INTRACRANIAL ATHEROSCLEROTIC DISEASE: EPIDEMIOLOGY, IMAGING, TREATMENT AND PROGNOSIS

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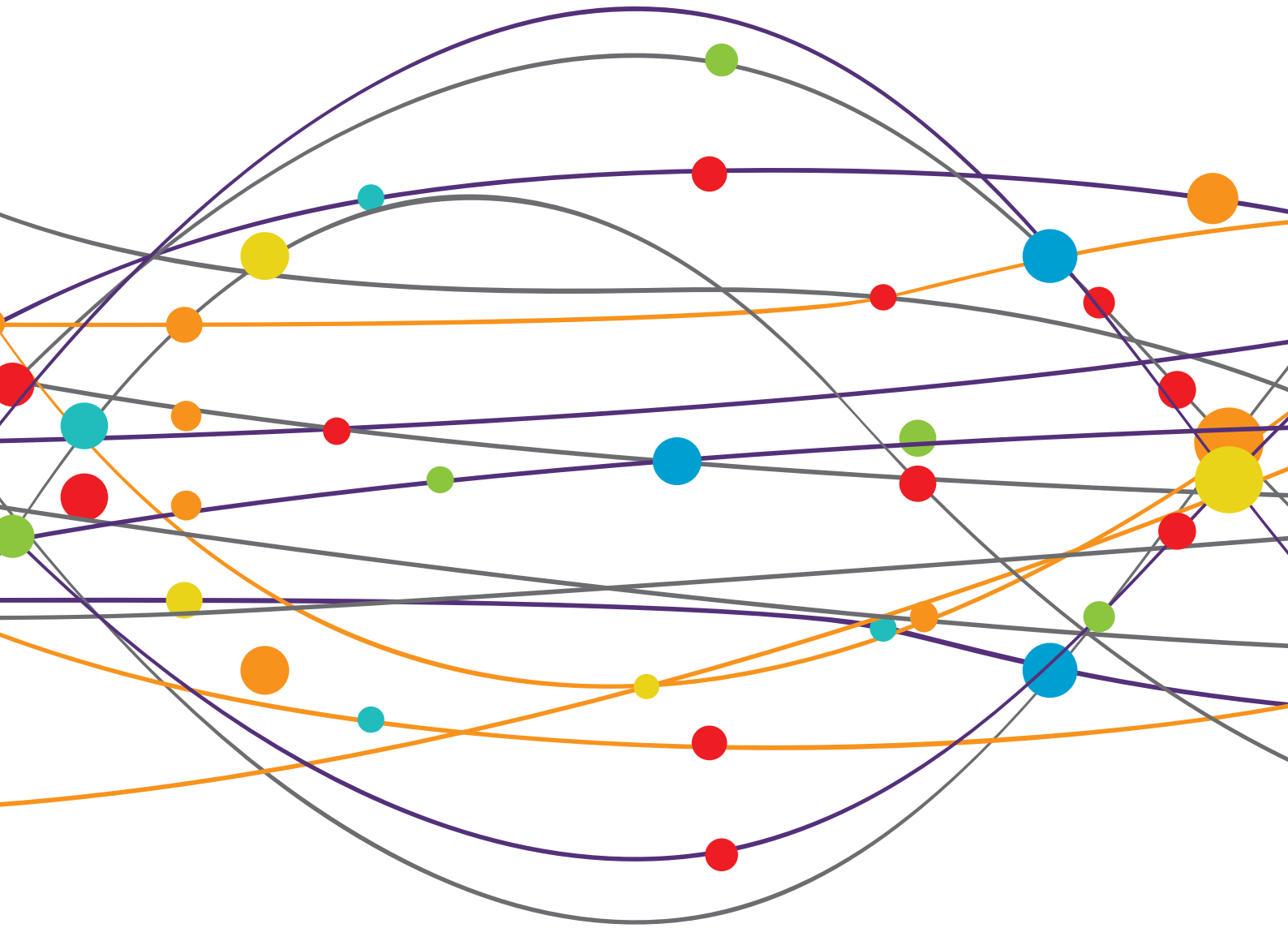

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INTRACRANIAL ATHEROSCLEROTIC DISEASE: EPIDEMIOLOGY, IMAGING, TREATMENT AND PROGNOSIS

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EDITORIAL
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Editorial: Intracranial Atherosclerotic Disease: Epidemiology, Imaging, Treatment and Prognosis

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Keywords: stroke, intracranial atherosclerotic disease, imaging, endovascular treatment, stenting

Editorial on the Research Topic

Intracranial Atherosclerotic Disease: Epidemiology, Imaging, Treatment and Prognosis

Intracranial atherosclerotic disease (ICAD) is an important cause of ischemic stroke and transient ischemic attack (TIA) worldwide (1). Patients with ischemic stroke attributed to ICAD face a considerable risk of stroke recurrence, despite guideline-recommended treatments, mostly based on findings from the SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) trial (2). To date, symptomatic ICAD is treated based on the severity of luminal stenosis in almost all trials and clinical practice, with 70–99% stenoses considered as "high-risk" lesions, despite the fact that nearly half of the recurrent strokes occur in those with "moderate" (50–69%) or even "mild" (<50%) stenosis.

In recent years, advanced imaging techniques have emerged to depict different aspects of ICAD and stroke, providing an extensive amount of data to illustrate the various mechanisms of stroke in ICAD and myriad factors involved in its dynamic evolution and prognosis (3). Yet, research on ICAD still falls far behind that on atherosclerotic disease in other vascular beds, such as coronary and carotid arteries. Numerous questions remain unanswered in this field, e.g., reasons underlying the ethnic difference in ICAD prevalence, evolution in patterns of the disease, differences in risk of stroke relapse and response to treatment in strokes of different mechanisms, differences in acute endovascular treatment (EVT) of large vessel occlusion (LVO) due to ICAD vs. other causes, potential benefit of stenting therapy in selected patients, and safety and efficacy of novel treatment methods.

In this collection, we have included several articles on conventional or novel imaging markers in ICAD and the clinical implications. Yang et al. reported a high prevalence of intracranial arterial calcification in patients with ischemic stroke or TIA, mostly affecting the intracranial portion of internal carotid artery (ICA); they also investigated the association of intracranial arterial calcification, in general or further classified as intimal or medial calcification, with presence of culprit and non-culprit plaques for the index cerebral ischemic event. Among patients with symptomatic or asymptomatic, unilateral, severe stenosis of middle cerebral artery (MCA), Lin et al. evaluated the velocity and extent of cortical venous filling by dynamic CT angiography, and discussed the importance of venous drainage in sustaining cerebral perfusion and affecting clinical outcomes of ICAD patients. In a *post-hoc* analysis of the Chinese IntraCranial AtheroSclerosis (CICAS) Study, Liu et al. found that coexisting ICAD and white matter hyperintensities was

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associated with an increased risk of unfavorable functional outcome (modified Rankin Scale 3–6) at 1 year, among 2,076 patients with acute ischemic stroke or TIA. With other accumulating studies on ICAD plaque characteristics, collateral circulation and cerebral hemodynamics, etc., these studies reinforced the need for comprehensive assessment of ICAD and coexisting conditions or imaging markers, for more accurate risk stratification of affected patients.

In *post-hoc* analysis of the Mechanisms of Early Recurrence in Intracranial Atherosclerotic Disease (MyRIAD) Study, Sangha et al. revealed a high risk (25%) of early new infarcts (with various manifestations, e.g., borderzone, cortical or territorial infarcts, or in a mixed pattern) within 8 weeks of an initial stroke in symptomatic ICAD patients, indicating the potential value of early imaging follow-up to reveal early, silent ischemic lesions and stroke mechanisms in such patients. In a single-center study, Zhang et al. reported a significantly higher risk of recurrence stroke/TIA in patients with symptomatic, posterior-circulation ICAD than anterior-circulation ICAD (25.5 vs. 14.2%), for which they argued various stroke mechanisms in the two groups as a key explanation, in addition to the differences in the baseline characteristics. These two studies have stressed the need to understand the pathophysiology in ICAD-related stroke and to treat ICAD and the stroke mechanism(s) rather than a single stenosis. This was also emphasized in a Mini Review article in this collection, which reviewed the potential effects of arterial hemodynamics and platelet activity in dominating the response to currently "optimal" medical treatment and outcomes of patients with symptomatic ICAD.

In the past few years, EVT has become a first line treatment in acute ischemic stroke with LVO, after a few successful randomized controlled trials (4). ICAD and embolic occlusion are two main causes of LVO stroke. In a multicenter registry, Lee et al. reported that ICAD as an underlying cause of LVO may not be associated with a higher rate of recanalization failure by mechanical thrombectomy, as compared with LVO with an embolic origin. However, Li et al. found a significantly higher risk of poor functional outcome after EVT associated with ICAD-related LVO than LVO of other causes. Previous studies had also reported conflicting findings (5). On the other hand, acute LVO stroke caused by ICAD or embolic origin may benefit from different EVT strategies. Baek et al. found that rescue endovascular strategy after failure of routine mechanical thrombectomy, preferably in combination with glycoprotein IIb/IIIa inhibitor infusion, may be associated with better imaging and clinical outcomes in ICAD-related LVO, compared with routine mechanical thrombectomy alone. Early identification of the etiology of LVO may help guide treatment strategies: among 164 patients with acute LVO who received EVT, Jin et al. identified the jet-like (pencil-tip-like or line-linked) appearance of contrast filling on the occlusion edge in pre-procedural angiography as an imaging marker of ICAD-related LVO. In addition, Liao et al. have found different pathological compositions of thrombi obtained by mechanical thrombectomy in LVO patients, atrial thrombi obtained during cardiac surgery and carotid plaques obtained by endarterectomy, which may have implications for acute reperfusion therapy in acute ischemic stroke.

Apart from acute EVT, there are several studies on angioplasty and stenting therapy for secondary stroke prevention in symptomatic ICAD patients in this collection. In a multicenter registry study, Guo et al. reported a 8.2% 1-year risk of stroke and vascular death, in patients with symptomatic, high-grade ICAD with imaging evidence of downstream hypoperfusion who received stenting treatment. The risk is comparable with that (8.5%) in the WEAVE (Wingspan Stent System Post Market Surveillance)/WOVEN (Wingspan One-year Vascular Events and Neurologic outcomes) study (6), but much lower than that (over 20%) in the stenting arms of SAMMPRIS (2) and VISSIT (Vitesse Intracranial Stent Study for Ischemic Therapy) trials (7). In a small case series, Hassan et al. reported a zero periprocedural complication rate, and a 7.7% risk of TIA but zero recurrent stroke or death within 6 month, upon using a new generation of drug-eluting balloon-mounted stent in treating medically refractory, symptomatic ICAD ($\geq$70% stenosis). However, symptomatic ICAD in the posterior circulation may bear a higher risk of periprocedural complications, recurrent stroke and death. For instance, Wang et al. reported a high risk (22.7%) of stroke, TIA and death during hospitalization in patients with symptomatic intracranial vertebrobasilar artery stenosis (70–99%) refractory to medical treatment. Luo et al. observed a 55% rate of new cerebral infarctions in diffusion-weighted MR imaging obtained at 72 h after angioplasty and/or stenting treatment of symptomatic basilar artery stenosis, but they did not identify significant associations between plaque characteristics by vessel wall MR imaging and new cerebral infarctions. All these investigations have echoed the rising voice of revisiting the safety and efficacy of stenting therapy (that was overruled as first-line treatment after SAMMPRIS), and associated beneficial and deleterious factors, in selective, symptomatic ICAD patients.

In summary, this collection includes review or original research articles on pathology, pathophysiology, imaging, treatment and prognosis of ICAD and ICAD-related stroke or TIA, with which we intend to elicit further attention on ICAD and more interest in ICAD research around the world. Hopefully in the near future, more accurate risk stratification, and more effective and individualized acute treatment and secondary stroke prevention of symptomatic ICAD will be developed, with the goal "to provide the right treatment, at the right dose or use, for the right patient, at the right time," as stated in the review article on "precision medicine" for ICAD in this collection.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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Differences in Pathological Composition Among Large Artery Occlusion Cerebral Thrombi, Valvular Heart Disease Atrial Thrombi and Carotid Endarterectomy Plaques

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Background and Purpose: Acute ischemic stroke (AIS) with large artery occlusion (LAO) may lead to severe disability or death if not promptly treated. To determine the source of cerebral artery occlusion thrombosis, we studied the pathological components of cerebral artery thrombosis with different etiological classifications to guide clinical formulation of preventive treatment.

Materials and Methods: Eighty-eight thrombi from AIS patients with LAO, 12 atrial thrombi from patients with valvular heart disease (VHD), and 11 plaques obtained by carotid endarterectomy (CEA) from patients with carotid artery stenosis were included in this retrospective study. The hematoxylin and eosin–stained specimens were quantitatively analyzed for erythrocytes, white blood cells (WBCs) and fibrin; platelets were shown by immunohistochemistry for CD31.

Results: The thrombi of VHD showed the highest percentage of fibrin, followed by those of cardioembolism (CE) and stroke of undetermined etiology (SUE), and these values were higher than those of the other groups. Plaques obtained by CEA showed the highest erythrocyte number, followed by the large artery atherosclerosis (LAA) thrombi, and showed significantly noticeable differences between other stroke subtypes. The proportions of fibrin and erythrocytes in the thrombi of CE and SUE were most similar to those in the thrombi of VHD, and the LAA thrombi were the closest to those obtained by CEA. CE thrombi and CEA plaques had a higher percentage of WBCs than thrombi of other stroke thrombus subtypes and VHD.

Conclusions: CE and most cryptogenic thrombi may originate from the heart, and the formation of carotid atherosclerotic plaques may be related to atherosclerotic cerebral embolism. Inflammation may be involved in their formation.

Keywords: stroke, mechanical thrombectomy, thrombus, red blood cells, white blood cells, fibrin, platelets

INTRODUCTION

Acute cerebral large artery occlusion (LAO) may lead to severe disability or even death if the patient does not have access to prompt treatment. In recent years, the benefit of endovascular therapy has been demonstrated in patients. Embolic clots of the cerebral large arteries may come from deciduous cardiac valvular thrombi or intracranial/extracranial large artery plaques. Thus, it is important to identify the etiology of LAO in clinical treatment (1). Although the TOAST classification is currently simple and easy to use and advances imaging and diagnostic methods, identifying a clear stroke etiology remains challenging for a certain percentage of stroke patients, especially for patients with atrial fibrillation and intracranial large vascular stenosis or paroxysmal atrial fibrillation, and the etiological mechanisms are difficult to obtain from clinical data (2–4). The study of thrombus properties and components provides good guidance in the selection of recanalization treatment. Previously, assessment of thrombus length by imaging has been used as an independent predictor of the success of vein recanalization, but no histopathological evidence has been verified.

Staessens et al. found that all thrombi were composed of platelet-rich regions and erythrocyte-rich regions by analyzing the composition and internal structure of AIS thrombi retrieved from endovascular therapy; platelet-rich areas are composed of fibrin, von Willebrand's factor (vWF) and platelets. They also suggested that platelet-rich thrombi based on vWF and DNA as well as dense fibrin were the main reason for the failure of intravenous thrombolysis, and the histological characteristics of platelets, vWF and fibrin networks in thrombi were observed by fluorescence microscopy (5). Recent studies have demonstrated that arterial thrombi are mainly composed of the following three components: fibrin/platelet aggregation, red blood cells and white blood cells (WBCs) (6, 7). However, the source of thrombi in patients with AIS is more complex than that of thrombi in the coronary arteries, mainly from the cardiac or large arteries. CE thrombi have higher proportions of fibrin, fewer red blood cells, and more WBCs than non-cardioembolic thrombi. The thrombus histology of cryptogenic strokes and CE strokes showed a strong overlap (8–10). However, Kim et al. observed that CE thrombi had higher proportions of red blood cells than LAA thrombi, and CE thrombi had fewer fibrin, platelets, and WBCs, although the differences were not statistically significant. There were also no statistically significant differences in the proportion of thrombi components between SUE, CE, and LAA causes (11). No consistent results have been reported regarding the association between thrombi compositions and stroke subtypes, and these studies focused on only thrombi with AIS, with relatively limited results. Based on this inconsistency, this is the first study to perform pathologic analysis of atrial thrombi, carotid atherosclerotic plaques, and LAO thrombi to compare the distribution of fibrin/platelets, red blood cells, and WBCs. We attempted to clarify the pathogenesis and origin of stroke thrombi by analyzing differences in thrombi composition.

METHODS

Patient Selection

(1) This retrospective study comprised 263 Chinese patients with LAO from January 2017 to March 2019. This study was conducted according to the recommendations of guidelines from the Institutional Review Board of the First Affiliated Hospital of Jinan University. All protocols and procedures of our research were carried out in conformity to the Helsinki Declaration. All patients who were treated in our hospital signed informed consent for medical research of their images and specimens.

The inclusion criteria included patients over 18 years old; all patients who had been treated by intra-arterial mechanical thrombectomy with thrombus were retrieved for histopathological analysis, and LAO patients who did not have visible thrombi for analysis were excluded from this study. Data regarding patient demographics, clinical presentation, treatment strategies, outcome, imaging findings, and stroke pathogenesis were collected. The stroke subtypes were classified using the Trial of Org 10172 in Acute Stroke Treatment classifications (12). Drinking as defined more than 50 ml per day. Long-term bedridden was defined as staying in bed for more than 3 months.

(2) Valvular heart disease (VHD) patients with a left atrial thrombus removed during cardiac valvectomy or replacement were enrolled retrospectively at the same time. The inclusion criteria were age >18 years old, patients who underwent valvular surgery for valve lesions such as mitral stenosis or aortic stenosis, and patients who had thrombus material for histopathological analysis.

(3) Patients who underwent carotid endarterectomy (CEA) and had carotid atherosclerotic plaque specimens were included retrospectively at the same time. Patients with carotid atherosclerotic plaque stenosis over 75% and >18 years of age were included.

Thrombus Sample Staining and Histopathological Analysis

Atrial thrombi were obtained during cardiac surgery, carotid atherosclerotic plaques were obtained from carotid endarterectomy, and emboli were retrieved during mechanical thrombectomy (stent-retriever and contact aspiration). All samples were flushed with 0.9% saline, gently placed on sterile gauze wipes, and then fixed in 10% buffer formalin for 2–8 h. The volume of the formaldehyde was approximately 10 times the size of the thrombus. After the sections were treated with solvents and embedded in paraffin, the thrombus organization was identified in the largest section of 6 serial sections that were each 4 μm; these sections were stained with hematoxylin and eosin. Another section was immunohistochemically stained for CD31 (mouse monoclonal, 1:100; Dako Denmark A/S, ready to use) by stepwise procedures. All thrombus slices were dried in a 60°C oven for 30 min, dewaxed in xylene and rehydrated in decreasing ethanol grades. A 6% solution of hydrogen peroxide in water and the biotin-blocking reagent were used to block endogenous peroxidase and endogenous biotin successively.

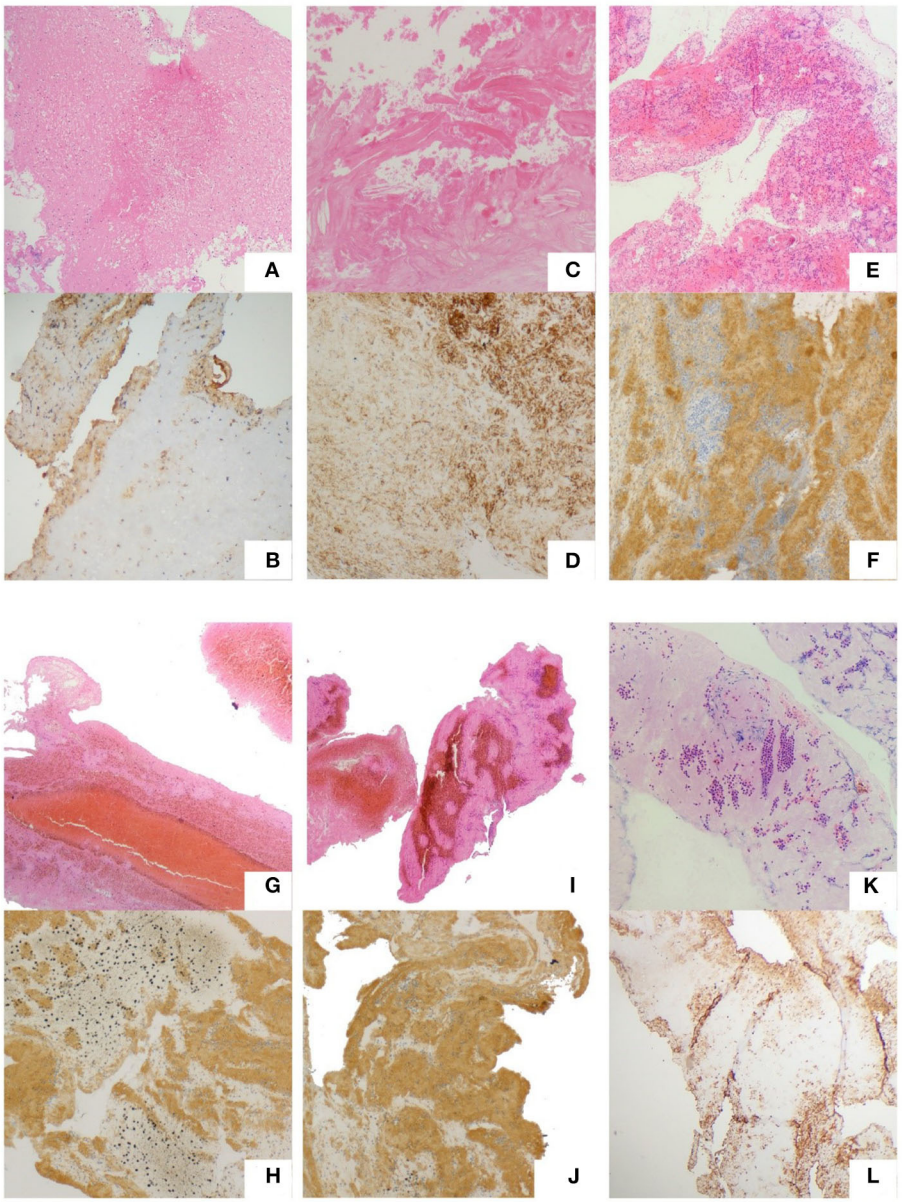

FIGURE 1 | Typical thrombi and plaques. Atrial thrombi of VHD patients. **(A,B)** Carotid atherosclerotic plaques of CEA patients. **(C,D)** Thrombi of CE. **(E,F)** LAA. **(G,H)** SOE. **(I,J)** SUE. **(K,L)** Hematoxylin and eosin staining. **(A,C,E,G,I,K)** Red color represents red blood cells; pink regions represent fibrin; and blue dots represent WBCs; CD31 immunostaining. **(B,D,F,H,J,L)** Dark brown represents platelets (magnification, 200◇).

Primary antibodies against CD31 were added and incubated for 22 min at normal temperature, followed by streptavidin-peroxidase conjugation and incubation for 22 min. The sections were counterstained with hematoxylin, dehydrated in increasing grades of ethanol, cleared in xylene and mounted.

For the H&E staining images, red represents red blood cells; pink regions represent fibrin; and blue dots represent WBCs. For CD31 immunohistochemical staining, dark brown represents platelets, and other components are not colored (**Figure 1**). Histological quantification was performed using ImageJ 1.52a (Image Processing and Analysis in Java; National Institutes of Health, USA) as per the standard operating procedure. The mean value of each clot component was calculated. All observers were blinded to the study groups. The calculation formulas are as follows:

$$\begin{aligned}\text{Target area proportion (\%)} &= \text{measurement target area} \\ &\quad (\text{fibrin/platelet/red blood cells})/ \\ &\quad -(\text{the total areof pictures the blank area}) * 100\% \\ \text{The number of WBCs} &= \text{WBC count}/ \\ &\quad (\text{the total area of pictures} - \text{the blank area}) * 10^6.\end{aligned}$$

TABLE 1 | Clinical patient characteristics.

	LAO ($n = 88$)	VHD ($n = 12$)	CEA ($n = 11$)	*P*
Age (years)	63.36 ± 15.97	60.25 ± 9.69	65.00 ± 4.69	0.71
Male	59 (67.05%)	7 (58.33%)	6 (54.55%)	0.63
Risk factors				
Hypertension	46 (52.27%)	1 (8.33%)	5 (45.45%)	0.39
Diabetes mellitus	38 (43.18%)	3 (25%)	5 (45.45%)	0.47
Coronary artery disease	29 (32.95%)	12 (100%)	4 (36.36%)	<0.001
Dyslipidemia	24 (27.27%)	3 (25%)	1 (9.09%)	0.42
Smoking	24 (27.27%)	1 (8.33%)	4 (36.36%)	0.27
Drinking	11 (12.5%)	0	3 (27.27%)	0.14
Atrial fibrillation	38 (43.18%)	9 (75%)	0	<0.001
History of stroke or TIA	18 (20.45%)	5 (41.67%)	2 (18.18%)	0.24
Long-term bedridden	4 (4.55%)	1 (8.33%)	0	0.63

Statistical Analysis

The data were assessed using ANOVA or the Kruskal-Wallis method, depending on the type of data. The correlation analysis between basic information about the participants and the structure of thrombosis was calculated by Spearman's method. All the analyses above were performed by SPSS (Version 23).

RESULTS

Patient Characteristics

There were 88 patients from whom thrombi were retrieved during mechanical thrombectomy; 175 with no thrombus were excluded from the study. The reasons of no thrombus retrieval including partial recanalization before thrombectomy, arterial sclerosis, too small thrombi, thrombi escaped to a distal blood vessel or thrombectomy failed. All patients in group VHD ($n = 12$) had valvular heart disease, and nine patients had atrial fibrillation. All patients in the CEA group ($n = 11$) had no atrial fibrillation. There were statistically noticeable differences among the VHD, CEA, and LAO groups in the proportion of patients with atherosclerotic coronary heart disease and atrial fibrillation. There were significantly more VHD patients with atherosclerotic coronary heart disease and atrial fibrillation in the VHD group than in the other two groups (**Table 1**). The cause of stroke was determined by two stroke neurologists based on all clinical information and imaging available for each patient. LAO patients were divided into these subtypes: (1) CE (83.3% of patients with atrial fibrillation, $n = 46$), (2) large artery atherosclerosis (LAA, $n = 25$), and (3) stroke of other determined etiology (SOE, $n = 6$), including patients with arterial dissection, (4) stroke of undetermined etiology (SUE, $n = 11$), (5) small-artery occlusion (SAO, $n = 0$). LAA is defined as artery-to-artery embolism in our study, excluding *in-situ* atherothrombosis. Among the LAO subtypes, the proportion of coronary atherosclerotic heart disease and atrial fibrillation in the CE group was significantly higher than that in the other three groups. The distribution of the National Institutes of Health Stroke Scale (NIHSS) score and Alberta Stroke Program Early CT Score (ASPECTS) before thrombectomy and the modified Rankin Scale (mRS) at 3 months after discharge were the same in each group. There was no significant difference among the subtypes (**Table 2**).

ANOVA was used for data conforming to a normal distribution, and the Kruskal-Wallis method was used for data not conforming to a normal distribution.

Histological Analysis

Stained slices were scanned by using an Olympus BX43 microscope and digital camera to take panoramic photos (magnification, 200◇). The quantification of fibrin, red blood cells and platelets was used to measure the area covered by various components in the image [%], and the WBCs were used to automatically measure the particle number of the threshold set (**Table 3**).

Differences in the Composition of Thrombi Among VHD, CEA, and LAO Patients

VHD thrombi showed the highest percentage of fibrin, the lowest percentage of red blood cells and the lowest WBC count. The percentage of CEA was the lowest, and CEA thrombi showed the highest numbers of red blood cells and WBCs. The percentage of LAO was between them and showed statistically noticeable differences.

Comparison of Stroke Subtypes and VHD and CEA

The percentages of fibrin in thrombi of the CE and SUE subtypes were higher than those in thrombi of the LAA and SOE subtypes, showing statistically noticeable differences between other stroke subtypes. LAA thrombi showed the highest red blood cell count among stroke subtypes but less fibrin (**Figure 2**). Thrombi of the CE subtype had more WBCs than those of the other stroke subtypes. CEA thrombi had significantly more WBCs than those of the VHD subtype (**Figure 3**). No statistically noticeable differences in platelets between groups were found.

DISCUSSION

In this study, we analyzed the histological characteristics of thrombi from patients with acute stroke of LAO and compared the histological composition with atrial thrombi and carotid atherosclerotic plaques for the first time, which showed a stronger reference. The sample size in the present study was larger than those in many previous studies.

In our cases, there were significantly more VHD patients with atherosclerotic coronary heart disease and atrial fibrillation than in the other two groups, suggesting that coronary heart disease and atrial fibrillation are both important risk factors for cardiac thrombosis. The age of the patients, sex, hypertension, diabetes, hyperlipidemia, smoking, alcohol consumption, history of stroke or transient ischemic attack, and

TABLE 2 | Clinical characteristics of stroke subtypes (TOAST).

	LAA ($n = 25$)	CE ($n = 46$)	SOE ($n = 6$)	SUE ($n = 11$)	*P*
Age (years)	64.19 ± 15.06	65.04 ± 14.43	55.80 ± 14.17	58.20 ± 21.70	0.37
Male	14 (56.00%)	24 (52.17%)	3 (50.00%)	7 (63.64%)	0.91
Risk factors					
Hypertension	15 (60.00%)	21 (45.65%)	1 (16.67%)	3 (27.27%)	0.43
Diabetes mellitus	12 (48.00%)	16 (34.78%)	1 (16.67%)	6 (54.55%)	0.32
Coronary artery disease	2 (8.00%)	21 (45.65%)	1 (16.67%)	3 (27.27%)	<0.001
Dyslipidemia	10 (40.00%)	9 (19.57%)	1 (16.67%)	3 (27.27%)	0.28
Smoking	7 (28.00%)	10 (21.74%)	1 (16.67%)	3 (27.27%)	0.90
Drinking	6 (24.00%)	3 (6.52%)	0	1 (9.09%)	0.12
Atrial fibrillation	2 (8.00%)	33 (71.74%)	0	0	<0.001
History of stroke or TIA	6 (24.00%)	10 (21.74%)	0	1 (9.09%)	0.44
Long-term bedridden	0	4 (8.70%)	0	0	0.28
Intravenous thrombolysis	5 (20.00%)	13 (28.26%)	1 (16.67%)	4 (36.36%)	0.69
Times of thrombectomy	2 ± 0.83	2 ± 2.00	2 ± 0.71	3 ± 2.81	0.41
Baseline NIHSS score	17 ± 8.65	16 ± 5.98	14 ± 6.20	18 ± 9.38	0.69
ASPECT score	9 ± 0.89	9 ± 2.12	8 ± 1.48	9 ± 1.25	0.60
mRS 0-2	10 (40.00%)	27 (58.70%)	4 (66.67%)	2 (18.18%)	0.06

TABLE 3 | Differences in the components among the six groups.

	Fibrin (%)*	Red blood cell (%)*	White blood cell*	Platelet (%)*
LAA ($n = 25$)	22.96 (17.81, 28.11)	53.44 (49.91, 56.97)	171.91 (120.01, 223.79)	23.48 (17.69, 29.27)
CE ($n = 46$)	35.91 (31.44, 40.39)	35.70 (32.04, 39.36)	198.47 (166.82, 230.12)	28.43 (22.68, 34.19)
SOE ($n = 6$)	26.33 (12.31, 40.36)	41.83 (25.95, 57.71)	158.92 (73.92, 243.94)	31.83 (20.82, 42.85)
SUE ($n = 11$)	39.73 (27.97, 51.49)	38.18 (31.01, 45.35)	155.24 (86.85, 223.64)	22.09 (10.69, 33.49)
VHD ($n = 12$)	40.83 (34.70, 46.97)	37.08 (31.70, 42.47)	107.38 (48.82, 165.93)	22.08 (16.00, 28.16)
CEA ($n = 11$)	19.91 (17.81, 28.11)	59.00 (47.93, 70.07)	206.11 (169.82, 242.41)	21.09 (7.94, 34.24)
P	0.000	0.000	0.127	0.513

**The data are presented as the median percentage (interquartile range, IQR).*

long-term bedridden status were not different among the LAO, VHD, and CEA groups. All included patients with different stroke subtypes had no significant differences in baseline data, preoperative NIHSS scores, ASPECT scores or mRS scores 3 days after the operation. The proportion of patients with CE thrombi with coronary atherosclerotic heart disease and atrial fibrillation was significantly higher than that among the other three subtypes, which was related to the TOAST classification criteria.

It is worth noting that thrombus composition plays a crucial role in recanalization therapy in LAO patients (13). We found that the percentage of fibrin in the VHD group was significantly higher than that in the other groups, and the contents of red blood cells and WBCs were lower. Previous studies have suggested that atrial thrombi are composed of extensive fibrin and a small number of embedded red blood cells and platelets (14). A study that examined the histopathology of atrial thrombus extraction during cardiac valve surgery in patients with atrial fibrillation and thrombus of cardiac embolization origin from the iliofemoral artery and the subclavian brachial artery during vascular surgery found that the fibrin area of most atrial thrombi was significantly larger than the platelet area (15). The pathogenesis of atrial thrombosis is multifactorial and is mainly related to blood stasis of the left atrium with poor contractility, followed by the hypercoagulable state of blood (16). Especially in mitral stenosis or atrial fibrillation, abnormal stagnation of blood flow in the left atrium and left atrial appendage is important for left atrial thrombosis (17–20). The larger the atrial thrombus is, the less likely it is to dissolve because the denser fibrin network in the thrombus is more resistant to endogenous thrombolysis (21). Boeckh-Behrens et al. (8) found that patients with cardiogenic embolism had a significantly higher proportion of fibrin/platelets in their thrombi than in thrombi from other stroke subtypes, similar to our findings. The fibrin in the CE group was as dominant as that in the VHD group and was significantly more abundant than that in the other stroke subtypes and the CEA group. The fibrin content of both CE and SUE thrombi was close to that of atrial thrombi. Yuki et al. (22) recently found in pig models that the histological characteristics of thrombus had an effect on the process and success of mechanical

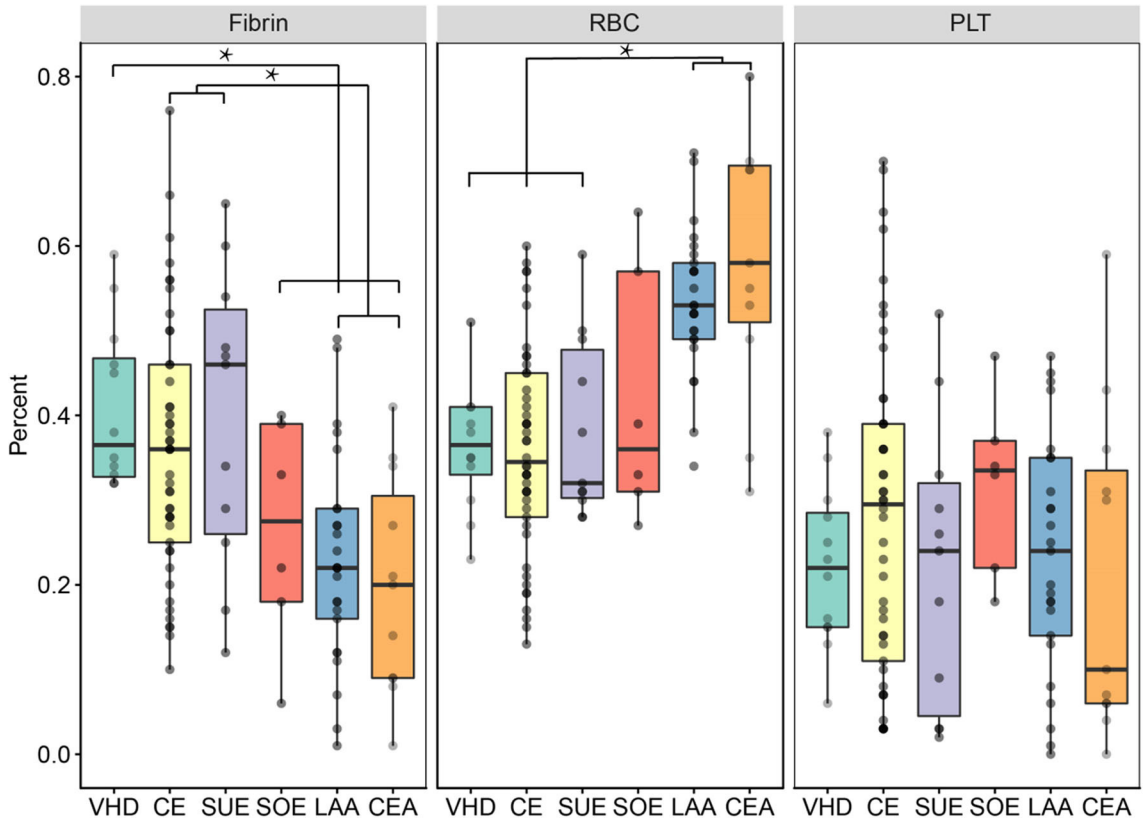

FIGURE 2 | Main sample components of VHD, CEA, and subtypes of TOAST. RBCs, red blood cells; PLT, platelets; VHD, valvular heart disease; CE, cardioembolic; SUE, stroke of undetermined etiology; SOE, stroke of other determined etiology; LAA, large artery atherosclerosis; CEA, carotid endarterectomy. *$P < 0.05$.

thrombectomy; in particular, high fibrin content increased the difficulty of thrombectomy and decreased the success rate of mechanical thrombectomy.

We found that the level of WBCs in the CE thrombus of LAO was significantly higher than that in the VHD group and higher than that in the other subtypes of acute LAO. Boeckh-Behrens et al. studied the histopathology of 34 patients with acute anterior circulative stroke and found that the WBC content of CE thrombi was significantly higher than that in thrombi of other causes of acute stroke (23), which was consistent with our findings. WBCs can improve the overall stability of thrombi with the help of newly discovered neutrophil extracellular traps (NETs) and thus enhance resistance to thrombolysis (24–30). In terms of thrombus composition, fibrin/platelet-rich thrombi have increased friction with the vessel wall, and the reduced fusion of this thrombus with the thrombus cutter makes these thrombi more resistant to mechanical thrombectomy and more difficult to remove (31, 32). Structurally, fibrin/platelet-rich thrombi include dense fibrin/vWF structures and WBCs. Large fibrin bundles can increase the hardness of the thrombus and affect the friction coefficient and physical compression level of the thrombus (5). NETs of WBCs can also change the structure of fibrin to make it more resistant to mechanical force (32–34). These thrombotic characteristics make it difficult for CE thrombi to achieve good results through thrombolysis or mechanical thrombectomy.

Our findings suggested that thrombi in the CEA group had the highest proportion of red blood cells, followed by those in the LAA group, whose red blood cell content was higher than that in thrombi of the other LAO subtypes. Niesten et al. (35) studied thrombi after mechanical thrombectomy in 22 patients with acute stroke. They found that thrombi originating from LAA had the highest proportion of red blood cells, while there was no statistically significant difference in the proportion of fibrin and platelets among the other stroke subtypes. A limitation of the study was the small number of patients. Red blood cells play a major role in the transition from stable atherosclerotic lesions to unstable lesions, leading to occlusion (8, 23, 32, 34). Therefore, the proportion of red blood cells originating from unstable atherosclerotic plaques is higher, especially in cerebral thrombi, and most LAA thrombi are acute thromboembolic events that occur after intraplaque hemorrhage (36–38). With age, the vascular wall is aging and prone to damage. After vascular endothelial cells are damaged, the production of coagulation kinases increases, and the anticoagulant prostacyclin decreases, leading to the formation of thrombi, which contain more red blood cells (6, 39). A study of 649 patients who underwent mechanical thrombectomy for AIS concluded that mechanical

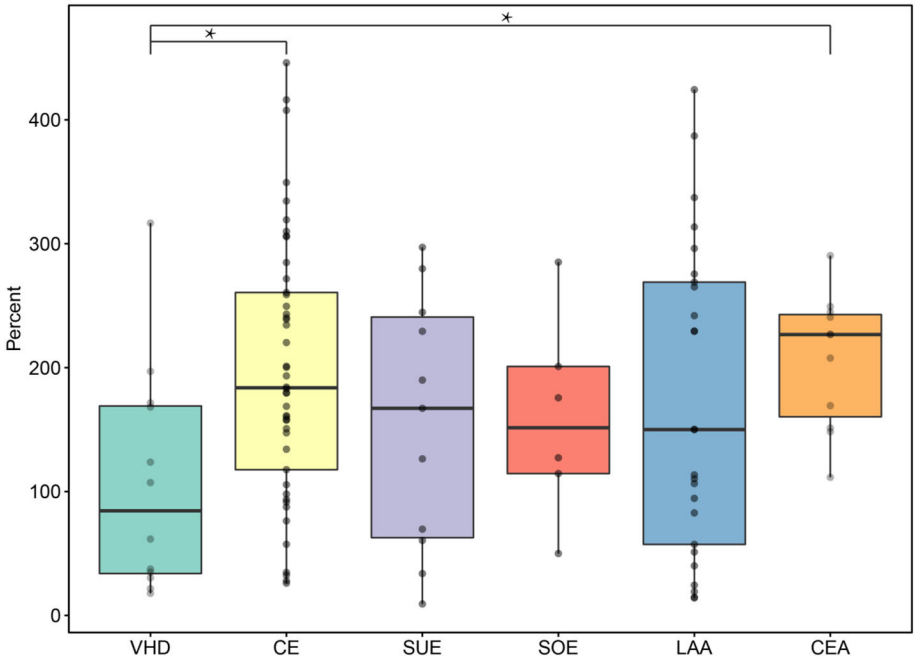

FIGURE 3 | WBC counts of VHD, CEA, and subtypes of TOAST. VHD, valvular heart disease; CE, cardioembolic; SUE, stroke of undetermined etiology; SOE, stroke of other determined etiology; LAA, large artery atherosclerosis; CEA, carotid endarterectomy. *$P < 0.05$.

thrombectomy may be more effective in the treatment of LAA stroke than CE stroke (40). Many studies have shown that compared with CE stroke, stroke thrombi rich in red blood cells are easier to obtain through intravascular treatment and easier to recanalize through rt-PA intravenous thrombolysis (41, 42).

Our study found that the plaques of the CEA group were rich in WBCs. Many studies have shown that inflammation plays many key roles in the development and progression of atherosclerosis (43, 44) and that infiltration of WBCs into the carotid plaque surface may be a key step in promoting plaque formation or carotid artery occlusion (45).

Currently, the SUE thrombi showed histological characteristics and compositions similar to those of cardiogenic thrombi seen in several studies (8–10), suggesting that a cardiac origin is the main cause of undetermined etiology stroke (10). Other studies have assessed the composition of thrombi in patients with SUE and found no significant difference between these thrombi and the proportion of cardiogenic or large artery atherosclerotic thrombi (23). However, our study found that the fibrin and red blood cell contents of SUE thrombi were very close to those of CE and LAA thrombi, which supported the current findings of stroke of undetermined etiology.

The SOE group in our study included patients with arterial dissection. These thrombi were characterized by a higher proportion of red blood cells and significantly less fibrin content than atrial thrombi of VHD, suggesting that such thrombi might be emboli caused by the formation and shedding of a hematoma in the arterial wall. In a previous study of three patients with arterial dissection, thrombi of mixed but predominantly red blood cells were observed (35), and thrombectomy in this group was relatively effective. The limitation of this histological analysis of thrombi is that the sample size is small, and further study is needed.

In conclusion, the proportions of fibrin and red blood cell content of CE and SUE thrombi were the closest to those of atrial thrombi in VHD. CE thrombi originated from cardiac thrombi, suggesting that most SUE thrombi may also originate from the heart. The proportions of red blood cells and fibrin in thrombi in the LAA group were close to those in thrombi in the CEA group, suggesting that the formation of carotid atherosclerotic plaques may be related to stroke of LAA. These results provide a reference for the study of embolus sources. There were significantly more WBCs in the CE group and plaque in the CEA group than in the atrial thrombus group, suggesting that in addition to traditional thrombolysis and thrombectomy, anti-inflammatory therapy may improve the success rate of recanalization in the treatment of CE stroke. For patients with carotid artery plaque and stenosis, early anti-inflammatory therapy may have a certain inhibitory effect on plaque rupture or carotid artery occlusion, which provides a theoretical basis for clinical treatment.

A limitation of this study is that it is a preliminary and retrospective study. Second, the composition statistics of thrombi or plaques in each group were averages, which cannot exclude the existence of the same type of thrombus in different subtypes of a cerebral thrombus. For example, red thrombi were found in both the LAA and CE groups; thus, it is not simply considered that red thrombi are from strokes of the LAA or CE. The results of this study provide only a reference for the etiological source of stroke. Furthermore, intravenous thrombolysis may also affect the composition of the thrombus, but the proportion

of such cases is small. However, the samples we selected were all previously treated with intravascular therapy after thrombolysis failure, and the proportion of thrombolysis was small; thus, this effect was excluded.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

ETHICS STATEMENT

All patients who were treated in our hospital signed informed consent for medical research of their images and specimens. This study was conducted according to the recommendations of guidelines from the Institutional Review Board of the First Affiliated Hospital of Jinan University. All protocols and procedures of our research were carried out in conformity to the Helsinki Declaration.

AUTHOR CONTRIBUTIONS

YL and MG performed all the pathological experiments, performed data analyses, and wrote the manuscript. DL and SH performed the patients' TOAST classification. YS and JL performed data analyses. XZ, XX, and DY wrote and edited the manuscript. LH and HQ contributed to the conception and design of the study and wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00811/full#supplementary-material

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Initial Experience With the Next-Generation Resolute Onyx Zotarolimus-Eluting Stent in Symptomatic Intracranial Atherosclerotic Disease

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Background and Purpose: Intracranial atherosclerotic disease (ICAD) is a common cause of stroke worldwide. Although there are different endovascular options for the treatment of symptomatic ICAD (sICAD), it is still controversial. Herein, we aim to study the safety and efficacy of a new generation of drug-eluting balloon-mounted stent (DES); Resolute (R) onyx DES in the treatment of sICAD.

Methods: A prospectively maintained neuroendovascular procedures database in a high-volume comprehensive stroke center was reviewed from October 2019 through January 2020. Patients were included if they had sICAD (≥70% stenosis), failed medical management, and underwent intracranial stenting with R-onyx DES. Technical success was defined as the ability to deploy the device at the desired location and achievement of <30% residual stenosis. The primary outcome was the occurrence of complications within 72 h of the procedure (strokes, ischemic or hemorrhagic; and mortality). Secondary outcomes included rates of symptomatic and angiographic recurrence within 6 months of the procedure.

Results: A total of 18 consecutive patients (mean age, 66.6 years; 44.4% were females and 94.4% were Hispanic) were eligible for the analysis. Indication for treatment was recurrent strokes in 13 and recurrent transient ischemic attack (TIA) in 5. A total of 22 symptomatic lesions with a mean baseline stenosis percent (84.9 ± 9.6) were treated using 23 R-onyx DES in 19 procedures. All procedures were done under general anesthesia with 100% technical success, and no reported periprocedural strokes or death. Among 13 patients who had clinical follow-up, 1 (7.7%) patient had TIA. There were no reported ischemic or hemorrhagic strokes. Angiographic follow-up for 9 (50%) patients showed no in-stent restenosis.

Conclusion: The use of R-onyx DES in the treatment of sICAD is safe with high technical success rates. Large prospective multicenter trials with long-term follow-up are warranted.

Keywords: intracranial atherosclerosis, angioplasty, stenting, drug eluting stent, stroke

INTRODUCTION

Intracranial atherosclerotic disease (ICAD) is a common cause of stroke worldwide, with variable prevalence among different races (1). Endovascular treatment (ET) has been controversial since the results of randomized clinical trials (RCTs) that compared medical treatment (MT) vs. ET, Stenting vs. Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) (2), and Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) (3) trials were terminated in advance because ET groups showed a significant increase in perioperative complications. On the other hand, a single-center RCT in China (4) found that ET could be a safe and efficient treatment modality for carefully selected patients with ICAD due to middle cerebral artery stenosis. The Wingspan Stent System Post Market Surveillance (WEAVE) trial (5) reported improved safety of intracranial stenting with a periprocedural event rate of stroke or death of 2.6% when stenting was performed using the Food and Drug Administration (FDA)–approved indication and by experienced operators. Different types of stents can be used in intracranial stenting: self-expandable stent (SES) (5, 6) and drug-eluting balloon-mounted stents (DES) (7–11). The former has a lower radial force; therefore, it is less suitable to achieve the ideal luminal dilatation, especially in those with calcified lesions and has higher rates of in-stent restenosis (ISR) (12, 13). Although DES reduces the risk of ISR (14) "by delivering an antiproliferative drug that prevents neointimal hyperplasia," the delivery system is usually stiff, hence navigation along tortuous intracranial vasculature could be difficult. Two generations of DES have evolved according to their antiproliferative agents, the first generation (paclitaxel/sirolimus-eluting stents) and the second generation (everolimus/zotarolimus-eluting stents), where the stent is more flexible than the latter.

In the present study, we aim to evaluate the safety and efficacy of a new generation of DES, Resolute (R) onyx DES (Medtronic, Santa Rosa, CA) in the treatment of sICAD.

MATERIALS AND METHODS

Patient Selection

We retrospectively reviewed a prospectively maintained neuroendovascular procedures database in a comprehensive stroke center from October 2019 through January 2020. Patients were included in the analysis if they had sICAD: ≥70% intracranial stenosis, recurrent strokes, or transient ischemic attacks (TIAs) in the territory of the affected artery despite aggressive MT[2] and baseline modified Rankin Scale (mRS) ≤3. The Institutional Review Board approved the study and written informed consent was obtained from all participants to use the off-label stent.

Device Description

R-onyx DES (Medtronic) Zotarolimus-Eluting Coronary Stent System consists of a balloon-expandable, intracoronary DES premounted on a Rapid Exchange or an Over-the-Wire stent delivery system. R-onyx DES is manufactured from a composite material of cobalt alloy and 90% platinum−10% iridium alloy and is formed from a single wire bent into a continuous sinusoid pattern that then laser fused back onto itself. The stents are available in multiple lengths and diameters. The delivery system has two radiopaque markers to aid in the placement of the stent during fluoroscopy and is compatible with 0.014-in. (0.36-mm) guidewires and 1.42-mm (5 Fr/0.056 in.) minimum inner diameter guide catheters. The strut thickness is 81 μm. R-Onyx has a swaged shape and a larger strut width-to-thickness ratio than the old generation (Resolute). Zotarolimus dose density and polymer are identical to the Resolute DES; however, because of the modified stent geometry, the overall drug load is slightly reduced in most sizes of the R-Onyx DES (15).

Endovascular Procedure

The decision to pursue with endovascular treatment was based on multidisciplinary discussion between vascular neurologists and neurointerventionalists. All procedures were performed under general anesthesia. A dose of 325 mg of acetylsalicylic acid (ASA) and 75 mg of clopidogrel was given at least 3 days before ET. Platelet function was assessed by P2Y12 reaction units (PRU) test with a target of 60–200; if it was above 200, a loading dose (180 mg) of ticagrelor was given then the patient was started on ticagrelor 90 mg BID and ASA 81 mg daily and discontinued clopidogrel. Femoral access was used for anterior circulation lesions, whereas posterior circulation lesions were approached through radial access. Two types of guiding catheters were used: ballast long sheath (Balt, Irvine, CA, USA) and Neuron 088 Max (Penumbra, Alameda, CA, USA), and the choice between the two devices was depending on operator's preference. Similarly, two types of distal access catheters were used: Navien 5Fr (Medtronic, Irvine, CA, USA) and Sofia 5Fr (MicroVention, Tustin, CA, USA). During the intervention, all patients were heparinized to activated clotting time from 250 to 300 s. A radiologic examination of the targeted vessel was performed using a biplane angiographic system (Innova IGS 630; GE Healthcare, Chalfont St Giles, UK), the vessel diameter adjacent to the stenosis and the diameter and length of the stenosis were determined for proper selection of the stent size. The degree of percent stenosis was determined as follows: percent stenosis = $[(1 - (D_{stenosis}/D_{normal}))] \times 100$, where $D_{stenosis}$ = the diameter of the artery at the site of the most severe stenosis and D_{normal} = the diameter of the proximal normal artery (16).

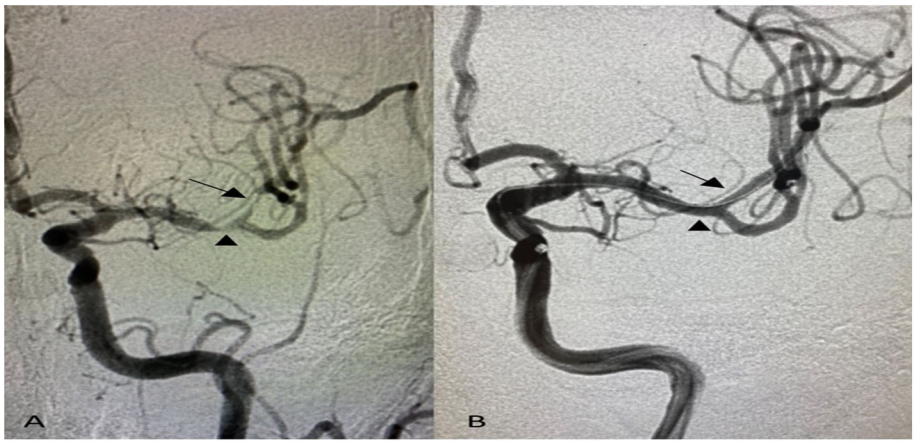

FIGURE 1 | Anterior–posterior projection of digital subtraction angiography shows **(A)** tandem intracranial significant stenoses of the left middle cerebral artery; distal M1 segment (arrowhead) and superior division of M2 segment (arrow), **(B)** post-angioplasty and stenting with no residual stenosis using 2 Resolute Onyx Drug-Eluting Stents 2 × 8 mm.

Under a road map, the vessel distal to the stenosis was catheterized with a microwire; in case of near occlusion of the targeted vessel, a pre-dilatation with a balloon (Gateway; Stryker, Kalamazoo, MI, USA) was performed, then the R-onyx DES was deployed at nominal pressure (12 atm) with a manometer. After deflation and withdrawal of the balloon catheter, a final DSA run was carried out to confirm stent deployment at the targeted stenosis and to exclude complications.

Dual antiplatelet therapy with either ticagrelor 90 mg plus ASA 81 mg or clopidogrel 75 mg plus ASA 81 mg continues indefinitely after the procedure.

Outcome and Follow-Up

The primary outcome was the incidence of strokes (ischemic, hemorrhagic) and death within 72 h post-stenting which was assessed clinically before patient discharge by a vascular neurologist and radiologically through head CT. Technical success was defined as the ability to deploy the device at the desired location and achievement of <30% residual stenosis. Patients underwent clinical and angiographic follow-up within 6 months after the procedure to assess for symptomatic and angiographic recurrence.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages. After normality testing through Shapiro–Wilk, continuous variables were expressed as mean ± SD for parametric and as median for non-parametric variables. The analysis was performed using SPSS 26 software (IBM, Armonk, NY, USA).

RESULTS

A total of 18 patients were eligible for the analysis. The mean age was 66.6 ± 12 years, 44.4% were females, and 94.4% were Hispanic. Stroke risk factors included hypertension in all patients (100%), diabetes mellitus in 12 (66.7%), hyperlipidemia in 9 (50%), and current cigarette smoking in 2 (11.1%). Moreover, 72.8% had recurrent strokes in the territory of the affected blood vessel, and 27.8% had recurrent TIA. Nineteen symptomatic lesions were treated with a mean baseline stenosis of 84.9 ± 9.6%. Also, 72.7% of the lesions located in the anterior circulation and 27.3% in the posterior circulation. Tandem intracranial lesions occurred in 16.7% of patients (**Figure 1**, **Table 1**).

A total of 19 procedures were performed under general anesthesia with median fluoroscopy time 12.2 (10–18.3) min; mean contrast volume, 50.4 ± 24 ml. The median time of stenting from the last stroke was 4.5 (1.8–67.5) days, with 10 (52.6%) patients being treated within 7 days of the last stroke. The lesion was accessed through a femoral puncture in 15 (78.9%) and radial puncture in 4 (21.1%) of the procedures. Pre-dilatation with a balloon was performed in four (21.1%) procedures. In-stent thrombosis occurred in one procedure, which was resolved with intra-arterial tirofiban without complications. A total of 23 stents were deployed, 1.3 per procedure and 9 (39.1%) were 2 × 8 mm in size. The overall procedural success rate was 100%, with no reported periprocedural ischemic or hemorrhagic strokes and death (**Table 2**).

Clinical and Angiographic Follow-Up

Among 13 patients who had clinical follow-up, one (7.7%) patient had transient ischemic attack in the same territory of the treated artery 2 months after the procedure. There were no reported ischemic/hemorrhagic strokes or medication-related complications. Nine (50%) patients underwent digital subtraction angiography on follow-up and showed no ISR (**Table 2**).

DISCUSSION

We successfully treated 18 patients with sICAD using the Medtronic Resolute Onyx drug-eluting balloon-mounted stent.

TABLE 1 | Patients' demographics, risk factors, and lesion characteristics.

All patients *n* (%)	***n* = 18**
Age (years) mean ± SD	66.6 ± 12
Female	8 (44.4)
Race	
Hispanic	17 (94.4)
White	1 (5.6)
Hypertension	18 (100)
Diabetes mellitus	12 (66.7)
Hyperlipidemia	9 (50)
Current cigarette smoking	2 (11.1)
Recurrent stroke	13 (72.2)
Recurrent TIA	5 (27.8)
Total lesions *n* (%)	***n* = 22**
Stenosis location	
Anterior circulation:	16 (72.7)
Supraclinoid ICA	3 (13.6)
Cavernous ICA	3 (13.6)
Petrous ICA	2 (9.1)
Middle cerebral artery	
M1 segment	4 (18.2)
M2 segment	4 (18.2)
Posterior circulation:	6 (27.3)
Vertebral artery V4 segment	3 (13.6)
Basilar artery	2 (9.1)
Posterior cerebral artery	1 (4.5)
Tandem intracranial lesions per subject	3 (16.7)
Baseline stenosis percent (%) mean ± SD	84.9 ± 9.6

ICA, internal carotid artery; TIA, transient ischemic attack.

TABLE 2 | Procedural characteristics and outcome.

Procedural characteristics *n* (%)	***n* = 19**
Time of stenting from the last stroke (days) median (IQR)	4.5 (1.8–67.5)
Procedures ≤7 days of the last stroke	10 (52.6)
Arterial access	
Femoral	15 (78.9)
Radial	4 (21.1)
General anesthesia	19 (100)
IA-tirofiban	1 (5.3)
R-onyx DES:	*n* = 23
Stent per procedure	1.3
Stent size:	
2×8 mm	9 (39.1)
Number of lesions planned for treatment	
1	16 (84.2)
2	3 (15.8)
Pre-stenting balloon angioplasty	4 (21.1)
Technical success	19 (100)
No residual stenosis	15 (78.9)
Non-significant residual stenosis	4 (21.1)
Total contrast (ml) mean ± SD	50.4 ± 24
Fluoroscopy time (min) median (IQR)	12.2 (10–18.3)
Outcome	
Procedural complication	
In-stent thrombosis	1 (5.3)
Ischemic stroke	0 (0)
Intracerebral hemorrhage	0 (0)
Follow-up	
Clinical (13 patients)	
TIA	1 (7.7)
Ischemic and hemorrhagic strokes	0 (0.0)
6-month angiogram (9 patients)	
In-stent stenosis	0 (0.0)

IQR, interquartile range; TIA, transient ischemic attack.

There was no periprocedural stroke or death within 72 h of stenting. Moreover, there were no reported cases of ISR among patients who had 6-month angiographic follow-up.

Currently, the Wingspan stent (Stryker) is the only FDA-approved stent for the treatment of sICAD under the strict indications applied in the WEAVE trial (5). Other applications of ET for sICAD include balloon angioplasty alone (17) or followed by SES (6), DES (7–11), and more recent use of a drug-eluting balloon (18). Angioplasty alone without stent placement is associated with higher rates of restenosis and procedural complications due to the elastic recoil of blood vessels and the risk of dissection (19).

The present case series reported high safety and technical success in the treatment of sICAD using the most recent generation of DES. R-onyx DES not only delivers zotarolimus with "a more potent with less systemic side effect than first-generation antiproliferative" (20) but also the stent geometry is different from the old generation [Resolute and previously studied Resolute Integrity (21)]. It has a swaged shape and thinner struts that substantially improve stent navigability while maintaining radial strength and lower overall drug load. These advantages, in addition to the use of a more biocompatible polymer, may improve the safety concern about late stent thrombosis (ST) with first-generation DES, which results from incomplete re-endothelialization and persistent fibrin deposition (22).

Periprocedural complications related to DES implantation could result from high-degree stenosis of the target vessel, difficult navigability of the stent due to its stiff nature especially in the elderly with tortuous anatomy, and in more distal lesions, deployment of the stent near a perforator and early treatment within 7 days after stroke that may cause reperfusion hemorrhage from the weakened capillary bed and recurrent stroke due to rupture of unstable plaque (23).

