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Insights in endovascular and interventional neurology: 2021

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ORIGINAL RESEARCH
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Hemodynamic Effects of Stent-Induced Straightening of Parent Artery vs. Stent Struts for Intracranial Bifurcation Aneurysms

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Objective: This study aims to compare the hemodynamic impact of stent-mesh and stent-induced straightening of the parent artery in intracranial bifurcation aneurysms using finite element method simulation.

Material and Methods: Three intracranial bifurcation aneurysms treated with different stent-assisted coil embolization were evaluated. Simulation using the finite element method was conducted for Solitaire, LVIS and Neuroform stents. Four models of each stent were established, including a pre-treatment baseline, stenting without parent artery straightening (presented as stent-mesh effect), no-stent with parent artery reconstruction (to reveal the straightening impact), and stenting with straightening (categorized as Models I–IV respectively). Hemodynamic characteristics of the four models for each stent were compared.

Results: In the Neuroform stent, compared with the pre-treatment model (100%), the mean WSS decreased to 82.3, 71.4, and 57.0% in Models II-IV, velocity to 88.3, 74.4, and 62.8%, and high flow volume (HFV, >0.3 m/s) to 77.7, 44.0, and 19.1%. For the LVIS stent, the mean WSS changed to 105.0, 40.2, and 39.8% in Models II to IV; velocity to 91.2, 58.1, and 52.5%, and HFV to 92.0, 56.1, and 43.9%. For the Solitaire stent, compared with the pre-treatment model (100%), the mean WSS of Models II-IV changed altered by 105.7, 42.6, and 39.4%, sac-averaged velocity changed to 111.3, 46.6, and 42.8%, and HFV 115.6, 15.1, and 13.6%.

Conclusion: The hemodynamic effect of straightening the parent artery of intracranial bifurcation aneurysms by stenting was noticeably improved over stent mesh diversion in all three stents tested. Therefore stent-induced remodeling of the parent artery appears to be the best method of decreasing recurrence in intracranial bifurcation aneurysms.

Keywords: stent, straightening, hemodynamics, intracranial bifurcation aneurysms, finite element method

INTRODUCTION

Stent-assisted coil embolization can decrease the recurrence rate compared with simple coiling in intracranial aneurysms (1). However, the stent has a scaffold function and can induce angular deformation of parent arteries in the intracranial bifurcation aneurysms (2–4). It can migrate the flow impingement away from the aneurysm neck to decrease recurrence (5–7). Meanwhile, a stent with its mesh has a flow diverter effect by reducing the WSS and velocity of the aneurysm sac (8). However, the hemodynamic impact of the stent mesh vs. stent-induced straightening of the parent artery of the intracranial bifurcation aneurysm is unknown. This study aims to assess and compare the hemodynamic characteristics of stent-meshes and stent-induced straightening of parent artery in intracranial bifurcation aneurysms based on computational simulations using the high-fidelity finite element method.

MATERIALS AND METHODS

Study Design

Three intracranial bifurcation aneurysms treated with three different stent-assisted coil embolization were evaluated. Stenting methods including Solitaire, LVIS, and Neuroform were simulated using the finite element method. Four models of each stent, including pre-treatment (Model I), stenting without parent artery deformation (Model II, presented as stent-mesh effect), no-stent with parent artery reconstruction (model III) to reveal the straightening effect, and stenting with straightening (model IV) were established (**Figure 1**). Hemodynamic characteristics of the four models in each stent were compared.

Patient Description and Aneurysm Model

Three patients with intracranial bifurcation aneurysms, treated with stent-assisted coiling in real life, were included in this study. In case 1, a 66-year-old male with an unruptured small anterior communicating artery aneurysm (maximal diameter: 4.8 mm; width: 2.53 mm) was treated with a Neuroform (Stryker, Kalamazoo, Michigan, USA; size: 2.5 × 15mm) stent-assisted coiling embolization. For case 2, a 48-year-old female with a ruptured anterior communicating artery aneurysm (maximal diameter: 5.49 mm; width: 4.09 mm) was treated with LVIS (MicroVention, Tustin, CA, USA; size: 2.5 × 17mm) stent-assisted coiling. For case 3, a 57-year-old female with an unruptured A2/3 bifurcation aneurysm (maximal diameter: 6.96 mm; width: 7.22 mm) was treated with Solitaire AB (Covidien, Irvine, California; size: 4 × 20 mm) stent-assisted coiling embolization.

3D rotational angiographic images were obtained, while 3D segmentation and isolation of the region of interest were performed through the open-source software VMTK (www.vmtk.org). The segmented geometry before treatment is shown in **Figure 1**. To simplify the simulation of stenting, part of the adjacent parent artery with the aneurysm sac was isolated from the whole parent vessel using the Geomagic tool (Geomagic Inc., Morrisville, North Carolina). Our institutional review board approved this retrospective study with consent waived.

Finite-Element Method Modeling of Stent Deployment

Solitaire, LVIS, and Neuroform stents were virtually generated using SolidWorks (Dassault Systems, SolidWorks Corp., MA) and transferred into FEM software ABAQUS v6.14 (SIMULIA, Providence, RI) to perform the remodeling of the aneurysm with adjacent parent vessels.

The FEM-based workflow for stent deployment modeling was conducted in ABAQUS/Explicit v6.14, where the stent was modeled as Nitinol alloy. The material properties were obtained from literature (9–11), as shown in **Table 1**. The simulation consists of three steps: crimping, delivery, and deployment. The crimping of the stent was performed and used for the initial condition for the delivery process using the predefined field tool in ABAQUS. The delivery path was generated with central points of cross-sections of the blood vessel. Crimped stent within the microcatheter was delivered through the path to the orifice of the aneurysm as the actual delivery process during clinical treatment. The crimped stent was assembled in a microcatheter in the global coordinate system and delivered to the aneurysm orifice of the pre-treatment model through a displacement load according to the central points of the arterial wall along the delivery path. The stent was released in the next step with the predefined stress-strain field. A "general contact" algorithm in ABAQUS was used for the complex interactions during the stent delivery and deployment procedures, with a friction coefficient value of 0.15 (12).

During FEM analysis, the parent vessel was modeled as a rigid wall in no deformation models (model I and II) and deformable wall in straightened models (model III and IV). In the latter models, Mooney-Rivlin's stress-strain constitutive relationship was implemented to simulate the hyperplastic behavior of the vessel wall (13). A set of parameter values from the human cerebral artery wall were adopted, where the parameters were chosen as C1 = 0.174 MPa, C2 = 1.88 MPa (13). The cerebral arterial wall and aneurysmal wall were modeled as membrane elements with a thickness of 0.3 mm (14) and 0.2 mm (15), respectively. In the end, the surface-based aneurysm and vessel geometry model with the 3D representation of the stent were used for the subsequent CFD analysis. The exact method can be referenced in our previous study (7). The FEM simulations matched the actual stent-deployment images, including the parent artery straightening (**Figure 2**).

CFD Simulation

Computational models meshed with polyhedral grids with a size of 0.1 mm for the aneurysm and vessel and 0.03 mm for the stent using STAR-CCM+ meshing tool (CD Adapco, Melville, NY). Incompressible Navier-Stokes equations under steady flow conditions were solved with the finite volume CFD solver, STAR-CCM+. The mean flow rate for the internal carotid artery inlet was 4.6 ml/s and this was used as the inlet boundary condition (16). Traction-free boundary conditions were applied at all outlets and, the mass flow rate through each outlet vessel was set to be proportional to the cube of its diameter based on the principle of optimal work (17). With a

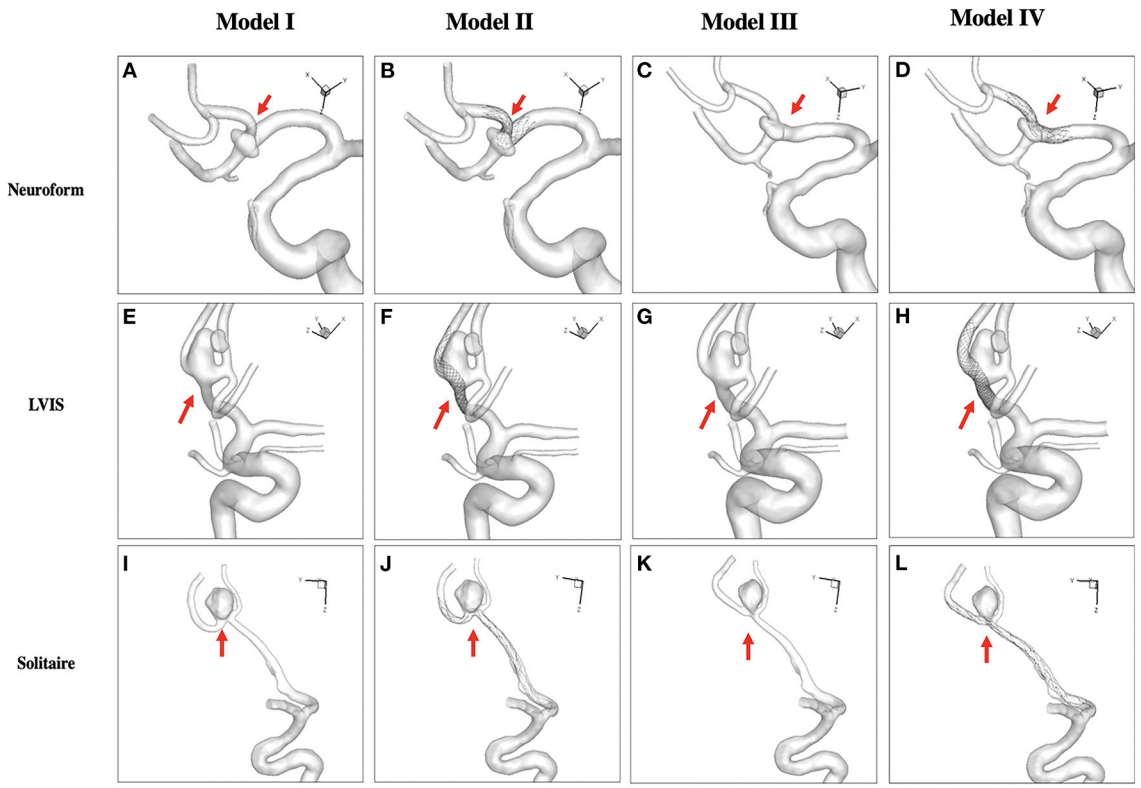

FIGURE 1 | Four models of each stent (Neuroform stent, **A-D**; LVIS stent, **E-H**; Solitaire stent, **I-L**) were simulated. Pre-treatment (Model I, **A,E,I**), stenting without straightening (Model II, **B,F,J**) presented as the stent-mesh effect, no-stent with reconstruction (Model III, **C,G,K**) to reveal the straightening effect, and stenting with straightening (Model IV, **D,H,L**) were established.

TABLE 1 | Superelastic shape-memory alloys material properties for the Auricchio/Taylor superelasticity model (9–11).

Thermoelastic properties							
E^A		E^M		ν^A		ν^M	
70 GPa		70 GPa		0.33		0.33	
Phase diagram properties							
σ^{M_s}	$\sigma_C^{M_s}$	σ^{M_f}	σ^{A_s}	σ^{A_f}	C^A	C^M	T_0
448 MPa	448 MPa	562 MPa	257 MPa	221 MPa	9.21 MPa/K	6.31 MPa/K	350 K
Transformation strain properties							
H					H_V		
4.7%					4.7%		

density of 1,056 kg/m^3 and a viscosity of 0.0035 N·s/m^2, the blood was modeled as a Newtonian fluid material (18), and the vessel walls were simulated as a rigid wall with no-slip boundary conditions (19).

Bifurcation angle was defined as the angle between the stented branch and the proximal main trunk of the aneurysm. The aneurysmal flow streamlines, iso-velocity surface (to measure high flow region around aneurysmal neck plane), and wall shear stress (WSS) were visualized for qualitative analysis. Iso-velocity surface was the surface with equal velocity. As the threshold value increased, the high flow region became focused on the aneurysm neck (**Figure 3**). In this study, the threshold value for velocity was set at 0.3 m/s. For quantitative analysis, the sac-averaged velocity, high flow volume using iso-velocity surface (>0.3 m/s), and sac-averaged WSS were calculated using the pre-treatment model as a baseline (100%).

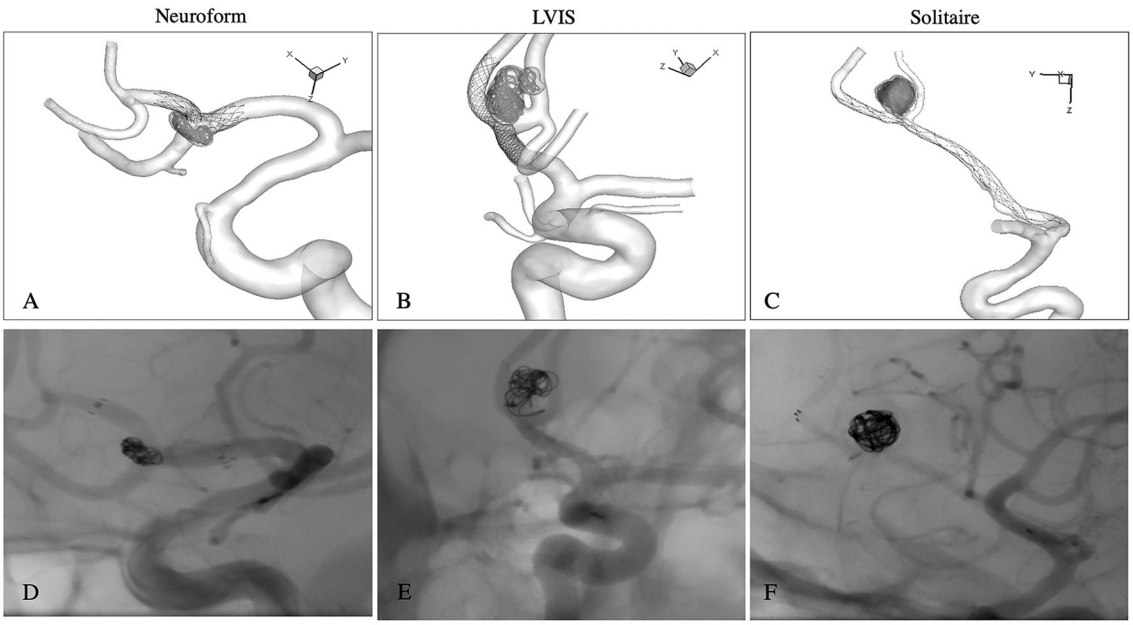

FIGURE 2 | The FEM simulations of each stent matched the actual post-operative non-subtracted DSA images, including parent artery straightening. Neuroform stent **(A,D)**; LVIS stent **(B,E)**; Solitaire stent **(C,F)**.

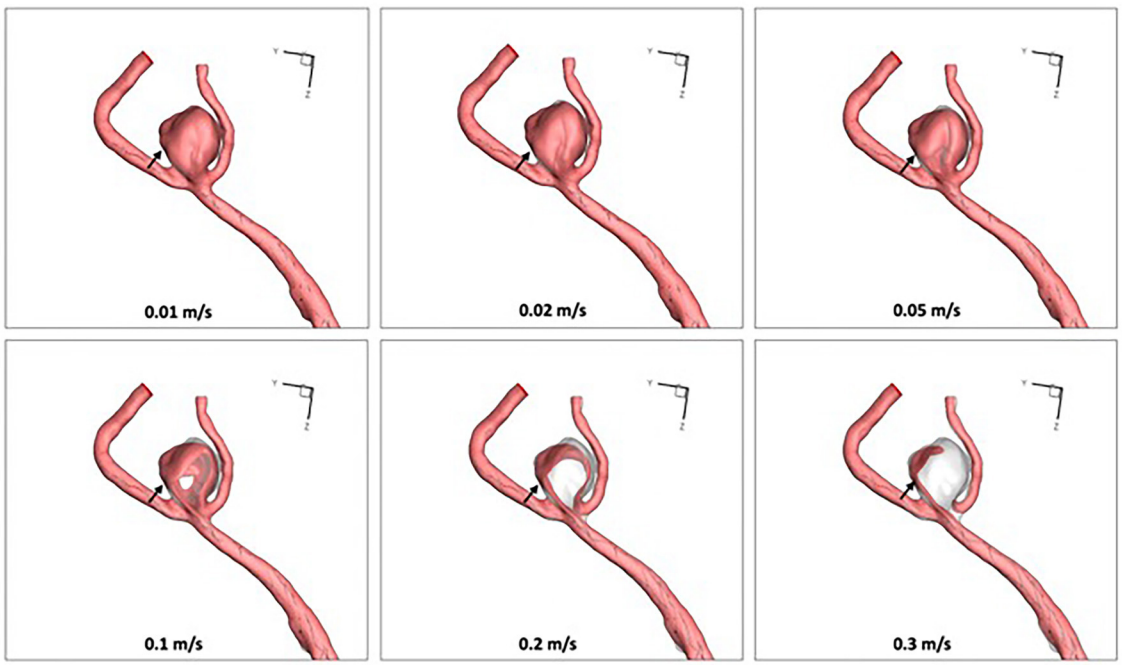

FIGURE 3 | As the threshold velocity value increased in the virtual stenting with parent artery straigtening (Model IV), the high flow region (0.3 m/s) focused on the inflow trunk of the aneurysm neck (arrows).

RESULTS

Bifurcation Angle Change

For the Neuroform stent model, the bifurcation angle change was 42.47° from pre-treatment 96.42° to post-stenting 138.89°. The aneurysm experienced no recurrence in the 20-month DSA follow-up. For the LVIS stent model, the bifurcation angle changed from 112.27 to 135.90° after stenting. Follow-up DSA after 30 months revealed no recurrence. The bifurcation change in the Solitaire stent model was most dramatic, from 58.5 to

TABLE 2 | Angular measurements and hemodynamics of four models in three different stents.

	Bifurcation angle (degrees)	WSS (Pa)	Velocity (m/s)	High flow volume (mm3)
Neuroform				
Model I	96.42	4.30 (100%)	0.180 (100%)	3.23 (100%)
Model II	96.42	3.54 (82.3%)	0.159 (88.3%)	2.51 (77.7%)
Model III	138.89	3.07 (71.4%)	0.134 (74.4%)	1.42 (44.0%)
Model IV	138.89	2.45 (57.0%)	0.113 (62.8%)	0.617 (19.1%)
LVIS				
Model I	112.27	12.72 (100%)	0.434 (100%)	51.0 (100%)
Model II	112.27	13.36 (105.0%)	0.396 (91.2%)	46.90 (92.0%)
Model III	135.90	5.11 (40.2%)	0.252 (58.1%)	28.60 (56.1%)
Model IV	135.90	5.06 (39.8%)	0.228 (52.5%)	22.4 (43.9%)
Solitaire				
Model I	58.50	9.70 (100%)	0.292 (100%)	64.2 (100%)
Model II	58.50	10.25 (105.7%)	0.325 (111.3%)	74.20 (115.6%)
Model III	168.27	4.13 (42.6%)	0.136 (46.6%)	9.67 (15.1%)
Model IV	168.27	3.82 (39.4%)	0.125 (42.8%)	8.70 (13.6%)

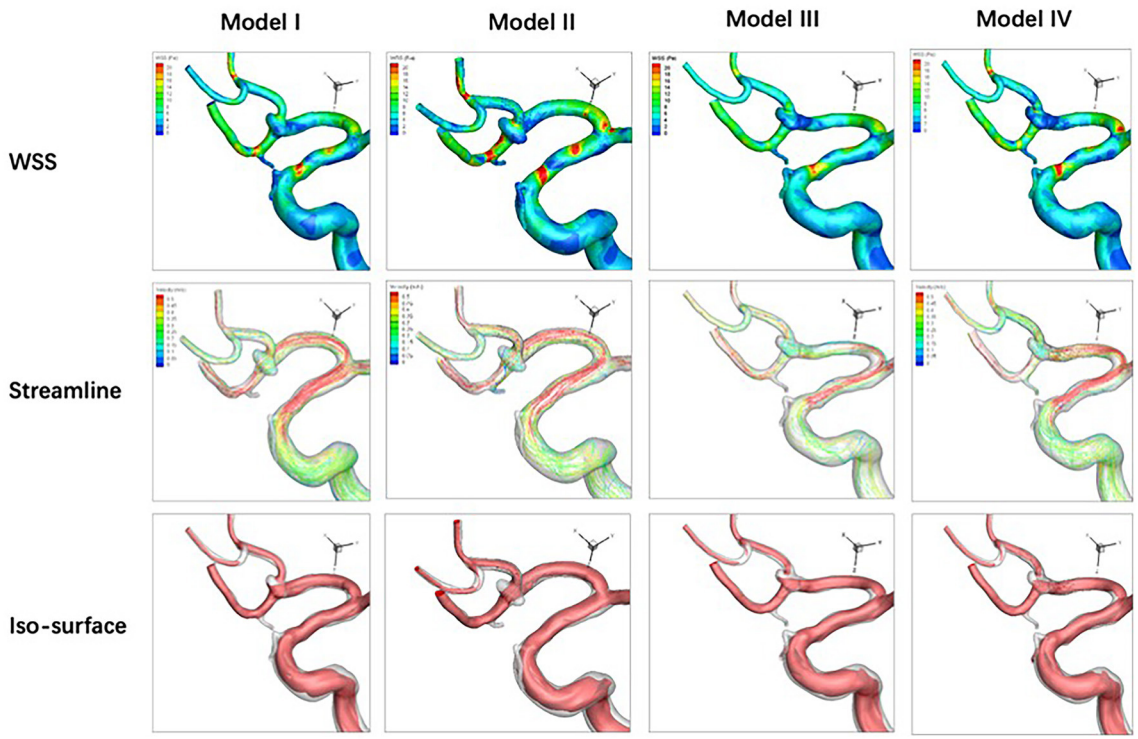

FIGURE 4 | For an anterior communicating artery aneurysm with Neuroform stenting, hemodynamic characteristics of four models are depicted. Wall shear stress, velocity, and high flow volume in Models III and IV decrease slightly compared with Models I and II.

168.27°, which almost became a side-wall aneurysm (**Table 2**). The aneurysm was not recurrent in the 10-month DSA follow-up.

Qualitative Analysis

Compared with the pre-treatment baseline (Model I), stenting with parent artery reconstruction (Model IV) in the three stents performed the best in decreasing mean WSS, velocity, and high flow volume. In LVIS and Solitaire stent groups, the WSS of stenting without parent artery reconstruction (Model II) increased compared with corresponding pre-treatment models. In the Solitaire stent, the velocity and high flow volume of Model II increased compared with Model I. In three stent groups, the

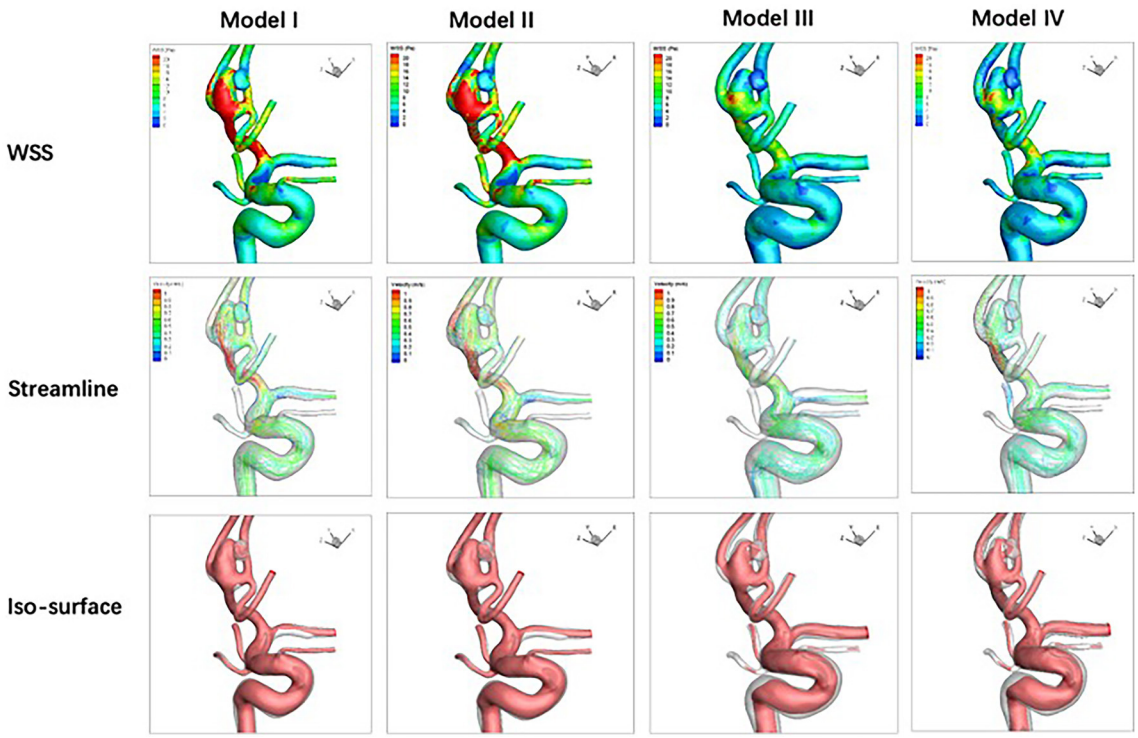

FIGURE 5 | Hemodynamic characteristics of four models are illustrated in LVIS stenting for an anterior communicating artery aneurysm with a daughter sac. Compared with Model I, wall shear stress increases, and velocity decreases while the high flow volume does not change significantly in Model II. Wall shear stress, velocity, and high flow volume in Models III and IV decreased significantly compared with Model I.

WSS, velocity, and high flow volume of Model III were lower than these of Model II (**Figures 4**-**6**).

Quantitative Analysis

For the Neuroform stent, compared with the pre-treatment model (100%), the mean WSS decreased to 82.3, 71.4, and 57.0% in models II-IV, velocity to 88.3, 74.4, and 62.8%, and HFV to 77.7, 44.0, and 19.1%. For the LVIS stent, the mean WSS changed to 105.0, 40.2, and 39.8% in models II-IV, velocity to 91.2, 58.1, and 52.5%, and HFV to 92.0, 56.1, and 43.9%. With the Solitaire stent, compared with the pre-treatment model (100%), the mean wall shear stress (WSS) of Models II-IV changed to 105.7, 42.6, and 39.4%, the sac-averaged velocity changed by 111.3, 46.6, and 42.8%, and the high flow volume (HFV, >0.3m/s) changed by 115.6, 15.1, and 13.6% (**Figure 7**).

DISCUSSION

This study simulated four models for each of three different stents to reveal the hemodynamics induced by the stent straightening effect. The hemodynamic effects of stent-induced parent artery straightening are better than the stent-mesh effect in different stent models. Hypothesized stenting without a parent artery straightening model could produce adverse effects. Fortunately, the actual stenting with the parent artery straighening model plays the best performance in modifying the aneurysm hemodynamics.

For the initiation of intracranial aneurysms, bifurcation angulation plays an important role (20–22), with Song et al. finding that a larger bifurcation angle was more prevalent on the aneurysmal branch compared with the contralateral non-aneurysmal middle cerebral artery bifurcation (23). Furthermore, intracranial aneurysm presence was associated with abnormal hemodynamics due to the abnormal bifurcation angle (23, 24). The stent-induced parent artery straightening concept has been increasingly adopted clinically to transform a bifurcation aneurysm into a sidewall aneurysm (25, 26). Stent-induced straightening of the parent artery can decrease recanalization, especially for intracranial bifurcation aneurysms (4, 26). In computational fluid dynamics, Gao et al. (6) revealed that stent-induced angular remodeling significantly altered bifurcation apex hemodynamics in a favorable direction and narrowed and migrated the flow impingement zone based on aneurysm-capped simulation. In our study, stenting after parent artery reconstruction (Model IV) directly confirmed that straightening the parent artery decreased the wall shear stress and velocity and migrate the high flow region in the aneurysm neck. Neointima formation and thrombus organization are concurrent processes during aneurysm healing (27). Conventional stents work as a scaffold for neointima formation (28). However, stent-induced straightening of the parent artery can decrease the high flow

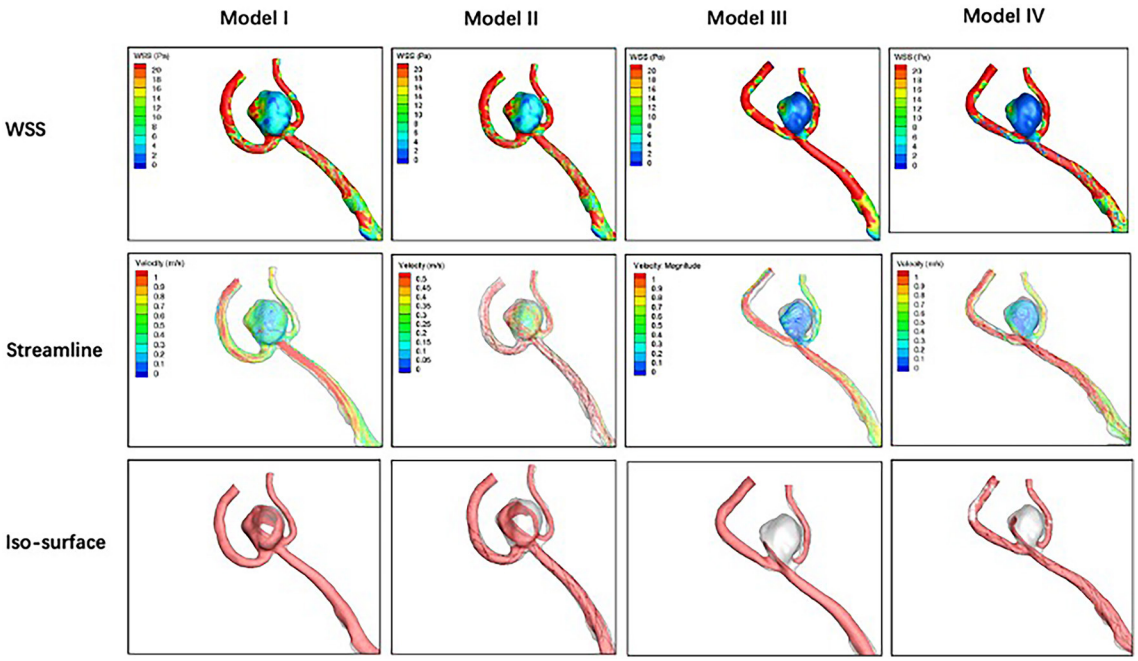

FIGURE 6 | Hemodynamic characteristics of four models for Solitaire stenting of an unruptured A2/3 bifurcation aneurysm are revealed. Velocity in Model II increased significantly while wall shear stress and high flow volume in Model II do not change significantly compared with Model I. Wall shear stress, velocity, and high flow volume in Models III and IV decreased significantly compared with Model I.

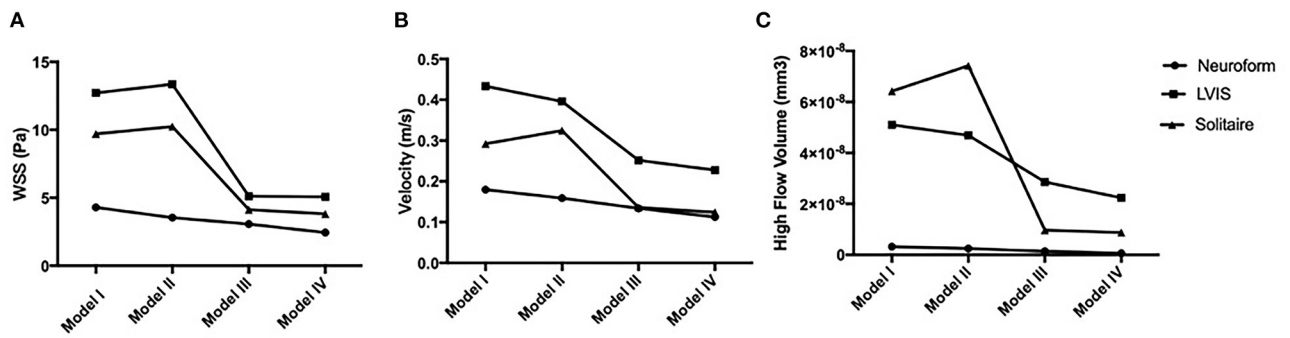

FIGURE 7 | Hemodynamic characteristics tendencies for the four models in three stents are analyzed. **(A)** Wall shear stress (WSS); **(B)** velocity (m/s); **(C)** high flow volume (mm3).

volume in the aneurysm sac, facilitating thrombus in the aneurysm sac.

Previous studies revealed that LVIS close mesh could divert flow and double LVIS induced flow diverter effect could surpass a Pipeline stent (8), although the unpredictability in overlapping stent use. In this study, the Solitaire stent-mesh size is the largest (29), indicating its weakest strut effect. However, the Solitaire stent straightened the parent artery significantly and transformed the bifurcation aneurysm into a sidewall one. The hemodynamic straightening effect increased while the parent artery angle changes increased. This study did not simulate a Pipeline stent and compared its flow diverter hemodynamic effect with straightening parent artery due to its off-label application in intracranial bifurcation aneurysms. Clinically, flow diverter embolization devices have been used in complex bifurcation aneurysms beyond the circle of Willis in some centers. However, the branch caliber reduction and asymptomatic occlusion of covered cortical branches and silent perforator stroke are not uncommon (30).

For sidewall aneurysms, a previous study demonstrated that stent struts had a dual effect on flow velocity reduction than straightening vessels (31). In contrast, our study revealed that the hypothesized stenting without straightening could generate an adverse hemodynamic impact in the bifurcation aneurysms. We theorized that the stent struts could narrow the inflow jet typically observed in bifurcation IAs and generate elevated flow inside the aneurysm sac. Jeong et al. (5) also found an adverse effect due to stenting of bifurcation aneurysms.

WSS indicates the frictional force between blood and arterial wall inner surface and can influence aneurysm initiation with high WSS (32), and ruptures with low WSS (33). A low aneurysmal WSS environment encourages inflammatory cell infiltration and has been correlated with aneurysm rupture status. Stagnant flow and excessively low WSS after stenting or flow diverter may induce focal inflammation and subsequent tissue destruction or degradation in the aneurysm dome, the usual rupture site. Low WSS accelerates unstable red thrombus formation, while high WSS facilitates stable white thrombus after stenting. The three aneurysms in this study were treated with stent-assisted coiling. Coiling may facilitate thrombus formation in the aneurysm sac before aneurysm wall degradation and rupture.

Some limitations must be noted. First, the sample is small, which needs further extensive sample studies to demonstrate. Second, we adopted several commonly used assumptions to make CFD tractable. Due to a lack of patient-specific information, we assumed a constant, location-based inlet flow rate. Inlet velocities were scaled according to the inlet diameter. This study utilized the pretreatment model as a baseline and evaluated the relative, not absolute hemodynamic change. Future studies should consider utilizing a pulsatile flow profile instead of steady-state to explore the detailed effect of vessel straightening and its impact on hemodynamics within the aneurysm.

CONCLUSION

The hemodynamic effect of straightening the parent artery induced by stenting was markedly better than that of stent mesh flow diversion in all three different stents tested. Stent-induced remodeling of the parent artery, transforming the bifurcation aneurysms into sidewall aneurysms, should decrease the recurrence rate in intracranial bifurcation aneurysms.

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 Huashan Hospital, Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XZ and JX had the idea for the article. HW and XL performed the computational fluid study. HW, LH, GL, LG, and YJ performed the literature search. HW and LH wrote the article. XZ and JX are the guarantors. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: XL and JX were employed by the company ArteryFlow Technology Co., Ltd.

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

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Plaque Characteristics in Young Adults With Symptomatic Intracranial Atherosclerotic Stenosis: A Preliminary Study

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Purpose: To determine how intracranial vascular wall and atherosclerosis plaque characteristics differ between young and old adults with sICAS.

Methods: Eighty-four consecutive patients with sICAS who underwent high-resolution magnetic resonance imaging (HRMRI) from December 2017 to July 2020 were retrospectively collected. These participants were divided into young adult group (18–50 years, $n = 28$) and old adult group (>50 years, $n = 56$). Reviewers were blinded to any clinical information and HRMRI scans were analyzed for qualitative and quantitative indicators of vascular walls and plaque at the maximal lumen narrowing site using the independent-sample *t*-test, Mann–Whitney *U*-test, chi-square test or Fisher exact test, and logistic regression analysis.

Results: Young patients with sICAS had significantly smaller maximum wall thickness (1.45 ± 0.38 vs.1.75 ± 0.51 mm^2, $P = 0.003$), higher prevalence of positive remodeling (53.57 vs. 21.43%, $P = 0.003$), and lower prevalence of diabetes mellitus (14.29 vs. 35.71%, $P = 0.04$) than old patients. Plaque burden and other plaque features were comparable between young and old patients.

Conclusion: Young patients with sICAS have smaller maximum wall thickness and greater ability to reconstruct, and are more likely to show positive remodeling, which may lead to some atherosclerotic lesions being missed. Young patients with evidence of vessel narrowing should be carefully examined for presence of high-risk atherosclerotic plaque.

Keywords: symptomatic intracranial atherosclerotic stenosis, high-resolution magnetic resonance imaging, ischemic stroke, young adult, plaque

INTRODUCTION

Symptomatic intracranial atherosclerotic stenosis (sICAS) is an important cause of ischemic stroke worldwide (1, 2). In the past, sICAS was generally reported in older individuals, but more and more young adults are being affected nowadays due to earlier appearance of traditional vascular risk factors (e.g., hypertension, diabetes, hyperlipidemia) as a result of rapid improvements in living standards (3, 4). In a recent large study from China, atherosclerosis accounted for 43.7% of ischemic strokes in young adults (5). In the young, the high risk of recurrence after a stroke and the many

ensuing years of disability and loss of productivity places a huge burden on family, society, and the economy; therefore, sICAS in the young is receiving increasing attention (6–9). However, current guidelines from the American Heart and Stroke Association and the Royal College of Physicians still have few specific recommendations for the management of stroke in young adults (10–12).

Atherosclerosis—including the formation of the atherosclerotic plaque, artery stenosis, and rupture of unstable plaque—is an important cause of ischemic stroke. Early interventions to limit the occurrence and development of atherosclerotic plaque can help prevent end-stage cerebrovascular events (13). Traditional arterial imaging techniques (such as CTA, MRA, DSA) can reveal the degree of stenosis of the affected vessels, but cannot evaluate the characteristics of atherosclerotic plaque. High-resolution MRI (HR-MRI) is increasingly being recognized as a useful modality for evaluating the characteristics of vascular wall lesions and the morphological and quantitative characteristics of plaques (14, 15). However, due to paucity of research on the topic, it is not clear whether there are differences in the characteristics of atherosclerotic plaque between young and old adults (6, 16–18). Therefore, the aim of this study was to determine whether the characteristics of intracranial vascular wall and atherosclerotic plaque differ between young and old adults and to establish the value of HR-MRI for evaluation of atheromatous plaque.

MATERIALS AND METHODS

Ethics

The study was approved by the Ethics Committee of our institution and was performed in accordance with the tenets of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Patients

The data of consecutive of patients with cerebrovascular symptoms who underwent HR-MRI at our hospital between December 2017 and July 2020 were collected from the hospital database and retrospectively analyzed. The inclusion criteria were (1) age 18–80 years; (2) clinical symptoms of classic transient ischemic attack (TIA) or ischemic stroke; (3) HR-MRI performed within 2 weeks of symptom onset; (4) at least one intracranial atherosclerotic plaque identified on HR-MRI; and (5) The clinical symptoms of TIA or ischemic stroke was attributed to plaques of atherosclerotic stenosis of intracranial portion. Classic TIA was defined as distinct focal neurologic dysfunction or monocular blindness lasting <24 h. Complete ischemic stroke was defined as one or more minor (non-disabling) completed strokes with persistence of symptoms or signs for more than 24 h (19). The exclusion criteria were (1) non-atherosclerotic intracranial artery stenosis (e.g., due to Moyamoya disease, arterial dissection, vasculitis, reversible cerebral vasoconstriction syndrome, antiphospholipid antibody syndrome, or hematological disorders.); 2) extracranial carotid artery stenosis ≥50%; (3) cardiogenic stroke; (4) incomplete clinical information or laboratory results; and (5) poor image quality. The 84 patients that met these criteria were divided into two groups according to age: a young group (18–50 years old; $n = 28$) and an old group (9) (≥50 years old; $n = 56$).

MRI Protocol

On admission, all patients underwent MRI (DWI, T1WI, T2WI, and FLAIR) on a 3.0T MR scanner (Ingenia CX, Philips Healthcare, The Netherlands) with a 32-channel neurovascular coil. HR-MRI scan was performed within 2 weeks of symptom onset. Scan included TOF-MRA angiography, BB-T1WI imaging, BB-T2WI imaging, PDWI Vista imaging, and postcontrast T1WI. The total scanning time was about 50 min. **Table 1** lists the MRI sequences and parameters.

All MRI images were transformed to semi-automatic software (tsimaging.net) and RadiAnt DICOM Viewer (version 2020.2; http://www.radiantviewer.com) for analysis. Morphology and quantitative index of intracranial plaque at the site of maximum lumen narrowing (MLN) were analyzed. First, multiplanar reformations tool in postprocessing software was used to reconstruct the postcontrast T1WI images in both long and short axes, according to the vascular orientation at the MLN site. Traditional measurements and analysis were performed on a workstation by two experienced neuroradiologists (with 12 and 6 years of experience, respectively) who were blinded to the clinical data. The inner lumen and outer wall were manually outlined at the MLN site on reconstructed postcontrast T1WI images of each patient. The reference site was the nearest plaque-free segments proximal or distal to the MLN site. Maximum wall thickness (MWT), total vessel area (TVA), and lumen area (LA) were each measured thrice, and the values were averaged. Then, wall area (WA), plaque area (PA), plaque burden (PB), degree of stenosis (DS), remodeling index (RI), and remodeling type were calculated using the following formulas:

$$\begin{aligned} \mathrm{WA} &= \mathrm{TVA} - \mathrm{LA} \\ \mathrm{PA} &= \mathrm{WA_{MLN}} - WA_{\mathrm{reference}} \\ \mathrm{PB} &= (1 - \mathrm{LA/TVA}) \times 100\% \\ \mathrm{DS} &= (1 - \mathrm{LA_{MLN}/LA_{reference}}) \times 100\% \\ \mathrm{RI} &= \mathrm{TVA_{MLN}/TVA_{reference}} \end{aligned}$$

RI ≥ 1.05 was considered as positive remodeling (PR), and RI < 1.05 as non-positive remodeling (20–23).

Intraplaque hemorrhage (IPH) was considered to be present if the T1WI signal within the plaque was ≥150% of the T1WI signal of adjacent muscle or pons (24). Eccentric stenosis was considered present if the thinnest part of the wall was <50% of the thickest point on at least one T1WI slice. Concentric stenosis

Abbreviations: CI, confidence interval; DS, degree of stenosis; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; HR-MRI, high-resolution MRI; ICC, intraclass correlation coefficient; IPH, intraplaque hemorrhage; LA, lumen area; LDL, low-density lipoprotein cholesterol; MLN, maximal lumen narrowing; MWT, maximum wall thickness; OR, odds ratio; PA, plaque area; PB, plaque burden; RI, remodeling index; sICAS, symptomatic intracranial atherosclerotic stenosis; TIA, transient ischemic attack; TVA, total vessel area; WA, wall area.

TABLE 1 | Imaging parameters for each sequence.

Imaging parameters	TR (ms)	TE (ms)	FOV (mm)	Matrix (mm)	Slice thickness (mm)	Slice gap (mm)
T1WI	2,000	20	230 × 180	480 × 480	6	1
T2WI	2,500	80	230 × 180	480 × 480	6	1
FLAIR	6,000	120	230 × 180	480 × 480	6	1
DWI	2,562	94	230 × 230	224 × 224	6	1
TOF-MRA	18	3	180 × 180	256 × 180	0.5	0
BB-T1WI	700	14	80 × 80	256 × 256	1.0	0.5
BB-T2WI	2,500	67	80 × 80	256 × 256	1.0	0.5
PDWI	2,400	17	80 × 80	256 × 256	1.0	0.5

TR, repetition time; TE, echo time; FOV, field of view.
Postcontrast T1WI was performed 5 min after the injection of a single dose (0.1 mmol/kg of body weight) of gadolinium-based contrast agent (Magnevist; Bayer HealthCare Pharmaceuticals).

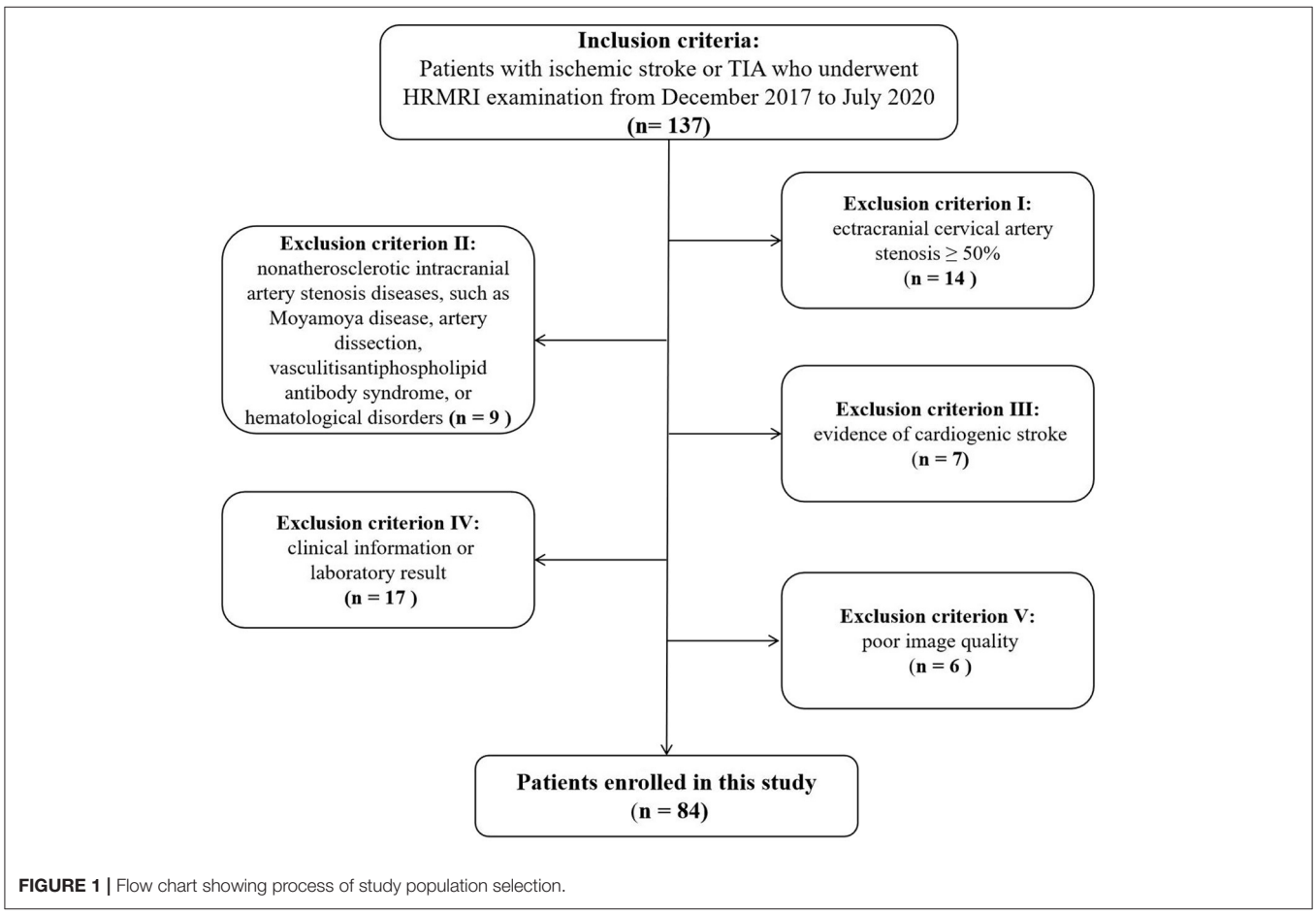

FIGURE 1 | Flow chart showing process of study population selection.

was diagnosed if the thinnest part of the wall was estimated to be no <50% of the thickest point on all image slices or a stenosis without wall thickening (22). Plaque enhancement on postcontrast T1WI was classified as "strong" if enhancement was equal to that of pituitary parenchymal enhancement or as "not strong" if enhancement was less than that of pituitary parenchymal enhancement (25). The irregular plaque surface was defined as the surface of uneven fluctuation (26) or ulceration that was identified on multicontrast MR vessel wall images with published criteria (27). Atherosclerotic plaque in the middle cerebral artery was defined as anterior circulation plaque and in the basal artery as posterior circulation plaque. The qualitative characteristics of intracranial arterial plaque were determined independently by two neuroradiologists who were blinded to the clinical data; disagreements were resolved by consensus.

Clinical Data Collection

Data were collected on age; sex; smoker; hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg); diabetes mellitus [fasting glucose ≥7.0 mmol/L,

TABLE 2 | Characteristics of patients in the two groups.

Characteristics	Young group (18–50 years, *n* = 28)	Old group (>50 years, *n* = 56)	*P*
Age (y)	39.07 ± 8.61	66.02 ± 8.96	<0.001
Males	24 (85.71)	46 (82.14)	0.679
Smoker	17 (60.71)	28 (50)	0.353
Hypertension	15 (53.57)	44 (78.57)	0.018
Systolic blood pressure (mmHg)	135.25 ± 19.86	147.57 ± 25.83	0.038
Diastolic blood pressure (mmHg)	85.21 ± 13.64	86.02 ± 15.79	0.962
Diabetes mellitus	4 (14.29)	20 (35.71)	0.040
HbA1c	5.96 ± 1.52	6.17 ± 1.17	0.023
Hyperlipemia	6 (21.43)	12 (21.43)	1.000
TC (mmol/L)	3.76 ± 1.3	3.63 ± 0.95	0.439
TG (mmol/L)	1.88 ± 1.38	1.34 ± 0.65	0.127
LDL (mmol/L)	2.02 ± 0.73	1.97 ± 0.99	0.510
HDL (mmol/L)	0.99 ± 0.23	1.08 ± 0.31	0.129
Hyperhomocysteinemia	19 (67.86)	24 (42.86)	0.031
Homocysteine (μmol/L)	31.28 ± 23.73	16.90 ± 6.38	0.023
History of coronary artery disease	3 (10.71)	8 (14.29)	0.744

Data are means ± standard deviation or n (%). P < 0.05 indicates significant difference. HbA1c, glycosylated hemoglobin; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglyceride.

random glucose ≥11.1 mmol/L, or hemoglobin A1c (HbA1c) ≥7%]; HbA1c; hyperlipidemia [total cholesterol ≥5.18 mmol/L, triglycerides ≥1.7 mmol/L, low-density lipoprotein cholesterol (LDL) ≥ 3.37 mmol/L, high-density lipoprotein cholesterol (HDL) ≤1.04 mmol/L]; hyperhomocysteinemia (homocysteine ≥15 μmol/L); history of coronary artery disease; and family history of cardiovascular disease.

Statistical Analysis

Intraclass correlation coefficient (ICC) was used to evaluate interobserver agreement in measurement of MWT, TVA, and LA, and was classified as very good ($r = 0.81$–1.00), good ($r = 0.61$–0.80), moderate ($r = 0.41$–0.60), fair ($r = 0.21$–0.40), or poor ($r < 0.20$).

Normally distributed continuous variables were expressed as means ± standard deviation and non-normally distributed continuous variables as medians (25th−75th percentiles); comparison between groups was performed using the independent sample *t*-test or the Mann–Whitney *U*-test, respectively. Categorical variables were summarized as counts and percentages and compared using the chi-square or Fisher exact test. Logistic regression (binary variable) analysis was performed to assess the differences in plaque features between young and old adults after adjusting for confounding factors, and the results were expressed by the regression slope (β) or odds ratio (OR) and corresponding 95% confidence intervals (CIs). Clinical risk factors were considered to be potential confounders when the *P*-value was <0.1 during comparison analysis between young and old adult. For all other tests, statistical significance was at $P < 0.05$. Statistical analysis was performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic Data

The flow diagram in **Figure 1** summarizes the patient selection process. A total of 84 patients (70 men; mean age, 56.6 ± 16.1 years) with sICAS were included in this study. While 51 (60.71%) patients had complete ischemic stroke (on DWI), the other 33 (39.28%) had TIA. The plaque was in the anterior circulation in 38 (45.24%) patients, and in the posterior circulation in 46 (54.76%) patients.

Of the 84 patients, 28 (33.33%) were assigned to the young adult group (22 men; mean age, 38 ± 8 years) and 56 (66.67%) patients to the old adult group (29 men; mean age, 64 ± 9 years). **Table 2** shows the characteristics of the two groups. The young group had significantly lower prevalence of hypertension (53.57 vs. 78.57%, $P = 0.018$) and diabetes mellitus (14.29 vs. 35.71%, $P = 0.04$); significantly lower mean systolic blood pressure (135.25 ± 19.86 mmHg vs. 147.57 ± 25.83 mmHg, $P = 0.038$) and HbA1c (5.96 ± 1.52% vs. 6.17 ± 1.17%, $P = 0.023$); significantly higher prevalence of hyperhomocysteinemia (67.86 vs. 42.86%, $P = 0.031$); and significantly higher mean homocysteine level (31.28 ± 23.73 μmol/L vs. 16.90 ± 6.38 μmol/L, $P = 0.023$). Prevalence of smoking, hyperlipidemia, and coronary artery disease, were similar in the two groups; mean diastolic blood pressure was also comparable between the two groups.

Plaque Characteristics

Figure 2 shows measurement of vessel plaque characteristics. Interobserver agreement in measurements of MWT, TVA, and LA was very good, with r values of 0.969 (95% CI, 0.952–980), 0.989 (95% CI, 0.982–0.993), and 0.919 (95% CI, 0.877–0.947), respectively. **Table 3** presents a comparison of plaque characteristics in the two groups. Mean MWT (1.45 ± 0.38 mm^2 vs.1.75 ± 0.51 mm^2, $P < 0.003$), TVA (12.0 ± 8.65 mm^2 vs. 14.28 ± 7.08 mm^2, $P < 0.029$), and WA (9.04 ± 5.31 mm^2 vs. 11.41 ± 5.95 mm^2, $P < 0.034$) were significantly lower in the young group than in the old group. Prevalence of PR was significantly higher in the young group (53.57 vs. 21.43%, $P < 0.003$). Prevalence of IPH was significantly lower in the young group (21.43 vs. 46.43%, $P < 0.026$).

Multivariable regression analysis revealed that MWT, PR, and prevalence of diabetes remained significantly different between young and old adult groups after adjusting for clinical confounding factors (both $P < 0.05$). MWT remained significantly lower (OR = 0.38; 95% CI: 0.002–0.635; $P = 0.023$), the prevalence of diabetes mellitus also remained significantly lower (OR = 0.173; 95% CI: 0.034–0.889; $P = 0.036$), while PR was significantly higher (OR = 5.416; 95% CI: 1.480–19.829; $P = 0.011$) in young group compared with old group. Prevalence of IPH ($P = 0.102$), hypertension ($P = 0.062$), and hyperhomocysteinemia ($P = 0.137$) were comparable between the two groups (**Table 4**).

