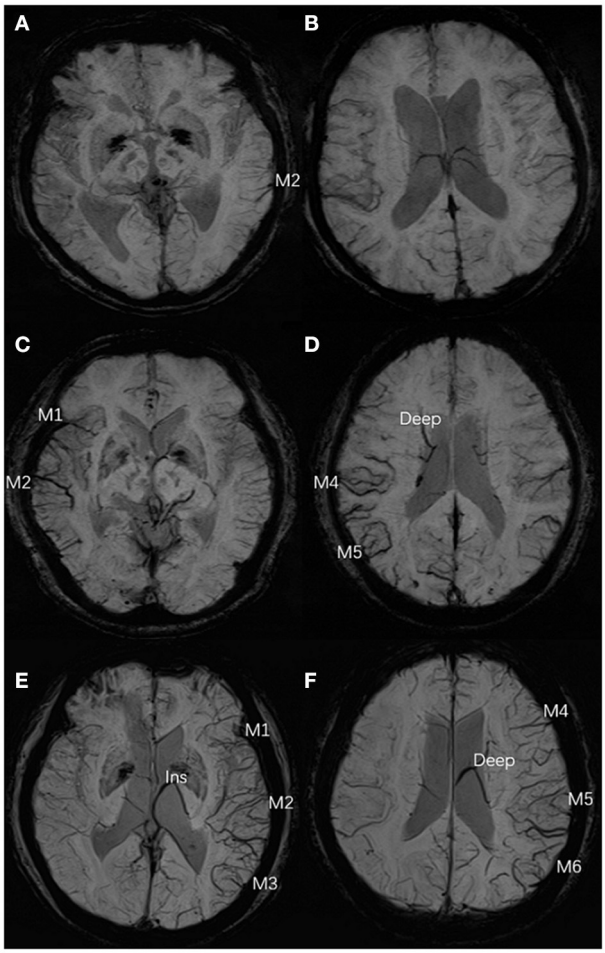


FIGURE 1 | Three typical cases of ACVS, graded as "mild," "moderate," and "severe" **(A,B)** In the left hemisphere, ACVS in M2 was evident on SWI and defined as "mild ACVS." **(C,D)** In the right hemisphere, ACVS in M1 and M2 and M4, M5, and Deep were evident on SWI, and defined as "moderate ACVS." **(E,F)** In the left hemisphere, ACVS in M1, M2, M3, and Ins and M4, M5, M6, and Deep were evident on SWI and defined as "severe ACVS". AIS, acute ischemic stroke; ACVS, asymmetric cortical vein sign; M1, anterior MCA cortex; M2, MCA cortex lateral to the insular cortex; M3, posterior MCA cortex; M4, M5, M6, the anterior, lateral and posterior MCA territories immediately superior to M1, M2 and M3, respectively; Deep, deep white matter; Ins, insula; MCA, middle cerebral artery; SWI, susceptibility-weighted imaging.

Evaluation of the Cerebral CC

The decision to undertake DSA was made according to the attending physician. DSA was done using an angiography unit (Allura; Philips Medical Systems, Amsterdam, the Netherlands) after MRI. Carotid and vertebrobasilar angiography were obtained by orthographic projection and lateral projection, and these two projections had a similar angiographic volume and injection rate. Arterial, capillary, and venous phases were imaged to evaluate slow-moving collateral vessels. All patients underwent DSA and MRI during hospitalization.

The parameters of DSA images were measured using the measurement tool of Neuosoft Picture Archive and Communication System (PACS)/Radiography Information System (RIS). The criteria for collateral flow map–based collateral grade were chosen based on the American Society of Interventional and Therapeutic Neuroradiology (ASITN) scale (20). ASITN score is the most commonly used to evaluate collateral circulation, which is widely used in the evaluation of collateral circulation on DSA. The latter can be divided into five grades: 0 (no visible CC in the ischemic site), 1 (slow CC around the ischemic site and persistent partial defect), 2 (rapid CC around the ischemic site), 3 (slow CC but complete blood flow to the ischemic bed in late vein), 4 (collateral blood flow can reach the ischemic bed completely and rapidly through retrograde perfusion). Grade 3–4 was designated a "good" CC. Grade 0–2 was designated as a "poor-to-moderate" CC. We chose three cases to describe this grading system (**Figure 2**). Y.H.Z. and G.P.L. assessed the DSA results independently and were blinded to the SWI results. Twenty cases were selected to test the intra-rater agreement and inter-rater agreement. The intra-rater agreement of DSA measurements was good (kappa = 0.82). The inter-rater agreement of the DSA measurements was

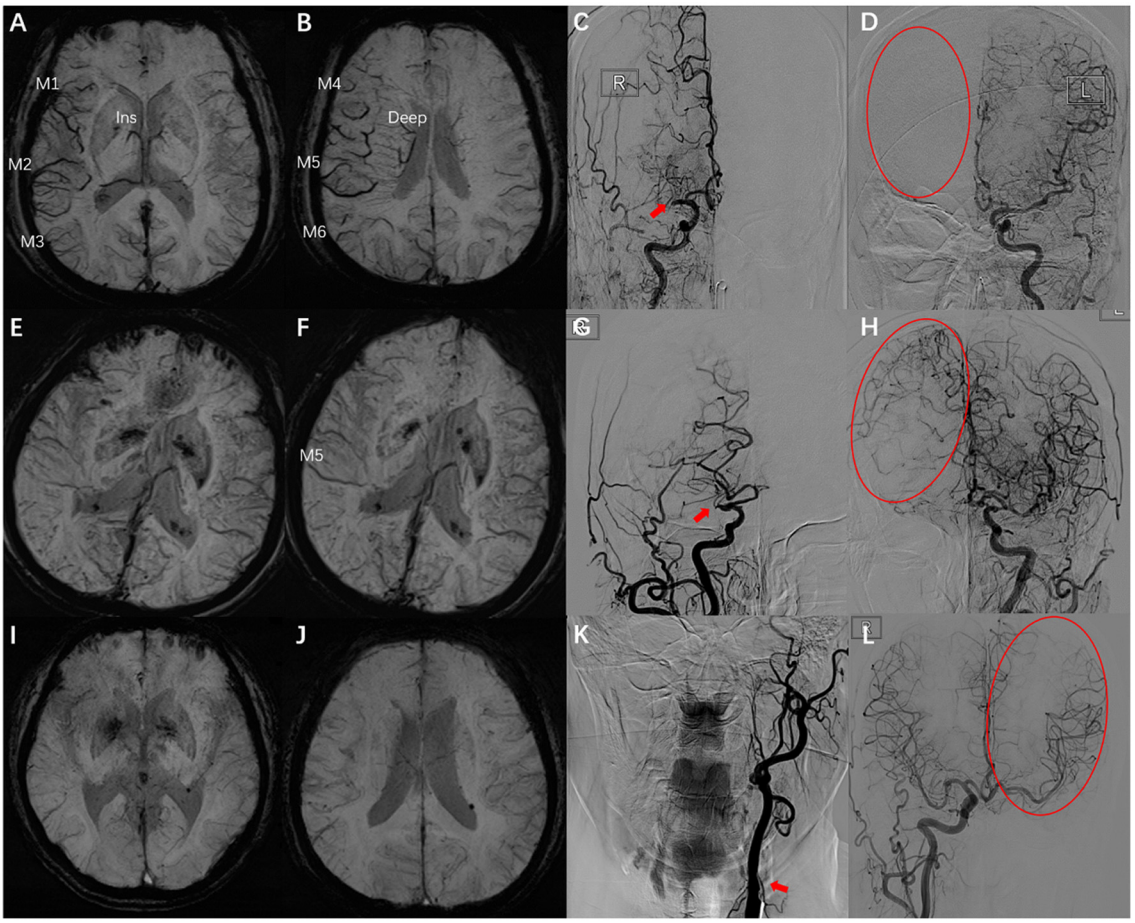


FIGURE 2 | Examples for case selection. **(A,B)** SWI images, ACVS in M1, M2, M3, and Ins and M4, M5, M6, and Deep were evident, ACVS grade was "severe." **(C,D)** DSA images showed the right MCA was occluded in horizontal segment (red arrow), no visible CC in the ischemic site (red circle), ASITN grade = 0. **(E,F)** SWI images, ACVS in M5 was evident, ACVS grade is "mild." **(G,H)** DSA images showed the slow CC but complete blood flow to the ischemic bed, ASITN grade = 3. **(I,J)** SWI images, no ACVS in any MCA cortical area, ACVS grade is "none." **(K,L)** DSA images showed the left ICA was occluded in start section (red arrow), the CC is rapidly and completely perfused to the whole ischemic vascular bed (red circle), ASITN grade = 4. SWI, susceptibility-weighted imaging; ACVS, asymmetric cortical vein sign; Ins, insula; Deep, deep white matter; MCA, middle cerebral artery; DSA, digital subtraction angiography; CC, collateral circulation; ASITN, American Society of Interventional and Therapeutic Neuroradiology; ICA, internal carotid artery; red arrow: responsible vessel; red circle: collateral circulation.

good (kappa = 0.74). If the raters disagreed, then a discussion was initiated until consensus was reached.

Statistical Analyses

Statistical analyses were conducted using SPSS 23.0 (IBM, Armonk, NY, USA). Participants were classified into two groups in terms of a good CC or a not good CC. Continuous variables with a normal distribution are reported as the mean ± SD. Variables with a non-normal distribution are reported as the median and interquartile range. Clinical variables and MRI variables were compared between the two groups using the χ^2 test, independent-samples *t*-test, Fisher's exact test, or Mann–Whitney *U*-test, as appropriate. Logistic regression analysis was conducted for a good CC confirmed by DSA. The power of ACVS prediction for a good CC was calculated using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. $P < 0.05$ (two-sided) was considered significant.

RESULTS

Sixty-two patients (mean age, 59.2 ± 10.6 years; 69.4% male) were evaluated. Thirty-one patients (50%) had occlusion of the internal carotid artery or M1 segment of the MCA. According to the ASITN scale score, 19 patients (30.65%) had a good CC (grade 3–4), and 43 (69.35%) patients had a poor-to-moderate CC (grade 0–2). Among the 30 patients with moderate-to-severe ACVS, only three (10%) patients had a good CC, and 27 (90%) patients had a poor-to-moderate CC; among the 32 patients with none or mild ACVS, 16 (50%) of them had a good CC and the other 50% had a moderate-to-severe CC. Patients with a good CC did not differ significantly from those with a poor-to-moderate CC in terms of age, sex, vascular risk factors, or previous stroke ($P > 0.05$ for all). Patients with a good CC were more likely to have large-artery occlusion (73.7 vs. 39.5%, $P = 0.013$) (**Table 1**).

We constructed two logistic regression models with ACVS grading and none or mild ACVS entered into the models,

TABLE 1 | Comparisons of clinical variables and neuroimaging variables between patients with a DSA-confirmed good collateral circulation or not.

	Whole sample *N* = 62	Good collateral circulation *N* = 19	Poor-to-moderate collateral circulation *N* = 43	*P*
Age* (years)	59.2 ± 10.6	61.58 ± 7.42	58.12 ± 11.60	0.059
Sex†	43(69.4%)	16(84.2%)	37(86.0%)	0.850
Hypertension†	53(85.5%)	18(94.7%)	35(81.4%)	0.169
Diabetes mellitus†	20(32.3%)	5(26.3%)	15(34.9%)	0.506
Smoker†	31(50.0%)	11(57.9%)	20(46.5%)	0.409
Atrial fibrillation†	3(4.8%)	1(5.3%)	2(4.7%)	0.918
Previous stroke history†	12(19.4%)	4(21.1%)	8(18.6%)	0.822
Hyperlipidemia†	31(50.0%)	11(57.9%)	20(46.5%)	0.409
NIHSS score on admission§	2(0–15)	3(0–13)	2(1–15)	0.423
SWI–MRI measures				
DWI-infarct volume (mm^3) §	6.5(0.3–115.6)	6.7(1–95.4)	5.8(0.3–115.6)	0.987
MRI timing(days) §	2(0.5–6)	2(0.5–6)	1(0.5–5)	0.024
ACVS grade†				0.006
None	20(32.3%)	9(47.4%)	11(25.6%)	
Mild	12(19.4%)	7(36.8%)	5(11.6%)	
Moderate	15(24.2%)	1(5.3%)	14(32.6%)	
Severe	15(24.2%)	2(10.5%)	13(30.2%)	
None or mild ACVS†	32(51.6%)	16(84.2%)	16(37.2%)	0.001
DSA timing(days) §	5(0.5–7)	5(0.5–7)	5(0.5–7)	0.691
DSA measures				
Occlusion†	31(50.0%)	14(73.7%)	17(39.5%)	0.013
ASITN grade¶	3(0–6.25)	4(3–4)	0(0–2)	< 0.001

*ASITN, American Society of Interventional and Therapeutic Neuroradiology; NIHSS, National Institutes of Health Stroke Scale; SWI, susceptibility weighted imaging; ACVS, asymmetric cortical vein sign; DSA, digital subtraction angiography. *mean (SD), t-test; † n(%), χ^2 test; ¶n(%), Fisher's exact test; §median (25Q−75Q), Mann–Whitney U-test.*

respectively, together with age and large-artery occlusion. In model 1, no ACVS (compared with severe ACVS, odds ratio (OR) = 40.329, 95% confidence interval (CI) = 2.817–577.422, $P = 0.006$), mild ACVS (compared with severe ACVS, OR = 17.186, 95%CI = 1.735–170.224, $P = 0.015$), and large-artery occlusion (OR = 45.645, 95%CI = 4.603–452.592, $P = 0.001$) correlated with a good CC. In model 2, none or mild ACVS (OR = 36.848, 95%CI = 5.516–246.171, $P < 0.001$) was significantly associated with a good CC judged by DSA, adjusted by age and large-artery occlusion (**Table 2**). We also conducted a logistic regression model with poor CC serving as a dependent variable. Moderate-to-severe ACVS did not significantly correlate with poor CC (**Supplementary Table 1**).

The ROC curve showed the predictive ability of ACVS grading and none or mild ACVS for CC. The AUC for predicting a good CC for none or mild ACVS and ACVS grading was 0.735 and 0.706, respectively (**Figure 3**).

A box plot shows the relationship between ACVS grading (abscissa) and NIHSS stroke score (ordinate) (**Figure 4**). ACVS grading correlated with the severity of stroke (Spearman r = 0.275, $P = 0.031$).

DISCUSSION

The main finding of our study was that, in AIS patients with ISSACS, ACVS grading (especially none or mild ACVS on SWI) strongly predicted a good CC on DSA. This finding is practical for physicians to acquire, in a prompt and non-traumatic way, CC status using only MRI without the need for contrast-agent injection.

The principle of SWI is dependent mainly on deoxyhemoglobin content in venous blood (21). In patients with AIS, the vasodilation caused by ischemia in the cerebral cortex on the affected side (as well as an imbalance in the supply and demand of oxygen in hypoperfused tissue after cerebral-artery occlusion) leads to a relative increase in the deoxyhemoglobin level in the corresponding draining veins and a relative decrease in the oxyhemoglobin level. This action leads to ACVS, which, as a new imaging marker of CC status, is discussed in a few studies (8, 13). A study on the mismatch between DWI and SWI indicates that the increased oxygen demand of hypoperfused brain tissue leads to an increase in the deoxyhemoglobin:oxyhemoglobin ratio. If the insufficiency of cerebral perfusion can be improved and blood vessels can be recanalized, the risk of irreversible ischemic injury can be reduced (13, 22).

The CC is the basis of ischemic penumbra. A good CC can provide sufficient perfusion for the affected hemisphere (23) and reduce the need of ischemic tissue for a metabolic reserve. Early and rapid identification of ischemic penumbra can help to decide whether intravenous thrombolysis or mechanical thrombectomy is indicated. We found that, in comparison with people with

TABLE 2 | Logistic regression analysis of a good collateral circulation confirmed by DSA.

	Univariate logistic regression			Multivariate logistic regression		
Variables	**OR**	**95%CI**	***P***	**OR**	**95%CI**	***P***
Model 1						
Age	1.035	0.978–1.095	0.236	1.048	0.966–1.136	0.257
DWI-infarct volume	1.000	0.978–1.023	0.987	0.962	0.912–1.016	0.162
MRI timing	1.706	1.043–2.788	0.033	1.536	0.767-3.073	0.225
DSA timing	0.954	0.758–1.201	0.689	0.825	0.534–1.275	0.825
Occlusion	7.407	1.875–29.265	0.004	45.645	4.603–452.592	0.001
ACVS grade			0.019			0.006
Severe	ref			ref		
None	5.318	0.943–29.993	0.058	40.329	2.817–577.422	0.006
Mild	9.100	1.318–59.619	0.021	17.186	1.735–170.224	0.015
Moderate	0.464	0.037–5.749	0.550	0.393	0.030–5.231	0.479
Model 2						
Age	1.035	0.978–1.095	0.236	1.056	0.975–1.144	0.178
Occlusion	7.407	1.875–29.265	0.004	32.260	4.791–217.233	<0.001
None or mild ACVS	9.000	2.265–35.755	0.002	36.848	5.516–246.171	<0.001

ACVS, Asymmetric cortical vein sign.

severe ACVS, those without or with only mild ACVS were more likely to have a good CC even if they had symptomatic ISSACS. In addition, none or mild ACVS seems to be a strong indicator for a good CC. These results are in accordance with data from a study by Verma *et al.* (8), which also found that the better the state of the CC, the smaller was the range of ACVS. However, that study had only 33 cases and conducted univariate comparisons only. Determination of ACVS is difficult if bilateral large arteries have severe stenosis/occlusion. Thus, we recruited only AIS patients with ISSACS. Furthermore, we also adjusted these results by age and large-artery occlusion and confirmed this strong association. However, we did not find that severity of ACVS could predict a poor CC. Moderate-to-severe ACVS commonly implicates hypoperfusion, which does not always mean the presence of poor CC. ACVS on MRI-SWI is a non-invasive technique without radiation and contrast allergy risk. Not every AIS patient with large arterial stenosis or occlusion needs a DSA evaluation. It can partially replace DSA assessment of CC in patients with contraindications or unwilling to have DSA for collateral circulation evaluation. However, ACVS is not suitable for patients with bilateral severe large arterial stenosis or occlusion.

In a study of dynamic changes of SWI signals in AIS, Baik et al. (15) found that ACVS was significantly lessened after revascularization. Also, the prognosis of these patients was, in general, not poor but, for patients with hypoperfusion who did not have brain improvement in a timely and complete manner, ACVS on SWI indicated that these patients would be more prone to early neurological deterioration. Previously, we also found that ACVS can predict early neurological deterioration effectively in AIS patients with symptomatic large-artery stenosis/occlusion after treatment with recombinant tissue plasminogen activator (24).

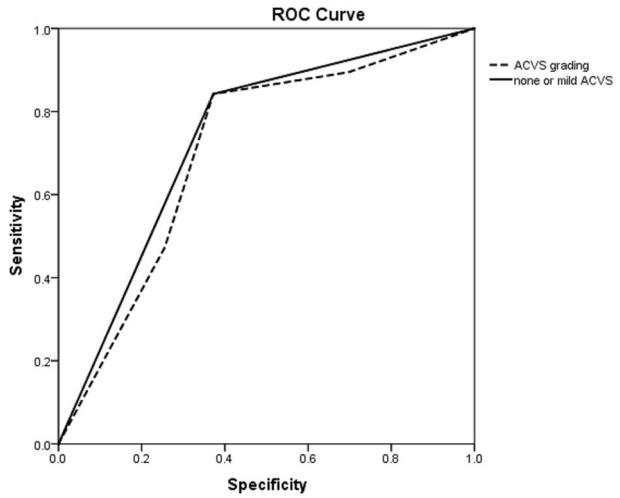


FIGURE 3 | ROC curve of ACVS to predict a good collateral circulation as confirmed by DSA. ROC curve showing the predictive ability of ACVS grading (dotted line) and none or mild ACVS (solid line) for a collateral circulation. ROC, receiver operating characteristic; ACVS, asymmetric cortical vein sign.

ACVS was difficult to quantify accurately. We used the ASPECT scoring to evaluate the range of ACVS. ASPECT scoring was initially used for the measures of the early CT ischemic changes range in predicting benefit with intravenous thrombolysis. A lower ASPECT score implicates a larger range of involvement. ACVS reflects the change of vein shape and number and is difficult to quantify. SWI-ASPECT scoring can be used to evaluate the range of ACVS as recommended by some studies. Only one study (25) attempted to define ACVS quantitatively using susceptibility percentage change. However, to the best of

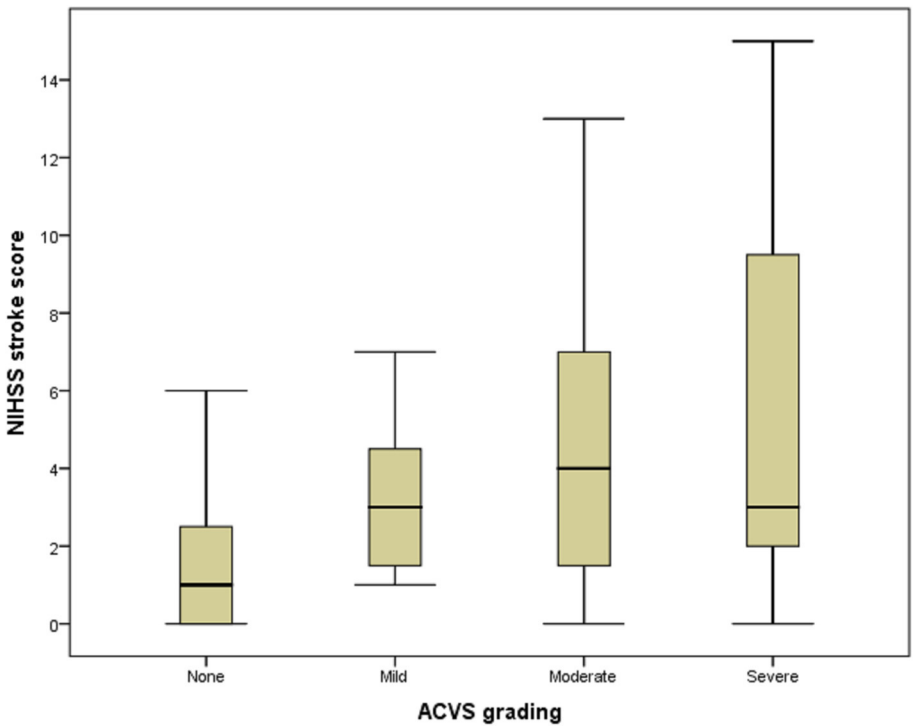


FIGURE 4 | Box plot of the relationship between ACVS and NIHSS stroke score. Box plot showing the relationship between ACVS grading (abscissa) and NIHSS stroke score (ordinate). ACVS, asymmetric cortical vein sign.

our knowledge, no studies have successfully quantified the extent of ACVS using objective methods.

The strengths of our study were that the CC was confirmed using DSA (the gold standard) and that we adjusted for confounders in our analyses. However, our study had four main limitations. First, the sample size of our study was small, and the regression model might have been not very stable. Second, we recruited only AIS patients with ipsilateral arterial lesions. Thus, this finding may be valuable only for unilateral severe stenosis/occlusion in the anterior circulation and not applicable for bilateral lesions. Third, as mentioned before, ACVS is difficult to quantify, and we assessed it *via* a semi-quantitative method. Last, we did not have dynamic evaluation of ACVS as no patients in our stroke center would have SWI examination before thrombolysis or thrombectomy according to the guideline of our stroke center.