Ye et al. (24) reported a 1.4% incidence of stroke or mortality within 30 days after DES implantation in a group with moderate stenosis <70% that increases to 12.1% if the stenosis was >70%. The present study demonstrated no periprocedural strokes or death with 84.9 ± 9.6% mean baseline stenosis and deployment of the R-onyx DES in different types of lesions; anterior circulation 72.7%, posterior circulation 27.3%, and tandem intracranial

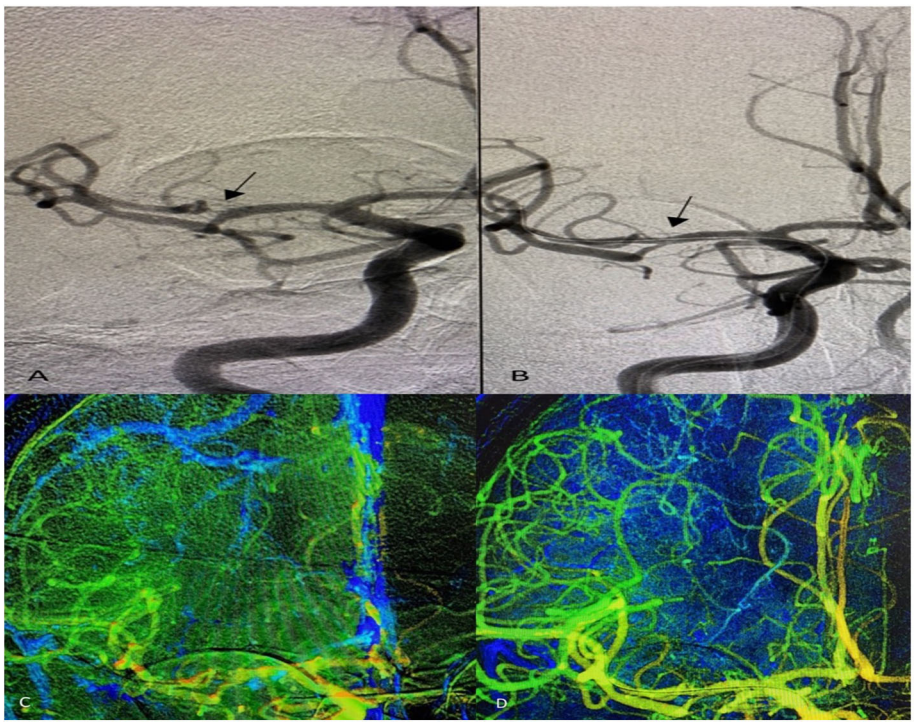

FIGURE 2 | Anterior–posterior projection of digital subtraction angiography shows **(A)** significant stenosis of the right middle cerebral artery–M2 segment (arrow), **(B)** post-angioplasty and stenting with no residual stenosis using Resolute Onyx Drug-Eluting Stents 2 × 8 mm. Two-dimensional parametric parenchymal blood flow demonstrates the difference in blood flow pre- **(C)** and post-angioplasty and stenting **(D)**.

lesions 16.7% of procedures (**Figure 1**). Moreover, more distal lesions (middle cerebral artery M2 segment) within small vessel diameter were treated using the smallest profile of R-onyx DES in the market (2 × 8 mm) with high technical success (**Figure 2**), and 52.6% of the procedures were performed within 7 days of the last stroke. Also, several studies in the literature (7–9) reported higher rates of periprocedural complications than the present study with a mean age of studied population lower than that demonstrated in our case series.

A major concern for using bare-metal stents has been the rate of ISR which is reported to be ∼24 to 45% (13, 25). Previous studies demonstrated several clinical and anatomical predictors of ISR after intracranial stenting including younger age, diabetes mellitus, long lesions, and stenting of small vessels (13, 25, 26). Because ISR is associated with a high rate of recurrent neurologic events (27), DES treatment of sICAD could be more effective especially if associated with the aforementioned risk factors. DES has less incidence of ISR (24); the underlying pathophysiological mechanism of this is inhibition of vessel overreaction after injury and reduction of neointimal thickness which is achieved by delivery of antiproliferative drugs (28).

The technological advances of R-onyx DES provide the unmet needs of intracranial stenting, and the thin strut thickness remains a crucial characteristic in stent platform, demonstrating better device conformability, easier navigability, and lesser strut malapposition. Also, thin struts are associated with low levels of inflammation at the lesion site resulting in rapid and almost complete arterial re-endothelialization and reduced neointimal growth (29). Furthermore, the slim 2-mm stent enables stenting of a small target vessel diameter which is associated with a high incidence of vessel injury, difficult accessibility, and higher rates of ISR. Despite the poor visibility of the slim-profile DES that has ultrathin struts under X-ray images, R-onyx DES was designed with a platinum–iridium core and a cobalt alloy shell to enhance its radiopacity (30).

The new technology of R-onyx DES could be a step forward in the treatment of sICAD if large prospective multicenter trials corroborate our results. The ongoing randomized clinical trial (31) of using dual antiplatelet therapy only for 1 month followed by single antiplatelet therapy after R-onyx DES implantation in patients undergoing percutaneous coronary intervention with high bleeding risk will likely be helpful in determining the adequate duration of antiplatelet regimen in a similar subgroup of sICAD patients.

Our study has all the typical limitations inherent of any single-center retrospective analysis. In addition, the small sample size where only 18 patients were included limits the generalizability of our findings. Similarly, only 50% of patients had follow-up imaging which limited the power to prove the efficacy in preventing ISR. However, the main aim of this study is to identify the periprocedural safety and technical success of the

deployment of a new DES that might help in the treatment of sICAD.

CONCLUSION

The present case series demonstrate that R-onyx DES can be used in the treatment of sICAD with different types of lesions with high procedural safety and technical success rates. Large multicenter studies are needed to further evaluate procedural safety, restenosis rates, and long-term efficacy.

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 Valley Baptist Medical Center. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

AH: study conception, design of the work, and critical revision of the article. MM: study conception, design of the work, interpretation of data, and drafting of the article. RR: data acquisition and critical revision of the article. WT: critical revision of the article. All authors gave final approval of the version to be published.

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Conflict of Interest: AH: Consultant/Honorarium/Scientific Advisor: Medtronic, Stryker, Penumbra, Genentech, Viz, Balt, Microvention, GE Healthcare, Scientia, and Cerenovus.

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Jet-Like Appearance in Angiography as a Predictive Image Marker for the Occlusion of Intracranial Atherosclerotic Stenosis

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Introduction: Identifying intracranial atherosclerotic stenosis-related occlusion (ICAS-O) in acute ischemic stroke has important clinical significance. Correct identification would help operators devise an optimal recanalization strategy. However, it is often hard to make accurate judgments in emergency situations before thrombectomy. Here, we propose a new image marker for ICAS-O based on the appearance of occluded vessels on baseline digital subtraction angiography.

Materials and Methods: We retrospectively reviewed patients with acute ischemic stroke who underwent endovascular therapy from August 2017 to February 2020 at our center. ICAS-O was identified by residual focal stenosis at occluded vessels after successful recanalization. The jet-like appearance was defined as appearance of pencil-tip-like or line-linked contrast filling of the occlusion edge. A non-jet-like appearance was defined as appearance of convex, concave, or flat edge contrast filling. The proportion of jet-like appearance in different occlusion etiologies and occluded vessels was determined. The diagnostic value of jet-like appearance for ICAS-O was assessed.

Results: A total of 164 patients diagnosed with ICAS-O were enrolled. Jet-like appearance was detected in 34 (20.7%) patients with younger age (68.0 ± 11.9 years vs. 62.7 ± 10.2, $p = 0.019$), patients with lower baseline NIHSS scores (16.6 ± 7.1 vs. 12.4 ± 6.5, $p = 0.002$) and patients with more past stroke or transit ischemic events (31.4 vs. 13.2%, $p = 0.011$). ICAS-O rate was higher in the jet-like appearance group (82.9 vs. 8.5%, $p < 0.001$), and rescue methods were more frequently used (74.3 vs. 12.4%, $p < 0.001$). Jet-like appearance was mostly found at the origin of the middle cerebral artery (MCA) (44.1%), followed by the first segment trunk of MCA (20.6%) and internal carotid artery (ICA) supraclinoid (11.8%). Logistic regression showed that jet-like appearance was independently associated with ICAS-O [OR 180.813, 95% CI (17.966, 1,819.733), $p < 0.001$]. The sensitivity, specificity, and accuracy values for predicting ICAS-O was 96, 78, and 83%.

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Jin X, Shi F, Chen Y, Zheng X and Zhang J (2020) Jet-Like Appearance in Angiography as a Predictive Image Marker for the Occlusion of Intracranial Atherosclerotic Stenosis. Front. Neurol. 11:575567. doi: 10.3389/fneur.2020.575567

Conclusion: The jet-like appearance on the angiogram was an image marker for ICAS-O, with relatively high sensitivity and specificity, which could help operators predict underlying intracranial atherosclerotic stenosis in a timely manner and choose the optimal intervention strategy during endovascular therapy.

Keywords: acute ischemic stroke, large vessel occlusion, endovascular therapy, intracranial atherosclerotic stenosis, image marker, diagnostic accuracy

INTRODUCTION

Endovascular revascularization therapy has become the first line treatment for acute ischemic stroke (AIS) with large vessel occlusion (LVO). With modern endovascular techniques, patients can achieve over 80% successful revascularization (1–7). However, good clinical outcomes represent ∼50%. Clinical outcome is affected by many factors, including time from onset to recanalization, ischemic core volume, collateral compensation status, and post-procedural management. Rapid recanalization is the critical factor for achieving a favorable outcome. In this regard, one of the most important modifiable factors is to set up an optimal endovascular strategy.

Embolic occlusion (Emb-O) and intracranial atherosclerotic stenosis occlusion (ICAS-O) are two main causes of AIS with LVO, and both of them are treated with endovascular therapy in acute settings. Unlike the case with Westerners, ICAS-O is a more common cause of AIS in Asians (8). The Chinese IntraCranial AtheroSclerosis study group determined that the prevalence of ICAS defined as a ≥50% reduction in diameter on magnetic resonance angiography was 46.6% among hospitalized AIS patients (9). Another study demonstrated that at least 25% of cases of Chinese patients with anterior circulation AIS with LVO who received mechanical thrombectomy were diagnosed as ICAS-O (10). ICAS-O leads to more cases of thrombectomy failure (11–14). The underlying stenosis cannot be solved by stent retrieval; however, the irritated endothelium after thrombectomy would result in instant spontaneous re-occlusion. Accordingly, more than one third of the cases of ICAS-O ended up with rescue technique during endovascular procedure (14), including intraarterial, or intravenous GP IIb/IIIa inhibitor infusion (11, 15), balloon angioplasty, stent retriever detachment, or another stent implantation (13, 16, 17). Thus, it is very important to differentiate ICAS-O from Emb-O before starting the procedure.

A variety of methods can be used to differentiate ICAS-O from Emb-O. Clinical history includes progressive or fluctuating symptoms, low median baseline National Institutes of Health Stroke Scale (NIHSS) score, male, hypercholesterolemia, smoking; posterior circulation involvement may possibly support ICAS-O (16, 18, 19), while atrial fibrillation strongly suggests Emb-O. Imaging features include hyper-density vessel sign on non-contrast CT scan (NCCT) (20) and susceptibility vessel sign on susceptibility-weighted magnetic resonance imaging, which are specific indications of Emb-O (21). However, the identification of ICAS-O before thrombectomy is still challenging, especially in patients with complicated clinical situations. Hereby, we propose a new method simply based on the angiographic appearance of occlusion artery with high specificity for identification of ICAS-O.

MATERIALS AND METHODS

Design and Population

We retrospectively reviewed cases of patients with AIS who underwent endovascular therapy (EVT) from August 2017 to February 2020 at our center. Patients were initially assigned to NCCT and CT angiography (<6 h) or CT perfusion (from 6 to 24 h) before EVT, based on the time from the onset of symptoms. The criteria for patients to receive EVT at our center were (1) age ≥18 years; (2) baseline NIHSS score ≥6; (3) large intracranial artery occlusion including distal internal carotid artery (ICA), first and second segment of middle cerebral artery (MCA), first segment of anterior cerebral artery (ACA), fourth segment of vertebral artery (VA), and basilar artery (BA); (4) baseline Alberta Stroke Program Early CT score (ASPECTS) ≥6, for symptoms onset within 6 h; demonstration of potentially salvageable brain tissue on CT perfusion (mismatch ratio of ≥ 1.2, absolute mismatch volume of >10 mL), as well as ischemic core <70 mL for symptoms onset more than 6 h.

First, an angiography of the target artery was used to evaluate the occluded appearance. We excluded patients without an angiography or if a clear angiography was not available prior to the thrombectomy, and patients with tandem disease or extracranial artery occlusion, which prevents visualization of the intracranial occlusion. Patients with failure of recanalization were excluded as well, since the etiology of the occlusion could not be identified. This study was approved by an institutional review committee and all participants provided their informed consent.

Protocol for Cerebral Digital Subtraction Angiography

Simplified digital subtraction angiography (Philips FD-20, Amsterdam, Netherland or Artis zee III biplane, Siemens, Erlangen, Germany) was performed before EVT. Patients had an aortic arch PA angiogram followed by target artery PA and lateral angiograms because LVO was already identified by CT angiography (CTA) or CT perfusion (CTP). An aortic angiogram was performed with 30 ml contrast administered at 20 ml/s under 600 psi. A target artery angiogram was performed with 8 ml contrast administered at 4 ml/s for ICA and 6 ml contrast administered at 3 ml/s for vertebral artery under 300 psi. DSA images were acquired at 6 frames per second using neurointervention software.

Image Analysis and Classification of the Etiology

Jet-like appearance was defined as the appearance of pencil-tip-like or line-linked contrast filling on the occlusion edge on DSA imaging (**Figures 1A**, **2A–F**). The tapering segment was either near the vessel wall or in the middle of the vessel lumen. A non-jet-like appearance was defined as visualization of convex, concave, or flat edge contrast filling (**Figures 1B–D**, **2G–L**).

Two neuroradiologists with at least 10 years of experience, blinded to the clinical information, retrogradely reviewed the initial angiograms and classified the appearance of the occlusions. Another neuroradiologist would determine the classification if a consensus could not be reached.

Occlusion etiology was classified as intracranial atherosclerotic stenosis occlusion (ICAS-O) or Emb-O. ICAS-O was identified by residual fixed stenosis >70% or lower-degree stenosis with a tendency for re-occlusion or flow impairment during the procedure (13). Emb-O was identified by a lack of fixed focal stenosis after successful recanalization, or temporary stenosis that recovered in angiography 20 min later without angioplasty (13).

Statistics

The analysis was performed using the SPSS 24.0 statistical program (IBM SPSS, Armonk, NY). Continuous values are expressed as median and inter-quartile range (IQR), and categorical values are expressed as counts and percentage. Continuous variables were compared with the Mann–Whitney test, and categorical variables were compared using the Chi square test or Fisher's exact test. Statistical significance was defined as $p < 0.05$ and variables with $p < 0.1$ on univariate analysis were included in logistic regression. Diagnostic parameters, including sensitivity, specificity, and accuracy value, were calculated to assess the value of the jet-like appearance when differentiating the etiology. The kappa statistic value was used to assess intraobserver and interobserver variability when assessing the jet-like appearance.

RESULTS

A total of 249 patients with LVO underwent thrombectomy during this period. After reviewing the images, 66 patients were excluded (49 patients did not have clear angiogram images, 13 patients had tandem disease, and 4 patients suffered severe intracranial hemorrhage and thrombectomy were ceased). A total of 183 patients were finally analyzed, 27 (14.7%) patients were under local anesthesia due to severe cardiac or pulmonary disease, 164 patients (93 males, mean age 66.8 ± 11.8 years, mean initial NIHSS 15.7 ± 7.2) achieved successful recanalization (final mTICI ≥ 2b). Among them, 42 (25.6%) suffered internal carotid artery occlusion, 98 (59.8%) had MCA occlusion, 18 (11.0%) had vertebral BAs occlusion, 40 (24.4%) were identified as ICAS-O, and 124 (75.6%) were identified as Emb-O.

Example illustrations of patients with and without jet-like appearance were shown in **Figure 1**. Jet-like appearance was observed in 34 (20.7%) patients. The intraobserver and interobserver kappa values for detection of jet-like appearance were 0.889 and 0.847, respectively.

As **Table 1** shows, patients with jet-like appearance were younger (68.0 ± 11.9 years vs. 62.7 ± 10.2, $p = 0.019$), and had lower baseline NIHSS scores (16.6 ± 7.1 vs. 12.4 ± 6.5, $p = 0.002$). A history of past stroke and transient ischemic attack was more frequent in patients with jet-like appearance ($p = 0.011$), and atrial fibrillation was more common in patients without jet-like appearance ($p = 0.001$). Stroke etiology was distributed differently in the two groups. Cardiac embolism was the most common etiology for patients without jet-like appearance. For patients with jet-like appearance, 71.4% were classified as having large artery atherosclerosis. The ICAS-O rate was higher in the jet-like appearance group as well (82.9 vs. 8.5%, $p < 0.001$), and rescue methods were more frequently used, including intraarterial tirofiban infusion, balloon angioplasty, and stent placement ($p < 0.001$).

The proportion of jet-like appearance and ICAS-O differed according to the occlusion site (**Table 2**). Jet-like appearance was mostly found at the origin of the MCA (44.1%), followed by the first segment trunk of the MCA (20.6%) and the supraclinoid of the ICA (11.8%). There was no jet-like appearance in the

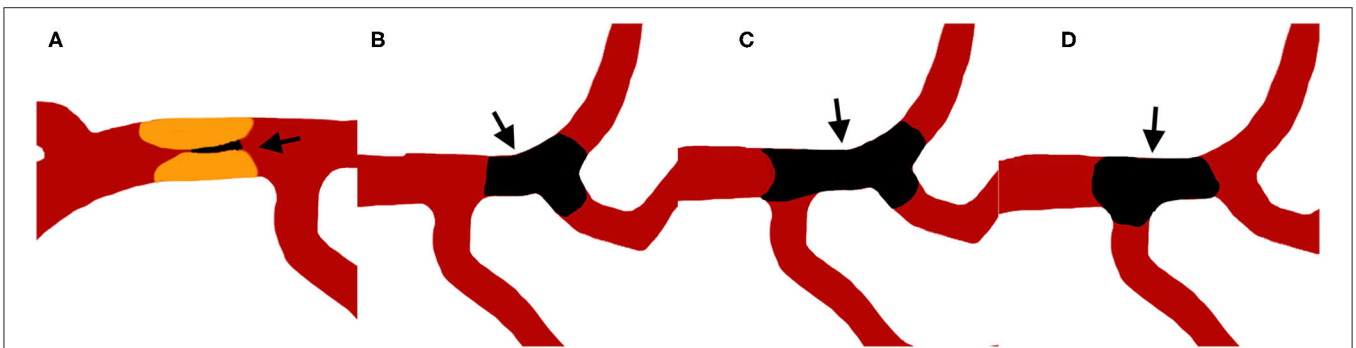

FIGURE 1 | Illustration of jet-like appearance and non-jet-like appearance, arrows point to the thrombus. **(A)** shows a typical jet-like appearance of intracranial artery stenotic occlusion. **(B–D)** shows non-jet-like appearance of embolic occlusion with flat **(B)**, convex **(C)**, and concave **(D)** appearance at the proximal edge of the occluded vessel.

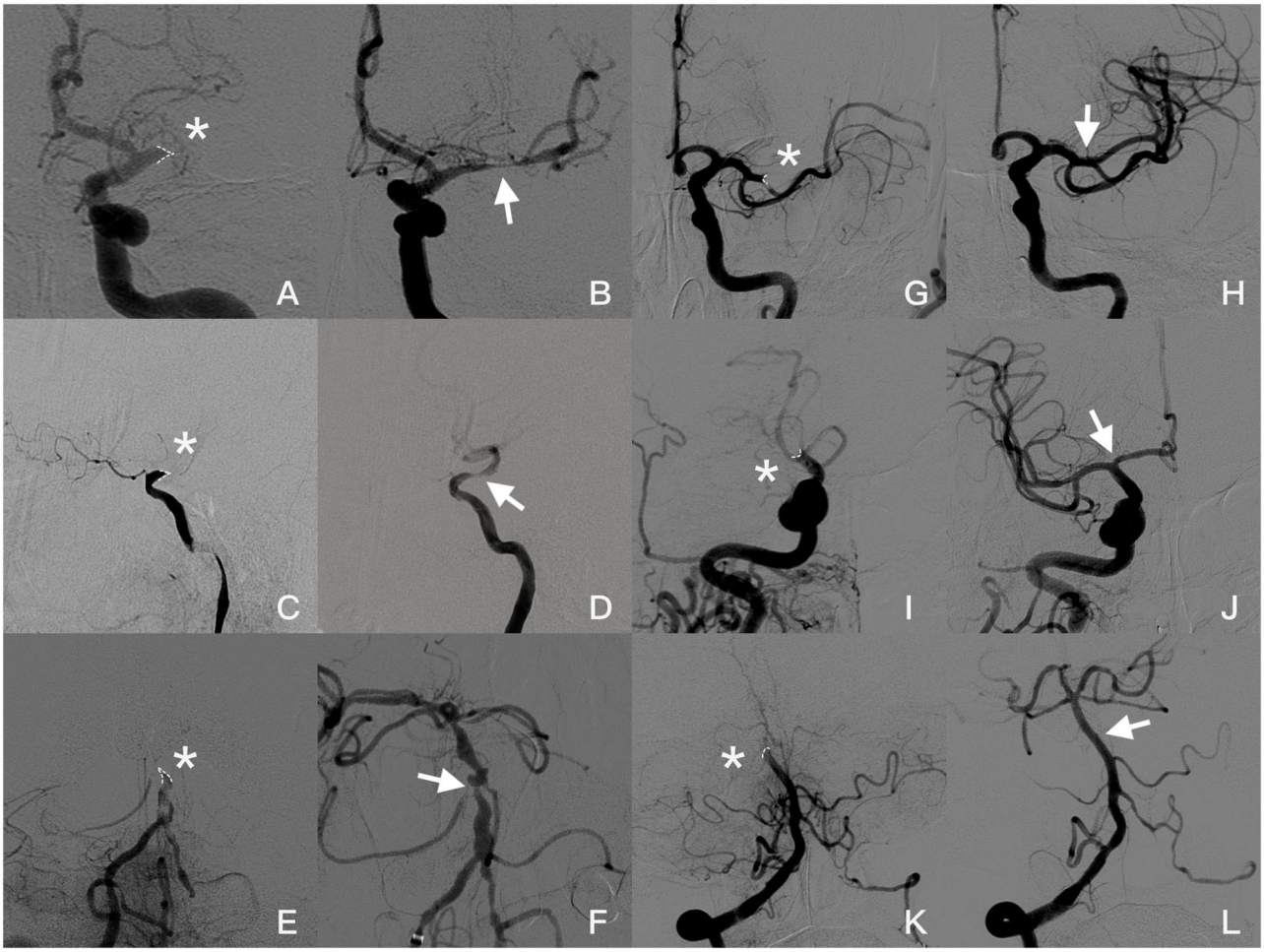

FIGURE 2 | Angiogram images of a patient with jet-like appearance **(A–F)**: **(A,B)** Jet-like appearance at the origin of the left MCA in late arterial phase (asterisk). Severe stenosis (arrow) was seen in the MCA after first attempted thrombectomy. **(C,D)** Occlusion at supraclinoid of ICA presented as a jet-like appearance (asterisk). After the small-volume thrombus was removed, severe stenosis is shown (arrow) after the ophthalmic artery was taken off and forward blood flow was significantly affected. **(E,F)** Basilar artery occluded at AICA take-off (asterisk). Severe stenosis was seen after two thrombectomy attempts; however, blood flow speed was normal, and no further angioplasty was required. Angiogram images of patients without jet-like appearance **(G–L)**. **(G,H)**: Concave appearance of the occluded left MCA (asterisk), and post-thrombectomy angiography showed recanalization of the superior branch of MCA without focal stenosis. **(I,J)** Occlusion at the end of ICA with concave appearance (asterisk). Both MCA and ACA were recanalized without focal stenosis (arrow). **(K,L)** Appearance of top of basilar artery occluded (asterisk) and recanalized (arrow) in a female with atrial fibrillation. Occlusion appearance in angiography was figured out by dotted line.

petro-cavernous segment of the ICA. In comparison, the origin of the MCA (35.0%), first segment trunk of the MCA (25.0%) and supraclinoid of the ICA (10.0%) were the most common sites for ICAS-O.

Thus, age, baseline NIHSS score, atrial fibrillation, history of stroke/TIA, and jet-like appearance were included in a binary logistic regression model to select predictors for ICAS-O. Binary logistic regression analysis (**Table 3**) revealed that jet-like infusion sign was independently associated with ICAS-O, after adjusting for age, baseline NIHSS score, atrial fibrillation, and history of stroke/TIA [OR 180.813, 95% CI (17.966, 1,819.733), $p < 0.001$].

Diagnostic indices are shown in **Table 4**. The sensitivity, specificity, and accuracy values for the jet-like infusion sign for predicting ICAS-O were 73, 95, and 90%, respectively, for all patients with ICAS-O. The accuracy of predicting ICAS-O at the origin of the MCA, and supraclinoid of the M1 trunk and ICA was 96, 78, and 83%, respectively.

DISCUSSION

Here, we proposed that the jet-like appearance at an occluded artery on angiography is an independent image marker for ICAS-O. Out of all patients with LVO, jet-like appearance was detected in 73% of patients with ICAS-O, and exhibited 95% specificity for ICAS-O, suggesting that the jet-like appearance is useful for predicting ICAS-O before thrombectomy.

TABLE 1 | Comparison of baseline characteristics between patients with and without Jet-like appearance.

Variables	No jet-like appearance ($n = 129$)	Jet-like appearance ($n = 35$)	*p*-value
Age, year	68.0 ± 11.9	62.7 ± 10.2	0.019
Male, *n* (%)	69 (53.4%)	24 (68.6%)	0.110
Baseline NIHSS score	16.6 ± 7.1	12.4 ± 6.5	0.002
ASPECTS, median (IQR)	8 (6–9)	8 (7–9)	0.124
Past medical history	17 (13.2)	11 (31.4)	0.011
Stroke/TIA, *n* (%)			
Atrial fibrillation, *n* (%)	75 (58.1)	9 (25.7)	0.001
Hypertension, *n* (%)	85 (65.9)	25 (71.4)	0.536
Diabetes, *n* (%)	22 (17.1)	8 (22.9)	0.431
Hyperlipidemia, *n* (%)	26 (20.2)	6 (17.1)	0.690
TOAST etiologies			<0.001
LAA, *n* (%)	10 (7.8)	25 (71.4)	
CE, *n* (%)	90 (69.8)	5 (14.3)	
Other, *n* (%)	4 (3.1)	0 (0)	
UE, *n* (%)	25 (19.4)	5 (14.3)	
Occlusion type			<0.001
ICAS-O, *n* (%)	11 (8.5)	29 (82.9)	
Emb-O, *n* (%)	118 (91.4)	6 (17.1)	
Door-Puncture time (min)	147.5 ± 61.4	153.8 ± 60.4	0.605
Puncture-Recanalization time (min)	74.9 ± 53.0	84.2 ± 65.7	0.424
Rescue methods			<0.001
None, *n* (%)	113 (87.6)	9 (25.7)	
IA Tirofiban, *n* (%)	4 (3.1)	3 (8.6)	
Balloon, *n* (%)	3 (2.3)	8 (22.9)	
Stent, *n* (%)	9 (7.0)	15 (42.9)	
SIH, *n* (%)	9 (7.0)	1 (2.9)	0.366
90d mRS, median (IQR)	3 (1–5)	2 (1–5)	0.414

NIHSS, National Institutes of Health Stroke Scale; LAA, large artery atherosclerosis; CE, cardiac embolism; UE, undetermined etiology; ICAS-O, intracranial atherosclerotic stenosis occlusion; Emb-O, embolic occlusion; IA, intraarterial; SIH, symptomatic intracranial hemorrhage; mRS, Modified Rankin Scale. Data was expressed as mean ± standard deviation for continuous variables.

TABLE 2 | Proportion of jet-like appearance and ICAS-O at different occlusion sites.

Occlusion site	Jet-like appearance ($n = 34$)	ICAS-O ($n = 40$)	Emb-O ($n = 124$)
ICA, *n* (%)			
Supraclinoid	4 (11.8)	4 (10.0)	19 (15.3)
Petro-cavernous	0 (0)	2 (5.0)	15 (12.1)
MCA, *n* (%)			
Origin	15 (44.1)	14 (35.0)	8 (6.5)
M1 trunk	7 (20.6)	10 (25.0)	26 (21.0)
M1 branch	3 (8.8)	3 (7.5)	26 (21.0)
VBA, *n* (%)			
VA after PICA	2 (5.9)	2 (5.0)	0 (0)
BA origin	1 (2.9)	1 (2.5)	1 (0.8)
BA after AICA	2 (5.9)	2 (5.0)	11 (8.9)
Other vessels, *n* (%)	0 (0)	0 (0)	18 (15.2)

ICAS-O, intracranial atherosclerotic stenosis occlusion; Emb-O, embolic occlusion; ICA, internal carotid artery; MCA, middle cerebral artery; M1, first segment of middle cerebral artery; VBA, vertebral basilar artery; VA, vertebral artery; PICA, posterior inferior cerebellar artery; BA, basilar artery; AICA, anterior inferior cerebellar artery.

TABLE 3 | Univariant and multivariant logistic regression of predictors for ICAS-O.

Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age	0.946 (0.916, 0.977)	1.019 (0.957, 1.084)
Baseline NIHSS score	0.846 (0.785, 0.912)	0.826 (0.718, 0.949)
Atrial fibrillation	0.061 (0.020, 0.183)	0.011 (0.001, 0.142)
History of stroke/TIA	2.893 (1.229, 6.810)	4.638 (0.620, 34.686)
Jet-like appearance	51.848 (17.705, 151.835)	180.813 (17.966, 1,819.733)

ICAS-O, intracranial atherosclerotic stenosis occlusion; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; OR, odds ratio; CI, confidence interval.

In our study, 24.4% of patients were determined as having ICAS-O, which was consistent with previous studies (10, 22). Patients with ICAS-O presented the same features as other studies, like younger age (17) and lower baseline NIHSS scores (16, 19). Furthermore, a history of stroke or TIA was more common among ICAS-O patients, while atrial fibrillation was more common in Emb-O patients.

Patients with jet-like appearance and ICAS-O shared similar characteristics of their medical histories and baseline NIHSS scores. After adjusting for other confounding factors, this study demonstrated that jet-like appearance before thrombectomy strongly indicated ICAS-O. Furthermore, the predictive value of jet-like appearance differed according to the occlusion site. Jet-like appearance was easily found where the occlusion occurred distal to a large branch take-off, such as the ICA supraclinoid (where ophthalmic artery take-off was performed), origin of the MCA (where ACA take-off was performed), or the fourth segment of the vertebral artery (where posterior inferior cerebellar artery take-off was performed). For occlusions occurring proximal to a large branch take-off, contrast agent was insufficient to reach the occlusion edge. This could explain why jet-like appearance was never seen in our study at the petro-cavernous segment of the ICA, where atherosclerotic stenosis frequently occurs. It also explained the low sensitivity of jet-like appearance in the trunk of the MCA first segment.

Occlusion caused by intracranial arterial dissection (ICAD) sometimes demonstrates a jet-like appearance and would be difficult to discriminate. "Intimal flap" and "double lumen" are the most characteristic findings associated with ICAD (23). However, these findings are visible in only a few cases. The "pearl and string sign" and retention of contrast media in the false lumen are often seen in conventional cerebral angiographies of ICAD. Furthermore, whether or not a fixed focal stenosis by single-stent retriever deployment in the occlusion can be the criterion for differentiating ICAD from ICAS-O.

Stent retrievers and contact aspiration devices both demonstrate significant efficacy as first line methods for mechanical thrombectomy (24). However, both are primarily

TABLE 4 | Diagnostic testing of Jet-like appearance for predicting ICAS-O.

	Jet-like infusion sign, n	Sensitivity 95% CI	Specificity 95% CI	Positive predictive value, 95% CI	Negative predictive value, 95% CI	Accuracy
All patients ($n = 164$)	34	0.73 (0.56, 0.85)	0.95 (0.90, 0.98)	0.83 (0.68, 0.92)	0.92 (0.87, 0.95)	0.90 (0.84, 0.94)
MCA origin occlusion ($n = 22$)	15	1.00 (0.77, 1.00)	0.87 (0.47, 1.00)	0.93 (0.69, 0.99)	1.00	0.96 (0.77, 1.00)
M1 trunk ($n = 36$)	7	0.40 (0.12, 0.74)	0.88 (0.70, 0.98)	0.57 (0.26, 0.83)	0.79 (0.69, 0.87)	0.75 (0.58, 0.88)
ICA supraclinoid ($n = 23$)	4	0.50 (0.07, 0.93)	0.89 (0.67, 0.98)	0.17 (0.05, 0.39)	0.50 (0.16, 0.84)	0.83 (0.61, 0.95)

ICAS-O, intracranial atherosclerotic stenosis occlusion; MCA, middle cerebral artery; M1, first segment of middle cerebral artery; ICA, internal carotid artery.

designed for embolism occlusion rather than ICAS-O (7, 25, 26). Stent retriever thrombectomy often results in instant spontaneous re-occlusion due to subsequent thrombosis at the site of ICAS (11). On the other hand, contact aspiration seems less effective than stent retrievers for ICAS-O, resulting in a longer time from puncture to reperfusion, longer procedure duration, and a higher rate of switching to an alternative thrombectomy technique (27, 28). As mentioned above, ICAS-O often requires intraarterial or intravenous GP IIb/IIIa inhibitor infusion, emergent balloon angioplasty, and stenting (11, 15–17, 29). Intraarterial infusion of GP IIb/IIIa inhibitor tirofiban at the occlusion site may be a reasonable therapeutic option since the major components of thrombi *in situ* of ICAS are rich in platelets and fibrin. Recent studies have shown that both intracranial angioplasty/stenting and intraarterial infusion of a glycoprotein IIb/IIIa inhibitor are effective and safe in the treatment of AIS patients with ICAS-O (30). In ACTUAL study, investigators found that patients with acute anterior ICAS-O, who received primary angioplasty treatment, showed favorable independent outcomes at 90 days and lower rates of asymptomatic intracranial hemorrhage compared to patients who received primary stent retriever thrombectomy (31). All this evidence suggest that the optimal early endovascular strategy for ICAS-O is quite different than that for Emb-O. Thus, early identification of ICAS-O may help operators modify the treatment approach before initiating intervention. Operators should reduce thrombectomy passes and switch to rescue methods in a timely manner once ICAS-O is determined. However, it is difficult for operators to make accurate judgment in emergent situations due to incomplete clinical information. Coexistence of ICAS and atrial fibrillation further increases the difficulty. Deng et al. (10) determined that 8.6% of anterior circulation LVO patients who received mechanical thrombectomy had both of them. In our study, the corresponding ratio was 1.8% (3/164). Yet, all 3 patients showed jet-like appearance and were classified as ICAS-O, indicating that jet-like appearance can predict ICAS-O effectively, even in complex clinical situations.

Occlusion type is a highly specific image marker for differentiating ICAS-O from Emb-O. Truncal type occlusion during thrombectomy post-stent deployment had 87.4% specificity to predict fixed focal stenosis (32). Microcatheter first-pass effect, a string-like blood flow observed in angiography after the microcatheter is retrieved from the occlusive vessel segment, indicates ICAS-O (33). First-pass effect can accurately predict ICAS-O in 88.5% of patients with LVO (33). These methods have a few limitations despite their high specificity. The main problem is that additional manipulations are required to determine the occlusion etiology; for example, microcatheter angiography beyond the occlusion, post-deployment angiography, or repeated microcatheter movement in the occlusion. All these manipulations implied the risk of irritating the inflamed plaque in ICAS-O (34). Besides, occlusion type practically depends on stent-through blood flow and cannot be determined in patients undergoing non-stent thrombectomy. In comparison, the jet-like appearance can help interventionists identify ICAS-O before the procedure, so that they can choose the most appropriate frontline instruments and strategies. Occlusion type based on CTA was another applicable method for determining ICAS-O before thrombectomy. However, conventional CTA imaging may vary depending on whether the scan phase is arterial, arteriovenous, or venous-weighted (35, 36). Unequal CTA quality would make ICAS-O identification difficult. Multiphase CTA or CTP could resolve this shortcoming but is not available at most centers (3, 37–40).

Our study has several limitations. Firstly, this study was performed at a single stroke center, with a relatively small number of ICAS-O patients. Secondly, 49 patients were excluded because of a lack of clear angiogram images. This accounts for 26.5% and may limit the level of rigor of the data. Among them, 35 patients did not undergo a first angiography, but a roadmap was available. A roadmap often shows images of the vessels in early arterial phase for clear navigation, while occlusion edges on DSA imaging can only be observed clearly in the late arterial phase due to decreased blood flow motivation. Furthermore, a roadmap is often not available for patients undergoing local anesthesia. Therefore, in our opinion, a clear angiography including complete arterial and venous phase would be crucial for detecting jet-like appearance. The main drawback of jet-like appearance is that it relies on the occlusion site and hemodynamic status. Jet-like appearance is rarely shown in the petro-cavernous segment of the ICA or the origin of the BAs. Therefore, jet-like appearance is not an appropriate marker for predicting ICAS-O in these areas. Finally, a larger sample size and multicenter study are required to verify the predictive value of jet-like appearance for ICAS-O.

CONCLUSION

The present study proposed jet-like appearance in angiogram as an image marker for ICAS-O, with relatively high

sensitivity and specificity. This could help operators predict underlying intracranial atherosclerotic stenosis in a timely manner and choose the best intervention strategy during thrombectomy.

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 Sir Run Run Shaw Hospital Ethics Committee School of Medicine, Zhejiang 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

JZ and XJ proposed the concept and designed the study. XJ, YC, and XZ performed data collection and image analysis. FS and XJ performed statistical analysis. XJ and JZ drafted the paper, and JZ approved the final paper for publication. All authors contributed to the article and approved the submitted version.

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Risk of Recurrence of Symptomatic Intracranial Atherosclerosis in Posterior Circulation Seen to Be Higher Than That in Anterior Circulation in Long-Term Follow-Up

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Background: Intracranial atherosclerotic stenosis (ICAS) is an important cause of ischemic stroke. In Asians, intracranial atherosclerotic disease leads to 33–50% of ischemic events. At present, treatment with medication vs. endovascular therapy (EVT) for symptomatic ICAS (sICAS) patients is still debatable. The clinical prognosis of patients who are not completely free of stroke symptoms despite regular medication and are not eligible for EVT for various reasons, is not yet investigated.

Aim: To report the long-term recurrence rate of stroke in a cohort of symptomatic ICAS patients who intended to undergo EVT upon admission but could not for various reasons after digital subtraction angiography (DSA) evaluation.

Method: This is a retrospective analysis of consecutive sICAS patients in a single center from January 1, 2016 to August 31, 2017 who underwent DSA assessment alone and were not eligible for further EVT. Demographic information, risk factors related to cerebrovascular disease, clinical comorbidities, medication, imaging data, and long-term outcomes were reported.

Results: A total of 218 patients were included in the study; 42 (19.2%) patients had recurrence of stroke/transient ischemic attack (TIA) at the 1-year follow up. Patients were divided into two groups according to lesions in anterior circulation (n = 120) or posterior circulation (n = 98). There was a higher stroke/TIA recurrence rate in the posterior circulation than anterior circulation group (25.5 vs. 14.2%, p = 0.035). Given the advanced age, higher prevalence of coronary heart disease, larger stenosis length, and poorer collateral circulation, the posterior circulation group showed a higher risk of recurrent stroke/TIA and death than the anterior circulation group [HR = 3.092, 95% CI (1.335–7.164), p = 0.0084], after adjusting for all confounding factors in the COX regression model. Kaplan–Meier analysis showed that sICAS recurrence and mortality risk in the posterior circulation group was consistently higher than that in the anterior circulation group (log-rank-test, p = 0.033).

Conclusions: Patients with posterior circulation sICAS have higher recurrence risk than those with anterior circulation managed with medication alone. Further, posterior circulation lesion is an independent risk factor for recurrence in sICAS patients.

Keywords: symptomatic intracranial atherosclerosis (sICAS), posterior circulation, recurrent stroke/TIA, medication, long-term outcomes

INTRODUCTION

Symptomatic intracranial atherosclerosis (sICAS) is one of the main causes of ischemic stroke in China and refers to the stenosis of one or more intracranial arteries with a stenosis rate of 50–99%, resulting in insufficient blood supply and transient or persistent neurological impairment, including transient ischemic attack (TIA) and ischemic stroke (1). In fact, the severity of vascular lesions in patients with ischemic cerebrovascular disease is not consistent with the clinical manifestations, as some patients still have a high risk of stroke recurrence after intensive medical treatment or endovascular therapy (EVT). In the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, the 1-year recurrent rate of ischemic stroke for patients with a stenosis ≥50% was up to 15% (aspirin group) and 14% (warfarin group), and the respective 2-year recurrent rates were 20.4 and 17% (2). A prospective study of symptomatic atherothrombotic intracranial stenoses (GESICA) study indicated that the 2-year stroke recurrence rate of sICAS patients treated with drugs alone was 38.2% (3). In China, the prevalence of intracranial atherosclerotic stenosis (ICAS) was 46.6% (4), with a high risk of stroke recurrence. Nowadays, the treatment for patients with sICAS comprises medication and EVT, pre-dominantly including balloon dilatation and stent implantation. However, the published outcomes of two vital trials—SAMMPRIS (5) and VISSIT (6)—that compared the efficacy and safety between medication and EVT highlighted an overwhelming preference for medication in clinical practice (7). Recently, the lower peri-procedural complication rate reported in the Wingspan Stent System Post-market Surveillance (WEAVE) trial seemed to rectify the benefit of EVT for sICAS patients (8). The guidelines recommended medication as the primary treatment for sICAS patients, then asked neurointerventionalists to select "proper" patients for further EVT as an alternative, such as those with severe stenosis, hypoperfusion, or poor collateral circulation and those in whom medication was ineffective (9). Considering that more individualized treatment is required for sICAS patients, neurointerventionalists are urged to identify the true prognosis and recurrence risk of sICAS, especially in those who are not completely free of stroke symptoms despite regular medication and who do not qualify for EVT either.

Therefore, the aim of our study is to report the long-term recurrent rate of stroke in a cohort of sICAS patients who intended to undergo EVT upon admission but could not for various reasons after digital subtraction angiography (DSA) evaluation. We mainly compared the different characteristics and prognosis between sICAS patients with lesions in the anterior and posterior circulation, as this is still poorly investigated.

MATERIALS AND METHODS

Study Design and Patients

This is a single-center, retrospective analysis of consecutive patients with sICAS who underwent DSA evaluation alone between January 1, 2016 and August 31, 2017. Demographic data, clinical characteristics, and imaging data were available in a prospectively developed local database. Patients with acute ischemic stroke, routine reexamination after cerebrovascular stenting, and concomitant extracranial artery stenosis and non-atherosclerosis stenosis were excluded. Those who underwent EVT within 1 year without new stroke/TIA onset after enrollment were also exclude from our analysis. A flow chart of patient screening is presented in **Figure 1**. Missing data were obtained from the patients' medical records. The study was approved by the institutional review board of the institution. All patients enrolled in the study signed informed consent for the procedure.

Procedure

Because most patients aim to seek further EVT upon admission, the DSA procedure was focused on evaluating the feasibility and peri-procedural complication rate based on magnetic resonance angiography (MRA) and/or computed tomography angiography (CTA). At the same time, most patients had undergone intracranial CT perfusion (CTP) examination and had confirmed perfusion defects in the responsible lesions. Some patients also underwent high-resolution MRI examination of intracranial vessels to determine the existence of plaque and wall of responsible vessels.

All DSA procedures followed the standard guidelines and were performed by experienced interventionalists. The DSA evaluation parameters focused on the responsible lesions causing vascular stenosis and included lesion location, lesion length, degree of stenosis, angulation, calcification, eccentric plaques, antegrade blood flow, and collateral circulation in the ischemic area.

EVT was considered for patients with the following: (1) angiographically measured degree of ICAS ≥70%, which was associated with ischemic stroke or TIA; (2) distal hypoperfusion with an TICI (Thrombolysis in Cerebral Ischemia Scale) score of 0-2a; and (3) poor collaterals with an American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASTIN/SIR) Collateral Flow Grading System score of <3.

When select proper sICAS patients to EVT, surgical indication, technical feasibility, and risk of peri-procedural complications are the main concern for neurointerventionalists.

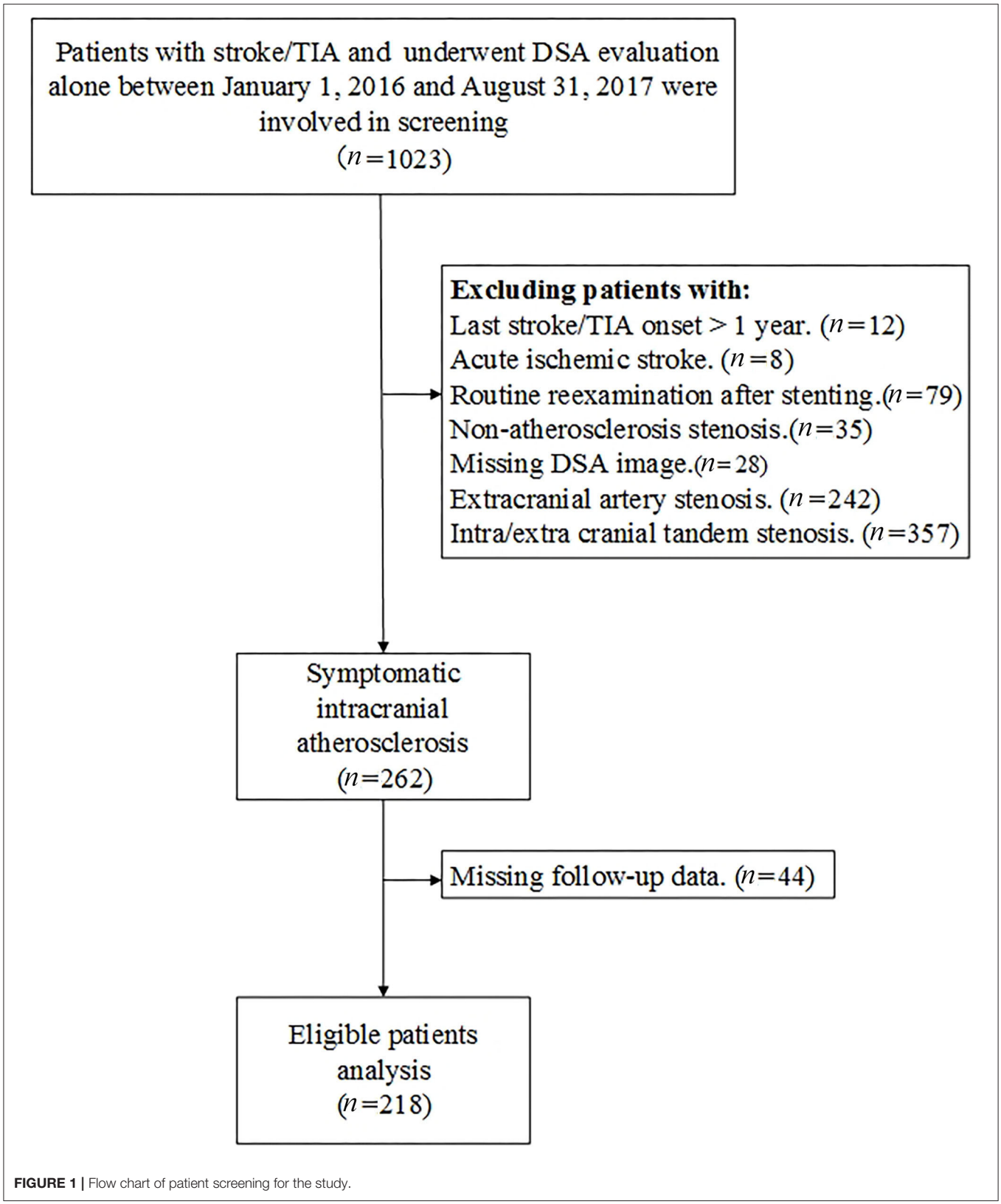

FIGURE 1 | Flow chart of patient screening for the study.

In our center, we thought that stenosis with severe atherosclerotic plaque, complete occlusion, severe tortuous artery, stenosis lesion longer than 10 cm, multiple stenosis and abundant perforating vessels near the lesion vessels, bleeding tendency or severe coagulation dysfunction would increase the risk of peri-procedural complications. We first judge whether a sICAS patient

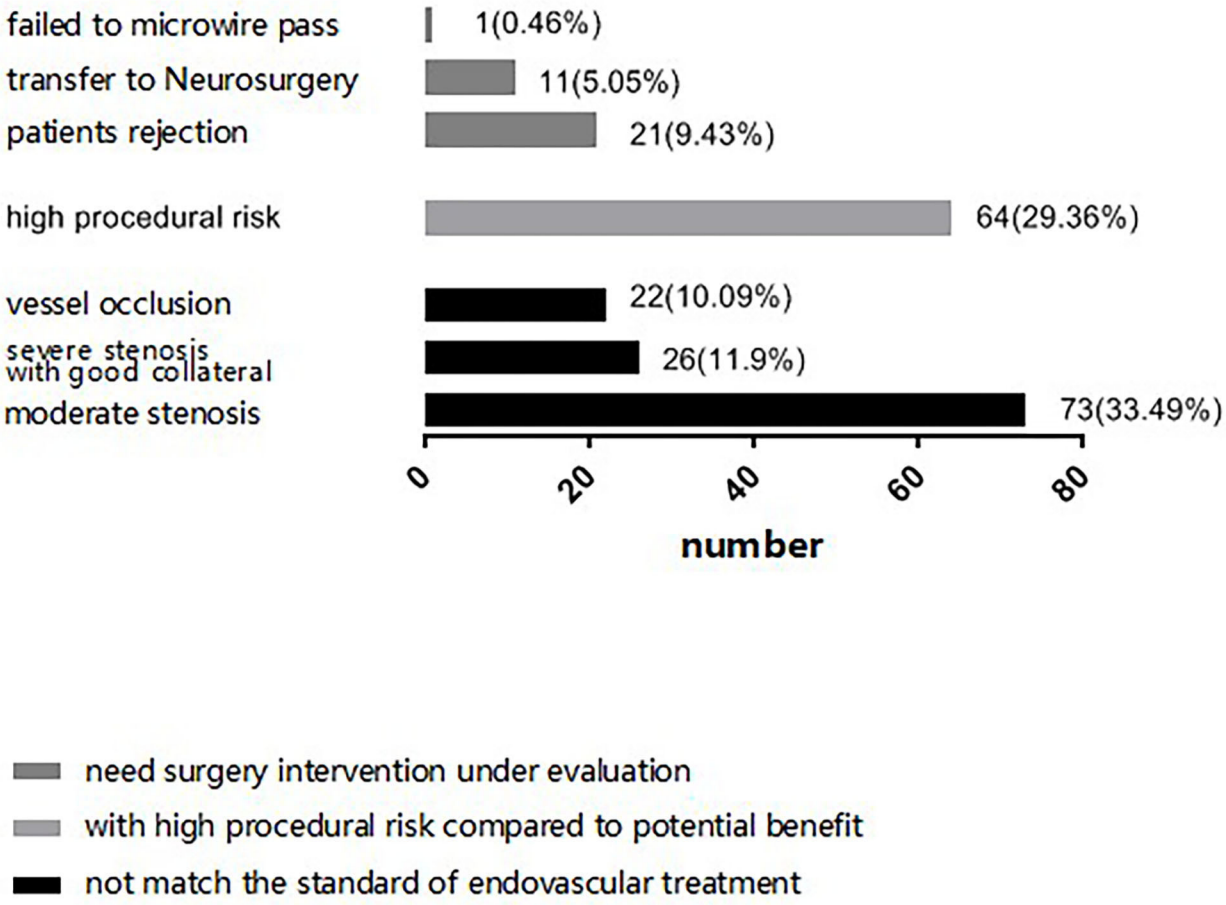

FIGURE 2 | Various reason of failing to further endovascular treatment.

has an indication of EVT, if yes, then assess technical feasibility, risk, and potential benefit. However, there were several patients rejected further EVT for economic distress although they were recommended to EVT by neurointerventionalists. And some patients were transferred to neurosurgery clinic because of failing to microwire pass or the condition of the stenosis distal vascular bed is poor. The final decision regarding further EVT depended on neurointerventionalists' evaluation and recommendation, as well as patients' and their family's preferences. The three situations in which patients were not eligible to receive further EVT are detailed in **Figure 2**.

Peri-Procedural Medications

All patients took at least one kind of antiplatelet drug, including aspirin (100 mg/day) and/or clopidogrel (75 mg/day) for more than 1 week after the onset of ischemic stroke or TIA, and other long-term oral drug therapy for individual complications. At discharge, all patients were re-recommended to adjust the antiplatelet drug dose according to Essen Stroke Risk Score (ESRS) or ABCD2 score and thromboelastogram (TEG) results, for long-term secondary prevention. The type and dose of statins were selected according to individual conditions and lipoprotein metabolism level. It was recommended that the target value of blood pressure be <140/90 mmHg, the target value of glycosylated hemoglobin (HbA1C) be lower than 7%, the target value of low-density lipoprotein cholesterol (LDL-C) be lower than 1.8 mmol/L. At the same time, we also reminded patients regarding health management which included quitting smoking, losing weight, and performing appropriate physical activity.

Follow-Up

Patients were followed-up at 3 months, 6 months, and 1 year after the procedure by means of clinic and telephone visits

by the interventionalist. In the outpatient clinic, the doctor asked the patient whether there were any new ischemic events during the visit period, then asked in detail the symptoms, duration and relief of neurological deficit. The patients took CTA and/or MRA for cerebrovascular assessment. For those patients relieved within 24 h who complaint with same symptom as initial ischemic onset or related to the symptomatic stenotic artery, we concluded it a recurrent TIA. We defined stroke as an outcome event mainly on the basis of symptom and imaging of patients. When the patient's symptom got worse with NIHSS added 4 points, or the patient had new symptoms, and there were indeed new lesions confirmed by imaging, we thought the patient had an outcome event. If a patient was suspected of having a stroke during the telephone interview, his or her imaging would be traced and collected. If the imaging was done in our center, it would be reviewed by interventionalists to be confirmed. If the imaging was done in other hospital, the patient would be required to provide the imaging or its report. All the images of patients with suspected stroke were available.

The medication, management of critical risk factors, and new clinical complications and treatment, any type of adverse events during the follow-up period were also recorded. The final follow-up was carried out in October 2018.

Imaging Review

All patients' DSA images were selected separately and reviewed by two interventionalists blinded to the patient details. Lesion location, length, degree of stenosis, TICI, and ASTIN/SIR grade were the main parameters. Stenosis was measured according to the standard of WASID. The consistency of both groups of measurement results was tested, and the results were reinterpreted by a third interventionalist in case of controversial interpretations.

Statistics

Baseline characteristics are presented as means, medians, or percentages based on types of variables. Univariate associations between demographic, clinical, procedural variables, and the 1-year recurrent stroke were evaluated. COX regression model was used for multivariate analysis, and the recurrence of stroke in anterior and posterior circulation was evaluated by Kaplan–Meier curve. Stepwise logistic regression analysis was used to assess the relationship between the factors and 1-year recurrent stroke in different groups. A multivariate model was constructed using variables with p-values < 0.1 in the univariate analysis by forward inclusion. The p-value for inclusion in the model was <0.05. All analyses were done in IBM SPSS V.24 (International Business Machines Corp).

RESULTS

A total of 218 patients were included in the analysis and were divided into two groups: anterior circulation sICAS ($n = 120$) and posterior circulation sICAS ($n = 98$). The degree of stenosis and type of ischemic type showed no significant intergroup differences. Compared with the anterior circulation, Patients in the posterior circulation sICAS group were older (60.5 ± 9.1 vs. 56.1 ± 9.5, $p = 0.0007$); had greater prevalence of coronary heart disease (26.5 vs. 12.5%, $p = 0.0084$); larger stenosis length (7.6 ± 6.1 mm vs. 5.66 ± 3.43 mm, $p = 0.0080$); less AcoA opened (28.6 vs. 50%, $p = 0.0013$); and more PcoA opened (except for embryonic posterior cerebral artery, both unilateral and bilateral) (37.8 vs. 29.2%, $p = 0.0137$). In addition, posterior circulation sICAS showed poorer collateral circulation than the anterior circulation, as the numbers of ASTIN/SIR score of 0-2 and the TICI grade 0-2a were increased to 90.8 vs. 80.8% ($p = 0.0380$) and 57.1 vs. 41.7% ($p = 0.0230$), respectively (**Table 1**).

We analyzed the reasons for not EVT between the two groups. There were 73 (60.8%) patients in anterior circulation group and 48 (49.0%) patients in posterior circulation group showed no indication for EVT, 28 (23.3%) patients in anterior circulation group and 36 (36.7%) patients in posterior circulation group with high procedural risk compared to penitential benefit, 19 (15.8%) patients in anterior circulation group and 14 (14.3%) patients in posterior circulation group were recommended EVT but they rejected or transferred to neurosurgery for treatment. There was no statistical difference between the two groups for not EVT ($\chi^2 = 1.049$, $p = 0.306$).

We recorded the medication and lifestyle management at each visit, partially referred to patients' self-reported blood pressure and blood glucose levels. Almost everyone took at least one type of antiplatelet drug at the 1-year follow-up. Patients with posterior circulation sICAS took aspirin for a longer time [12 months (IQR: 12–12) vs. 12 months (IQR: 3–12), $p = 0.0121$] and had a lower chance of stopping the antiplatelet drug (4.08 vs. 15.13%, $p = 0.0073$) than those with anterior circulation. Lifestyle management showed no differences between the two groups and were not satisfactory either (**Table 2**).

Overall, 42 (19.2%, eight stroke and 34 TIA) patients suffered stroke/TIA recurrence and five (2.29%) patients died of other non-ischemic cerebrovascular diseases by the 1-year follow-up. The posterior circulation group showed a higher stroke/TIA recurrence rate than the anterior circulation group (25.5 vs. 14.2%, $p = 0.035$). However, the type of ischemic event and recurrent-enrolment time showed no difference between the two groups. Further, majority had an independent functional prognosis (mRS $\leq$ 2) in both groups (**Table 3**).

COX regression model was used for multivariate analysis; the posterior circulation group still showed a higher risk of recurrent stroke/TIA and death than the anterior circulation group without any adjustment [HR = 1.932, 95% CI (1.043–3.578), $p = 0.0362$]; by adjusting only age and sex [HR = 2.221, 95% CI (1.170–4.217), $p = 0.0147$]; and by adjusting for all confounding factors [HR = 3.092, 95% CI (1.335–7.164), $p = 0.0084$; **Table 4**]. Kaplan–Meier analysis showed that the posterior circulation sICAS recurrence and mortality risk were consistently higher than the anterior circulation group in the long-term (log-rank-test, $p = 0.033$; **Figure 3**).

TABLE 1 | Baseline characteristics.

Characteristic	Anterior circulation (*n* = 120)	Posterior circulation (*n* = 98)	*p*
Age (y)	56.1 ± 9.5	60.5 ± 9.1	0.0007
Male (*n*, %)	84 (70.0)	77 (78.6)	0.1520
BMI	25.7 ± 2.9	26.2 ± 2.8	0.2196
Hypertension (*n*, %)	85 (70.8)	77 (78.6)	0.1933
Hypercholesterolemia (*n*, %)	64 (53.3)	57 (58.2)	0.4750
Diabetes mellitus (*n*, %)	49 (41.0)	38 (38.8)	0.7580
CAD (*n*, %)	15 (12.5)	26 (26.5)	0.0084
Smoker (*n*, %)	66 (55.0)	55 (56.7)	0.8019
INR	0.97 ± 0.07	1.02 ± 0.28	0.0519
TEG-AA	89.51 ± 21.18	94.01 ± 14.83	0.1530
TEG-ADP	50.75 ± 24.73	55.45 ± 25.18	0.2540
Ischemic type			0.8922
TIA (*n*, %)	54 (45.0)	45 (45.9)	
Stroke (*n*, %)	66 (55.0)	53 (54.1)	
Onset to DSA procedure (*d*)	52 (30–94)	45 (26–96)	0.6371
Lesion location (*n*, %)			
ICA	42 (35.0)		
MCA M1	73 (60.8)		
MCA M2	5 (4.2)		
VA		39 (39.8)	
BA		59 (60.2)	
Stenosis rate	66.5 ± 20.9	69.5 ± 21.0	0.2930
Stenosis rank			0.2110
Mild (*n*, %)	28 (23.3)	12 (12.2)	
Median (*n*, %)	44 (36.7)	43 (43.9)	
Severe (*n*, %)	27 (22.5)	24 (24.5)	
Occlusion (*n*, %)	21 (17.5)	19 (19.4)	
Stenosis length	5.66 ± 3.43	7.60 ± 6.10	0.0080
AcoA	60 (50.0)	28 (28.6)	0.0013
PcoA (unilateral of bilateral)	35 (29.2)	37 (37.8)	0.0137
Complete Willis Circle	9 (7.5)	5 (5.1)	0.4735
Leptomeningeal collateral	99 (83.2)	69 (70.4)	0.0250
ASTIN 0-2 (*n*, %)	97 (80.8)	89 (90.8)	0.0380
TICI 0-2a (*n*, %)	50 (41.7)	56 (57.1)	0.0230

Data are median (IQR) or n (%). BMI, Body Mass Index; CAD, Coronary Artery Disease; INR, International standard ratio; TEG-AA, Thromboelastogram platelet mapping arachidonic acid inhibition; TEG-ADP, Thromboelastogram platelet mapping adenosine diphosphate inhibition; TIA, Transient Ischemic Attack; DSA, Digital Subtraction Angiography; ICA, internal carotid artery; MCA M1, Middle Cerebral Artery M1 segment; MCA M2, Middle Cerebral Artery M2 segment; VA, Vertebral Artery; BA, Basilar Artery; AcoA, Anterior Communicating Artery; PcoA, Posterior Communicating Artery; TICI, Thrombolysis in Cerebral Ischemia Scale; ASTIN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology Collateral Flow Grading System.

Multivariate logistic regression analysis was performed in the two groups separately. In the posterior circulation sICAS group, good antegrade flow (TICI 3/4) could seemed to lower the recurrence risk [OR = 0.228 95% CI (0.067–0.776), $p = 0.018$]. No remarkable risk factors were found in the anterior circulation group (**Figure 4**).