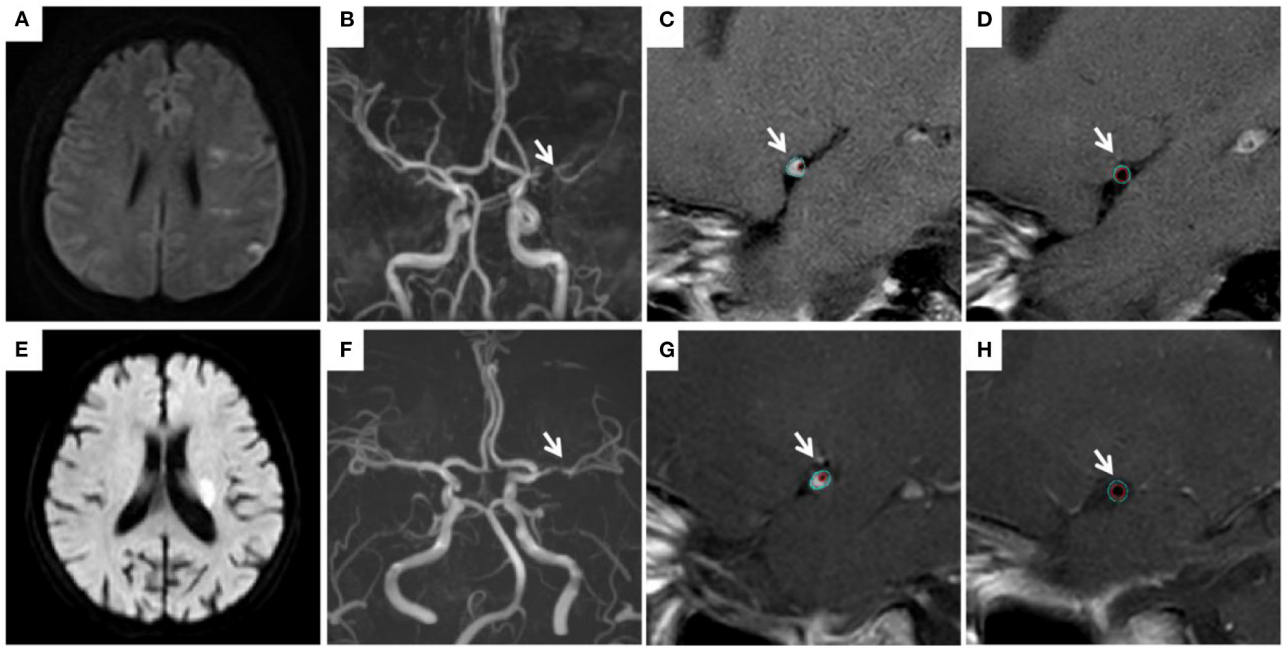

FIGURE 2 | Measurement of vessel plaque characteristics. In a young patient (31 years old) with an infarction in the left hemisphere **(A)**, left MCA stenosis **(B)** was observed. TVA was 7.81 mm^2 at the MLN site **(C)** vs. 7.10 mm^2 at the reference site **(D)**. RI is 1.1. In a old patient (68 years old) with an infarction in the left basal ganglia **(E)**, left MCA stenosis **(F)** was observed. TVA was 7.46 mm^2 at the MLN site **(G)** vs. 8.12 mm^2 at the reference site **(H)**. RI is 0.92. MCA, middle cerebral artery; MLN, maximum lumen narrowing; TVA, total vessel area; RI, remodeling index.

DISCUSSION

This study compared intracranial atherosclerotic plaque characteristics (identified with HR-MRI) and clinical factors between the young and old adult patients with sICAS and found significant differences between the two groups. Young individuals with sICAS had smaller MWT and were more likely to have PR; other plaque characteristics were similar in the two groups. Among clinical factors, diabetes mellitus was significantly less likely to be present in young patients than in old patients; other clinical factors were not significantly different between the two groups.

In this study, MWT, TVA, and WA were smaller in young patients with sICAS than in old patients but, after adjusting for potential confounders in multivariable analysis, only MWT remained significantly associated with sICAS in the young. Previous studies have also reported smaller MWT in younger patients. Cogswell et al. used 3T HR-MRI to measure internal carotid wall thickness and vessel outer wall diameter in healthy participants and found that both increase significantly with age (28). A study by de Freitas et al. (29) also showed that aging is independently related to increase in carotid intima-media thickness. The increase of MWT with age may represent the progression of atherosclerosis with age. Furthermore, instability and healing constantly alternate in atherosclerotic plaque, the repeated re-endothelialization of plaque surface and fibrosis leads to increase in MWT over time (13).

In this study, we found that PR was more likely in young patients with sICAS than in old patients. This suggests that the type of remodeling may be related to the plaque formation process. The duration of atherosclerotic plaque formation will be shorter in young patients than in old patients; because plaque development will still be in the early stage, the vessel will be more inclined to PR. However, the development of vessel tends to negative remodeling with the expand of life. Our result is consistent with reports of plaque remodeling in previous studies (30). Vessel wall compliance is better in young patients (as reflected by the lower systolic blood pressure) and so, when lumen stenosis occurs, vascular remodeling occurs more readily (31). This suggests that young patients with no stenosis or only mild stenosis, but having risk factors for early onset of large artery atherosclerosis, deserve special attention as PR may mask the presence of high-risk plaque. HR-MRI can be beneficial in such patients. In addition, PR is known to be a marker of plaque vulnerability (34), and our results showed that PR rate of young patients was higher than that of old patients, indicating that such patients had a higher incidence of vulnerable plaques, a higher risk of subsequent plaque rupture, and a higher possibility of cerebrovascular events eventually. Therefore, more attention should be paid to these patients clinically.

In the present study, young patients were found to be less likely to have diabetes mellitus than old patients; mean HbA1c was also significantly lower in young patients. It may suggests thatdiabetes mellitus has less effect on plaque' s development in young groups which has sICAS. A previous meta-analysis

TABLE 3 | Plaque features in the two groups.

Plaque features	Young group ($n = 28$)	Old group ($n = 56$)	*P*
MWT (mm)	1.45 ± 0.38	1.75 ± 0.51	0.003
TVA (mm^2)	12.0 ± 8.65	14.28 ± 7.08	0.029
LA (mm^2)	2.96 ± 5.09	2.88 ± 2.50	0.194
WA (mm^2)	9.04 ± 5.31	11.41 ± 5.95	0.034
PA (mm^2)	4.36 ± 3.57	4.59 ± 3.31	0.715
PB (%)	39.04 ± 18.43	32.43 ± 17.49	0.163
DS (%)	60.14 ± 27.97	59.09 ± 25.29	0.680
RI	0.98 ± 0.41	0.79 ± 0.38	0.042
Plaque morphology			
PR	15 (53.57)	12 (21.43)	0.003
IPH	6 (21.43)	26 (46.43)	0.026
Strong enhancement	17 (60.71)	38 (67.86)	0.516
Surface irregularity	17 (60.71)	36 (64.28)	0.749
Eccentric distribution	17 (60.71)	42 (75)	0.177
Anterior circulation	15 (53.57)	23 (41.07)	0.278

Data are means ± standard deviation or n (%). P < 0.05 indicates a significant difference. MWT, maximum wall thickness; TVA, total vessel area; LA, lumen area; WA, wall area; PA, plaque area; PB, plaque burden; DS, degree of stenosis; RI, remodeling index; IPH, intraplaque hemorrhage.

TABLE 4 | Results of multivariable regression analysis showing factors associated with sICAS in the young individual.

	OR	95% CI	*P*
MWT	0.38	0.002–0.635	0.023
TVA	1.008	0.871–1.167	0.914
WA	1.129	0.853–1.494	0.397
PR	5.416	1.480–19.829	0.011
IPH	0.305	0.073–1.268	0.102
Hypertension	0.276	0.071–1.067	0.062
Diabetes mellitus	0.173	0.034–0.889	0.036
Hyperhomocysteinemia	2.485	0.748–8.256	0.137

P < 0.05 indicates a significant difference.
OR, odds ratio; CI, confidence interval; MWT, maximum wall thickness; TVA, total vessel area; WA, wall area; PR, positive remodeling; IPH, intraplaque hemorrhage.

of 23 studies found that patients with type 2 diabetes mellitus and impaired glucose tolerance had greater carotid intima-media thickness than control patients (32). Further, Sun et al. showed that patients with high HbA1c had larger plaque burden (percent wall volume, max wall thickness) (33). This is consistent with our finding that diabetes and large MWT were less likely in young patients than in old patients.

LIMITATIONS

Our study has several limitations. First, this was a cross-sectional study with a small sample size. Second, we did not include severely disabled patients or those with severe cardiovascular disease treated with stents, pacemakers, or implantable cardioverter defibrillators; the selection bias might have affected our results. Future longitudinal studies on large samples are warranted to clarify the impact of age on plaque characteristics. Third, measurement of quantitative plaque indices is prone to subjective errors; however, we found excellent inter-reader consistency.

CONCLUSIONS

In conclusion, young patients with sICAS have smaller MWT and a greater ability for positive remodeling. Special attention is necessary to avoid missing the presence of high-risk plaque in these patients. HR-MRI appears to be a useful and reliable tool for evaluation of plaque characteristics.

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

Ethical review and approval was not required for the current study in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

AUTHOR CONTRIBUTIONS

LL and MT drafted the manuscript and designed the study. LL performed the statistical analysis. XY and JG contributed to conducting the study and revised the manuscript. MT and KA provided technical support. LL, NM, XS, YN, and YW collected the data. XZ and XL helped design the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Pre-Existing Non-Disabling Encephalomalacia Confers Risk to Stroke Outcomes After Endovascular Treatment

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Background: Patients with previous stroke episodes tend to have poor outcomes after an endovascular treatment (EVT). Encephalomalacia (EM) is an objective indicator of previous strokes but has not been systematically investigated. The fundamental aim of this exploration is to investigate the effects of a pre-existing non-disabling EM on clinical outcomes after EVT.

Methods: Consecutive patients undergoing an EVT due to the anterior circulation large vessel occlusion (LVO) strokes were enrolled in the study. The pre-existing EM was defined as the focal hypodense lesions ($\geq$ 3 mm in maximum diameter) on a non-contrast cranial CT using axial images before EVT. The primary outcome was the 90-day functional assessment using the modified Rankin Scale (mRS) score. The safety outcome was the incidence of symptomatic intracranial hemorrhage (sICH) defined as any hemorrhage within 24 h after an EVT, which is responsible for an increase of $\geq$ 4 points in the score of National Institutes of Health Stroke Scale (NIHSS).

Results: Of the 433 patients analyzed in this investigation, a pre-existing non-disabling EM was observed in 106 (24.5%) patients. After adjusting for potential confounding factors, patients with contralateral EM (OR = 2.68, 95% CI = 1.13–6.31; $P = 0.025$) and with an EM+ > 20 mm in maximum diameter (OR = 2.21, 95% CI = 1.01–4.85; $P = 0.048$) were substantially associated with unfavorable outcomes (mRS > 2). For the sICH, we did not observe any association with the pre-existing EM ($P > 0.05$).

Conclusions: A pre-existing non-disabling EM is common and safe in patients undergoing EVT. However, a contralateral EM and the large size of EM may predict an unfavorable outcome at 90 days, which should receive more attention before EVT.

Keywords: stroke, encephalomalacia, CT, recanalization, odds ratio

INTRODUCTION

Endovascular treatment (EVT) is commonly used as the standard of care treatment for patients with large vessel occlusion (LVO) in the anterior circulation stroke (1–7). However, the therapeutic effect of EVT varies greatly among individuals and the clinical outcomes are unpredictable, and more than half of the patients did not achieve functional independence (8). Further exploring the

risk factors and optimizing the patient selection strategies are of importance in clinical practice.

Several studies have shown that the history of previous strokes may predict poor outcomes in patients with LVO who are undergoing an EVT (9–11). However, the results may be confounded by the inclusion of those patients with pre-existing disability and with different levels of baseline neurological deficits. Also, most of the stroke history data provided by the families of the patients may be inaccurate, particularly for patients without a previous disabling stroke.

Encephalomalacia (EM) on non-contrast cranial CT (NCCT) may be a better alternative to stroke history. The NCCT was used as a pretreatment screening modality for almost all the thrombectomy candidates. This approach can identify EM that occurs before the acute index stroke which could provide an objective indicator of a previous brain injury (mainly strokes). However, its relationship with clinical outcomes has not yet been investigated.

Herein, we assessed the influence of a pre-existing EM on stroke consequences after an EVT in a cohort of consecutive cases with functional independence before the index stroke. The different sides, size, and number of pre-existing EM were also analyzed.

METHODS

Study Population

We retrospectively evaluated the information from patients with acute ischemic stroke undergoing an EVT from a prospectively collected database generated from May 2015 to August 2021. The treatment protocols for EVT have been described previously (12). The criteria for inclusion in this research were as follows: (1) age $\geq$ 18 years; (2) diagnosis of an acute ischemic stroke with proven proximal LVO (internal carotid artery or the M1 segment of middle cerebral artery) confirmed by digital subtraction angiography (DSA); (3) patients undergoing EVT; and (4) patients with a pre-stroke modified Rankin Scale (mRS) score $\leq$ 1.

The exclusion criteria for the study were as follows: (1) patients with blurring NCCT data or missing data before EVT; and (2) patients with multiple vessel occlusion (MVO) confirmed by DSA. The present survey was confirmed by the Ethics Committee of Yijishan Hospital. A written informed consent for EVT was acquired from all the patients or their guardians.

Identification of EM on Non-Contrast Cranial CT Before EVT

A non-contrast cranial CT (NCCT) was performed on a dual-source CT scanner (SOMATOM Definition FLASH, Siemens Healthcare, Forchheim, Germany) with a slice thickness of 5 mm. The EM was defined as focal hypodense lesions ($\geq$ 3 mm in maximum diameter) on NCCT using axial images (13, 14). We calculated the number of EM for each patient, recorded the laterality of each EM corresponding to the responsible lesion for the index stroke, and measured the maximum diameter of each EM in millimeters. In case of multiple EM, the largest maximum diameter of each patient was used for further analysis.

Baseline Clinical and Radiologic Assessment

The demographics, medical history, and other clinical data of enrolled patients were prospectively recorded. Collateral circulation was evaluated by a retrograde contrast filling of the vessels within the occluded territory on the pretreatment DSA images. The good collaterals were defined as collateral supply filling of $>$ 50% in the affected vascular area (15). A successful recanalization was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) grade of 2b or 3 (16). The symptomatic intracranial hemorrhage (sICH) was defined as any hemorrhage confirmed by CT within 24 h that was responsible for an increase of $\geq$ 4 points in the score of NIHSS according to the European Cooperative Acute Stroke Study (ECASS) criteria (17). All the brain imaging data was interpreted based on the consensus of two skilled neurologists who were blinded to the clinical data of the patients and the group assignment.

Follow-Up

The follow-up was performed by stroke neurologists through the scheduled visits or telephone interviews at 3 months following the onset of stroke. The functional outcomes were assessed using a modified Rankin Scale (mRS) score. We dichotomized the patients into favorable (mRS 0 to 2) and unfavorable outcome (mRS 3 to 6) groups.

Statistical Analysis

The categorical variables were presented as the frequencies (percentages) and were analyzed by employing a $\chi 2$ or Fisher exact assessments as appropriate. By the mean (standard deviation, SD) or median (interquartile range, IQR), continuous variables were described and respectively analyzed using the unpaired Student *t*-tests or Mann-Whitney *U*-tests as appropriate. The analysis of logistic regression was conducted to explore the predictors of clinical outcomes. All variables with $P < 0.1$ in the analysis of univariate regression were entered into a multivariable logistic regression model in which the odds ratio (OR) with 95% CIs were evaluated. The level of statistical meaningful level was set at a two-sided $P < 0.05$. The statistical assessments were executed by implementing SPSS computer program version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Of the 519 consecutive cases with anterior circulation LVO strokes processed with an EVT during the period of research, 86 cases were excluded due to the occlusion site being located at the M2 segment of the middle cerebral artery ($n = 42$), anterior cerebral artery ($n = 7$), or MVO ($n = 32$), or due to blurring or missing pretreatment imaging data ($n = 5$) (**Figure 1**). A total of 433 patients were enrolled in our study. Two patients who did not have postoperative CT scans for the analysis of sICH were discharged due to a sudden neurological deterioration. The baseline characteristics of studied patients are detailed in **Table 1** and **Supplementary Table 1**.

In the study cohort, 24.5% (106/433) of the cases were assigned to the EM+ group. In comparison with cases in the EM– group, cases in the EM+ group were considerably older (70.6 $\pm$ 10.9 vs.

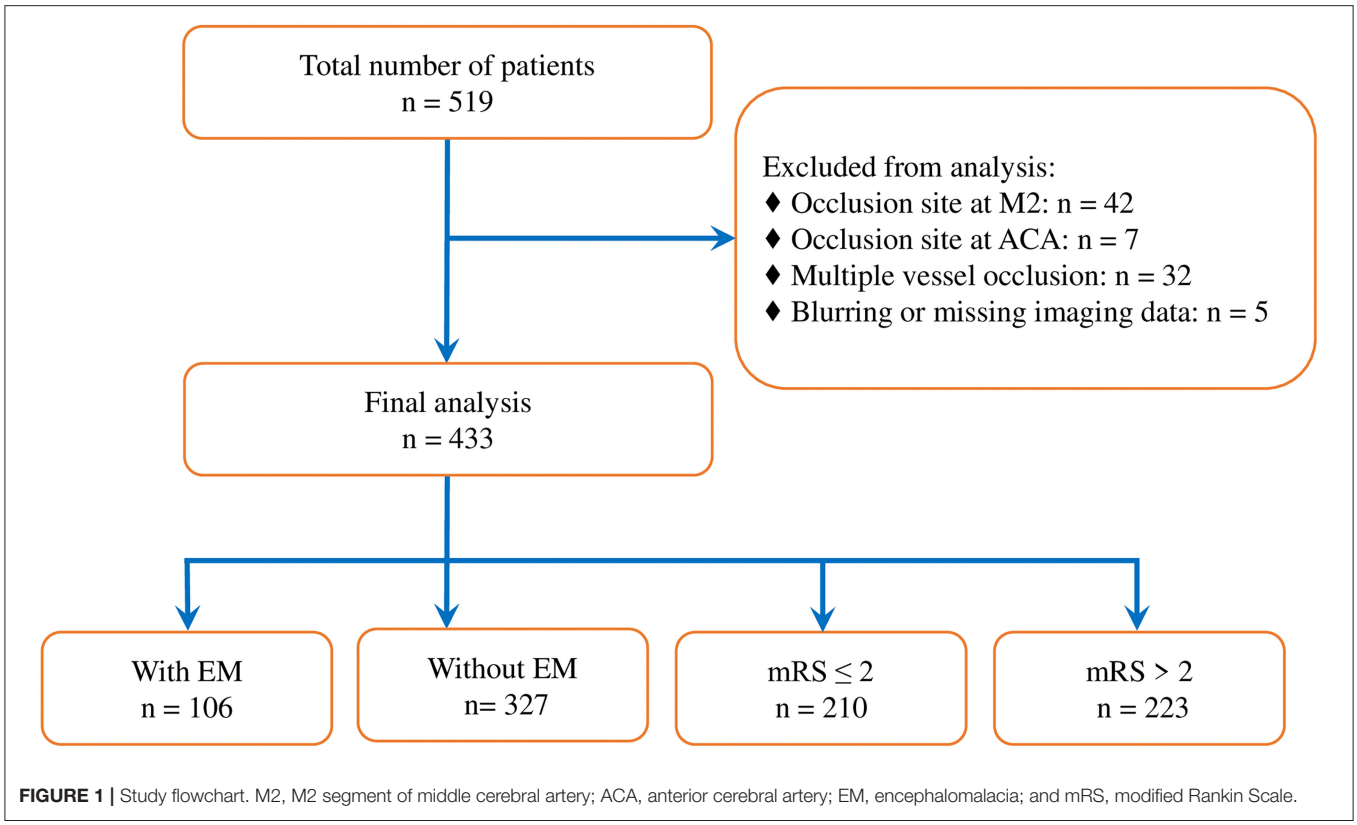

FIGURE 1 | Study flowchart. M2, M2 segment of middle cerebral artery; ACA, anterior cerebral artery; EM, encephalomalacia; and mRS, modified Rankin Scale.

67.5 ± 11.1 years; $P = 0.015$), possessed a greater rate of anti-thrombotic use (33 vs. 22.9%; $P = 0.038$), higher systolic blood pressure on admission (157 ± 23 vs. 149 ± 23 mmHg; $P = 0.004$), shorter onset to puncture time (250 vs. 290 min; $P = 0.028$), shorter procedural time (54 vs. 60 min; $P = 0.041$), higher rates of successful reperfusion (87.7 vs. 78.0%; $P = 0.028$), and lower rates of favorable outcomes (39.6 vs. 51.4%; $P = 0.035$).

The univariate assessment suggested that patients in the unfavorable outcome group demonstrated a greater rate of EM+ compared to those in the favorable outcome group (28.7 vs. 20%, $P = 0.035$; **Table 2** and **Figure 2**). A contralateral EM (corresponding to the side of index event) and a larger size EM [grouped by maximum diameter of 15 mm or 20 mm which was the usual size limit for lacunes of presumed vascular origin (13, 14)] were significantly associated with unfavorable outcomes ($P < 0.05$ for all three; **Table 2**). However, no meaningful correlation was detected between the number of EM and stroke outcomes (**Table 2**). For the sICH, no association with pre-existing EM was observed ($P > 0.05$, **Supplementary Table 1**). After adjusting for potential confounding factors (details are provided in **Supplementary Table 2**), patients with contralateral EM (OR = 2.68, 95% CI = 1.13–6.31; $P = 0.025$; **Table 3**) or with EM+ > 20 mm in maximum diameter (OR = 2.21, 95% CI = 1.01–4.85; $P = 0.048$; **Table 3**) were considerably associated with unfavorable outcomes.

DISCUSSION

Our study demonstrated that the size and the sides of a pre-existing non-disabling EM are associated with a functional outcome, whilst no significant association was observed for the number of pre-existing non-disabling EMs. Also, the presence of pre-existing, non-disabling EM did not significantly change the incidence of sICH after the EVT.

In this study, patients in the EM+ group had initial strokes with similar severity but with worse functional outcomes compared to those in the EM– group (**Table 1**). The combined findings of a shorter onset to puncture time, shorter procedure times, and a higher rate of successful recanalization in the EM+ group indicate that a pre-existing non-disabling EM may impact the patient benefit from the EVT. Older age (18, 19) and higher systolic blood pressure on admission (20, 21) in the EM+ group may in part contribute to the unfavorable outcomes. Also, we hypothesize that the structural and functional changes caused by the contralateral EM, combined with the responsible focus for index stroke, may damage the bilateral brain tissues and may impair the reserve and recovery capacity. In contrast, changes caused by the ipsilateral EM might be covered by a larger focus of the index stroke. Similarly, an increased impairment of the brain reserve and recovery capacity was made in the group of EM+ (> 20 mm in maximum diameter), resulting in a relatively poor outcome after the EVT.

Previous randomized controlled studies (4–6) reported that 11–12.4% of patients with LVO undergoing an EVT had clinical documentation of previous strokes. These data were lower than the observed incidence (24.5%) of patients with a pre-existing non-disabling EM on NCCT in our study. Imaging EM in patients with minor or silent ischemia strokes is usually ignored or unrecognized during the collection of medical history and may contribute to this difference. Leker et al. (9)

TABLE 1 | Baseline characteristics between patients with and without pre-existing encephalomalacia (EM).

Variables	EM– (*n* = 327)	EM+ (*n* = 106)	*P*
Demographic characteristics			
Age, y, mean (SD)	67.5 (11.1)	70.6 (10.9)	0.015
Female sex, *n* (%)	141 (43.1)	46 (43.4)	0.960
Medical history, *n* (%)			
Hypertension	209 (63.9)	77 (72.6)	0.099
Diabetes mellitus	42 (12.8)	20 (18.9)	0.124
Current smoking	91 (27.8)	35 (33.0)	0.307
Atrial fibrillation	164 (50.2)	59 (55.7)	0.324
Antithrombotics	75 (22.9)	35 (33.0)	0.038
Clinical data			
Admission SBP, mean (SD)	149 (23)	157(23)	0.004
Admission DBP, mean (SD)	83(14)	83(16)	0.614
Admission NIHSS, median, (IQR)	15 (12–18)	15 (12–19)	0.567
ASPECT score ≥ 6	303 (92.7)	96 (90.6)	0.486
IV-rtPA, *n* (%)	37 (11.3)	14 (13.2)	0.599
Occlusion site, *n* (%)			0.783
ICA	150 (45.9)	47(44.3)	
MCA-M1	177 (54.1)	59 (55.7)	
TOAST type, *n* (%)			0.193
LAA	99 (30.3)	30 (28.3)	
CE	184 (56.3)	68 (64.2)	
Others	44 (13.5)	8 (7.5)	
Procedure process			
OTP, median (IQR)	290 (223–347)	250 (219–316)	0.028
PT, median (IQR)	60 (42–90)	54 (38–81)	0.041
Good collaterals, *n* (%)	168 (51.4)	50 (47.2)	0.452
Procedural modes, *n* (%)			0.541
Solitaire FR first	192 (58.7)	68 (64.2)	
Inspiration first	90 (27.5)	27 (25.5)	
Others	45 (13.8)	11 (10.4)	
mTICI (2b/3), *n* (%)	255 (78.0)	93 (87.7)	0.028
Outcomes			
Sich	31 (9.5)	8 (7.6)	0.557
90-d mRS score ≤ 2	168 (51.4)	42 (39.6)	0.035

EM, encephalomalacia; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; IQR, Interquartile range; ASPECTS, the Alberta Stroke Program Early Computed Tomography Score; IV-rtPA, intravenous recombinant tissue plasminogen activator; ICA, internal carotid artery; MCA, middle cerebral artery; TOAST, Trial of Org 10172 in acute stroke treatment; LAA, large artery atherosclerosis; CE, cardioembolic; OTP, onset to puncture time; PT, procedural time; mTICI, modified Thrombolysis in Cerebral Infarction; sICH, symptomatic intracranial hemorrhage; and mRS, modified Rankin Scale.

TABLE 2 | Univariate analysis between a pre-existing encephalomalacia (EM) and a stroke outcome at 90 days.

Variables	mRS ≤ 2 (*n* = 210)	mRS > 2 (*n* = 223)	*P*
EM–	168 (80.0)	159 (71.3)	
Compared with EM–			
EM+	42 (20.0)	64 (28.7)	0.035
EM+ grouped by areas			0.011
Ipsilateral EM+	20 (9.5)	13 (5.8)	
Contralateral EM+	12 (5.7)	30 (13.5)	
EM+ on posterior circulation	3 (1.4)	6 (2.7)	
EM+ involving ≥ 2 above areas	7 (3.3)	15 (6.7)	
EM+ grouped by sizes			0.049
EM+ ≤ 15 mm in maximum diameter	19 (9.0)	21 (9.4)	
EM+ > 15 mm in maximum diameter	23 (11.0)	43 (19.3)	
EM+ grouped by sizes			0.012
EM+ ≤ 20 mm in maximum diameter	28 (13.3)	29 (13.0)	
EM+ > 20 mm in maximum diameter	14 (6.7)	35 (15.7)	
EM+ grouped by number			0.085
Number =1	31 (14.8)	43 (19.3)	
Number > 1	11 (5.2)	21 (9.4)	

EM, encephalomalacia; mRS, modified Rankin Scale.

found that previous strokes were not associated with sICH but predicted an unfavorable outcome, which is in agreement with our findings. Kang et al. (11) reported that history of stroke/TIA was the only independent predictor of unfavorable outcomes following the EVT in cases with LVO owing to a severe intracranial atherosclerotic stenosis. These observations also supported our results.

Our results extend these findings to the patients with proximal LVO, who are undergoing an EVT, showing that a pre-existing non-disabling EM on NCCT is not a rare finding. More importantly, we provided evidence that the presence of a pre-existing non-disabling EM may confer risk to unfavorable outcomes, which may enable the further development of optimized management strategies for patients undergoing EVT. In patients with a non-disabling EM detected during the routine medical checkups, even if when there is no indication of a long-term antithrombotic use for primary prevention, an improved management of vascular risk factors and a healthy lifestyle should be advocated to prevent the occurrence of stroke. All patients and their families commonly expect favorable outcomes after stroke onset. They should be prepared to accept that patients with a pre-existing contralateral EM or a large EM may have a relatively lower rate of favorable outcomes at 90 days after EVT. If EVT is performed in these patients, a close monitoring of systolic blood pressure after admission and measures to preserve collaterals should be performed as these characteristics are important predictors for the stroke outcomes (21, 22). The prevention of hypo- and hypertension (23, 24), hypovolemia (25), hyperglycemia (24), and hyperuricemia (26) should also be considered as primary targets for intervention.

There were several restrictions that should be considered when interpreting our achievements. This study was performed retrospectively at a single-center investigation with a relatively small sample size in subgroup assessment and requires further validation in prospective multi-center studies with larger sample sizes. Due to the retrospective nature of this study, we failed to investigate the clinical relevance of a pre-existing EM according to its etiology, and the incomplete data of previous stroke history was not included in this study. The identification of a pre-existing ipsilateral EM may be disturbed in patients that have an early

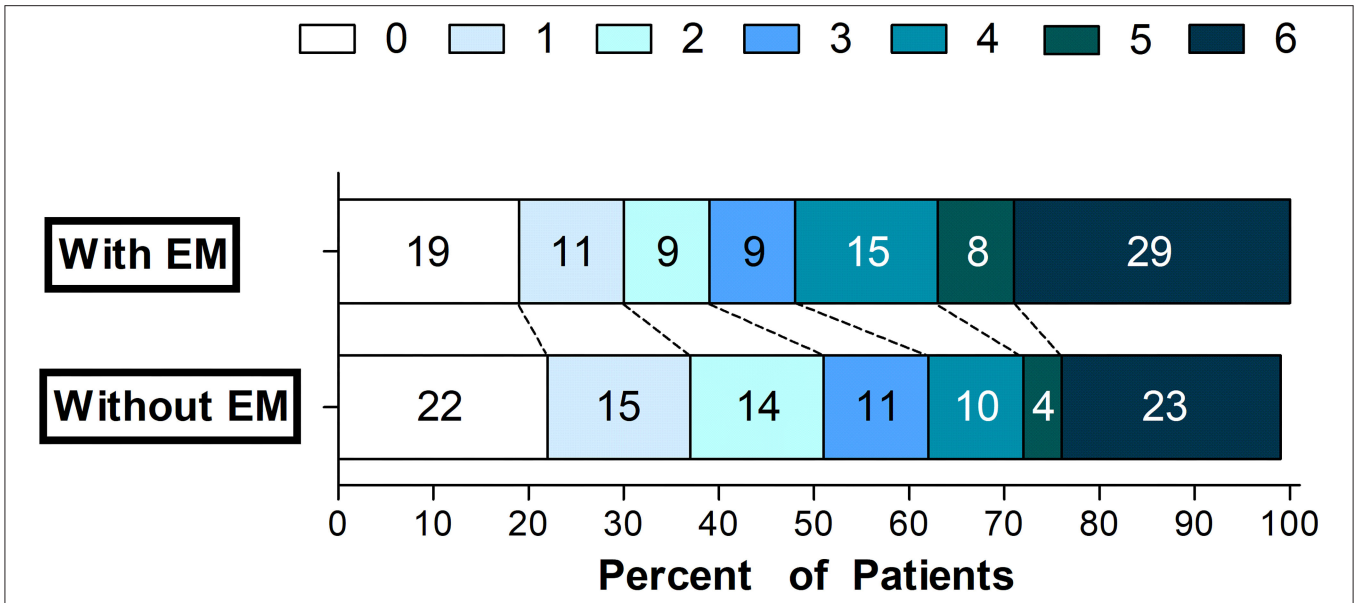

FIGURE 2 | Scores on the mRS grouped by the presence of a pre-existing encephalomalacia. EM, encephalomalacia; and mRS, modified Rankin Scale.

TABLE 3 | Multivariable logistic regression between pre-existing encephalomalacia (EM) and outcome stroke outcome at 3 months.

Variables	mRS > 2		
	Odds ratio	Confidence interval	*P*-value
Compared with EM–			
EM+	1.70	0.97–2.96	0.063
EM+ grouped by areas			0.043
Ipsilateral EM+	0.74	0.31–1.76	0.493
Contralateral EM+	2.68	1.13–6.31	0.025
EM+ on posterior circulation	4.34	0.91–20.78	0.066
EM+ involving ≥ 2 above areas	1.92	0.58–6.40	0.286
EM+ grouped by sizes			0.177
EM+ ≤ 15 mm in maximum diameter	1.64	0.71–3.76	0.244
EM+ > 15 mm in maximum diameter	1.74	0.88–3.42	0.112
EM+ grouped by sizes			0.118
EM+ ≤ 20 mm in maximum diameter	1.37	0.67–2.78	0.384
EM+ > 20 mm in maximum diameter	2.21	1.01–4.85	0.048
EM+ grouped by number			0.176
Number =1	1.73	0.92–3.27	0.091
Number > 1	1.61	0.61–4.26	0.336

EM, encephalomalacia; mRS, modified Rankin Scale.
Adjusted for age, sex, hypertension, diabetes mellitus, current smoking, atrial fibrillation, antithrombotics, admission systolic blood pressure (SBP), National Institutes of Health Stroke Scale (NIHSS) score, occlusion site, Trial of Org 10172 in acute stroke treatment (TOAST), the Alberta Stroke Program Early Computed Tomography Score (ASPECTS), procedural time (PT), collateral score, procedural modes, and modified Thrombolysis in Cerebral Infarction (mTICI).

space-occupying effect due to a large area of cerebral infarction (7.9% patients with ASPECTS < 6 in this study). The laterality of each EM, instead of the exact localization, was investigated in this study, which may affect the evaluation of neurological status. For patients with multiple pre-existing EM, the larger maximum diameter was selected for the analysis, which may have ignored the effects of the small functional lesions. However, all patients with a pre-existing EM were non-disabled in our study, which reduced the impact of the exact location and size on the evaluation of baseline neural function.

A pre-existing non-disabling EM is an objective imaging marker that is common in patients undergoing an EVT. The contralateral EM and large size of EM may predict unfavorable outcomes at 90 days and should be considered in the clinic before EVT. Larger prospective studies are warranted to validate our findings.

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 Yijishan Hospital, Wuhu, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZL, QL, and YJ designed the study, analyzed all data, and prepared the manuscript. XH and QY conceptualized the study, interpreted study data, and revised the manuscript. ZZ and SZ performed interventional procedure. ZC conducted the statistical

analysis. LM collected clinical data and image data. All authors approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.833737/full#supplementary-material

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General Anesthesia vs. Local Anesthesia During Endovascular Treatment for Acute Large Vessel Occlusion: A Propensity Score-Matched Analysis

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Objective: To date, no consensus still exists on the anesthesia strategy of endovascular treatment (EVT) for acute ischemic stroke (AIS) due to large vessel occlusion (LVO). We aimed to compare the 90-day outcomes, puncture-to-recanalization time (PRT), successful recanalization rate, and symptomatic intracranial hemorrhage (sICH) of patients undergoing general anesthesia (GA) or local anesthesia (LA) ± conscious sedation (CS) during the procedure.

Methods: We selected patients from the Acute Ischemic Stroke Cooperation Group of Endovascular Treatment (ANGEL) registry and divided them into the GA group and the LA ± CS group. The two groups underwent 1:1 matching under propensity score matching (PSM) analysis. Then, we compared the primary outcome including the 90-day modified Rankin Scale (mRS) 0–2, secondary outcome including the 90-day mRS, the 90-day mRS 0–1, the 90-day mRS 0–3, PRT, and successful recanalization rate as well as the safety outcome including sICH, any ICH, and 90-day mRS 6.

Results: Among the 705 enrolled patients, 263 patients underwent GA and 442 patients underwent LA ± CS. After 1:1 PSM according to the baseline characteristics, each group has 216 patients. Patients with GA had the higher median 90-day mRS [3 (1–5) vs. 2 (1–4), p <0.001], the lower 90-day mRS 0–2 rate (43.5 vs. 56.5%, $p = 0.007$), higher mortality (19.9 vs.10.2%, $p = 0.005$), and longer PRT [92 (60–140) vs. 70 (45–103) min, $p < 0.001$]. There were no differences in sICH and successful recanalization rate between both the groups.

Conclusion: In the real-world setting, LA ± CS might provide more outcomes benefits than GA in patients with AIS-LVO during the procedure.

Keywords: general anesthesia, local anesthesia, endovascular treatment, large vessel occlusion, propensity score matching

INTRODUCTION

Endovascular treatment (EVT) has become the standard for acute ischemic stroke (AIS) due to large vessel occlusion (LVO) (1–5). However, the most suitable anesthetic approach is still unknown. Recently, three well-known randomized controlled trials (RCTs) [Sedation vs Intubation for Endovascular Stroke Treatment (SIESTA), General or Local Anesthesia in Intra Arterial Therapy (GOLIATH), and Anesthesia During Stroke (ANSTROKE)] showed no significant difference in the outcome between different anesthetic approaches (6–8). Surprisingly, a meta-analysis of these three trials demonstrated different results; the use of protocol-based general anesthesia (GA) was significantly associated with less disability at 3 months (9). Conversely, analysis from the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaborators demonstrated an association between poor outcome and GA (10). The finding from the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trial *post-hoc* analysis supported this result (11).

In a real-world scenario, the result might be different. Hence, the objective of this study was to compare the safety and efficacy outcomes between different anesthetic approaches, mainly GA vs. local anesthesia (LA) ± conscious sedation (CS) in patients with AIS-LVO undergoing EVT using data from the prospective multicenter Acute Ischemic Stroke Cooperation Group of Endovascular Treatment (ANGEL) registry.

METHODS

Patient Population and Data Collection

We retrospectively reviewed patients from a multicenter, prospective study of the ANGEL registry from June 2015 to December 2017 (12). Inclusion criteria in this study were described as the following: (1) Age more than 18 years; (2) Clinical diagnosis of ischemic stroke in which the stroke symptoms last for more than 30 min and no improvement prior to treatment; (3) The modified Rankin Scale (mRS) less than 2 before the current stroke; (4) Large vessel occlusion in the internal carotid artery (ICA), middle cerebral artery (MCA) (M1/M2 segment), and anterior cerebral artery (ACA); and (5) Informed consent form was obtained from the patient or legally authorized representative of the patient after receiving information about data collection.

Of all the patients, we excluded 210 patients due to posterior circulation stroke ($n = 203$) and no thrombectomy procedure [only digital subtraction angiography (DSA) or fragment, $n = 7$]. Finally, we classified 705 patients with GA ($n = 263$) and LA ± CS ($n = 442$). There were 61 (8.7%) patients who received CS in this study. GA was defined as induction and maintenance with sedation drugs, analgesic agents, and muscle relaxants, with controlled ventilation under tracheal intubation or laryngeal mask, from the time of puncture to the end of the procedure. CS was defined as LA and spontaneous breathing, with administration of sedatives during the procedure. LA is defined as subcutaneous anesthesia at the arterial puncture site with or without administration of sedatives throughout the procedure (13).

We recorded the demographics, medical history, prior treatment [antiplatelet therapy and intravenous thrombolysis (IVT)], systolic blood pressure (SBP), the National Institutes of Health Stroke Scale (NIHSS) score, the Alberta Stroke Program Early CT Score (ASPECTS) (14), occlusion sites [ICA, MCA (M1, M2/M3), ACA, and tandem occlusion] (15), the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) stroke subtypes (16), procedural characteristics, and the time points of working flow of the patient. All the pretreatment imaging data, including noncontrast CT, MRI, and DSA images during EVT and follow-up CT or MRI of the head, were anonymized and reviewed centrally by two independent physicians. A consensus between the physicians was obtained to resolve any disagreements; if no agreement was achieved, then a third physician blinded to this study was introduced for a final consensus.

Outcomes

The primary functional outcome was the 90-day mRS 0–2. Meanwhile, the safety endpoints were symptomatic intracranial hemorrhage (sICH) within 24 h post hours, which was diagnosed according to the European Cooperative Acute Stroke Study (ECASS-II) (17), any ICH within 24 h post-EVT, and mortality (mRS 6). Secondary outcomes included the 90-day mRS, the 90-day mRS 0–1, the 90-day mRS 0–3, successful recanalization of the modified Tissue Thrombolysis in Cerebral Ischemia (mTICI) 2b/3, and time from puncture to recanalization (18). At 3 months after endovascular therapy, we assessed the prognoses of all the patients through telephone follow-up. The follow-up was based on a shared standardized interview protocol and centrally conducted by a third-party Clinical Research Organization (CRO) blinded to the clinical details or anesthesia method.

Statistical Analysis

We described the categorical variables as numbers and percentages. We expressed the continuous variables as median with [interquartile range (IQR)]. We use the Wilcoxon rank-sum test for continuous variables and the Pearson's chi-squared test or the Fisher's exact test for categorical variables to perform univariate analysis to find the different characteristics between the GA and LA groups. Then, we performed propensity score matching (PSM) analysis using the caliper size of 0.02 to reduce selection bias and confounding variables between the two groups at a 1:1 ratio. All the significant baseline characteristics in univariate analysis ($p < 0.05$) and the baseline variables likely to influence the outcome were in the multivariate logistic regression model to calculate the propensity score including age, SBP, the NIHSS, the ASPECTS, IVT, and antiplatelet therapy before EVT, large artery atherosclerosis (LAA) stroke subtype, cardioembolism (CE) stroke subtype, tandem lesion, occlusion location, and time from door to puncture. Following the score generation, the neighboring matching algorithm without replacement was used to match the GA group and the LA ± CS group. After PSM, we used the same statistical methods to compare the two groups. A $p < 0.05$ (two-sided) was considered as statistically significant. We used the SPSS version 25.0 (IBM Incorporation, Armonk, New York, USA) to analyze the data.

TABLE 1 | Comparison of baseline, procedure, and outcome characteristics between the two groups before PSM.

Variables/clinical findings	All Patients ($n = 705$)	GA ($n = 263$)	LA ± CS ($n = 442$)	*P*-value
Age, y, median (IQR)	64 (55–73)	65 (58–73)	64 (55–73)	0.170
Men, *n* (%)	495 (64.5)	165 (62.7)	290 (65.6)	0.441
Medical history, *n* (%)				
Hypertension	364 (51.6)	131 (49.8)	233 (52.7)	0.455
Diabetes mellitus	107 (15.2)	35 (13.3)	72 (16.3)	0.286
Atrial fibrillation	145 (20.6)	57 (21.7)	88 (19.9)	0.575
Stroke	72 (10.2)	25 (9.5)	47 (10.6)	0.632
Current smoking	237 (33.6)	87 (33.1)	150 (33.9)	0.816
Current drinking	101 (14.3)	40 (15.2)	61 (13.8)	0.606
Prior treatment, *n* (%)				
Antiplatelet therapy	150 (21.3)	72 (27.4)	78 (17.6)	**0.002**
IVT	263 (37.3)	63 (24.0)	143 (32.4)	**0.018**
Baseline measurements				
SBP, mmHg	145 (130–161)	147 (130–164)	144 (130–160)	0.287
Admission NIHSS, median (IQR)	15 (10–20)	17 (13–21)	13 (9–18)	**<0.001**
ASPECTS, median (IQR)	8 (7–8)	8 (7–8)	8 (7–8)	**0.024**
Occlusion site, *n* (%) 0.093				
ICA	285 (40.4)	113 (43.0)	172 (38.9)	
M1	333 (47.2)	128 (48.7)	205 (46.4)	
M2/3	82 (11.6)	21 (8.0)	61 (13.8)	
ACA	5 (0.7)	1 (0.4)	4 (0.9)	
Tandem occlusion	126 (17.9)	35 (13.3)	91 (20.6)	**0.015**
Stroke subtype, *n* (%)				
LAA	486 (68.9)	164 (62.4)	322 (72.9)	**0.004**
CE	144 (20.4)	71 (27.0)	73 (16.5)	**0.001**
Procedure process, *n* (%)				
GP IIb/IIIa receptor inhibitor	213 (30.2)	106 (40.3)	107 (24.2)	**<0.001**
Stent retriever	528 (74.9)	237 (90.1)	291 (65.8)	**<0.001**
Aspiration	51 (7.2)	24 (9.1)	27 (6.1)	0.135
IAT	230 (32.6)	82 (31.2)	148 (33.5)	0.528
Angioplasty	53 (7.5)	18 (6.8)	35 (7.9)	0.601
Stenting	98 (13.9)	43 (16.3)	55 (12.4)	0.147
Time intervals, min, median (IQR)				
Onset-to-door time	180 (95–270)	180 (105–255)	180 (90–278.5)	0.642
Door-to-puncture time	110 (69.5–156)	115 (74–165)	105 (57–140)	**0.007**
Onset-to-recanalization time	385 (300–505)	393.5 (301.75–487.25)	380 (296–510)	0.655
Primary outcome, *n* (%)				
90-day mRS 0–2	369 (52.3)	107 (40.7)	262 (59.3)	**<0.001**
Secondary outcomes				
90-day mRS, median (IQR)	3 (1–4)	3 (1–5)	2 (1–4)	**<0.001**
90-day mRS 0–1, *n* (%)	292 (41.4)	82 (31.2)	210 (47.5)	**<0.001**
90-day mRS 0–3, *n* (%)	465 (66.0)	146 (55.5)	319 (72.2)	**<0.001**
Puncture-to-recanalization time, median (IQR)	80 (50–112)	89.5 (60–140)	75 (50–110)	**<0.001**
Successful recanalization (mTICI 2b/3), *n* (%)	649 (92.1)	244 (92.8)	405 (91.6)	0.586
Safety outcomes, *n* (%)				
sICH	44 (6.2)	22 (8.4)	22 (5.0)	0.072
Any ICH	166 (23.5)	69 (26.2)	97 (21.9)	0.194
90-day mRS 6	110 (15.6)	56 (21.3)	54 (12.2)	**0.001**

PSM, propensity score matching; IQR, interquartile range; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; M1, middle cerebral artery M1 segment; M2, middle cerebral artery M2 segment; M3, middle cerebral artery M3 segment; ACA, anterior cerebral artery; SBP, systolic blood pressure; LAA, large artery atherosclerosis; CE, cardioembolism; IAT, intra-arterial thrombolysis; ICH, intracranial hemorrhage; sICH, symptomatic ICH; mRS, modified Rankin Scale; GA, general anesthesia; LA, local anesthesia, CS, conscious sedation. Bold values indicates statistical significance.

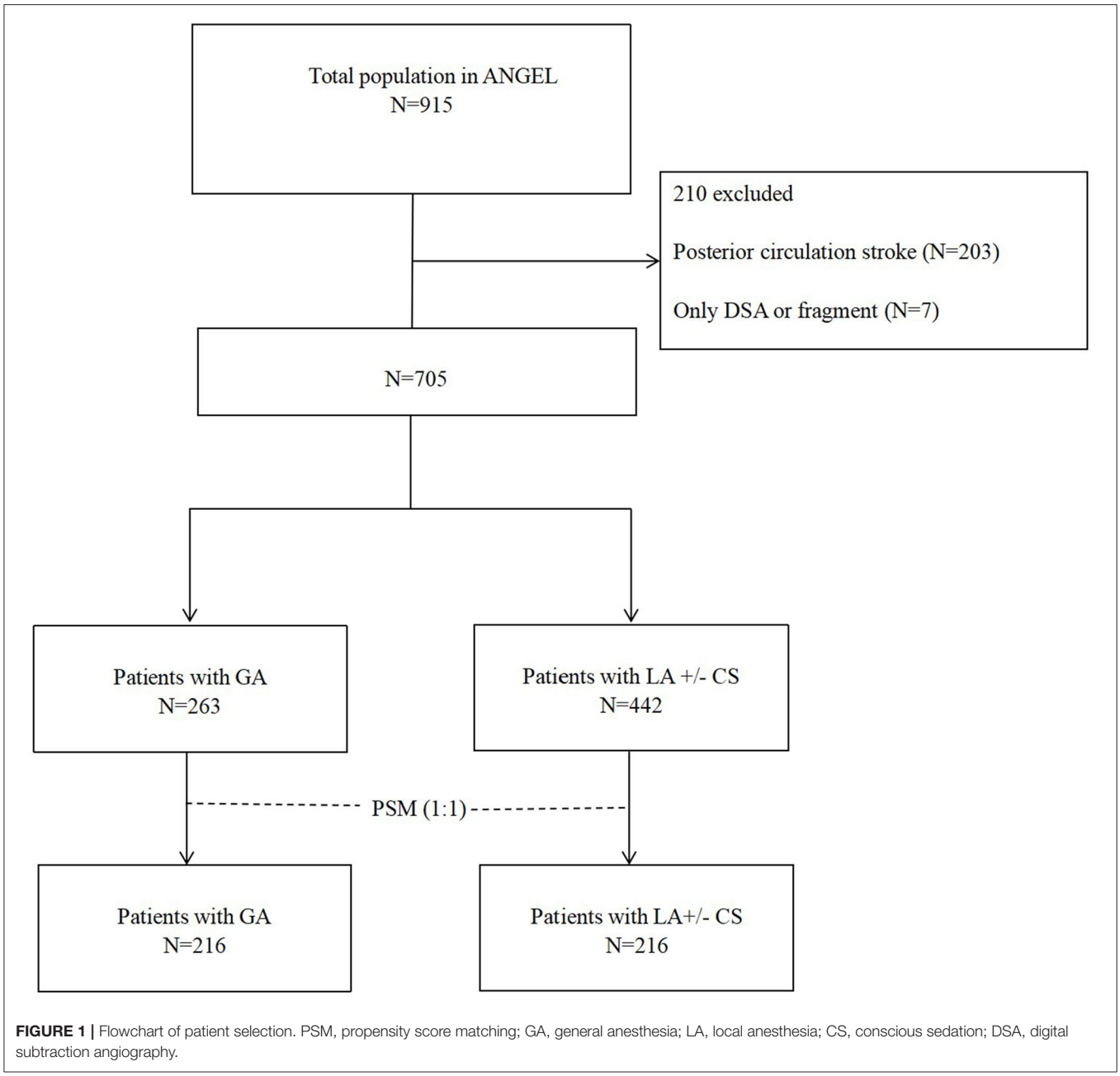

FIGURE 1 | Flowchart of patient selection. PSM, propensity score matching; GA, general anesthesia; LA, local anesthesia; CS, conscious sedation; DSA, digital subtraction angiography.

RESULTS

Table 1 shows that 705 patients with AIS in anterior circulation underwent EVT were included in this study. During EVT, 263 patients received GA and 442 patients received LA (**Figure 1**). Antiplatelet therapy was significantly different before EVT, IVT before EVT, the admission NIHSS, the admission ASPECTS, tandem occlusion, LAA subtype, CE subtype, and time from door to puncture between the two groups. Compared to the LA ± CS group, patients in the GA group had the higher median NIHSS, the longer median time from door to puncture, and the median ASPECTS. Besides antiplatelet therapy and CE subtype, IVT before EVT, LAA subtype, and tandem occlusion occurred less frequently in the GA group.

Table 2 shows that 216 patients in each group were matched 1:1 according to the baseline characteristics. After PSM, the covariates were statistically similar between the two groups. The proportion of patients receiving antiplatelet therapy (25.5 vs. 28.2%, $p = 0.515$) and IVT (28.2 vs. 29.6%, $p = 0.750$) before EVT in the GA group was similar to the LA ± CS group. There was no significant difference in tandem occlusion (14.8 vs. 13.9%, $p = 0.784$), LAA subtype (67.1 vs. 47.3%, p

TABLE 2 | Comparison of baseline, procedure, and outcome characteristics between the two groups after PSM.

Variables/clinical findings	All patients (*n* = 432)	GA (*n* = 216)	LA ± CS (*n* = 216)	*P*-value
Age,y, median (IQR)	64 (55–73)	64 (56–73)	63 (54–74.8)	0.472
Men, *n* (%)	277 (64.1)	137 (63.4)	140 (64.8)	0.763
Medical history, *n* (%)				
Hypertension	217 (105)	105 (48.6)	112 (51.9)	0.501
Diabetes mellitus	69 (16.0)	31 (14.4)	38 (17.6)	0.358
Atrial fibrillation	92 (21.3)	41 (19.0)	51 (23.6)	0.240
Stroke	44 (10.2)	20 (9.3)	24 (11.1)	0.525
Current smoking	155 (35.9)	78 (36.1)	77 (35.6)	0.920
Current drinking	62 (14.4)	36 (16.7)	26 (12.0)	0.170
Prior treatment, *n* (%)				
Antiplatelet therapy	116 (26.9)	55 (25.5)	61 (28.2)	0.515
IV thrombolysis	125 (28.9)	61 (28.2)	64 (29.6)	0.750
Baseline measurements, median (IQR)				
Systolic blood pressure, mmHg	146 (130–162)	148.5 (130.0–163.5)	145.5 (130.0–162.0)	0.738
Admission NIHSS	16 (13–21)	16 (13–21)	16 (13–22)	0.589
ASPECTS, median	8 (7–8)	8 (7–8)	8 (7–8)	0.523
Occlusion site, *n* (%)				
ICA	174 (40.3)	94 (43.5)	80 (37.0)	0.163
M1	205 (47.5)	102 (47.2)	103 (47.7)	
M2/3	51 (11.8)	19 (8.8)	32 (14.8)	
ACA	2 (0.5)	1 (0.5)	1 (0.5)	
Tandem occlusion	62 (14.4)	32 (14.8)	30 (13.9)	0.784
TOAST, *n* (%)				
LAA	275 (63.7)	145 (67.1)	130 (47.3)	0.134
CE	100 (23.1)	50 (23.1)	50 (23.1)	1.000
Procedure process, *n* (%)				
GP IIb/IIIa receptor inhibitor	147 (34.0)	83 (38.4)	64 (29.6)	0.054
Stent retriever	357 (82.6)	192 (88.9)	165 (76.4)	**0.001**
Aspiration	40 (9.3)	20 (9.3)	20 (9.3)	1.000
IA thromblysis	118 (27.3)	73 (33.8)	45 (20.8)	0.002
Angioplasty	40 (9.3)	18 (8.3)	22 (10.2)	0.507
Stenting	69 (16.0)	38 (17.6)	31 (14.4)	0.358
Time intervals, min, median (IQR)				
Onset-to-door time	160 (90–255)	170 (90.5–241.0)	154.0 (87.8–266.0)	0.510
Door-to-puncture time	106 (60.8–150)	110 (60–145)	104.5 (65.0–150.0)	0.669
Onset-to-recanalization time	374.5 (284.5–470)	397 (300–487)	360 (277–460)	**0.012**
Primary outcome, *n* (%)				
90-day mRS 0–2	216 (50.0)	94 (43.5)	122 (56.5)	**0.007**
Secondary outcomes				
90-day mRS, median (IQR)	3 (1–4)	3 (1–5)	2 (1–4)	**<0.001**
90-day mRS 0–1, *n* (%)	169 (39.1)	72 (33.3)	97 (44.9)	**0.014**
90-day mRS 0–3, *n* (%)	276 (63.9)	125 (57.9)	151 (69.9)	**0.009**
Puncture-to-recanalization time, median (IQR)	80 (50–115)	92 (60–140)	70 (45–103)	**<0.001**
Successful recanalization (mTICI 2b/3), *n* (%)	390 (90.3)	200 (92.6)	190 (88.0)	0.104
Safety outcomes, *n* (%)				
Any ICH	112 (25.9)	56 (25.9)	56 (25.9)	1.000
sICH	28 (6.5)	17 (7.9)	11 (5.1)	0.241
90-day mRS 6	65 (15.0)	43 (19.9)	22 (10.2)	**0.005**

PSM, propensity score matching; IQR, interquartile range; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; M1, middle cerebral artery M1 segment; M2, middle cerebral artery M2 segment; M3, middle cerebral artery M3 segment; ACA, anterior cerebral artery; SBP, systolic blood pressure; LAA, large artery atherosclerosis; CE, cardioembolism; IAT, intra-arterial thrombolysis; ICH, intracranial hemorrhage; sICH, symptomatic ICH; mRS, modified Rankin Scale; GA, general anesthesia; LA, local anesthesia, CS, conscious sedation. Bold values indicates statistical significance.