CONCLUSIONS

Our study provides evidence for the reliability of ACVS in judging the CC in treatment of AIS in the anterior circulation. Further longitudinal studies using larger patient cohorts and more objective ACVS quantification, e.g., using machine-learning methods, are warranted to justify this finding.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Affiliated Dongguan Hospital, Southern Medical University. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

Y-HZ and Y-KC conceptualized and designed the study, acquired and analyzed data, and drafted the manuscript for intellectual content. Y-HZ and G-PL took measurements. Y-LL and C-QX measured SWI data. R-XL, Z-QW, W-MX, and W-DH selected and recruited the patients. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Guangdong Province Science and Technology Plan Project Public Welfare Fund and Ability Construction Project, China (2017A020215002).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.691430/full#supplementary-material

REFERENCES

1. Dargazanli C, Fahed R, Blanc R, Gory B, Labreuche J, Duhamel A, et al. Modified thrombolysis in cerebral infarction 2c/thrombolysis in cerebral infarction 3 reperfusion should be the aim of mechanical thrombectomy: insights from the aster trial (contact aspiration versus stent retriever for successful revascularization). *Stroke.* (2018) 49:1189–96. doi: 10.1161/STROKEAHA.118.020700
2. Singer OC, Berkefeld J, Nolte CH, Bohner G, Reich A, Wiesmann MK, et al. Collateral vessels in proximal middle cerebral artery occlusion: the ENDOSTROKE study. *Radiology.* (2015) 274:851–8. doi: 10.1148/radiol.14140951
3. Liebeskind DS. Collateral circulation. *Stroke.* (2003) 34:2279–84. doi: 10.1161/01.STR.0000086465.41263.06
4. Liu LP, Xu AD, Wong LK, Wang DZ, Wang YJ. e Expert consensus group of the, and s intervention of collateral circulation for ischemic, Chinese consensus statement on the evaluation and intervention of collateral circulation for ischemic stroke. *CNS Neurosci Ther.* (2014) 20:202–8. doi: 10.1111/cns.12226
5. Liebeskind DS. Collaterals in acute stroke: beyond the clot. *Neuroimaging Clin N Am.* (2005) 15:553–73, x. doi: 10.1016/j.nic.2005.08.012
6. Jansen IGH, Berkhemer OA, Yoo AJ, Vos JA, Lycklama ANGJ, Sprengers MES. et al. Comparison of CTA- and DSA-based collateral flow assessment in patients with anterior circulation stroke. *AJNR Am J Neuroradiol.* (2016) 37:2037–42. doi: 10.3174/ajnr.A4878
7. Maier IL, Scalzo F, Leyhe JR, Schregel K, Behme D, Tsogkas I, et al. Validation of collateral scoring on flat-detector multiphase CT angiography in patients with acute ischemic stroke. *PLoS One.* (2018) 13:e0202592. doi: 10.1371/journal.pone.0202592
8. Verma RK, Hsieh K, Gratz PP, Schankath AC, Mordasini P, Zubler C, et al. Leptomeningeal collateralization in acute ischemic stroke: impact on prominent cortical veins in susceptibility-weighted imaging. *Eur J Radiol.* (2014) 83:1448–54. doi: 10.1016/j.ejrad.2014.05.001
9. Morofuji Y, Horie N, Tateishi Y, Morikawa M, Yamaguchi S, Izumo T, et al. Arterial spin labeling magnetic resonance imaging can identify the occlusion site and collateral perfusion in patients with acute ischemic stroke: comparison with digital subtraction angiography. *Cerebrovasc Dis.* (2019) 48:70–6. doi: 10.1159/000503090
10. Leng X, Fang H, Leung TW, Mao C, Xu Y, Miao Z, et al. Impact of collateral status on successful revascularization in endovascular treatment: a systematic review and meta-analysis. *Cerebrovasc Dis.* (2016) 41:27–34. doi: 10.1159/000441803
11. Haacke EM, Mittal S, Wu Z, Neelavalli J, Cheng YC. Susceptibility-weighted imaging: technical aspects and clinical applications, part 1. *AJNR Am J Neuroradiol.* (2009) 30:19–30. doi: 10.3174/ajnr.A1400
12. Zhang S, Lai Y, Ding X, Parsons M, Zhang JH, Lou M. Absent filling of ipsilateral superficial middle cerebral vein is associated with poor outcome after reperfusion therapy. *Stroke.* (2017) 48:907–14. doi: 10.1161/STROKEAHA.116.016174
13. Park MG, Yeom JA, Baik SK, Park KP. Total mismatch of diffusion-weighted imaging and susceptibility-weighted imaging in patients with acute cerebral ischemia. *J Neuroradiol.* (2017) 44:308–12. doi: 10.1016/j.neurad.2017.04.002
14. Weiqiang Q, Tikun S, Qiongqiong Q, Jinge Z, Chunchao X, Yi L, et al. Asymmetric cortical vessel sign indicates hemodynamic deficits in adult patients with moyamoya disease. *World Neurosurg.* (2019) 127:e137–41. doi: 10.1016/j.wneu.2019.02.187
15. Baik SK, Choi W, Oh SJ, Park KP, Park MG, Yang TI, et al. Change in cortical vessel signs on susceptibility-weighted images after full recanalization in hyperacute ischemic stroke. *Cerebrovascular Diseases.* (2012) 34:206–12. doi: 10.1159/000342148
16. Li W, Xiao WM, Luo GP, Liu YL, Chen YK. Asymmetrical cortical vein sign predicts early neurological deterioration in acute ischemic stroke patients with severe intracranial arterial stenosis or occlusion. *BMC Neurol.* (2020) 20:331. doi: 10.1186/s12883-020-01907-w
17. Xu Z, Duan Y, Yang B, Huang X, Pei Y, Li X. Asymmetric deep medullary veins in patients with occlusion of a large cerebral artery: association with cortical veins, leptomeningeal collaterals, and prognosis. *Front Neurol.* (2019) 10:1292. doi: 10.3389/fneur.2019.01292
18. Puetz V, Dzialowski I, Hill MD, Demchuk AM. The alberta stroke program early CT Score in clinical practice: what have we learned? *Int J Stroke.* (2009) 4:354–64. doi: 10.1111/j.1747-4949.2009.00337.x
19. Park MG, Yang TI, Oh SJ, Baik SK, Kang YH, Park KP. Multiple hypointense vessels on susceptibility-weighted imaging in acute ischemic stroke: surrogate marker of oxygen extraction fraction in penumbra? *Cerebrovasc Dis.* (2014) 38:254–61. doi: 10.1159/000367709
20. 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
21. Haacke EM, Xu Y, Cheng YC, Reichenbach JR. Susceptibility weighted imaging (SWI). *Magn Reson Med.* (2004) 52:612–8. doi: 10.1002/mrm.20198
22. Yuan T, Ren G, Quan G, Gao D. Fewer peripheral asymmetrical cortical veins is a predictor of favorable outcome in MCA infarctions with SWI-DWI mismatch. *J Mag Reson Imaging.* (2018) 48:964–70. doi: 10.1002/jmri.25965
23. Liebeskind DS, Bracard S, Guillemin F, Jahan R, Jovin TG, Majoie CB, et al. eTICI reperfusion: defining success in endovascular stroke therapy. *J Neurointerv Surg.* (2019) 11:433–8. doi: 10.1136/neurintsurg-2018-014127
24. Liu YL, Yin HP, Qiu DH, Qu JF, Zhong HH, Lu ZH, et al. Multiple hypointense vessels on susceptibility-weighted imaging predict early neurological deterioration in acute ischaemic stroke patients with severe intracranial large artery stenosis or occlusion receiving intravenous thrombolysis. *Stroke Vascular Neurol.* (2020) 5:361–7. doi: 10.1136/svn-2020-000343
25. Luo Y, Gong Z, Zhou Y, Chang B, Chai C, Liu T, et al. Increased susceptibility of asymmetrically prominent cortical veins correlates with misery perfusion in patients with occlusion of the middle cerebral artery. *Eur Radiol.* (2017) 27:2381–90. doi: 10.1007/s00330-016-4593-y

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 09 September 2021
doi: 10.3389/fneur.2021.695085

Efficacy of a Direct Aspiration First-Pass Technique (ADAPT) for Endovascular Treatment in Different Etiologies of Large Vessel Occlusion: Embolism vs. Intracranial Atherosclerotic Stenosis

Geng Liao[1], Zhenyu Zhang[1], Guangzhi Zhang[1], Weijie Du[1], Chaomao Li[1] and Hanxiang Liang[2]*

[1] Department of Neurology, Maoming People's Hospital, Maoming, China, [2] Department of Magnetic Resonance Imaging, Maoming People's Hospital, Maoming, China

OPEN ACCESS

Edited by:
Osama O. Zaidat,
Northeast Ohio Medical University,
United States

Reviewed by:
Alhamza R. Al-Bayati,
Emory University, United States
Nabil Kitchener,
General Organization for Teaching Hospitals and Institutes, Egypt
Alberto Maud,
Texas Tech University Health Sciences Center El Paso, United States
Qazi Zeeshan,
University at Buffalo, United States

***Correspondence:**
Geng Liao
legendv@126.com

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: 14 April 2021
Accepted: 14 July 2021
Published: 09 September 2021

Citation:
Liao G, Zhang Z, Zhang G, Du W, Li C and Liang H (2021) Efficacy of a Direct Aspiration First-Pass Technique (ADAPT) for Endovascular Treatment in Different Etiologies of Large Vessel Occlusion: Embolism vs. Intracranial Atherosclerotic Stenosis. Front. Neurol. 12:695085. doi: 10.3389/fneur.2021.695085

Background and Aims: Aspiration thrombectomy is an effective method of recanalizing large vessel occlusion (LVO). However, the efficacy of a direct aspiration first-pass technique (ADAPT) for recanalization of LVO of different etiologies is not properly understood.

Methods: The prospectively collected database on ADAPT was reviewed retrospectively. We defined two groups of enrolled patients: the embolism-related occlusions (EMB-O) group and the intracranial atherosclerotic stenosis (ICAS)-related occlusion (ICAS-O) group. Baseline characteristics, procedural variables, and post-procedural variables were collected. Multivariate logistic regression analysis was used to identify first-pass recanalization predictors.

Results: Of 114 registered patients, 94 were eligible for this study (51 patients in the EMB-O group and 43 patients in the ICAS-O group). Achieving successful reperfusion immediately after direct aspiration was more frequent in the EMB-O group than in the ICAS-O group (64.71 vs. 27.91%, respectively, $p = 0.006$), with fewer additional rescue treatments needed (35.29 vs. 70.09%, respectively, $p = 0.001$). The EMB-O group also showed a higher final successful reperfusion rate (96.8 vs. 74.41%, $p = 0.006$). However, the 90-day good functional outcomes were not affected by the groups. Independent predictors of first-pass success of aspiration included the isolated middle cerebral artery site of occlusion, embolic etiology, and use of larger bore catheters.

Conclusions: The efficacy of ADAPT recanalization approach was better in EMB-O than in ICAS-O. In case of embolic etiology and the isolated MCA site of occlusion, using a larger aspiration catheter for direct aspiration thrombectomy may be reasonable.

Keywords: etiology, endovascular treatment, mechanical thrombectomy, embolism, intracranial atherosclerotic stenosis, stroke

INTRODUCTION

A direct aspiration first-pass technique (ADAPT) as first-line therapy for stroke thrombectomy has shown non-inferior functional outcome at 90 days compared with stent retriever first-line thrombectomy (1). However, the efficacy of aspiration thrombectomy as a first-line approach for the recanalization of large vessel occlusions (LVOs) of different etiologies is not properly understood. There have been only a few studies about the endovascular treatment (EVT) of intracranial atherosclerotic stenosis (ICAS)-related LVO (ICAS-O) (2). They revealed that mechanical thrombectomy (MT) with a stent retriever or contact aspiration was less effective and more time-consuming in ICAS-O than in embolic LVO (EMB-O). In this study, we aimed to evaluate the efficacy of using ADAPT in LVO of different etiologies.

MATERIALS AND METHODS

Study Populations

We performed a retrospective analysis of our prospectively gathered EVT database of patients with acute ischemic stroke (AIS). The intention was to identify patient cohorts in whom aspiration had been used as a first-line EVT approach in the anterior and posterior circulation (internal carotid artery, middle cerebral artery M1 and M2 segments, basilar artery, and vertebral artery in the V4 segment) and in whom the etiology of occlusion was identified. The database included all patients who presented with AIS due to LVO and who were treated with EVT between January 1, 2018, and June 30, 2020. The inclusion criteria were as follows:

- patients with intracranial large artery occlusions;
- underlying etiology classified as ICAS or embolism; and
- the onset time was defined as time from symptom onset to puncture $\leq$ 24 h. The onset time was defined as the last time when patient was still well.

Exclusion criteria encompassed the following:

- the etiology of LVO was classified as dissection, chronic total occlusion, moyamoya disease, vasculitis, or undetermined; and
- patients referred for pre-onset modified Rankin Scale (mRS) score $>$ 2.

Patient demographics, comorbidities, premorbid functional status, conventional vascular risk factors, and laboratory findings assessed during admission, National Institutes of Health Stroke Scale (NIHSS), arterial occlusion site and lateralization, time from onset to puncture, Alberta Stroke Program Early CT Score (ASPECTS), intravenous thrombolysis before MT, angiographic, the number of passes with the aspiration device, time from puncture to reperfusion, and clinical data were collected. The location of initial occlusion site was determined using baseline computed tomography angiography or digital-subtraction angiography (DSA). Reperfusion performance was evaluated using the modified Thrombolysis in Cerebral Infarction grade (mTICI) grade (3). Successful reperfusion was defined as mTICI grade 2b or higher. First attempt recanalization (FAR) was defined as successful recanalization at the first attempt (4). All patients had a computed tomography (CT) at the end of the procedure and a CT or magnetic resonance image (MRI) scan 24 h after treatment onset to assess hemorrhagic complications. Intracerebral hemorrhages were classified in accordance with the European Cooperative Acute Stroke Study criteria (5). Subarachnoid hemorrhage (SAH) was classified using the modified Fisher scale (6). Symptomatic intracranial hemorrhage was defined as parenchymal hematoma type 2 using the ECASS III grading (European Cooperative Acute Stroke Study) according to imaging at 24 h, associated with an increase of at least four NIHSS points within 24 h, or resulting in death (7). New embolism in other vessels was defined as an occlusion of a previously unaffected non-downstream vascular territory observed on the angiogram after clot removal.

Endovascular Procedure

In the current study, we divided patients into two groups based on the etiology of occlusion: the EMB-O group and ICAS-O group. ADAPT was used as the first-line approach for MT in both groups. In brief, a large-bore guide catheter such as a MPA1 0.088 inches (Cordis, USA) or 8-9F balloon guide catheter (Stryker, CA, USA) was advanced as far safely as possible into the internal carotid artery for anterior circulation thrombi and to the largest caliber vertebral artery in the posterior circulation thrombi. Then, the aspiration catheter was advanced and inserted into the internal thrombosis, usually over a microcatheter and micro guidewire. Dual aspiration was applied, and the clot was either ingested within the catheter or it was affixed at the catheter tip and then withdrawn under continuous vacuum exerted by a 50 or 60-ml syringe. If aspiration alone failed three times, access was maintained through the aspiration catheter, and then the second-line option was considered with the use of a stent retriever. Rescue treatments were allowed, including angioplasty, intra-arterial infusion of antithrombotics, and intracranial stenting. A control angiogram was performed to confirm reperfusion. Devices were selected at the discretion of neurointerventionalists based on the consensus of the stroke team.

Etiologic Classification of Target Occlusive Lesions

The etiology of target LVO was determined by an independent core laboratory imaging analysis group based on medical history, angiography, and magnetic resonance imaging. Two experienced neurointerventionalists who were blinded to patient identification independently reviewed the clinical and image data of all the patients to determine the etiology of target LVO, and an experienced neurologist solved disparities. Interrater agreement for etiology of LVOs was assessed using Cohen's kappa coefficient (Cohen κ). Vasospasm caused by catheter and uncommon cerebral arterial diseases such as chronic total occlusion, dissection, and moyamoya disease were excluded. Etiological identification referred to TOAST criteria (Trial of Org 10172 in Acute Stroke Treatment) (8): if the occluded vessel was

completely recanalized after primary thrombectomy, the etiology was classified as embolic occlusion, and a remnant stenosis >50% was classified as ICAS-O. In addition, the etiology of LVO in some patients was further evaluated by high-resolution magnetic resonance vascular wall analysis following MT during admission. Consequently, the EMB-O and ICAS-O groups were included in the analyses.

Outcome Measures

The primary outcome was the rate of immediate and final successful reperfusion (mTICI score of 2b or 3) after the use of aspiration thrombectomy as the first-line approach; secondary outcomes included safety issues (procedural complications), procedural times (onset and femoral puncture to reperfusion), and 90-day all-cause mortality. Favorable outcome was defined by an modified Rankin Scale score (mRS) of 0 to 2 as evaluated by an independent senior vascular neurologist during face-to-face interviews or *via* telephone conversations at the 90th day of follow-up. Otherwise, since the clinical outcome may differ between the anterior and posterior circulation occlusions, the occlusion site as a subgroup was also included in the analysis of clinical outcomes.

Statistical Analysis

Baseline characteristics and outcome measures were compared using univariate comparison and descriptive statistics. Variables were expressed as means ± standard deviations, medians (interquartile ranges), or numbers (percentages). Variables were compared using a non-parametric alternative for *t*-test (Mann-Whitney *U*-test) for non-continuous or non-normally distributed variables, Student's *t*-test for continuous variables, and χ^2 test for categorical variables. Multivariate logistic regression was used to identify first-pass effect predictors in overall patients. *p*-values were two-tailed, and variables were considered significant at the < 0.05 level. Analysis was performed using PASWstat 18.0 (IBM Corporation, New York, USA).

RESULTS

From January 2018 to June 2020, a total of 429 patients were screened for EVT of LVO ischemic stroke. Of these, 114 patients were treated with aspiration thrombectomy as first-line approach, and they constituted the study sample. Among them, 94 patients were included in the final analysis. The patient inclusion flowchart is shown in **Figure 1**. There was a good agreement on identification of the etiology of target LVO (Cohen κ: 0.871) between two independent neurointerventionalists. Overall, FAR and successful recanalization rates after simple contact aspiration were achieved in 44.68% (42/94) and 47.87% (45/94) of patients, respectively. The final successful recanalization rate was 86.17% (81/94).

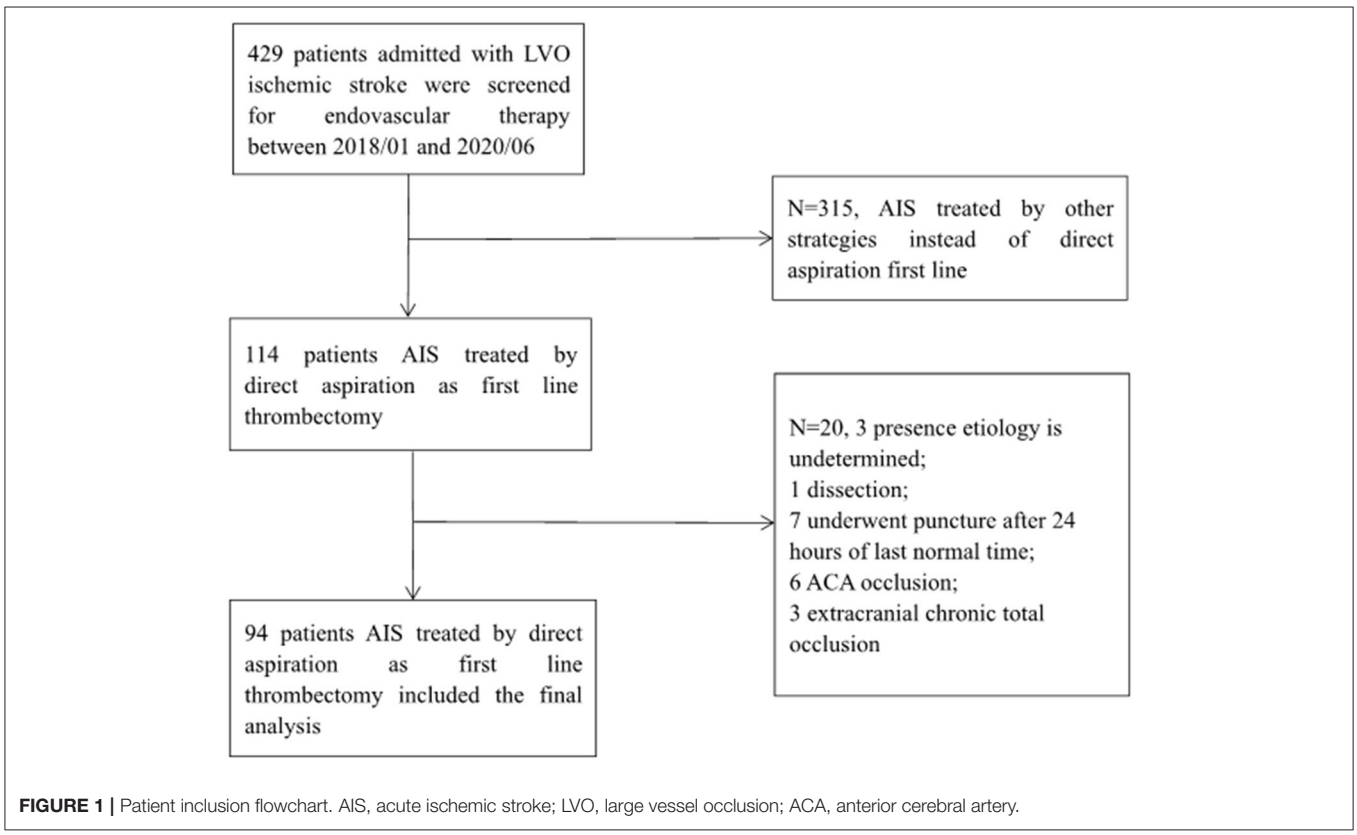


FIGURE 1 | Patient inclusion flowchart. AIS, acute ischemic stroke; LVO, large vessel occlusion; ACA, anterior cerebral artery.

Baseline Characteristics

The characteristics of study sample are described in **Table 1**.

Demographics and comorbidities showed that the risk factors for atherosclerosis, such as hypertension (74.4 vs. 37.3%; $p = 0.001$) and diabetes (32.6 vs. 9.8%; $p = 0.013$), were higher in the ICAS-O group than in the EMB-O group. The risk factors for atrial fibrillation in the EMB-O group were much more common than in the ICAS-O group (72.5 vs. 4.7%, respectively; $p < 0.001$). Time from onset to main hospital arrival and puncture time were shorter in the EMB-O group. Other demographic variables and comorbidities revealed no significant differences between the two groups.

Effects of ADAPT for MT

Table 2 summarizes comparative results regarding the treatment.

Successful reperfusion after first pass of aspiration was more common in the EMB-O group than in the ICAS-O group (56.86 vs. 30.23%, $p = 0.017$). Immediate successful reperfusion after aspiration was achieved more frequently in the EMB-O group (64.71%) than in the ICAS-O group (27.91%; $p = 0.006$), as well as the complete reperfusion (mTICI 2C-3) rate (51.94 vs. 23.26%, $p = 0.003$). The rate of total switching to another thrombectomy device was more frequent in the ICAS-O group than in the EMB-O group (70.09 vs. 35.29%, $p = 0.001$). As rescue treatments, balloon angioplasty and permanent stenting were performed more frequently in the ICAS-O group. Tirofiban/eptifibatide infusion was performed in both groups with no significant difference.

The final successful reperfusion rate was higher in the EMB-O group than in the ICAS-O group (EMB-O, 96.8% vs. ICAS-O, 74.41%; $p = 0.006$). The time from puncture to final revascularization was longer in the ICAS-O group.

Intracerebral hemorrhagic transformation of any type and parenchymal hematoma type 2 occurred at similar rates in the two groups. The occurrence of new embolism in other vessels and iatrogenic dissection or rupture were similar between the two groups.

TABLE 1 | Comparison of baseline characteristics in 94 patients with aspiration thrombectomy as first-line approach.

Variable	Overall	Embolism-related occlusions	ICAS-related occlusions	*p*-values*
No. of patients	94	51	43	
Age, years; mean ± SD	68.71 ± 13.33	68.82 ± 13.36	67.28 ± 11.20	0.307
Men	56 (59.6)	27 (52.9)	29 (67.4)	0.224
Hypertension	51 (54.3)	19 (37.3)	32 (74.4)	0.001
Diabetes mellitus	19 (20.2)	5 (9.8)	14 (32.6)	0.013
Dyslipidemia	12 (12.8)	3 (5.9)	9 (20.9)	0.062
Atrial fibrillation	39 (41.5)	37 (72.5)	2 (4.7)	0.000
Cardiovascular disease	18 (19.1)	10 (19.6)	8 (18.6)	1.000
Current smoking	8 (8.50)	4 (7.80)	4 (9.30)	1.000
Site of occlusion				
ICA siphon	28 (29.79)	18 (35.29)	10 (23.26)	NA
ICA siphon and MCA tandem	16 (17.02)	10 (19.61)	6 (13.95)	NA
Middle cerebral artery, M1	20 (21.28)	9 (17.65)	11 (25.58)	NA
Middle cerebral artery, M2	4 (4.26)	3 (5.88)	1 (2.33)	NA
Basilar artery	18 (19.15)	10 (19.61)	8 (18.60)	NA
Vertebral artery	8 (8.51)	0	8 (18.60)	NA
Initial NIHSS score, median (IQR)	14.95 (10–25)	15.73 (10–21)	14.30 (10–19)	0.345
ASPECTS, median (IQR)	8.44 (7–10)	8.0 (5–10)	8.91 (8–10)	0.078
Previous use of IV thrombolysis	15 (16.0)	10 (19.6)	5 (11.6)	0.441
Onset-to-door time, min, median (IQR)	256 (120–360)	224 (120–300)	293 (180–390)	0.040
Onset-to-puncture time, min, median (IQR)	353 (201–481)	320 (217–444)	394 (259–513)	0.029
The number of passes with the aspiration device (mean ± SD)	1.11 ± 0.373	1.10 ± 0.300	1.12 ± 0.448	0.815
Use of BGC	11	9	2	NA
Use of larger bore catheters (≥060)	29	23	6	NA
SOFIA PLUS 070	19	16	3	NA
Catalyst 060	8	6	2	NA
NAVIEN 072	2	1	1	NA
HR-MR following MT	19	2	17	NA

*Values expressed as n (%) unless otherwise indicated. NA, not applicable; ICAS, intracranial atherosclerotic stenosis; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; HR-MR, high-resolution magnetic resonance vascular wall analysis; BGC, balloon guide catheter; MT, mechanical thrombectomy. *p-values calculated using Student's t-test or Mann–Whitney U-test or χ^2 test, as appropriate.*

TABLE 2 | Procedure details.

Variable	Embolism-related occlusions ($n = 51$)	ICAS-related occlusions ($n = 43$)	*p*-values
Immediate effects following first-line thrombectomy of direct aspiration			
mTICI 2b or greater on first pass of aspiration	29 (56.86)	13 (30.23)*	0.017
mTICI 2c-3 on first pass of aspiration	27 (51.94)	10 (23.25)	0.003
mTICI 2b or greater after aspiration	33 (64.71)	12 (27.91)	0.006
Time from groin puncture to first revascularization, min, median (IQR)	27 (20–30)	42 (30–60)	0.000
Rescue treatments after first-line thrombectomy of direct aspiration	18 (35.29)	31 (70.09)	0.001
Switching to stent retriever device	18 (35.29)	11 (25.58)	0.429
Balloon angioplasty	1 (1.96)	18 (41.86)	0.000
Permanent stenting	2 (3.92)	10 (23.26)	0.013
Tirofiban/Eptifibatide infusion	18 (35.29)	25 (58.14)	0.344
Final endovascular treatment results			
Final mTICI flow [*n* (%)]			
2b−3	49 (96.8)	32 (74.41)	0.006
0–2a	2 (3.92)	11 (25.58)	0.000
Time from groin puncture to final revascularization, min, median (IQR)	42 (29–50)	83 (60–103)	0.000
Complications			
Hemorrhage, all types	6 (11.76)	3 (6.98)	0.876
Hemorrhage, PH2	3 (5.88)	2 (4.65)	0.791
SAH, grade 3 or 4	1 (1.96)	1 (2.33)	0.903
New embolism in other vessels	6 (11.76)	2 (4.65)	0.546
Iatrogenic dissection or rupture	0	1 (2.33)	0.932
Spasm	3 (5.88)	2 (4.65)	0.791

*Data presented as n (%, 95% confidence interval), median (95% confidence interval), n (%), or mean (SD). mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health stroke scale; IQR, interquartile range; PH2, parenchymal hematoma type 2; SAH, subarachnoid hemorrhage. *One patient was treated successfully by aspiration, but due to re-occlusion after 10 min, another round of rescue therapy was required.*

Clinical Outcomes After EVT

There was no significant difference in favorable clinical outcome at 3 months (**Table 3**). To investigate the clinical outcome, we divided patients into two subgroups based on the location of the occlusion (anterior circulation vs. posterior circulation). The subgroup analysis showed that the location of the occlusion did not affect good clinical outcome at 3 months (**Table 3**, **Figure 2A**). However, 90-day mortality in patients with occlusion in the posterior circulation was higher in the ICAS-O than in the EMB-O group (16.28 vs. 1.96%, $p = 0.012$; **Table 3**, **Figure 2B**).