TABLE 2 | Medication and lifestyle control at the 1-year follow-up.

Measures	Anterior circulation (*n* = 120)	Posterior circulation (*n* = 98)	*p*
Antiplatelet drugs (*n*, %)	108 (90.8)	95 (98.0)	0.0560
Time of aspirin (*m*)	12 (3–12)	12 (12–12)	0.0121
Time of clopidogrel (*m*)	12 (2.5–12)	6 (3–12)	0.1628
Discontinuation of antiplatelet (*n*, %)	18 (15.13)	4 (4.08)	0.0073
Discontinuation of statins (*n*, %)	26 (22.03)	17 (17.40)	0.3904
BP control (*n*, %)[a]	58 (68.24)	54 (70.13)	0.5240
Blood sugar control (*n*, %)[b]	18 (36.7)	14 (36.8)	0.8174
Quit smoking (*n*, %)	24 (45.28)	22 (45.83)	0.9558

[a] *Recommended target value of blood pressure be <140/90 mmHg.*
[b] *Target value of glycosylated hemoglobin (HbA1C) be lower than 7%.*

TABLE 3 | Comparison of the 1-year outcome in both groups.

Endpoint events	Anterior circulation (*n* = 120)	Posterior circulation (*n* = 98)	*p*
New territorial ischemic event	17 (14.2)	25 (25.5)	0.035
TIA	13 (76.5)	21 (84.0)	0.542
Stroke	4 (23.5)	4 (16.0)	
Time of recurrence to onset (*d*)	312 (164.5–393.5)	277 (81–397.5)	0.412
Independent outcome (mRS ≤ 2)	116 (99.2)	91 (94.8)	0.056
New ischemic cardiovascular events	2 (1.7)	4 (4.1)	0.278
Any hemorrhagic disease	7 (5.8)	10 (10.2)	0.231
Death	4 (3.3)	1 (1.02)	0.256

TABLE 4 | Different HR values in survival analysis.

	HR	95% CI	*p*
Unadjusted	1.932	1.043–3.578	0.0362
Only age and sex adjusted	2.221	1.170–4.217	0.0147
All confounding factors adjusted*	3.092	1.335–7.164	0.0084

**Contained age, sex, CAD, stenosis length, stenosis rate, TICI, ASTIN/SIR, AcoA, and PcoA.*

DISCUSSION

Because of the considerable controversy with respect to optimum treatment for sICAS patients (medication vs. EVT), in this study, we evaluated a cohort of sICAS patients who intended to undergo EVT upon admission, but could not after DSA evaluation for various reasons. It is worthwhile to identify specific patients with different lesions, recurrent risk, and clinical outcomes for a precise therapy. Our study is a simple retrospective observational study, more like a description of the real state.

In our study, all patients received early standard medical drug therapy such as with antiplatelets and statins, and other risk factor intervention after initial ischemic event onset, and then

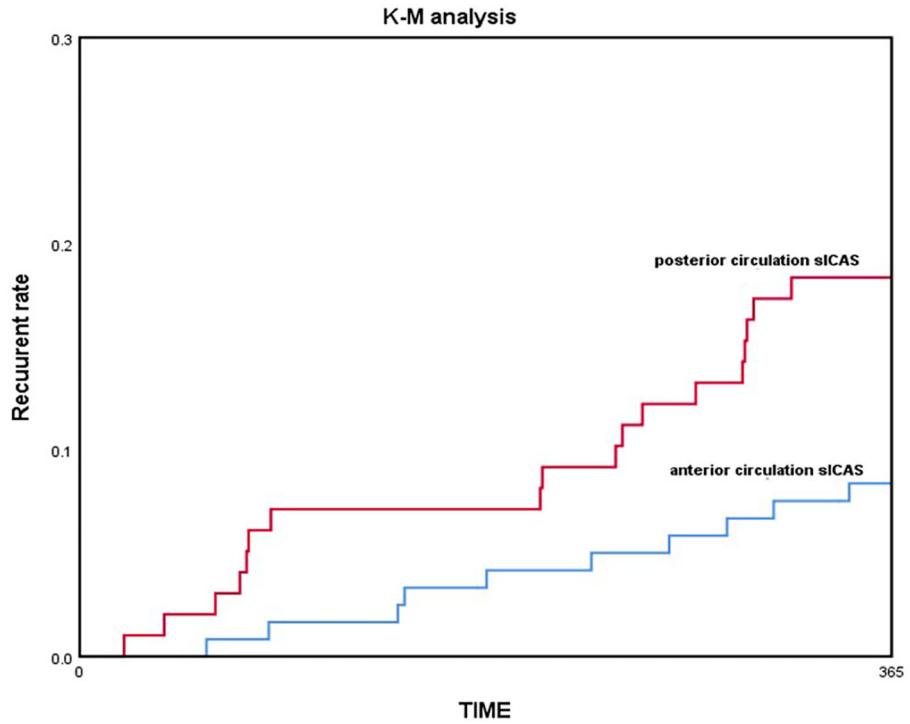

FIGURE 3 | The 1-year recurrent rate compared between two groups using the Kaplan-Meier method.

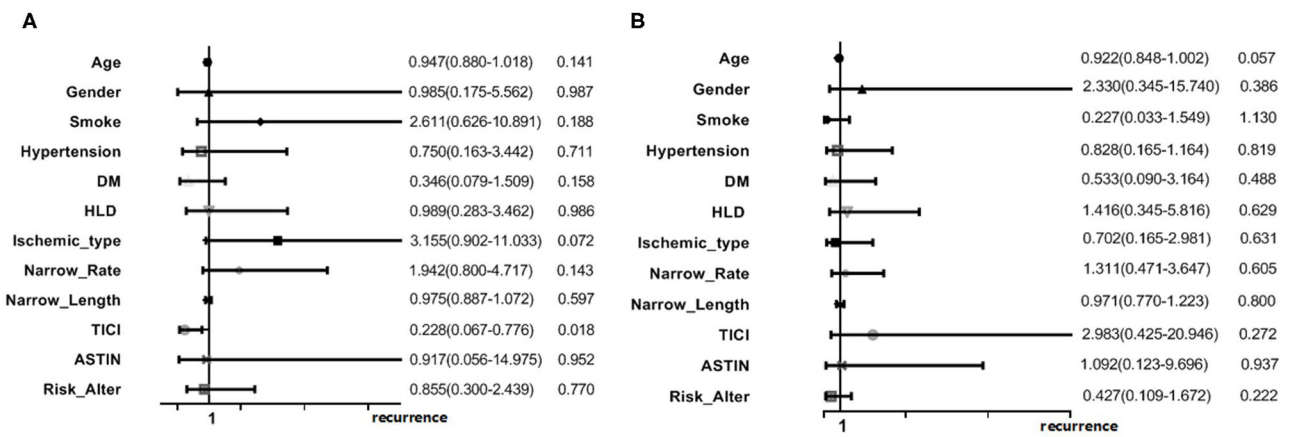

FIGURE 4 | Multivariate analysis in posterior **(A)** and anterior **(B)** circulation sICAS.

sought EVT as a rescue treatment when regular medication did not help. Regardless of the exact reasons for not undergoing further EVT, these sICAS patients who did not benefit from medical management may benefit from EVT (10, 11).

Consistent with previous studies, most patients in our study were male (73.9%), and majority showed common risk factors of ischemic stroke, which was consistent with the characteristics of intracranial atherosclerosis. However, there were a few differences. First, the median time of onset to enrollment was 51 days (IQR: 28–94), which is significantly longer than the 30-day time window of the classic SAMMPRIS and VISSIT study and the 7-day time window of the CICAS study. Second, majority lesions caused mild-to-moderate (74.56 ± 20.43%) stenosis that could be the potential sICAS population worthy of intensive treatment. According to CISS classification (12), the pathogenesis of ischemic stroke was classified from high to low as parent artery-perforator lesion in 47 cases (39.5%), low perfusion in 44 cases (37.5%), artery-to-artery embolism in 17 cases (14.3%), and mixed mechanism in 11 cases (9.2%), which is slightly different from previous studies: low perfusion accounted for 52.4% in the

SAMMPRIS and artery-to-artery embolism accounted for 50.7% in the WASID trials.

Ischemic recurrence was observed in 42 (19.2%) patients at the 1-year follow-up in our study, higher than that in the medical arms of the SAMMPRIS (12.2%) and VISSIT (15.1%) trials. This may be because more than half of the patients (64.7%) in our study were complicated with multiple ICAS, and several studies indicated that the increased burden of ICAS was an independent risk factor for recurrent stroke (13–15). Another potential reason is that the proportion of patients with posterior circulation sICAS was 45% in our study, which was also higher than that reported in previous studies. Patients with posterior circulation sICAS showed more ischemic recurrence than those with anterior circulation (25.5 vs. 14.2%), which has not been proven in previous studies. Despite the many differences between the two groups at baseline, posterior circulation sICAS were found to be independent risk factors for stroke recurrence in patients with sICAS in the COX survival analysis. In addition, the effect of early drug treatment was not good in our study. Although antiplatelet drugs and statins were prescribed and risk factor intervention was emphasized upon after admission, there were no Aggressive Medical Measures like in the SAMMPRIS trial in real life (16), which has been proved in follow-up, medication and lifestyle control is not qualified as requested. Based on a large sample of Chinese ICAS patients, the CICAS registration study pointed out that the risk of stroke recurrence increases with the increase of the number of risk factors (4).

Since sICAS patients with unsatisfactory treatment have a high risk of recurrent ischemic events, it is more clinically meaningful to identify specific populations with a high risk of recurrence. A subgroup analysis based on the WASID study (17) showed that the 1-year stroke recurrence occurred more frequently in ICAS patients with >70% stenosis and within 17 days from onset to enrollment. Different lesion locations and subtypes of ischemic events did not seem to have an influence. However, previous studies preferred to choose patients with anterior circulation sICAS, because the diverse clinical symptoms caused by posterior circulation are challenging to determine.

In our study, we found that posterior circulation sICAS patients are older and more commonly have coronary atherosclerosis disease than those with anterior circulation. According to the DSA results, lesion length is significantly larger in posterior circulation and collateral circulation is poorer than when compared to AcoA/PcoA existence and TICI/ASTIN score. Maybe the limit of sample size and hospital bias, no more different characteristics were found as former study. Without doubt, there are differences between anterior and posterior circulation sICAS (18, 19), not only in demographic characteristics and pathogenesis of ischemic stroke but also in risk of recurrence. In our study, the comparison of primary outcome showed that the recurrence rate is higher in the posterior circulation group than the anterior circulation group (25.5 vs. 14.2%, $p = 0.035$), but there was no difference in the type of ischemic events. It was seen that the recurrence risk (including 1-year recurrent ischemic events and death) in the posterior circulation sICAS group was higher than that in the anterior circulation group throughout, by gradually adjusting the confounding factors in the COX survival analysis. Kaplan–Meier analysis also indicated that recurrence was more likely in posterior circulation sICAS than anterior circulation sICAS with increasing time. This points toward the need for a larger prospective trial that will exclusively focus on the prognosis and treatment of posterior circulation sICAS.

We tried to assess the potential factors related to the recurrent ischemic events in the posterior circulation sICAS patients by multiple analysis. The logistic regression model showed good antegrade flow (TICI 3/4) could lower the recurrence risk in posterior circulation sICAS, [OR = 0.228, 95% CI (0.067–0.776), $p = 0.018$]. Hypoperfusion is most likely a feature connected with recurrent stroke. The time from onset to DSA was 45 days (IQR: 26–96) in the posterior circulation group, and the collateral circulation was also poor. Regardless of whether the cerebral blood flow reserve and regulation differ in anterior and posterior circulation stroke, this is a bold hypothesis. Maybe a limit of traditional collateral circulation measurements which are applied for anterior circulation stroke more properly.

Former studies also showed other risk factors in patients with posterior circulation sICAS. A stroke registration study on a Taiwanese population pointed that the increased degree of vertebrobasilar artery (VBA) stenosis was associated with stroke recurrence. The 1-year stroke recurrence risk of patients with moderate-to-severe VBA stenosis was 1.21-times higher than that of patients with mild VBA stenosis [95% CI (1.01–1.45), $p < 0.05$] (20). Patients with basilar artery stenosis had a higher risk of recurrent stroke than those with vertebral artery stenosis according to a meta-analysis (21). Another retrospective study of a small sample pointed out that most cases of posterior circulation stroke were caused by parent artery-perforator lesion, in which case the likelihood of recurrence was the least (22).

The main limitation of our study is the retrospective nature and small sample size. Moreover, patient enrollment bias and department bias caused by hospital cannot be eliminated. We only selected patients who underwent DSA evaluation in our department for 20 months. In fact, most patients missed screening because of the difficulty of continuous follow-up. Another limitation is the collection of follow-up information. Most recurrent ischemic events in our study are TIA-related, with the majority being repeat TIA attacks since the initial onset. After enrollment, although medication did not greatly resolve patient symptoms, risk-factor intervention was not feasible. Maybe we should have compared sICAS patients treated with EVT in the same period to determine whether recovery of blood flow has any effect on recurrence. A further study is on-going to clarify the prognosis of sICAS and precise therapy.

CONCLUSION

Patients with posterior circulation sICAS have higher recurrence risk than those with anterior circulation on medication alone, and posterior circulation lesion is an independent risk factor for recurrence in sICAS patients. Further studies

should be performed exclusively on patients with posterior circulation sICAS.

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

ZM designed and supervised the study. JZ and KZ was responsible for data analyses, drafting, and revising the article. BJ and ZQ was responsible for data acquisition. DM, NM, and FG were involved in revising the article for important intellectual content. All authors critically reviewed the article and approved the final version.

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Neutrophil Count, Intracranial Atherosclerotic Stenosis, and Prognosis of Ischemic Stroke After Endovascular Treatment: A Mediation Analysis

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Background and Purpose: Data on the relationship among neutrophil count, intracranial atherosclerotic stenosis (ICAS), and functional outcomes after endovascular thrombectomy (EVT) for ischemic stroke patients remains unclear. We aimed to evaluate the association between neutrophil count and prognosis of EVT patients and to determine whether the association was mediated by ICAS.

Methods: We retrospectively analyzed consecutive patients who underwent EVT at two comprehensive stroke centers between June 2016 and December 2019. A remaining stenosis >70%, or a lesser degree of stenosis with a tendency toward re-occlusion or flow impairment during the procedure, was classified as ICAS. A poor outcome was defined as a 90-day modified Rankin Scale score of 3–6.

Results: Of the 221 patients (mean age, 65.9 years; males, 61.1%) included in this study, 81 (36.3%) had ICAS, and 120 (54.3%) experienced a poor outcome at 90 days, respectively. In the multivariate adjustment for potential confounders, neutrophil count (odds ratio [OR], 1.19; 95% confidence interval [CI], 1.04–1.36; $P = 0.012$) and presence of ICAS (OR, 2.65; 95CI%, 1.28–5.45; $P = 0.008$) were risk factors of poor outcomes. Furthermore, mediation analysis indicated that total ICAS mediated the association between increased neutrophil count and worse functional outcome after EVT (the regression coefficient was changed by 11.7% for poor outcome, and 17.1% for modified Rankin Scale score, respectively).

Conclusions: Our study demonstrated that a higher neutrophil count might increase the risk of a poor outcome among ischemic stroke patients who underwent EVT, which was partially mediated by ICAS.

Keywords: stroke, endovascular treatment, neutrophil, intracranial atherosclerosis, mediation analysis

INTRODUCTION

Several randomized controlled trials and meta-analyses have confirmed that endovascular thrombectomy (EVT) with stent retriever was a safe and effective way or achieving reperfusion in anterior circulation ischemic stroke caused by occlusion of the proximal anterior artery (1–5). Large-artery occlusion is generally due to embolism from proximal sources in Caucasians, whereas intracranial atherosclerotic stenosis (ICAS) with *in situ* thrombus occlusion are much more common in Asian patients (6). ICAS may challenge the passage of the retriever devices to the targeting lesions (7). Moreover, EVT with stent retrievers for ICAS may produce blood vessel injury and lead to re-occlusion caused by subsequent platelet aggregation at the site of the intracranial atherosclerotic lesion (8). Therefore, uncertainties remain regarding the benefit of EVT in patient with ICAS-related occlusion, especially in the Chinese population.

Neutrophils, as the indicator of acute and chronic inflammation, are the first cells that migrate from the peripheral vessel into the brain ischemic zone after stroke (9). The increased neutrophil count may accelerate inflammatory response by releasing proinflammatory cytokines and chemokines, in which the ischemic injury is intricately aggravated (10). Recent experimental studies have also found that acute ischemic stroke thrombi contain neutrophil extracellular traps and that their numbers were associated with intravenous thrombolysis and EVT resistance (11, 12). Neutrophils are not only associated with clinical outcomes in ischemic stroke after EVT (13), but also play a pivotal role in ICAS (14). Even in a healthy population, the baseline neutrophil-lymphocyte ratio was reported to be linked to the progression of ICAS (15). However, the relationship between neutrophil count, presence of ICAS, and functional outcomes after EVT is still unclear. We therefore performed this retrospective multicenter cohort study to assess the association between neutrophil count and prognosis of ischemic stroke patients treated with EVT, and to determine whether the association was mediated by ICAS-related occlusion.

METHODS

Study Design and Subjects

We retrospectively analyzed consecutive ischemic stroke patients who underwent EVT at two comprehensive stroke centers (Shuguang Hospital and Mianyang Central Hospital) between June 2016 and December 2019. Patients were recruited in this study if they: (1) had acute intracranial large artery occlusion of the anterior circulation confirmed by computed

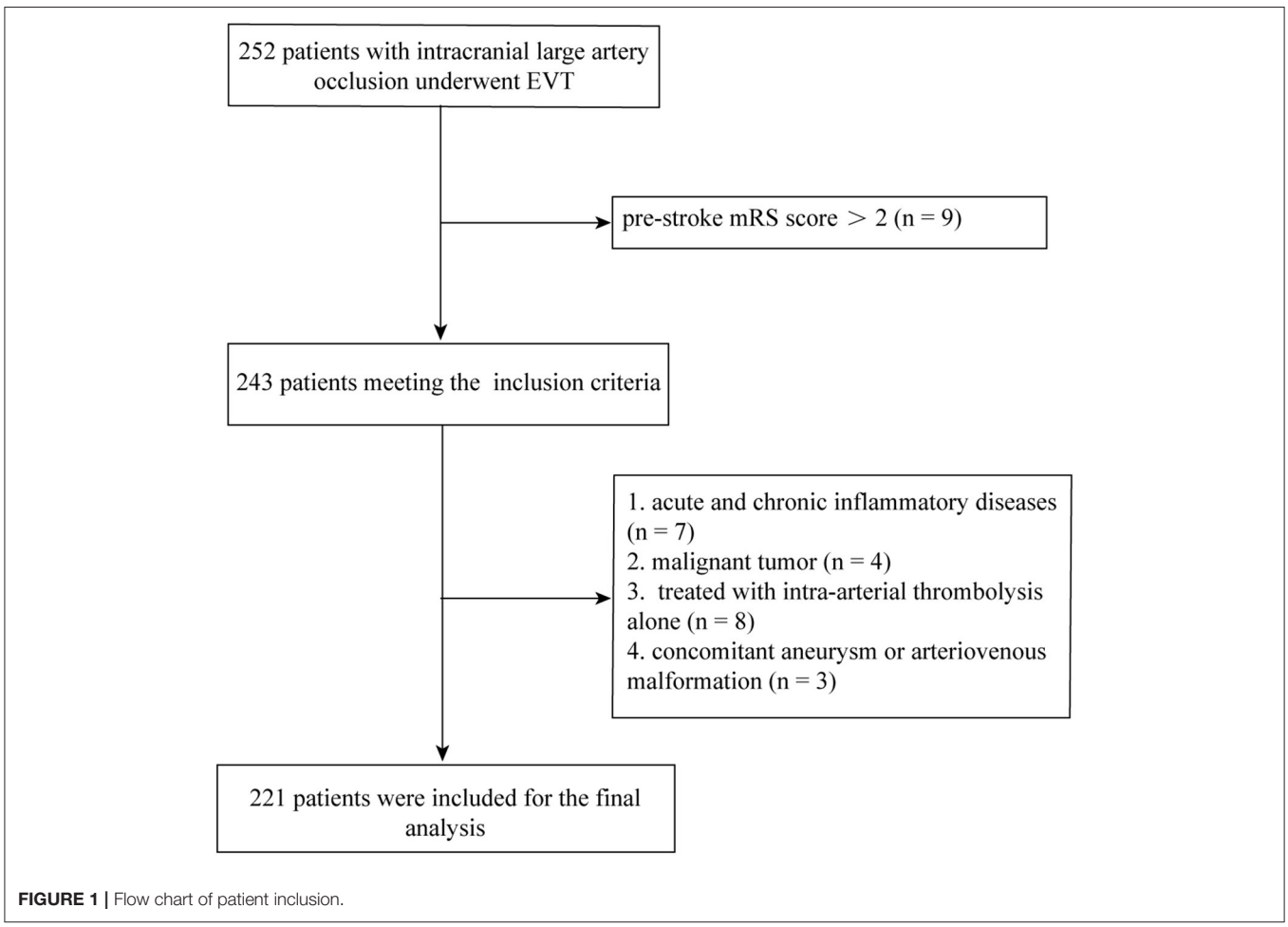

FIGURE 1 | Flow chart of patient inclusion.

tomographic angiography, magnetic resonance angiography, or digital subtracted angiography (DSA); (2) were aged 18 years or older; (3) had a pre-stroke mRS score $\leq$ 2. The intracranial internal carotid artery, and M1 and M2 segment of middle cerebral artery were defined as intracranial large vessels. The exclusion criteria were acute and chronic inflammatory diseases such as pneumonia, urinary tract infection, pelvic inflammatory disease and nephritis, autoimmune disease, malignant tumor, or severe renal and hepatic insufficiency. To maintain the homogeneity of the enrolled patients, we excluded patients treated with intra-arterial thrombolysis alone or those diagnosed with concomitant aneurysm or arteriovenous malformation. This study was approved by the ethics committee of each participating center, and due to its retrospective nature; patient consent was waived.

Baseline Data Collection

Demographics characteristics, clinical data, procedural characteristics and imaging data were recorded after admission. Neurological deficit was assessed by the National Institutes of Health Stroke Scale (NIHSS) (16). The Alberta stroke program early computed tomography Score (ASPECTS) was used to evaluate the extent of preoperative early cerebral ischemia (17). The symptomatic intracranial hemorrhage (sICH) was defined using the criteria of the Heidelberg Bleeding Classification within 24 h after EVT (18). Collateral circulation was determined based on the DSA using the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology grading system, with grade 0–1 representing a poor collateral status, and grade 2–4 representing a moderate to excellent status (19). Successful reperfusion was defined as a modified Thrombolysis in Cerebral Infarction score of 2b or 3 (20).

TABLE 1 | Comparison of baseline data stratified by the neutrophil count.

Variables	All subjects, $n = 221$	Higher neutrophil, $n = 109$	Lower neutrophil, $n = 112$	*P*-value
Demographic characteristics				
Age, years	65.9 ± 13.1	65.8 ± 13.6	66.0 ± 12.7	0.925
Male, *n* (%)	135 (61.1)	67 (61.5)	68 (60.7)	0.909
Risk factors				
Hypertension, *n* (%)	137 (62.0)	67 (61.5)	70 (62.5)	0.874
Diabetes mellitus, *n* (%)	56 (25.3)	34 (31.2)	22 (19.6)	0.048
Hyperlipidemia, *n* (%)	20 (9.0)	12 (11.0)	8 (7.1)	0.317
Coronary heart disease, *n* (%)	23 (10.4)	14 (12.8)	9 (8.0)	0.242
Current smoker, *n* (%)	79 (35.7)	36 (33.0)	43 (38.4)	0.405
Clinical data				
Systolic blood pressure, mmHg	152.8 ± 23.7	151.8 ± 22.7	153.7 ± 22.8	0.548
Diastolic blood pressure, mmHg	80.5 ± 13.3	79.8 ± 12.6	81.2 ± 14.0	0.448
Onset to groin puncture, min	225.0 (189.0, 270.0)	221.0 (188.0, 283.0)	225.0 (188.5, 250.0)	0.578
Baseline NIHSS, score	15.0 (11.0, 20.0)	17.0 (12.0, 20.0)	14.0 (10.0, 17.0)	0.003
Baseline ASPECTS, score	9.0 (9.0, 10.0)	9.0 (9.0, 10.0)	9.0 (9.0, 10.0)	0.907
ICSA (vs. Non-ICAS), *n* (%)	81 (36.3)	49 (45.0)	32 (28.6)	0.012
ICA (vs. MCA), *n* (%)	84 (38.0)	63 (57.8)	74 (66.1)	0.205
Prior IVT, *n* (%)	148 (67.0)	71 (65.1)	77 (68.8)	0.568
Poor collateral status, *n* (%)	90 (40.7)	40 (40.4)	46 (41.1)	0.915
Stent retriever with rescue therapy, *n* (%)	61 (27.6)	32 (29.4)	29 (25.9)	0.565
Passes with retriever	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	0.218
Successful reperfusion, *n* (%)	165 (74.7)	76 (69.7)	89 (79.5)	0.106
sICH, *n* (%)	22 (10.0)	15 (13.8)	7 (6.3)	0.062
Poor outcome at 90 days	120 (54.3)	72 (66.1)	48 (42.9)	0.001
Laboratory data				
Total cholesterol, mmol/L	4.1 ± 1.0	4.0 ± 0.9	4.1 ± 1.1	0.531
Triglyceride, mmol/L	1.6 (1.3, 3.1)	1.7 (1.3, 2.2)	1.6 (1.3, 1.9)	0.520
Low density lipoprotein, mmol/L	3.0 (2.4, 3.5)	3.0 (2.5, 3.7)	2.9 (2.5, 3.3)	0.235
High density lipoprotein, mmol/L	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	1.2 (1.1, 1.4)	0.163
Baseline blood glucose, mmol/L	7.9 ± 3.1	8.2 ± 3.1	7.9 ± 3.0	0.504
Hs-CRP, mg/L	1.8 (1.2, 3.5)	1.8 (1.2, 3.9)	2.0 (1.4, 3.2)	0.318
Platelet, 10^9/L	180.6 ± 70.2	184.3 ± 77.3	176.5 ± 62.7	0.383

ASPECTS, alberta stroke program early computed tomography score; Hs-CRP, hyper-sensitive C-reactive protein; ICAS, intracranial atherosclerotic stenosis; ICA, internal carotid artery; IVT, intravenous thrombolysis; MCA, middle cerebral artery; NIHSS, national institute of health stroke scale; sICH, symptomatic intracranial hemorrhage.

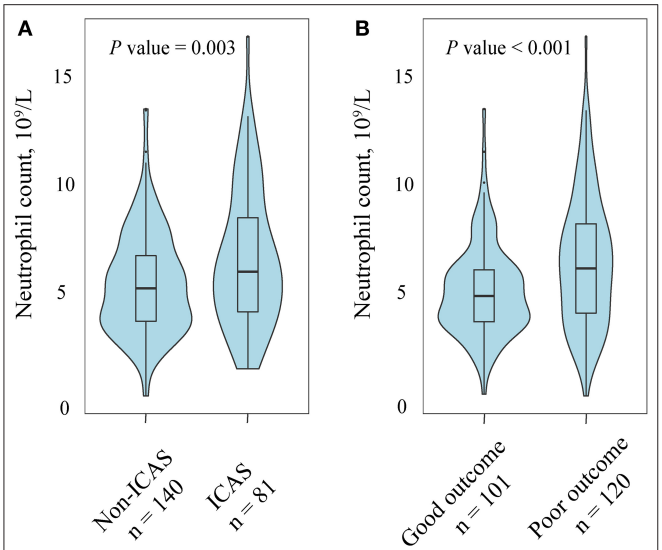

FIGURE 2 | Association of neutrophil count with intracranial atherosclerotic stenosis (ICAS) and functional outcome at 90 days. **(A)** Patients with ICAS tended to have a higher neutrophil count compared with those without ICAS. **(B)** Compared with patients with a favorable outcome patients, the group of patients with an unfavorable outcome had a high level of neutrophil.

Blood samples were obtained from each subject after admission. Laboratory data were also recorded including neutrophil count, platelet count, hyper-sensitive C-reactive protein (hs-CRP), and the lipid profile.

The etiology of target large vessel occlusion was assessed by stepwise angiographic analysis with the results of DSA. If no stenosis was observed and the lumen was smooth, the occlusion was considered to be caused by embolism. ICAS-related occlusion was defined as a remaining stenosis >70%, or a lesser degree of stenosis with a tendency toward re-occlusion or flow impairment during the procedure (7). All neuroimaging data were reviewed by two physicians who were blinded to the clinical data. In case of disagreement, a joint reading was performed, and a consensus decision was reached.

Functional outcome was assessed using the modified Rankin Scale score (mRS) at 90 days after stroke onset. A poor outcome was defined as a modified Rankin Scale score of 3–6. Functional outcome was primarily evaluated by stroke neurologists during the patient's routine clinic follow-up at 3 months. If a patient could not come to the clinic, mRS was determined *via* telephone by interviewing the patient or their family.

Endovascular Procedures

EVT were performed under local anesthesia or general anesthesia. The type of EVT procedure was selected at the discretion of the treating physician. EVT was performed using different approved modalities, including aspiration with separators, stent retrievers, and aspiration thrombectomy. If recanalization of the targeting artery failed, rescue therapies, such as balloon angioplasty, stent implantation, intra-arterial thrombolysis, or intracatheter tirofiban administration were implemented as needed.

TABLE 2 | Comparison of baseline data in patients with and without unfavorable outcome at 90 days.

Variables	Poor outcome, *n* = 120	Good outcome, *n* = 101	*P*-value
Demographic characteristics			
Age, years	65.8 ± 14.2	65.9 ± 11.8	0.978
Male, *n* (%)	70 (58.3)	65(64.4)	0.360
Risk factors			
Hypertension, *n* (%)	78 (65.0)	59 (58.4)	0.315
Diabetes mellitus, *n* (%)	37 (30.8)	19 (18.8)	0.041
Hyperlipidemia, *n* (%)	12 (10.2)	8 (7.9)	0.591
Coronary heart disease, *n* (%)	14 (11.7)	9 (8.9)	0.504
Current smoker, *n* (%)	43 (35.8)	36 (35.6)	0.977
Clinical data			
Systolic blood pressure, mmHg	154.6 ± 23.9	150.5 ± 23.4	0.199
Diastolic blood pressure, mmHg	81.4 ± 13.5	79.4 ± 13.1	0.269
Onset to groin puncture, min	240.0 (209.0, 283.0)	215.0 (176.0, 248.0)	<0.001
Baseline NIHSS, score	16.0 (11.0, 21.0)	14.0 (10.0, 17.0)	0.002
Baseline ASPECTS, score	9.0 (8.0, 10.0)	10.0 (9.0, 10.0)	0.003
ICSA (vs. Non-ICAS), *n* (%)	54 (45.0)	27 (26.7)	0.005
ICA (vs. MCA), *n* (%)	54 (45.0)	30 (29.7)	0.022
Prior IVT, *n* (%)	76 (63.3)	72 (71.3)	0.210
Poor collateral status, *n* (%)	66 (55.0)	24 (23.8)	<0.001
Stent retriever with rescue therapy, *n* (%)	35 (29.2)	26 (25.7)	0.571
sICH, *n* (%)	21 (17.5)	1 (1.0)	<0.001
Passes with retriever	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	0.013
Successful reperfusion, *n* (%)	70 (58.3)	95 (94.1)	<0.001
Laboratory data			
Total cholesterol, mmol/L	4.0 ± 1.1	4.1 ± 1.0	0.367
Triglyceride, mmol/L	1.7 (1.2, 2.2)	1.6 (1.4, 1.9)	0.381
Low density lipoprotein, mmol/L	2.8 (2.5, 3.7)	3.2 (2.6, 3.3)	0.671
High density lipoprotein, mmol/L	1.2 (1.1, 1.2)	1.2 (1.1, 1.4)	0.107
Baseline blood glucose, mmol/L	8.3 ± 3.1	7.8 ± 3.2	0.350
Hs-CRP, mg/L	1.8 (1.2, 5.4)	2.3 (1.3, 3.0)	0.892
Platelet, 10^9/L	179.1 ± 75.4	182.3 ± 63.8	0.743
Neutrophil count, 10^9/L	6.7 ± 3.0	5.3 ± 2.1	<0.001

ASPECTS, alberta stroke program early computed tomography score; Hs-CRP, hyper-sensitive C-reactive protein; ICAS, intracranial atherosclerotic stenosis; ICA, internal carotid artery; IVT, intravenous thrombolysis; MCA, middle cerebral artery; NIHSS, national institute of health stroke scale; sICH, symptomatic intracranial hemorrhage.

Statistical Analysis

Continuous variables were reported as means (standard deviation, SD) or medians (interquartile range, IQR). Proportions were calculated for categorical variables. Differences in baseline characteristics between groups were explored using independent sample *t*-tests, Mann–Whitney *U*-tests, chi-square test, or fisher's exact test, where appropriate. To identify the independent risk factors of a poor outcome, a logistic regression

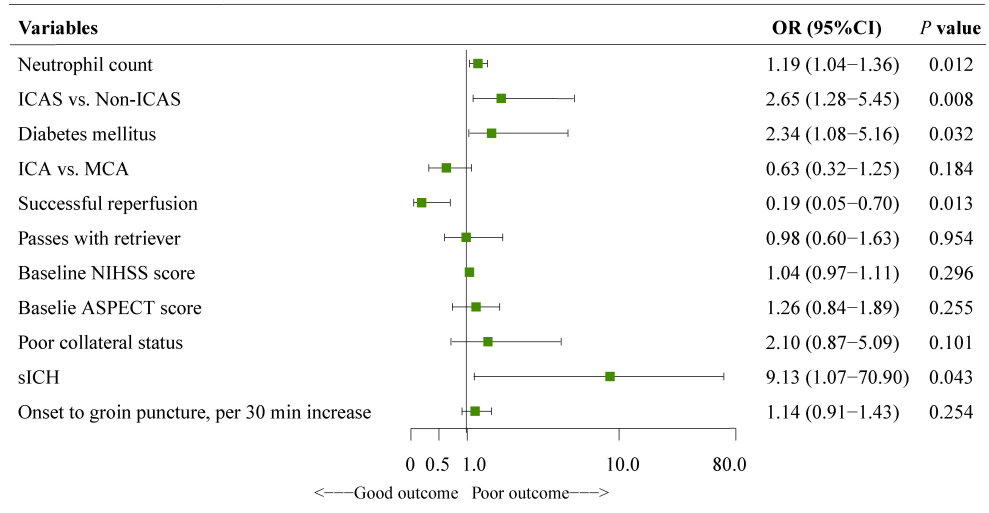

FIGURE 3 | Results of the logistic regression model evaluating the risk factors of poor outcome at 90 days. Multivariate logistic regression was adjusted for potential confounders with $P < 0.1$ in the univariate analysis. ASPECTS, the albert stroke program early CT score; CI, confidence interval; NIHSS, national institutes of health stroke scale; ICAS, intracranial atherosclerotic stenosis; ICA, internal carotid artery; MCA, middle cerebral artery; sICH, symptomatic intracranial hemorrhage.

model was performed using a forward stepwise method that included all variables with a probability value <0.10 in the univariate analysis. Adjusted odd ratios (OR) and their 95% confidence intervals (CI) were calculated.

To determine whether ICAS could mediate the effect of increased neutrophil count on the risk of poor outcome after EVT, we conducted a mediation analysis to calculate the proportion mediated and to test its significance using the Sobel test (21, 22). A mediation analysis consists of a four-step procedure and seeks to explain a relationship between an independent variable (neutrophil count) and a dependent variable (poor outcome) *via* the inclusion of a third hypothetical variable (presence of ICAS). A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software, version 24.0 (IBM, New York, NY).

RESULTS

Patient Baseline Characteristics

A total of 221 patients (mean age, 65.9 years; males, 61.1%) treated with EVT were recruited for the final analysis. The flow chart of patient inclusion is presented in **Figure 1**. Among them, 81 had ICAS-related occlusion whereas the other 140 had no ICAS (122 for cardioembolic, and 18 for undetermined or others, respectively). General and clinical characteristics of the subjects by median of neutrophil count (5.8×10^9/L) are presented in **Table 1**. Participants with a higher neutrophil count had an increased baseline NIHSS score (median, 17.0 vs. 14.0; $P = 0.003$), and were more likely to have diabetes mellitus (31.2 vs. 19.6%; $P = 0.048$), ICAS-related occlusion (45.0 vs. 28.6%; $P = 0.012$), and a poor outcome at 90 days (66.1 vs. 42.9%; $P = 0.001$). Similar significant findings were observed when the neutrophil count was analyzed as a continuous variable (**Figure 2**).

Multivariate Analysis for the Predictors of Poor Outcome at 90 Days

During the 90-day follow-up, 120 (54.3%) patients had a poor functional outcome. A comparison of baseline data in patients with and without an unfavorable outcome at 90 days is shown in **Table 2**. The univariate analysis revealed that patients with a poor outcome had a higher neutrophil count (mean, 6.7×10^9/L vs. 5.3×10^9/L; $P < 0.003$), onset to groin puncture time (median, 240.0 min vs. 215.0 min; $P < 0.003$), baseline NIHSS score (median, 16.0 vs. 14.0; $P = 0.002$), and passes with retriever (median, 2.0 vs. 2.0; $P = 0.013$); and had a lower ASPECTS (median, 9.0 vs. 10.0; $P = 0.003$) than patients with a favorable outcome. The prevalence of diabetes mellitus (30.8% vs. 18.8%; $P = 0.041$), ICAS-related occlusion (45.0 vs. 26.7%; $P = 0.005$), occlusion site in internal carotid artery (45.0 vs. 29.7%; $P = 0.022$), poor collateral circulation (55.0 vs. 23.8%; $P < 0.001$), sICH (17.5 vs. 1.0%; $P < 0.001$) and unsuccessful reperfusion (41.7 vs. 5.9%; $P < 0.012$) was also significantly higher in patients with a poor outcome than in patients with a favorable outcome.

In the multivariate adjustment for potential confounders (including variables with P value < 0.1 in the univariate analysis), neutrophil count (OR, 1.19; 95%CI, 1.04–1.36; $P = 0.012$), ICAS-related occlusion (OR, 2.65; 95CI%, 1.28–5.45; $P = 0.008$), diabetes mellitus (OR, 2.34; 95CI%, 1.08–5.16; $P = 0.032$), successful reperfusion (OR, 0.19; 95CI%, 0.05–0.70; $P = 0.013$), and sICH (OR, 9.13; 95CI%, 1.07–70.90; $P = 0.043$) were significant predictors of a poor outcome (**Figure 3**).

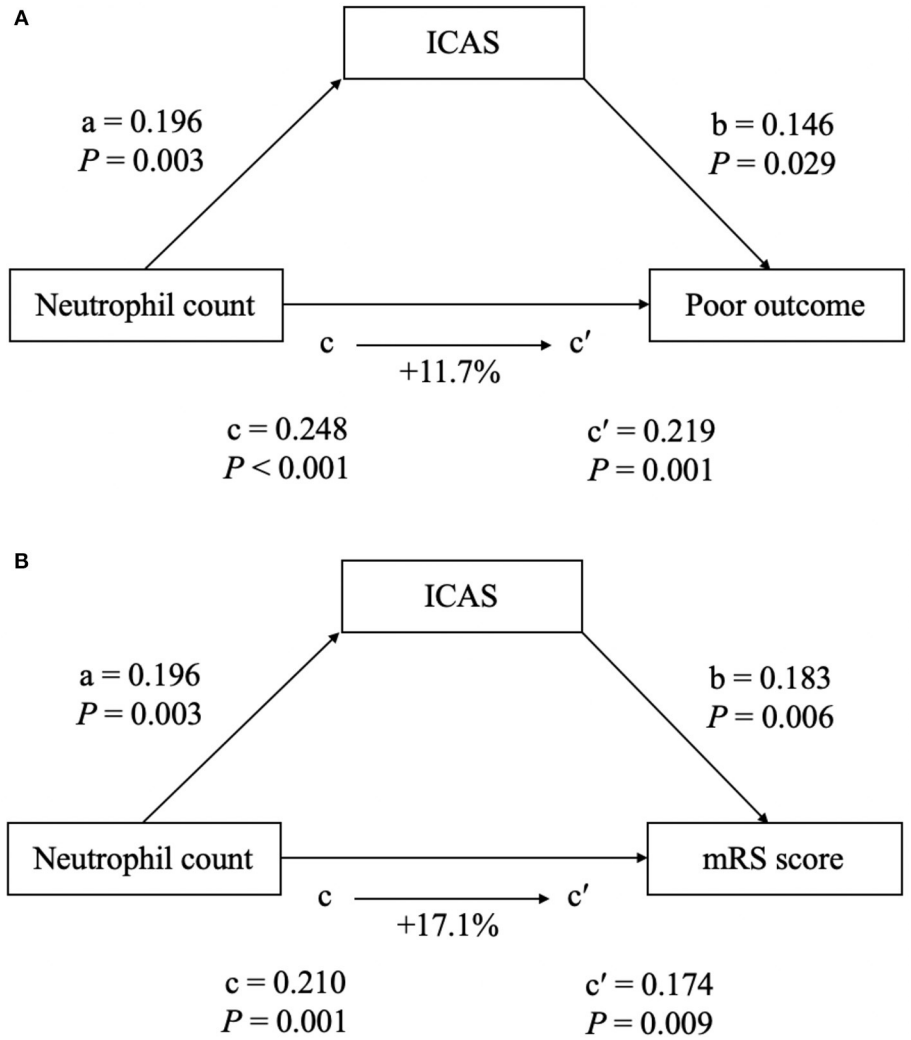

FIGURE 4 | The mediation analysis by intracranial atherosclerotic stenosis (ICAS) of the association between neutrophil count and clinical outcome [**(A)** for poor outcome at 90 days; **(B)** for mRS score at 90 days). a, regression coefficient of the association between neutrophil count and ICAS; b, regression coefficient of the association between ICAS and clinical outcome, using neutrophil count and ICAS as independent variables; c, regression coefficient of the association between neutrophil count and clinical outcome; c′, regression coefficient of the association between neutrophil count and clinical outcome, using neutrophil count and ICAS as independent variables. The percentage difference of the coefficients (1–c/c′) is shown.

Mediation by ICAS-Related Occlusion of the Association Between Neutrophil Count and Functional Outcome

To further test the potential mediating effects of ICAS-related occlusion on the association between increased neutrophil count and a worse functional outcome, we conducted a causal mediation analysis. After including ICAS-related occlusion as a mediator, we observed a significant partial mediation effect for ICAS on higher neutrophil count-related effects on the 90-day functional outcome after EVT in ischemic stroke patients. The estimated proportion mediated by ICAS-related occlusion was 11.7% for a poor outcome and 17.1% for the mRS score, respectively (**Figure 4**).

DISCUSSION

The results of this observational study demonstrated that an elevated neutrophil count and the presence of ICAS-related occlusion were associated with a higher risk of a 90-day poor outcome in ischemic stroke patients who underwent EVT. Our data further indicated that worse functional outcomes associated with the higher neutrophil count, could be partially explained by the presence of ICAS-related occlusion.

To date only a few studies have reported the clinical outcomes of patients who underwent EVT for ICAS-related occlusion. Furthermore, the results of functional outcomes have been inconsistent (7, 23–25). Data from the Acute Stroke due to

Intracranial Atherosclerotic occlusion and Neurointervention-Korean Retrospective registry, found that ICAS-related occlusion could predict the 3-month functional dependence after EVT treatment (7). Also, Lee et al. (25) confirmed that patients with ICAS-related occlusion had much worse outcome than those without it. However, other studies showed no significant difference or a protective factor of ICAS-related occlusion on the prognosis of EVT patients (23, 24). Because the optimal EVT strategy for ICAS-related occlusion was not uniformly established, patients with ICAS-related occlusion were treated according to the neuro-interventionist's judgement, which resulted in a comparable rate of recanalization and poor prognosis. Similar to previous studies that focused on Asian patients, our retrospective multicenter cohort demonstrated that ICAS-related occlusion was associated with an increased risk of a 90-day poor outcome in ischemic stroke patients treated with EVT. The lower rate of recanalization, longer procedure time, and higher rate of using rescue therapy and re-occlusion may partly contribute to the relatively poor outcome in the ICAS-related occlusion after EVT (26).

Mounting evidence has confirmed that inflammation plays a vital role in the worsening of a stroke outcome (27). Our study added to the existing evidence by demonstrating that a higher neutrophil count was positively correlated with an increased risk of a poor outcome among EVT patients. However, the underlying mechanisms by which neutrophils contribute to a worse outcome in patients treated with EVT, remain poorly understood. Neutrophil, as the important factor of inflammatory response, recruits into the ischemic zone and initiates the inflammatory and immune cell migration by releasing detrimental molecules, such as proinflammatory cytokines, chemokines, and reactive oxygen species, which are all involved in infarct growth and are caused symptom deterioration (10, 28). Moreover, in the setting of inflammation, an activated neutrophil can contribute to thrombus formation through neutrophil extracellular traps (NETs) (29). Recent experimental studies reported that ischemic stroke thrombi contain NETs and that their number was associated with the resistance of EVT treatment (12). This could partly explain why an increased neutrophil count is associated with a poor clinical outcome after EVT. In addition, increased neutrophils may contribute to the development and progression of atherosclerosis, and lead to the carotid plaque destabilization (30, 31). Moreover, compelling evidence in total white blood cell count, neutrophil count, and the presence of ICAS have been reported in prior clinical studies (14, 15, 25). Even in a healthy population, the baseline neutrophil-lymphocyte ratio has been reported to be associated with the development of ICAS (15). Therefore, ICAS-related occlusion may play a crucial role in the presence of a poor outcome in EVT patients caused by a higher neutrophil count. Interestingly, our mediation analysis showed that ICAS mediated a modest but significant proportion (11.7% for poor outcome and 17.1% for increased mRS score) of the above-mentioned association, suggesting that atherosclerosis plays an intermediating role. The data from a previous study support the need for new therapies focusing on DMT by targeting NETs, for example, with recombinant DNAse 1 or platelet activation (13). The management of neutrophil counts within an appropriate range could improve the functional outcome after EVT and is a possible future area of inquiry.

Some limitations of the present study must be addressed when interpreting the results. First, this was a retrospective study with data taken from two comprehensive stroke centers, which may have generated system biases. This cohort also included relatively few cases with ICAS-related occlusion. We therefore could not rule out a type I error in the present study. Second, this study did not include all outcome-related variables for mediation analysis, such as blood pressure variation, use of an antiplatelet regime, and infarct volume. Thus, selection biases might have occurred. Third, the neutrophil count was measured only once, at baseline, so we were unable to explore the association between the dynamic change of albumin and prognosis after EVT. Finally, the results of the present study are confined to Chinese patients, and thus, the findings may not be generalized to other ethnicities.

In conclusion, our study found a significant correlation between increased neutrophil count and a higher risk of a 90-day poor outcome after EVT treatment in ischemic stroke patients. The association could be partially mediated by the presence of ICAS-related occlusion.

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 approved by the Ethics Committee of Shuguang Hospital and Mianyang Central Hospital, and due to its retrospective nature; patient consent was waived.

AUTHOR CONTRIBUTIONS

TL, DL, and XY contributed to overall study design. XZ, XT, FG, MW, HZ, YG, JZ, YL, BQ, ZZ, and ZF contributed to clinical data collection. SP contributed to Image data collection. ZC, TL, and DL designed and conduced data analysis. ZC and DL contributed to data analysis and interpretation. ZC wrote the manuscript. WP was involved in the review of the paper. All authors approved the submitted version of the article.

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Intracranial Atherosclerosis Coexisting With White Matter Hyperintensities May Predict Unfavorable Functional Outcome in Patients With Acute Cerebral Ischemia

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Background and Purpose: This study aimed to assess the effect of baseline white matter hyperintensities (WMH) on 1-year stroke recurrence and the functional outcome for patients with intracranial atherosclerosis (ICAS).

Methods: We analyzed 2,076 patients who were enrolled in the Chinese IntraCranial AtheroSclerosis (CICAS) study. ICAS and WMH were diagnosed by baseline magnetic resonance angiography. The primary outcomes were stroke recurrence and unfavorable functional outcome (modified Rankin Scale score 3–6) at 1 year.

Results: Of the 2,076 patients included in this study, 1,370 (65.99%) were men, and the mean age was 61.70 years. In total, 224 (10.79%) patients had no WMH and no ICAS, 922 (44.41%) patients had WMH and no ICAS, 157 (7.56%) patients had ICAS and no WMH, and 773 (37.24%) had both WMH and ICAS. During the follow-up period, 87 patients had a recurrent stroke and 333 had unfavorable outcomes at 1 year. Compared to WMH (–) ICAS (–) group, the adjusted odd ratios and 95% confidence interval for unfavorable functional outcome were 0.791 (0.470–1.332; $p = 0.3779$) in the WMH (+) ICAS (–) group, 1.920 (1.024–3.600; $p = 0.0421$) in the WMH (–) ICAS (+) group, and 2.046 (1.230–3.403; $p = 0.0058$) in the WMH (+) ICAS (+) group. There was no significant difference in stroke recurrence risk among the four groups.

Conclusion: ICAS coexisting with WMH may predict an unfavorable functional outcome at 1 year, but not stroke recurrence.

Keywords: white matter hyperintensities, intracranial atherosclerosis (ICAS), stroke recurrence, small vessel disease (SVD), outcome

INTRODUCTION

Intracranial atherosclerosis (ICAS) is likely to be the most common stroke subtype worldwide (1). It accounts for about 15% of Caucasian patients with ischemic attack or stroke (2) and nearly 50% of ischemic strokes in Asia (1, 3, 4). Cerebral small vessel disease (SVD) is another kind of common cerebrovascular disease, which manifests as recent small subcortical infarcts, lacunes, white matter hyperintensities (WMH), perivascular spaces, microbleeds, and brain atrophy on neuroimaging (5). SVD may also have racial differences, and an observational study found that Han Chinese had a higher prevalence of confluent WMH than white Australians, but had a similar prevalence of lacunes and microbleeds (6). Some studies have suggested that patients with ICAS may be particularly prone to having coexistent SVD (7–9). Patients with multiple ICAS lesions, occlusive lesions, and atherosclerotic lesions in the posterior circulation were more likely to coexist with WMH (10). Previous studies have found that WMHs were associated with risk of incident stroke, ischemic stroke, intracerebral hemorrhage, dementia, Alzheimer's Disease, and death (11). A study from the PICASSO (Prevention of Cardiovascular Events in Ischemic Stroke Patients with High Risk of Cerebral Hemorrhage) trial showed that the severity of WMH on baseline brain magnetic resonance imaging scans may be associated with a 2.15-fold risk of stroke, 2.11-fold risk of ischemic stroke, and 3.72-fold risk of hemorrhagic stroke (12).

It is still uncertain whether the presence of SVD on baseline magnetic resonance imaging could affect the stroke recurrent risk and functional outcome of patients with ICAS. A subgroup analysis of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) showed that the SVD image markers are not independently associated with an increased risk of stroke in patients with ICAS (13). Lau et al. validated a total small vessel disease score in two independent prospective studies and found that a higher score was associated with an increased risk of recurrent ischemic stroke and intracerebral hemorrhage (14). A study from the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial, indicated that SVD and ICAS may have different levels of risk for future strokes. SVD was associated with more disability and bleeding events, and ICAS was associated with an increased risk of stroke and disability in patients with minor stroke and TIA at 3 months (15).

This study hypothesized that ICAS and WMH may interact with each other, resulting in an increased risk of unfavorable functional outcome and stroke recurrence. The study aimed to assess the effect of baseline WMH on 1-year stroke recurrence and the functional outcome for patients with acute cerebral ischemia in the Chinese Intracranial Atherosclerosis (CICAS) study database.

MATERIALS AND METHODS

Subjects

From October 2007 to June 2009, a total of 2,864 patients were recruited into the CICAS study (4). We excluded 444 patients who did not have interpretable images for the presence of white matter changes and 344 patients with extracranial large artery stenosis or occlusion. Finally, 2,076 patients were included in this study. The CICAS study was a multicenter, hospital-based cohort study that included 22 hospitals in mainland China and the Hong Kong Special Administrative Region. The study was approved by the Institutional Review Boards of the participating hospitals. Details of the CICAS study design and the definition of baseline characteristics have been published previously (4). This study recruited patients with cerebral ischemia, aged from 18 to 80, admitted within 7 days of symptom onset. We excluded patients who were clinically unstable and those that required close monitoring or were disabled before admission, physically or subjectively unable to comply with magnetic resonance (MR) examination or had severe comorbidity, and those who were presumed to have had a cardioembolic stroke such as atrial fibrillation.

Brain MRI Assessment

All MR images were stored in digital format and were read by two readers blinded to the clinical information of subjects (4). Intracranial stenosis or occlusion was estimated by 3-dimensional time-of-flight MR angiography (3D TOF MRA). ICAS was defined as stenosis more than or equal to 50% on MRA for the main intracranial arteries. Intracranial arterial segments included the distal internal carotid artery (ICA), middle cerebral artery (MCA) (M1 and M2 segment), anterior cerebral artery (ACA) (A1 and A2 segment), posterior cerebral artery (PCA) (P1 and P2 segment), and basilar artery (BA). Duplex color Doppler ultrasound or contrast-enhanced MRA were used for extracranial carotid vessels. WMH was defined as a hyperintense lesion on both T2-weighted imaging and FLAIR but was usually not seen on T1-weighted imaging or showed faint hypointensity (5). DWI was used to differentiate acute ischemic stroke lesions from WMH. The severity of WMH was assessed according to the Fazekas scale (16). Scores in periventricular white matter hyperintensities (PWMH) and deep white matter hyperintensities (DWMH) were evaluated separately and summed together as Fazekas scores. The total Fazekas score was classified into two categories: 0–3 and 4–6. According to the presence of ICAS or WMH, the patients were classified into four groups: WMH (–) ICAS (–), WMH (+) ICAS (–), WMH (–) ICAS (+), and WMH (+) ICAS (+). WMH (–) was defined as a Fazekas score equal to 0.

Follow-Up Assessment

We monitored the included patients for 1 year through telephone or face to face consultations with trained research personnel from the follow-up center of the Beijing Tiantan Hospital and the Hong Kong Prince of Wales Hospital. The primary outcomes were stroke recurrence and unfavorable functional outcome (modified Rankin Scale score 3–6). Stroke recurrence was defined as sudden functional deterioration in neurological status with a decrease in the National Institutes of Health Stroke Scale (NIHSS) score of four or more, or a new focal neurological deficit of vascular origin lasting >24 h, including recurrent ischemic or hemorrhagic stroke (4).

Statistical Methods

All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA). Two-sided *P*-values <0.05 were considered statistically significant. Continuous variables were summarized as median (interquartile range) or mean (SD). Categorical variables were presented as numbers (percentages). The χ^2 test (or Fisher exact test, when appropriate) was used to test differences in proportions for categorical variables. A Wilcoxon signed rank test was used to test differences in median for the continuous variables. The cumulative probabilities of stroke recurrence over time were estimated by the Kaplan–Meier product-limit method and were compared among WMH (–) ICAS (–), WMH (+) ICAS (–), WMH (–) ICAS (+), and WMH (+) ICAS (+) group using the log-rank test. Cox proportional hazards regression analyses were used to estimate the hazards ratio of each group for stroke recurrence adjusted by potential confounders. For the unfavorable functional outcome at 1 year, odds ratio (OR), and 95% confidence interval (CI) were given and logistic regression was used for adjusting confounders. All tests were two-sided with a significance level fixed at 5%.

TABLE 1 | Baseline characteristics of participants.

Characteristics	WMH (–) ICAS (–) (*n* = 224)	WMH (+) ICAS (–) (*n* = 922)	WMH (–) ICAS (+) (*n* = 157)	WMH (+) ICAS (+) (*n* = 773)	*P*-value
Male sex, *n* (%)	151 (67.41)	611 (66.27)	120 (76.43)	488 (63.13)	0.0136
Age, mean (SD), y	53.73 (10.71)	63.09 (10.53)	52.33 (11.74)	64.25 (10.28)	<0.0001
BMI, mean (SD), kg/m^2	24.82 (3.43)	24.53 (3.09)	25.08 (3.29)	24.37 (3.03)	0.2333
Diabetes, *n* (%)	51 (22.77)	301 (32.65)	55 (35.03)	315 (40.75)	<0.0001
Hypertension, *n* (%)	132 (58.93)	734 (79.61)	92 (58.60)	654 (84.61)	<0.0001
Hyperlipidemia, *n* (%)	170 (75.89)	689 (74.73)	123 (78.34)	582 (75.29)	0.8047
Hyperhomocystinemia, *n* (%)	48 (21.43)	189 (20.50)	38 (24.20)	233 (30.14)	<0.0001
Family history of stroke, *n* (%)	26 (11.61)	72 (7.81)	25 (15.92)	73 (9.44)	0.0080
Current smoker, *n* (%)	82 (36.61)	308 (33.41)	82 (52.23)	226 (29.24)	<0.0001
Heavy drinker, *n* (%)	12 (5.36)	37 (4.01)	15 (9.55)	29 (3.75)	0.0103
History of stroke, *n* (%)	25 (11.16)	219 (23.75)	22 (14.01)	255 (32.99)	<0.0001
Heart disease, *n* (%)	7 (3.13)	79 (8.57)	9 (5.73)	66 (8.54)	0.0277
Peripheral vascular disease, *n* (%)	1 (0.45)	7 (0.76)	1 (0.64)	4 (0.52)	0.9132
NIHSS score at admission, median (IQR)	2 (0–5.5)	3 (2–5)	4.5 (2–9)	4 (2–8)	<0.0001
Pattern of infarct, *n* (%)					<0.0001
No infarct	83 (37.73)	245 (27.01)	23 (14.65)	128 (16.67)	
Cortical infarct	8 (3.64)	20 (2.21)	7 (4.46)	42 (5.47)	
Subcortical infarct	69 (31.36)	439 (48.40)	43 (27.39)	289 (37.63)	
Cortical and subcortical	18 (8.18)	39 (4.30)	60 (38.22)	141 (18.36)	
Infratentorial	41 (18.64)	160 (17.64)	22 (14.01)	149 (19.40)	
Supratentorial and infratentorial	1 (0.45)	4 (0.44)	2 (1.27)	19 (2.47)	
Number of acute infarcts, *n* (%)					<0.0001
No acute infarct	83 (37.73)	245 (27.01)	23 (14.65)	127 (16.54)	
Single infarct	125 (56.82)	621 (68.47)	97 (61.78)	530 (69.01)	
Multiple infarct	12 (5.45)	41 (4.52)	37 (23.57)	111 (14.45)	
In-hospital treatment, *n* (%)					
Thrombolysis therapy	11 (4.91)	24 (2.60)	12 (7.64)	19 (2.46)	0.0021
Antithrombotic therapy	215 (95.98)	879 (95.34)	153 (97.45)	755 (97.67)	0.0634
Dual Antiplatelet	21 (9.38)	62 (6.72)	25 (15.92)	92 (11.90)	0.0001
Statins	164 (73.21)	684 (74.19)	121 (77.07)	602 (77.88)	0.2560
Blood pressure-lowering therapy	89 (39.73)	550 (59.65)	54 (34.39)	406 (52.52)	<0.0001

ICAS, intracranial atherosclerosis; WMH, white matter hyperintensities; BMI, Body Mass Index; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SD, Standard Deviation.

TABLE 2 | Predictors of recurrent stroke in 2,076 patients (Univariate analysis).

Characteristics	No recurrent stroke (*n* = 1989)	Recurrent stroke (*n* = 87)	*P*-value
Male sex, *n* (%)	1,317 (66.21)	53 (60.92)	0.3075
Age, mean (SD), y	61.55 (11.29)	65.20 (11.39)	0.0027
BMI, mean (SD), kg/m^2	24.53 (3.11)	24.82 (3.59)	0.8559
Diabetes, *n* (%)	685 (34.44)	37 (42.53)	0.1210
Hypertension, *n* (%)	1,535 (77.17)	77 (88.51)	0.0130
Hyperlipidemia, *n* (%)	1,495 (75.16)	69 (79.31)	0.3798
Hyperhomocystinemia, *n* (%)	490 (24.64)	18 (20.69)	0.4021
Family history of stroke, *n* (%)	184 (9.25)	12 (13.79)	0.1561
Current smoker, *n* (%)	682 (34.29)	16 (18.39)	0.0021
Heavy drinker, *n* (%)	92 (4.63)	1 (1.15)	0.1250
History of stroke, *n* (%)	484 (24.33)	37 (42.53)	0.0001
Heart disease, *n* (%)	147 (7.39)	14 (16.09)	0.0030
Peripheral vascular disease, *n* (%)	13 (0.65)	0	1.0000*
NIHSS score at admission, median (IQR)	3 (1–6)	5 (3–10)	<0.0001
Pattern of infarct, *n* (%)			0.0649
No infarct	469 (23.87)	10 (11.49)	
Cortical infarct	74 (3.77)	3 (3.45)	
Subcortical infarct	804 (40.92)	36 (41.38)	
Cortical and subcortical	245 (12.47)	13 (14.94)	
Infratentorial	348 (17.71)	24 (27.59)	
Supratentorial and infratentorial	25 (1.27)	1 (1.15)	
Number of acute infarcts, *n* (%)			0.0044
No acute infarct	468 (23.82)	10 (11.49)	
Single infarct	1,311 (66.72)	62 (71.26)	
Multiple infarct	186 (9.47)	15 (17.24)	
ICAS, *n* (%)	879 (44.19)	51 (58.62)	0.0081
Fazekas score, median (IQR)	2 (1–4)	3 (2–4)	0.0008
In-hospital treatment, *n* (%)			
Thrombolysis therapy	60 (3.02)	6 (6.90)	0.0435
Antithrombotic therapy	1,925 (96.78)	77 (88.51)	<0.0001
Dual Antiplatelet	186 (9.35)	14 (16.09)	0.0370
Statins	1,503 (75.57)	68 (78.16)	0.5808
Blood pressure-lowering therapy	1,052 (52.89)	47 (54.02)	0.8360

**p-value was calculated by Fisher's exact test; ICAS, intracranial atherosclerosis; WMH, white matter hyperintensities; BMI, Body Mass Index; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SD, Standard Deviation.*

RESULTS

Among the 2,076 patients included in this study, 1,370 (65.99%) were men, and the mean (SD) of age was 61.70 (11.32) years. Two hundred and twenty-four (10.79%) patients had no WMH and no ICAS, 922 (44.41%) patients had WMH and no ICAS, 157 (7.56%) patients had ICAS and no WMH, and 773 (37.24%) had both WMH and ICAS. The baseline characteristics for each group are shown in **Table 1**. Patients with both WMH and ICAS were older and more likely to have diabetes, hypertension, hyperhomocysteinemia, and a history of stroke. The median (interquartile range) of baseline Fazekas score in the WMH (+) group was 3 (2–4).