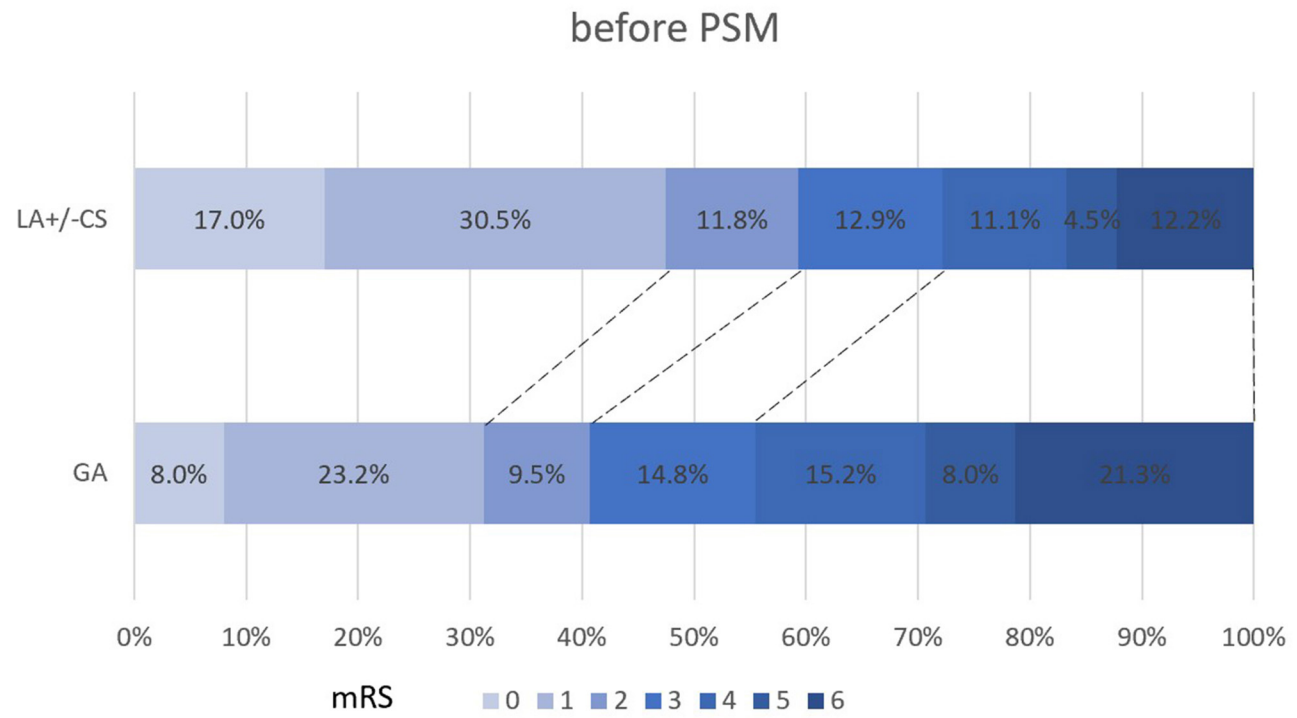

FIGURE 2 | Shift on the 90-day mRS score stratified by LA and GA before PSM. PSM, propensity score matching; mRS, modified Rankin Scale.

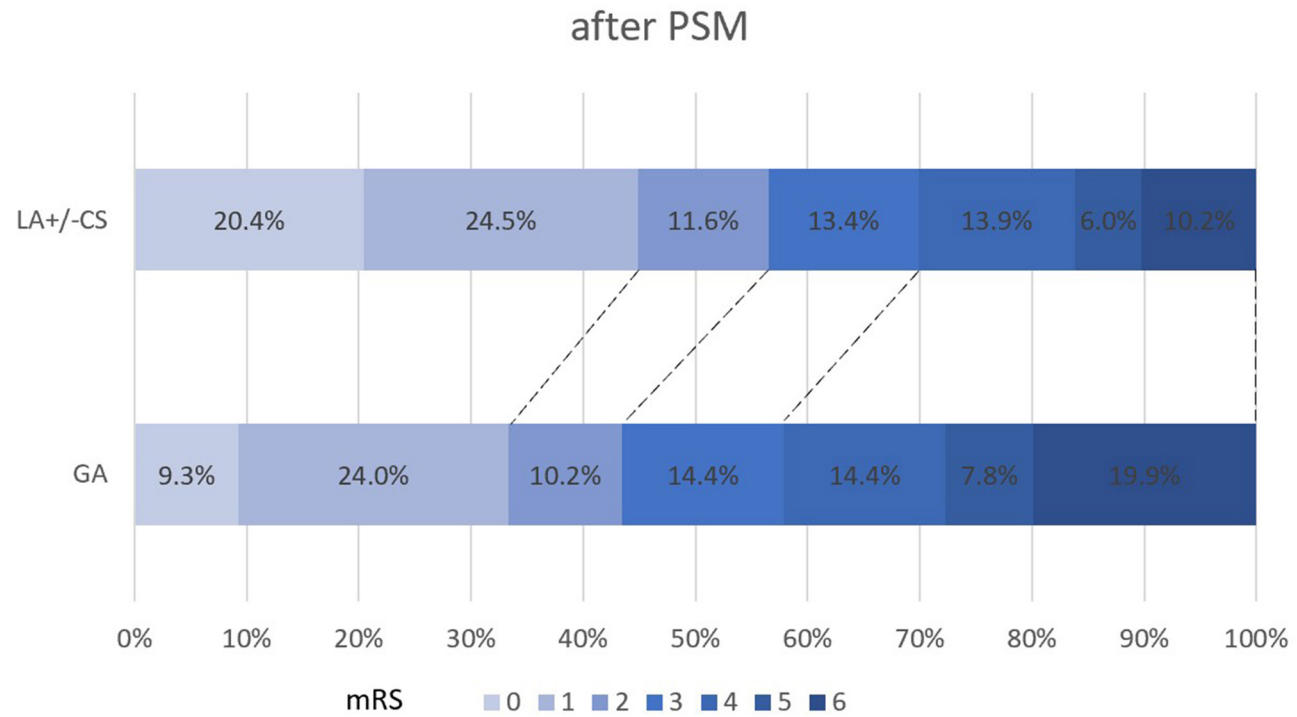

FIGURE 3 | Shift on the 90-day mRS score stratified by LA ± CS and GA after PSM. PSM, propensity score matching; mRS, modified Rankin Scale; GA, general anesthesia; LA, local anesthesia; CS, conscious sedation.

= 0.134) and CE subtype (23.1 vs. 23.1%, $p = 1.000$) between the two groups. The admission NIHSS (16 vs. 16, $p = 0.589$), the ASPECTS (8 vs. 8, $p = 0.523$), and time from door to puncture (110 vs. 104.5 min, $p = 0.669$) were similar between the two groups.

The propensity score-adjusted outcomes of the two groups are shown in **Table 2**. Time from puncture to recanalization (92 vs. 70 min, $p = 0.000$) and time from onset to recanalization (397 vs. 360 min, $p = 0.012$) were longer in the GA group than the LA ± CS group. The median mRS at 90 days was higher in the GA group than the LA ± CS group (3 vs. 2, $p = 0.000$). Compared to the LA ± CS group, excellent outcome rate at 90 days (33.3 vs. 44.9%, $p = 0.014$), good outcome rate at 90 days (43.5 vs. 56.5%, $p = 0.007$), and favorable outcome rate at 90 days (57.9 vs. 69.9%, $p = 0.009$) were lower, while mortality at 90 days (19.9 vs. 10.2%, $p = 0.005$) was higher in the GA group (**Figures 2**, **3**). There was no difference in successful recanalization rate, any ICH incidence, and sICH incidence between the two groups.

DISCUSSION

In this multicenter study, in patients with AIS-LVO who had successful recanalization, LA may provide more functional benefit at 3 months follow-up than GA. A shorter time workflow from LA might attribute to this outcome result.

There is still inconsistency regarding the anesthetic approach during EVT. A study using PSM to reduce the impact of confounding factors reported that CS might reduce the in-hospital mortality, rates of complications, hospital costs, and lengths of stay than those who had GA (19). Another cohort study reported a similar result (20). In contrast, the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) investigators (21) demonstrated that GA has a comparable time to treatment initiation and successful revascularization. Although, their study also demonstrated the negative effect of GA such as lower rates of functional independence and an increase in periprocedural hypotension and postoperative pneumonia.

Later, three well-known RCTs demonstrated that anesthesia patterns might not significantly impact clinical treatment after EVT (7–9). However, the lack of sample size and centers involved limited the result to be generalized into the global population. Surprisingly, the meta-analysis of these three RCTs showed different results (9). GA is associated with clinical benefits in this study. The higher reperfusion rates in the GA group might attribute this result, suggesting that more optimal procedural condition during EVT is essential to the functional outcome.

On the contrary, a meta-analysis of individual data by the HERMES collaborators demonstrated that the non-GA approach showed better functional outcomes after EVT than those with the GA approach (10). Nevertheless, the largely unbalanced baseline parameters increase the risk for bias and confounding. Furthermore, the incomplete anesthesia pattern and hemodynamic management information further limited their interpretability.

Particular caution is needed when interpreting those results of studies. Either GA or non-GA both has advantages and disadvantages. GA may have the advantage in achieving a higher recanalization rate, as operators were more convenient to perform more complex EVT procedures confronting complex lesions in the presence of patient agitation and discomfort. Besides, the circumstances might lower the probability of procedural complications such as arterial perforation. These advantages might be less provided by non-GA (22). On the other hand, hypotension and blood pressure variability were more common in those who had GA, exacerbating the functional outcomes (9, 22).

While most studies compared the effect of GA and non-GA, the most non-GA approach was CS. To date, there is still a lack of study investigating the impact of LA in patients with AIS-LVO undergoing EVT. Recently, only two studies using PSM analysis investigated the impact of LA and non-LA on EVT outcomes (22, 23). Both studies demonstrated that non-LA was associated with better clinical outcomes. Nevertheless, the lower reperfusion rates in the LA ± CS group might influence this result. Inconsistent with that, LA demonstrated better functional outcomes at 90-day follow-up in this study. Despite similar reperfusion rates achieved in the LA and GA groups, LA showed a significantly shorter duration of time workflow. This result highlighted the importance of time workflow in modifying the outcome in different anesthesia approaches.

This study could not conclude which anesthesia approach is the best for EVT. However, we recommended that the procedure for anesthesia should be individualized according to the preoperative integrative assessment of the status of the patient. Non-GA, particularly LA, is first recommended. However, if the conditions were not allowed, there should be no argument for choosing GA. In the circumstances, attempts should be made to avoid the delay of the anesthesia procedure and hypotension to optimize the treatment outcomes.

This study has several limitations. First, the nonrandomized design. Despite using propensity score analysis to minimize the impact of confounding factors, other unmentioned factors may also impact the treatment outcome. Second, the small sample size and this study is limited to the Chinese population. Thus, this result could not be generalized to the global population. Third, LA is the first recommended anesthesia approach and GA was preferred in patients with more severe stroke. Therefore, there was a high probability of selection bias, which may affect the treatment result.

CONCLUSION

Our multicenter study data suggest that LA ± CS could be superior to GA for those who achieved successful recanalization. Future trials are needed to determine

the best anesthetic approach for AIS-LVO in different patient stratification.

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

AUTHOR CONTRIBUTIONS

FC and QZ supervised and performed quality control for the study. HH performed statistical analysis and acquired the data and wrote the manuscript with input from all the co-authors. All the authors contributed to the article and approved the submitted version of the manuscript.

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Posterior Circulation ASPECTS on CT Angiography Predicts Futile Recanalization of Endovascular Thrombectomy for Acute Basilar Artery Occlusion

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Background: Acute basilar artery occlusion (BAO) is the most potentially disastrous outcome and has a high risk of recurrence stroke in posterior circulation infarction (PCI). However, the rate of futile recanalization remains high despite successful recanalization. The objective of this study was to investigate 90 days functional outcomes among patients with BAO who underwent endovascular thrombectomy (EVT) and to identify the risk factors associated with futile recanalization.

Methods: We retrospectively analyzed 72 patients with acute BAO who received EVT from January 2018 to June 2021. CT angiography source images posterior circulation Acute Stroke Prognosis Early CT Score (CTA-SI pc-ASPECTS) evaluated the extensive hypoattenuation in patients with BAO. Futile recanalization defined an modified Rankin Scale (mRS) of 3-6 at 90 days despite a successful recanalization. Logistic regression analysis was performed to investigate the predictors of futile recanalization.

Results: Our sample included a total of 55 eligible patients. Patients with poor outcomes showed that the pc-ASPECTS score was lower in patients with poor outcomes than that in patients with good outcomes ($P = 0.017$). Longer time from symptoms onset-to-the puncture ($P = 0.014$) and elevation of leucocytes ($P = 0.012$) were associated with poor outcomes. The multivariable logistic analysis showed that pc-ASPECTS and onset-to-puncture time (OPT) were independent predictors of futile recanalization.

Conclusions: This study suggested that pc-ASPECTS and OPT are independent predictors of futile recanalization after EVT in patients with BAO. The lower pc-ASPECTS score and longer puncture time will have a poor clinical outcome.

Keywords: basilar artery occlusive, endovascular thrombectomy, futile recanalization, CT angiography, posterior circulation Acute Stroke Prognosis Early computed tomography score, onset-to-puncture time

INTRODUCTION

Posterior circulation infarction (PCI) accounts for 20–25% of all incidents of acute ischemic stroke (AIS) (1) and has complex clinical presentations. Acute basilar artery occlusive (BAO) is the most devastating form of PCI (2), with potentially disastrous outcomes and a high risk of recurrent stroke (3). The mortality of patients with AIS caused by BAO is more than 85%. In the past few decades, the availability and technical improvement of endovascular thrombectomy (EVT) have changed this devastating scenario (4). BAO has developed from an almost fatal disease to become a treatable disease. However, there is a phenomenon that despite a successful recanalization, the outcome is poor; we define it as futile recanalization. The recent completed ENDOSTROKE study showed that only 34% of patients with BAO achieved good clinical outcomes despite a 79% rate of recanalization with EVT (5). Besides this, the results of a recent study suggested that this phenomenon occurred more often in BAO than in anterior circulation large-vessel occlusion (LVO) (6). Although the mechanism of futile recanalization has not yet been clarified, it might be associated with age, stroke severity, time from stroke onset to treatment, infarct distribution and volume, brain edema, leukoaraiosis, collateral status, subacute re-occlusion, microvascular compromise, impaired cerebral autoregulation, etc (7). In addition, pre-treatment imaging changes, both on MRI and CT, were indicated as independent predictors of clinical outcomes in recent studies (5, 8–10), highlighting the importance of applying initial prognostic markers for patient selection to avoid futile recanalization (4). Therefore, it is very important to select appropriate patients with BAO to receive EVT to avoid futile recanalization.

Recent studies found that the appropriate selection of patients for EVT upon imaging criteria helps improve prognosis (7). Areas of hypoattenuation on CT angiography (CTA) delineate regions of brain tissue with ischemic damage (11, 12). Compared with non-contrast CT, CTA source images (CTA-SI) is more accurate in predicting the final extent of infarction and clinical outcomes (8, 11, 12). The posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS), first proposed by Puetz et al. (13), is a semi-quantitative method to grade irreversible ischemia in the vertebrobasilar artery system (14). Several studies that have applied pc-ASPECTS to CTA-SI have validated its usefulness and demonstrated that it could predict functional outcomes in patients with AIS caused by BAO (12, 13, 15). Previous studies have emphasized the importance of pc-ASPECTS on the outcomes of patients with BAO after EVT; a high pc-ASPECTS (pc-ASPECTS $\geq$8) on the initial image usually implies a higher quality of life and lower mortality rates. Nevertheless, recent data demonstrated that a large number of patients with scores below this threshold may still recover well after EVT if recanalization occurs rapidly.

In this study, we aimed to assess the 90-day functional outcomes among patients with BAO who underwent EVT and to identify the risk factors associated with futile recanalization, focused on pc-ASPECTS and OPT, for screening out patients who cannot benefit significantly from EVT.

METHODS

Patients

We retrospectively analyzed 72 consecutive patients with acute BAO who received EVT from January 2018 to June 2021 in Zhongnan Hospital of Wuhan University.

The inclusion criteria included: (1) patients were confirmed of BAO by CTA; (2) $\geq$18 years old; (3) onset within 24 h; (4) successful recanalization after EVT [modified Thrombolysis in Cerebral Infarction (mTICI) $\geq$2b]; (5) complete 90-day follow-up was available; (6) all signed informed consent for treatment.

The exclusion criteria included: (1) pre-stroke modified Rankin Scale (mRS) > 3; (2) patients with anterior circulation stroke; (3) CTA were a known history of contrast medium allergy or any degree of renal failure; (4) intracranial hemorrhage or tumor. The flow chart for the inclusion of patients is summarized in **Figure 1**.

This study was carried out in compliance with the Declaration of Helsinki (10) and was approved by the ethics committees of Zhongnan Hospital of Wuhan University. All of the information was anonymous and confidentiality of information was assured (10).

Clinical Data Collection

Including demographic data, the severity of symptoms [National Institute of Health Stroke Scale (NIHSS)], stroke risk factors (hypertension, diabetes mellitus, previous stroke, smoke, hyperlipidemia, and atrial fibrillation), OPT, surgical methods, mTICI, [successful recanalization was defined as final mTICI of 2b to 3 (14)], hemorrhagic transformation [small or confluent petechiae, with or without a space-occupying effect in the infarcted area with or without clinical deterioration (16)], and mRS at 90 days [functional outcome at 90 days were derived from telephone or outpatient follow-up with patients or their relatives (13)].

Ischemic events were identified by two experienced neurologists based on the medical history description and brain CT or MRI (10). Clinical evaluations were conducted by three professional investigators, without knowledge of the baseline performance and surgical details, through clinical interviews or standardized telephone interviews with patients or their relatives (17). mRS was used to record the EVT treatment of the patient's clinical state. A favorable outcome was defined as an mRS score of 0–2, a poor outcome was defined as 3–6 (17).

Imaging Analysis

Posterior circulation Acute Stroke Prognosis Early CT Score (Pc-ASPECTS) allots the posterior circulation with 10 points (13). Pc-ASPECTS was scored early ischemic changes by evaluating hypoattenuation areas in posterior circulation territories on CTA-SI. One point each is subtracted for early ischemic changes in the left or right thalamus, cerebellum, or posterior cerebral artery (PCA) territory, respectively, and two points in any part of the midbrain or pons (18) (**Figure 2**). A pc-ASPECTS score of 10 indicates the absence of visible posterior circulation ischemia, a score of 0 indicates hypoattenuation in all pc-ASPECTS territories.

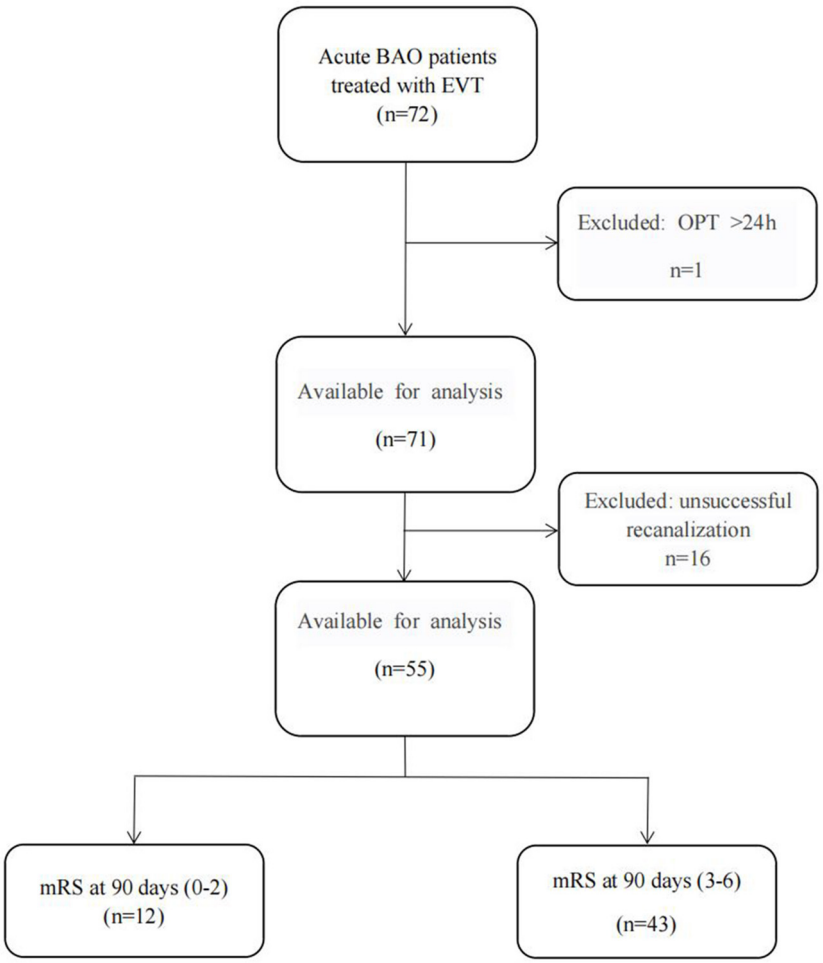

FIGURE 1 | The flow chart for the inclusion of patients. (BAO, basilar artery occlusive; EVT, endovascular thrombectomy; OPT, Onset-to-Puncture Time; mRS, the modified Rankin scale).

The imaging data were evaluated by two experienced neuro-radiologists without knowing the clinical data in advance. In cases of disagreement, a higher-level neuro-radiologist will review and make the final judgment. We rated the perfusion of the entire basilar artery (BA) with a delayed flow or full perfusion with a normal BA flow as described in the digital subtraction Angiography (DSA) results (according to mTICI 2b to 3 flow grades) as BA recanalization (19).

Clinical Outcomes

The mRS was used to assess the 90-day functional outcomes (20). Without knowing the patient's clinical information, a follow-up was conducted by professional medical researchers according to developed interview protocols. The primary outcome was futile recanalization after EVT defined as an mRS of 3–6 at 90 days despite successful recanalization.

Statistical Analysis

Data were collected on standard forms, evaluated for completeness (21). Continuous variables were presented as mean ± SD or median with interquartile range (IQR). Categorical variables were presented as counts and percentages. In the univariate analysis, the continuous variable is abnormally distributed, the Mann-Whitney *U*-test or student *t*-test was used to determine differences between the two groups. The differences between the two groups of categorical variables were tested by χ^2 test or Fisher's exact test. For variables with $P < .1$ in the univariate analysis, multivariate logistic regression with a forward stepwise method was performed. The receiver operating characteristic (ROC) test was used to evaluate the predicted area under the curve (AUC) and identify the best cutoff value to distinguish between poor and favorable clinical outcomes.

A two-sided *P*-value of .05 or less was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 26 software (Version 26.0; IBM) (17).

RESULTS

The baseline characteristics of the patients are presented in **Table 1**. A total of 55 patients who fulfilled the inclusion

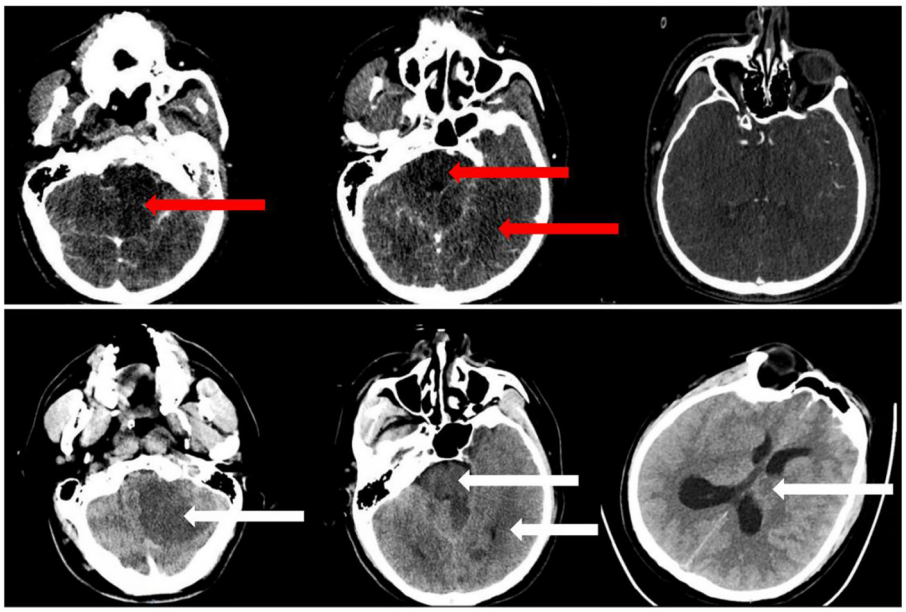

FIGURE 2 | Example of a patient with BAO in our study. We rated CT angiography (CTA) source images (CTA-SI) (upper row) posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS) score 6 (hypoattenuation left PCA territory, left cerebellum, midbrain) and follow-up non-contrast CT (NCCT) (lower row) pc-ASPECTS score 5 (additional ischemic change left thalamus).

criteria were included. The average age of the patients was 64 years (ranging from 39 to 90), including 47 males (85.4%). The pretreatment NIHSS score for all patients was 35 (IQR, 20–35). The median pc-ASPECTS was 8 (IQR, 7–9), and the time from stroke onset-to-puncture was 480 min (IQR, 345–700). Among them, 12/55 patients (21.8%) were classified into the favorable outcome and 43/55 patients (78.2%) had a poor outcome. Comparison of predictors of clinical outcomes by univariate analysis (favorable vs. poor). The pc-ASPECTS scores in patients with poor outcomes was lower than those of patients with good outcomes [8 (7–9) vs. 9 (8–10); $P = 0.017$]. The time from symptoms onset to the puncture [510 (410–770) vs. 383 (227–490); $P = 0.014$] and leukocyte (10.1 (7.6–12.2) vs. 7.0 (6.3-9.1); $P = .012$) were associated with clinical outcomes. The predictors of the functional outcome by multiple logistic regression analysis were listed in **Table 2**. The pc-ASPECTS (OR,.476; 95% CI,.227-.998, $P = .049$) and OPT (OR, 1.004; 95% CI, 1.000–1.007, $P = .048$) were independent predictors for functional outcome. As a result of ROC curve analysis (22), the AUC for the pc-ASPECTS was.726 (95% CI,.566–0.885) and for the time from onset-to-puncture was.734 (95% CI,.582–0.885). The best cutoff value respectively was 8 score and 476 min, to maximize the sensitivity and specificity for discriminating patients with good outcomes and poor outcomes (22) (**Figure 3**, **Table 3**). The distribution of 90-day-mRS according to the categorized pc-ASPECTS score are presented in **Figure 4**. We can see that patients with lower pc-ASPECTS (0–7) accounts for a larger proportion of poor outcome.

DISCUSSION

Severe ischemic cerebrovascular diseases (ICD) not only bring physical diseases but also life pressure to patients and their families. BAO accounts for about 1% of all strokes (22) and for 5% of all intracranial large vessel occlusions (LVO) (18). Although the efficacy of EVT for BAO has been demonstrated in multiple observational studies (6, 9, 14, 23), its positive impact on the BA is still a matter of debate (23). Even if successful recanalization is strongly associated with a high mortality rate and a high risk of disability, these treatments are often expensive, with a poor outcome. Reliable predictions of futile recanalization are important to identify patients with BAO who do not benefit significantly from EVT and assist in the personalized formulation.

The main 2 findings of the study were as follows. (1) the onset-to-puncture time and pc-ASPECTS on CTA-SI before treatment were independent risk factors in predicting futile recanalization for patients with BAO who underwent EVT. (2) The best cutoff value for differentiation between favorable outcomes and poor clinical outcomes was a score of 8 for pc-ASPECTS and 476 min (≈8 h) for the time from onset-to-puncture before treatment.

The recently published studies found that the appropriate selection of patients for EVT upon imaging criteria helps improve prognosis (2, 4, 12, 16). In this retrospective study, our study demonstrates that pc-ASPECTS on CTA-SI can help predict the functional outcomes 15 after BAO successful recanalization (OR, 0.476; 95% CI, 0.227–0.998, $P = 0.049$) and being dichotomized at ≥8 vs. <8 to predict favorable outcome and poor

TABLE 1 | Characteristics and clinical data of the BAO patients treated with EVT.

Variables	All patients ($n = 55$)	Favorable outcome ($n = 12$)	Poor outcome ($n = 43$)	*P*-value
Male, *n* (%)	47 (85.4%)	9 (75.0%)	38 (88.4%)	0.485
Age, y (median, IQR)	64 (57–75)	69 (63–75)	62 (57–75)	0.103
Hypertension, *n* (%)	38 (69.1%)	8 (66.7%)	30 (69.8%)	1.000
Diabetes, *n* (%)	14 (25.4%)	3 (25.0%)	11 (25.6%)	1.000
Prior stroke, *n* (%)	11 (20.0%)	4 (33.3%)	7 (16.3%)	0.369
Smoking, *n* (%)	18 (32.7%)	4 (33.3%)	14 (32.6%)	1.000
Hyperlipidemia, *n* (%)	6 (10.9%)	3 (25.0%)	3 (25.0%)	0.212
Atrial fibrillation, *n* (%)	8 (14.5%)	2 (16.7%)	6 (14.0%)	1.000
Coronary heart disease, *n* (%)	9 (16.4%)	4 (33.3%)	5 (11.6%)	0.175
pc-ASPECTS, (median, IQR)	8.0 (7.0–9.0)	9.0 (8.0–10.0)	8.0 (7.0–9.0)	0.017*
NIHSS score, (median, IQR)	35.0 (20.0–35.0)	34.5 (18.0–36.0)	35.0 (20.0–35.0)	0.532
Blood glucose, mmol/L (median, IQR)	8.6 (7.0–10.2)	8.3 (6.7–9.4)	8.8 (7.0–10.7)	0.354
Leukocyte, 10^9/L(median, IQR)	9.5 (7.2–11.8)	7.0 (6.3–9.1)	10.1 (7.6–12.2)	0.012*
Intravenous r-tPA, *n* (%)	17 (30.9%)	5 (41.7%)	12 (27.9%)	0.576
Onset to puncture, min (median, IQR)	480 (345–700)	383 (227–490)	510 (410–770)	0.014*
Onset to recanalization, min (median, IQR)	594 (475–867)	551 (319–686)	604 (524–907)	0.053*
Puncture to recanalization, min (median, IQR)	104 (75–151)	90 (66–219)	110 (75–141)	0.610
mTICI, 2b or 3, *n* (%)				0.162
2b	21 (38.2%)	2 (16.7%)	19 (44.2%)	
3	34 (61.8%)	10 (83.3%)	24 (55.8%)	
Type of procedure, *n* (%)				0.276
Aspiration alone	14 (25.5%)	5 (41.7%)	9 (20.9%)	
Stent retrieve	17 (30.9%)	2 (16.7%)	15 (34.9%)	
Angioplasty	24 (43.6%)	5 (41.7%)	19 (44.2%)	
Hemorrhagic transformation, *n* (%)	8 (14.5%)	2 (16.7%)	6 (14.0%)	1.000

**Variables with p-value < 0.1.*

BAO, basilar artery occlusive; EVT, endovascular thrombectomy; pc-ASPECTS, the posterior circulation Acute Stroke Prognosis Early CT Score; NIHSS, National Institutes of Health Stroke Scale; mTICI, modified Thrombolysis in Cerebral Infarction Score; IQR, interquartile range.

TABLE 2 | Independent risk factors for poor outcome at 90 days.

Variables	β	Odds Ratio	Standard Error	95% CI	*P*-value
pc-ASPECTS, median (IQR)	−0.743	0.476	0.378	0.227–0.998	0.049*
OPT, median (IQR), min	0.004	1.004	0.002	1.000–1.007	0.048*
Leukocyte,median (IQR), $\times 10^9$/L	0.351	1.421	0.180	0.998–2.023	0.051

**Variables with p-value < 0.05.*

IQR, interquartile range; OPT, onset to puncture time; β, regression coefficient; 95% CI, 95% Confidence Interval.

outcome at 90 days. Patients with lower scores often represented extensive brain ischemic infarction lesions, suggesting that despite successful recanalization, it is difficult to achieve good functional outcomes.

It has shown that the quantification of hypoattenuation on CTA-SI predicts clinical outcomes in patients with posterior circulation stroke (PCS) (12). Using a systematic approach with a novel CT score (12, 13), pc-ASPECTS is a semi-quantitative grading system for PCS suggested by Puetz et al. in 2008 (13). It is relatively simple and easy to apply (24). Based on previous findings indicating that the numbers of regions involved and the involvement of the pons and midbrain are the most critical issues in functional outcome in patients with PCS (25). Applied on CTA-SI, pc-ASPECTS predicted clinical outcomes in patients with suspected BAO. Patients with extensive hypoattenuation defined by a CTA-SI pc-ASPECTS score <8 usually represent futile recanalization (7). In our study, patients with lower pc-ASPECTS (0–7) accounts for a larger proportion of poor outcome, the overall functional outcome was comparable to the average outcome reported in the literature (26, 27).

Basilar artery (BA) recanalization, thrombus location, length of BA obstruction, and state of collaterals have been identified as independent variables affecting functional outcomes in several studies (28, 29). However, no criteria are currently available to identify patients who will likely benefit from EVT. MRI with

diffusion-weighted imaging (DWI) sequences is considered the diagnostic "Gold standard" in patients with PCS (30). However, the feasibility of MRI may be limited in these frequently unstable patients (29), and it takes a long time and costs a lot. A completely normal non-contrast CT (NCCT) scan seems ideal in terms of potential benefit (because no damage at that time) from any possible therapies but may introduce diagnostic uncertainty for the stroke neurologist (12). The comparison of CTA, CTP, and multimodal MRI to predict outcomes and treatment response in patients with BAO could be the subject of future studies (13, 31) and more research is needed to investigate the most reliable scoring system.

Another key finding was the strong effect of time to treatment on poor clinical outcomes. There is an old saying that goes that time is money and in our research, we were surprised to find that time is also life. The time to treatment initiation is generally held as the single most dominant determinant of the fate of ischemic brain tissues (32); some centers with smaller cohorts of BAO have found an association between OPT and outcomes (28). Furthermore, Mokin et al. (33) reported that the 6 h window cutoff might be an important criterion for the prediction of outcomes in patients with PCS treated with EVT (32). But, in our analysis, the 476 min (8 h) window cutoff from symptom onset-to-puncture was statistically significant. The longer the puncture time, the more likely to have a poor outcome (OR, 1.004; 95% CI, 1.000–1.007; $P = 0.048$). This result first suggests that each patient may have a unique best treatment time window and we should make the right decision as soon as possible to reduce transport and preoperative preparation time. Secondly, due to the misleading nature of prodromal symptoms related to BAO, clinical diagnosis is often delayed, leading to prolonged time intervals to imaging evaluation and treatment (18). Finally, currently known puncture methods include radial artery and femoral artery puncture. The radial artery is small and difficult to find, which is more difficult for inexperienced doctors. Therefore, whether femoral artery puncture is more rapid and safe needs further study. In fact, our findings were markedly different from the BEST trial, which failed to show benefit of EVT within 8h. In the BEST registry, patients typically had higher clinical severity (34), which increased the chance of selection bias, and the study that had been completed 10 years ago was not applicable to contemporary clinical. Moreover, the results may have been confused by a loss of balance during the study.

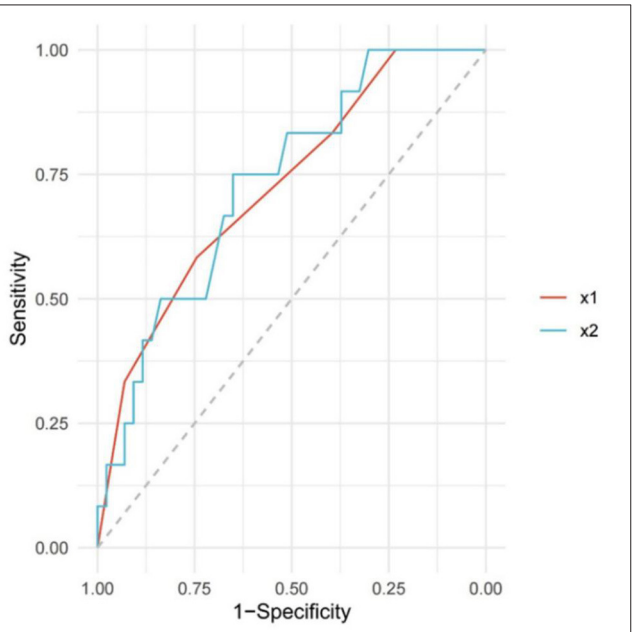

FIGURE 3 | Receiving operating characteristic (ROC) curve of pc-ASPECTS and OPT. The red solid line (x1) represents the boundary of the pc-ASPECTS area under the curve (AUC), and the blue band (x2) represents the boundary of onset-to-puncture time (OPT). The predictive performance indexes of this scale at different cutoff values are shown in **Table 3**. ROC, Receiver-operating Characteristic; OPT, Onset-to-puncture time; AUC, Authentication Center.

Evidence showed that pc-ASPECTS was a more critical factor influencing the benefits from EVT over time (35). This is probably due to the patients who survived several hours after symptom onset, there may be a robust collateral arterial network maintaining brittle patency of brain stem perforators, which may improve treatment benefits from delayed recanalization (36, 37). However, each patient likely has a unique optimal time window for therapy because of inherent variability in collateral support (14). Hence, it is necessary to receive treatment as soon as possible. Moreover, patients with lower pc-ASPECTS often had a much longer time from onset-to-puncture, as indicated by our results, providing evidence that the chance of a favorable pc-ASPECTS ($\geq$8) will probably decrease with time delay, resulting in deleterious effects (14). We have reason to assume that the longer the time spent, the larger the ischemic area is. If the OPT occurs rapidly, even patients with extensive cerebral ischemia and below the best cutoff point can still benefit from EVT. Compared to the previous reports (34, 38), the BEST trial and BASICS trial showed that there were no significant differences in the acute BAO outcome. Imaging selection was not clearly mentioned in the two trials that

TABLE 3 | ROC curve analysis of pc-ASPECTS and OPT.

Variables	AUC value	95% CI	Best Cutoff Value	Sensitivity	Specificity
pc-ASPECTS, median (IQR)	0.726	0.566–0.885	8	0.583	0.744
OPT, min, median (IQR)	0.734	0.582–0.885	476	0.651	0.75

AUC indicates area under the curve; mRS, modified Rankin Scale; pc-ASPECTS, the posterior circulation Acute Stroke Prognosis Early CT Score; OPT, onset to puncture time; IQR, interquartile range; 95% CI, 95% Confidence Interval.

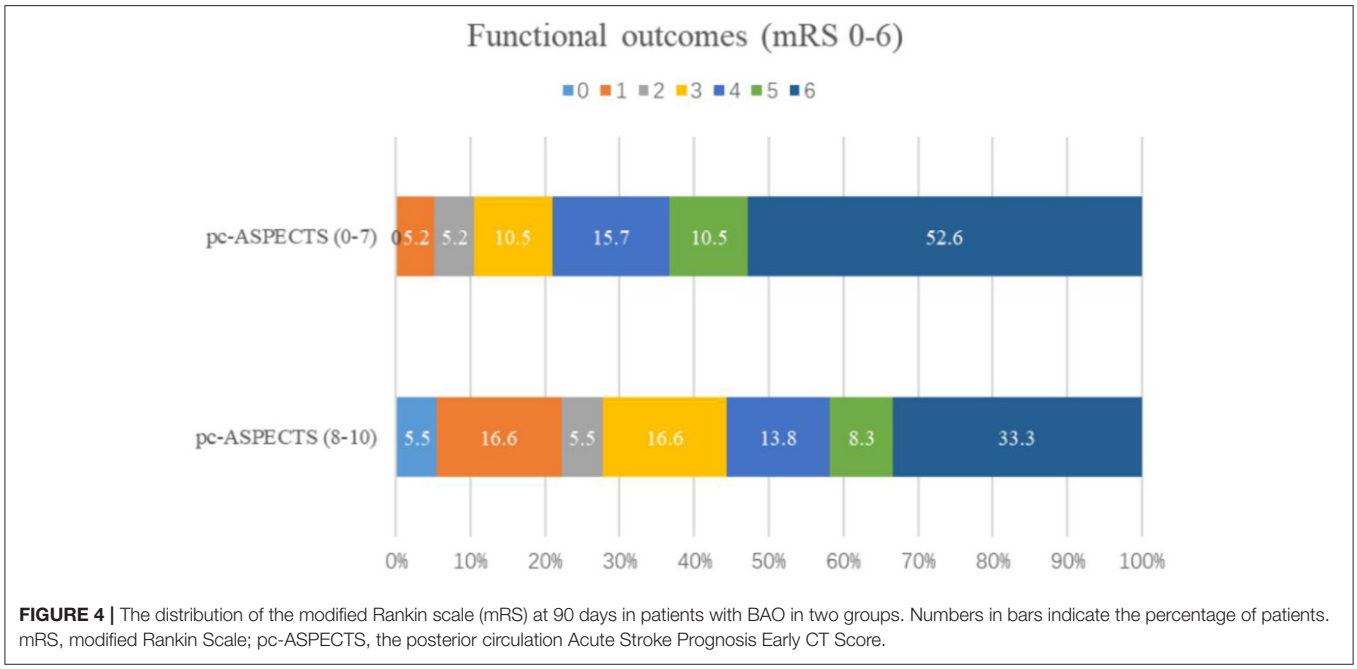

FIGURE 4 | The distribution of the modified Rankin scale (mRS) at 90 days in patients with BAO in two groups. Numbers in bars indicate the percentage of patients. mRS, modified Rankin Scale; pc-ASPECTS, the posterior circulation Acute Stroke Prognosis Early CT Score.

might be the cause of the negative outcomes, and the two trials recruitment programs were largely flawed, resulting in a large selection bias that could offset the potential benefits of EVT.

However, the effectiveness of pc-ASPECTS in its application on patients with acute BAO selection remains controversial, although it is might be the most widely used scale for PCS. Several DWI scoring systems have been published for the assessment of early ischemic injury in patients with BAO (13, 39–41). The Pons-Midbrain and Thalamus (PMT) score was published recently. It was a DWI-based semi-quantitative scale in which the infarctions of pons, midbrain, and thalamus were fully considered in assessing the outcome of EVT in patients with BAO (39). Future studies should reinforce assessing whether multimodal scores provide superior prognostic information in patients.

The major limitations of this study are the single-center retrospective design and that the clinical outcome was identified retrospectively and requires prospective validation in another cohort. Secondly, the lack of data regarding the etiology of the occlusion (embolism vs. thrombotic), thrombus volume, and collateral circulation (32). Finally, the relatively small sample size and selection bias (2).

CONCLUSIONS

The results of this study indicate that pc-ASPECTS and OPT are independent predictors of futile recanalization after EVT in patients with BAO. We describe pc-ASPECTS which quantifies early ischemic changes in the posterior circulation (13). Applied on CTA-SI, pc-ASPECTS predicts futile recanalization after EVT and identifies patients with BAO who potentially benefit from EVT. The effect of OPT on EVT outcome is also described in our study; extending OPT not only increases the incidence of futile recanalization but also decreases functional independence. We consider that the chance of favorable pc-ASPECTS will probably decrease with OPT delay, resulting in detrimental effects.

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

AUTHOR CONTRIBUTIONS

KO and ZK contributed to the conception and design of the study. YX revised some of the manuscript. YL conducted statistical analysis. KO, ZK, and JF organized the database. All authors participated in revising the article, reading it, and approving the submitted version.

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Impact of Pre-operative Embolization With Onyx for Brain Arteriovenous Malformation Surgery

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Objective: To clarify the safety and efficacy of pre-operative embolization using Onyx liquid embolic agent (Onyx; ev3) compared with *N*-butyl cyanoacrylate (NBCA; Cordis Neurovascular, Inc.) or coils in cerebral arteriovenous malformation (AVM) surgery.

Methods: This was a retrospective review of a prospectively collected clinical database of brain AVMs treated at our institute from January 2005 to March 2021. A total of 38 consecutive patients who underwent AVM resection after pre-operative embolization were included. Based on pre-operative embolization materials, the patients were divided into the pre-Onyx group ($n = 16$), in which NBCA or coils were used for embolization, and the Onyx group ($n = 22$). Patient characteristics and treatment results were compared between the two groups.

Results: Patient characteristics were comparable between the two groups in terms of age, sex, and rupture status. While the Spetzler–Martin grade was also similar between the two groups, the location of the AVM nidus in the eloquent area was slightly higher in patients in the Onyx group (72.7%) than in patients in the pre-Onyx group (43.8%) ($P = 0.09$). The embolization rate was higher in the pre-Onyx group (mean: 63.0%; range: 12.7–100%) than in the Onyx group (mean: 50.0%; range: 15.8–100%), but the difference was not statistically significant ($P = 0.06$). The time needed for surgical removal was shorter in the Onyx group (mean: 354.8 min; range: 144–884 min) than in the pre-Onyx group (mean: 457.9 min; range: 240–1,294 min); however, this difference was not statistically significant ($P = 0.13$). The amount of intraoperative bleeding was significantly lower in the Onyx group (mean: 129.8 ml; range: 20–540 mL) than in the pre-Onyx group (mean: 448.8 mL; range: 120–1,550 ml) ($P = 0.0008$). The surgical complication rates were comparable between the two groups (pre-Onyx group, 18.8%; Onyx group, 4.5%; $P = 0.29$).

Conclusions: Pre-operative embolization with Onyx can significantly reduce the amount of intraoperative bleeding in AVM resection and may contribute to safe AVM surgery.

Keywords: Onyx, *N*-butyl cyanoacrylate, coils, neurosurgery, cerebral arteriovenous malformation (cAVM)

INTRODUCTION

Pre-operative endovascular embolization for brain arteriovenous malformation (AVM) has been widely performed in recent years, and good treatment results have been reported (1–3). Various materials have been conventionally used for embolization of AVMs (4–6). In Japan, *N*-butyl cyanoacrylate (NBCA; Cordis Neurovascular, Inc., Miami, FL) has been widely used for pre-operative embolization of AVMs, but after the approval of the Onyx liquid embolic system (Onyx; ev3, CA, USA) by the Japanese Ministry of Health, Labor and Welfare in 2008, this embolic material is being increasingly used in the treatment of AVMs. Compared with NBCA, Onyx has slower cast formation, flow-independent delivery, cohesiveness, and smaller minimum diameter of embolized vessel (7–9). These features enable the usage of the plug and push method and penetration into smaller microvasculature, leading to nidus occlusion. For these reasons, pre-operative embolization for AVM surgery using Onyx is expected to be more effective than using NBCA (10, 11). According to a review of 1,042 AVM cases from Japan that underwent embolization, coils were used in 165 embolization procedures (15.8%); NBCA in 627 (60.2%); and Onyx in 432 (41.5%) (11). However, a multicenter randomized controlled trial and some observational studies that directly compared Onyx and NBCA failed to show that pre-operative embolization using Onyx resulted in superior surgical outcomes (1, 8, 12).

The purpose of this study was to investigate the safety and efficacy of pre-operative embolization using Onyx by comparing it with coils or NBCA in cerebral AVM surgery using real-world data.

MATERIALS AND METHODS

Study Population and Data Analysis

This study was carried out in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Nagasaki University Hospital (No. 21081606). Written informed consent was obtained from all participants.

Between January 2005 and March 2021, 38 consecutive patients with AVMs who were treated at our hospital with endovascular embolization and microsurgical resection were included in this study. The data were prospectively maintained in the AVM database. All embolization procedures were performed by two board-certified neuroendovascular therapists (H.K. and N.H.) of the Japan Neuroendovascular Therapy Society. All surgeries were performed by two board-certified neurosurgeons (I.N. and T.I.) of the Japan Neurosurgical Society.

Onyx became available at our institution on May 1, 2014; since then, we have changed the first choice of embolization materials from NBCA to Onyx for the pre-operative embolization of brain AVMs. Our basic policy was to aim for nidus embolization using the plug and push method with Onyx embolization. Thus, the patients included in this study were divided into pre-Onyx and Onyx groups, depending on the embolization material. The prospectively collected clinical data were reviewed and analyzed by a single neurosurgeon (T.I.). The following data were included: age, sex, symptoms at presentation, Spetzler–Martin grade, rupture status, embolic material, number of embolized feeding arteries, number of embolization sessions, embolization rate, endovascular procedure complications, operative time, intraoperative blood loss, obliteration rate after surgery, surgical complications, and pre-operative and post-operative (at discharge) modified Rankin Scale (mRS) score.

The pre-embolized and post-embolized nidus of the AVM was manually traced in each of the anterior-posterior (AP) and lateral (LAT) views in the digital subtraction angiogram (DSA) image using Synapse Vincent software (Fujifilm, Japan), and the area was automatically calculated (mm^2). The embolization rate was calculated for each AP and LAT view and is described as the average value. After surgery, the obliteration rate was defined utilizing post-operative DSA performed after 10 days. A good neurological outcome was defined as an mRS score <3, and a poor outcome was defined as an mRS score ≥ 3.

Statistical Methods

Statistical analyses were performed to compare the two patient groups. Continuous variables are presented as the mean and standard deviation (SD) and as the median and range, while categorical variables are presented as frequencies. Statistical analysis was conducted using the Student's *t*-test or Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables, as appropriate. All statistical analyses were performed using SPSS for Windows (version 24.0; IBM, Armonk, NY, USA). Differences were considered statistically significant at $P < 0.05$.

RESULTS

Baseline Characteristics of Participants

There were 16 patients in the pre-Onyx group and 22 in the Onyx group. Patient characteristics at baseline were similar between the two groups (**Table 1**). The mean age was 40.9 ± 20.3 years in the pre-Onyx group and 41.4 ± 22.9 years in the Onyx group ($P = 0.95$). The proportion of female patients was 25.0% (4/16) in the pre-Onyx group and 45.5% (10/22) in the Onyx group ($P = 0.31$). The most frequent symptom at presentation was disturbance of consciousness in both groups. Seizure was observed slightly more frequently in the pre-Onyx group. One patient in the Onyx group was asymptomatic.

Baseline Characteristics of AVMs

Baseline AVM characteristics were comparable between the two groups (**Table 2**). In the pre-Onyx group the AVMs most frequently in the right side, while in the Onyx group the AVMs were located equally in the right and left side; however, this difference was not significant ($P = 0.64$). There were no significant difference in Spetzler-Martin grades between the Onyx and pre-Onyx grous ($p = 0.32$). Conversely, there were increasing trends of patients with the AVM nidus in the eloquent area in the Onyx group (72.7%) compared with those in the pre-Onyx group (43.8%) ($P = 0.09$). The proportion of patients presenting with AVM rupture was 87.5% in the pre-Onyx group and 91% in the Onyx group ($P = 1.00$). A good pretreatment mRS score (0–2)

TABLE 1 | Patient demographics.

	Pre-onyx group	Onyx group	*P*-value
No. of patients	16	22	
Age, years			
Mean ± SD	40.9 ± 20.3	41.4 ± 22.9	0.95
Median (range)	49.5 (8–67)	46 (7–81)	
Sex (%)			
Female	4 (25)	10 (45.5)	0.31
Male	12 (75)	12 (54.5)	
Presenting symptoms			
Consciousness disturbance	7	10	
Hemiparesis	4	9	
Sensory disturbance	0	1	
Seizure	4	1	
Headache	6	6	
Nausea/vomiting	5	2	
Visual field defect	2	2	
Vertigo	1	1	
None	0	1	

SD, standard deviation.

TABLE 2 | AVM characteristics.

	Number (%)		
	Pre-onyx group	Onyx group	*P*-value
No. of patients	16	22	
AVM location			0.64
Left	6 (37.5)	10 (45.5)	
Right	8 (50)	10 (45.5)	
Midline	2 (12.5)	2 (9.0)	
Spetzler-Martin grade			0.32*
I	4 (25)	3 (13.6)	
II	6 (37.5)	6 (27.3)	
III	5 (31.3)	10 (45.5)	
IV	1 (5.2)	3 (13.6)	
AVM size, maximum diameter			0.34
<3 cm	10 (62.5)	10 (45.5)	
3–6 cm	6 (37.5)	11 (50)	
>3 cm	0 (0)	1 (4.5)	
Nidus in eloquent area	7 (43.8)	16 (72.7)	0.09
Deep venous drainage	6 (37.5)	6 (27.3)	0.72
Rupture status			1.00
Ruptured	14 (87.5)	20 (91.0)	
Unruptured	2 (12.5)	2 (9.0)	
Preop mRS score			0.52
0–2	10 (62.5)	11 (50)	
3–5	6 (37.5)	11 (50)	

**I + II/III + IV.*
AVM, arteriovenous malformation; mRS, modified Rankin Scale.

TABLE 3 | Embolization materials.

Pre-onyx group		Onyx group	
NBCA	7	Onyx	21
coils	5	Onyx + NBCA	1
NBCA + coils	4		
Total	16		22

NBCA, N-butyl cyanoacrylate.

was found in 62.5% of patients in the pre-Onyx group and 50% in the Onyx group ($P = 0.52$).

Embolization Results

In the pre-Onyx group, NBCA alone was used in seven patients, coil (the Guglielmi detachable coil; Stryker Neurovascular, MI, USA or ED coil, Kaneka Medix, Japan) alone was used in four patients, and a combination of NBCA and coil was used in five patients (**Table 3**). In the Onyx group, Onyx alone was used in 21 patients and a combination of Onyx and NBCA was used in one patient. The mean number of embolized arteries was 1.94 ± 0.33 in the pre-Onyx group and 2.27 ± 0.28 in the Onyx group ($P = 0.45$) (**Table 4**). The mean number of embolization sessions was 1.06 ± 0.069 in the pre-Onyx group and 1.09 ± 0.059 in the Onyx group ($P = 0.76$). The mean embolization rate was lower in the Onyx group (50.0 ± 4.43%) than in the pre-Onyx group (63.0 ± 5.20%), but the difference was not significant ($P = 0.06$). Pre-operative embolization complications occurred in two patients (both in the Onyx group). One patient experienced transient aphasia due to cerebral infarction caused by migration of Onyx to a passing artery, and one patient experienced a stuck microcatheter. Thus, the complication rate was 0% in the pre-Onyx group and 9.1% in the Onyx group; the difference was not statistically significant ($P = 0.50$).

Surgical Results

The mean operative time was comparable between the two groups (457.9 ± 50.4 min in the pre-Onyx group and 354.8 ± 43.0 min in the Onyx group, $P = 0.13$) (**Table 4**). On the other hand, mean intraoperative bleeding was significantly less in the Onyx group (129.8 ± 117.0 mL) than in the pre-Onyx group (448.8 ± 388.6 mL) ($P = 0.0008$). Total removal was achieved in all patients in both groups. Surgical complications occurred in three patients in the pre-Onyx group and one patient in the Onyx group. In the pre-Onyx group, symptomatic hemorrhage occurred in two patients. Among them, one patient underwent re-craniotomy and hematoma removal, and one patient underwent ventricular drainage. The other patient experienced wound infection. In the Onyx group, post-operative intracerebral hemorrhage occurred in one patient who underwent re-craniotomy and hematoma removal. Thus, the surgical complication rate was 18.8% in the pre-Onyx group and 4.5% in the Onyx group ($P = 0.29$). No post-operative worsening of the mRS was observed in either group. A good post-operative outcome (mRS 0–2) was achieved in 68.8% (11/16) of the pre-Onyx group and 68.4% (15/22) of the Onyx group ($P = 1.00$).

TABLE 4 | Treatment results.

	Pre-Onyx group	Onyx group	*P*-value
No. of patients	16	22	
Number of embolized arteries			
Mean ± SD	1.94 ± 0.33	2.27 ± 0.28	0.45
Median (range)	2 (1–3)	2 (1–4)	
Number of embolization sessions			
Mean ± SD	1.06 ± 0.069	1.09 ± 0.059	0.76
Median (range)	1 (1–2)	1 (1–2)	
Embolization rate (%)			
Mean ± SD	63.0 ± 5.20	50.0 ± 4.43	0.06
Median (range)	62.0 (12.7–100)	52.6 (15.8–100)	
Complications of embolization			
No. (%)	0 (0)	2 (9.1)	0.50
Operative time (minutes)			
Mean ± SD	457.9 ± 50.4	354.8 ± 43.0	0.13
Median (range)	379 (240–1,294)	311 (144–884)	
Intraoperative bleeding (ml)			
Mean ± SD	448.8 ± 388.6	129.8 ± 117.0	0.0008
Median (range)	300 (120–1,550)	97 (20–540)	
Total removal no. (%)	16 (100)	22 (100)	1.00
Surgical complication			
No. (%)	3 (18.8)	1 (4.5)	0.29
Post-operative mRS score			1.00
0–2	11 (68.8)	15 (68.4)	
3–5	5 (31.2)	7 (31.6)	

SD, standard deviation; mRS, modified Rankin Scale.