TABLE 3 | Clinical outcomes at 90 days after endovascular treatment.

	Embolism-related occlusions ($n = 51$)	ICAS-related occlusions ($n = 43$)	OR (95% CI)	*p*-values
mRS 0–2 at 90 days	24 (47.06)	15 (34.88)	1.659 (0.721–3.821)	0.233
Anterior circulation	18 (35.29)	11 (25.58)	1.587 (0.649–3.879)	0.310
Posterior circulation	6 (11.76)	4 (9.30)	1.064 (0.281–4.022)	0.928
Mortality at 90 days	10 (19.61)	13 (30.23)	0.563 (0.218–1.455)	0.233
Anterior circulation	9 (17.65)	6 (13.95)	1.321 (0.43–4.064)	0.626
Posterior circulation	1 (1.96)	7 (16.28)	0.101 (0.012–0.856)	0.012

Data presented as n (%) or median (IQR). OR, odds ratio; mRS, modified Rankin Scale; CI, confidence interval; ICAS, intracranial atherosclerotic stenosis.

Predictors of FAR Using ADAPT

To investigate predictors of FAR, multivariate logistic regression analysis was applied in all cases of the two groups. Embolic etiology, isolated MCA occlusion, and the use of larger aspiration catheters were predictors of FAR (**Table 4**). Multivariate logistic regression analysis was applied in all cases of the two groups.

DISCUSSION

Our study demonstrates that ADAPT is more successful to achieve full recanalization in embolic LVO compared to intracranial atherosclerotic stenosis LVO. Additionally, we also found that independent predictors of FAR of aspiration included the isolated middle cerebral artery site of occlusion, embolic etiology, and use of larger bore catheters. Subgroup analysis showed that trends for the mortality of ICAS-O patients were higher than those of EMB-O in the posterior circulation.

ICAS is one of the main causes of acute stroke in Asian, Hispanic, and African populations (9). Furthermore, some studies have documented that ICAS-O is responsible for ∼12–34% of all causes of LVO in east Asia (2, 10) and 1.9%−5.5% in Western countries (11, 12). It has been shown that the pathomechanism of ICAS-O is likely due to *in situ* thromboocclusion (13). Some studies have shown that stent retriever thrombectomy for obtaining initial recanalization is equally effective in ICAS-O and EMB-O, although reocclusion is frequent after an initial recanalization in ICAS-O (2). Unlike stent retriever thrombectomy, aspiration first seemed less effective for the recanalization of ICAS-O (14).

In this cohort, baseline characteristics of the two groups were different in many risk factors for stroke, such as

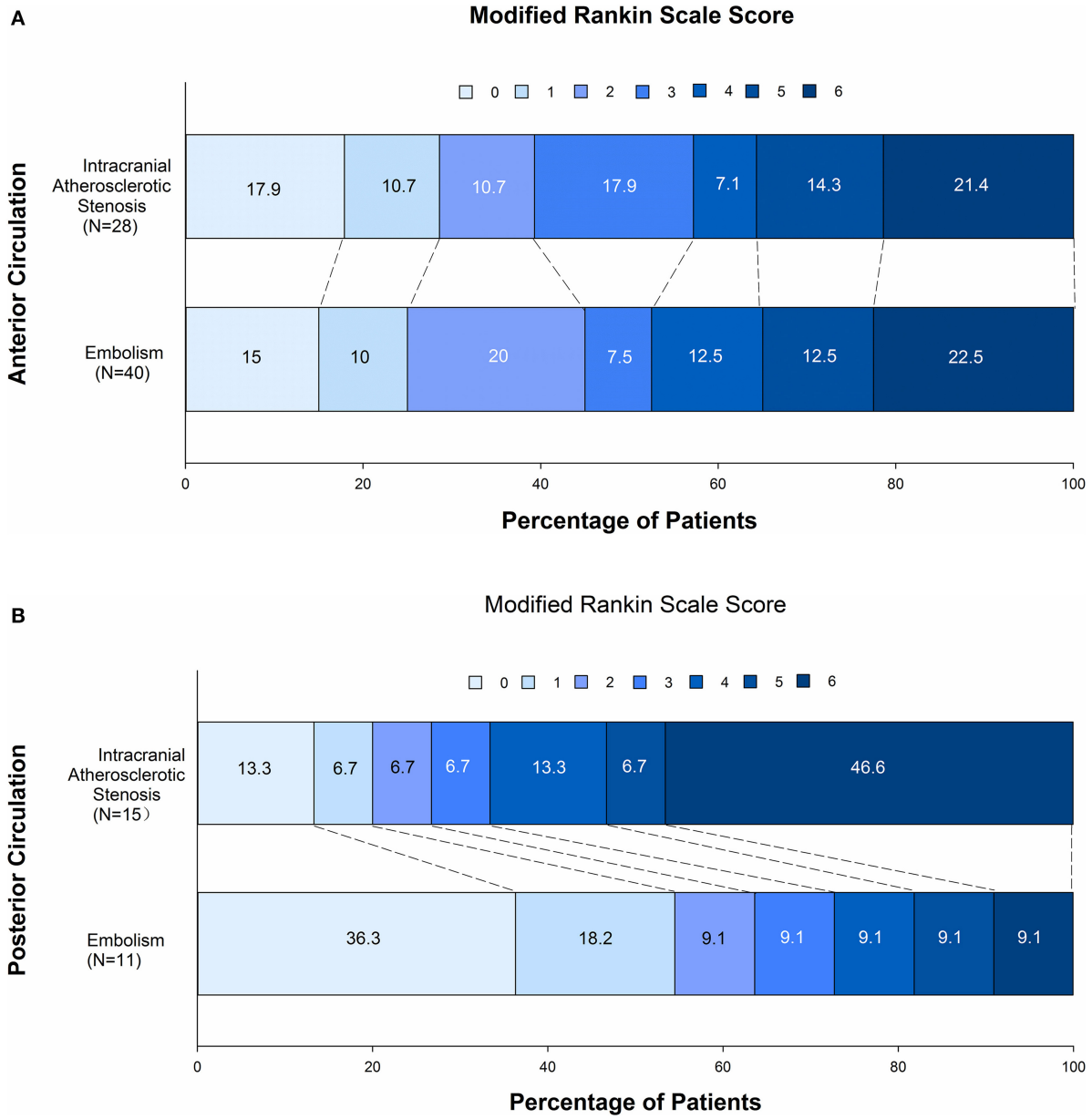


FIGURE 2 | Comparison of clinical outcome at 90 days after a direct aspiration first-pass technique (ADAPT) for the endovascular treatment of stroke in embolism-related occlusions and intracranial atherosclerotic stenosis-related occlusions in the anterior circulation **(A)** and in the posterior circulation **(B)**.

hypertension, diabetes mellitus, and atrial fibrillation, which stems from the fact that the grouping was based on etiology. It is noteworthy that the onset-to-door time in the ICAS-O group was much higher than in the EMB-O group. Indeed, neurologic deficit at onset was mild in some ICAS-O cases, which, along with insufficient health education, resulted in delayed visit to hospital. Underlying ICAS was identified in approximately a third of patients, which is consistent with the previous reports in Asia (2, 10). The primary outcomes of this study, immediate (56.86%) and final reperfusion (96.8%) performance, were better in the EMB-O group. In addition, time from groin puncture to final revascularization in the EMB-O group (42 min) was significantly lower than in the ICAS-O group (83 min). Interestingly, the higher rescue treatment (70.09%) involving the use of other devices in the ICAS-O group matches those from the other reports (40–59.7%) (2, 14, 15). It is suggested that ICAS-O may require a different first-line treatment strategy compared with a direct aspiration thrombectomy.

MT may cause vessel damage, which has been confirmed by clinical and animal studies (16, 17). In the current study, there were no inter-group differences in all and severe complications.

TABLE 4 | Multivariate regression analysis for predictors of first attempt recanalization of ADAPT.

Variable*	OR	95% CI	*p*-values
Age	0.997	0.956–1.039	0.871
Male gender	0.585	0.196–1.743	0.336
Diabetes	1.870	0.487–7.181	0.362
Hypertension	1.201	0.330–4.263	0.777
Hyperlipidemia	0.970	0.207–4.556	0.969
Pre-stroke mRS score	0.753	0.038–14.802	0.753
Baseline NIHSS score	0.939	0.865–1.019	0.133
IV tPA	1.764	0.397–7.846	0.456
Onset-to-puncture time	1.001	0.998–1.004	0.364
Site of occlusion			
Isolated MCA	4.506	1.066–19.045	0.041
Isolated VBA	3.5	0.887–13.807	0.074
Isolated ICA	0.560	0.194–0.615	0.284
Tandem occlusions	0.313	0.057–1.721	0.182
Etiology: embolism	3.505	1.031–11.917	0.045
Use of larger bore catheters (≥060)	9.167	2.6–32.322	0.001

**Variables showing statistical significance ($p < 0.05$) are shown in bold font. ADAPT, a direct aspiration first-pass technique; IV tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; VBA, vertebral basilar artery; ICA, internal carotid artery.*

However, new embolism to previously uninvolved territory (8.5%) was more frequent in this study than in previous reports (1, 14, 15). This may be attributed to the lesser application of the balloon guide catheter (11.7%), and associated with histological clot composition.

Despite many disadvantages in the ICAS-O compared with the EMB-O group, 3-month favorable outcomes and mortality did not differ between the groups. The enhanced lateral circulation of atherosclerotic stenosis occlusion and ischemic preconditioning compared to embolic occlusion may play crucial roles, as the ASPECTS in the ICAS-O group was higher than that of EMB-O (8.9 vs. 8.0), indicating the better collaterals in the ICAS group, though it may not be statistically significant. Of note, this study included the patients with posterior circulation LVO. It is not clear whether revascularization of posterior circulation occlusion can benefit from EVT (18, 19). Therefore, the clinical outcome was further analyzed in two subgroups separately (anterior and posterior circulation groups). To our surprise, although there was no difference in good outcomes between the two subgroups, we revealed that mortality was significantly higher in the posterior circulation subgroup of ICAS-O than EMB-O. Although the exact mechanism has not been illuminated, it is likely that shorter recanalization time plays a role here.

Successful recanalization using ADAPT depends on multiple factors such as location of the occlusion, vascular anatomy, clot characteristics, device characteristic, and underlying etiology (4, 20). Previous studies have shown that clots from cardioembolism had a significantly higher proportion of erythrocyte and a lower proportion of fibrin compared with those from large-artery atherosclerosis, and erythrocyte components were positively related to successful reperfusion (21–23). In our study, the presence of embolic etiology, isolated MCA occlusion, and the use of larger aspiration catheters were independent predictors of FAR with aspiration first-line approach. In contrast, underlying atherosclerosis has been shown to be a predictor of unsuccessful recanalization. Given that ACE catheters have not yet been allowed for application in our stroke center, we mainly use the Sofia catheter as a primary aspiration catheter. Sofia catheter is a distal aspiration catheter with a specific hybrid design. Its braid and coil construction combines different softness segments with a distal inner lumen of 0.055–0.070 inches in 5F and 6F Plus versions, respectively (24). The safety and efficacy of the Sofia aspiration catheter in a large population with first-line use has been reported (25). Our experience shows that a large inner lumen aspiration catheter such as Sofia 6F PLUS (0.070 inches) works better than a small one. Besides we found that the embolic etiology of LVO was a positive FAR predictor with direct aspiration thrombectomy, which may be a useful point for clinical reference.

The limitations of this study were as follows. First, since this was a single-center study, the sample size and representativeness are insufficient. Second, it is difficult to determine whether ICAS was really the cause of LVO. Although we had collected the clots in this study, we are not yet providing histopathological analysis due to technical limitations, which requires further research. Thus, the diagnosis of underlying ICAS after thrombectomy mainly depended on the imaging characteristics of the local lesion during the procedure. Third, we used an unblinded approach for the evaluation of NIHSS and mRS. At present, due to time constraints, it is difficult to design a randomized controlled study based on the etiology of LVO stroke before intervention. Future prospective and multicentric studies with blinded endpoint registration are warranted.

CONCLUSIONS

The evaluation of the efficacy of ADAPT showed higher immediate and final reperfusion in EMB-O than in ICAS-O. However, there were no significant differences in the 90-day outcomes between the two etiological groups of LVO. In case of embolic etiology and isolated MCA site of occlusion, using a larger aspiration catheter pretreatment for direct aspiration thrombectomy may be reasonable.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Ethics Committee of Maoming

People's Hospital. They granted approval for our work (2019027). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GL designed the report, completed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript, and took overall responsibility. GL, ZZ, WD, CL, and GZ contributed to the acquisition of data. GL, ZZ, and HL managed the literature searches and analyses. All authors have provided a substantial contribution to the study.

FUNDING

This work was supported by grants from the High-level Hospital Construction Research Project of Maoming People's Hospital (Reference No. Yueweihan 2018413) and the Special Fund of Science and Technology of Guangdong Province, China (Reference No. 2020S00050).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.695085/full#supplementary-material

REFERENCES

1. Turk AS, 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
2. 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
3. Tomsick T, Broderick J, Carrozella J, Khatri P, Hill M, Palesch Y, et al. Revascularization results in the interventional Management of Stroke II trial. *AJNR Am J Neuroradiol*. (2008) 29:582–7. doi: 10.3174/ajnr.A0843
4. Anadani M, Alawieh A, Vargas J, Chatterjee AR, Turk A, Spiotta A. First attempt recanalization with ADAPT: rate, predictors, and outcome. *J Neurointerv Surg*. (2018) 2018:1–6. doi: 10.1136/neurintsurg-2018-014294
5. Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European cooperative acute stroke study I (ECASS I) cohort. *Stroke*. (1999) 30:2280–4.
6. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurgery*. (2006) 59:21–7. doi: 10.1227/01.Neu.0000218821.34014.1b
7. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al. SITS-MOST Investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. (2007) 369:275–82. doi: 10.1016/S0140-6736(07)60149-4
8. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke*. (1993) 24:34–41. doi: 10.1161/01.str.24.1.35
9. Wong LK. Global burden of intracranial atherosclerosis. *Int J Stroke*. (2006) 1:158–9. doi: 10.1111/j.1747-4949.2006.00045.x
10. 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*. (2017) 2017:1–6. doi: 10.1136/neurintsurg—2017-013489
11. Gascou G, Lobotesis K, Machi P, Maldonado I, Vendrell JF, Riquelme C, et al. Stent retrievers in acute ischemic stroke: complications and failures during the perioperative period. *AJNR Am J Neuroradiol*. (2014) 35:734–40. doi: 10.3174/ajnr.A3746
12. 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
13. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Song D, et al. Importance of truncal-type occlusion in stentriever-based thrombectomy for acute stroke. *Neurology*. (2016) 87:1542–50. doi: 10.1212/WNL.0000000000003202
14. Yoo J, Lee SJ, Hong JH, Kim YW, Hong JM, Kim CH, et al. Immediate effects of first-line thrombectomy devices for intracranial atherosclerosis-related occlusion: stent retriever versus contact aspiration. *BMC Neurol*. (2020) 20:283–92.
15. Lapergue B, Blanc R, Guedin P, Decroix JP, Labreuche J, Preda C, et al. A direct aspiration, first pass technique (ADAPT) versus stent retrievers for acute stroke therapy: an observational comparative study. *AJNR Am J Neuroradiol*. (2016) 37:1860–5. doi: 10.3174/ajnr.A4840
16. Liao G, Zhang Z, Che X, Liang H. Mechanical thrombectomy using a stent retriever with an intermediate catheter for partially occluded middle cerebral artery fenestration. *World Neurosurg*. (2020) 138:355–9. doi: 10.1016/j.wneu.2020.03.096
17. Koge J, Kato S, Hashimoto T, Nakamura Y, Kawajiri M, Yamada T. Vessel wall injury after stent retriever thrombectomy for internal carotid artery occlusion with duplicated middle cerebral artery. *World Neurosurg*. (2019) 123:54–8. doi: 10.1016/j.wneu.2018.11.223
18. 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*. (2020) 19:115–22. doi: 10.1016/S1474-4422(19)30395-3
19. Siebert E, Bohner G, Zweynert S, Maus V, Mpotsaris A, Liebig T, et al. Revascularization techniques for acute basilar artery occlusion: technical considerations and outcome in the setting of severe posterior circulation steno-occlusive disease. *Clin Neuroradiol*. (2019) 29:435–43. doi: 10.1007/s00062-018-0683-3
20. Blanc R, Redjem H, Ciccio G, Smajda S, Desilles JP, Orng E, et al. Predictors of the aspiration component success of a direct aspiration first pass technique (ADAPT) for the endovascular treatment of stroke reperfusion strategy in anterior circulation acute stroke. *Stroke*. (2017) 48:16149. doi: 10.1161/STROKEAHA.116.016149
21. Kamalian S, Morais LT, Pomerantz SR, Aceves M, Sit SP, Bose A, et al. Clot length distribution and predictors in anterior circulation stroke: implications for intra-arterial therapy. *Stroke*. (2013) 44:3553–6. doi: 10.1161/STROKEAHA.113.003079
22. Kim SK, Yoon W, Kim TS, Kim HS, Heo TW, Park MS. Histologic analysis of retrieved clots in acute ischemic stroke: correlation with stroke etiology and gradient-echo MRI. *AJNR Am J Neuroradiol*. (2015) 36:1756–62. doi: 10.3174/ajnr.A4402
23. Hashimoto T, Hayakawa M, Funatsu N, Yamagami H, Satow T, Takahashi JC, et al. Histopathologic analysis of retrieved thrombi associated with successful reperfusion after acute stroke thrombectomy. *Stroke*. (2016) 47:3035–7. doi: 10.1161/STROKEAHA.116.015228

24. Wong JHY, Do HM, Telischak NA, Moraff AM, Dodd RL, Marks MP, et al. Initial experience with SOFIA as an intermediate catheter in mechanical thrombectomy for acute ischemic stroke. *J Neurointerv Surg.* (2017) 9:1103–6. doi: 10.1136/neurintsurg-2016-012750
25. Marnat G, Barreau X, Detraz L, Bourcier R, Gory B, Sgreccia A, et al. First-line sofia aspiration thrombectomy approach within the endovascular treatment of ischemic stroke multicentric registry: efficacy, safety, and predictive factors of success. *Am J Neuroradiol.* (2019) 40:1006–12. doi: 10.3174/ajnr.A6074

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 13 September 2021
doi: 10.3389/fneur.2021.688019

Can Tirofiban Improve the Outcome of Patients With Acute Ischemic Stroke: A Propensity Score Matching Analysis

Lingxin Cai[1], Xiaobo Yu[1], Jun Yu[1], Jing Xu[1], Liang Xu[1], Chenhan Ling[1], Min Lou[2], Cheng Yu[3] and Cong Qian[1]**

[1] Department of Neurological Surgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China, [2] Department of Neurology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China, [3] Department of Neurosurgery, The Second People's Hospital, Quzhou, China

OPEN ACCESS

Edited by:
QinJian Sun,
Shandong University, China

Reviewed by:
Shashvat M. Desai,
University of Pittsburgh, United States
Kristen Sanfilippo,
Washington University School of Medicine in St. Louis, United States

***Correspondence:**
Cheng Yu
Yc661070@163.com
Cong Qian
congqian@zju.edu.cn

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: 30 March 2021
Accepted: 28 July 2021
Published: 13 September 2021

Citation:
Cai L, Yu X, Yu J, Xu J, Xu L, Ling C, Lou M, Yu C and Qian C (2021) Can Tirofiban Improve the Outcome of Patients With Acute Ischemic Stroke: A Propensity Score Matching Analysis. Front. Neurol. 12:688019. doi: 10.3389/fneur.2021.688019

Objective: To evaluate the efficacy and safety of tirofiban for patients with acute ischemic stroke (AIS), especially posterior circulation stroke (PCS).

Methods: We enrolled consecutive patients with AIS who suffered large artery occlusion (LAO) and underwent mechanical thrombectomy (MT) between January 2016 and May 2020. Patients were divided into two groups according to whether tirofiban was used during MT. The primary efficacy outcome was a favorable functional outcome, defined as a modified Rankin Scale (mRS) score of 0–2 at 3 months. The safety outcomes were the rate of mortality at 3 months and the presence of intracranial hemorrhage (ICH) and symptomatic intracranial hemorrhage (sICH). Cohorts were balanced using 1:1 propensity score matching (PSM). Subgroup analysis was further performed to compare the efficacy and safety of tirofiban between the anterior circulation stroke (ACS) and PCS groups.

Results: A total of 292 patients were eligible for this study and divided into the tirofiban group ($n = 51$) and the no-tirofiban group ($n = 241$). In the propensity-score-matched cohort, the tirofiban group had a higher rate of favorable outcomes than the no-tirofiban group (49.0 vs. 25.5%, $p = 0.014$), and the mortality at 3 months showed a greater downward trend in the tirofiban group than the no-tirofiban group (15.6 vs. 33.3% $p = 0.064$). The risk of sICH and ICH was the same between the tirofiban and control groups (17.6 vs. 27.4% $p = 0.236$, 31.3 vs. 45.1% $p = 0.154$, respectively). Tirofiban use was predictive of favorable outcomes [adjusted odds ratio (aOR) = 2.87, 95% confidence interval (CI) 1.52–6.44, $p = 0.043$] after multiple logistic regression analysis. Subgroup analysis revealed that tirofiban use was significantly associated with favorable outcomes in ACS (aOR = 3.66, 95% CI 1.24–5.22, $p = 0.019$) but not in PCS (aOR = 1.12, 95% CI 0.47–7.52, $p = 0.570$).

Conclusion: We demonstrated that tirofiban may be associated with improving favorable outcome for the AIS patients who underwent MT, without increasing ICH or sICH. Furthermore, our results indicated that for PCS patients tirofiban may not be associated with favorable outcome, and more comprehensive randomized controlled trials are needed to confirm this finding.

Keywords: tirofiban, acute ischemic stroke, propensity score matching, mechanical thrombectomy, posterior circulation stroke

INTRODUCTION

A number of randomized clinical trials have shown the benefit of mechanical thrombectomy (MT) in the treatment of acute ischemic stroke (AIS) that is due to large-vessel occlusion (LVO) (1, 2). However, this endovascular recanalization approach may lead to endothelial injury, plaque rupture, and subsequent platelet activation, leading to early re-occlusion and poor prognosis. Tirofiban is a non-peptide selective glycoprotein (GP) IIb/IIIa receptor inhibitor that reversibly inhibits fibrinogen-dependent platelet aggregation and subsequent formation of thrombi, which contribute to the major atherosclerotic complications in the progression of AIS (3).

Clinical trials in patients with AIS initially demonstrated the safety and efficacy of tirofiban as an adjunct to MT for AIS patients. However, the results of these trials have been controversial; some studies have shown that tirofiban does not improve prognosis and may even increase intracranial hemorrhage (ICH) and mortality. Therefore, more data are needed to confirm further the benefits and risks of tirofiban. A series of follow-up studies have reported a number of clinically valuable findings about the tirofiban regimen following MT, including the specific dose (4), injection method (5), and patient selection according to etiology (6). However, the specific indications and patient selection are still under debate. Considering the different clinical characteristics of posterior circulation stroke (PCS) and anterior circulation stroke (ACS) (7), as well as the different postoperative prognoses of patients with MT between the two groups (8), there is a hypothesis that tirofiban may have inconsistent risks and benefits in PCS and ACS. At present, there are some studies about the benefit of MT in PCS patients and the administration of tirofiban following MT (9, 10), but there are few studies exploring tirofiban in patients with PCS.

The main aim of this study was to test the safety and efficacy of tirofiban following MT in AIS patients. Propensity score matching (PSM) was used to match tirofiban- and no-tirofiban-treated patients for potential confounders. Regression analysis after PSM was performed to identify independent associations with the outcomes. The secondary aims were to compare the risks and benefits of tirofiban following MT between PCS and ACS.

METHODS

Patient Selection

In this retrospective study, a total of 292 patients who underwent MT secondary to large artery occlusion (LAO) between January 2015 and May 2019 were enrolled. The inclusion criteria were as follows: (1) patients with AIS secondary to LAO confirmed by computed tomographic angiography (CTA), (2) patients with neurological deficits with a National Institutes of Health Stroke Scale (NIHSS) score of 6 or higher at presentation, (3) patients who were 18 years of age or older, and (4) patients who underwent MT.

The exclusion criteria were as follows: (1) cerebral hemorrhage confirmed by computed tomography; (2) platelet count $<100 \times 109$/L, blood glucose concentration <2.8 or >22.0 mmol/L, and severe hepatic or renal dysfunction; and (3) incomplete data or loss to follow-up. This study was approved by the Ethics Committee of Zhejiang University School of Medicine Second Affiliated Hospital.