During the follow-up period, 87 patients had a recurrent stroke and 333 had unfavorable outcomes at 1 year. The predictors of recurrent stroke in 2,076 patients are shown in **Table 2**. Patients with recurrent stroke were older and a higher percentage had hypertension, history of stroke, heart disease, multiple infarction, and ICAS. The stroke recurrence rate was 6 (2.68%) in the WMH (–) ICAS (–) group, 30 (3.25%) in the WMH (+) ICAS (–) group, 5 (3.18%) in the WMH (–) ICAS (+) group, 46 (5.95%) in the WMH (+) ICAS (+) group. Compared to the WMH (–) ICAS (–) group, the hazard ratio (HR) and 95% confidence interval (CI) was 0.682 (0.270–1.721), 1.124 (0.340–3.719), and 1.263 (0.510–3.131) in each group, respectively, after adjustment by age, sex, diabetes, hypertension, hyperhomocysteinemia, family history of stroke, current smoker, heavy drink, history of stroke, and heart disease. There was no significant difference between groups for recurrent risk of stroke at 1 year. For patients with ICAS, the stroke recurrent rate had no significant difference between Fazekas score 0–3 and 4–6. The HR (95%CI) of stroke recurrence in the patients in each group are shown in **Table 3**. Kaplan-Meier curves of recurrent stroke showed in **Figure 1**.

For unfavorable functional outcome at 1 year, there were 21 (10.05%) patients in the WMH (–) ICAS (–) group, 96 (28.83%) in the WMH (+) ICAS (–) group, 26 (7.81%) in the WMH (–) ICAS (+) group, and 190 (26.46%) in the WMH (+) ICAS (+) group. Compared to the WMH (–) ICAS (–) group, the adjusted odd ratios (OR) and 95% CI were 0.791 (0.470–1.332), 1.920 (1.024–3.600), 2.046 (1.230–3.403) in the other three groups, respectively. The OR (95%CI) of unfavorable outcomes in patients from each group are shown in **Table 4**. The distribution of Functional Scores at 1 year are shown in **Figure 2**.

DISCUSSION

The findings of this study are consistent with those of other recently reported trials (13, 15), which indicated that the presence of WMH on baseline magnetic resonance imaging is not independently associated with an increased risk of stroke recurrence in patients with ICAS. The coexistence of intracranial atherosclerosis with changes in white matter may predict an unfavorable functional outcome at 1 year. Although the 1-year stroke recurrence rate in the ICAS and WMH group was higher than that of other groups, there was no significant difference after adjusting by confounders, suggesting that age, baseline NIHSS score, the number of acute infarctions, and medical history may be more relevant in stroke recurrence than WMH alone. For patients with ICAS, the severity of WMH had no

TABLE 3 | Recurrent stroke in patients with WMH or ICAS.

	Stroke recurrence, *n* (%)	HR (95%CI)	*P*-value	Adj. HR (95%CI)*	*P*-value
WMH (–) ICAS (–)	6 (2.68)	1 (Reference)		1 (Reference)	
WMH (+) ICAS (–)	30 (3.25)	1.058 (0.437–2.563)	0.9004	0.682 (0.270–1.721)	0.4176
WMH (–) ICAS (+)	5 (3.18)	1.146 (0.350–3.755)	0.8216	1.124 (0.340–3.719)	0.8477
WMH (+) ICAS (+)	46 (5.95)	2.171 (0.926–5.089)	0.0745	1.263 (0.510–3.131)	0.6140
ICAS (+) Fazekas score 0–3	21 (3.48)	1 (Reference)		1 (Reference)	
ICAS (+) Fazekas score 4–6	30 (9.20)	2.658 (1.516–4.661)	0.0006	1.850 (0.977–3.505)	0.0591

**The number of patients included was 2,061. Adjusted by age, sex, diabetes, hypertension, hyperhomocysteinemia, family history of stroke, current smoker, heavy drink, history of stroke, heart disease.*

ICAS, intracranial atherosclerosis; WMH, white matter hyperintensities; CI, confidence interval; HR, hazard ratio.

significant correlation with the risk of stroke recurrence and functional outcome.

WMH is a common imaging feature that is associated with small-vessel disease (SVD) and related to stroke incidence, dementia, or death (11). SVD is common in patients with ICAS. Kwon et al. (13) observed that nearly half of ICAS patients had SVD on a baseline MRI. Lee et al. (9) reported a significant association between WMH and stroke subtypes. The large-artery-disease group in this study had a higher prevalence of WMH than other groups (55.4% in the large-artery-disease group, 30.3% in the lacunar group, and 14.3% in the cardioembolic). In a CICAS study, 41.45% of acute ischemic stroke or TIA patients had WMH at baseline MRI and patients with ICAS had a higher percentage of WMH than those without (45.77% vs. 37.67%) (4). However, there are limited data on the effect of WMH on stroke recurrence or functional outcome in patients with acute cerebral ischemia. A study from the SAMMPRIS trial showed that the presence of SVD on baseline magnetic resonance imaging was not independently associated with an increased risk of stroke in patients with ICAS (13). Data from the CHANCE trial found that SVD was associated with more disability and bleeding events and that ICAS is associated with an increased risk of stroke and disability in patients with minor stroke and TIA at 3 months, which implies that SVD and ICAS may represent different vascular pathologies and play distinct roles in stroke outcomes (15).

How to explain the results by the pathogenesis? The mechanisms of ICAS-related stroke include parent artery atherosclerosis occluding penetrating artery, artery to artery embolism, hypoperfusion, and mixed mechanisms). Different pathogenesis has different recurrence risk. Previous reports showed that ICAS with multiple infarctions (indicated by an artery to artery mechanism) (17), borderzone infarcts and impaired collateral flow (hemodynamic markers) (18), or a mixed mechanism of artery to artery embolism and hypoperfusion (19) were more likely to have recurrent stroke. WMHs are often considered to be a consequence of chronic hypoperfusion (20). Patients with hemodynamically more severe ICAS are more likely to have more severe ipsilateral WMH (21). Some researchers believe that impaired cerebral blood flow is one of the physiopathology mechanisms of WMH (22). However, the relationship between WMH and ICAS is still not clear. A meta-analysis study reviewed available published (and unpublished) research on cerebral blood flow (CBF) in small vessel disease, and data showed that a high WMH load is associated with lower CBF, but they are not causally related. In cross-sectional studies, low CBF was observed in most patients with more WMHs. The association was less pronounced after removing non-age matched subjects and those with dementia, which suggests that the underlying association is between reduced CBF and age or dementia rather than just WMH (20). Therefore, ICAS and WMH represent different types of pathophysiology. The ICAS-related recurrence of stroke correlates with plaque stability, hemodynamics, and collateral circulation, while the mechanisms of stroke recurrence related to WMH are more complex and involve arteriolar tortuosity, reduced vessel density, and occlusive venous collagenosis (23). WMH is usually associated with brain dysfunction, and ICAS is associated with stroke recurrence.

This study had several limitations. First, the included data was, in some cases, older, which could cause bias due to the advancement of medical treatment strategies such as dual anti platelet and high intensity statin. This was also a hospital-based study involving upper first-class hospitals, and most of the enrolled patients had a minor stroke, meaning that selective bias affects the included population. Second, the study included patients within seven days of onset, the rate of stroke recurrence might have been underestimated. Third, we did not distinguish the subtypes of recurrent stroke. Finally, other manifestations of cerebral small vessel disease (recent small subcortical infarcts, lacunes, perivascular spaces, microbleeds, and brain atrophy on neuroimaging) were not analyzed in this study.

In conclusion, the presence of WMH on baseline magnetic resonance imaging is not an independent predictor of stroke recurrence for patients with acute cerebral ischemia. The co-existence of intracranial atherosclerosis with changes in white matter may predict an unfavorable functional outcome at 1 year. For patients with ICAS, the severity of WMH had no significant correlation with the risk of stroke recurrence and functional outcome. The manifestations of WMH with different pathophysiological mechanisms may be different in images and the visual features of ICAS-related WMH need to be further explored in future studies.

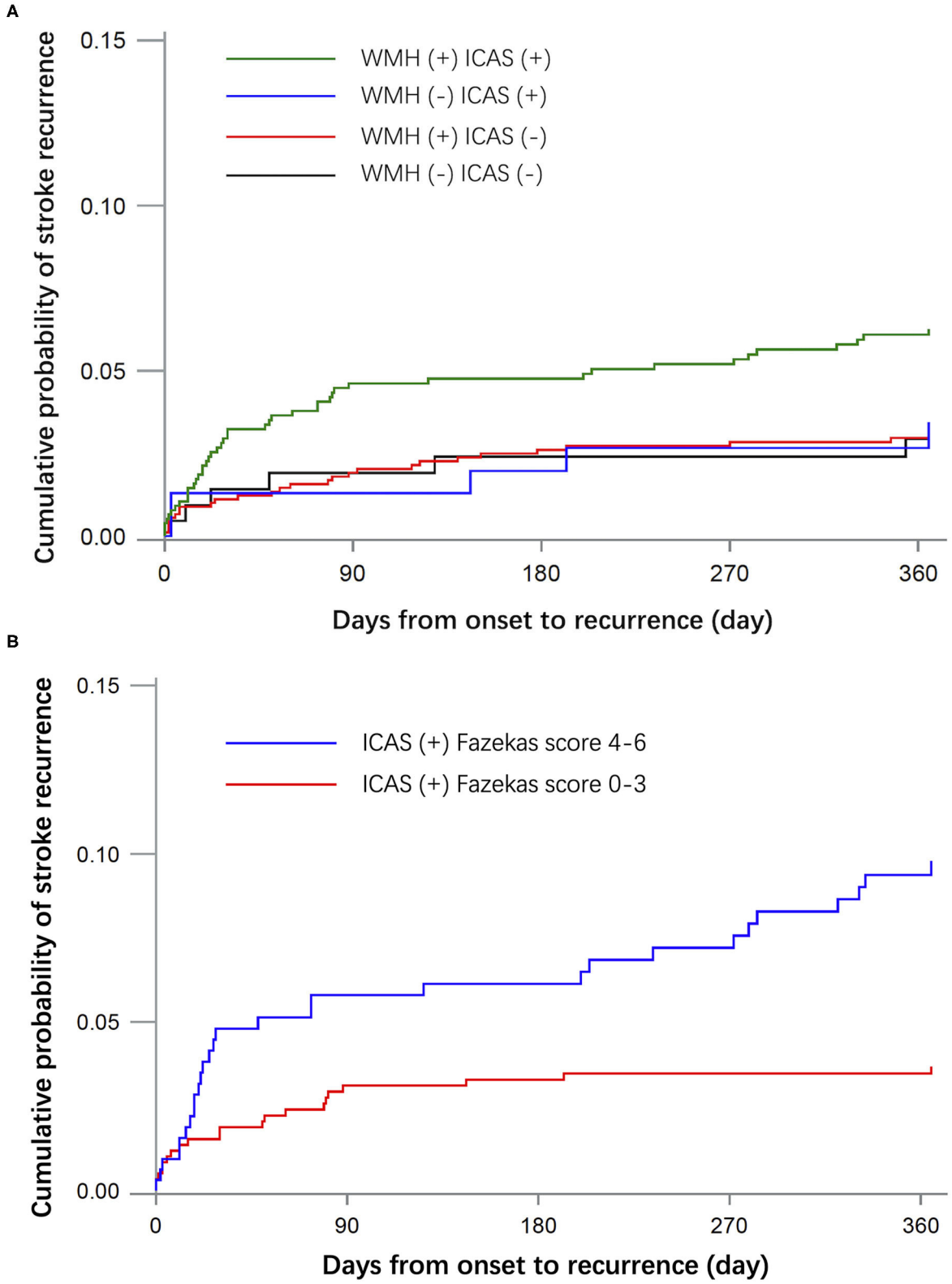

FIGURE 1 | Kaplan-Meier curves of recurrent stroke within 1 year. **(A)** Shows the cumulative incidence of recurrent stroke in groups WMH (–) ICAS (–), WMH (+) ICAS (–), WMH (–) ICAS (+) and WMH (+) ICAS (+). **(B)** Shows the cumulative incidence of recurrent stroke in patients with ICAS by different severity of WMH.

TABLE 4 | Unfavorable functional outcome at 1 year in patients with WMH or ICAS.

	mRS 3–6, *n* (%)	OR (95%CI)	*P*-value	Adj. OR (95%CI)*	*P*-value
WMH (–) ICAS (–)	21 (10.05)	1 (Reference)		1 (Reference)	
WMH (+) ICAS (–)	96 (28.83)	1.118 (0.679–1.840)	0.6620	0.791 (0.470–1.332)	0.3779
WMH (–) ICAS (+)	26 (7.81)	1.877 (1.012–3.483)	0.0459	1.920 (1.024–3.600)	0.0421
WMH (+) ICAS (+)	190 (26.46)	3.221 (1.992–5.209)	<.0001	2.046 (1.230–3.403)	0.0058
ICAS (+) Fazekas score 0–3	132 (23.04)	1 (Reference)		1 (Reference)	
ICAS (+) Fazekas score 4–6	84 (28.47)	1.330 (0.967–1.830)	0.0797	1.006 (0.701–1.445)	0.9732

**The number of patients included was 1,942. Adjusted by age, sex, diabetes, hypertension, hyperhomocysteinemia, family history of stroke, current smoker, heavy drink, history of stroke, heart disease.*

ICAS, intracranial atherosclerosis; WMH, white matter hyperintensities; CI, confidence interval; OR, odds ratio.

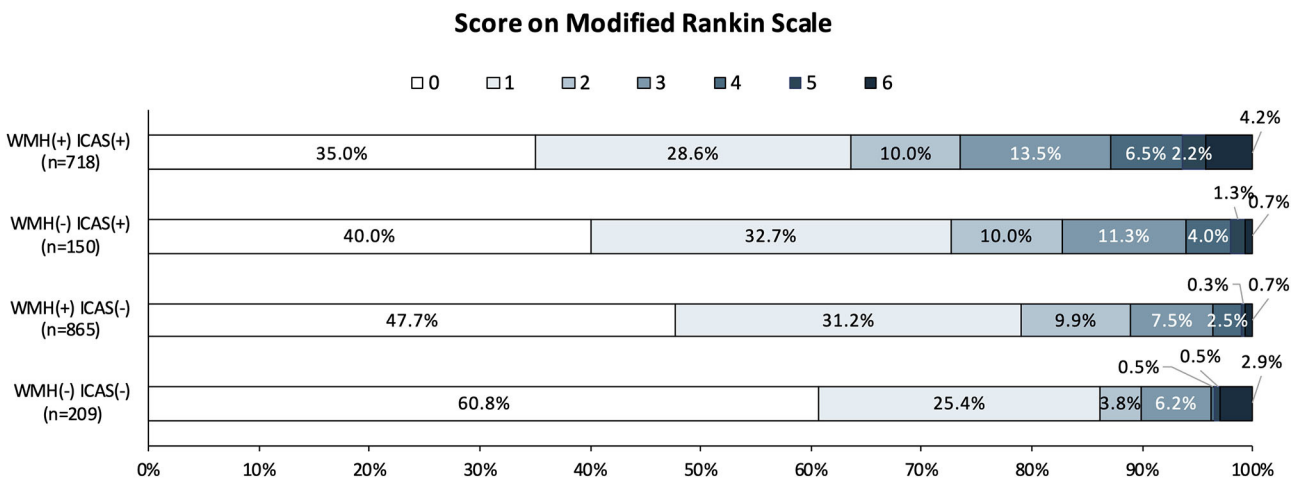

FIGURE 2 | Distribution of mRS score at 1 year in the four groups. Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help, but able to walk unassisted; 4, moderately severe disability (unable to attend body needs and unable to walk); 5, severe disability (requiring constant nursing care and attention); and 6, death. mRS scores at 1 year were missing in 134 cases.

DATA AVAILABILITY STATEMENT

Requests for access to the data reported in this paper will be considered by the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing Tiantan Hospital of Capital Medical University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HL and YPu undertook the literature search, data analysis and interpretation, figures, and wrote the manuscript. LL, XZh, YiW, YoW, TL, and KW contributed to the study design, data analysis, data interpretation, and provided comments on the manuscript. XZo and YS contributed to data collection and image analysis and interpretation. CZ contributed to the image interpretation of white matter lesions. YPa contributed to data analysis and interpretation and figures. All authors contributed to the article and approved the submitted version.

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Etiological Approach to Understanding Recanalization Failure in Intracranial Large Vessel Occlusion and Thrombectomy: Close to Embolism but Distant From Atherosclerosis

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Introduction: In patients with intracranial large vessel occlusion (LVO) who undergo endovascular treatment (EVT), recanalization failure may be related to intracranial atherosclerotic stenosis (ICAS). We evaluated whether the risk factors of recanalization failure could possibly be a marker of ICAS among various types of LVO.

Methods: From a multicenter registry, patients with middle cerebral artery M1 segment occlusions who underwent thrombectomy within 24 h were included. Based on the on-procedure and post-procedure angiographic findings, patients were classified into embolic, ICAS-related, tandem occlusion, and recanalization failure groups. Recanalization failure was defined if the occluded vessel could not be recanalized by stent retrieval, contact aspiration, or local lytics treatment. Risk factors, imaging markers, and EVT methods were compared between groups.

Results: Among 326 patients, 214 were classified as embolism, 76 as ICAS, 16 as tandem, and 20 as recanalization failure. The group with recanalization failure showed higher scores on the National Institutes of Health Stroke Scale (NIHSS) (median, 16.0 vs. 14.5 vs. 14.0 vs. 17.0, $p = 0.097$), frequent atrial fibrillation (59.3 vs. 18.4 vs. 0 vs. 40.0% $p < 0.001$), and elevation in erythrocyte sedimentation rate (ESR) (14.5 ± 15.7 vs. 15.0 ± 14.1 vs. 21.2 ± 19.5 vs. 36.0 ± 32.9, $p < 0.001$) among the groups. The rate of computed tomography angiography-based truncal-type occlusion in recanalization failure group was not as high as that in the ICAS group (8.1 vs. 37.5 vs. 0 vs. 16.7%, $p < 0.001$). Balloon guide catheters (BGC) were less frequently utilized in the recanalization

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failure group as compared to their use in the other groups (72.0 vs. 72.4 vs. 62.5 vs. 30.0%, $p = 0.001$). In the multivariable analysis, initial higher NIHSS [odds ratio (OR), 1.11 95% confidence interval (CI), 1.01–1.22 $p = 0.027$], higher ESR (OR, 1.03 CI, 1.01–1.05 $p = 0.006$), and non-use of BGCs (OR, 3.41 CI, 1.14–10.17 $p = 0.028$) were associated with recanalization failure. In M1 occlusions, the predominant mechanism of recanalization failure was presumed to be embolic in 80% and due to ICAS in 20%.

Conclusion: The analysis of recanalization failures does not suggest an underlying predominant ICAS mechanism. Sufficient utilization of thrombectomy devices and procedures may improve the rates of recanalization.

Keywords: intracranial large vessel occlusion, recanalization failure, thrombectomy, middle cerebral artery, endovascular treatment

INTRODUCTION

Endovascular treatment (EVT) is an effective treatment for acute ischemic stroke due to large vessel occlusion (LVO) (1). Nevertheless, recanalization is not successful in all patients. Possible causes of recanalization failure include tandem occlusion, clot characteristics and its burden, or different occlusion pathomechanisms (atherosclerotic occlusions) apart from anatomical challenges that limit the initiation of mechanical thrombectomy itself (2–4).

More specifically, underlying intracranial atherosclerotic stenosis (ICAS) in LVO is associated with recanalization failure. It was reported that truncal-type occlusion (TTO), which is a marker of ICAS, was associated with stent retriever failure (5). Additionally, clot characteristics can be an important hurdle for recanalization. Despite recent studies regarding clots, it is difficult to evaluate which clot characteristics would result in recanalization failure because sufficient clot burden could not be retrieved. Instead, a hyperdense artery sign (HAS) on computed tomography (CT) may indirectly show some characteristic differences among clots in LVO.

In the current study, we first categorized acute stroke patients with large vessel occlusion into embolic, intracranial atherosclerosis-related, tandem occlusion, and recanalization failure groups. Thereafter, we aimed to identify the clinical features and imaging findings with clues for the identification of occlusion etiology in the recanalization failure group with special focus on ICAS etiology in LVO, thrombus characteristics, and EVT methods.

METHODS

Study Population

Patients were retrospectively identified from the Acute Stroke due to Intracranial Atherosclerotic Occlusion and Neurointervention-Korean Retrospective (ASIAN KR) registry (6–8). Between January 2011 and May 2016, 720 patients who had undergone EVT for emergent large vessel occlusion were identified. From this registry, patients were included in the current study when (1) they had middle cerebral artery (MCA) M1 occlusion on baseline non-invasive angiography and underwent thrombectomy and (2) if the onset to puncture time was <24 h. Patients were excluded if the etiology of M1 was determined as dissection, Moyamoya disease, or vasculitis. After de-identification and blinding of clinical data, core laboratory imaging analysis was performed to ensure consistent grading and to eliminate bias. Initial large vessel occlusion location was identified on baseline CT or magnetic resonance angiography (S.J.L.). Infarct burden was measured using the Alberta Stroke Program Early CT Score (ASPECTS) (S.I.S.). Successful reperfusion was defined as a modified Treatment In Cerebral Ischemia grade of 2b−3 (9) (J.S.L. and Y.H.H.). The data collection protocol was approved by the Institutional Review Board of each hospital. This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Classification of Intracranial Large Vessel Occlusion Etiology

The etiology of MCA M1 occlusion was classified into four groups. The judgment of etiology was based on procedural angiography according to previous reports (Y.H.H. and J.S.L.) (6, 10). In brief, after confirmation of arterial occlusion, uncommon cerebral arterial diseases such as dissection, Moyamoya disease, and vasculitis were evaluated. If the occluded vessel was completely recanalized after primary thrombectomy such as stent retrieval, aspiration method, or local lytic methods but it was not involved in extracranial atherosclerosis, etiology was classified as embolic occlusion. If the occlusion was associated with extracranial atherosclerosis (i.e., tandem occlusion) and was completely recanalized, it was classified as tandem. Intracranial remnant stenosis of over 70%, moderate stenosis with tendency of re-occlusion, or flow impairment after successful recanalization through primary thrombectomy or additional lytic treatment was classified as ICAS. If the degree of recanalization could not be evaluated due to thrombectomy

Abbreviations: ASPECTS, alberta stroke program early CT score; BGC, balloon guide catheters; BSO, branching-site occlusion; CT, computed tomography; ESR, erythrocyte sedimentation rate; EVT, endovascular treatment; HAS, hyperdense artery sign; ICAS, intracranial atherosclerotic stenosis; LVO, large vessel occlusion; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; TTO, truncal-type occlusion.

failure after stent retrieval, aspiration method, or lytic treatment, it was classified as recanalization failure. In this group, partial or complete reperfusion could be achieved by balloon angioplasty or permanent stent deployment, but their classification as recanalization failure was not altered. After the procedure, the occlusion etiology was further confirmed by evaluating repeat angiography during admission after EVT (J.Y.) to exclude possible dissection or vasospasm. Finally, the following groups were included in the analysis: (1) embolic, (2) ICAS, (3) tandem, and (4) recanalization failure groups.

Imaging Analysis of Occlusion Types and Thrombus Characteristics

Previous studies have reported imaging markers to predict embolic occlusions and ICAS-related occlusions. A TTO sparing the major branches and their bifurcation sites beyond the occlusive segment was a predictive marker for ICAS-related LVO, while branching-site occlusion (BSO) involving the bifurcation site was a predictive marker for embolic origin of LVO (11, 12). For the current study, occlusion types were classified as either TTO or BSO based on baseline CT angiography by two individual interventional neurologists (S.J.L. and J.Y.) with consensus on discrepancy. For the MCA M1, if the bifurcation point and most proximal point of both M2 segments were visible, it was regarded as a TTO. Cases in which CT angiography images were not of sufficient quality to enable the differentiation between the two occlusion types were classified as inconclusive.

To analyze differences in thrombus burden (13), occlusion location (14), and evaluation of occlusion pathomechanism (15), HAS on non-contrast CT was evaluated (S.Y.P.). The location and distribution of HAS were evaluated by assessing involvement among four segments of the M1, and the total burden was scored on a scale of 0 to 4. The average Hounsfield units for the HAS were also evaluated.

Statistical Analysis

Frequency and distribution were compared among embolic, atherosclerotic, and undetermined groups. Differences between the groups were analyzed using the χ^2 test for categorical variables or analysis of variance. Direct comparison of frequency analyses and *post-hoc* Bonferroni test for continuous variables among groups were performed. A multiple logistic regression analysis was performed with clinically relevant variables for identification of risk factors for recanalization failure. A *p*-value of <0.05 was considered significant. Statistical analysis was performed using the SPSS statistical package (version 22.0, Chicago, IL).

Analysis of Recanalization Failure

In cases with recanalization failure, the patient data and imaging and procedural findings were carefully reviewed by experts to empirically conclude upon a presumed mechanism. A number of factors were considered into this analysis. Presence of atrial fibrillation favored cardioembolic etiology. Occlusion type on pre-procedure non-invasive angiographic images and upon stent retriever deployment was reviewed. TTO favored ICAS-related LVO, while BSO favored embolic etiology (11, 12). Presence of tandem occlusions proximal or distal to the main intracranial segment was evaluated. An atherosclerotic occlusion of the proximal ICA favored artery-to-artery embolisms, while distal ICA occlusions that completely recanalized, or tandem occlusions distal to main occlusions, were considered evidence for embolic etiology (16). Any thrombus migration distal to the initial occlusion site before or during EVT with no culprit stenosis was considered suggestive of embolic occlusions. The post-procedure non-invasive angiography performed usually on the next day was evaluated for delayed recanalization. If the delayed recanalization revealed a focal stenosis, it was considered evidence for ICAS, while complete recanalization was considered evidence for embolic occlusions (17).

RESULTS

Baseline Demographics and Risk Factors

A total of 326 patients were included in the analysis. Among them, 214 (65.6%) were classified as embolism, 76 (23.3%) as ICAS, 16 (4.9%) as tandem, and 20 (6.1%) as recanalization failure (**Figure 1**). Overall, embolic and failure groups shared similar clinical distributions, while tandem group and ICAS group shared some features (**Table 1**). Among the groups, atrial fibrillation was more frequent in embolic and failure groups (embolic, ICAS, tandem, and failure groups: 59.3, 18.4, 0, and 40.0%, respectively $p < 0.001$). National Institutes of Health Stroke Scale (NIHSS) scores tended to be higher in the failure group (15.9 ± 5.2, 14.5 ± 5.5, 14.6 ± 5.8, and 17.4 ± 7.8 $p = 0.097$), and the erythrocyte sedimentation rate (ESR) was the highest in the failure group (14.5 ± 15.7, 15.0 ± 14.1, 36.0 ± 32.9, 21.2 ± 19.5 $p < 0.001$). In contrast, male sex was more predominant in the ICAS and tandem groups (52.8 %, 67.1 %, 75.0 %, and 45.0 % $p = 0.047$). Smoking was more frequent in the ICAS and tandem groups (19.2 %, 35.5 %, 50.0 %, and 15.0 % $p = 0.002$), and low-density lipoprotein levels were also higher in the ICAS and tandem groups (99 ± 38, 118 ± 40, 107 ± 42, and 91 ± 34 mg/dl $p = 0.001$). Patients tended to be younger in the ICAS group (67 ± 13, 63 ± 14, 67 ± 8, and 67 ± 12 years $p = 0.095$).

Differences in Imaging Factors

Initial infarct burden as measured using the ASPECTS did not differ among the groups ($p = 0.253$) (**Table 1**). In terms of occlusion type, a TTO was more frequently observed in the ICAS group than in the other groups (8.1 vs. 37.5 vs. 0 vs. 16.7% $p < 0.001$). In the analysis of HAS distribution along the four segments of M1, HAS was most frequent in ICAS on the proximal first (38.4, 62.3, 25.0, and 26.3% $p = 0.001$) and the second segments (50.5, 69.6, 37.5, and 52.6% $p = 0.024$), while it was similarly frequent on the third segment among groups (75.3, 65.2, 75.0, and 68.4% $p = 0.424$), and it was less frequent in the ICAS group on the distal fourth segment (79.3, 62.3, 81.3, and 78.9% $p = 0.038$). The distribution of embolic, tandem, and recanalization failure groups did not differ (**Figure 2**). There were no differences in terms of total burden for the four points along the M1 segments (2 [2–3] vs. 2 [2–4] vs. 2 [2–2.75] vs. 2 [2–3] $p = 0.404$) or mean Hounsfield units of the HAS (60.7 ± 9.0 vs.

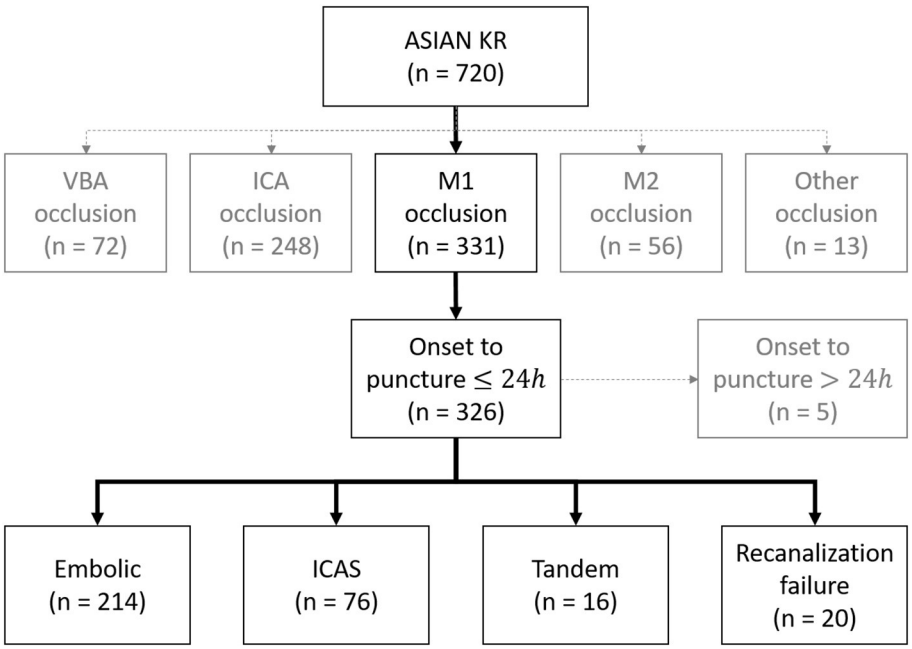

FIGURE 1 | Classification of acute intracranial occlusion based on EVT. ASIAN KR, acute stroke due to intracranial atherosclerotic occlusion and neurointervention-korean retrospective; VBA, vertebrobasilar artery; ICA, internal carotid artery; ICAS, intracranial atherosclerotic stenosis.

59.5 ± 8.7 vs. 60.2 ± 5.9 vs. 58.8 ± 6.7 $p = 0.668$), suggesting that there was no difference in thrombus characteristics.

EVT Findings

Procedure time was the longest in the recanalization failure group (63 ± 37, 79 ± 40, 72 ± 36, and 110 ± 54 min $p < 0.001$). The use of a balloon guide catheter (BGC) was significantly less frequent in the failure group (72.0, 72.4, 62.5, and 30.0% $p = 0.001$). Final reperfusion success (modified Treatment in Cerebral Ischemia grade 2b−3) was less frequent in the failure group (81.3, 77.6, 75.0, and 10.0% $p < 0.001$), and 3-month good outcome (modified Rankin Scale 0–2) was less frequent in the failure group (60.1, 53.9, 62.5, and 15.0% $p = 0.001$) (**Table 2**).

Factors Associated With Recanalization Failure and Presumed Pathomechanism

In the multivariable analysis of factors associated with recanalization failure, factors associated with occlusion etiology such as atrial fibrillation, proximal M1 involvement, or TTO patterns did not predict recanalization failure. Instead, significant factors were NIHSS [odds ratio (OR): 1.11, 95% confidence interval (CI): (1.01–1.22), $p = 0.027$], ESR [OR: 1.03, 95% CI: (1.01–1.05), $p = 0.006$], and non-use of BGC [OR: 3.41, 95% CI: (1.14–10.17), $p = 0.028$], suggesting the influence of systemic inflammation and procedural factors (**Table 3**). Upon careful review of each recanalization failure case, 16/20 (80.0%) were presumed to be embolic in origin, while 4/20 (20.0%) were presumed to be ICAS-related occlusions (**Table 4**). In cases of follow-up angiography, delayed recanalization was rare.

DISCUSSION

In the current study, the major finding was that recanalization failure in mechanical thrombectomy for LVO was not associated with underlying ICAS based on angiographic evaluation or thrombus characteristics based on CT HAS. Instead, initial high severity score, initial high ESR levels, and non-use of BGC were proven to be associated with recanalization failure.

How recanalization failure is defined is an important issue that needs to be addressed because its definition has been varied among previous studies. First, recanalization should be distinguished from reperfusion, although both terms represent the same situations in most cases (18). For intracranial LVO, complete reperfusion does not always follow complete recanalization, especially when small branches are occluded. In contrast, partial recanalization can be followed by complete reperfusion in the underlying ICAS cases among LVOs. Even though reocclusion of partial recanalization repeatedly occurs during mechanical thrombectomy, complete reperfusion can be achieved after the remnant stenosis site is stabilized by intra-arterial antiplatelet treatments (19, 20). During the neurointervention, an unfavorable response to intracranial EVT may fall into the three categories as follows (3–5, 21): (1) access failure due to vascular tortuosity or external carotid artery stenosis (2) thrombectomy refractoriness possibly due to fibrin clot and (3) partial recanalization or reocclusion on stent retrieval or contract aspiration. For the current study, partial recanalization was classified into the ICAS group. In addition, intracranial balloon angioplasty or stent insertion upon recanalization

TABLE 1 | Baseline characteristics and risk factors of the four etiologic groups.

	Embolism ($n = 214$)	ICAS ($n = 76$)	Tandem ($n = 16$)	Recanalization failure ($n = 20$)	*P*
Clinical characteristics					
Age	67 ± 13	63 ± 14	67 ± 8	67 ± 12	0.095
Male sex	113 (52.8%)	51 (67.1%)	12 (75%)	9 (45%)	0.047
Initial NIHSS	16.0 [13.0–20.0]	14.5 [11.0–18.8]	14.0 [10.0–20.5]	17.0 [12.3–21.0]	0.097
Hypertension	128 (59.8%)	43 (56.6%)	10 (62.5%)	15 (75%)	0.514
Diabetes mellitus	45 (21.0%)	22 (28.9%)	8 (50%)	3 (15%)	0.031
Dyslipidemia	63 (29.4%)	18 (23.7%)	6 (37.5%)	3 (15%)	0.345
Smoking	41 (19.2%)	27 (35.5%)	8 (50%)	3 (15%)	0.002
Atrial fibrillation	127 (59.3%)	14 (18.4%)	0 (0%)	8 (40%)	<0.001
CAOD	25 (11.7%)	2 (2.6%)	2 (12.5%)	1 (5%)	0.105
Prior antiplatelet	62 (29.0%)	9 (11.8%)	5 (31.3%)	5 (25%)	0.027
Prior anticoagulant	33 (15.4%)	6 (7.9%)	1 (6.3%)	1 (5%)	0.194
Hemoglobin (g/dl)	13.3 ± 1.84	14.0 ± 1.9	13.2 ± 1.4	13.1 ± 1.8	0.024*
Hematocrit (%)	39.5 ± 5.3	41.2 ± 5.2	38.3 ± 4.1	38.5 ± 4.3	0.027†
Platelet ($\times 10^3$)	214.6 ± 65.9	238.1 ± 66.7	282.8 ± 119.5	237.8 ± 95.3	0.001‡
WBC ($\times 10^3$)	8.1 ± 2.8	9.7 ± 3.8	10.0 ± 3.4	9.2 ± 3.0	<0.001*
Initial glucose (mg/dl)	139.9 ± 52.1	149.8 ± 61.2	151.8 ± 63.0	136.1 ± 36.3	0.395
HbA1c	6.2 ± 1.3	6.3 ± 1.4	6.5 ± 1.5	6.5 ± 1.0	0.644
Total cholesterol (mg/dl)	166.7 ± 65.1	185.4 ± 43.2	179.6 ± 44.6	161.0 ± 41.7	0.091
TG (mg/dl)	105.3 ± 59.5	137.9 ± 158.6	224.4 ± 390.5	104.6 ± 74.0	0.002‡
HDL (mg/dl)	45.1 ± 11.0	45.0 ± 10.4	42.8 ± 12.6	44.1 ± 8.4	0.854
LDL (mg/dl)	99.4 ± 37.6	118.4 ± 39.6	107.3 ± 42.0	91.4 ± 34.0	0.001§
ESR (mm/h)	14.5 ± 15.7	15.0 ± 14.1	21.2 ± 19.5	36.0 ± 32.9	<0.001|
CRP (mg/dl)	0.7 ± 1.4	1.3 ± 4.4	1.5 ± 3.3	1.02 ± 2.2	0.227
Imaging characteristics					
ASPECTS	7.0 [5.0–9.0]	8.0 [6.0–9.0]	6.0 [4.0–7.0]	6.0 [6.0–8.8]	0.253
TTO on baseline angiography	14 (8.1%)	24 (37.5%)	0 (0%)	3 (16.7%)	<0.001
HAS burden	2 [2–3]	2 [2–4]	2 [2–2.75]	2 [2–3]	0.404
Hounsfield unit inHAS	60.7 ± 9.0	59.5 ± 8.7	60.2 ± 5.9	58.8 ± 6.7	0.668

The data are presented as the mean ± standard deviation, frequency (percentage), or median [interquartile range].

**Embolism vs. ICAS, $p < 0.05$, Bonferroni post-hoc test; †embolism vs. ICAS, $p = 0.07$, Bonferroni post-hoc test; ‡embolism vs. tandem, $p < 0.05$, Bonferroni post-hoc test; §ICAS vs. embolism & recanalization failure, $p < 0.05$, Bonferroni post-hoc test; |recanalization failure vs. embolism & ICAS, $p < 0.05$, Bonferroni post-hoc test.*

ICAS, intracranial atherosclerotic stenosis; NIHSS, National Institutes of Health Stroke Scale; CAOD, coronary artery obstructive disease; WBC, white blood cell count; HbA1c, glycated hemoglobin; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; TTO, truncal-type occlusion; HAS, hyperdense artery sign.

failure without partial recanalization was classified into the failure group.

Another finding of our study is that recanalization failure in mechanical thrombectomy for LVO was not predominated by underlying ICAS. In the early generations of mechanical thrombectomy, the frequency of underlying atherosclerotic occlusions and its effect on recanalization failure were not completely understood. However, with primary stent retrieval, temporary bypass is usually seen in most patients (19). Analysis of large cohort data further showed that with appropriate rescue therapy such as intra-arterial tirofiban, angioplasty, or stent placement, the rates of reperfusion, or outcomes, may be similar when compared to those of embolic occlusions (6, 22). However, in cases where even temporary bypass is not achieved, how much does ICAS account for recanalization failure remains to be understood. The results of our study show that there is no predominance of atherosclerosis. The risk factors of recanalization failure were closer to embolic occlusion rather than ICAS-related occlusion. The frequency of atrial fibrillation, a major embolic source, was higher in both embolic and failure groups but less in the ICAS group. Well-known risk factors of atherosclerosis were not predominant in the failure group. In terms of imaging findings, the TTO pattern, a marker for ICAS in LVO, was less frequent in the failure group. Upon the HAS localization along the MCA M1 segment, it was found to be proximally located in the ICAS group, whereas it was more distally located in the embolic, tandem, and failure groups. Additionally, the assessment of presumed mechanism, which was evaluated *post-hoc* by expert opinion, showed that embolic occlusion might account for 80% of recanalization failure groups, while ICAS LVO accounts for 20%. These findings do not support the notion

that recanalization failure may be primarily associated with ICAS LVO.

In contrast, non-use of BGC was a significant predictor of recanalization failure. Along with contemporary mechanical thrombectomy devices such as stent retrieval and large-bore aspiration catheters, our results provide further evidence that BGCs significantly contribute to improvements in recanalization (23, 24). These consistent results highlight the importance of improvements in devices and thrombectomy techniques in achieving higher rates of reperfusion. In a study wherein stent-retriever thrombectomy was performed, no reperfusion was

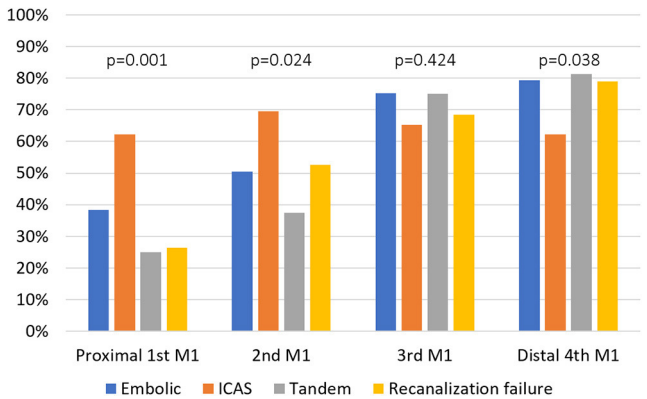

FIGURE 2 | Comparison of hyperdense artery signs on the four respective segments of M1 segment between the groups. MCA, middle cerebral artery; ICAS, intracranial atherosclerotic stenosis.

TABLE 3 | Predictors for recanalization failure.

Variables	Odds ratio (95% CI)	*P*
Age	–	
Atrial fibrillation	–	
NIHSS	1.11 (1.01–1.22)	0.027
ESR, per 1 mm/h increase	1.03 (1.01–1.05)	0.006
Truncal-type occlusion on baseline angiography	–	
HAS burden	–	
HAS M1 first segment involvement	–	
Non-use of balloon guide catheter	3.41 (1.14–10.17)	0.028

NIHSS, National Institutes of Health Stroke Scale; ESR, erythrocyte sedimentation rate; HAS, hyperdense artery sign.

TABLE 2 | Treatment and outcomes according to the four etiologic groups.

	Embolism (*n* = 214)	ICAS (*n* = 76)	Tandem (*n* = 16)	Recanalization failure (*n* = 20)	*P*
Intravenous thrombolysis	118 (55.1%)	33 (43.4%)	8 (50.0%)	10 (50.0%)	0.371
Onset to puncture (min)	308 ± 208	408 ± 271	393 ± 315	347 ± 240	0.010*
Procedure time (min)	63 ± 37	79 ± 40	72 ± 36	110 ± 54	<0.001†
Onset to final angiography	371 ± 212	487 ± 253	464 ± 310	457 ± 253	0.001*
Use of balloon guide catheter	154 (72.0%)	55 (72.4%)	10 (62.5%)	6 (30.0%)	0.001
Stent retrieval, *n* (%)	115 (53.7%)	62 (81.6%)	3 (18.8%)	14 (70.0%)	<0.001
Direct aspiration, *n* (%)	148 (69.2%)	40 (52.6%)	10 (62.5%)	12 (60.0%)	0.075
Intracranial balloon, *n* (%)	0 (0%)	6 (7.9%)	0 (0%)	1 (5.0%)	<0.001
Intracranial stenting, *n* (%)	1 (0.5%)	7 (9.2%)	2 (12.5%)	1 (5.0%)	<0.001
First EVT method					<0.001
Penumbra 1st	94 (43.9%)	27 (35.5%)	3 (18.8%)	9 (45.0%)	
Penumbra MAX	38 (17.8%)	9 (11.8%)	1 (6.3%)	2 (10.0%)	
Solitaire	59 (27.6%)	30 (39.5%)	1 (6.3%)	5 (25.0%)	
Trevo	10 (4.7%)	7 (9.2%)	0 (0.0%)	0 (0.0%)	
Lytic infusion	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Angioplasty	5 (2.3%)	3 (3.9%)	7 (43.8%)	2 (10.0%)	
Remote aspiration	7 (3.3%)	0 (0.0%)	4 (25.0%)	1 (5.0%)	
Others	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	
Number of techniques, median [IQR]	1 [1–2]	2 [1.25–2.75]	2 [1–2]	2 [1–3]	<0.001
Successful recanalization (AOL 2–3)	207 (96.7%)	53 (69.7%)	11 (78.6%)	3 (15%)	<0.001
Successful reperfusion (mTICI 2b−3)	174 (81.3%)	59 (77.6%)	12 (75.0%)	2 (10.0%)	<0.001
PH2 or SAH 3–4	11 (5.1%)	5 (6.6%)	1 (6.3%)	5 (25%)	0.009
Favorable outcomes	128 (60.1%)	41 (53.9%)	10 (62.5%)	3 (15.0%)	0.001

The data are presented as the mean ± standard deviation, frequency (percentage), or median [interquartile range].
**Embolism vs. ICAS, $p < 0.05$, Bonferroni post-hoc test; †Recanalization failure vs. embolism & ICAS & tandem, ICAS vs. embolism, $p < 0.05$, Bonferroni post-hoc test.*
ICAS, intracranial atherosclerotic stenosis; IQR, interquartile range; AOL, arterial occlusive lesion score; mTICI, modified Treatment in Cerebral Ischemia score; PH, parenchymal hematoma; SAH, subarachnoid hemorrhage.

TABLE 4 | Description of the 20 recanalization failure patients according to etiologic classification and expert opinion on presumed etiology.

Number	Age	Sex	NIHSS	ASPECTS	A-fib	Baseline occlusion pattern	Procedure findings	Post-procedure angio	Presumed mechanism
1	69	F	31	2	Y	TTO	Tandem distal ICA and M1 without ECAS	NA	Embolic (CE)
2	83	M	14	4	Y	BSO	Thrombus migration Culprit ulcerative ICA stenosis	Recanalization	Embolic (AA)
3	57	M	12	9	N	BSO	TTO on stent deployment, reocclusion	Occlusion	ICAS
4	70	M	23	6	Y	BSO	Visible thrombus	Occlusion	Embolic (CE)
5	77	F	19	6	N	BSO	BSO on stent deployment, procedural A1 embolization	NA	Embolic (Cryp)
6	64	F	19	3	Y	BSO	Ulcerated carotid plaque	Occlusion	Embolic (AA)
7	65	M	21	2	N	BSO	Persistent occlusion	NA	Embolic (Cryp)
8	82	F	18	6	N	TTO	Persistent occlusion	NA	ICAS
9	70	M	14	9	Y	BSO	BSO on stent deployment	Occlusion	Embolic (CE)
10	64	F	4	10	N	NA	BSO on stent deployment	Partial recanalization	ICAS
11	43	F	11	8	N	BSO	BSO on stent deployment, visible thrombus	NA	Embolic (Cryp)
12	73	M	11	6	N	BSO	Reocclusion, ICAS or dissection	Occlusion	ICAS
13	63	F	21	6	N	BSO	Thrombus migration	NA	Embolic (Cryp)
14	75	F	5	8	Y	NA	BSO on stent deployment	Occlusion	Embolic (CE)
15	65	F	13	6	Y	BSO	Thrombus migration	Occlusion	Embolic (CE)
16	34	M	19	7	N	BSO	Persistent occlusion	NA	Embolic (Cryp)
17	75	F	16	6	N	BSO	BSO on stent deployment, thrombus migration	NA	Embolic (Cryp)
18	71	M	24	7	N	BSO	BSO on stent deployment	Occlusion	Embolic (Cryp)
19	76	F	37	10	Y	TTO	Tandem distal ICA and M1 occlusion without ECAS	Occlusion	Embolic (CE)
20	73	M	16	9	N	BSO	Tandem distal ICA and MCA occlusion	Occlusion	Embolic (AA)

NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; A-fib, atrial fibrillation; TTO, truncal-type occlusion; ICA, internal carotid artery; ECAS, extracranial atherosclerotic stenosis; CE, cardioembolic; BSO, branching-site occlusion; AA, artery-to-artery; ICAS, intracranial atherosclerotic stenosis; Cryp, cryptogenic source.

achieved in 10.6% cases (25). Among these failures, most were due to technical difficulties, stent-retriever failure, and inability to reach target occlusion. We agree that technical development and scientific effort should focus on thrombectomy efficacy as well as tools and alternative access routes to improve cervical and intracranial access. In addition to ICAS cases, when encountered with an intractable occlusion, the rational method would be to increase efforts for thrombus removal, rather than angioplasty of the vessel wall, until there is evidence otherwise.

Further, in our study, thrombus characteristics were not associated with a specific occlusion etiology such as embolism or ICAS, which is in agreement with a previous meta-analysis (26). It is generally considered that a red blood cell-dominant clot shows higher attenuation and is more responsive to mechanical thrombectomy, while an intractable fibrin clot is likely to have more hypoattenuation and absence of HAS (26). However, large published cohorts evaluating thrombus attenuation have not shown increased rates of reperfusion (27, 28). Research is needed to establish if thrombus composition affects reperfusion outcomes and if CT-based attenuation evaluation is the most sufficient way to detect thrombus composition.

Elevated ESR was associated with recanalization failure in this study. There is evidence that various inflammation-based scores are associated with outcomes after mechanical thrombectomy (29). Furthermore, inflammation is associated with thrombus formation. There is evidence that neutrophil extracellular traps, a form of neutrophil-mediated immunity, contribute to ischemic stroke thrombi (30). Clots associated with large artery atherosclerosis showed significantly higher interleukin-1β expression tumor necrosis factor-α and matrix metalloproteinase-9 expression was significantly higher in clots with a negative susceptibility vessel sign than in those with a positive susceptibility vessel sign (31). We can extrapolate from our results that an inflammatory mechanism may play a role in thrombi with recanalization failure. Targeting such mechanisms may have potential.

This study has some limitations. First, as the classification of pathomechanism is not based on pathologic confirmation,

it may be subject to errors. Nevertheless, the ICAS definition of the current study has been utilized numerous times in similar studies (6, 10, 15). For recanalization failure, we focused on recanalization failure without treatment methods that can potentially alter the morphology of the arterial structure, as such would result in alteration of the classification of pathomechanism. We clearly define this in the *METHODS* section. Second, while we performed analysis of thrombus characteristics by evaluation of HAS and vessel attenuation, the CT analysis used was 5-mm thick and may introduce a certain margin of error due to partial volume effect (32). The best imaging methods to describe thrombus characteristics and if thrombus characteristics indeed affect the response to mechanical thrombectomy need further study. Third, while we used preprocedure CT-based occlusion-type analysis in this study, the sensitivity for detection of fixed focal stenosis in the MCA vascular bed is modest, while the specificity is high (12). Application of TTO on a case-by-case basis may be liable to errors. Occlusion-type analysis after stent retriever deployment could not be applied to our study due to the heterogeneous reperfusion modality used and was used only for clues of occlusion etiology in the recanalization failure group. However, in the recanalization failure group, the rates of CTA-based TTO were much lower than those of the ICAS group and approached that of the embolic group. Fourth, our results regarding thrombus burden may be biased by our selection criteria, which included only patients with M1 occlusions. In terms of thrombus burden, poor outcomes (33) have been reported with increasing thrombus burden, while other studies have shown no association between clot burden score and outcomes or reperfusion (34). It is generally understood that thrombectomy is effective in achieving successful recanalization and good clinical outcomes throughout the entire range of clot burden score values. Further studies are needed to address these issues.

In conclusion, through a stepwise approach to evaluate occlusion etiology and thrombus imaging analysis in acute ischemic stroke patients with MCA M1 occlusion, we could identify that recanalization failure was neither predominantly due to differences in target vessel pathology such as ICAS nor was it associated with differences in thrombus characteristics. Improvements in mechanical thrombectomy devices and procedures, such as BGCs, and addressing the role of inflammation in thrombus formation may be potential targets to improve recanalization.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ajou university hospital IRB. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

S-JL, SP, and JL contributed to the conception and design of the study, acquisition and analysis of data, and preparation of the manuscript. Y-HH, S-IS, JH, JC, D-HK, Y-WK, Y-SK, J-HH, JY, and C-HK contributed to acquisition and analysis of data and reviewed the manuscript for critical intellectual content. RN reviewed the manuscript for critical intellectual content. All authors contributed to the article and approved the submitted version.

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Risk Factors of New Cerebral Infarctions After Endovascular Treatment for Basilar Artery Stenosis Based on High-Resolution Magnetic Resonance Imaging

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Objective: The current study aims to analyze the risk factors of new cerebral infarctions in the distribution of basilar artery (BA) detected by diffusion-weighted imaging (DWI) after endovascular treatment in patients with severe BA stenosis.

Methods: Data was collected from the electronic medical records of patients with severely atherosclerotic basilar artery stenosis (≥70%) who underwent endovascular treatment. The plaque characteristics, including the plaque distribution, plaque burden, plaque enhancement index, remodeling ratio, and stenosis degree, were evaluated qualitatively and quantitatively using high-resolution magnetic resonance imaging (HR-MRI) and digital subtraction angiography (DSA). The characteristics of the procedure, such as the type of treatment, balloon diameter, balloon length, stent diameter, and stent length, were analyzed.

Results: A total of 107 patients with severe basilar artery stenosis (≥70%) who underwent endovascular treatment were enrolled. The study participants included 77 men and 30 women, with an average age of 61.6 ± 8.1 years. The rate of postoperative new cerebral infarctions was 55.1% (59/107), of which 74.6% (44/59) were caused by artery-to-artery embolism, 6.8% (4/59) due to perforator occlusion, and 18.6% (11/59) were caused by a mixed mechanism. Twelve of 59 patients had ischemic events, with nine cases of stroke and three cases of transient ischemic attacks (TIA). The plaque burden in the DWI-positive group was significantly larger than that in the DWI-negative group (3.7% vs. −8.5%, $p = 0.016$). Positive remodeling was more common in the DWI-positive group than in the DWI-negative group (35.6% vs. 16.7%, $p = 0.028$). Smoking was inversely correlated with the rate of new cerebral infarctions (odds ratio, 0.394; 95% confidence interval, 0.167–0.926; $p = 0.033$).

Conclusion: The plaque characteristics are not associated with new cerebral infarctions in the distribution of BA, although a large plaque burden and positive remodeling are more

likely to appear in patients with new cerebral infarctions after BA stenting, which warrants further studies with a larger sample size. As for smoking, the inverse correlation with new cerebral infarctions in the BA territory needs large-scale prospective randomized controlled trials to verify.

Keywords: basilar artery stenosis, new cerebral infarctions, high-resolution magnetic resonance imaging, smoking, plaque burden, remodeling index

INTRODUCTION

Basilar artery (BA) atherosclerotic stenosis is a common cause of transient ischemic attacks (TIA) and stroke, accounting for approximately 20% of symptomatic ischemic infarctions of the posterior circulation (1). Endovascular therapy is an effective alternative treatment for drug-refractory BA stenosis. However, endovascular treatment for BA atherosclerotic stenosis has a high perioperative complication rate. The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial described that the stroke or death rate due to BA atherosclerotic stenosis was as high as 21.6% after BA stenting (2). However, the new cerebral infarction rate detected by diffusion-weighted imaging (DWI) may be higher given that the definition of stroke is the combination of new cerebral infarctions on DWI and clinical symptoms of neurological deficits, as well as some new cerebral infarctions that have no clinical symptoms and are only detected by DWI (3). Indeed, some studies have reported that the prevalence of new cerebral infarctions discovered by DWI is as high as 70% after endovascular treatment (4, 5).

Although most new cerebral infarctions after endovascular treatment are silent without clinical symptoms, the long-term risk of neurological deficits is enormous. Several studies have found that silent infarctions can lead to subcortical cavities, cortical atrophy, and glial cell proliferation, resulting in long-term complications such as cognitive decline, impaired motor coordination, poor visual reactivity, mental disorders, and even a high risk of long-term stroke (6, 7). Indeed, previous studies have reported that silent infarctions increase the risk of recurrent stroke by 2–3-fold, despite strict control of vascular risk factors (8). Therefore, it is crucial to identify the risk of new cerebral infarctions after endovascular treatment.

Previous studies have shown that silent cerebral infarctions are associated with advanced age, hypertension, and diabetes mellitus in the natural course (7, 9). However, few studies have focused on exploring the risks of new cerebral infarctions in the BA territory after endovascular treatment for BA stenosis, in particular, the relationship between plaque characteristics and new cerebral infarctions. High-resolution magnetic resonance imaging (HR-MRI) is an imaging evaluation technology for plaque characteristics that has emerged in recent years. HR-MRI has advantages including high resolution, visualization of the vascular wall structure, and non-invasiveness, and is considered a reliable evaluation method for evaluating plaque characteristics (10). Furthermore, HR-MRI can be used to assess the plaque location, burden, enhancement ratio, size, length, and area, as well as the remodeling index both qualitatively and quantitatively (11–13). In the current study, we retrospectively explored the risk factors of new cerebral infarctions in the BA territory detected by DWI after endovascular treatment for BA stenosis based on HR-MRI in Chinese individuals. We also sought to determine the risk factors associated with patient demographics and the endovascular treatment procedure.

MATERIALS AND METHODS

This study was conducted in accordance with the Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of our center, and given the retrospective nature of the study and the fact that data were analyzed anonymously, the study was exempted from obtaining consent from patients. The demographic characteristics, plaque imaging features, and procedure characteristics were examined to analyze the risk of new cerebral infarctions detected by DWI.

Study Populations and Demographics

We retrospectively enrolled patients with basilar atherosclerotic stenosis who were treated by endovascular therapy between January 1, 2012, and December 31, 2019. The inclusion criteria were as follows: (1) Patients with symptomatic atherosclerotic stenosis of the BA aged from 18 to 80 years, (2) the degree of stenosis of the lesions was more than 70% confirmed by digital subtraction angiography (DSA), (3) HR-MRI was performed before intervention, and (4) the sequence of DWI was performed 72 h before and after the surgery. Some patients were excluded based on the following criteria: (1) Acute BA occlusion treated by endovascular therapy; (2) endovascular therapy for another intracranial and extracranial vessel disease simultaneously; (3) BA stenosis accompanied with moderate-to-severe stenosis of the vertebral artery; (4) non-atherosclerotic cause of BA stenosis, such as Moyamoya disease, vasculitis, or vascular dissection; and (5) preoperative DWI suggested large-area cerebral infarctions ($\geq$1/2).

The demographic data of patients were collected, including age, gender, body mass index (BMI), vascular risk factors (hypertension, diabetes, hyperlipidemia, coronary heart disease [CHD], qualifying events, smoking history, and drinking history), modified Rankin score (mRS) at admission and discharge, and preoperative and postoperative results of DWI. The evaluation of the new infarction was based on a new high signal on DWI and a new low signal on apparent diffusion coefficient (ADC) imaging after 72 h of intervention compared with pre-operative imaging. If a new infarction was

detected in the blood supply area of the BA, such as the brainstem, cerebellum, occipital lobe, or thalamus, the patient was classified as DWI positive (DWI+). If the patient had new infarctions in other districts or no new infarction, the patient was classified as DWI negative (DWI–). As for smoking history, non-smokers were defined as not smoking currently or previously, or as smokers.

Imaging Protocol and Analysis

All eligible patients were examined by a 1.5T or 3.0T magnetic resonance imaging (MRI) system (MAGNETOM Avanto; Siemens Healthineers) with a standard 8-channel head coil to assess the characteristics of BA stenosis. Multi-sequence scans were performed as follows: time-of-flight magnetic resonance angiography (TOF-MRA), fast spin-echo T1-weighted imaging (T1WI-FSE), and T1-weighted enhanced imaging (T1WI + C). The coronal acquisition parameters were as follows: repetition time, 550 ms; echo time, 27 ms; field of view, 200 × 200 cm; layer thickness, 0.6 mm, and echo-train length, 158. The T1WI + C sequence was scanned 5 min after the intravenous injection of gadopentetate meglumine. All images required reconstruction for image analysis from axial, coronal, and sagittal views.

All plaque images were analyzed using CMRtools (Cardiovascular Imaging Solutions Ltd., UK) by two experienced neuroradiologists who were not involved in statistical analyses. The original data with the type of digital imaging and communications in medicine (DICOM) were required for image analysis. The measurements of the vessel area (VA) and lumen area (LA) were performed on cross-sectional T1-weighted BA images at the maximal lumen narrowing (MLN) or reference sites after zooming in 400 times. We used two lines to divide the axial lumen into four quadrants: ventral, dorsal, left, and right (11, 13). The plaque was considered to belong in the quadrant which had the thickest part of the plaque. If the plaque had a large span and the thickest part was between two quadrants, it was defined as being distributed in more than two quadrants. The reference site was selected at the normal segment of proximal or distal stenosis according to the criteria of WASID (Warfarin vs. Aspirin for Symptomatic Intracranial Disease) where the proximal segment was preferred, but the distal vessel was considered when the proximal segment was diseased (14). Wall area (WA) was measured using VA–LA, and the plaque burden was defined as, $[(WA_{MLN}\text{-}WA_{reference})/VA_{MLN}] \times 100\%$. The remodeling index (RI) was defined as, $[VA_{MLN}/VA_{reference}]$; RI $\geq$ 1.05 was defined as positive remodeling, RI $\leq$ 0.95 as negative remodeling, and RI between 0.95 and 1.05 as intermediate remodeling. The contrast enhancement ratio was measured at the slice of the MLN that was normalized by the signal from adjacent gray matter. The enhancement ratio was calculated by, [signal of plaque (post-contrast)/signal of gray matter (post-contrast)]/[signal of plaque (pre-contrast)/signal of gray matter (pre-contrast)] × 100% (15).