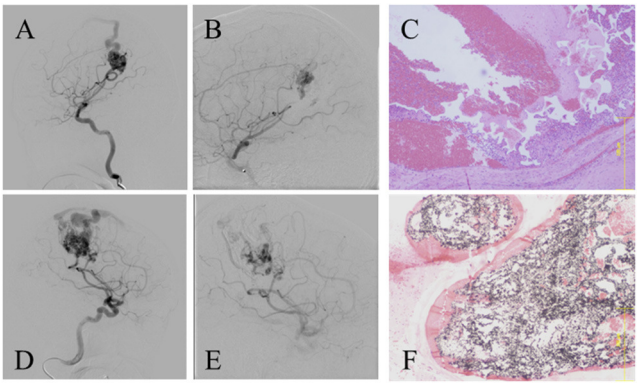

FIGURE 1 | (A,B) Lateral projection digital subtraction angiogram (DSA) showing Spetzler-Martin grade 1 AVM pre-embolization and post embolization using NBCA, respectively. The calculated embolization rate was 68.8%. **(C)** pathological findings of resected angiographically disappeared nidus showing remarkable red blood cells in the microvasculatures (Hematoxylin-Eosin staining, ×25). **(D,E)** Lateral projection DSA showing Spetzler-Martin grade 3 AVM pre-embolization and post embolization with Onyx, respectively. The calculated embolization rate was 52.1%. **(F)** Pathological findings of resected angiographically disappeared nidus showing the Onyx cast without red blood cells in the microvasculatures (Hematoxylin-Eosin staining, ×25). AVM, arteriovenous malformation; NBCA, *N*-butyl cyanoacrylate.

Representative Cases Presentation

We compared the post-operative histopathological findings between patients who underwent NBCA pre-operative embolization (**Figures 1A–C**) and Onyx (**Figures 1D–F**). The first case was a Spetzler–Martin grade 1 right parietal unruptured AVM. The patient underwent pre-operative embolization with NBCA, and the embolization rate was 68.8%. The post-operative pathological findings of the NBCA-embolized nidus revealed that there were significant red blood cells (RBCs) in some areas of the removed nidus. This area had disappeared on cerebral angiography after the NBCA-embolization. The second case was a Spetzler–Martin grade 3 ruptured AVM. The patient underwent pre-operative embolization with Onyx, and the embolization rate was 52.1%. The post-operative pathological findings of the angiographically disappeared area of the nidus showed the Onyx cast in the AVM microvasculature and sparse RBCs.

DISCUSSION

In this study, pre-operative embolization with Onyx significantly reduced bleeding in AVM surgery compared with NBCA or coil embolization. In addition, the operation time tended to be shorter in the Onyx group, although the difference was not significant. The Onyx group tended to have more lesions in the eloquent area; however, no cases with worsened functional status were observed after surgery, and the same treatment prognosis as in the pre-Onyx group could be achieved.

Intraoperative bleeding is a significant risk factor for surgical complications after surgery for cerebral AVMs. Therefore, it is crucial to suppress the bleeding to a small amount using a precise maneuver (13–17). Wong et al. studied 977 surgical cases of cerebral AVM and reported that early neurological sequelae and permanent complications were observed in 9.3 and 3.4% of patients, respectively (18). Multivariate analysis revealed that two or more units of red blood cell transfusions or 1,000 mL or more of intraoperative bleeding were significant risk factors for complications (18). Thus, performing surgery for AVMs with a small amount of intraoperative bleeding contributes to improved prognosis for post-operative patients.

The usefulness of pre-operative embolization to reduce intraoperative bleeding in brain AVM surgery has been widely reported. Spetzler et al. reported the effectiveness of surgical removal following multiple pre-operative embolizations for Spetzler–Martin high-grade classification of brain AVMs (19). As a result, pre-operative embolization shortened the surgical time and reduced the amount of bleeding, leading to a reduction in surgical complications and improved long-term neurological outcomes. DeMeritt et al. reported that 70% of patients in the pre-operative embolization with surgery group had no signs of neurological loss 1 week after surgery, compared with 41% ($P < 0.05$) in the surgery alone group (20). Thus, pre-operative embolization seems to be an essential procedure for improving the safety of surgery for brain AVMs (21).

Conventionally, NBCA has been widely used as an embolic substance for endovascular embolization. Several reports have

shown that the effect of embolization with NBCA on brain AVMs is beneficial. Meisel et al. investigated the impact of partial embolization on brain AVMs using NBCA and reported a 31% reduction in the annual bleeding rate compared to pretreatment (22). Moreover, Wikholm et al. followed up 150 cases of cerebral arteriovenous malformation that underwent embolization with NBCA for an average of 6.3 years and reported a high occlusion rate of at least 90% and stable neurological signs (23).

On the other hand, pre-operative embolization using NBCA requires obliteration of at least two-thirds or more volume of the nidus to be effective in brain AVM surgery (24). Multiple embolization sessions are mandatory when using NBCA, especially for large brain AVMs, to achieve adequate nidus obliteration in radiation exposure and hemodynamic safety. However, some reports have shown that an increase in the number of treatment sessions is a significant factor in the post-operative neurological complication rate, and aggressive treatment using NBCA should be modestly applied to select cases (2, 25). NBCA has been used for a long time; however, medical professionals have waited a long time for the emergence of an embolic substance with greater maneuverability and better safety to replace it.

To overcome this, a new liquid embolic substance, the Onyx liquid embolic system, has been developed and launched on the market. Compared to the NBCA, Onyx has (1) slower cast formation, (2) blood flow-independent delivery, (3) cohesiveness, and (4) allows for penetration into a smaller vessel size (7–9). These characteristics enable the plug-and-push method and embolization of the brain AVM microvasculature. Several observational studies have reported that pre-operative embolization with Onyx may improve surgical outcomes for brain AVMs (9, 10, 26–28). On the other hand, a multicenter randomized controlled trial and some observational studies that directly compared Onyx and NBCA failed to show that pre-operative embolization using Onyx resulted in superior surgical outcomes (1, 8, 12). Thus, the effectiveness of pre-operative embolization with Onyx in AVM surgery is unclear.

In the present study, pre-operative embolization with Onyx significantly reduced intraoperative bleeding during AVM surgery compared to NBCA or coils. In addition, although the difference was not significant, the operation time tended to be shorter when using Onyx. We believe that the nidus occlusion technique makes the most of the unique characteristics of Onyx, which made it possible to achieve these results. As shown in **Figure 1**, when pre-operative embolization using NBCA was performed, even if the blood flow of the nidus appeared to disappear on cerebral angiography, the histopathological image revealed prominent RBCs in the nidus. This phenomenon is a result of the NBCA characteristics, which make it difficult to reach the microvessels of the nidus. In other words, NBCA embolization results in feeder occlusion, and blood flow from different routes results in persistent blood flow into the nidus.

On the other hand, the pathological findings in the Onyx-embolized nidus revealed Onyx cast in the microvessels instead of the erythrocytes, which result from the characteristic of Onyx to reach the microvasculature by the plug-and-push method: its ability to continuously inject and fill the nidus after the formation of the plug. These differences in the penetration of Onyx and NBCA into microvessels were the leading cause of the significant reduction in intraoperative bleeding in the Onyx group compared to the pre-Onyx group in this study. In other words, the nidus occlusion policy with the plug-and-push method is crucial for achieving a significant reduction in intraoperative bleeding during AVM surgery *via* pre-operative embolization with Onyx.

The morbidity and mortality rates of the combined strategy, which included Onyx pre-operative embolization and surgery, were reported to be 0–21% and 0–2%, respectively (8, 10, 12, 26, 29). In the present study, the post-operative morbidity rate was 4.5%, and mortality did not occur, indicating good treatment results equivalent to those in the aforementioned studies. Moreover, although the Onyx group had a more eloquent location nidus than the pre-Onyx group, the post-operative prognosis was similar. There were no cases showing deterioration of the mRS score in the Onyx group. As mentioned above, accurate dissection around the nidus in a bloodless field is crucial for safe AVM surgery, especially for eloquent lesions (13–15, 17, 18, 30). We believe that our plug-and-push method with Onyx pre-operative embolization contributed to the achievement of an excellent post-operative prognosis due to reduced intraoperative bleeding because of the nidus occlusion policy.

Some of the limitations of this study were (1) the small sample size, (2) retrospective analysis, (3) patients recruited from a few centers, (4) absence of randomization, and (5) outcome assessment by neurosurgeons at our institutes, without external validation. The sample size was also insufficient for subgroup analysis based on the Spetzler–Martin grade of the AVMs and/or other characteristics. Moreover, two neurosurgeons (T.I. and N.I.) operated on all the patients in this series. Thus, care should be taken when generalizing our results to patients with AVM.

Although further studies will be needed to conclusively demonstrate the impact of Onyx pre-operative embolization for AVM surgery, this is the first study to show that presurgical embolization using Onyx results in significantly less intraoperative blood loss and a marginally shorter operation time compared with the pre-Onyx era, with favorable post-treatment outcomes.

CONCLUSIONS

Pre-operative embolization with Onyx could significantly reduce the amount of intraoperative bleeding in AVM resection and marginally shorten the operative time compared with the pre-Onyx era. The favorable treatment outcomes of the Onyx group were comparable with those of previous reports. We believe that these results could be achieved by our nidus occlusion policy using the plug-and-push method with Onyx. Pre-operative embolization using Onyx may contribute to safe AVM surgery.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Nagasaki University Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

TI: conceptualization, methodology, visualization, and writing—original draft preparation. TI, KO, RT, YMatsun, ES, and HM: data curation. TI, NH, and KH: formal analysis. TI and TM: funding acquisition. TI and YMo: investigation. TI, IN, and TM: project administration. YMatsum, IN, and TM: supervision. NK and YT: validation. TI, SY, SB, TH, and TA: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Hemodynamic Comparison of Treatment Strategies for Intracranial Vertebral Artery Fusiform Aneurysms

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Objective: This study comparatively analyzed the hemodynamic changes resulting from various simulated stent-assisted embolization treatments to explore an optimal treatment strategy for intracranial vertebral artery fusiform aneurysms. An actual vertebral fusiform aneurysm case treated by large coil post-stenting (PLCS) was used as a control.

Materials and Methods: A single case of an intracranial vertebral artery fusiform aneurysm underwent a preoperative and eight postoperative finite element treatment simulations: PLCS [single and dual Low-profile Visualized Intraluminal Support (LVIS)], Jailing technique (single and dual LVIS both simulated twice, Pipeline Embolization Device (PED) with or without large coils (LCs). Qualitative and quantitative assessments were performed to analyze the most common hemodynamic risk factors for recurrence.

Results: Jailing technique and PED-only had a high residual flow volume (RFV) and wall shear stress (WSS) on the large curvature of the blood flow impingement region. Quantitative analysis determined that PLSC and PED had a lower RFV compared to preoperative than did the jailing technique [PED+LC 2.46% < PLCS 1.2 (dual LVIS) 4.75% < PLCS 1.1 (single LVIS) 6.34% < PED 6.58% < Jailing 2.2 12.45% < Jailing 1.2 12.71% < Jailing 1.1 14.28% < Jailing 2.1 16.44%]. The sac-averaged flow velocity treated by PLCS, PED and PED+LC compared to preoperatively was significantly lower than the jailing technique [PED+LC = PLCS 1.2 (dual LVIS) 17.5% < PLCS 1.1 (single LVIS) = PED 27.5% < Jailing 1.2 = Jailing 2.2 32.5% < Jailing 1.1 37.5% < Jailing 2.1 40%]. The sac-averaged WSS for the PLCS 1.2 (dual LVIS) model was lower than the PED+LC, while the high WSS area of the Jailing 1 model was larger than for Jailing 2 [PLCS 1.2 38.94% (dual LVIS) < PED+LC 41% < PLCS 1.1 43.36% (single LVIS) < PED 45.23% < Jailing 2.1 47.49% < Jailing 2.2 47.79% < Jailing 1.1 48.97% < Jailing 1.2 49.85%].

Conclusions: For fusiform aneurysms, post large coil stenting can provide a uniform coil configuration potentially reducing the hemodynamic risk factors of recurrence. Flow diverters also may reduce the recurrence risk, with long-term follow-up required, especially to monitor branch blood flow to prevent postoperative ischemia.

Keywords: coil, flow diverter, stent, hemodynamics, recurrence

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INTRODUCTION

Fusiform aneurysms are more prone to occur in the posterior circulation (1). Intracranial aneurysm recurrence is related to the degree of the parent artery involved (2). Fusiform aneurysms have more extensive wall enhancement than the saccular variety indicating wall inflammation and vulnerability (3, 4). Vulnerable vessel walls exposed to abnormal hemodynamics are susceptible to aneurysm growth, rupture, and recurrence (5–7). For highly involved parent artery aneurysms, coils cannot be safely and effectively used for vascular reconstruction (8). Revascularization therapy mainly relies on various stent-assisted embolization techniques presenting different procedures and recurrence risks (9, 10). Currently, our center's most commonly used stent-assisted embolization techniques include Jailing, post-large-coil stenting (PLCS), and Pipeline Embolization Device (PED) combined with or without large-coil techniques. Jailing techniques with conventional stents present a relatively low procedure-related risk with a high recurrence exposure (11). PLCS proposed in our center can be used to embolize fusiform aneurysms and lower their recurrence rate. Increased off-label use of flow diverters presents some extent ischemic risk for intracranial vertebral artery fusiform aneurysms (12). Unclear hemodynamic effects among the various reconstructive strategies for intracranial vertebral fusiform aneurysms make it difficult to nominate an optimal approach.

Hemodynamically, wall shear stress (WSS) is an important risk factor for aneurysm rupture. Low WSS induces destructive remodeling caused by inflammatory cells, resulting in aneurysm instability. Higher than normal WSS also can result in the enlargement and rupture of aneurysms based on other mechanisms (6). This study focused on the recanalization risk induced by blood inflow for the unruptured aneurysm. To elucidate the issue of postoperative recurrence, high WSS and velocity, larger residual flow volume (RFV), and other hemodynamic characteristics from large blood inflow were correlated with recanalization and recurrence (13–18). Luo et al. (16) reported high WSS and flow velocity in partially occluded saccular aneurysms prone to recanalization. Umeda et al. (18) found that RFV predicts the recurrence of coiled paraclinoid aneurysms. For large narrow-necked aneurysms, PED with coils treatment can accelerate thrombotic efficiency, favoring aneurysm occlusion in the competition with delayed rupture (19).

However, no CFD mechanism-related studies exist on the potential recurrence risk among different reconstruction techniques for intracranial vertebral artery fusiform aneurysms. This present study modeled an actual case of vertebral artery fusiform aneurysm treated with PLCS without considering thrombosis, simulating and comparing the preoperative hemodynamic effects and eight post-operative finite element treatment simulations– PLCS x 2 (single and dual Low-profile Visualized Intraluminal Support (LVIS)), Jailing technique x 4 (single and double LVIS both simulated twice with different coil configurations), and 2x Pipeline Embolization Device (PED) with or without large coils (LCs) – to analyze the most common hemodynamic risk factors for recurrence.

MATERIALS AND METHODS

Population

A man in his 40 s with an intracranial fusiform aneurysm in the dominant vertebral artery experienced a sudden headache once 2 months ago. The left vertebral artery fusiform aneurysm diagnosed on MRI in a local hospital was treated with PLCS techniques (schematic **Figure 1** for details). Three large coils compared to aneurysmal width (two Microplex-10 8 mm x 30 cm and one 7 mm x 30 cm) plus two LVIS stents (4.5 x 20 mm and 4.5 x 15 mm) were implanted with a modified Raymond IIIa outcome (**Figure 2**). The 12-month DSA follow-up showed no recurrence or remnant (Raymond I).

Model Reconstruction

Raw data was generated from DSA rotational angiography (high-pressure injector rate 3 ml/s, time 5 s, total volume 15 ml) using Siemens equipment Axiom Artis Zeego, Siemens Medical Solutions, Erlangen, Germany). The acquired raw data were reconstructed in Mimics 17 software (Materialise, Leuven, Vlaams-Brabant, Belgium) to generate STL files subsequently imported into Geomagic 12 software for model repair, trimming, and smoothing (**Figure 3A**).

Finite Element Simulation

A two-step finite element simulation of stent deployment was devised (20). Firstly, LVIS and Pipeline models were generated in SolidWorks (Dassault Systems, SolidWorks Corp., MA) according to geometric information (21). Secondly, stent deployment was simulated in ABAQUS v6.14 (SIMULIA, Providence, RI) using the Dynamic Explicit Method and B31 element type, which was also done for the coils. Stent-specific parameters obtained from a previous study (22) were divided into three steps: compression, delivery, and release of the stent. Initially, the stent in its fully released state was inserted into a round tube and compressed to a state where it can be inserted into the micro-catheter model by allocating the displacement load of the outer wall. Then, the stent followed the delivery path of the micro-catheter by providing the displacement load to be delivered to the target area. Finally, the micro-catheter was withdrawn, and the stent was released using a predefined stress-strain field allowing the stent to expand in the designated area to fit the inner wall of the artery. The delivery path was generated by connecting the center points of the blood vessel cross-section, while the stent release point was determined by the surgical image. The "general contact" algorithm was used in ABAQUS to deal with the complex interactions during stent release, with the friction coefficient assigned to 0.15 (23).

The simulation of the coil insertion process was carried out in ABAQUS (20). The process involved both pulling in and pushing out the coil. The coils were generated in MATLAB (MathWorks, Natwick, MA) using centerlines to simplify the coil shape (22). First, a coil-microcatheter-aneurysm model was built using NX12.0, and then the model was imported into ABAQUS. The coil is pulled into the microcatheter by distributing a displacement load at one end of the coil, while the coil inside the microcatheter is pushed out into the aneurysm using a

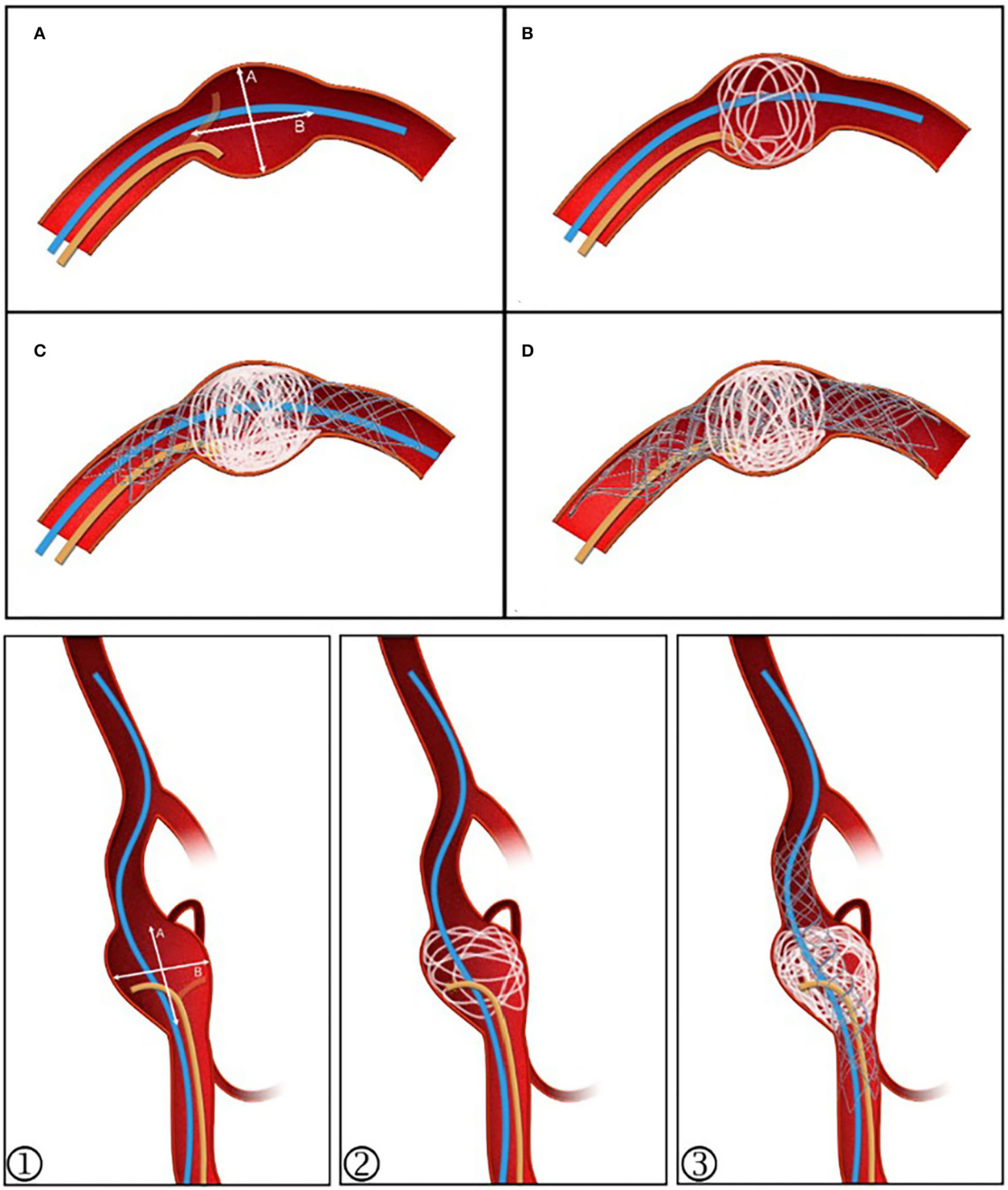

FIGURE 1 | Post-large coil stenting technique schematic diagram. **(A)** The stenting microcatheter (blue) and unshaped coiling microcatheter (yellow) are positioned. **(B)** Coil diameter is selected with reference to the value ≥A. The aneurysm sac is evenly filled. **(C)** Continued embolization using 2–4 coils, then deploying the stent and placing the stenting microcatheter at the distal segment as a backup. **(D)** If the sac is not densely embolized or coil protrusion into the stent occurs, a second stent can be released to provide flow diversion, allowing further embolization to proceed. ①–③ For those with branches or an irregular sac, the stent can be semi-released to assist in forming a basket while protecting the branches.

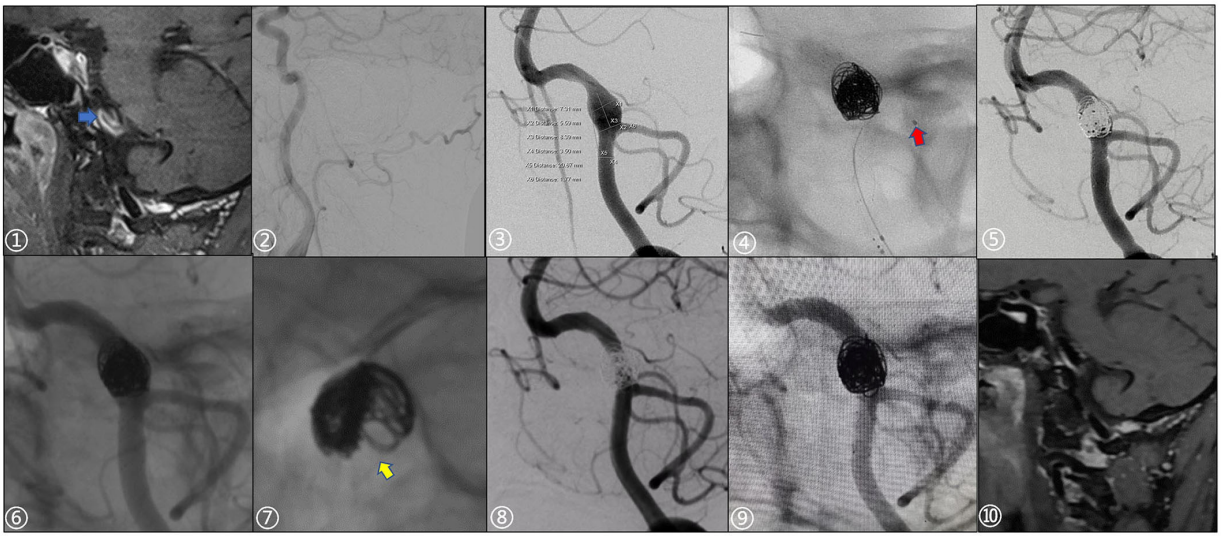

FIGURE 2 | A 49-year-old male patient presented with a sudden severe headache once 2 months prior. ① Preoperative high-resolution MRI showed significant enhancement of the vessel wall with the intraluminal slow flow (blue arrow). ② Right vertebral artery dysplasia. ③ Preoperative measurement of aneurysm and parent artery, aneurysm size: 7.31 x 8.39 mm. ④ Echelon-10 microcatheter (red arrow) was used to protect the posterior inferior cerebellar artery during operation. ⑤, ⑥ Stents were post-deployed, Immediate postoperative angiography and non-subtraction images showed slight stagnation in the aneurysm sac (Raymond IIIa; Microplex-10 coils: two 8 x 30 cm and one 7 x 30 cm; LVIS stents: 4.5 x 20 mm, 4.5 x 15 mm). ⑦ The distribution of the coils along the wall was not well-uniform. ⑧, ⑨ 12-month follow-up showed that there was no recurrence of the aneurysm (Raymond I) and the parent artery was patent. ⑩ 12-month follow-up with HR-MRI, the vortex in the sac disappeared, while the aneurysm wall was still partially enhanced.

pre-defined stress-strain field via creating a displacement load on the other end of the coil. Finally, the coil was placed in the aneurysm sac and then scanned in three dimensions according to the centerlines after placement (24, 25). The coil exhibited the following physical properties: a density of 2.13×10^{-8}kg/m^3, Young's modulus of 10,000 Pa, and Poisson's ratio of 0.39 (26). The three-dimensional stent and coil models obtained by finite element simulation were output as STL format files, maintaining the same spatial coordinate system as the blood vessel model in the next step of the hemodynamic simulation.

The simulated hemodynamics of the preoperative untreated model was adopted as baseline parameters. The jailing technique with coiling was conducted twice, to simulate both separated and connected coils. A total of eight postoperative treatment options were simulated (**Figure 3**): 1. PED implantation; 2. PED + large coils; 3–6. Jailing technique with two coiling simulations (1.1 single/1.2 dual LVIS with separated coils and 2.1 single/2.2 dual LVIS with connected coils); 7–8. For post-large-coil stenting (PLCS1.1 single/1.2 dual LVIS). Three large-coils (two Microplex-10 8 mm x 30 cm and one 7 mm x30 cm) and two stents (LVIS 4.5 mm x 20 mm and 4.5 mm x 15 mm) were selected. The PED size (3.75*20 mm) was determined by two neuro-interventionists with over 10-year experience.

Hemodynamic Simulation

The virtual treatment model is subjected to CFD simulation analysis. To generate mesh files, the preoperative and eight postoperative models were imported into ANSYS ICEM CFD version 16.2 (ANSYS Inc, Canonsburg, PA, USA). A grid independence test was performed to determine the appropriate grid size for the stability of the calculation outcomes and the efficiency calculation. Due to the different geometric dimensions of vessels, stents, and coils, the mesh sizes of different object surfaces are determined to various values. The grid size for the stent wire surface was finally set to 1/6 of the circumference of the wire. The artery and coil surface were 0.16 mm along with the 0.03 mm LVIS surface and the 0.015 mm PED surface grid. A three-layer boundary mesh was added to improve the accuracy of the simulation results in the near-surface region of the model. Final mesh calculations were generated as follows: 3 million for the preoperative model; 96 million for PED and PED with large coil; 45 million for Jailing1.1, 1.2, and PLCS1.1; 65 million for Jailing 2.1, 2.2, and PLCS1.2. The hemodynamic simulations were fitted with the Navier-Stokes equations for steady-state simulations using ANSYS CFX version 2019 (ANSYS Inc, Canonsburg, PA, USA). The blood was designed as an incompressible, laminar flow, Newtonian fluid with a density of 1,056 kg/m^3 and a viscosity of.0035 kg/m·s (27). The vessel wall was designed to be rigid with no slip. The flow rate for the vertebral artery inlet was set at 1.3 ml/s (28). Outlet conditions were calculated according to Murray's law of flow distribution (29). A steady coupled solver was used for laminar simulation. The residual target of the convergence criterion was 0.00001.

Statistical Analysis of the Various Approaches

Qualitative and quantitative methods were used to analyze and compare the flow velocity, WSS, and RFV (v >0.03 m/s) (19)

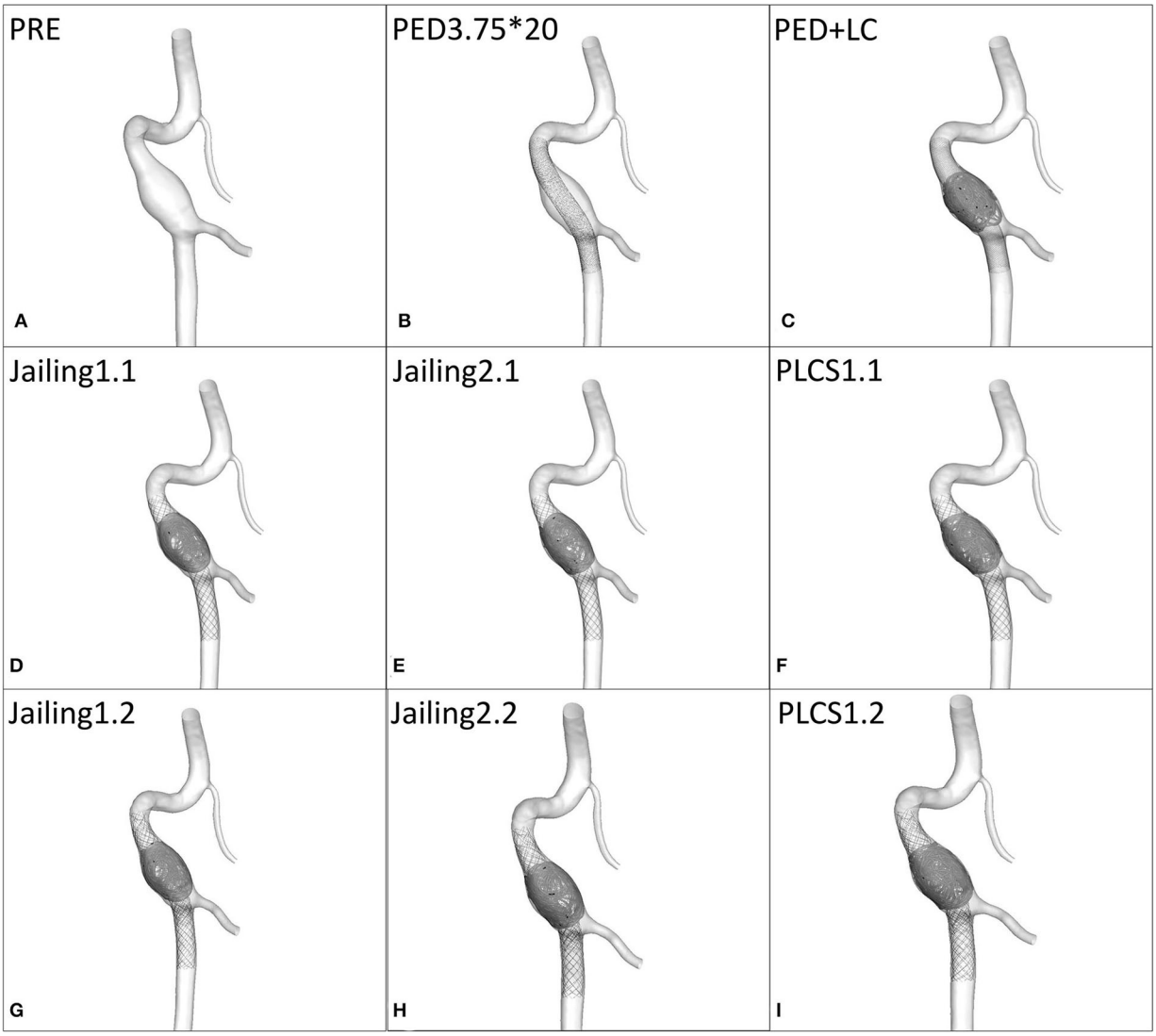

FIGURE 3 | Simulation reconstruction model of aneurysm preoperatively and for eight different treatment approaches. **(A)** Preoperative aneurysm model. **(B)** Pipeline device (PED) 3.75*20 mm implantation model. **(C)** Large coil; Microplex-10 8 x 30 cm x 2 + 7 x 30 cm and PED-3.75 x 20 mm. **(D–F)** Single LVIS stent 4.5 x 20 mm (Jailing 1.1, Jailing 2.1, and PLCS 1.1). **(G–I)** Dual LVIS stent 4.5 x 20 mm, 4.5 x 15 mm (Jailing 1.2, Jailing 2.2, and PLCS 1.2).

in the aneurysm sac among nine simulations (preoperative and eight postoperative simulations). The vascular segment covered by the stents was intercepted and the aneurysm sac volume was defined as the space between the vascular wall and the stent surface. Defining the preoperative hemodynamic parameters as 100%, the hemodynamic changes for each of the treatment strategies were analyzed and compared.

RESULTS

Residual Blood Flow Volume (RFV)

Qualitative Analysis

RFV was discerned in the sac after PED implantation alone. According to the simulated projection and down-the-barrel view, the Jailing technique had a higher RFV on the large curved side due to the non-uniformity of the coil embolization, more similar to PED-only implantation than the RFV values of the PED+LC and PLCS techniques (**Figures 4**, **5**).

Quantitative Analysis

Both PLCS and PED with or without large-coils had lower residual percentages of RFV than the Jailing technique compared with pre-operation. The residual percentage of RFV of for dual stents in PLCS and Jailing are smaller than for the single stent [PED + LC 2.46% < PLCS 1.2 (dual LVIS) 4.75% < PLCS 1.1 (single LVIS) 6.34% < PED 6.58% < Jailing 2.2 12.45% < Jailing 1.2 12.71% < Jailing 1.1 14.28 % < Jailing 2.1 16.44%; **Table 1**, **Figure 6**].

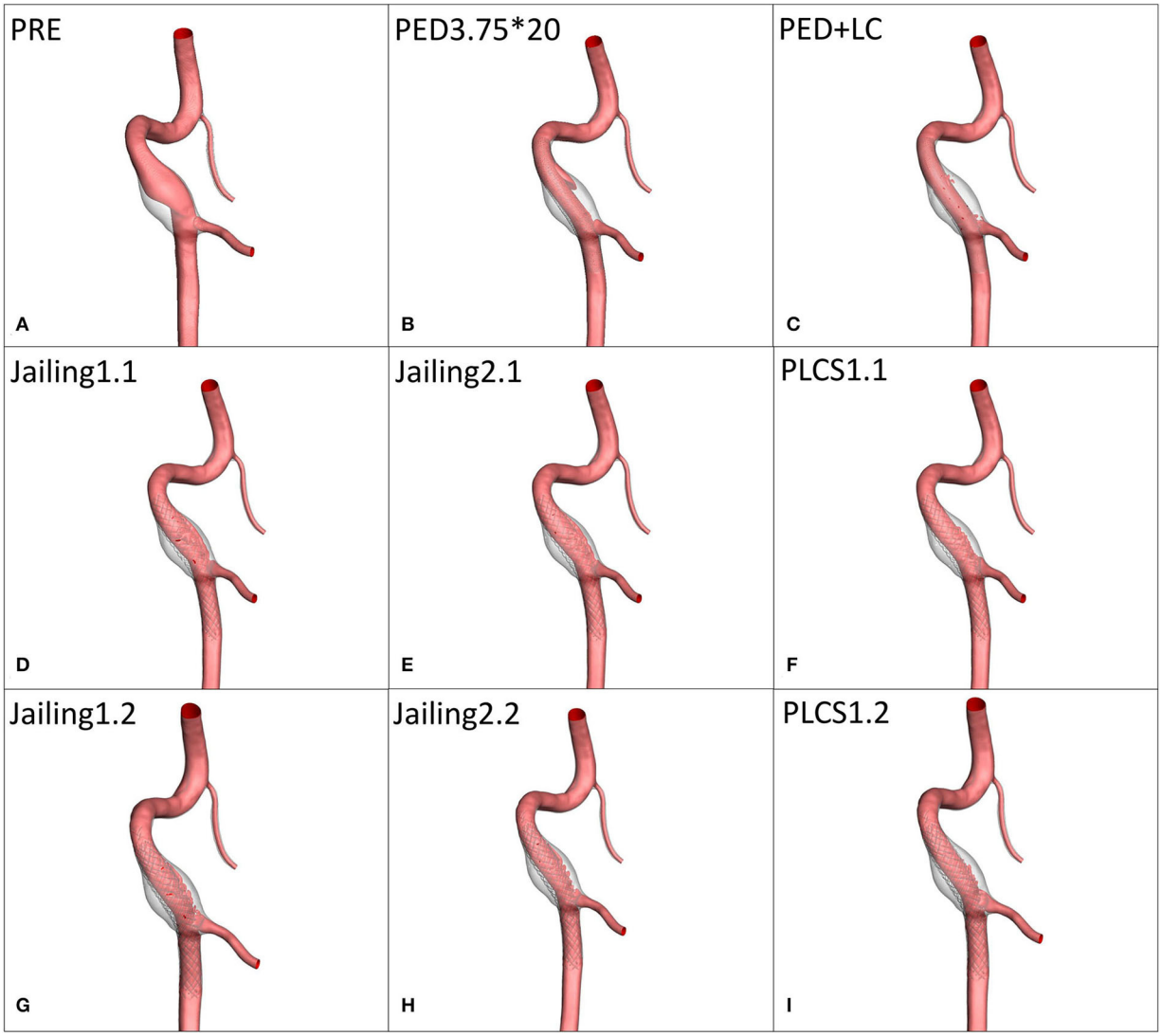

FIGURE 4 | (A) Preoperative high-velocity region (v > 0.03 m/s). **(B–I)** RFV maps for different stent-assisted techniques.

The Average Flow Velocity of the Aneurysm Sac

The streamline diagram and quantitative analysis showed that the averaged flow velocity in the aneurysm sac after PLCS for PED with and without large-coils decreased significantly more than for the Jailing technique. The sac-averaged flow velocity for dual stents in PLCS and Jailing technique are smaller than single stent [PED+LC = PLCS1.2 (double LVIS) 17.5% < PLCS1.1 (single LVIS) = PED 27.5% < Jailing1.2 = Jailing2.2 32.5% < Jailing1.1 37.5% < Jailing2.1 40%; **Table 1**, **Figures 6**, **7**].

Average WSS of the Aneurysm Wall

Qualitative Analysis

WSS values of all postoperative models decreased significantly compared with pre-operation. Jailing 1 experienced a larger high WSS region than Jailing 2 (**Figure 8**).

Quantitative Analysis

WSS from the PLCS 1.2 (double LVIS) had the largest decline [PLCS1.2 (Dual LVIS) 38.94% < PED+LC 41% < PLCS1.1 (Single LVIS) 43.36% < PED 45.23% < Jailing2.1 47.49% < Jailing 2.2 47.79% < Jailing 1.1 48.97% < Jailing1.2 49.85 %; **Table 1**, **Figures 6**, **8**].

DISCUSSION

The main conclusion of this study is that PLCS and PED with or without large-coils can significantly decrease the hemodynamic risk factors of recurrence in the treatment of fusiform vertebral aneurysm compared with the jailing technique. Hemodynamic studies have shown that high WSS, large RFV, and high-velocity areas after interventional treatment are risk factors for aneurysmal recurrence (17, 19, 30). Chatziprodromou et al. and

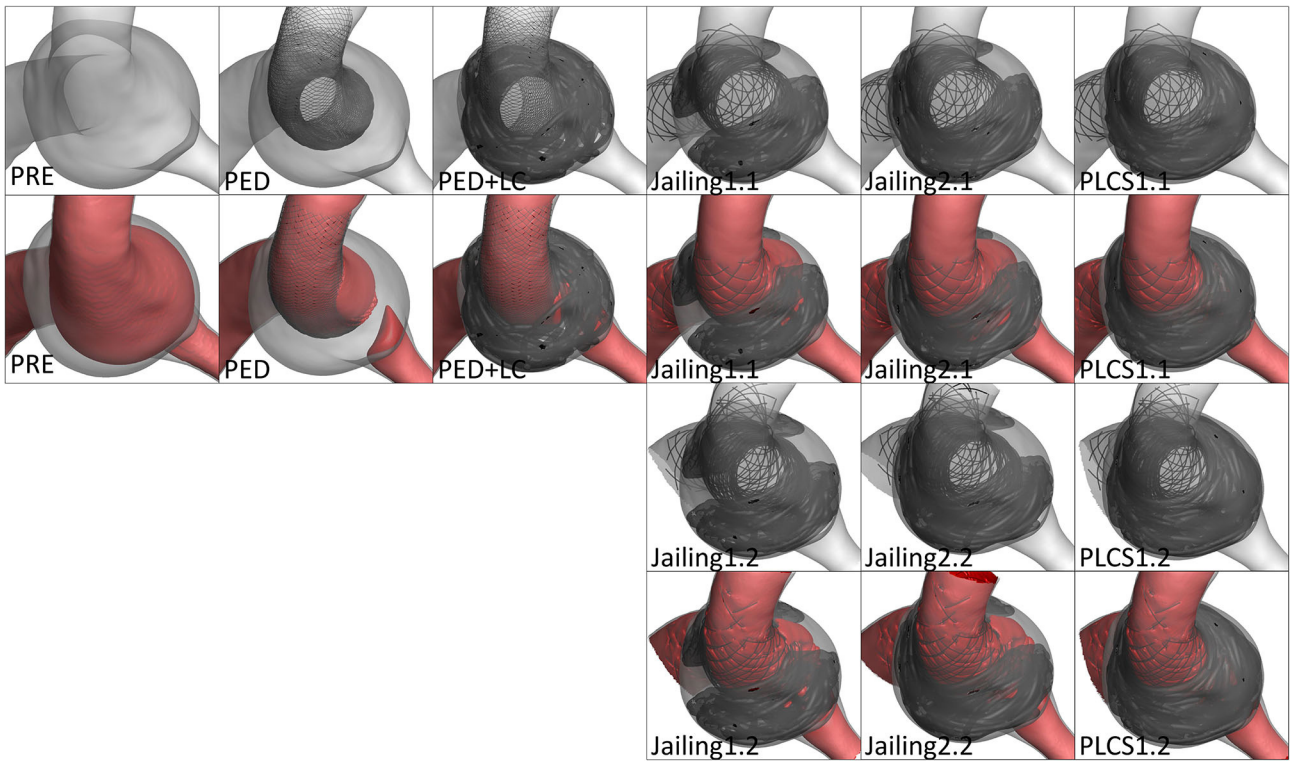

FIGURE 5 | The down-the-barrel view of preoperative and different stent-assisted technique simulation treatment.

TABLE 1 | Hemodynamic parameters pre-and post-operative stimulation treatment for various stent-assisted techniques.

Parameters	Pre	PED	PED+LC	Jailing1.1	Jailing1.2	Jailing2.1	Jailing2.2	PLCS1.1	PLCS1.2
Sac-averaged WSS (Pa)	0.339	0.154	0.139	0.166	0.169	0.161	0.162	0.147	0.132
Sac-averaged velocity (m/s)	0.040	0.011	0.007	0.015	0.013	0.016	0.013	0.011	0.007
RFV (mm^3; v > 0.03m/s)	121.12	7.964	2.975	17.300	15.397	19.907	15.074	7.678	5.753

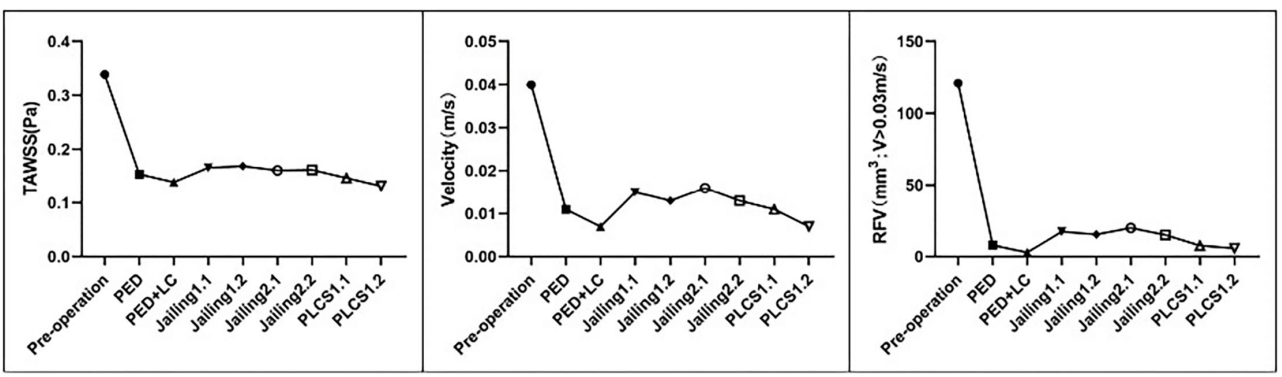

FIGURE 6 | Quantitative assessment of the sac-averaged WSS, sac-averaged velocity, and RFV of the simulated preoperative and various stent-assisted models.

Rayz et al. (31, 32) reported that high blood flow velocity and high WSS are often accompanied, which is not conducive to thrombosis in the aneurysm sac and has an adverse impact on the long-term stability after embolization. Hemodynamic risk parameters – WSS, RFV, and high-velocity regions – were lower for PLCS than those for jailing, thus reducing the recurrence

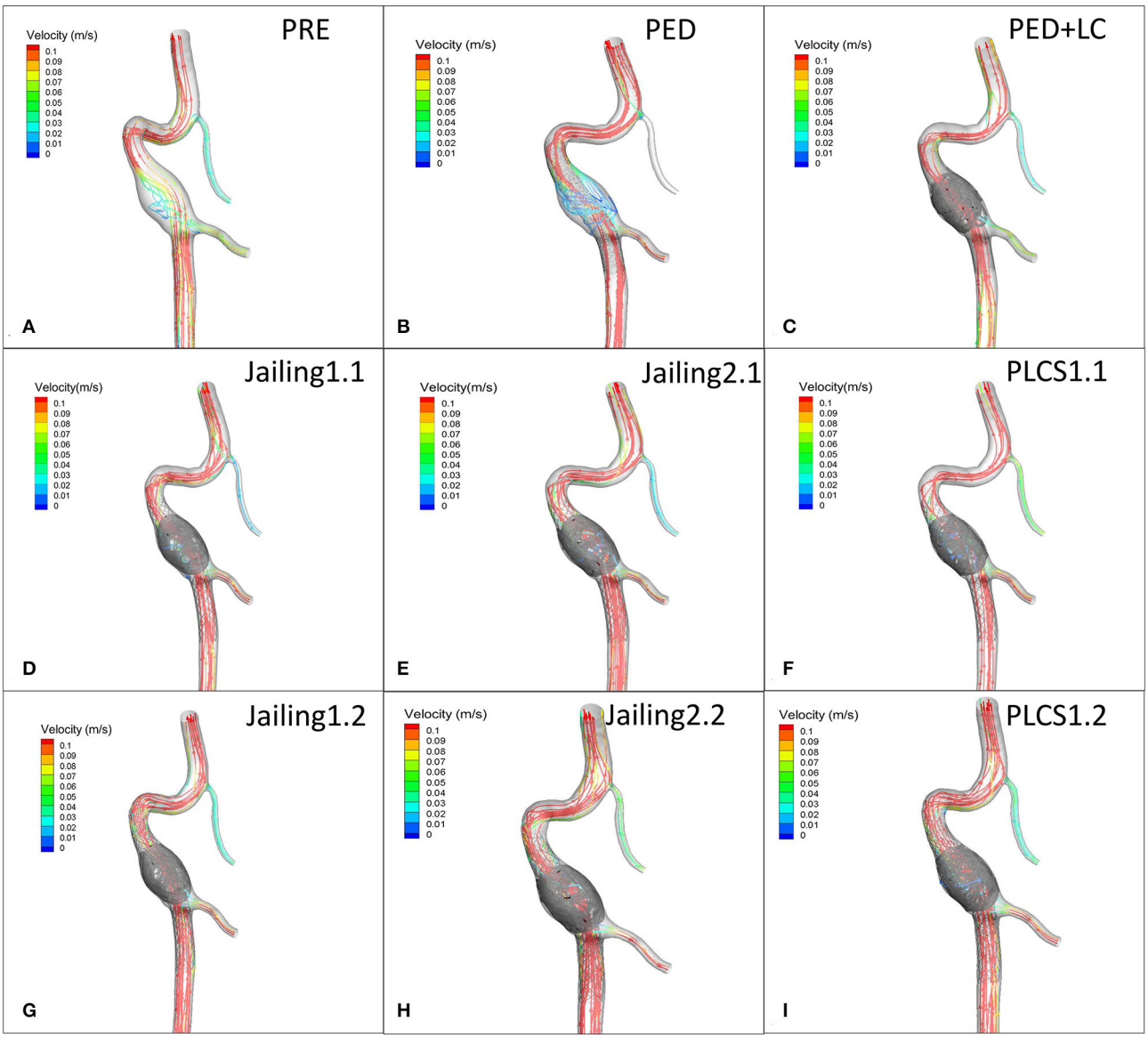

FIGURE 7 | (A) Preoperative velocity streamlines. **(B–I)** Post-operative velocity streamlines for PED, PED+LC, Jailing, and PLCS models.

risk. In both jailing and PLCS technique, the hemodynamic risk factors of the single LVIS stent were larger than those for dual LVIS stents. Therefore, the overlapping stent technique is a beneficial option to reduce the potential risk of recurrence compared with a single stent. At present, few studies analyze the recurrence of vertebral artery aneurysms based on CFD (33, 34). These studies indicated that hemodynamics played a role in vertebral fusiform aneurysms similar to saccular aneurysms. Although the data, in this case, are based on the vertebral artery, the results should be generalizable to other aneurysms with similar morphological characteristics.

Quantitative analysis showed hemodynamic risk factors for recurrence after jailing was also confirmed higher than PLCS and PED techniques due to incomplete embolization from the micro-catheter fixed by the stent (35). Hong et al. (36) proposed that the semi-Jailing technique could help improve the maneuverability of the micro-catheter during the treatment of wide-necked complex aneurysms. Chen et al. (10) advocated a modified balloon-in-stent technique for the treatment of fusiform aneurysms. Prolonged balloon inflation and stent malposition potentially lead to thromboembolic events. The wide extent of inflammation on the fusiform aneurysm wall indicated vulnerability to recurrence (3, 37). The uniform distribution of coils helps create a local flow diversion effect which can reduce recurrence. The inflow tract WSS for Jailing 1 is larger than Jailing 2 mainly due to a failure to fully pack the impingement area, consistent with the recurrence of saccular aneurysms after embolization (38, 39). This suggests that more emphasis should be placed on the inflow tract.

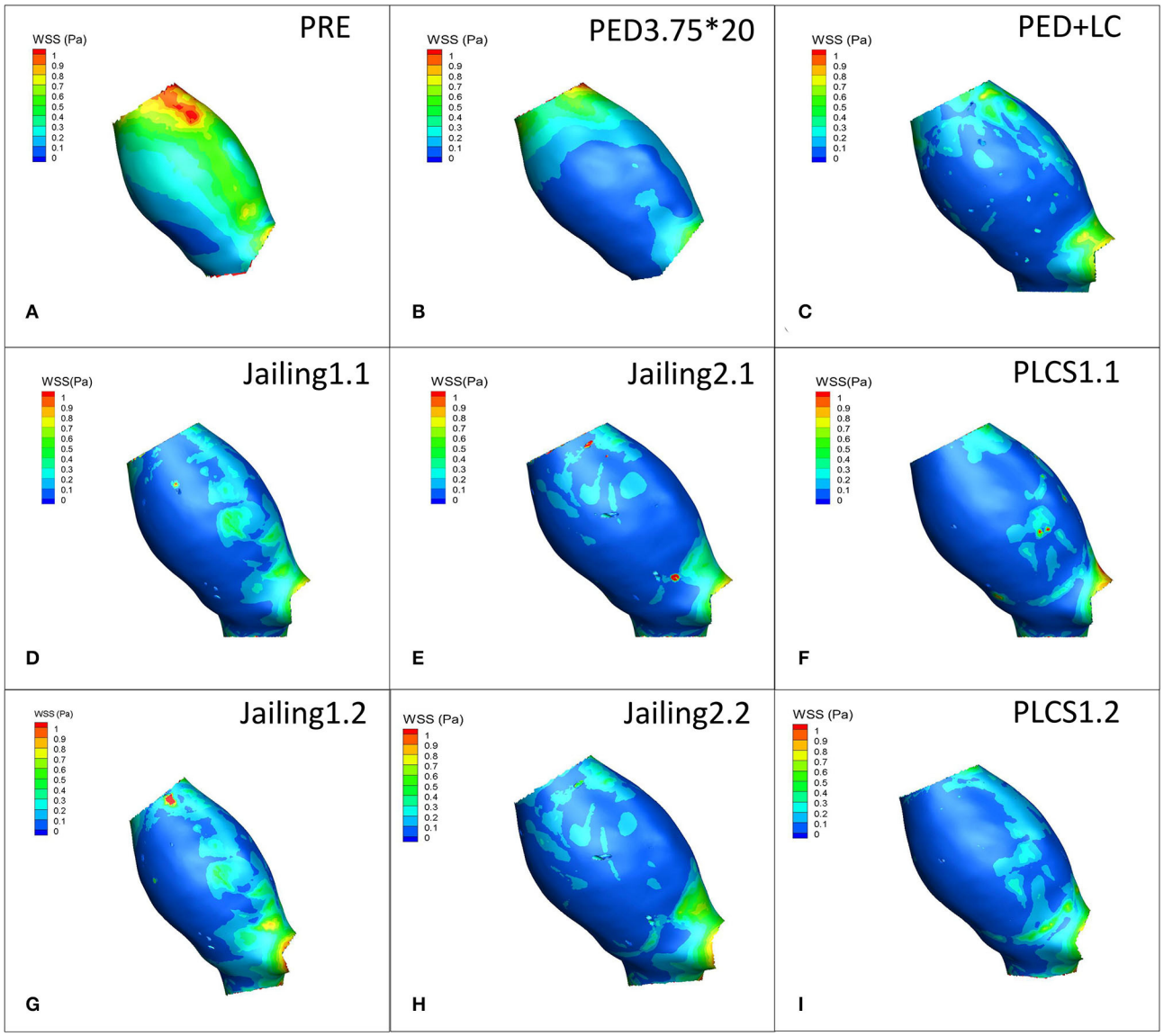

FIGURE 8 | (A) Preoperative WSS. **(B–I)** WSS of PED, PED+LC, Jailing, and PLCS post-operative models.

Procedure critical points of the PLCS technique on coil, stent, and embolizing microcatheter selection should be emphasized for fusiform aneurysms. Coil packing has some inherent randomness in clinical practice. Coil configuration for PLCS should achieve a more even distribution than the jailing technique. The framing coils (diameter $\geq$ aneurysm width) often require repeated adjustment contributing to uniform coil distribution. While protecting the patency of the involved branches, semi-deployment of the stent can assist in framing the large coils. Soft coils with a smaller primary helix diameter were preferred to result in stent well-apposition. The proper amount of large-coils (2–4) is normally used to prevent stent opening failure. Small coils with a rivet technique may result in stenosis or delayed occlusion of the parent artery. LVIS stents were more usually selected for the PLCS technique due to a number of advantages. LVIS stents can be re-sheathed and pushed during the deployment process (9) allowing for the uniform distribution of large coils. Further, LVIS stent is tied to lower thrombogenicity than Pipeline stents. Finally, LVIS stents are more cost-effective than Pipelines (10). However, due to the local dense coverage rate, antiplatelets should be rigorously confirmed to avoid any delayed vessel occlusion. Previous studies have reported a wide range of LVIS in-stent stenosis rates between 17.5 and 86.7% (40, 41). According to previous studies, multiple flow diverters without coils were not recommended for ruptured lesions due to the necessity of strict antiplatelet therapy (42). On the other hand, treatment with overlapping PEDs also presents a high ischemic risk (12), such that non-overlapping stents

might be preferable. Multiple flow diverters were not simulated in this present study. Using a Pipeline device with large coils is a promising technique for fusiform aneurysms, especially for aneurysms without evident perforators or branches. An unshaped or 45-degree tip can provide sway to the micro-catheter permitting greater maneuverability and thus the creation of more uniform baskets. For such patients, antiplatelet medication should be administered cautiously in the peri- and postoperative phase, with timely adjustment according to TEG and CYC2P19 gene results.