Procedures

All enrolled patients were treated according to current guidelines for AIS and underwent MT employed second-generation stent-retriever devices (Solitaire AB/FR, Covidien/ev3, Irvine, CA; Trevo Proview, Stryker, CA). Alternative rescue therapies, including balloon angioplasty and rescuing stent, were determined by the operators during the procedure based on the characteristics of the lesion and access. Following thrombectomy, all patients underwent postprocedural computed tomography (CT) within 12–24 h, and the presence of hemorrhage on CT was determined and scored by a blinded neuroradiologist.

Tirofiban was considered for application in the following situations: (1) rescue treatment with emergency stenting and balloon angioplasty for residual artery stenosis or failed thrombectomy, (2) successful mechanical recanalization with ≥ 3 passes with stent retriever, (3) severe *in situ* atherosclerosis with high risk of early re-occlusion, and (4) other recanalization refractory conditions and presumed endothelial damage. Tirofiban was continuously given at a rate of 8 μg/kg·h after an intravenous bolus of 10 μg/kg if there was no evidence of ICH on immediate head CT after MT. Twenty-four hours later, dual antiplatelet therapy was given after ICH was ruled out by another head CT.

Baseline Assessment and Outcome Measures

Data were extracted through a retrospective review of patient charts, procedure notes, image data, and follow-up notes. Baseline characteristics were collected, including age, sex, presenting NIHSS score, Alberta Stroke Program Early

Computed Tomography Score (ASPECTS) or posterior circulation ASPECTS (pc-ASPECTS), comorbidities (diabetes, hypertension, atrial fibrillation, hyperlipidemia, and a history of prior stroke), antiplatelet drug and anticoagulation drug use, and coagulation function indicators. Procedural variables included time from symptom onset to groin puncture, time from symptom onset to reperfusion, tissue plasminogen activator (t-PA) use, retrieval times ≥3, rescue therapy including balloon angioplasty and rescuing stent, and Thrombolysis in Cerebral Infarction (TICI) grading. A TICI grade better than 2b was defined as successful recanalization. The arterial occlusion site was recorded as ACS and PCS. The stroke etiology was classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria: large artery atherosclerosis (LAA), cardioembolism (CE), and stroke of other determined or undetermined causes.

The primary outcome measure was functional outcome, which was measured by the modified Rankin Scale (mRS) at 3 months. A favorable outcome was defined as an mRS score of 0–2. The scores were collected by a stroke neurologist during routine follow-up visits at 90 days (±14) after stroke for the majority of patients. Telephone discussions with patients or their families were used to obtain information. ICH was considered present when head CT revealed a region consistent with newly developed blood extravasation. Correspondingly, symptomatic intracranial hemorrhage (sICH) was defined as any hemorrhage with neurological deterioration, indicated by an NIHSS score of ≥4 points above the baseline value, or as any hemorrhage leading to mortality. Two investigators, who were blinded to all clinical information, independently reviewed the CT and magnetic resonance imaging (MRI) images to determine the presence of ICH or sICH.

Statistical Analysis

Statistical analyses were performed using SPSS V.25 for the majority of the data. Patient variables were analyzed using descriptive statistics and univariate comparisons. Comparisons were performed using the *t*-test for continuous measures, for non-continuous variables, and χ^2 test for categorical measures. All tests were two sided, and an $\alpha < 0.05$ was considered significant.

PSM was performed with R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) to ensure an even distribution of possible confounders between the two groups. A 1:1 matched analysis using nearest-neighbor matching with a caliper distance of 0.1 without replacement was performed based on the estimated propensity score of each patient. After matching patient characteristics, these were analyzed again to confirm successful matching. Multivariate logistic regression analysis was used to assess the odds ratio (OR) and corresponding 95% confidence interval (CI) to explore whether tirofiban can independently affect favorable clinical outcomes (mRS scores 0–2) and safety outcomes, including ICH, sICH, and mortality at 3 months.

RESULTS

Patient Characteristics

A total of 292 patients were eligible for this study. The baseline characteristics and outcomes of the patients are presented in **Table 1** and were compared between the tirofiban group ($n = 51$) and the no-tirofiban group ($n = 241$). There was no significant between-group difference with respect to age, sex, or NIHSS score at presentation ($p > 0.05$). Coagulation function was assessed by preoperative and postoperative coagulation indicators, including prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count, which were similar between the two groups. PCS was more common in the tirofiban group (25.5 vs. 12.9%, $p = 0.038$). LAA was the cause of stroke in 74.5% of tirofiban patients, compared with 50.6% in the no-tirofiban group ($p < 0.001$). In contrast, CE was lower in the tirofiban group (29.4 vs. 58.9%, $p < 0.01$). Other medical histories and comorbidities showed no between-group differences.

The analysis of procedural variables showed that ∼88.1% of patients received t-PA, without a significant difference between the two groups. The mean times from symptom onset to recanalization were comparable (414.2 ± 394.3 vs. 314.6 ± 172.2, $p > 0.05$), but the time from symptom onset to reperfusion in the tirofiban group was longer (515.78 ± 394.34 vs. 393.97 ± 182.95, $p = 0.035$). Furthermore, the patients with tirofiban were more often to accept the rescue therapies including balloon angioplasty (13.7 vs. 7.5%, $p = 0.062$) and permanent stenting (11.8 vs. 4.5%, $p = 0.046$) and undergo MT with retrieval times ≥3 (9.8 vs. 3.7%, $p = 0.018$). The overall rate of recanalization was 90.8%, and it was not significantly different between the two groups.

Safety and Efficacy Outcomes

The efficacy and safety outcome measures were not significantly different. The rates of favorable outcomes (mRS 0–2) were 49.0 and 36.1%, respectively, in the tirofiban and no-tirofiban groups, but $p > 0.05$. The overall mortality at 3 months was 18.50% across both groups and was slightly, but not significantly, lower in the tirofiban group than in the no-tirofiban group (15.6 vs. 19.1%, $p > 0.05$). Procedure-related complications in the tirofiban group, including ICH (31.4 vs. 41.1%, $p = 0.197$) and sICH (17.65 vs. 21.58%, $p = 0.531$), did not occur more frequently than in the no-tirofiban group.

Variables in the PSM were selected based on previous univariate analysis, including age, NIHSS score, time from symptom onset to reperfusion, involved vessel site TOAST classification, and ASPECTS. Finally, 51 cases were successfully matched, and the standard deviation indicated that the matching effect was satisfactory. After PSM, the characteristics of the two groups were relatively the same after matching (**Table 1**). After PSM, tirofiban significantly improved the rates of favorable outcomes in the tirofiban and no-tirofiban groups (49.0 vs. 25.5%, $p = 0.014$) (**Figure 1**). No difference was found in mortality and the rates of ICH and sICH ($p > 0.05$).

Stepwise regression was performed to identify the factors associated with the safety and efficacy outcomes (**Supplementary Table 1**). In the overall patients, tirofiban tended to improve the rates of favorable outcomes independently

TABLE 1 | Patient characteristics and outcomes before and after PSM.

	Before PSM			After PSM		
	Tirofiban ***n*** **= 51**	**No tirofiban** ***n*** **= 241**	***p***	**Tirofiban** ***n*** **= 51**	**No tirofiban** ***n*** **= 51**	***p***
Age (year)	66.2 ± 11.4	68.5 ± 14.3	0.262	66.2 ± 11.4	66.7 ± 8.7	0.954
Female, *n* (%)	18 (35.3)	97 (40.2)	0.617	18 (35.3)	21 (41.2)	0.541
Involved vessel, *n* (%)			0.038*			0.818
ACS	38 (74.5)	210 (87.1)		38 (74.5)	39 (80.4)	
PCS	13 (25.5)	31 (12.9)		13 (25.5)	12 (19.6)	
TOAST, *n* (%)			0.001*			0.089
LAA	38 (74.5)	122 (50.6)		38 (74.5)	31 (60.8)	
CE	7 (13.7)	106 (44.0)		7 (13.7)	14 (27.5)	
Other	6 (11.8)	13 (5.4)		6 (11.8)	6 (11.7)	
NIHSS, median (IQR)	14 (11–18)	12 (9–16)	0.078	14 (11–18)	13 (9–18)	0.638
ASPECTS/pc-ASPECTS, median (IQR)	8 (7–9)	8 (7–9)	0.788	8 (7–9)	8 (7–9)	0.832
Systolic BP (mm Hg)	144.6 ± 22.6	144.1 ± 18.1	0.869	144.6 ± 22.6	147.2 ± 18.3	0.553
Glucose (mmol/L)	7.17 ± 2.08	8.69 ± 22.91	0.638	7.17 ± 2.08	7.32 ± 1.84	0.709
Medical history						
Atrial fibrillation, *n* (%)	15 (29.4)	142 (58.9)	0.001*	15 (29.4)	36 (70.6)	0.043*
Hyperlipidemia, *n* (%)	1 (2.0)	4 (1.7)	1.000	1 (2.0)	1 (2.0)	1.000
Hypertension, *n* (%)	37 (72.5)	157 (65.1)	0.393	37 (72.5)	35 (68.6)	0.828
Diabetes mellitus, *n* (%)	7 (13.7)	38 (15.8)	0.878	7 (13.7)	9 (17.6)	0.785
Previous stroke, *n* (%)	11 (21.6)	40 (16.6)	0.518	11 (21.6)	8 (15.7)	0.445
Pre-antiplatelet, *n* (%)	6 (11.8)	35 (14.5)	0.769	6 (11.8)	8 (15.7)	0.774
Pre-anticoagulation, *n* (%)	2 (3.9)	21 (8.7)	0.385	2 (3.9)	2 (3.9)	1.000
Smoker, *n* (%)	9 (17.6)	30 (12.4)	0.444	9 (17.6)	4 (7.8)	0.138
Coagulation function						
Pre-platelet (10^9/L)	178.8 ± 49.7	178.2 ± 60.5	0.945	178.8 ± 49.7	171.4 ± 53.5	0.476
Post-platelet (10^9/L)	186.7 ± 61.8	185.7 ± 65.3	0.916	186.7 ± 61.8	183.1 ± 62.8	0.771
Procedural variables						
t-PA treated, *n* (%)	42 (82.4)	215 (89.2)	0.257	42 (82.4)	46 (90.2)	0.388
Time 1 (min)	414.2 ± 394.3	314.5 ± 172.2	0.083	414.2 ± 394.3	390.8 ± 233.2	0.716
Time 2 (min)	515.7 ± 394.3	393.9 ± 182.9	0.035*	515.7 ± 394.3	493.8 ± 241.5	0.738
Retrieval times ≥3, *n* (%)	5 (9.8)	9 (3.7)	0.018*	5 (9.8)	1 (2.0)	0.092
Balloon angioplasty, *n* (%)	7 (13.7)	18 (7.5)	0.062	7 (13.7)	2 (3.9)	0.081
Permanent stenting, *n* (%)	6 (11.8)	11 (4.5)	0.046*	6 (11.8)	2 (3.9)	0.141
TICI 2b−3, *n* (%)	44 (86.3)	221 (91.7)	0.342	44 (86.3)	43 (84.3)	0.780
Clinical outcome						
Favorable outcome, *n* (%)	25 (49.0)	87 (36.1)	0.085	25 (49.0)	13(25.49)	0.014*
sICH, *n* (%)	9 (17.6)	52 (21.5)	0.531	9 (17.6)	14(27.45)	0.236
ICH, *n* (%)	16 (31.3)	99 (41.0)	0.197	16 (31.3)	23 (45.1)	0.154
Mortality at 3 months, *n* (%)	8 (15.6)	46 (19.0)	0.570	8 (15.6)	17 (33.3)	0.064

Data are mean ± SD, n (%), or median (IQR). Factors matched by PSM included age, NIHSS score, time from symptom onset to reperfusion, involved vessel site, TOAST classification, retrieval times ≥3, permanent stenting, and ASPECTS.

**Statistically significant.*

PSM, propensity score matching; ACS, anterior circulation stroke; PCS, posterior circulation stroke; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, large artery atherosclerosis; CE, cardioembolism; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; pc-ASPECTS, posterior circulation ASPECTS; BP, blood pressure; t-PA, tissue plasminogen activator; Time 1, time from symptom to groin puncture; Time 2, time from symptom to reperfusion; TICI, Thrombolysis in Cerebral Infarction grading; sICH, symptomatic intracranial hemorrhage; ICH, intracranial hemorrhage.

[adjusted odds ratio (aOR) = 1.45, 95% CI 1.67–3.43, $p = 0.024$]. Furthermore, tirofiban did not show any association with the incidences of ICH, sICH, or mortality ($p = 0.605$, 0.353, and 0.362, respectively).

The results remained stable after PSM for potential confounders. The use of tirofiban showed an independent association with better outcomes (aOR = 2.87, 95% CI 1.52–6.44, $p = 0.043$). Tirofiban was not associated with a

FIGURE 1 | Distribution of mRS at 3 months categories before PSM **(A)** and after PSM **(B)**. The lines indicate differences in favorable outcome (mRS 0–2) between groups. *$p < 0.05$. mRS, modified Rankin Scale; PSM, propensity score matching.

risk of ICH (aOR = 0.67, 95% CI 0.37–2.13, $p = 0.451$), sICH (aOR = 0.55, 95% CI 0.67–1.23, $p = 0.263$), or mortality at 3 months (aOR = 0.45, 95% CI 0.57–1.43, $p = 0.728$). And the multivariate regression models were adjusted, respectively, for the favorable outcome and safety outcome (**Table 2**).

Effects on ACS and PCS

Based on the above regression analysis results, we performed a subgroup analysis according to location to explore further the association between tirofiban and favorable outcomes. First, the main characteristics and clinical outcomes of patients with ACS and PCS were compared with univariate analysis, and there were many differences between the two groups (**Table 3**). Patients with PCS had higher NIHSS scores on admission than those with ACS (21.9 ± 13.1 vs. 14.4 ± 5.9, $p = 0.001$), a longer time from symptom onset to groin puncture (494.0 ± 448.6 vs. 303.2 ± 146.5, $p = 0.008$), and a longer time from symptom onset to reperfusion (587.0 ± 450.7 vs. 384.7 ± 158.0, $p = 0.005$). A total of 63.6% of patients with PCS had LAA stroke, compared with 52.4% of patients with ACS ($p = 0.005$). Relatedly, tirofiban administration was more common in PCS patients (29.5 vs. 15.3%, $p = 0.001$). In terms of comparison with the outcomes of the two groups, patients in the PCS group had significantly worse favorable clinical outcomes (20.4 vs. 41.5%, $p = 0.008$).

TABLE 2 | Multivariate regression analysis of effects of tirofiban on safety and efficacy outcomes.

	Before PSM ($n = 294$)		After PSM ($n = 102$)	
	aOR (95% CI)	*p*	aOR (95% CI)	*p*
Favorable outcome[a]	1.45 (1.67–3.43)	0.024*	2.87 (1.52–6.44)	0.043*
ICH[b]	0.24 (0.29–1.19)	0.605	0.67 (0.37–2.13)	0.451
sICH[b]	0.67 (0.27–1.49)	0.353	0.55 (0.67–1.23)	0.263
Mortality at 3 months[b]	0.66 (0.25–1.55)	0.362	0.45 (0.57–1.43)	0.728

[a]*Model 1 adjusted for age, ASPECTS/pc-ASPECTS, tirofiban, baseline NIHSS, glucose, TOAST classification, and location (posterior or anterior circulation).*
[b]*Model 2 adjusted for age, ASPECTS/pc-ASPECTS, tirofiban, baseline NIHSS, TOAST classification, involved vessel site (posterior or anterior circulation), and previous stroke.*
**Statistically significant.*
PSM, propensity score matching; aOR, adjusted odds ratio; CI, confidence interval; ICH, intracranial hemorrhage; sICH, symptomatic intracranial hemorrhage; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; pc-ASPECTS, posterior circulation ASPECTS; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

TABLE 3 | Patient characteristics and outcomes on patients with ACS and PCS.

	ACS $n = 248$	PCS $n = 44$	*p*
Characteristics			
Age (year)	69 ± 9.8	65 ± 11.3	0.122
NIHSS, *n* (%)	14.4 ± 5.9	21.9 ± 13.1	0.001*
ASPECTS/pc-ASPECTS, median (IQR)	8 (7–9)	8 (7–9)	0.436
TOAST, *n* (%)			0.005*
LAA	130 (52.4)	28 (63.6)	
CE	104 (42.7)	9 (20.4)	
Other	12 (4.8)	7 (15.9)	
Tirofiban, *n* (%)	38 (15.3)	13 (29.5)	0.022*
Time 1 (min)	303.2 ± 146.5	494.0 ± 448.6	0.008*
Time 2 (min)	384.7 ± 158.0	587.0 ± 450.7	0.005*
TICI 2b−3	229(92.3)	36(81.8)	0.026*
Clinical outcome			
Favorable outcome, *n* (%)	103 (41.5)	9 (20.4)	0.008*
ICH, *n* (%)	100 (40.2)	15 (34.0)	0.436
sICH, *n* (%)	51 (20.5)	10 (22.7)	0.745
Mortality#, *n* (%)	42 (16.9)	12 (27.2)	0.104

Values are n (%), mean ± SD.
**Statistically significant.*
ACS, anterior circulation stroke; PCS, posterior circulation stroke; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; pc-ASPECTS, posterior circulation ASPECTS; IQR, interquartile range; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, large artery atherosclerosis; CE, cardioembolism; Time 1, time from symptom to groin puncture; Time 2, time from symptom to reperfusion; TICI, Thrombolysis in Cerebral Ischemia; ICH, intracranial hemorrhage; sICH, symptomatic intracranial hemorrhage.

There were no significant differences in ICH, sICH, or risk of death between the two groups.

A multivariate analysis was performed to adjust the confounders and to identify the use of tirofiban as the independent predictor of favorable outcomes in the overall group (aOR = 1.45, 95% CI 1.67–3.43, $p = 0.024$). In the ACS patients, tirofiban was associated with favorable outcomes (aOR = 3.66, 95% CI 1.24–5.22, $p = 0.019$); however, such an association was not observed in PCS patients (aOR = 1.12, 95% CI 0.47–7.52, $p = 0.570$). Detailed information on the regression coefficients and *p*-values is presented in **Supplementary Table 2**. The comparison between subgroups is more intuitively reflected in **Figure 2**.

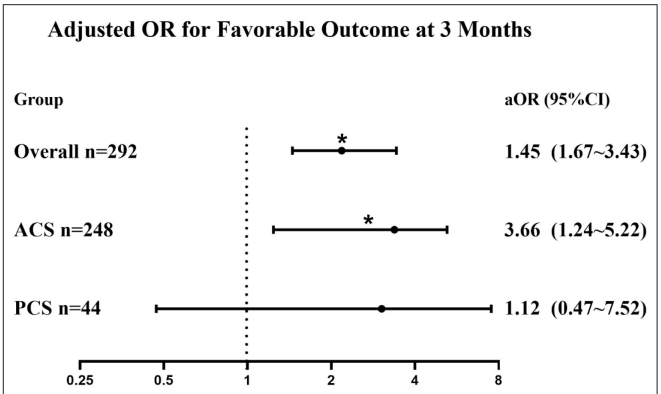


FIGURE 2 | Forest plot of adjusted OR for the association between tirofiban administration and favorable outcomes (mRS 0–2) in patients with posterior circulation stroke (PCS) and anterior circulation stroke (ACS). Adjusted for age, ASPECTS/pc-ASPECTS, tirofiban, baseline NIHSS, glucose, TOAST classification, and location (posterior or anterior circulation). aOR, adjusted odds ratio; mRS, modified Rankin Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; pc-ASPECTS, posterior circulation ASPECTS; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment. *$p < 0.05$.

DISCUSSION

In this study, we evaluated the safety and efficacy of tirofiban as an adjuvant therapy for MT in AIS patients. The main findings of our study are as follows: (1) more patients in the tirofiban group had favorable clinical outcomes after PSM matching, and ICH and mortality did not differ between the two groups; (2) multivariate regression analysis demonstrated that tirofiban was positively associated with favorable clinical outcomes but not with ICH, mortality, or other safety indicators; and (3) tirofiban was associated with increasing favorable clinical outcomes in patients with ACS but not in patients with PCS.

The purpose of therapy for AIS patients is to achieve rapid cerebral vascular recanalization to restore cerebral blood flow (10), and MT has become the first-line treatment for LVO (11). However, many patients who achieve rapid vascular recanalization by MT are still at high risk of acute reocclusion, especially LAA patients (12, 13). The potential cause may be *in situ* atherosclerotic occlusion, local platelet aggregation, and broken plaques (14). LAA strokes are the most common stroke type in China, so it is urgent to find ways to prevent reocclusion (15).

Tirofiban is a relatively short-acting and reversible GP IIb/IIIa receptor inhibitor that inhibits fibrinogen binding to platelets, effectively preventing platelet aggregation and

secondary thrombosis (16). There have been a number of clinical trials demonstrating the safety and efficacy of tirofiban administration in AIS patients undergoing MT, but with controversial results. Most studies have demonstrated that tirofiban has great clinical application prospects in MT, and tirofiban has proved to be an independent predictor of favorable outcomes (17–19). A multicenter retrospective cohort confirmed that the safety of tirofiban was not associated with ICH or mortality (20). In contrast, other studies have shown that tirofiban does not improve clinical outcomes (21) and may be associated with an increased risk of fatal ICH (22, 23). The reasons for the controversial results are complex, including the heterogeneity of experiments, relatively small sample sizes, patient selection bias, and different tirofiban application regimens (5, 24). In our study, tirofiban was continuously given at a rate of 8 μg/kg·h after an intravenous bolus of 10 μg/kg if there was no evidence of ICH. The dose of tirofiban was not consistent in previous studies, but it did not vary extensively. And the total amount of tirofiban infusion was low and only varied from 0.5 to 2.0 mg in most centers (3). Nevertheless, the specific dose may affect the results especially for the risk of ICH, and further research about the dose is needed.

In this study, the use of tirofiban did not lead to significantly more benefits before PSM. We found the patients in the tirofiban group were more often with rescuer therapies, repeated attempts of thrombectomy, and longer time from symptom onset to reperfusion, which were associated with difficulty of vascular recanalization. Additionally, in our study tirofiban was more selectively adopted for patients with LAA stroke rather than CE stroke (74.5 vs. 13.7%, $p = 0.01$). This patient selection bias may explain the lower rate of recanalization in the tirofiban group (86.3 vs. 91.7%, $p = 0.342$). After the correction of these confounding factors by PSM, the rate of recanalization has become similar in the matched cohort, and the use of tirofiban significantly improved the rate of favorable outcomes in AIS patients.

A number of studies have noted the differences between ACS and PCS in clinical characteristics, treatment, and prognosis (25). PCS accounts for 5–19% of AIS patients (26, 27). A large clinical trial including 90,484 patients treated with t-PA demonstrated that PCS was associated with worse outcomes (28). Some studies have suggested that MT for PCS is a safe and feasible treatment option (29). MT is widely used in PCS clinically, and our study results showed that more PCS patients than ACS patients were treated with tirofiban (29.5 vs. 15.3%). However, few studies have focused on whether tirofiban administration in MT has consistent safety and efficacy between ACS and PCS. Subgroup analysis was performed, and we found that PCS patients had an obviously worse prognosis than ACS patients (20.4 vs. 41.5%, respectively), and they also had a higher NIHSS score at admission and a longer time from symptom onset to reperfusion. Further analysis by logistic regression illustrated that tirofiban was associated with increasing favorable clinical outcomes in patients with ACS but not in patients with PCS. However, Alawieh et al. thought that patients with PCS benefit equally from tirofiban administration compared with ACS (30). Given the limited sample size, our results only indicated that the effect of tirofiban may be modified by the occlusion sites and the PCS patients seemed to benefit less. Whether tirofiban treatment can affect efficacy outcomes of PCS patients treated with MT requires future research.

There are also the limitations in this study. First, this experiment included only patients in the past 5 years from a single center, which reduced the changes and differences in perioperative patient care procedures but also resulted in a small sample size. Additionally, this is a retrospective study with inevitable patient selection bias. Even though we used advanced statistical methods, including PSM and multivariate adjustment, we cannot correct residual or unmeasured confounding. Furthermore, the balloon angioplasty and stenting are more commonly used in tirofiban groups, which may exaggerate the effect of tirofiban. Considering these limitations, these results should be analyzed with more caution, and larger multicenter data will be required to study this effect further.