Interventional Procedure and Analysis

The culprit lesions were treated by neurosurgeons who had more than 15 years of experience with endovascular treatment, including primary angioplasty, balloon-mounted stent placement (Apollo), and self-expansion stent placement (Gateway-Wingspan system). The therapeutic strategies were decided by the operators according to the characteristics of the lesion and their own experience; more details are provided in a previous study (16). All patients received preoperative medication with a combination of aspirin (100 mg daily) and clopidogrel (75 mg daily) started 5 d prior to the procedure, or a loading dose of aspirin and clopidogrel (300 mg each) 1 d before the procedure. During the procedure, systematic heparin was administered by intravenous injection at a dose of 2/3 mg per kg of body weight. The standard of procedure was referred to as the protocol of CASSISS (China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis) (17). The three types of intervention, primary angioplasty, self-expansion stent (SES), and balloon-mounted stent (BMS), had different procedures. Angiography with a high-pressure contrast agent was followed by balloon pre-expansion during primary angioplasty. As for SES placement, the procedure was similar to that for primary angioplasty except for the self-expansion stent placement after angiography. As for BMS placement, the balloon expanded the stent mostly without the need for pre-expansion.

The parameters of the procedure were collected, including the vessel diameter (VD) at the most stenotic site and reference site, length of the lesion, intervention method, diameter and length of the balloon and/or stent, and pressure (P) before and/or after expansion. The degree of stenosis was defined as $[(1\text{-}VD_{MLN}/VD_{reference}) \times 100\%]$ in accordance with the standard of WASID (14). We also defined new composite variables to explore the relationship between the lesion and instruments. The diameter ratio was defined as the maximal diameter of the implant divided by the VD_{MLN} and $VD_{reference}$, respectively.

The BA was divided into three segments according to the branch of the anterior inferior cerebellar artery and the superior cerebellar artery: low, middle, and high segments (18).

Statistical Analysis

Statistical analyses were performed using SPSS 25.0 (IBM). Continuous variables are described as means ± SD and categorical variables as frequency and percentage. Student's *t*-test or Mann–Whitney *U* test was used for the comparison of continuous variables, and the chi-square test was used for categorical variables. Covariates with a univariate p-value < 0.10 were subsequently enrolled in multivariate logistic regression analysis. The odds ratio (OR) with 95% confidence interval (CI) was determined using a logistic regression model. P-values < 0.05 were considered to indicate statistical significance.

RESULTS

Demographic Characteristics

A total of 376 consecutive patients with BA stenosis underwent endovascular treatment at our center from January 1, 2012, to December 31, 2019; among them, 107 patients were eligible after screening (see **Figure 1**). The patients comprised 77 men and 30 women with an average age of 61.6 ± 8.1 years. The success rate of endovascular therapy was 100%. The mRs of most patients ranged from 0 to 1, with a proportion

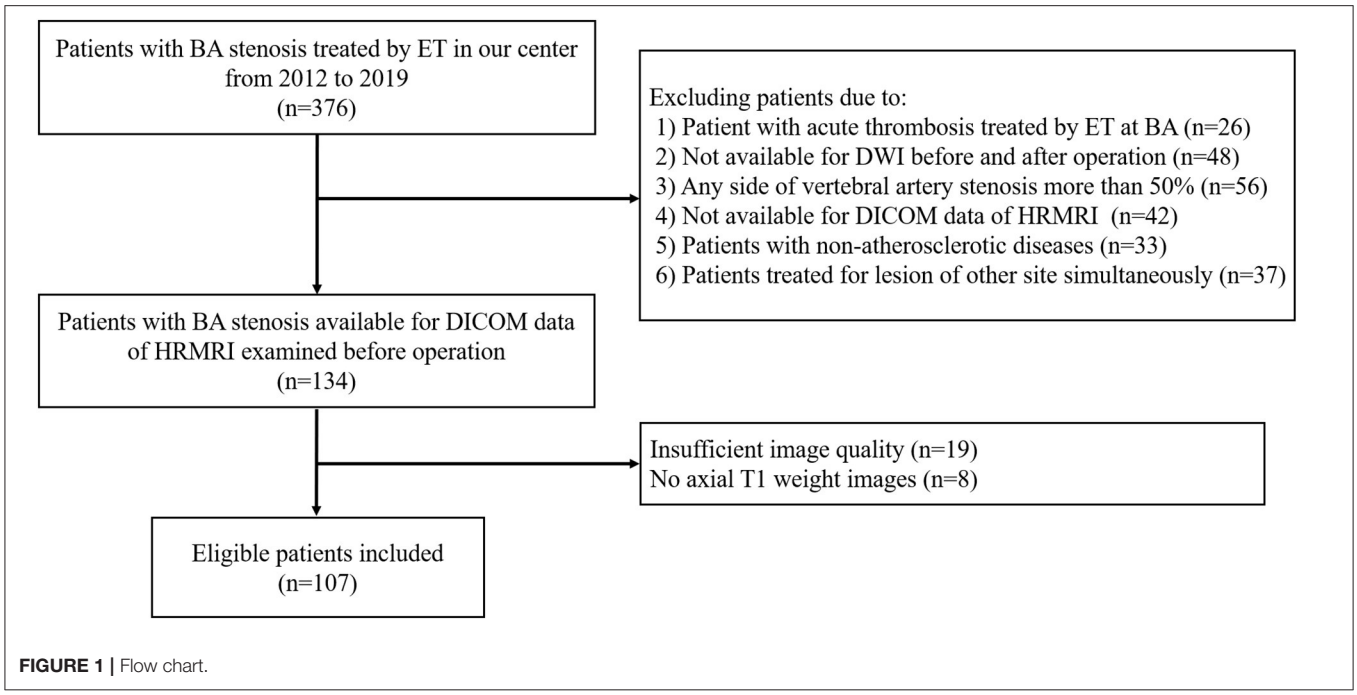

FIGURE 1 | Flow chart.

of 86.3%. Fifty-nine patients (55.1%) developed new cerebral infarctions after endovascular therapy as evaluated by DWI; among these, 12 patients had ischemic events, with nine cases of stroke and three cases of TIA. There was no death at discharge. As for the mechanisms of infarctions, 74.6% of infarctions (44/59) were caused by artery-to-artery embolism, 6.8% (4/59) by perforator occlusion, and 18.6% (11/59) by a mixed mechanism. There was a significant difference in smoking history ($p = 0.021$) between DWI– and DWI+ patients. The detailed demographic characteristics are described in **Table 1**.

TABLE 1 | Demographic Characteristics.

Variables	All patients ($n = 107$)	DWI– ($n = 48$)	DWI+ ($n = 59$)	*P*-value
Age (y)	61.6 ± 8.1	60.7 ± 8.3	62.4 ± 7.9	0.296
Male	77 (72.0%)	37 (77.1%)	40 (67.8%)	0.287
BMI	26.4 ± 3.0	26.3 ± 3.0	26.4 ± 3.0	0.875
Hypertension	88 (82.2%)	39 (81.3%)	49 (83.1%)	0.808
Diabetes Mellitus	46 (43.0%)	18 (37.5%)	28 (47.5%)	0.301
Hyperlipidemia	19 (17.8%)	9 (18.8%)	10 (16.9%)	0.808
CHD	13 (12.1%)	3 (6.3%)	10 (16.9%)	0.092
Arrhythmia	4 (3.7%)	2 (4.2%)	2 (3.4%)	0.609
Smoking history	47 (43.9%)	27 (56.3%)	20 (33.9%)	0.021
Drinking history	29 (27.1%)	13 (27.1%)	16 (27.1%)	0.997
Qualifying event				0.487
TIA	13 (12.1%)	7 (14.6%)	6 (10.2%)	
Stroke	94 (87.9%)	41 (85.4%)	53 (89.8%)	
Pre-operation mRs				0.059
<2	93 (86.9%)	45 (93.8%)	48 (81.4%)	
≥2	14 (13.1%)	3 (6.2%)	11 (18.6%)	

BMI, body mass index; CHD, coronary heart disease; mRS, modified Rankin Scale.

Characteristics Based on HRMRI, DSA, and the Procedure of Endovascular Treatment

The average stenosis of patients was 77.8 ± 6.8%, with 57.9% of lesions presented at the middle segment of BA from the coronal view and 34.6% at the ventral BA from the axial view. Half of the lesions were eccentric, while the rest presented as either C type or circular type. Most lesions had non-positive remodeling, with a proportion of 72.9%. More than half of the BA stenosis (57.9%) was treated with self-expansion stenosis. The most common site of the lesions was the middle segment of the BA (57.9%) and the ventral region of the BA (34.6%) (**Figures 2**, **3**). There were significant differences in wall area of the reference vessel (17.1 mm^2 vs. 15.1 mm^2, $p = 0.040$), plaque burden (−8.5% vs. 3.7%, $p = 0.016$), and positive remodeling (16.7% vs. 35.6%, $p = 0.028$) between DWI– and DWI+ patients. More details are presented in **Tables 2**, **3**.

Multivariate Analysis

According to the results of conventional statistical analysis with $p < 0.10$, these covariates, including CHD, smoking history, preoperative mRs, plaque burden, and remodeling index, were included in the multivariate logistic regression analysis. Although the *p*-values of the vessel area and wall area at the reference site were <0.10, they were not included in the multivariate analysis because the plaque burden and remodeling type were calculated. Multivariate analysis demonstrated that smoking was an independent factor for new cerebral infarctions (OR, 0.394; 95% CI, 0.167–0.926, $p = 0.033$). More details are presented in **Table 4**.

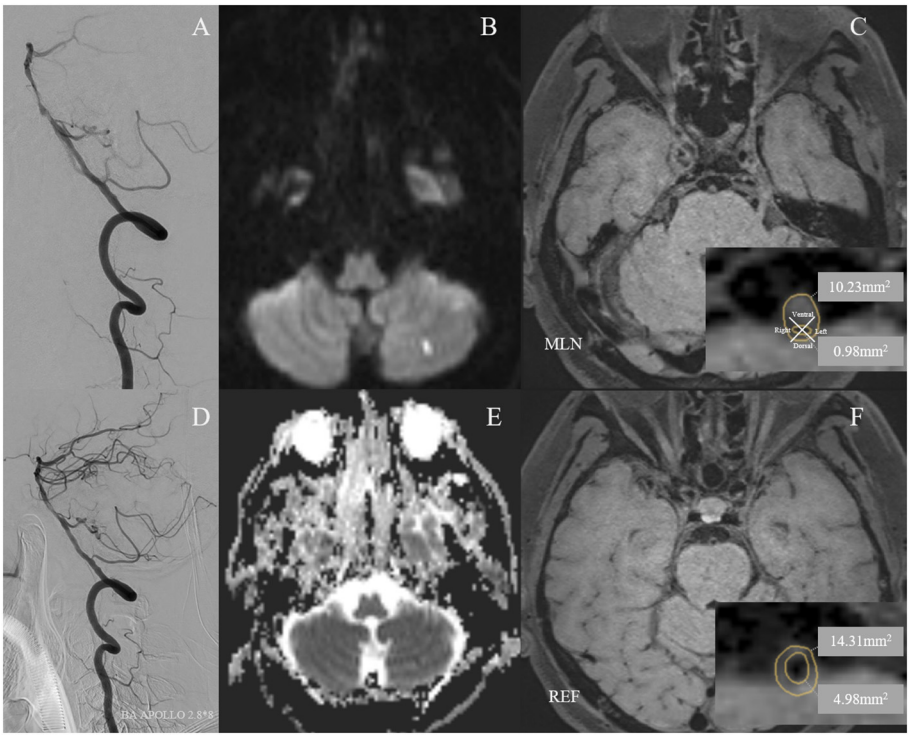

FIGURE 2 | A 59-year-old man with cigarette smoking history and drinking history presented with recurrent transient attacks of dizziness for 2 months. **(A)** Pre-operative digital subtraction angiography (DSA) showed stenosis at the middle segment of the basilar artery (BA) with 75.5% of degree. **(D)** A 2.8×8 mm Apollo balloon-mounted stent (MicroPort NeuroTech, Shanghai, China) was placed at the stenotic segment. The patient had a new cerebral infarction at the left cerebellum within 72 h after stenting without clinical symptoms, which was detected by diffusion-weighted imaging with a new high signal **(B)** and apparent diffusion coefficient imaging with a new low signal **(E)**. Figures of the right column are cross-sectional T1-weighted BA images at the maximal lumen narrowing (MLN) **(C)** and reference (REF) **(F)** sites. The plaque was eccentric and belonged to the ventral side of the BA **(C)**. Vessel area (VA) and lumen area (LA) at the MLN (**C**, VA 10.23 mm^2, LA 0.98 mm^2) or REF (**F**, VA 14.31 mm^2, LA 4.98 mm^2) sites were manually traced for measuring after zooming in 400 times. Wall area (WA) at the MLN or REF sites was calculated by VA-LA. The plaque burden was calculated as $[(WA_{MLN}\text{-}WA_{REF})/VA_{MLN}] \times 100\%$ and the remodeling index was calculated as VA_{MLN}/VA_{REF}. Therefore, the plaque burden was −0.78%. The remodeling index of the vessel at MLN was 0.71, which was categorized as negative remodeling.

DISCUSSION

The impact of new cerebral infarctions has been largely ignored in clinical practice, especially those cases without clinical symptoms. Most clinical studies, including multicenter randomized controlled studies, only regarded symptomatic cerebral infarctions (stroke) or TIA as the endpoint, which reduces the public's knowledge of new cerebral infarctions without clinical symptoms, known as silent cerebral infarctions (19, 20). Although some new cerebral infarctions have no symptoms, they still pose as a high-risk factor for stroke in the future (8). In addition, silent cerebral infarctions can cause long-term cognitive impairment, impaired motor coordination, and mental illness (6, 21, 22). Therefore, some experts have suggested that the definition of silent cerebral infarctions should be replaced by covert cerebral infarctions, which are difficult to detect by contemporary evaluation methods (23).

The history of endovascular treatment may rapidly increase the probability of new cerebral infarctions without clinical symptoms. However, few studies have reported the incidence of new cerebral infarction after endovascular treatment for BA stenosis. In the current study, the incidence of new cerebral infarctions in the distribution of BA was 55.1%, with 43.9% of them being silent cerebral infarctions, which is consistent with the rate of 15–70% of new cerebral infarctions after carotid stenting (5, 24). Artery-to-artery embolism was the most common infarction mechanism, similar to the findings of previous studies (25). The results demonstrated that smoking, plaque burden, and positive remodeling may be the influencing factors for new cerebral infarctions. Smoking was independently associated with new cerebral infarctions.

Smoking Is Inversely Associated With the Risk of New Cerebral Infarctions After Endovascular Treatment

As we all know, smoking is a classic risk factor for cardiovascular diseases. Indeed, some studies have reported that the 10-year risk of death was 2-fold in smokers compared to that in non-smokers; smoking has been shown to be the most important risk factor for premature death (26, 27). The damaging effect of smoking has been attributed to several dysfunctions, including endothelial dysfunction, inflammation, and a state of prothrombotic formation (28, 29).

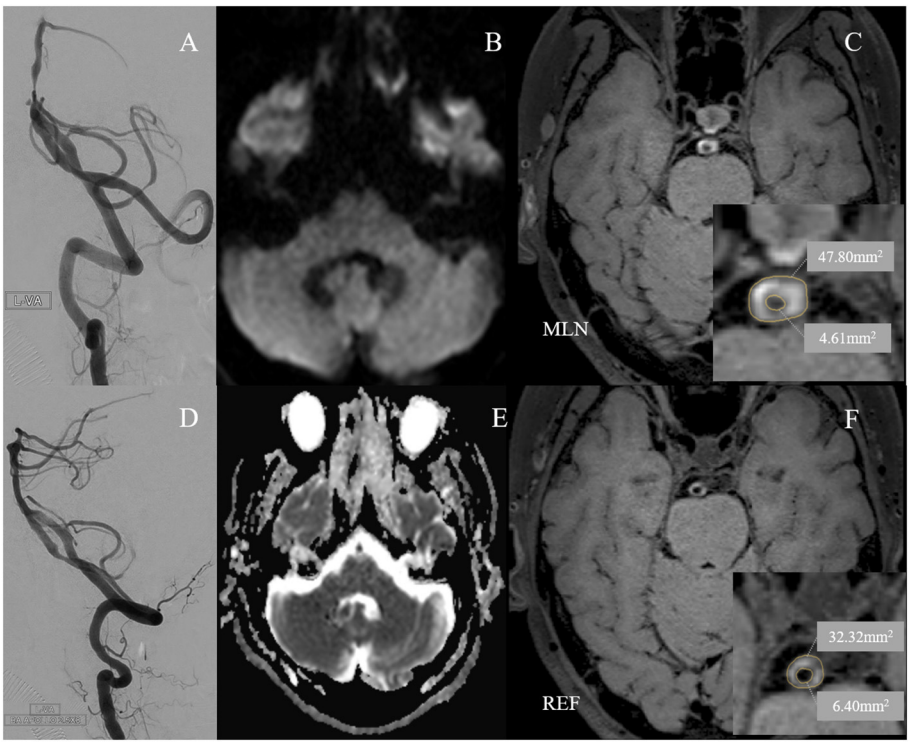

FIGURE 3 | A 60-year-old man with cigarette smoking history presented with recurrent transient attacks of vertigo for 1 month. **(A)** Pre-operative digital subtraction angiography (DSA) showed stenosis at the low segment of the basilar artery (BA) with 77.7% of degree. **(D)** A 2.5 × 8 mm Apollo balloon-mounted stent (MicroPort NeuroTech, Shanghai, China) was placed at the stenotic segment. There was no new cerebral infarction confirmed by diffusion-weighted imaging **(B)** and apparent diffusion coefficient imaging **(E)** within 72 h after stenting. Figures of the right column are cross-sectional T1-weighted BA images at the maximal lumen narrowing (MLN) **(C)** and reference (REF) **(F)** sites. The plaque was concentric and belonged to the circular type **(C)**. Vessel area (VA) and lumen area (LA) at the MLN (**C**, VA 47.80 mm^2, LA 4.61 mm^2) or REF (**F**, VA 32.32 mm^2, LA 6.40 mm^2) sites were manually traced for measuring after zooming in 400 times. Wall area (WA) at the MLN or REF sites was calculated by VA-LA. The plaque burden was calculated as [(WA_{MLN}-WA_{REF})/VA_{MLN}] × 100% and the remodeling index was calculated as VA_{MLN}/VA_{REF}. Therefore, the plaque burden was 36.1%. The remodeling index of the vessel at MLN was 1.48, which was categorized as positive remodeling.

Unexpectedly, there was a paradoxical phenomenon similar to our finding in a large number of studies. Some studies on fibrinolytic therapy for cardiovascular diseases have shown that smokers are associated with better in-hospital and short-term follow-up outcomes. The results of the multivariate analysis demonstrated that smoking was associated with better short-term outcomes (adjusted OR, 0.80; 95% CI, 0.72–0.90) (30). One of the hypotheses was that thrombosis formation was more common in smokers. Another interpretation was that smokers with acute stroke were younger than non-smokers and had lower rates of complications, such as diabetes mellitus and hypertension. Similarly, in the era of endovascular treatment for cardiovascular diseases, the paradoxical effect of smoking was demonstrated in landmark clinical trials, where the short-term prognosis for smokers with acute cardiovascular diseases after mechanical thrombectomy was better than that for non-smokers (adjusted OR: 0.54, 95% CI: 0.38–0.76) (31, 32). Furthermore, previous studies of a subgroup analysis of the International Carotid Stenting Study (ICSS) demonstrated a reduced incidence of 30-day postoperative major adverse events in smokers compared with non-smokers (adjusted OR, 0.33; 95% CI, 0.13–0.85) (33). Some studies have given some explanations for this phenomenon. Dual antiplatelet therapy, including aspirin and clopidogrel, is an essential preoperative preparation for endovascular treatment with conventional or loading doses. Tobacco smoking could enhance the antiplatelet effects of clopidogrel by affecting the enzyme responsible for converting clopidogrel into its active form, which increases the ability to resist platelet aggregation and reduces the probability of thrombogenesis (34, 35). Meanwhile, some researchers suspected that smoking may create a vascular disease state that is more responsive to clopidogrel, even when the patients have not smoked for several years (36).

Plaque Characteristics Associated With New Cerebral Infarctions After Endovascular Treatment

Although plaque characteristics were insignificant in the multivariate analysis, we found that large plaque burden and positive remodeling was higher in the DWI+ group than in the DWI− group in accordance with univariate analysis. The greater the plaque burden with a large lipid core, the higher the risk of new cerebral infarctions after endovascular treatment, because the risk of the plaque breaking increases during

TABLE 2 | Lesion characteristics based on HRMRI and DSA.

Variables	All patients (n = 107)	DWI– (n = 48)	DWI+ (n = 59)	*P*-value
Stenosis site (coronal view)				0.506
Low	40 (37.4%)	19 (39.6%)	21 (35.6%)	
Middle	62 (57.9%)	28 (58.3%)	34 (57.6%)	
Low & Middle	5 (4.7%)	1 (2.1%)	4 (6.8%)	
Stenosis site (axial view)				0.141
Ventral	37 (34.6%)	11 (22.9%)	26 (44.1%)	
Side	31 (29.0%)	16 (33.3%)	15 (25.4%)	
Dorsal	18 (16.8%)	9 (18.8%)	9 (15.5%)	
≥2 quadrant	21 (19.6%)	12 (25.0%)	9 (15.3%)	
Plaque morphology				0.245
Eccentric	58 (54.2%)	29 (60.4%)	29 (49.2%)	
C type and circular	49 (45.8%)	19 (39.6%)	30 (50.8%)	
Tandem lesion	8 (7.5%)	2 (4.2%)	6 (10.2%)	0.240
Stenosis (%)	77.8 ± 6.8%	77.8 ± 6.2%	77.8 ± 7.5%	0.961
Diameter at MLN (mm)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.723
Diameter at reference (mm)	2.8 ± 0.6	2.7 ± 0.6	2.7 ± 0.5	0.565
Plaque length (mm)	6.6 ± 3.2	6.2 ± 2.8	6.9 ± 3.5	0.369
Plaque length/Degree of stenosis	8.5 ± 3.8	8.0 ± 3.5	8.9 ± 4.1	0.273
VA at MLN (mm^2)	18.6 ± 7.6	18.4 ± 7.9	18.5 ± 7.1	0.666
LA at MLN (mm^2)	1.2 ± 0.7	1.2 ± 0.8	1.2 ± 0.7	0.757
WA at MLN (mm^2)	17.4 ± 7.4	17.2 ± 7.8	17.3 ± 6.8	0.539
VA at reference (mm^2)	21.9 ± 7.0	23.2 ± 7.3	20.8 ± 6.7	0.076
LA at reference (mm^2)	5.9 ± 2.6	6.1 ± 2.6	5.7 ± 2.6	0.324
WA at reference (mm^2)	16.0 ± 5.0	17.1 ± 5.4	15.1 ± 4.5	0.040
Plaque burden (%)	−1.8 ± 40.1	−8.5 ± 33.2	3.7 ± 44.4	0.016
Remodeling type				0.028
Positive remodeling	29 (27.1%)	8 (16.7%)	21 (35.6%)	
Non-positive remodeling	78 (72.9%)	40 (83.3%)	38 (64.4%)	
Enhancement ratio	1.7 ± 0.6	1.7 ± 0.6	1.8 ± 0.7	0.965

MLN, maximal lumen narrowing; VA, vessel area; LA, lumen area; WA, wall area.

TABLE 3 | Characteristics of procedure.

Variables	Total (n = 107)	DWI– (n = 48)	DWI+ (n = 59)	*P*-value
Treatment type				
PA	21 (19.6%)	10 (20.8%)	11 (18.6%)	0.943
BMS	24 (22.4%)	11 (22.9%)	13 (22.0%)	
SES	62 (57.9%)	27 (56.3%)	35 (59.3%)	
Diameter $_{max}$ of PTAS (mm)	3.1 ± 0.8	3.0 ± 0.8	3.1 ± 0.8	0.641
Length $_{max}$ of PTAS (mm)	13.6 ± 4.2	13.5 ± 4.3	13.7 ± 4.2	0.832
Pressure $_{max}$ of PTAS (atm)	6.4 ± 1.5	6.4 ± 1.4	6.4 ± 1.6	0.869
Diameter ratio of stenosis*	5.8 ± 2.9	5.5 ± 2.5	6.0 ± 3.2	0.446
Diameter ratio of reference*	1.2 ± 0.3	1.0 ± 0.3	1.2 ± 0.3	0.441

PA, primary angioplasty; BMS, balloon-mounted stent; SES, self-expansion stent; PTAS, percutaneous transluminal angioplasty with or without stenting.
**The diameter ratio was defined as the maximal diameter of implant divided by vessel diameter of stenosis and reference.*

TABLE 4 | Risks for post-operative new cerebral infarction assessed by multivariate analysis.

	OR (95%CI)	*P*-value
Age	1.003 (0.952–1.057)	0.905
Smoking history	0.394 (0.167–0.926)	0.033
CHD	4.109 (0.973–17.354)	0.055
Pre-operative mRs		
<2	–	
≥2	2.710 (0.66–11.120)	0.166
Plaque burden	1.001 (0.988–1.014)	0.988
Remodeling ratio		
Non-positive remodeling	–	–
Positive remodeling	2.807 (0.832–9.472)	0.096

CHD, coronary heart disease.

endovascular treatment with external force (37). Similarly, the remodeling index was associated with the risk of new cerebral infarctions. Most studies have defined a remodeling index >1.05 as positive remodeling with plaque advance outward, and a remodeling index <0.95 as negative remodeling with plaque advance inward. In the current study, more than half of patients (65.4%) were negative remodeling, followed by positive remodeling (27.1%) and intermediate remodeling (8.4%). The plaque burden in positive remodeling was larger than that in negative remodeling. Therefore, the risk of new cerebral infarctions was higher in patients with positive remodeling. Some studies have demonstrated that plaque stability is associated with a small plaque burden and negative remodeling. The unstable plaque increased the risk of plaque breakage during endovascular treatment and the rate of new postoperative infarctions (38–40). Furthermore, previous studies have suggested that positive remodeling is more common in patients with advanced BA stenosis (38). However, we found that negative remodeling was a common condition in patients with symptomatic BA stenosis treated by endovascular therapy. The reason for the difference in results was the diversity of eligible patients enrolled in the study. Non-acute, stable patients with symptomatic severe BA stenosis were admitted to our center for endovascular treatment. Studies have found that the development of atherosclerosis is a process that proceeds from positive remodeling to negative remodeling; negative remodeling is a late remodeling form of plaque, with a relatively stable state (41). Some lipid cores may outflow at the onset of an ischemic event due to the instability of the plaque during positive remodeling (39). Therefore, negative remodeling is more common in patients with severe symptomatic stenosis (namely late disease). Therefore, large plaque burden and positive remodeling may be the influencing factors of new cerebral infarctions in the BA territory, although there were insignificances in the multivariate analysis. The small sample size may be the cause of these results, which warrants verification through further studies with larger sample sizes.

Limitation

The current study has several limitations. First, the study data were limited due to the retrospective nature of the study. It was difficult to subdivide the smoking state of the patients into

currently smoking and previously smoking without more details of smoking, however, it has been found that the devastating effects of tobacco smoking on vessels are lasting and do not subside easily after quitting (31). Several studies have reported better short-term outcomes in smokers, including previously and currently smoking compared with non-smokers (42). Second, the evaluation of plaque characteristics is given increasing attention nowadays. HR-MRI is an effective non-invasive method to assess plaque characteristics. However, it was not easily available for patients in our center at the early stage of the study. Third, serum biochemical tests, such as TNF-α levels and intra-arterial oxidative stress, and white matter damage may be related to new cerebral infarctions (43). However, the availability of these examinations was limited in the current analysis.

CONCLUSION

Few studies have investigated the risk factors for new cerebral infarctions in the BA territory after endovascular treatment for BA stenosis in Chinese individuals. The plaque characteristics are not associated with new cerebral infarctions in the distribution of BA, although a large plaque burden and positive remodeling are more likely to appear in patients with new cerebral infarctions after BA stenting, which warrants further studies with larger sample sizes. As for smoking, the inverse correlation with new cerebral infarctions in the BA territory should be verified by large-scale prospective randomized controlled 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 Xuanwu Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JL contributed to the preparation of the manuscript and data collection. JL, LL, YF, and RY contributed to the data collection. KY and TW contributed to data analysis and interpretation. LJ, YM, PG, and BY contributed to the experimental design and manuscript revision. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Imaging Patterns of Recurrent Infarction in the Mechanisms of Early Recurrence in Intracranial Atherosclerotic Disease (MyRIAD) Study

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Introduction: While much is known about recurrent clinical events in patients with intracranial atherosclerotic disease (ICAD), there is limited data on characteristics of recurrent infarcts.

Methods: The NIH-funded MyRIAD prospective, observational study was designed to identify mechanisms of ischemia and predictors of recurrence in ICAD. Recurrent infarction was assessed on MRI at 6–8 weeks. We reviewed the DWI/ADC and FLAIR sequences in patients with recurrent stroke and characterized the number of infarcts, infarct location, size, and patterns based on whether they were borderzone (BZ), perforator (SC/P), cortical or territorial (C/T), and mixed. Temporal characteristics were delineated by ADC/FLAIR correlation.

Results: Of the 89 patients with 6–8 weeks MRI, 22 (24.7%) had recurrent infarcts in the territory of the symptomatic artery. Recurrent infarcts were evident on DWI in 63.6% and single infarcts in 54.5%. The median recurrent infarct volume was 2.0 cm^3 compared to median index infarct volumes of 2.5 cm^3. A mixed infarct pattern was most common (40.9%), followed by borderzone (22.7%), cortical or territorial (27.3%), while only 9.1% were in a perforator artery distribution. Amongst those with a mixed pattern, 8/9 had a borderzone distribution infarct as part of their mixed infarct pattern.

Conclusion: These findings provide novel data on the characteristics of early recurrent infarcts in patients with symptomatic ICAD.

Keywords: ischemic stroke, intracranial atherosclerosis, stroke mechanisms, recurrent infarction pattern, infarct size

INTRODUCTION

Intracranial atherosclerotic disease (ICAD) is the most common cause of ischemic stroke globally and carries the highest risk of stroke recurrence with an estimated 1 year rate of ∼12% despite aggressive medical therapy (1–3). The Mechanisms of Early Recurrence in Intracranial Atherosclerotic Disease (MyRIAD) Study (NIH/NINDS) aimed to determine the mechanisms of ischemic stroke in ICAD using imaging biomarkers and determine the rate of early recurrent infarction (4).

Recurrent infarct characteristics may provide valuable information regarding the mechanisms of ischemic recurrence. Previous studies have investigated the correlations between mechanisms of ischemic stroke and infarct patterns on brain imaging in patients with ICAD (5–7). Analysis of infarct patterns in patients with ICAD have demonstrated a correlation between borderzone infarcts and poor distal perfusion (8). In this secondary analysis of MyRIAD, we aimed to describe recurrent infarct characteristics patients enrolled in MyRIAD.

METHODS

Study Design

The MyRIAD study design has been previously described (4). Eligible patients had a recent (<21 days) ischemic stroke or a transient ischemic attack (TIA) caused by ICAD of the intracranial carotid artery, middle cerebral artery M1 segment, basilar artery, or vertebral artery V4 segment, with 50–99% stenosis, in the absence of proximal cervical arterial stenosis >50% or a cardioembolic source. Ischemic stroke required symptoms lasting >24 h with imaging confirmation of an infarct; TIA had either diffusion weighted imaging (DWI) abnormality or two or more stereotypical events with unequivocally ischemic symptoms. The degree of stenosis was calculated by established methods (9) on digital subtraction angiography ($n = 23$), CT angiography ($n = 69$) or MR angiography ($n = 26$); a flow gap on MR angiography was considered eligible. Eligibility for vascular imaging was reviewed centrally. Eligible patients were >30 years of age, but those of age 30–49 years had either established atherosclerosis in another vascular bed or 2 or more vascular risk factors, and signed informed consent. We excluded those with contraindications to MRI, MR contrast agents, including allergy, creatinine >1.5 mg/dL or GFR <30 mL/min/1.73 m^2, and those with planned endovascular treatment for ICAD. All enrolled patients were treated with aggressive medical therapy based on the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial medical regimen (10). The primary outcome in the MyRIAD study was to assess the incidence of ischemic stroke in the territory of the stenotic artery; secondary outcomes included recurrent TIA and new infarct on MRI at 6–8 weeks.

Clinical and Imaging Data

We recorded demographic and clinical characteristics, medications, laboratory tests at the time of the index event, and collected all eligibility brain parenchymal and vascular imaging. A brain MRI with FLAIR and DWI/ADC sequences was obtained at 6–8 weeks. Clinical follow-up occurred at 6–8 weeks, 3 months + 15 days, 6 months + 15 days, and 12 months + 21 days to determine if an endpoint had occurred and to record treatment adherence.

Infarct Patterns and Imaging Characteristics of Recurrent Infarcts

The baseline study imaging was evaluated by central readers. Patterns of recurrent infarcts were analyzed by reviewing the MRI FLAIR and DWI sequences by two central adjudicators (R.S.S and D.L). We classified recurrent infarct patterns using a methodology used prior studies of ICAD (5) as follows: (1) Perforator (**Figure 1**)—single subcortical lesions that result from perforating vessels originating at the site of the stenosis; (2) Borderzone (**Figure 2**)—lesions that occur in the corona radiata or centrum semiovale and or between cortical borderzone territories, such as between the middle cerebral artery and anterior cerebral artery or the middle cerebral artery and the posterior cerebral artery; (3) Cortical/Territorial (**Figure 3**)—lesions that occur distal to the region of stenosis but are located in the region supplied by the corresponding intracranial artery; and (4) Mixed (**Figure 4**)—a combination of cortical and subcortical lesions.

Recurrent infarcts were considered when new DWI/ADC or FLAIR sequence lesion developed compared to the baseline MRI ascertained by 2 independent experienced vascular neurologists (EF, RSS) who reviewed clinical data and imaging studies, including that obtained at baseline, 6–8 weeks, and at the time of a clinical endpoint. Recurrent infarcts were also analyzed for

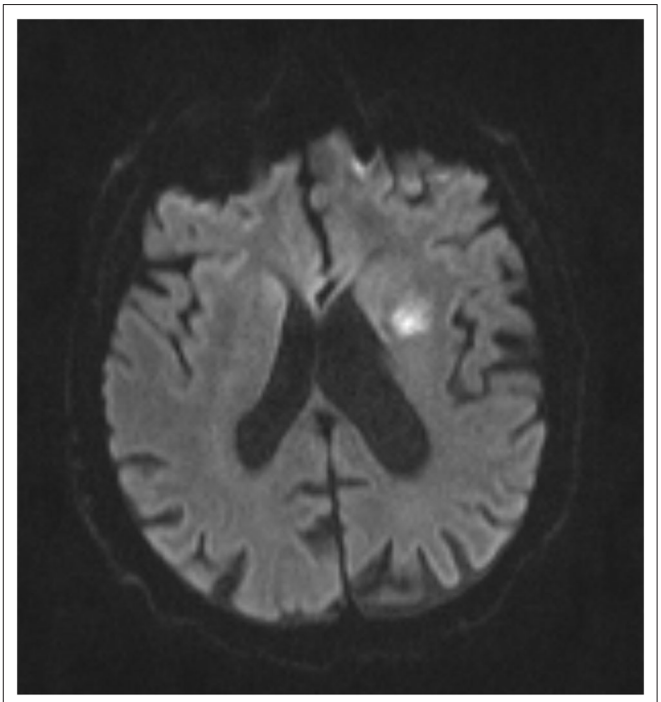

FIGURE 1 | MRI DWI sequence of Perforator Infarct.

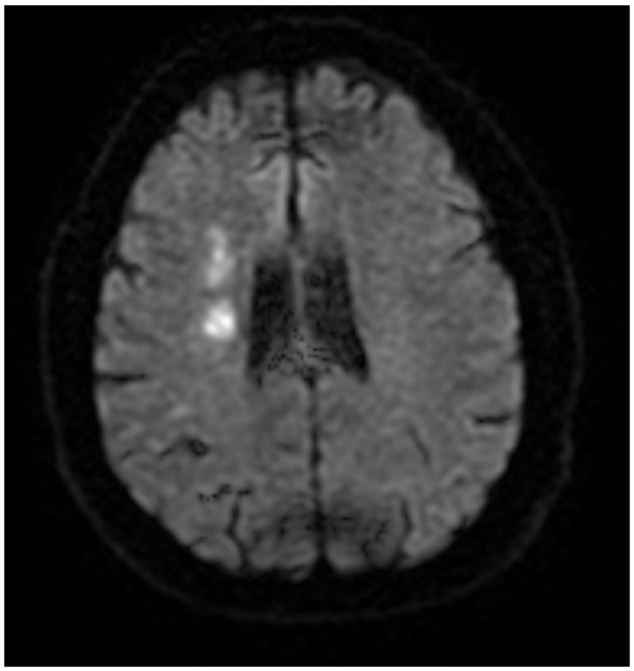

FIGURE 2 | MRI DWI sequence of Borderzone Infarct.

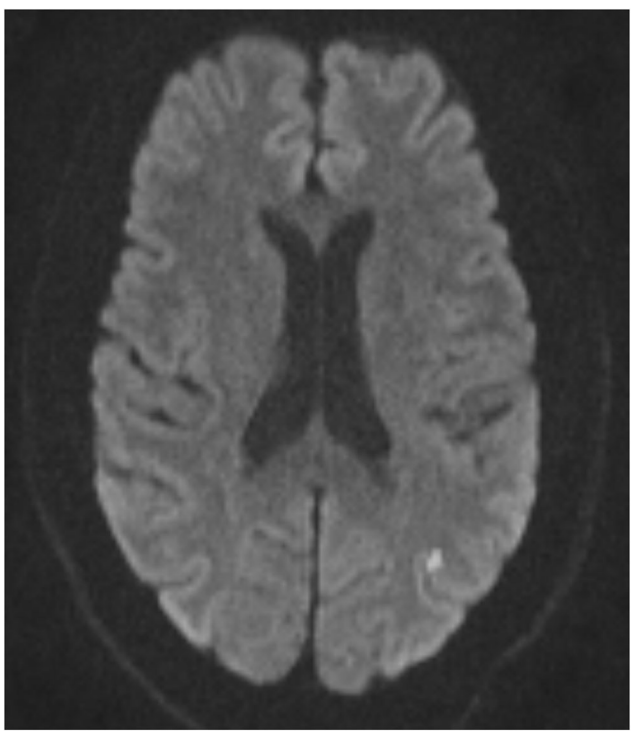

FIGURE 3 | MRI DWI sequence of Cortical/Territorial Infarct.

volume of infarcts by comparing the original volume of infarct measured on FLAIR (cm^3) as well as the volume of FLAIR and DWI lesions at 6–8 weeks MRI or clinical endpoint MRI.

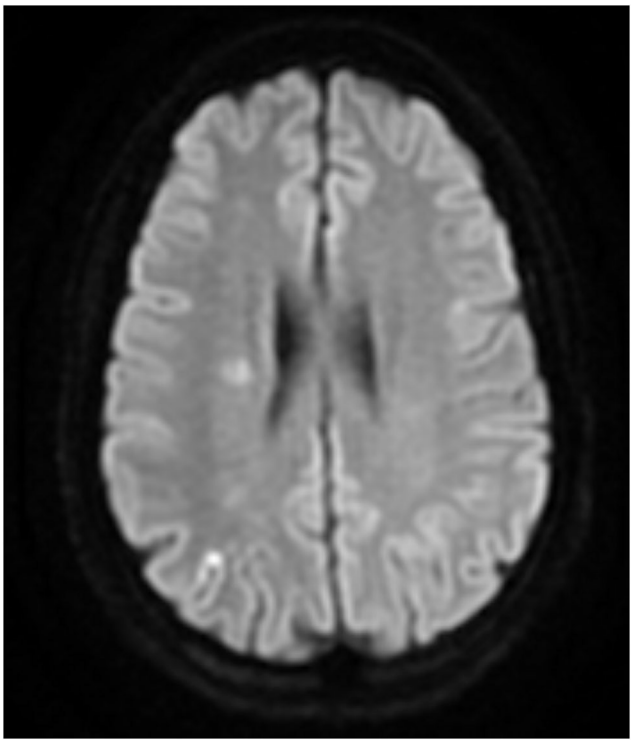

FIGURE 4 | MRI DWI sequence of Mixed Infarct.

Oleasphere 3.0 was used to co-register the baseline and 6–8 weeks MRI FLAIR sequences. Volumes of new infarction were calculated from the subtraction maps after visual verification to remove any artifacts.

Continuous measurements are summarized as mean ± standard deviation, or median ± interquartile range for attributes with skewed distributions.

MyRIAD is supported through a grant by the NIH/NINDS (R01 NS084288). The institutional review board/ethics committee at each participating institution approved this study, which is registered at ClinicalTrials.gov (NCT02121028).

RESULTS

Of 89 patients with 6–8 weeks MRI, 22 (24.7%) had recurrent infarcts in the territory of the symptomatic artery. The mean age was 57.7 ± 12.2 (mean, SD) years with 14/22 (64%) male, 13/22 (59%) White, 8/22 (36%) African American, 1/22 (5%) Asian, and 4/22 (18%) Hispanic. The location of stenosis was the middle cerebral artery in 14 (63.6%), intracranial carotid artery in 4 (18.2%) and basilar artery in 3 (13.6%). The mean degree of stenosis was 83% (±9%) in 21 cases while 1 had a flow gap on MRA.

The recurrent infarct was evident on DWI in 14 of the 22 (63.6%) patients while in 8 of 22 (36.4%) they were apparent only on FLAIR. Only 5/22 (22.7%) patients had symptomatic presentations in this time period. Recurrent ischemic lesions

TABLE 1 | Characteristics of patients with recurrent infarct in the MyRIAD cohort.

Age (years)	Sex	Eligible event	Target vessel	Stenosis (%)	Recurrent infarct pattern
48.2	Female	Stroke	LMCA	95	Cortical/Territorial
81.2	Female	Stroke	LMCA	85	Borderzone
35.8	Male	Stroke	RMCA	100	Mixed (B/P)
66.3	Male	Stroke	RMCA	73	Mixed (B/P)
71.9	Female	Stroke	RMCA	89	Mixed (B/P)
65.7	Male	Stroke	LMCA	69	Borderzone
72.1	Male	Stroke	RICA	Flow Gap	Cortical/Territorial
45.3	Female	Stroke	RICA	77	Borderzone
77.1	Male	Stroke	LMCA	99	Perforator
54.7	Male	Stroke preceding TIA	LMCA	84	Cortical/Territorial
54.0	Male	Stroke	LMCA	78	Mixed (B/C)
37.7	Male	Stroke followed by TIA	LMCA	85	Mixed (B/C)
46.8	Female	Stroke preceding TIA	LICA	80	Mixed (B/P)
55.7	Male	Stroke preceding TIA	Basilar	86	Cortical/Territorial
61.2	Male	Stroke	RMCA	94	Borderzone
58.8	Male	Stroke followed by TIA	Basilar	82	Cortical/Territorial
58.0	Female	Stroke	RMCA	79	Mixed (B/C)
52.1	Male	Stroke preceding TIA	RMCA	75	Perforator
44.4	Female	Stroke	RICA	82	Mixed (B/C)
70.2	Male	Stroke	LICA	70	Mixed (P/C)
58.1	Male	Stroke	LMCA	71	Borderzone
54.4	Female	TIA	Basilar	83	Cortical/Territorial

were single in 12/22 (54.5%) and multiple in 10/22 (45.5%) patients. The median volume of infarcted tissue was 2.0 cm^3 with interquartile range 5.3 cm^3 (minimum and maximum volumes 0 and 25.2 cm^3, respectively). Index infarct volumes were median 2.5 cm^3 with interquartile range 7 cm^3 (minimum and maximum 0 and 30.3 cm^3).

The infarct patterns are exemplified in **Table 1**. We found a mixed pattern in 9/22 (40.9%), borderzone distribution in 5 (22.7%), cortical or territorial in 6 (27.3%), while only 2 (9.1%) were in a perforator artery distribution. Amongst those with a mixed pattern, 8/9 had a borderzone distribution infarct as part of their mixed infarct pattern.

DISCUSSION

In this secondary analysis of the MyRIAD study, we describe characteristics of recurrent infarcts, with interesting observations. First, patients were noted to have recurrent infarcts that were similar in size to the original index event. Both the index event and recurrent events had lesion volumes of 2–2.5 cm^3. These data suggest that that a quarter of patients with ICAD will accrue infarcts within 8 weeks with similar volumetric impact on the brain as the index infarct. These cumulative effects of overt and covert infarcts may lead to long-term cognitive and other neurologic consequences and requires further study. Previous studies have shown that infarct size is a predictor of poor outcome in ischemic stroke patients (11). It should be noted that while infarct size and outcome has been reported in lacunar strokes (12), this is the first study to report the size of recurrent infarcts in patients with ICAD. Further studies should focus on determination of patient functional and cognitive outcomes with temporal relation to changes in infarct size.

Second, nearly two thirds of recurrent infarcts had restricted diffusion, indicating that the infarcts were acute and not merely evolution and extensions of the original infarcts. A prior study suggested that while early lesion recurrence may be secondary to a progression of the initial ischemic event, delayed occurrence is a more accurate reflection of a recurrent ischemic event (13). Given that only five of the 22 cases had a clinical stroke recurrence, MRI-defined ischemic lesion recurrence could be a more sensitive and objective marker for stroke recurrence and should be considered in future clinical trials of ICAD (13). It is possible that earlier small recurrent infarcts within areas of baseline FLAIR/T2 signal abnormality could go undetected at the time frame of repeat imaging as the DWI signal abnormality may have normalized. The time course of early infarction recurrence should be evaluated in future studies with earlier repeat imaging. Furthermore, it is difficult to ascertain the effects of silent ischemic lesions (SIL) without clinical manifestations on patient outcomes; further analysis is required to assess changes in patient cognition, physical phenotypes, and quality of life to fully understand whether SIL's will require further changes in medical therapy or medical approaches for patients with symptomatic ICAD.

Finally, the majority of patients with recurrent infarcts had had a borderzone distribution infarct, either alone or in combination with other patterns, at the index event. This suggests that hypoperfusion is a significant mechanism for recurrent

events. Similar patterns have been seen in previous analysis of ICAD patients and recurrent patterns of infarcts (5). Patients with a perforator pattern of infarct were less common. This is different from other studies (5) and may be explained by the small sample size.

There are limitations to this study. With a small sample size, it is difficult to draw definitive conclusions regarding the mechanisms of recurrent infarcts. This analysis was also completed *post-hoc* with attendant biases. This study also has some important strengths, including volumetric analysis of recurrent infarct volume and careful ascertainment of infarct recurrence in a meticulously analyzed ICAD cohort.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

RS, SP, JR, and DL: formulation of research question, data collection, data review, writing manuscript, and editing of manuscript. EF, TH, GC, and IC-B: data collection. AN: statistical analysis, data collection, and editing of manuscript. All authors contributed to the article and approved the submitted version.

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Long-Term Risk Factors for Intracranial In-Stent Restenosis From a Multicenter Trial of Stenting for Symptomatic Intracranial Artery Stenosis Registry in China

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Guo X, Ma N, Gao F, Mo D-P, Luo G and Miao Z-R (2021) Long-Term Risk Factors for Intracranial In-Stent Restenosis From a Multicenter Trial of Stenting for Symptomatic Intracranial Artery Stenosis Registry in China. Front. Neurol. 11:601199. doi: 10.3389/fneur.2020.601199

Background: For patients with symptomatic intracranial artery stenosis (sICAS), endovascular treatment has been shown to be feasible and safe in recent studies. However, in-stent restenosis (ISR) risks the recurrence of ischemic stroke. We attempt to elucidate the risk factors for ISR.

Methods: We retrospectively analyzed 97 patients with sICAS from a prospective registry trial that included 20 centers from September 2013 to January 2015. Cases were classified into the ISR $\geq$ 50% group or the ISR $<$ 50% group. The baseline characteristics and long-term follow-up were compared between the two groups. Binary logistic regression analyses were identified as an association between ISR and endovascular technique factors.

Results: According to whether ISR was detected by CT angiography, 97 patients were divided into the ISR group ($n = 24$) and the non-ISR group ($n = 73$). The admission baseline features and lesion angiography characteristics were similar, while plasma hs-CRP (mg/L) was higher in the ISR $\geq$ 50% group at admission (8.2 ± 11.4 vs. 2.8 ± 4.1, $p = 0.032$). Binary logistic regression analysis identified the longer stents (adjusted OR 0.816, 95% CI 0.699–0.953; $p = 0.010$), balloon-mounted stents (adjusted OR 5.748, 95% CI 1.533–21.546; $p = 0.009$), and local anesthesia (adjusted OR 6.000, 95% CI 1.693–21.262; $p = 0.006$) as predictors of ISR at the 1-year follow-up.

Conclusions: The longer stents, balloon-mounted stents implanted in the intracranial vertebral or basilar artery, and local anesthesia were significantly associated with in-stent restenosis. Further studies are required to identify accurate biomarkers or image markers associated with ISR in ICAS patients.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT01968122.

Keywords: cerebrovascular disease, stroke, endovascular treatment, interventional neurology, intracranial in-stent restenosis

INTRODUCTION

The prevalence of intracranial atherosclerotic stenosis (ICAS) in Chinese patients was up to 46.6% in symptomatic ischemic stroke patients (1). Symptomatic ICAS (sICAS) is associated with recurrent ischemic stroke (2). SAMMPRIS and VISSIT trials have shown that aggressive medical management has been more effective and safer than endovascular therapy in the past decade (3, 4). However, a recent Wingspan Stent System Post Market Surveillance Study (WEAVE) indicated that the perioperative complication rate is quite low for on-label patients (2.6%). Patients enrolled in this study, including patients with symptomatic and severe ICAS lesions, had suffered at least two ischemic strokes (5). It is obvious that patients with sICAS who failed the best medical treatment would benefit from endovascular therapy.

As we reported, the 30-days rate of primary endpoints, including stroke, transient ischemic attack, and death, was 4.3% in a multicenter prospective registry study of stenting for sICAS in China (6). The incidence of the composite endpoint in this study at 1 year was 8.1%, and restenosis $\geq$50% was found in 27.6% of patients at the 12-months follow-up. Although the majority of patients (78.9%) were asymptomatic (7), restenosis would be a risk factor for ischemic stroke, causing acute large vessel occlusion or transient ischemic attack (TIA) (2). Therefore, in the present study, according to the inflammatory index (hs-CRP), features of the lesion in angiography, and characteristics of the stent in the operation procedure, we aimed to identify risk factors for in-stent restenosis of endovascular treatment in intracranial atherosclerotic stenosis in a 12-months follow-up.

METHODS

Overall Design

Details of the protocol of the Aire/Wire-China trial were published (8). This study was a new subgroup *post-hoc* analysis of a multicenter prospective non-randomized registry trial that included 20 participating centers from September 2013 to January 2015. Approval by each site's institutional review board or ethics committee was obtained. Written informed consent was required from each patient or their legally authorized representative. All reported endpoints were evaluated and confirmed by a central adjudication committee composed of designated neurologists, neurosurgeons, and radiologists blinded to the treatment choices. An independent Data and Safety Monitoring Board (DSMB) oversaw the conduction, safety, and efficacy of the study.

Study Population

Inclusion and exclusion criteria were established by the executive committee. Patients were aged 18–85 years and had a symptomatic ICAS of 70–99% with a lesion length of $\leq$15 mm and a target vessel diameter of $\geq$2.0 mm in the intracranial internal carotid artery, middle cerebral artery, intracranial vertebral artery, or basilar artery. The measurements were made on digital subtraction angiography (DSA) using the warfarin–aspirin symptomatic intracranial disease method with normal distal vessels as the reference (9). The symptoms could be transient ischemic attack (TIA) or stroke onset within the past 3 months but had to be attributable to hypoperfusion in the territory of the target lesion. Hemodynamic impairment in the territory of the culprit artery was determined on imaging within 2 weeks before the operation using any one of the following methods: (1) Hypoperfusion in the target anterior or posterior circulation territory by computer tomography perfusion (CTP) or single-photon emission CT (SPECT); (2) An American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology Collateral Flow Grading System score of $<$3 on DSA (10); (3) Hemodynamic ischemic lesion by magnetic resonance imaging (MRI); and (4) A peak systolic velocity of $\geq$200 cm/s and $\leq$1 collateral vessel that could be insonated on transcranial Doppler examination (11). In this study, hemodynamic ischemic lesions on MRI were defined as small ischemic infarcts in a watershed distribution in the culprit vessel territory (12). Lesions that could be entirely explained as an embolic phenomenon or lacunar infarcts were excluded from this category. The images were centrally reviewed by at least two physicians who were allowed to resolve the disagreement through discussion. The patients were excluded from the study if the raters could not agree on the classification.

Patients were excluded if they had an acute ischemic stroke within 3 weeks, severe arterial tortuosity precluding the deployment of endovascular devices, non-atherosclerotic on an MRI, embolic or perforator stroke on MRI or CT, or a baseline modified Rankin Scale Score $>$3. Only patients without risk factors for intracranial atherosclerosis or patients with lesions suspected of being non-atherosclerotic by regular CT, MRI, or DSA had high-resolution MRI. All images were centrally reviewed by at least two radiologists who would also adjudicate any disagreement. All data were reviewed centrally by the executive committee to determine the patient's eligibility for enrollment. A flow chart illustrating the number (n) of cases included and excluded can be viewed in **Figure 1**.

Endovascular Device and Procedure

Operators were instructed to choose the devices based on the following guidelines, also taking into consideration their experience and preference to ultimately select what they thought were best suited for the patients. For patients with smooth arterial access and Mori A lesions (13), the Apollo balloon-mounted stent (MicroPort Neuro Tech, Shanghai, China) was selected. For patients with tortuous arterial access, Mori C lesion, or a lesion with a significant mismatch in the diameter between the proximal and distal segments, balloon predilation plus self-expanding stent (Gateway balloon plus Wingspan stent system) (Stryker Neurovascular, Fremont, California, USA) was preferred.

The procedures were performed by experienced neurointerventionists at each participating site. Either general anesthesia or local anesthesia was chosen depending on the operators' experience and preference. Intravenous heparin was administered after the placement of vascular access using a bolus of 75 U/kg followed by half the dose 1 h later. The guiding catheter was advanced into the cervical vertebral or internal carotid artery as high as the vessel tortuosity allowed.

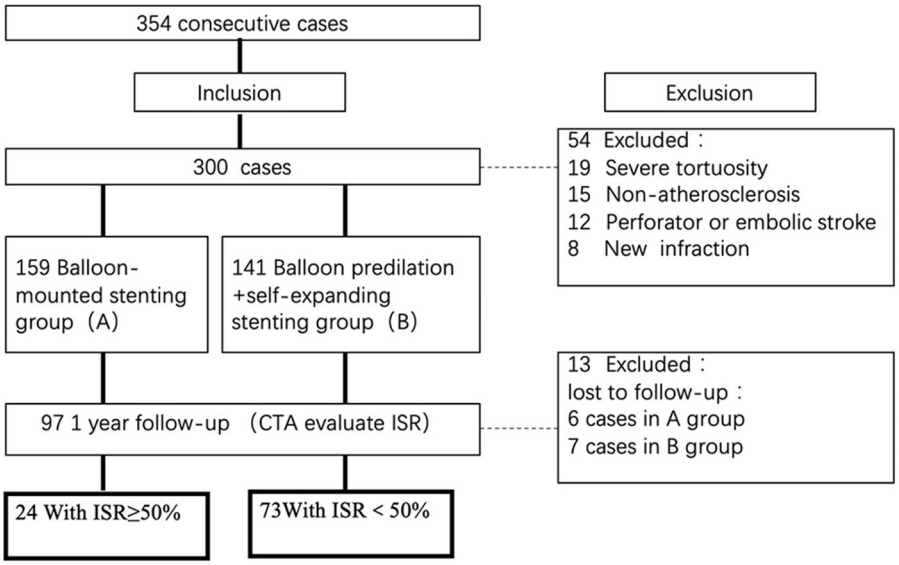

FIGURE 1 | Flow chart of the study. Flow chart illustrating the numbers (n) of cases included and excluded in this analysis. ISR, in-stent restenosis; CTA, computed tomography angiography.

Perioperative systolic blood pressure was kept between 100- and 120-mm Hg. Non-contrast head CT was obtained to exclude potential hemorrhage after the procedure. All patients were given a weight-based dose of 0.4–0.6-mL Fraxiparine (Sanofi Winthrop Industry) every 12 h subcutaneously for 3 days and monitored closely until discharge.

Perioperative Management

All patients received aspirin (100 mg/d) and clopidogrel (75 mg/d) for >5 days before the operation or a loading dose of 300 mg clopidogrel if the procedure was considered urgent. All of the cases tested the ADP-induced platelet inhibition rate (ADP%). Based on the result of ADP%, we switched to P2Y12-receptor inhibitors. They were maintained on aspirin (100 mg/d) plus clopidogrel (75 mg/d) for 90 days after stenting. Aggressive medical therapy was implemented to achieve the following long-term goals: systolic blood pressure of <140 mm Hg (or <130 mm Hg in patients with diabetes mellitus), low-density lipoprotein of <70 mg/dL (1.81 mmol/L) or a decrease by 50%, diabetes control, smoking cessation, and lifestyle modification for obesity and sedentary state.

Follow-Up

Follow-up information on clinical outcomes was collected and reviewed by trained personnel who were blinded to treatment assignment at study entry, the day of discharge, 30-days follow-up, and a face-to-face interview every 3 months. All follow-up visits were in person unless the patient could not return for the visit, in which case a telephone follow-up was completed. DSA or CT angiography (CTA) was obtained at the 12-months follow-up after the procedure. ISR was defined as a lesion demonstrating stenosis of >50% adjacent to the stent (i.e., within or immediately adjacent 5 mm) on follow-up imaging (12, 14).

Statistical Analysis

Continuous variables, such as demographic, clinical, and characteristics of stenosis lesions and imaging findings, were described as the mean ± standard deviation (*SD*), and categorical variables were expressed as the frequency and percentage of the group. The median and inter-quartile range (IQR) were used to describe the univariable distribution, including admission NIHSS and mRS. Comparative analyses between the ISR ≥ 50% and ISR < 50% groups were analyzed using *T*-tests for continuous variables, Mann-Whitney *U* non-parametric tests for ordinal variables (NIHSS, mRS, hs-CRP, length of the stent), and chi-square tests for categorical variables. Binary logistic regression analyses were conducted to test the relationship between ISR and the variables including length of the stent, stent type, anesthesia mode, and Mori type. All statistical analyses, including crude and adjusted odds ratios and 95% confidence intervals (OR, 95% CI), were performed using SPSS software (IBM, SPSS Statistics 25.0, Armonk, New York, USA), and $P < 0.05$ were considered statistically significant.

RESULT

Baseline Characteristics

Of 354 consecutive cases who underwent endovascular treatment in the designated period time, 300 patients were recruited, including 159 patients treated with a balloon-mounted stent and 141 patients with balloon predilation plus self-expanding stent. Ninety-seven patients finally fulfilled the inclusion criteria and performed CTA images in a median of 12.7 months (IQR 11.0–15.1 months). Twenty-four cases were identified with ISR ≥ 50%, while 73 cases had ISR < 50%.

TABLE 1 | Baseline demographic and clinical characteristics.

Variables	All ($n = 97$)	Patients with ISR ≥ 50% ($n = 24$)	Patients with ISR < 50% ($n = 73$)	*P*-value
Demographics				
Age, years, mean (*SD*)	57.12 (10.53)	59.21 (9.57)	56.44 (10.80)	0.266
Male sex	75 (77.32%)	18 (75.00%)	57(78.08%)	0.754
Risk factors				
Hypertension	27 (27.8%)	17 (70.8%)	53 (72.6%)	0.867
Diabetes mellitus	31 (32.0%)	9 (37.5%)	22 (30.1%)	0.502
Hypercholesterolemia	37 (38.1%)	10 (41.7%)	27 (37.0%)	0.682
Current smoking	28 (28.9%)	6 (25.0%)	22 (30.1%)	0.153
Features on admission				
BMI, mean (*SD*)	25.6 (2.9)	25.9 (2.6)	25.5 (3.0)	0.601
Systolic BP, mmHg (*SD*)	137 (18)	139 (18)	137 (18)	0.670
Diastolic BP, mmHg (*SD*)	81 (11)	81 (11)	81 (11)	0.995
Glucose, mmol/L (*SD*)	6.4 (3.5)	6.8 (2.7)	6.3 (3.8)	0.559
LDL-C, mmol/L (*SD*)	2.3 (0.9)	2.5 (1.0)	2.3 (0.9)	0.231
hs-CRP (mg/L)[a]	4.0 (6.8)	8.2 (11.4)	2.8 (4.1)	0.032
NIHSS score	0.0 (0–1.5)	0.0 (0.0–1.8)	0.0 (0.0–1.5)	0.403
mRS score	1.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1)	0.538
Lesion				
Anterior circulation	45 (46.4%)	11 (45.8%)	34 (46.6%)	0.950
Posterior circulation	52 (53.6%)	13 (54.2%)	39 (53.4%)	
Length of lesion (mm)	7.8 (3.0)	8.1 (2.9)	7.8 (3.0)	0.675
Degree of stenosis (%)	85.2 (6.6)	84.9 (7.1)	85.3 (6.4)	0.791

ISR, in-stenting restenosis; BMI, body mass index; LDL-C, low density-lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.
[a]*31 missing values.*

All patients were confirmed by DSA before the endovascular procedure, while CTA was confirmed in a 12-months follow-up in 97 patients. These patients had an average age of 57.12 years (SD 10.53), and male sex accounted for 77.32%. There was no significant difference between the two groups concerning the risk factors, admission features, and blood tests, except for hs-CRP levels. Lesions in 45 cases were located at the anterior circulation, including intracranial internal carotid artery (12 cases) and middle cerebral artery (33 cases), while the other 52 cases were located at the posterior circulation, including intracranial vertebral artery (23 cases) and basilar artery (29 cases). The mean length of the lesion and stenosis degree in both groups had no statistical significance. At the 12-months follow-up, TIA and cerebral infarction in ISR ≥ 50% and ISR < 50% were 8/72 (11.1%) and 4/24 (16.7%), respectively ($p = 0.704$). Baseline demographic and clinical characteristics are displayed in **Table 1**.