Limitations

This study has the following limitations. This proof-of-concept study was a single case. However, it effectively demonstrates hemodynamic effects after treatment for different stent-assisted techniques. Comprehensive intracranial stents such as Solitaire and Neuroform were not tested. In addition, not all treatment strategy combinations were simulated such as Jailing + Pipeline. Since a Murray flow outlet was employed in this study, the flow rate change of the PICA branch was inapplicable. The pressure outlet should be a feasible way to evaluate the influence on the flow rate of PICA. Flow change may be affected by thrombus and stent endothelialization. This study did not address the degree of vascular curvature which can affect the different stent-assisted strategies. The coil distribution from the PLCS technique is somewhat random and the simulation cannot be completely consistent with actual placement. This CFD study used common assumptions such as rigid walls and a lack of specific inflow and outflow tract flow conditions.

CONCLUSIONS

For fusiform aneurysms of the intracranial vertebral artery, the PLCS technique can more uniformly pack aneurysm sacs and may reduce the hemodynamic risk factors of recurrence similar to flow diverters, though long-term follow-up is still required. Attention should be paid to the impact on any perforators or branches to lessen the ischemic risk.

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 Institution Review Board of Huashan Hospital affiliated to Fudan University approved this retrospective study and waived the requirement for informed consent. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XZ and JX conceived and designed the research and handled the funding and supervision. YJ acquired the data and drafted the manuscript. YJ, GLu, LG, GLi, and RZ analyzed and interpreted the data. YJ, XL, and HW performed the statistical analysis. All authors made critical revisions to the manuscript for important intellectual content and reviewed the final version of the manuscript.

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Conflict of Interest: GLi, RZ, XL, and JX were employed by the company ArteryFlow Technology Co., Ltd.

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

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Intra-Arterial Thrombolysis Vs. Mechanical Thrombectomy in Acute Minor Ischemic Stroke Due to Large Vessel Occlusion

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Background: The efficacy and safety of mechanical thrombectomy (MT) in acute large vessel occlusion (LVO) patients with minor stroke (NIHSS $\leq$ 5) remains undetermined. We aimed to compare the efficacy and safety of intra-arterial thrombolysis (IAT) alone vs. MT for LVO patients with minor stroke.

Methods: Patients were selected from the Acute Ischemic Stroke Cooperation Group of Endovascular Treatment (ANGEL) registry, a prospective multicenter registry study, and divided into MT and IAT alone groups. We compared the outcome measures between the two groups, including 90-day functional outcome evaluated by the modified Rankin Scale (mRS), the final recanalization level, intracranial hemorrhage, and mortality within 90-days by logistic regression models with adjustment. Besides the conventional multivariable analysis, we performed a sensitivity analysis by adjusting the propensity score to confirm our results. The propensity score was derived using a logistic regression model.

Results: Of the 120 patients, 63 received IAT alone and 57 received MT as the first-line treatment strategy. As compared to MT group, patients in the IAT alone group were associated with a higher chance of 90-day mRS 0-2 [93.7% vs. 71.9%, odds ratio (OR) = 4.75, 95% confidence interval (CI): 1.20–18.80, $P = 0.027$], a high chance of 90-day mRS 0-3 (96.8% vs. 86.7%, OR = 11.35, 95% CI: 1.93–66.86, $P = 0.007$), a shorter median time from puncture to recanalization (PTR) (60 min vs. 100 min, $\beta = -63.70$, 95% CI: −81.79– −45.61, $P < 0.001$), a lower chance of any intracranial hemorrhage (ICH) within 48 h (3.2% vs. 19.3%, OR = 0.15, 95% CI: 0.03–0.79, $P = 0.025$), and a lower chance of mortablity within 90 days (1.6% vs. 9.2%, OR = 0.05, 95% CI: 0.01–0.57, $P = 0.016$). Similarly, the sensitivity analysis showed the robustness of the primary analysis.

Conclusions: Compared with MT, IAT may improve 90-day clinical outcomes with decreased ICH rate and mortality in LVO patients with minor stroke.

Keywords: minor ischemic stroke, large vessel occlusion, outcome, mechanical thrombectomy, intra-arterial thrombolysis

INTRODUCTION

Minor stroke is not uncommon, occuring in about two-thirds of the entire acute ischemic stroke (AIS) population (1). An underlying large vessel occlusion (LVO) may increase the risk of further clinical deterioration in this population (2). Several well-known randomized controlled trials (RCT) have demonstrated the clinical benefit of mechanical thrombectomy (MT) over standard medical care in AIS patients with large vessel occlusion (3). Confirming this, the international stroke guidelines (4, 5) have also provided a high level of evidence and treatment recommendations. However, a majority of these trials enrolled patients with baseline National Institutes of Health Stroke Scale (NIHSS) scores of >5 (3, 6), and therefore the efficacy and safety of MT for LVO patients with a minor stroke (NIHSS $\leq$ 5) remain unclear.

Previous studies report that, compared to standard medical treatment, MT could result in similar clinical outcomes and a higher risk of intracranial hemorrhage (ICH) in LVO patients with minor stroke (7, 8). Unlike MT, which has an invasive characteristic concerning arterial wall damage, non-MT treatment, such as intra-arterial thrombolysis (IAT), seems to be an appropriate treatment option for LVO with minor stroke. Additionally, IAT had a better rate of recanalization when compared with standard medical treatment (9) and could also enhance the microcirculatory reperfusion of the target occlusion artery (10).

Therefore, we sought to compare the efficacy and safety of IAT alone vs. MT for acute LVO patients with minor stroke from a multicenter prospective registry in China.

METHODS

Study Population

Patients from the Acute Ischemic Stroke Cooperation Group of Endovascular Treatment (ANGEL) registry, a multicenter, prospective registry study from June 2015 to December 2017, were included in the data analysis (11). They were screened further to meet the following criteria: (1) age more than 18 years; (2) clinical diagnosis of ischemic stroke in which the stroke symptoms lasted for more than 30 min and showed no improvement before treatment; (3) patients with minor stroke (NIHSS 0-5); (4) patients with large vessel occlusion confirmed by digital subtraction angiography (DSA) including the internal carotid artery, the middle cerebral artery (M1/2/3 segment), the anterior cerebral artery, the basilar artery, or the dominant vertebral artery, and the posterior cerebral artery; and (5) patients who underwent IAT alone or MT.

Data Collection

We prospectively collected all the variables, including (1) clinical: age, sex, vascular risk factors, medical history, baseline NIHSS, procedure details, periprocedural management, the time points of working flow, and functional outcomes [e.g., modified Rankin scale (mRS)] and (2) imaging: baseline CT/ magnetic resonance (MR) and CT angiography/MR angiography imaging, DSA, and postprocedural CT.

The imaging data were evaluated by the imaging core laboratory consisting of three trained and experienced neuroradiologists blinded to the clinical data and outcomes. Two neuroradiologists reviewed all imaging independently, with a third available for adjudication when needed.

The imaging core laboratory assessed the Alberta Stroke Program Early CT Score (ASPECTS) on baseline CT (12), modified Thrombolysis in Cerebral Infarction (mTICI) (13), procedure-related complications (e.g., intraprocedural embolization, arterial perforation, arterial dissection, and vasospasm requiring treatment) on DSA, and intracranial hemorrhage (ICH) after EVT on postprocedural CT.

Endovascular Treatment

Patients from the MT group underwent MT (stent retriever or/and contact aspiration) as the first-line endovascular treatment strategy. The rescue treatment, such as balloon angioplasty or stenting, was allowed at the surgeon's discretion. Patients from IAT alone group received only IAT as the sole endovascular treatment.

IAT can be conducted on patients from the ANGEL registry based on the surgeon's discretion. According to PROACT-II (Prolyse in Acute Cerebral Thromboembolism II) (9) and MELT (Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial) (14) studies, we performed intra-arterial thrombolysis before or next to and distal to the thrombus by injecting urokinase (UK) or recombinant tissue plasminogen (r-tPA) manually *via* the microcatheter. The best dose and rate were not fixed, and we suggested 1 mg/min r-tPA for no more than 40 mg or intra-arterial (IA) 10–30 thousand unit/min urokinase for no more than 1 million units. If the patients had received intravenous r-tPA previously, we suggested an intra-arterial dosage of <30 mg alteplase or 400,000 U urokinase (11).

Outcome Measurement

We assessed 90-day functional outcomes using the mRS by a standardized telephone interview performed by trained investigators blinded to clinical information. The primary outcome was 90-day mRS 0-2. The secondary outcomes were 90-day mRS 0-1, 90-day mRS 0-3, time from puncture to recanalization (PTR), time from onset to recanalization (OTR), successful recanalization, and complete recanalization. The safety outcomes were any ICH within 48 h and mortality (mRS 6) within 90 days. Successful recanalization was defined as mTICI 2b-3 at the end of the procedure, and complete recanalization was defined as mTICI 3 at the end of the procedure.

Statistical Analysis

Categorical variables were expressed as numbers (percentage), and continuous variables were expressed as median (interquartile range [IQR]). We performed an univariable analysis using the Mann-Whitney *U*-test for continuous variables and χ^2 or Fisher's exact test for categorical variables to identify the difference between the IAT alone and MT groups. For comparing the outcome measures, all the significant baseline characteristics in

the univariate analysis ($P < 0.05$) and the baseline variables likely to influence clinical outcomes as potential confounders (age, sex, NIHSS, bridging IVT, tirofiban during the procedure, heparin during the procedure, and occlusion location) were adjusted by binary logistic regression model or generalized linear model as appropriate to analyze the adjusted odds ratios (OR) or β-coefficients with their 95% confidence intervals (CI).

In addition to conventional multivariable analysis, we performed a sensitivity analysis by adjusting the propensity score, derived using a logistic regression model that included all the potential confounders above. A two-sided *P*-value of < 0.05 was considered to be statistically significant. SPSS version 26.0 (IBM, Armonk, NY, USA) was used to analyze the data.

RESULTS

As shown in **Figure 1**, 797 of the 917 patients were excluded for the following reasons: (1) incomplete baseline data (n =2); (2) NIHSS ≥ 6 (n = 784); (3) stenting alone (n = 6); (4) balloon angioplasty alone (n = 1); and (4) only stenting and balloon angiography (n = 4). Finally, our study included 120 patients. Of the 120 patients, 63 were in the IAT alone group and 57 were in the MT group.

Baseline Characteristics

Table 1 shows the baseline characteristics according to the MT and IAT alone group. Patients in the IAT alone group were younger than the MT group [60(52–65) vs. 65(59–75), P = 0.001]. Patients in the IAT alone group had a lower rate of bridging IVT (6.3% vs. 24.6%, P = 0.005), a lower dose of tirofiban during EVT (25.4% vs. 49.1%, P = 0.007), and a lower dose of heparin during EVT (17.5% vs. 38.6%, P = 0.010) than patients in the MT group.

Outcome Measures

Table 2 shows the comparison of the outcome measures between the IAT alone and MT groups. Regarding the primary outcome

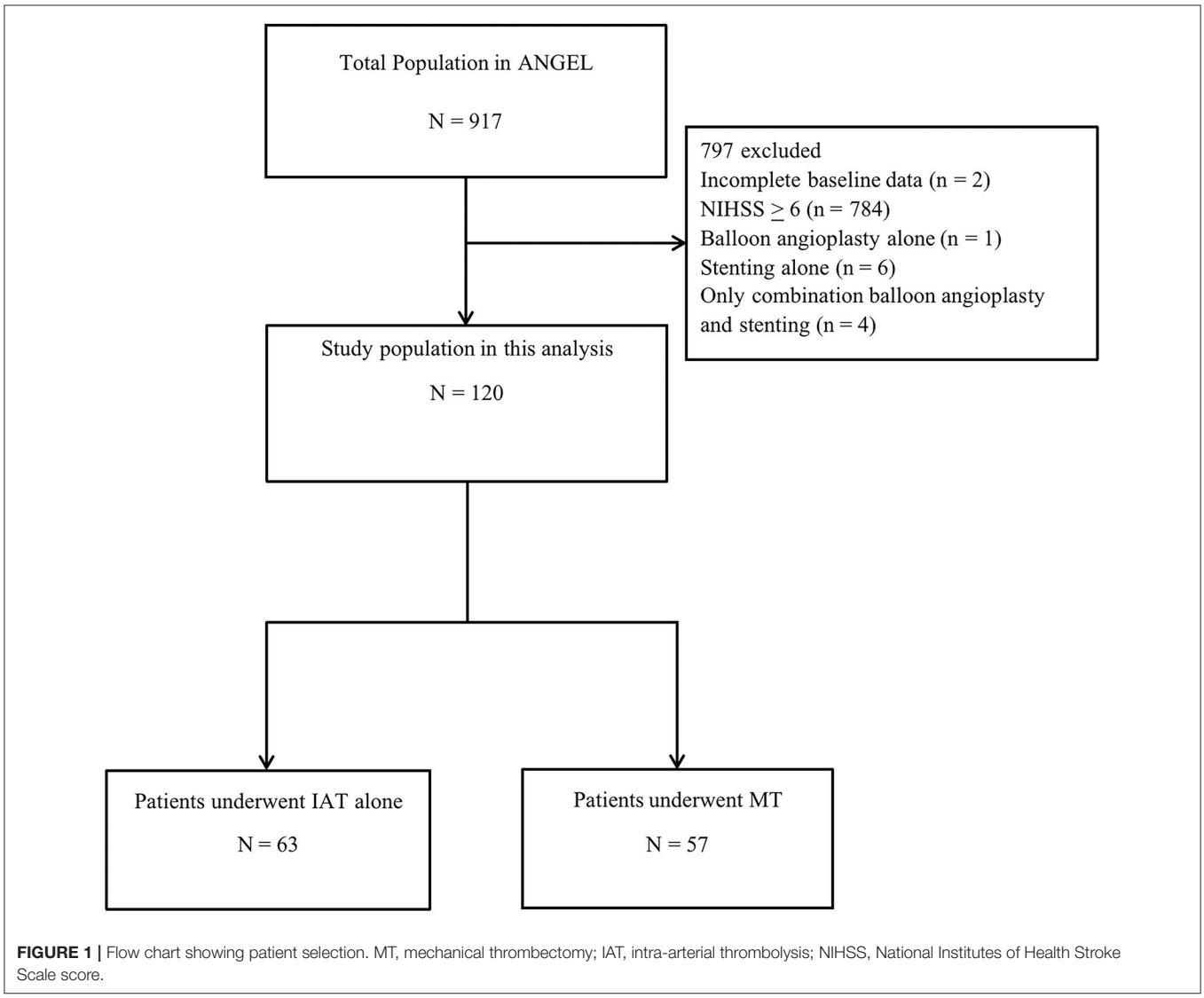

FIGURE 1 | Flow chart showing patient selection. MT, mechanical thrombectomy; IAT, intra-arterial thrombolysis; NIHSS, National Institutes of Health Stroke Scale score.

TABLE 1 | Baseline characteristics of IAT alone and MT group in LVO patients with minor stroke.

Characteristics	Total ($n = 120$)	IAT alone ($n = 63$)	MT ($n = 57$)	*P*-value
Age–year, median (IQR)	62 (53–70)	60 (52–65)	65 (59–75)	**0.001**
Male sex–no (%)	89 (74.2)	45 (71.4)	44 (77.2)	0.471
SBP–mmHg, median (IQR)	145 (133–160)	140 (135–160)	148 (130–166)	0.613
ASPECTS, median (IQR)	8 (7–8)	8 (7–8)	8 (7–8)	0.174
NIHSS score, median (IQR)	3 (1–4)	3 (1–4)	3 (1–4)	0.829
Current or previous smoking–no (%)	46 (38.3)	24 (38.1)	22 (38.6)	0.955
Current or previous drinking–no (%)	27 (22.5)	14 (22.2)	13 (22.8)	0.939
Medical history–no (%)				
Atrial Fibrillation	4 (3.3)	1 (1.6)	3 (1.9)	0.345
Diabetes Mellitus	26 (21.7)	10 (15.9)	16 (28.1)	0.105
Previous stroke	8 (6.7)	2 (3.2)	6 (10.5)	0.148
Hypertension	68 (56.7)	32 (50.8)	36 (63.2)	0.172
TOAST classification–no (%)				
Large artery atherosclerosis	102 (85.0)	56 (88.9)	46 (80.7)	0.210
Cardiogenic	3 (2.5)	0 (0)	3 (5.3)	0.104
Other etiology or unknown etiology	15 (12.5)	7 (11.1)	8 (14.0)	0.692
Occlusion site confirmed by DSA–no (%)				0.238
ICA	36 (30.0)	17 (27.0)	19 (33.3)	
M1	19 (15.8)	12 (19.1)	7 (12.3)	
M2/3	7 (5.8)	4 (6.3)	3 (5.3)	
ACA	3 (2.5)	2 (3.2)	1 (1.8)	
PCA	8 (6.7)	7 (11.1)	1 (1.8)	
V-BA	47 (39.2)	21 (33.3)	26 (45.6)	
Anterior circulation–no (%)	65 (54.2)	35 (55.6)	30 (52.6)	0.748
Posterior circulation–no (%)	55 (45.8)	28 (44.4)	27 (47.4)	
OTD time, median (IQR), min	264 (180–328)	281 (180–360)	250 (153–301)	0.198
DTP time, median (IQR), min	131 (109–200)	130 (92–199)	131 (119–203)	0.130
OTP time, median (IQR), min	430 (343–550)	443 (330–670)	430 (360–493)	0.499
Peri-procedural antithrombotic and anticoagulant–no (%)				
Prior use of antiplatelet agents	29 (24.2)	13 (20.6)	16 (28.1)	0.342
Bridging IVT	18 (15.0)	4 (6.3)	14 (24.6)	**0.005**
Tirofiban during the procedure	44 (36.7)	16 (25.4)	28 (49.1)	**0.007**
Heparin during the procedure	33 (27.5)	11 (17.5)	22 (38.6)	**0.010**

MT, mechanical thrombectomy; SD, standard deviation; SBP, systolic blood pressure; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale score; ASPECTS, Alberta Stroke Program Early CT score, TOAST, trial of ORG 10172 in acute stroke treatment; ICA, internal carotid artery; M1, middle cerebral artery M1 segment; M2/3, middle cerebral artery M2/3 segment; ACA, anterior cerebral artery; PCA, posterior cerebral artery; V-BA, vertebrobasilar artery; OTD, time from onset to door; DTP, time from door to puncture; PTR, time from puncture to recanalization; OTP, time from onset to puncture; OTR, time from onset to recanalization; IVT, intravenous thrombolysis; IAT, intra-arterial thrombolysis. Bold values indicates statistical significance.

(90-day mRS 0-2), patients in the IAT alone group had a higher 90-day mRS 0-2 rate than patients in the MT group (93.7% vs. 71.9%, OR = 4.75, 95% CI: 1.20–18.80, $P = 0.027$) (**Figure 2**). Regarding the secondary outcomes, the IAT alone group had higher rates of 90-day mRS 0-3 (96.8% vs. 75.4%, OR = 11.35, 95% CI: 1.93–66.86, $P = 0.007$) and shorter PTR [60(40–80) min vs. 100(80–157) min, $\beta = -63.70$, 95% CI: −81.79– −45.61, $P < 0.001$] than the MT group. Regarding the safety outcomes, the IAT alone group had less ICH within 48 h (3.2% vs. 19.3%, OR = 0.15, 95% CI: 0.03–0.79, $P = 0.025$) and mortality (mRS 6) within 90 days (1.6% vs. 17.5%, OR = 0.05, 95% CI: 0.01–0.57, $P = 0.016$). However, the angiographic outcomes (successful recanalization and complete recanalization) were similar between the two groups (all $P > 0.05$).

Sensitivity Analysis

After the sensitivity analysis, we also found that the IAT alone group was independently associated with a higher chance of 90-day mRS 0-2 (OR = 4.17, 95% CI: 1.17–14.89, $P = 0.028$) and 90-day mRS 0-3 (OR = 9.79, 95% CI: 1.89–50.60, $P = 0.006$), a lower chance of any ICH within 48 h (OR = 0.13, 95% CI: 0.03–0.71, $P = 0.019$) and mortality within 90 days (OR = 0.06, 95% CI: 0.01–0.52, $P = 0.011$), and shorter PTR ($\beta = -61.44$, 95% CI:

−80.05– −42.82, $P < 0.001$) as compared with the MT group (**Table 3**).

DISCUSSION

Our study showed that in LVO patients who presented with minor stroke, the IAT alone group had better 90-day functional outcomes, less mortality within 90 days, and less ICH rate within 48 h compared to the MT group.

Several RCTs have demonstrated the benefits of MT for LVO patients with NIHSS > 6 (3). However, the safety and efficacy of IAT for LVO were still unclear. Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) (15) and Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trails (16) allowed the use of IAT, but no subgroup analyses have been published so far. Kaesmacher et al. (2020) reported that IA urokinase, after failed, unsuccessful, or incomplete MT for anterior circulation LVO with NIHSS ≥

TABLE 2 | Comparison of outcomes between IAT alone and MT groups.

Variables	Overall population $n = 120$			Unadjusted model		Adjusted model[a]	
	Total ($n = 120$)	IAT alone($n = 63$)	MT ($n = 57$)	Effect size(95% CI)	*P*–value	Effect size(95% CI[a])	*P*-value
Primary outcome-no (%)							
90-day mRS 0-2	100 (83.3)	59 (93.7)	41 (71.9)	5.76 (1.79–18.47)	0.003	4.75 (1.20–18.80)	**0.027**
Secondary outcomes							
90-day mRS 0-1- no (%)	87 (72.5)	53 (84.1)	34 (59.6)	3.59 (1.52–8.46)	0.004	2.44 (0.88–6.71)	0.085
90-day mRS 0-3- no (%)	104 (86.7)	61 (96.8)	43 (75.4)	9.93 (2.15–45.96)	0.003	11.35 (1.93–66.86)	**0.007**
Successful recanalization-no (%)	108 (90.0)	57 (90.5)	51 (89.5)	1.12 (0.34–3.69)	0.855	0.29 (0.06–1.49)	0.285
Complete recanalization-no (%)	87 (72.5)	47 (74.6)	40 (70.2)	1.25 (0.56–2.79)	0.588	0.73 (0.28–1.91)	0.517
PTR, median (IQR), min	80 (50–110)	60 (40–80)	100 (80–157)	−50.18 (−66.89–33.48)[b]	<0.001	−63.70 (−81.79–−45.61)[b]	<0.001
OTR, median (IQR), min	514 (433–664)	510 (395–730)	528 (450–648)	3.48 (−84.03–90.99)[b]	0.938	−11.90 (−104.09–80.30)[b]	0.800
Safety outcomes-no (%)							
Any ICH within 48 h	13 (10.8)	2 (3.2)	11 (19.3)	0.14 (0.03–0.65)	0.012	0.15 (0.03–0.79)	**0.025**
Mortality within 90 days (mRS 6)	11 (9.2)	1 (1.6)	10 (17.5)	0.08 (0.01–0.61)	0.016	0.05 (0.01–0.57)	**0.016**

ICH, intracranial hemorrhage; mTICI, modified thrombolysis in cerebral infarction; mRS, modified Rankin scale; IAT, intra-arterial thrombolysis; MT, mechanical thrombectomy; PTR, time from puncture to recanalization; OTR, time from onset to recanalization; OR, odds ratio; CI, confidence interval.

[a]*Adjusted for age, sex, NIHSS, intravenous thrombolysis, tirofiban and heparin use during the procedure, and occlusion location.*

[b]*The β-coefficients were calculated using a generalized linear model.*

Bold values indicates statistical significance.

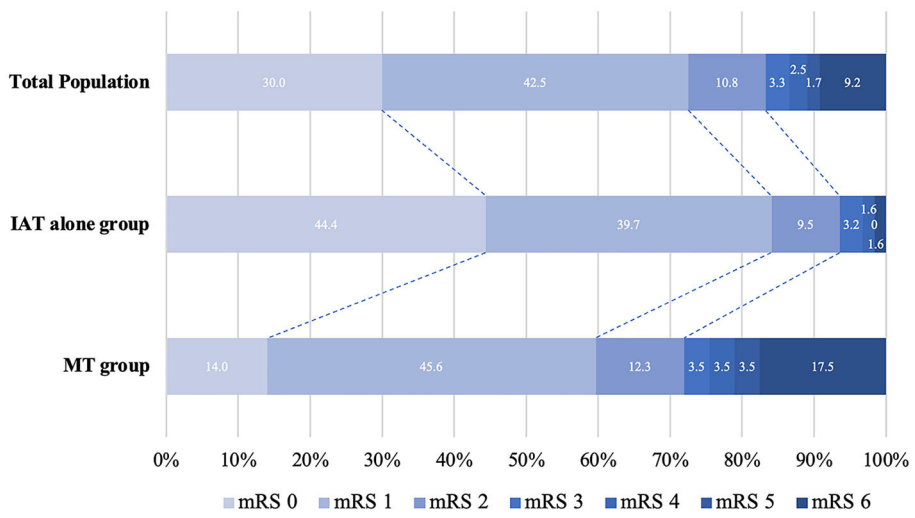

FIGURE 2 | Distribution of modified Rankin Scale (mRS) scores at 3 months between IAT alone and MT group. MT, mechanical thrombectomy; IAT, intra-arterial thrombolysis; NIHSS, National Institutes of Health Stroke Scale score; mRS, modified Rankin scale.

TABLE 3 | Sensitivity analysis: comparison of outcomes between IAT alone and MT groups with adjustment for the propensity score.

Variables	Overall population $n = 120$			Adjusted model[a]	
	Total ($n = 120$)	IAT alone ($n = 63$)	MT ($n = 57$)	Effect size (95% CI[a])	*P*-value[a]
Primary outcome- no (%)					
90-day mRS 0-2	100 (83.3)	59 (93.7)	41 (71.9)	4.17 (1.17–14.89)	**0.028**
Secondary outcomes					
90-day mRS 0-1- no (%)	87 (72.5)	53 (84.1)	34 (59.6)	2.38 (0.91–6.19)	0.076
90-day mRS 0-3- no (%)	104 (86.7)	61 (96.8)	43 (75.4)	9.79 (1.89–50.60)	**0.006**
Successful recanalization- no (%)	108 (90.0)	57 (90.5)	51 (89.5)	0.30 (0.07–1.36)	0.118
Complete recanalization- no (%)	87 (72.5)	47 (74.6)	40 (70.2)	0.73 (0.29–1.87)	0.514
PTR, median (IQR), min	80 (50–110)	60 (40–80)	100 (80–157)	−61.44 (−80.05–−42.82)[b]	**<0.001**
OTR, median (IQR), min	514 (433–664)	510 (395–730)	528 (450–648)	−7.89 (−107.71–91.94)[b]	0.877
Safety outcomes- no (%)					
Any ICH within 48 h	13 (10.8)	2 (3.2)	11 (19.3)	0.13 (0.03–0.71)	**0.019**
Mortality within 90 days (mRS 6)	11 (9.2)	1 (1.6)	10 (17.5)	0.06 (0.01–0.52)	**0.011**

ICH, intracranial hemorrhage; mTICI, modified thrombolysis in cerebral infarction; mRS, modified Rankin scale; IAT, intra-arterial thrombolysis; MT, mechanical thrombectomy; PTR, time from puncture to recanalization; OTR, time from onset to recanalization; OR, odds ratio; CI, confidence interval.

[a]*Adjusted for the propensity score.*

[b]*The β-coefficients were calculated using a generalized linear model.*

Bold values indicates statistical significance.

6, was safe and improved angiographic reperfusion (17). The Chemical Optimization of Cerebral Embolectomy (CHOICE) RCT demonstrated that adjunct IA r-tPA after successful reperfusion following thrombectomy was more likely to yield an excellent neurological outcome at 90 days in patients with LVO (18).

In contrast to the two studies mentioned above, we compared the clinical and angiographic outcomes between IAT alone and MT for LVO patients with minor stroke and found that IAT was more beneficial than MT, with lower mortality within 90 days and ICH rate within 48 h. Several reasons could explain our findings: (1) High recanalization rate was achieved in the IAT alone group despite no significant difference between the two groups regarding the recanalization rate in our study. It has been confirmed by previous well-known studies that recanalization rate is an essential factor for better outcomes (3, 19, 20). (2) IAT is easier to perform than MT, and the relatively less complex procedure could result in shorter PTR. In this study, IAT could reduce almost one-third of the recanalization time (40 min), in which delayed treatment time is the predictive factor for increased disability and bleeding rate (21). Thus, reducing the recanalization time might be an important factor in improving clinical prognosis. (3) MT procedure is more invasive, and arterial wall injury is inevitable. Moreover, the longer the retriever or aspiration times, the greater the injury to the arterial wall, which might also increase the risk of bleeding (22). (4) In our study, large artery atherosclerosis (LAA) accounted for 85.0% of all patients; LAA might exacerbate the injury during thrombus retrieval (2, 23).

Interestingly, the IAT alone group had similar angiographic outcomes to MT groups despite their clinical outcomes being superior to the MT group. One possible explanation for this result is that LAA is the most common etiology of stroke in our study. The patients with LAA generally had good collateral (24) and a low clot burden (25). Thus, it was relatively easy to achieve vascular recanalization with IAT or MT. Another notable finding in the current study is the very high rate (93.7%) of 90-day mRS 0-2 in the IAT alone group, which may be because IAT not only could achieve successful recanalization but also improved the distal microcirculation reperfusion (10).

There are several limitations to our study. First, our study was not an RCT, which could lead to selection bias. Second, the small sample size may decrease the statistical power to reflect the actual effects of the study. In addition, the small sample size also resulted in inflated confidence intervals due to a large number of adjustments for the limited number of patients. This may impact the precision of the studies and warrant confirmation in larger cohorts. Third, the thrombolytic agents and dosage were not unique, which could confound our results. Finally, due to the high prevalence of LAA in our cohort, our results could not be easily extrapolated to other populations.

CONCLUSIONS

IAT may prove safer and more effective than MT in patients with minor strokes. However, a large multicenter cohort or randomized controlled trial is urgently needed to clarify the results further. Furthermore, in addition to MT, it might also be worthwhile to explore IAT as an alternative to standard medical treatment in future trials.

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

AUTHOR CONTRIBUTIONS

ZM supervised and performed quality control for the study. AW performed the statistical analysis. DS, XH, and R acquired the data and wrote the manuscript with input from all co-authors. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.860987/full#supplementary-material

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Transvenous embolization of hemorrhagic brain arteriovenous malformations: Case reports and literature review

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Introduction: Transvenous embolization (TVE) has been proven to be safe and feasible as an alternative management of brain arteriovenous malformations (AVMs). We presented four patients with a hemorrhagic brain AVM who underwent TVE and reviewed the relevant literature.

Methods: Four patients underwent TVE of a hemorrhagic brain AVM in our center between July 2019 and July 2020. We retrospectively collected and analyzed the clinical and imaging data of these patients and those reported in previously published studies.

Results: Four patients with a hemorrhagic brain AVM were included. Nidus sizes ranged from 0.79 to 2.56 cm. Spetzler-Martin grade ranged from grade II to grade III. The AVM nidus was located in a deep brain region in three patients. One patient underwent TVE alone and three underwent combined transarterial and transvenous approaches. Digital subtraction angiography (DSA) demonstrated complete obliteration of the vascular malformation after embolization in all four patients. Three patients were independent [modified Rankin Scale (mRS) score $\leq$2] at discharge. All four patients were independent at the last follow-up. AVM obliteration was confirmed in all four patients at the last angiographic follow-up.

Conclusion: Transvenous embolization can be used as an alternative treatment for contemporary management of brain AVMs, appropriate patient selection is essential to achieve a good clinical outcome.

KEYWORDS

transvenous embolization, brain arteriovenous malformations, hemorrhage, endovascular treatment, obliteration

Introduction

Brain arteriovenous malformations (AVMs) are congenital lesions characterized by anomalous high-flow abnormal connections between cerebral arteries and veins (1, 2). Intracranial hemorrhage and seizure are the two most common clinical manifestations of brain AVMs; hemorrhage is the main cause of AVM-related mortality (3–5). Treatment of brain AVMs is still challenging because of their complicated anatomy and an uncertain prognosis. The optimal therapeutic strategy remains ill-defined, contemporary approaches include microsurgery, endovascular embolization, stereotactic radiosurgery, or various combinations of these modalities (6–9).

Since the publication of the Unruptured Brain Arteriovenous malformations (ARUBA) trial in 2014, the management of AVMs remains ill-defined. At present, there is insufficient pragmatic evidence to provide clear guidelines (10, 11). The introduction of liquid embolic agents and detachable tip microcatheters and significant advances in endovascular techniques and devices have brought remarkable clinical benefits to the curative therapy of AVMs (12–14). The traditional approach is transarterial, the main objective of endovascular treatment is to completely obliterate the nidus while preserving normal vessel architecture (15–17). However, the complete obliteration of the lesion may not be achievable with the absence of an arterial approach. The introduction of transvenous embolization (TVE) using Onyx (Covidien/ev3, Irvine, California) as a novel treatment modality has addressed this dilemma (18). The aim of this study was to report our preliminary experience with four patients with a hemorrhagic brain AVM who underwent TVE and review the relevant TVE literature.

Materials and methods

Study design and participants

The Institutional Ethics Committee of Beijing Tiantan Hospital approved this study. Between November 2019 and August 2020, TVE was introduced as an alternative treatment modality at the institution on a trial basis and implemented for consecutive patients with ruptured brain AVMs. The prospective database of 4 patients with ruptured brain AVMs who underwent TVE combined with transarterial support was retrospectively analyzed. Clinical and imaging data were retrospectively obtained from the medical records. Demographics, clinical presentation, neurological examination findings, medical history, and AVM characteristics of patients were recorded (Table 1). Each case in this report was discussed by a multidisciplinary committee that included at least one experienced neurosurgeon, one experienced neurointerventionalist, and one experienced radiosurgeon. The main inclusion criteria were as follows: (1) patients with ruptured brain AVMs; (2) patients who were not suitable for transarterial embolization due to lack of arterial access, tiny arterial branches, extremely tortuous course, and excessive feeding branches; (3) patients with lesions that were not amenable to surgery or radiosurgery or who refused to undergo surgery or radiosurgery; (4) patients with favorable venous angioarchitecture and single draining vein; and (5) patients who can understand and accept the risks associated with the procedure.

Technical description

All patients were placed under general endotracheal anesthesia with full heparinization and proper neurological monitoring by the same team of experienced interventional neuroradiologists and supporting personnel. Catheterization was performed using a femoral access with a 6-F sheath, and selective angiograms were performed before each treatment in all patients. A 6-F transarterial guiding catheter (Envoy; Codman & Shurtleff, Inc., Raynham, MA, USA), used for angiographic control injections during the procedure, was positioned in the cervical internal artery. Subsequently, a 6-French sheath was placed in the femoral vein, and another transvenous 6-F guiding catheter (Navien; Covidien/ev3, Irvine, California or Envoy, Cordis Neurovascular, Miami Lakes, FL, USA) was advanced into the intracranial venous sinus under roadmap guidance obtained through the arterial side. The distal tip of the guiding catheter was placed close to the origin of the AVM main drainage vein. A microcatheter (Marathon [Medtronic]; Apollo [Medtronic]; Echelon [Medtronic]; or Headway DUO [MicroVention, Inc., Aliso Viejo, CA, USA]) was advanced over a guidewire (0.08-inch Mirage; Covidien/ev3/0.014-inch Synchro; Stryker Neurovascular, Fremont, CA, USA), and the tip of the microcatheter was then navigated through the draining vein of the brain AVM and placed as close as possible to the nidus. Another transvenous microcatheter was then used to move through the draining vein of the brain AVM and placed next to the nidus. Microangiography was then performed to better visualize the angioarchitecture of draining veins and adjust the position of the microcatheter tip. Prior to TVE, three measures were taken to selectively control the supply arteries to the AVM in the brain. (1) Mean arterial pressure was reduced to 45–50 mm Hg. (2) To minimize the risk of the procedure, transarterial embolization was performed to reduce AVM flow and size prior to TVE in the presence of a feeding artery accessible by a microcatheter. Feeding arteries were embolized with Glubran® (GEM SRL, Viareggio, Italy) in the presence of a feeding artery accessible by a microcatheter. (3) The main feeding artery was blocked using a compliant balloon (HyperGlide; Medtronic). When two transvenous microcatheters navigated through the draining

TABLE 1 Patients and arteriovenous malformation characteristics.

Case	Age, y, sex	Previous rupture	Nidus size, cm	AVM location	S-M score	Technique	Venous collector	mRs score on admission	Postoperative mRs scores	mRs final score	Clinical outcome
1	36/F	Yes	1.98	L, basal ganglia, Deep	3	TAE+TVE	1	2	2	0	Cure
2	10/F	Yes	2.56	R, basal ganglia, Deep	3	TAE+TVE	1	2	3	2	Cure
3	17/F	Yes	2.24	R, basal ganglia, Deep	3	TVE	1	2	2	2	Cure
4	47/F	Yes	0.79	L, temporal lobe, Superficial	2	TAE+TVE	2	2	2	2	Cure

vein, the coils were placed in the draining vein next to the nidus through the transvenous microcatheter to create a plug. Another microcatheter in the nidus was ready for injecting Onyx. This was the typical transvenous pressure cooker technique (PCT) that can be accomplished with two microcatheters (19). Onyx was injected into the nidus *via* intravenous access, and once Onyx reflux was obtained, Onyx penetrated all the way through to the arterial branches. The microcatheter was withdrawn after full retrograde filling of the nidus with Onyx and anatomic obliteration of the AVM. Dyna computed tomography (CT) was performed routinely after embolization to confirm that no intracranial hemorrhage occurred. No additional anticoagulation was performed, and postoperative care followed the standard practice of transarterial embolization.

Case reports

Case 1

A 36-year-old man was hospitalized because of sudden severe headache and disturbed consciousness. Head CT showed intracerebral hemorrhage (ICH). The patient underwent digital subtraction angiography (DSA), which demonstrated a left basal ganglia AVM, Spetzler-Martin grade III. Nidus size was 1.98 cm and venous drainage was deep (Figure 1A). The feeding arteries included the anterior choroidal artery (AChA) and perforating arteries arising from the middle cerebral artery (MCA). The AVM drainage was through a single deep vein into the straight sinus. During the first stage procedure, superselective arteriography *via* the AChA and Glubran® (GEM SRL, Viareggio, Italy) was injected into the nidus under fluoroscopic guidance (Figure 1B). Afterward, DSA showed a Glubran® cast and a smaller nidus volume (Figure 1C). Two weeks later, the second stage procedure was performed. Two microcatheters were positioned through the straight sinus within the origin of the venous collector, and a balloon microcatheter was placed in the ipsilateral internal carotid artery (Figure 1D). After the balloon was inflated to provisionally occlude the internal carotid artery, we used the typical transvenous PCT to occlude the nidus completely (Figure 1E). No clinical complications were associated with the procedure, and the patient was discharged from the hospital with slight right limb weakness and a modified Rankin Scale (mRS) score of 2, which was unchanged as compared to the preoperative period. DSA 4 months later confirmed AVM obliteration (Figure 1F). At the 4-month follow-up, the patient was asymptomatic with an mRS score of 0.

Case 2

A 10-year-old boy was presented to the emergency department with an acute headache and disturbed

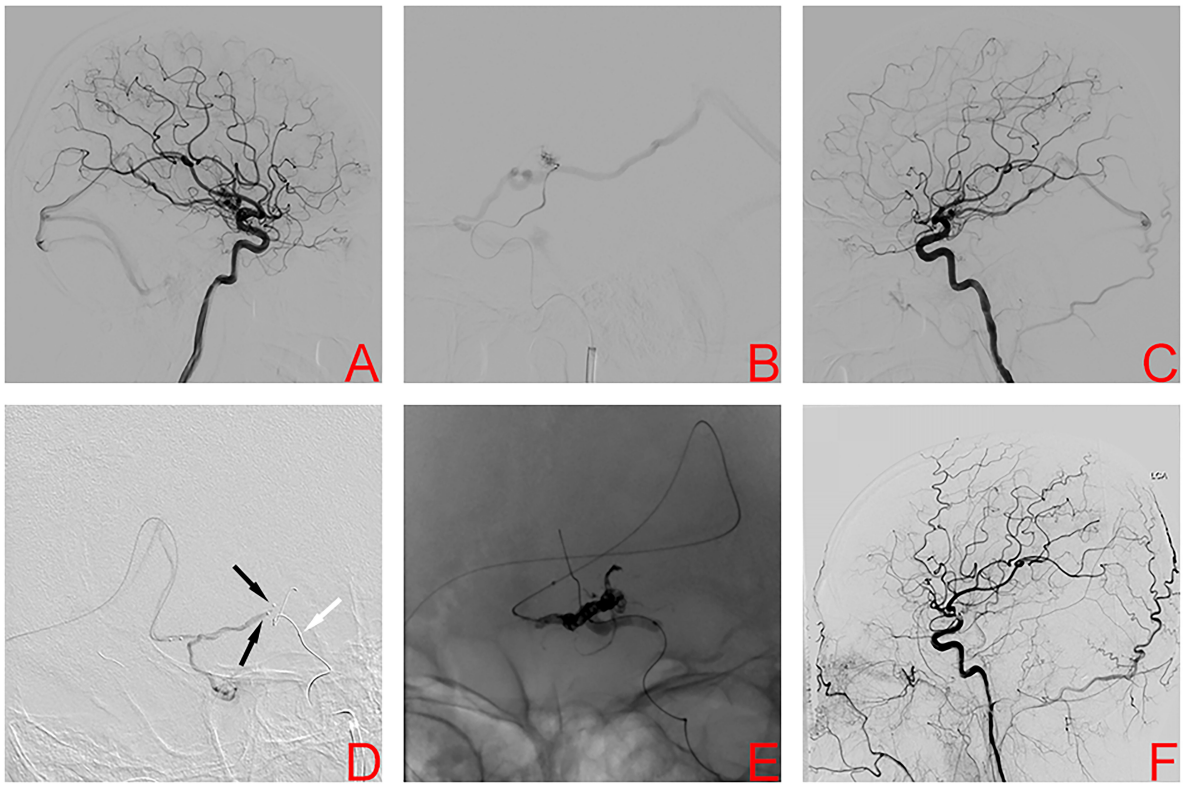

FIGURE 1
Digital subtraction angiography left internal carotid artery (ICA) demonstrated the left basal ganglia arteriovenous malformation in case 1 **(A)**. Superselective arteriography and embolization *via* the anterior choroidal artery **(B)**. Immediate angiography of left ICA after transarterial embolization showed a residual small nidus **(C)**. TVE was performed due to the lack of optimal arterial access. Dual microcatheters (black arrows) were positioned in the origin of the venous collector and a balloon microcatheter (white arrow) was placed in the ipsilateral internal carotid artery **(D)**. After the balloon was inflated to provisionally occlude the internal carotid artery, we used the PCT to occlude the nidus **(E)**. Digital subtraction angiography 4 months later confirmed AVM obliteration **(F)**.

consciousness. ICH was confirmed on head CT. DSA showed a right basal ganglia AVM, Spetzler-Martin grade III. Nidus size was 2.56 cm and venous drainage was deep (Figure 2A). Feeding arteries included branches arising from the posterior communicating artery (PCA) and the lenticulostriate arteries (LSAs) originating from the MCA. As in case 1, a two-stage procedure was planned. During the first stage procedure, superselective arteriography demonstrates the AVM angioarchitecture (Figure 2B). Glubran® was injected *via* the PCA, and DSA after the first stage shows the partially embolized AVM (Figure 2C). In the second stage, the PCT was used again. Two microcatheters were positioned at the origin of the venous collector, microangiography was then performed to better visualize the angioarchitecture of draining veins and adjust the position of the microcatheter tip (Figure 2D). After the balloon was inflated to provisionally occlude the internal carotid artery, Onyx was injected transvenously into the AVM nidus through the microcatheter, and ~2 cm of embolysate reflux (black arrow) was encountered prior to achieving sufficient retrograde nidal penetration (Figure 2E). The final DSA showed complete obliteration of the AVM (Figure 2F). Unfortunately, the child awoke with difficulty from anesthesia, Dyna CT showed AVM hemorrhage (Figure 2G). The patient then underwent craniotomy for evacuation of intracranial hematoma and nidus resection. After surgery, the patient was awake and conscious with stable vital signs (mRS score, 3). One year later, DSA confirmed complete AVM obliteration and mRS score was 2 (Figure 2H). Gratifyingly, the patient is currently being educated in the regular class with a big group of normal peers.

Case 3

A 17-year-old boy was referred to our center because of sudden severe headache and disturbed consciousness. Head CT showed ICH. DSA demonstrated a right basal ganglia AVM, Spetzler-Martin grade III. Nidus size was 2.24 cm and venous drainage was deep (Figures 3A,B). The nidus was supplied by

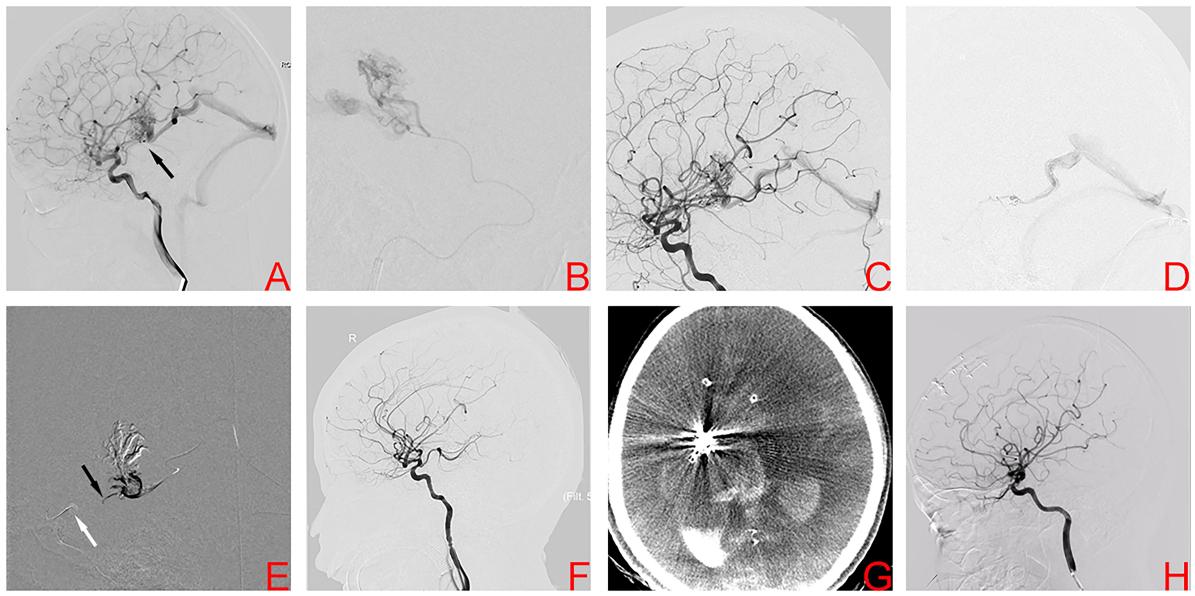

FIGURE 2
Digital subtraction angiography demonstrates the right basal ganglia arteriovenous malformation in case 2 **(A)**. Superselective arteriography and embolization *via* the posterior communicating artery **(B)**. Angiography after transarterial embolization shows a partially embolized arteriovenous malformation **(C)**. TVE was performed due to the lack of optimal arterial access. Transvenous microcatheter injection angiography confirmed an optimal position of the microcatheter tip **(D)**. After the balloon (white arrow) was inflated to provisionally occlude the ipsilateral internal carotid artery, Onyx was injected transvenously into the AVM nidus through the microcatheter, and ~2 cm of embolysate reflux (black arrow) was encountered prior to achieving sufficient retrograde nidal penetration **(E)**. Postoperative angiography showed complete embolization **(F)**. However, postoperative CT confirmed intracranial hemorrhage **(G)**. Angiography 1 year later showed complete embolization of the arteriovenous malformation **(H)**.

the AChA and LSAs. After provisional balloon occlusion of the ICA, the PCT was successfully used (Figures 3C,D). Final DSA confirmed complete obliteration of the AVM (Figures 3E,F). Postoperative head CT showed no hemorrhage. After 1 day of observation, the patient was discharged without complication. At the 6-month clinical follow-up visit, mRS score of patient had improved to 2.

Case 4

A 47-year-old man presented with acute severe headache and disturbed consciousness. Head CT scan showed ICH with midline brain shift and the patient underwent emergency surgical treatment. A left temporal AVM was encountered during surgery. Its nidus was resected incompletely and the hematoma was evacuated. After the patient was medically stable, DSA confirmed a left temporal AVM, Spetzler-Martin grade II. Nidus size was 0.79 cm and venous drainage was superficial (Figure 4A). The patient underwent conventional transarterial embolization *via* the temporal branches of the MCA using Onyx 18^{TM} (Figure 4B). Postembolization DSA showed a residual nidus (Figure 4C). TVE was performed due to the lack of optimal arterial access. A microcatheter was positioned at the origin of the venous collector, microangiography was then performed to better observe the angioarchitecture of draining veins and adjust the position of the microcatheter tip (Figure 4D). Onyx 18^{TM} was injected transvenously into the AVM nidus through a microcatheter until anatomic obliteration of the AVM (Figure 4E). Six months later, the patient was independent with mRS score of 2 and in a good condition. DSA confirmed complete AVM obliteration (Figure 4F).

Review of previous cases

The study searched PubMed databases with the terms "TVE of hemorrhagic brain AVMs" and "hemorrhagic brain AVMs treated with TVE from 2011 to 2021." After the full-text screening, 12 relevant studies were included (18, 20–30). Table 2 summarizes 12 previously published studies of TVE and our single-center experience. These studies included 246 AVMs in 245 patients (125 men, 120 women). The average patient age was 36.8 years. The mean nidus diameter was 2.53 cm. The most frequent clinical manifestation was ICH. A single draining vein was noted in 212 patients (86.5%). Among the 241 AVMs that were classified according to the Spetzler-Martin system, 90 were classified as grade I or

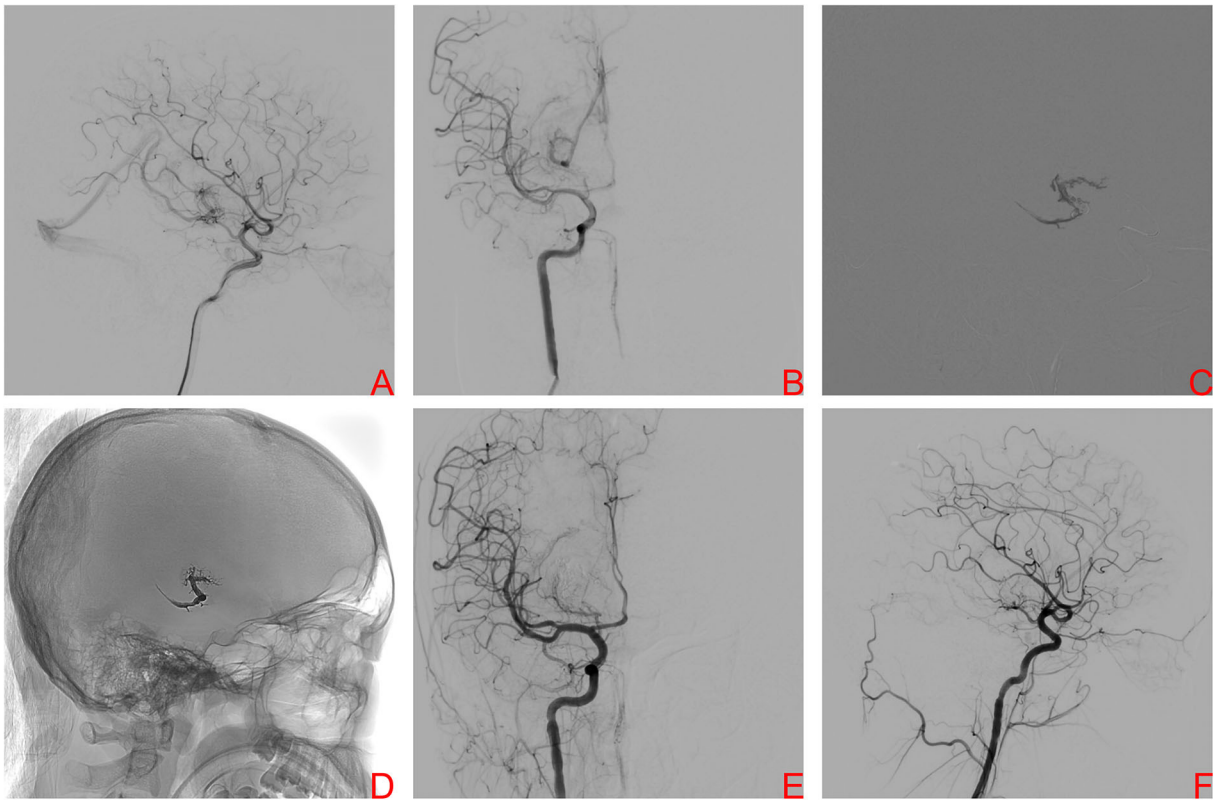

FIGURE 3
A right internal carotid artery (ICA) angiogram, anteroposterior projection **(A)** and lateral projection **(B)**, demonstrating a Spetzler–Martin grade III brain arteriovenous malformation (BAVM) located in the right basal ganglia drained by the basal vein of Rosenthal, the nidus was supplied by the right AChA and LSAs. After provisional balloon occlusion of theright ICA, Onyx was injected transvenously into the AVM nidus and sufficient retrograde nidal penetration was achieved **(C)**. The Onyx cast is visualized at the end of the procedure **(D)**. Final angiography of right ICA, anteroposterior projection **(E)** and lateral projection **(F)**, showed complete obliteration of BAVM.

II (37.3%). Treatment approach data were available in 173 patients. The transvenous approach was used in 93 (53.8%) and the combined transarterial and transvenous approach in the remaining 80 patients (46.2%). Angiographic follow-up was available in 244 patients. The rate of complete embolization at the last angiographic follow-up was 90.6%. Complications occurred in 26 of 245 patients (10.6%). The most common complication was ICH (9.8%). Procedure-related bleeding other than perforation was occurred in 17 patients (6.9%) and perforation was occurred in six (2.4%). One patient (0.41%) experienced a pulmonary embolism not related to the procedure. Intraoperative bleeding and peri-procedural bleeding were the most frequent complications. The latest hemorrhage occurred 96 h after the procedure. Overall, the rate of complete embolization was high (90.6%) and the rates of hemorrhagic events (9.8%), permanent morbidity (1.6%), and mortality (0.41%) were low, suggesting that TVE is safe and effective.

Discussion

The management of brain AVMs is challenging and the optimal treatment modality remains ill-defined (6, 7). ABUBA is the first randomized controlled clinical trial on the treatment of AVMs, but it does not address this issue. Contemporary methods include microsurgery, endovascular embolization, and stereotactic radiosurgery. The goal of AVM treatment is to eliminate the nidus to prevent hemorrhage while preserving the surrounding normal vessels. The role of endovascular intervention in the management of AVMs is generally regarded as adjunctive to microsurgery or radiosurgery. Embolization *via* the transarterial approach is the most common.