CONCLUSION

We demonstrated that tirofiban may be associated with improving favorable outcome for the AIS patients who underwent MT, without increasing ICH or sICH. Furthermore, our results indicated that for PCS patients tirofiban may not be associated with favorable outcome, and more comprehensive randomized controlled trials are needed to confirm this finding.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

LC, LX, and JX collected the data and drafted the manuscript. JY, CL, and XY analyzed the data and performed all statistical analyses. ML, CY, and CQ conceived the study and made critical revisions to the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Natural Science Foundation of China (Grant nos. 81701152 and 81971097), Natural Science Foundation of Zhejiang Province (LY19H090022), and Medical and Health Science and Technology Program of Zhejiang Province (2016KYA199).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.688019/full#supplementary-material

REFERENCES

1. Martins SO, Mont'Alverne F, Rebello LC, Abud DG, Silva GS, Lima FO, et al. Thrombectomy for stroke in the public health care system of Brazil. *N Engl J Med.* (2020) 382:2316–26. doi: 10.1056/NEJMoa2000120
2. Saver J, Goyal M, Bonafe A, Diener H, Levy E, Pereira V, 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
3. Yang M, Huo X, Miao Z, Wang Y. Platelet Glycoprotein IIb/IIIa receptor inhibitor tirofiban in acute ischemic stroke. *Drugs.* (2019) 79:515–29. doi: 10.1007/s40265-019-01078-0
4. Zhao W, Che R, Shang S, Wu C, Li C, Wu L, et al. Low-dose tirofiban improves functional outcome in acute ischemic stroke patients treated with endovascular thrombectomy. *Stroke.* (2017) 48:3289–94. doi: 10.1161/STROKEAHA.117.019193
5. Yang J, Wu Y, Gao X, Bivard A, Levi C, Parsons M, et al. Intraarterial versus intravenous tirofiban as an adjunct to endovascular thrombectomy for acute ischemic stroke. *Stroke.* (2020) 51:2925–33. doi: 10.1161/STROKEAHA.120.029994
6. 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
7. Kim JT, Park MS, Choi KH, Kim BJ, Han MK, Park TH, et al. Clinical outcomes of posterior versus anterior circulation infarction with low national institutes of health stroke scale scores. *Stroke.* (2017) 48:55–62. doi: 10.1161/STROKEAHA.116.013432
8. Caplan L, Wityk R, Glass T, Tapia J, Pazdera L, Chang H, et al. New England medical center posterior circulation registry. *Ann Neurol.* (2004) 56:389–98. doi: 10.1002/ana.20204
9. Weber R, Minnerup J, Nordmeyer H, Eyding J, Krogias C, Hadisurya J, et al. Thrombectomy in posterior circulation stroke: differences in procedures and outcome compared to anterior circulation stroke in the prospective multicentre REVASK registry. *Eur J Neurol.* (2019) 26:299–305. doi: 10.1111/ene.13809
10. Berkhemer O, Fransen P, Beumer D, van den Berg L, Lingsma H, Yoo A, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* (2015) 372:11–20. doi: 10.1056/NEJMoa1411587
11. Yajima H, Kanaya H, Ogino M, Ueki K, Kim P. Middle meningeal artery embolization for chronic subdural hematoma with high risk of recurrence: a single institution experience. *Clin Neurol Neurosurg.* (2020) 197:106097. doi: 10.1016/j.clineuro.2020.106097
12. Kang D, Yoon W, Kim S, Baek B, Lee Y, Kim Y, et al. Endovascular treatment for emergent large vessel occlusion due to severe intracranial atherosclerotic stenosis. *J neurosurg.* (2018) 130:1—8. doi: 10.3171/2018.1.JNS172350
13. Kim Y, Sohn S, Yoo J, Hong J, Kim C, Kang D, et al. Local tirofiban infusion for remnant stenosis in large vessel occlusion: tirofiban ASSIST study. *BMC Neurol.* (2020) 20:284. doi: 10.1186/s12883-020-01864-4
14. Mosimann P, Kaesmacher J, Gautschi D, Bellwald S, Panos L, Piechowiak E, et al. Predictors of unexpected early reocclusion after successful mechanical thrombectomy in acute ischemic stroke patients. *Stroke.* (2018) 49:2643–51. doi: 10.1161/STROKEAHA.118.021685
15. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, incidence, and mortality of stroke in china: results from a nationwide population-based survey of 480 687 adults. *Circulation.* (2017) 135:759–71. doi: 10.1161/CIRCULATIONAHA.116.025250
16. Sun X, Zhang H, Tong X, Gao F, Ma G, Miao Z. Effects of periprocedural tirofiban vs. oral antiplatelet drug therapy on posterior circulation infarction in patients with acute intracranial atherosclerosis-related vertebrobasilar artery occlusion. *Front Neurol.* (2020) 11:254. doi: 10.3389/fneur.2020.00254
17. Yang M, Huo X, Gao F, Wang A, Ma N, Shi H, et al. Low-dose rescue tirofiban in mechanical thrombectomy for acute cerebral large-artery occlusion. *Eur J Neurol.* (2020) 27:1056–61. doi: 10.1111/ene.14170
18. Yi HJ, Sung JH, Lee DH. Safety and efficacy of intra-arterial tirofiban injection during mechanical thrombectomy for large artery occlusion. *Curr Neurovasc Res.* (2019) 16:416–24. doi: 10.2174/1567202616666191023154956
19. Huo X, Yang M, Ma N, Gao F, Mo D, Li X, et al. Safety and efficacy of tirofiban during mechanical thrombectomy for stroke patients with preceding intravenous thrombolysis. *Clin Interv Aging.* (2020) 15:1241–8. doi: 10.2147/CIA.S238769
20. Zhao L, Jian Y, Li T, Wang H, Lei Z, Sun M, et al. The safety and efficiency of tirofiban in acute ischemic stroke patients treated with mechanical thrombectomy: a multicenter retrospective cohort study. *Biochem Res Int.* (2020) 2020:5656173. doi: 10.1155/2020/5656173
21. Pan X, Zheng D, Zheng Y, Chan P, Lin Y, Zou J, et al. Safety and efficacy of tirofiban combined with endovascular treatment in acute ischaemic stroke. *Eur J Neurol.* (2019) 26:1105–10. doi: 10.1111/ene.13946
22. Kellert L, Hametner C, Rohde S, Bendszus M, Hacke W, Ringleb P, et al. Endovascular stroke therapy: tirofiban is associated with risk of fatal intracerebral hemorrhage and poor outcome. *Stroke.* (2013) 44:1453–5. doi: 10.1161/STROKEAHA.111.000502
23. Wu Y, Yin C, Yang J, Jiang L, Parsons M, Lin L. Endovascular thrombectomy: tirofiban increases bleeding risk in acute stroke patients. *Stroke.* (2018) 49:2783–5. doi: 10.1161/STROKEAHA.118.022919
24. Goyal M, Menon B, van Zwam W, Dippel D, Mitchell P, Demchuk A, 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
25. Dornák T, Král M, Sedláčková Z, Šanák D, Cecháková E, Divišová P, et al. Predictors for intracranial hemorrhage following intravenous thrombolysis in posterior circulation stroke. *Transl Stroke Res.* (2018) 9:582–8. doi: 10.1007/s12975-018-0608-0
26. Frid P, Drake M, Giese AK, Wasselius J, Schirmer MD, Donahue KL, et al. Detailed phenotyping of posterior vs. anterior circulation ischemic stroke: a multi-center MRI study. *J Neurol.* (2020) 267:649–58. doi: 10.1007/s00415-019-09613-5
27. Sarraj A, Medrek S, Albright K, Martin-Schild S, Bibars W, Vahidy F, et al. Posterior circulation stroke is associated with prolonged door-to-needle time. *Int J Stroke.* (2013) 10:672–8. doi: 10.1111/j.1747-4949.2012.00952.x
28. Sommer P, Posekany A, Serles W, Marko M, Scharer S, Fertl E, et al. Is functional outcome different in posterior and anterior circulation stroke? *Stroke.* (2018) 49:2728–32. doi: 10.1161/STROKEAHA.118.021785
29. Meyer L, Stracke C, Jungi N, Wallocha M, Broocks G, Sporns P, et al. Thrombectomy for primary distal posterior cerebral artery occlusion stroke: the TOPMOST study. *JAMA Neurol.* (2021) 78:434–44. doi: 10.1001/jamaneurol.2021.0001
30. Alawieh A, Vargas J, Turner RD, Turk AS, Chaudry MI, Lena J, et al. Equivalent favorable outcomes possible after thrombectomy for posterior circulation large vessel occlusion compared with the anterior circulation: the MUSC experience. *J NeuroInterv Surg.* (2018) 10:735–40. doi: 10.1136/neurintsurg-2017-013420

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 29 September 2021
doi: 10.3389/fneur.2021.677630

Trevo 6 × 25 mm vs. 4 × 30 mm in Mechanical Thrombectomy of M1 LVO

Marion John Oliver[1], Emily Brereton[2], Muhib A. Khan[3], Alan Davis[3] and Justin Singer[3]*

[1] Department of Neurology, University of Toledo, Toledo, OH, United States, [2] College of Human Medicine, Michigan State University, East Lansing, MI, United States, [3] Spectrum Health, Grand Rapids, MI, United States

Objectives: Our primary objective was to determine the successful rate of recanalization of M1 large vessel occlusion using either the Trevo 4 × 30 mm or 6 × 25 mm stent during mechanical thrombectomy. Our secondary objectives were to determine differences between the use of these two stent retrievers regarding first-pass effect, periprocedural complications, and mortality in the first 90 days.

Methods: This is a retrospective cohort study. Data regarding the stent used, recanalization, number of passes, periprocedural complications, and mortality were determined *via* our mechanical thrombectomy database along with chart review.

Conclusion: When comparing Trevo 4 × 30 mm to 6 × 25 mm stent retrievers used in mechanical thrombectomy for middle cerebral artery large-vessel occlusion causing stroke, there is no statistically significant difference in successful recanalization rates, first-pass effect, perioperative complications, or mortality at 90 days. Studies like this will hopefully lead to further prospective, randomized controlled trials that will help show experts in the field an additional way to perform this procedure effectively and safely.

Keywords: stent retreiver, large vessel occlusion, neurointervention, mechanical thrombectomy, stroke

OPEN ACCESS

Edited by:
Osama.O Zaidat, Northeast Ohio Medical University, United States

Reviewed by:
Tareq Kass-Hout, Rush University Medical Center, United States
Vikas Gupta, Texas Tech University Health Sciences Center El Paso, United States
Ido Van Den Wijngaard, Haaglanden Medical Center, Netherlands

****Correspondence:***
Marion John Oliver
marionjolivermd@gmail.com

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *08 March 2021*
Accepted: *04 June 2021*
Published: *29 September 2021*

Citation:
Oliver MJ, Brereton E, Khan MA, Davis A and Singer J (2021) Trevo 6 × 25 mm vs. 4 × 30 mm in Mechanical Thrombectomy of M1 LVO. Front. Neurol. 12:677630. doi: 10.3389/fneur.2021.677630

INTRODUCTION

Acute ischemic stroke secondary to large-vessel occlusion accounts for a significant amount of morbidity and mortality in the world (1). In the USA, stroke is the fifth leading cause of death (2). Of the people that die from stroke, an overwhelming proportion of them are due to large-vessel occlusion (LVO) (3, 4).

Recent clinical trials have shown improved functional outcomes of mechanical thrombectomy in patients with LVO (5–9). The success of these recent trials as compared to earlier studies is related to the evolution of mechanical thrombectomy technology along with improved patient selection. Specifically, trials like SWIFT and TREVO II show the importance of stent retrievers like Solitaire and Trevo compared to Merci catheters (10).

These stent retrievers differ in various ways, including but not limited to size, shape, and material. There is paucity of data on which Trevo stent retriever is better for achieving recanalization efficiently. Our study looked to answer the question of which Trevo stent retriever is superior, Trevo 4 × 30 mm or 6 × 25 mm, in recanalization of M1 LVO.

TABLE 1 | Demographic and clinical characteristics.

	4 x 30 mm stent retriever	6 x 25 mm stent retriever	*p*-value
Age*	69.1+18.3	70.4+18.7	0.745
Sex (% female)	30/50 (60.0%)	12/36 (33.3%)	0.015
Hypertension	37/50 (74.0%)	28/36 (77.8%)	0.687
HLD	25/50 (50.0%)	23/36 (63.9%)	0.201
Diabetes	7/50 (14.0%)	8/36 (22.2%)	0.322
Afib	19/50 (38.0%)	13/36 (36.1%)	0.858
Tobacco use			0.881
Former	9/50 (18.0%)	8/36 (22.2%)	
Current	14/50 (28.0%)	10/36 (27.8%)	
Never	27/50 (54.0%)	18/36 (50.0%)	
Tpa	21/50 (42.0%)	11/36 (30.6%)	0.367
Vessel			0.799
LMCA	25/50 (50.0%)	19/36 (52.8%)	
RMCA	25/50 (50.0%)	17/36 (47.2%)	
BGC	34/50 (68.0%)	2/36 (5.60%)	< 0.001
Puncture to perfusion time†	20 (12, 28)	20 (11, 41)	0.996
Initial NIHSS†	15 (10, 22)	19 (11.5, 24.5)	0.146
Passes†	1 (1, 2)	1 (1, 2)	0.888

HLD, Hyperlipidemia; Afib, Atrial fibrillation; tPA, Tissue plasminogen activator; LMCA, Left main coronary artery; RMCA, Right main coronary artery; BGC, Balloon guided catheterization; NIHSS, National Institutes of Health Stroke Scale.
**mean + SD.*
† median (25th percentile, 75th percentile).

METHODS

Design

This was a retrospective cohort study based out of a single comprehensive stroke center setting. Retrospective chart and mechanical thrombectomy database review was performed over a 2-year period between 2018 and 2019. IRB approval was obtained, and due to the retrospective nature of the study, informed consent was not necessary.

Patient Selection

There were 86 patients included in this retrospective study from 2018 to 2019. Inclusion criteria were the following: patients >18 years of age, have had a mechanical thrombectomy between the time from 2018 to 2019, have LVO in the M1 segment confirmed on CTA and CTP causing acute ischemic stroke, ≤24 h from the last known well, only mechanical thrombectomy done with Trevo 4 × 30 mm or 6 × 25 mm stent retrievers, and all or a portion of subjects care at a primary stroke center.

Data Collection

Patients were divided into two main groups based on which stent retriever was used, and their revascularization was recorded based on their TICI score (11). The TICI score was recorded by the interventionalist that performed the procedure. Additional information that was collected included the following: number of passes, initial NIHSS, discharge NIHSS, change in NIHSS, patient's age, tobacco use, atrial fibrillation, diabetes, hypertension, hyperlipidemia, re-occlusion, groin hematoma, vasospasm, dissection, intracerebral hemorrhage, subarachnoid hemorrhage, use of balloon guided catheterization (BGC), tPA administration, specific vessel occlusion, and 90-day mortality (see **Table 1**).

Primary Outcome Variable

The primary outcome variable was successful recanalization, as defined by thrombolysis in cerebral infarction (TICI) score of IIb–III.

Secondary Outcome Variables

Secondary outcome variables are first-pass effect, perioperative complications, and mortality at 90 days.

Statistical Methods

Summary statistics were calculated. Age is expressed as the mean ± SD, while all other quantitative data are expressed as the median, with the interquartile range in parentheses (25th percentile, 75th percentile). Nominal data are expressed as a percentage. Comparison between groups for age was performed using the *t*-test, while comparisons for all other quantitative variables were performed using the Mann–Whitney U test. Nominal variables were evaluated using the chi-square test or the Fisher's exact test, as appropriate. Significance was assessed at $p < 0.05$. Analyses were performed using Stata v. 15.1 (StataCorp, College Station, TX, USA).

RESULTS

- Eighty-six patients were included in this retrospective study from 2018 to 2019.
- Trevo 4 × 30 mm and 6 × 25 mm had successful recanalization 96.0 and 91.7%, respectively, $p = 0.645$.
- Ninety-day mortality was 16.0% for 4 × 30 mm and 27.8% for 6 × 25 mm, $p = 0.185$.
- tPA was used in 42% of the 4 × 30 mm group and 30.6% of the 6 × 25 mm group.
- Vessels occluded were 50.0% LMCA for 4 × 30 mm, 52.8% 6 × 25mm, and RMCA 50.0% 4 × 30 mm group, 47.2% 6 × 25 mm group.
- BGC was used 68% of the 4 × 30 mm and 5.6% of the 6 × 25 mm groups, $p < 0.001$.
- SAH was a complication in 4% in the 4 × 30 mm group and 2.80% in the 6 × 25 mm, $p > 0.999$.
- ICH was a complication in 2% in the 4 × 30 mm group and 0% in the 6 × 25 mm group, $p > 0.999$.
- Groin hematoma was a complication 0% of the 4 × 30 mm group and 2.8% of the 6 × 25 mm group, $p = 0.419$.
- Vessel perforation took place in 2% of the 4 × 30 mm group and 0% of the 6 × 25 mm group, $p > 0.999$.
- Arterial dissection, vasospasm, and re-occlusion were not complications in either group (see **Table 2**).

DISCUSSION

There are many combinations of techniques that are used in mechanical thrombectomy. *In this study, we included two*

TABLE 2 | Outcomes.

	4 x 30 mm stent retriever	6 x 25 mm stent retriever	*p*-value
90 day mortality	8/50 (16.0%)	10/36 (27.8%)	0.185
Successful recanalization*	48/50 (96.0%)	33/36 (91.7%)	0.645
SAH	2/50 (4.00%)	1/36 (2.80%)	>0.999
ICH	1/50 (2.00%)	0/36 (0.00%)	>0.999
Dissection	0/50 (0.00%)	0/36 (0.00%)	>0.999
Vasospasm	0/50 (0.00%)	0/36 (0.00%)	>0.999
Groin hematoma	0/50 (0.00%)	1/36 (2.80%)	0.419
Re-occlusion	0/50 (0.00%)	0/36 (0.00%)	>0.999
Vessel perforation	1/50 (2.00%)	0/36 (0.00%)	>0.999
Discharge NIHSS†	6 (1, 11.5)	5 (2, 14)	0.550
Delta NIHSS†,‡	8 (3, 14)	13 (2, 18)	0.135

SAH, Subarachnoid hemorrhage; ICH, Intracerebral hemorrhage; TICI, Thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale.
** TICI of 2b or 3.*
† median (25^{th} percentile, 75^{th} percentile).
‡ Initial NIHSS – Discharge NIHSS.

operators that used continuous aspiration prior to intracranial vascular embolectomy (CAPTIVE) and stent retriever-assisted vacuum-locked extraction (SAVE) techniques. One preferred the Trevo 6 × 20 mm stent without the use of BGC and the other Trevo 4 × 30 mm stent with the use of BGC. All other equipment was identical.

Limited data is available for guidance as to which stent retriever to use for M1 LVO mechanical thrombectomy. Interventionalists make stent size decisions based on how they were trained, which vessel is affected, their own personal experiences, and/or the measurement of the vessel itself on imaging. We had two operators that used both.

This study initially proposed that the larger stent diameter would achieve greater revascularization compared to the smaller stent diameter. This hypothesis was based on the larger stent diameter having greater radial force in the artery of interest.

One study by Machi et al. evaluates properties of various stent retrievers as well as their effectiveness. One specific parameter measured was radial force, both outward and inward. Outward radial force was greater in the larger-diameter stent retriever compared to the smaller-diameter stent retriever. Inward radial force varied considerably based on the diameter of the tube it was tested in (12). Additional Trevo data along with one retrospective study by Yi et al. state that larger stent diameter has larger radial force regardless of the vessel size, which in turn leads to better angiographic and clinical outcomes (13, 14).

Another point to consider is the length of the stent. Expert opinion in the field states that the longer the length of the stent, the greater the odds of proper clot integration, thus yielding a greater revascularization rate. This concept leaves radial force behind. The STRATIS registry publication by Zaidat et al. showed that increased length of Solitaire stent retrievers demonstrates a higher rate of first-pass effect and modified first-pass effect compared to larger-diameter or shorter-stent retrievers. However, final revascularization or significant differences in functional dependence/mortality at 90 days post procedure were not seen (15). Our results show us that neither the diameter nor the length of the Trevo stent retriever has a statistically significant effect on successful revascularization, first-pass effect, perioperative complications, or mortality at 90 days. *Mortality of 27.8% in the Trevo 6 × 20 mm group compared to 16.0% was not statistically significant; however, we do believe it is important to be noted.*

The use of balloon-guided catheterization (BGC) was statistically significant in the 4 × 30 group compared to the 6 × 25 group. Despite the statistical significance of the use of BGC in 4 × 30 group, there was no statistical significance achieved in terms of primary endpoint compared to 6 × 25 without the use of BGC. Several studies have shown that regardless of thrombectomy techniques used by the interventionalist (ADAPT, SAVE, CAPTIVE, etc.), the use of BGC is an independent predictor of higher rate of successful revascularization, first-pass effect, and mRS 0–2 at 90 days. The advantages of BCG are flow arrest proximal to the clot and the decreasing arterial pressure that impacts the clot. This leads to a reduction in distal embolization along with enhancement of the actual thrombectomy technique (16).

Our study does have its limitations. It was retrospective, had a limited sample size due to our strict exclusion criteria, and was not a randomized control trial. Additionally, the use of BGC and a lack of control in length or width of stent size were limitations as well. Perhaps our primary endpoint results would have been different if the 4 × 30 group had not used BCG or the 6 × 25 group had used BGC.

Despite these limitations, this study challenges us to think about which technique/tools for this procedure are best. Additional randomized trials are needed to further best clarify the optimal approach for angiographic outcomes, first pass, perioperative outcomes, and 90-day mortality.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

Lead author MO. Principle investigator was JS. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.677630/full#supplementary-material

REFERENCES

1. Global Heatlh Estimates. Geneva: World Health Organization; (2012). Available online at: http://www.who.int/healthinfo/global_burden_disease/en
2. Murphy SL, Xu JQ, Kochanek KD, Arias E. Moratlity in the United States, 2017 NCHS Data Brief, no 328. Hyattsville, MD: National Center for Health Statistics. (2018)
3. Malhotra K, Gornbein J, Saver JL. Ischemic Strokes Due to Large-Vessel Occlusions Contribute Disproportionately to Stroke-Related Dependence and Death: A Review. *Front Neurol*. (2017). 8:651. doi: 10.3389/fneur.2017.00651
4. Rai AT, Seldon AE, Boo S, Link PS, Domico JR, Tarabishy AR, et al. A population-based incidence of acute large vessel occlusions and thrombectomy eligible patients indicates significant potential for growth of endovascular stroke therapy in the USA. *J Neuro-Interventional Surgery*. (2017) 9:722–6.
5. 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
6. 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
7. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke, March 12, 2015. N *Engl J Med*. (2015). 372:1019–30. doi: 10.1056/NEJMoa1414905
8. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EL, Pereira CM, 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
9. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 Hours after Symptom Onset in Ischmic Stroke. *N Engl J Med*. (2015) 372:2296–306. doi: 10.1056/NEJMoa1503780
10. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, et al. Trevo versus Merci retrievers for thrombectomy revascularization of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomized trial. *The Lancet*. (2012) 380:1231-40. doilink[10.1016/S0140-6736(12)61299-9]10.1016/S0140-6736(12)61299-9
11. Fugate JE, Klunder AM, Kallmes DF. What Is Meant by "TICI"? *Am J Neuroradiol*. (2013) 34:1792–7. doi: 10.3174/ajnr.A3496
12. Machi P, Jourdan F, Ambard D, Reynaud C, Lobotesis K, Sanchez M, et al. Experimental evaluation of stent retrievers' mechanical properties and effectiveness. *J Neurointerventional Sur*, (2017) 9:257–63. doi: 10.1136/neurintsurg-2015-012213
13. Yi HJ, Sung JH, Lee DH, Hong JT, Lee SW. Single-center experience of mechanical thrombectomy with the Trevo XP ProVue 6 × 25 mm stent retriever in middle cerebral artery occlusion: comparison with Trevo XP ProVue 4 × 20 mm. *World Neurosurg*. (2017) 107:649–56. doi: 10.1016 /j.wneu.2017.08.043.
14. Features and Benefits: High radial force at smallest diameters. Available online at: https://www.strykerneurovascular.com/products/ais/trevo-xp-provue-retriever
15. Zaidat OO, Haussen DC, Hassan AE, Jadhav AP, Mehta BP, Mokin M, et al.Impact of stent retriever size on clinical and angiographic outcomes in the STRATIS stroke thrombectomy registry.*Stroke*. (2019) 50:441–7. doi: 10.1161/STROKEAHA.118.022987
16. Zaidat OO, Mueller-Kronast NH, Hassan AE, Haussen DC, Jadhav AP, Froehler MT, et al. Impact of balloon guide catheter use on clinical and angiographic outcomes in the STRATIS stroke thrombectomy registry. *Stroke*. (2019) 50:697–704. doi: 10.1161/STROKEAHA.118.021126

Conflict of Interest: JS is a consultant for Stryker and Medtronic.

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.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 26 October 2021
doi: 10.3389/fneur.2021.692128

Imaging Predictors for Endovascular Recanalization of Non-acute Occlusion of Internal Carotid Artery Based on 3D T1-SPACE MRI and DSA

*Liu Chao[1], Meng Qingbin[1], Xu Haowen[1], Xie Shanshan[2], Fu Qichang[2], Chen Zhen[1] and Guan Sheng[1]**

[1] Department of Interventional Neuroradiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China,
[2] Department of Magnetic Resonance Imaging, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Objectives: To investigate the predictive factors for successful recanalization based on digital subtraction angiography and three-dimensional T1W sampling perfection with application-optimized contrasts using different flip angle evolutions (3D T1-SPACE) high-resolution magnetic resonance imaging (MRI) signal features.

Methods: Consecutive internal carotid artery occlusion cases with ipsilateral ischemic stroke refractory to therapy who visited our institution between February 2017 and August 2020 were retrospectively analyzed. Epidemiology, symptomatology, imaging morphology on angiography and MRI, peri-procedural complications, technical success rate, and follow-up results were summarized. Factors related to technical success were analyzed using univariate and multivariate analyses.

Results: In total, 75 cases (53 men, mean age 57.51 ± 9.71 years) were included. The total successful recanalization rate was 72.00% (54/75), with a complication rate of 13.33% (9/75). Through multivariate analysis, first ischemic stroke in <3 months (OR: 2.57; 95% CI: 1.13–4.58), tapered stump (OR: 4.31; 95% CI: 1.37–13.55), reversed flow of the ophthalmic artery (OR: 2.99; 95% CI: 1.06–8.49), high intraluminal signal on unenhanced T1-SPACE sequence (OR: 16.15; 95% CI: 3.40–76.72), no vessel wall collapse (OR: 17.00; 95% CI: 3.57–81.02), short occlusion length (OR: 9.87; 95% CI: 2.09–46.64), and primary occlusion site at the cervical internal carotid artery (OR: 8.42; 95% CI: 1.04–68.19) were associated with successful recanalization.

Conclusion: Besides traditional features such as short ischemic event time, tapered stump, and distal ICA reconstitution by the ophthalmic artery, our study demonstrates that luminal and mural changes determined by 3D SPACE high-resolution MRI could also predict successful endovascular recanalization. Endovascular recanalization for non-acute internal carotid artery occlusion is feasible, but prudent case selection is mandatory considering the high periprocedural complication rate.