Procedural Features and Treatment

Among these patients, the incidence of ISR ≥ 50% was higher in patients who underwent local anesthesia than in those who underwent general anesthesia (11/23 vs. 12/74, $P = 0.003$). The rate of ISR ≥ 50% was significantly higher in patients who underwent balloon-mounted stents than in those who underwent balloon-predilation plus self-expanding stents (19/57 vs. 5/40, $p = 0.019$). The mean stent lengths were longer in the ISR ≥ 50% group than in the ISR < 50% group (11.0 ± 3.9 vs. 12.8 ± 3.4, $p = 0.020$). Mori type, residual stenosis rate, or primary outcome at the 12-months follow-up did not have a significant intergroup difference. Details of the interventional procedure results are displayed in **Table 2**.

Risk Factors Associated With ISR

Binary logistic regression analysis of predictors for the longer stent (adjusted OR 0.816, 95% CI 0.699–0.953; $p = 0.010$), balloon-mounted stent (adjusted OR 5.748, 95% CI 1.533–21.546; $p = 0.009$), or local anesthesia (adjusted OR 6.000, 95% CI 1.693–21.262; $p = 0.006$) were significantly associated with in-stent restenosis. The results of the binary logistic regression analysis are shown in **Table 3**.

DISCUSSION

In recent evidence, the WEAVE study demonstrated that the incidence of the peri-procedural event was only 2.6% because of on-label stent use for ICAS patients (5). In this year, the Wingspan One-Year Vascular Events and Neurologic Outcomes (WOVEN) trial that consequently studied the WEAVE trial presented in 2020 ISC. A total of 107 of 129 imaging follow-up results showed that 16.8% of patients had restenosis of 70%

TABLE 2 | Comparison of interventional procedural results stratified by ISR.

Variables	All ($n = 97$)	Patients with ISR ≥ 50% ($n = 24$)	Patients with ISR < 50% ($n = 73$)	*P*-value
Mori type				0.229
A	24 (24.7%)	3 (12.5%)	21 (28.8%)	0.109
B	54 (55.7%)	15 (62.5%)	39 (53.4%)	0.438
C	19 (19.6%)	6 (25.0%)	13 (17.8%)	0.636
Mode of anesthesia				0.003
General anesthesia	74 (76.3%)	13 (54.2%)	61 (83.6%)	
Local anesthesia	23 (23.7%)	11 (45.8%)	12 (16.4%)	
Stent type				0.019
Wingspan	40 (41.2%)	5 (20.8%)	35 (47.9%)	
Apollo	57 (60.6%)	19 (79.2%)	38 (52.1%)	
Length of stent, *SD* (mm)	12.3 (3.6)	12.8 (3.4)	11.0 (3.9)	0.020
Residual stenosis, *SD* (%)	8.6 (8.1)	7.7 (10.2)	8.9 (7.3)	0.519
Events				
Composite endpoint[a]	8 (8.2%)	2 (8.3%)	6 (8.2%)	1.000
Any stroke	3 (3.1%)	0 (0.0)	3 (2.3%)	0.572
Ischemic stroke	3 (10.2)	0 (0.0)	3 (4.1%)	0.188

ISR, in-stenting restenosis.
[a] *The composite endpoint includes ischemic stroke within the territory of the target vessel, hemorrhagic stroke and vascular death.*

TABLE 3 | Binary logistic regression analysis of the association between risk factors and ISR.

Variables	cOR	95% CI	*P*-value	aOR	95% CI	*P*-value
Length of stenosis	1.034	0.887–1.204	0.671	1.018	0.849–1.220	0.847
Length of stent	0.872	0.761–0.998	0.046	0.816	0.699–0.953	0.010
Stent type	3.500	1.180–10.378	0.024	5.748	1.533–21.546	0.009
Anesthesia mode	4.301	1.561–11.885	0.005	6.000	1.693–21.262	0.006

ISR, in-stenting restenosis; cOR, crude odds ratio; aOR, adjust odds ratio.

or greater in the mean time of 5 months (range 1–11 months) (15). In our study, the rate of in-stent restenosis is higher than in the WOVEN trial. This could be due to several reasons: (1) There were different ISR definitions (≥70% in the WOVEN trial vs. > 50% in our study); (2) The different patterns of images in the WOVEN trial included TCD, CTA, MRA, and DSA, while there was uniform CTA follow-up in our study; (3) The mean time of imaging follow-up in WOVEN was shorter (5 vs. 12.7 months).

Generally, the conventional predictors of in-stent restenosis of ICAS included risk factors of stroke and endovascular procedure related factors. To our knowledge, our study includes the largest sample to analyze endovascular procedure risk factors for in-stent stenosis for ICAS with uniform follow-up images in prospective controlled trials, although patients were retrospectively analyzed from a prospectively collected database in multiple centers. According to the analysis of the level of hs-CRP, characteristics of the intracranial stenosis lesion, mode of anesthesia, and features of the stent in the endovascular procedure, we tried to identify the risk factors for ISR of endovascular treatment in intracranial atherosclerotic stenosis.

The Type and Length of the Stent

In our controlled study, the rate of ISR ≥ 50% was significantly higher in the balloon-mounted stent group than in the self-expandable stent group (33.3 vs. 12.5%). The rate of restenosis was slightly higher than that in our earlier study (20.3%) with coronary artery stents and the VISSIT study (26.5%) (4, 16), but was similar to Jin's study, which showed that the restenosis rate with the Apollo stent was 27.5% (24/87) vs. the Wingspan, which was 24.6% (17/69). In a recent study, Baik et al. reported insertion of a balloon-expandable stent (BES) with symptomatic middle cerebral artery stenosis, and the overall incidence of restenosis or reocclusion was 14.7% (5/34) with long-term follow-up (17). We concluded that 19 patients presented restenosis by performing balloon-mounted stents, including seven cases with basilar artery stenosis and four cases with intracranial vertebral artery stenosis. Therefore, in-stent restenosis of endovascular treatment for stenosis with this type of stent could be associated with the location of lesions, particularly in the posterior circulation.

In our study, the length of the stent, but not lesion length or residual stenosis, was a predictor of in-stent restenosis. Albuquerque reported that Wingspan-related ISR typically occurs as a focal shorter lesion, but more than a quarter of cases

(26.8%) developed 50% of the length of the stented segment restenosis. The longer stent implantation, the more likely the ISR is to occur (18). We hypothesized that longer stents are associated with endothelial dysplasia, inflammatory responses, and the formation of new plaques, thus accelerating in-stent restenosis. In our further analysis, the difference in length between the self-expanding stent group and the balloon-expandable stent group was not significantly different (12.00 ± 3.62 mm vs. 8.40 ± 0.55 mm, $P = 0.088$).

With the development of new neurointerventional devices in recent years, stents delivered *via* microcatheters and assisted aneurysm embolization have increasingly been performed in ICAS. The report from Feng et al. supported the use of the more flexible Enterprise stent (Codman & Shurtleff, Raynham, Massachusetts, USA) for complex symptomatic ICAS, i.e., tortuous vessel pathways, longer than 15 mm stenosis lesions, or arterial bifurcation. Except for the feasibility and safety of this stent used for ICAS in the small sample observed study, only three cases (6.81%) presented >50% ISR compared to 86.4% (38/42) of patients who underwent a mean 22-months period of image follow-up (19). The drug-eluting balloon or stent has been used for stenosis of the coronary artery, and several observational studies have focused on the effectiveness and safety of endovascular treatment for ICAS. According to a systematic review and meta-analysis of the drug-eluting stent or drug-eluting balloon predilation with wingspan stent for ICAS studies, the ISR rate is 4.1 and 13%, respectively, which is lower than our study (20, 21). These studies are not high-level recommendations, but may be used to advance endovascular therapy and reduce the ISR rate in long-term image follow-up.

There is a paradox in our result that the complication rate of stroke in patients with ISR ≥ 50% is lower than that in patients with ISR < 50%. There was no statistical significance in the incidence of complications of stroke or ischemic stroke in both groups. We identified a downstream artery embolism due to in-stent intraplaque hemorrhage in a patient with ISR < 50% by HR-MRI. However, other reasons for symptomatic ISR in patients with ICAS need to be further investigated. Additional clinical and radiographic long-term follow-up cases could clarify the association between ISR and ischemic stroke.

Modality of Anesthesia

Management of anesthesia in the endovascular procedure for non-acute stroke patients with ICAS was not discussed in recent literature. Although more RCTs or other trials have been published since 2015 on mechanical thrombectomy for acute stroke with large vessel occlusion, the feasibility and safety of any type of anesthesia, including general anesthesia, conscious sedation, or local anesthesia, are currently in doubt (22, 23). According to this study, ISR in groups between patients who underwent intubation and local anesthesia was 17.6%, 13/74, vs. 33.3%, 11/33, $P = 0.003$, respectively. Local anesthesia is easy to perform during the operation procedure, offering the advantages of being low in cost, being less time consuming, and allowing for earlier detection of patient detoriation (24). However, general anesthesia could minimize patient movement during the procedure, perform plentiful submaximal inflation, and reduce complications of technical operations, such as iatrogenic perforation or dissection.

hs-CRP

Hs-CRP, as an inflammatory biomarker, has been proven to be associated with ISR in patients implanted with coronary or carotid artery stents (25, 26). Moreover, high CRP levels are a predictor of the asymmetric growth of restenotic tissue because of the differential distribution of shear stress and its effect on neointimal tissue shape mediated by the inflammatory process (27). Our analysis suggested a significant association between elevated serum hs-CRP and ISR. However, limited samples need to be expanded in further studies.

Limitation

Finally, our study has some limitations. We retrospectively reviewed the large multicenter, prospective, observative database which only allows us to suggest association rather than causation. Based on the characteristics of ICAS lesions and operators' experience or preference, interventionists individually selected a balloon-mounted stent or balloon plus a self-expanding stent. It is difficult to eliminate selection bias in the allocation of the two groups accurately. Second, despite analysis as a predictor of different locations in anterior or posterior circulation of ISR, details of different segments of the intracranial artery that underwent endovascular treatment may be a predictor of ISR. Third, 95% CI for balloon-mounted stents and local anesthesia is very large because of our retrospective analysis of available information, and this may be subject to selective bias. The analysis result needs to be interpreted cautiously. Furthermore, based on our data, 13 patients performed both follow-up CTA and DSA examinations (the consistent rate of CTA and DSA results was statistically tested to be 84.6%). However, CTA was used for the evaluation of ISR as a uniform modality of follow-up image in our study, but DSA was not, because generally patients were reluctant to accept more convenient and less invasive imaging procedures.

CONCLUSION

Our study suggested that a higher hs-CRP level, longer stents, balloon-mounted stents implanted in the intracranial vertebral or basilar artery, and local anesthesia were significantly associated with in-stent restenosis. Owing to advances in this new era of neuro-endovascular devices, technology, and neuroradiology, further studies are required to identify novel and accurate biomarkers or image markers associated with ISR in ICAS patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethics committee of Beijing Tiantan Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XG: study design, literature search, data collection, database establishment, and chief writer of this manuscript. NM, FG, and D-PM: data analysis. GL: manuscript reviewing, modification, and data analysis. Z-RM: study design, chief writer of this manuscript, and guarantor. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Precision Medicine for Intracranial Atherosclerotic Disease

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Diagnostic and therapeutic strategies for intracranial atherosclerotic disease (ICAD) have vastly expanded within the last several years. Challenges and concrete initiatives have emerged in the implementation of precision medicine for ICAD, focusing personalized treatment for the prevention of stroke and cognitive impairment around pathophysiology. Theranostics for ICAD incorporates an integrated diagnostic and therapeutic approach tailored to a specific individual. The ICAS 2019 meeting provided a roadmap for accelerating global innovation, underscoring the epidemiology, prior scientific evidence from trials, diagnostic tools or imaging, novel biomarkers, management approaches, and a broad range of treatments including many new medications, endovascular, and surgical strategies. This thematic overview provides perspective on current definitions for arterial stenosis, symptomatic lesions and outcomes or endpoints in clinical trials. Imaging correlates are reviewed, from routine multimodal CT or MRI to advanced angiographic techniques. The temporal features of ICAD and longitudinal observation are considered with respect to management and risk factor modification. The evolving science of multivariable interactions in ICAD and use of big data are explored, followed by an overview of recently launched clinical trials.

Keywords: intracranial atherosclerosis, stroke, hemodynamic, precision medicine, imaging

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INTRODUCTION

Recurrent stroke due to intracranial atherosclerotic disease (ICAD), the leading cause of stroke worldwide, causes an overwhelming burden of disability (1, 2). As the most common etiology of ischemic stroke, effective treatment strategies for acute ischemia and secondary stroke prevention are greatly needed. The neurological impact of ICAD is likely vastly underestimated by the incidence of recurrent stroke, as relatively mild clinical severity, involvement of secondary or less apparent functional regions of the brain and lack of continuity of care decrease reported recurrent events. Furthermore, recurrent ischemia may not cause clinical stroke events, yet cognitive and other neurological impairment may ensue (3). Despite this public health priority, there remain no proven treatments for acute or recurrent ischemia due to ICAD (4). Brain or cerebrovascular health is a relatively novel concept, unlike the established prominence of cardiovascular health. Given the prevalence and impact of ICAD on neurological disability, developing effective treatment for ICAD represents a key goal in sustaining brain health. The preponderance of "silent" ischemia without overt clinical stroke syndromes makes the use of imaging surveillance more important. More detailed clinical and imaging evaluation of individuals with ICAD is therefore necessary to properly tackle this disease.

Precision medicine for ICAD may leverage the extensive data that exist from routine imaging and clinical data (5–9). Although precision medicine in other disorders evolved from genomics, such phenotypic data may provide exquisite delineation of individual risk and disease trajectory. Advancing the field of ICAD at the population level may be fueled by understanding individual patient management with a focus on granular details. Theranostics of precision medicine entails a combination of diagnostic and therapeutic considerations, tailoring one to the other, based on specific details of a given patient. Even more so, such details are focused on the exact clinical presentation and timecourse, whether acute or chronic. The goal of such an approach is to provide the right treatment, at the right dose or use, for the right patient, at the right time. Such an approach is conceptually the converse of the data provided by a randomized, controlled trial of ICAD. Rather than controlling for individual distinctions in myriad variables from subject to subject and looking solely at class-level response to the investigational treatment, precision medicine studies of ICAD would focus first on the extensive variables that distinguish one individual from the next.

Trials of ICAD have demarcated the landscape of stroke prevention in this subtype, delineating few conclusions about what strategies are most effective. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial compared aspirin to warfarin, leaving no clear answer (2). The subsequent Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial tested the role of angioplasty and stenting with dual anti-platelet therapy (DAPT) compared to DAPT alone (10). SAMMPRIS demonstrated an unfavorable risk of early stroke after stenting, yet the annual risk of stroke in these cases with >70% stenosis was still considerable. After SAMMPRIS in 2011, blanket statements about ICAD treatment followed, citing a "failure" of stenting and "best medical therapy" as 90 days of DAPT after an index ischemic stroke or TIA. For the last decade since SAMMPRIS, it has been difficult to study ICAD. ICAD studies have many facets that are relatively more complex than trials in acute ischemic stroke. ICAD is difficult to diagnose underlying complete occlusion of a proximal artery, the extent of acute ischemia is relatively modest and the longer-term outcomes of prevention studies are more challenging. The seminal ICAD trials, however, provided a wealth of data for important subgroup analyses.

INTRACRANIAL ATHEROSCLEROSIS 2019

Despite almost a decade elapsing since the last largescale therapeutic trial in ICAD, the research community has maintained interest in tackling this influential cause of stroke. Last year, the ICAS 2019 meeting provided a roadmap for accelerating global innovation, underscoring the epidemiology, prior scientific evidence from trials, diagnostic tools or imaging, novel biomarkers, management approaches, and a broad range of treatments including many new medications, endovascular and surgical strategies (11). At ICAS 2019, the global epidemiology of ICAD, including subclinical disease was assessed. Cognitive impairment due to ICAD was discussed and a variety of novel imaging diagnostics were scrutinized, ranging from ultrasonography to vessel wall imaging and computational fluid dynamics (CFD). Recent trials were reviewed including statins, PCSK9 inhibitors and a variety of new anti-platelet therapies. Endovascular and surgical studies were reviewed, underscoring promising future trial designs. Genetic factors and the role of precision medicine in ICAD were also debated. Despite this extensive list of potential avenues for future investigation, several limitations exist in trial design (6, 7).

TARGETS AND DEFINITIONS

Precise definitions and therapeutic targets are needed to properly study ICAD, yet numerous hurdles remain in how we define and characterize ICAD. Almost the entire field of ICAD has defined the disease substrate and therapeutic target as a focal stenosis of a proximal artery in the brain (4). Focal stenosis or luminal narrowing across a discrete arterial segment is only one manifestation of underlying atherosclerosis. ICAD has been equated with focal stenosis as it is easiest to identify, yet paradoxically the obsession with exact percentage of luminal stenosis has little significance when other variables such as hemodynamics are considered. Other imaging features such as perfusion in the downstream arterial territory or collateral status have rarely been considered. Indications for endovascular therapy remain ill-defined, as well. Although we colloquially refer to "best medical therapy," it remains unclear which anti-platelet therapy combination should be used, for how long, and how we should tailor statins or PCSK9 inhibitors. Perhaps the greatest quandary relates to optimal management of blood pressure: what are target goals; what treatments are indicated; and how these factors relate to actual blood pressure response. Finally, it remains unclear whether endpoints should solely revolve around recurrent ischemic stroke or whether we should consider cognitive trajectories.

The designation of symptomatic vs. asymptomatic lesions in ICAD has been variably defined. Although strict definitions have been applied in randomized, controlled trials where an index stroke or TIA must be accompanied by focal neurological symptoms referrable to the downstream arterial territory, such strict definitions are rarely adjudicated. Furthermore, imaging evidence of ischemia in the downstream territory is seldomly used to define symptomatic arterial lesions.

Imaging definitions for ICAD have not been validated (12). On CT or MRI perfusion studies, definitions of infarct core and penumbra have been appropriated from acute ischemic stroke, without validation. For example, perfusion delays measured by time-to-peak or Tmax are radically different in ICAD when residual antegrade flow is present, compared to complete occlusion in acute ischemic stroke where the delays reflect several additional seconds of delayed arrival due to retrograde pial collateral flow. In ICAD with residual antegrade flow across a stenotic lesion, milder Tmax and other perfusion delays carry distinct significance (**Figure 1**). Arterial stenoses are typically diagnosed only when there is extreme narrowing of the arterial

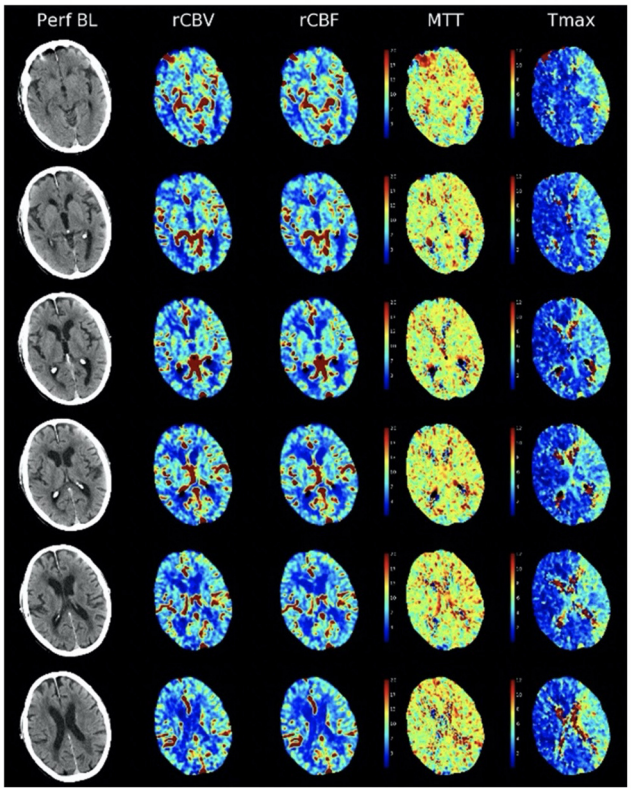

FIGURE 1 | Non-contrast CT and CT perfusion maps of ICAD in the proximal left middle cerebral artery. A small, subcortical stroke is seen on non-contrast CT (left column, Perf BL). CT perfusion (right columns) reveals residual antegrade flow across the stenotic lesion, with preserved blood volume (rCBV), blood flow (rCBF), and mean transit time (MTT) with extensive areas of Tmax delays <6 s (Tmax).

lumen, as most lesions below 70% stenosis are considered "mild" without consideration of downstream consequences. Even when downstream ischemia or perfusion delays are manifest, many lesions are designated as "mild."

Our clinical definition of symptomatic ICAD lesions has been narrowed to index stroke events, as classification of TIAs often remains unclear. Clinical status is highly dependent on reporting of clinical events, leaving many gaps in management of patients with ICAD. Serial or continued evaluation of patients with ICAD is relatively uncommon, as we rely on patients reporting recurrent symptoms and we rarely assess sequelae, such as cognitive dysfunction, beyond symptomatic clinical complaints. In the overwhelming majority of cases, serial imaging evaluation is rarely pursued to detect recurrent ischemia.

BEYOND FOCAL STENOSIS

Focal arterial stenosis is simply one subtype of ICAD, as a subset of a systemic atherosclerotic disorder. It reflects a particular manifestation of ICAD, much as coronary stenoses are a subtype of atherosclerotic coronary artery disease (CAD). Perhaps not surprisingly, many datasets have demonstrated a correlation between the presence of ICAD and co-existent CAD. When diffuse ICAD is present, it may be difficult to discern a focal arterial stenosis as the entire arterial segment may have concentric narrowing (13). As a result, even "mild" lesions of <70% stenoses may be difficult to diagnose, despite the presence of overt ICAD. Similarly, other subtypes of ICAD are neglected, such as dolichoectasia and intracranial calcifications that do not encroach on the arterial lumen. Dolichoectasia in the proximal arterial segments of the intracranial circulation may result from positive or outward remodeling of the arterial lumen due to atherosclerosis. Similarly, intracranial arterial calcifications may be apparent in the carotid siphon or distal vertebral arteries, reflecting a specific flow-related disease manifestation, distinct from focal stenosis. In sum, the resolute definition of ICAD as focal stenosis is likely overzealous, limiting our insight on the broader spectrum of atherosclerosis in the brain.

HEMODYNAMICS

The hemodynamic impact of arterial lesions due to ICAD may be quantified by flow aberrations at the site of the arterial lesion or by blood flow delivery in the downstream arterial territory. ICAD stenoses of varying degree or percentage narrowing of the artery result in different effects on blood flow across the lesion and in the downstream bed. At the site of stenosis, high wall shear stress is often noted with post-stenotic vortices, low shear stress zones associated with prothrombotic, pro-inflammatory stimuli and oscillatory shear indices that may promote platelet aggregation (**Figure 2**) (14). In WASID, downstream patterns of residual antegrade blood flow and collateral circulation were shown to be an important predictor of subsequent stroke in the territory (15, 16). These blood flow patterns were more important predictors of recurrent stroke than the degree of narrowing. In SAMMPRIS (ICAD >70%), conventional angiography of collaterals was available in 376 subjects, revealing decreased antegrade flow in 50% and complete collateral compensation in 31% (10). More robust collaterals were noted in younger subjects, those with higher HDL, those participating in moderate exercise and non-smokers (all $p < 0.05$). Confirming the findings of WASID, more robust collaterals in SAMMPRIS were associated with markedly reduced rates of recurrent stroke.

COUNTING STROKES—ACUTE-ON-CHRONIC ISCHEMIA

The nature of ICAD as an acute-on-chronic condition defies traditional approaches to trial design where it is assumed that the index hospitalization reflects the first stroke associated with the arterial stenosis. In a subset of cases, individuals presenting initially with symptomatic ICAD have no imaging evidence of prior infarction, however, many others have underlying evidence of prior strokes in the territory. MRI of acute ischemic stroke due to ICAD often shows relatively small DWI lesions (~1 cc) yet FLAIR may reveal much more extensive chronic ischemic

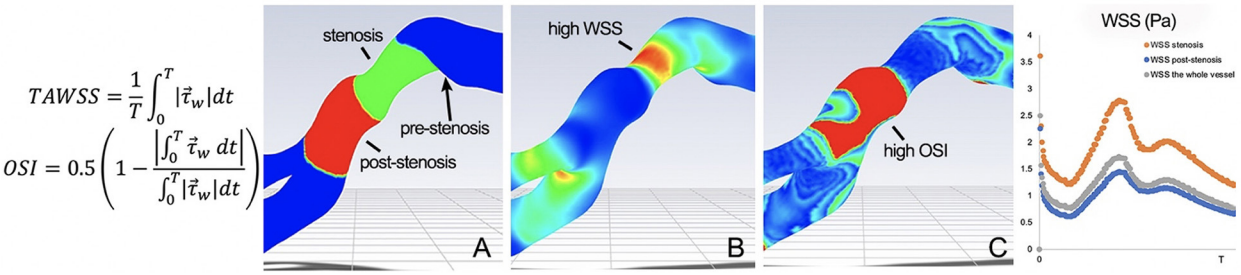

FIGURE 2 | Pulsatile CTA CFD of MCA ICAD, revealing **(A)** a 4.9 mm stenotic segment (green) and corresponding 4.9 mm post-stenotic segment (red). The WSS map **(B)** depicts high TAWSS and WSSR in the stenotic segment. The OSI map **(C)** shows mean OSI of 0.31 in the post-stenotic segment. $\vec{\tau}_w$ represents the WSS vector and T represents the period of the cardiac cycle.

lesions in the territory (17). Clinical definitions of stroke are applied, counting only events where focal symptoms have been ascribed to a discrete episode. As a result, ICAD patients may have had a varying degree of prior strokes in the territory, yet trials have neglected to count such strokes. A history of "old stroke" has been associated with worse prognosis. After SAMMPRIS, the U.S. Food and Drug Administration (FDA) warned that stenting should only be considered after 2 strokes, when a subject is at imminent risk of a third stroke (18). Counting such strokes, however, is therefore quite vague without detailed clinical and imaging data over time. These findings suggest that it is important to ascertain the temporal profile or history of disease with serial imaging and clinical data over time. In clinical practice, however, the lack of proven medical or endovascular treatments has been interpreted by some as an unproven need to follow ICAD patients over time.

MYRIAD MECHANISMS AND MULTIPLE VARIABLES

The complexity of ICAD is rooted in the myriad mechanisms of ischemic stroke and the extensive list of variables that may affect such outcomes. Several biological mechanisms of stroke in ICAD have been invoked, including residual flow across the stenosis, decreased compensatory collateral perfusion, impaired vasomotor reactivity (VMR), plaque growth, distal emboli and perforator occlusion. Each of these mechanisms may be demonstrated with neuroimaging modalities, as in the MyRIAD prospective, observational study, yet interactions between these factors and the role of independent mechanisms remains an open question (17, 19). Even when using detailed imaging of ICAD, the cutpoints or thresholds for disease severity remain unclear, much as with percent arterial stenosis. For instance, it remains unclear what should be considered abnormal or deleterious with respect to blood flow velocities, fractional flow measures, Tmax perfusion thresholds, degree of VMR impairment, or number of emboli. Combining these imaging definitions with numerous other clinical, serological, or even genomic variables markedly increases complexity, yet likely improves prediction of disease course.

ENDPOINTS AND FAILURE IN STROKE PREVENTION

Defining the failure of stroke prevention or what constitutes an endpoint in studies of ICAD remains unanswered. Similar to controversy regarding the inclusion of TIA with acute stroke as an index event for entry into ICAD trials, the role of TIA as an endpoint is unclear. Recurrent TIAs may be difficult to adjudicate and may not carry the same clinical significance. It may be argued that recurrent TIAs without infarction may promote ischemic conditioning and impart better prognosis, overall. When stroke is used as an endpoint, the relationship to the parent artery stenosis is key. Stroke in the territory, rather than other stroke subtypes must be evaluated. The nature of each stroke, with respect to neurological deficits or severity and subsequent disability, should also be defined. Cognitive impairment has rarely been the focus of endpoints in ICAD studies. Interestingly, ∼55% of subjects in SAMMPRIS had decreased cognitive performance, measured by the Montreal Cognitive Assessment (MOCA) (3). In ICAD, such cognitive dysfunction has been linked with impaired perfusion and the likelihood of recurrent stroke. These measures of failed stroke prevention must be qualified, however, as they relate to particular therapies or interventions and whether recurrent strokes may have been diminished rather than averted altogether. Recurrent stroke often prompts clinicians to switch a variety of anti-thrombotic strategies, without proven failure of such approaches compared with other therapies. Similarly, restenosis after stenting is often seen as a failure that prompts repeat endovascular therapy even when clinical symptoms may be inapparent.

BIG DATA IN ICAD

The extent of potential informative data in ICAD, including a wide range of clinical, imaging and other variables over time is seemingly boundless (6, 7, 20–22). The seminal WASID and SAMMPRIS trials incorporated voluminous amounts of data, even without detailed imaging variables explored in MyRIAD. Genomics of ICAD and serological measures remain largely unexplored. Only recently have any studies begun to explore

the role of resistance or pharmacologic response to anti-platelet therapies. Blood pressure management has rarely been studied and physiological data on blood pressure variability or continuous measures over time is untouched. ICAD patients often keep blood pressure diaries, yet such data is often uncaptured. The volume, depth and dimensions of potential big data in ICAD is daunting yet carry the potential to serve as the basis for precision medicine approaches, delineating the optimal treatment of individual patients. Fortunately, monitoring of blood pressure, physical activity, and even cognition may now be tracked with mobile technologies. Data management in ICAD will undoubtedly be important in future studies. The incremental value of each variable is often questioned, yet this remains unknown at the outset. Observational studies of ICAD will play an important role, missing data is inevitable and advanced analytic approaches that consider an array of variables and clustering of data will be important to discern subtle, yet important interactions. Longitudinal evaluation and follow-up data are imperative. Selection biases must be accounted for and survival bias must be avoided when analyzing endpoint or long-term outcomes. Capturing data on the largest population of ICAD is most important for generalizability. These approaches should capture both the acute and chronic phases of ICAD disease course. Although the annual recurrent stroke risk of ICAD is relatively high, the majority of ICAD patients may remain stable over the course of 1 year. Ascertaining the serial trajectory of ICAD is a key priority for future research. The role of changes in neurological status or imaging features at two timepoints will be important in predicting the subsequent course, as well.

DISCUSSION OF EMERGING STUDIES AND FUTURE TRIALS IN ICAD

The issues, gaps and corresponding opportunities for precision medicine in ICAD leave many approaches available for future research. Parallel approaches, incorporating observational studies and innovative interventional trial designs will likely emerge. Treatment or interventional studies may leverage novel methods such as platform trials (23). Both research strategies will require detailed and intensive data methodology for precision medicine insight. Such methods must entail relatively easy or practical data collection, including non-invasive, serial, and angiographic imaging studies. Available technologies may be leveraged to capture serology, genomics, routine imaging, blood pressure, physical activity and cognitive data. Infrastructure for such studies may build upon existing frameworks developed in recent studies like MyRIAD (17).

Ongoing imaging studies such as MyRIAD will be able to discern the interaction various biological mechanisms with recurrent ischemic stroke in ICAD. Incorporation of perfusion imaging will disclose the role of hemodynamics and collateral flow at various timepoints. Vessel wall imaging studies will reveal how such atherosclerotic plaques change over time, while illustrating which imaging features such as enhancement or lipid-laden core are most relevant in clinical outcomes. The RISER study, including both asymptomatic and symptomatic patients with ICAD will explore such changes over 18 months, correlating imaging features with PCSK9 inhibitor treatment[1].

Future ICAD studies are poised to leverage the extensive list of variables and availability of such data in routine clinical practice. Randomized, controlled trials should account for these individual-specific characteristics and clinical aspects when analyzing impact of the investigational treatment. Observational studies should ideally capture real-world data that is multidimensional, including imaging and diagnostics that measure underlying pathophysiology and physiologic response to treatments commonly employed for secondary stroke prevention in ICAD. Longitudinal or serial evaluation of patients will be essential to discern long-term clinical and imaging outcomes. ICAD is an ideal prototype for establishing precision medicine, capitalizing on the myriad variables commonly encountered.

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DL conceived and designed the manuscript, analyzed and interpreted the data, handled funding and supervision, drafted the manuscript, and made critical revision of the manuscript for important intellectual content.

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ORIGINAL RESEARCH
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Stenting for Symptomatic Intracranial Vertebrobasilar Artery Stenosis in Northeast of China: A Single-Center Study

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Wang Z, Wang C, Li C, Shi M, Wang S and Yang Y (2021) Stenting for Symptomatic Intracranial Vertebrobasilar Artery Stenosis in Northeast of China: A Single-Center Study. Front. Neurol. 11:609286. doi: 10.3389/fneur.2020.609286

Objective: We described the incidence of surgery-related complications to evaluate the safety of endovascular therapy for severe symptomatic intracranial vertebral basilar artery stenosis (IVBS) in our stroke center in Northeast of China.

Methods: Consecutive patients with symptomatic IVBS caused by 70–99% stenosis despite standard medical treatment of antiplatelet agents plus statin were enrolled. Either balloon-mounted stent or balloon predilation plus self-expanding stent was performed. Clinical adverse events such as stroke, transient ischemic attack (TIA), and death after the surgery were documented. Radiological events such as in-stent thrombosis, dissection, and guide-wire perforation during the process were recorded as complications as well. The baseline characteristics and outcomes of patients among different Mori types were compared.

Results: From January 2017 to December 2018, 97 patients with stroke or TIA due to intracranial IVBS were treated by stenting, including 30 patients with basilar artery (BA) stenosis, 55 patients with intracranial vertebral artery (V4) stenosis, and 12 patients with V4-BA stenosis. The primary events include two intracranial hemorrhage (2.1%, 2/97), seven ischemic events (7.2%, 7/97), and two death (2.1%, 2/97). The successful stent deployment rate was 98.9% (96/97). The Apollo stents were used more for Mori A lesions. Self-expanding stents were more used in Mori C lesions. Mori C lesions were more vulnerable to endovascular procedure and showed higher rate of complications than A ($p = 0.008$) and B type ($p = 0.047$).

Conclusion: A high technical success rate of IVBS stenting could be achieved, and the safety was acceptable, whereas Mori C lesions were more vulnerable to endovascular procedure and showed a higher rate of complications than A and B types.

Keywords: symptomatic intracranial vertebrobasilar artery stenosis, stenting, outcome, complication, safety

INTRODUCTION

Posterior circulation stroke takes ∼25% of all ischemic stroke cases, and unlike anterior stroke, symptomatic vertebrobasilar atherosclerotic disease is more challenging and has a relatively higher annual recurrence of stroke despite standard medical treatment of antiplatelet agents and statin (1–3), and the symptoms caused by large artery stenosis or occlusion are often devastating. Also, it was associated with a risk of stroke > 20%, as was shown in a pooled data analysis from two studies (4, 5). Stenting is becoming a promising therapeutic method for recurrent ischemic events refractory to best medical treatment, but there are also side effects such as procedure-related ischemic stroke or transient ischemic attack (TIA), intracranial hemorrhage, and even death (6, 7). Former researches such as the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke (SAMMPRIS) study (8) and the Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT) trial (9) used stents, either self-expanding or balloon-expandable ones, and demonstrated higher perioperative stroke and death rate compared with medical therapy, showing less favorable outcome of this procedure. However, not only advanced devices have emerged, but also more experienced hands have grown, making this technique more applicable and favorable (10). Because of different anatomy and function, the posterior circulation arteries might have different characteristics compared with that of anterior circulation for endovascular treatment (1). Moreover, intracranial artery stenosis is more frequently seen in Asian population than in white and black patients (11), and the northeast area of China holds people with one of the highest rates of stroke in the world, whose profiles have rarely been published. Thus, we aimed to investigate the safety of stenting for patients with severe intracranial vertebral BA stenosis (IVBS) refractory to medical treatment.

METHODS

Participants

This study was approved by the ethics committee of the First Hospital of Jilin University. Written informed consent was obtained from all patients and/or their relatives. Patients' baseline characteristics and outcomes were collected. Inclusion criteria for endovascular stenting were as follows (5): (1) 18 to 85 years old; (2) vertebral artery V4 segment or basilar artery atherosclerotic stenosis 70% or greater as defined by the Warfarin Aspirin Symptomatic Intracranial Disease Trial criteria (12) and a lesion length of ≤15 mm on digital subtraction angiography (DSA), with normal distal vessel; (3) recent non-disabling stroke or TIA of the vertebrobasilar vascular territory within 90 days refractory to standard medical therapy (stroke or TIA recurrence due to severe stenosis of VA and basilar artery (BA) under strict control of risk factors such as hypertension and diabetes mellitus [DM] and more than 3 months' use of at least one antiplatelet drug and statin, or stroke or TIA recurrence due to hypoperfusion < 3 months even under aggressive medical treatment: dual antiplatelet drugs and control of low-density lipoprotein cholesterol <1.8 mmol/L or >50% decrease); (4) a modified Rankin score (mRS) ≤3; (5) at least one atherosclerotic risk factor (hypertension, DM, hyperlipidemia, and cigarette smoking); and (6) hypoplastic posterior communicating artery (PcomA) and/or posterior cerebral artery P1 segment, and for V4 segment lesion, the contralateral vertebral artery should be hypoplastic or occluded. Exclusion criteria included (1) non-atherosclerotic stenosis; (2) patients with stroke symptoms that were not thromboembolic or hemodynamic (including perforator strokes); (3) intracranial hemorrhage in the territory of the stenotic artery within 6 weeks; (4) potential source of cardiac embolism; (5) concurrent intracranial tumor, aneurysm, and cerebral arteriovenous malformation; (6) tandem ≥50% stenosis of extracranial carotid or vertebral artery; (7) known contraindication to heparin, aspirin, clopidogrel, anesthesia, and contrast media; (8) platelet count <100,000; (9) international normalized ratio >1.5 (irreversible) and uncorrectable bleeding diathesis; (10) and life expectancy <1 year because of other medical conditions.

We use Mori classification of intracranial artery stenosis to differentiate lesion morphology (13): type A (<5 mm in length, concentric or moderately eccentric lesions not totally occlusive), type B (tubular, 5–10 mm in length, extremely eccentric or totally occluded lesions), and type C (10–15 mm in length, extremely angulated lesions with excessive tortuosity of the proximal segment, or totally occluded lesions). The medical treatment for risk factor control was based on the SAMMPRIS study and the Chinese ischemic stroke guideline. Clinical and radiological adverse events such as stroke, TIA, death, in-stent thrombosis, dissection, and guide-wire perforation were recorded as complications. Technical success was defined angiographically as <30% residual stenosis (5). TIA was defined as a reversible neurological deficit that lasts for at least 10 min and completely resolved within 24 h regardless of the diffusion-weighted imaging changes.

Outcome Measures

The primary outcome was any stroke (including ischemic or hemorrhagic), TIA, and death caused by the endovascular procedure during hospital stay. The secondary outcome was successful revascularization (residual stenosis <30%) rate, 90-day mRS of patients with complications after stenting. Other radiological events, including in-stent thrombosis and dissection, were also recorded as adverse events. If a new posterior circulation stroke was suspected, computed tomography (CT) or magnetic resonance imaging scans were arranged for documentation.

Follow-Up

Radiological and clinical follow-up information of patients with complications after surgery was obtained during in hospital. Ninety-day clinical outcomes were reviewed and collected by a trained neurologist who was blinded to treatment via face-to-face or telephone interview.

Statistical Analysis

Statistics analysis was performed with the SPSS version 16.0 (SPSS, Chicago, IL, USA). The baseline, imaging, and stenting

TABLE 1 | Complication profile and prognosis.

No.	Gender	Age	Meri type	Target artery	Intervention method	Complication	Remedial measure	Pre-NIHSS	Post-NIHSS	New symptoms after stenting	90d mRS
1	M	60	B	V4-BA	Ballon mounted stent	Perforator injury	Drug therapy	0	0	Numbness of left extremities	0
2	M	68	B	V4	Ballon + balloon mounted stent	Perforator injury	Drug therapy	2	2	Nystagmus, nausea	0
3	M	47	B	V4	Ballon mounted stent	Thrombosis	IA urokinase	0	0	None	0
4	M	52	A	V4	Ballon + self-expending stent	Hemorrhage	BP control	0	0	Mild headache	0
5	M	70	B	V4	Ballon + self-expending stent	Perforator injury	Drug therapy	2	2	Mild weakness of right limbs	0
6	F	71	B	V4	Ballon + self-expending stent	Perforator injury	Drug therapy	0	0	Stroke recurrence 2 months later	3
7	M	54	A	V4	Ballon + self-expending stent	Perforator injury	Drug therapy	0	35	Coma	6
8	F	61	C	BA	Fail	Hemorrhage	Protamine + BP control	2	25	Paralysis, disturbance of consciousness, dyspnea	6
9	M	55	B	V4	Ballon + self-expending stent	Thrombosis	IA urokinase	0	0	Dizziness, nausea	1
10	M	53	A	V4	Ballon + self-expending stent	Thrombosis	IA urokinase	0	0	Transient dysarthria	0
11	M	49	B	BA	Ballon + self-expending stent	Perforator injury	Drug therapy	2	15	Right limbs paralysis	5
12	M	61	C	BA	Ballon + self-expending stent	Dissection	Stenting	1	9	Right limbs paralysis	5
13	M	66	A	V4	Ballon + self-expending stent	Perforator injury	Drug therapy	2	3	Dysarthria, dizziness	2
14	M	44	B	V4	Balloon mounted stent	Thrombosis	Mechanical thrombectomy	0	3	Ataxia, nystagmus	2
15	M	59	A	BA	Ballon + self-expending stent	Dissection	Stenting	0	0	None	0
16	F	54	B	BA	Ballon + self-expending stent	Hyper-perfusion	BP control	1	1	Headache, restlessness	0
17	F	65	A	V4	Ballon + self-expending stent	Hyper-perfusion	BP control	2	2	Headache, nausea	1
18	M	67	B	BA	Ballon + self-expending stent	Thrombosis	IA tirofiban	0	5	Left limb and facial paralysis	1
19	M	59	A	V4	Ballon + self-expending stent	Thrombosis	IA tirofiban + urokinase	4	6	Right limbs paralysis	3
20	M	43	B	V4-BA	Ballon + self-expending stent	Dissection	Stenting	1	1	Transient paralysis of left limbs	2
21	M	49	A	V4	Ballon + self-expending stent	Thrombosis	IA urokinase	0	1	Transient nystagmus, nausea, dysarthria	1
22	M	53	A	V4	Ballon + self-expending stent	Thrombosis	IA tirofiban + urokinase	3	3	None	0

data of all patients are presented as means (± SD) or median interquartile range for continuous variables and number for categorical data. Continuous variables were tested with the Student *t*-test, whereas categorical data were tested with χ^2 test or Fisher exact test (when the expected cell frequency was <5). When continuous variables had skewed distributions, the Mann–Whitney *U*-test was used to identify the difference in the continuous variables. The significant *P*-value was set at < 0.05.

RESULTS

From January 2017 to December 2018, 97 patients (67 males, aged 64.4 ± 8.6) with stroke or TIA due to IVBS were treated by stenting, including 30 patients with BA stenosis, 55 patients with V4 stenosis, and 12 patients with V4-BA stenosis. Vertebrobasilar artery stenosis and poor collaterals were all confirmed by DSA before stenting.

The successful stent deployment rate was 98.9% (96/97). Taking all the other adverse events into account, the rate of overall complication was 22.7% (22/97). And the primary events include two cases of intracranial hemorrhage (2.1%, 2/97): one was caused by wire penetration of BA during the surgery and the other one was due to intimal damage confirmed by postoperative CT scan. Seven ischemic events happened within 24 h after the surgery including one TIA and six strokes (7.2%, 7/97), all caused by perforator injury: two happened in V4 group and five happened in BA group. Two patients died (2.1%, 2/97) during hospital stay, one was caused by subarachnoid hemorrhage due to wire penetration, and the other one was caused by medulla oblongata infarction due to perforator injury. Other complications included eight (8.2%, 8/97) patients with thrombosis during the procedure process, three (3.1%, 3/97) patients with dissection after balloon dilation, and two (2.1%, 2/97) patients with hyperperfusion. Among all the 22 patients, nine (40.9%) showed deterioration by increasing at least one National Institutes of Health Stroke Scale (NIHSS) score during in-hospital stay, whereas 17 patients (77.3%) recovered to independence (mRS <3) (**Table 1**) in 90 days' follow-up.

The baseline characteristics of patients with or without surgery-related complications are presented in **Table 2**. We found no statistical differences on rate of hypertension, DM, coronary heart disease, atrial fibrillation, prior ischemic stroke, smoking, and alcohol drinking between these two groups.

As for whether the site of the stent would influence the rate of complication, we found no difference among patients who had stenting for BA (6/30, $p = 0.508$), V4 (14/55, $p = 0.716$), or V4-BA (2/12, $p = 1$). Nor did we find statistical difference of interventional techniques (balloon-mounted stent or balloon+ balloon-mounted stent or balloon+ self-expanding stent) in these segments of arteries on complication occurrence (3/23 vs. 1/6 vs. 17/66; $p = 0.53$ vs. 1.0 vs. 0.086).

While Mori C lesions were more vulnerable to endovascular procedure and showed higher rate of complications than A type ($p = 0.008$) and B type ($p = 0.047$). **Tables 3**, **4** show that as for BA and Mori C type lesion stenting, self-expanding stent such as Wingspan or Enterprise were more frequently applied ($p = 0.029$, $p = 0.018$). Compared to types B and C lesions, Mori A and V4 lesions were more likely to receive balloon-mounted stent ($p = 0.006$).

TABLE 2 | Clinical characteristics and complications.

Characteristic		Complication		*P*
		Yes *n* = 22	No *n* = 75	
Age	y ± SD	57.3 ± 8.3	58.9 ± 8.5	0.423
Male sex	%(n)	72.7 (16)	68.0 (51)	0.673
Coronary heart disease	%(n)	22.7 (5)	16.0 (12)	0.329
Atrial fibrillation	%(n)	13.6 (3)	10.7 (8)	0.708
Cerebral infarction/TIA	%(n)	18.2 (4)	22.7 (17)	0.451
Hypertension	%(n)	81.8 (18)	61.3 (46)	0.075
Diabetes mellitus	%(n)	45.5 (10)	26.7 (20)	0.08
Alcohol drinking	%(n)	50.0 (11)	59.2 (45)	0.404
Cigarette smoking	%(n)	59.0 (13)	48.0 (36)	0.421
BA	n	6	24	0.508
V4	n	14	41	0.716
V4-BA	n	2	10	1
Balloon-mounted stent	n	3	20	0.53
Balloon + balloon-mounted stent	n	1	5	1
Balloon + self-expanding stent	n	17	49	0.086
Mori A	n	5	33	0.538
Mori B	n	7	29	0.047
Mori C	n	10	13	0.008*
Lesion length	mm ± SD	8.9 ± 4.16	6.8 ± 3.4	0.141
Stenosis percentage	% ± SD	86.4 ± 7.69	84.7 ± 8.21	0.787

**P < 0.05 for comparing between two groups.*

TABLE 3 | Lesion distribution and stenting method.

Lesion location	Self-expanding stent	Balloon-mounted stent	*P*-value
BA	25	4	0.029*
V4	35	20	0.843
V4-BA	8	4	0.202

**P < 0.05 for comparing between two groups.*

TABLE 4 | Lesion type and stenting method.

Lesion type	Self-expanding stent	Balloon-mounted stent	*P*-value
A	20	18	0.006*
B	29	6	0.980
C	19	4	0.018*

**P < 0.05 for comparing between two groups.*

DISCUSSION

The rate of overall complications in our study was 22.7% (22/97), which was higher than that reported in literature (14), because we included both radiological and clinical abnormalities

during and after the procedure. Patients with radiological complications may not necessarily present clinical symptoms, but these abnormalities could compromise the integrity of the vessel wall or interfere the blood flow especially when occurring on the opening of an artery (15, 16). Thus, we took into account all these radiological changes as complications even if they did not necessarily show clinical symptoms as to present the characteristics of a lesion. For instance, we found type C lesions were more vulnerable to endovascular procedure and showed a higher rate of these complications, which means higher risks of symptom deterioration or new infarction that also have a clinical meaning: It is a reminder that we could not be too cautious when dealing with it.

Previous studies have shown that stenting for IVBS was challenging because of its higher complication rate and severe symptoms once it happened. Levy et al. (17) treated 11 IVBS patients; three suffered periprocedural deaths and one died of pontine stroke. Tsang et al. (18) conducted a systematic review and random-effects meta-analysis of all available randomized controlled trials evaluating the safety and efficacy of percutaneous transluminal angioplasty and stenting (PTAS), in comparison with medical therapy, for symptomatic intracranial artery stenosis (sICAS) and found a higher risk of any stroke or death within 2 years in the sICAS subgroup located in posterior circulation than medical treatment. SAMMPRIS (8) and VISSIT trial (9) both demonstrated higher perioperative stroke and death rate compared with medical therapy, showing less favorable outcome of this procedure. It was obvious that stenting for IVBS was no easy thing, and complications could occur; none of these results recommended stenting as first-line treatment for IVBS, but with the advancement of neurointervention devices and more experienced neurointerventionists, safety of PTAS for IVBS seemed to be acceptable. Miao et al. (19) treated 159 intracranial atherosclerotic disease (ICAD) patients with balloon-mounted stent and 141 ICAD patients with balloon plus self-expanding stent. The 30-day rate of stroke, TIA, and death was 4.3%. Ding et al. (15) analyzed 19 ICAD stenting series after SAMMPRIS trial, including 2,196 patients with 2,314 lesions, showing the median rate of postprocedural ischemic events was 9.4% (range, 0–25%). Thus, we believe that after a thorough clinical assessment and exquisite surgery procedure, a particular group of patients would benefit from IVBS stenting with high successful rate of stent deployment and low rate of complication occurrence such as stroke or death.

We collected and compared clinical data of patients with or without any kind of complications in order to distinguish patients who might suffer from surgery-related complications. As for medical history, we found no statistical difference of these factors between groups, but patients with hypertension and DM seemed to have a higher occurrence of complications, which explains that these patients have higher rates of perforator stroke and poor collateral status.

The practice that perforator stroke was more likely to happen after BA stenting was also reported in previous literatures (19). We assumed that compared with intracranial vertebral arteries, the BA had much more perforating branches and poor collateral circulation, which made it extremely sensitive to ischemia. Also, neurological deficits caused by the occlusion of perforator orifice of BA were severe and sometimes even lethal. This may be caused by atherosclerotic debris being displaced over the perforator origins during angioplasty or stent deployment. The SAMMPRIS trial concluded that the occlusion of perforating arteries was the most common cause of ischemic stroke especially after BA PTAS.

The rate of successful stent deployment in our center was 98.9% (96/97), and device selection of self-expandable stent or balloon-mounted stent depended on arterial access and lesion morphology (7, 20). From our experience, the Gateway–Wingspan system with its excellent flexibility in traversing curvatures is more suitable for tortuous lesions, whereas the Apollo stent is preferred for patients with smooth arterial access, which does not require exchanging. Therefore, for patients with smooth arterial access and Mori A lesion, the balloon-mounted stent would be convenient. For patients with tortuous arterial access and a Mori B or C lesion, Gateway balloon plus self-expandable stents such as Wingspan stent system is preferred. And if perforator arteries originated near the stenotic site, predilation of small-sized balloon plus self-expandable stent is also preferred out of protection for the orifice of the perforator artery, as we believed that balloon-mounted stent might hurt the perforator arteries more easily, which could cause devastating result. Following these easy strategies while doing the endovascular procedure, we did not find difference of complication rate among patients who had stenting for BA, V4, or V4-BA. Nor did we find any difference of interventional techniques (balloon-mounted stent or balloon + self-expanding stent) in these segments of artery. But we did have seven ischemic events happened, including one TIA and six strokes, all caused by perforator injury. Among all the 22 patients, nine (40.9%) showed NIHSS deterioration by increasing at least 1 point. Two patients died (2.1%, 2/97): one was caused by subarachnoid hemorrhage due to wire penetration, and the other one was caused by medulla oblongata infarction due to perforator injury, whereas 17 patients (77.3%) recovered to independence (mRS <3). Patients may show symptoms such as dizziness, nausea, and nystagmus, and mostly reached recession very soon. Our study showed even IVBS was challenging because of its higher complication rate; the majority could recovery to independency.

Some limitations should be considered when interpreting the findings because this is a single-center observational study with a relatively small size of patients. And we analyzed only the clinical data we collected during the hospital stay; thus, the long-term prognosis of this treating strategy such as stroke recurrence or restenosis is still to be investigated. Nevertheless, we described our experience and findings of stenting for IVBS in the population of northeast China.

CONCLUSIONS

A high technical success rate of IVBS stenting could be achieved, and the safety was acceptable, whereas Mori C lesions were more vulnerable to endovascular procedure and showed higher rate of complications than A and B types.

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 Human and Research Ethics committees of the First Hospital of Jilin University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZW and CW conceived and designed the study, acquired the data, and drafted and revised the manuscript. All authors analyzed and interpreted the data and critically revised the manuscript for important intellectual content.

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Endothelial Shear Stress and Platelet FcγRIIa Expression in Intracranial Atherosclerotic Disease

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Intracranial atherosclerotic disease (ICAD) has been characterized by the degree of arterial stenosis and downstream hypoperfusion, yet microscopic derangements of endothelial shear stress at the luminal wall may be key determinants of plaque growth, vascular remodeling and thrombosis that culminate in recurrent stroke. Platelet interactions have similarly been a principal focus of treatment, however, the mechanistic basis of anti-platelet strategies is largely extrapolated rather than directly investigated in ICAD. Platelet FcγRIIa expression has been identified as a potent risk factor in cardiovascular disease, as elevated expression markedly increases the risk of recurrent events. Differential activation of the platelet FcγRIIa receptor may also explain the variable response of individual patients to anti-platelet medications. We review existing data on endothelial shear stress and potential interactions with the platelet FcγRIIa receptor that may alter the evolving impact of ICAD, based on local pathophysiology at the site of arterial stenosis. Current methods for quantification of endothelial shear stress and platelet activation are described, including tools that may be readily adapted to the clinical realm for further understanding of ICAD.

Keywords: intracranial atherosclerosis, stroke, shear stress, FcγRIIa receptor, platelet activation and reactivity

INTRODUCTION

Intracranial atherosclerotic disease (ICAD) is the most common cause of stroke worldwide (1, 2). The devastating consequences of ICAD reflect racial, sex and ethnic disparities, impact a broad age group and lack strategies for prevention (3). Overwhelming recurrent risk amounts to an excessive burden of disease and public health priority (4). ICAD engenders a ∼12.5% rate of recurrent clinical strokes within 1 year (5, 6). The impact of "silent" strokes, evident only on surveillance imaging, may be even greater when one considers cognitive or other impairment.

Recurrent ischemic stroke due to ICAD is extremely common despite treatment with anti-platelet medications. Heterogeneity of the arterial architecture and associated blood flow changes in ICAD-related stenoses result in different patterns of wall shear stress (WSS) from

one individual to the next. Such wall shear stress can be readily quantified with computational fluid dynamics (CFD) from non-invasive CT angiography (CTA), routinely acquired in patients with minor stroke or transient ischemic attack (TIA) due to ICAD. These shear stress changes in blood flow promote platelet aggregation and thereby alter the response to anti-platelet therapy. Additionally, greater platelet FcγRIIa expression increases platelet reactivity and promotes thrombosis when platelets are exposed to increased shear stress. In coronary artery disease (CAD), greater platelet expression of FcγRIIa identifies patients at greater risk of recurrent cardiovascular events, including stroke. Numerous mechanisms have been invoked in the recurrence of ischemia in ICAD, yet focused research on the pathophysiology of shear stress and platelet activation has not been evaluated to explain the high rate of imaging evidence and clinical strokes following minor stroke or TIA due to ICAD. Given the shared pathology of coronary artery disease and ICAD, the data suggest that individual differences in CFD-derived WSS and platelet FcγRIIa expression may inform a precision medicine strategy to prevent recurrent stroke.

SHEAR-INDUCED PLATELET AGGREGATION IN ICAD

More than 25 years ago, stroke research underscored the pathophysiology of shear-induced platelet aggregation (7–9). *In vitro* studies showed a protective effect of thienopyridines (e.g., clopidogrel), creating parallel approaches to ICAD and CAD, based on anti-platelet effects. These studies revealed that aspirin has limited effect on platelet aggregation, modified largely by local hemodynamics, forming the rationale for dual anti-platelet therapy (DAPT) in ICAD and CAD. Distinct zones in the region of arterial narrowing or stenosis and immediately downstream in the post-stenotic segment influence platelet activation, modulated by shear stress. As in **Figure 1**, wall shear stress (WSS, calculated as t_s) increases as blood flows tangentially to the arterial wall of the narrowed lumen or stenosis, measured by the residual radius. As blood flow volume asymmetrically exits the stenosis, flow vortices create oscillating gradients in both direction and intensity of WSS. High shear stress and the oscillatory shear index (OSI) can be measured with CTA techniques and are closely linked to platelet activity (10–13).

PLATELET REACTIVITY AND PLATELET EXPRESSION OF FCγRIIA

Increased platelet reactivity has identified patients with minor stroke or TIA who are at greater risk of recurrent stroke (14). Similarly, increased platelet reactivity has consistently identified patients with CAD who are at greater risk of subsequent cardiovascular events (15–17). Two large clinical trials in CAD failed to demonstrate that currently available non-specific

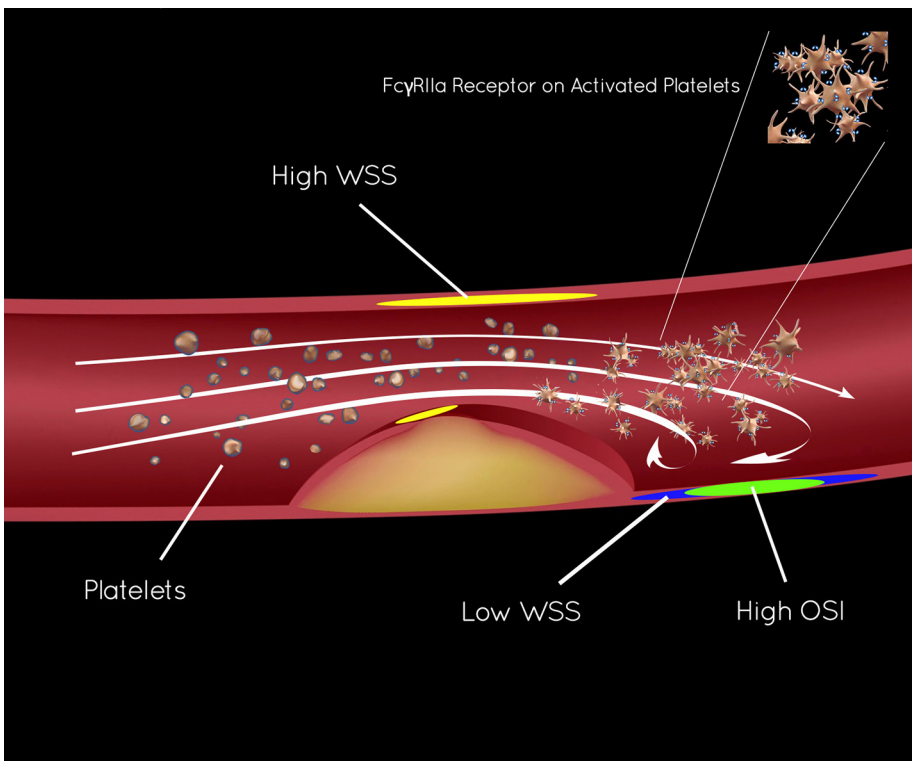

FIGURE 1 | Endothelial shear stress in ICAD and activation of platelet FcγRIIa.

platelet function tests can be used to guide treatment (18, 19). Intra-individual variability in platelet function over time is substantial and likely to be a major contributor to the failure (20–22). Because of the failure of platelet function tests to effectively guide treatment in patients with CAD, it is unlikely that existing platelet function tests will be able to guide individualized care in ICAD.

FcγRIIa is a member of the Fc family of proteins that is expressed on the surface of platelets and amplifies platelet activation (23, 24). The Schneider Lab has pioneered the platelet biology of FcγRIIa and established it as a potential marker of risk for secondary thrombotic events in circulatory disorders. FcγRIIa amplifies activation of platelets in response to any stimulus or agonist. Importantly, platelet FcγRIIa expression amplifies thrombosis in the setting of shear forces (25). In a single center study, we found that high platelet FcγRIIa expression ($\geq$11,000/platelet) is associated with a greater risk (odds ratio $>$ 4) of myocardial infarction (MI), stroke and death (26). Platelet FcγRIIa expression does not require activation of platelets and does not exhibit the magnitude of intra-individual variability seen with platelet function tests (27). The emphasis on platelet activation directly focuses our stroke prevention efforts in ICAD where anti-platelets have been paramount and shear-induced platelet aggregation pivotal. FcγRIIa may identify those at high or low risk of recurrent stroke and serve as an effective tool to guide precision medicine in ICAD.