The curative effect is limited by variation in the size, location, pattern, and number of arterial feeders, as well as the number and location of draining veins. A systematic review that included 15 studies with 597 patients and 598 AVMs treated with transarterial embolization demonstrated the

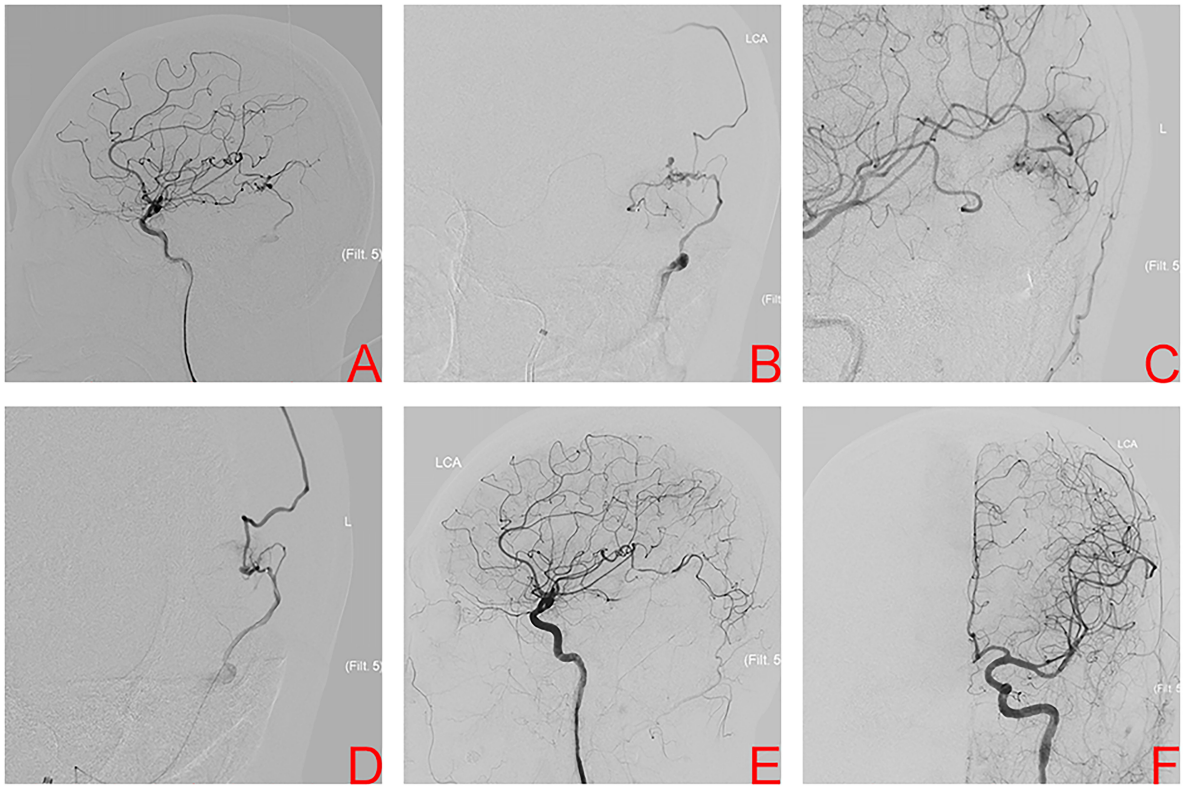

FIGURE 4
Digital subtraction angiography of left internal carotid artery (ICA) after incomplete nidus resection and hematoma evacuation shows the left temporal arteriovenous malformation in case 4 **(A)**. Superselective arteriography and embolization *via* the temporal branches of the middle cerebral artery **(B)**. Immediate angiography of left ICA after transarterial embolization showed a residual small nidus **(C)**. TVE was performed due to the lack of optimal arterial access. Superselective arteriography confirmed an optimal position of the microcatheter tip **(D)**, Onyx was injected transvenously into the AVM nidus through microcatheter. Final angiography of left ICA, anteroposterior projection **(E)** and lateral projection **(F)** confirmed complete obliteration.

complete obliteration in 45.8% of AVMs in the entire patient cohort, the complication rate was 24.1%, and procedure-related mortality was 1.5% (31). Furthermore, outcomes of conventional transarterial embolization of unruptured brain AVMs have been inferior to conservative management (10, 32). To be noted, the role of radiosurgery is clearly a valid option for the treatment of unruptured cases, especially in low Spetzler-Martin grade brain arteriovenous malformations (bAVMs) (33–35). For patients with ruptured lesions, the risk of re-bleeding was increased after the first hemorrhage. A fast eradication of the nidus should be the goal of treatment and long latency periods for a cure seem to be less desirable because the patient is not protected against re-rupture during this time. In addition, previous studies have indicated that surgical treatment achieves better outcomes than transarterial embolization (1, 36, 37). The AVM cure rate rarely exceeds 50% with stand-alone transarterial embolization (16). The emergence of TVE has the potential to improve endovascular treatment outcomes. According to our knowledge, Mullan first proposed TVE as a curative standalone modality in the treatment of AVMs in 1994 (38). Kessler et al. confirmed that patients harbored with AVMs treated *via* TVE achieved 80% of complete obliteration (18). Compared with the transarterial route, AVMs embolization performed *via* TVE achieves complete obliteration by directly and facilely targeting the nidus. Nidal embolisate penetration is facilitated by control of arterial inflow *via* systemic or local hypotension. TVE significantly improved complete obliteration rates. Previous studies demonstrated angiographic obliteration in 95% of AVMs patients treated with TVE (28, 39).

The transvenous approach has provided new insights into brain AVM management. However, occlusion of AVM venous collectors alone without controlled hypotension is associated with hemorrhagic complications and high mortality. Massoud and Hademenos first proposed transvenous retrograde nidus sclerotherapy under controlled hypotension (TRENSH) as an AVM treatment strategy in 1999 (40). With this

TABLE 2 Literatures review of endovascular treatment of AVMs *via* transvenous approach.

No	References	Case no	Sex ratio F:M	Mean age	Ruptured case	Nidus size*	S-M score 1–2	Single draining vein	TAE+TVE	Complications	Hemorrhage	Complete occlusion rate
1	Koyanagi et al. (20)	51	20:31	47	42 (82%)	N/A	15	50	N/A	3	3	42
2	De Sousa et al. (21)	57	29:28	38.05	38 (66.6%)	2.44	23	37	40	10	10	52
3	He et al. (22)	21	14:7	29.9	21 (100%)	2.76	7	20	N/A	6	5	18
4	He et al. (23)	10	2:8	24.5	10 (100%)	4.16	2	9	8	2	2	9
5	Viana et al. (24)	12	7:5	33.4	9 (75%)	1.9	9	10	1	0	0	10
6	Mendes et al. (25)	40	22:18	37.7	27 (67.5%)	2.8	17	31	7	2	1	38
7	Mendes et al. (26)	9	5:4	34.9	8 (88.9%)	2.3	0	9	1	0	0	9
8	Mendes et al. (30)	7	4:3	13.6	7 (100%)	2	5	7	4	0	0	7
9	Renieri et al. (27)	4	2:2	11	1 (25%)	1.5	4	3	1	0	0	4
10	Iosif et al. (28)	20	10:10	36.8	20 (100%)	2.3	4	19	11	2	2	20
11	Consoli et al. (29)	5	3:2	33.4	5 (100%)	1.7	4	4	3	0	0	5
12	Kessler et al. (18)	5	2:3	41.8	4 (80%)	N/A	0	5	1	0	0	4
	Our study	4	0:4	27.5	4 (100%)	1.97	1	4	3	1	1	3
Total		245	120:125	36.8	196 (80%)	2.52	91 (37%)	212 (86.5%)	80 (46.2%)	26 (10.6%)	24 (9.8%)	221 (90.6%)

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technique, arterial inflow to the nidus is lowered using systemic hypotension with or without the aid of a balloon, and sclerosant is injected into the nidus *via* a retrograde transvenous route. This allows more complete permeation of sclerosant throughout the nidus (6, 40). The advent of liquid embolic agents (particularly Onyx) has facilitated the clinical use of TRENSH. Unlike cyanoacrylates, Onyx is a non-adhesive embolic agent with glue-like characteristics, its low adherence allows injection of a higher volume of the liquid embolic agent into the nidus. These features have led to its widespread use in clinical practice. Furthermore, advances in embolization techniques have also occurred. Chapot et al. first described the PCT in 2014, which creates an anti-reflux plug using coils or glue to obtain wedge-flow conditions (19). This controls reflux and allows more comprehensive, forceful, continuous, and safe Onyx embolization, which achieves a better clinical outcome. The PCT also allows a better understanding of AVM angioarchitectural features, may extend the indications for AVM embolization, and may decrease the number of treatments required.

Here, we summarized our knowledge on TVE: consistent with previous studies, our experiences indicated that good control of the reflux along the venous collector is critical. The use of PCT makes it possible to have sufficient control of their retrograde filling, determining a slow alteration of the hemodynamic balance throughout the duration of the procedures. The appropriate position of the venous microcatheter is crucial to prevent occlusion of the venous collector before the liquid embolic reaches the nidus, preventing hemorrhagic complications (26, 29). To be noted, the injection of Onyx was primarily *via* venous approach. To decrease nidus inflow and achieve sufficient retrograde nidal penetration of Onyx, prior to TVE, the transarterial embolization was performed in cases 1, 2, and 4. These results emphasize the importance of using an initial arterial approach to shrink the nidus. A procedure-related complication was noted for one patient. Hemorrhagic complications were commonly seen during microcatheterization or microcatheter retrieval. To our best knowledge, microcatheter perforation during navigation or arterial tear at catheter retrieval is the potential reason for hemorrhage (41, 42). Fortunately, the patient made a full recovery without any neurological sequelae thus far.

Based on our experience and the relevant studies, we have concluded that appropriate patient selection is the key to good outcomes after TVE. Indications for TVE are as follows: (a) tortuous arterial approach and accessible transvenous approach; (b) single venous collector [multiple venous collectors are associated with an 8.7-fold increase in odds of hemorrhagic complications (21)]; (c) nidus size <3 cm [small and compact architecture is more easily penetrated (3, 22)]; (d) Spetzler-Martin grade I or II (25, 43, 44); and (e) deep location.

Conclusion

The TVE with good clinical outcomes emerged as a novel concept in the management of brain AVMs in the condition that the conventional transarterial route is not accessible or not safe. The positive clinical outcomes make it a promising therapeutic alternative modality. Appropriate patient selection, accurate assessment of preoperative data, and extensive experience are the key points to achieve a good clinical outcome.

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 in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

XC and LZ performed the manuscript writing. XC edited the figure of the article. HZ acquired the data. YW, LF, LN, and LD analyzed and interpreted the data. ML and PL conceived and designed the research. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Endovascular treatment of intracranial vertebral artery unruptured dissecting aneurysms: Comparison of flow diversion and stent-assisted coiling or stenting alone

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Purpose: To investigate the effect and safety of flow diverters in the treatment of unruptured dissecting intracranial aneurysms of the vertebral artery in comparison with stent-assisted coiling or stenting alone.

Materials and methods: Patients with unruptured dissecting intracranial aneurysms of the vertebral artery treated with the flow diverter, stent-assisted coiling, or stenting alone were retrospectively enrolled. The clinical data were analyzed and compared.

Results: Twenty-five patients were enrolled in the flow diversion group and 42 patients in the stenting group. Twenty-six flow diverters were deployed in the flow diversion group. Immediate angiography revealed contrast agent retention within the aneurysm cavity in all patients. In the stenting group, 48 stents were deployed, and immediate angiographic outcome showed O'Kelly-Marotta (OKM) grade D in 18 (42.9%) aneurysms, grade C in 16 (38.1%), and grade B in 8 (19.0%). Periprocedural ischemic complications of thrombosis occurred in two (4.8%) patients and were treated with thrombolysis. In the flow diversion group, 19 (76%) patients underwent angiographic follow-up 3–46 (median 24) months after the procedure, with the OKM grade D in 11 (57.9%) patients, C in two (10.5%), and B in six (31.6%). The aneurysm recurrence rate was zero, and all diverters remained patent. Asymptomatic instent stenosis occurred in two (10.5%) patients. In seven of the ten patients with mild or moderate parent artery stenosis before the procedure who experienced angiographic follow-up, the stenosis was improved in five (71.4%) patients. In the stenting group, angiographic follow-up was carried out in 33 (78.6%) patients 6–58 months (median 34) after the procedure, with OKM grade D in 22 (66.7%) patients, grade C in five (15.2%), grade B in three (9.1%), and aneurysm recurrence (grade B, with increased contrast agent into the aneurysm cavity) in three (9.1%). Five (16.7%) patients experienced asymptomatic instent stenosis, and six of the 12 patients (50%) with parent artery stenosis were improved.

Conclusion: Flow diverters with or without selective adjunctive coiling for the treatment of unruptured dissecting intracranial aneurysms of the vertebral artery may be safe and effective with good occlusion effects not inferior to those of stent-assisted coiling and stenting alone even though the long-term effect still warrants confirmation.

KEYWORDS

intracranial aneurysms, dissecting, vertebral artery, flow diverter, effect

Introduction

As a cause of stroke, spontaneous dissection of the intracranial vertebral artery may present with varied symptoms in young adults like ischemic symptoms, subarachnoid hemorrhage, brainstem compression, and local symptoms (headache), and has been increasingly recognized with improvement of imaging technology (1, 2). Arterial dissection is probably caused by a disruption of arterial internal elastic lamina and media, resulting in penetration of flowing blood into the arterial wall and formation of an intramural hematoma (3, 4). Arterial dissection may exhibit different shapes like dilatation, stenosis, or both based on the tear depth, with luminal stenosis or occlusion caused by subintimal dissection and luminal dilatation by subadventitial dissection (dissecting aneurysm). Dissecting aneurysms on the intracranial segment of the vertebral artery occur mostly in male young adults and are the most important reason for subarachnoid hemorrhage and posterior circulation stroke (1). Currently, there are no established treatment approaches for unruptured dissecting aneurysms of the vertebral artery. Even if unruptured intracranial dissecting aneurysms of the vertebral artery have been thought to have a benign clinical course (2, 5–10), the natural course of these dissections are still unknown and treatment guidelines remain controversial and debatable (5, 11, 12). Moreover, some researchers believed that the risk of bleeding from unruptured dissecting aneurysms of the vertebral artery was higher than previous reports (6, 12). Patients with these dissecting aneurysms may experience serious neurological deficits after hemorrhage and secondary ischemic events, and early management of these aneurysms is necessary because rebleeding after rupture is common (2, 8, 9). However, intracranial dissecting aneurysms of the vertebral artery are usually wide-necked and involve a long segment and the posterior inferior cerebellar artery, which makes it difficult for traditional treatment approaches. Anticoagulation is preferred for conservative treatment of hemodynamically stable dissecting aneurysms (13), however, use of anticoagulation or antiplatelet therapy in patients with ischemic presentations of unruptured vertebral arterial dissections may exacerbate aneurysmal dissection and cause a rupture of the dissecting aneurysm (12). One randomized trial had demonstrated no difference in the effect of antiplatelet and anticoagulant therapy at preventing stroke and death in patients with symptomatic vertebral and carotid artery dissections (14). A deconstructive approach is to surgically or endovascularly occlude the dissecting segment, but some disadvantages may be involved, including ischemic events in the case of the dominant vertebral artery being occluded, and the need of a bypass in the case of involvement of the posterior inferior cerebellar artery by the dissecting aneurysm (12). As a reconstructive technique, stent placement and stent-assisted coiling have been applied to treat intracranial vertebral artery dissecting aneurysms, with good outcomes being achieved (15–17). Flow diverting devices are used to reconstruct the parent artery of the aneurysm and have achieved good prognoses in the treatment of complex anterior circulation aneurysms, but their application in the posterior circulation is still in the exploratory stage. It was hypothesized that the flow diverters could be safely applied to effectively treat the intracranial dissecting aneurysms of the vertebral artery. This study was consequently conducted to investigate the safety and effect of flow diverters in the treatment of this condition in comparison with stent placement or stent-assisted coiling.

Materials and methods

This retrospective case-control single-center study was approved by the ethics committee of our hospital, with the written informed consent obtained from all patients to participate. Patients with unruptured dissecting intracranial aneurysms of the vertebral artery who were treated with stent placement, stent-assisted coiling or flow diverters were enrolled between May 2014 and October 2019. The inclusion criteria were patients with imaging-confirmed unruptured dissecting intracranial aneurysms on the intracranial segment of the vertebral artery, with increased dissecting size on repeated angiographic imaging, and sustained contrast stagnation in the dissecting aneurysms, which were treated with stent placement, stent-assisted coiling or flow diverters. The exclusion criteria were patients with infectious or traumatic intracranial aneurysms, non-dissecting aneurysms, history of endovascular or surgical treatment, and concomitant with intracranial tumors or other diseases affecting management of intracranial

aneurysms. Patients were divided into the stent group to receive stent-assisted coiling or stent placement alone and the flow diversion group who were to receive flow diverting treatment. Generally, in some complex lesions, in which there was no clear aneurysm sac to effectively fill the coil, the lesion segment was long, and the dissection shown by on magnetic resonance imaging was larger than that shown on digital subtraction angiography, the Pipeline device would be considered as the first choice even though ordinary stents might also be selected because of their low price.

Before the endovascular embolization procedure, patients were given dual antiplatelet therapy (aspirin 100 mg/d and clopidogrel 75 mg/d), administered orally for 3–5 days. Thromboelastography (TEG) was conducted 3 days after the administration of the therapy, and the dose was adjusted according to the TEG test results so as to maintain the inhibition rate of arachidonic acid (AA) > 50%, the inhibitive rate of adenosine diphosphate (ADP) > 30%, and the maximal amplitude of ADP curve at 31–47 mm. Intravenous bolus injection of heparin 50–70 U / kg was administered before the endovascular treatment, and heparin was then maintained at 1,000 U / h. After the embolization, dual antiplatelet therapy was continued at the same dosage for 6 months before switching to aspirin at the same dosage for at least 1 year.

The endovascular procedure was performed under general anesthesia. After a 6F long sheath was inserted into the right femoral artery, a 6F Navien intermediate catheter (Medtronic, USA) was navigated to the aneurysm. The stent delivery system was sent over a micro-guidewire to the appropriate location for deployment of a stent (Neuroform stent, Stryker, Kalamazoo, Michigan, USA, or Enterprise stent, Codman & Shurtleff, Raynham, Massachusetts, USA) with or without coiling or flow diverting device (Pipeline, Medtronic, USA or Tubridge, MicroPort, China). In deploying the flow diverter, it was possible to avoid covering the orifice of the contralateral vertebral artery. For patients with coil embolization, an embolization microcatheter was navigated into the aneurysm cavity for coiling. After embolization, digital subtraction angiography was performed to check the adherence of the flow diverters or stent to the vascular wall, and balloon expansion of the stent was conducted in poor wall adherence. For patients with apparent parent artery stenosis, the stenosis was expanded using a balloon catheter after stent embolization. Procedure success was defined as complete coverage of the aneurysm neck by the stent or flow diverter, good wall adherence, and patent parent artery. Computed tomographic scan was conducted immediately after endovascular treatment so as to exclude possible intracranial hemorrhage.

Clinical follow-up was performed 3, 12 and 24 months after the procedure to check possible adverse events which were defined as cerebral hemorrhage, infarction, and any neurological symptoms. The patients were evaluated with the modified Rankin scale (mRS) score. Angiographic follow-up was conducted with the magnetic resonance imaging angiography or digital subtraction angiography. The aneurysm occlusion status on imaging was assessed with the O'Kelly-Marotta (OKM) grading system (17), with the aneurysm filling grade of A - complete filling (>95%), B - incomplete (5%-95%), C - neck remnant (<5%), or D - no filling (0%).

Statistical analysis

The statistical analysis was performed with the SPSS 19.0 (IBM, Chicago, IL, USA). Measurement data were presented as mean ± standard deviation if in normal distribution and tested with the *t*-test or median and interquartile range if in skew distribution and tested with the Mann-Whitney U test. Enumeration data were presented as numbers and percentages and tested with the Chi square test. A $P < 0.05$ was considered statistically significant.

Results

Twenty-five patients with unruptured dissecting intracranial aneurysms of the vertebral artery treated with flow diverters were enrolled as the flow diversion group, including 16 males and 9 females, with an age range of 29–72 (mean 52 ± 11.3) years (Table 1). The symptoms were headache or neck pain in 13 (52%) patients and cerebral infarction or transient ischemic attack in six (24%), and the other six (24%) patients were incidentally found to have dissecting intracranial aneurysms of the vertebral artery. Primary hypertension was found in nine (36%) patients and diabetes mellitus in five (20%). The aneurysm was on the left side in 10 (40%) patients and on the right side in 15 (60%). The aneurysm involved the posterior inferior cerebellar artery in eight (32%) patients, and concomitant stenosis existed in the parent artery proximal or distal to the aneurysm in ten (40%) patients.

Forty-two patients with intracranial unruptured dissecting aneurysms of the vertebral artery treated with stent alone or stent-assisted coiling were also enrolled as the stent group, including 15 female and 27 male patients with an age range of 32–75 (mean 53 ± 9.2) years (Table 1). The symptoms were headache or neck pain in 22 (52.4%) patients and cerebral infarction or transient ischemic attack in 13 (31.0%), and the other seven (16.7%) patients were incidentally found. Hypertension was found in twelve (28.6%) patients and diabetes mellitus in six (14.3%). The aneurysm was on the left side in 25 (59.5%) patients and on the right side in 17 (40.5%). The aneurysm involved the posterior inferior cerebellar artery in 15 (35.7%) patients, and concomitant stenosis existed in the parent artery proximal or distal to the aneurysm in 12 (28.6%) patients. No significant ($P > 0.05$) difference was found in the basic information of patients between two groups.

TABLE 1 Demography (n, %).

Variables		Flow diversion ($n = 25$)	Stent ($n = 42$)	P
F/M		9/16	15/27	0.78
Age (y, range and mean)		29–72 (52 ± 11.3)	32–75 (53 ± 9.3)	0.36
Symptoms	Headache or neck pain	13 (52%)	22 (52.4%)	0.87
	Cerebral infarction or TIA	6 (24%)	13 (31.0%)	0.56
	Incidentally found	6 (24%)	7 (19.0%)	0.23
History	Hypertension (n, %)	9 (36%)	12 (28.6%)	0.54
	Diabetes mellitus	5 (20%)	6 (14.3%)	0.27
Features of aneurysms	Left vertebral artery	10 (40%)	25 (59.5%)	0.56
	Right vertebral artery	15 (60%)	17 (40.5%)	0.21
	Involvement of PICA	8 (32%)	15 (35.7%)	0.66
	Concomitant parent artery stenosis	10 (40%)	12 (28.6%)	0.27

PICA, Posterior inferior cerebellar artery.

TABLE 2 Endovascular treatment and follow-up.

Variables	Flow diverter	Stent
Devices deployed (n)	26	48
Technical success rate	100%	100%
Type of device	PED 16 (64%)	NF 28 (58.3%)
	Tubridge 9 (36%)	EP 20 (41.7%)
Treatment mode (*n*, %)		
Patients with 1 device	24 (96%)	36 (85.7%)
Patients with 2 devices	1 (4%)	6 (14.3%)
Additional coiling	2 (8%)	36 (85.7%)
Immediate occlusion outcomes		
OKM grade D	0	18 (42.9%)
OKM grade C	0	16 (38.1%)
OKM grade B	25 (100%)	8 (19.0%)
Clinical follow-up Duration (m)	3–46 (median 22)	6–58 (median 37)
Hemorrhagic complications	1	0
Ischemic complications	0	0
Angiographic follow-up duration (m)	3–46 (median 24)	6–58 (median 34)
No. of patients with follow-up	19 (76%)	33 (78,6%)
DSA	18 (94.7%)	19 (57.6%)
CTA	1 (5.3%)	11 (33.3%)
OKM grade D	11 (57.9%)	22 (66.7%)
OKM grade C	2 (10.5%)	5 (15.2%)
OKM grade B	6 (31.6%)	3 (9.1%)
Recurrence	0	3 (9.1%)
Asymptomatic instent stenosis	2 (10.5%)	5 (16.7%)
Parent artery stenosis improved	5 (71.4%)	6 (20%)

PED, Pipeline embolization device; DSA, digital subtraction angiography; CTA, computed tomography angiography; OKM grade, O'Kelly-Marotta grading system.

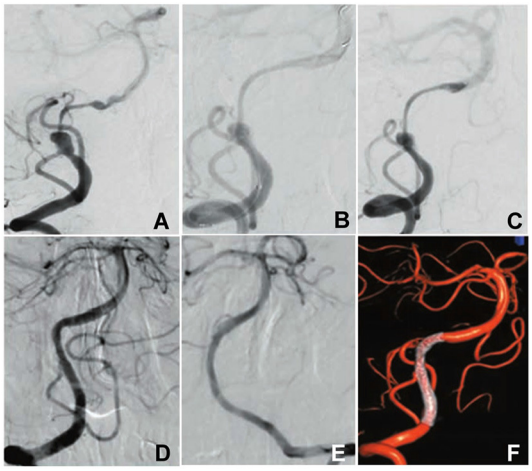

FIGURE 1
A patient with intermittent headache was hospitalized. **(A)** Cerebral angiography revealed a dissecting aneurysm at the intracranial vertebral artery concomitant with distal long-segment stenosis. **(B,C)** A flow diverter was deployed to cover the aneurysm. **(D)** Angiography 3 months later demonstrated complete occlusion of the dissecting aneurysm with the stenosis being relieved and patent posterior inferior cerebellar artery. **(E)** The left vertebral artery was normal. **(F)** Three-dimensional angiography of reconstruction showed complete occlusion of the dissecting aneurysm and patent flow diverter.

The endovascular stenting procedure was technically successful in all patients receiving the flow diverters, stent alone, or stent-assisted coiling. In the flow diversion group, twenty-six flow diverting devices were deployed in 25 patients, including 16 Pipeline embolization devices (PEDs) deployed in 16 (64%) patients and ten Tubridge devices in nine (36%) patients (Table 2 and Figure 1). One flow diverter was deployed in 24 (96%) patients each, and two Tubridge devices were deployed in one (4%) patient, and additional coiling was performed in two (8%) patients after deployment of one diverter. The diverter deployment technical success was 100%, with complete coverage

of the aneurysm neck, good wall adherence, and patent parent artery. Immediate angiography revealed contrast agent retention within the aneurysm cavity in all patients. In ten (40%) patients with moderate parent artery stenosis, no predilatation was needed, and in one (4%) patient with concomitant parent artery stenosis, postdilatation was performed within the stent. In ten (40%) patients, the flow diverter covered the orifice of the posterior inferior cerebellar artery after deployment. No relevant neurological complications Occurred in this cohort of patients.

In the stent group, 48 stents were deployed in 42 patients, including 36 Neuroform (75%) and 20 Enterprise (25%) stents (Table 2). One stent was deployed in each of 36 patients (85.7%) for stent-assisted coiling, and two stents were deployed without additional coiling in each of the other six patients (14.3%). The technical success rate of stenting was 100%. Immediate angiographic outcome showed OKM grade D with no aneurysm filling in 18 (42.9%) aneurysms, OKM grade C with a neck remnant in 16 (38.1%), and OKM grade B with incomplete occlusion in 8 (19.0%). No pre- or postdialation of the stent was performed in these patients. Periprocedural ischemic complications with thrombosis occurred in two (4.8%) patients, and no neurological deficits were left after appropriate thrombolysis.

In the flow diversion group, all 25 (100%) patients underwent clinical follow-up 3–54 months (median 22). In one (4%) patient with sudden headache 8 months after the embolization procedure, hemorrhage of the caudate nucleus was demonstrated on computed tomography to break into the ventricle, and the patient recovered completely after drug treatment. Nineteen (76%) patients underwent angiographic follow-up 3–46 (median 24) months after the procedure, including digital subtraction angiography in 18 (94.7%) patients and computed tomographic angiography in one (5.3%). The OKM grade was D in 11 (57.9%) patients, C in two (10.5%), and B in six (31.6%). No aneurysm recurrence was detected. Asymptomatic instent stenosis occurred in two (10.5%) patients including one patient with deployment of two Tubridge devices. All the other stents remained patent. Seven (70%) of the ten patients with the flow diverter covering the orifice of the posterior inferior cerebellar artery underwent angiographic follow-up, and the posterior inferior cerebellar artery remained patent. In seven of ten patients with mild or moderate parent artery stenosis who experienced angiographic follow-up, the stenosis was improved in five (71.4%) patients.

In the stent group, clinical follow-up was performed 6–58 months after the procedure through clinic visit or telephone contact, with no additional complications. Angiographic follow-up was carried out in 33 (78.6%) patients 6–58 months (median 34) after the procedure, with the OKM grade D in 22 (66.7%) patients, grade C in five (15.2%), grade B in three (9.1%), and recurrence in three (9.1%). Five (16.7%) patients experienced asymptomatic instent stenosis, and six of 12 patients (50%) with parent artery stenosis were improved.

In comparison between the flow diversion and stent groups (Table 2), no significant ($P>0.05$) differences were found in the number of devices deployed, treatment mode, immediate occlusion outcomes, complications, clinical and angiographic follow-up, follow-up angiographic modes, and follow-up outcomes (OKM grade and stenosis).

Discussion

In this study investigating the effect and safety of flow diverters in the treatment of unruptured dissecting intracranial aneurysms of vertebral artery in comparison with stent-assisted coiling or stenting alone, it was found that the use of flow diverters for the treatment of unruptured dissecting intracranial aneurysms of vertebral artery was safe and effective with good occlusion effects no less than those of stent-assisted coiling and stenting alone.

Surgical and endovascular techniques can both be used to treat the intracranial dissecting aneurysms of the vertebral artery, however, the surgical approach has been applied less often because the deep location, long segment, fusiform shape, and frequent involvement of the posterior inferior cerebellar artery and brain stem perforators make surgical treatment much more difficult and increase the risk of severe complications (18). Thus, as a microinvasive approach, the endovascular approach has become the primary method of treatment, including arterial reconstruction and occlusion. For unruptured intracranial dissecting aneurysms of vertebral artery, arterial reconstruction is the main treatment approach, including covered stent implantation, stent implantation only, and stent-assisted coil embolization. A covered stent can isolate the aneurysm from the parent artery flow by reconstructing the parent artery, however, the covered stent is less compliant and limited in the stent length and diameter, unsuitable for aneurysms involving perforating arterial branches, longer arterial segment, or larger diameter of the parent artery. Moreover, endoleak, thrombosis, and stent occlusion may occur after deployment of the covered stent, limiting its wide application (19). Stent deployment alone has a certain role in diverting blood flow by partially occluding the intimal tear and limiting blood flow into the aneurysm to promote healing of the dissecting aneurysms, but may not be able to prevent the recurrence and rebleeding (20). Compared with sole stenting, stent-assisted coiling can reconstruct the parent artery, ensure arterial patency, and embolize the aneurysm cavity to decrease the risk of rebleeding, achieving good short-term results even though the primary issue with this technique is still aneurysm recurrence. Because the number of stents deployed correlates with the flow diverting effect and improved hemodynamics, which is beneficial to the prevention of rupture and recurrence of dissecting aneurysms, an increasing number of researchers tend to use multiple stents to assist coiling of dissecting aneurysms (21, 22). The use of

multiple stents with or without concomitant coiling may had a similar effect to that of flow diverters. However, the number of stents deployed is also closely related to periprocedural ischemic events, and certain technical difficulties exist in the use of stent-assisted coiling for dissecting aneurysms involving perforating arteries.

The treatment of intracranial aneurysms is changed from intrasaccular embolization to reconstruction of the parent artery by flow diverting devices, which is in line with the treatment idea of multiple stent placement for dissecting aneurysms. Coiling operation within the aneurysm sac is dangerous and may puncture the aneurysm wall, resulting in intra-procedural aneurysm rupture, severe complications or death. Moreover, flow diverters have significantly decreased porosities with an improved effect of flow diversion, reduced blood flow into the aneurysm sac to facilitate thrombosis (23–25), and provided a physical scaffold across the aneurysm neck to promote neointimal growth (23, 26, 27), thus demonstrating a great advantage in the treatment of dissecting aneurysms. Natarajian et al. (28) have reported good outcomes in applying the PED device to treat 12 patients with fusiform vertebrobasilar artery aneurysms sized 13.25 ± 4.5 mm, and at the minimum follow-up duration of 1 year, all 12 aneurysms were occluded, the PED devices were patent, and no patient experienced delayed hemorrhage, stroke, or in-stent stenosis. Zhang et al. (29) have explored the feasibility of PED device compared with stent-assisted coiling in the treatment of non-saccular intracranial vertebral artery aneurysms. They found that the PED device achieved similar procedural complications, angiographic results, and favorable clinical outcomes, with aneurysms treated with PED being more prone to complete occlusion over time than aneurysms treated with the stent-assisted coiling technique, suggesting a safe and feasible strategy of the PED device in the treatment of these aneurysms. In our study, the proportion of dissecting aneurysms obtaining near complete occlusion was 68% (13/19), with no aneurysm recurrence at follow-up. This near complete occlusion rate may be low for some reasons. Firstly, the follow-up time may not be long enough because the complete occlusion degree increases with the follow-up time in flow diversion treatment of cerebral aneurysms. Secondly, most of the dissecting aneurysms were fusiform with a wide aneurysm neck, which may affect the endothelialization of the flow diverter at the neck. Thirdly, fewer cases were treated with overlapped flow diverters, with only two flow diverters deployed in one (4%) patient. Two overlapped flow diverters can increase the metal coverage area and is beneficial to thrombosis within the aneurysm cavity and complete aneurysm occlusion. Adjunctive coiling after deployment of a diverter was performed only in two (8%) patients, and most other patients had deployment of only one flow diverter. Adjunctive coiling will promote aneurysm thrombosis and complete occlusion. The above reasons may account for the low complete occlusion degree in our study.

Because of the rich perforating branches in the basilar artery, more periprocedural complications may occur in the use of flow diverters for the treatment of basilar artery aneurysms (30). However, there are few branches and perforating vessels in the intracranial segment of the vertebral artery, so ischemic complications of flow diverters in the treatment of unruptured intracranial dissecting aneurysms of the vertebral artery are less likely to occur. In our study, no ischemic complications occurred in the periprocedural period or at follow-up. Flow diverters can effectively protect the patency of perforators involved by the aneurysm while completely occluding the aneurysm. In the flow diversion group in our study, among ten patients whose posterior inferior cerebellar artery was covered by the flow diverter, seven patients had cerebral angiographic follow-up which proved patency of the artery. In the stenting group, no ischemic complications occurred at follow-up. In a study by Catapano et al. (5) reporting the endovascular treatment of unruptured vertebral artery dissecting aneurysms (VADAs) and ruptured dominant VADAs using flow diverters and stent-assisted coiling, it was found that the use of flow diverters for the treatment of VADAs seemed to be associated with lower retreatment and complication rates than stenting-assisted coiling (complications 2/29 vs. 4/15, P=0.008 and retreatment 4/29 vs. 6/15, $P = 0.002$) and that endovascular treatment of unruptured VADAs was safe with favorable angiographic and neurological outcomes. This study supports our outcomes.

Compared with the clinoid segment of the internal carotid artery, the intracranial segment of the vertebral artery is relatively straight and smooth, which enables easy deployment of the flow diverter. However, a dissecting aneurysm at this segment is usually fusiform and wide-necked and involves a longer segment, and a longer flow diverting device with a greater diameter than that of the parent artery should be chosen to cover the aneurysm neck with sufficient anchoring area at the distal end. When releasing the device at the aneurysm neck, the delivery micro-catheter should maintain a certain tension, and the device should be mainly pushed to prevent the distal end from sliding downward. For larger aneurysms, loose coil packing is needed to promote the closure of aneurysms.

Intracranial dissecting aneurysms of the vertebral artery may be accompanied by stenosis of the parent artery. In our study, ten (40%) patients exhibited mild and moderate stenosis of the parent artery. Predilatation of moderate stenosis is not necessary because the stenosis will be alleviated after deployment of the flow diverter, and further alleviation of the stenosis will be achieved at follow-up with repair and reconstruction of the parent artery. In seven of these patients who had angiographic follow-up, the stenosis was improved in five (71.4%) patients. In some patients with parent artery stenosis which did not improve after deployment of the flow diverter, postdilatation may be needed to relieve the stenosis as demonstrated in one patient in our study.

Instent stenosis or occlusion is another issue worthy of attention after the placement of a flow diverter. The study by Chalouhi et al. (31) showed that the rate of instent stenosis was as high as 15.8%, but most of the stenoses were asymptomatic. In our study, instent stenosis occurred in two patients, and in one patient with two Tubridge devices deployed in the "bridging form," the stent was occluded at 3 months after the procedure, which was probably caused by deployment of multiple devices (32).

The involvement of the origin of the posterior inferior cerebellar artery is an independent risk factor affecting recurrence of intracranial vertebrobasilar dissecting aneurysms (33). In our study, patients with the OKM grade B occlusion degree at follow-up had the involvement of the posterior inferior cerebellar artery origin, and long-term effects of these patients remain to be determined. In one patient with hemorrhage of the caudate nucleus to break into the ventricle, the hemorrhage was probably related to poor control of the blood pressure and high blood concentration of antiplatelet therapy.

In the use of flow diverters or intracranial stents to treat cerebral aneurysms, dual antiplatelet therapy is necessary to prevent stent-related thromboembolic events. Recently, an antithrombotic polymer coating has been developed for coating a flow diverter (the p48MW HPC), and this coated flow diverter allows application of a single antiplatelet function medication for endovascular treatment of cerebral aneurysms, especially ruptured ones (34–36). Recent exploring studies have proved that deployment of this coated flow diverter is able to decrease thrombogenicity safely and effectively, and achieves good early aneurysm occlusion rates in cerebral aneurysms in the proximal intracranial circulation, complex bifurcation aneurysms in the anterior and posterior circulation, and distally located cerebral aneurysms even though further larger comparative studies are essential to confirm these outcomes and optimize the perioperative antiplatelet treatment (34–36).

This study had some limitations, including the one-center and retrospective design, the small cohort of patients, the enrollment of only Chinese patients, and the lack of randomization, which may all affect the generalization of the outcomes. Further studies will be needed to resolve these issues for better outcomes.

Conclusion

In conclusion, the use of flow diverters with or without selective coiling for the treatment of unruptured dissecting intracranial aneurysms of vertebral artery may be safe and effective with good occlusion effects not inferior to those of stent-assisted coiling and stenting alone, even though the long-term effect still warrants confirmation.

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 Ethics Committee of Henan Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

B-LG and T-XL: study design. LL, H-LG, G-QX, KZ, and Z-LW: data collection. G-QX, B-LG, and T-XL: data analysis. LL: writing of the original version. B-LG: revision. All authors: validation and approval.

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Conflict of interest

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

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Independent predictors and risk score for intraprocedural rupture during endovascular treatment of small ruptured intracranial aneurysms (<5 mm)

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Background and purpose: Intraprocedural rupture (IPR) is a devastating complication of endovascular treatment (EVT). Small-sized and ruptured aneurysms are independent predictors of IPR, which presents a technical challenge during EVT. We aimed to develop a score to quantify the individual patient risk of IPR in the EVT of small (<5 mm) ruptured aneurysms (SRAs).

Methods: A retrospective review was conducted to interrogate databases prospectively maintained at two academic institutions in China from January 2009 to October 2016. We collected intraoperative angiograms and medical records to identify independent predictors of IPR using univariate and multivariable analyses. A risk score for IPR was derived using multivariable logistic regression analyses.

Results: Of the 290 enrolled patients, IPR occurred in 16 patients (5.5%). The univariate analysis showed that the rate of IPR was significantly higher in patients having aneurysms with a small basal outpouching (SBO), in patients having aneurysms concomitant with adjacent moderate atherosclerotic stenosis (ACAMAS), and in former or current smokers. Multivariate analyses showed that SBO [odds ratio (OR): 3.573; 95% confidence interval (CI): 1.078–11.840; $p = 0.037$], vascular eloquence (VE; OR: 3.780; 95% CI: 1.080–13.224; $p = 0.037$), and ACAMAS (OR: 6.086; 95% CI: 1.768–20.955; $p = 0.004$) were significantly and independently associated with IPR. A three-point risk score (S-V-A) was derived to predict IPR [SBO (yes = 1), VE (yes = 1), and ACAMAS (yes = 1)].

Conclusions: Intraprocedural rupture occurred in 5.5% of the patients during EVT of SRA. SBO, VE, and ACAMAS were independent risk factors of IPR in the EVT of SRA. Based on these variables, the S-V-A score may be useful in predicting IPR daily, but more confirmation studies are required.

KEYWORDS

intraprocedural rupture, small, intracranial aneurysms, endovascular treatment, risk score

Introduction

Intraprocedural rupture (IPR) during endovascular treatment (EVT) of ruptured intracranial aneurysms (RIAs) is one of the most feared complications with an incidence rate of 1%−8% and a modality rate of up to 40% (1–3). Several studies reported that aneurysm size (<5 mm) and ruptured aneurysm are important independent predictors of IPR (4–6). However, no study has focused on IPR predictors during EVT of small ruptured aneurysms (SRA, <5 mm).

In addition, EVT for SRA has technical challenges, including instability of the distal microcatheter, coil conformability, and the reliability of coil detachment (1, 7), which may lead to IPR. Based on a large number of studies, a common assumption to date was that the size and location of aneurysms, technical aspects, and basal morphology might be associated with the risk of IPR (1, 5, 6). However, those studies did not take into account the heterogeneity of EVT between small and big aneurysms. In this study, we conducted a retrospective analysis of consecutive patients with SRA to identify independent predictors of IPR during EVT.

Methods

Patient selection and data acquisition

This retrospective multicenter study was carried out at Beijing Tiantan Hospital and Beijing Hospital. This study included all patients who had a saccular SRA and underwent EVT at the two Chinese stroke centers from January 2009 to October 2016. In this study, the exclusion criteria were (1) patients with fusiform, traumatic, blood blister-like, and dissecting aneurysm; (2) those with aneurysms related to arteriovenous malformation (AVM), arteriovenous fistula (AVF), and moyamoya disease; (3) those with incomplete data (for example, missing digital subtraction angiography (DSA) or progress note); (4) ambiguous information about which aneurysm is ruptured in patients with multiple aneurysms; and (5) patients who did not originally undergo EVT at these two stroke centers.

We obtained these prospectively maintained databases *via* medical records and a detailed inquiry. These data included sex, age, hypertension, diabetes mellitus, dyslipidemia, heart comorbidities, history of smoking, history of drinking, history of subarachnoid hemorrhage (SAH), prehospital delay after SAH, preprocedural delay after SAH and EVT, Hunt and Hess Grade and Fisher Grade at admission, treatment modality, Raymond Scale (RS) score (8), and the modified Rankin Scale (mRS) score at discharge. The RS score demonstrates the occlusion degree of aneurysms at the end of embolization, including complete occlusion (RS1), residual neck (RS2), and residual aneurysm (RS3) (8). We recorded the morbidity and mortality rates associated with the treatment at 1 month after discharge treatment. Morbidity was categorized as an mRS score of 2–5 or at least a one-point increase during hospitalization.

Imaging of variable definitions

Aneurysm-specific characteristics included aneurysm location, aneurysm size, neck size (9), aspect ratio (AR) (10), and aneurysm shape, aneurysms concomitant with adjacent atherosclerotic stenosis (ACAAS) (2), multiplicity, vascular eloquence (VE) (11), and small basal outpouching (SBO) (12). Aneurysm location was categorized as distal vessels (A2, M2, P2 aneurysms and beyond) (13); VE (parent arteries of IAs <20 mm from the internal carotid artery or located in the first segment of cerebral arteries, e.g., A1, M1, and P1 segments) (11), cerebral bifurcation vessels (internal carotid artery bifurcation and basilar artery) and important vascular branches (posterior inferior cerebellar and anterior choroidal arteries) supporting the brain stem and the basal ganglia area; communicating arteries (anterior and posterior communicating artery); and other areas. SBO was defined as the daughter sac, or bleb, which is located near the base of a ruptured aneurysm (12). ACAAS was defined as aneurysms with proximal parent artery stenosis (2). The degree of stenosis in the proximal parent artery was defined as mild, moderate, and severe ACAAS (i.e., ACAIAS, adjacent moderate atherosclerotic stenosis (ACAMAS), and ACASAS), which correspond to <50, 50–70, and >70%, respectively.

Endovascular procedures

Each center was equipped with green channels for emergency patients in the acute stage (SAH within 72 h). Patients with SRA underwent endovascular or surgical treatment, which was determined by the neurosurgical team of each center according to the patient's characteristics and aneurysm features. All EVT procedures were performed under general anesthesia and systemic heparinization. After deployment of the first coil, an initial bolus of 50 U/kg heparin was given, and the activated clotting time was maintained at two times the normal range. For wide-neck aneurysms, (14) coiling with a stent or a balloon was performed by interventionalists with 20 years of experience at each center. During the procedure of stent-assisted coiling, patients would be allocated 300 mg clopidogrel and 300 mg aspirin. When IPR occurred, heparin was reversed by protamine sulfate, and rapid coil deposition was always considered until contrast medium extravasation disappeared. Blood pressure would be controlled at baseline. If needed, a balloon would be inflated near the proximal artery in case of massive hemorrhage, and emergency ventricular drainage (EVD) would be performed to reduce intracranial pressure. In case of acute thrombotic events, the glycoprotein Iib/IIIa inhibitor (Tirofifiban, Grand Pharma, Wuhan, China) was used. After the EVT procedure, immediate brain computed tomography (CT) scans were always performed for each patient. Moreover, patients received 75 mg of clopidogrel daily for 1 month and 100 mg of aspirin daily for 5 months.

IPR definition

Digital subtraction angiography or immediate post-operative CT scans demonstrated that IPR was defined as extravasation of the contrast medium. Two experienced interventionalists (15 and 20 years of experience in neuroradiology, respectively) who were blinded to patients' clinical information reviewed the angiograms. Any disagreements were resolved through negotiation. Considering the missing DSA reports of four cases of IPR, those cases were classified as unclear. We classified the occurrence of IPR into three phases: during aneurysm access, during coil placement, and other phases. The causes of IPR were classified into four categories: coil, microguide wire, microcatheter, and other categories.

Statistical analysis

Data related to categorical variables were analyzed using Fisher's exact test or Pearson's chi-squared test. Data related to continuous variables were analyzed using two-tailed *t*-tests or the Kruskal–Wallis *H*-test. A univariate analysis was used to compare each variable value between the IPR and non-IPR groups. Variables with a *p*-value $\leq$0.20 would be included in the multivariate analysis. We followed the current guidelines for risk score models (15). A *p*-value $\leq$0.05 (two-tailed) was prospectively considered statistically significant. Statistical analyses were performed with SPSS (version 23.0; IBM Corp., Armonk, NY).

Risk score derivation

In the final fitted multivariable model, the regression coefficient of each variable was performed to develop the point score to predict the rate of IPR during EVT of SRAs. The final risk score of IPR for each patient was defined as the sum of all points for each variable. The evaluation of the derived score was based on discrimination and calibration. Discrimination, which indicates the ability to discriminate between the IPR and non-IPR groups, was assessed using the C-statistic (areas under receiver operating characteristics curves, AUC; 0.5 indicates no ability and 1.0 indicates perfect ability). Calibration was carried out by comparing the observed probability of IPR against the predicted risk through the Hosmer–Lemeshow goodness-of-fit test (nonsignificant *p*-value of the test indicating a good fit).

Results

Study population and baseline characteristics

In total, 362 patients with RIAs (<5 mm) underwent EVT during the study period in the databases. Approximately, 72 patients were excluded, as seen in Figure 1. Finally, 290 patients with SRAs were included. The median age was 53.5 $\pm$ 0.69 years (ranging from 14 to 79), and 55.5% were women. The number of patients with SRA located in the VE, distal vessels, communicating arteries, and other arteries was 6 (20.6%), 28 (9.7%), 29 (10.0%), and 173 (59.7%), respectively. The number of patients treated with coiling only, stent-assisted coiling, and balloon-assisted coiling was 191 (65.9%), 83 (28.6%), and 16 (5.5%), respectively. The basic characteristics of patients and aneurysms are presented in Table 1.

Characteristics of IPR

The characteristics of IPR are summarized in Table 2. IPR occurred in 16 out of 290 endovascular procedures, and the incidence of IPR was 5.5%. According to the timing of IPR, two cases (12.5%) occurred during aneurysm access, eight cases (50%) occurred during coil placement, and six cases (37.5%) occurred during unclear stages. Additionally, among the causes

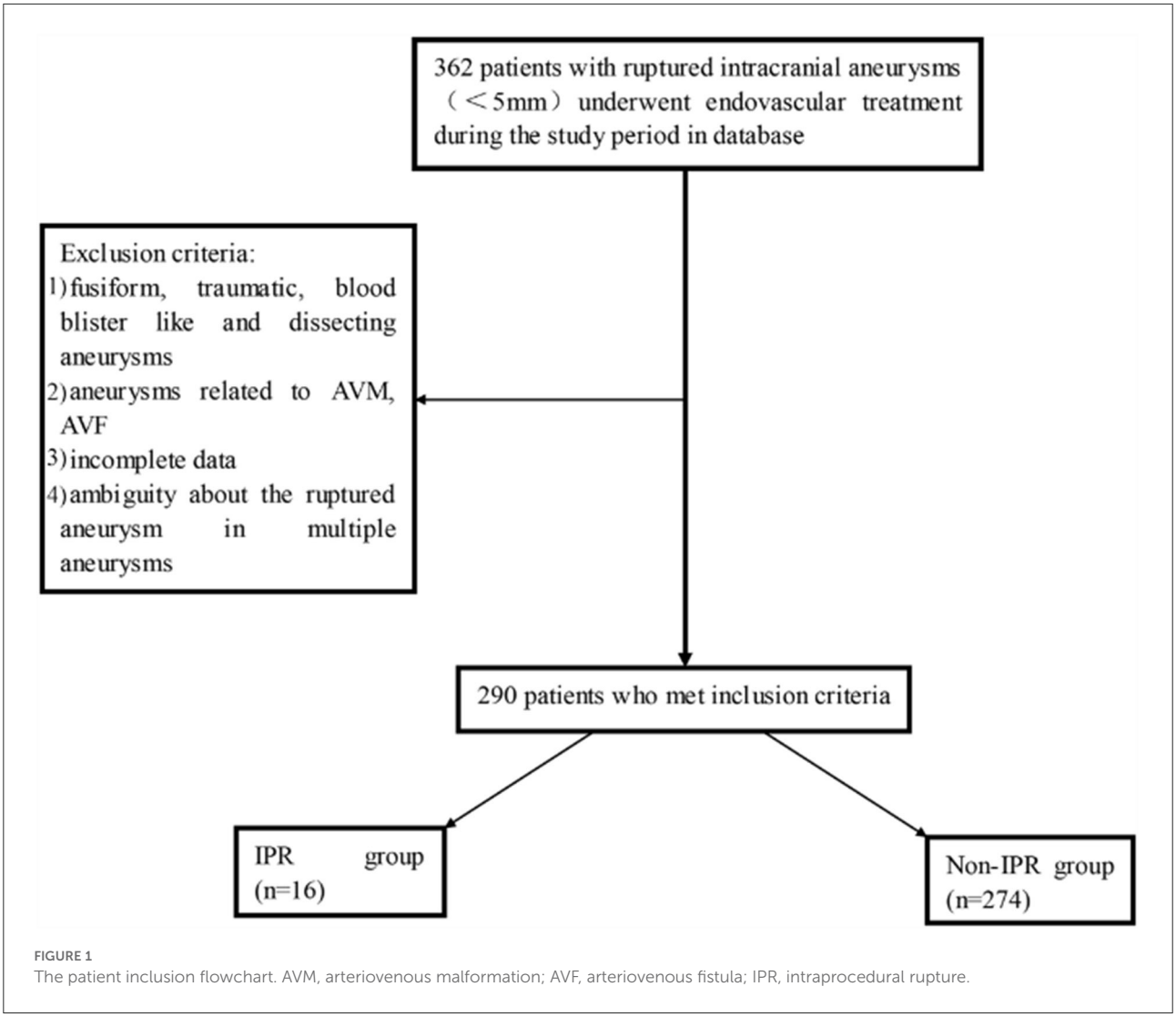

FIGURE 1
The patient inclusion flowchart. AVM, arteriovenous malformation; AVF, arteriovenous fistula; IPR, intraprocedural rupture.

of IPR, eight were coils, one was a microguide wire, one was a microcatheter, and the other six were other reasons (a case of ruptured aneurysm after stent deployment; a case of ruptured aneurysm from an unclear reason before the microcatheter in position, and four cases with no angiography reports).

Among patients with IPR, post-procedural symptoms are shown in Table 2. Eight patients (50%, eight in 16) had morbidity, while four patients (50%, eight in 16) had mortality. The overall morbidity and mortality rates were 38.8 and 2.8%, respectively.

Univariate analysis and multivariate analyses for risk factors of IPR

The following factors from an univariate analysis were significant ($p < 0.20$) and subsequently included in the multivariable analyses: SBO ($p = 0.027$), the shape of an aneurysm ($p = 0.183$), acute stage ($p = 0.118$), smoking status ($p = 0.031$), ACAAS ($p = 0.010$), hypertension ($p = 0.188$), and VE ($p = 0.114$). Multivariate analyses showed that aneurysms with an SBO [odds ratio (OR): 3.573; 95% confidence interval (CI): 1.078–11.840; $p = 0.037$], with ACAMAS (OR: 6.086; 95% CI: 1.768–20.955; $p = 0.004$), and in VE (OR: 3.780; 95% CI: 1.080–13.224; $p = 0.037$) were independently associated with IPR, which were entered into the finally adjusted multivariable logistic regression model (Table 3).

Risk score derivation

According to the multivariate analyses, a three-point IPR score was derived (Table 4). The discriminative power of the

TABLE 1 Baseline characteristics of patients and aneurysms in IPR and non-IPR groups.

Characteristic	Total	IPR(100%)	P-value
Female	161	10(6.2)	0.615
Age≥ 50 (years)	172	7(4.1)	0.202
Hypertension	177	7(4.0)	0.188
Diabetes mellitus	26	1(3.8)	1.000
Dyslipidemia	87	4(4.6)	0.771
Heart comorbidities	26	0(0.0)	0.376
Smoking atatus			0.031
Never smoking	204	15(7.4)	
Current smoking	79	0(0.0)	
Former smoking	7	1(14.3)	
History of drinking	73	4(5.5)	1.000
History of SAH	31	3(9.7)	0.393
Acute stage	167	6(3.6%)	0.118
Prehospital delay after SAH			0.300
≤3 days	165	7(4.2)	
3-14 days	63	3(4.8)	
15-28 days	22	3(13.6)	
>28 days	40	3(7.5)	
Preprocedure dalay after SAH			0.841
≤3 days	135	7(5.2)	
3-14 days	73	3(4.1)	
15-28 days	39	3(7.7)	
>28 days	43	3(7.0)	
Hunt Hess Grade			0.726
1-2	244	13(5.3)	
3-5	46	3(6.5)	
Fisher Grade			1.000
1-2	230	13(5.7)	
3-5	60	2(5.0)	
Treatment modality			0.608
Coiling	191	11(5.8)	
Stent-assisted coiling	83	5(6.0)	
Balloon-assisted coiling	16	0(0.0)	
Raymond scale (RS)			0.663
RS1	214	13(6.1)	
RS2	62	2(3.2)	
RS3	14	1(7.1)	
mRS score on discharge			0.162
≤2	239	11(4.6)	
>2	49	5(10.2)	
Location of distal vessels	28	2(7.1)	0.659
Communicating arteries	168	9(5.4)	1.000
VE	61	6(9.8)	0.114
neck size			0.374
<4mm	224	11(4.9)	
≥4mm	66	5(7.6)	
Aspect ratio			0.609
<1.3	157	10(6.4)	
≥1.3	133	6(4.5)	
aneurysm size			0.569
≤3mm	82	3(3.7)	
3-5mm	208	13(6.3)	
shape of aneurysm			0.183
Lobular	13	0(0.0)	
Regular	135	5(3.7)	
Daughter sac	54	6(11.1)	
Other irregularity	88	5(5.7)	
ACAAS			0.010
ACAIAS	243	10(4.1)	
ACAMAS	38	6(15.8)	
ACASAS	9	0(0.0)	
multiplicity	43	3(7.0)	0.715
SBO	46	6(13.0)	0.027

VE, vascular eloquence (parent arteries was <20 mm from the internal carotid artery or the first segment of cerebral arteries, eg, A1, M1, P1 segments); SBO, small basal outpouching; ACAAS, aneurysms concomitant with adjacent moderate atherosclerotic stenosis; ACAIAS, the mild of ACAAS; ACAMAS, the moderate of ACAAS; ACASAS, the severe of ACAAS.

IPR score was statistically significant (AUC: 0.716; CI: 0.575–0.856; $p = 0.004$), as seen in Figure 2. The Hosmer–Lemeshow χ^2 statistics were 0.159 ($p = 0.650$) in the cohorts, indicating good calibration. Figure 3 reports observed and predicted probabilities of the IPR rate according to the IPR risk score. The predicted IPR rates for patients with a score of 0, 1, 2, and 3 were 2.1, 7.4, 23.0, and 53.0% respectively, which were significantly correlated with their actually observed IPR rates (2.4, 6.7, 21.1, and 100% respectively; Pearson $r = 0.975$, $p = 0.025$; Figure 3).

Discussion

The rate of IPR in patients with ruptured aneurysms ranges from 2.73 to 9.52% (5, 16). We observed a comparable rate of 5.5% in the present study. Smaller aneurysm size (<5 mm) and ruptured IAs were reported as independent predictors of IPR. However, very few studies were designed to identify independent predictors of IPR during the coiling of small and ruptured IAs (1, 3, 17). In this study, we found that SBO, VE, and ACAMAS were independent risk factors of IPR in the EVT of SRA.

Small basal outpouching (i.e., a daughter sac or bleb that is located near the base of a ruptured aneurysm) is a common morphological configuration in cases of basal rupture. Park et al.

TABLE 2 Characteristics, management, and outcomes of IPR (n = 16).

Characteristics	n	Incidence (%)
Timing of perforation		
Access	2	12.5
Coils placement	8	50.0
Others	6	37.5
Causes of IPR		
Coil	8	50.0
Microguidewire	1	6.3
Microcatheter	1	6.3
Others	6	37.5
Symptoms		
Headache	4	25.0
Disturbance of consciousness	3	18.8
Double vision	1	6.3
Limb weakness	2	12.5
Complications		
Ischemia	9	56.3
Bleeding	2	12.5
Clinical outcome		
Morbidity	8	50.0
Mortality	4	12.5

TABLE 3 Multivariate analysis of risk factors for intraprocedural rupture.

Variable	OR(95%CI)	*P value*
Hypertention	0.308(0.095-0.996)	0.049
Smoking	2.797(0.277-28.262)	0.383
VE	3.780(1.080-13.224)	0.037
SBO	3.573(1.078-11.840)	0.037
ACAMAS	6.086(1.768-20.955)	0.004

SBO, small basal outpouching; ACAMAS, aneurysms concomitant with adjacent moderate atherosclerotic stenosis.

(18) reported that the incidence of SBO in ruptured aneurysms was 8.7%, and in some cases, the basal rupture could be induced by the SBO. Kang et al. (12) suggested that the chance of IPR could increase when the coil or microcatheter was placed near the SBO. The presence of the microcatheter and the microguide wire would likely cause repeated wear and tear of the SBO during the procedure, which also increases the risk of IPR. Similarly, in our study, the risk of IPR in aneurysms with an SBO was three times more than that of an aneurysm without SBO.

Several previous studies reported a case series of IAs concomitant with ACAAS (2, 19, 20). In this study, of 16 IPR cases, it was found that six (37.5%) had ACAAS and all of them had a moderate degree. It was reported that moderate or severe stenosis adjacent to the aneurysm may increase the risk of aneurysm rupture due to pressure changes caused by balloon or stent implantation (19). One possible explanation is that atherosclerosis could increase vascular susceptibility to mechanical injury (21), and the rebleeding event may be triggered by the coil implanted near the aneurysm neck, which was proximal to the stenosis. However, of the nine cases with ACASAS, none of them had IPR. One possible explanation is that the occlusion rate of was higher in SRAs with ACAMAS (92.1%) than SRAs with ACASAS (55.6%). Moreover, we should be more careful in treating proximal severe stenosis cases and use coil occlusion as much as possible to avoid the occurrence of a thromboembolic event, which may further reduce the contact with the aneurysmal wall and decrease the risk of IPR.

TABLE 4 Risk score (S-V-A score, 0-3 points) for IPR.

Clinical variables	Assigned points
SBO	
No	0
Yes	1
VE involvement	
No	0
Yes	1
ACAMAS	
No	0
Yes	1

VE, which is demonstrated as the arterial segments often having iatrogenic complications (i.e., occlusion or injury), was first used to assess the curative risk of EVT for AVM (11). Here, VE is regarded as the parent vessel close to the internal carotid artery or the first segment of cerebral arteries. As reported in the A1 segment of the internal carotid artery bifurcation, EVT of small aneurysms faces a great challenge (17). In this study, six IPR cases (9.8%) occurred in the VE group, which was more than two times that in the non-VE group (4.4%). Among the six IPR cases, four cases (66.7%) occurred in the procedure of coiling. For small-sized aneurysms, the incidence of "close contact" between the coils and the perforators or vessel branches may increase, which may further increase the chance of IPR (17).

It is therefore beneficial to establish a risk score to identify patients who are at high risk of IPR before EVT decision for SRAs. Based on the above three significant and important factors, we established this S-V-A score system. Our receiver operating characteristic (ROC) analysis demonstrated that the application of the endovascular S-V-A score provides good discriminatory power to evaluate IPR rates (AUC = 0.716). The Hosmer–Lemeshow χ^2 statistics were 0.159 ($p = 0.650$) across cohorts, indicating good calibration. The analysis of predicted risk and observed probability of IPR demonstrated that the predicted IPR rate was significantly correlated with the observed IPR rate (Pearson $r = 0.975$; $p = 0.025$; Figure 3). This score would be helpful to identify patients with a high risk of IPR, thereby taking protective interventions before EVT.

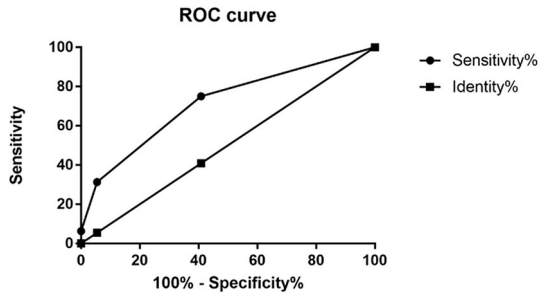

FIGURE 2
Receiver operating characteristic (ROC) curves for the IPR score. The AUC value was 0.716 (95% CI: 0.58–0.86) for this model. AUC, area under the curve; CI, confidence interval. IPR, intraprocedural rupture.

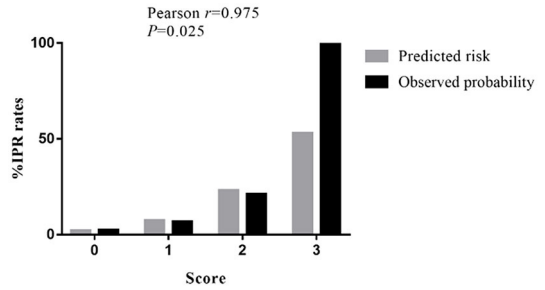

FIGURE 3
Rates of IPR by the clinical score for patients with SRAs. The predicted rates of patients with SRAs with a score of 0, 1, 2, and 3 have IPR rates of 2.1, 7.4, 23.0, and 53.0%, respectively. The observed rates of patients with SRAs with a score of 0, 1, 2, and 3 have IPR rates of 2.4, 6.7, 21.1, and 100%, respectively. IPR, intraprocedural rupture; SRAs, small ruptured aneurysms.

Notably, 50% (eight of 16) of IPR events occurred because of the attempt to reach a complete occlusion. In the procedure of coiling, as the degree of embolization increases, the operation time and the difficulty of operation also increase, which therefore increases the likelihood of IPR. Several factors such as anterior communicating artery (ACoA), posterior communicating arteries (PCoA), history of SAH, (17, 22) coronary artery disease, and dyslipidemia were reported to be the risk factors of IPR in previous studies (4). However, in our study, these risk factors were nonsignificant. Vessel wall disease may be responsible for IPR as it is reported that IPR may be due to vascular rupture (22). However, not all the patients performed high-resolution magnetic resonance imaging (HR-MRI) prior to EVT. Moreover, the vessel wall abnormality was also rarely considered in several previous studies and clinical practice. So, we suggest that there is a need for prospective cohort studies in the future to investigate the association between IPR and vessel wall abnormality demonstrated by HR-MRI or other photographic methods. Many studies found that aneurysms ($\leq$3 mm) were associated with an increased incidence of IPR (3, 17). In our study, three cases (3.7%) in the $\leq$3 mm group and 11 cases (5.3%) in the 3–5-mm group had IPR. The IPR rate in the 3-mm group was lower than that in the 3–5-mm group ($p = 0.569$), which was different from their results. The reason may be the limited sample in our study and the heterogeneity of operative techniques in different operators.

Strengths and limitations

This is the first study to develop a simple scoring system to predict IPR risk in the EVT of SRA. To avoid selection bias, we included information from two major stroke centers in China. Moreover, we included new risk factors, including prehospital delay after SAH and preprocedural delay after SAH, SBO, VE, and ACAAS. In the meantime, we also acknowledge some potential limitations. First, the study has 16 IPR events and offers many predictive variables in the model for this number of events (general rule one variable for 10 events). Second, our study can be limited due to its retrospective nature because data were prospectively recorded with limited data size. Third, the S-V-A score system is designed for SRAs (<5 mm), which may not fit for all ruptured aneurysms. Fourth, some potential risk factors are missing such as softness and the shape of the coils used, vascular wall disease with high-resolution MRI, and stent design and deployment technique. Thus, the S-V-A score requires external validation using a large series in other centers or countries.

Conclusions

In this study, SBO, VE, and ACAMAS were independent risk factors of IPR in EVT of SRA. This indicates that SBO and ACAMAS are important morphological risk factors for predicting a higher risk of IPR, but more confirmation studies on these results are required. In addition, the S-V-A score may be useful to predict the risk of IPR based on variables used in daily practice.

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 Beijing Tiantan Hospital, Capital Medical University. The patients/participants provided

their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FP drafted the manuscript for intellectual content. XF and XH designed the study and analyzed and interpreted the data. HN, HZ, XT, BZ, JX, XC, BX, PQ, and JL collected the data in each center. DW and AL strictly revised this manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Predictors of futile recanalization in patients with acute ischemic stroke undergoing mechanical thrombectomy in late time windows

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Background and purpose: Futile recanalization (FR), defined as functional dependence despite successful reperfusion, is common in patients who experience an acute stroke after thrombectomy. We aimed to determine the predictors of FR in patients who underwent thrombectomy in late time windows (6 h or more after symptom onset).

Methods: This retrospective review included patients who underwent thrombectomy for acute anterior circulation large vessel occlusion from October 2019 to June 2021. Successful reperfusion was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b/3. Functional dependence at 90 days was defined as a modified Rankin scale score of 3–6. Multivariate analysis and a receiver operating characteristic (ROC) curve were used to identify the predictors of FR in patients treated in delayed time windows.

Results: Of the 99 patients included, FR was observed in 51 (51.5%). In the multivariate analysis, older age (OR, 1.12; 95% CI, 1.04–1.22; $P = 0.005$), female sex (OR, 3.79; 95% CI, 1.08–13.40; $P = 0.038$), a higher National Institutes of Health Stroke Score (NIHSS) score upon admission (OR, 1.11; 95% CI, 1.02–1.22; $P = 0.023$), and an increased number of passes per procedure (OR, 2.07; 95% CI, 1.11–3.86; $P = 0.023$) were independently associated with FR after thrombectomy. The ROC curve indicated that the model that combined age, female sex, baseline NIHSS score, and the number of passes per procedure (area under the curve, 0.84; 95% CI, 0.75–0.90, $P < 0.001$) was able to predict FR accurately.

Conclusions: Older age, female sex, higher NIHSS score upon admission, and an increased number of passes per procedure were independent predictors of FR in patients who experienced acute ischemic strokes after thrombectomy in late time windows.

KEYWORDS

futile recanalization, mechanical thrombectomy, acute ischemic stroke, late time windows, predictors

Introduction

Mechanical thrombectomy (MT) is widely accepted as a standard approach for acute large-vessel occlusions (LVOs) in the anterior circulation in patients with acute ischemic stroke (AIS) (1). Recently, the results from the DAWN and the DEFUSE-3 trials have demonstrated the safety and efficacy of MT in late time windows in patients with AIS selected by perfusion imaging (2, 3). However, a substantial proportion of patients experience futile recanalization (FR; defined as poor clinical outcomes despite successful recanalization) after thrombectomy in late time windows, even though these patients are screened with rigorous imaging (2–4). A real-world study showed that patients who underwent endovascular treatment more than 6 h after symptom onset had a relatively higher rate of poor outcomes despite successful reperfusion compared with those treated within 6 h of symptom onset (4). Thus, predicting FR in these specific populations could help select a population of patients treated with MT that would potentially benefit more of adjunctive therapies to maximize the benefit of MT.

Many previous studies have identified predictors of FR after endovascular treatment in early time windows in patients with AIS (5–12). However, few studies have investigated the predictors of FR in patients treated with MT in late time windows. Therefore, this study aimed to identify the potential predictors of FR in patients with AIS who underwent thrombectomy in late time windows.

Materials and methods

Population selection

From October 2019 to June 2021, 321 patients who underwent MT for acute LVO in the anterior circulation were retrospectively reviewed using the stroke database. The selection criteria were as follows: (1) age of ≥18 years; (2) a modified Rankin scale (mRS) score of 0–1 before stroke; (3) an initial National Institutes of Health Stroke Scale (NIHSS) score of ≥6; (4) MT performed 6 to 24 h after symptom onset; (5) occlusion of the internal carotid artery (ICA) and/or middle cerebral artery (MCA) M1 or proximal M2; (6) fulfillment of DAWN or DEFUSE-3 criteria in CT perfusion (CTP) imaging; and (7) successful recanalization. The exclusion criteria were as follows: (1) occlusion of posterior circulation or anterior cerebral artery; (2) MT performed within 6 h of symptom onset; (3) failed recanalization; (4) stroke recurrence during hospitalization; and (5) loss of clinical data or follow-up results. Ultimately, 99 patients were included in the study. This study was approved by the local institutional review board, and because of the retrospective study design, the requirement for informed consent from patients was waived. Figure 1 shows the workflow for patient selection.

Clinical and imaging data evaluation

The following clinical data were collected: demographic features (age and sex), medical history (hypertension, hyperlipidemia, diabetes mellitus, myocardial infarction, atrial fibrillation, smoking history, ischemic stroke history, and blood pressure on admission), procedure details, and outcomes. The baseline NIHSS score was used to assess stroke severity. All patients underwent computed tomography (CT) scans immediately and 24 h after MT. The follow-up magnetic resonance (MR) imaging, including the additional sequences of MR angiography and perfusion, was also performed approximately 1 week after MT if the patient cooperated. A non-contrast CT scan was performed immediately to exclude intracranial hemorrhage if any deterioration in the patient's neurological status was observed. Hemorrhagic transformation (HT) was evaluated according to the European Cooperative Acute Stroke Study II (ECASS II) criteria, and symptomatic intracranial hemorrhage (sICH) was defined as a hemorrhage observed on the CT scan accompanied by a deterioration in the patient's neurologic status, defined as an increase in NIHSS score by ≥4 (13). The clinical outcome was assessed using the mRS score; the 90-day mRS score was obtained from the clinic or through telephonic interviews. Successful reperfusion was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b/3. FR was defined as a poor clinical outcome (a 90-day mRS of 3–6) despite successful recanalization, and patients were divided into FR and meaningful recanalization groups.

At our institution, multimodal CT-based images are routinely conducted in late time windows in patients with suspected stroke, including non-contrast CT, CTP, and post-processed series. Automated Alberta Stroke Program Early Computed Tomography Scores (ASPECTS) were obtained from a non-contrast CT. Perfusion images were processed using the commercial software RAPID (iSchemaView, Menlo Park, California, USA), which automatically provided colored parametric CTP maps. The ischemic core volume (cerebral blood flow [CBF] < 30%), hypoperfusion volume (Tmax > 6 s), and mismatch volume were obtained from CTP maps. The collateral status evaluated on angiography was divided into two categories according to the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) guidelines: good collaterals (grade 3–4) and poor collaterals (grade 0–2). The imaging parameters were assessed by two experienced neuroradiologists who were blinded to the clinical treatment and outcomes; if any discrepancies arose

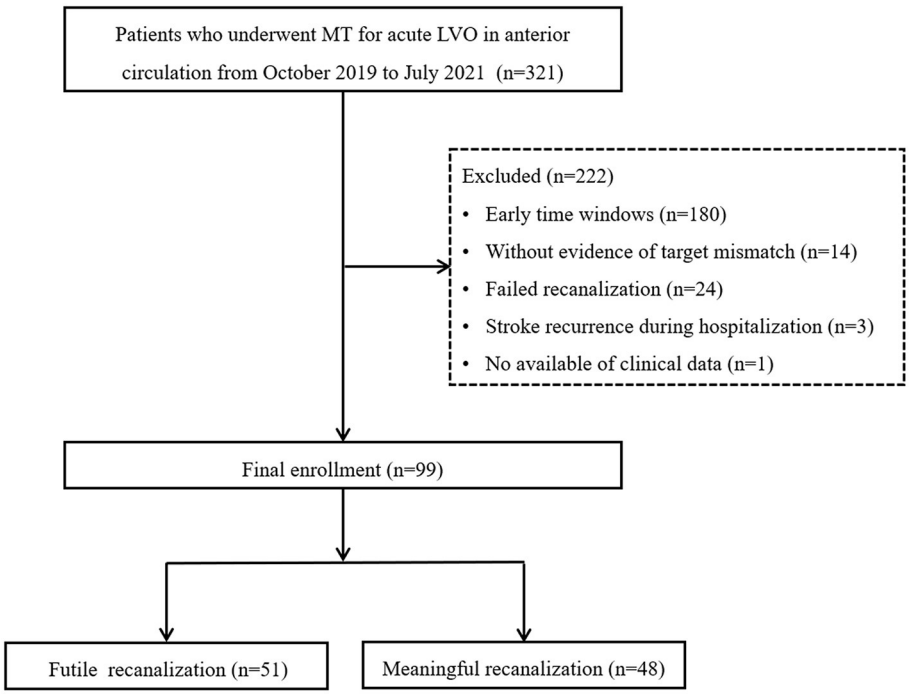

FIGURE 1
Flowchart of patient selection. MT, mechanical thrombectomy; LVO, large vessel occlusion.

between the two readers, a consensus was achieved with the help of a third neuroradiologist.

Endovascular procedure

According to the current guidelines, patients are eligible to receive an intravenous recombinant tissue plasminogen activator before MT within 4.5 h after stroke onset. MT was performed under local anesthesia/conscious sedation. A stent retriever thrombectomy was recommended as the first-line thrombectomy technique, but other devices were also permitted. Rescue therapies were defined as interventions performed after a failed MT, including permanent stent placement, balloon angioplasty, and use of glycoprotein IIb/IIIa antagonists.

Statistical analysis

Continuous variables are described as means (standard deviation, SD) or medians (interquartile range, IQR) and categorical variables are presented as frequencies (%). The Shapiro-Wilk test and histograms were used to assess the normality of the distributions. A Student's *t*-test or a Mann-Whitney *U*-test was performed to analyze continuous data. The Fisher exact or χ^2 test was used to analyze categorical data. Significant clinical factors ($P < 0.1$) identified using univariate logistic regression analyses were included in the multivariate logistic regression model to determine odds ratios (ORs) and confidence intervals (CIs). Multicollinearity was assessed by calculating variance inflation factors (VIFs) for variables included in the final model, and substantial multicollinearity was defined as a VIF < 10. Considering that rescue therapies may bring a bias to the results, a sensitivity analysis was undertaken in the subgroup of patients not treated with rescue therapies. Receiver operating characteristic (ROC) curve analyses were applied to identify the effectiveness of significant variables in predicting FR. SPSS 26.0 (IBM, Armonk, NY, USA) and MedCalc (version 11.0, Solvusoft Corporation, Los Angeles, CA, USA) software packages were used for analysis. A *P*-value of <0.05 was considered statistically significant.

Results

The mean age of the 99 patients who met the inclusion criteria was 72 years (IQR, 66–80) and 50.5% of these patients were women. The median baseline NIHSS score was 16 (11–22), and the median baseline ASPECTS score was seven (IQR, 5–8). The numbers of patients who had occlusions in the ICA (isolated, T- or L-shaped, and tandem occlusions), M1, and M2 were 35 (35.4), 53 (53.5), and 11 (11.1%), respectively. The median volumes of ischemic core

and hypoperfusion were 9 mL (IQR, 0–27) and 139 mL (IQR, 89–179), respectively. Intravenous tissue plasminogen activator (tPA) was administered in 20 patients (20.2%) at local hospitals before MT was performed. The etiologies of stroke were cardiac embolism (50, 50.5% of patients), large artery atherosclerosis (33, 33.3% of patients), and undetermined etiology or others (16, 16.2% of patients). The median onset-to-puncture (OTP) and puncture-to-recanalization (PTR) times were 572 min (IQR, 431–793) and 67 min (IQR, 49–100), respectively. Rescue therapy was performed in 24 patients (24.2%), including stent-retriever detachment alone in two, balloon angioplasty alone in 13, and balloon angioplasty plus stenting in 9. The rates of HT and sICH were 40.4% (40/99) and 16.2% (16/99), respectively, and 90-day mortality was observed in 18 patients (18.2%).

FR was observed in 51 patients (51.5%). Table 1 shows a comparison of the characteristics and clinical outcomes between the futile and meaningful recanalization groups. Patients with FR were older (median age of 76 years vs. 68, $P < 0.001$), and a higher proportion of them were women (60.8 vs. 39.6%, $P = 0.035$); those in the FR group also had a higher prevalence of atrial fibrillation (62.7 vs. 33.3%, $P = 0.003$), a lower incidence of smoking history (3.9 vs. 22.9%, $P = 0.012$), a higher median NIHSS score at admission (19 vs. 12, $P = 0.001$), a lower median ASPECTS score (7 vs. 8, $P = 0.039$), and a higher median number of passes per procedure (2 vs. 1, $P = 0.041$). In addition, a larger proportion of patients in the FR group had cardiac embolism stroke ($P = 0.001$) and poor collaterals ($P = 0.021$). Furthermore, there were significant differences in terms of HT, sICH, and mortality rates ($P < 0.001$).

After further adjustment of the variables (including age, female sex, smoking, baseline systolic blood pressure, ASPECTS, ischemic core volume, stroke etiology, and poor collaterals) in multivariate logistic regression analyses (Table 2), we found that older age (OR, 1.12; 95% CI, 1.04–1.22; P = 0.005), female sex (OR, 3.79; 95% CI, 1.08–13.40; $P = 0.038$), a higher NIHSS score on admission (OR, 1.11; 95% CI, 1.02–1.22; $P = 0.023$), and an increased number of passes per procedure (OR, 2.07; 95% CI, 1.11–3.86; $P = 0.023$) were independently associated with the occurrence of FR after thrombectomy. Supplementary Table 1 shows multicollinearity testing for the variables included in the final logistic regression model.

In addition, in the sensitivity analysis that excluded patients not treated with rescue therapies, the results did not change substantially (Supplementary Table 2).

Using the ROC curves from the logistic regression analysis, we identified the predictive accuracy of age, female sex, NIHSS score on admission, and the number of passes per procedure for predicting FR (Figure 2). The area under the curve (AUC) for age, sex, NIHSS score on admission, and the number of passes per procedure were 0.77 (95% CI, 0.67–0.85), 0.59 (95% CI, 0.48–0.68), 0.70 (95% CI, 0.60–0.79), and 0.61 (95% CI, 0.51–0.71). The model combining age, female sex, baseline NIHSS score, and the number of passes per procedure had the highest AUC (0.84; 95% CI, 0.75–0.90).

Discussion

In this cohort of patients treated in late time windows, we observed an FR incidence of 51.5% after thrombectomy. The main finding of this study was that advanced age, female sex, a higher NIHSS score on admission, and an increased number of passes per procedure were independently associated with FR after adjusting for confounders. The combination of these independent risk factors increased the model's ability to predict FR in these patients.

The results from the DAWN and the DEFUSE-3 trials led to prolonged time windows for MT in patients with AIS selected by perfusion imaging and changed the guidelines for the early management of these patients (1–3). However, a substantial proportion of patients in both these trials had poor clinical outcomes despite successful recanalization, even after rigorous imaging screening. Reperfusion in delayed time windows may carry harmful consequences, such as severe ischemia-reperfusion injury, and the chances of functional independence may decline. Therefore, predicting FR in patients treated with MT in late time windows may help clinicians select more personalized therapy for patients undergoing MT and identify patients who need other timely adjuvant treatments. Predictors of FR in early time windows have received widespread attention, and several predictors have previously been identified, such as age, female sex, systolic blood pressure upon admission, serum glucose, baseline NIHSS score, time from onset to treatment, and post-procedural complication events (5–12). In this study, we confined our analysis to patients with stroke who underwent treatment in late time windows and identified several clinical markers as independent predictors of poor outcomes after successful recanalization; these predictors could help manage these patients.

Consistent with most previous studies (5, 10–12, 14), we found that advanced age was associated with functional dependence despite successful recanalization, which may be explained by the higher prevalence of underlying diseases, higher incidence of complications, and lower potential for rehabilitation in older age groups compared with younger ones. In addition, older adults are more likely to have leukoaraiosis and poor collateral status than younger individuals, which may be linked to the occurrence of intracranial hemorrhage and poor outcomes after successful reperfusion (15). Nevertheless, older patients could still benefit from endovascular treatment despite their higher rate of FR compared with younger patients. Thus, it seems unjustified to exclude older adults from thrombectomy, but this poor prognostic indicator could help inform discussions with patients' families about the likely prognosis after stroke.

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TABLE 1 Comparisons of characteristics and clinical outcomes between futile and meaningful recanalization groups.

Variables	Total ($n = 99$)	Futile recanalization ($n = 51$)	Meaningful recanalization ($n = 48$)	*P*-value
Age (years), median (IQR)	72 (66–80)	76 (71–83)	68 (57–74)	<0.001
Female sex, *n* (%)	50 (50.5)	31 (60.8)	19 (39.6)	0.035
Arterial hypertension, *n* (%)	65 (65.7)	36 (70.6)	29 (60.4)	0.287
Diabetes mellitus, *n* (%)	17 (17.2)	11 (21.6)	6 (12.5)	0.232
Myocardial infarction, *n* (%)	13 (13.1)	8 (15.7)	5 (10.4)	0.438
Hyperlipidemia, *n* (%)	5 (5.1)	3 (5.9)	2 (4.2)	1.000
Atrial fibrillation, *n* (%)	48 (48.5)	32 (62.7)	16 (33.3)	0.003
History of ischemic stroke, *n* (%)	14 (14.1)	8 (15.7)	6 (12.5)	0.649
Smoking, *n* (%)	13 (13.1)	2 (3.9)	11 (22.9)	0.012
Glucose (mmol/L), median (IQR)	6.4 (5.1–8.4)	6.7 (5.3–8.6)	6.1 (4.6–8.3)	0.786
Baseline SBP (mm Hg), mean (SD)	149 (22.5)	152 (23.2)	144 (21.2)	0.078
Baseline NIHSS score, median (IQR)	16 (11–22)	19 (14–23)	12 (9–17)	0.001
Baseline ASPECTS, median (IQR)	7 (5–8)	7 (6–8)	8 (7–9)	0.039
Ischemic core (mL), median (IQR)	9 (0–27)	9 (0–23)	5 (0–16)	0.056
Hypoperfusion (mL), median (IQR)	139 (89–179)	142 (99–176)	139 (85–186)	0.657
Mismatch (mL), median (IQR)	121 (70–156)	123 (81–146)	126 (68–179)	0.908
Treatment with IV alteplase, *n* (%)	20 (20.2)	9 (17.6)	11 (22.9)	0.191
Local anesthesia, *n* (%)	99 (100.0)	51 (100.0)	48 (100.0)	1.000
Etiology, *n* (%)				0.001
Cardio–embolism	50 (50.5)	34 (66.7)	16 (33.3)	
Large artery atherosclerosis	33 (33.3)	9 (17.6)	24 (50.0)	
Undetermined etiology or others	16 (16.2)	8 (15.7)	8 (16.7)	
Occlusion site, *n* (%)				0.779
ICA	35 (35.4)	17 (33.3)	18 (37.5)	
M1	53 (53.5)	29 (56.9)	24 (50.0)	
M2	11 (11.1)	5 (9.8)	6 (12.5)	
Poor collaterals, *n* (%)	51 (51.5)	32 (62.7)	19 (39.6)	0.021
OTP time (min), median (IQR)	572 (431–793)	604 (445–762)	520 (410–809)	0.949
PTR time (min), median (IQR)	67 (49–100)	65 (52–102)	71 (49–99)	0.798
Number of passes per procedure, median (IQR)	1 (1–2)	2 (1–3)	1 (1–2)	0.041
Rescue therapy, *n* (%)	24 (24.2)	9 (17.6)	15 (31.3)	0.114
HT, *n* (%)	40 (40.4)	30 (58.8)	10 (20.8)	<0.001
sICH, *n* (%)	16 (16.2)	16 (31.4)	0 (0)	<0.001
Mortality, *n* (%)	18 (18.2)	18 (35.3)	0 (0)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; OTP, onset to puncture; PTR, puncture to reperfusion, HT, hemorrhagic transformation; sICH, symptomatic intracranial hemorrhage.

It is generally accepted that the baseline NIHSS score is a strong predictor of FR after thrombectomy. Our study confirmed that a higher NIHSS score on admission (≥12) was associated with FR in delayed windows patients, which was in line with previous studies (5, 7–11, 14). However, Lee et al. found that the clinical benefit of reperfusion after thrombectomy increased with the progression of stroke severity despite the increased rate of FR (8). Similarly, a meta-analysis showed that patients with severe stroke (an NIHSS score of more than 20) experienced greater benefits from thrombectomy than from pharmaceutical treatment (16). This may be because patients with severe stroke tend to have a higher likelihood of functional dependence if untreated, and a proportion of patients with sufficient salvageable brain tissue could recover after reperfusion. According to these findings, when considered as a non-modifiable risk factor, a high NIHSS score should not be considered an exclusion criterion for thrombectomy.

TABLE 2 Logistic regression analysis identifying the risk factors associated with futile recanalization.

Variables	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age	1.11 (1.06–1.17)	<0.001	1.12 (1.04–1.22)	0.005
Female sex	2.37 (1.06–5.30)	0.036	3.79 (1.08–13.40)	0.038
Arterial hypertension	1.57 (0.68–3.63)	0.288	–	–
Diabetes mellitus	3.33 (0.65–17.15)	0.150	–	–
Myocardial infarction	1.60 (0.49–5.28)	0.441	–	–
Hyperlipidemia	1.44 (0.23–9.00)	0.698	–	–
Atrial fibrillation	3.37 (1.48–7.69)	0.004	–	–
History of ischemic stroke	1.30 (0.42–4.08)	0.650	–	–
Smoking	0.14 (0.03–0.66)	0.013	–	–
Glucose	1.06 (0.78 −1.54)	0.782	–	–
Baseline SBP	1.02 (0.99–1.04)	0.082	–	–
Baseline NIHSS score	1.10 (1.04–1.17)	0.002	1.11 (1.02–1.22)	0.023
Baseline ASPECTS	0.82 (0.68–0.99)	0.043	–	–
Ischemic core volume	1.03 (1.00–1.05)	0.028	–	–
Hypoperfusion volume	1.00 (0.99–1.00)	0.775	–	–
Mismatch volume	1.00 (0.99–1.00)	0.436	–	–
Treatment with IV alteplase	0.72 (0.27–1.93)	0.515	–	–
Etiology (cardio–embolism vs. others)	4.00 (1.73–9.23)	0.001	–	–
Occlusion site of ICA	0.83 (0.37–1.90)	0.665	–	–
Poor collaterals	2.57 (1.14–5.78)	0.022	–	–
OTP time	1.00 (0.99–1.00)	0.747	–	–
PTR time	1.00 (0.99–1.01)	0.806	–	–
Number of passes per procedure	1.49 (1.00–2.24)	0.052	2.07 (1.11–3.86)	0.023

SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; OTP, onset to puncture; PTR, puncture to reperfusion.

Our analysis also showed that female sex was associated with FR in patients treated in late time windows. The impact of sex on FR is still unclear. Hussein et al. (7) reported similar results: women had a lower rate of favorable outcomes despite successful recanalization compared with men (38.7 vs. 56.5%). In a *post hoc* analysis of the MR CLEAN trial, women had worse treatment outcomes after intra-arterial treatment, although no difference in the recanalization rate was observed (17). In this analysis, the association between female sex and FR was significant after adjusting for confounders. A possible explanation is that women have a higher incidence of atrial fibrillation, and different stroke etiologies may influence the treatment strategies and clinical outcomes (7). This observed difference in treatment outcomes between men and women should be further analyzed with a larger sample size to rule out coincidence.

Several procedure-related factors have been associated with poor outcomes after thrombectomy, including the first-pass effect (18, 19), the number of stent retriever passes (20, 21), and the PTR time (10). The present study showed that an increased number of passes per procedure was associated with 90-day functional dependence despite successful reperfusion after MT. However, the PTR time was not associated with functional dependence in our study. In addition, we did not find a significant association between the OTP time and FR, which was consistent with the data from DEFUSE-3 (22). Despite this, the importance of shortening OTP and PTR time should be stressed in clinical practice.

According to the recently published studies, the effect of collateral status on the functional outcome after recanalization is still controversial. Pan et al. (14) observed a lower rate of FR in patients with good collateral circulation before endovascular treatment. Conversely, a meta-analysis found no significant difference in collateral status between the FR and meaningful recanalization groups (23). Our analysis did not observe a strong association between collateral status and FR after adjusting for the available variables. These contradictory results may be explained by the differences in approaches used to assess collateral circulation and the existence of heterogeneity. In addition, a large final infarct volume was shown to be associated with FR after endovascular therapy in patients with stroke (12). However, no analysis has yet identified an association

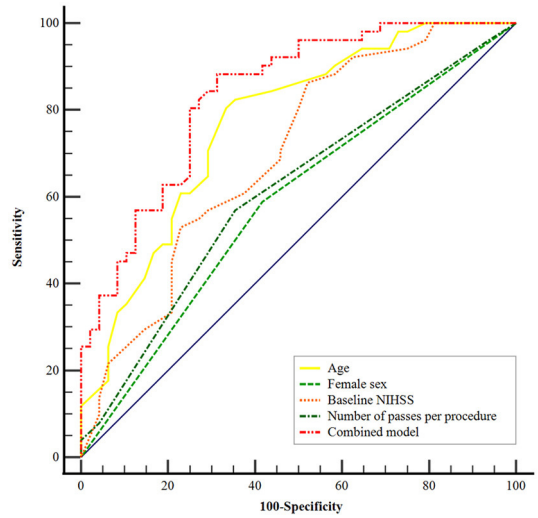

FIGURE 2
Receiver operating characteristic curves were generated to evaluate the efficacy of age, female sex, baseline NIHSS score, and number of passes per procedure independently and combined for the prediction of futile recanalization after mechanical thrombectomy. The area under the curve of the combined model was 0.84 (95% CI, 0.75–0.90; $P < 0.001$). NIHSS, National Institute of Health Stroke Scale.

between preoperative ischemic core volume on CTP imaging and FR. Ribo et al. (24) indicated that patients with lesion core volumes of >39 mL upon admission had poor outcomes after endovascular treatment. By contrast, Heit et al. reported no difference in the ischemic core between the FR and meaningful recanalization groups (22). We found that patients with FR had a slightly larger ischemic core, but this result was not statistically significant. It should be noted that a small ischemic core was observed in most patients included in this study after selection by perfusion imaging, and core volumes larger than 50 mL were rare (10/99, 10.1% of patients). Further studies with a larger sample size are needed to evaluate the prognostic value of these variables (collaterals and core) for futile recanalization.

This study has several potential limitations. First, it has limitations inherent to the retrospective study design. Second, the relatively small sample size may limit the interpretation of the results; some variables with a trend toward significance may show significant associations in analyses with larger sample sizes. Third, post-procedural complications, such as the occurrence of sICH and pneumonia, were not analyzed in the multivariate model because we mainly focused on evaluating preoperative clinical factors and procedural details, and the data on pneumonia were not collected. Finally, the lack of independent core laboratory adjudication for imaging parameters may affect the reliability of the results.

Conclusions

Although the benefits of MT have been demonstrated in many trials and meta-analyses, the incidence of FR remains a major concern in emerge thrombectomy. In patients with acute stroke treated in late time windows, our results suggest that older age, female sex, higher NIHSS score on admission, and an increased number of passes per procedure are independent predictors of FR after thrombectomy. This finding could help select a population of patients who may potentially benefit more of adjunctive therapies to maximize the benefit of MT, but not for selecting patients for MT treatment. Further studies are needed to validate the predictive value of this model for futile recanalization in this specific subset of acute 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 Ethical Standards of the Institutional Research Committee of Jiangsu Province Hospital, the First Affiliated Hospital of Nanjing Medical University (IRB number: 2021-SR-516). Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional requirements.

Author contributions

HN and XL analyzed the data and drafted the manuscript. SL designed the study and helped to revise this manuscript. LZ conceived the study and made final approval of this manuscript. YH, ZJ, YC, and HS helped to perform the analysis with constructive discussions. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.958236/full#supplementary-material

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Stent-assisted coiling using the Neuroform Atlas stent for treatment of aneurysms that recur after coil embolization

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Objective: To evaluate the safety and efficacy of stent-assisted coiling (SAC) using the Neuroform Atlas stent for aneurysms that recur after coil embolization.

Methods: We retrospectively reviewed patients who underwent SAC using the Neuroform Atlas stent to treat aneurysms that recurred after coil embolization from November 2020 to November 2021. Patient and aneurysm characteristics, procedural details, complications, and angiographic and clinical follow-up outcomes were recorded and analyzed.

Results: Eleven patients with 11 recurrent aneurysms were included for analysis. Atlas stent deployment was successful in all cases. Angiography immediately after the SAC procedure and at last follow-up showed complete occlusion in 10 patients (90.9%) and a residual neck in one (9.1%). Mean angiographic and clinical follow-ups were 9.2 and 10 months, respectively. A single procedure-related complication occurred, mildly blurred vision in the left eye, which recovered completely. No permanent morbidity or mortality occurred.

Conclusion: SAC using the Atlas stent to treat aneurysms that recur after coil embolization is safe and effective. Large-scale studies with long-term follow-up are warranted to confirm our results.

KEYWORDS

Neuroform Atlas stent, recurrent aneurysms, stent-assisted coiling, endovascular treatment, previously coiled

Introduction

Endovascular treatment of intracranial aneurysms is effective; however, recurrence is a known complication that requires re-treatment to reduce the risk of aneurysm growth and hemorrhage (1–3). The reported rates of aneurysm recurrence and re-treatment after coiling are 20% and 10%, respectively (4). Intracranial stents can reduce the incidence of recurrence by preventing coil protrusion into the parent artery, maintaining high coil

density within the aneurysm sac, and creating a scaffold for endothelial coverage (5, 6). Several studies have shown that stent-assisted coiling (SAC) is associated with a lower recurrence rate than coiling alone (7).

Since the introduction of the Neuroform stent (Stryker Neurovascular, Fremont, CA, USA) in 2002, intracranial stents have been continually refined. New-generation stents designed with varying structures, lower profile, and improved delivery systems have been introduced to improve aneurysmal occlusion and reduce recurrence (8–10). The self-expanding Neuroform Atlas stent (Stryker Neurovascular) is the successor of the Neuroform stent. This laser-cut stent is made of nitinol and has a mixed open-cell/closed-cell design. Delivery is via microcatheter (0.0165–0.017 inch). The Atlas stent can be used in small distal vessels, which has increased the number of aneurysms amenable to endovascular treatment.

Although efficacy of the Atlas stent has been established in several multicenter studies, to the best of our knowledge, SAC using the Atlas stent for treatment of recurrent aneurysms after coil embolization has not been evaluated (11–13). This study reports our experience.

Materials and methods

Patient population

We retrospectively reviewed all patients with intracranial aneurysms treated using the Atlas stent between November 2020 and November 2021 at Beijing Tiantan Hospital. Patients who met the following criteria were included for analysis: (1) age 18 to 80 years; (2) intracranial aneurysm confirmed by digital subtraction angiography (DSA) and previously treated with coiling alone; (3) aneurysm recurrence diagnosed on initial follow-up DSA; (4) re-treatment with SAC using the Atlas stent; and (5) clinical and angiographic follow-up were available after re-treatment. Institutional review board approval was obtained and all patients provided written informed consent.

The following data regarding patient and aneurysm characteristics were recorded: age; sex; hypertension; diabetes mellitus; smoking and alcohol use; symptoms before treatment; history of subarachnoid hemorrhage (SAH); aneurysm location (including bifurcation); irregular aneurysm; aneurysm size; aneurysm neck width; dome/neck ratio; modified Rankin scale (mRS) score before treatment, at discharge, and at follow-up; immediate and follow-up angiographic results; number of stents placed; stent size; procedure-related complications; and interval between initial treatment and re-treatment.

Endovascular procedure and antiplatelet regimen

Patients with unruptured aneurysms were premedicated with a dual-antiplatelet regimen (clopidogrel 75 mg/d and aspirin 100 mg/d) for at least 5 days. For patients with ruptured aneurysms, we administered loading doses of clopidogrel 300 mg and aspirin 300 mg orally or through a stomach tube 4 h before the procedure. All SAC procedures were performed *via* the femoral approach under general anesthesia and full anticoagulation with heparin (targeted activated clotting time was two to three times above the patient's baseline value). A triaxial guide-catheter system using a 6-Fr Cook (Cook Medical, Bloomington, IN, USA) or 6-Fr Neuron MAX (Penumbra, Alameda, California, USA) long sheath, 5-Fr or 6-Fr Navien (Covidien, Irvine, California, USA) intermediate support catheter, and Excelsior SL-10 or XT-17 microcatheter (Stryker Neurovascular) was used to deploy the stent. Aneurysm morphology and parent arterial structure were assessed using three-dimensional rotational angiography and the proper working projection was selected. An Echelon-10 microcatheter (Medtronic, Dublin, Ireland) was then placed into the aneurysm lumen. An Excelsior SL-10 or XT-17 microcatheter was placed into the parent artery under microguidewire guidance. Aneurysm coiling was performed using the jailing technique. Clopidogrel 75 mg and aspirin 100 mg daily were continued for at least 3 months after the procedure, then aspirin alone for 6 months or life.

Clinical and angiographic evaluations

Procedure-related complications were categorized as ischemic or hemorrhagic. Ischemic complications were defined as thromboembolic events associated with re-treatment, namely persistent focal neurological deficit, transient ischemic attack, or cerebral infarction. Hemorrhagic complications were defined as visualization of contrast leakage from the aneurysm or ruptured vessel during the procedure or visualization of intracranial hemorrhage on an imaging study performed in the periprocedural period.

Clinical outcome was assessed based on mRS score at last follow-up and was classified as favorable (mRS score 0–2) or poor (mRS score 3–6). Morbidity was defined as any procedure-related neurological deterioration that caused an increase in mRS score.

Angiographic outcomes were evaluated immediately and 6 and 12 months after the procedure using the Raymond–Roy (RR) occlusion classification system: class I, complete occlusion; class II, residual neck; class III, residual aneurysm (14). The outcomes were independently determined by two experienced

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neuro-interventionalists. Follow-up outcomes were categorized based on comparison with the outcomes immediately after the procedure: (1) improvement, decreased contrast filling in the aneurysm sac; (2) stable, no change in contrast filling; and (3) recurrence, increased contrast filling.

Results

Patient and aneurysm characteristics

Eleven patients met inclusion criteria. Median patient age was 49.1 years (range, 31–65) and 8 patients were women. Nine aneurysms presented initially with a rupture. Aneurysm location was anterior communicating artery in 5 patients, posterior communicating artery in 3, pericallosal artery in 2, and superior hypophyseal artery in 1. Mean aneurysm size and neck width was 4.8 ± 2.2 mm (range, 2.7–7.2) and 3.8 ± 1.2 mm (range, 2.5–4.9), respectively. Dome/neck ratio was <2 in all aneurysms and therefore considered wide-necked. Patient and aneurysm characteristics at the time of initial treatment are summarized in Table 1.

Technical and angiographic outcomes

Characteristics of the recurrent aneurysms, SAC procedural details, and follow-up outcomes are shown in Table 2. Among the 11 patients with recurrent aneurysms, only one patient (Case 9) presented with a ruptured aneurysm on admission. Atlas stent deployment was successful in all patients. Intraprocedural Dyna computed tomography (Siemens, Munich, and Germany) demonstrated satisfactory vessel wall apposition for all stents. Other than coils, no additional devices such as flow diverters or balloons were used during re-treatment. Immediate postprocedural angiographic showed that complete occlusion (RR class I) was achieved in 10 patients (90.9%), residual neck (RR class II) in 1 patient (9.1%). All patients underwent angiographic follow-up at least once. After a mean of 9.2 months of angiographic follow-up, 10 patients (90.9%) showed complete occlusion (RR class I), and 1 patient showed neck remnant (RR class II).

Complications and clinical outcomes

The only complication was minor visual impairment in one patient who developed mildly blurred vision in the left eye after the procedure (mRS score 1). Therefore, clinical outcome was favorable (mRS score 0–2) in all patients at discharge. Mean clinical follow-up was 10 months (range, 6–15). During follow-up, the patient who experienced blurred vision recovered completely (mRS score 0) and the others reported no new

TABLE 1 Patient and aneurysm characteristics and procedural details at the time of initial endovascular treatment.

Patient No.	Age (yrs)/Sex	Vascular risk factors	Initial presentation	Aneurysm location	Aneurysm type	Aneurysm size (mm)	Aneurysm neck (mm)	Dome/neck ratio	RROC scores of the initial treatment	Time from initial treatment to Atlas stent placement
1	65/M	HTN, S,	UIA	PComA	Saccular	7.2	3.4	1.9	1	21 Months
2	57/M	HTN, S, D	RIA	AComA	Saccular	5.3	3.7	0.8	1	54 Months
3	45/M	DM	RIA	Hypophyseal	Saccular	3.8	3.6	0.9	1	117 Months
4	48/F	HTN	RIA	Pericallosal	Saccular	4.3	2.9	0.7	1	11 Months
5	55/F	HTN	UIA	AComA	Saccular	2.7	2.5	0.7	1	14 Months
6	47/F	HTN, S	RIA	Pericallosal	Saccular	3.1	3.0	1.0	1	9 Months
7	48/F	No	RIA	PComA	Saccular	4.3	4.3	0.5	1	20 Months
8	36/F	No	RIA	AComA	Saccular	3.3	3.3	0.7	1	15 Months
9	51/F	HTN	RIA	PComA	Saccular	5.2	4.9	1.1	1	56 Months
10	57/F	HTN	RIA	AComA	Saccular	3.8	3.8	0.7	1	16 Months
11	31/F	No	RIA	AComA	Saccular	3.4	3.4	0.6	1	14 Months

AComA, anterior communicating artery; D, history of drinking alcohol; DM, diabetes mellitus; HTN, hypertension; PComA, posterior communicating artery; RIA, ruptured intracranial aneurysm; S, history of smoking; SAC, stent-assisted coiling; SAH, subarachnoid hemorrhage; UIA, unruptured intracranial aneurysm.

TABLE 2 Characteristics of recurrent aneurysms, procedural details of stent-assisted coiling, and follow-up outcomes.

Patient No.	Retreatment presentation	Retreatment strategy	Procedure-related complications	Clinical outcome (mRS Score)		Angiographic outcome (RROC Score)		
				Pre mRS	Last F/U mRS	Immediate	Last F/U	F/U Period
1	UIA	Atlas 3.0 × 21 mm, 10 Coils	No	0	0	1	1	10 Months
2	UIA	Atlas 3.0 × 15 mm, 4 Coils	No	0	0	1	1	8 Months
3	UIA	Atlas 4.5 × 21 mm, 2 Coils	No	0	0	1	1	12 Months
4	UIA	Atlas 3.0 × 21 mm, 5 Coils	No	0	0	1	1	7 Months
5	UIA	Atlas 3.0 × 15 mm, 2 Coils	No	0	0	1	1	8 Months
6	UIA	Atlas 3.0 × 21 mm, 6 Coils	No	0	0	1	1	10 Months
7	UIA	Atlas 4.0 × 15 mm, 2 Coils	No	0	0	1	1	11 Months
8	UIA	Atlas 3.0 × 15 mm, 4 Coils	No	0	0	1	1	7 Months
9	RIA	Atlas 3.0 × 21 mm, 9 Coils	Diplopia after intervention	1	0	2	2	12 Months
10	UIA	Atlas 3.0 × 21 mm, 6 Coils	No	0	0	1	1	9 Months
11	UIA	Atlas 3.0 × 15 mm, 4 Coils	No	0	0	1	1	7 Months

F/U, follow-up; mRS, modified Rankin Scale; RIA, ruptured intracranial aneurysm; RROC, Raymond–Roy occlusion classification; UIA, Unruptured intracranial aneurysm.

neurologic deficits. Follow-up clinical outcome was favorable in all patients without morbidity or mortality.

Case presentations

Case 1

A 65-year-old man presented to an outside hospital with a 1-month history of dizziness and headache. Magnetic resonance angiography showed a left posterior communicating artery aneurysm and he was transferred to our hospital. DSA confirmed the aneurysm (4.8 × 6.7 mm) and RR class I occlusion was achieved with coil embolization (Figures 1A,B). Aneurysm recurrence was diagnosed 21 months later (Figure 1C) and SAC using the Atlas stent (3.0 × 21 mm) was performed without complications. Intraprocedural angiography showed the three radiopaque markers at the proximal and distal ends of the Atlas stent (Figure 1D). Angiography immediately after the procedure revealed RR class I occlusion and dense coil packing within the aneurysm (Figure 1E). Follow-up DSA 10 months later still showed complete aneurysmal occlusion and a patent posterior communicating artery (Figure 1F).

Case 2

A 57-year-old man was admitted to the hospital with a severe headache. Computed tomography showed SAH in the longitudinal and right Sylvian fissures as well as around the brainstem (Figure 2A). DSA showed a saccular anterior communicating artery aneurysm (Figure 2B). Coil embolization was performed, which achieved RR class I occlusion and relieved the headache (Figure 2C). Follow-up angiography 54 months later showed contrast within the aneurysm neck (Figure 2D). During re-treatment, an Echelon 10 microcatheter (Medtronic, Dublin, Ireland) was delivered into the aneurysm sac to place the coils with stent assistance (Figure 2E). Intraprocedural

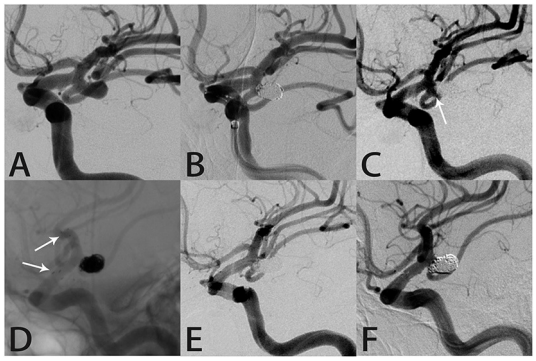

FIGURE 1
Images from a 65-year-old man with a left posterior communicating artery aneurysm (case 1). **(A)** Preoperative angiography showed a left posterior communicating artery aneurysm. **(B)** The aneurysm was occluded completely after coil embolization. **(C)** Follow-up angiography 21 months after the procedure revealed a mild recurrence in the aneurysm neck (white arrow). **(D)** Angiography during re-treatment showed the deployed Atlas stent (3.0 × 21 mm) covering the aneurysm neck and coils densely packed within the sac (white arrow indicates the end of the stent). **(E)** Angiography immediately after the procedure showed the aneurysm was occluded completely. **(F)** Follow-up angiography 10 months later showed complete aneurysmal occlusion and parent artery patency.

angiography showed the three radiopaque markers at the proximal and distal ends of the Atlas stent (3.0 × 15 mm) and coils within the sac (Figure 2F). Angiography immediately after embolization showed RR class I occlusion (Figure 2G). The aneurysm remained completely occluded and the parent artery was patent on follow-up angiography 8 months later (Figure 2H).

Case 4

A 48-year-old woman presented with severe headache. Computed tomography showed SAH in the longitudinal fissure (Figure 3A). DSA showed a right pericallosal aneurysm (Figure 3B). Coil embolization was performed (Figure 3C). RR class I occlusion was shown on angiography performed immediately after treatment (Figure 3D). Aneurysm recurrence was diagnosed 11 months later on follow-up angiography (Figure 3E). Because of the complexity of the aneurysm, we elected to perform SAC using the Atlas stent, which was successful without complications. Intraprocedural angiography showed the three radiopaque markers at the proximal and distal ends of the Atlas stent (3.0 × 21 mm) and coils within the sac (Figure 3F). Post-embolization angiography showed RR class I occlusion (Figure 3G). Seven months later, the aneurysm remained completely occluded and the parent artery was patent (Figure 3H).

Case 9

A 51-year-old woman suddenly developed a severe headache with nausea and vomiting, followed by loss of consciousness, and was conscious for about 1 h later. Computed tomography performed in our hospital showed SAH in the brain basal cistern, lateral fissure cistern, longitudinal fissure cistern, and ambient cistern (Figure 4A). DSA showed a left posterior communicating artery aneurysm (Figure 4B). We performed coil embolization of the aneurysm, and immediate post-procedural angiographic showed that the aneurysm achieved RR class I occlusion (Figure 4C). The patient recovered well after the procedure, and the headache symptoms recovered at the time of discharge. However, the patient was re-admitted with severe headache 56 months after the initial coil embolization. Computed tomography confirmed that the patient was re-bleeding, and the SAH involved the lateral fissure cistern and sulcus (Figure 4D). The patient had Fisher score of grade 3 and a WFNS score of grade 1. DSA showed recurrence of the left posterior communicating artery aneurysm (Figure 4E). Considering that this patient was re-bleeding and led to recurrence 56 months after the initial coil embolization, after the discussion of several experts in our group, we finally decided to adopt the Atlas stent-assisted coiling treatment strategy. Atlas stents can reduce the incidence of recurrence by preventing coil protrusion into the parent artery, and the low metal coverage rate of the stent may also reduce the incidence of thromboembolic complications. Thus, we performed SAC using the Atlas stent (3.0 × 21 mm), and angiography immediately after re-treatment showed RR class II occlusion (Figure 4F), and the patient developed mildly blurred vision in the left eye after the procedure. Twelve months later, the follow-up angiography showed the aneurysm remained RR class II occlusion and the Atlas stent was stable (Figures 4G,H). Notably, the patient's vision was completely recovered.

Discussion

The effectiveness of the Atlas stent in assisting coil embolization to achieve aneurysm occlusion with low rates of recurrence and morbidity has made it an appealing adjunct when treating intracranial aneurysms (12, 15, 16). As the incidence of aneurysm recurrence has increased in conjunction with increased use of endovascular treatment, so has the use of SAC with the Atlas stent to treat these recurrences. Currently, few data are available regarding SAC using the Atlas stent for treatment of recurrent aneurysms. Thus, in this study, we describe our experience spanning 1 year at a single center with the safety and efficacy of SAC using the Atlas stent to treat recurrent aneurysms after coil embolization.

Since the publication of the International Subarachnoid Aneurysm Trial, the paradigm for intracranial aneurysm treatment has gradually shifted from microsurgical clipping to

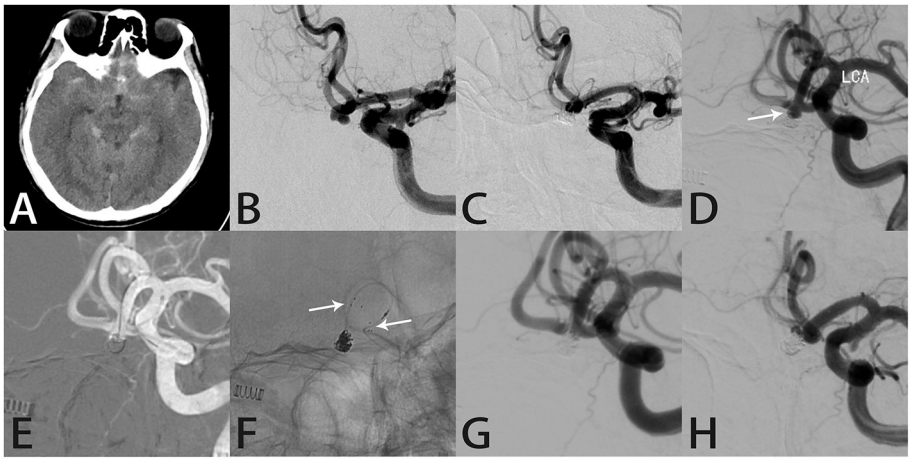

FIGURE 2
Images from a 57-year-old man with an anterior communicating artery aneurysm (case 2). **(A)** Computed tomography showed subarachnoid hemorrhage in the longitudinal and right Sylvian fissures as well as around the brainstem. **(B)** Preoperative angiography showed an anterior communicating artery aneurysm. **(C)** The aneurysm was occluded completely after coil embolization. **(D)** Follow-up angiography 54 months later showed an obvious recurrence in the aneurysm neck (white arrow). **(E)** During re-treatment, an Echelon 10 microcatheter (Medtronic, Dublin, Ireland) was delivered into the aneurysm sac to place the coils. **(F)** Intraprocedural angiography showed the three radiopaque markers (white arrows) at the proximal and distal ends of the Atlas stent (3.0 × 15 mm) and the coils within the aneurysm sac. **(G)** Angiography immediately after the procedure showed the aneurysm was occluded completely. **(H)** Follow-up angiography 8 months later showed complete aneurysmal occlusion and parent artery patency.

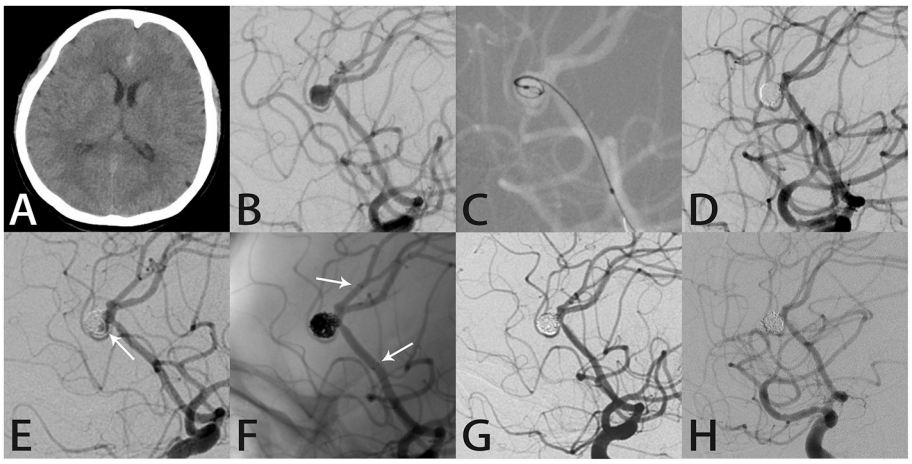

FIGURE 3
Images from a 48-year-old woman with a right pericallosal aneurysm (case 4). **(A)** Computed tomography showed subarachnoid hemorrhage in the longitudinal fissure. **(B)** Angiography showed a right pericallosal aneurysm. **(C)** During treatment, an Echelon 10 microcatheter (Medtronic, Dublin, Ireland) was delivered into the aneurysm sac to place the coils. **(D)** The aneurysm was occluded completely after coil embolization. **(E)** Follow-up angiography 11 months later showed recurrence in the aneurysm neck (white arrow). **(F)** Intraprocedural angiography showed the deployed Atlas stent (3.0 × 21 mm) covering the aneurysmal neck and coils densely packed within the sac (white arrows indicate the ends of the stent). **(G)** Angiography immediately after the procedure showed the aneurysm was occluded completely. **(H)** Follow-up angiography 7 months later showed complete aneurysmal occlusion with the coils densely packed within the aneurysm.

endovascular intervention (17). Endovascular coil embolization is now widely used and is well-known for its low morbidity and mortality (18). However, risk of recurrence remains a major concern. A systematic review reported that 10% to 33.6% of all cerebral aneurysms treated with endovascular coil embolization recur and re-treatment rates range between 4.7 and 12.3% (19). In addition, recurrent aneurysms are associated with a higher rate of intracranial hemorrhage. Slob et al. (20) reported a 6.9% hemorrhage rate in patients with incompletely occluded aneurysms after initial coiling who were not re-treated; however,

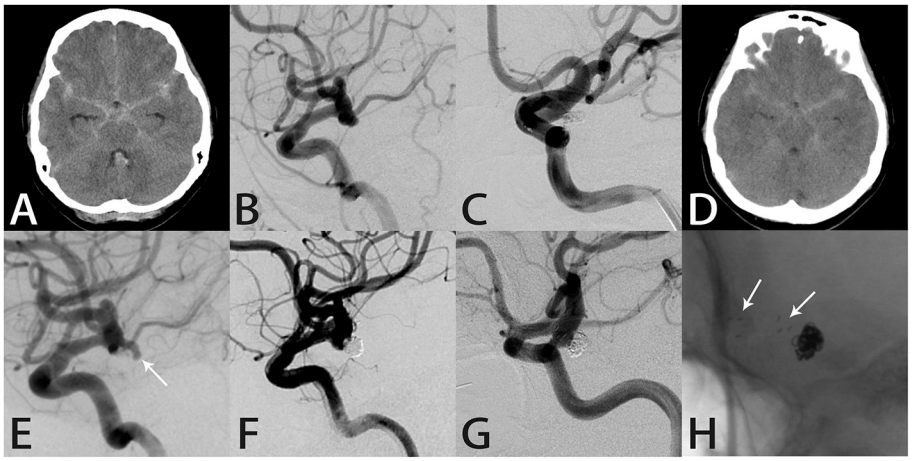

FIGURE 4
Images from a 51-year-old woman with a left posterior communicating artery aneurysm (case 9). **(A)** Computed tomography showed subarachnoid hemorrhage in the brain basal cistern, lateral fissure cistern, longitudinal fissure cistern, and ambient cistern. **(B)** Angiography showed a left posterior communicating artery aneurysm. **(C)** The aneurysm was occluded completely after coil embolization. **(D)** Computed tomography showed subarachnoid hemorrhage in the lateral fissure cistern and sulcus. **(E)** Angiography showed recurrence of the left posterior communicating artery aneurysm. **(F)** Angiography immediately after re-treatment showed RR class II occlusion. **(G)** Follow-up angiography 12 months later showed the aneurysm remained RR class II occlusion. **(H)** Intraprocedural angiography showed the Atlas stent remained stable and the three radiopaque markers (white arrows) could be seen at the proximal and distal ends of the Atlas stent (3.0 × 21 mm).

the rate was zero in those who underwent additional coiling. Therefore, re-treatment of recurrent aneurysms appears to reduce the risk of future hemorrhage.

Several endovascular treatment modalities are available to manage recurrent aneurysms, including re-coiling, SAC, and placement of a flow diverter. Previous studies have found that re-embolization using coils alone is associated with a higher rate of recurrence (21, 22). Stent assistance stabilizes the inserted coils, maintains parent artery patency, and provides protection against recurrence (22). Therefore, SAC may be a better alternative. Daou et al. (23) reported an 86.7% complete or near-complete occlusion rate after placement of the Pipeline embolization device (Medtronic, Dublin, and Ireland) in previously coiled recurrent aneurysms, demonstrating the efficacy of flow diversion. However, another study reported high rates of complications (17.2%) and permanent morbidity (6.9%) with this approach (24). Therefore, neurointerventionalists should carefully consider the appropriate treatment modality on an individual basis when managing recurrent aneurysms.

Re-treating recurrent aneurysms is frequently technically challenging. Accurate measurement of the recurrent lumen may be difficult owing to the previously inserted coils (25). Furthermore, if thrombus has formed within the lumen, it may dislodge into the parent artery and cause a serious thromboembolic complication (25). Moreover, many recurrent aneurysms have a wide neck and relatively shallow depth because of coil compaction (22). Therefore, the procedure may require complex manipulations through multiple microcatheters and stent assistance may be necessary to prevent coil protrusion and migration. Our technical success rate for SAC using the Atlas stent was 100%, which is comparable to previously reported rates for treatment of naïve aneurysms (5, 26). The Atlas stent can be successfully used for SAC of previously coiled aneurysms.

Our rates of RR class I and II occlusion immediately after the procedure were 90.9 and 9.1%, respectively, and these rates remained stable at the last follow-up. We attribute the favorable angiographic outcomes to our use of Atlas stent assistance. These rates compare favorably with other multicenter studies that have evaluated Atlas stent performance in SAC of naïve aneurysms (12, 16, 27). The rate of complete occlusion in these studies ranged from 81.3 to 86.7%. In addition, our results are comparable to those achieved in a multicenter study of SAC using the Acclino stent (Acandis GmbH, Pforzheim, Germany) to treat recurrent and residual aneurysms; this study reported a 94.7% complete occlusion rate immediately after the procedure that decreased to 76.9% at last angiographic follow-up (28). Previous studies of SAC using the LVIS Jr (MicroVention, Aliso Viejo, California, USA) and LEO Baby (Balt Extrusion, Montmorency, France) stents have focused on the treatment of naïve aneurysms (8, 29); they have not been examined yet for treatment of recurrent aneurysms.

Procedure-related complications occurred in only one patient (9.1%), a 51-year-old woman with a recurrent left posterior communicating artery aneurysm who developed mildly blurred vision in the left eye. Angiography immediately after re-treatment showed RR class II occlusion. Although her vision completely recovered, follow-up angiography remained

RR class II occlusion. We believe her blurred vision may be attributed to oculomotor nerve palsy (ONP). Unilateral ONP occurs in approximately 25% of patients with a posterior communicating artery aneurysm (30) and often occurs at the time of aneurysm rupture. The cause may be rupture-related trauma to the nerve or the presence of localized hematoma and/or subarachnoid blood (31). However, ONP may also be observed in association with unruptured aneurysms because of direct mechanical compression from the aneurysm sac and/or aneurysm pulsatility (32). Considering that this patient's aneurysm was relatively small and unruptured, we presume that the most likely cause was aneurysm pulsatility. A previous study reported that coiling can eliminate aneurysmal pulsations, which allows more complete nerve recovery (31). This patient's vision recovery supports this hypothesis.

Two previous studies of SAC using the Atlas stent for treatment of naïve aneurysms have reported thromboembolic complication rates of 3.8 and 2.3%, respectively, and hemorrhagic complication rates of 0.8 and 0.8%, respectively (33, 34). Reported thromboembolic complication rates in SAC studies using the Neuroform and Enterprise (Codman Neurovascular, Raynham, MA, USA) stents were 8.8 and 8.7%, respectively (35, 36). The Atlas stent appears to be associated with a lower rate of thromboembolic complications than conventional stents. One possible explanation is that its miniaturized design and delivery system reduces exposure of the metal-covered surfaces to blood flow, which reduces thrombus formation.

All patients who initially presented with SAH in our study were treated using coil embolization alone, suggesting that most neurointerventionalists are reluctant to use stent assistance when embolizing acutely ruptured aneurysms. This is understandable because the body is in a hypercoagulable state in the acute stage of SAH and introduction of a stent into the cerebral vasculature may increase the risk of thromboembolism. Furthermore, the antiplatelet therapy that is generally associated with stent placement may increase the risk of re-hemorrhage, especially in patients with an intraventricular catheter. In patients with a ruptured aneurysm, the rate of ventriculostomy-related re-hemorrhage is 3.4 times higher in those who undergo SAC than in those who undergo coiling alone (37). Therefore, stent use should be considered with caution in ruptured aneurysm patients.

Although the results of this study are encouraging, future large-scale studies with long-term follow-up are needed to fully evaluate the efficacy of SAC using the Atlas stent for recurrent aneurysms.

Limitations

This study has several limitations. Its retrospective single-center design lacked a control group and selection bias may have been introduced. In addition, its sample size was small and the follow-up period was short; therefore, our reported occlusion rates may not accurately reflect the true rates.

Conclusion

SAC using the Atlas stent to treat aneurysms that recur after coil embolization is safe and effective. However, large-scale studies with long-term follow-up are necessary to validate 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

This study was reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital. Written informed consent to participate in this study was provided by the patients or their legal guardian/next of kin.

Author contributions

JW, ML and PL: conception and design. XC, LZ, ZZ, QP, and ZJ: data analysis and interpretation. LD and JW: manuscript writing. The final version was approved by ML on behalf of all authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Publisher's note

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Effects of stent-assisted coiling in comparison with flow diversion on intracranial aneurysms

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Objective: The aim of this study was to investigate the efficacy and complications of stent-assisted coiling in comparison with flow diversion for wide-necked intracranial aneurysms.

Methods: Patients with wide-necked intracranial aneurysms who were treated with stent-assisted coiling or flow diversion were respectively, enrolled into the stent-assisted coiling or flow diversion treatment group. The clinical and angiographic data were analyzed.

Results: A total of 61 patients with intracranial aneurysms underwent stent-assisted coiling, including 35 (57.4%) female and 26 (42.6%) male patients with 21 (34.4%) ruptured and 40 (65.6%) unruptured aneurysms. Also, 53 patients underwent deployment of flow-diverting devices, including 30 (56.6%) female and 23 (43.4%) male patients with 25 (47.2%) ruptured and 28 (52.8%) unruptured aneurysms. Stent-assisted coiling was performed successfully in 60 patients with 63 stents deployed, and immediate aneurysm occlusion was complete occlusion in 38 (62.3%) aneurysms, residual neck in 12 (19.7%), and residual aneurysm in 10 (16.4%). Procedure-related complications included in-stent thrombosis in three (4.9%) patients, coil protrusion in three (4.9%), and re-rupture of one (1.6%) aneurysm, with a total complication rate of 11.5%. In the flow diversion group, a pipeline embolization device alone was deployed in each of the 24 (45.3%) patients, adjunctive coiling combined with a pipeline device in 29 (54.7%), and double pipeline devices in each of the 6 (11.3%) patients. Immediately after treatment, complete occlusion was achieved in 3 (5.7%) patients with adjunctive coiling, residual neck in 3 (5.7%), and residual aneurysm in 47 (88.7%). Procedure-related complications included aneurysm rebleeding in one patient (1.9%). Clinical and angiographic follow-up was performed 13–49 months (median 29) after the procedure for 49 (80.3%) patients with stent-assisted coiling, with complete aneurysm occlusion in 27 (55.1%) aneurysms, residual neck in 3 (6.1%), residual aneurysm in 5 (10.2%), and recurrence in 14 (28.6%). Follow-up was performed for 14–37 (median 25) months in 45 (84.9%) patients with flow diversion treatment, with complete occlusion in 39 (86.7%) patients, residual neck in 5 (11.1%), residual aneurysm in 1 (2.2%), and no aneurysm recurrence.

Conclusions: Stent-assisted coiling comes with more complications but fewer permanent aneurysm occlusions than flow diverters, and flow diverters are superior to stent-assisted coiling in the treatment of wide-necked intracranial aneurysms, especially in the long-term effect.

KEYWORDS

wide-neck, intracranial aneurysms, stent-assisted embolization, flow diversion, effect

Introduction

The publication of the international subarachnoid aneurysm trial of neurosurgical treatment vs. endovascular coiling in 2,143 patients with ruptured intracranial aneurysms has established the role of endovascular embolization in treating cerebral aneurysms, and since then, endovascular embolization has been applied as a routine for cerebral aneurysms, especially ruptured aneurysms (1). However, endovascular management of wide-necked cerebral aneurysms remains a technical challenge because of the risk of coil protrusion, possibly leading to thrombosis and parent artery compromise. Several endovascular techniques have been applied for wide-necked aneurysms, including balloon- or stent-assisted coiling, flow diversion, and the WEB aneurysm embolization system (Sequent Medical, Aliso Viejo, CA, USA) (2–5). A stent can have an endurable support for coils within the aneurysm sac and prevent coils from escaping out of the sac. With use of flow diverters or stents, complication rates may be higher than those with selective coil embolization or balloon-assisted coiling due to thrombogenicity of the devices and a need for dual-antiplatelet administration. Use of antiplatelet therapy in stent-assisted coiling or flow diversion in acute subarachnoid hemorrhage may cause high rates of early adverse events, elevated thromboembolic complications, increased risks of intracranial hemorrhage and rebleeding from a ruptured aneurysm, increased morbidity and mortality, and potential of infarction secondary to vasospasm (2, 6–8). Stent-assisted coiling was initially developed to overcome the limitations of coiling alone such as aneurysmal neck remnant and coil protrusion into the artery (9). However, technical challenges remain with the stent-assisted coiling technique, including difficulty navigating the coiling microcatheter through the interstices of the stent, stent malposition, and incomplete coiling besides long-term recurrence of aneurysms. The advent of flow-diverting devices has facilitated the treatment of cerebral aneurysms. However, few studies have been performed to directly compare the safety and efficiency of stent-assisted coiling with flow diversion for the treatment of wide-necked ruptured and unruptured intracranial aneurysms. It was thus hypothesized that both stent-assisted coiling and flow diversion could be safely and efficiently applied to treat ruptured and unruptured cerebral aneurysms. This study was consequently performed to investigate the safety and effect of stent-assisted coiling and flow diversion in the treatment of wide-necked intracranial aneurysms.

Materials and methods

This retrospective one-center study was approved by the ethics committee of our hospital, and all patients or their family members provided signed informed consent to participate. Patients who underwent stent-assisted coiling or deployment of flow-diverting devices using the pipeline embolization device (PED, Medtronic, Irvine, CA, USA) for wide-necked intracranial aneurysms between January 2016 and June 2020 were enrolled into two groups, namely, stent-assisted coiling and flow diversion treatment. Wide-necked aneurysms were referred to those with a neck diameter of $\geq$ 4 mm or a dome-to-neck ratio of <2. The inclusion criteria were consecutive patients with wide-necked ruptured or unruptured aneurysms confirmed by computed tomography angiography (CTA) or digital subtraction angiography, who were treated with stent-assisted coiling or flow diversion, and who were without contraindiction to the endovascular treatment or contrast agent. The exclusion criteria were patients with subarachnoid hemorrhage caused by other non-aneurysmal diseases or trauma, ruptured cerebral aneurysms treated without use of stents, with contraindications for use of contrast agents, and with severe heart, renal, and liver diseases. In this study, wide-necked intracranial aneurysms were treated either with stent-assisted coiling or flow diversion, and assignment of the patients into these two groups was based on the desire and selection of the patients after informed consent. In the initial period of this study, stent-assisted coiling was performed more frequently while, in the later period, more patients with wide-necked cerebral aneurysms experienced deployment of flow diverters with a better understanding of the advantages of these flow diverters.

In patients with unruptured aneurysms, thromboelastography was performed 3 days before the embolization procedure to test the response of antiplatelet medications, and the dosage of dual antiplatelet medications was adjusted according to the test outcome to maintain the

inhibition rate of arachidonic acid more than 50%, the inhibitive rate of adenosine diphosphate over 30%, and the maximal amplitude of adenosine diphosphate curve at 31–47 mm.

Stent-assisted coiling and flow diversion treatment of cerebral aneurysms were performed by neurosurgeons with 5–10 years of experience in endovascular treatment, with the patient in supine position under general anesthesia. In patients with ruptured aneurysms, aspirin (300 mg) and clopidogrel (300 mg) were administered *via* nasogastric feeding 3 h before the embolization procedure, and in patients with unruptured aneurysms, aspirin 100 mg/day and clopidogrel 75 mg/day were administered 5 days before the procedure. After puncture of one common femoral artery and insertion of an arterial sheath and a guiding catheter, cerebral angiography was performed. In patients with deployment of a PED device alone, an appropriate PED device was selected and deployed to cover the aneurysm neck, with the PED device long enough to anchor at both the proximal and distal sides of the aneurysm neck. For aneurysms treated with stent-assisted coiling or PED plus adjunctive coiling, an appropriate stent or PED device was selected according to the size of the parent artery and aneurysm and sent to the vessel distal to the aneurysm. After deployment of coils within the aneurysm sac, the stent or PED device was navigated to the aneurysm and deployed partially or completely. After stent deployment, 2,000 IU heparin was slowly injected intravenously for systemic heparinization. If the procedure exceeded 2 h, 1,000 IU heparin was injected intravenously once every hour. Immediately or within 24 h after embolization, all patients underwent head CT scan and repeated head CT scan was performed within 72 h for monitoring possible subarachnoid hemorrhage and hydrocephalus. Anticoagulation was continued with low molecular heparin 4,000 IU injected subcutaneously twice daily for 2 days and continued afterward with aspirin 100 mg administered orally once per day for 3 months. Clopidogrel at the dose of 75 mg was administered orally once daily for 1 month.

Periprocedural complications, stents used, occlusion status, rebleeding of aneurysms, thrombosis, coil escape, and clinical outcomes were recorded. Angiographic follow-up was performed once half a year, 1, 3, and 5 years following embolization. Aneurysm occlusion was evaluated with the Raymond–Roy grade, with complete occlusion as grade I, residual neck as grade II, and residual aneurysm as grade III (10). Aneurysm recanalization was diagnosed if opacification of the aneurysm was seen to increase in amount.

Statistical analysis

The SPSS 19.0 software (IBM, Chicago, IL, USA) was used for statistical analysis. Measurement data were expressed as mean ± standard deviation and tested with the *t*-test if in normal distribution. If not in normal distribution, the measurement data were presented as median (range) and tested with the Wilcoxon rank-sum test. Enumeration data were presented as numbers and percentages and tested with the chi-square test or Fisher's exact probability method. $p < 0.05$ was set as the statistically significant level.

Results

Patient's data

Among 61 patients undergoing stent-assisted coiling, there were 35 (57.4%) female and 26 (42.6%) male patients, with an age range of 34–76 (mean ± 15) years, including 21 (34.4%) with ruptured and 40 (65.6%) with unruptured aneurysms (Table 1). The most frequent location of aneurysm was internal carotid artery (ICA) ($n = 36$ or 59.0%), especially the posterior communicating artery (Pcom) segment ($n = 22$, 36.1%), followed by intracranial vertebral artery ($n = 9$ or 14.8%). Among 21 patients with ruptured aneurysms, the Hunt–Hess grade was I in 5 (23.8%) patients, II in 13 (61.9%), III in 1 (4.8%), and IV in 1 (4.8%). Most aneurysms were between 3 and 10 mm ($n = 40$, 65.6%), 14 (23.0%) aneurysms were between 10 and 25 mm, with 6 (9.8%) aneurysm ≤ 3 mm and 1 (1.6%) aneurysm > 25 mm.

Among 53 patients undergoing deployment of flow-diverting devices, there were 30 (56.6%) female and 23 (43.4%) male patients with an age range of 29–80 (mean 55 ± 12) years, including 25 (47.2%) patients with ruptured and 28 (52.8%) with unruptured aneurysms. The most frequent location of aneurysm was ICA ($n = 27$ or 50.9%), especially the Pcom segment ($n = 16$ or 30.2%), followed by the middle cerebral artery ($n = 8$ or 15.1%). Among 25 patients with ruptured aneurysms, the Hunt–Hess grade was I in 9 (36%) patients, II in 11 (44%), and III in 5 (20%). Most aneurysms ($n = 30$, 56.6%) were between 3 and 10 mm, and 18 (34.0%) were between 10 and 25 mm, with 4 (7.5%) aneurysms ≤ 3 mm and 1 (1.9%) aneurysm > 25 mm.

No significant ($p > 0.05$) difference existed in the age, sex, aneurysm size and location, and the Hunt–Hess grade.

Endovascular treatment

In patients who underwent stent-assisted coiling, two patients experienced deployment of double stents each, but the other patients had only one stent deployed each. The total number of stents deployed was 63 stents, including 36 (57.1%) Solitaire AB stents (Medtronic, Irvine, CA, USA), 22 (34.9%) Enterprise stents (Codman & Shurtleff, Raynham, MA, USA), and 5 (7.9%) Neuroform stents (Stryker, Fremont, CA, USA) (Table 2 and Figures 1, 2). Stent deployment was failed in one patient, with the technical success rate of stenting as 98.4%. The procedure was 169 ± 41 min. Immediate

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TABLE 1 Demography and treated aneurysms.

Variables		Stent-assisted coiling (61)	Flow diversion (53)	P
F/M		35/26	30/23	0.56
Age (y)		34–76 (mean 56 ± 15)	29–80 (mean 55 ± 12)	0.54
Unruptured/ruptured		40/21	28/25	0.32
ICA	Pcom	22 (36.1%)	16 (30.2%)	0.87
	Cavernous segment	4 (6.6%)	7 (13.2%)	
	OOP segment	8 (13.1%)	4 (7.5%)	
	ICA bifurcation	2 (3.3%)	0	
	ACA A1 segment	1 (1.6%)	2 (3.8%)	
	Acom	6 (9.8%)	5 (9.4%)	
	MCA M1 segment	3 (4.9%)	8 (15.1%)	
	Intracranial VA	9 (14.8%)	6 (11.3%)	
	BA	6 (9.8%)	5 (9.4%)	
Aneurysm size	≤3 mm	6 (9.8%)	4 (7.5%)	0.87
	3 mm<D ≤ 10 mm	40 (65.6%)	30 (56.6%)	
	10 mm<D ≤ 25 mm	14 (23.0%)	18 (34.0%)	
	D > 25 mm	1 (1.6%)	1 (1.9%)	
Hunt-Hess grade	I	5 (23.8%)	9 (36%)	0.87
	II	13 (61.9%)	11 (44%)	
	III	1 (4.8%)	5 (20%)	
	IV	1 (4.8%)	0	

ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; OOP, ophthalmic or Paraclinoid; Pcom, posterior communicating artery; Acom, anterior communicating artery; VA, vertebral artery; BA, basilar artery.

TABLE 2 Treatment and occlusion degrees of aneurysms.

Variables		Stent-assisted coiling ($n = 61$)	Flow diversion ($n = 53$)	*P*
Treatment modality (*n*)	Stent+coiling	61 (100%)	29 (54.7%)	0.94
	Stent alone	0	24 (45.3%)	
	Double stents	2 (3.3%)	6 (11.3%)	
No. of stents (*n*)		63	59	
Immediate occlusion	Complete occlusion	38 (62.3%)	3 (5.7%)	0.59
	Residual neck	12 (19.7%)	3 (5.7%)	
	Residual aneurysm	10 (16.4%)	47 (88.7%)	
	Failed	1 (1.6%)	0	
Complications	Instent thrombosis	3 (4.9%)	0	0.18
	Coil protrusion	3 (4.9%)	0	
	Rebleeding	1 (1.6%)	1 (1.9%)	
Follow-up	Duration (m, median)	13–49 (29)	14–37 (25)	
	Number	49 (80.3%)	45 (84.9%)	
Follow-up occlusion	Complete occlusion	27 (55.1%)	39 (86.7%)	0.85
	Residual neck	3 (6.1%)	5 (11.1%)	
	Residual aneurysm	5 (10.2%)	1 (2.2%)	
	Recurrence	14 (28.6%)	0	

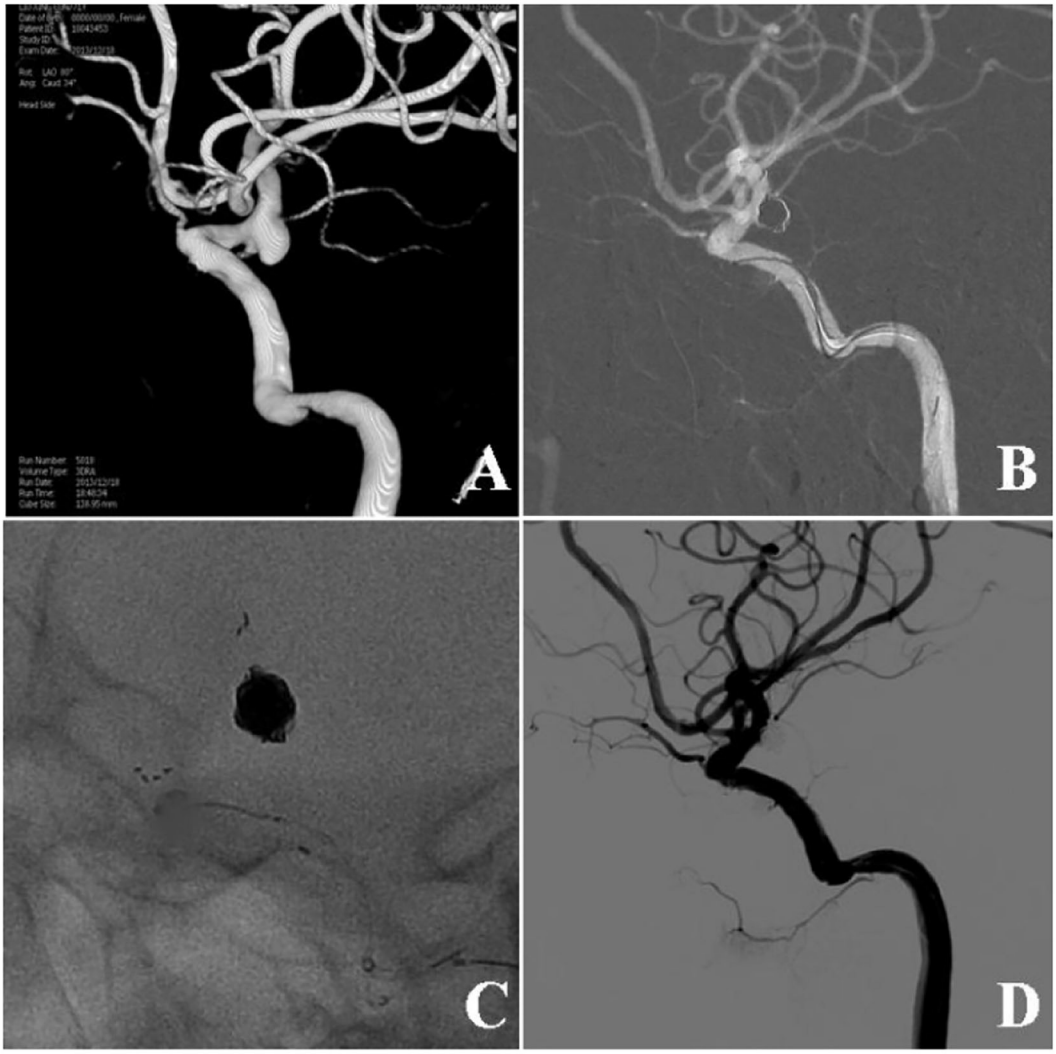

FIGURE 1
Stent-assisted coiling of a wide-necked ruptured aneurysm at the posterior communicating artery (Pcom). **(A)** Three-dimensional digital subtraction angiography showed a wide-necked aneurysm at the Pcom. **(B)** An Enterprise stent was used for assisting aneurysm coiling. **(C)** The stent and the coil mass are shown. **(D)** Six months following embolization, the aneurysm remained totally occluded.

aneurysm occlusion after the treatment was complete in 38 (62.3%) aneurysms, residual neck in 12 (19.7%), and residual aneurysm in 10 (16.4%). In case of failed stent deployment (1.6%) for an aneurysm at the ICA ophthalmic segment, the microcatheter was dislocated and could not be repositioned within the aneurysm sac. Procedure-related complications included in-stent thrombosis in three (4.9%) patients, coil protrusion in three (4.9%), and re-rupture of one (1.6%) aneurysm caused by microcatheter puncture of the aneurysm wall, with a total complication rate of 11.5%. For in-stent thrombosis, 100,000–200,000 units of urokinase were given through a microcatheter for thrombolysis, resulting in complete recanalization 15–30 min later. All complications were managed appropriately without causing any severe sequela.

In patients experiencing flow diversion treatment, deployment of PED devices alone was performed in each of the 24 (45.3%) patients, flow diversion plus adjunctive coiling in 29 (54.7%), and double PED devices in each of the 6 (11.3%) patients. The total number of PED devices deployed was 59, with the technical success rate of PED deployment of 100% (Table 2 and Figures 3, 4). The procedure time was 122 ± 48 min, which was significantly shorter than that in the stent-assisted coiling group. Immediately after endovascular treatment, complete occlusion was achieved in 3 (5.7%) patients with adjunctive coiling, residual neck in 3 (5.7%), and residual aneurysm in 47 (88.7%). Procedure-related complications included rebleeding of an ophthalmic segment aneurysm in one patient (1.9%) while inserting coils into the aneurysm.

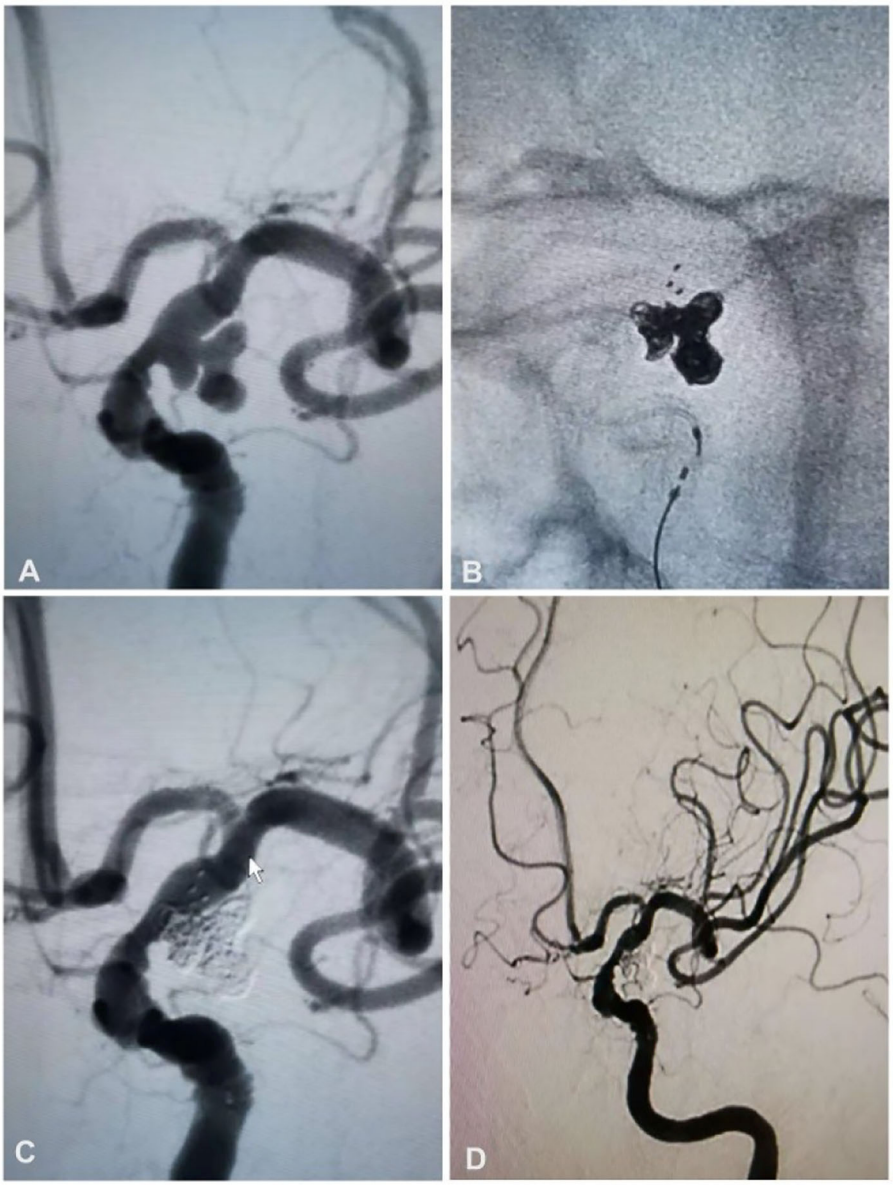

FIGURE 2
A 63-year-old woman had a ruptured aneurysm at the posterior communicating artery (Pcom) of the left internal carotid artery and was treated with stent-assisted coiling. **(A)** Angiography revealed an aneurysm at the left Pcom. **(B)** Stent-assisted coiling was performed with a Solitaire AB stent (4 × 20 mm) and six coils. **(C)** The aneurysm was totally occluded. **(D)** Follow-up angiography at 6 months revealed that the aneurysm was still totally occluded.

Follow-up results

Clinical and angiographic follow-up was performed 13–49 months (median 29) after the procedure for 49 (80.3%) patients with stent-assisted coiling. No new neurological symptoms that were related to the stent-assisted coiling procedure were found. Angiographic examination revealed complete occlusion of the aneurysm in 27 (55.1%) aneurysms, residual neck in 3 (6.1%), residual aneurysm in 5 (10.2%), and recurrence in 14 (28.6%), with no symptomatic in-stent stenosis or occlusion. Follow-up was performed 14–37 (median 25) months after the procedure in 45 (84.9%) patients with deployment of flow-diverting devices. No neurological sequela was found in this group. Angiographic imaging demonstrated complete occlusion in 39 (86.7%) patients, residual neck in 5 (11.1%), residual aneurysm in 1 (2.2%), and no aneurysm recurrence.

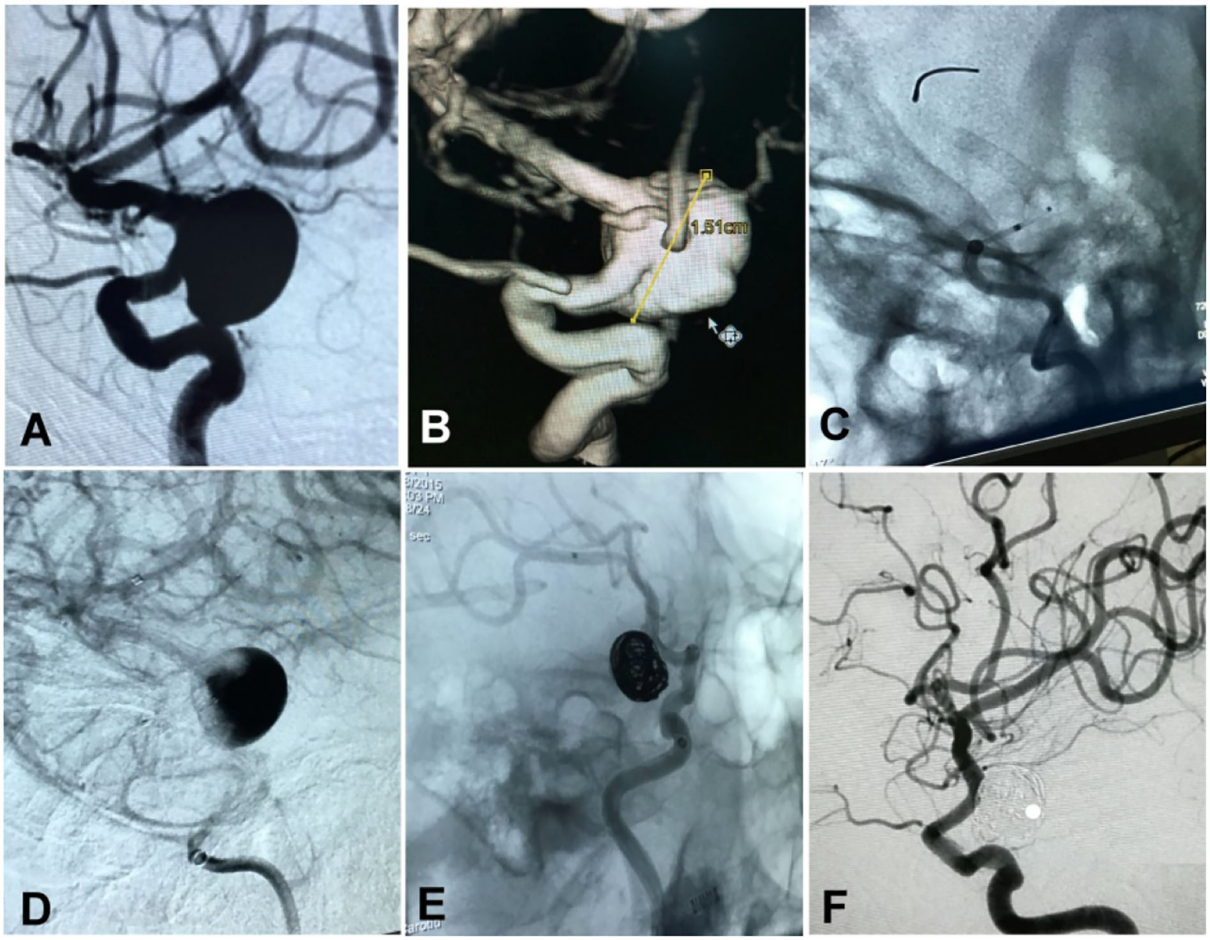

FIGURE 3
A woman in her 50's had a ruptured aneurysm (Hunt–Hess grade II) measuring 15 × 17 mm at the posterior communicating segment of the internal carotid artery treated with a Pipeline embolization device plus adjunctive coiling. **(A,B)** The aneurysm is shown. **(C)** A Pipeline embolization device of 3.5 × 25 mm was deployed. **(D)** After deployment of the stent, blood flow into the aneurysm cavity was significantly reduced. **(E)** The aneurysm was loosely occluded at the end of embolization. **(F)** At 25-month follow-up, the aneurysm was completely occluded.

No in-stent stenosis or occlusion was detected. No significant ($p > 0.05$) difference existed in the occlusion status between the two groups.

Discussion

In this study, investigating the efficacy and safety of stent-assisted coiling in comparison with flow diversion for the treatment of wide-necked intracranial aneurysms, it was found that stent-assisted coiling and flow diversion were both safe and effective for the treatment of wide-necked intracranial aneurysms; however, flow diversion seemed more efficient with more complete occlusion but few recurrence of aneurysms in the long run.

Due to micro invasiveness, few complications, and fast recovery, endovascular embolization has become the first choice of treatment for cerebral aneurysms. Endovascular treatment has been increasingly applied for unruptured wide-necked cerebral aneurysms, with good clinical and angiographic outcomes (2, 5, 6, 11–15). However, ever since the introduction of flow diversion into practice for the treatment of intracranial aneurysms, the use of stent-assisted coiling has been decreasing. Crobeddu et al. have reported a marked decrease from 14.7 to 6.9% ($p = 0.04$) over a 4-year period in the use of stent-assisted coiling in their institute following introduction of the flow diversion technology (16). Flow diversion is a technological advantage compared with the stent-assisted coiling technique because it is a method of reconstruction of the parent artery, encompassing many advantages over stent-assisted coiling such as avoiding coil access to the aneurysm sac with subsequently reduced risk of iatrogenic aneurysm rupture caused by endovascular devices within the aneurysm

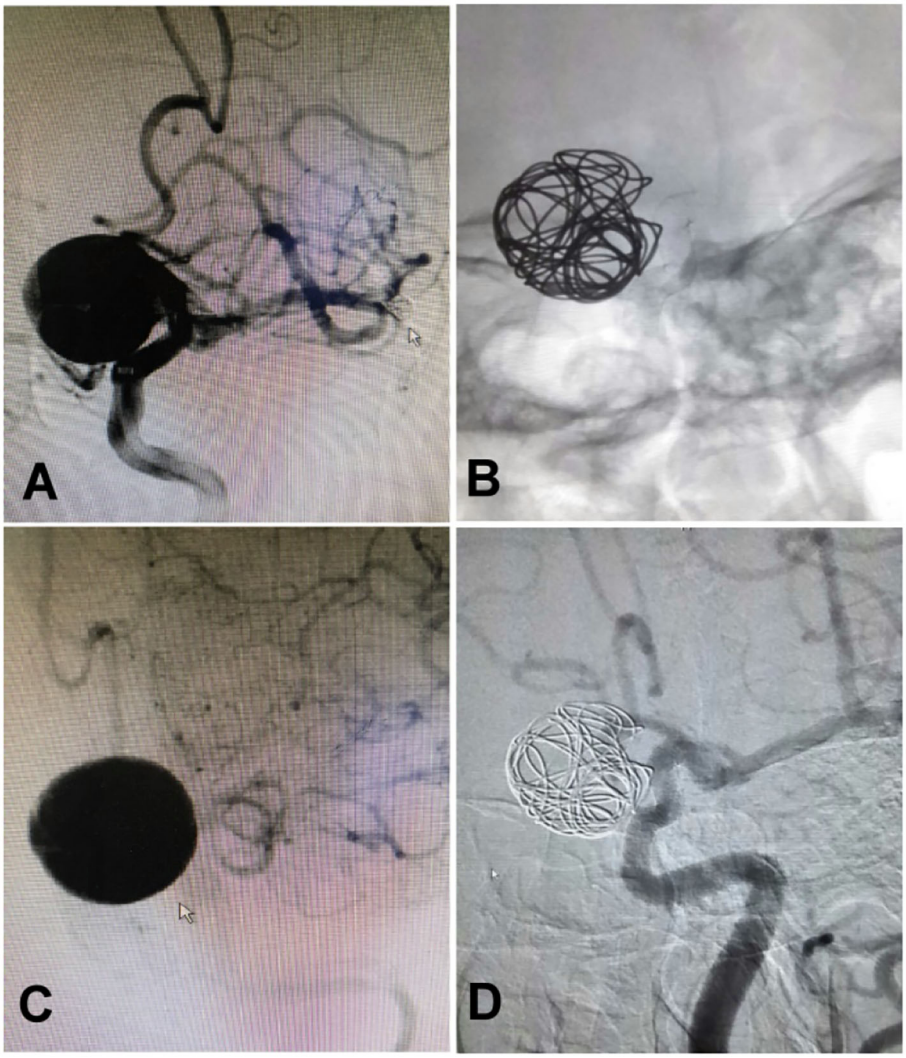

FIGURE 4
A woman in her 40's with intermittent headache for half a year was found to have an aneurysm measuring 15 × 15 mm at the ophthalmic segment of the internal carotid artery treated with deployment of a Pipeline embolization device and adjunctive coiling. **(A)** The aneurysm was found at the ophthalmic segment. **(B)** A 4.0 × 25 mm Pipeline embolization device was deployed before adjunctive coiling. **(C)** The aneurysm was shown at the end of the embolization. **(D)** One year after embolization, the aneurysm was completely occluded.

sac (17). Moreover, adjacent multiple aneurysms can be covered and treated simultaneously in a single procedure with one PED, and the ability to remodel an entire vessel with flow diversion is able to prevent aneurysm recanalization and *de novo* aneurysm formation in the setting of a dysplastic parent vessel (17). In case of large and giant cerebral aneurysms, the technique of stent-assisted coiling may necessitate insertion of a large mass of coils within the aneurysm sac to achieve complete aneurysm occlusion, which may likely aggravate the mass effect-related symptoms caused by the densely packed coils (18, 19). Nonetheless, the flow diverters are able to reconstruct the parent artery lumen and can eliminate the mass effect-related symptoms without inserting coils within the aneurysm sac. Simply deploying a flow diverter at the defect parent artery also means simplification of endovascular embolization operation and decreased radiological irradiation. These advantages have resulted in an increased application of flow diversion but a concurrent decrease in the use of stent-assisted coiling in the treatment of cerebral aneurysms (16, 20).

In one study investigating the effectiveness and safety between the PED and stent-assisted coiling for the treatment of ICA Pcom segment aneurysms (21), including 17 aneurysms treated with the stent-assisted coiling and 21 with PED devices, complete occlusion was achieved in 82.4% of aneurysms in the stent-assisted coiling and 71.4% in the PED devices with no

significant ($p > 0.05$) difference at the first angiographic follow-up half a year after the procedure. At the second angiographic follow-up at a median time 8.3 months for the PED group but 27 months for the stent-assisted coiling, complete occlusion was achieved in 70.6% of aneurysms in the stent-assisted coiling but 81% for the PED group. This study (21) confirmed the increased aneurysm recurrence rate but decreased complete aneurysm occlusion rate in patients treated with stent-assisted coiling as well as the increased complete aneurysm occlusion rate but no recurrence in the flow diversion group. In a multicenter cohort study comparing the effect of stent-assisted coiling for 62 aneurysms and PED embolization for 106 aneurysms in the ICA ophthalmic segment (17), the immediate complete occlusion was achieved in 58.1% of aneurysms treated with stent coiling. At the median follow-up of stent-assisted coiling vs. flow diversion (22.5 vs. 8.7 months, $p = 0.0002$), complete occlusion was achieved in 75.9% and 81.1% of aneurysms treated with stent-coiling and PED, respectively, with no significant difference ($p = 0.516$). The need for retreatment was higher with stent coiling. In a study comparing the safety and efficacy of flow diversion and stent-assisted coiling in the treatment of large and giant aneurysms based on a propensity score-matched analysis (22), the complete occlusion rate was significantly higher in the PED cohort than in the conventional stent-coiling cohort at 6-month follow-up. The PED cohort achieved significantly greater improvement but a lower recurrence rate. In our study, the complete occlusion rate of aneurysm immediately after embolization was high in the stent-assisted coiling cohort but lower in the flow diversion group. However, at follow-up of ∼2 years, the complete occlusion rate was higher in the flow diversion group but lower in the stent-assisted coiling cohort, which experienced an increased aneurysm recurrence rate.

Our study included aneurysms at different locations like the ICA, anterior and middle cerebral artery, intracranial vertebral artery, and basilar artery, with different sizes of aneurysms treated from small to giant aneurysms. Ruptured and unruptured aneurysms were also involved in our study. Currently, most studies comparing the effect and safety of stent-assisted coiling vs. flow diversion involved only unruptured (23, 24) or ruptured (25) aneurysms, posterior (26) or anterior (27) circulation, small or tiny aneurysms (28). In the procedure-related complications, the stent-assisted coiling involved more complications than those with flow diversion even though there were no significant differences (11.5 vs. 1.9%). The procedure-related complication rate of stent-assisted coiling in comparison with flow diversion had been reported to be of no significant difference (24–28). Chalouhi et al. reported the complication rate in the stent-assisted coiling vs. flow diversion to be 3 vs. 5% (27), including four ischemic events and one rebleeding event in the stent-assisted coiling cohort but one ischemic and one rebleeding event in the PED group, with no procedure-related mortality in either group. Zhang et al. (28) studied 77 small and tiny aneurysms treated with PED deployment in comparison with 281 small and tiny aneurysms treated with stent-assisted coiling but did not find a significant ($p > 0.05$) difference in the complication rate between these two treatment approaches (11.1 vs. 6.1%).

Retreatment is less likely for cerebral aneurysms treated with flow-diverting devices than those treated with the stent-assisted coiling technique because of the high rate of aneurysm occlusion and minimal risk of recurrence achieved with the flow-diverting device (21, 29). Enriquez-Marulanda et al. found no recanalization in the PED group compared with that in the stent-assisted coiling cohort (21). Chalouhi et al. found that a significantly lower rate of retreatment in the PED group than that in the coiling group (5 vs. 32.5%, $p = 0.003$) of patients with small non-complex intracranial aneurysms (30). Xin et al. also found significantly lower rates of retreatment in patients treated with flow diversion than in patients treated with stent-assisted coiling for unruptured cerebral aneurysms (24). In our study, no recurrence was found in 2-year follow-up of aneurysms treated with the flow diverter, consistent with the findings of the above studies.

Studies with three-dimensional models demonstrated that stents deployed at the aneurysm neck can significantly decrease the peak velocity, strengths of vortices and wall shear stress on the inner wall of aneurysms, and that deployment of an additional stent will further decrease these hemodynamic stresses (31, 32). Moreover, experimental and clinical data have demonstrated that the placement of a stent alone across the neck (33–35) of side-wall or fusiform aneurysms could change the intra-aneurysmal hemodynamic status, leading to thrombosis and final obliteration of the aneurysm from blood circulation. Stenting alone provides a novel treatment option for selected cerebral aneurysms, especially the PED flow-diverting device that provides ∼30–35% metal surface coverage at nominal expansion–a much higher percent coverage than that provided by conventional intravascular stents (36). The Neuroform stent and the Enterprise stent provide between 6.5 and 9% metal surface coverage when fully deployed in the artery. These properties have enabled the stents to significantly reduce the wall shear stress and flow velocity entering the aneurysm cavity (37). Wang et al. studied the effect of stenting on the wall shear stress and flow velocity into the aneurysm and found that a single PED stent caused less reduction in wall shear stress (51.08%, 0.96 Pa) and velocity (37.87%, 0.0503 m/s), but double PED devices resulted in the most greater reduction in wall shear stress (72.37%, 1.36 Pa) and velocity (54.26%, 0.0721 m/s) (37).

Currently, the PED devices have been refined. The PED Classic device that was the first generation approved in 2011 did not support retrieval after release and had demonstrated some difficulties in deployment as well as poor adherence to arterial wall at tortuous segments of intracranial arteries, which may all increase technique-related procedural complications including arterial dissection and intracranial hemorrhage (38–41). The PED Flex device is the second refined version approved in

2015 to address the disadvantages of the previous-generation device, with improved releasing system, improved resheathing capability, and modified pusher wire (42, 43). Studies have shown improved clinical outcomes of the PED Flex device, with decreases in the surgical time, technical failure, and procedural complications (44–46). With the development of science and technology, flow diverters may be further refined, and the risk profile of flow diverters may be decreased over the years with newer iteration of the devices, resulting in better clinical outcomes. Nonetheless, in the technique of conventional stent-assisted coiling, a conventional stent is still needed to be deployed before inserting coils within the aneurysm sac. No further development in the stent-assisted coiling has been reported in the literature. The stent-assisted coiling technique persists to have a high recurrence rate of aneurysms after embolization because this technique does not significantly decrease the hemodynamic stresses within the parent artery or the aneurysm neck as the flow diverter does. This is probably because the conventional stent does not have a higher metal surface coverage area to reconstruct the parent artery lumen (36), which may constitute the fundamental reason for its higher recurrence rate at follow-up.

Some limitations existed in this study, including a retrospective and single-center study, no randomization, Chinese patients enrolled only, and a small cohort of patients, which may all affect the generalization of the outcomes. Moreover, multiple stents with different brands (Neuroform, Enterprise, and Solitaire) were used in the stent-assisted coiling group, and aneurysms at the posterior and anterior circulation or aneurysms with or without rupture were included in the study, which may also affect the generalization of the study outcome. However, these limitations may better reflect the real clinical setting of endovascular treatment of wide-necked aneurysms using either stent-assisted coiling or flow diversion. Nonetheless, future randomized, multicenter, prospective studies will have to be performed to resolve these issues for better outcomes.

Conclusion

Stent-assisted coiling may come with more complications but fewer permanent aneurysm occlusions than flow diverters, and flow diverters may be superior to stent-assisted coiling in the treatment of wide-necked intracranial aneurysms, especially in the long-term effect. Nonetheless, further randomized controlled clinical trials are necessary to assess and confirm the advantages and disadvantages of these treatment approaches for wide-necked cerebral aneurysms.

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 Ethics Committee of First Hospital of Hebei Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

C-HL and B-LG: study design and data analysis. HG, J-FL, C-HL, J-WW, and HL: data collection. HL: supervision. All authors: validation. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

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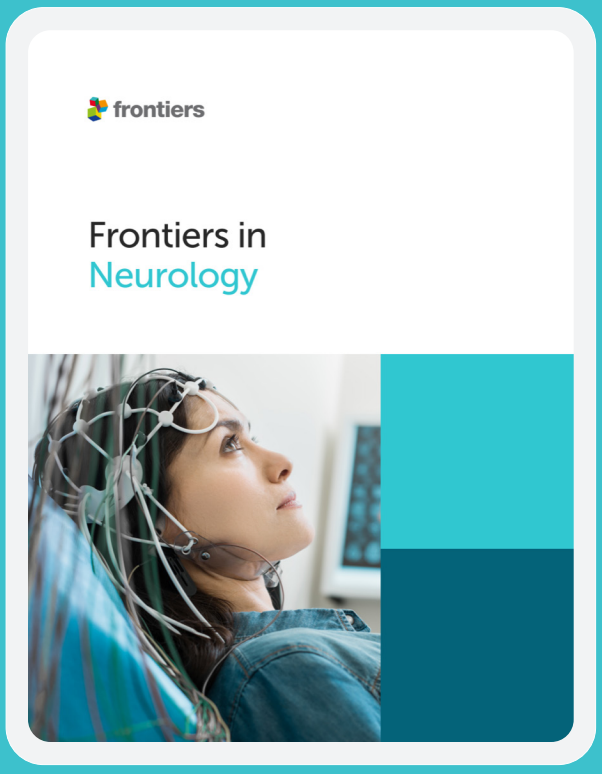

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