Keywords: non-acute occlusion, internal carotid artery, endovascular recanalization, magnetic resonance imaging, 3D T1-SPACE

OPEN ACCESS

Edited by:
Liqun Jiao,
Capital Medical University, China

Reviewed by:
Yukiko Enomoto,
Gifu University Hospital, Japan
Luis Rafael Moscote-Salazar,
University of Cartagena, Colombia

****Correspondence:***
Guan Sheng
gsradio@126.com

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *07 April 2021*
Accepted: *20 September 2021*
Published: *26 October 2021*

Citation:
Chao L, Qingbin M, Haowen X, Shanshan X, Qichang F, Zhen C and Sheng G (2021) Imaging Predictors for Endovascular Recanalization of Non-acute Occlusion of Internal Carotid Artery Based on 3D T1-SPACE MRI and DSA. Front. Neurol. 12:692128. doi: 10.3389/fneur.2021.692128

INTRODUCTION

A non-acute occluded internal carotid artery (NAOICA) accounts for a 6–20% risk of developing ipsilateral ischemic stroke, despite patients receiving optimal medical treatment (1). Propagation of clots into the circle of Willis and compromised cerebral perfusion are regarded as the major causes of recurrent neurological events (2).

Treatment of the chronically occluded internal carotid artery is challenging. Surgical revascularization with extracranial–intracranial bypass was found to be ineffective compared to medical therapy in patients with hemodynamic impairment and showed no benefit during two follow-ups (3, 4). Carotid endarterectomy could revascularize the short cervical occlusive internal carotid artery, but was ineffective for long segmental or tandem lesions (5). Hybrid surgery seems to compensate for such drawbacks (6), but concerns of increased stroke and death rates due to complicated post-procedural management between open surgery and intensive antiplatelet/anticoagulant protocols should be considered (7).

Recently, endovascular revascularization was reported to have a 70% success rate, with a 13% complication rate and 5% morbidity (8–10). However, technical skills are required for complex occluded vessels, such as complicated routes, collapsed vessel walls, propagated thrombi, and vulnerable plaques. Precise preprocedural appraisal of the occluded vasculature to rule out dangerous conditions can help achieve safe and successful recanalization.

At present, no studies have focused on the relationship between dynamic changes in the lumen and vessel wall of NAOICA and recanalization results. Here, we hypothesized that vessel wall and lumen changes are also important for successful recanalization. Therefore, we conducted a retrospective analysis of all patients with NAOICA who visited our center and underwent vessel three-dimensional T1W sampling perfection with application-optimized contrasts using different flip angle evolutions (3D T1-SPACE) magnetic resonance imaging (MRI) before endovascular recanalization to identify the predictive factors of vessel wall imaging (VWI) for successful recanalization in order to select appropriate candidates for such procedures. To the best of our knowledge, this is the first study to assess this.

METHODS

Patients

Basic and radiological data of patients with NAOICA who underwent attempted endovascular recanalization from January 2017 to August 2020 at our institution were analyzed. The inclusion criteria were as follows: (1) had ipsilateral recurrent ischemic stroke and were refractory to medical treatment, (2) had hypoperfusion confirmed by computed tomography (CT) perfusion or MR perfusion weighted imaging, and (3) underwent all endovascular procedures 2 weeks after the latest ischemic event. The exclusion criteria were as follows: (1) acute occlusion of the carotid artery, (2) asymptomatic lesions, (3) severe disabling strokes (modified Rankin Scale (mRS) score >2), (4) Alberta stroke program early CT (ASPECT) score <6, (5) history of a bleeding disorder, (6) any coexisting condition that limited life expectancy to <1 year, (7) allergy or contraindication contrast media, anesthesia, or heparin, and (8) intolerable to high-resolution MRI.

3D T1-Space MRI

All VWIs were performed on a three T MRI system (Magnetom Prisma, Siemens, Erlangen, Germany) with a 64-channel coil. The parameters for VWI were: TR 900 ms, TE 15.0 ms, field of view 230 × 230 mm, matrix 256 × 265, and spatial resolution 0.6 mm (isotropic). The MRI protocol also included standard sequences such as T1WI, T2WI, FLAIR, DWI, and a 3D TOF MRA sequence of the arteries above the aortic arch.

Magnevist was used as the contract media (Bayer Schering Pharma AG, Germany).

Interventional Procedure

All patients received dual antiplatelet drugs (clopidogrel 75 mg/d and aspirin 100 mg/d) for at least 5 days. Patients with an AA > 70% and ADP > 30% on the thromboelastogram were considered suitable for undergoing the operation.

The procedure was performed on digital subtraction angiography (DSA) panel (FD2020; Philip, Netherlands) under monitored anesthesia. A thorough 6-vessel diagnostic angiogram was obtained to confirm the occlusion characteristics and state of the collaterals. After two interventional neurologists checked all basic and radiological data, endovascular reconstruction of the ICA was initiated. After intravenous administration of a bolus of heparin (100 mg/kg), a 7 F 90-cm long sheath (Terumo, Japan) was deployed at the distal common carotid artery *via* the femoral artery to provide sufficient backup and facilitate the delivery of multiple devices. Given that passing through the occluded site to the true lumen without injury to the intima was challenging, several protocols were adopted at our institution. First, a microcatheter (Echelon, SL, Excelsior XT-27, etc.) and a microwire (Synchro, Transcend, Traxcess, etc.) used employed to probe the tapered stump or vulnerable spot. If the attempts were unsuccessful, a Progreat microcatheter (Terumo, Japan) designed for the peripheral artery or 5-F vertebral angiographic catheter combined with a 0.035-inch guidewire was used to perform the same process. Once the wire crossed the occlusion site and angiographic projections confirmed its position in the true lumen, an embolus protection device was considered if the occlusion was short without tandem lesions. However, if long segmental occlusion with a propagated thrombus or tortuous vasculature was encountered, a 300-mm microwire (Synchro or Transcend) was carefully navigated to the ipsilateral middle cerebral artery as a rail to deliver different devices. Angiographic projections with large-bore microcatheters (Excelsior XT-27, rebar-27) were performed through the wire from C7 to C1 downstream to detect the primary occlusion site and occlusion length. If the thrombus load was high, direct aspiration or stent thrombectomy with aspiration catheters (Penumbra, Sofia, Catalyst, etc.) and stents (Solitaire FR, Trevo, EmboTrap, etc.) would be adopted first. If not, a small-diameter angioplasty balloon was used to dilate the occluded segments from the distal

part to the proximal part. Any proper stents were acceptable, as determined by the operating surgeons to scaffold the elastically recoiled vessel. Post-stenting balloon angioplasty was necessary if the residual stenosis was >30%. Thrombolysis in cerebral infarction classification (TICI) 2b-3 on DSA findings was considered successful recanalization.

Systolic blood pressure was rigorously maintained at 100–120 mmHg after the procedure to prevent hyperperfusion syndrome. Regular dual antiplatelet agent (aspirin 100 mg/day and clopidogrel 75 mg), proper control of risk factors, and effective rehabilitation training were also prescribed after the procedure.

The post-procedural neurological state was assessed by the mRS score, which was obtained by a telephone call or face-to-face follow-up. Computed tomography angiography (CTA) or DSA was routinely prescribed 6 months after the procedure.

Image Analysis

Two interventional neurologists (CZ and MQ) reviewed all DSA images. The morphological characteristics included stump type (tapered or blunt), distal internal carotid artery reconstituted by the ophthalmic artery, and occlusion length (≥3 segments or less according to Bouthillier segmentation). Two magnetic resonance physicians (XS and FQ) analyzed the MRI images, including the collapsed wall, the occlusion segments, and the intraluminal signal. In case of disagreement, two senior researchers (GS and XH) were chosen as the third reviewer to resolve the discrepancy.

Statistical Analysis

SPSS software for Windows 26.0 version (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous data are presented as mean ± SD, and categorical data are presented as counts and percentages. The chi-square test or Fisher's test (if the group's number was five or less) was used to compare the categorical data. An ANOVA test or Mann–Whitney test was used to compare groups of continuous data with equal variances. The Wilcoxon–Mann–Whitney *U*-test was used to compare groups of continuous data with heterogeneous variances. Binary logistic regression models were used to assess the correlation between radiological features and recanalization success rates. Statistical significance was set at a 2-sided probability value of <0.05.

RESULTS

In total, 75 patients (53 men, mean age 57.51 ± 9.71 years) with symptomatic NAOICA who underwent attempted endovascular recanalization were included. The flow chart selection chart is demonstrated in **Figure 1**. Demographic and clinical data are listed in **Table 1**. The angiographic findings and 3D T1-SPACE MRI features are listed in **Table 2**.

Among the 75 patients, 54 (72.00%) achieved successful recanalization. The perioperative complication rate was 13.3% (10/75), including two cases of intracranial hemorrhage followed

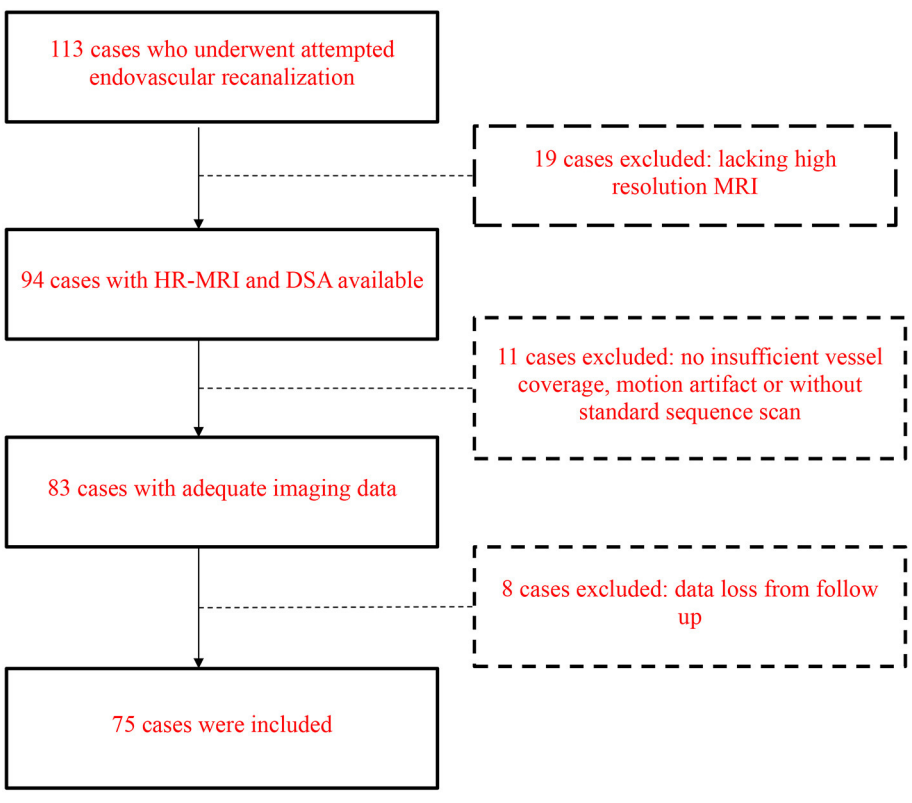


FIGURE 1 | Flow chart of case selection.

TABLE 1 | Basic characteristics of the patients.

	Successful	Failed	Total	*p*-value
Male (n, %)	42 (77.8%)	11 (52.4%)	53 (70.7%)	0.059
Age (years)	56.07 ± 10.33	61.19 ± 6.80	57.51 ± 9.71	0.015
Hypertension (n, %)	24 (44.4%)	13 (61.9%)	37 (49.3%)	0.174
Diabetes mellitus (n, %)	13 (24.1%)	3 (14.3%)	16 (21.3%)	0.532
Coronary disease (n, %)	8 (14.8%)	2 (9.5%)	10 (13.3%)	0.716
Hyperlipidemia (n, %)	17 (31.5%)	7 (33.3%)	24 (32.0%)	0.877
Hyperhomocysteinemia (n, %)	29 (53.7%)	9 (42.9%)	38 (50.7%)	0.399
Alcohol	15 (27.8%)	4 (19.0%)	19 (25.3%)	0.435
Smoking	16 (29.6%)	3 (19.3%)	19 (25.3%)	0.170
LDL (mmol/L)	2.06 ± 0.77	2.28 ± 0.86	2.12 ± 0.80	0.277
Homocysteine (μmol/L)	15.94 ± 4.48	16.19 ± 7.23	16.01 ± 5.34	0.861
HbA1c (%)	6.47 ± 1.34	6.01 ± 0.85	6.34 ± 1.23	0.147
D-dimer (mg/L)	0.25 ± 0.52	0.27 ± 0.73	0.26 ± 0.58	0.882
First ischemic event				0.040
≤3 months	36 (66.7%)	12 (57.1%)	48 (64.0%)	
>3 months	18 (33.3%)	9 (42.9%)	27 (36.0%)	
Last ischemic event				0.340
≤3 months	51 (94.4%)	18 (85.7%)	69 (92.0%)	
>3 months	3 (5.6%)	3 (14.3%)	6 (8.0%)	

LDL, low density lipoprotein.

TABLE 2 | Radiologic characteristics of the patients.

	Successful	Failed	Total	*p*-value
Stumped	48 (88.9%)	17 (81.0%)	65 (86.7%)	0.452
Tapered	46 (85.2%)	12 (57.1%)	58 (77.3%)	0.014
Reversed flow of the ophthalmic artery	35 (64.8%)	8 (38.1%)	43 (57.3%)	0.036
Distal ICA reconstitution by the circle of Willis	40 (74.1%)	16 (76.2%)	56 (74.7%)	0.850
High signal on 3D-SPACE MRI	34 (63.0%)	2 (9.5%)	36 (48.0%)	0.000
Collapse of vessel wall	20 (37.0%)	19 (90.5%)	39 (52.0%)	0.000
Long occlusion length	26 (49.1%)	19 (90.5%)	45 (60.8%)	0.001
Occlusion site at intracranial ICA	38 (70.4%)	20 (95.2%)	58 (77.3%)	0.021
Concomitant intracranial artery stenosis or occlusion	12 (22.2%)	2 (9.5%)	14 (18.7%)	0.324

ICA, internal carotid artery; MRI, magnetic resonance imaging.

TABLE 3 | Logistic regression for predictors of technique success.

	OR (95% CI)	*p*-value
Hypertension	2.23 (0.23 – 21.97)	0.492
Diabetes mellitus	1.90 (0.48 – 7.50)	0.358
Hyperlipidemia	0.92 (0.31 – 2.69)	0.877
Hyperhomocysteinemia	1.55 (0.56 – 4.27)	0.400
Smoking	2.53 (0.65 – 9.79)	0.180
Alcohol	1.64 (0.47 – 5.66)	0.438
First ischemic event time (≤3 months)	2.57 (1.13 – 4.58)	0.042
Short T1 signal on 3D-SPACE MRI	16.15 (3.40 – 76.72)	0.000
No vessel wall collapse	17.00 (3.57 – 81.02)	0.000
Occlusion length ≤3 segments	9.87 (2.09 – 46.64)	0.004
Reversed flow of ophthalmic artery	2.99 (1.06 – 8.49)	0.039
Distal ICA reconstituted by Willis's circle	0.25 (0.04 – 2.57)	0.850
Primary occlusion site at cervical ICA	8.42 (1.04 – 68.19)	0.046
Concomitant lesions of cerebral artery	2.71 (0.55 – 13.33)	0.219
Tapered	4.31 (1.37 – 13.55)	0.012

3D-SPACE MRI three-dimensional T1W sampling perfection with application-optimized contrasts using different flip angle evolutions. MRI, magnetic resonance image; ICA, internal carotid artery.

by microwire perforation, three cases of asymptomatic carotid-cavernous fistula (CCF), and three cases of asymptomatic dissection. No complications resulted in severe disability or death.

All cases were followed up by telephone, and the median follow-up duration ranged from 6 to 26 months. In the successful recanalization group, 43 (81.13%) patients underwent CTA or DSA examination at 6 months after the procedure; 1 (1.88%) patient experienced recurrent ischemic stroke for severe in-stent restenosis; and 8 (18.60%) patients developed moderate to severe silent restenosis. In the failed recanalization group, 6 (28.57%) patients experienced ipsilateral ischemic stroke under regular medical treatment. No hemorrhage or death occurred in either group.

Multivariate analysis with logistic regression suggested several independent positive predictive factors for successful recanalization (**Table 3**). The technical success rate was higher in the following conditions: first ischemic stroke in <3 months (OR: 2.57; 95% CI: 1.13–4.58), tapered stump (OR: 4.31; 95% CI: 1.37–13.55), reversed flow of the ophthalmic artery (OR: 2.99; 95% CI: 1.06–8.49), short intraluminal signal on non-enhanced T1-SPACE sequence (OR: 16.15; 95% CI: 3.40–76.72), no vessel wall collapse (OR: 17.00; 95% CI: 3.57–81.02), short occlusion length (OR: 9.87; 95% CI: 2.09–46.64), and primary occlusion site at the cervical internal carotid artery (OR: 8.42; 95% CI: 1.04–68.19).

DISCUSSION

The incidence of internal carotid artery occlusion is ∼6 per 100,000 individuals. Neurovascular event rates range from 0 to 26% (11). In cases of insufficient collateral compensation, the risk of ischemic stroke may be as high as 30% per year (12). A recent report by Janko et al. (13) suggested that the occluded carotid artery is more frequently associated with neurovascular

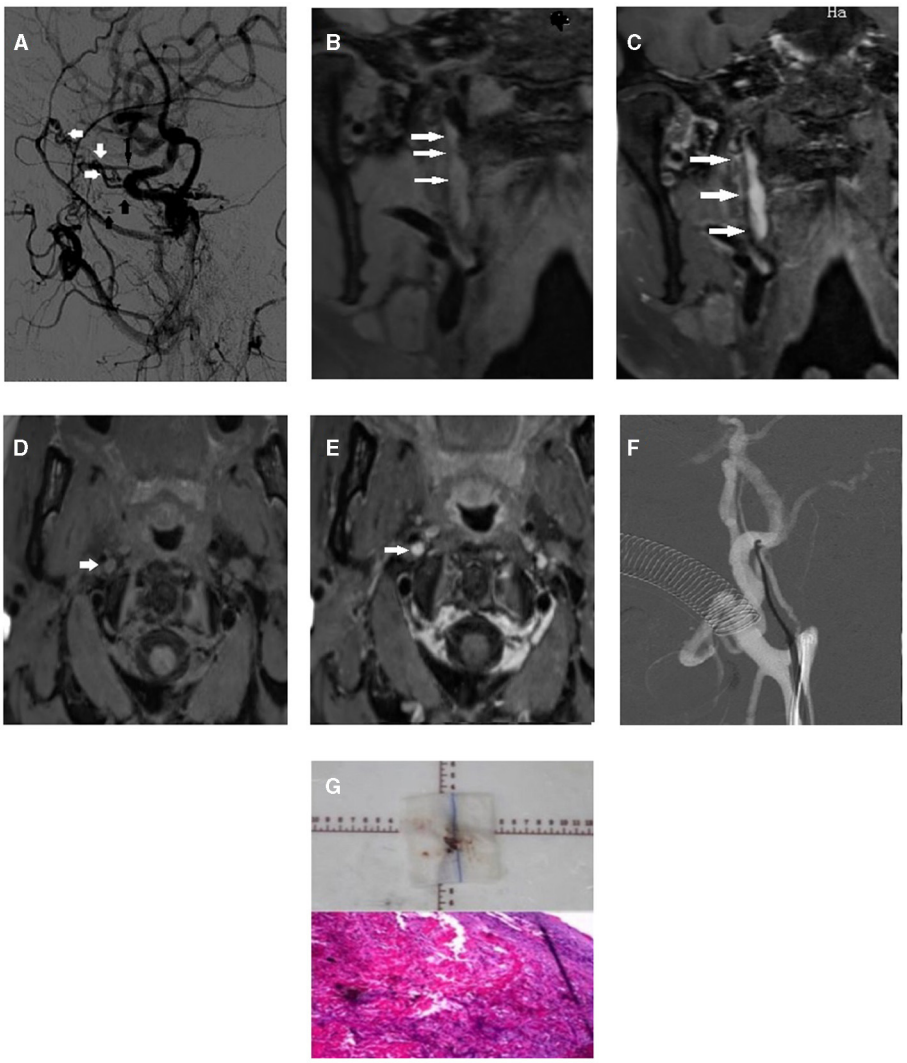


FIGURE 2 | First illustrative case of right internal carotid artery chronic occlusion with border zone infarction. **(A)** Lateral image of occluded internal carotid artery on DSA exhibited multiple collaterals from extracranial carotid artery (white arrow: recurrent meningeal artery, short black arrow: artery of the foramen rotundum, long black arrow: ophthalmic artery). **(B)** Long atresia lumen was detected on coronal scan of unenhanced 3D SPACE MRI (white arrow). **(C)** On enhanced coronal scan, intraluminal slight enhancement was detected (white arrow). **(D)** On unenhanced cross-section, occluded internal carotid lumen was exhibited (white arrow). **(E)** Intraluminal enhancement after contrast injection (white arrow). **(F)** After all attempts with multiple guidewires, passing through the occluded site was still failed. **(G)** Biopsy from carotid endarterectomy revealed old thrombosis at the occlusion site.

events than moderately severe carotid stenosis, despite similar overall cost and readmission rates. At present, a consensus has been reached that chronic occlusion is not as benign as previously thought (1, 14). Thus, an optimal recanalization protocol is necessary.

Chen et al. (15) developed a scoring system with a sensitivity of 80.3% and a specificity of 67.9% based on angiographic features and symptoms (15), such as non-tapered stump, distal ICA reconstituted by the ophthalmic artery or communicating artery, and absence of neurologic events. In addition, based on DSA angiography, Hasan et al. divided the occluded ICA into four groups (A: tapered stump with patent distal ICA filling by collaterals; B: non-tapered stump with patent distal ICA; C: no ICA stump with patent distal lumen filling by collaterals; D: no ICA stump with occluded distal lumen). Type A and type B were more amenable to safe revascularization than type C and type D. Meimo et al. modified the radiological features of the four groups according to their institutional data and achieved the same results as the study by Hasan et al. In summary, a short occlusion time, tapered ICA stump, and long patent lumen of the distal ICA filled by collaterals are positive predictors of successful recanalization.

In our study, tapered stump and patent distal lumen with reversed ophthalmic artery flow were associated with successful

recanalization, which was consistent with previous studies. While these studies did not consider the pathological changes to the vessel wall and lumen, their drawbacks were obvious. In the coronary artery, wall imaging techniques, such as intravascular ultrasound and optical coherence tomography, improved periprocedural and long-term outcomes compared with angiography-guided percutaneous coronary intervention (16). We also illustrate a case of type A lesion, which was expected to have a 100% success rate, but ultimately had failed recanalization (**Figure 2**). The lumen collapsed with no short signal on the unenhanced T1-SPACE sequence, suggesting a longtime occlusion or even congenital atresia of the vessel.

With the advent of the vessel wall and lumen imaging by high-resolution MRI, the collapsed vessel wall, propagated thrombus, and occlusion length could be clearly visualized, especially in the 3D T1-SPACE sequence. Chai et al. (17) found that high-resolution MRI could correctly detect tandem lesions and the extent of occlusion length of chronic occluded ICA compared with DSA (17). Vessel wall MRI was also performed to detect pseudo-occlusion or false dissection, but was only diagnosed by super-selective microcatheter angiography (18).

In our study, 64.00% (34/54) of cases exhibited high intraluminal signals on the unenhanced T1-SPACE sequence, while this was only 9.50% (2/21) in the failed recanalization group. A high signal portion was then confirmed as unstable thrombosis by stent thrombectomy or aspiration (**Figure 3**). In total, 90.50% (19/21) of cases manifested a collapsed vessel wall in the failed recanalization group, while this was only 37.0% (20/54) in the successful recanalization group. These results indicated their relationship with safe and effective revascularization.

We also detected six long segmental mural hematoma cases that were characteristic of dissection (19, 20), and direct stent implantation was performed to reconstruct the vessel wall and finally restore normal blood flow.

The technical success rate was 72.00% in our study. Although bypass surgery presented a relatively lower incidence of complications, less benefits were exhibited on neurological function improvement and recurrent ischemic stroke. While endovascular recanalization was characterized by a relatively lower technical success and higher complications, long-term functional improvement and lower recurrence of ischemic events were achieved. Hybrid surgery plays the same role as endovascular treatment. Therefore, future prospective randomized trials should focus on endovascular treatment and hybrid surgery in selected cases.

Migration of thrombus was rarely reported in previous literatures. Usually, chronic vessel occlusion was deemed with stable mural thrombus. But in our institution, we encountered three cases that did not perform high resolution MRI encountered thrombus migration. Therefore, thrombectomy with a stent retriever and aspiration catheter was performed in 24 cases (32.00%) with intraluminal high signals to prevent thrombus migration. Although no benefit on recanalization rate was observed ($p = 0.343$), the feasibility and safety were confirmed.

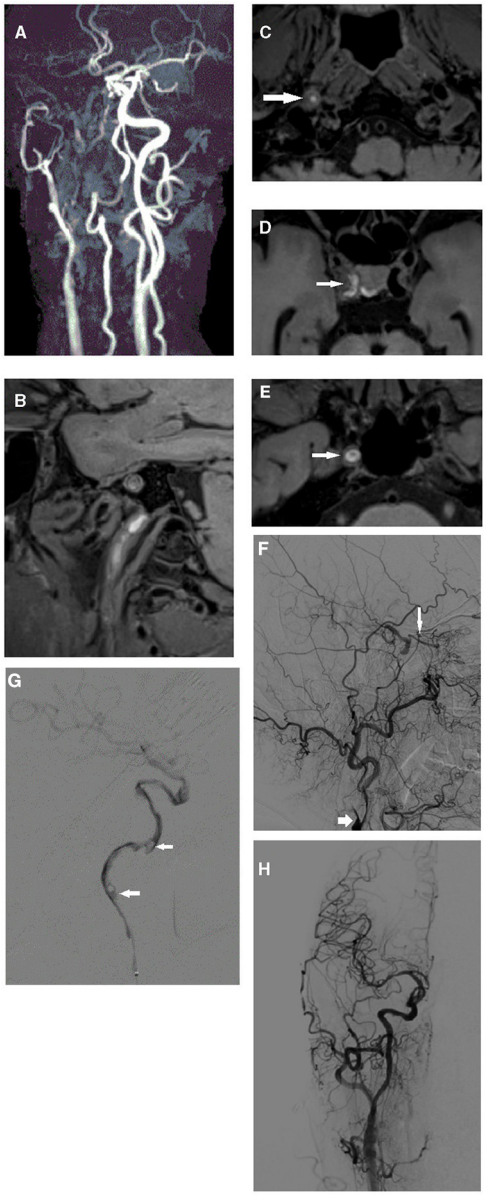


FIGURE 3 | Second illustrative case of right internal carotid occlusion with recurrent ischemic events: **(A)** Long segmental occlusion of right internal carotid artery was detected by TOF MRA. **(B–D)** Intraluminal high signals were detected from cervical segment to clinic segment (white arrow) on 3D SPACE sequence. **(E)** After contrast injection intravenously, enhanced patent wall was delineated (white arrow). **(F)** Lateral images on DSA exhibited the tapered stump (short white arrow) and reversed ophthalmic artery (long white arrow). **(G)** Microcatheter angiograph exhibited long segmental filling defect sign (white arrow). **(H)** After aspiration with Sofia catheter (Microvention, Terumo, Japan), we retrieved a long old thrombus and restored the normal blood flow.