FCγRIIA AS A MARKER OF PLATELET REACTIVITY AND RISK OF CARDIOVASCULAR EVENTS

FcγRIIa was identified as a low-affinity receptor for the fragment constant (Fc) portion of immunoglobulin (Ig) G (28, 29). FcγRIIa markedly enhances thrombus formation when platelets are perfused over a collagen-coated flow chamber under conditions of arterial and venous shear (30). Phosphorylation of FcγRIIa amplifies the activation of platelets (23, 24). We demonstrated that platelets with more FcγRIIa exhibited greater activation in response to sub-maximal concentrations of multiple agonists (31). FcγRIIa may therefore be a novel biomarker capable of identifying patients with increased platelet reactivity. A prospective trial was designed to determine the prognostic implications of platelet FcγRIIa expression (26). Patients (n = 197) were enrolled shortly before discharge from hospitalization for myocardial infarction (MI, both ST elevation and non-ST elevation were included). All patients were treated with aspirin (81 mg) and treatment with clopidogrel (∼64%) and ticagrelor (∼36%) was balanced in patients with high and low platelet expression of FcγRIIa (26). Clinical characteristics were well-balanced with the exception of older age, diabetes, and prior revascularization being more prominent in the high expression group. Patients with platelet expression of FcγRIIa $\geq$11,000 had a greater risk of heart attack, stroke, and death that became apparent after 6 months. Cox regression analysis was performed and platelet expression of FcγRIIa was the sole covariate (hazard ratio 3.9, $p = 0.035$) associated with freedom from MI, stroke, and death. The sensitivity of high expression to identify patients with cardiovascular events was 0.82 (95% confidence intervals 0.57 to 0.92) and the specificity was 0.51 (95% confidence intervals 0.43 to 0.58). Cardiovascular events (heart attack, stroke, and death) were uncommon (8% of all patients experienced an event). The negative predictive value of low platelet expression of FcγRIIa was 0.97 (95% confidence intervals 0.89 to 0.98). Based on preliminary retrospective studies it has been hypothesized that a threshold of 11,000 molecules of FcγRIIa/platelet may identify high and low risk of subsequent cardiovascular events. Analysis of patients with heart attack confirmed that this threshold discriminated high and low risk most efficiently (26). As platelet expression of FcγRIIa is a continuous variable, a larger study will be required to address whether the relationship between cardiovascular events and FcγRIIa expression is continuous.

DEFINING PLATELET ACTIVITY AND ANTI-PLATELET STRATEGIES IN SECONDARY STROKE PREVENTION

Anti-platelet therapies have been the mainstay of secondary stroke prevention for decades. In ICAD, "best medical therapy" is currently defined as DAPT with aspirin and clopidogrel for 90 days after stroke or TIA as in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial (6). Determining platelet activity, defining long-term "best medical therapy" and establishing criteria for "failure" of anti-platelet strategies remain unaddressed. Extensive variation exists in combinations of anti-platelet strategies used and platelet activity monitoring remains a quandary. The measures in **Table 1** are used sporadically, imparting bias without systematically assaying platelet activity, offering a role for FcγRIIa.

ARTERIAL HEMODYNAMICS OF ICAD WITH CTA COMPUTATIONAL FLUID DYNAMICS (CFD)

For more than a decade, routinely acquired, non-invasive CTA has been used to generate CFD measures of arterial hemodynamics in the coronary and cerebral circulations. CTA CFD has measured fractional flow reserve (FFR), elevated wall shear stress associated with arterial stenoses and post-stenotic flow aberrations, including focal areas of atherogenic low shear stress. In ICAD, almost all cases are treated with medical therapy with very few undergoing endovascular revascularization or alteration of the arterial lesion. As a result, CTA CFD can be used to characterize the local arterial hemodynamics that may predict future events. Our group has pioneered the use of CFD to quantify specific arterial hemodynamic parameters in ICAD for more than a decade (32–40). Our collaborative efforts with investigators in Beijing and Hong Kong have yielded insight on WSS in ICAD stenoses and subsequent clinical events. In a multicenter study of 245 patients (median age = 61 years, 63.7% men) we demonstrated the pivotal prognostic implication of high WSS in the stenosis (35). Stroke in the territory (SIT)

TABLE 1 | Platelet assays and potential use in anti-platelet stroke prevention strategies.

Biomarker	Description	Role	Pro	Con
Platelet Count	• Indication of total mass of platelet	• Platelets are key to hemostasis over a wide range (150,000–400,000/μl) • Hemostasis maintained with platelet count even below 50,000/μl	• High platelet mass predisposes to exaggerated thrombosis in response to vascular injury	• Most stroke patients have normal platelet count • Increased platelet count often transient, not reflective of long-term risk
Platelet Indices	• Mean platelet volume (MPV) is a measure of platelet size • Young platelets are larger and more reactive	• Young platelets are first responders to vessel injury and critical in hemostasis • High MPV reflects more young platelets	• High MPV predisposes to exaggerated thrombosis in response to vascular injury	• High MPV in stroke patient likely due to release of new platelets after thrombosis • Increased MPV is transient, not reflective of long-term risk
Genotyping (CYP2C19)	• Genotyping for CYP2C19 will identify patients who poorly metabolize clopidogrel to form the active metabolite	• Decreased metabolism of clopidogrel to form the active metabolite leads to less antiplatelet effects	• If clopidogrel is poorly metabolized, less antiplatelet effect will occur predisposing to more events • Useful to guide alternative treatment to clopidogrel	• CYP2C19 genotyping is specific to clopidogrel • Genotyping has not been shown to predict underlying thrombotic risk
Platelet Function Testing (Verify Now)	• Measures activation of platelets in response to an agonist or combinations	• High platelet reactivity (more activation in response to an agonist) identifies subjects who are likely to have an exaggerated thrombotic response to vascular injury	• High platelet reactivity has been consistently associated with a greater risk of heart and stroke	• Platelet function tests have failed to effectively guide therapy • Platelet function tests exhibit high intra-individual variability • Platelet function tests determine response to a selected agonist/combination
Platelet FcγRIIa	• Platelet surface marker quantified with the use of flow cytometry	• Amplifies activation of platelets exposed to vessel injury/agonist/activating signal • Marker of high platelet reactivity	• Leverages implications of high platelet reactivity identified with platelet function tests • Marker of consistent increased platelet reactivity	• Requires additional validation in larger cohorts

occurred in 20 (8.2%) patients, mostly with multiple infarcts in the borderzone and/or cortical regions. In multivariate Cox regression, high WSS ratio (WSSR) of stenotic WSS to pre-stenotic WSS was independently associated with SIT (adjusted HR = 3.05, $p = 0.014$). These data suggest that high WSS will predict recurrent stroke, yet many other instrumental variables were not captured in that study, including post-stenotic shear force. In our most recent shear stress and endothelial pathophysiology study, we are investigating post-stenotic foci of low shear stress as a nidus for specific endothelial genotype expression, laden with atherogenic and pro-thrombotic stimuli (41). Our collaborative work integrating CFD of ICAD with microfluidic and endothelial expertise has analyzed the CTA subset acquired in the SAMMPRIS trial, showing low shear stress in the post-stenotic segment due to flow vortices proving our ability to extract and define WSS ratios at various arterial lesion sites. These retrospective analyses of SAMMPRIS are limited in ability to prove recurrent stroke due to post-stenotic low shear stress, particularly as they lack systematic MRI follow up to discern interval ischemic injury. These studies focus on only 70–99% stenoses of the proximal MCA and other potentially critical variables regarding platelet biology, anti-platelet treatment, and platelet resistance or response were not collected. *In vitro* work on shear-induced platelet aggregation strongly suggests that not just elevated WSS, but immediate downstream fluctuations in shear stress are instrumental. We have used the OSI in the post-stenotic segment to calculate, map and quantify this influential variable on *in silico* models of ICAD with CTA CFD.

DISCUSSION

Poor understanding of ICAD pathophysiology has been a critical barrier to progress in the field of stroke prevention. Targeting specific mechanisms of recurrent ischemia may enable clinicians to match diagnostic findings of ICAD in a given patient with the most effective therapies. Such strategies have been limited due to gaps in clinical trial design, dearth of observational studies, simplistic definitions of ICAD lesion type, empiric use of "best medical therapy," choice of endpoints and failure to maximally leverage patient-level information from diagnostic imaging. ICAD trials increasingly focus on the most severe (70–99%) stenosis, yet almost half of ischemic strokes due to ICAD occur in milder (50–69%) lesions (42). We have previously shown that hemodynamics in ICAD are pivotal for risk stratification. Dual anti-platelet treatment (DAPT) is often used for variable durations after stroke without recognizing individual anti-platelet response or effects.

It may be possible to tackle these weaknesses using precise individual platelet biology, arterial hemodynamics of shear force

across a spectrum of ICAD lesions to ascertain effect on both clinical and imaging ischemic endpoints in a multicenter cohort study. Preliminary data have established that increased platelet FcγRIIa expression is a stable measure of increased platelet reactivity. FcγRIIa can now be quantified for comparison across centers. Unlike platelet function tests, platelet FcγRIIa expression is not substantially affected by assay conditions. Finally, FcγRIIa $\geq$ 11,000/platelet identifies patients with ∼4-fold greater risk of MI, stroke and death. Using the baseline CTA routinely acquired in our recently completed MyRIAD study, we calculated the time averaged WSS in the ICAD lesion, WSS ratio and post-stenotic OSI under pulsatile flow conditions. This preliminary research enabled us to develop standard methodology for quantification of these variables in circumferential bands of the stenosis and equivalent length post-stenosis. A larger study may extend these findings to ICAD patients, show key interplay between platelet FcγRIIa expression and WSS, providing these markers as a basis to guide individualized ICAD stroke prevention.

We have been ardently detailing a vision for precision medicine approaches to stroke and ICAD for many years now (43–56). We have described the potential of imaging features, novel assays and individual clinical characteristics of patients with acute stroke and chronic ICAD to identify therapeutic opportunities based on an *n* of 1. At a population level, we have advocated for innovative statistical methods such as clustering to discern key predictors of not just risk, but also of propensity for benefit with specific therapeutics. In retrospective analyses, we have leveraged clustering and principal component analyses to reclassify and stratify patient subsets at heightened risk of recurrent events in the datasets of past stroke randomized, controlled trials (44, 49, 57). We developed a novel approach to validate CTA CFD values of WSS in stenoses in ICAD with precision 3D cerebrovascular models, including data from the landmark SAMMPRIS trial. In other collaborations, we have separately studied the potential impact of elevated WSS on stroke recurrence in ICAD and conducted an observational multicenter study on mechanisms of recurrent stroke in ICAD. It has been demonstrated that greater platelet FcγRIIa expression increases the activation of platelets in response to agonists and shear stress. These synergies now enable investigation of how the interaction of anti-platelet therapies with individual platelet expression of FcγRIIa and WSS calculated from patient-specific CTA CFD may explain recurrent ischemia after minor stroke or TIA due to ICAD. The culmination of parallel work on shear stress-induced platelet activation in ICAD leverages preliminary data on FcγRIIa, CTA CFD of WSS and precision medicine analytics in stroke.

AUTHOR CONTRIBUTIONS

DL conceived and designed the manuscript, analyzed and interpreted the data, handled funding and supervision, drafted the manuscript, and made critical revision of the manuscript for important intellectual content. JH, NK, HK, TH, AD, EF, RN, SP, PC, and DS analyzed and interpreted the data and made critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Evaluating the Velocity and Extent of Cortical Venous Filling in Patients With Severe Middle Cerebral Artery Stenosis or Occlusion

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Objective: To investigate the velocity and extent of cortical venous filling (CVF) and its association with clinical manifestations in patients with severe stenosis or occlusion of the middle cerebral artery (MCA) using dynamic computed tomography angiography (CTA).

Methods: Fifty-eight patients (36 symptomatic and 22 asymptomatic) with severe unilateral stenosis (≥70%) or occlusion of the MCA M1 segment who underwent dynamic CTA were included. Collateral status, antegrade flow, and CVF of each patient were observed using dynamic CTA. Three types of cortical veins were selected to observe the extent of CVF, and the absence of CVF (CVF-) was recorded. Based on the appearance of CVF in the superior sagittal sinus, instances of CVF, including early (CVF_1), peak (CVF_2), and late (CVF_3) venous phases, were recorded. The differences in CVF times between the affected and contralateral hemispheres were represented as rCVFs, and CVF velocity was defined compared to the median time of each rCVF.

Results: All CVF times in the affected hemisphere were longer than those in the contralateral hemisphere ($p < 0.05$). Patients with symptomatic MCA stenosis had more ipsilateral CVF- ($p = 0.02$) and more delayed CVF at $rCVF_2$ and $rCVF_{21}$ ($rCVF_2$-$rCVF_1$) ($p = 0.03$ and 0.001, respectively) compared to those with asymptomatic MCA stenosis. For symptomatic patients, fast CVF at $rCVF_{21}$ was associated with poor collateral status (odds ratio [OR] 6.42, 95% confidence interval [CI] 1.37–30.05, $p = 0.02$), and ipsilateral CVF- in two cortical veins was associated with poor 3-month outcomes (adjusted OR 0.025, 95% CI 0.002–0.33, $p = 0.005$).

Conclusions: Complete and fast CVF is essential for patients with symptomatic MCA stenosis or occlusion. The clinical value of additional CVF assessment should be explored in future studies to identify patients with severe MCA stenosis or occlusion at a higher risk of stroke occurrence and poor recovery.

Keywords: cortical venous filling, middle cerebral artery, severe stenosis, occlusion, dynamic computed tomography angiography

INTRODUCTION

A series of studies have shown that patients with severe intracranial atherosclerotic stenosis (≥70%) or occlusion are at elevated risk of stroke occurrence and recurrence, regardless of whether the best medical therapy is received (1–3). For patients with symptomatic intracranial stenosis, the gradual development of collateral circulation plays a role in protecting perfusion and stabilizing cerebral blood flow (4, 5), including arterial collateral compensation as well as cerebral venous autoregulation (6). The intracranial venous system, a vital component of the vascular neural network, accounts for up to 70% of the total cerebral blood volume (7). However, vascular assessment in intracranial atherosclerosis is mainly based on arterial collateral recruitment, ignoring the significant element of intracranial venous drainage (8).

In recent years, imaging-based venous biomarkers such as cortical veins have been widely reported to play an essential role in acute ischemic events (7, 9–11). The presence of cortical venous filling (CVF) is related to a reduction in infarct volume and decreased severity of hemiparesis (10). Slow or poor CVF of the affected territory probably represents a delayed transmission of cerebral microcirculation, which is more prevalent in strokes in patients with poor collaterals (12–14). Several studies have demonstrated that the asymmetry of CVF can accurately predict clinical prognosis (15–18). In acute stroke patients with severe intracranial arterial stenosis or occlusion, the asymmetrical prominent cortical vein sign is associated with early neurological deterioration (19). However, there have been no reports on the combined assessment of the extent and velocity of CVF in patients with chronic atherosclerosis.

As a non-invasive technique, dynamic computed tomography angiography (CTA)/whole-brain CT perfusion (CTP) is a potential adjunct to traditional digital subtraction angiography (DSA) if time-resolved imaging is required (20). Dynamic CTA/CTP is widely used to evaluate vascular filling from arterial to venous phases because both the velocity and the extent of vessel filling can be considered at the same time, showing high diagnostic accuracy (21–27). To our knowledge, cortical veins, such as the superficial middle cerebral vein (SMCV) and the veins of Trolard (VOT) and Labbe (VOL), receive drainage from most of the arterial supply territories of the middle cerebral artery (MCA) and drain into the superior sagittal sinus (10, 28, 29). This study aimed to investigate the extent and velocity of these key venous fillings and determine whether there is an association between CVF and clinical manifestations in patients with severe unilateral MCA stenosis or occlusion using dynamic CTA/CTP.

MATERIALS AND METHODS

Subjects

The Ethics Committee of the First Affiliated Hospital of Jinan University approved this study. From January 2018 to March 2020, we prospectively screened consecutive patients in the Department of Neurology of the First Affiliated Hospital of Jinan University, with unilateral MCA M1 segment stenosis (≥70%) or occlusion confirmed by DSA or CTA. These patients were divided into symptomatic and asymptomatic groups. Symptomatic patients were those with ischemic stroke or transient ischemic attack within 2 weeks following the onset of symptoms in the distribution of severe stenotic MCA or occlusion. Asymptomatic patients were considered for inclusion if there was no history of cerebrovascular events related to the internal carotid system but still had unilateral MCA M1 segment stenosis (≥70%) or occlusion detected by DSA or CTA. All patients received antiplatelet medication with aggressive risk factors control after admission. Written informed consent was obtained, and dynamic CTA/CTP examinations were performed for each patient.

Patients with any of the following conditions were excluded: (1) internal carotid artery stenosis (≥50%) or contralateral MCA stenosis (≥50%); (2) previous internal carotid artery or MCA stenting, balloon dilatation, or endarterectomy; (3) non-atherosclerotic vasculopathy, such as dissection, moyamoya disease, or vasculitis; (4) evidence of cardiogenic embolism; (5) poor image quality hindering further image analysis; and (6) CT examination-related contraindications. For symptomatic patients, the National Institutes of Health Stroke Scale (NIHSS) score was assessed at the time of admission, and the modified Rankin score (mRS) was obtained at 3 months by telephone interview or outpatient visit.

CT Protocol

All patients underwent dynamic CTA/CTP examination with a 320-slice multidetector (Aquilion ONE; Cannon Medical Systems, Tokyo, Japan). A total volume of 50 mL of contrast material with an iodine content of 370 mg/mL (Ultravist 370; Bayer, Leverkusen, Germany) was injected at a flow rate of 6 mL/s. The CT scanning parameters were as follows: tube voltage, 80 kV; matrix, 512 × 512; field of view, 320 mm; rotation time, 0.35 s; and collimator, 0.5 mm × 320. A total of 19 whole-brain volume data were obtained for every patient and loaded into a Vitrea Fx 6.3 workstation (Vital Images, Minnetonka, MN). Based on the separation of the arterial and venous time attenuation curves (TACs) using contrast enhancement of the contralateral MCA and the superior sagittal sinus (25), the maximum intensity projection (MIP) images at different phases were reconstructed. We defined the time point with the best contrast opacification of the bilateral MCA, which was less affected by cortical veins and venous sinuses as the arterial phase (A-TAC) and the time point at the peak points of the venous TAC as the venous phase (V-TAC) (**Figure 1A**). The stenotic degree of the MCA M1 segment was calculated using 3D CTA with dedicated imaging software (**Figure 1B**) or verified by DSA (30).

Image Analysis

Using the reconstructed three-dimensional (3D) CT venography (CTV) MIP images, we observed contrast enhancement of all cortical veins that drained into the superior sagittal sinus. We defined CVF_1 as the time point when any cortical vein began to appear, CVF_2 as when most cortical veins reached maximum contrast opacification, and CVF_3 as the first moment when all cortical veins had completely disappeared (13). In addition, the difference between CVF_2 and CVF_1 (CVF_{21}) represented the

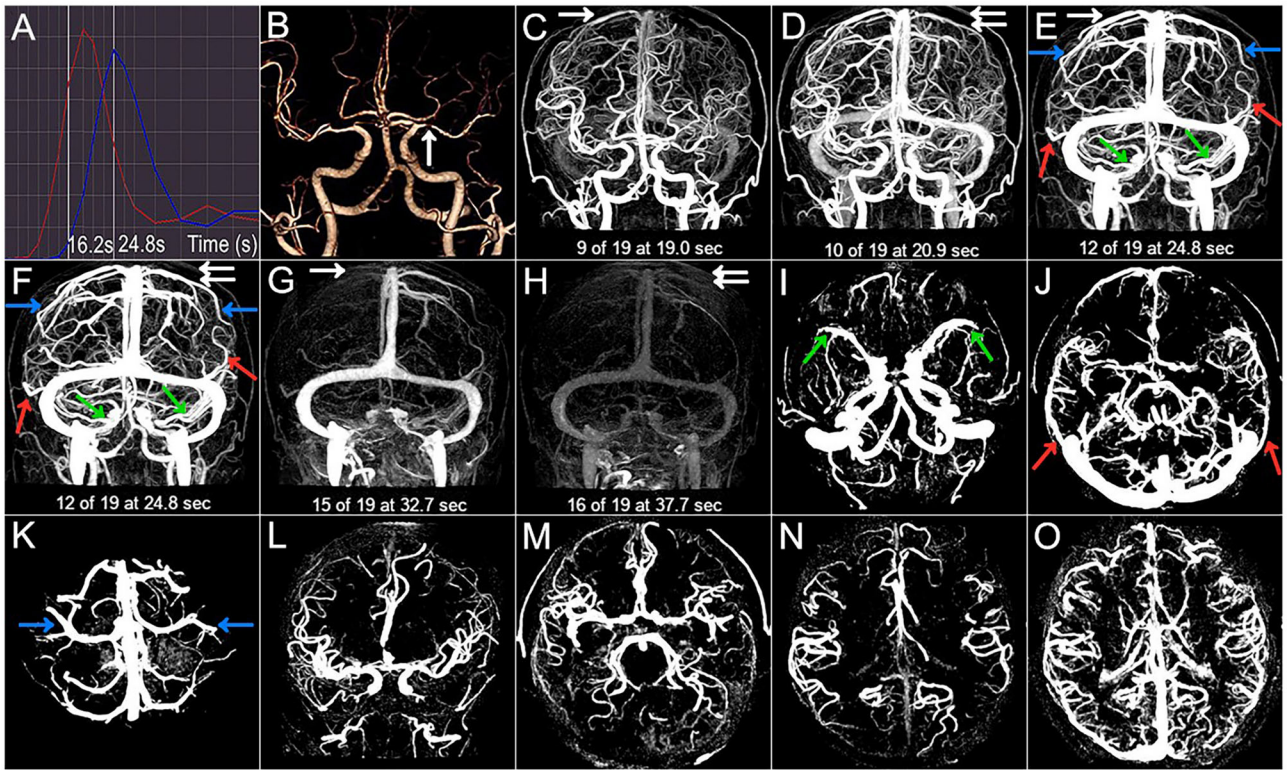

FIGURE 1 | Case 1. A 66-year-old man with a history of hypertension and lipid disorder presented with dizziness for 3 days. **(A)** The arterial and venous time attenuation curves (TACs; red and blue, respectively). The selected arterial phase on TAC (A-TAC) was 16.2 s, and the time-to-peak on the venous TAC (V-TAC) was 24.8 s. **(B)** The arrow points to the left MCA M1 severe stenosis at A-TAC on three-dimensional (3D) computed tomographic angiography (CTA). **(C–H)** The 3D computed tomography venography (CTV) shows cortical venous filling (CVF) draining into the superior sagittal sinus at early (CVF_1), peak (CVF_2), and late venous phases (CVF_3) in the affected (double white arrow) and contralateral (white arrow) hemispheres. Cortical veins begin to be visible in the contralateral (C, CVF_1, 19.0 s) and affected hemispheres (D, CVF_1, 20.9 s). The maximum contrast opacification of all cortical veins in the contralateral (E, CVF_2, 24.8 s) and affected hemispheres (F, CVF_2, 24.8 s) appear at the same time, and contrast medium in all cortical veins disappears in the contralateral (G, CVF_3, 32.7 s) and affected hemispheres (H, CVF_3, 37.7 s). CVF_{21} and CVF_{31} of the contralateral hemisphere are 5.8 s and 13.7 s, respectively, while the CVF_{21} and CVF_{31} of the affected hemisphere are 3.9 s and 16.8 s, respectively. The mean difference between the affected and contralateral hemispheres is 1.9 s for $rCVF_1$, 0 s for $rCVF_2$, 5 s for $rCVF_3$,−1.9 s for $rCVF_{21}$, and 3.1 s for $rCVF_{31}$. The presence (color arrow) and absence (circle) of SMCV (green), VOL (red), and VOT (blue) across all whole venous phases (marked as SMCV+/VOL+/VOT+ and SMCV-/VOL-/VOT-, respectively) are displayed in the 3D CTV and **(I–K)** axial planes of the V-TAC. SMCV-, VOL-, and VOT- are not found in the bilateral hemispheres. **(L,M)** Antegrade flow assessment at TAC in the coronal and axial planes. Contrast filling of the MCA M1 segment and its distal branches in the affected hemisphere is more than two-thirds of the contralateral hemisphere. the contralateral hemisphere, and antegrade flow is preserved. **(N,O)** Collateral status assessment at A-TAC and V-TAC in the axial plane. Complete contrast enhancement of collateral flow at V-TAC in the affected hemisphere with good collateral status.

early to peak-venous phase, and the difference between CVF_3 and CVF_1 (CVF_{31}) represented the whole venous phase. We calculated the above CVF times for both hemispheres according to the timing collection of the 19 volumes (**Figures 1C–H**). Moreover, the difference in CVF times between the affected and contralateral hemispheres was calculated (rCVFs). To further assess CVF velocity, the fast CVF was defined as a point in time that was less than or equal to the median rCVF, and slow CVF was the opposite (13).

To assess the extent of CVF, we first observed contrast filling of the three cortical veins on 3D CTV, including SMCV, VOT, and VOL. Subsequently, we assessed the MIP reconstruction of the cortical veins above the V-TAC in the axial plane (**Figures 1I–K**). The presence of CVF at any time point in the venous phase was defined as CVF+ (SMCV+/VOL+/VOT+), whereas the absence of CVF during the whole venous phase was defined as CVF- (SMCV-/VOL-/VOT-) (31). Because CVF- could be seen in the unaffected hemisphere in subjects with anatomical variations (32), we defined the condition of CVF- in the affected hemisphere and CVF+ in the contralateral hemisphere as ipsilateral CVF-. If there was ipsilateral CVF-, the type and number of ipsilateral CVF- were recorded in symptomatic and asymptomatic patients.

The antegrade flow across the stenotic MCA was evaluated in both the coronal and axial planes at A-TAC by referring to the thrombolysis in cerebral infarction scale based on DSA (33, 34) (**Figures 1L,M**). We reported antegrade flow as preserved or compromised according to whether the vessel filling of the MCA in the affected hemisphere was more than two-thirds of the contralateral hemisphere. Moreover, the collateral status in the affected hemisphere was evaluated at the level of the basal ganglia and thalamus in the axial plane at A-TAC and V-TAC by comparing it with that in the

contralateral hemisphere (35) (**Figures 1N,O**). For our analysis, we reported good collateral status if the collaterals presented complete contrast enhancement at V-TAC or A-TAC and poor collateral status if no contrast enhancement or peripheral contrast enhancement was observed with V-TAC or A-TAC. Two experienced neuroradiologists (Z.Y.C and X.R.C), blinded to all clinical information, independently interpreted and measured the imaging data of all patients. In case of disagreements further judgment was made by consulting a neuroimaging radiologist with higher qualifications.

Statistical Analyses

Statistical analyses were conducted using SPSS version 21.0 (IBM Corp., Armonk, NY). Variables conforming to the contralateral distribution were reported as mean ± standard deviation, and a *t*-test was conducted for comparison between groups. Categorical variables were expressed as frequencies, and Pearson's chi-square test was used for comparisons between groups. The time from symptom onset or admission to the dynamic CTA/CTP examination, NIHSS score at admission, and CVF times were expressed as the median of the interquartile range (IQR) and were compared using the Mann-Whitney *U* test between groups. To study the relationship between CVF, collateral status, and clinical outcome in the symptomatic group, univariate and multivariate logistic models were used. Results are expressed as odds ratios (ORs) with 95% CIs. *P*-values of <0.05 were considered as statistically significant.

TABLE 1 | Baseline demographics of symptomatic and asymptomatic patients.

	Symptomatic patients ($n = 36$)	Asymptomatic patients ($n = 22$)	*p*
Age, years	58.3 ± 9.2	61.3 ± 11.0	0.28
Female	9 (25%)	6 (27%)	0.85
HbA_{1c}, %	6.7 ± 2.2	6.2 ± 1.3	0.35
LDL cholesterol, mmol/L	2.7 ± 1.1	2.4 ± 0.9	0.14
HDL cholesterol, mmol/L	1.4 ± 1.4	0.9 ± 0.2	0.06
Cholesterol, mmol/L	4.5 ± 1.6	4.1 ± 1.3	0.35
Triglyceride, mmol/L	2.1 ± 1.0	1.6 ± 1.1	0.14
Hypertension	16 (44%)	12 (55%)	0.46
Diabetes mellitus	12 (33%)	7 (32%)	0.91
Smoking history	23 (64%)	10 (46%)	0.17
Drinking	9 (25%)	8 (36%)	0.36
Lipid disorder	26 (72%)	12 (71%)	0.9
Stenosis of MCA			0.56
Severe stenosis (70–99%)	24 (67%)	13 (59%)	
Occlusion (100%)	12 (33%)	9 (41%)	
Time from admission to dynamic CTA/ CTP, days, median (interquartile range)	3 (1–7)	5 (3–7)	0.12

HbA_{1c}, hemoglobin A_{1c}; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MCA, middle cerebral artery; CTA, computed tomography angiography; CTP, computed tomography perfusion.

RESULTS

Patient Characteristics

A total of 66 consecutive patients underwent dynamic CTA/CTP scanning. Due to poor image quality, eight patients were excluded. Among the 58 patients included in the study, 36 were symptomatic (31 with ischemic stroke in the MCA territory and five with transient ischemic attack) and 22 were asymptomatic. The median time from symptom onset to dynamic CTA/CTP examination of symptomatic patients was 11 days. The traditional risk factors for intracranial atherosclerosis, the stenotic degree of MCA, and the median time from admission to dynamic CTA/CTP scanning were similar between the symptomatic and asymptomatic groups (**Table 1**). **Figure 1** shows a representative asymptomatic patient, and **Figures 2**, **3** show two representative symptomatic patients.

Comparison of CVF Between Symptomatic and Asymptomatic Patients

The CVF times and instances of CVF- of the affected and contralateral hemispheres in both symptomatic and asymptomatic patients were compared, and the results are listed in **Table 2**. In symptomatic patients, CVF-, SMCV-, VOT-, and VOL- in the affected hemisphere were more common than in the contralateral hemisphere ($p < 0.001$, $p = 0.02$, 0.004, and 0.03, respectively), while there was no significant difference in the proportion and type of CVF- between the affected and contralateral hemispheres in the asymptomatic group. In addition, the CVF times of the affected hemisphere were all significantly longer than those of the contralateral hemisphere in both the symptomatic and asymptomatic groups ($p < 0.05$ for all CVF times).

Imaging findings of symptomatic and asymptomatic patients are listed in **Table 3**. Since there was no ipsilateral SMCV-, VOT-, or VOL- at the same time in either group, we divided the number of instances of ipsilateral CVF- into two groups: CVF- = 1 and CVF- = 2. Patients with symptomatic MCA stenosis had longer CVF times at $rCVF_2$ and $rCVF_{21}$ ($p = 0.03$ and 0.001, respectively; e.g., 0 s in **Figure 1** vs. 2 s in **Figures 2**, **3** for $rCVF_2$; −1.9 s in **Figure 1** vs. 0 s in **Figure 2**, 0.1 s in **Figure 3** for $rCVF_{21}$) and more ipsilateral CVF- ($p = 0.02$; e.g., ipsilateral CVF+ in **Figure 1** vs. ipsilateral CVF- in **Figures 2**, **3**) in the MCA territory of the affected hemisphere, but were similar in the type and number of ipsilateral CVF- compared to the asymptomatic group. In addition, there was no significant difference in collateral status or antegrade flow between the groups.

CVF Velocity and Collateral Status in Symptomatic Patients

It can be concluded from **Table 3** that the mean difference between the affected and contralateral hemisphere was 2.0 s for $rCVF_1$, 2.5 s for $rCVF_2$, 2.7 s for $rCVF_3$, 1.9 s for $rCVF_{21}$, and 1.7 s for $rCVF_{31}$ in symptomatic patients. Therefore, we selected fast $rCVF_{21}$ if the difference in CVF time was ≤1.9 s compared to that in the contralateral hemisphere. In patients with symptomatic

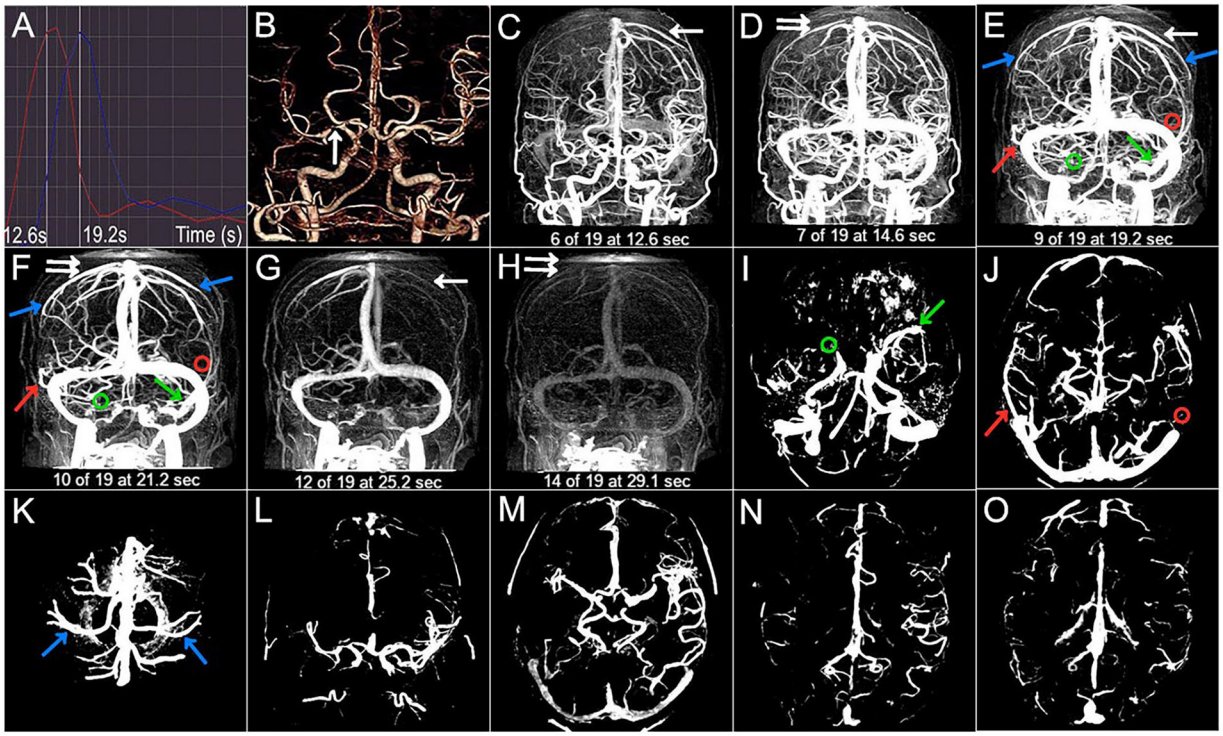

FIGURE 2 | Case 2. A 54-year-old woman with a history of hypertension and diabetes presented with left-sided and left facial droop hemiparesis. The NIHSS score was 5 on admission. 3 months mRS score was 1 (good outcome). **(A)** The selected arterial and venous phases are 12.6 s and 19.2 s, respectively. **(B)** The arrow points to the right M1 severe stenosis. **(C–H)** The CVF_1, CVF_2, CVF_3, CVF_{21}, and CVF_{31} of the contralateral hemisphere (white arrow) are 12.6 s, 19.2 s, 25.2 s, 6.6 s, and 12.6 s, respectively, while the CVF_1, CVF_2, CVF_3, CVF_{21}, and CVF_{31} of the affected hemisphere (double white arrow) are 14.6 s, 21.2 s, 29.1 s, 6.6 s, and 14.5 s, respectively. The mean difference between the affected and contralateral hemisphere is 0 s for $rCVF_{21}$. **(C–K)** The presence (color arrow) and the absence (circle) of SMCV (green), VOL (red), and VOT (blue). SMCV- is found in the affected hemisphere, and VOL- is found in the contralateral hemisphere. **(L–O)** Compromised antegrade flow and poor collateral status.

MCA stenosis, 22 had good collateral status and 14 had poor collateral status. The relationship between CVF velocity and collateral status at each time point is shown in **Table 4**. Fast CVF at $rCVF_{21}$ was present in 8 (36%) patients with good collateral status, whereas it was found in 11 (79%) patients with poor collateral status ($p = 0.02$). In univariate analysis, fast CVF (only at $rCVF_{21}$, i.e., early to peak-venous phase) was positively associated with poor collateral status (OR 6.42, 95% CI 1.37–30.05, $p = 0.02$; e.g., fast CVF at $rCVF_{21}$ and poor collateral status in **Figures 2**, **3**).

CVF and Neurological Outcomes at 3 Months in Symptomatic Patients

At 3 months after discharge, 25 patients had a favorable prognosis (mRS score 0–2), while 11 had a poor outcome (mRS score > 2). **Table 5** shows the associations between clinical and imaging variables and clinical outcomes at the 3-month follow-up. There was no significant relationship between baseline characteristics and clinical prognosis. The proportion of patients with poor outcomes was greater in those with higher NIHSS scores after admission ($p = 0.04$). Four patients underwent elective endovascular angioplasty for severe stenotic MCA within 3 months; however, there was a non-significant trend toward a good prognosis. Ipsilateral CVF-, type of ipsilateral CVF-, absence of filling of one cortical vein, poor collateral status, and compromised antegrade flow were not significantly related to poor clinical outcomes. Among the 11 patients with poor outcomes, the absence of filling of the two cortical veins was found in six cases (56%) ($p < 0.001$). In univariate analysis, the absence of filling of the two cortical veins was associated with clinical results (OR 0.04, 95% CI 0.003–0.36, $p = 0.005$). Furthermore, multivariate analysis showed that the absence of filling of the two cortical veins was still related to the poor outcome at the 3-month follow-up (adjusted OR 0.025, 95% CI, 0.002–0.33, $p = 0.005$) (**Figure 2** vs. **Figure 3**).

DISCUSSION

To the best of our knowledge, this is the first prospective study to describe the velocity and extent of CVF in patients with severe stenosis or occlusion of the MCA responsible or not responsible for recent ischemic stroke or transient ischemic attack. Prolonged CVF times were commonly found at different stages of the venous phase in the affected hemisphere. Patients with symptomatic MCA stenosis also had longer CVF times and more ipsilateral CVF- than those with asymptomatic MCA

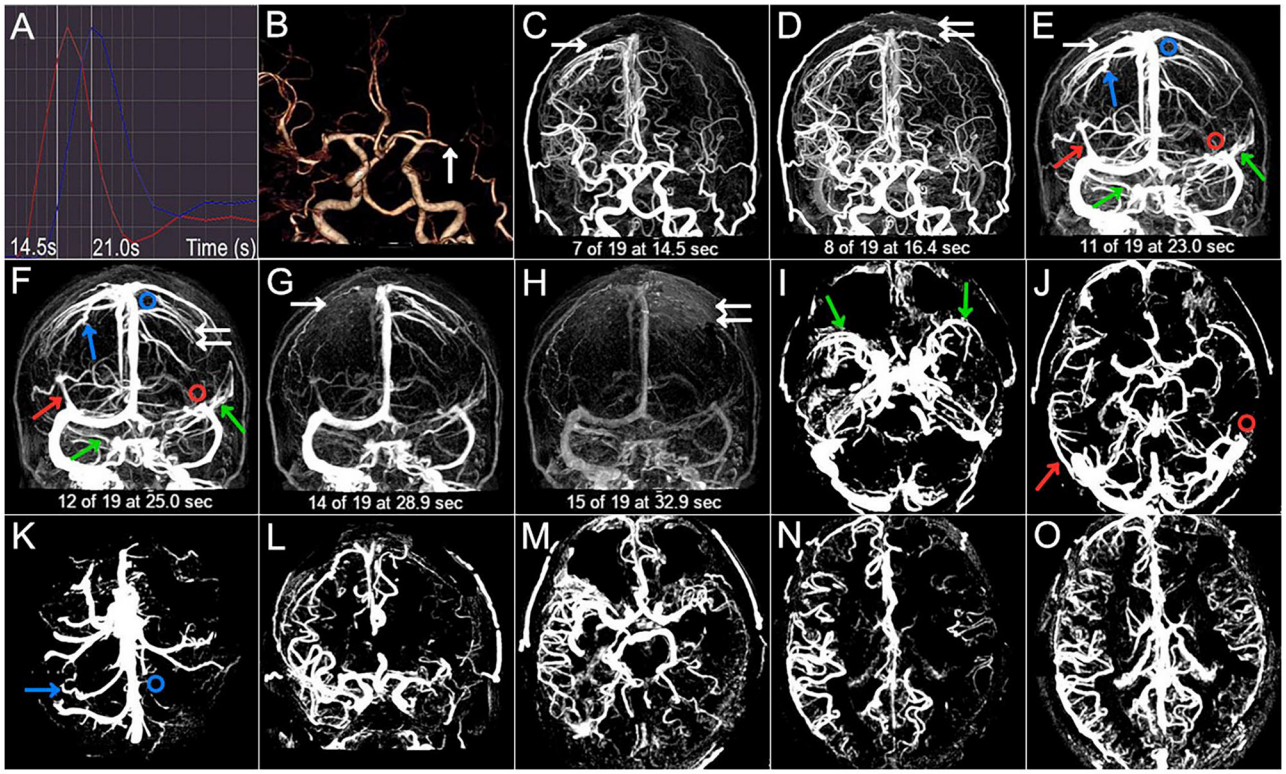

FIGURE 3 | Case 3. A 50-year-old man with a history of hypertension, diabetes, and smoking presented with dysarthria and right-sided hemiparesis. NIHSS score was 6 on admission and 3-month mRS score was 3 (poor outcome). **(A)** The selected arterial phase and the venous phase are 14.5 s and 21.0 s, respectively. **(B)** The arrow points to the left M1 occlusion. **(C–H)** The CVF_1, CVF_2, CVF_3, CVF_{21}, and CVF_{31} of the contralateral hemisphere (white arrow) are 14.5 s, 23.0 s, 28.9 s, 8.5 s, and 14.4 s, respectively, while CVF_1, CVF_2, CVF_3, CVF_{21}, and CVF_{31} of the affected hemisphere (double white arrow) are 16.4 s, 25.0 s, 32.9 s, 8.6 s, and 16.5 s, respectively. The mean difference between the affected and contralateral hemisphere is 0.1 s for $rCVF_{21}$. **(C–K)** SMCV-, VOL-, and VOT- are not found in the contralateral hemisphere (color arrow), while VOL- (red circle) and VOT- (blue circle) are shown in the affected hemisphere. **(L–O)** Compromised antegrade flow and poor collateral status.

TABLE 2 | Instances of CVF- and CVF times of the affected and contralateral hemispheres.

	Symptomatic patients ($n = 36$)			Asymptomatic patients ($n = 22$)		
	Affected hemisphere	**Contralateral hemisphere**	***p***	**Affected hemisphere**	**Contralateral hemisphere**	***p***
Instances of CVF-						
CVF-	19 (53%)	2 (6%)	<0.001	4 (18%)	5 (23%)	1
SMCV-	7 (19%)	0 (0%)	0.02	1 (5%)	1 (5%)	1
VOT-	9 (25%)	0 (0%)	0.004	2 (9%)	0 (0%)	0.47
VOL-	10 (28%)	2 (6%)	0.03	1 (5%)	4 (18%)	0.34
CVF times, s, medians (interquartile range)						
CVF_1	14.7 (13.2–17.9)	12.8 (11.5–14.5)	<0.001	14.2 (10.0–17.0)	12.2 (9.8–14.5)	<0.001
CVF_2	21.3 (19.7–26.8)	19.1 (17.3–23.0)	<0.001	21.5 (17.8–23.3)	18.5 (16.9–22.0)	<0.001
CVF_3	29.0 (24.8–33.1)	25.6 (23.2–30.0)	<0.001	30.9 (26.6–33.5)	26.9 (23.0–30.3)	<0.001
CVF_{21}	8.8 (6.6–11.7)	6.6 (5.0–7.9)	<0.001	6.3 (4.8–8.3)	6.0 (4.6–8.3)	0.003
CVF_{31}	12.9 (11.8–16.0)	12.5 (7.8–16.3)	0.04	15.3 (13.7–19.4)	14.4 (12.4–16.9)	0.02

CVF-, absence of cortical venous filling; SMCV-, absence of the superficial middle cerebral vein; VOT-, absence of the vein of Trolard; VOL-, absence of the vein of Labbé; CVF, cortical venous filling; CVF_1, early venous phase; CVF_2, peak venous phase; CVF_3, late venous phase; CVF_{21}, early to peak-venous phase; CVF_{31}, whole venous phase.

TABLE 3 | Imaging findings in symptomatic and asymptomatic patients.

	Symptomatic patients ($n = 36$)	Asymptomatic patients ($n = 22$)	*p*
Ipsilateral CVF-	19 (53%)	4 (18%)	0.02
Type of ipsilateral CVF-			
SMCV-	7 (19%)	1 (5%)	0.23
VOT-	9 (25%)	2 (9%)	0.25
VOL-	10 (28%)	1 (5%)	0.07
Number of ipsilateral CVF-			
CVF- = 1	12 (33%)	4 (18%)	0.34
CVF- = 2	7 (19%)	0 (0%)	0.07
CVF times, s, medians (interquartile range)			
$rCVF_1$	2.0 (1.2–3.0)	1.8 (0.3–2.0)	0.16
$rCVF_2$	2.5 (1.9–3.9)	2.0 (0.8–2.6)	0.03
$rCVF_3$	2.7 (0.3–4.0)	2.1 (0.0–4.0)	0.79
$rCVF_{21}$	1.9 (0.4–4.5)	0.1 (0.0–0.5)	0.001
$rCVF_{31}$	1.7 (−1.9–4.7)	0.2 (0.0–2.2)	0.5
Collateral status			0.2
Good	22 (61%)	17 (77%)	
Poor	14 (39%)	5 (23%)	
Antegrade flow			0.78
Preserved	15 (42%)	10 (45%)	
Compromised	21 (58%)	12 (55%)	

CVF-, absence of cortical venous filling; SMCV-, absence of the superficial middle cerebral vein; VOT-, absence of the vein of Trolard; VOL-, absence of the vein of Labbé; CVF- = 1, absence of one cortical vein; CVF- = 2, absence of two cortical veins; CVF, cortical venous filling; $rCVF_1$, relative difference in the early venous phase; $rCVF_2$, relative difference in the peak venous phase; $rCVF_3$, relative difference in the late venous phase; $rCVF_{21}$, relative difference in the early to peak-venous phase; $rCVF_{31}$, relative difference in the whole venous phase.

TABLE 4 | Relationship between CVF velocity and collateral status in symptomatic patients.

	Good collateral status ($n = 22$)	Poor collateral status ($n = 14$)	*p*	OR	95% CI	*p*
CVF velocity						
$rCVF_1$			1			
Fast	14 (64%)	8 (64%)				
Slow	8 (36%)	5 (36%)				
$rCVF_2$			0.31			
Fast	9 (41%)	8 (64%)				
Slow	13 (59%)	5 (36%)				
$rCVF_3$			0.09			
Fast	8 (36%)	10 (71%)				
Slow	14 (64%)	4 (29%)				
$rCVF_{21}$			0.02	6.42	1.37-30.05	0.02
Fast	8 (36%)	11 (79%)				
Slow	14 (64%)	3 (21%)				
$rCVF_{31}$			0.74			
Fast	11 (50%)	8 (57%)				
Slow	11 (50%)	6 (43%)				

CVF, cortical venous filling; $rCVF_1$, relative difference in the early venous phase; $rCVF_2$, relative difference in the peak venous phase; $rCVF_3$, relative difference in the late venous phase; $rCVF_{21}$, relative difference in the early to peak-venous phase; $rCVF_{31}$, relative difference in the whole venous phase.

TABLE 5 | Univariate associations of baseline characteristics and clinical outcomes at 3 months.

	Good outcomes ($n = 25$)	Poor outcomes ($n = 11$)	*p*	OR	95% CI	*p*
Age, years	57.0 ± 9.2	61.5 ± 8.6	0.18			
Hypertension	10 (40%)	6 (55%)	0.48			
Diabetes	7 (28%)	5 (46%)	0.45			
Smoking history	16 (64%)	7 (64%)	1			
Drinking	6 (24%)	3 (27%)	1			
Lipid disorder	18 (72%)	8 (73%)	1			
NIHSS, median (interquartile range)	3 (2–4)	5 (2–8)	0.04	1.36	1.00–1.86	0.05
Angioplasty	3 (12%)	1 (9%)	1			
Ipsilateral CVF-	11 (44%)	8 (73%)	0.16			
Ipsilateral SMCV-	4 (16%)	3 (27%)	0.65			
Ipsilateral VOT-	6 (24%)	3 (27%)	0.57			
Ipsilateral VOL-	5 (20%)	5 (45%)	0.12			
CVF- = 1	9 (36%)	3 (27%)	0.71			
CVF- = 2	1 (4%)	6 (56%)	< 0.001	0.04	0.003–0.36	0.005
Slow $rCVF_1$	11 (44%)	2 (18%)	0.26			
Slow $rCVF_2$	12 (48%)	6 (55%)	1			
Slow $rCVF_3$	11 (44%)	7 (64%)	0.47			
Slow $rCVF_{21}$	11 (44%)	6 (55%)	0.41			
Slow $rCVF_{31}$	11 (44%)	6 (55%)	0.72			
Poor collateral status	11 (44%)	3 (27%)	0.47			
Compromised antegrade flow	13 (52%)	8 (73%)	0.3			

NIHSS, National Institutes of Health Stroke Scale; CVF-, absence of cortical venous filling; SMCV-, absence of the superficial middle cerebral vein; VOT-, absence of the vein of Trolard; VOL-, absence of the vein of Labbé; CVF- = 1, absence of one cortical vein; CVF- = 2, absence of two cortical veins; $rCVF_1$, relative difference in the early venous phase; $rCVF_2$, relative difference in the peak venous phase; $rCVF_3$, relative difference in the late venous phase; $rCVF_{21}$, relative difference in the early to peak-venous phase; $rCVF_{31}$, relative difference in the whole venous phase.

stenosis. Moreover, our preliminary study demonstrated that fast CVF was associated with poor collateral status, and the absence of filling of the two cortical veins was linked with poor outcome, suggesting the essential and irreplaceable role of cortical veins in patients with symptomatic high-grade MCA stenosis or occlusion.

In this study, we noticed an obvious relationship between delayed filling of the ipsilateral cortical veins and severe stenosis or occlusion of the MCA. Adequate collateral perfusion requires arterial and venous autoregulation to redistribute cerebral blood flow and maintain cerebral perfusion (6, 7), which might indicate a slowdown of venous drainage to varying degrees in response to chronic cerebral hypoperfusion. However, there was a similar proportion of CVF- in the bilateral hemispheres of asymptomatic patients. A possible explanation is that compensatory venous collaterals can extensively communicate at the cortical surface (36, 37), resulting in delayed venous drainage, but the presence of cortical vein collaterals (SMCV, VOT, VOL).

Similar to previous research studies on acute MCA occlusion (10, 38), our study demonstrated that symptomatic patients were more likely to experience slower and asymmetrical CVF in the affected MCA territory. No serial studies have assessed changes in the cortical veins over time after qualifying ischemic events. If ischemic strokes occur under the condition of chronic stenosis, a compensatory hemodynamic function of venous collaterals associated with increased venous blood volume and cerebral vasodilation may be continuously and seriously impaired (39), resulting in slower or even absent ipsilateral CVF for a long time. Additionally, a previous study has shown that VOL and VOT are often seen in a certain hemisphere in contralateral subjects (40), which may partially explain why the type and number of ipsilateral CVF- between the symptomatic and asymptomatic groups were not enough to contribute to a statistical difference.

We also found that fast CVF was closely related to poor arterial collateral in symptomatic patients. This finding was not in line with that of a previous study, which demonstrated a trend toward slow CVF with a worse collateral grade in patients with acute MCA occlusion (10). It is important to mention that the clinical correlations of arterial collaterals in this study were not evident, indicating that the rapid and effective drainage of cortical veins may be beneficial in compensating for potential arterial hemodynamic damage. Moreover, once chronic atherosclerosis reaches a stage with severe stenosis or complete occlusion, it will lead to insufficient and slow venous drainage far beyond the nearby arterial collaterals, even if good collateral flow tends to compensate circulation. Interestingly, delayed drainage of cortical veins in the early to peak-phase, not the late venous phase (41), was related to arterial collateral status and stroke occurrence in this study. The CVF time lag in the affected hemisphere has been proven to be associated with prolonged mean transit time (12), which probably reflects compromised perfusion through microcirculation at an earlier stage of venous drainage due to progressive microvascular obstruction (16).

Our results support the effect of asymmetric CVF on the prognosis of ischemic stroke demonstrated in previous studies (15–18). In contrast to acute occlusion, the number of ipsilateral CVF-, rather than the type of ipsilateral CVF- has superior prognostic value in patients with symptomatic MCA stenosis in this study, which might be explained by hemodynamic mechanisms. First, the lower extent of CVF during chronic stenosis may be explained by the upregulation of vascular endothelial cell adhesion molecules and the downregulation of tight junction proteins to weaken the blood-brain barrier in hypoperfusion (42). Other explanations include active venous contraction (43), leukocyte-platelet aggregation obstruction (44, 45), and passive thin-walled venule compression (46). In addition, the respective collateral pathways of venous drainage are irrevocably impaired when the number of ipsilateral CVF- is high (47). Furthermore, the severely impaired venous drainage pathway around the lesions, accompanied by long-term cerebral hypoperfusion, will ultimately damage the required perfusion and upstream arterial regulation (48), causing subsequent pathophysiological consequences that are difficult to correct.

In conclusion, we used dynamic CTA/CTP to investigate the relationships between various stages of cortical venous flow, symptom occurrence, and clinical prognosis in the present study. An increased proportion of CVF- or prolonged CVF times in the early to peak-phase in the affected hemisphere are more likely to be associated with recent ischemic events in patients with severe MCA stenosis or occlusion. Moreover, a lower extent of CVF is associated with worse short-term clinical outcomes, and fast CVF is likely to be a reaction to poor collateral flow, suggesting the importance of complete and fast cortical venous drainage in symptomatic MCA stenosis. Further prospective studies are warranted to validate the feasibility of CVF assessment in identifying patients with high-grade MCA stenosis or occlusion at a higher risk of stroke occurrence and poor prognosis.

However, this study had several shortcomings. First, the sample size collected in this study was small. Larger sample sizes will be critical for moving the field forward. Second, the period between symptom onset and imaging acquisition could not be determined for asymptomatic patients without clinical symptoms. Third, CVF-related MIP images were acquired in the target subjects with unilateral MCA severe stenosis or occlusion, which may be difficult to rule out patients with multifocal intracranial atherosclerotic stenosis. Therefore, a contralateral MCA with $<50\%$ stenosis was used as a control. Fourth, there is a certain proportion of CVF- in healthy individuals. Considering the physiological differences in each patient, our study mainly focused on the asymmetry of CVF in the affected hemisphere and evaluated whether ipsilateral CVF- had any effect on the occurrence and prognosis of stroke. Finally, the time interval of commonly used clinical image acquisition was quite long because of the clinical limitations of dynamic CTA/CTP. Therefore, it is necessary to carefully compare the CVF times at different stages of venous drainage.

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 the First Affiliated Hospital of Jinan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LH contributed to the conception and design of the study and edited the manuscript. JL performed data analyses and wrote the manuscript. JL and YS contributed toward the patient

recruitment. ZC and XC interpreted and measured the imaging data. All authors contributed to the article.

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Combination of Rescue Stenting and Antiplatelet Infusion Improved Outcomes for Acute Intracranial Atherosclerosis-Related Large-Vessel Occlusion

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Background and Purpose: Intracranial atherosclerosis-related large-vessel occlusion caused by *in situ* thrombo-occlusion (ICAS-LVO) has been regarded an important reason for refractoriness to mechanical thrombectomy (MT). To achieve better outcomes for ICAS-LVO, different endovascular strategies should be explored. We aimed to investigate an optimal endovascular strategy for ICAS-LVO.

Methods: We retrospectively reviewed three prospective registries of acute stroke underwent endovascular treatment. Among them, patients with ICAS-LVO were assigned to four groups based on their endovascular strategy: (1) *MT alone*, (2) rescue intracranial stenting after MT failure (*MT-RS*), (3) glycoprotein IIb/IIIa inhibitor infusion after MT failure (*MT-GPI*), and (4) a combination of MT-RS and MT-GPI (*MT-RS+GPI*). Baseline characteristics and outcomes were compared among the groups. To evaluate whether the endovascular strategy resulted in favorable outcome, multivariable analysis was also performed.

Results: A total of 184 patients with ICAS-LVO were included. Twenty-four patients (13.0%) were treated with MT alone, 25 (13.6%) with MT-RS, 84 (45.7%) with MT-GPI, and 51 (27.7%) with MT-RS+GPI. The MT-RS+GPI group showed the highest recanalization efficiency (98.0%). Frequency of patent arteries on follow-up (98.0%, $p < 0.001$) and favorable outcome (84.3%, $p < 0.001$) were higher in the MT-RS+GPI group than other groups. The MT-RS+GPI strategy remained an independent factor for favorable outcome (odds ratio, 20.4; 95% confidence interval, 1.97–211.4; $p = 0.012$).

Conclusion: Endovascular strategy was significantly associated with procedural and clinical outcomes in acute stroke by ICAS-LVO. A combination of RS and GPI infusion might be an optimal rescue modality when frontline MT fails.

Keywords: stroke, endovascular treatment, atherosclerosis, stent, angioplasty

INTRODUCTION

Intracranial atherosclerosis-related large-vessel occlusion (ICAS-LVO) caused by *in situ* thrombo-occlusion is a common etiology in endovascular treatment (EVT) for acute stroke. ICAS-LVO was frequently reported in ∼17–30% of patients who underwent EVT in Asia, although the incidence varied, depending on race or occlusion site (1). Importantly, mechanical thrombectomy (MT) techniques, including stent retriever thrombectomy (SRT) and contact aspiration thrombectomy (CAT), are ineffective in EVT for acute stroke primarily caused by ICAS-LVO (2–5). Owing to the refractoriness, the number of device passes can be increased in ICAS-LVO, which could delay time to recanalization and also make patient's prognosis worse (6, 7). Furthermore, arterial injury can be possible when stent retriever is indiscriminately applied to ICAS-LVO (8). Stent retriever is also likely to provoke platelet activation on atheromatous plaque, leading to reocclusion of partially recanalized artery (3).

To overcome occlusions refractory to treatment, specific rescue treatments appropriate for ICAS [ICAS-specific modalities (ISMs)], including intracranial stenting, balloon angioplasty, and glycoprotein IIb/IIIa inhibitor (GPI) infusion, can be considered (9–13). In several previous studies, ISMs were associated with higher possibility of successful recanalization, shorter time to recanalization, and better patient outcome (14–18). Although the necessity and feasibility of ISMs have been widely recognized, a practical endovascular strategy for ICAS-LVO has not yet been established. Reliable information regarding which ISM is optimal when the frontline MT fails is lacking. For example, GPI is an efficient rescue modality for the reocclusive ICAS-LVO; however, we do not know exactly when we need a more aggressive modality such as emergent intracranial stenting after GPI injection. While intracranial stenting may ultimately offer a successful recanalization, it might not always be the case. If further intracranial stenting cannot guarantee a successful recanalization, one may have to reconsider the type of ISMs. To determine a practical endovascular strategy for ICAS-LVO, procedural and clinical benefits of each ISM for MT failure should be investigated. Accordingly, the procedural efficiencies and clinical outcomes were evaluated in the present study based on endovascular modality for treatment of acute ICAS-LVO.

METHODS

Participants

Consecutive acute stroke patients with an intracranial LVO of anterior circulation, who underwent EVT between January 2010 and December 2018 in three comprehensive stroke centers, were retrospectively reviewed. The intracranial internal carotid artery and M1 segment of middle cerebral artery were defined as intracranial large vessels. In the present study, patients who met the following criteria were selected from the prospective registry: (1) first endovascular modality was MT (SRT and/or CAT); (2) age ≥18 years; (3) initial National Institutes of Health Stroke Scale (NIHSS) score ≥4; (4) presentation to the hospital within 8 h from stroke onset; patients within 8–12 h were also considered if they had an Alberta Stroke Program Early CT Score (ASPECTS) ≥7; and (5) premorbid modified Rankin Scale (mRS) score ≤2. Patients whose occlusion etiology was ICAS-LVO were finally included in this study. ICAS-LVO was determined angiographically. Residual fixed focal stenosis >70% of the target vessel or occlusion at arterial trunk on digital subtraction angiography was defined as ICAS-LVO (12, 14). ICAS-LVO was assessed by two independent neurointerventionalists. The κ-value for the interrater reliability was 0.91. Discrepant cases were resolved by consensus.

Endovascular Procedure

All endovascular procedures were performed under local anesthesia. Conscious sedation was allowed as necessary. The MT procedures were performed according to common recommendations and previous reports (9, 19). Rescue treatments were performed when occlusion was refractory even after several attempts using the frontline MT device; the occlusion segment was recanalized with severe stenosis leading to significant flow limitation, or the occlusion tended to reocclude. Rescue endovascular modalities included switching to the other MT modality (SRT to CAT or *vice versa*), a combination of SRT and CAT, intra-arterial urokinase infusion, balloon angioplasty, intracranial stenting, and/or intra-arterial or intravenous GPI infusion. Selection of the optimal rescue modality depended on the operator's judgment. However, when ICAS was suspected as the cause of LVO, the patient was treated by one of the following endovascular modalities: (1) intracranial rescue stenting with or without balloon angioplasty (RS), (2) GPI infusion, or (3) both modalities. Typically, 5–10 mg of abciximab (1–2 mg/min) or 0.3–1.5 mg of tirofiban (0.05 mg/mL concentration with 0.1 mg/min) was used. A sequence of RS and GPI infusion was not specified. For RS, Solitaire® (Medtronic, Dublin, Ireland) or Wingspan® (Stryker, Kalamazoo, MI, USA) was used. To secure the stability of arterial patency achieved using RS and/or GPI infusion, serial delay angiograms were taken for at least 20 min after recanalization was achieved. When significant angiographic worsening in arterial patency and perfusion were not observed, the procedure was finished.

Successful recanalization was defined as achieving modified TICI grade 2b or 3 and no reocclusion observed on delayed angiograms during the procedure. Dichotomized modified TICI grades (0–2a vs. 2b−3) were assessed by two independent neurointerventionalists blinded to clinical information and follow-up imaging. The κ-value for the interrater reliability was 0.81. All discrepant cases were resolved by consensus.

Postprocedural Antithrombotic Medication and Follow-Up Examinations

The types and timing of postprocedural antithrombotic medication were determined by consensus of neurointerventionalists and stroke neurologists from each participating center. Although not regulated under specific protocols, the postprocedural antithrombotic medication was summarized as follows: (1) no antithrombotic medication until intracranial hemorrhage was excluded based on brain imaging on the next day of EVT, (2) administration of single (aspirin 100–300 mg or clopidogrel 75 mg) or dual oral antiplatelets

(aspirin 100–300 mg with clopidogrel 75 mg) immediately after completion of the EVT procedure, and (3) intravenous infusion of GPI after completion of the EVT procedure for at least 12 h, then administration of dual antiplatelets after exclusion of intracranial hemorrhage based on brain imaging on the next day of EVT.

Arterial patency of recanalized arteries was evaluated on follow-up magnetic resonance angiograms (MRAs) and routinely performed at 1–7 days after EVT. For some patients who were medically unstable, CTA was obtained instead of MRA. The artery was considered patent when significant distal flow was observed on time-of-flight MRA. The arterial patency on follow-up was assessed by two independent physicians who were blinded to final recanalization status and clinical symptoms. The κ-value for the interrater reliability was 0.89. Discrepant cases were resolved by consensus.

Clinical Variables

All clinical parameters, including functional outcome, death, and symptomatic intracerebral hemorrhage (sICH), were collected from the prospective registries. Functional outcome and death were assessed based on the mRS score at 3 months after stroke onset. A favorable outcome was defined as mRS score of 0–2. The ICH was assessed on CT or MRI scans obtained 24 ± 6 h after EVT. If the patient's neurological status worsened, the CT or MRI scans were obtained anytime to evaluate ICH. The ICH was defined as symptomatic if the patient's NIHSS score increased ≥4.

Statistical Analyses

Based on the different types of endovascular modalities used to recanalize ICAS-LVO, endovascular strategies were classified into four groups: (1) EVT performed only with MT modalities (*MT-alone group*); (2) among ISMs, RS performed after MT failure (*MT-RS group*); (3) GPI infused after MT failure (*MT-GPI group*); and (4) both RS and GPI infusion performed after MT failure (*MT-RS+GPI group*).

First, demographics, risk factors for stroke, procedural details and outcomes, follow-up arterial patency, and clinical outcomes, including functional outcome, death, and sICH, were compared among the groups. Analysis of variance, Kruskal–Wallis test, χ^2 test, and Fisher exact test were used as appropriate. Second, to evaluate whether endovascular strategy was independently associated with functional outcome, a multivariable binary logistic regression analysis was performed for favorable outcome. Variables with potential association ($p < 0.2$ in univariable analyses) were entered into the multivariable model. For the univariable analyses, Student *t*-test, Mann–Whitney *U*-test, χ^2 test, and Fisher exact test were used as appropriate.

A $p < 0.05$ was considered statistically significant for 95% confidence interval (CI). All statistical analyses were performed using SPSS software (version 23; IBM, Armonk, NY, USA).

RESULTS

Among the 1,311 acute stroke patients who met the inclusion criteria for this study, 192 (14.6%) had ICAS-LVO. After excluding patients without a 3-month mRS score, 184 patients (95.8% of all patients with ICAS-LVO; mean age, 67.9 ± 14.0 years; male, 57.6%) were included in the final analysis (**Figure 1**). Twenty-four patients (13.0%) were treated only with MT modality (MT-alone group). ISMs were used in 160 patients (87.0%): 25 (13.6%) treated with RS (MT-RS group), 84 (45.7%) with GPI infusion (MT-GPI group), and 51 (27.7%) with both RS and GPI infusion (MT-RS+GPI group). Age, initial NIHSS score, and time from stroke onset to puncture differed among the groups (**Table 1**). SRT was the predominant frontline MT modality in all groups, and CAT was used as the frontline modality in ∼30% of patients in MT alone and MT-RS groups.

Recanalization Results Based on Endovascular Modality

A successful recanalization was achieved in 168 patients [91.3% (168 of 184)]. MT was successful in only 9.8% (18 of 184) of all ICAS-LVO patients as a frontline modality (**Table 1**). Among the remaining 166 patients who did not experience a successful recanalization with the frontline MT treatment, 160 were further treated with ISM. Rescue treatment with ISM was effective in 150 patients [150 of 160 (93.8%); overall recanalization efficiency of ISM after MT failure]. Recanalization efficiency in the MT-RS group (80.0%) was significantly lower than in the MT-GPI (95.2%, $p = 0.028$) and MT-RS+GPI groups (98.0%, $p = 0.013$).

Outcomes Based on Endovascular Modality

On the follow-up examination, 89.9% of recanalized arteries (151 of 168) were patent. The frequency of patent arteries on follow-up was different based on endovascular modality ($p < 0.001$; **Table 1**) and most frequent in the MT-RS+GPI group (98.0%). Patent arteries in the MT-RS+GPI group were significantly more frequent than in the MT alone (70.8%, $p = 0.001$), MT-RS (56.0%, $p < 0.001$), and MT-GPI groups (83.3%, $p = 0.009$; **Figure 2A**). The frequency of patent arteries on follow-up in the MT-RS group was significantly lower than in the MT-GPI group ($p = 0.004$) and not significantly different from the MT-alone group.

Functional outcome was also different based on endovascular modality ($p < 0.001$; **Table 1**). Favorable outcome was observed most in the MT-RS+GPI group (84.3%) and the least in the MT-alone group (29.2%). Furthermore, favorable outcome in the MT-RS+GPI group was significantly more frequent than in MT alone ($p < 0.001$), MT-RS (44.0%, $p < 0.001$), and MT-GPI groups (65.5%, $p = 0.017$; **Figure 2B**). Favorable outcome in the MT-GPI group was significantly more frequent than in the MT-alone group ($p = 0.002$). However, functional outcomes in the MT-RS group were not significantly different from the MT-alone group. Mortality was different based on endovascular modality, which was highest in the MT-RS group. The sICH did not differ among the groups.

The type of endovascular modality used for treating ICAS-LVO was also an independent factor for favorable outcome compared with using only the MT modality. Multivariable analysis showed the MT-RS+GPI modality [odds ratio (OR), 20.4; 95% CI, 1.97–211.4; $p = 0.012$] remained an independent factor for favorable outcomes, in addition to younger age,

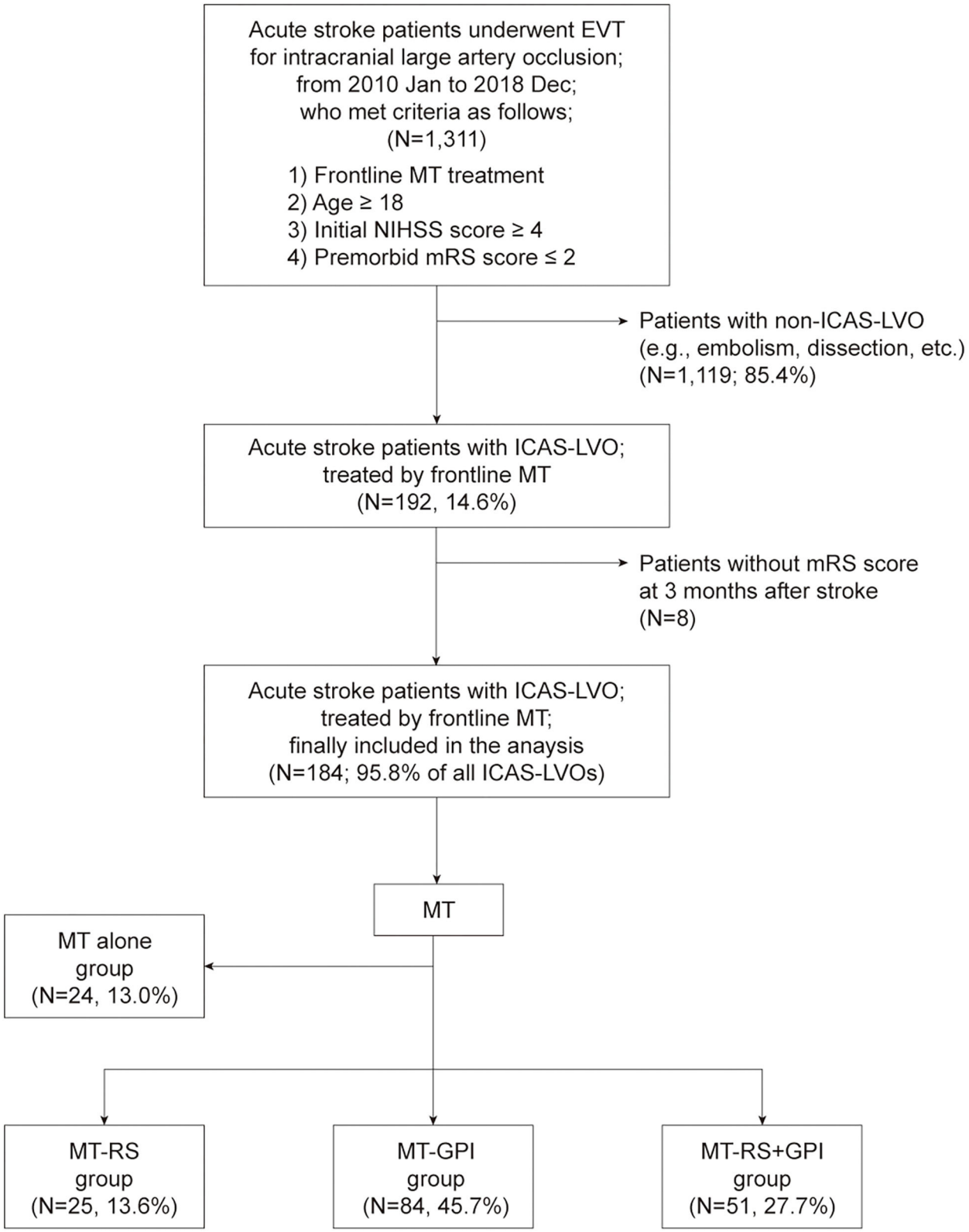

FIGURE 1 | Patient selection flow and grouping. EVT, endovascular treatment; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ICAS-LVO, intracranial atherosclerosis-related large-vessel occlusion; MT-RS, rescue stenting after mechanical thrombectomy failure; MT-GPI, glycoprotein IIb/IIIa infusion after mechanical thrombectomy failure; MT-RS+GPI, rescue stenting with glycoprotein IIb/IIIa infusion after mechanical thrombectomy failure.

TABLE 1 | Clinical and procedural characteristics and outcomes based on endovascular modality for intracranial atherosclerosis-related large-vessel occlusion.

	MT alone ($n = 24$)	MT-RS ($n = 25$)	MT-GPI ($n = 84$)	MT-RS+GPI ($n = 51$)	p-Value
Characteristics					
Age, years	74.6 (± 11.9)	69.7 (± 15.6)	65.8 (± 13.2)	67.4 (± 14.6)	0.045
Male	11 (45.8)	16 (64.0)	52 (61.9)	27 (52.9)	0.412
Hypertension	18 (75.0)	14 (56.0)	61 (72.6)	34 (66.7)	0.388
Diabetes	8 (33.3)	8 (32.0)	24 (28.6)	13 (25.5)	0.887
Hypercholesterolemia	7 (29.2)	6 (24.0)	25 (29.8)	12 (23.5)	0.849
Smoking	5 (20.8)	6 (24.0)	30 (35.7)	14 (27.5)	0.414
Coronary artery disease	1 (4.2)	1 (4.0)	5 (6.0)	4 (7.8)	0.890
Atrial fibrillation	3 (12.5)	3 (12.0)	10 (11.9)	5 (9.8)	0.680
Initial NIHSS score	15.5 [11.8; 19.3]	17.0 [15.5; 18.0]	12.0 [7.0; 15.0]	15.5 [12.5; 17.0]	<0.001
Occlusion site					0.403
Internal carotid artery	9 (37.5)	5 (20.0)	18 (21.4)	13 (25.5)	
Middle cerebral artery	15 (62.5)	20 (80.0)	66 (78.6)	38 (74.5)	
ASPECTS	7.5 [6, 9]	8 [7, 9]	8 [7,8]	8 [7,9]	0.174
Use of IV tPA	11 (45.8)	5 (20.0)	25 (29.8)	22 (43.1)	0.101
Frontline MT modality					0.003
Stent retriever	17 (70.8)	18 (72.0)	78 (92.9)	47 (92.2)	
Contact aspiration	7 (29.2)	7 (28.0)	6 (7.1)	4 (7.8)	
No. of MT passes	2.9 (± 1.5)	3.2 (± 2.0)	2.6 (± 1.7)	2.4 (± 1.1)	0.186
Time of onset to puncture, min	290 [183; 412]	259 [222; 375]	488 [211; 922]	290 [240; 444]	0.005
Total procedure time, min	66 [53; 93]	95 [90; 99]	133 [83; 156]	144 [104; 166]	0.035
Post-procedural antithrombotics					<0.001
None	18 (75.0)	17 (68.0)	10 (11.9)	7 (13.7)	
Oral antiplatelets immediately after procedure	6 (25.0)	7 (28.0)	1 (1.2)	0 (0.0)	
IV GPI infusion followed by oral antiplatelets	0 (0.0)	1 (4.0)	73 (86.9)	44 (86.3)	
Outcome					
Recanalization					
Successful recanalization	18 (75.0)	20 (80.0)	80 (95.2)	50 (98.0)	0.001
Patent artery on follow-up	17 (70.8)	14 (56.0)	70 (83.3)	50 (98.0)	<0.001
Favorable outcome	7 (29.2)	11 (44.0)	55 (65.5)	43 (84.3)	<0.001
Symptomatic ICH	2 (8.3)	2 (8.0)	2 (2.4)	1 (2.0)	0.323
Mortality	3 (12.5)	5 (20.0)	2 (2.4)	1 (2.0)	0.003

MT, mechanical thrombectomy; MT-RS, rescue stenting after mechanical thrombectomy failure; MT-GPI, glycoprotein IIb/IIIa infusion after mechanical thrombectomy failure; MT-RS+GPI, rescue stenting with glycoprotein IIb/IIIa infusion after mechanical thrombectomy failure; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; IV tPA, intravenous tissue plasminogen activator; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale.
Values in parentheses represent the standard deviation or the number of patients (%). Brackets represent first and third quartiles.

low initial NIHSS score, lower number of MT device passes, successful recanalization, patent artery on follow-up, and use of intravenous infusion of GPI followed by oral antiplatelets (**Table 2**).

DISCUSSION

In this study, frontline MT was not very effective in ICAS-LVO and resulted in <10% of successful recanalization rate. For patients who experienced failed frontline MT modality, successful recanalization was achieved in ∼94% of patients treated with ISM. Recanalization efficiency using a combination of RS and GPI infusion was relatively higher than with other ISMs. Among ISMs, a combination of RS and GPI infusion resulted in significantly more patent arteries on follow-up and significantly more favorable outcomes, which was an independent factor for favorable outcome.

In several previous reports, conventional MT modalities were shown to be ineffective for ICAS-LVO; thus, alternative or special strategies for ICAS-LVO are necessary for better EVT outcomes (9–12, 20). Based on a small number of retrospective studies in which the procedural details and outcomes were analyzed, most rescue modalities for ICAS-LVO included immediate intracranial stenting, percutaneous balloon angioplasty, GPI infusion, and combinations of the modalities (referred to as ISMs) (3–5, 13, 14, 21–23). The necessity of ISMs in EVT for ICAS-LVO is generally recognized; however, unfortunately, the optimal ISM remains unknown. In clinical practice, one type of ISM should be chosen after frontline MT device fails. To make

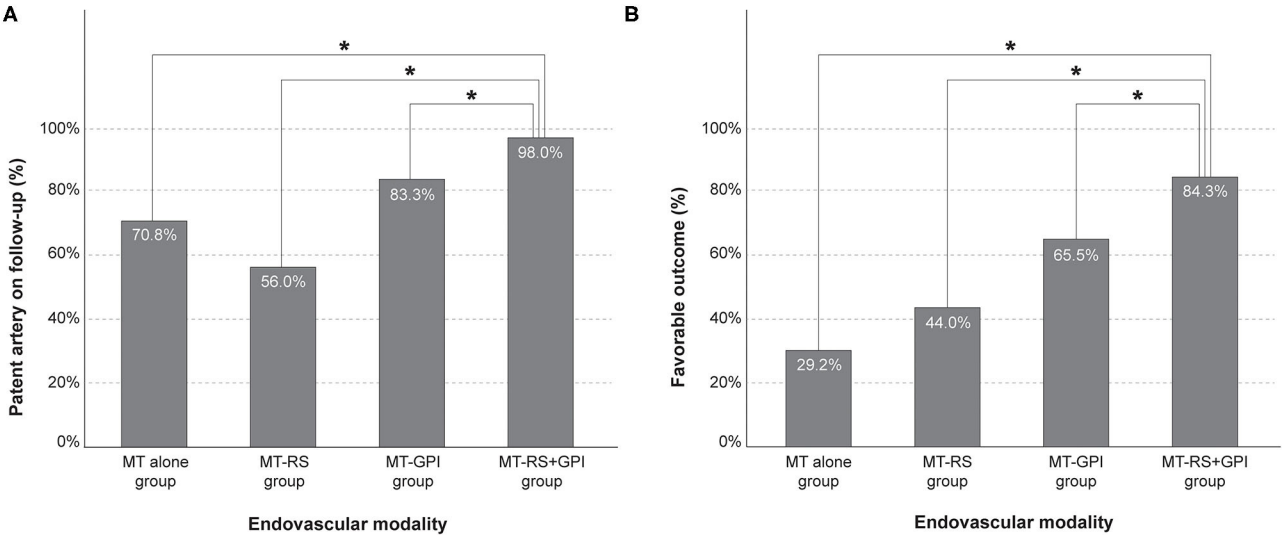

FIGURE 2 | Frequency of **(A)** patent artery on follow-up and **(B)** favorable outcome based on endovascular modality. MT-RS, rescue stenting after mechanical thrombectomy failure; MT-GPI, glycoprotein IIb/IIIa infusion after mechanical thrombectomy failure; MT-RS+GPI, rescue stenting with glycoprotein IIb/IIIa infusion after mechanical thrombectomy failure. *Significantly different between groups.

the best decision, many factors should be considered including which ISM provides a greater possibility to obtain a successful recanalization, whether the recanalized target artery will be well-maintained (or patent) after the endovascular procedure, whether the chosen ISM will cause intracranial hemorrhage, and whether patient's clinical outcome will be guaranteed when the specific ISM is used. If more information regarding these factors is known, the decision would likely be easier and more rational.

From a strategic viewpoint, the results from this study indicated that RS alone was not appropriate as the rescue endovascular modality. RS alone performed after frontline MT failure (MT-RS group) was not significantly more beneficial regarding arterial patency on follow-up and functional outcome. In addition, patients in the MT-RS group showed the lowest recanalization efficiency among ISMs, and mortality was rather high. Conversely, several beneficial effects were observed when using a combination of RS and GPI infusion after MT failure (MT-RS+GPI group) such as recanalization efficiency, follow-up arterial patency, and favorable outcome. Approximately 98% of patients had a successful recanalization with the combination of RS and GPI infusion. Patent artery on follow-up and favorable outcome were significantly more frequent in the MT-RS+GPI group. Furthermore, use of a combination of RS and IA GPI infusion was an independent factor for favorable outcome. Unlike common anxiety regarding hemorrhagic risk, GPI infusion was not associated with sICH development, which is in agreement with the results from previous studies (22–25). Because successful recanalization and patent artery on follow-up were significant factors affecting favorable outcome, a combination of RS and GPI infusion might result in a better patient clinical outcome due to higher recanalization efficiency and more patent arteries observed on follow-up. In fact, delayed reocclusion after EVT was highly associated with poor functional outcome, which was represented by a quite low OR for favorable outcome (0.035; 95% CI, 0.005–0.243) (26). According to a recent large registry, worsening of arterial patency was significantly associated with all kinds of negative clinical outcomes including early neurological deterioration, short- and long-term mortality, and poor functional status (OR, 5.37; 95% CI, 2.70–8.49) (27).

Although favorable outcome in the MT-GPI group was not comparable with the MT-RS+GPI group (the absolute difference was ∼20%), patients in the MT-GPI group experienced relatively good recanalization efficiency and follow-up arterial patency. On multivariable analysis, the OR in the MT-GPI group showed a tendency for a favorable outcome, although not significantly. Compared with the MT-RS group, patients in the MT-GPI group had better recanalization efficiency, follow-up arterial patency, and more favorable outcome. Therefore, GPI infusion may play a role in MT failure. To examine the role of GPI infusion after MT failure, further prospective studies are necessary.

The MT-RS+GPI group showed a much higher rate of favorable outcome than expected in general. Although this study did not focus on the specific factors for the remarkable clinical outcome in the MT-RS+GPI group, we think that patent artery on follow-up, active and immediate administration of postprocedural antithrombotics, or a kind of bias such as the selection of a smaller lesion for further use of ISM might affect the outstanding clinical outcome. However, interpretation should be cautious as the rate of favorable outcome in the MT-RS+GPI group was not statistically different from that in the MT-GPI group in multiple comparisons.

TABLE 2 | Factors associated with favorable outcome.

	Univariable			Multivariable	
	Favorable outcome (n = 116)	**Unfavorable outcome (n = 68)**	***p*-value**	**Odds ratio* (95% CI)**	***p*-value**
Age, years	64.2 (± 14.8)	74.1 (± 9.9)	<0.001	0.95 (0.91–0.99)	0.018
Male	76 (65.5)	30 (44.1)	0.005	0.79 (0.30–2.08)	0.636
Hypertension	78 (67.2)	49 (72.1)	0.514		
Diabetes	28 (24.1)	25 (36.8)	0.091	0.69 (0.24–1.98)	0.488
Hypercholesterolemia	28 (24.1)	22 (32.4)	0.235		
Smoking	44 (37.9)	11 (16.2)	0.002	3.19 (0.97–10.5)	0.056
Coronary artery disease	5 (4.3)	6 (8.8)	0.334		
Atrial fibrillation	10 (8.6)	11 (16.2)	0.150	0.45 (0.11–1.88)	0.275
Initial NIHSS score	13.0 [8.0; 16.0]	16.0 [12.0; 20.0]	<0.001	0.90 (0.82–0.98)	0.017
Occlusion site			0.903		
Internal carotid artery	28 (24.1)	17 (25.0)			
Middle cerebral artery	88 (75.9)	51 (75.0)			
Use of IV tPA	45 (38.8)	18 (26.5)	0.108	1.69 (0.62–4.66)	0.308
Time of onset to puncture, min	320 [239; 609]	290 [202; 710]	0.631		
Total procedure time, min	94 [60; 157]	104 [84; 147]	0.781		
Frontline MT modality			0.024		
Stent retriever	106 (91.4)	54 (79.4)		Reference	
Contact aspiration	10 (8.6)	14 (20.6)		0.71 (0.15–3.30)	0.667
No. of MT passes	2.2 (± 1.0)	3.5 (± 2.1)	<0.001	0.47 (0.31–0.71)	<0.001
Endovascular modalities			<0.001		
MT alone	7 (6.0)	17 (25.0)		Reference	
MT-RS	11 (9.5)	14 (20.6)		1.41 (0.07–27.9)	0.822
MT-GPI	55 (47.4)	29 (42.6)		3.21 (0.44–23.5)	0.250
MT-RS+GPI	43 (37.1)	8 (11.8)		20.4 (1.97–211.4)	0.012
Successful recanalization	113 (97.4)	55 (80.9)	<0.001	8.48 (1.01–71.8)	0.049
Patent artery on follow-up	109 (94.0)	42 (61.8)	<0.001	14.1 (2.05–97.4)	0.007
Postprocedural antithrombotics			<0.001		
None	18 (15.5)	34 (50.0)		Reference	
Oral antiplatelets immediately after procedure	8 (6.9)	6 (8.8)		1.62 (0.26–9.96)	0.603
IV GPI infusion followed by oral antiplatelets	90 (77.6)	28 (41.2)		22.8 (1.09–475.9)	0.044

IV tPA, intravenous tissue plasminogen activator; MT, mechanical thrombectomy; MT-RS, rescue stenting after mechanical thrombectomy failure; MT-GPI, glycoprotein IIb/IIIa infusion after mechanical thrombectomy failure; MT-RS+GPI, rescue stenting with glycoprotein IIb/IIIa infusion after mechanical thrombectomy failure; IV GPI, intravenous glycoprotein IIb/IIIa inhibitor; NIHSS, National Institutes of Health Stroke Scale.

Values in parentheses represent the standard deviation or the number of patients (%). Brackets represent first and third quartiles.

**Odds ratio for favorable outcome.*

This study had several limitations. First, because of the retrospective nature of this study, procedural decisions were not regulated under a specific protocol. The timing of frontline MT failure was determined according to operators' best judgment. Thus, successful recanalization using the frontline MT procedure might have been underestimated. However, the mean number of MT passes in all groups was not significantly different. More importantly, the main focus in this study was rescue endovascular modalities specific to ICAS-LVO, not MT failure. Second, the choice of ISM may be biased. Hemorrhagic risk is the most common consideration when using ISM. Many physicians are concerned that GPI infusion or postprocedural antithrombotics after emergent stenting elicit intracranial bleeding. Therefore, the use of ISM may be biased in patients with less risk of hemorrhagic complications. A few clinical factors relevant to hemorrhagic risk, such as a lesion size, might also affect the choice of ISM. However, lesion sizes representing initial ASPECTS were not significantly different between groups in this study. Moreover, the focus of this study was on the type of ISM and not on whether to use ISM itself; all types of ISM used in this study were thought equivalent, at least when hemorrhage was considered. Third, the sequence of GPI infusion and RS was not specified in this study. One might first consider using an easier or pharmacologic one and thus conduct an escalating method—GPI infusion first, then RS if GPI fails. In other cases, GPI can be infused after RS. However, this study focused only on the type of further ISM, but not on its sequence. Thus, we did not distinguish the different sequences of combination. A prospective study is necessary to verify the treatment effectiveness according to its sequence. Fourth, this study was conducted in an Asian country, where

ICAS is more prevalent than in Western countries. However, ICAS is also an important issue for Hispanic and African populations. Furthermore, overcoming refractoriness to modern MT techniques should be discussed regardless of patient's race. Consequently, more specific improvements to the endovascular strategy for ICAS-LVO are necessary. Evaluating and comparing procedural and clinical outcomes based on the types of rescue modalities would be of great importance in the field of EVT for acute stroke.

CONCLUSIONS

Rescue endovascular strategy after MT failure was significantly associated with procedural and clinical outcomes in acute stroke caused by ICAS-LVO. Use of a combination of RS and GPI infusion showed the highest rate of recanalization efficiency, patent arteries on follow-up, and favorable outcome. A combination of RS and GPI infusion might be an optimal rescue modality when frontline MT fails in EVT of ICAS-LVO.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Boards of all participating centers. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

BMK established the study idea and analyzed the study data. J-HB and CJ contributed to acquisition of the study data, interpretation of the analysis, and draft of this manuscript. BMK, JHH, DJK, HSN, YDK, EHL, J-HK, JYK, and JHK contributed to acquisition of the study data, interpretation of the analysis, and critical revisions to the manuscript. All authors contributed to the article and approved the submitted version.

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Understanding the Clinical Implications of Intracranial Arterial Calcification Using Brain CT and Vessel Wall Imaging

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Background and Purpose: Intracranial arterial calcification (IAC) has been the focus of much attention by clinicians and researchers as an indicator of intracranial atherosclerosis, but correlations of IAC patterns (intimal or medial) with the presence of atherosclerotic plaques and plaque stability are still a matter of debate. Our study aimed to assess the associations of IAC patterns identified on computed tomography (CT) with the presence of plaque detected on vessel wall magnetic resonance imaging and plaque stability.

Materials and Methods: Patients with stroke or transient ischemic attack and intracranial artery stenosis were recruited. IAC was detected and localized (intima or media) on non-contrast CT images. Intracranial atherosclerotic plaques were identified using vessel wall magnetic resonance imaging and matched to corresponding CT images. Associations between IAC patterns and culprit atherosclerotic plaques were assessed by using multivariate regression.

Results: Seventy-five patients (mean age, 63.4 ± 11.6 years; males, 46) were included. Two hundred and twenty-one segments with IAC were identified on CT in 66 patients, including 86 (38.9%) predominantly intimal calcifications and 135 (61.1%) predominantly medial calcifications. A total of 72.0% of intimal calcifications coexisted with atherosclerotic plaques, whereas only 10.2% of medial calcifications coexisted with plaques. Intimal calcification was more commonly shown in non-culprit plaques than culprit plaques (25.9 vs. 9.4%, $P = 0.008$). The multivariate mixed logistic regression adjusted for the degree of stenosis showed that intimal calcification was significantly associated with non-culprit plaques (OR, 2.971; 95% CI, 1.036–8.517; $P = 0.043$).

Conclusion: Our findings suggest that intimal calcification may indicate the existence of a stable form of atherosclerotic plaque, but plaques can exist in the absence of intimal calcification especially in the middle cerebral artery.

Keywords: calcification, atherosclerosis, intracranial disease, computed tomography, magnetic resonance imaging

INTRODUCTION

Intracranial atherosclerotic disease is a leading cause of ischemic stroke worldwide, accounting for 10% of ischemic strokes in Caucasians and 30–50% in Asians (1, 2). Identification of an imaging marker of vulnerable plaques that are prone to rupture and lead to downstream thromboembolic events is of vital importance in the early detection of high-risk patients (3). Intracranial artery calcification (IAC) is a highly prevalent finding on non-contrast enhanced head CT scans in both stroke patients (4) and the general population (5). Several epidemiological studies have shown that IAC is an independent risk factor of future ischemic cerebrovascular events (5, 6). Although IAC seen on CT is traditionally thought as a surrogate marker for atherosclerosis, the association between IAC and plaque stability is controversial.

Calcification is located not only in the tunica intima (intimal calcification) as typically seen with atherosclerotic plaque but also in the tunica media or around the internal elastic lamina (medial calcification), which is not a typical feature of atherosclerotic plaque (7). Previous studies have found that intimal and medial calcification show differences in the neurovascular risk factor profile, with intimal calcification being related to smoking and hypertension whereas medial calcification more associated with diabetes, older age, and chronic kidney disease (8–10). This indicates that the two distinct morphological patterns of IAC may represent different pathological processes that have distinct clinical outcomes including cerebrovascular ischemic events (11). Our recent pathological study examining large intracranial arteries showed that intimal calcification existed in advanced atherosclerotic lesions and could be used as a marker for intracranial atherosclerosis, whereas medial calcification was not associated with atherosclerosis (12). Despite the histologic evidence, it remains unclear in clinical practice if intimal calcification should be considered as a feature of plaque stability.

High-resolution vessel wall magnetic resonance imaging (VWMRI) has gained notoriety as an imaging approach to reliably visualize the intracranial vessel wall, leading to the non-invasive characterization of intracranial atherosclerotic plaques (13–15). While VWMRI can detect soft plaque components (e.g., intraplaque hemorrhage, lipid core) (16–18), CT is superior for characterizing calcification (19, 20). Therefore, in this study, we aimed to identify the patterns of IAC on CT to determine their associations with the presence of plaque detected by VWMRI and plaque stability.

MATERIALS AND METHODS

Subjects

Patients admitted to the stroke center at the Prince of Wales Hospital from 2014 to 2018 were recruited for the VWMRI exams, with the following inclusion criteria: (1) ischemic stroke confirmed by MRI or clinical evidence of TIA within 30 days; (2) Moderate or severe luminal stenosis in at least one intracranial artery as confirmed by magnetic resonance angiography; (3) one or more atherosclerotic risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and smoking. The exclusion criteria for the VWMRI exams were as follows: (1) contraindications to MRI; (2) non-atherosclerotic vasculopathies, such as arteritis, dissection, or Moyamoya disease; (3) evidence of cardioembolism, such as atrial fibrillation. Patients who had good VWMRI images and underwent routine CT were recruited in this study. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

CT Acquisition and Processing

Routine CT was performed at the admission on a 64-slice multi-detector row CT system (Light speed 64 plus, General Electric, Milwaukee, WI, USA) without contrast administered. All unenhanced brain CT scans were acquired in axial mode with tilting along the occipito-meatal line, covering the base of the skull to the vertex region. Imaging acquisition parameters were as follows: slice thickness 5 mm, 120 kVp, 170 mAs, 1 s per rotation. Axial images were reconstructed at 0.625-mm intervals.

The presence and morphologic characteristics of IAC were assessed for the major cerebral arteries: cavernous segment (C3) of the intracranial carotid artery (ICA), supraclinoid segment (C4) of the ICA, M1 segment of the middle cerebral artery (MCA), the basilar artery (BA), and the intracranial segment (V4) of the vertebral artery (VA). For all patients, the assessment was done on the reconstructed three dimensional (3D) CT images by one of two readers (WJ. Y. and ZQ. H.) with at least 2 years of experience reading CT images, who were blinded to the clinical data and MRI results. The presence of IAC was defined as hyperdense foci with a density of more than 130 Hounsfield units (HU). The patterns of calcification were categorized based on a previously established calcification scoring model (21), in which scores were assigned for morphologic patterns of calcification as follows: circularity (1 for dots, 2 for $<90^{\circ}$, 3 for 90–270°, and 4 for 270–360°), thickness (1 for thick $\geq$1.5 mm, and 3 for thin $<$1.5 mm), and continuity of calcification over the long axis of arterial segments (0 for indistinguishable, 1 for irregular/patchy, and 4 for continuous) (**Figure 1**). The cumulative calcification score was used to localize the calcification on a spectrum from intimal to medial, with predominantly intimal ranging from 1 to 6 points and predominantly medial ranging from 7 to 11 points. To assess the inter-reader reliability, two raters (WJ. Y. and ZQ. H.) reviewed 20 randomly selected CT images independently, and graded all calcifications using the above scoring system.

MRI Acquisition and Processing

VWMRI was performed using a 3T Achieva MR system (Philips Healthcare, Cleveland, OH, USA) with an 8-channel head coil. The protocol included a transverse 3D T1-weighted Volumetric ISotropic Turbo spin-echo Acquisition (VISTA) sequence and a time-of-flight MR angiography (MRA) sequence, as described before (22, 23). The following scan parameters were used for the T1-weighted VISTA: field-of-view $200 \times 167 \times 45$ mm^3, acquired resolution $0.6 \times 0.6 \times 1.0$ mm^3, reconstructed resolution $0.5 \times 0.5 \times 0.5$ mm^3, TR 1,500 ms, TE 36 ms, SENSE factor 1.5 (phase-encode direction), echo spacing 4.0 ms, TSE + startup echoes 56 + 6. VWMRI images were repeated 20 min after the intravenous

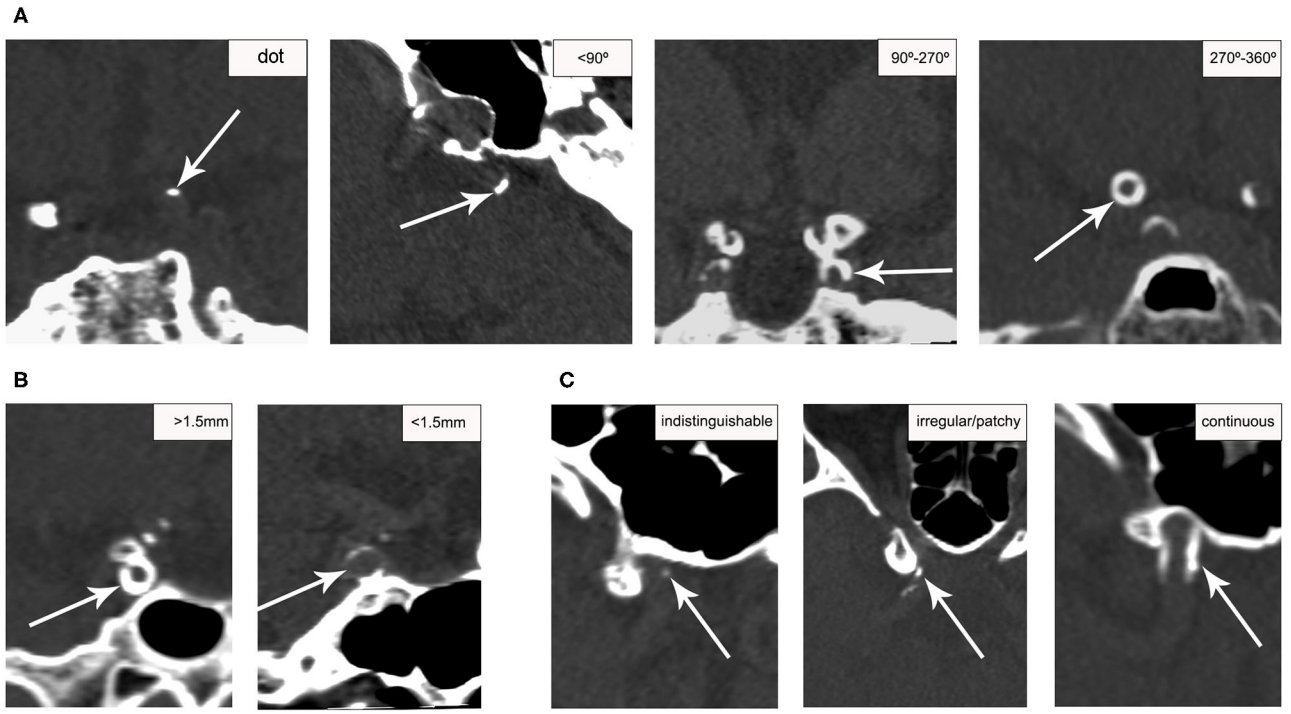

FIGURE 1 | Examples of calcification score for categorizing ICA calcification patterns. Calcification (arrows) was scored based on circularity **(A)**, thickness **(B)**, and continuity **(C)** on CT. Circularity and thickness were assessed on the short axis; continuity was assessed on the long axis.

injection of 0.2 mL/kg of a gadolinium-containing gadolinium-containing contrast agent (Dotarem; Guerbet, Roissy CdG Cedex, France) at an injection rate of 3.5 ml/s. Scan parameters for the time-of-flight MRA sequence were as follows: FOV 200 × 200 × 56 mm^3, acquired resolution 0.4 × 0.6 × 0.7 mm^3, TR/TE 23/3.5 ms.

VWMRI was acquired within 30 days after the onset of ischemic events. The presence of atherosclerotic plaque was identified independently by 2 analysts (WJ. Y. and L. Z.) with more than 3 years of experience in VWMRI who were blinded to the clinical data and CT results. Discrepancies were resolved by consensus with a third analyst (XY. C.). The 3D VW images were reconstructed orthogonal to the vessel axis at 0.5-mm intervals. An atherosclerotic plaque was defined as wall thickening identified on the short axis on both pre- and post-contrast VWMRI. Each detected plaque was classified as a culprit, non-culprit, or indeterminate lesion according to its likelihood of causing the downstream ischemic cerebrovascular events, as previously described (24). A culprit lesion was defined if it was the only lesion within the vascular territory relative to the stroke. If there were multiple plaques in the same affected vascular territory, the most stenotic plaque was classified as a culprit lesion, and the others as indeterminate lesions. A non-culprit lesion was defined as one that was not within the vascular territory of the stroke. The degree of stenosis for each atherosclerotic plaque was measured on maximum intensity projection images reformatted from time-of-flight MRA, following methods established by the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial (25): percent stenosis = $(1- D_{stenosis}/D_{normal}) *100$.

Matching Calcification With Atherosclerotic Plaques

After the identification of plaques on VWMRI and calcification patterns (intimal or medial) on CT, a side-by-side analysis was performed, in which the rater was shown the co-registered CT and MRI images to check if the identified IAC corresponds to any detected plaques.

Statistical Analysis

Continuous quantitative variables are described as mean ± SD and a percentage is used to describe the categorical variables. The data were analyzed using the SPSS 20.0 software package (SPSS, Inc., USA). Fisher's exact test was used for comparing the prevalence of calcification between culprit and non-culprit lesions. Multivariate logistic regression (adjusted for the degree of stenosis) was used to assess the association between calcification and culprit plaques, with mixed models to account for repeated measurements within subjects. Inter-reader agreements were estimated using Cohen κ. Reliabilities below 0.4 were characterized as poor, 0.4–0.75 as fair to good, and above 0.75 were considered as excellent. $P < 0.05$ was considered to indicate a statistically significant difference.

TABLE 1 | Clinical characteristics of the study population ($n = 75$).

Age	63.4 ± 11.6
Male	46 (61.3%)
Hypertension	52 (69.3%)
Diabetes	19 (25.3%)
Hyperlipidemia	37 (49.3%)
Smoking	
Current	7 (9.3%)
Ex-smoker	20 (26.7%)
Ischemic stroke	67 (89.3%)
Transient ischemic attack	8 (10.7%)

Values are presented as mean ± SD or number (%).

TABLE 2 | Distributions of calcification assessed on CT and atherosclerotic plaques assessed on VWMRI in the segments of large intracranial arteries.

	Calcification			Plaques
	Intimal	Medial	Total	
ICA				
C3	24 (27.9%)	68 (50.4%)	92 (41.6%)	19 (6.7%)
C4	30 (34.9%)	48 (35.6%)	78 (35.3%)	67 (23.6%)
M1	3 (3.5%)	0 (0.0%)	3 (1.4%)	110 (38.7%)
V4	26 (30.2%)	18 (13.3%)	44 (19.9%)	47 (16.5%)
BA	3 (3.5%)	1 (0.7%)	4 (1.8%)	41 (14.4%)
Total	86	135	221	284

ICA, internal carotid artery; C3, cavernous segment; C4, supraclinoid segment; M1, M1 segment of the middle cerebral artery; V4, V4 segment of the vertebral artery; BA, basilar artery.

RESULTS

In total, 75 patients (mean age, 63.4 ± 11.6; male, 46) were included in this study. The clinical characteristics of the study population are shown in **Table 1**.

Distribution of Calcification on CT and Plaques on VWMRI

A total of 637 segments were examined (on average 8.5 segments per patient), out of which 221 (34.7%) segments with calcification were identified on CT from 66 (88.0%) subjects. Of the 66 subjects showing calcification, most had 1 to 4 segments with calcification (21.2, 21.2, 15.2, 16.7%, respectively), and few patients (3.0%) had as many as 8 segments with calcification. Calcification predominantly occurred in the cavernous (41.6%) and supraclinoid segments (35.3%) of the ICA, followed by the V4 segment (19.9%), BA (1.8%), and MCA (1.4%) (**Table 2**).

Among the 221 segments with calcification, 86 (38.9%) calcifications were categorized as predominantly intimal calcification (**Figure 2**, **Supplementary Figures 1**, **2**) and the other 135 (61.1%) as predominantly medial calcification (**Figure 3**). The majority of calcifications involving the cavernous and supraclinoid segments were medial calcification [68/92 (73.9%) and 48/78 (61.5%), respectively]. In comparison, among V4 segments with calcification, 18 out of 44 (40.9%) showed medial calcification.

There were a total of 284 plaques detected on VWMRI in all participants, most commonly involving the M1 segment (38.7%), followed by the cavernous and supraclinoid segments of the ICA (30.3%), the V4 segment (16.5%), and then BA (14.4%) (**Table 2**).

Correlation Between Calcification Patterns and Plaques

Since the distal V4 segment was not imaged by VWMRI for 31 patients, there was no corresponding VWMRI for 18 VA segments harboring calcification, including 11 intimal calcifications and 7 medial calcifications. In the remaining 203 segments with calcification, 75 (36.9%) segments showed intimal patterns and 128 (63.1%) showed medial patterns of calcification. Of the 75 intimal calcifications, 54 (72.0%) were co-existent with atherosclerotic plaques. In comparison, only a minority of medial calcifications (13/128, 10.2%) corresponded with atherosclerotic plaques (**Table 3**). Among the 67 atherosclerotic plaques with calcification (54 intimal and 13 medial), only 6 (9.0%) were culprit, 49 (73.1%) were non-culprit, and 12 were indeterminate lesions (17.9%).

Sixty-four (22.5%) out of the 284 detected plaques were culprit, 189 (66.5%) were non-culprit, and 31 (10.9%) were indeterminate lesions. There was a higher prevalence of calcification in non-culprit lesions than in culprit lesions (25.9 vs. 9.4%, $P = 0.008$). When we categorized calcification by intimal and medial calcification, 5 (7.8%) plaques with intimal calcification were culprit lesions and 39 (20.6%) plaques with intimal calcifications were non-culprit ($P = 0.021$). Only 1 (1.6%) medial calcification was found in culprit lesions and 10 (5.3%) were observed in non-culprit lesions. No significant difference in the prevalence of medial calcification was found between culprit and non-culprit plaques ($P = 0.299$) (**Table 4**). Culprit plaques showed significantly higher degree of stenosis than non-culprit plaques in lesions with (64.3 ± 28.1 vs. 30.6 ± 24.9, $P = 0.003$) and without calcification (65.6 ± 32.5 vs. 28.4 ± 23.8, $P < 0.001$).

The mixed logistic regression model adjusting for the degree of stenosis showed that calcification was associated with non-culprit plaques [odds ratio (OR), 3.068; 95% confidence interval (CI), 1.171–8.037; $P = 0.023$]. After categorizing calcification to intimal and medial patterns, intimal calcification was associated with non-culprit plaques (OR, 2.971; 95% CI, 1.036–8.517; $P = 0.043$), whereas medial calcification was not associated with non-culprit plaques (OR, 2.423; 95% CI, 0.303–19.354; $P = 0.606$).

Reliability Assessment

Inter-reader agreement for the presence of calcification was excellent (κ: 0.911). Inter-reader agreement for classifying calcification was excellent (κ: 0.803). Inter-reader agreement for the presence of plaques was also excellent (κ: 0.735).

DISCUSSION

In this study, we found that IAC was common in patients with ischemic cerebrovascular disease, and the ICA was most frequently affected. Continuous, thin, and circular IAC detected

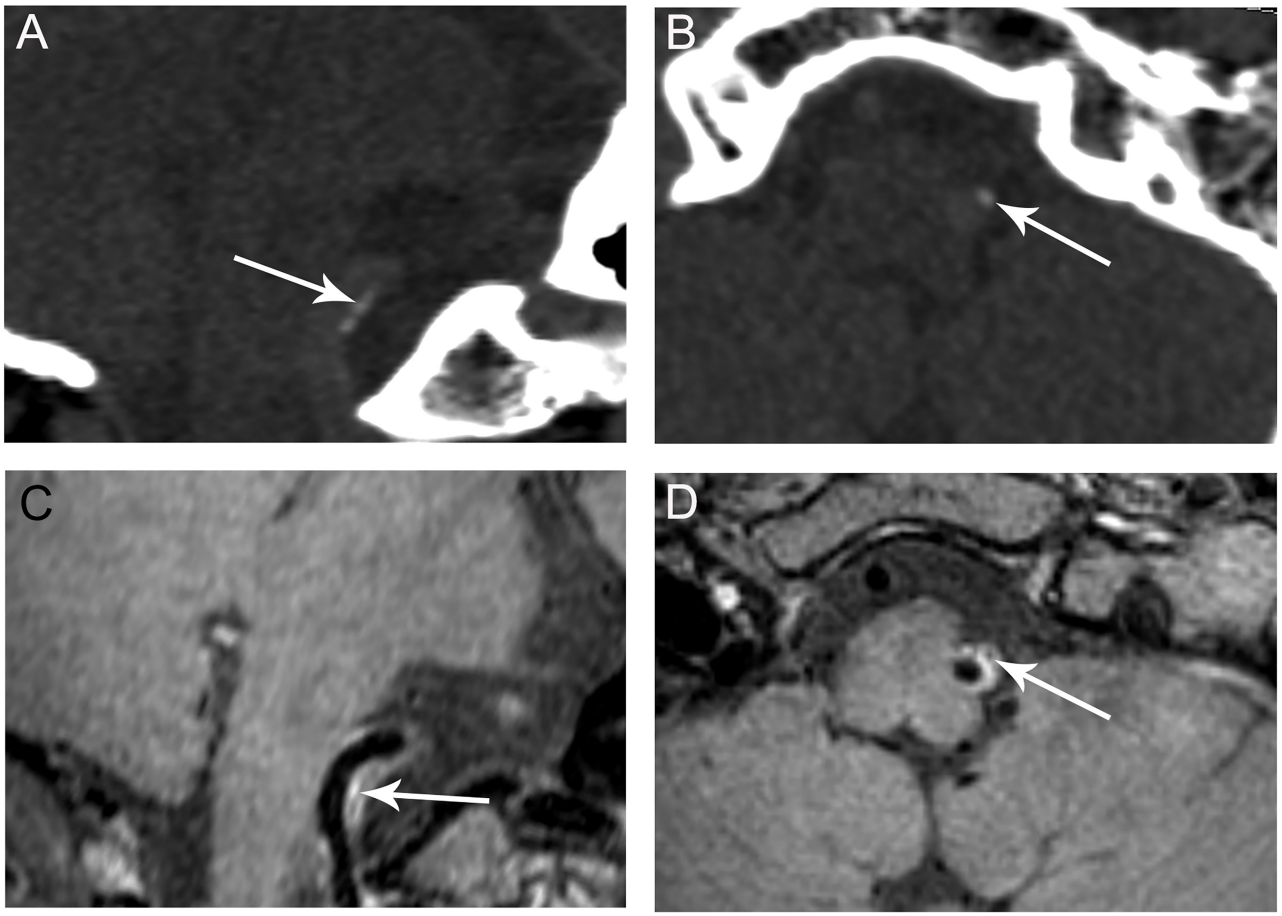

FIGURE 2 | Representative images of predominant intimal VA calcification. CT shows a small clustered calcification on the long (**A**, arrow) and short axes (**B**, arrow) of the right VA indictive of intimal calcification. The calcification corresponds to a hypointensity area (**C,D**, arrows) within an atherosclerotic plaque observed on VWMRI.

on CT indicative of medial calcification was less likely to be co-existent with atherosclerotic plaques. In contrast, discontinuous, thick, and focal IAC that suggests intimal calcification was mostly observed in plaques and might be a feature of plaque stability.

A previous CT study has reported that ICA was the most common site affected by calcification (60%) in Chinese patients, followed by the VA (20%), MCA (5%), and BA (5%) (26). We found 77% calcification involving the cavernous segment and supraclinoid segments of the ICA in the present study, which is higher than the 60% reported in the literature because the cavernous segment and supraclinoid segment were calculated separately. Despite the high prevalence of plaques (38.7%) involving the MCA in our study, calcification was not common (1.4%) in the MCA, which indicates that the absence of CT calcification in MCA territory cannot exclude the presence of MCA plaques. A CT study of 1,132 stroke patients showed the presence of dominant intimal calcification in 30.9% of participants and dominant medial calcification in 46.9% (8). Using the same grading system, we found that medial calcification accounted for 60% of all calcifications. Medial calcification was especially high in the intracranial ICA (68.2%), concordant with the histopathological finding that 71% of ICA calcifications are medial (27). Medial calcification was only observed in ICA and VA, suggesting that specific vascular beds might behave differently in terms of the pathogenesis of plaque and related vascular events (28).

Consistent with our prior histopathological study (12), the present clinical study demonstrated that most intimal calcification was observed in atherosclerotic plaques, whereas the majority of medial calcification was not related to plaques. Intimal calcifications were more commonly found in non-culprit lesions than in culprit lesions. Ischemic cerebrovascular events in patients with intracranial atherosclerosis are frequently caused by rupture of vulnerable plaque and the subsequent thromboembolism (29). Therefore, the more frequent intimal calcification in non-culprit lesions may indicate the stabilized effect of IAC on intracranial atherosclerosis.

In extracranial arteries, a calcified plaque is considered more biomechanically stable than a non-calcified plaque (30). Huang et al. (31) showed that calcification did not increase fibrous cap stress in either ruptured or stable coronary atherosclerotic plaques, and thus did not contribute to plaque rupture and

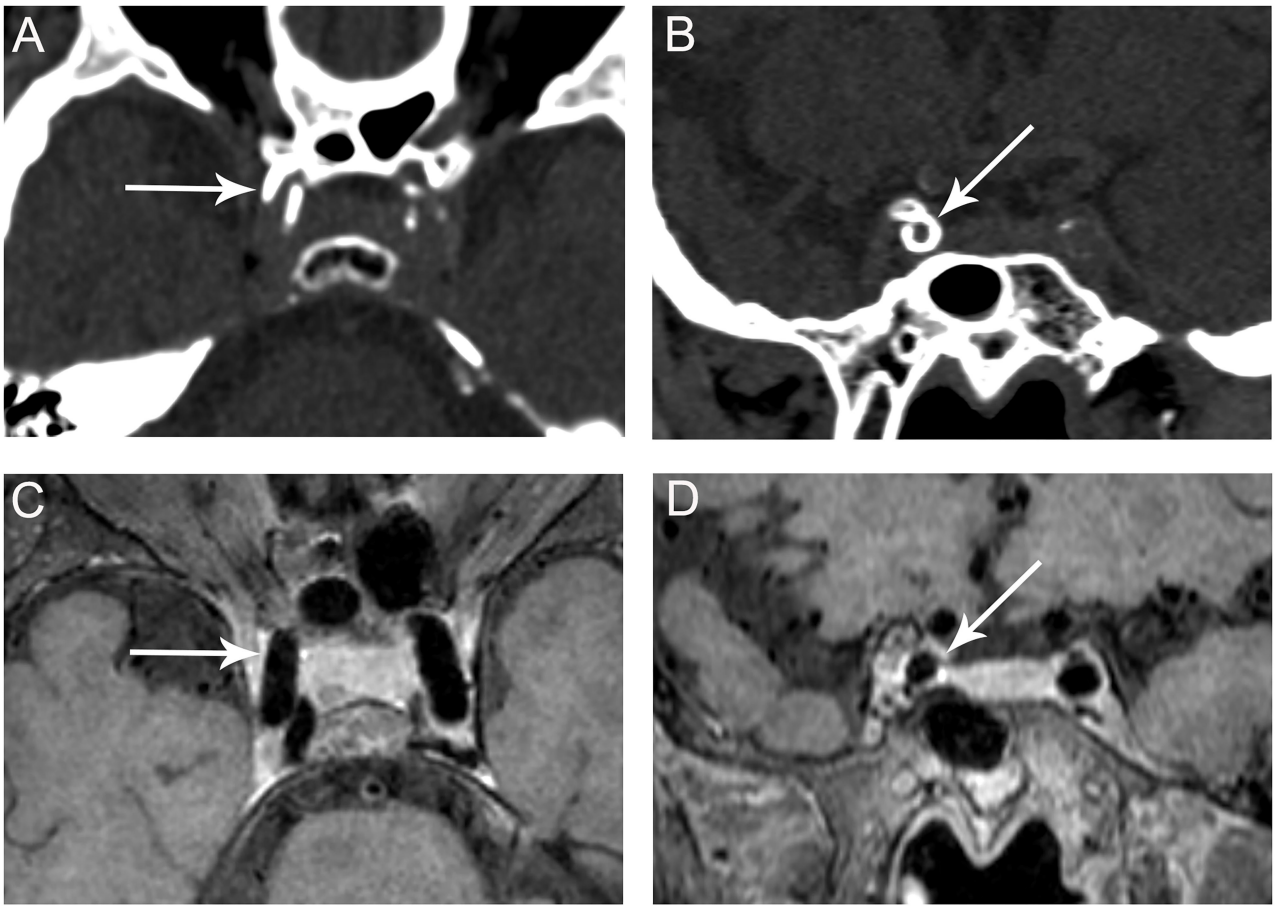

FIGURE 3 | Representative images of predominant medial ICA calcification. CT shows a continuous, circumferential calcification on the long (**A**, arrow) and short axes (**B**, arrow) of the right cavernous segment of the ICA suggesting medial calcification. No corresponding plaque is observed on VWMRI (**C**, **D**, arrows).

the subsequent thrombotic events. Another carotid plaque study found the extent of plaque calcification was inversely related to plaque fibrous cap inflammation and symptomatic plaques were less calcified (32). However, the effect of calcification on plaque stability remains controversial in intracranial arteries. A recent clinical study of patients with acute stroke in the MCA territory showed that the presence of calcification in the MCA was less frequent in the symptomatic group, which suggests that calcification might have a protective effect on symptomatic MCA infarction (33). Nonetheless, the symptomatic lesion in their study was defined as a stenotic MCA detected on MRA upstream from an infarction, but angiographic imaging may underestimate the stenosis and severity of atherosclerosis (34), highlighting the value of plaque detection using VWMRI. In the present study, by matching calcification detected on CT with atherosclerotic plaque seen on VWMRI, we showed that intimal calcification was associated with non-culprit lesions, independent of the degree of stenosis, indicating that intimal calcification may help to stabilize atherosclerotic plaques. In contrast to our results, some prior studies suggested that plaque calcification may predict stroke risk (4, 35). The discrepancies may be explained by the hypothesis that the presence of IAC seen on CT may only denote a cumulative imaging marker of atherosclerosis burden (36), but IAC itself is not a source of embolism or thrombosis (37–39).

TABLE 3 | Correlation between calcification patterns on CT and the presence of plaques on VWMRI.

		Presence of plaques on VWMRI		
		Yes	**No**	**Total**
Patterns of calcification on CT	Intimal	54 (72.0%)	21 (28.0%)	75
	Medial	13 (10.2%)	115 (89.8%)	128
	Total	67 (33.0%)	136 (67.0%)	203

Of note, some segments with intimal calcification did not show any corresponding atherosclerotic plaques. In this study, medial calcification was defined as circumferential, thin, and continuous whereas intimal calcification was clustered, thick, and scattered. However, according to prior pathological studies, medial calcification progresses along the internal elastic lamina

TABLE 4 | Association between calcification patterns and culprit plaques.

	Culprit ($n = 64$)	Non-culprit ($n = 189$)	*P*-value*
All calcification	6 (9.4%)	49 (25.9%)	0.008
Intimal calcification	5 (7.8%)	39 (20.6%)	0.021
Medial calcification	1 (1.6%)	10 (5.3%)	0.299

%, percentage of all calcification, intimal calcification, and medial calcification in culprit (n = 64) and non-culprit (n = 189) plaques, respectively.
**P-values were generated by using Fisher's exact test.*

from a scattered spotty pattern in its early stage to a confluent circumferential pattern in its late-stage (7). Therefore, some early granular medial calcifications could be misclassified as intimal in the present study. Moreover, Vos et al. (27) reported that a small proportion of intimal calcification occurred in early atherosclerotic lesions (intimal thickening and intimal xanthoma) that could appear as normal or minimal wall thickening on VWMRI. Given that CT is more sensitive to calcification than VWMRI to plaques, it is very likely that intimal calcifications were detected on CT while the corresponding plaques were too small to resolve on VWMRI. VWMRI was performed at a field strength of 3T, which is needed to accurately differentiate pathological vessel wall changes from a normal arterial wall compared with VWMRI at 1.5 T that is more common in regional and community hospitals (40). Some small plaques identified on 3 T MRI may become undetectable on 1.5 T scanner, so we would expect a higher frequency of intimal calcification without corresponding plaques detected on 1.5 T VWMRI.

There are several limitations to our study. First, since the calcification types were classified based on a prior CT scoring system that was developed and validated in the ICA calcification in only 16 patients, caution should be taken when extrapolating these findings to other intracranial arteries. We have validated the scoring system in the basilar and vertebral arteries in a prior histology study (12). Although only 11 calcifications (9 intimal and 2 medial calcifications) were included in that study, all of them were accurately classified based on this CT score, indicating that the scoring system can be generalized to the vertebrobasilar system. Further studies with a larger sample size are warranted to test the reliability of the scoring system in categorizing calcification involving other intracranial arteries. Second, the prevalence of intracranial plaques was underestimated because the V4 segment was not covered by VWMRI in 31 patients. Third, we qualitatively assessed the presence or absence of calcification but did not quantify the volume and assess the morphology of calcification. Priors studies have demonstrated that compared with the deep, coalescent calcification, superficial and scattered calcification was more associated with plaque instability (41, 42). Furthermore, some scattered micro-calcifications that may be more related to culprit plaques (43) are beyond the resolution of a CT scan (44), which may lead to an underestimation of the prevalence of calcification in plaques. Lastly, since IAC is more prevalent in Asians, African Americans, and Hispanics than in Caucasians (20, 26), larger studies involving other populations are needed to increase the generalizability of these findings.

CONCLUSIONS

In summary, our study indicates that intimal calcification, unlike medial calcification, is a CT maker of atherosclerotic plaque, but a lack of intimal calcification on CT does not exclude its presence, especially in the MCA. Intimal calcification is more associated with non-culprit plaques and may be a potential marker of plaque stability. Our study results may provide basis for the management of stroke patients with calcification.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board of the Chinese University of Hong Kong. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

W-JY recruited patients, analyzed data, and drafted the manuscript. BW participated in the study design and revised the manuscript. LZ recruited patients and analyzed imaging data. Z-QH and JL analyzed the data. JA, SW, and MY acquired the VWMRI data. WC, LW, and TL participated in the design and coordination of the study. X-YC conceived the study, participated in its design and coordination, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.619233/full#supplementary-material

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