Complication rate in our study was 13.33%, mostly iatrogenic lesions related to technical skills, such as perforation, CCF, and dissection, but no permanent neurological symptoms were leftover. Federrico Caggnazzo et al. performed a meta-analysis including 13 studies and 568 patients. The complications were 18%, and the morbidity was ∼5%. Therefore, prudent

case selection and individualized recanalization protocol are crucial.

LIMITATIONS

(1) The main limitations of our study were related to its retrospective design and relatively small sample size, and these limitations may interfere with the statistical analysis and may have contained correlative variables; however, our sample size was relatively larger than that of previous studies. (2) Histopathological data were unavailable, and the correlation between MRI signals and tissue characteristics remains unknown. We obtained several thrombus samples; however, these require further analysis. (3) Few studies have focused on the mural and intraluminal signals on high-resolution MRI; therefore, a precise criterion to confirm the occlusion type would be controversial.

CONCLUSIONS

First ischemic events in <3 months, tapered stump, reversed flow of the ophthalmic artery, short intraluminal signal on non-enhanced T1-SPACE MRI, no vessel wall collapse, short occlusion length, and primary occlusion site at the cervical internal carotid artery were independent predictors for successful endovascular recanalization of NAOICA. These results may help predict effective recanalization of the NAOICA, but further randomized trials with a large cohort are necessary to verify our results.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Zhengzhou University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GS designed the research. LC collected the data and performed the manuscript writing. XH, CZ, XS, and MQ interpreted the data. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Morris-Stiff G, Teli M, Khan PY, Ogunbiyi SO, Champ CS, Hibberd R, et al. Internal carotid artery occlusion: its natural history including recanalization and subsequent neurological events. *Vasc Endovasc Surg.* (2013) 47:603–7. doi: 10.1177/1538574413500539
2. Grubb RL, Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, et al. Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. *JAMA*. (1998) 280:1055–60. doi: 10.1001/jama.280.12.1055
3. Powers WJ, Clarke WR, Grubb RL, Videen TO, Adams HP, Derdeyn CP, et al. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the carotid occlusion surgery study randomized trial. *JAMA*. (2011) 306:1983–92. doi: 10.1001/jama.2011.1610
4. Nahab F, Liu M, Rahman HA, Rangaraju S, Barrow D, Cawley CM, et al. Recurrent hemispheric stroke syndromes in symptomatic atherosclerotic internal carotid artery occlusions: the carotid occlusion surgery study randomized trial. *Neurosurgery*. (2020) 87:137–41. doi: 10.1093/neuros/nyz352
5. Bigliardi G, Dell'Acqua ML, Vallone S, Barbi F, Pentore R, Picchetto L, et al. 'Opening the unopenable': endovascular treatment in a patient with three months' internal carotid artery occlusion and hemispheric symptomatic hypoperfusion. *J Stroke Cerebrovasc Dis*. (2016) 25:2016–18. doi: 10.1016/j.jstrokecerebrovasdis.2016.04.019
6. Shih YT, Chen WH, Lee WL, Lee HT, Shen CC, Tsuei YS. Hybrid surgery for symptomatic chronic total occlusion of carotid artery: a technical note. *Neurosurgery*. (2013) 73(1 Suppl Operative):onsE117–23. doi: 10.1227/NEU.0b013e31827fca6c
7. Stewart LM, Spangler EL, Sutzko DC, Pearce BJ, McFarland GE, Passman MA, et al. Carotid endarterectomy with concomitant distal endovascular intervention is associated with increased rates of stroke and death. *J Vasc Surg.* (2021) 73:960–7.e1. doi: 10.1016/j.jvs.2020.07.062
8. Cagnazzo F, Lefevre PH, Derraz I, Dargazanli C, Gascou G, Riquelme C, et al. Endovascular recanalization of chronically occluded internal carotid artery. *J NeuroIntervent Surg.* (2020) 12:946–51. doi: 10.1136/neurintsurg-2019-015701
9. Hasan D, Zanaty M, Starke R, Atallah E, Chalouhi N, Jabbour P, et al. Feasibility, safety, and changes in systolic blood pressure associated with endovascular revascularization of symptomatic and chronically occluded cervical internal carotid artery using a newly suggested radiographic classification of chronically occluded cervical internal carotid artery: pilot study. *J Neurol Surg.* (2018) 130:1–10. doi: 10.3171/2018.1.JNS172858
10. Mo L, Ma G, Dai C, Wang S, Li C, Ma T, et al. Endovascular recanalization for symptomatic subacute and chronically occluded internal carotid artery: feasibility, safety, a modified radiographic classification system, and clinical outcomes. *Neuroradiology*. (2020) 62:1323–34. doi: 10.1007/s00234-020-02458-0
11. Flaherty ML, Flemming KD, McClelland R, Jorgensen NW, Brown RD. Population-based study of symptomatic internal carotid artery occlusion: incidence and long-term follow-up. *Stroke*. (2004) 35:e349–e52. doi: 10.1161/01.STR.0000135024.54608.3f
12. Xu B, Li C, Guo Y, Xu K, Yang Y, Yu J. Current understanding of chronic total occlusion of the internal carotid artery. *Biomed Rep*. (2018) 8:117–25. doi: 10.3892/br.2017.1033
13. Janko M, Moore R, Kim AH, Shevitz AJ, Morrow KL, Johnson DJ, et al. Carotid occlusion is associated with more frequent neurovascular events than moderately severe carotid stenosis. *J Vasc Surg.* (2017) 66:1445–9. doi: 10.1016/j.jvs.2017.04.041
14. Powers WJ, Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, et al. Benign prognosis of never-symptomatic carotid occlusion. *Neurology*. (2000) 54:878–82. doi: 10.1212/WNL.54.4.878
15. Chen YH, Leong WS, Lin MS, Huang CC, Hung CS, Li HY, et al. Predictors for successful endovascular intervention in chronic carotid artery total occlusion. *JACC Cardiovasc Intv.* (2016) 9:1825–32. doi: 10.1016/j.jcin.2016.06.015

16. Maehara A, Matsumura M, Ali ZA, Mintz GS, Stone GW. IVUS-guided versus OCT-guided coronary stent implantation: a critical appraisal. *JACC Cardiovasc Imaging.* (2017) 10:1487–503. doi: 10.1016/j.jcmg.2017.09.008
17. Chai S, Sheng Z, Xie W, Wang C, Liu S, Tang R, et al. Assessment of apparent internal carotid tandem occlusion on high-resolution vessel wall imaging: comparison with digital subtraction angiography. *AJNR Am J Neuroradiol.* (2020) 41:693–9. doi: 10.3174/ajnr.A6452
18. Grossberg JA, Haussen DC, Cardoso FB, Rebello LC, Bouslama M, Anderson AM, et al. Cervical carotid pseudo-occlusions and false dissections: intracranial occlusions masquerading as extracranial occlusions. *Stroke.* (2017) 48:774–7. doi: 10.1161/STROKEAHA.116.015427
19. Coppenrath E, Lenz O, Sommer N, Lummel N, Linn J, Treitl K, et al. Clinical significance of intraluminal contrast enhancement in patients with spontaneous cervical artery dissection: a black-blood MRI study. *Rofo.* (2017) 189:624–31. doi: 10.1055/s-0043-104632
20. Hakimi R, Sivakumar S. Imaging of carotid dissection. *Curr Pain Headache Rep.* (2019) 23:2. doi: 10.1007/s11916-019-0741-9

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 24 December 2021
doi: 10.3389/fneur.2021.706645

High-Resolution MR for Follow-Up of Intracranial Steno-Occlusive Disease Treated by Endovascular Treatment

Junjie Wang[1†], *Shun Zhang*[1,2†], *Jun Lu*[1], *Peng Qi*[1], *Shen Hu*[1], *Ximeng Yang*[1], *Kunpeng Chen*[1] *and Daming Wang*[1*]

[1] Department of Neurosurgery, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China, [2] Graduate School of Peking Union Medical College, Beijing, China

Background and Purpose: An endovascular recanalization is an alternative option for symptomatic intracranial atherosclerotic steno-occlusive disease (ICAD). Accurate non-invasive alternatives to digital subtraction angiography (DSA) for follow-up imaging after endovascular treatment are desirable. We aimed to evaluate the image quality and diagnostic performance of high-resolution magnetic imaging in follow-up using DSA as a reference.

Materials and Methods: From January 2017 to June 2021, data from 35 patients with 40 intracranial steno-occlusive lesions who underwent endovascular recanalization and received high-resolution magnetic resonance (HR-MR) follow-up were retrospectively collected in our prospective database. Studies were evaluated for the quality of visualization of the vessel lumen, restenosis rate, and accuracy of high-resolution magnetic resonance (HR-MR) with DSA used as the reference standard. Intraclass correlation coefficient (ICC) analyses were performed to assess the agreement between the two different readers.

Results: In total, 40 intracranial steno-occlusive lesions in 35 patients, with 34 lesions undergoing balloon angioplasty [including 16 drug-coated balloons (DCBs)] and 8 lesions undergoing stenting were enrolled. The median age was 63.6 years (IQR 58.5–70.0 years), and the mean imaging follow-up time was 9.5 months (IQR 4.8–12.5 months). The median degrees of preprocedural and residual stenosis were 85.0% (IQR 75.0–99.0%) and 32.8% (IQR 15.0–50.0%), respectively. Intracranial periprocedural complications occurred in 1 (3.6%) patient. In the case of a stainless-steel stent ($n = 1$), there was a signal drop at the level of the vessel, which did not allow evaluation of the vessel lumen. However, this was visible in the case of nitinol stents ($n = 7$) and angioplasty ($n = 34$). The overall restenosis rate was 25.8% ($n = 9$). The DCB subgroup showed a lower rate of restenosis than the percutaneous transluminal angioplasty (PTA) subgroup [5.3% (2/13) vs. 35.7% (5/14)].

Conclusion: High-resolution magnetic resonance may be a reliable non-invasive method for demonstrating the vessel lumen and diagnostic follow-up after endovascular

OPEN ACCESS

Edited by:
QinJian Sun,
Shandong University, China

Reviewed by:
Edgar A. Samaniego,
The University of Iowa, United States
Bu-Lang Gao,
Second Hospital of Hebei Medical University, China

****Correspondence:***
Daming Wang
dm.wang@bjhmoh.cn

[†] These authors share first authorship

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *07 May 2021*
Accepted: *15 November 2021*
Published: *24 December 2021*

Citation:
Wang J, Zhang S, Lu J, Qi P, Hu S, Yang X, Chen K and Wang D (2021) High-Resolution MR for Follow-Up of Intracranial Steno-Occlusive Disease Treated by Endovascular Treatment. Front. Neurol. 12:706645. doi: 10.3389/fneur.2021.706645

recanalization for ICAD. Compared with MR angiography (MRA), HR-MR showed a higher inter-reader agreement and could provide more information after endovascular recanalization, such as enhancement of the vessel wall.

Keywords: HR-MRI (high-resolution MRI), ICAD (intracranial artery disease), DSA (digital subtraction angiography), follow-up, endovascular recanalization

INTRODUCTION

Intracranial artery disease (ICAD) is one of the major causes of ischemic stroke and neurologic symptoms, especially in Asians (1–4). Endovascular treatment (EVT) has been an alternative option for patients refractory to medication, as it can restore blood flow and shows promise to prevent the recurrence of stroke. However, EVT for ICAD is associated with a high-restenosis rate (up to 30%), which accounts for most subsequent recurrence of ischemic events (5).

Lumenography, such as digital subtraction angiography (DSA), CT angiography (CTA), and MR angiography (MRA), has been essential and widely used in the diagnosis of ICAD and follow-up imaging (6). Among these methods, DSA is thought to be the standard criterion tool because of its superior spatial and temporal resolution (7, 8). However, it is also an invasive procedure with the risk of neurologic complications and radiation exposure (9, 10). Conventional MRA and CTA can be used as minimally invasive methods to assess intracranial stenosis, but artifacts can be a problem in the luminal evaluation compared with DSA. Accurate non-invasive alternatives to DSA for follow-up imaging after EVT are desirable.

High-resolution magnetic resonance (HR-MR) imaging has been recently introduced as a minimally invasive-advanced imaging technique for directly identifying the intracranial arterial wall (11, 12), which may correlate with luminal angiography (13–15). In the recent years, some studies have shown the feasibility of HR-MR in the evaluation and characterization of intracranial atherosclerosis and steno-occlusive lesions (12, 16, 17). However, data on follow-up after EVT based on HR-MR are limited. Therefore, we report our initial experience using HR-MR for evaluating angiographic follow-up outcomes of ICAD after EVT.

This retrospective study was approved by our institutional review board and information of the patient was anonymized and reidentified before the assessment.

METHODS

Patient Selection

The studies involving human participants were reviewed and approved by the institutional ethics committee at Beijing Hospital. The patients provided written informed consent to participate in this study. Prior to the intervention, patients gave their informed consent to the operation. Patients ($\geq$18 years) with symptomatic, intracranial high-grade stenosis (WASID $\geq$ 70%) or occlusion and elective [ipsilateral hypoperfusion ($\geq$40% decrease in cerebral blood flow in the territory distal to the target lesion in CT perfusion)] endovascular recanalization between January 2017 and June 2020 who underwent HR-MR follow-up were included in this retrospective data analysis. Patients with hyperacute (0–24 h) stroke or with asymptomatic steno-occlusive lesions and without follow-up were excluded.

Data Collection and Follow-Up Outcomes

Demographical, clinical, angiographical, and periprocedural data were collected. The primary follow-up outcomes were angiographic restenosis, ISR, and recurrent ischemic events. Restenosis or ISR was defined as >50% stenosis within or immediately adjacent (within 5 mm) to the treated segment and >20% absolute luminal loss. Symptomatic restenosis was defined as restenosis associated with ischemic symptoms of the offending vessel territory.

Strategy of Endovascular Treatment

Digital subtraction angiography was performed for all the patients and the strategy of endovascular treatment was decided according to the site and characteristics of the target lesions and based on the experience and preference of the operators. In general, drug-coated balloons (DCBs) (SeQuent Please, Braun Medical, Melsungen, Germany) with balloon predilatation were selected in lesions with tortuous arterial access or with a significant mismatch in the diameter between the proximal and distal segments or lesions in vessels with small reference diameters. Balloon dilation (BD) alone (Tazuna, Terumo, Japan; Ryujin, Terumo, Japan; Gateway, Stryker Neurovascular, USA; Sprinter, Medtronic, USA) was performed in patients with more tortuous arterial access for which DCB or stenting was considered improper by operators. Stenting (Wingspan, Stryker Neurovascular, USA; Solitaire, Medtronic, USA; Apollo, MicroPort Medical, China) was preferred in lesions with straightforward arterial access or was deployed for the treatment of dissection after balloon dilation.

Procedure and Periprocedural Management

Endovascular procedures were performed by experienced neurointerventionists with the patients under general anesthesia. Prior to the intervention, all the patients were under dual antiplatelet therapy (DATP) with aspirin and clopidogrel. An intravenous heparin regimen was administered to maintain an activated clotting time between 250 and 300 s during the procedure. A 6F-guiding catheter was introduced through the common femoral artery and guided into the ICA or VA proximal to the target lesion. The precise length and diameter of the lesion were assessed by three-dimensional (3D) DSA prior to the recanalization procedure. Under the fluoroscopic guidance, a microwire was first passed through the intracranial steno-occlusive lesion. Then, one of the three kinds of interventional

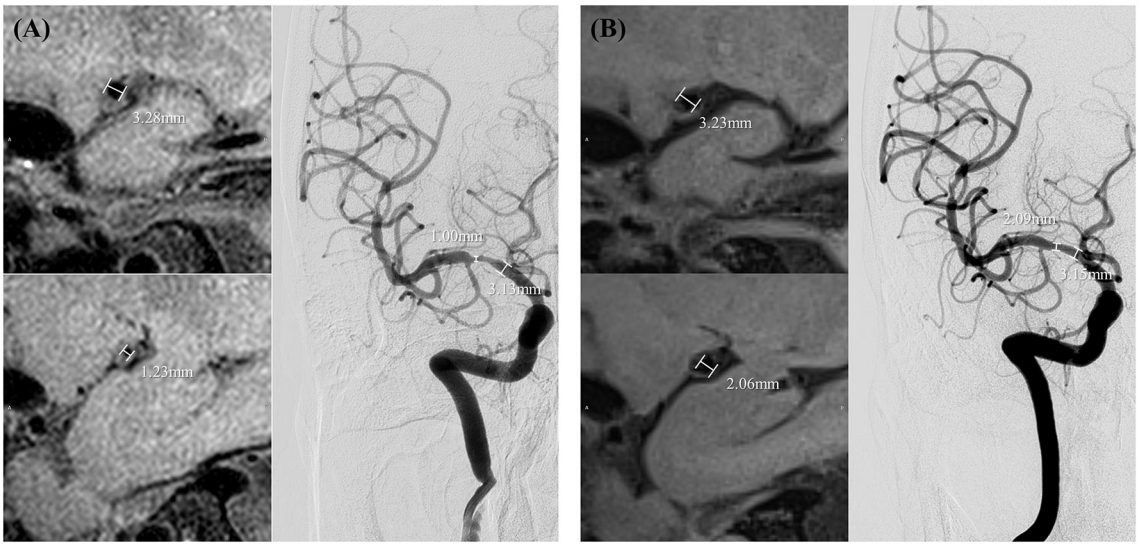


FIGURE 1 | Measurements of the degree of stenosis and minimal luminal diameter in preprocedural high-resolution magnetic resonance (HR-MR) and digital subtraction angiography (DSA) **(A)** and follow-up HR-MR and DSA **(B)**.

TABLE 1 | Characteristics of patients who underwent endovascular recanalization and received high-resolution magnetic resonance (HR-MR) follow-up.

Characteristics	Overall	DCB	PTA	Stenting
Age (years)	63.6(58.5-70.0)	62.7(58.8-69.5)	61.8(57.0-67.0)	69.8(68.0-75.5)
Gender (male)	62.9% (22/35)	56.3% (9/16)	61.5% (8/13)	83.3% (5/6)
Radiological follow-up time (months)	9.5(4.8–12.5)	9.5(6.0–12.0)	7.6(2.8–11.0)	13.5(5.8–17.8)
Pre-procedural degrees of stenosis	85% (75.0–99.0%)	80.0% (70.0–86.3%)	91.3% (85.0–99.3%)	81.8% (73.8–92.3%)
Residual degree of stenosis	32.8% (15.0–50.0%)	29.0% (15.0–40.0%)	44.0% (28.8–60.0%)	18.0% (10–18.8%)
Periprocedural complication	2.9% (1/35)	0.0% (0/16)	6.3% (1/16)	0.0% (0/8)
Restenosis	25.8% (9/35)	12.5% (2/16)	31.2% (5/16)	25.0% (2/8)
Symptomatic restenosis	2.9% (1/35)	0.0% (0/16)	0.0% (0/16)	25.0% (2/8)
Asymptomatic restenosis	20.0% (7/35)	12.5% (2/16)	31.2% (5/16)	0.0% (0/8)
Wall enhancement change				
weakened	53.6% (15/28)	75.0% (9/12)	36.4% (4/11)	40.0% (2/5)
constant	42.9% (12/28)	25.0% (3/12)	63.7% (7/11)	40.0% (2/5)
obvious	3.6% (1/28)	0.0% (0/12)	0.0% (0/11)	20.0% (1/5)

procedures (DCB, BD, and stenting) was performed based on the experience of the operators. The choice of strategy is as described earlier.

Dual antiplatelet therapy was maintained for at least 6 months and aspirin or clopidogrel alone was continued daily afterward. Long-term management of individual medical risk factors, such as blood pressure, cholesterol, and diabetes mellitus, was implemented.

Imaging Protocol

High-resolution magnetic resonance was performed with a 3.0-T MR scanner (Achieva; Philips Health care, Best, The Netherlands) with a 16-channel NV coil. The HR-MRI sequences included 3D time of flight MRA and pre and postcontrast T1W imaging (VISTA). The parameters were as follows for time-of-flight MRA: repetition time = 25 ms; echo time = 3.45 ms; field-of-view = 180 mm × 180 mm; and acquired resolution = 0.55 mm × 0.55 mm × 1.1 mm. For T1W imaging, the parameters were: repetition time = 800 ms; echo time = 18 ms; field of view = 200 mm × 180 mm × 40 mm; and acquired resolution = 0.6 mm × 0.6 mm × 0.6 mm. Gadoteric acid meglumine (Dotarem; Guerbet, Aulnay-sous-Bois, France) was intravenously injected (0.1 mmol/kg of bodyweight). T1W imaging was repeated 5 min after injection.

Digital subtraction angiography was performed in 4 vessels using a biplane system, including high-resolution 3D rotational angiography (FD20; Philips Health care, Best, The Netherlands). Transfemoral access was used, and selective injection of a contrast medium, either iohexol (350 mg

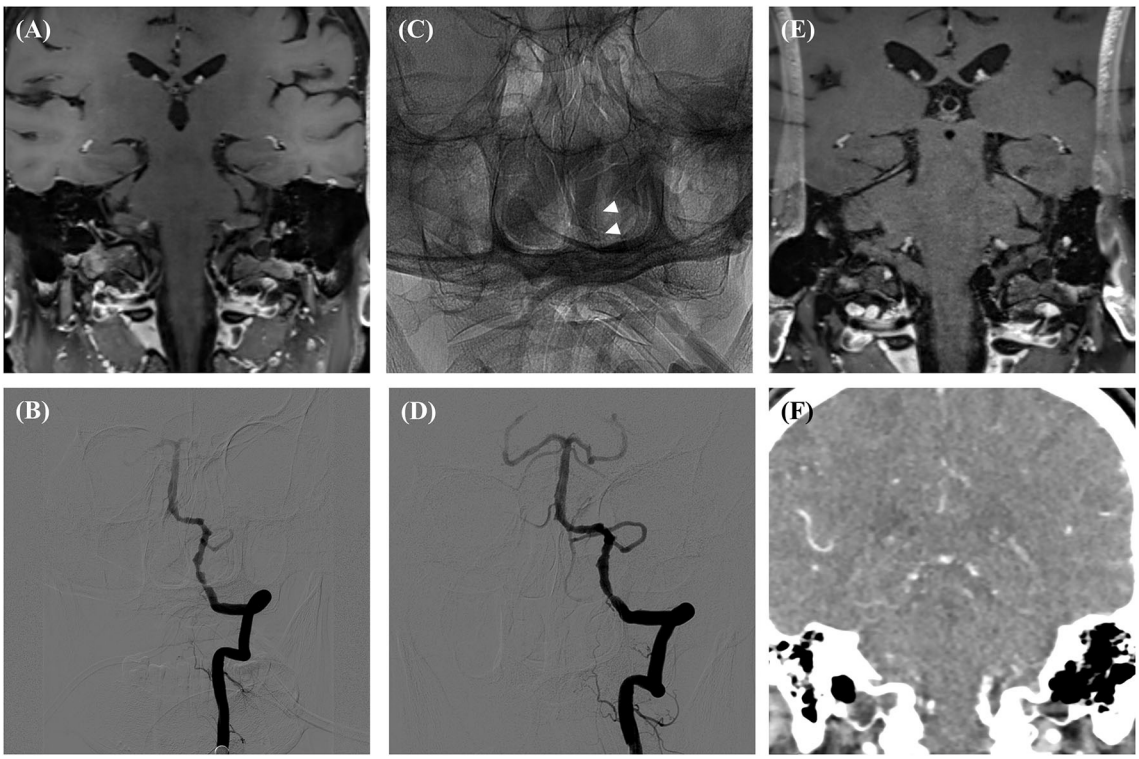


FIGURE 2 | Preprocedural HR-MR **(A)**, Preprocedural DSA **(B)**, DSA immediately after the procedure **(C,D)**, follow-up HR-MR **(E)** and CTA **(F)**. There was a signal drop at the level of the vessel in the follow-up HR-MR images. White arrows showed the Apollo stent.

of iodine/ml; Beijing Beilu Pharmaceutical Corporation, China) or iodixanol (320 mg of iodine/ml, Visipaque; GE Healthcare, USA), was performed at a rate of 4 ml (for internal carotid artery) or 3 ml (for vertebral artery) per second using an injector (Liebel-Flarsheim Angiomat Illumina, USA). The parameters were as follows: matrix, 1,024; FOV, 310 mm.

Imaging Analysis

Two neuroradiologists independently assessed images on the basis of the PACS workstation (Neusoft, Shenyang, China; version 5.5.0) for MR images and the interventional workspot (Philips Medical Systems, Best, The Netherlands; Version 1.4.1) for 3D rotational DSA data.

The image quality of HR-MR was first assessed by an experienced reviewer using a 3-point scale, where 1 = poor [low signal-to-noise (SNR) and obscured vessel wall or lumen boundaries], 2 = fair (passable SNR with a few motions or blood artifacts, distinguishable vessel wall, but partially obscured vessel lumen and wall boundaries), and 3 = good (high SNR without artifacts, clearly displaying vessel lumen boundary and wall). Images with an image quality of 1 were excluded from further analyses.

The following parameters were measured: (1) the arterial luminal diameter (i.e., stenosis diameter and reference diameter). MR data were measured manually in 0.6-mm-thick cross-sections reformatted from HR-MR and 0.6-mm-thick cross-sections from 3D tetralogy of fallot (TOF). Data of DSA were collected from 3D reconstruction of images (when 3D images were not available, data were measured manually in 2-dimensional DSA images); (2) stenosis degree (%) calculated according to the Warfarin–Aspirin Symptomatic Intracranial Disease trial criteria; (3) presence and change of wall enhancement at the site of steno-occlusive lesions in HR-MR. According to the enhancement in the follow-up images compared with the preprocedural images, the images were evaluated as: increase, little change, or less (**Figure 1**).

Statistical Analysis

Continuous variables are presented as the mean ± SD and categorical variables are reported as the frequencies (percentages), as appropriate. For continuous variables, the agreement between HR-MR and DSA was assessed by using the intraclass correlation coefficient (ICC) and the Bland–Altman analyses. The level of agreement was categorized as follows: poor (ICC = 0–0.20), fair (ICC = 0.21–0.40), moderate (ICC = 0.41–0.60), good (ICC = 0.61–0.80), and excellent (ICC = 0.81–1.00). Differences between proportions were assessed by chi-squared analysis. All the statistical analyses were performed using R Statistical Software version 3.6.2 (Foundation for Statistical Computing, Vienna, Austria). $p < 0.05$ was considered to indicate statistically significant.

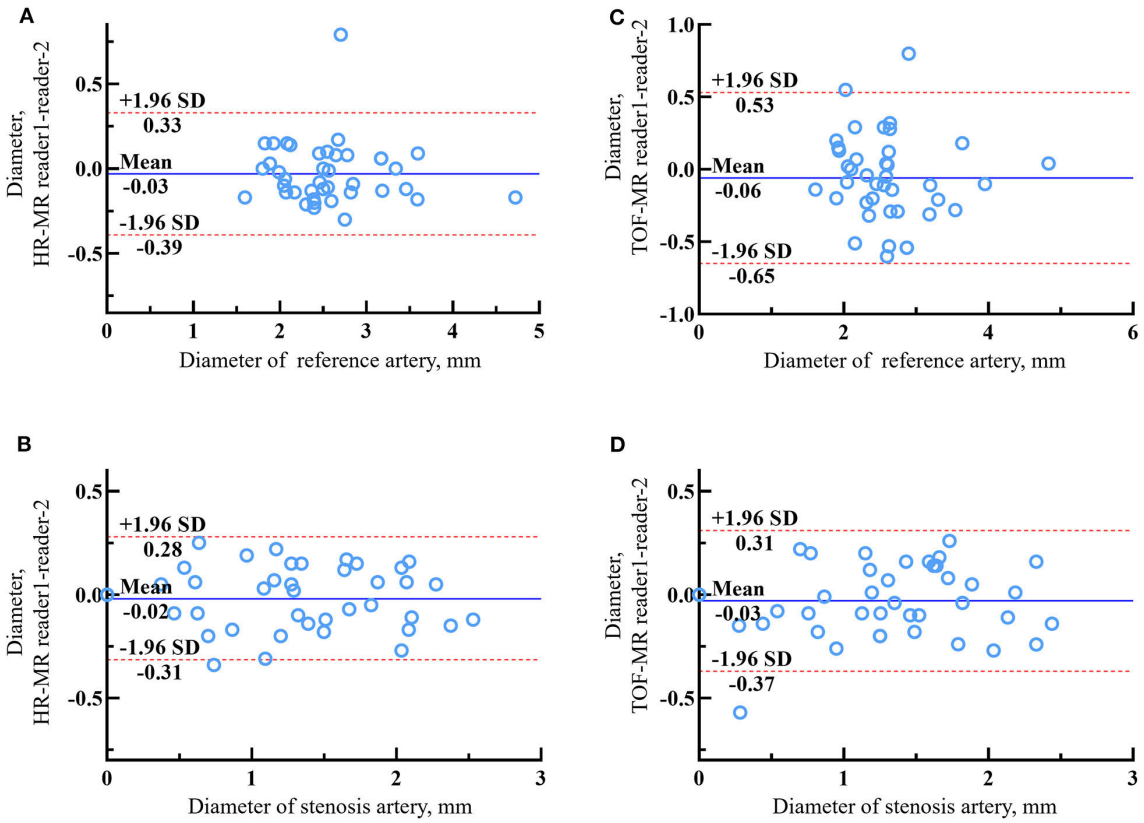


FIGURE 3 | The Bland–Altman plots of lumen diameter measurements between reader 1 and reader 2 of reference artery and stenosis artery on HR-MR images **(A,B)** and tetralogy of fallot (TOF)-MR images **(C,D)**. The solid lines represent the mean difference and the dashed lines indicate the 95% limits of agreement.

RESULTS

Patient Characteristics

Overall, 40 intracranial steno-occlusive lesions in 35 patients (22 males, 13 females; median age, 63.6 years, IQR 58.5–70.0 years), with 32 lesions undergoing balloon angioplasty (including 16 DCB) and 8 lesions undergoing stenting, were identified. Most treated lesions were located in the anterior circulation. The median preprocedural and residual degrees of stenosis were 85.0% (IQR 75.0–99.0%) and 32.8% (IQR 15.0–50.0%), respectively. In one patient, dissection of the M2 segment of the MCA with consecutive subarachnoid hemorrhage occurred during the interventional maneuver. However, the patient recovered completely from this incident. The median radiological follow-up was 9.5 months (IQR 4.8–12.5 months, range 1.8–29.0 months).

On follow-up, the overall restenosis rate was 25.8% ($n = 9$). Of these 9 patients with restenosis, 2 patients were in the stent group (25.0%, 2/8). The other 7 cases were in the angioplasty group (21.9%, 7/32). One patient in the stent group suffered from symptomatic restenosis and he received further revascularization with the insertion of another stent in the intracranial vertebral artery. The other 8 patients were asymptomatic and received medical treatment. The DCB subgroup showed a lower rate of restenosis than the percutaneous transluminal angioplasty (PTA) subgroup [12.5 (2/16) vs. 31.2% (5/16)] (**Table 1**).

Image Quality

The overall image quality for HR-MR was 2.8 ± 0.4 (1 point in 1 case, 2 points in 5 cases, and 3 points in 34 cases). In one case with a stainless-steel stent (Apollo; MicroPort Medical, Shanghai, China), there was a signal drop at the level of the vessel, which did not allow evaluation of the vessel lumen (**Figure 2**).

Inter-Reader Agreement of HR-MR and TOF-MR

In 39 lesions with sufficient image quality, two observers measured the diameter of the stenosis and reference vessel. The ICCs of the HR-MR group were 0.956 and 0.973, and the ICCs of the TOF–MRI group were 0.890 and 0.962, respectively. The Bland–Altman plots of the diameter of the stenosis and reference vessel between reader 1 and reader 2 are shown in **Figure 3**. The mean differences were −0.015 and −0.027 mm in the HR-MRI group and −0.034 and −0.061 mm in the TOF–MR group (**Table 2**).

TABLE 2 | Inter-reader agreement of arteries without total occlusion on time-of-flight magnetic resonance (TOF-MR) and HR-MR images.

Measurement methods	ICC	*P*-value	Reader 1	Reader 2	Mean difference ± SE	Limits of agreement
TOF MR						
Reference diameter	0.890	$P < 0.001$	2.574 ± 0.627	2.635 ± 0.653	−0.061 ± 0.047	−0.646, 0.525
Stenosis diameter	0.962	$P < 0.001$	1.290 ± 0.650	1.324 ± 0.626	−0.034 ± 0.027	−0.375, 0.367
HR MR						
Reference diameter	0.956	$P < 0.001$	2.563 ± 0.608	2.590 ± 0.621	−0.027 ± 0.028	−0.386, 0.332
Stenosis diameter	0.973	$P < 0.001$	1.320 ± 0.650	1.336 ± 0.657	−0.015 ± 0.024	−0.314, 0.283

Data are presented as mean eaSD. Numbers in parentheses are 95% CI.
ICC, intraclass correlation coefficient.

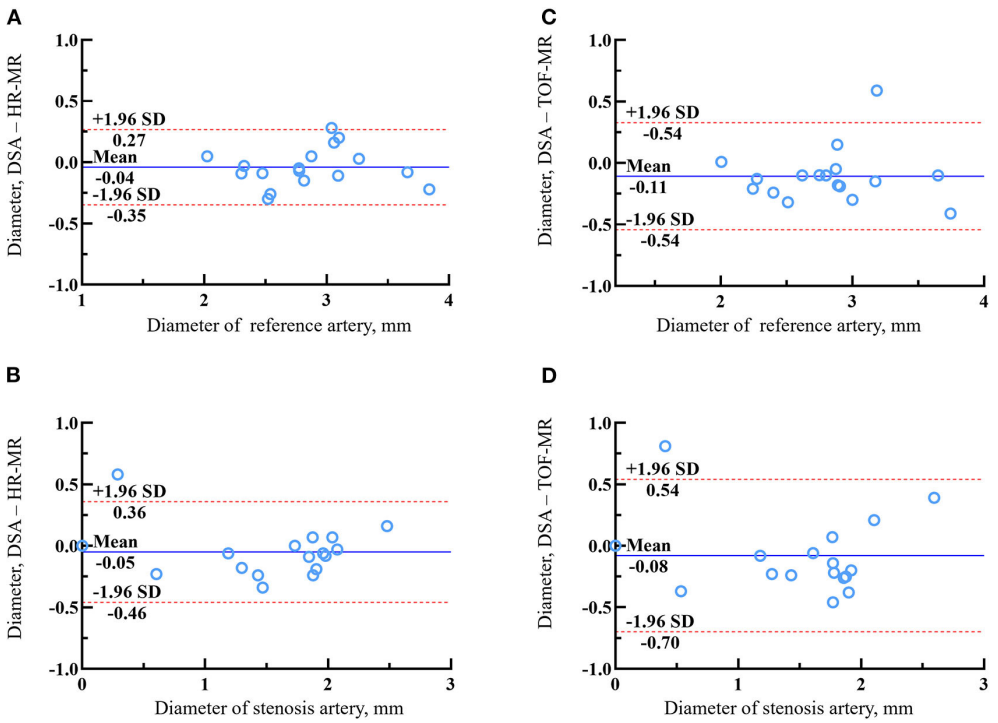


FIGURE 4 | The Bland–Altman plots of lumen diameter measurements of reference artery and stenosis artery between HR-MR images **(A,B)** or TOF-MR images **(C,D)** and DSA. The solid lines represent the mean difference and the dashed lines indicate the 95% limits of agreement.

Agreement Between HR-MR TOF-MR and DSA

Of the 40 arteries, 16 arteries were followed-up by DSA. The agreements in the quantitative measurements between HR-MR and DSA and between TOF-MR and DSA are given in **Table 3**. The Spearman correlation coefficient indicated excellent agreement for all metrics (all the coefficients ≥0.90) between HR-MR and DSA. The Bland–Altman plots of the vessel diameter between HR-MR and between DSA and TOF-MR are presented in **Figure 4**. In the HR-MR group, the absolute (relative) difference of stenosis diameter and absolute (relative) difference of reference diameter were −0.051 (3.3%) mm and −0.040 (1.4%) mm, respectively. In addition, the values were −0.083 mm (5.3%) and −0.108 mm (3.8%) in the TOF-MR group, respectively (**Table 4**).

Diagnostic Accuracy of HR-MR Imaging

Using DSA as the reference, the sensitivity; specificity; positive predictive value; negative predictive value; and accuracy of HR-MR for detecting stenosis at >50, >70%, and restenosis are presented in **Table 5**. HR-MR had a high level of sensitivity and specificity for detecting stenosis >50%, stenosis >70%, and total occlusion.

Wall Enhancement During Follow-Up

Of the 28 stenotic lesions with both the preprocedural and follow-up HR-MR images, wall enhancement was seen in 22 (78.6%) at baseline. During follow-up, the enhancement weakened in 15 lesions and remained constant in 12, but was clear in 1 case. Compared with the PTA subgroup, more lesions weakened in the DCB subgroup [75.0 (9/12) vs. 36.4% (4/11), $p = 0.06$].

DISCUSSION

This study found that HR-MR had good accuracy for the assessment of intracranial reference vessels and lesion vessels in the follow-up of patients with ICAD after EVT. The measurement results of HR-MR were highly consistent with DSA. Accurate lumen information can be provided even after most stents are placed. In addition, HR-MR can also provide tube wall images, which is helpful to further evaluate the postoperative situation. Therefore, HR-MR may be a useful imaging option comparable to DSA for the evaluation of stenosis and the detection of restenosis after EVT.

In this study, we evaluated the consistency of HR-MR between the two readers. Our results showed excellent interobserver reproducibility for the measurement of the lumen diameter of stenosis and reference vessels (ICC $>$ 0.9). At the same time, HR-MR showed good agreement (ICC $>$ 0.9) and significant correlations (Spearman R $>$0.8) with DSA regarding the degree of stenosis and the minimal luminal diameter. Using DSA as a reference, HR-MR performed a high level of sensitivity and specificity at diagnostic of stenosis. Compared with TOF-MR, HR-MR seems to have higher interobserver reproducibility and agreement with DSA. This may be because HR-MR can provide better resolution and visualize the boundaries of the vessel wall that can help readers distinguish the vascular boundaries.

High-resolution magnetic resonance may be a useful imaging method regarding the diagnosis and might also help to compensate for the limitations of luminal angiography due to the additional information beyond the luminal characterization. Atherosclerotic plaque enhancement may be associated with neovessel formation, active inflammatory cells, and fibrous cap thinning (18, 19). Several studies have reported that enhancing atherosclerotic plaque is more common in patients with ischemic symptoms or positive DWI findings, suggesting its instability and vulnerability (20–22). Antiproliferative drugs in DCBs can inhibit smooth muscle cell proliferation due to the natural immune inflammatory response (23). Recent data have shown some convincing results in reducing the restenosis rate after EVT in patients with ICAD (24–28). This study demonstrated a higher proportion of plaque enhancement weakening during follow-up in the DCB group. This may be related to the low rate of restenosis.

High-resolution magnetic resonance may have some impact on clinical practice. It may characterize the nature of the occlusion lesion and distinguish different etiologies. Furthermore, it can trace the vessel course and calibrate the distal lumen even in areas of stasis flow. This may be helpful in the therapeutic planning, guiding the selection of balloon or stent size at the occlusive segment that is invisible on DSA. HR-MR can also be used as an alternative follow-up method after EVT of ICAD due to its high accuracy for restenosis and non-radioactivity. For restenosis cases, the characteristics of the vessel wall may guide us to choose a comprehensive treatment (including lipid-lowering, anti-inflammatory, and DCB) rather than just angioplasty.

There are several limitations in this study. First, a retrospective study with a small number of cases may have resulted in

TABLE 3 | Correlation coefficient between digital subtraction angiography (DSA) and HR-MR in the different measurement metrics.

Measurement metrics	Spearman's correlation coefficient
Pre-procedural	
Luminal diameter of reference vessel	0.924
Luminal diameter of stenotic lesion	0.964
Degree of stenosis	0.936
Follow-up	
Luminal diameter of reference vessel	0.988
Luminal diameter of stenotic lesion	0.960
Degree of stenosis	0.809

TABLE 5 | Prediction performance of HR-MR in different stenosis degrees.

Stenosis degree	SEN	SPN	PPV	PNV	ACC
Stenosis >50%	1	0.86	0.75	1	0.917
Stenosis >70%	1	1	1	1	1
Restenosis	1	0.86	0.75	1	0.917

SEN, SPN, PPV, PNV, and ACC are short of sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.

TABLE 4 | Summary of agreement between TOF-MR or HR-MR images and DSA.

Measurement methods	ICC	*P*-value	Reader 1	Reader 2	Mean difference ± SE	Limits of agreement
TOF MR						
Reference diameter	0.890	$P < 0.001$	2.574 ± 0.627	2.635 ± 0.653	−0.061 ± 0.047	−0.646,0.525
Stenosis diameter	0.962	$P < 0.001$	1.290 ± 0.650	1.324 ± 0.626	−0.034 ± 0.027	−0.375,0.367
HR MR						
Reference diameter	0.956	$P < 0.001$	2.563 ± 0.608	2.590 ± 0.621	−0.027 ± 0.028	−0.386,0.332
Stenosis diameter	0.973	$P < 0.001$	1.320 ± 0.650	1.336 ± 0.657	−0.015 ± 0.024	−0.314,0.283

Data are presented as mean eaSD. Numbers in parentheses are 95% CI.
ICC, intraclass correlation coefficient.

limitations in selection bias and statistical power. The accuracy of HR-MR has yet to be confirmed by data from larger series. Second, not all follow-up images were 3D. In 2D images, the eccentricity of the stenotic lesion may have biased the lumen diameter measurement. Third, almost all the cases in this study were atherosclerotic lesions. The conclusions drawn from this series of cases are not necessarily applicable to cases of other causes, such as dissection. The imbalance of analyzed arterial segments may have led to selection bias. However, stratified analysis was not available due to the small sample size. Despite these limitations, we believe that our study reflects exploration in actual clinical practice. We hope that further research can be extended to larger samples and other diverse etiologies and apply HR-MR to the clinical prognosis field.

CONCLUSION

High-resolution magnetic resonance can provide high-resolution images of both the vessel wall and lumen. It could be a reliable non-invasive method for demonstrating the vessel lumen and diagnostic follow-up after endovascular recanalization for ICAD.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Beijing Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW and SZ reviewed the image data. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the Beijing Hospital Clinical Research 121 Project (BJ-2018-086 and BJ-2018-202), Capital's Funds for Health Improvement and Research (2020-4-4053).

REFERENCES

1. Bang OY. Intracranial atherosclerosis: current understanding and perspectives. *J Stroke.* (2014) 16:27–35. doi: 10.5853/jos.2014.16.1.27
2. Sacco RL, Boden-Albala B, Gan R, Chen X, Kargman DE, Shea S, et al. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. *Am J Epidemiol.* (1998) 147:259–68. doi: 10.1093/oxfordjournals.aje.a009445
3. Liu LH, Caplan LR, Kwan E, Beldon JR, Ke DS, Nien CK. Racial differences in ischemic cerebrovascular disease: clinical and magnetic resonance angiographic correlations of white and Asian patients. *J Stroke Cerebrovasc Dis.* (1996) 6:79–84. doi: 10.1016/S1052-3057(96)80007-3
4. Wong KS, Huang YN, Gao S, Lam WW, Chan YL, Kay R. Intracranial stenosis in Chinese patients with acute stroke. *Neurology.* (1998) 50:812–3. doi: 10.1212/WNL.50.3.812
5. Jin M, Fu X, Wei Y, Du B, Xu XT, Jiang WJ. Higher risk of recurrent ischemic events in patients with intracranial in-stent restenosis. *Stroke.* (2013) 44:2990–4. doi: 10.1161/STROKEAHA.113.001824
6. Kinoshita T, Ogawa T, Kado H, Sasaki N, Okudera T. CT angiography in the evaluation of intracranial occlusive disease with collateral circulation: comparison with MR angiography. *Clin Imaging.* (2005) 29:303–6. doi: 10.1016/j.clinimag.2005.01.030
7. Wang Y, Lou X, Li Y, Sui B, Sun S, Li C, et al. Imaging investigation of intracranial arterial dissecting aneurysms by using 3 T high-resolution MRI and DSA: from the interventional neuroradiologists' view. *Acta Neurochir (Wien).* (2014) 156:515–25. doi: 10.1007/s00701-013-1989-1
8. Leng X, Wong KS, Liebeskind DS. Evaluating intracranial atherosclerosis rather than intracranial stenosis. *Stroke.* (2014) 45:645–51. doi: 10.1161/STROKEAHA.113.002491
9. Kaufmann TJ, Huston J, Mandrekar JN, Schleck CD, Thielen KR, Kallmes DF. Complications of diagnostic cerebral angiography: evaluation of 19,826 consecutive patients. *Radiology.* (2007) 243:812–9. doi: 10.1148/radiol.2433060536
10. Chung TS, Joo JY, Lee SK, Chien D, Laub G. Evaluation of cerebral aneurysms with high-resolution MR angiography using a section-interpolation technique: correlation with digital subtraction angiography. *AJNR Am J Neuroradiol.* (1999) 20:229–35.
11. Xu WH, Li ML, Niu JW, Feng F, Jin ZY, Gao S. Intracranial artery atherosclerosis and lumen dilation in cerebral small-vessel diseases: a high-resolution MRI Study. *CNS Neurosci Ther.* (2014) 20:364–7. doi: 10.1111/cns.12224
12. Hui FK, Zhu X, Jones SE, Uchino K, Bullen JA, Hussain MS, et al. Early experience in high-resolution MRI for large vessel occlusions. *J Neurointerv Surg.* (2015) *7*:509–16. doi: 10.1136/neurintsurg-2014-011142
13. Liu Q, Huang J, Degnan AJ, Chen S, Gillard JH, Teng Z, et al. Comparison of high-resolution MRI with CT angiography and digital subtraction angiography for the evaluation of middle cerebral artery atherosclerotic steno-occlusive disease. *Int J Cardiovasc Imaging.* (2013) 29:1491–8. doi: 10.1007/s10554-013-0237-3
14. Kim YS, Lim SH, Oh KW, Kim JY, Koh SH, Kim J, et al. The advantage of high-resolution MRI in evaluating basilar plaques: a comparison study with MRA. *Atherosclerosis.* (2012) 224:411–6. doi: 10.1016/j.atherosclerosis.2012.07.037
15. Qiao Y, Anwar Z, Intrapiromkul J, Liu L, Zeiler SR, Leigh R, et al. Patterns and implications of intracranial arterial remodeling in stroke patients. *Stroke.* (2016) 47:434–40. doi: 10.1161/STROKEAHA.115.009955
16. Qiao Y, Zeiler SR, Mirbagheri S, Leigh R, Urrutia V, Wityk R, et al. Intracranial plaque enhancement in patients with cerebrovascular events on high-spatial-resolution MR images. *Radiology.* (2014) 271:534–42. doi: 10.1148/radiol.13122812
17. Wang Z, Lu M, Liu W, Zheng T, Li D, Yu W, et al. Assessment of carotid atherosclerotic disease using three-dimensional cardiovascular magnetic resonance vessel wall imaging: comparison with digital subtraction angiography. *J Cardiovasc Magn Reson.* (2020) 22:18. doi: 10.1186/s12968-020-0604-x
18. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation*. (2004) 109:Ii2–10. doi: 10.1161/01.CIR.0000129535.04194.38
19. Cai J, Hatsukami TS, Ferguson MS, Kerwin WS, Saam T, Chu B, et al. *In vivo* quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. *Circulation.* (2005) 112:3437–44. doi: 10.1161/CIRCULATIONAHA.104.528174
20. Vakil P, Vranic J, Hurley MC, Bernstein RA, Korutz AW, Habib A, et al. T1 gadolinium enhancement of intracranial atherosclerotic plaques associated

with symptomatic ischemic presentations. *AJNR Am J Neuroradiol.* (2013) 34:2252–8. doi: 10.3174/ajnr.A3606
21. Gupta A, Baradaran H, Al-Dasuqi K, Knight-Greenfield A, Giambrone AE, Delgado D, et al. Gadolinium enhancement in intracranial atherosclerotic plaque and ischemic stroke: a systematic review and meta-analysis. *J Am Heart Assoc.* (2016) 5:e003816. doi: 10.1161/JAHA.116.003816
22. Lou X, Ma N, Ma L, Jiang WJ. Contrast-enhanced 3T high-resolution MR imaging in symptomatic atherosclerotic basilar artery stenosis. *AJNR Am J Neuroradiol.* (2013) 34:513–7. doi: 10.3174/ajnr.A3241
23. Tesfamariam B. Local arterial wall drug delivery using balloon catheter system. *J Control Release.* (2016) 238:149–56. doi: 10.1016/j.jconrel.2016.07.041
24. Remonda L, Diepers M, Berberat J, Kahles T, Anon J, Nedeltchev K, et al. Drug-coated balloon treatment in symptomatic intracranial high grade stenosis : a retrospective study of 33 patients. *Clin Neuroradiol.* (2021) 31:45–9. doi: 10.1007/s00062-020-00936-9
25. Gruber P, Garcia-Esperon C, Berberat J, Kahles T, Hlavica M, Anon J, et al. Neuro Elutax SV drug-eluting balloon versus Wingspan stent system in symptomatic intracranial high-grade stenosis: a single-center experience. *J Neurointerv Surg.* (2018) 10:e32. doi: 10.1136/neurintsurg-2017-013699
26. Gruber P, Braun C, Kahles T, Hlavica M, Anon J, Diepers M, et al. Percutaneous transluminal angioplasty using the novel drug-coated balloon catheter SeQuent Please NEO for the treatment of symptomatic intracranial severe stenosis: feasibility and safety study. *J Neurointerv Surg.* (2019) 11:719–22. doi: 10.1136/neurintsurg-2018-014378
27. Han J, Zhang J, Zhang X, Zhang J, Song Y, Zhao W, et al. Drug-coated balloons for the treatment of symptomatic intracranial atherosclerosis: initial experience and follow-up outcome. *J Neurointerv Surg.* (2019) 11:569–73. doi: 10.1136/neurintsurg-2018-014237
28. Zhang J, Zhang X, Zhang J, Song Y, Zheng M, Sun L, et al. Drug-coated balloon dilation compared with conventional stenting angioplasty for intracranial atherosclerotic disease. *Neurosurgery.* (2020) 87:992–8. doi: 10.1093/neuros/nyaa191

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership