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Safety and efficacy of stents and flow diverters used for embolization of acutely-ruptured intracranial aneurysms in the acute stage

Edited by
Robert Ostrowski, Cong-Hui Li, Bu-Lang Gao, Hongqi Zhang and Xianli Lv

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Safety and efficacy of stents and flow diverters used for embolization of acutely-ruptured intracranial aneurysms in the acute stage

Topic editors

Robert Ostrowski — Mossakowski Medical Research Institute, Polish Academy of Sciences, Poland

Cong-Hui Li — The First hospital of Hebei Medical University, China

Bu-Lang Gao — Hebei Medical University, China

Hongqi Zhang — Capital Medical University, China

Xianli Lv — Tsinghua University, China

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EDITED AND REVIEWED BY
Osama O. Zaidat,
Northeast Ohio Medical University,
United States

*CORRESPONDENCE
Conghui Li
✉ 13363880072@163.com
Bulang Gao
✉ browngao@163.com

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Editorial: Safety and efficacy of stents and flow diverters used for embolization of acutely-ruptured intracranial aneurysms in the acute stage

Bulang Gao[1]*, Hongqi Zhang[2], Xianli Lv[3], Robert P. Ostrowski[4] and Conghui Li[5]*

[1]Department of Medical Research, Shijiazhuang People's Hospital, Hebei Medical University, Shijiazhuang, China, [2]Department of Neurosurgery, Xuanwu Hospital of Capital Medical University, Beijing, China, [3]Department of Neurosurgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China, [4]Department of Experimental and Clinical Neuropathology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland, [5]Department of Neurosurgery, Hebei Medical University First Hospital, Shijiazhuang, Hebei, China

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Editorial on the Research Topic
Safety and efficacy of stents and flow diverters used for embolization of acutely-ruptured intracranial aneurysms in the acute stage

Currently, the treatment of acutely-ruptured intracranial aneurysms (ARIAs) using stents or flow diverters for endovascular embolization is controversial. Some authors favor the use of stents and flow diverters, but others do not. For one thing, the standardized embolization procedure has not been established for the use of stents or flow diverters. For another, the use of stents or flow diverters may cause additional adverse events in the acute phase of aneurysm rupture compared with coils only. Nonetheless, because ARIAs may have unfavorable morphology for endovascular embolization, the use of stents or flow diverters is necessary.

In different countries and regions across the world, the development of skills using stents or flow diverters for ARIAs is not balanced. In China with a large population and a great number of aneurysm patients, endovascular treatment with stents or flow diverters is necessary because of the micro-invasiveness and fast recovery, and a great deal of experience using the stents or flow diverters has been accumulated. With accumulation of such experience, standardized embolization procedures should be established to improve the safety and efficacy of stents or flow diverters for ARIAs. Treatment of ARIAs in the acute phase is critical to the prognosis of these patients, and timely treatment is able to prevent a secondary rupture and will promote further aggressive treatment, beneficial to the recovery.

In this Research Topic of 10 articles, the aim is to bring together the latest quality articles and provide an up-to-date and comprehensive overview of the latest research hotspots from researchers for the treatment of ARIAs using intracranial stents and flow diverters with or without adjunctive coiling. In particular, the following specific themes have been touched upon: periprocedural complication rates, re-rupture of ARIAs, angiographic and clinical outcomes, and ischemic events when using intracranial stents and flow diverters for ARIAs.

Four articles focused on traditional intracranial stents in assisting coiling of ARIAs (Liu et al.; Wu et al.; Zhang, Wu et al.; Zhang, Zhang et al.), one meta-analysis on staged stenting of intracranial stents and Pipeline embolization device (PFD) for wide-necked ARIAs (Wei et al.), two articles on the PED treatment of intracranial aneurysms (Li et al.; You et al.), one meta-analysis of efficacy and safety on the use of the Willis covered stent in the treatment of blood blister-like aneurysm (Tan et al.), one bibliometric study of worldwide productivity and research trends of publications concerning stent application in ARIAs (Chen et al.), and one on automatic risk prediction of intracranial aneurysm on CTA image with convolutional neural networks and radiomics analysis (Xie et al.).

In the bibliometric study of worldwide productivity and research trends of publications concerning stent application for ARIAs (Chen et al.), 275 publications were included, the research focus was ARIAs and application of stents during interventional procedures, and the main trends of research were development of materials and safety of stent application in ARIAs.

In the study of stent-assisted coiling vs. coiling alone for tiny ARIAs (Zhang, Wu et al.), it was found that stent-assisted coiling may increase the incidence of hemorrhagic events with favorable angiographic outcomes and comparable clinical outcomes as compared with stand-alone coiling and that the low-profile visualized intraluminal support (LVIS) stent may improve the safety compared with the lazer-cut stent. Two other studies (Liu et al.; Wu et al.) confirmed the effect of the LVIS stent for ARIAs with favorable angiographic and clinical outcomes. In one study with 41 patients with ARIAs (Liu et al.), the complete aneurysm occlusion rate was 70.7% immediately after embolization and 83.3% at 13.9-month angiographic follow-up, the favorable clinical outcome rate at follow-up was 92.7%, and intraoperative thrombosis and hemorrhage occurred in two (4.9%) and one (2.4%) patients, respectively. In the other study with a LVIS stent being deployed within an Enterprise stent for the treatment of 30 patients with 34 acutely-ruptured intracranial vertebrobvasilar artery-dissecting aneurysms (Wu et al.), all aneurysms were successfully treated in the acute stage, six patients (20.0%) experienced severe in-hospital adverse events (two deaths, 6.7%), aneurysm rebleeding occurred in one patient (3.3%), and three ischemic events happened. At 12-month follow-up, the complete aneurysm occlusion rate was 93.3%, and the incidence of dependence of death (mRS score of 3–6) at discharge and at the last follow-up was 16.7 and 14.3%, respectively.

Two studies (Zhang, Zhang et al.; Wei et al.) investigated staged stenting for ARIAs with initial coiling followed by scheduled delayed stenting, resulting in comparable or better angiographic complete occlusion rates, procedure-related complication rate, and clinical outcomes at follow-up. In one study (Zhang, Zhang et al.), the propensity score-matched method was used to balance the data in the staged stenting arm and the conventional stent-assisted coiling arm, without using the flow diverters, and comparable clinical, angiographic, and procedure-related complication rates were obtained in both arms. In the other study of a meta-analysis and systematic review including both conventional intracranial stents and flow diverters in 5 studies with 143 patients with ARIAs (Wei et al.), a high aneurysm occlusion rate, favorable clinical outcomes and lower procedure-related complication rates have been achieved in the staged stenting group.

Two articles investigated the effect of the PED vs. traditional coils in embolization of intracranial aneurysms (Li et al.) or the incidence and prediction of in-stent stenosis after PED deployment for intracranial aneurysms treatment (You et al.). In one study of a meta-analysis with 10 studies and 1,400 patients enrolled (Li et al.), the PED had higher rates of complete aneurysm occlusion but lower rates of aneurysm retreatment in comparison with traditional coils, but traditional coils was superior to the PED group in terms of procedure-related intracranial hemorrhage and other procedure-related complications, and favorable functional outcome (mRS $\leq$ 2). In the other study with 240 patients and 252 aneurysms (You et al.), it was found that in-stent stenosis is a common angiographic finding after PED implantation for intracranial aneurysms and is presented as a largely benign course through long-term follow-up and that younger patients and longer procedure durations were risk factors for developing in-stent stenosis.

A meta-analysis of efficacy and safety of the Willis covered stent for treating blood blister-like aneurysms including eight studies and 104 patients (Tan et al.) found that the Willis covered stent could be effectively and safely applied for the treatment of this kind of aneurysms. In the last article exploring automatic risk prediction of intracranial aneurysm on CTA image with convolutional neural networks (CNN) and radiomics analysis (Xie et al.), the incorporation of CNN and radiomics analysis can improve the prediction performance, and the selected optimal feature set can provide essential biomarkers for the determination of rupture risk.

In conclusion, this Research Topic provides an up-to-date and comprehensive overview of the latest research hotspots regarding the use of intracranial stents and flow diverters for the treatment of intracranial aneurysms and it is a great step forward even though not all fields have been covered.

Author contributions

BG: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—review and editing. HZ: Conceptualization, Resources, Validation, Visualization, Writing—review and editing. XL: Conceptualization, Formal analysis, Validation, Visualization, Writing—review and editing. RO: Conceptualization, Validation, Visualization, Writing—review and editing. CL: Conceptualization, Validation, Visualization, Writing—review and editing.

Conflict of interest

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

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EDITED BY
Cong-Hui Li,
The First Hospital of Hebei Medical University, China

REVIEWED BY
Bu-Lang Gao,
Hebei Medical University, China
Kun Zhang,
Henan Provincial People's Hospital, China
Tianxiao Li,
Henan Provincial People's Hospital, China

*CORRESPONDENCE
Erqing Chai
happybirds998@126.com

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

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Efficacy of pipeline embolization device vs. traditional coils in embolization of intracranial aneurysms: A systematic review and meta-analysis

Wei Li[1,2,3†], Zaixing Xiao[1,2,3†], Kaixuan Zhao[2,3], Shijie Yang[2,3], Yichuan Zhang[2,3], Bin Li[2,3], Yu Zhou[3,4], Yong Ma[2,3] and Erqing Chai[2,3*]

[1]The First Clinical Medical College of Gansu University of Chinese Medicine, Lanzhou, China, [2]Cerebrovascular Disease Center of Gansu Provincial People's Hospital, Lanzhou, China, [3]Key Laboratory of Cerebrovascular Diseases in Gansu Province, Lanzhou, China, [4]The First Clinical Medical College of Lanzhou University, Lanzhou, China

Introduction: In recent years, the Pipeline embolization device (PED) has been widely used in the embolization of intracranial aneurysms, but there are some inconsistent findings on whether its efficacy and safety are superior to those of traditional coils embolization (coils alone, stent-assisted coils and balloon-assisted coils). The purpose of this meta-analysis was to evaluate the safety and efficacy of PED in intracranial aneurysm embolization by comparing with traditional coils.

Methods: We systematically searched PubMed, Embase, Web of Science, and The Cochrane Library databases for randomized controlled trials and observational studies (case-control studies and cohort studies) comparing the efficacy of PED with traditional coils in intracranial aneurysm embolization published before April 1, 2022. The endpoints observed in this meta-analysis were procedure-related intracranial hemorrhage, procedure-related intracranial ischemia, other procedure-related complications (e.g., aneurysm rupture, neurological impairment, etc.), retreatment rate, complete occlusion (100%) of the aneurysm at the last follow-up, and favorable functional outcome (MRS $\leq$ 2).

Results: A total of 10 studies with a total of 1,400 patients (PED group: 576 and Traditional coils: 824) were included in this meta-analysis. A comprehensive analysis of the included literature showed that the PED group had a higher rate of complete aneurysm occlusion [OR = 2.62, 95% CI (1.94, 3.55), $p < 0.00001$] and Lower re-treatment rate [OR = 0.20, 95% CI (0.12, 0.34 $p < 0.00001$)] compared with the traditional coil embolization group at the last follow-up. In terms of procedure-related intracranial hemorrhage [OR = 3.04, 95% CI (1.08, 8.57), $p = 0.04$] and other procedure-related complications [OR = 2.91, 95% CI (1.48, 5.57), $p = 0.002$], the incidence of PED was higher than that of the traditional coil embolization group. Moreover, in terms of favorable functional outcome [OR = 0.4, 95% CI (0.22, 0.71), $p = 0.002$] of patients at the last follow-up, the PED group was lower than the traditional coil embolization group. There

was no statistically significant between the two groups in terms of surgery-related intracranial ischemia complications [OR = 0.88, 95% CI (0.47, 1.64), $p = 0.68$].

Conclusion: PED had higher rates of complete aneurysm occlusion and lower rates of aneurysm retreatment compared with traditional coils, but traditional coils was superior to the PED group in terms of procedure-related intracranial hemorrhage complication and other procedure-related complications (aneurysm rupture, neurological impairment), and favorable functional outcome (mRS $\leq$ 2). This result still needs to be further confirmed by additional large-sample, multicenter, prospective randomized controlled trials.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier: CRD42022325673.

KEYWORDS

PED vs. traditional coils efficacy pipeline embolization device (PED), traditional coils, intracranial aneurysm, comparative efficacy, systematic review, meta-analysis

Introduction

Ruptured intracranial aneurysms can lead to severe subarachnoid hemorrhage and threaten patients' life (1). In recent years, researchers have focused on finding treatments to reduce the morbidity and mortality of intracranial aneurysms. With the rapid development of endovascular techniques, endovascular treatment provides new treatment options for aneurysms and has become the preferred modality for the treatment of certain intracranial aneurysms.

Pure coil embolization is mainly used for small and uncomplicated aneurysms. Stent-assisted spring coil (SAC) is an alternative technique for the treatment of giant, wide-necked, and spindle-shaped aneurysms that have failed to respond to pure coil embolization therapy, where the propped-up stent prevents the coil from entering the aneurysm-carrying artery (2). However, this traditional coils embolization technique has significant treatment limitations, and numerous studies have found that ~12–14.5% of aneurysms after coils embolization therapy are recanalized after occlusion, increasing the risk of aneurysm re-rupture (3, 4). The pipeline embolization device (PED; Covidien, Medtronic) was the first vascular diversion device approved for the treatment of large or large wide carotid aneurysms from the carotid to the superior segment of the pituitary in the internal carotid artery (ICA).The PED diverts the blood flow into the aneurysm, leading to thrombosis in the interior of the aneurysm lumen, and subsequently reconstructs the lumen of the aneurysm-carrying artery by endothelialization of the stent (5) to achieve the purpose of aneurysm occlusion. With the development of PED technology, its clinical indicators are gradually expanding (the so-called "out-of-indication" use), and it is necessary to compare PED with the traditional coils embolization technique to assess safety and efficacy.

However, the most appropriate strategy for the endovascular treatment of aneurysms depends mainly on clinical factors and the aneurysm's anatomical characteristics. The choice of the best endovascular approach for treatment remains to be determined. In several studies compared with conventional coil embolization, PED treatment significantly increases the rate of aneurysm occlusion and decreases the rate of retreatment and complications (6, 7). However, there are also studies showing that PED treatment is not as safe and effective as assumed (8). In this study, a meta-analysis was performed to evaluate the safety and efficacy of PED in intracranial aneurysm embolization through a randomized controlled trial and an observational study comparing the efficacy of PED with traditional coils in intracranial aneurysm embolization.

Methods

Search strategy

This meta-analysis was performed according to the PRISMA guidelines. We systematically searched PubMed, Embase, Web of Science, and The Cochrane Library databases for randomized controlled trials and observational studies (case-control studies and cohort studies) comparing the efficacy of PED with traditional coils in embolization of intracranial aneurysms published before April 1, 2022. A literature search was conducted independently by two investigators, and we used a combination of the following terms: Intracranial Aneurysm (Mesh), Aneurysm, Anterior Communicating Artery, Aneurysm, Basilar Artery, Aneurysm, Middle Cerebral Artery, Aneurysm, Posterior Cerebral Artery, Berry Aneurysm, Brain Aneurysm, Cerebral Aneurysm, Giant Intracranial Aneurysm Mycotic Aneurysm, Intracranial, Aneurysm, Anterior Cerebral Artery, Aneurysm, Posterior Communicating Artery, Pipeline embolization device, Flow diverter device, PED, Pipeline Flex, primary coil, balloon-assisted coiling, stent-assisted coiling.

References generated from these searches were imported into the reference manager EndNote X9.3.1 (Thompson Reuters, Philadelphia, PA) and duplicate references were removed. Then, journal article titles and abstracts were systematically screened by two researchers independently according to the following inclusion and exclusion criteria. This meta-analysis has been registered in PROSPERO (ID: CRD42022325673).

Inclusion criteria

(1) Patients with confirmed intracranial aneurysms (ruptured and unruptured intracranial aneurysms) (2) Vascular treatment: with PED and traditional coils embolization (coils alone, stent-assisted coils, balloon-assisted coils) (3) Data for two treatment groups can be clearly provided in the literature: the PED treatment group and the traditional coils embolization group (4) Randomized controlled trials and observational studies (case-control studies and cohort studies).

Exclusion criteria

(1) unpublished studies, conference abstracts, letters, reviews, correspondence, and animal studies; (2) studies with duplicate or overlapping data; (3) lack of outcome data outside of hospitalization; and (4) literature that did not provide data for both treatment groups: the PED treatment group and the traditional coils embolization group (5) case series of <10 patients for both.

Antiplatelet therapy strategy

Prior to PED or stent-assisted coil embolization, patients were given a loading dose of 325–650 mg aspirin and 600 mg clopidogrel as antiplatelet therapy for patients with acute ruptured aneurysms. For non-emergency patients, 1–2 weeks before treatment, patients were started on daily aspirin (ASA) 100–325 mg and clopidogrel 75 mg antiplatelet aggregation. Use light transmittance aggregometr (LTA) or thromboelastography (TEG) to perform platelet function tests, and determine whether to adjust the drug dose or replace antiplatelet drugs according to the test results. Dual antiplatelet therapy was generally continued for 6 months after device placement, followed by aspirin indefinitely (5–7). The choice of oral antiplatelet drug timing and aspirin dose for treatment initiation varies by patient ethnicity and other differences and is selected according to national guidelines.

Data extraction and efficacy metrics

Data for each eligible literature were extracted independently by 2 investigators, and any disagreements were resolved by discussion and consultation with a 3rd senior neurosurgeon. Basic information such as first author's name, study design, sample size, mean age, sex ratio, size of the aneurysm, width of the aneurysm neck, location of the aneurysm, and endovascular treatment modality were extracted using a pre-developed form. The main indicators analyzed: procedure-related intracranial hemorrhage, procedure-related intracranial ischemia, other procedure-related complications (e.g., aneurysm rupture, impaired neurological function, etc.), retreatment rate, complete occlusion (100%) of the aneurysm at the last follow-up, and favorable functional outcome (MRS ≤ 2).

Literature quality assessment

Each of the two trained researchers read all the titles and abstracts of the literature, firstly screened out the literature that clearly did not meet the inclusion criteria, and then read the full text of the literature to initially identify the literature that could be included in the study. Finally, the screening results of the two researchers were cross-checked, and the two evaluators discussed the questionable literature and combined the third-party opinions to decide whether to include it or not. The quality of randomized controlled trials was evaluated using the Cochrane Risk of Bias tool, and the quality of observational studies was evaluated using the Newcastle-Ottawa Scale (NOS).

Statistics analysis

Statistical analyses were performed using Review Manager (v.5.3), and differences were considered statistically significant at $P \leq 0.05$ if not explicitly stated. We calculated the odds ratio (OR) of categorical variables using a random-effects model, and heterogeneity was evaluated using chi-square tests and I^2 tests, and we considered data to be significantly heterogeneous when I^2 $>50\%$, and we performed meta-analysis using a random-effects model, otherwise, a fixed-effects model was performed. Sensitivity analyses were performed by omitting studies one by one to assess the effect of each study on the overall outcome. Symmetry was assessed using Begg's and Egger's tests, and significant publication bias was defined as $p < 0.1$, and publication bias was assessed with sensitivity analysis using STATA (v.12).

Results

Search results and selection of research subjects

Searching from the database identified 385 articles (Pubmed: 28, Embase: 114, Cochrance: 6, Web of Science: 237), of

which 118 duplicates were excluded. The titles and abstracts of the shortlisted articles were reviewed and excluded An additional 237 papers were reviewed, and the remaining 30 papers were read in detail to determine whether they met the inclusion/exclusion criteria. Ultimately, 10 eligible papers were included in this meta-analysis (7, 9–17) (shown in Figure 1).

Basic characteristics of the research object

One thousand four hundred patients from 10 (7, 9–17) studies (0 randomized controlled trials and 10 observational studies) were included in this study, of whom 576 were treated with PED and 824 with traditional coils embolization. Demographic characteristics and details regarding the type of literature included in the study are shown in Table 1.

Quality evaluation of the included literature

A total of 10 (7, 9–17) studies were included, and all 10 studies were observational, using NOS quality assessment of non-randomized controlled trials (Supplementary Table 1). In conclusion, the quality scores of the included literature were high, describing the selection of the study population and comparability between groups.

PED vs. traditional coils for efficacy

Procedure-related intracranial hemorrhage

In the evaluation of procedure-related intracranial hemorrhage, a total of seven (7, 9–11, 14–16) studies were included, with a total of 460 patients in the PED group with 15 (3.3%, 15/460) patients with procedure-related intracranial hemorrhage and a total of 460 patients in the traditional coils group with three (0.7%, 3/460) patients with procedure-related intracranial hemorrhage, with low heterogeneity ($I^2 = 0\%$, $P = 0.90$), so a fixed-effects model was used. The incidence of Procedure-related intracranial hemorrhage was higher in the PED group than in the conventional coil embolization group, with a statistically significant difference between the two groups [OR = 3.04, 95% CI (1.08, 8.57), $p = 0.04$; shown in Figure 2].

Procedure-related intracranial ischemia

In the evaluation of procedure-related intracranial ischemia, a total of nine (7, 9–12, 14–17) studies were included, with a total of 521 patients in the PED group and 23 (4.4%, 23/521) patients with procedure-related intracranial ischemia, and a total of 524 patients in the traditional coils group and 26 (4.9%, 26/524) patients with procedure-related intracranial ischemia, with low heterogeneity ($I^2 = 0\%$, $P = 0.53$), so a fixed-effects model was used. There was no statistically significant difference between the two groups in terms of Procedure-related intracranial ischemia [OR = 0.88, 95% CI (0.47, 1.64), $p = 0.68$; shown in Figure 3].

Other procedure-related complications

In the evaluation of other procedure-related complications, a total of nine (7, 9–15, 17) studies included a total of 441 patients in the PED group with 30 (6.8%, 30/441) patients with other procedure-related complications and a total of 794 patients in the traditional coils group with 12 (1.5%, 12/794) patients with other procedure-related complications, with low heterogeneity ($I^2 = 0\%$, $P = 0.74$), so a fixed-effects model was used. In terms of other procedure-related complications (aneurysm rupture, neurological deficit), the PED group had a higher incidence than the traditional coil embolization group, and there was a statistically significant difference between the two groups [OR = 2.91, 95% CI (1.48, 5.57), $p = 0.002$; shown in Figure 4].

Aneurysm retreatment rate

Aneurysm retreatment rates from a total of 998 intracranial aneurysms included in eight studies (7, 9–12, 14, 16, 17), heterogeneous ($p = 0.28$, $I^2 = 18\%$), using a fixed effects model, with a retreatment rate of 4.6% (25/547) in the PED group and 21.5% (95/441) in the traditional coils group, using PED compared to traditional coils had a lower retreatment rate, with a statistically significant difference between the two [OR = 0.20, 95% CI (0.12, 0.34), $p < 0.00001$; shown in Figure 5].

Favorable functional outcome of patients at last follow-up (MRS ≤ 2)

In the evaluation of favorable functional outcome of patients at follow-up, a total of nine (7, 9, 11–17) studies were included, with 539 patients in the PED group with a MRS 0–2 score of 505 (93.7%, 505/539) and 592 patients in the traditional coils group with a MRS ≤2 score of 569 (96.1%, 569/592), with low heterogeneity ($I^2 = 18\%$, $P = 0.29$), using a fixed-effects model. Compared with the traditional coil embolization group, the PED group had fewer patients with MRS ≤ 2 at last follow-up, and the difference between the two was statistically significant [OR = 0.4, 95% CI (0.22, 0.71), $p = 0.002$; shown in Figure 6].

Complete occlusion rate (100%) of aneurysm in patients at last follow-up

A total of 10 studies were included in the comparison of patients with complete occlusion of aneurysms in the two groups at last follow-up (7, 9–17), with high heterogeneity ($P < 0.0001$, $I^2 = 74\%$), with 575 aneurysms followed in the PED group

TABLE 1 Baseline characteristics of the included studies.

References	Study design	Sample size		Aneurysm size (mm)		Aneurysm neck size (mm)		Aneurysm location	Mean age, years (P/T)	Gender (M/F)		Endovascular therapy
		P	T	P	T	P	T			P	T	
Chalouhi et al. (7)	Observational	40	120	14.9 ± 4.7	14.9 ± 5.9	5.0 ± 1.2	4.9 ± 1.7	OA, VA, MCA, PcomA, cavernous, paraclinoid, petrous	60.7/60.3	7/33	17/103	PED, coiling, SAC, BAC
Di Maria et al. (9)	Observational	77	61	8.7 + 6.3	6.7 + 3.6		Na	Carotid-ophthalmic aneurysms	49.7/49.2	17/60	10/51	PED, coiling, SAC, BAC
Zanaty et al. (10)	Observational	51	106	16.75	14.27		Na	Carotid cavernous aneurysms	63.0/60.42	4/47	7/99	PED, coiling, SAC
Adeeb et al. (11)	Observational	106	62	6.4	7.1	4	5.1	Ophthalmic segment aneurysms	57/57	8/98	1/61	PED, SAC
Chalouhi et al. (12)	Observational	40	40	6.3 ± 2.7	6.3 ± 2.8		Na	Paraclinoid, PcomA, OA, carotid cave	54.8/54.9	4/40	4/40	PED, coiling, SAC, BAC
Zhang et al. (13)	Observational	55	300	4.3 ± 1.4	4.0 ± 1.3		Na	Cavernous, OA, paraclinoidal	54.1/53.4	9/55	50/250	PED, coiling, SAC
Enriquez-Marulanda et al. (14)	Observational	21	17	4.9	8.6		Na	Communicating segment ICA	61/58	4/17	2/15	PED, SAC
Zhang et al. (15)	Observational	30	64	11	11.6		Na	Intradural vertebral artery aneurysms	51/53	24/6	57/7	PED, SAC
Salem et al. (16)	Observational	135	30	4.9	5.2		Na	ICA, carotid bifurcation	58/60.5	22/135	5/25	PED, SAC
Suzuki et al. (17)	Observational	21	24	12.3 ± 3.6	12.9 ± 3.2	6.1 ± 1.8	6.9 ± 2.5	Paraclinoid aneurysms	59/60.6	4/17	7/17	PED, coiling, SAC, BAC

P, pipeline embolization device (PED); T, traditional coils embolism; OA, ophthalmic segment; VA, vertebrobasilar; MCA, middle cerebral artery; PcomA, middle cerebral artery; ICA, internal carotid artery.

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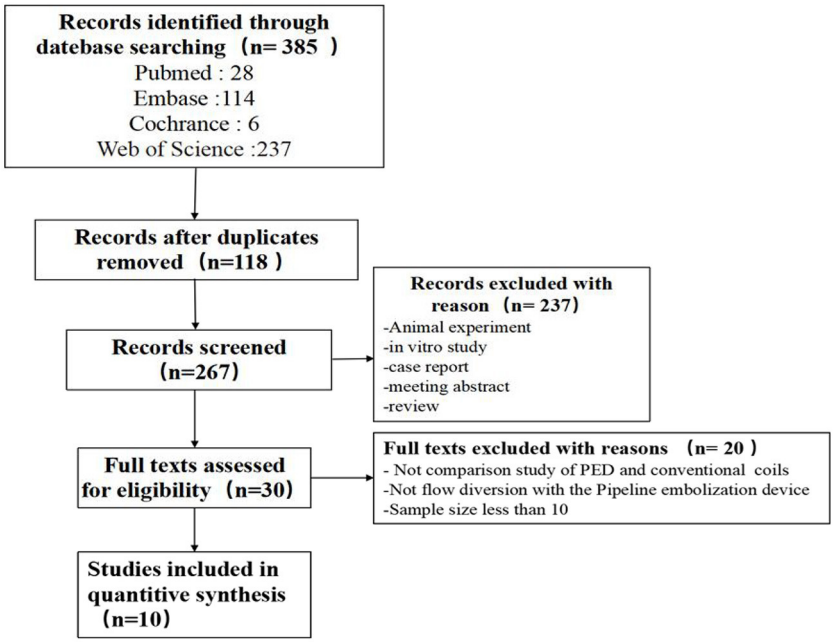

FIGURE 1
Flow chart of the search and inclusion of literature.

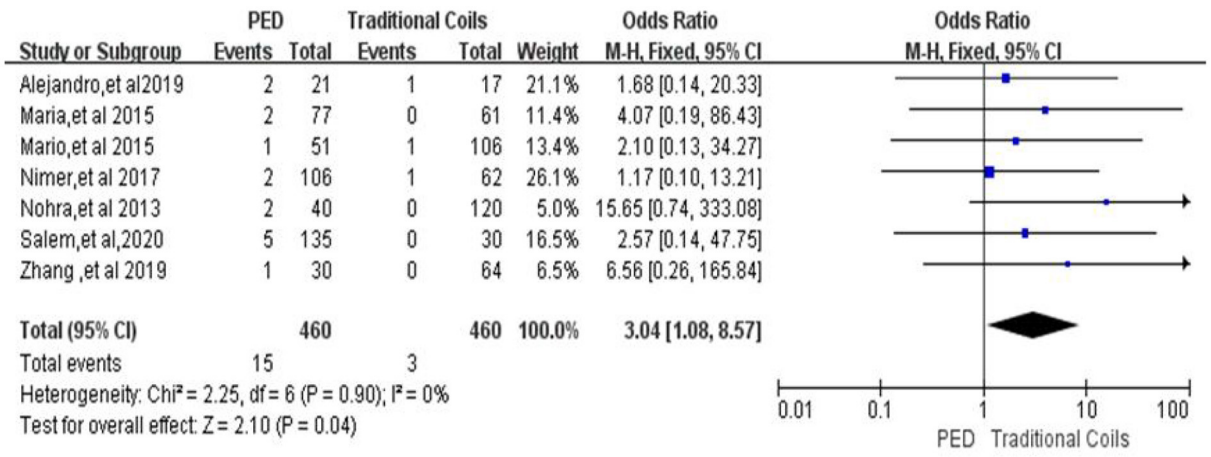

FIGURE 2
Forest plot and meta-analysis of procedure-related intracranial hemorrhage.

and 454 complete occlusion, with a complete occlusion rate of 78.96%, and 690 aneurysms followed in the traditional coils group and 460 complete occlusion, with a complete occlusion rate was 66.67%, and PED had a higher occlusion rate compared to traditional coils, with a statistically significant difference between the two [OR = 2.04, 95% CI (1.12, 3.70), $p = 0.02$, shown in Figure 7A]. After excluding the study by Zhang et al. (13), the heterogeneity of this analysis was significantly lower ($I^2 = 40\%$, $p = 0.1$), with complete occlusion rates of 79.3% (410/517) in the PED group and 57.6% (285/495) in the traditional coils group, without affecting the final outcome [OR = 2.62, 95% CI (1.94, 3.55), $p < 0.00001$, shown in Figure 7B].

Sensitivity analysis and publication bias

In this meta -analysis, the results of the sensitivity analysis for effectiveness and safety were consistent with the results of the

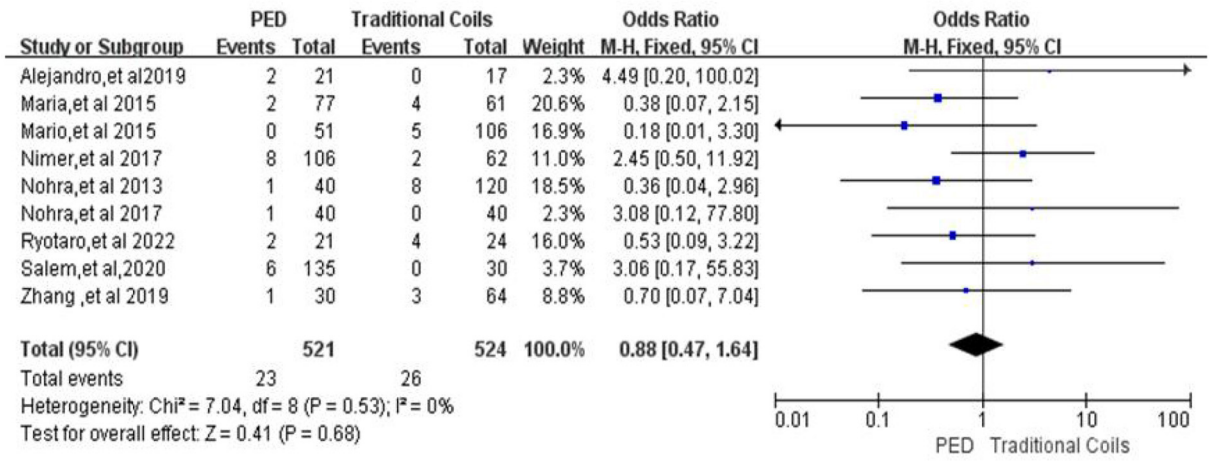

FIGURE 3
Forest plot and meta-analysis of procedure-related intracranial ischemia.

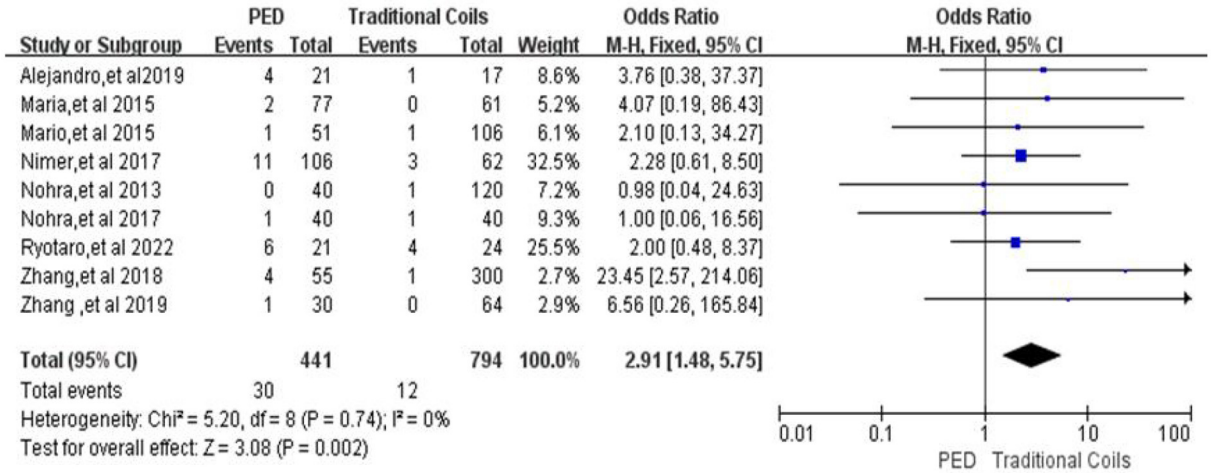

FIGURE 4
Forest plot and meta-analysis of other procedure-related complications.

combined analysis; we used the Begg's and Egger's tests to assess the effect of publication bias, and the funnel plots were both symmetrical, with no significant evidence of publication bias.

Discussion

PED is the earliest blood flow diverting device used for intracranial aneurysm embolization, and it was mainly used to treat large and giant wide-necked aneurysms of the internal carotid artery in the early stage. With the maturation of PED treatment technology in recent years, PED treatment has also started to be used super-indicated for small aneurysms, but the feasibility and advantages of the treatment are still controversial. The traditional coils embolization treatment modality has shown acceptable safety and effectiveness (18, 19), which makes it necessary to compare PED with traditional coils (coils alone, stent-assisted coils, balloon-assisted coils) safety and efficacy in the treatment of intracranial aneurysms. A total of 10 studies comparing the two treatment modalities involving 1,400 patients were included in this meta-analysis. After a comprehensive analysis it was shown that the PED group had a lower retreatment rate and a higher rate of complete aneurysm occlusion (100%) compared to the traditional coils embolization group. The traditional coils embolization group was superior to the PED group in terms of procedure-related intracranial

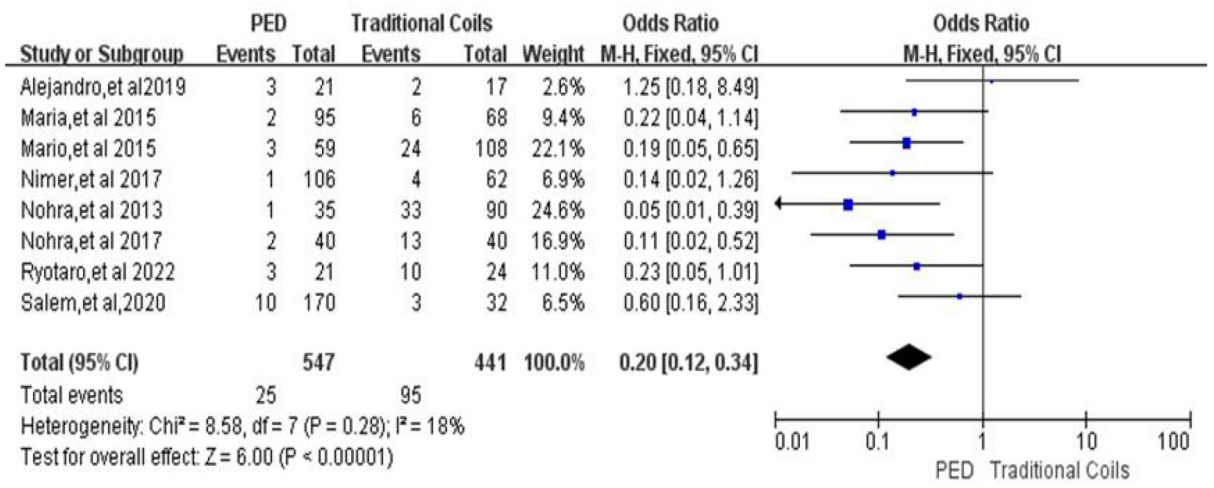

FIGURE 5
Forest plot and meta-analysis of aneurysm retreatment rate.

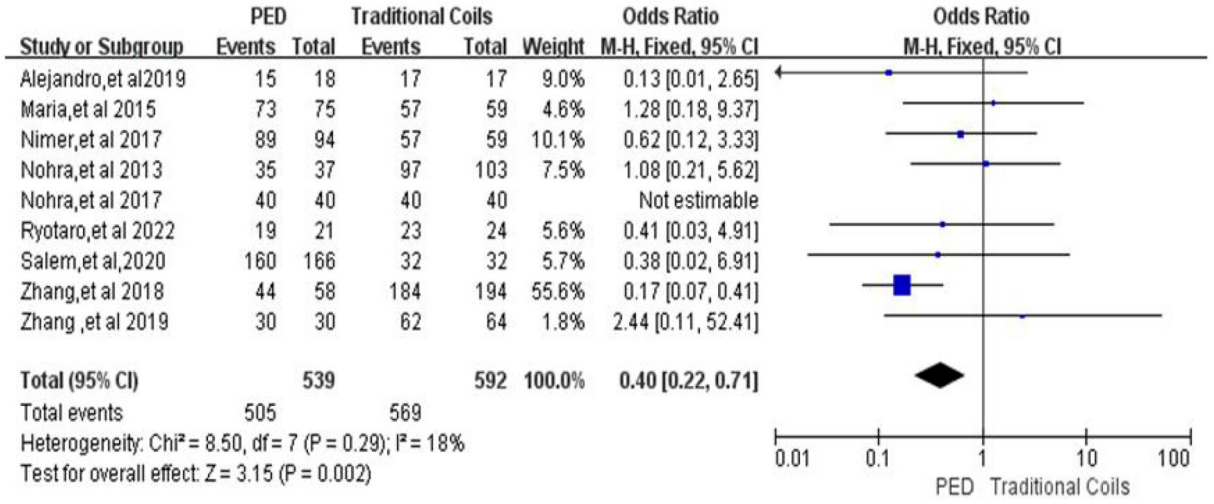

FIGURE 6
Forest plot and meta-analysis of favorable functional outcome of patients at last follow-up.

hemorrhage, other procedure-related complications (aneurysm rupture, neurological impairment, etc.), and favorable functional outcome at last follow-up (MRS $\leq$ 2), but no significant differences were seen between the two groups in terms of procedure-related intracranial ischemic complications.

Endovascular therapy is now the key treatment for most different types of intracranial aneurysms. Coil embolization is traditionally one of the most popular treatment modalities and is primarily indicated for the treatment of small (<10 mm), unruptured and morphologically simple anterior circulation intracranial aneurysms. Stent-assisted coil embolization is based on simple coil embolization to solve the problems of residual aneurysm neck and coil protruding into the parent artery through stent-assisted embolization, and can be used as the core of endothelial cell growth and aneurysm healing (20, 21). Compared with coil embolization alone, stent-assisted spring coil embolization has a higher rate of complete occlusion and a lower rate of recurrence (22). Although stent-assisted coils have wider indications and better efficacy than coils alone, there are still technical challenges, such as difficulty in passing microguidewires and microcatheters through the stent gap, stent misalignment, and incomplete coiling leading to residual

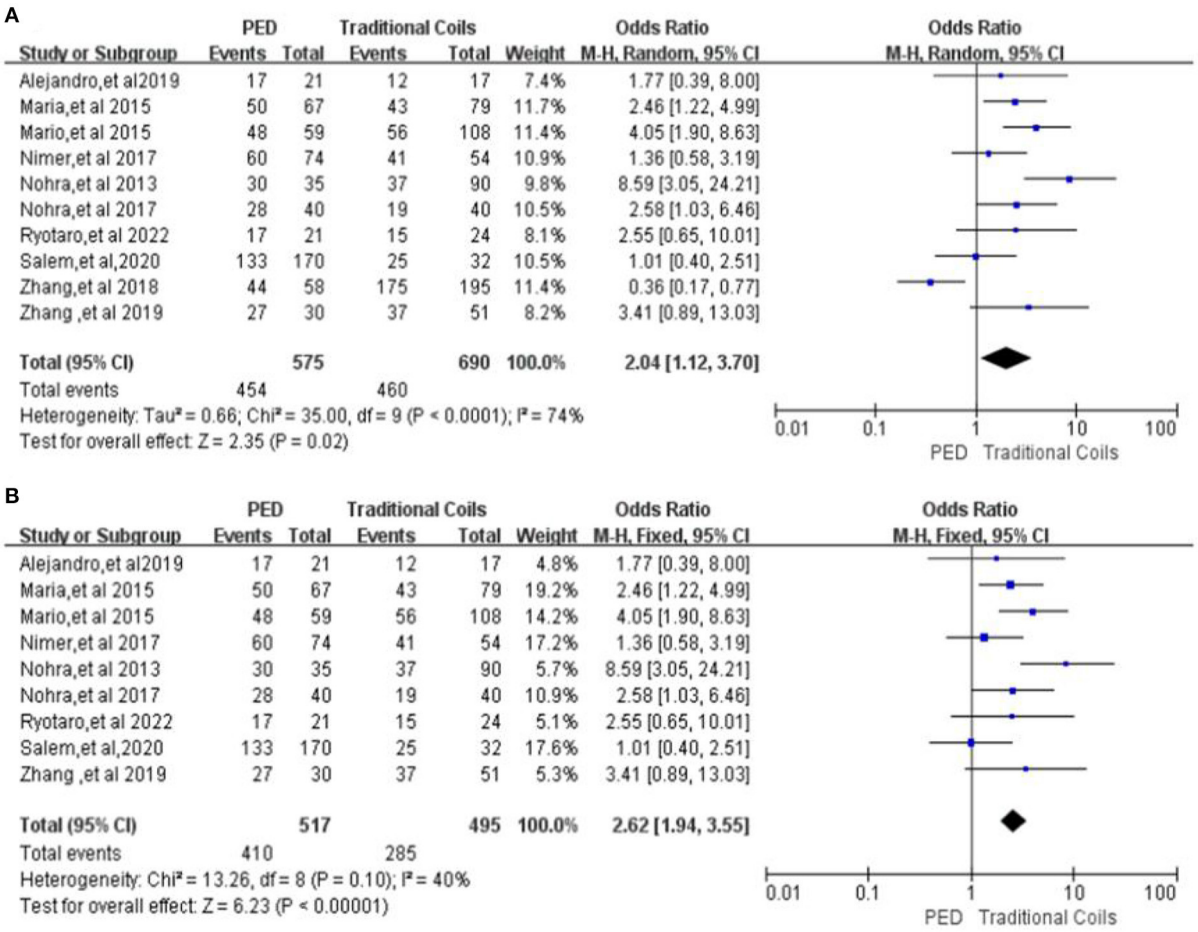

FIGURE 7
(A) Forest plot and meta-analysis of complete occlusion rate (100%) of aneurysm in patients at last follow-up. **(B)** Forest plot and meta-analysis of Complete occlusion rate (100%) of aneurysm in patients at last follow-up after excluding the study by Zhang et al. to reduce heterogeneity.

aneurysm neck, making the persistence of aneurysm occlusion still a concern. The introduction of PED technology overcomes some of the technical challenges of conventional spring coil embolization. PED is a specialized shunt approved by the U.S. Food and Drug Administration (FAD) in 2011. It works to rebuild the parent artery, thereby Diverts blood flow away from the aneurysm, resulting in interruption and stagnation of blood flow within the aneurysm, subsequent thrombus formation, and occlusion of the aneurysm, while the vital arterial branches covered by the shunt remain open (23). The safety and efficacy of PEDs have also been confirmed in several recent series, but most of these series were not comparative studies with patients treated with traditional embolization strategies (6, 24, 25). In 2013, Crobeddu et al. (26) reported that in the 4 years since PEDs were first introduced, the use of SAC decreased from 14.7 to 6.9%. The reason why PED technology is welcomed by the majority of operators may be mainly due to its technical advantages. PED can avoid entering the aneurysm sac, thereby reducing the risk of iatrogenic rupture when placing the coil, especially for smaller aneurysms. In addition, multiple nearby aneurysms can be treated in a single operation, which can re-establish the Plastics the entire vessel, thereby preventing aneurysm recanalization and formation of new aneurysms in the context of dysplastic parent vessels.

Whether the safety and efficacy of PED treatment of intracranial aneurysms is superior to that of traditional coils embolization is controversial. The most appropriate strategy for aneurysm embolization depends largely on clinical factors and the anatomic characteristics of the aneurysm. Previous studies have found a 1–8.6% incidence of procedure-related complications and a 5–23% re-treatment rate for traditional coils embolization of intracranial aneurysms (27–29). In the study of this meta-analysis, the incidence of procedure-related intracranial hemorrhage in the traditional coils embolization group was found to be 0.7%, the incidence of intracranial ischemia was 4.9%, the incidence of other procedure-related complications was 1.5%, and the re-treatment rate was 21.5%, which is similar to the results of previous studies. In contrast,

regarding PED treatment, previous studies have reported rates of 3.4–31.7% for neurosurgery-related complications and 0.9–15% for retreatment (11, 30, 31). In the study of this meta-analysis, the incidence of procedure-related intracranial hemorrhage was 3.3%, the incidence of intracranial ischemia was 4.4%, the incidence of other procedure-related complications was 6.8%, and in the treatment rate was 4.6%. The results of previous studies were also similar. Because of the sample size of the original study, this meta-analysis did not include separate subgroup analyses of aneurysm size and location. In terms of the overall outcome of aneurysm treatment, the traditional coils embolization group was superior to the PED group in terms of procedure-related complications. However, in another study conducted by Zhang et al. (32), a propensity score analysis was performed to compare the safety and efficacy of PED vs. SAC in large and giant aneurysms, and procedure-related complications were similar between the two groups. Alejandro et al. (14) also compared PED and SAC for the treatment of aneurysms located in the traffic segment of the internal carotid artery, and the results showed that procedure-related complications were not significant between the two groups. This is inconsistent with our findings. We speculate that the main reason is that the aneurysms studied in this meta-analysis originate from blood vessels in various parts of the brain, and the sizes are different, which affects the consistency of the results. But we cannot ignore the unique complications of PED itself, such as delayed migration of the device, distal parenchymal hemorrhage, aneurysm rupture due to aneurysm wall degeneration or endoleakage (33–35). Large samples and randomized trials are still needed to validate for surgical complications. As for the re-treatment rate, our findings are consistent with those of previous studies, with the PED group was significantly better than the traditional coil embolization group (12, 17).

The rate of complete aneurysm occlusion during post-operative aneurysm follow-up is a key observation in the course of aneurysm treatment. In 2013, a matched study comparing PEDs and traditional coils for intracranial aneurysms found significantly higher occlusion rates for PED-treated aneurysms (86 vs. 41%) (7). Several single-center and multicenter studies have also demonstrated a higher rate of complete occlusion of intracranial arteries treated with PEDs compared with traditional aneurysm embolization strategies (7, 36). In the Di Maria et al. (9) comparative study found that the occlusion rate was also significantly higher in the PED group than in the traditional coils embolization group at 12 months follow-up (85.3 vs. 54%). However, some studies (14) also found no difference in complete aneurysm occlusion between the PED and traditional coils embolization groups. The mean duration of follow-up was 10 months in the PED group and 23 months in the traditional coils embolization group in the studies included in this meta-analysis, and the rate of complete aneurysm occlusion was significantly higher in the PED group than in the traditional coil embolization group at the last follow-up, which is consistent with the results of some of the previous studies. With regard to favorable functional outcome at the follow-up, several comparative studies on PED vs. stent-assisted coil treatment of aneurysms found no difference in favorable functional outcome (mRS $\leq$ 2) between the two groups during follow-up (11, 13, 16). This meta-analysis study found that the traditional coils embolization group was superior to the PED group with regard to favorable functional outcome at the last follow-up of the patients. We speculate that this has a certain relationship with the incidence of surgery-related complications in patients, and adverse complications lead to permanent neurological damage in patients. PED technique may have different efficacy for aneurysms of different sizes and locations, but in terms of overall results, PED still has a significant advantage in terms of complete aneurysm occlusion and aneurysm retreatment.

Limitations

In interpreting the results, some limitations should be highlighted. First, most of the included studies were non-randomized, selection bias is inevitable, and different sizes and sites of aneurysms can affect the validity of the findings. Secondly, not all studies had the data required to assess the efficacy of PED vs. conventional spring coil embolization studies. Third, the overall sample size of this study was small, which may have affected the results.

Conclusion

PED had higher rates of complete aneurysm occlusion and lower rates of aneurysm retreatment compared with traditional coils embolization, but traditional coils embolization was superior to the PED group in terms of procedure-related intracranial hemorrhagic complications and other procedure-related complications (aneurysm rupture, neurological impairment), and favorable functional outcome (mRS $\leq$ 2) at the last follow-up. This result still needs to be further confirmed by additional large-sample, multicenter, prospective randomized controlled trials.

Data availability statement

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

Author contributions

WL and ZX participated in the design of the study, collected and analyzed the data, and drafted and revised the manuscript. KZ, SY, YZha, BL, YZho, and YM analyzed the data, interpreted

the results, and performed the statistical analysis. EC designed the study, supervised the study inclusion and data extraction, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.978602/full#supplementary-material

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EDITED BY
Cong-Hui Li,
The First Hospital of Hebei Medical University, China

REVIEWED BY
Yong Cao,
Beijing Tiantan Hospital, Capital Medical University, China
Chaofan Zeng,
Beijing Tiantan Hospital, Capital Medical University, China

*CORRESPONDENCE
Qiao Zuo
dr_zuo@126.com
Jianmin Liu
chstroke@163.com

†These authors have contributed equally to this work

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Worldwide productivity and research trends of publications concerning stent application in acutely ruptured intracranial aneurysms: A bibliometric study

Rundong Chen†, Yanpeng Wei†, Guanghao Zhang†, Renkun Zhang, Xiaoxi Zhang, Dongwei Dai, Qiang Li, Rui Zhao, Yi Xu, Qinghai Huang, Pengfei Yang, Qiao Zuo* and Jianmin Liu*

Neurovascular Center, Changhai Hospital, Naval Medical University, Shanghai, China

Background: Stenting is a common clinical practice to treat acutely ruptured intracranial aneurysm (RIA). Although multiple studies have demonstrated its long-term safety and effectiveness, there is currently a lack of bibliometric analysis on stent application in acutely RIA. This study sought to summarize the current status of research in this field and lay a foundation for further study.

Materials and methods: Related publications were searched in the Web of Science Core Collection (WoSCC) database. Data analysis and visualization were performed by R and CiteSpace software.

Results: A total of 275 publications published in English from 1997 to 2022 were included in this study. The growth of publications slowed down. The reference co-citation network identified 13 clusters with a significant network ($Q = 0.7692$) and convincing clustering ($S = 0.9082$). The research focus was acutely RIA and the application of stents during interventional procedures. The main trends of research were: (1) development of materials, and (2) safety of stent application in acutely RIA. The United States contributed the most articles, and Jianmin Liu was the most prolific author. Mayo Clinic was the leading institution in this field. Most articles were published in Interventional Neuroradiology.

Conclusions: This study analyzed the research trends, hotspots and frontiers of stent application in acutely RIA. It is our hope that the results obtained could provide useful information to researchers to get a clearer picture about their future research directions in this field.

KEYWORDS

stent application, stent-assisted coiling, ruptured intracranial aneurysms, bibliometric, cluster analysis, Citespace

Introduction

The past decades have witnessed remarkable advances in the endovascular treatment of acutely ruptured intracranial aneurysms (RIA), and the safety and effectiveness of stent application in acutely RIA have been explored (1). RIA is the most common cause of subarachnoid hemorrhage (SAH), which is often a devastating event with high mortality and morbidity (2). About 4% and 1% SAH patients have an increased risk of rebleeding in the first 24 h and every day in the first month respectively (3). Endovascular and surgical treatments are available for aneurysm repair, which are the only effective treatments to prevent rebleeding at present (4). However, for some complex aneurysms, giant aneurysms and aneurysms with a low fundus-to-neck ratio, specialized skills are required to obtain satisfactory embolization, including stent-assisted coiling (SAC), balloon-assisted coiling (BAC), flow diverters (FD), and the use of new embolic materials including liquids (5–7). Stent placement has been commonly applied in acutely RIA, including classic laser-cut stents, braided stents, drug-eluting stents, and covered stents (8–10). These skills are expected to enable aneurysms previously considered unsuitable for the endovascular procedure to be treated in the future (5, 11). Early studies suggested a high incidence of adverse events with stent application in acutely RIA, including stent-related thrombosis and hemorrhagic complications due to the use of antiplatelet drugs (12–14). However, with the progress in endovascular skills, materials, devices and antiplatelet strategies, the perioperative safety of stent application in acutely RIA has been continuously improved (1, 15–17). Exploration and summary of the research trends of stent application in acutely RIA treatment is significant to those who want to carry out this research.

Bibliometrics uses statistical methods to analyze publications, especially those of scientific content. Bibliometric mapping allows data to be presented in ways that make relationships more understandable and provide researchers with relatively macro information (18). The method of bibliometric analysis has become increasingly mature and has been widely used in clinical disease research (19).

However, there is a lack of data on bibliometric analysis of stent application in acutely RIA. To fill this gap, we conducted a bibliometric study to discuss publications on stent application in acutely RIA from 1997 to 2022 both quantitatively and qualitatively. In addition, we summarized the main research trends and frontiers, provided the latest insights and findings, and looked forward to the future development of this field.

Materials and methods

Objectives

The primary objective of the study was to systematically map how stenting is evolved in the treatment of patients with acutely RIA, and identify the main trends and hot topics of research in this field by constructing networks of co-cited references and co-occurring keywords. The secondary objective was to render the research network in terms of countries, authors, institutions and journals.

Data collection

We searched publications from the Web of Science Core Collection (WoSCC) through the Science Citation Index Expanded (SCI-E). The search terms combined Medical Subject Headings words and keywords:[TS = (stent*) OR TS=("stent assisted")] AND TS=("ruptured intracranial aneurysm*"). The language was limited to "English." The main document type was "articles" and "reviews" with no time limitation. All the search result records, including the title, author information, keyword, abstract and reference were exported in TXT format for analysis on July 15, 2022.

Data analysis

The raw files were analyzed by R software (4.1.3) and Citespace software (6.1.R2). The "bibliometrix" R package is an open-source tool for quantitative research in bibliometrics. It summarizes the preliminary information, country scientific production, and the cumulate occurrence of journal articles in this study. CiteSpace is a Java application for visualizing patterns and trends in scientific publications by focusing on identifying critical points in developing a particular field. It was used to explore networks of co-cited references and co-occurring keywords, as well as collaboration networks between countries, authors, institutions, and journals.

Results

General overview

A total of 275 publications about stent application in acutely RIA from 1997 to 2022 were included in this study, of which 236 were original articles, and 39 were review articles (Figure 1). The growth of the overall number of articles and the mean article citations per year slowed down. The COVID-19 pandemic may lead to a decline. The cumulative number of citations for these publications was 5,041 (4,464 without self-citations), with a mean number of citations per item of 18.33. The mean H-index in this field was 38. The analysis showed significant progress in this field in the past 20 years, especially in 2013 and 2019.

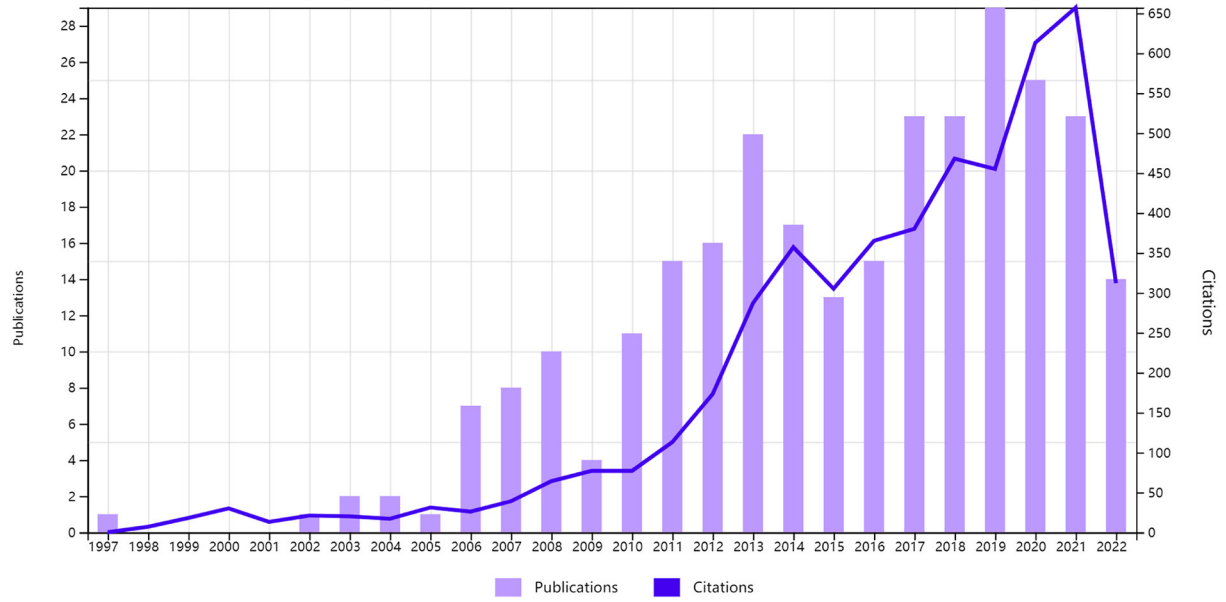


FIGURE 1
Annual scientific production and citation.

Co-cited references and references

Co-citation references were two or more articles appearing simultaneously in the references of other documents. The association of co-citations may reveal how groupings have evolved independently from the original publication (19). The top 10 most cited documents and the top 10 most cited references were shown in Tables 1, 2 respectively. There were 693 nodes and 2,830 links constructed by Citespace for a map of reference co-citations with corresponding clusters (Figures 2A,B). The first article was issued in 1997 (20). At that time, stenting was attempted for the treatment of acutely RIA through endovascular therapy. Thirteen clusters were identified in this network with significant modularity Q scores and silhouette scores (Q = 0.7692, S = 0.9082). We found a research focus and two different research trends in this map. The research focus was acutely SAH and the application of stents during interventional procedures. These clusters, with the indication of the label, silhouette score, size, the mean year of publications, and most representative reference were: cluster#5 (cerebrovascular disease, S = 0.912, size = 49, mean year = 2009) (21), cluster#3 (subarachnoid hemorrhage, S = 0.903, size = 71, mean year = 2011) (22), cluster #7 (interventional radiology, S=0.864, size = 32, mean year = 2016) (23), and cluster#15 (stent, S = 0.994, size = 5, mean year = 2018) (24). The first trend was concerned with the development of materials. It started with cluster #6 (liquid embolic agents, S = 0.993, size = 48, mean year = 2002) (25), which developed research on cluster #2 (neuroform stent, S = 0.908, size = 81, mean year = 2007) (26) and cluster #10 (matrix coil, S = 0.959, size = 16, mean year = 2008) (27). More recently, these clusters became cluster #0 (pipeline embolization device, S = 0.851, size = 92, mean year = 2014) (28), with strong links to cluster#1 (woven endobridge, S = 0.875, size = 89, mean year = 2020) (29). The second major research trend was concerned with the safety of stent application in acutely RIA. This trend began with cluster #9 (vascular accident, S = 0.952, size = 17, mean year = 2014) (30) and cluster #14 (para-ophthalmic, S = 0.996, size = 10, mean year = 2016) (31), which has currently evolved into cluster#4 (safety, S = 0.941, size = 59, mean year = 2019) (32).

Keywords and hotspots

We extracted the timeline of the co-occurring keywords network (1997–2022) by Citespace (Figure 3A). Eleven clusters of keywords were identified with modularity Q score = 0.3962 and silhouette score = 0.7111. The most critical cluster was "clopidogrel," followed by "intracranial aneurysm," "coil embolization," "isat" (international subarachnoid aneurysm trial), "covered stent," "dsa," "antiplatelet therapy," "aneurysm coiling," "stent assisted coiling," "retreatment," and "antiplatelet drug resistance." We further extracted the same network from 2015 to 2022 (Figure 3B), and identified nine clusters of keywords with modularity Q score = 0.3924 and silhouette score = 0.7414. The most essential cluster was "ruptured intracranial aneurysm," followed by "coil embolization," "flow diversion," "stent assisted coiling," "vascular disorders,"

TABLE 1 The top 10 most cited documents.

Local citations[a]	Global citations[b]	Year	Source	Title	Doi
43	171	2011	American Journal of Neuroradiology	Stent-assisted coiling in acutely ruptured intracranial aneurysms: a qualitative, systematic review of the literature	10.3174/ajnr.A2478
27	75	2012	Neurosurgery	Stent-assisted coiling of wide-necked aneurysms in the setting of acute subarachnoid hemorrhage: experience in 65 patients	10.1227/NEU.0b013e318246a4b1
23	62	2015	American Journal of Neuroradiology	Complications in Stent-Assisted Endovascular Therapy of Ruptured Intracranial Aneurysms and Relevance to Antiplatelet Administration: A Systematic Review	10.3174/ajnr.A4365
18	57	2014	Journal of Neurosurgery	Stent-assisted coil embolization of ruptured wide-necked aneurysms in the acute period: incidence of and risk factors for periprocedural complications	10.3171/2014.4.JNS131662
16	85	2015	Journal of NeuroInterventional Surgery	Utilization of Pipeline embolization device for treatment of ruptured intracranial aneurysms: US multicenter experience	10.1136/neurintsurg-2014-011320
15	31	2012	Journal of NeuroInterventional Surgery	Stent assisted coiling of the ruptured wide necked intracranial aneurysm	10.1136/neurintsurg-2011-010035
14	344	1997	Journal of NeuroInterventional Surgery	Intravascular stent and endovascular coil placement for a ruptured fusiform aneurysm of the basilar artery. Case report and review of the literature	10.3171/jns.1997.87.6.0944
14	95	2012	American Journal of Neuroradiology	Immediate and midterm results following treatment of recently ruptured intracranial aneurysms with the Pipeline embolization device	10.3174/ajnr.A2797
13	99	2011	Neurosurgery	Stent-associated flow remodeling causes further occlusion of incompletely coiled aneurysms	10.1227/NEU.0b013e3182181c2b
11	99	2012	Neurosurgery	Safety and efficacy of endovascular treatment of basilar tip aneurysms by coiling with and without stent assistance: a review of 235 cases	10.1227/NEU.0b013e318265a416

[a]Number of citations in the network of 275 literature.
[b]Number of citations in the literature according to the journal where the paper was published.

"therapy," "endovascular occlusion," "cerebrovascular disease," and "neuroradiography." Moreover, keyword bursts represented keywords that were frequently cited over a period of time (Figure 3C). The earliest burst keyword was "Gugliemi detachable coil," which began in 2002 and lasted 8 years. Subsequently emerging keywords were "neuroform stent," "trial isat," "endovascular coiling," and "reconstruction," all of which focused on the feasibility of the stent application in acutely RIA. These keywords further evolved into "stent," "single center experience," "outcome," and "stent assisted coiling" in 2013, which were mainly concerned with the safety of stent application in acutely RIA. More recently, these keywords became "flow diversion," "complication," "therapy," "risk," and "efficacy."

Countries and regions

Based on the analysis of cooperation networks across countries or regions, 37 countries or regions were identified, of which the United States (US) contributed the most with 102 publications, followed by the People's Republic of China (n = 57), South Korea (n = 29), Germany (n = 22), and France (n = 21) (Supplementary Table 1). A country scientific production map was shown in Figure 4A and the cooperation networks across countries were mapped in Figure 4B. The US, as the landmark node, had extensive collaborations with other countries or regions worldwide.

TABLE 2 The top 10 most cited references.

Local citations	Global citations	Year	Source	Title	Doi
127	2,444	2002	Lancet	International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping vs. endovascular coiling in 2,143 patients with ruptured intracranial aneurysms: a randomized trial	10.1016/s0140-6736(02)11314-6
105	1,518	2005	Lancet	International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping vs. endovascular coiling in 2,143 patients with ruptured intracranial aneurysms: a randomized comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion	10.1016/S0140-6736(05)67214-5
68	1,061	2003	Stroke	Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils	10.1161/01.STR.0000073841.88563.E9
43	171	2011	American Journal of Neuroradiology	Stent-assisted coiling in acutely ruptured intracranial aneurysms: a qualitative, systematic review of the literature	10.3174/AJNR.A2478
43	444	2010	Stroke	Stent-assisted coiling of intracranial aneurysms: clinical and angiographic results in 216 consecutive aneurysms	10.1161/STROKEAHA.109.558114
43	2,380	2003	Lancet	Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment	10.1016/S0140-6736(03)13860-3
39	596	2003	Journal of Neurosurgery	Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience	10.3171/JNS.2003.98.5.0959
33	298	2004	Neurosurgery	Endovascular occlusion of wide-necked aneurysms with a new intracranial microstent (Neuroform) and detachable coils	10.1227/01.NEU.0000124484.87635.CD
33	246	2013	Stroke	Stent-assisted coiling of intracranial aneurysms: predictors of complications, recanalization, and outcome in 508 cases	10.1161/STROKEAHA.111.000641
31	121	2009	Radiology	Wide-necked intracranial aneurysms: treatment with stent-assisted coil embolization during acute (<72 h) subarachnoid hemorrhage–experience in 61 consecutive patients	10.1148/RADIOL.2531081923

Authors and institutions

The cooperation network between authors is shown in Figure 5A, and the top 10 influential authors are shown in Supplementary Table 2. There were 477 nodes and 1,075 links, and the results showed that Jianmin Liu contributed the largest number (n = 16) of publications with the highest centrality (0.17), followed by Jeongjun Lee (n = 9), NohraChalouhi (n = 9), Robert M Starke (n = 8), and David J Fiorella (n = 7). Jianmin Liu and Jeongjun Lee constituted the two pivot nodes that connected the network diagram, which was why these two authors had a higher degree of centrality. The collaboration between other authors was relatively decentralized. The cooperation network between institutions is shown in Figure 5B. The top 5 institutions by citation counts were Mayo Clinic (n = 9), Thomas Jefferson University (n = 9), Shanghai Jiao Tong University (n = 8), Capital Medical University (n = 8), and Jefferson Hospital for Neuroscience (n = 7) (Supplementary Table 3).

Journals

The top five journals with the most references were the American Journal of Neuroradiology (n = 26), Journal of

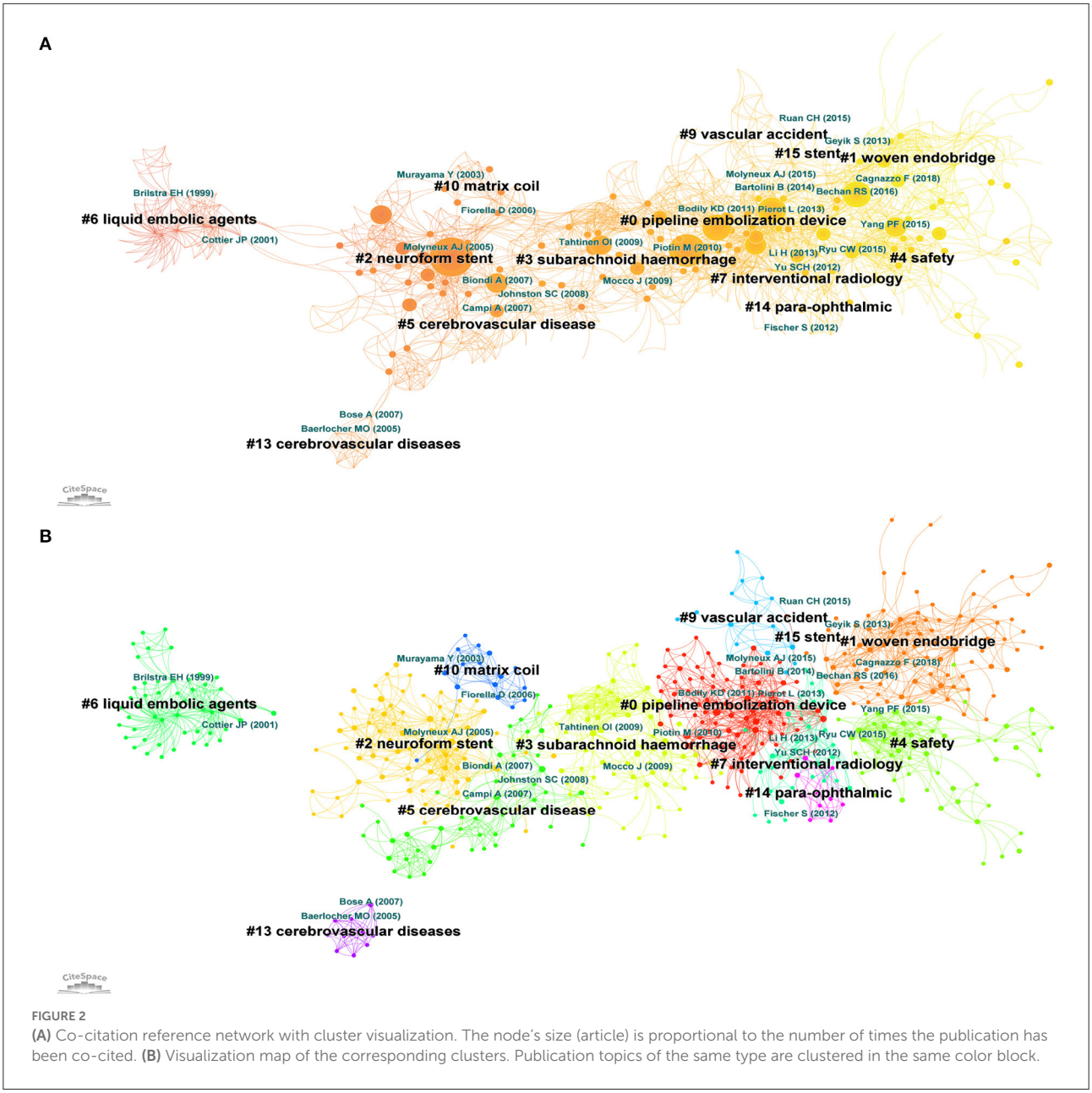
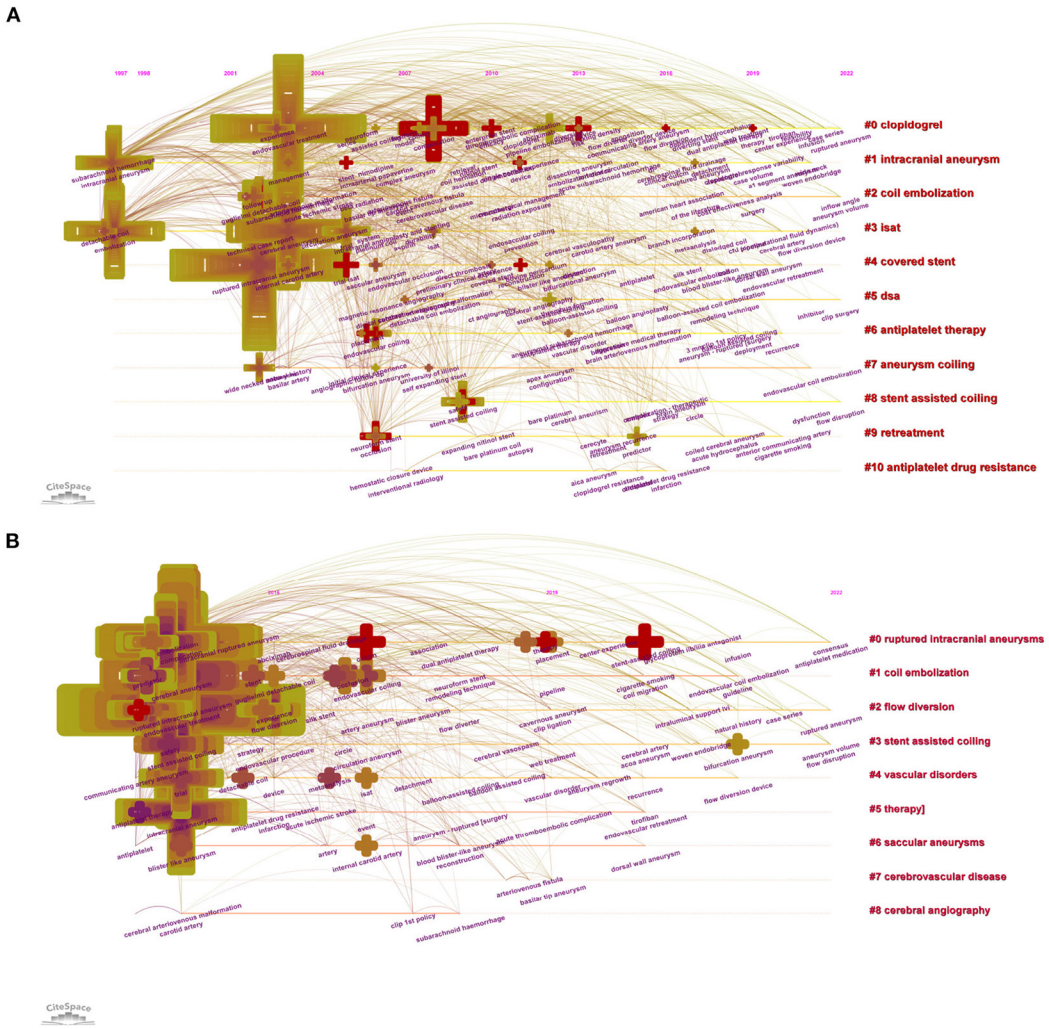


FIGURE 2
(A) Co-citation reference network with cluster visualization. The node's size (article) is proportional to the number of times the publication has been co-cited. **(B)** Visualization map of the corresponding clusters. Publication topics of the same type are clustered in the same color block.

NeuroInterventional Surgery (n = 25), Neurosurgery (n = 24), interventional Neuroradiology (n = 21), and World Neurosurgery (n = 16) (Figure 6A, Supplementary Table 4). The co-cited journal network over the past 20 years is shown in (Figure 6B). The American Journal of Neuroradiology, Neurosurgery, Journal of Neurosurgery, Stroke and Lancet were the top five journals that enjoyed the largest number of citations (Supplementary Table 5). This shows that the American Journal of Neuroradiology made the most outstanding contribution and had the greatest influence in this field.

Discussion

This study revealed the overall research results of stent application in acutely RIA in the past 25 years. The annual number of papers and literature trends may reflect the development speed and progress of research in this field. Before 2006, the number of publications in this field was roughly the same yearly. From 2006 to 2019, the number of publications increased obviously, reflecting the growing interest in this field, especially the evolution of materials and the safety in acutely RIA.



C

Top 14 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1997 - 2022
guglielmi detachable coil	1997	5.37	2002	2010	
neuroform stent	1997	4.94	2007	2013	
trial isat	1997	5.5	2010	2014	
endovascular coiling	1997	5.14	2010	2011	
reconstruction	1997	4.88	2011	2012	
stent	1997	3.33	2013	2018	
single center experience	1997	3.4	2014	2017	
outcm	1997	3.33	2014	2019	
stent assisted coiling	1997	3.79	2015	2016	
flow diversion	1997	3.52	2016	2022	
complication	1997	4.42	2017	2020	
therapy	1997	3.78	2019	2020	
risk	1997	3.59	2019	2022	
efficacy	1997	3.37	2019	2022	

FIGURE 3
Timeline visualization of co-occurring author keyword networks [**(A)** 1980–2021 and **(B)** 2015–2022]. The size of a cross is proportional to the burstness of keywords co-occurrence. The co-occurring keyword network is weighted on total link strength across different keyword nodes and scored on the mean publication years. The clusters are labeled in red at the right of the timeline maps. **(C)** Top14 keywords with the strongest citation bursts.

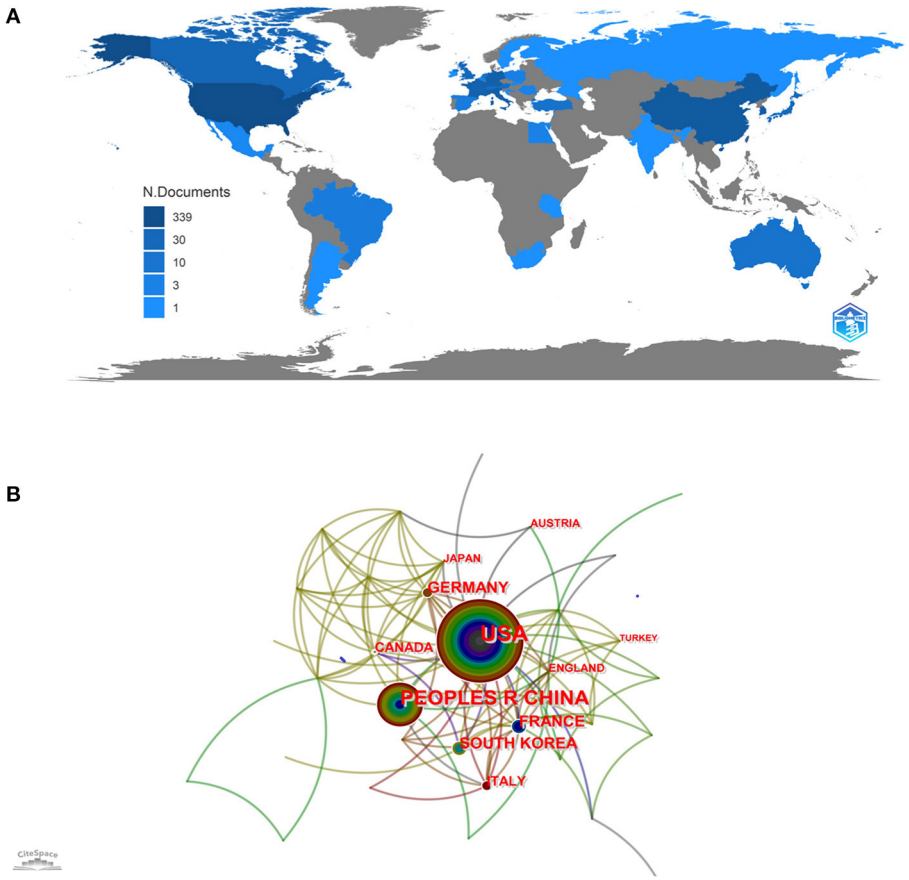


FIGURE 4
(A) Country-specific production. Dark blue = high productivity. Gray = no documents. **(B)** Country cooperation network map. The size of each node represents the number of publications published by the country, and the thickness of each link represents the strength of the cooperative relationship between two countries.

The co-cited references with the corresponding cluster network (1997–2022) described the coherent links between 13 different clusters and revealed the evolution of research trends about stent application in acutely RIA. The first trend was the evolution of materials, from liquid embolic agents to neuroform stents, then pipeline embolization devices and woven endobridge (WEB). The development of these new and exciting devices and materials has helped neurointerventionalists successfully treat aneurysmal SAH (16, 33, 34). But as the surface of the current stents is highly thrombotic, a dual antiplatelet regimen is required, which is still a controversial issue in the acute stage of SAH (35, 36). Therefore, the second major trend is the safety of stent application research in acutely RIA. In this aspect, the most concerned issues of researchers are the risk of increased hemorrhagic complications and acute stent thrombosis or even thromboembolic occlusion (37, 38), especially the ophthalmic artery (39). In addition, the focus on the past seven years showed that the latest research trends also aimed at developing materials and exploring technical security (Supplementary Figure 1). Analysis of the co-occurring keyword networks and burst keywords such as clopidogrel, ISAT, covered stent and antiplatelet resistance also verified these findings. The burst keywords in recent years, including flow diversion, complications, therapy, risk, and efficacy, also confirmed the current hot topic and research focus (Supplementary Figure 2). The safety and efficacy of stent application in acutely RIA have been a hot topic of discussion in recent years (32, 40, 41). Antiplatelet strategies have been found to be closely related to increased hemorrhagic complications. Furthermore, early use of anticoagulants after stent application in acutely RIA was identified as a risk factor for postoperative hemorrhagic complications. And dual antiplatelet agents were preferred by DELPHI consensus as a standard approach with aspirin and a glycoprotein IIb/IIIa receptor (35). Alternations based on anti-thrombogenic device coating might make stents used safely in the treatment of RIA (42). In terms of material selection, stents and coils made from LVIS and hydrogel are safer in the treatment of ruptured aneurysms because they

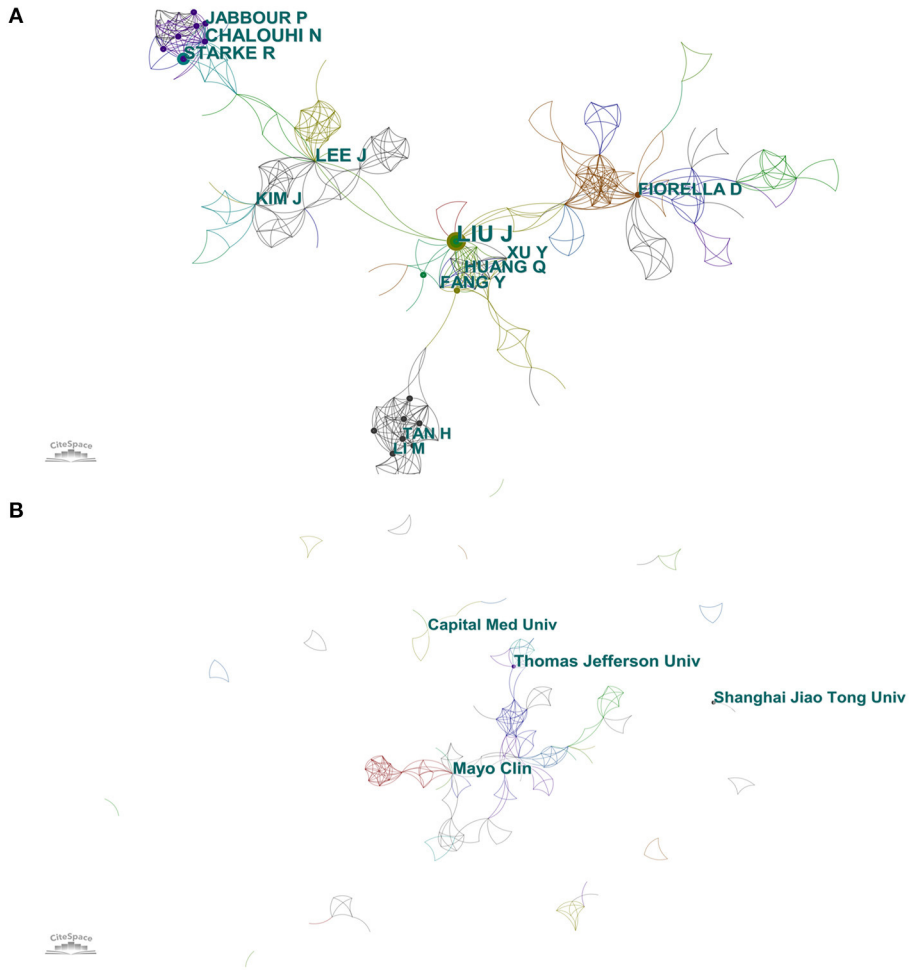


FIGURE 5
(A) Author cooperation network map. **(B)** Institution cooperation network map.

can provide a higher immediate embolization rate (43, 44). For blood blister-like aneurysms, FD was a more sensible choice at present, owing to its high metal coverage and the change in blood flow to promote intrasaccular thrombosis for better isolating blood from entering the aneurysm (45). Although a wealth of experience and treatment guidelines have been gleaned from 25 years of research into stent application in acutely ruptured intracranial aneurysms, many questions still need to be further addressed. Future research may focus on the development of novel stent materials which would reduce the reliance on antiplatelet drugs during the perioperative period and consequently reduce the potential risk of hemorrhagic complications.

As shown in Supplementary Table 1, the country with the most significant number of publications was the US. Centrality represents the algorithm that calculates unweighted shortest paths between all pairs of nodes in a graph. The US had the highest centrality of 0.87, indicating that the US occupied a leading position in this field. The further cluster analysis revealed that the US and the People's Republic of China mainly focused on preoperative evaluation of stent application in acutely RIA (46) (Supplementary Figure 3). The most productive author was Jianmin Liu, and the author team headed by him was mainly concerned with stent placement (1). Studies by other authors were more concerned with endobridge devices and balloon remodeling (47) (Supplementary Figure 4). Among the top ten research institutions, five were in the US, four were in the People's Republic of China, and the rest in South Korea. However, the centrality of institutions is low, indicating a lack of academic collaboration between institutions. Nevertheless, cluster analysis suggested that some institutional collaborations still contributed to the multicenter experience and perioperative preparation of stent application in acutely RIA (48) (Supplementary Figure 5). Publication source analysis can

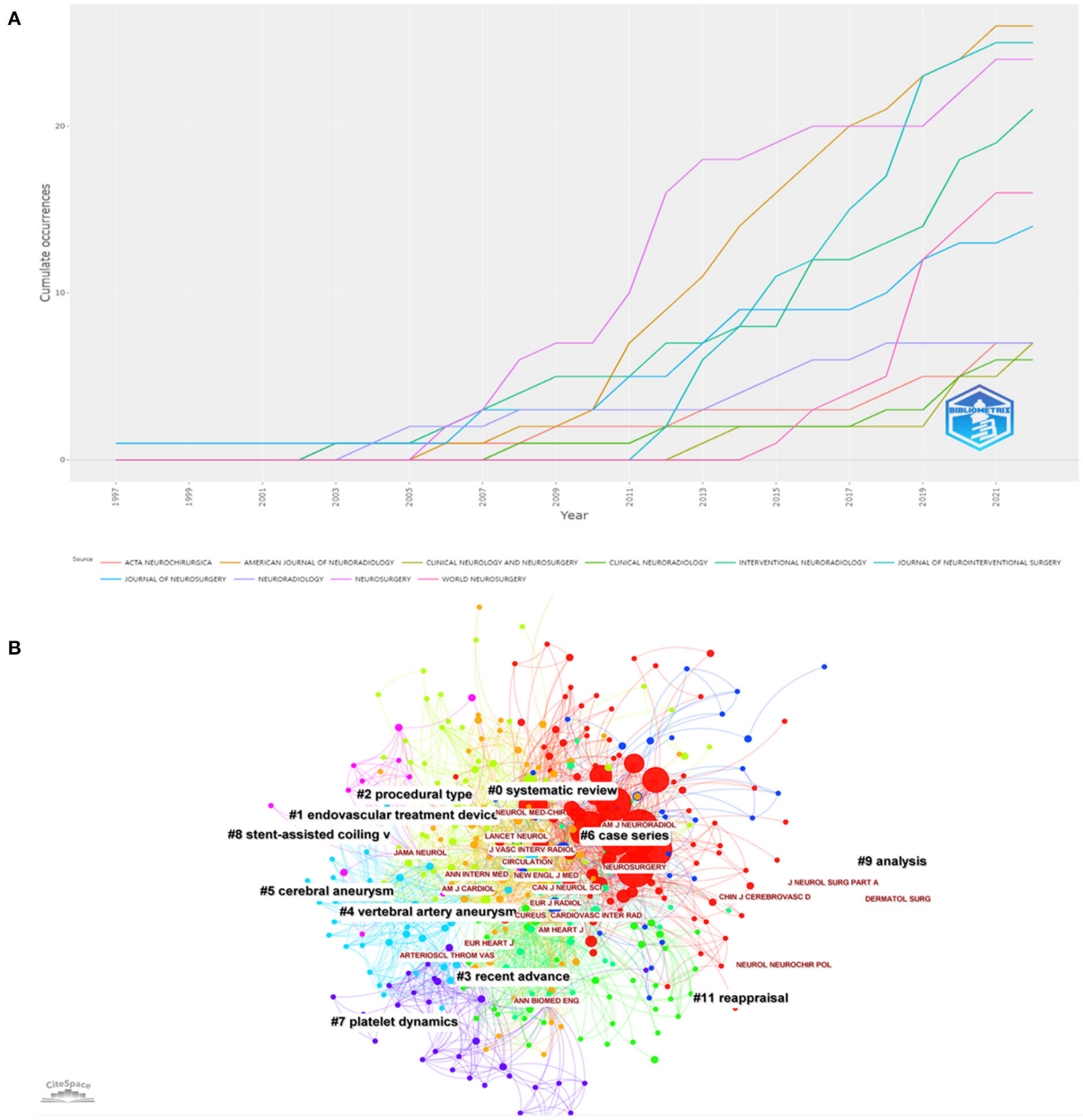


FIGURE 6
(A) Source growth of publications. **(B)** The co-cited journal network with cluster visualization.

help researchers identify core journals in their fields, and top-ranked co-cited journals can serve as authoritative references. The American Journal of Neuroradiology had the greatest number of articles published and the greatest number of articles cited simultaneously. In addition, those top co-cited and prolific journals mainly published systematic reviews, endovascular treatment devices, and recent advances in this field (29, 49) (Supplementary Figure 6).

This study inevitably had some limitations. The data were simply retrieved from the WoSCC database, which may lead to incomplete literature collection. In addition, the literature retrieved was limited to articles published in English, leading to some linguistic bias in the study results. With further research and exploration in this field, the findings of this study may be different from the realistic results in the future.

Conclusion

To the best of our knowledge, this is the first systematic and multidimensional analysis of the research trends, hotspots and frontiers of stent application in acutely RIA in an objective way, which we hope can be used as a comprehensive guide for clinicians and scholars engaged in this field, and help researchers get a clearer picture of their future research directions.

Data availability statement

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

Author contributions

RC, YW, and GZ made substantial contributions to the conception and design, acquisition of data, analysis, and drafting of the manuscript. QZ, JL, RZhang, XZ, DD, QL, RZhao, YX, QH, and PY assisted in the evaluation of analysis and their interpretation. All authors read and approved the final manuscript.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1029613/full#supplementary-material

SUPPLEMENTARY FIGURE 1
(A) Co-citation reference network with cluster visualization from 2015 to 2022. **(B)** Visualization map of the corresponding clusters from 2015 to 2022. **(C)** Timeline visualization of co-citation references network. **(D)** Top 12 references with the strongest citation bursts.

SUPPLEMENTARY FIGURE 2
Co-occurring author keyword networks with cluster visualization [**(A)** 1980–2021 and **(C)** 2015–2022]. Visualization map of the corresponding clusters [**(B)** 1980–2021 and **(D)** 2015–2022].

SUPPLEMENTARY FIGURE 3
(A) Country cooperation network with cluster visualization. **(B)** Timeline visualization of the country cooperation network.

SUPPLEMENTARY FIGURE 4
(A) Author cooperation network with cluster visualization. **(B)** Timeline visualization of the author cooperation network.

SUPPLEMENTARY FIGURE 5
(A) Institution cooperation network with cluster visualization. **(B)** Timeline visualization of the institution cooperation network.

SUPPLEMENTARY FIGURE 6
(A) Co-cited journal network map. **(B)** Timeline visualization of the co-cited journals network map.

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EDITED BY
Cong-Hui Li,
The First Hospital of Hebei Medical University, China

REVIEWED BY
Zhaohui He,
First Affiliated Hospital of Chongqing Medical University, China
Wenqiang Li,
First Affiliated Hospital of Zhengzhou University, China

*CORRESPONDENCE
Qiao Zuo
dr_zuo@126.com
Jianmin Liu
chstroke@163.com

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

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Stent-assisted coiling vs. coiling alone of ruptured tiny intracranial aneurysms: A contemporary cohort study in a high-volume center

Guanghao Zhang†, Yina Wu†, Yanpeng Wei†, Gaici Xue, Rundong Chen, Nan Lv, Xiaoxi Zhang, Guoli Duan, Ying Yu, Qiang Li, Yi Xu, Qinghai Huang, Pengfei Yang, Qiao Zuo* and Jianmin Liu*

Neurovascular Center, Changhai Hospital, Naval Medical University, Shanghai, China

Objective: This study aims to compare the safety and efficacy of stent-assisted coiling (SAC) with those of coiling alone (CA) for the treatment of ruptured tiny intracranial aneurysms.

Methods: We enrolled 245 patients with ruptured tiny intracranial aneurysms treated with coil embolization. Patients were grouped into SAC and CA groups. Baseline characteristics, periprocedural complications, clinical outcomes, and angiographic results were compared between the two groups. In addition, a subgroup analysis was conducted in the SAC group, and patients were regrouped into low-profile visualized intraluminal support (LVIS) and laser-cut groups to compare the perioperative procedure-related complications and clinical and angiographic follow-up outcomes.

Results: All baseline characteristics were equivalent between the two groups except for aneurysm size and dome-to-neck aspect ratio. The rates of overall procedure-related complications, intraprocedural rupture, postoperative early rebleeding, intraprocedural thrombosis, postprocedural thrombosis, and procedure-related mortality were comparable between the two groups (P = 0.105, 0.145, 0.308, 1.000, 1.000, 0.160, respectively). Nevertheless, the rate of hemorrhagic complication in the SAC group was significantly higher ($P = 0.023$). The angiographic follow-up outcomes showed that the SAC group had a higher complete occlusion rate and lower recurrence rate (88.2 vs. 67.1%, 5.4 vs. 15.2%, P = 0.001). The clinical outcomes at discharge and follow-up between the two groups demonstrated no significant differences ($P = 0.192$ and $P = 0.085$, respectively). For subgroup analysis, LVIS stents were associated with a significantly higher rate of complete occlusion ($P = 0.014$) and a lower rate of intraprocedural rupture ($p = 0.021$). Moreover, multivariate analysis showed that there were no predictors for the overall, hemorrhagic, and ischemic procedure-related complications, while Raymond class was an independent predictor of retreatment (OR = 3.508, 95% CI 1.168–11.603; $P = 0.029$).

Conclusion: Stent-assisted coiling may increase the incidence of hemorrhagic events with favorable angiographic results and comparable clinical outcomes compared with stand-alone coiling. Nevertheless, LVIS stent could improve the safety compared with lazer-cut stent. Simultaneously, considering the better long-term effect, LVIS stent-assisted coiling may be a preferable choice for ruptured tiny intracranial aneurysms.

KEYWORDS

endovascular treatment, tiny ruptured intracranial aneurysms, low-profile visualized intraluminal support stent, procedure-related complications, vascular disorders

Introduction

Subarachnoid hemorrhage (SAH) caused by ruptured intracranial aneurysms is one of the most common cerebrovascular diseases (1). Among patients with ruptured aneurysms, 6.2–15.1% are tiny intracranial aneurysms (2, 3). Notably, the unique structural characteristics of tiny intracranial aneurysms, such as very small size, thin aneurysm wall, and relatively wide neck, make it difficult and challenging for both clipping and endovascular treatment (4).

With the advances in neuroimaging and endovascular devices, several recent studies corroborated comparable effectiveness and better prognosis when using endovascular treatment as compared to microsurgical clipping (5, 6) for ruptured tiny intracranial aneurysms. Simultaneously, previous studies indicated that the stent-assisted coiling (SAC) technique was associated with a higher complete occlusion rate and lower recurrence rate at follow-up compared with coiling alone (CA) in ruptured intracranial aneurysms (7, 8). However, studies on aneurysm occlusion, recurrence, and procedural complication rates of SAC treatment for ruptured tiny intracranial aneurysms were limited and heterogeneous (9, 10). The safety and efficacy of SAC in the treatment of ruptured tiny intracranial aneurysms need to be further investigated.

Since its debut as an endovascular aid, Neuroform stents (Stryker, Kalamazoo, MI, USA) were quickly followed by other stents, and each stent targets aneurysms of specific shapes and parent patterns (11). Given the diversity of stents available, tailored therapeutics may be employed based on the angioanatomic conditions and configurations to improve perioperative safety and long-term sustainability. The low-profile visualized intraluminal support (LVIS) device (MicroVention, Tustin, CA, USA) is a self-expandable braided stent with higher metal coverage and less porosity than laser-cut stents (Enterprise, Neuroform stents, Solitaire stent, etc.). Our previous efforts suggested that perioperative procedure-related complications and aneurysm occlusion rates in intracranial aneurysms proved more favorable when using LVIS stents (7, 12). However, whether similar complications, angiographic outcomes, and clinical outcomes were achieved in ruptured tiny intracranial aneurysms subjected to LVIS SAC is not well-known.

In the present study, we compared SAC with CA in a high-volume center to further evaluate the safety and efficacy of SAC for the treatment of acutely ruptured tiny intracranial aneurysms. Then, we focused on the safety and efficacy of different stents, making a direct comparison between LVIS and laser-cut stents to comment on the periprocedural complications and occlusive status at follow-up. We further analyzed the in?uential factors associated with the perioperative complications and recurrence rate of these patients.

Methods

Study design

In this retrospective study, we collected the clinical data of 245 consecutive patients who were hospitalized for ruptured tiny intracranial aneurysms and treated endovascularly between January 2014 and December 2018 in our center. Among them, 93 patients underwent SAC, and 152 patients underwent CA. The study protocol was approved by the Ethics Committee of the Shanghai Changhai Hospital. Written informed consent was waived given the retrospective nature of the analysis.

The inclusion criteria were as follows: (1) Aneurysm rupture diagnosed by CT or lumbar puncture and ruptured tiny intracranial aneurysms diagnosed *via* digital subtraction angiography (DSA); (2) aneurysm treated within 28 days after SAH; (3) maximum aneurysm diameter was $\leq$3 mm *via* performing 3D rotational angiography; and (4) aneurysm treated by SAC or CA (including balloon-assisted coiling). The exclusion criteria were as follows: (1) Fusiform, traumatic, dissecting, pseudo-, and blood blister-like aneurysms; (2) reruptured aneurysms with previous treatment; (3) parent artery occlusion, simple stent placement alone, and coiling with other embolization materials; (4) multiple aneurysms but failed to identify the ruptured one; (5) staged stent placement; and (6) incomplete clinical data.

We collected baseline data from the patients, including age, sex, medical history, aneurysm location, preoperative Hunt-Hess grade, aneurysm size, Modified Fisher Grading Scale, and Modified Rankin Scale (mRS) score. In addition, other clinical data were also obtained on aneurysm size, dome-to-neck aspect ratio, and location.

An endovascular procedure and medications

All included patients were treated by eight endovascular neurosurgeons with experience of more than 10 years. All procedures were performed under general anesthesia. After systemic heparinization, rotational DSA and 3D reconstruction were performed routinely. The size of the aneurysm and the diameter of the distal and proximal aneurysmal parent artery were measured to select the appropriate coil and stent. During the procedures, the activated clotting time was maintained at 2–3 times the baseline level. All stents (LVIS, MicroVention Terumo, USA; Enterprise, Cordis, USA; Solitaire, Covidien, USA; Neuroform, Boston Scientific, USA) and coils were deployed according to the standard procedure recommended by the manufacturer. After the decision to deploy a stent was made, a loading dose of aspirin (300 mg) and clopidogrel (300 mg) was given orally or rectally to patients who had stent-assisted coil embolization. A loading dose (5 μg/kg for 3 min) of glycoprotein IIb/IIIa inhibitor (tirofiban; Grand Pharma, China) was intravenously injected to prevent platelet aggregation before stent release and maintained at a rate of 0.075 μg/kg/min for 6 h. For patients who underwent SAC, dual-antiplatelet therapy (100 mg aspirin and 75 mg clopidogrel) was maintained for 6 weeks after the procedure, followed by aspirin (100 mg) alone for at least 12 months. The antiplatelet protocol was adjusted according to the angiographic results and the patient's results of thromboelastography during the follow-up period. In case of acute thrombosis in the stent during the procedure, tirofiban was injected intraarterially at a dose of 0.075 ug/kg/min through a microcatheter. If intraprocedural rupture occurred, heparin was neutralized by using protamine sulfate immediately, and dense embolization of the aneurysm was performed as much as possible through packing coils quickly.

Clinical and angiographic follow-up

Clinical follow-up was typically scheduled at the 3rd, 6th, and 12th months, and the results were evaluated using the modified Rankin Scale (mRS). Favorable clinical outcomes were defined as an mRS score of 0 to 2, and poor clinical outcomes were defined as an mRS score of 3 to 6. Angiographic follow-up was assessed by magnetic resonance angiography or DSA routinely in the 6th month after the procedure and yearly thereafter and was classified using the Raymond–Roy occlusion classification. The cases in the CA group who underwent salvage stent placement because of coil protrusion were counted as the SAC group at follow-up.

Statistical analysis

Statistical analysis was performed using R version 4.1.3 software. Independent samples *t*-test, Pearson's χ^2 test, Fisher's exact test, or non-parametric test was used for statistical analysis as appropriate. Categorical variables were presented as frequency, and continuous variables were expressed as mean ± standard deviation ($x \pm s$) for normally distributed variables and median (IQR) for non-normally distributed variables, respectively. Univariate and multivariate analyses were performed to identify the association between procedure-related complications and predictive risk factors. The univariate analysis cutoff for inclusion in the multivariate analysis was $p < 0.20$. A p-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 245 patients with ruptured tiny intracranial aneurysms were enrolled in this study. The SAC group and CA group were statistically comparable with respect to age, sex, disease history, location, neck size, parent artery configuration, WNFS, Hunt-Hess, modified Fisher grading, interval between aneurysm rupture and procedure and surgery (Table 1). The SAC group had a smaller aneurysm size [median (IQR) 2.3 (1.9–2.6) vs. 2.5 (2.2, 2.8)] and a bigger dome-to-neck aspect ratio [1.180 (1.0–1.4) vs. 1.4 (1.1–1.7)] (Table 1).

Immediate embolization results and clinical outcomes at discharge

All stents were successfully deployed in the SAC group, whereas the salvage stent technique was used in 1 case (1.0%, 1/93) in the CA group due to the coil protrusion. The immediate angiographic results showed that Raymond class I was achieved in 59 cases (63.4%, 59/93), Raymond class II–III in 9 cases (9.7%, 9/93), and Raymond class III in 25 cases (26.9%, 25/93) in the SAC group, compared with 85 cases (55.9%, 85/152), 41 cases (27.0%, 41/152), and 26 cases (17.1%, 26/152) in the CA group, respectively, which showed no statistically significant difference between the two groups ($P = 0.078$). A total of 89.25% (83/93) of patients in the SAC group and 82.2% (125/152) of patients in the CA group had favorable neurological outcomes at discharge,

TABLE 1 Characteristics of patients at baseline.

Characteristics	Group		*P*-value
	SAC ($n = 93$)	CA ($n = 152$)	
Age, yrs	55.366 (10.410)	55.855 (12.592)	0.753
Sex			
Female	59 (63.44)	94 (61.84)	0.909
Male	34 (36.56)	58 (38.16)	
Hypertension, *n* (%)	44 (47.31)	82 (53.95)	0.381
Coronary heart disease, *n* (%)	3 (3.23)	5 (3.29)	1.000
Diabetes mellitus, *n* (%)	7 (7.53)	10 (6.58)	0.981
Smoking (%)	10 (10.75)	20 (13.16)	0.721
intracranial hematoma (%)	10 (10.75)	17 (11.18)	
Size(median [IQR])	2.300 [1.940, 2.620]	2.500 [2.152, 2.762]	0.007
Neck (median [IQR])	1.900 [1.500, 2.260]	1.815 [1.400, 2.092]	0.160
Dome-to-neck aspect ratio (median [IQR])	1.180 [1.010, 1.360]	1.360 [1.128, 1.662]	0.000
Intraventricular hematoma (%)	29 (31.18)	48 (31.58)	
Location (%)			
ICA	20 (21.51)	14 (9.21)	0.074
PcomA	20 (21.51)	26 (17.11)	
ACA	6 (6.45)	14 (9.21)	
AcomA	32 (34.41)	71 (46.71)	
MCA	9 (9.68)	19 (12.50)	
PC	6 (6.45)	8 (5.26)	
Parent artery configuration			
Bifurcation	47 (50.54)	87 (57.24)	0.374
Side wall	46 (49.46)	65 (42.76)	
WFNS (%)			
1	65 (69.89)	106 (69.74)	0.306
2	14 (15.05)	13 (8.55)	
3	3 (3.23)	3 (1.97)	
4	8 (8.60)	20 (13.16)	
5	3 (3.23)	10 (6.58)	
Hunt-Hess (%)			
1	11 (11.83)	18 (11.84)	0.613
2	47 (50.54)	68 (44.74)	
3	29 (31.18)	49 (32.24)	
4	6 (6.45)	17 (11.18)	
modified Fisher grade (%)			
1	18 (19.35)	35 (23.03)	0.221
2	62 (66.67)	82 (53.95)	
3	9 (9.68)	26 (17.11)	
4	4 (4.30)	9 (5.92)	
Interval between aneurysm rupture and procedure			
<72 h	60 (64.52)	111 (73.03)	0.303
72 h−14 d	30 (32.26)	35 (23.03)	
>14 d	3 (3.23)	6 (3.95)	
Surgery			
EVD	9 (9.68)	12 (7.89)	1.000
VP shunt	3(3.23)	4(2.61)	1.000
Other	3(3.23)	2(1.32)	0.373

mm, millimeter; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; ACoA, anterior communicating artery; PCoA, posterior communicating artery; PC, posterior circulation; EVD, external ventricular drainage; VP shunt, ventriculoperitoneal shunt.
Unless indicated otherwise, data are presented as the number of patients (%).

TABLE 2 Angiographic and clinical outcomes for patients treated with SAC and CA.

Outcomes	Group		*P*-value
	SAC ($n = 93$)	CA ($n = 152$)	
Immediate embolization result			
Raymond class I	59 (63.44)	85 (55.92)	0.246
Raymond class II-III	34 (36.56)	67 (44.08)	
Clinical outcome at discharge			
mRS score 0 to 2	83 (89.25)	125 (82.24)	0.193
mRS score 3 to 6	10 (10.75)	27 (17.76)	
Angiographic follow-up			
Complete occlusion	66 (89.19)	57 (67.06)	0.001
Improvement	2 (2.70)	1 (1.18)	
Stability	2 (2.70)	14 (16.47)	
Recurrence	4 (5.4)	13 (15.29)	
Retreatment	1 (1.35)	9 (10.59)	0.094
Clinical follow-up[a]			
mRS score 0 to 2	80 (97.56)	124 (90.51)	0.085
mRS score 3 to 6	2 (2.44)	13 (9.49)	
Clinical follow-up[b]			
mRS score 0 to 2	80 (88.89)	124 (84.35)	0.432
mRS score 3 to 6	10 (11.11)	23 (15.65)	

a Excluding patients who died at discharge.
b Including patients who died at discharge.

showing no statistically significant difference between the two groups ($P = 0.193$) (Table 2).

In the SAC group, Raymond class I and Raymond class II-III were achieved in 45 (67.2%) and 22 (22.84%) patients treated with LVIS and were achieved in 14 (53.9%) and 12 (46.2%) patients treated with laser-cut stents, which showed no significant difference between the two groups ($P = 0.33$); 59 (88.1%) patients treated with LVIS had an mRS of 0 to 2

TABLE 3 Angiographic and Clinical Outcomes for patients treated with LVIS and laser-cut stent.

Outcomes	Group		*P*-value
	LVIS ($n = 67$)	Laser-cut ($n = 26$)	
Immediate embolization result			
Raymond class I	45 (67.16)	14 (53.85)	0.339
Raymond class II-III	22 (32.84)	12 (46.15)	
Clinical outcome at discharge			
mRS score 0 to 2	59 (88.06)	24 (92.31)	0.825
mRS score 3 to 6	8 (11.94)	2 (7.69)	
Angiographic follow-up			
Complete occlusion	51 (94.44)	15 (75.00)	0.014
Improvement	0 (0.00)	2 (10.00)	
Stability	2 (3.70)	0 (0.00)	
Recurrence	2 (3.6)	2 (10.0)	
Retreatment	0 (0.00)	1	0.257
Clinical follow-up[a]			
mRS score 0 to 2	58 (96.7)	22 (100)	1.000
mRS score 3 to 6	2 (3.33)	0 (0)	
Clinical follow-up[b]			
mRS score 0 to 2	58 (87.9)	22 (91.7)	1.000
mRS score 3 to 6	8 (12.1)	2 (8.3)	

TABLE 4 Perioperative Complications for patients treated with SAC and CA.

Perioperative complications	Group		*P*-value
	SAC ($n = 93$)	CA ($n = 152$)	
Procedure-related complications	11 (11.8)	8 (5.3)	0.105
Hemorrhagic	8 (8.60)	3 (1.97)	0.023
Intraprocedural rupture	5 (5.38)	2 (1.32)	0.145
Postprocedural early rebleeding	3 (3.23)	1 (0.66)	0.308
Surgical procedure-related hemorrhagic event	0	0	1
Ischemic	3 (3.23)	5 (3.29)	1
Intraprocedural thrombosis	2 (2.15)	4 (2.63)	1
Postprocedural thrombosis	1 (1.1)	1 (0.7)	1
Coil protrusion	0	0	1
Salvage technique	0	1 (0.7)	1
Cerebral vasospasm	6 (6.5)	14 (9.2)	0.599
Procedure-related mortality	5 (5.38)	3 (1.97)	0.160

Unless indicated otherwise, data are presented as the number of patients (%).

compared with 24 (92.3%) patients treated with laser-cut stents without statistical significant difference ($P = 0.83$) (Table 3).

Periprocedural complications and mortality

Overall, perioperative procedure-related complications occurred in 11 patients (11.8%, 11 of 93) in the SAC group and in eight patients (5.3%, 8 of 152) in the CA group, which were comparable ($p = 0.106$). Specifically, the hemorrhagic complication rate of the SAC group was higher than those of the CA group ($P = 0.023$), while the ischemic complications were comparable ($P > 0.99$).

For hemorrhagic complications, intraprocedural rupture, aneurysm rebleeding, and surgical procedure-related hemorrhagic events occurred in five patients (3.0%, 4 of 133), three patients (1.5%, 2 of 133), and no patient (0.8%, 1 of 133) of the SAC group and two patients (1.0%, 3 of 289), one patient (1.4%, 4 of 289), and no patient of the CA group, respectively ($P = 0.145$, $P = 0.308$, and $P > 0.99$, respectively).

For ischemic complications, intraprocedural thrombosis and postprocedural thrombosis occurred in two patients (2.2%, 2/93) and one patient (1.1%, 1/93) of the SAC group, respectively, compared with four patients (2.6%, 4/152) and no patient of the CA group, respectively ($P > 0.99$ and $P = 0.804$, respectively).

Procedure-related mortality rates for patients who had the above complications were 5.4% (5/92) in the SAC group (four cases of aneurysm rebleeding and one case of postprocedural thrombosis) and 1.97% (3/152) in the CA group (two cases of intraoperative rupture and one case of postoperative rebleeding). No coil protrusion into the parent artery occurred (Table 4).

Among the patients who were treated with SAC, overall procedure-related complications were more common in patients with laser-cut stents than in those with LVIS without statistical significance (23.1%, 6/26 vs. 7.5%, 5/67, $P = 0.067$). The hemorrhagic complication rates in the LVIS group (4.4%, 5/67) were significantly lower compared with the laser-cut group (23.1%, 6/26) ($P = 0.031$), while the ischemic complication rates were similar. Regarding hemorrhagic complications, an intraprocedural rupture occurred in one patient in the LVIS group and four patients in the laser-cut group ($P = 0.021$). Postprocedural early rebleeding occurred in 2 patients (1.5%) in the LVIS group and one patient (3.8%) in the laser-cut group, but the difference was not statistically significant ($P > 0.99$). For ischemic complications, intraprocedural thrombosis and postprocedural thrombosis occurred in two patients (3.0%) and no patient in the LVIS group, compared with no patient and one patient (3.8%) in the laser-cut group ($P > 0.99$ and $=0.280$, respectively). Patients with LVIS carried a slightly

TABLE 5 Perioperative Complications for patients treated with LVIS and laser-cut stent.

Perioperative complications	Group		*P*-value
	LVIS ($n = 67$)	Lazer-cut ($n = 26$)	
Procedure-related complications	5 (7.5)	6 (23.1)	0.067
Hemorrhagic	3 (4.4)	5 (19.2)	0.036
Intraprocedural rupture	1 (1.5)	4 (15.4)	0.021
Post-procedural early rebleeding	2 (3.0)	1 (3.8)	1.000
Surgical procedure-related hemorrhagic event	0	0	1.000
Ischemic	2 (3.0)	1 (3.8)	1.000
Intraprocedural thrombosis	2 (3.0)	0	1.000
Postprocedural thrombosis	0	1 (3.8)	0.280
Cerebral vasospasm	4 (6.0)	2 (7.7)	0.671
Procedure-related mortality	2 (3.0)	3 (11.5)	0.131

lower procedure-related mortality (3.0 vs. 11.5%); however, this difference was not statistically significant ($P = 0.131$) (Table 5).

Clinical and angiographic follow-up

In total, eight patients in the SAC group and 10 patients in the CA group passed away before discharge. Therefore, a total of 227 patients survived the initial SAH at discharge. Among them, 159 patients (70.0%, 159 of 227) had been followed up angiographically, ranging from 6 to 2,260 days (mean, 423 days). Angiographic follow-up data demonstrated that complete occlusion, improvement, stability, recurrence, and retreatment were achieved in 66 cases (89.2%, 66 of 74), two cases (2.7%, 2 of 74), two cases (2.7%, 2 of 74), four cases (5.4%, 4 of 74), and one case (1.4%, 1 of 74), respectively, in the SAC group compared with 57 cases (67.1%, 57/85), one case (1.2%, 1/85), 14 cases (16.5%, 14/85), 13 cases (15.3%, 13/85), and nine cases (10.6%, 9/85), respectively, in the CA group. The SAC group showed a higher complete occlusion rate and a lower recurrence rate than the CA group ($P < 0.001$) (Table 2, Figures 1, 2).

Among these surviving patients, 219 patients (96.5%, 219 of 227) had been followed up clinically for 180 to 2,304 days (mean, 1,305 days); of which, four patients (4.7%, 4 of 86) had poor neurological outcomes (mRS score of 3–6) in the SAC group, whereas 13 patients (10.0%, 13 of 130) had poor neurological outcomes in the CA group ($P = 0.242$). All parent arteries were patent without clinically significant in-stent stenosis, and no aneurysm rebleeding or thrombosis events occurred during the follow-up period (Table 2).

For the SAC group, at least one angiographic follow-up was performed in 54 patients (80.6%, 54/67) in the LVIS group and 21 patients (76.9%, 20/26) in the laser-cut group. Follow-up angiograms showed complete occlusion in 51 cases (94.44%,51/54), improvement in no (0%, 0/54) case, stability in 2 (3.7%, 2/54) cases, and recurrence in one case (1.85%, 1/54) in the LVIS group, compared with 15 cases (75.0%, 15/20), two cases (10.0%, 2/20), no case (0%, 0/20), 3 cases (15.0%, 3/20) in the laser-cut group, showing statistically significant difference between the two groups ($P = 0.014$) (Table 3).

Multivariate analysis for risk factors of procedure-related complications

Univariate analysis showed that the intracranial hematoma ($P = 0.018$), intraventricular hematoma ($P = 0.157$), sidewall ($P = 0.18$), and SAC group ($P = 0.074$) were associated with overall perioperative procedure-related complications; intracranial hematoma ($P = 0.001$), intraventricular hematoma ($P = 0.028$), external ventricular drainage ($P = 0.11$), and SAC group ($P = 0.074$) were associated with hemorrhagic procedure-related complications; smoking ($P = 0.105$), size ($P = 0.102$), SAC group ($P = 0.054$), Raymond class ($P = 0.027$), and the interval between aneurysm rupture and procedure ($P = 0.172$) were associated with retreatment; and no risk factor was associated with ischemic procedure-related complications. Moreover, multivariate analysis showed that there were no predictors for the overall, hemorrhagic, and ischemic procedure-related complications, while Raymond class was an independent predictor of retreatment (OR = 3.508, 95% CI 1.168–11.603; $P = 0.029$).

Discussion

In this single-center retrospective cohort study, perioperative complications and treatment outcomes of tiny ruptured intracranial aneurysms were compared between the SAC group and the CA group. Moreover, in the SAC group, a direct comparison between LVIS and laser-cut stents was conducted to assess the effect between these two stents on the periprocedural safety and occlusive status during follow-up. The procedure-related hemorrhagic complication rate was higher in the SAC group than that in the CA group, whereas the ischemic complication rate was comparable. Moreover, the SAC group showed a significantly higher complete occlusion rate and a significantly lower retreatment rate compared with the CA group at follow-up. The favorable clinical outcome rate was similar in both groups. Further analysis indicated that although the univariate analysis showed

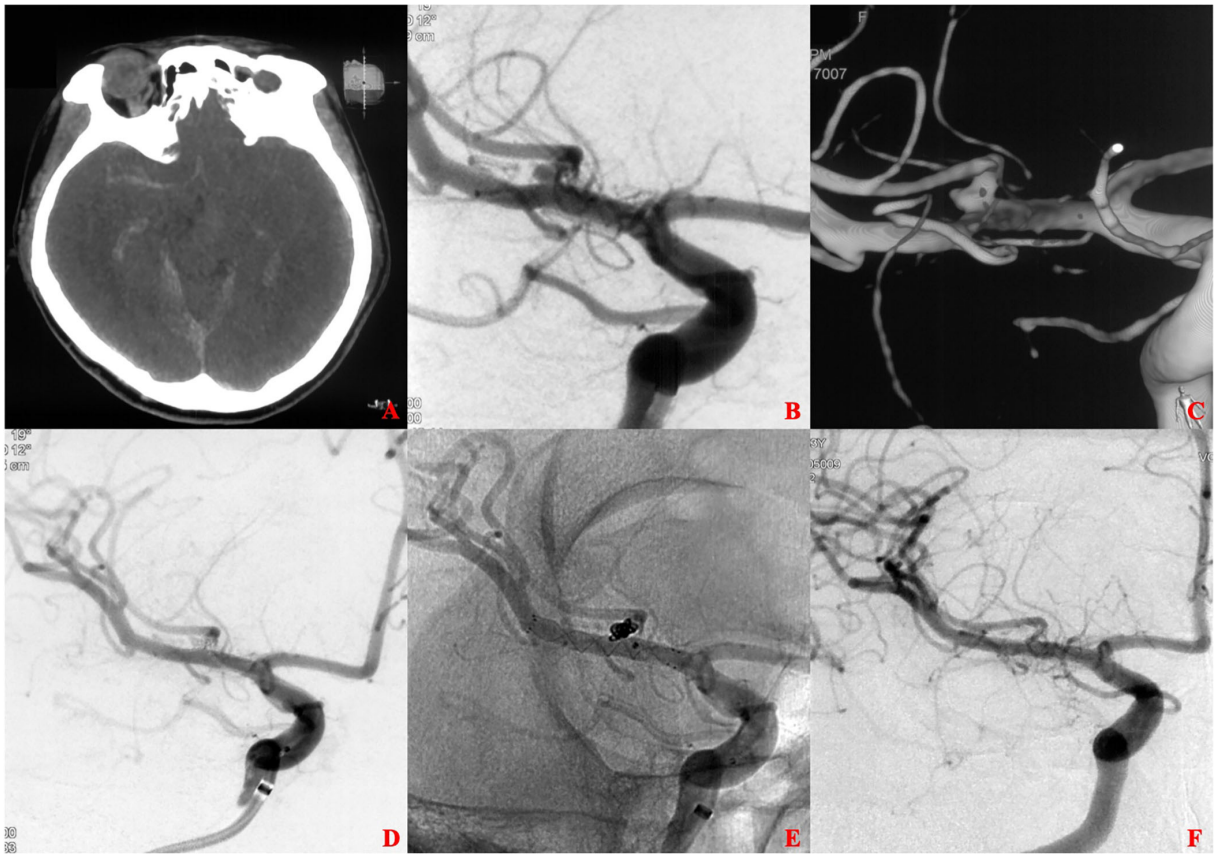

FIGURE 1
A ruptured tiny middle cerebral artery (MCA) intracranial aneurysm treated with stent-assisted coiling (SAC). **(A)** The patient was admitted with spontaneous subarachnoid hemorrhage. **(B,C)** Cerebral angiography and 3D reconstruction revealed a tiny MCA bifurcation aneurysm. **(D,E)** The aneurysm was treated with SAC embolization using an LVIS stent (3.5 × 15 mm). Immediate angiography showed that the aneurysm was completely occluded. **(F)** 13 months later, angiographic images showed complete occlusion of the aneurysm without in-stent artery stenosis.

an increased incidence of procedure-related hemorrhagic events in the SAC group, the multivariate analysis showed that SAC was not an independent risk factor. Besides, the multivariate analysis also showed that SAC was not a predictor for overall perioperative procedure-related complications and ischemic procedure-related complications of acutely ruptured tiny intracranial aneurysms. Among the SAC group, we observed significantly lower overall procedure-related complications, hemorrhagic complications, and intraprocedural aneurysm rupture in the LVIS group than those in the laser-cut group. In addition, follow-up angiographic results suggested that LVIS SAC was associated with a higher occlusion rate compared with laser-cut SAC. Favorable clinical outcomes at discharge and during long-term follow-up were comparable between the two groups of different stents. Summarizing these results, SAC might increase the risk of intracranial hemorrhagic events; however, these were mostly minor incidents associated with low morbidity. In addition, the SAC strategy has better long-term angiographic outcomes when compared to the CA strategy. When considering only patients treated with SAC, our cohort showed that LVIS SAC performed more safely and effectively than the laser-cut SAC for the treatment of tiny ruptured intracranial aneurysms.

Consistent with previous reports (9, 13), the majority of tiny aneurysms in our series were wide-necked. To avoid coil protrusion into the parent vessel and subtotal occlusion of the aneurysm, several studies reported that the aneurysm with a wider neck is more likely to use the SAC technique (14, 15). In addition, the very small size of tiny aneurysms limits the operation space of the microcatheter tip and has higher requirements for the stability of delivery systems (16, 17). Therefore, for the aneurysm with a relatively smaller size, to reduce the risk of intraoperative rupture, our center prefers to use SAC. The comparison of background characteristics between SAC and CA groups in our cohort demonstrated the expected differences. The variability of treatment strategy reflects the skill and experience of the operator and highlights the lack of specific

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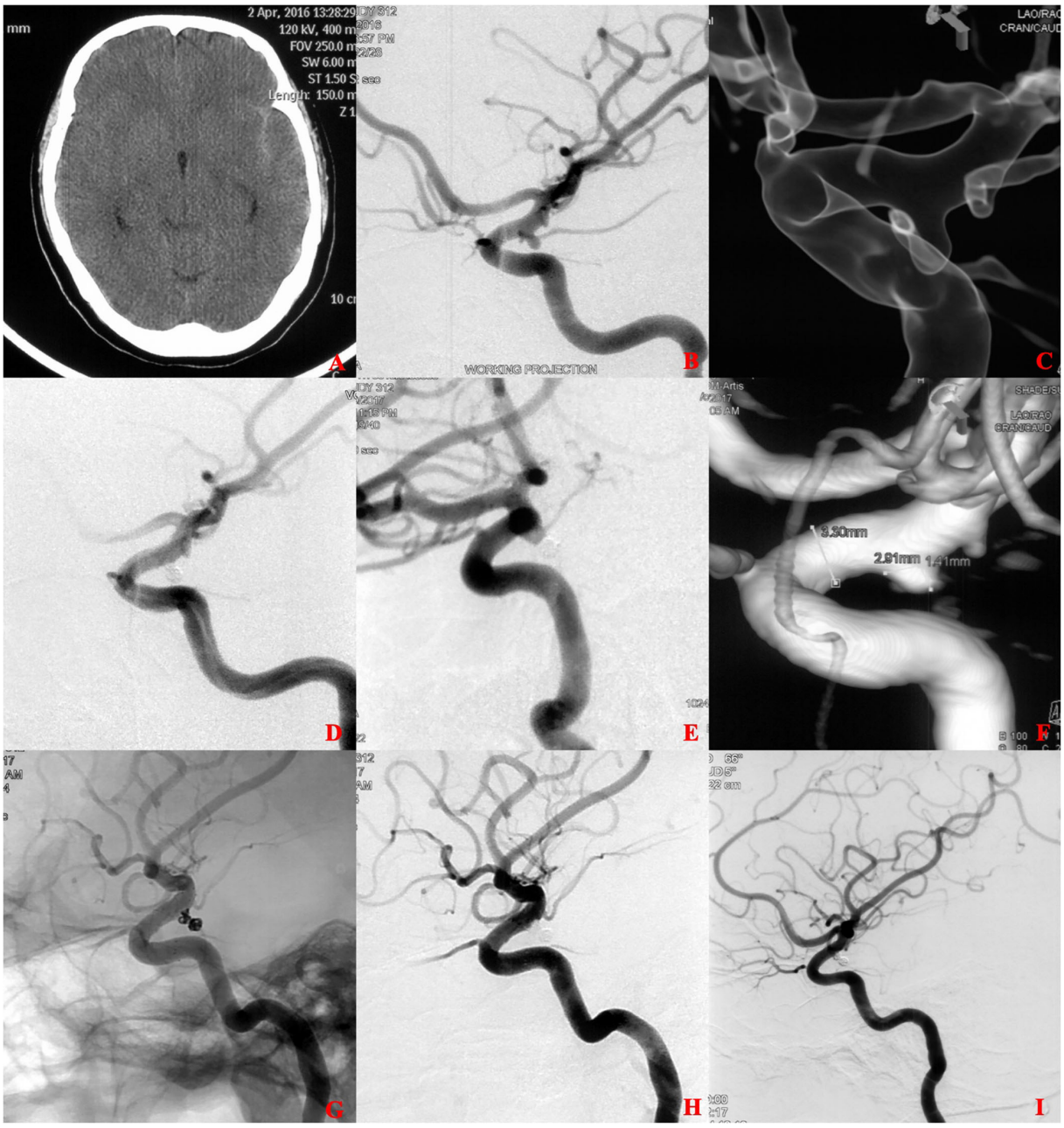

FIGURE 2
A ruptured tiny posterior communicating artery (PCOM) aneurysm treated with coiling alone (CA). **(A)** The patient was admitted with spontaneous subarachnoid hemorrhage. **(B,C)** Cerebral angiography and 3D reconstruction revealed a tiny PCOM aneurysm. **(D)** The aneurysm was treated with coiling embolization only. Immediate angiography showed that the aneurysm was completely occluded. **(E,F)** 6 months later, angiographic images showed postoperative recurrence of the aneurysm. **(G,H)** The aneurysm retreated with additional coiling embolization and an LVIS stent (4.5 × 15 mm). Immediate angiography showed that the aneurysm was completely occluded. **(I)** 12 months later, angiographic images showed complete occlusion of the aneurysm.

evidence on which structural characteristics of RIA are suitable for SAC.

Endovascular treatment-related hemorrhagic events and thromboembolism are the most common complications of morbidity and mortality caused by intravascular treatment of intracranial aneurysms. Ruptured intracranial aneurysms seem to be more susceptible to endovascular treatment-related hemorrhagic events than unruptured lesions (18). In addition, SAC, which requires antiplatelet medication in the setting of acutely ruptured aneurysms, increases the theoretical risk of

hemorrhagic complications. A multicenter retrospective cohort confirmed this concern. The authors reported that the aneurysm rebleeding rate in the SAC group was significantly higher than that of the CA group (17.4 vs. 1.9%, $P < 0.007$) (19). A meta-analysis of eight retrospective cohort studies with 909 RIA patients who underwent CA and 499 RIA patients who underwent SAC suggested the incidence of hemorrhagic events increased in the SAC group (OR 1.6, 95% CI 1.1–2.4, $P = 0.319$), but the favorable clinical outcome rate was comparable between the two groups (OR 0.95, 95% CI 0.88–1.02, $P = 0.338$) (20). In the present study, the risk of hemorrhagic complications was significantly higher in the SAC group than in those under CA therapy. In the SAC group, hemorrhagic events occurred in eight patients. Among them, one patient died before discharging due to a poor clinical grade at presentation and comorbidity. Of the remaining seven patients, five had good outcomes (MRS 0–2) at discharge, and two had poor outcomes (mRS 3–6). MRS of all patients did not improve during the follow-up period. In the CA group, three patients experienced hemorrhagic complications and had poor outcomes at discharge. Among them, two patients died due to multiple organ failures during the follow-up period, and one patient had no change in clinical outcome. A total of 86 patients in the SAC group and 122 patients in the CA group received clinical follow-up. The favorable clinical outcome rate at follow-up was similar between the two groups (84/86 vs. 119/122, 97.67 vs. 97.54%, $P = 1.000$), which was consistent with previous studies (7). Another two studies suggested that antiplatelet medication during SAH increased the risk of ventriculostomy-related hemorrhagic complications, but without further impact on the course and outcome of SAH (21, 22). Nevertheless, in our study, probably due to the limited sample size, there were no surgery-related hemorrhagic complications in the two groups, and this issue needs to be further investigated. On the contrary, thromboembolic complications of SAC are also a matter of concern. Several early studies showed that perioperative thromboembolic risk increased in the SAC group (23, 24). However, the recent reports for endovascular treatment of tiny ruptured intracranial aneurysms showed a low thromboembolic complication rate in both SAC and CA groups without a significant difference between them (10, 13). In the present study, our results further confirm this observation.

The performance of each stent type depends on structures or manufacturing processes, showing different behaviors in delivery method, neck protection, and flow diversion. When it comes to the SAC group, various clinical and angiographic outcomes in braided and laser-cut SAC for intracranial aneurysms have been observed in several studies (12, 25, 26). Nevertheless, the performance of these two stent types in terms of perioperative procedure-related complications is still controversial. Ge et al. reported 96 intracranial aneurysms in the braided stent (LVIS) group and 159 aneurysms in the laser-cut stent (Enterprise) group and found that the rate of hemorrhagic complication and thromboembolic events was comparable between the two groups (25). In addition, similar results have been reported in other studies (27, 28). According to our present study, intraprocedural rupture rates of patients treated with SAC proved significantly lower when using LVIS stent (vs laser-cut stent) ($P = 0.02$), and thromboembolism rates were slightly lower without statistical significance ($P = 1.000$). Our previous study on ruptured aneurysms observed similar results regarding periprocedural safety for treated aneurysms involving LVIS and laser-cut stents (12). Compared with laser-cut stents, smaller coils are available to be combined with LVIS stents with smaller mesh to improve the safety of the procedure. This factor may account for the highly statistically significant increase in the rate of intraprocedural rupture for laser-cut stents. To prevent thromboembolism, the modified antiplatelet regimen described in previous studies was adopted in our center (12). In the present study, the thromboembolism rates were comparable between LVIS and laser-cut groups and lower than those reported previously (12, 29, 30).

Our results agree with previous studies showing an immediate complete occlusion rate of 40.6–69.0% and a follow-up complete occlusion rate of 60.0–91.7% after SAC of ruptured tiny aneurysms (13, 31–33). In addition, we observed that the immediate complete occlusion rate in the SAC groups was higher than that in the CA group (63.44% vs. 55.92), although the difference was not significant ($P = 0.246$); the follow-up complete occlusion rate was significantly higher (88.19 vs. 67.06%, $P = 0.001$); and the retreatment rate was significantly lower (1.35 vs. 10.59%, $P = 0.004$) when using SAC treatment. These results are possible due to a continuous thrombosis process toward a more complete occlusion in the SAC group.

The low-profile visualized intraluminal support improves flow diversion effect and promotes reendothelialization due to its higher metal coverage (23%) and smaller mesh (1 mm) compared with laser-cut stents, theoretically, which could promote delayed aneurysm thrombosis and obtain a favorable occlusion rate in long-term follow-up (34). Nevertheless, a recent systematic review showed that the follow-up complete occlusion and recurrence in the LVIS group were comparable with the laser-cut group ($P = 0.454$, 0.056, respectively) (26). Lim et al. (35) reported a cohort study and demonstrated similar outcomes in follow-up and recurrence rates between the LVIS group and the Enterprise group. Our cohort study showed that for ruptured tiny intracranial aneurysms, patients treated with LVIS yielded significantly higher follow-up complete occlusion and lower recurrence rates ($P = 0.014$), while the retreatment rate was lower without statistical significance ($P = 0.27$). The results were similar to those reported by previous studies (25, 28). Notably, although the recurrence rate was higher in the laser-cut group compared with the LVIS group in the present study (10.0%), it was still comparable with previous studies on aneurysms treated with laser-cut stents (25, 36, 37).

The present study has some limitations. First, this study from one single center is non-randomized and retrospective, with an inherent selection bias. Second, our findings need to be

interpreted with caution due to the relatively small sample size of each stent group and the low incidence of retreatment.

Conclusion

Stent-assisted coiling may increase the incidence of hemorrhagic events with favorable angiographic results and similar clinical outcomes compared with stand-alone coiling. Nevertheless, LVIS stent appears to improve the safety compared with lazer-cut stent. Simultaneously, considering the better long-term effect, LVIS SAC may be a preferable choice for ruptured tiny intracranial aneurysms. Prospective studies with larger sample sizes are needed to further confirm the safety and efficacy of the SAC treatment.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of the Changhai Hospital of Naval Medical University (No. CHEC2022-149). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Conception or design of the work: JL and QZ. Acquisition of data: RC, GX, and NL. Analysis of data: QL, XZ, and GD. Interpretation of data: PY and QH. Drafting the work: GZ and YWu. Revising the work: YX, YY, and QZ. Final approval of the version: JL. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Cong-Hui Li,
The First Hospital of Hebei Medical University, China

REVIEWED BY
Kun Zhang,
Henan Provincial People's Hospital, China
Jonathan Cortese,
Bicêtre Hospital, France
Justin Moore,
Beth Israel Deaconess Medical Center and Harvard Medical School, United States

*CORRESPONDENCE
Qiao Zuo
✉ dr_zuo@126.com
Jianmin Liu
✉ chstroke@163.com

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

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Comparison of staged-stent and stent-assisted coiling technique for ruptured saccular wide-necked intracranial aneurysms: Safety and efficacy based on a propensity score-matched cohort study

Guanghao Zhang†, Renkun Zhang†, Yanpeng Wei†, Rundong Chen, Xiaoxi Zhang, Gaici Xue, Nan Lv, Guoli Duan, Chuanchuan Wang, Ying Yu, Dongwei Dai, Rui Zhao, Qiang Li, Yi Xu, Qinghai Huang, Pengfei Yang, Qiao Zuo* and Jianmin Liu*

Neurovascular Center, Changhai Hospital, Naval Medical University, Shanghai, China

Background: Application of stent-assisted coiling and FD in acute phase of ruptured wide-necked aneurysms is relatively contraindicated due to the potential risk of ischemic and hemorrhagic complications. Scheduled stenting after initial coiling has emerged as an alternative paradigm for ruptured wide-necked aneurysms. The objective of this study is to evaluate the safety and efficacy of a strategy of staged stent-assisted coiling in acutely ruptured saccular wide-necked intracranial aneurysms compared with conventional early stent-assisted coiling strategy *via* propensity score matching in a high-volume center.

Methods: A retrospective review of patients with acutely ruptured saccular wide-necked intracranial aneurysms who underwent staged stent-assisted coiling or conventional stent-assisted coiling from November 2014 to November 2019 was performed. Perioperative procedure-related complications and clinical and angiographic follow-up outcomes were compared.

Results: A total of 69 patients with staged stent-assisted coiling and 138 patients with conventional stent-assisted coiling were enrolled after 1:2 propensity score matching. The median interval time between previous coiling and later stenting was 4.0 weeks (range 3.5–7.5 weeks). No rebleeding occurred during the intervals. The rate of immediate complete occlusion was lower with initial coiling before scheduled stenting than with conventional stent-assisted coiling (21.7 vs. 60.9%), whereas comparable results were observed at follow-up (82.5 vs. 72.9%; $p = 0.357$). The clinical follow-up outcomes, overall procedure-related complications and procedure-related mortality between the two groups demonstrated no significant differences ($P = 0.232$, $P = 0.089$, $P = 0.537$, respectively). Multivariate analysis showed that modified Fisher grades (OR = 2.120, $P = 0.041$) were independent predictors for overall procedure-related complications and no significant predictors for hemorrhagic and ischemic complications.

Conclusions: Staged stent-assisted coiling is a safe and effective treatment strategy for acutely ruptured saccular wide-necked intracranial aneurysms, with comparable complete occlusion rates, recurrence rates at follow-up and overall

procedure-related complication rates compared with conventional stent-assisted coiling strategy. Staged stent-assisted coiling could be an alternative treatment option for selected ruptured intracranial aneurysms in the future.

KEYWORDS

endovascular treatment, intracranial aneurysm, procedure-related complications, ruptured wide-necked aneurysm, acute subarachnoid hemorrhage (SAH), staged stent-assisted coiling

Introduction

Stent-assisted coiling (SAC) and Flow-diversion (FD) treatments have been demonstrated to be amenable paradigms for unruptured intracranial aneurysms with parent artery preservation (1–3). However, for the treatment of acutely ruptured wide-necked aneurysms, the deployment of stents and FD in the acute phase remains controversial (4, 5), and has 3 main issues. First, these device-implanted techniques may contribute to perioperative thromboembolic and hemorrhagic events due to the hypercoagulable status in the setting of subarachnoid hemorrhage (SAH) (6). Second, mandatory antiplatelet medication potentially increases the risk of symptomatic hemorrhagic complications from additional procedures (such as external ventricular drainage and craniotomy) and aggravates bleeding during the acute period (7, 8). Third, early cerebral vasospasm of SAH makes microwire navigation, microcatheter positioning, device distribution, and deployment challenging (9). For these issues, applications of SAC and FD are limited. Simultaneously, the option of protecting against rebleeding and accepting neck remnants instead of complete occlusion of the aneurysm in the acute phase has emerged, although it is controversial (10).

In these situations, the efficacy of the application of stents or FD with or without coils after initial coiling of acutely ruptured wide-neck intracranial aneurysms, so-called staged treatment, has been revealed recently (10–14). However, previous studies have included various subtypes of ruptured wide-necked aneurysms with different hemodynamic situations, angioarchitecture, and perioperative risk (such as saccular, fusiform, dissecting, pseudo-, and blood blister-like aneurysms), resulting in great heterogeneity in the safety and efficacy of this technique. Meanwhile, there is a lack of published reports directly comparing the safety and effectiveness profiles of conventional and staged treatment. Therefore, this study focused on staged stenting with or without additional coils after initial coiling of acute ruptured saccular wide-neck intracranial aneurysms and presented herein a propensity score-matched cohort study comparing staged stent-assisted coiling (s-SAC) with conventional SAC (c-SAC) in a high-volume center to further evaluate the safety and efficacy of staged stent placement for the treatment of acutely ruptured saccular wide-necked intracranial aneurysms.

Methods

Institutional experience

This retrospective, observational study conducted in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) was approved by our local institutional review board (the Medical Ethics Committee of Changhai Hospital). Given the retrospective nature of the analysis, the requirement for written informed consent was waived.

Patient selection and population

The inclusion criteria were as follows: (1) Spontaneous SAH diagnosed by CT or lumbar puncture and ruptured wide-necked aneurysms diagnosed by digital subtraction angiography (DSA); (2) dome-to-neck ratio <2 or a neck width of at least 4 mm measured by DSA; (3) aneurysm treated <3 d after the initial rupture; and (4) aneurysm treated by c-SAC or s-SAC technique. The exclusion criteria were as follows: (1) fusiform, traumatic, dissecting, pseudo-, and blood blister-like aneurysms; (2) parent artery occlusion, simple coiling or stent placement alone; (3) multiple aneurysms but failed to identify the ruptured one; and (4) incomplete clinical data.

Clinical and angiographic data of 403 patients with ruptured intracranial aneurysms (RIA) from November 2014 to December 2019 were retrospectively reviewed by 2 experienced neurologists, including 70 patients who underwent s-SAC and 333 patients who underwent c-SAC. Propensity score matching (PSM) (1:2 matching) was used to adjust the potential differences in age, sex, hypertension, aneurysm location, aneurysm size, aneurysm neck, Hunt–Hess scale and stent type with a matching accuracy of 0.02. Finally, 69 and 138 propensity score-matched cases were included in this study, respectively (Figure 1).

Endovascular procedure and medications

All procedures were performed *via* the femoral approach with the patient under general anesthesia by experienced endovascular neurosurgeons. Systemic heparinization was administered immediately after femoral sheath placement to maintain an activated clotting time of 2–3 times the baseline during the procedure. A 6F guiding catheter was placed into the distal internal carotid artery or vertebral artery. For accurate measurement, three-dimensional reconstruction was performed to assess the aneurysm and parent artery morphology. All stents (LVIS, MicroVention Terumo, USA; Enterprise, Cordis, USA; Solitaire, Covidien, USA; Neuroform, Boston Scientific, USA) and coils were deployed according to the standard procedure recommended by the manufacturer.

For the c-SAC group, in the acute phase, a loading dose of aspirin (300 mg) and clopidogrel (300 mg) was administered orally or rectally after stent placement. For the s-SAC group, in the acute phase, conventional coiling was performed without antiplatelet

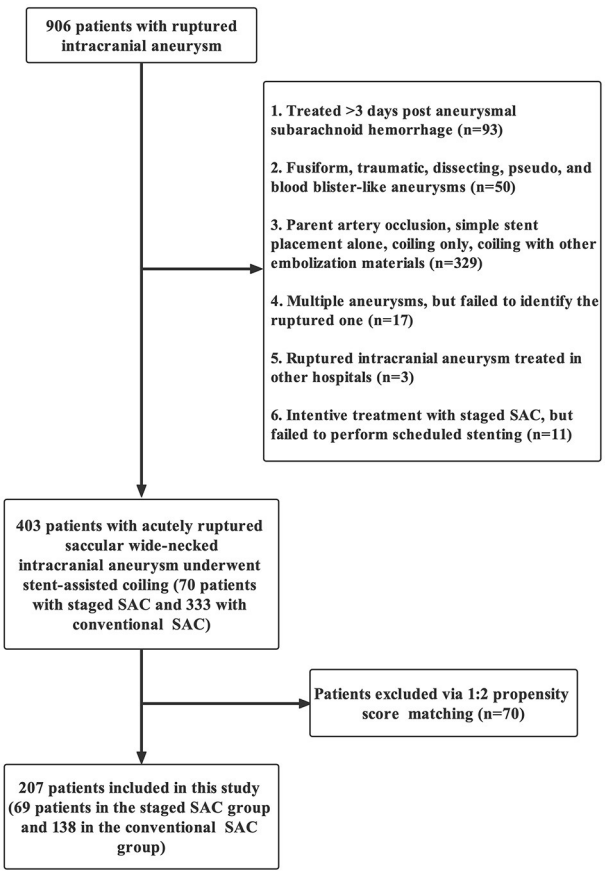

FIGURE 1
Flow diagram of patient selection according to the inclusion and exclusion criteria.

administration, the purpose of which was to embolize the ruptured site of the target aneurysm to avoid early rebleeding, then embolize as far as possible up to the neck remnant in the initial coiling.

Once patients neurologically recovered from the acute phase after SAH, stent implantation was scheduled after a required period of time (4 weeks). Thromboelastogram tests were performed in all patients in the s-SAC group on the day of scheduled admission for stenting. Dual antiplatelet drugs (aspirin 100 mg/day plus clopidogrel 75 mg/day or ticagrelor 180 mg/day according to whether the platelet response is adequate or not) were administered for at least 3 days before stenting. For both groups, dual antiplatelet drugs were recommended for 6 weeks post-procedure, followed by aspirin alone indefinitely.

Clinical and angiographic outcomes

Clinical evaluations and follow-up assessments were performed by two experienced neurologists. The modified Rankin Scale (mRS) was retrospectively used to describe the extent of patient disability at the time of discharge from hospital and at clinical follow-up visits. Favorable clinical outcomes were defined as a mRS score of 0 to 2, and poor clinical outcomes were defined as a mRS score of 3 to 6. Angiographic follow-up was assessed by magnetic resonance angiography or DSA routinely at 6 months. After the procedure and yearly thereafter and was classified using the Raymond–Roy occlusion classification: Raymond 1 (complete occlusion), 2 (residual neck), and 3 (residual aneurysm).

Statistical analysis

Statistical analysis was performed using R software (4.0.3). PSM was performed using MatchIt package to adjust the potential differences in age, sex, hypertension, aneurysm location, aneurysm size, aneurysm neck and Hunt-Hess scale. Continuous variables are expressed as mean values ± standard deviation (SD). Categorical variables are reported as proportions. And Pearson χ^2 test, Fisher exact test, independent samples *t*-test, or non-parametric test was used for statistical, analysis as appropriate. A *P*-value <0.05 was considered statistically significant. Univariate and multivariable analyses were performed to identify the association between procedure-related complications and predictive risk factors. The univariate analysis cutoff for inclusion in the multivariable analysis was $P < 0.20$. A *P*-value <0.05 was considered statistically significant.

Results

Baseline characteristics

There were no statistically significant differences in all baseline characteristics after PSM between the two groups. Of the 207 patients, 89 (43%) patients were male. The mean age was 54.1 ± 10.7 years (range 33–88). The mean aneurysm size, aneurysm neck, and dome-to-neck ratio were 4.67 mm (IQR 3.4–6.0), 3.0 mm (IQR 2.2–4.0), and 1.63 (IQR 1.35–1.90), respectively. A total of 192 (92.75%) were in the anterior circulation, and 15 (7.25%) were in the posterior circulation. Clinical and demographic patient data before and after propensity score matching are summarized in Table 1.

Periprocedural complications

The rate of overall perioperative procedure-related complications in the s-SAC group was lower than that in the c-SAC group without statistical significance (4.3% vs. 8.9%, $P = 0.394$). Among the hemorrhagic complications, intraprocedural rupture, post-procedural early rebleeding and surgical procedure-related hemorrhagic events occurred in 1 case (1.4%), 0 case and 0 case in the s-SAC group, compared with 2 cases (1.4%), 2 cases (1.4%) and 3 cases (2.2%) in the c-SAC group ($P = 1.000$, 0.802, and 0.537), respectively. Among the ischemic complications, the rates of intraprocedural thrombosis and post-procedural thrombosis were comparable between the two groups (1.4 vs. 2.9%, $P > 0.873$; 0 vs. 1.4%, $P = 0.802$). One patient in the s-SAC group (1.4%, 1 of 69) suffered coil protrusion into the parent artery without clinical symptoms. The procedure-related mortality rate was 2.2% (3/138) in the c-SAC group, including 1 case of intraprocedural aneurysm rupture and 2 cases of post-procedural early rebleeding, compared with 0% in the s-SAC group ($P = 0.537$) (Table 2).

TABLE 1 Angiographic and clinical characteristics before and after propensity score matching ($n = 473$).

Characteristics	Total population		*P*-value	Propensity score matching		*P*-value
	s-SAC ($n = 70$)	c-SAC ($n = 403$)		s-SAC ($n = 69$)	c-SAC ($n = 138$)	
Age, yrs	54.6 (9.6)	59.2 (11.8)	0.002	54.6 (9.6)	53.8 (11.2)	0.597
Sex						
Male	29 (41.4)	123 (30.5)	0.071	28 (40.6)	61 (44.2)	0.728
Female	41 (58.6)	280 (69.5)		41 (59.4)	77 (55.8)	
Hypertension, *n* (%)	46 (65.7)	212 (52.6)	0.042	45 (65.2)	81 (58.7)	0.450
Coronary heart disease, *n* (%)	3 (4.3)	20 (5.0)	1	3 (4.3)	6 (4.3)	1.000
Diabetes mellitus, *n* (%)	6 (8.6)	33 (8.2)	0.914	6 (8.7)	11 (8.0)	1.000
Smoking (%)	12(17.1)	40 (9.9)	0.075	11 (15.9)	21 (15.2)	1.000
Intraventricular hematoma (%)	20 (28.6)	150 (37.2)	0.164	20 (28.99)	43 (31.2)	0.873
Size [median (IQR)]	4.7 [3.4, 6.1]	4.5 [3.2, 6.2]	0.209	4.7 [3.4, 6.0]	4.3 [3.0, 6.6]	0.260
Neck [median (IQR)]	3.0 [2.2, 4.0]	3.3 [2.4, 4.3]	0.245	3.0 [2.2, 4.0]	3.0 [2.2, 4.0]	0.424
Dome to neck radio [median (IQR)]	1.6 [1.4, 1.9]	1.4 [1.1, 1.6]	0.001	1.6 [1.4, 1.9]	1.5 [1.3, 1.8]	0.160
Location (%)						
ICA	10 (14.3)	62 (15.4)	0.373	10 (14.5)	17 (12.3)	0.835
ACA	1 (1.4)	15 (3.7)		1 (1.5)	0 (0.0)	
AcomA	21 (30.0)	87 (21.6)		20 (29.0)	41 (29.7)	
MCA	12 (17.1)	49 (12.2)		12 (17.4)	23 (16.7)	
PcomA	22 (31.4)	156 (38.7)		22 (31.9)	46 (33.3)	
PC	4 (5.7)	34 (8.4)		4 (5.8)	11 (8.0)	
Parent artery configuration						
Bifurcation	40 (57.1)	212(52.6)	0.483	39 (56.5)	76 (55.1)	0.961
Side wall	30 (42.9)	191 (47.4)		30 (43.5)	62 (44.9)	
Multiple aneurysms						
Single	52 (74.3)	306 (75.9)	0.767	51 (73.9)	103 (74.6)	1.000
Multiple	18 (25.7)	97(24.1)		18 (26.1)	35(25.4)	
Hunt-Hess (%)						
1	35 (50.0)	202 (50.1)	0.779	34 (49.3)	67(48.6)	1.000
2	24 (34.3)	119 (29.5)		24 (34.8)	49(35.5)	
3	8 (11.4)	47 (11.7)		8 (11.6)	16(11.6)	
4	3 (4.3)	33 (8.2)		3 (4.4)	6(4.4)	
Stent type (%)						
LVIS	51(72.9)	279 (60.8)	0.312	51(73.9)	82(59.4)	0.053
Enterprise	17(24.3)	150 (32.8)		17(24.6)	45(32.6)	
Neuroform	2 (2.9)	25 (5.5)		1(1.5)	11(8.0)	
Solitaire	0 (0)	5 (1.0)		0 (0)	0 (0.0)	
Modified Fisher grade (%)						
1	11 (15.7)	78 (19.4)	0.423	11 (15.9)	25 (18.1)	0.789
2	43 (61.4)	241 (60.0)		42 (60.9)	88 (63.8)	
3	15 (21.4)	65 (16.2)		15 (21.7)	22 (15.9)	
4	1 (1.4)	18 (4.5)		1 (1.5)	3 (2.2)	

(Continued)

TABLE 1 (Continued)

Characteristics	Total population		*P*-value	Propensity score matching		*P*-value
	s-SAC ($n = 70$)	c-SAC ($n = 403$)		s-SAC ($n = 69$)	c-SAC ($n = 138$)	
Surgical procedure						
EVD	9 (12.9)	20 (4.5)	0.012	8 (11.6)	5 (3.6)	0.054
Other	8 (11.4)	16 (3.5)	0.001	8 (11.6)	5 (3.6)	0.054

mm, millimeter; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; ACoA, anterior communicating artery; PCoA, posterior communicating artery; PC, posterior circulation; EVD, external ventricular drainage.
Unless indicated otherwise, data are presented as the number of patients (%).

TABLE 2 Perioperative complications.

Perioperative complications	Group		*P*-value
	s-SAC ($n = 69$)	c-SAC ($n = 138$)	
Procedure-related complications	3 (4.3)	12 (8.9)	0.394
Hemorrhagic	1 (1.4)	6 (4.3)	0.497
Intraprocedural rupture	1 (1.4)	2 (1.4)*	1.000
Aneurysm rebleeding	0 (0.0)	2 (1.4)*	0.802
Surgical procedure-related hemorrhagic event	0 (0.0)	3 (2.2)	0.537
Ischemic	1 (1.4)	6 (4.3)	0.497
Intraprocedural thrombosis	1 (1.4)	4 (2.9)	0.873
Post-procedural thrombosis	0 (0.00)	2 (1.4)	0.802
Coil protrusion	1 (1.4)	0 (0.00)	1.000
Salvage technique	0	0	1.000
Cerebral vasospasm	4 (5.8)	9 (6.5)	1.000
Procedure-related mortality	0 (0.00)	3 (2.2)	0.537

*One patient have two complications.

Clinical and angiographic results

The immediate embolization results showed that in the s-SAC group following initial coiling, Raymond class I occlusion was achieved in 15 patients (21.7%), Raymond class II in 36 patients (52.2%), and Raymond class III in 18 patients (26.1%), compared with 84 patients (60.9%), 18 patients (13.0%), and 36 patients (26.1%) in the c-SAC group, respectively, demonstrating a statistically significant difference between the two groups ($P < 0.001$). For the s-SAC group, the median time between initial coiling and later stent treatment was 4.0 weeks (range 3.5–7.5 weeks). No rebleeding occurred during the intervals. Stents were implanted successfully in all 69 patients, resulting in 100% technical success. A total of 97.1% (67/69) of patients in the s-SAC group and 90.6% (125/138) of patients in the c-SAC group had favorable neurologic outcomes at discharge, and the difference between the two groups was not statistically significant ($P = 0.155$).

A total of 6 patients died at discharge in the two groups. In addition to the three patients who died of procedure-related complications mentioned above, the remaining three patients died of poor clinical grade at presentation and comorbidity. Therefore, a total of 201 patients survived at discharge. Among them, 188 patients (93.5%, 188 of 201) had been followed up clinically for 345–1,965 d (mean, 1,205 d). In addition, 61 patients (95.3%, 61/64) had favorable clinical outcomes in the s-SAC group, while 112 (90.3%, 112/124) patients had favorable clinical outcomes in the c-SAC group ($P = 0.232$).

A total of 188 (90.0%, 181/201) patients had at least one angiographic follow-up (mean 565 days), including 63 in the s-SAC group and 118 in the c-SAC group. Angiographic follow-up results showed that in the s-SAC group, 52 patients (82.5%, 52/63) were successfully occluded (Figure 2), 3 patients (4.8%, 3/63) improved, 6 patients (9.5%, 6/63) were stable, and 2 patients (3.2%, 2/63) were recanalized, compared with 86 patients (72.9%, 86/118), 8 patients (6.8%, 8/118), 12 patients(10.2%, 12/118), and 12 patients (10.2%, 12/118) in the c-SAC group, showing no statistically significant difference between the two groups ($P = 0.357$) (Table 3). The aneurysm occlusion rates in the s-SAC group including immediate results after coiling before stent implantation, immediate results after stent implantation and the outcomes at the last follow-up are summarized in Figure 3.

Univariate and multivariate analysis of risk factors for perioperative procedure-related complications

The following factors were included in the univariate analysis of perioperative procedure-related complications: patient age, sex, history of hypertension, smoking history, history of diabetes, history of coronary heart disease, Hunt-Hess grade, modified Fisher grade, aneurysm size, neck size, dome-to-neck ratio, aneurysm location, treatment strategy, stent type, and immediate embolization results. Univariate analysis showed that modified Fisher grade ($P = 0.025$), bifurcation (0.044) and a history of diabetes ($P = 0.043$) were associated with overall procedure-related complications; neck size ($P = 0.038$) and a history of diabetes ($P = 0.013$) were associated with ischemic complications; modified Fisher grade and dome-to-neck ratio were associated with hemorrhagic complications. Multivariate analysis showed that modified Fisher grade (OR = 2.120, 95% CI 1.036–4.440 $P = 0.041$) was an independent predictor of overall procedure-related complications, while there were no predictors for the hemorrhagic and ischemic procedure-related complications.

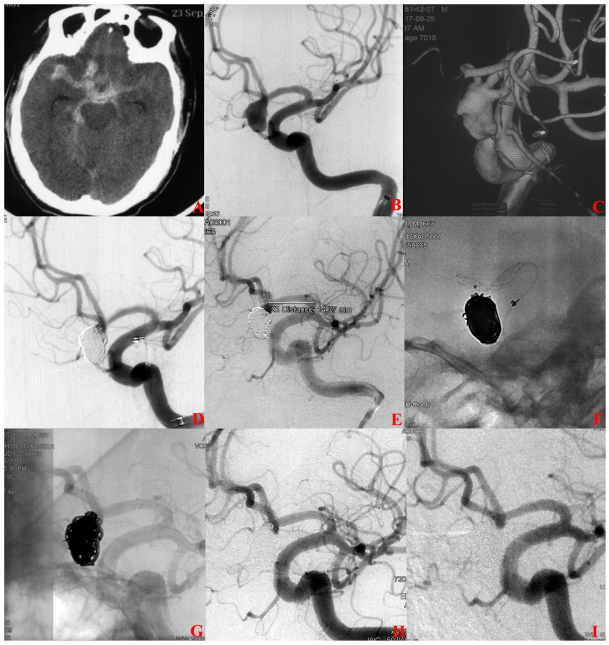

FIGURE 2
A ruptured anterior communicating aneurysms (AcomA) intracranial aneurysm treated with staged stent-assisted coiling. **(A)** The patient was admitted with spontaneous subarachnoid hemorrhage. **(B, C)** Cerebral angiography and 3D reconstruction revealed a AcomA aneurysm. **(D)** The aneurysm was treated with coiling embolization only at the initial stage. Immediate angiography showed the residual neck of the aneurysm. **(E–G)** 28 days later, the 3.5-mm * 15-mm LVIS stent adjunctive coils were deployed as scheduled. **(H)** Immediate angiography showed that the aneurysm was completely occluded. **(I)** Eleven months later, angiographic images showed complete occlusion of the aneurysm.

Discussion

In this propensity score-matched cohort study, the rates of overall procedure-related complications were slightly lower in the s-SAC group than in c-SAC group, while the differences were not statistically significant ($P = 0.394$). The angiographic follow-up results showed that the s-SAC group had a higher occlusion rate and lower recurrence rate than the early stent group, but the difference was not statistically significant. In addition, the rates of favorable clinical outcomes at discharge and during long-term follow-up were comparable between the two groups. Multivariate analysis revealed that c-SAC was an independent predictor of overall procedure-related complications. These results suggest that s-SAC has lower perioperative complication rates and comparable long-term angiographic outcomes when compared with the c-SAC strategy.

Despite evidence from prior research suggesting that conventional SAC for treating certain patients with intracranial aneurysms may be safe (15, 16), SAC of saccular wide-necked aneurysms is still controversial due to the uncertain incidence of procedure-related complications (17). Mandatory dual antiplatelet medication in the setting of acutely ruptured aneurysms increases the theoretical risk of hemorrhagic complications. A multicenter retrospective cohort confirmed this concern (18). The authors reported that the aneurysm rebleeding rate in the SAC group was significantly higher than that of coiling only group (17.4 vs. 1.9%, $P < 0.007$). Another 2 retrospective analyses suggested that antiplatelet therapy during SAH was associated with the risk of external ventricular drainage-related hemorrhagic complications (19, 20). Additionally, the potential risk of in-stent thrombosis makes conventional SAC disadvantageous due to the hypercoagulation condition in the acute phase of SAH. Our previous meta-analysis indicated that the thrombosis rate in the SAC group was significantly higher than that of the coiling-only group for RIA treatment (29.9 vs. 17.5%; RR = 2.71; 1.95–3.75) (21). A study with 55 cases of SAC and 394 cases of coiling alone for the treatment of acutely RIA without antiplatelet premedication showed that antiplatelet premedication-free SAC increased the risk of thromboembolism compared with coiling alone (22). Moreover, it is worth noting that cerebral vasospasm induced by acute SAH may present an extra obstacle when attempting to perform conventional SAC treatment. The structural thinness of the parent or branch arteries caused by cerebral vasospasm can have a negative impact on the navigation and delivery of stent catheters during procedures, which may lead to a decline in the technical success rate, stent migration and poor stent tolerance. In this study, for early coiling treatment before scheduled stenting, we did not use any antiplatelet therapy and relatively complex intravascular manipulation during the acute period of SAH and were more prone to accept a neck remnant if we consider that the primary purpose of early RIA management is to prevent rebleeding. Thus, theoretically, the incidence of procedure-related hemorrhagic events and thromboembolism can be reduced.

There were several studies implying that the s-SAC paradigm may be a favorable alternative in RIA treatment. Feng et al. reported 47 patients of s-SAC for acute ruptured wide-necked intracranial aneurysms and found that no hemorrhagic and ischemic complication was observed, and all patients demonstrated favorable clinical outcomes (mRS 0-2) at follow-up (11). Mine et al. evaluated the same strategy in 23 cases. No rebleeding occurred during the mean delay of 24.3 days between the initial coiling and stenting and clinical status was unchanged in all patients (10). However, the near-excellent results need additional case-control and larger

TABLE 3 Angiographic and clinical Outcomes.

Outcomes	Group		*P*-value
	s-SAC ($n = 69$)	c-SAC ($n = 138$)	
Angiographic outcome			
Immediate embolization			
Raymond class I	15 (21.7)	84 (60.9)	<0.001
Raymond class II	36 (52.2)	18 (13.0)	
Raymond class III	18 (26.1)	36 (26.1)	
Before stent implantation			
Raymond class I	4 (5.8)		
Raymond class II	42 (60.9)		NA
Raymond class III	23 (33.3)		
After stent implantation			
Raymond class I	22 (31.9)		
Raymond class II	34 (49.3)		NA
Raymond class III	13 (18.8)		
Follow-up			
Complete occlusion	52 (82.5)	86 (72.9)	0.357
Improvement	3 (4.8)	8 (6.8)	
Stability	6 (9.5)	12 (10.2)	
Recurrence	2 (3.2)	12 (10.2)	
Retreatment	1 (1.6)	6 (5.2)	0.424
Clinical outcome at discharge			
0–2	67 (97.1)	125 (90.6)	0.155
3–6	2 (2.9)	13 (9.4)	
Clinical follow-up[a]			
0–2	61 (95.3)	112 (90.3)	0.232
3–6	3 (4.7)	12 (9.7)	
Clinical follow-up[b]			
0–2	61 (92.4)	112 (87.5)	0.296
3–6	5 (7.6)	16 (12.5)	

[a]Excluding patients who died at discharge.
[b]Including patients who died at discharge.

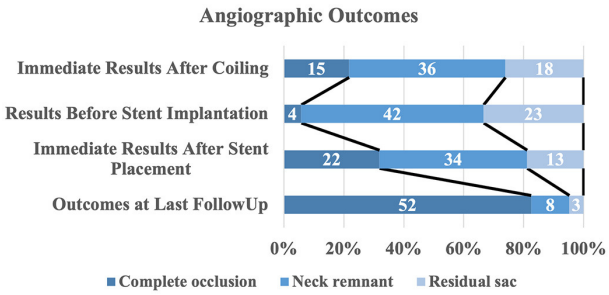

FIGURE 3
Distribution of angiographic outcomes by treatment stage. The raw distribution of results is shown.

sample studies to confirm the current observations. Our retrospective propensity score-matched cohort study suggested that the s-SAC treatment seems to be associated with a decreased risk of overall perioperative procedure-related complications compared with c-SAC treatment without statistical significance (4.3% vs. 8.9%, $P = 0.394$). The hemorrhagic and ischemic complications rates were lower in the s-SAC group than that in the c-SAC group, although the differences were not significant statistically. Notably, a total of 26 patients were treated with surgical procedures before or after endovascular treatment during SAH acute phase and we observed that the rate of hemorrhagic complications associated with surgical procedures in the c-SAC group was higher than that in the s-SAC group (3/10 vs. 0/16; 30.0 vs. 0%, $p = 0.046$). On the other hand, long-term clinical outcome was comparable between the two groups ($p = 0.272$). Our study results may be considered evidence of s-SAC treatment being a safe paradigm in this setting.

In terms of occlusion rates at follow-up, the s-SAC group yielded higher rates of complete occlusion and lower recurrence than the c-SAC group (82.54 vs. 72.88% and 3.17 vs. 10.17%, respectively). The long-term stability of s-SAC appeared to be superior to that of c-SAC, even though the difference did not meet the criteria for statistical significance ($P = 0.357$). We believe a complete obliteration rate of 82.54% in the s-SAC group to be rather satisfying and comparable with those reported in the previous research (10, 11). However, because of the lack of similar research in terms of study design and case scenario, poor comparability existed in the outcomes of different cohorts. Therefore, additional comparison studies are required to assess the safety and efficacy of the two SAC strategies for the treatment of acutely ruptured wide-necked intracranial aneurysms.

Since it is difficult to achieve complete occlusion of the wide-necked aneurysm using coiling alone without stent assistance, most neuroradiologists are concerned about early rebleeding during the interval between initial and complementary treatment due to the cerebral aneurysm rerupture after treatment study indicating that the degree of aneurysmal occlusion was strongly related to rerupture (23). However, recent studies have led to controversy regarding the feasibility of total aneurysm occlusion in the acute phase of SAH. Brinjikji et al. reported only one early rebleeding (3.22%) without additional morbidity in a cohort of 31 patients treated with complementary flow diverters (13). Recent literature on staged treatments of RIAs with scheduled implantation of stents or various approaches observed no early rebleeding (10–12). In the current study, our results further confirm this observation. For initial coiling treatment, our primary goal is to achieve enough packing density at the most likely rupture point and embolize as far as possible up to the neck remnant in the initial coiling (51/69, 73.91%). The immediate embolization outcome of initial coiling achieved Raymond I and Raymond II was comparable with the conversational SAC group (104/138, 75.36%, $P = 0.821$). The previous study has demonstrated that ruptured aneurysms with coiling only could be decreased to 2.0% with neck remnant occlusion. Based on the above facts, we consider the technique safe and effective for preventing early rebleeding.

The interval time between the initial coiling and scheduled SAC may be significant. The previous studies have demonstrated that the incidence of early rebleeding within 30 days after coiling

of a saccular RIA is very low, ranging from 1.9 to 3.6% (24–26). And data on antiplatelet management for stent-assisted coiling/flow diversion in the acute stage of ruptured intracranial aneurysms are relatively scarce. It is difficult to provide neurosurgeons with practical guidance based on the limited data available, and the availability and accessibility of certain antiplatelet agents vary depending on the country/region. We consider that without antiplatelet administration during this period, there is no need to weigh the risk of thrombotic complications against the risk of rebleeding caused by inadequate antiplatelet drugs. Therefore, we set the time interval between initial coiling and scheduled stenting as 4 weeks, which is consistent with the previous studies (11, 12). However, there is no consensus on this issue due to the scarcity of data. Further exploration is still needed in this field.

Alternately, temporary stent-assisted coil embolization (coiling assisted by temporary stenting, CATS) and intra-aneurysmal flow disruption (IAFD) paradigms have been proposed, with the benefit that blood flow is not disrupted during treatment and no implants are left in the parent channel (27, 28). Since the first report on CATS in 2013, few reports have been published about the safety and effectiveness of this technique for RIA. A retrospective study of CATS using Comaneci device (Rapid Medical, Israel) for 118 saccular wide-necked RIA suggested that the technical success rate was 100% and 66.9% (75 of 112) and 8.73% (11 of 118) of the patients demonstrated favorable complete occlusion at follow-up and procedure-related complications (29). IAFD was specifically designed to treat wide-necked bifurcation aneurysms (28). According to a recent retrospective case-control study of patients with RIA treated with the IAFD or conventional coiling, IAFD yielded a similar procedural complication rate (19.2 vs. 22.7%, $P = 0.447$) and potentially improved angiographic outcome at follow-up (93.9 vs. 76.2% $P = 0.058$) (30). Although in our current study, compared with these studies, s-SAC also showed satisfactory complete occlusion at follow-up (82.5%) and procedure-related complications (4.3%), methodological and study design differences between the two studies limit comparability.

Limitations

The present study has some limitations. First, the retrospective nature may have resulted in selection bias. In addition, we did not include other therapeutic devices and techniques in this study, particularly staged FD and surgical clipping. Therefore, it is difficult to determine if our treatment strategy would be superior to other treatment strategies in addition to conventional SAC. Lastly, due to the limited number of aneurysms in each location as a result of the small sample size, confirmation of our findings requires a large prospective study.

Conclusion

s-SAC is a safe and effective treatment strategy for acutely ruptured saccular wide-necked intracranial aneurysms, with comparable complete occlusion rates, recurrence rates at follow-up, and overall procedure-related complication rates compared with the c-SAC strategy. s-SAC could be an alternative treatment option for selected RIA in the future. Prospective studies with larger sample sizes are required to further determine the safety and efficacy of this strategy.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Changhai Hospital. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

GZ, RZhan, and YW made substantial contributions to the conception and design, acquisition of data, analysis, and drafting of the manuscript. QZ, JL, NL, GD, XZ, QL, RZhao, YX, QH, and PY assisted in the evaluation of analysis and their interpretation. All authors read and approved the final manuscript.

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Conflict of interest

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

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EDITED BY
Bu-Lang Gao,
Hebei Medical University, China

REVIEWED BY
Ansaar Rai,
West Virginia University, United States
Wei Ni,
Huashan Hospital, Fudan University, China
Bing Zhao,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Qiao Zuo
✉ dr_zuo@126.com
Jianmin Liu
✉ chstroke@163.com

†These authors have contributed equally to this work

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Staged stenting strategy of acutely wide-neck ruptured intracranial aneurysms: A meta-analysis and systematic review

Yanpeng Wei†, Xiaoxi Zhang†, Renkun Zhang†, Guanghao Zhang, Chenghao Shang, Rundong Chen, Dan Li, Meihua Huyan, Congyan Wu, Kang Zong, Zhengzhe Feng, Dongwei Dai, Qiang Li, Qinghai Huang, Yi Xu, Pengfei Yang, Rui Zhao, Qiao Zuo* and Jianmin Liu*

Neurovascular Center, Changhai Hospital, Naval Medical University, Shanghai, China

Objective: In the study, we explored the safety and effectiveness of staged stenting strategy for acutely wide-neck ruptured intracranial aneurysms.

Methods: Online databases, including PubMed, EMBASE, the Cochrane database, and Web of Science, were retrospectively and systematically searched. The main observation indicators were the procedure-related complication rate, complete occlusion rate, and favorable clinical outcome. Meta-analysis was performed using a random or fixed effect model based on heterogeneity.

Results: A total of 5 studies with 143 patients were included. The hemorrhagic complication rate of the initial coiling and staged stenting was 2.8% (4 of 143) and 0, respectively. The ischemic complication rate of the coiling and supplemental stenting was 3.5% (5 of 143) and 2.9% (4 of 139), respectively. There were no deaths due to procedure-related complications in two stages. The aneurysm complete occlusion rate was 25% (95% CI, 0.13–0.03; $I^2 = 4.4\%$; $P = 0.168$) after initial coiling, 54% (95% CI, 0.63–0.64; $I^2 = 0\%$; $P = 0.872$) after staged stenting, and 74% (95% CI, 0.66–0.81; $I^2 = 56.4\%$; $P = 0.562$) at follow-up, respectively. Favorable clinical outcome rate 74% (95% CI, 0.61–0.86; $I^2 = 50.5\%$; $P = 0.133$) after discharge of initial coiling treatment, and 86% (95% CI, 0.80–0.92; $I^2 = 0$; $P = 0.410$) after discharge from stenting, and 97% (95% CI, 0.93–1.01; $I^2 = 43.8\%$; $P = 0.130$) at follow-up.

Conclusion: Staged stenting treatment of wide-neck RIA with coiling in the acute phase followed by delayed regular stent or flow-diverter stent had high aneurysm occlusion rate, favorable clinical outcome rate and low procedure-related complication rate. A more dedicated and well-designed controlled study is warranted for further evaluation of staged stenting treatment compared to SCA in wide-neck RIA.

KEYWORDS

wide-neck, ruptured intracranial aneurysms (RIA), staged stenting, complications, initial coiling

Introduction

Endovascular embolization has become the standard treatment strategy for ruptured intracranial aneurysms (RIA) (1). The indications of endovascular embolization are increasingly well defined, however it remains controversial for the wide-neck RIA (2). For wide-neck RIA, stents are often necessary to provide permanent protection for the coil inside the aneurysm sac, which may prevent coil prolapse or migration during the procedure (3). Stent assisted coiling (SAC) also allows to obtain a better immediate occlusion, however, the application of stent and antiplatelet medication can lead to more unexpected ischemic and hemorrhagic complications in the acute phase of subarachnoid hemorrhage (SAH) (4, 5). The overall rate of perioperative complications of SAC in RIA was about 20.2% as we previously reported, which was significantly higher than coiling only (6).

To avoid the high complication risk of SAC due to antiplatelet medication use in acute phase of SAH for wide-neck RIA, staged stenting strategy was gradually being applied. In a recent study, acute coiling followed by staged stenting in the treatment of 20 RIA showed that the perioperative complication during acute coiling was 3.7% and the staged treatment was no complication occurred, which suggested that staged stenting could avoid the potential risk of stent placement in the acute phase of SAH (7). As reported, staged stenting strategy was divided into two stages (7–11). The patients underwent conventional coiling in the acute phase of SAH, the purpose of which was to embolize the target aneurysms to avoid early rebleeding without stenting. Then adequate antiplatelet medication and supplemental stenting treatment (regular stent or flow-diverter stent) were scheduled after 2 weeks at least when the patient's condition was stable. Considering the distinctive characteristics of wide-neck RIA, the argument of whether staged stenting strategy would be more appropriate for managing wide-neck RIA remains unclear. Therefore, we performed a meta-analysis to evaluate the safety and outcomes of staged stenting treatment for wide-neck RIA.

Materials and methods

Literature search strategy

This systematic review and single-arm meta-analysis was conducted in accordance with the PRISMA guidelines (12). A systematic search and critical review of the reported data were from January 2006 to June 2022. A thorough search of published English language literature was performed using PubMed, EMBASE, the Cochrane database, and Web of Science. The terms "ruptured", "intracranial aneurysms", "cerebral aneurysms", "intracranial aneurysm", "cerebral aneurysm", "staged", "subtotal", "planned", "partial", "targeted", "stent", and "flow-diverter" were combined as either keywords or Medical Subject Headings terms to identify all eligible studies. The reference lists of included studies were searched manually. All identified articles were systematically evaluated using the inclusion and exclusion criteria.

Selection criteria

The inclusion criteria were: (1) studies reported patients with wide-neck RIA verified by CT scan and CTA /MRA/DSA, who underwent staged stenting (regular stent or flow-diverter stent)

TABLE 1 Joanna Briggs institute scale.

Parameter	Feng et al. (8)	Benjamin et al. (10)	Brinjikji et al. (9)	Mehm et al. (7)	Howard et al. (11)
1. Clear criteria for inclusion	√	√	√	√	√
2. Condition measured in a standard, reliable way	√	√	√	√	√
3. Valid methods used for identification of the condition	√	√	√	√	√
4. Consecutive inclusion of participants	√	※	√	※	※
5. Complete inclusion of participants	√	※	√	※	※
6. Clear reporting of the demographics	√	√	√	√	√
7. Clear reporting of clinical information	√	√	√	√	√
8. Clear reporting outcomes or follow up results	√	√	√	√	※
9. Clear reporting of the presenting site(s)/clinic(s)	√	√	√	√	√
10. Appropriate statistical analysis	√	√	√	√	√

Studies with 6 positive answers were defined as good quality.

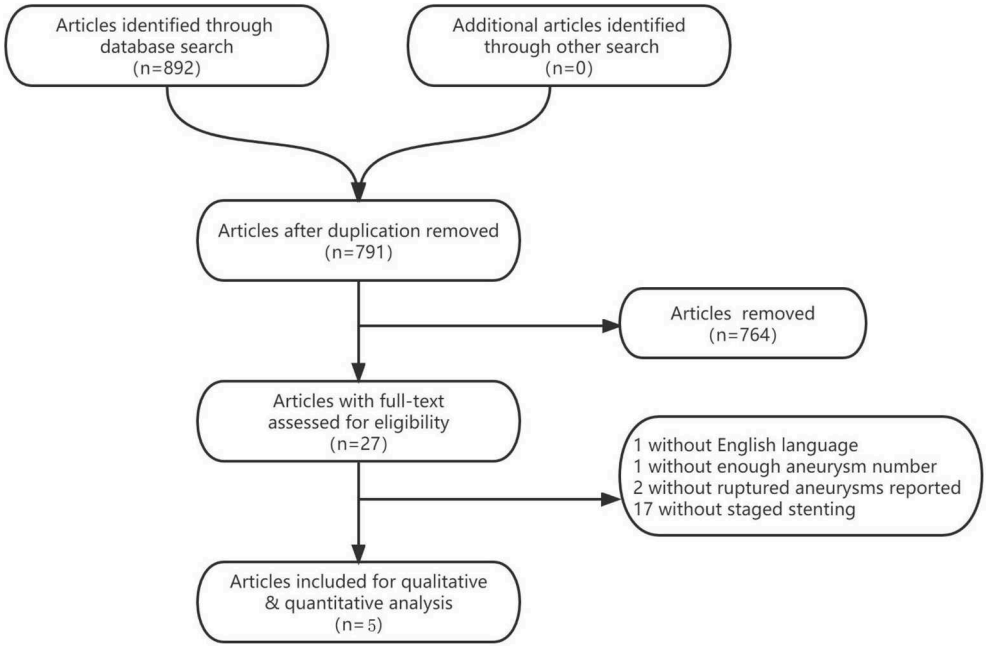

FIGURE 1
Flowchart of study selection.

treatment; (2) studies included at least 10 patients; (3) studies reported the clinical or angiographic outcomes of aneurysms. The exclusion criteria were as follows: (1) unextractable or unclear data; (2) second staged treatment using alternative modalities; (3) duplicated reports; (4) fusiform, dissecting, mycotic aneurysms; (5) unpublished studies, reviews, meta-analyses, comments, letters, pilot studies, conference-only reports, technical notes, case reports, and abstract only and non-English language studies. The database search and study selection were performed by two junior physicians (Wei and Zhang) independently, with disagreements settled by the senior physicians (Zuo and Liu).

Data extraction and item definition

The following information was extracted for the included studies: author, country, publication year, number of patients, baseline patient information, time between coiling and stent, complications, and so forth. The investigators were contacted if additional data were necessary.

The main observation indicators include the following: (1) Perioperative procedure-related complications and mortality in both phases. Procedure-related complications included hemorrhagic and ischemic complications. Hemorrhagic complications were defined as intraoperative aneurysm rupture and early rebleeding in two stages. Ischemic complications included acute in-stent thrombus formation, thromboembolic event, parent or branch artery occlusion. Procedure-related mortality was defined as death caused by a procedure-related complication other than deterioration of a severe condition. (2) The intracranial aneurysms complete occlusion rate immediately after both procedures and at follow-up. The intracranial aneurysm occlusion was evaluated using Raymond-Roy grade scale: (I) complete occlusion, (II) neck remnant, and (III) incomplete occlusion (13). (3) Favorable clinical outcome after both procedures immediately and at follow-up. Favorable clinical outcomes were defined as a modified Rankin scale score of 0–2.

Quality assessment and statistical analysis

Assessment of study quality was performed using a Joanna Briggs institute scale for 6 studies (Table 1).

A meta-analysis was performed using Stata, version 16 (Stata Corp., College Station, Texas, USA). Continuous variables are presented as mean values or median and range. Dichotomous variables are presented as risk ratios with 95% confidence intervals (CI). Statistical heterogeneity was assessed using I^2, a random effect model was used for analysis if the I^2 was >50%, and a sensitivity analysis was further performed. For analysis with an $I^2 < 50\%$, a fixed-effect model was used and a sensitivity analysis was not performed. Significance was set at $P < 0.05$.

Results

Literature search, study characteristics, and quality assessment

The literature search process was presented in a Preferred Reporting Items for flow chart showing the number of studies screened and excluded at each stage (Figure 1). The basic characteristics of the included eligible studies were summarized in Table 2. All included studies were retrospective studies using data from retrospective or prospective databases. The quality of the included studies using a Joanna Briggs institute scale (score range,

TABLE 2 The basic characteristics of the included eligible studies.

Investigator	Study period	Country	Patient number in initial coiling	Age (years)	Female sex *n* (%)	Anterior circulation *n* (%)	Aneurysm size (mm)	Neck size (mm)	Patient number in staged stenting	Time between coiling and stent (days)	Follow-up month (Angiographic)	Moderate clinical status*
Feng et al. (8)	2006/11–2016/9	China	47	55.4 ± 11.6	28 (59.57%)	46 (98%)	4.9 ± 4.0	4.2 ± 2.9	47	29.4	6.7∼36.4	38.30%
Benjamin et al. (10)	2012/1–2017/6	Belgium	23	50	15 (65.2%)	21 (91%)	7.1	3.4	23	24.3	6	82.6%*
Brinjikji et al. (9)	2009/4–2014/8	Italy	31	52.1 ± 11.1	17 (55%)	25 (84%)	15.8 ± 7.9	NA	27	119 (8–700)$^{\Delta}$	19.2 ± 12.0	64.50%
Mehm et al. (7)	2016/9–2020/12	Turkey	20	51.6 ± 14.2*	49 (45%)*	17 (85%)	8.97 ± 3.57	4.29 ± 0.85	20	87.71 ± 36.89	6	55%
Howard et al. (11)	NA	USA	22	57 (36–83)$^{\Delta}$	19 (86%)	21 (95%)	8.8 (2.3–24)$^{\Delta}$	4.7 (1.8–8.3)$^{\Delta}$	22	24.5 (3.5–105) $^{\Delta}$	6.0 (1.8–8.3)$^{\Delta}$	23.80%

Data presented as mean or mean ± standard deviation or *n* (%), unless otherwise stated; *, The description includes other groups; NA, not reported; $^{\Delta}$, median (range); Moderate clinical status. *, Hunt-Hess(1–2)/WFSN(1–2)/GCS(9–15).

TABLE 3 Perioperative procedure-related complications and mortality in both stages.

Feng et al. (8)	47	0	0	0	47	0	0	0
Benjamin et al. (10)	23	0	0	0	23	0	1	0
Brinjikji et al. (9)	31	3	4	0	27	0	2	0
Mehm et al. (7)	20	1	0	0	20	0	0	0
Howard et al. (11)	22	0	1	0	22	0	1	0
Total	143	4	5	0	139	0	4	0

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TABLE 4 The aneurysm complete occlusion rate immediately after both stages and at follow-up.

Investigator	Immediate outcomes after coiling			Complete occlusion rate	Immediate outcomes after stenting			Complete occlusion rate (%)	Outcomes at follow up			Complete occlusion rate
	I	II	III		I	II	III		I	II	III	
Feng et al. (8)	14	22	11	30%	24	18	5	51%	38	6	3	81.0%
Benjamin et al. (10)	7	13	3	30%	12	11	0	52%	14	6	1	67.0%
Brinjikji et al. (9)	3	13	15	10%			NA		15	3	4	68.0%
Mehm et al. (7)	0	0	20	0%	9	5	6	45%	11	4	1	68.0%
Howard et al. (11)	0	2	20	0%			NA		14	3	4	67.0%

0∼10), with 6 positive answers taken to define a good quality study (Table 1).

We identified 892 studies through the database search, and a total of 5 studies (7–11) were included in the present meta-analysis, with 143 ruptured intracranial aneurysms patients (Table 2).

Analysis of safety and outcomes

In all the 5 studies, the patients underwent conventional coiling in the acute phase of SAH without antiplatelet therapy. In 3 studies, the researchers described detailed antiplatelet strategy when patients underwent the supplemental stenting treatment. The regular dual antiplatelet drugs were administered for at least 3 days before stenting or a loading dose of dual antiplatelet drugs was used before the procedure.

The hemorrhagic complications only occurred in 4 patients (4 of 143, 2.8%) in perioperative of coiling. Among them the intraoperative aneurysm bleeding rate was 2.1% (3/143), and the early rebleeding rate was 0.7% (1 of 143). The ischemic complications occurred in 5 patients (5 of 139, 3.5%) in perioperative of coiling and 4 patients (4 of 139, 2.8%) in perioperative of stenting. There were no deaths due to procedure-related complications in two stages (Table 3).

The aneurysm complete occlusion rate was 25% (95% CI, 0.13–0.03; $I^2 = 4.4\%$; $P = 0.168$) after initial coiling, 54% (95% CI, 0.63–0.64; $I^2 = 0\%$; $P = 0.872$) after staged stenting, and 74% (95% CI, 0.66–0.81; $I^{2=}$ 56.4%; $P = 0.562$) at follow-up, respectively (Table 4, Figure 2).

Favorable clinical outcome rate was 74% (95% CI, 0.61–0.86; $I^2 = 50.5\%$; $P = 0.133$) after discharge of initial coiling treatment, and 86% (95% CI, 0.80–0.92; $I^2 = 0$; $P = 0.410$) after discharge from stenting, and 97% (95% CI, 0.93–1.01; $I^2 = 43.8\%$; $P = 0.130$) at follow-up, respectively (Table 5, Figure 3).

Sensitivity analysis and publication bias

The results of a funnel plot analysis of favorable clinical outcome at discharge was shown in Figures 4, 5, which indicated obvious publication bias. Similar results were also obtained for the immediate occlusion rate (Figures 4, 5).

Discussion

Endovascular treatment has long been part of the standard strategies in the treatment of RIA to prevent aneurysm rebleeding after ISAT trial (14). With the development of skills and devices, the use of intracranial stents for endovascular treatment of intracranial aneurysms has dramatically widened its indications to wide-neck RIA (15, 16). However, SAC is not the first option for treating wide-neck RIA in the acute phase of SAH. Studies related to SAC of RIA have been performed in several centers, and the use of intracranial stents may be associated with a higher risk of ischemic and hemorrhagic complications if the antiplatelet therapy is not proper (4, 17). In our previous study on SAC, the ischemic complication rate was 3.1–8.1% and the hemorrhagic complication rate was 4.5–6.2% in different periods and with different stents (3, 18). Meanwhile, antiplatelet therapy may also increase the risk of hemorrhagic complications

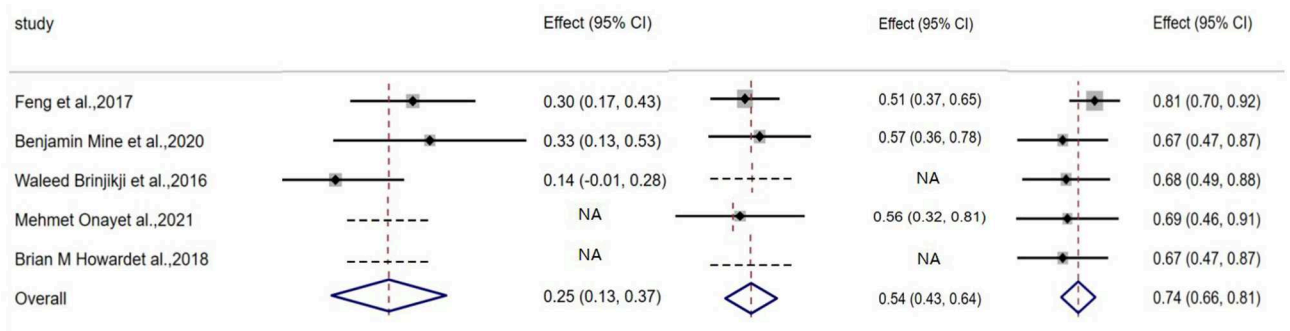

FIGURE 2
Plot showing complete occlusion rate after coiling, stenting and at follow up.

TABLE 5 Favorable clinical outcome immediately after both procedures and at follow-up.

Investigator	Favorable clinical outcomes (*n* %)		
	After discharge from coiling	After discharge from stenting	Follow-up
Feng et al. (8)	83.0%	89.3%	93.6%
Benjamin et al. (10)	NA	78.2%	100.0%
Brinjikji et al. (9)	67.7%	88.9%	92.6%
Mehm et al. (7)	NA	75.0%	93.8%
Howard et al. (11)	63.6%	NA	95.4%

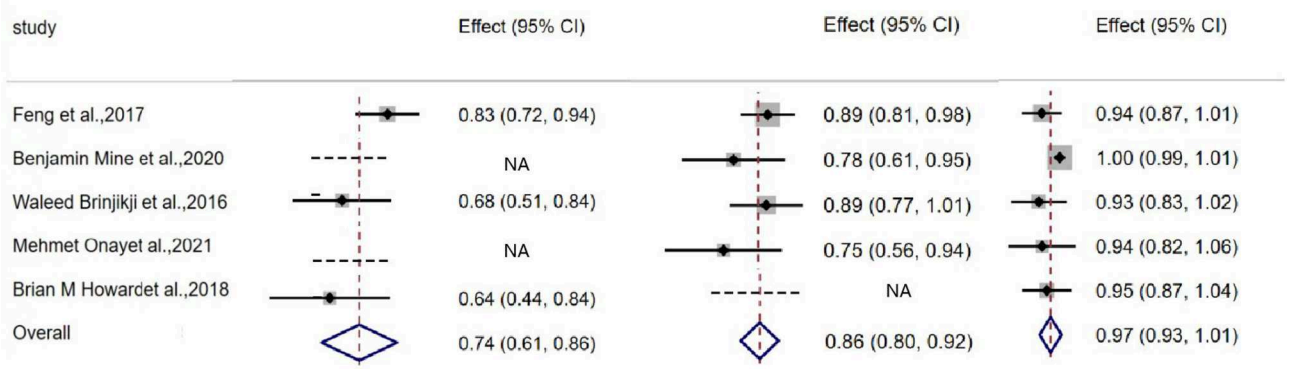

FIGURE 3
Plot showing favorable clinical outcome after coiling, stenting and at follow up.

during invasive surgeries that may be necessary within the early time of severe SAH such as ventricular drainage, hematoma clearance, or decompressive craniectomy. The study of Kung et al. (19) showed that the surgery-related bleeding risk was approximately three times higher in patients who used dual antiplatelet drugs with RIA than in those without dual antiplatelet drugs use (95% CI 1.46–8.04, $p = 0.0048$).

To effectively reduce the high rate of hemorrhagic and ischemic complications, several studies have reported the staged treatment of wide-neck RIA with coiling in the acute phase followed by delayed stenting, which may be a safe and effective strategy compared to SAC for acutely ruptured aneurysms. It allowed patients to avoid dual antiplatelet therapy during the acute phase and allowed for transitioning of the patients to a more subacute phase when the patient and aneurysm were stabilized, and dual antiplatelet therapy was safer.

Waldau et al. (20) firstly described the staged stent strategy for wide-neck RIA in 2010, with 5 patients who had complex ruptured aneurysms receiving intentional partial coiling dome protection and staged stent placement, and none of them experienced aneurysm rerupture before the supplementary stent treatment. We previously reported a series of 47 RIA patients with staged stenting treatment, and the results showed that no perioperative procedure-related complications and related death in both phases (8). Moreover, Onay et al. (7) proposed a different and radical technique of only targeted aneurysm bleb embolization and staged stenting treatment. They used small coils to embolize the bleb only instead of embolizing the aneurysm sac, which may lead to an increase in the formation of

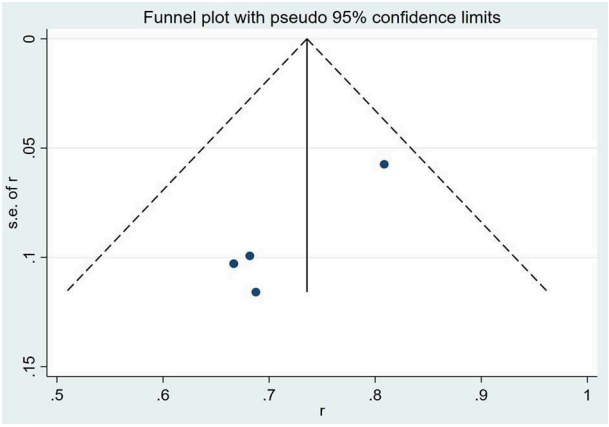

FIGURE 4
Funnel plot analysis of complete occlusion rate at follow up.

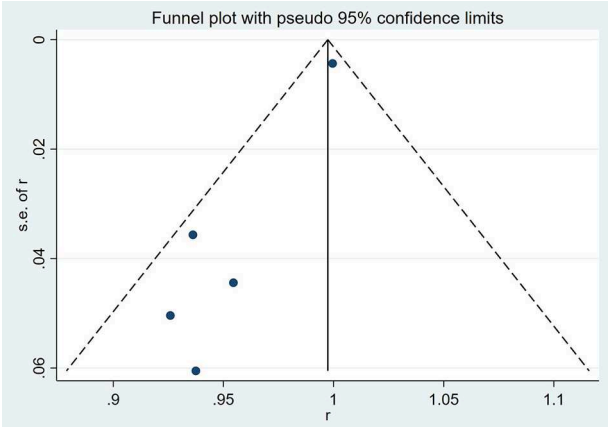

FIGURE 5
Funnel plot analysis of favorable clinical outcome at follow up.

thromboses at the bleb and ensure the stabilization of the bleb to avoid early rebleeding as they considered. In their study, although the early occlusion rate was 0, no patient suffered rebleeding before the second-stage stenting and the occlusion rate was 68% at follow-up. The safety of this new approach needs to be further validated with more studies.

Among the 143 included patients in this meta-analysis, only 4 (2.8%) patients had hemorrhagic events, and 5 (3.5%) patients had ischemic events, with no deaths due to procedure-related complications. The rate of complications seemed lower than our previous study about SAC (3, 18). Also in Mehmet's study, the staged stenting strategy had significantly lower complication rates compared to the SAC ($p = 0.047$).

In the previous meta-analysis of wide-neck RIA, the immediate occlusion rate of single coiling was 64.2% (6). It was indeed an interesting result that a low rebleeding rate was observed after the staged stenting strategy even with a relatively low rate of aneurysm immediate occlusion (25%). We shared the view of these researchers that non-dense embolization of wide-neck RIA may provide adequate protection against aneurysms rerupture in the acute phase. More evidence is still needed on whether non-dense embolization could prevent aneurysm rerupture.

At the same time, compared with our previous study about SAC of wide-neck RIA, the results of this meta-analysis showed similar rate of favorable clinical outcome (94 vs. 85.6%) and long-term angiographic complete occlusion (75 vs. 74%) at follow-up (3). Thus, staged stenting strategy may be a safe and effective way for wide-neck RIA treatment without antiplatelet management in the acute phase and with adequate antiplatelet preparation before the second-stage stent placement.

There were some limitations in the meta-analysis. First, in these 5 searched publications, the sample size was small. And only in 1 study the results of the staged stenting strategy were compared with SAC in acute phase. Therefore, we only performed a single-arm meta-analysis to summarize the preliminary results and experiences about the staged stenting strategy for wide-neck RIA. Second, the enrolled patients were carefully selected and treated with staged stenting strategy. These results may not truly represent the safety and effectiveness of staged stenting strategy. That was an unavoidable drawback of retrospective studies.

Third, the antiplatelet strategies differed across these studies, which may affect complications when supplementing stents. A more dedicated and well-designed controlled study is warranted for further evaluation of staged treatment with stent compared to SAC in acute phase of wide-neck RIA.

Conclusion

Staged stenting strategy of wide-neck RIA with coiling in the acute phase followed by delayed regular stent or flow-diverter stent had low procedure-related complication rates, favorable clinical outcome and high aneurysms occlusion rate at follow-up based on this single arm meta-analysis. We advocate for future prospective, randomized controlled trials of this promising therapy.

Data availability statement

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

Author contributions

YW, XZ, and RZhan made substantial contributions to the conception and design, acquisition of data, analysis, and drafting of the manuscript. GZ, CS, RC, DL, MH, CW, and KZ searched for relevant studies and selected the studies. ZF, DD, QL, QH, YX, PY, RZhao, QZ, and JL assisted in the evaluation of analysis and their interpretation. All authors read and approved the final manuscript.

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Conflict of interest

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

Publisher's note

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EDITED BY
Robert Ostrowski,
Mossakowski Medical Research Institute (PAN), Poland

REVIEWED BY
Oumei Cheng,
First Affiliated Hospital of Chongqing Medical University, China
Anatol Manaenko,
Innsbruck Medical University, Austria
Carmen Parra-Farinas,
University of Toronto, Canada

*CORRESPONDENCE
Zhaohui He
✉ geno_he@163.com

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Willis covered stent treatment for blood blister-like aneurysm: A meta-analysis of efficacy and safety

Jiahe Tan[1], Rui Song[2], Siyue Luo[3], Wenqiao Fu[1], Jun Su[1] and Zhaohui He[1]*

[1]Department of Neurosurgery, First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [2]Key Laboratory of Molecular Biology for Infectious Diseases (Ministry of Education), Department of Infectious Diseases, Institute for Viral Hepatitis, Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, [3]Clinical Medicine, Second Clinical College of Chongqing Medical University, Chongqing, China

Background: Blood blister-like aneurysm (BBA) is a rare and special type of intracranial aneurysm with extremely high rates of rupture, morbidity, mortality, and recurrence. Willis Covered Stent (WCS) is a new device that is specifically designed for the treatment of intracranial complex aneurysms. However, the efficacy and safety of WCS treatment for BBA remain controversial. Thus, a high level of evidence is required to prove the efficacy and safety of WCS treatment.

Methods: A systematic literature review was performed using a comprehensive literary search in Medline, Embase, and Web of Science databases to identify studies related to WCS treatment for BBA. A meta-analysis was then conducted to incorporate the efficacy and safety outcomes, including intraoperative situation, post-operative situation, and follow-up data.

Results: Eight non-comparative studies containing 104 patients with 106 BBAs met the inclusion criteria. In the intraoperative situation, the technical success rate was 99.5% [95% confidence interval (CI), 0.958, 1.000], the complete occlusion rate was 98.2% (95% CI, 0.925, 1.000), and the side branch occlusion rate was 4.1% (95% CI, 0.001, 0.114). Vasospasm and dissection occurred in 9.2% (95% CI, 0.000, 0.261) and 0.1% (95% CI, 0.000, 0.032) of the patients, respectively. In the post-operative situation, the rebleed and mortality rates were 2.2% (95% CI, 0.000, 0.074) and 1.5% (95% CI, 0.000, 0.062), respectively. In the follow-up data, recurrence and parent artery stenosis occurred in 0.3% (95% CI, 0.000, 0.042) and 9.1% (95% CI, 0.032, 0.168) of the patients, respectively. Ultimately, 95.7% (95% CI, 0.889, 0.997) of the patients had a good outcome.

Conclusions: Willis Covered Stent could be effectively and safely applied for BBA treatment. The results provide a reference for clinical trials in the future. Well-designed prospective cohort studies must be conducted for verification.

KEYWORDS

covered stent, blood blister-like aneurysm, efficacy, safety, meta-analysis

Introduction

Blood blister-like aneurysm (BBA), a name derived from its bright red, blood-blistered appearance under direct vision, refers to the aneurysm located at the non-branching sites of the anterior or the dorsal wall of the intracranial internal carotid artery and accounts for 1% of all intracranial aneurysms (1, 2). Owing to its features of a histologically fragile wall and a morphologically wide neck, BBA is prone to rupture, may lead to subarachnoid hemorrhage, and has high morbidity, mortality, and recurrence rates (3). Hence, its treatment is extremely challenging.

With the improvement in endovascular treatment techniques and the development of new materials, especially the flow diverter (FD) and the covered stent, BBA treatment has changed from "embolization of aneurysm" to "repair of parent artery" (4). However, optimal management remains controversial.

Willis Covered Stent (WCS), which was developed in China, is a new device that is specifically designed for the treatment of intracranial complex aneurysms. By isolating the aneurysm cavity and the parent artery, this "China Option" could reconstruct the anatomy and restore the normal hemodynamics of the parent artery to treat aneurysms (5).

Although WCS has been applied to treat BBA in several clinical centers, its efficacy and safety remain unclear (6). Thus, a high level of evidence is required to prove the efficacy and safety of WCS treatment. Here, the present study aimed to conduct a systematic review of current studies related to the WCS treatment for BBA and a meta-analysis to incorporate the outcomes of efficacy and safety.

Materials and methods

The review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022377151).

Literature search

Studies related to WCS treatment for BBA were identified after a comprehensive literature search in Medline, Embase, and Web of Science databases until November 14, 2022. Search terms included "blood blister like aneurysm," "blood blister-like aneurysm," "blood-blister-like aneurysm," "blister like aneurysm," "blister-like aneurysm," "blood blister aneurysm," "blood-blister aneurysm," "blister aneurysm," "BBA," "covered stent," "willis covered stent," and "WCS" in "AND" and "OR" combinations. The year of publication and language were not restricted.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) non-comparative studies analyzing the efficacy and safety of WCS treatment for BBA; (2) clear definition and same diagnostic criteria of BBA; (3) use of only WCS treatment performed by experienced interventional physicians, and the perioperative management of patients must be standard, especially the antiplatelet therapy strategy; (4) single study including more than two patients; and (5) studies reporting initial data of the outcomes, including intraoperative situation, postoperative situation, and follow-up data. The exclusion criteria were as follows: (1) repetitive articles or cohorts, (2) co-treatment of BBA, (3) lack of initial data, and (4) studies other than the non-comparative study. Studies were independently selected by two authors (Tan and Song) on the basis of the mentioned criteria. Disagreements were resolved by consensus with a third author (Luo).

Data extraction

Data included baseline characteristics (such as the first author, publication year, number of patients and BBAs, mean age, sex, and mean BBA size); intraoperative situation (number of technical successes, aneurysm complete occlusion, side branch occlusion, vasospasm, and dissection); postoperative situation (number of rebleeds and mortality); and follow-up data (duration, number of patients, recurrence, parent artery stenosis, and good outcome). The evaluation indicators for efficacy were technical successes, aneurysm complete occlusion, recurrence, and good outcome. The evaluation indicators for safety were side branch occlusion, vasospasm, dissection, rebleed, mortality, and parent artery stenosis. Technical success was defined as WCS successfully implanted in the parent artery of BBA. Occlusion, vasospasm, dissection, recurrence, stenosis, and rebleed were confirmed by the imaging examination [digital subtraction angiography, computed tomography (CT), computed tomography angiography (CTA), or magnetic resonance angiography (MRA)]. A good outcome was defined as a modified Rankin Scale score (mRS) of 0–2. Data were extracted independently by two authors (Tan and Song), and disagreements were resolved by consensus with a third author (Luo).

Abbreviations: BBA, blood blister-like aneurysm; FD, flow diverter; WCS, Willis Covered Stent; AHRQ, Healthcare Research and Quality; CI, confidence interval; I^2, I-squared; MOOSE, Meta-analysis of Observational Studies in Epidemiology; OA, ophthalmic artery; AChA, anterior choroidal artery.

Quality assessment

The methodological quality of each study was independently evaluated by two authors (Tan and Song), according to the Agency for Healthcare Research and Quality (AHRQ) 11-item checklist (7). One point was given for "YES" of each of the following criteria: (1) define the source of information (survey, record review), (2) list inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications, (3) indicate time period used for identifying patients, (4) indicate whether or not subjects were consecutive if not population-based, (5) indicate if the evaluators of subjective components of study were masked to other aspects of the status of the participants, (6) describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements), (7) explain any patient exclusions from analysis, (8) describe how confounding was assessed and/or controlled, (9) if applicable, explain how missing data were handled in the analysis, (10) summarize patient response rates and completeness of data collection, and (11) clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained. On the contrary, no point was given to "NO" or "UNCLEAR" answers. The quality of studies was ranked low ($\leq$3 points), moderate (4–7 points), and high ($\geq$8 points). Disagreements were resolved by consensus with a third author (Luo).

Statistical analysis

Data management, the transformation of the effect size, calculation of the pooled risk difference, and corresponding 95% confidence interval (CI) were performed using the "metaprop" code in the Stata statistical software (version 16.0) (8). For consideration of data compatibility, a random effects model was chosen to pool the event rates for overall outcomes. Heterogeneity across the studies was tested by calculating the I-squared (I^2) statistic (9). I^2 of $<$50% represented low heterogeneity and I^2 of $\geq$50% represented high heterogeneity. Forest plots were used to illustrate the results graphically. Owing to limitations caused by the non-comparative nature of the included studies, sensitivity analysis and tests for publication bias were not completed (10).

Results

Systematic review and meta-analysis were conducted following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (11).

Literature search

After a search of comprehensive literature, 68 records were identified. After the deletion of duplicate records, 38 records remained for the title and abstract review. After studying the title and abstract review, 14 records remained for full-text examination. Of these, three records were excluded because they were single studies that included only one or two patients, and two other records were excluded because not all the treated aneurysms were BBAs. One of the studies was a review. Ultimately, eight non-comparative studies were included in the meta-analysis (12–19). A flow diagram is shown in Figure 1.

Characteristics of included studies

A total of 104 patients with 106 BBAs were identified in the eight selected studies that were published from 2016 to 2022. The mean age of the patients in the seven selected studies ranged from 49.2 to 54.5 years, the men-to-women ratio in the seven selected studies was 48.3% (28/58), and the mean BBA sizes were clear in the six selected studies. Intraoperative situation, post-operative situation, and follow-up data were described in detail in all of the included studies. The characteristics of included studies are summarized in Table 1.

Quality assessment

All of the included studies were assessed for methodological quality in accordance with the AHRQ checklist. Details of the quality index are presented in Table 2. The scores ranged from 6 to 10 with a mean value of 7.9. The five selected studies were of high quality, and the three selected studies were of moderate quality. No low-quality study was included in the present research.

Outcomes of BBA treated by WCS

In the intraoperative situation, the technical success rate was 99.5% (95% CI, 0.958, 1.000) (Figure 2A), the complete occlusion rate was 98.2% (95% CI, 0.925, 1.000) (Figure 2B), and the side branch occlusion rate was 4.1% (95% CI, 0.001, 0.114) (Figure 2C). Vasospasm and dissection occurred in 9.2% (95% CI, 0.000, 0.261) (Figure 2D) and 0.1% (95% CI, 0.000, 0.032) (Figure 2E) of the patients, respectively. In the postoperative situation, the rebleed and mortality rates were 2.2% (95% CI, 0.000, 0.074) (Figure 3A) and 1.5% (95% CI, 0.000, 0.062) (Figure 3B), respectively. In the follow-up data, recurrence and parent artery stenosis occurred in 0.3% (95% CI, 0.000, 0.042) (Figure 4A) and 9.1% (95% CI, 0.032, 0.168) (Figure 4B) of the patients, respectively. Ultimately, 95.7% (95% CI, 0.889, 0.997)

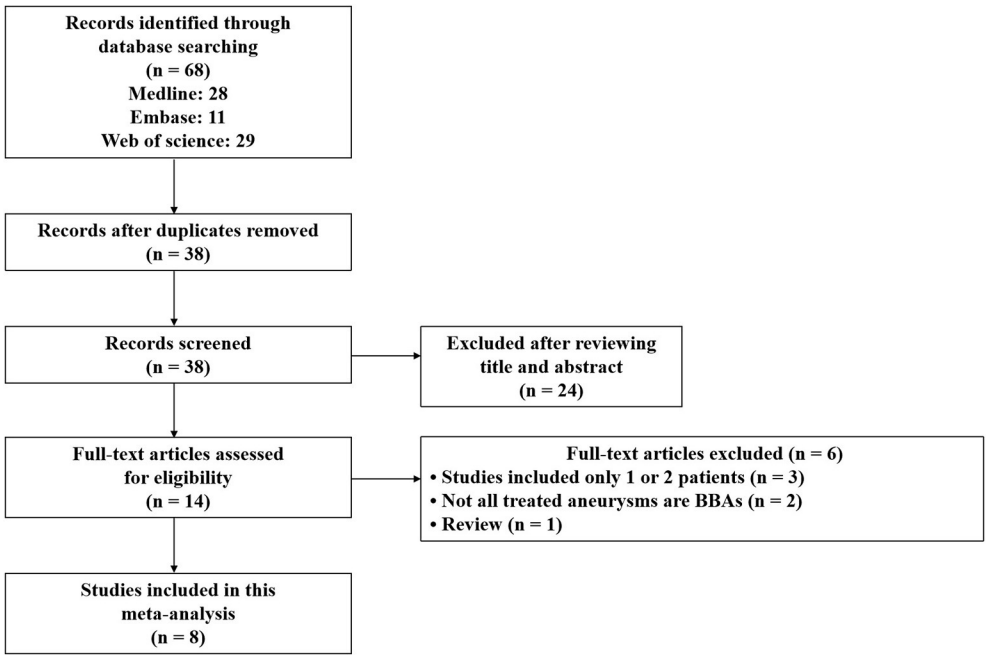

FIGURE 1
A flowchart of the literature search performed.

(Figure 4C) of the patients had a good outcome. The overall outcomes are summarized in Table 3.

Discussion

To the best of our knowledge, this study is the first systematic review and meta-analysis that has explored the efficacy and safety of WCS treatment for BBA. After the strict screening, eight eligible studies including 106 BBAs in 104 patients were selected. The estimated pooled results showed that WCS had a high success rate of implantation. While ensuring a complete occlusion rate, the WCS treatment exhibited a low rate of intraoperative and post-operative complications, a high BBA cure rate, and a low recurrence rate. The vast majority of patients could obtain a good prognosis.

Owing to its features of a histologically fragile wall and a morphologically wide neck, the BBA treatment remains extremely challenging (3). Microsurgery, endovascular therapy, or a combination of the two comprises the treatment options for BBA. The prevailing views are reconstructing the anatomy and restoring the normal hemodynamics of the parent artery. Endovascular therapy has been recognized as the first choice of BBA treatment. The options are mainly endovascular coiling, multiple overlapping stents with or without coiling, FD, and covered stent (20). Since the first report on WCS treatment for intracranial pseudoaneurysm, studies on WCS treatment for BBA have increased with clinicians' experience and the maturity of technology (21).

In our systematic review, the men-to-women ratio was 28:58 (48.3%). Gonzalez et al. conducted a systematic literature review of BBAs in 2014. A total of 322 patients were evaluated, and the men-to-women ratio was 89:233 (38.2%). The results showed that BBA tended to have female predominance, but no statistical analysis was performed. In the present comprehensive literature review of the BBA, no report has been found on the statistically significant effect of gender on the formation of BBA. Based on the combination of statistics and medical opinion, the possible reason can be that BBA is extremely rare and its pathogenesis is unknown. In addition, the risk factor analysis cannot be completed in studies with small sample sizes (22).

In the meta-analysis, the technical success rate of WCS implantation was close to 100%. Though WCS has relatively poor flexibility and requires rapid intraoperative catheter exchange upon release (14), experienced interventional physicians find it simple and easy to implant WCS successfully into the parent artery of BBA. Aneurysm complete occlusion and unrupture are the most important indicators to evaluate intraoperative efficacy. According to the meta-analysis, WCS treatment had a satisfying complete occlusion rate of 98.2%, and no BBA had ruptured during surgery. On the contrary, the rate of endoleak was 1.8%. Endoleak is an important issue of WCS treatment for BBA. It is extremely dangerous because blood flow from the aneurysm cavity is not smooth and will increase

TABLE 1 Characteristics of included studies.

	Baseline characteristics					Intraoperative situation	
References	Patients (BBAs), *n*	Mean age, y	Males/ females, *n*	Mean BBA size, mm	Technical success, *n*	Complete occlusion, *n*	Side branch occlusion, *n*
Wang et al. (12)	8/8	49.2	1/7	NA	7	7	0
Fang et al. (13)	13/15	52.8	7/6	2.3 * 3.3	13	12	3
Gu et al. (14)	20/20	50.6	5/15	3.3 * 5.1	19	15	0
Liu et al. (15)	14/14	54.5	9/5	4.3 * 2.8	14	14	2
Liu et al. (16)	7/7	53.9	1/6	5.7 * 6.0	7	7	0
Chang et al. (17)	18/18	NA	NA	3.5 * 4.3	18	18	0
Fang et al. (18)	16/16	50.6	5/11	3.3 * 2.8	16	16	1
Qi et al. (19)	8/8	50.3	0/8	NA	8	8	1

	Intraoperative situation		Post-operative situation			Follow-up data			
References	Vasospasm, *n*	Dissection, *n*	Rebleed, *n*	Mortality, *n*	Patients, *n*	Duration, m	Recurrence, *n*	Parent artery stenosis, *n*	Good outcome, *n*
Wang et al. (12)	0	0	0	0	7	3–6	0	1	7
Fang et al. (13)	0	0	0	0	13	4–6	0	2	13
Gu et al. (14)	4	0	1	1	17	3–36	0	2	14
Liu et al. (15)	8	0	1	1	13	3–15	2	1	13
Liu et al. (16)	0	0	0	0	7	6–10	0	0	7
Chang et al. (17)	6	1	0	0	17	3–6	0	3	14
Fang et al. (18)	0	0	1	1	13	3–30	0	1	12
Qi et al. (19)	0	0	1	0	8	1–6	0	0	8

y, year; BBA, blood blister-like aneurysm; n, number; mm, millimeter; m, month; NA, not available.

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TABLE 2 AHRQ checklist.

References	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	Total
Wang et al. (12)	★		★	★		★				★	★	6
Fang et al. (13)	★	★	★	★		★				★	★	7
Gu et al. (14)	★	★	★	★	★	★	★			★	★	9
Liu et al. (15)	★	★	★	★		★	★			★	★	8
Liu et al. (16)	★	★	★	★		★		★		★	★	8
Chang et al. (17)	★	★	★	★	★	★	★	★		★	★	10
Fang et al. (18)	★	★	★	★		★	★			★	★	8
Qi et al. (19)	★	★	★	★		★				★	★	7

AHRQ, Agency for Healthcare Research and Quality; y, year. (1) Define the source of information (survey, record review). (2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications. (3) Indicate the time period used for identifying patients. (4) Indicate whether or not subjects were consecutive if not population-based. (5) Indicate if evaluators of subjective components of the study were masked to other aspects of the status of the participants. (6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements). (7) Explain any patient exclusions from the analysis. (8) Describe how confounding was assessed and/or controlled. (9) If applicable, explain how missing data were handled in the analysis. (10) Summarize patient response rates and completeness of data collection. (11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained. ★Represents one point.

the internal pressure of the aneurysm, thus increasing the risk of aneurysm rupture (14). Therefore, various methods should be used during surgery to improve the complete occlusion rate and avoid endoleak. The side branch occlusion rate was 4.1%, and five cases of ophthalmic artery (OA) occlusion and two cases of anterior choroidal artery (AChA) occlusion occurred among the 102 patients. The majority of OA occlusion may not cause an important neurological dysfunction because the blood flow after OA occlusion can be compensated by the external carotid artery system due to extensive anastomosis in these two conditions (23). Nevertheless, AChA occlusion can cause catastrophic events, such as hemiparesis, hemianopsia, and hemihypesthesia (24). Although all patients with side branch occlusion were asymptomatic in all of the included studies, doctors cannot rely on luck. A pre-operative evaluation of the important side branch of the parent arteries is very important. The choice of WCS should be abandoned if the implantation leads to serious ischemic events due to the close relationship between the aneurysm and the side branch. In addition, the rate of intraoperative vasospasm in the present study was 9.2%. Though high heterogeneity (I^2=77%) could make this result unreliable, vasospasm remains a significant intraoperative complication. The stimulation caused by WCS for the arterial wall is the reason for aggressive vasospasm (14). Handling includes enhancing the support by positioning the catheter, speeding up the procedure of surgery, and intravenously injecting nimodipine. If the vasospasm persists without relief, then it may increase the risk of post-operative rebleeding (15). Only one patient had a mild dissection that occurred due to the guiding catheter but disappeared at the 3-month follow-up. Dissection can be avoided through gentle manipulation during the operation (17).

In the post-operative situation, the rebleed and mortality rates were 2.2 and 1.5%, respectively. All the deceased patients experienced rebleeding. The mentioned values were comparable with the rebleed and mortality rates of stent-assisted coil embolization for saccular aneurysms (20). Meanwhile, no infarction was reported in all of the included studies. All of these findings confirmed the safety of WCS treatment for BBA. The reason for rebleeding remains uncertain but may be attributed to one of the following: (1) rupture of the WCS membrane, (2) intraoperative or postoperative endoleak (endoleak might occur after the vasospasm disappeared after surgery), and (3) angiography may reveal only a part of the lesions of BBA, and thus WCS covers only a part of the diseased area (15). To prevent rebleeding as much as possible, the development of materials, accumulation of experience, and improvement of techniques are all indispensable.

The follow-up data revealed that, after 1–36 months of follow-up, only 2 of the 95 patients developed mild recurrence, and their recurrent aneurysms remained persistent after 12 months of conservative treatment. The recurrent aneurysms were all saccular aneurysms and significantly smaller than the original BBAs (15). For the underlying reason, the WCS membrane is only adherent at several points of the alloy stent struts. After surgery, part of the WCS membrane may expand, leading to the recurrence of an aneurysm located in the central area of WCS (25). Parent artery stenosis occurred in 9.1% of the patients, possibly because of the short follow-up time. Although none of these patients had clinical symptoms, in-stent stenosis remains a problem that cannot be ignored. Mechanical injury caused by the balloon-expandable stent and resistance to antiplatelet therapy can lead to stenosis (26). In addition, chronic diseases, such as hyperlipemia, hypertension, and diabetes, are risk factors for in-stent stenosis (27, 28). Given that most of the factors mentioned are difficult to control, a regular and long-term angiography follow-up is necessary. No hemorrhage, infarction, or death was reported in all of the included studies.

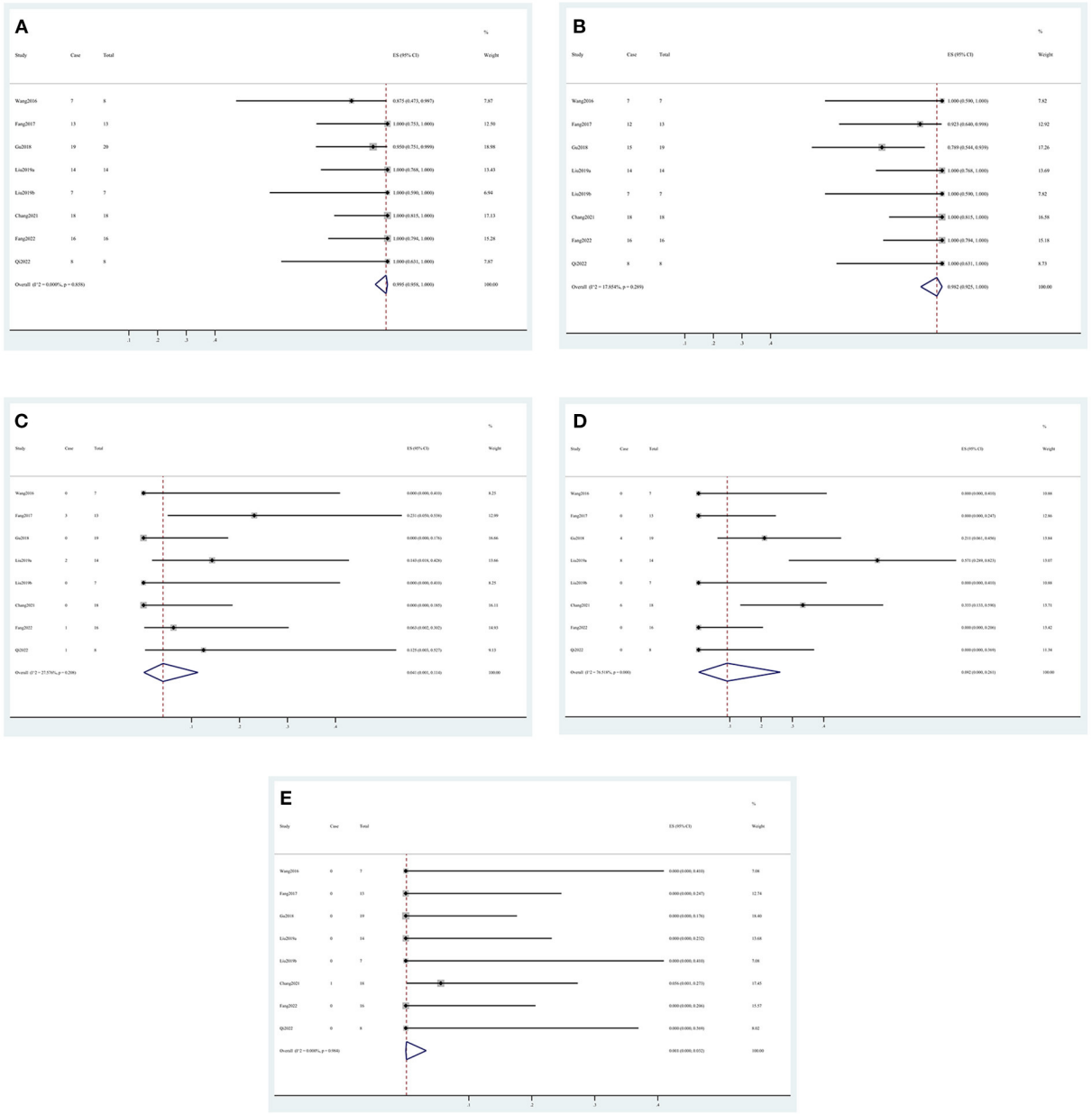

FIGURE 2
Forest plots of the intraoperative outcome rate. **(A)** Technical success, **(B)** complete occlusion, **(C)** side branch occlusion, **(D)** vasospasm, and **(E)** dissection.

Ultimately, 95.7% of the patients had a good outcome, but the rest of them were in poor health before the treatment. Zhu et al. (10) conducted a meta-analysis on the efficacy of FD treatment for BBA in 2018 and found that, among the 150 patients with BBA, 83.0% had a good outcome by the same definition. Despite being limited by the nature of non-comparative studies, no statistical comparison can be performed between the two rates. Along with its high technical success rate, a high aneurysm complete the occlusion rate and a low recurrence rate, and the efficacy of WCS treatment for BBA was confirmed.

The meta-analysis of the present study achieved positive results, but there are still some limitations. As a rare disease, the characteristics of BBA vary greatly among individuals: every patient has a different condition after the BBA rupture. In addition, the application time of WCS is too short, making it difficult to conduct studies with a large sample size and control

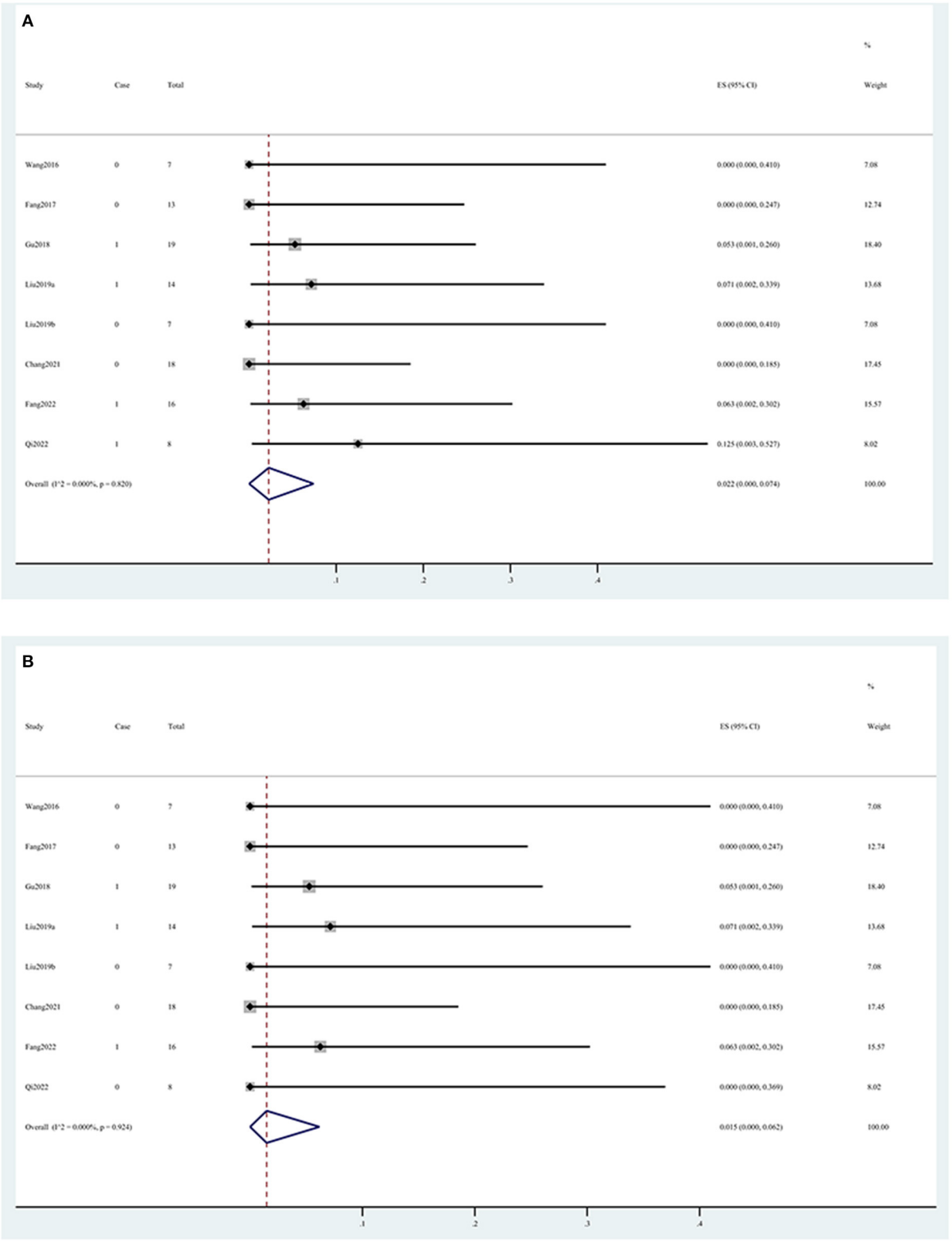

FIGURE 3
Forest plots of the post-operative outcome rate. **(A)** Rebleed and **(B)** mortality.

FIGURE 4
Forest plots of the follow-up outcome rate. **(A)** Recurrence, **(B)** parent artery stenosis, and **(C)** good outcome.

TABLE 3 Overall outcomes.

Outcome	Risk difference (95% CI)	Raw proportion	I^2 (%)
Technical success	0.995 (0.958, 1.000)	102/104	0
Complete occlusion	0.982 (0.925, 1.000)	97/102	18
Side branch occlusion	0.041 (0.001, 0.114)	7/102	28
Vasospasm	0.092 (0.000, 0.261)	18/102	77
Dissection	0.001 (0.000, 0.032)	1/102	0
Rebleed	0.022 (0.000, 0.074)	4/102	0
Mortality	0.015 (0.000, 0.062)	3/102	0
Recurrence	0.003 (0.000, 0.042)	2/95	0
Parent artery stenosis	0.091 (0.032, 0.168)	10/95	0
Good outcome	0.957 (0.889, 0.997)	88/95	9

CI, confidence interval; I^2, I-squared.

the selection bias. Randomized controlled trials or comparative studies are also difficult to perform. WCS is so expensive that some patients cannot afford it and are forced to choose other treatments, and this situation magnifies the selection bias further. Owing to the nature of non-comparative studies, this meta-analysis failed to complete the sensitivity analysis and the test for publication bias, thus affecting the authenticity of the results to a certain extent. Given that WCS has only been recently used to treat BBA, raw data available for analysis on long-term follow-up outcomes are currently lacking. Hence, the results of the present study are relatively one-sided.

Conclusion

Although this study demonstrated that WCS could be effective and safe for BBA treatment, the available evidence is indefinite. With the continuous promotion of WCS, clinical centers should have comprehensive BBA treatment options that would allow them to choose the most appropriate treatment option in accordance with the patient's condition. The results provide a reference for clinical trials. Well-designed prospective cohort studies must be conducted for verification.

Data availability statement

The original contributions presented in the study are included in the article/supplementary

material, further inquiries can be directed to the corresponding author.

Author contributions

The concept and design of the present study were performed by JT and ZH. The first draft of the manuscript was written by JT. Acquisition, analysis, and interpretation of data were performed by RS, SL, WF, and JS. Supervision of the study was conducted by ZH. All authors read and approved the final manuscript.

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Conflict of interest

The reviewer [OC] declared a shared affiliation with the authors to the handling editor at the time of review.

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

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EDITED BY
Robert Ostrowski,
Polish Academy of Sciences, Poland

REVIEWED BY
Ruben Mühl-Benninghaus,
Klinikum Lüneburg, Germany
Albert Acewicz,
Institute of Psychiatry and Neurology (IPiN), Poland

*CORRESPONDENCE
BangJiang Fang
✉ fangbji@163.com
Xuebin Hu
✉ huxuebin1227@163.com

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

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Utility of low-profile visualized intraluminal support (LVIS™) stent for treatment of acutely ruptured bifurcation aneurysms: A single-center study

Changya Liu[1†], Kaikai Guo[2†], Xinxin Wu[3], Linguangjin Wu[1], Yike Cai[2], Xuebin Hu[2*‡] and BangJiang Fang[1,4*‡]

[1]Department of Emergency, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [2]Department of Neurosurgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, [3]Shanghai Skin Disease Hospital, Skin Disease Hospital of Tongji University, Shanghai, China, [4]Emergency and Critical Care Institute of Shanghai University of Traditional Chinese Medicine, Shanghai, China

Objective: Stent-assisted coiling has been increasingly used in the treatment of intracranial aneurysms. However, its application in ruptured bifurcation aneurysms remains controversial and challenging. This study aimed to present the safety and feasibility of low-profile visualized intraluminal support (LVIS™, LVIS, and LVIS Jr.) stent for acutely ruptured bifurcation aneurysms.

Methods: A total of 41 patients with acutely ruptured intracranial aneurysms arising at the bifurcation were treated with LVIS™ stent-assisted coiling in our hospital between January 2017 and December 2021. The clinical data and angiographic results of the patients were analyzed.

Results: Among these patients, all stents were successfully implanted. According to the immediate angiographic results, 29 aneurysms (70.7%) were completely occluded. Intraoperative thrombosis and hemorrhage occurred in two and one cases, respectively. No post-operative thrombosis or rebleeding events were observed. The clinical follow-up of all patients revealed that 38 (92.7%) cases had favorable outcomes (modified Rankin scale: 0–2). The angiographic results available for the 36 patients during the follow-up period revealed complete occlusion was achieved in 30 patients (83.3%) and residual neck in six patients.

Conclusion: The LVIS™ stent-assistant coiling is a safe and feasible option for acutely ruptured bifurcation aneurysms. Further studies with a prospective design, a larger sample size, and long-term follow-up are needed to validate these findings.

KEYWORDS

stent-assisted coiling, ruptured aneurysms, bifurcation, low-profile visualized intraluminal support, LVIS

Introduction

The treatment goal for intracranial aneurysms is to reconstruct the morphological structure and restore the hemodynamics of the parent artery (1, 2). With the advances in minimally invasive techniques, endovascular treatment has emerged as a crucial treatment approach for managing intracranial aneurysms (3–5). The safety and effectiveness of stents

have been assessed in cases with complex lesions and unruptured aneurysms (6, 7), such as those with wide necks, located distally, or of small size. However, the stent implementation for the management of acutely ruptured intracranial aneurysms situated at the bifurcation site remains debatable and poses a challenge, given the intricate anatomical structures comprising broad necks, the inclusion of vital branches, and diminutive vessels (8), such as anterior cerebral artery (ACA), anterior communicating artery (AcomA), middle cerebral artery (MCA), and basilar tip (9, 10). Furthermore, apprehensions have arisen regarding the potential for thromboembolic complications during stent deployment and the possibility of rebleeding in patients who have experienced subarachnoid hemorrhage and are undergoing dual-antiplatelet medication management (11).

The low-profile visualized intraluminal support (LVIS^{TM}, Microvention, Tustin, CA, USA) stent, which has two variations (LVIS and LVIS Jr.), is a recently developed self-expandable device that assists in the coiling process of intracranial aneurysms (12, 13). The braided structure provides high metal coverage and a smaller cell structure (14), which protects the aneurysm neck and important branch arteries. This structure affords stable support for density packing coils and good wall apposition to the parent artery, particularly in curved vessels (15). As a result, the utilization of this stent may augment the level of occlusion of the aneurysm and, in theory, lower the probability of aneurysm rebleeding (16–18). Recent scholars have documented some studies associated with the employment of LVIS stents for ruptured intracranial aneurysms and have considered LVIS stent-assisted coiling as an option for ruptured intracranial aneurysm endovascular management (19, 20). However, a limited amount of research is focused specifically on the implementation of LVIS for acutely ruptured aneurysms located at the bifurcation. Herein, we present a cohort of patients with acutely ruptured bifurcation aneurysms treated with LVIS stent-assisted coiling. We analyzed the clinical and angiographic data to determine the safety and feasibility of this therapeutic approach.

Materials and methods

The institutional review board of our hospital approved this study (No. SOP-016-03-01), and informed consent has been obtained from all patients.

Subjects

Surgery or endovascular procedures were chosen in interdisciplinary discussions for patients admitted to our institution with aneurysms. Endovascular treatment was the preferred procedure option, except for those who required open surgery or aneurysm clipping. For patients diagnosed with ruptured aneurysms, endovascular treatment was conducted promptly upon admission. Additionally, endovascular procedures in our present cohort were all performed within 3 days of disease onset. The therapy strategy was dependent on anatomical circumstances and the treating interventionalist.

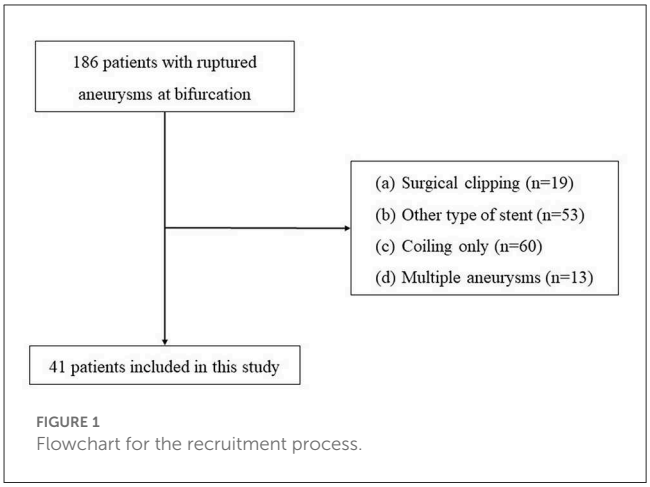

FIGURE 1
Flowchart for the recruitment process.

Between January 2017 and December 2021, 186 patients were admitted to our hospital with ruptured bifurcation aneurysms. We included patients based on the following exclusion criteria: patients (1) with blood blister-like aneurysms or multiple intracranial aneurysms; (2) who required double or multiple stents; (3) with a Hunt-Hess grade of IV–V before the procedure; (4) who received other embolization methods; and (5) who needed a craniectomy. Finally, a sample of 41 patients diagnosed with acutely ruptured aneurysms located at the bifurcation of the middle cerebral artery (MCA), anterior cerebral artery (ACA), anterior communicating artery (AcomA), or basilar tip and who underwent LVIS stent-assisted coiling was collected for the present study (Figure 1). In contrast, the other 145 patients, including 19 who received aneurysm clipping, 53 who received other types of stents, 60 who underwent coiling only, and 13 with multiple aneurysms who were also treated with other embolization methods, were excluded.

Endovascular procedure

The endovascular treatment was performed for patients under general anesthesia. A bolus of 50 IU/kg of heparin was given and routinely administered during the procedure to achieve an activated clotting time of >250 s. The femoral artery was introduced with a 6 Fr short sheath (Terumo, Japan), and a 6 Fr guiding catheter (Envoy; Johnson & Johnson, USA) was advanced to the proximal arterial lesion to establish a pathway. The structure of the lesion was assessed by 3D digital subtraction angiography using a standard biplane machine (Artis Zee Biplane; Siemens, Germany). Then, a microcatheter (Headway; Microvention, CA, USA) was placed in the parent artery to deliver the LVIS stent. The decision between selecting the LVIS or LVIS Jr. is contingent upon a multifactorial assessment, taking into account the diameter of the parent artery as well as the clinical experience of the surgeon involved. The structural characteristics of these two variations

Abbreviations: LVIS, low-profile visualized intraluminal support; LVIS Jr., low-profile visualized intraluminal support junior; EVD, external ventricular drainage; MCA, middle cerebral artery; ACA, anterior cerebral artery; AcomA, anterior communicating artery; CT, computed tomography; mRS, modified Rankin scale.

TABLE 1 Structural characteristics of the LVIS/LVIS Jr. stent.

	Recommended vessel diameter (mm)	Microcatheter for delivery (inch)	Cell size (mm)	Radiopaque visualization structure
LVIS	2.0 to 5.0	0.021	1.0	8 markers and 2 helical strands
LVIS Jr.	2.0 to 3.0	0.017	1.5	6 markers and 3 helical strands

are summarized in Table 1. Another microcatheter (Echelon-10; Medtronic, USA) was carefully introduced into the aneurysm sac. The semi-jailing technique (21) was applied to assist in the coiling packing density. The stent was fully deployed following the completion of the embolization procedure.

Antiplatelet therapy

Antiplatelet therapy was not prescribed before the operation. Furthermore, P2Y12 or other tests were not routinely used to measure individual responses to antiplatelet agents. When stent deployment was initiated, the patients were intravenously administered the glycoprotein IIb/IIIa inhibitor (Tirofiban, 100 ml/5 mg; Grand Pharma, Wuhan, China) at a dose of 0.10 μg/(kg/min) for 12 h. At the 9th h of infusion, a dosage of 75 mg clopidogrel and 100 mg aspirin was administered, either orally or *via* a nasogastric tube, daily for 3 months. Aspirin (100 mg/day) was maintained for at least 12 months. When post-procedural external ventricular drainage (EVD) was needed, surgical management was performed without discontinuing the antiplatelet medication.

For patients with intraoperative thrombus, as shown by stent thrombosis, slow blood flow in the parent artery during angiography, or the absence of distal arterial visualization, another microcatheter was employed, and intra-arterial tirofiban infusion was performed through the microcatheter, with the total dose of tirofiban not exceeding 1 mg.

Evaluation of complications, angiographic results, and clinical outcomes

Incidents of perioperative hemorrhage and thromboembolic complications were documented. Intraoperative hemorrhage was defined as contrast extravasation from the aneurysm or parent artery during angiography. Post-operative rebleeding was defined as increased hemorrhage after the operation in computed tomography (CT). Intraoperative thromboembolism was determined by the manifestation of stent thrombosis, sluggish blood flow of the parent artery observed during angiography, or the absence of visualization of the distal arteries. Post-operative thromboembolism was delineated as novel symptoms or signs of thromboembolism that were corroborated by magnetic resonance or CT imaging.

The angiographic results were evaluated immediately after the operation and during the follow-up, using the Raymond-Roy scale: class I indicated complete occlusion, class II represented residual neck, and class III indicated dome filling. The clinical outcomes were assessed upon discharge and subsequently scheduled at 3, 6, and 12 months using the modified Rankin scale (mRS). Good clinical outcomes for the mRS scores were defined as scores ranging from 0 to 2, whereas poor clinical outcomes were categorized as scores ranging from 3 to 6. The clinical follow-up was evaluated by an outpatient interview. A 6-month angiographic follow-up was recommended, and each year after the operation, using digital subtraction angiography.

Statistical analysis

The SPSS software version 22.0 (IBM SPSS Software, USA) was used for the statistical analysis. Continuous variables were presented as mean ± standard deviation, and categorical variables were presented in percentage. A P-value of < 0.05 was considered statistically significant.

Results

Of the 41 patients, 24 (58.5%) were women, and the mean age of the entire cohort was 52.3 ± 8.9 years. Furthermore, 8 patients (19.5%) had combined hypertension, four (9.8%) patients were diagnosed with diabetes, and three patients had a history of smoking. Among these patients, 21 aneurysms were located at the MCA. Additionally, one aneurysm was found to be situated at the basilar tip and ACA, respectively. Furthermore, 18 aneurysms were observed to be located at the AcomA. The mean length diameter of these aneurysms was 5.4 ± 2.0 mm, and the mean neck width was 3.3 ± 0.6 mm. Prior to the operation, the Hunt-Hess scale scores indicated that 10 cases (24.4%) were classified as grade I, 17 cases (41.5%) were classified as grade II, and 14 cases (34.1%) were classified as grade III (Table 2).

The LVIS devices were successfully deployed in all 41 cases, including 33 LVIS stents and ten LVIS Jr. stents (illustrative cases are presented in Figures 2, 3). All procedures were completed. Intraoperative thromboembolism with in-stent thrombosis incidence was observed in two cases (4.9%), and this was successfully resolved by intra-arterial tirofiban infusion without the occurrence of associated neurological deficits after treatment. Intraoperative hemorrhage occurred in one case (2.4%), and this incidence was successfully managed by neutralizing heparin, rapidly packing small coils for dense embolization to achieve hemostasis, and finally deploying the stent successfully, without substantial neurological deterioration after treatment. Post-operative complications, such as thromboembolic or rebleeding events, were not observed. After the endovascular treatment, 18 patients received lumbar cisterna drainage, while 12 patients underwent lumbar puncture. None of the cases underwent an EVD procedure.

TABLE 2 Baseline characteristics of the series of patients.

Characteristics	Value
Gender	
Male	17
Female	24
Age	52.3 ± 8.9
Lesion location	
Anterior communicating artery	18
Anterior cerebral artery	1
Middle cerebral artery	21
Basilar tip	1
Aneurysm size (millimeter)	
Length diameter	5.4 ± 2.0
Neck	3.3 ± 0.6
Comorbid disease	
Hypertension	8
Diabetes	4
Smoking history	3
Clinical manifestation	
Subarachnoid hemorrhage (SAH)	41
Hunt-Hess grade	
I	10
II	17
III	14

The data are presented in *n* (%) or mean ± standard deviation.

Following the immediate post-operative angiogram, 29 cases (70.7%) demonstrated complete occlusion (Raymond-Roy class I), 12 cases (29.3%) exhibited residual neck (Raymond-Roy class II), and no case was categorized as residual sac (Raymond-Roy class III). At discharge, 35 patients (85.4%) achieved mRS scores within the range of 0–2, four patients (9.8%) obtained a score of 3, and two patients (4.9%) scored 4.

Clinical follow-up data were obtained from all patients. Among these patients, 38 (92.7%) achieved good clinical outcomes with mRS scores of 0–2, while three (7.3%) had scores of 3. The angiographic follow-up data were available for 36 patients, with a mean follow-up time of 13.9 months. Among these patients, complete occlusion was achieved in 30 patients (83.3%), while an aneurysm neck remained in six patients. No recanalization was observed. In addition, no significant in-stent stenosis or parent artery occlusion was observed.

Discussion

A total of 41 cases of acutely ruptured bifurcation aneurysms were treated with LVIS stent-assisted coiling in our cohort. All of the LVIS devices were completely deployed. Notably, 83.3% of the aneurysms were occluded completely, and 92.7% of cases had good clinical outcomes. These findings suggest that using the LVIS stent is safe and feasible for patients with acutely ruptured bifurcation aneurysms.

With the development of devices and techniques, such as remodeling balloons, laser-cut expandable stents, and multicatheter coiling techniques, endovascular procedures have been widely applied for managing intracranial aneurysms. However, considering the protection of branch arteries incorporated in the aneurysm base and sac, the rate of occlusion and recurrence, and the paradox of antiplatelet therapy with rebleeding risk remains a challenge when treating ruptured bifurcation aneurysms with stent-assisted coiling.

The augmentation of metallic coverage across the neck of an aneurysm through the use of a low-porosity structure potentially represents an effective approach to reducing blood flow within the aneurysm sac, promoting intra-aneurysmal thrombus formation, and facilitating vessel wall reconstruction. As such, the implementation of this approach may lead to better wall apposition, a heightened degree of immediate and subsequent aneurysm occlusion, and a decreased prevalence of both rebleeding and recurrence that might result in better outcomes (22). The LVIS stent has a relatively high surface metal coverage rate (23) when compared to laser-cut stents such as the Enterprise stent and Neuroform stent (24). In a study conducted by McEachern et al. (25), a total of 196 patients, including 21 ruptured aneurysms, received endovascular treatment with the LVIS Jr. stent, resulting in a long-term complete occlusion outcome for 85% of the cohort. Fiorella et al. (26) assessed the efficacy of the LVIS stent system in 153 non-acute onset patients and demonstrated a complete occlusion rate of 79.1% on angiographic outcomes at 12 months. In a retrospective analysis by Ge et al. (27), 190 patients with unruptured intracranial aneurysms who underwent stent implantation were assessed, wherein the LVIS stent group exhibited notably higher initial complete and near-complete obliteration rates in comparison to the Enterprise stent group (96.9%, 93/96 vs. 88.4%, 99/112; $P = 0.034$). Moreover, the angiographic follow-up revealed a lower recurrence rate in the LVIS stent cohort (2.8%, 1/36 vs. 10.7%, 6/56). Conversely, some studies have yielded disparate findings. Feng et al. (28) conducted a study with 142 patients, analyzing the occlusion status of aneurysms, and discovered no significant differences in angiographic outcomes between the LVIS stent group and the Enterprise stent group. However, logistic regression analysis indicated that the LVIS device may result in a lower rate of recanalization than the Enterprise stent. Zhang et al. (29) reviewed data from 56 studies published between 2015 and 2020 and reported comparable angiographic outcomes between the application of laser-cut and braided stents. However, they also found that the recurrence rate in the laser-cut stent cohort was higher than that of braided stents (6.87 vs. 5.52%). Recently, Mokin et al. (30) analyzed 659 patients, comparing the outcomes of endovascular management using Neuroform, Enterprise, and LVIS stents. The study presented significant differences in the complete occlusion rate on post-procedure imaging (LVIS 64.4%, 210/326; Neuroform 56.2%, 95/169; and Enterprise 47.6%, 68/143; $P = 0.008$) and follow-up imaging (LVIS

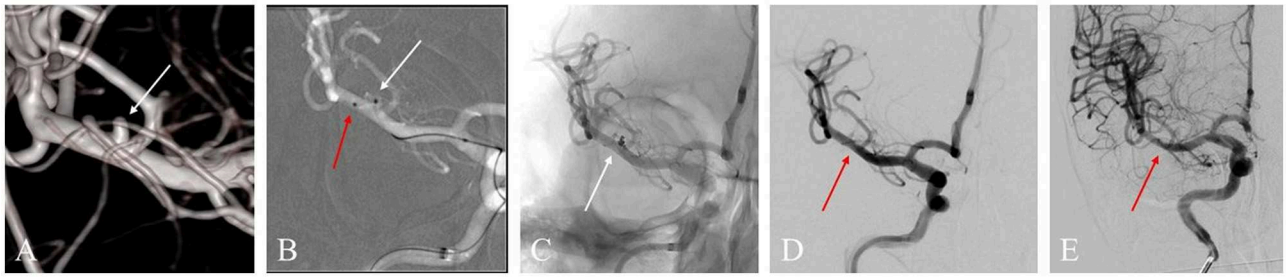

FIGURE 2
(A) A 53-year-old woman with a ruptured right middle cerebral artery (MCA) bifurcation aneurysm (white arrow) in the three-dimensional reconstruction image. **(B)** The roadmap image shows one sharp microcatheter catheterizing the aneurysm sac (white arrow) and another microcatheter placed in the parent artery (red arrow) for delivering astent device. **(C)** An LVIS Jr. stent (3.5 * 23 mm) was successfully delivered, and the aneurysm showed density packing from the coils (white arrow). **(D)** The final angiographic image manifested that the complete occlusion was achieved (red arrow). **(E)** DSA image follow-up in 12 months shows complete occlusion of the aneurysm (red arrow).

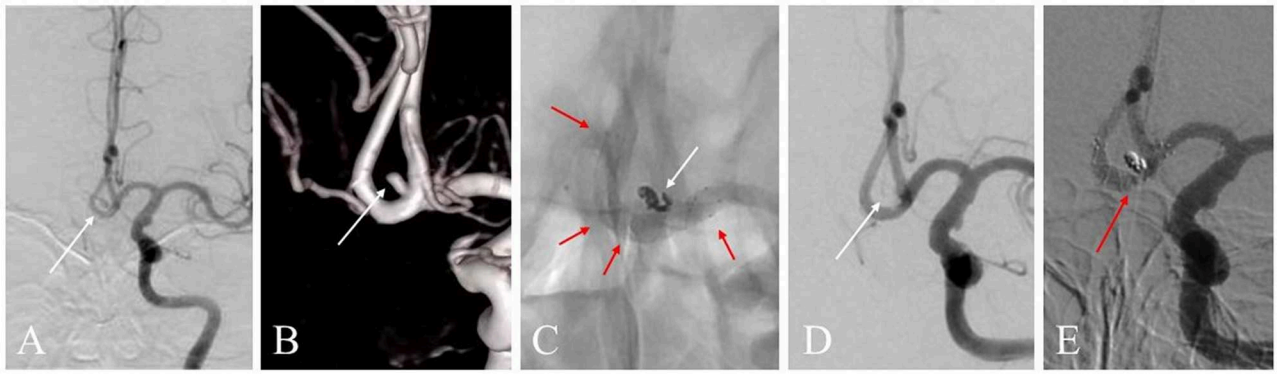

FIGURE 3
(A) A 59-year-old woman with a ruptured anterior communicating artery (AcomA) aneurysm treated with LVIS stent-assisted coiling strategy. Angiogram shows the AcomA aneurysm (white arrow). **(B)** Three-dimensional reconstruction imaging of the aneurysm (white arrow). **(C)** The LVIS stent (3.5 * 15 mm) was deployed during the procedure. The marks and the structure of the stent are presented (red arrow). The aneurysm showed density packing from the coils (white arrow). **(D)** Angiographic image shows the complete occlusion of the aneurysm (white arrow). **(E)** Digital subtraction angiography image of the aneurysm follow-up in 12 months shows the complete occlusion was achieved (red arrow).

84%, 251/299; Neuroform 78%, 117/150; Enterprise 67%, 83/123; $P = 0.004$). In addition, their subgroup analysis for ruptured aneurysms revealed a higher complete occlusion outcome in the LVIS stent application group, including 76 aneurysms, compared to the laser-cut stent group at baseline (LVIS 80%, Neuroform 52%, and Enterprise 42%, $P < 0.001$) and follow-up (LVIS 86%, Neuroform 63%, and Enterprise 58%, $P = 0.018$). Unfortunately, their study did not distinguish the specific location of ruptured aneurysms. Consistent with previous research, our investigation of ruptured aneurysms located at bifurcations demonstrated a 70.7% complete occlusion rate in the immediate post-operative angiogram, with an 83.3% complete occlusion rate on angiographic follow-up. These findings indicate that the use of LVIS stent-assisted coiling is an effective approach for treating acutely onset bifurcation lesions.

The incidence of perioperative complications during the stent application for acutely ruptured aneurysms, specifically periprocedural thromboembolic complications and rebleeding while undergoing antiplatelet therapy, is a significant concern that hinders neurosurgeons from considering this treatment option. A previous study revealed that stent implanting in ruptured aneurysms arising at the location in small vessels beyond the circle of Willis may increase the rate of perioperative complications (31). Fan et al. (32) reported that the rate of perioperative bleeding and thrombus incidence was 9.5 and 15.9%, respectively, among 63 patients with ruptured aneurysms in the AcomA and treated with stent-assisted coiling. According to Zhou et al. (33), the procedure-related complication rate of stent implantation in the acute stage was 25.9%. These studies indicated the need for careful consideration of the benefits and drawbacks of stent implantation in managing acutely ruptured aneurysms. Furthermore, incomplete expansion of the stent in the lumen of the parent artery is a risk factor for periprocedural thromboembolic complications (17). Cho et al. (34) reported five of 27 (18.5%) patients with incomplete stent expansion during LVIS stent deployment. Poncyljusz et al. (35) reported

the technical success rate of complete LVIS stent deployment as 91%.

The present study demonstrated 100% technical success with stent deployment, in which 4.9% (2/41) of cases had intraoperative thrombosis and 2.4% (1/41) of cases had an intraoperative hemorrhage. To the best of our knowledge, various factors may account for the low incidence of complications. Among these, the presence of a braided structure could offer some advantages for the management of complex aneurysms. The LVIS stents exhibit radiographic opacity and possess the capacity to be resheathed and repositioned, thus enabling convenient handling and accurate deployment. Second, the utilization of the "pull-push" technique during the stent deployment process, as well as the "bulging" technique, which entails the partial protrusion of the stent into the aneurysm's neck by pushing it across (36), provides good protection for both wide-necked aneurysms and their associated side-branches, facilitating improved attachment of the stent to the vessel wall. Third, the development of treatment materials such as the recently introduced more pliant coil materials may reduce the force applied to the aneurysm sac, potentially lowering the risk of rupture intraoperatively. Furthermore, the relatively low Hunt-Hess grade of our cohort and the use of intra-procedural cone-beam CT scans to monitor the stent expansion may contribute to a procedural facility in operation and improve clinical outcomes. In addition, the antiplatelet regimen and the usage of intravenous tirofiban in the present study, which were consistent with previous articles (37, 38), may be advantageous to the low rates of hemorrhage complications and thrombotic events.

In recent years, some novel devices have been developed for managing bifurcation aneurysms at the AcomA, MCA, and basilar tip, such as the Woven EndoBridge device (Sequent Medical, CA, USA), the PulseRider device (Pulsar Vascular, CA, USA), and the pCONus device (Phenox, Bochum, Germany) (39, 40). However, only the Woven EndoBridge device has been approved for clinical use in China but not for treating ruptured intracranial aneurysms. A prospective multicenter assessment of the Woven EndoBridge device in ruptured aneurysms conducted by Spelle et al. (41) presented a complete occlusion rate of 41.3% (19/46) at 1 year follow-up. Another study by Youssef et al. (42) revealed that 61.5% of cases achieved complete occlusion in follow-up. A systematic review conducted by Rooij et al. (43) revealed the rate of procedure-related complications in cases with ruptured intracranial aneurysms treated with the Woven EndoBridge device ranged between 1.8 and 27.3%, with the incidence rate of thromboembolic complications ranging between 1.8 and 21.0%. The follow-up occlusion rate ranged between 33.3 and 80.8%. Overall, the application of these new devices for ruptured intracranial aneurysms at the bifurcation warrants further evaluation.

The present study has some limitations. These included the retrospective and single-center design of the study and the relatively small sample size due to the highly selective cases treated with a relatively low Hunt-Hess grade, a specific stent, and an antiplatelet protocol. These may have introduced bias into the results.

Conclusion

The present study reviewed 41 patients with acutely ruptured bifurcation aneurysms treated with LVIS stent-assistant coiling. The results revealed that the LVIS stent is a safe and feasible option for patients with ruptured bifurcation aneurysms, with a high complete occlusion rate and low complication incidence. Large-scale, multi-center investigations with longer follow-ups are needed to validate these present findings.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design and final approval of the version to be published: BF, XH, and CL. Analysis and interpretation of the data and review of the submitted version of the manuscript: CL and XW. Drafted the article: CL and KG. Critically revised the article: BF and XH. Statistical analysis: LW and XW. Administrative, technical, and material support: LW, YC, and KG. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

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EDITED BY
Xianli Lv,
Tsinghua University, China

REVIEWED BY
Xiangyu Cao,
People's Liberation Army General Hospital, China
Bing Zhao,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Pei Wu
✉ wupei@hrbmu.edu.cn
Huaizhang Shi
✉ shihuaizhang@hrbmu.edu.cn

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

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LVIS-within-enterprise double-stent technique with coil embolization in the treatment of patients with acutely ruptured intracranial vertebrobasilar artery-dissecting aneurysms

Qiaowei Wu†, Yuxiao Meng†, Aixia Chen, Shancai Xu, Chunlei Wang, Zhiyong Ji, Jingtao Qi, Kaikun Yuan, Jiang Shao, Huaizhang Shi* and Pei Wu*

Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China

Objective: This study aimed to evaluate the feasibility of the low-profile visualized intraluminal support (LVIS)-within-enterprise double-stent technique for patients with acutely ruptured intracranial vertebrobasilar artery-dissecting aneurysms (ari-VBDAs).

Methods: A total of 30 patients with ari-VBDAs who underwent reconstructive treatment using LVIS-within-enterprise double-stent technique with coil embolization between January 2014 and May 2022 were retrospectively enrolled. Patients' characteristics and clinical and imaging outcomes were reviewed. The functional outcomes were assessed using the modified Rankin scale (mRS).

Results: A total of 34 ari-VBDAs were identified, including seven (20.6%) basilar artery aneurysms and 27 (79.4%) vertebral artery aneurysms. All aneurysms were successfully treated in the acute phase. In total, six (20.0%) patients experienced in-hospital serious adverse events, including two deaths (6.7%). The median clinical follow-up time of the remaining 28 patients was 20.0 (IQR, 7.3–40.8) months. The incidences of dependency or death (mRS score of 3–6) at discharge and at the last follow-up were 16.7% and 14.3%, respectively. Aneurysm rebleeding occurred in one (3.3%) patient periprocedurally. In total, three (10.0%) patients had ischemic events, one of which occurred during the periprocedural period and two occurred during follow-up. A total of two patients (6.7%) underwent ventriculoperitoneal shunt. Imaging follow-up was available for 14 patients at the median of 12.0 (IQR, 7.0–12.3) months, with a complete occlusion rate of 93.3% (14/15). In total, one patient experienced parent artery occlusion, and no aneurysm was recanalized.

Conclusion: LVIS-within-enterprise double-stent technique with coil embolization for the treatment of patients with ari-VBDAs could be performed with a good safety profile and high technical success rate. The rate of complete aneurysm occlusion during follow-up seemed to be satisfactory.

KEYWORDS

vertebrobasilar artery, dissecting aneurysms, ruptured, subarachnoid hemorrhage, stent-assisted coiling

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Introduction

The prognosis of posterior circulation aneurysmal subarachnoid hemorrhage is poor (1, 2). For patients with acutely ruptured intracranial vertebrobasilar artery-dissecting aneurysms (ari-VBDAs), if untreated, Mizutani et al. (3) reported that approximately 70% of patients subsequently underwent rebleeding, and it most commonly occurred within the first 24 h, resulting in the deaths of approximately half of those patients. Previous studies have shown that endovascular therapy tended to have better outcomes than neurosurgical clipping in the treatment of posterior circulation aneurysms (4, 5). Deconstructive treatment and single stent-assisted or multilayer stent-assisted coiling of ari-VBDAs have been described in published studies (6, 7). However, ari-VBDAs are rare, and there are limited data on the treatment outcomes regarding the imaging results and the benefits/risks of different endovascular techniques. The safety and efficacy of different endovascular treatment techniques for ari-VBDAs remain to be further explored.

A low-profile visualized intraluminal support (LVIS) device has been demonstrated to be beneficial in assisting the coil embolization of intracranial aneurysms (8). However, due to the nature of the braided stent, the LVIS stent will expand outward along the neck when treating fusiform-dissecting aneurysms, and an uneven distribution of metal coverage along the neck may affect the flow-diverting effect (9). To avoid this shortcoming, in this study, we attempted to use LVIS-within-enterprise double-stent technique with coil embolization in the treatment of ari-VBDAs. The enterprise stent was used as an external frame to limit the expansion of the LVIS stent to increase metal coverage in the aneurysmal neck (Figure 1). The current study aimed to assess the feasibility of the LVIS-within-enterprise double-stent technique with coil embolization in the treatment of ari-VBDAs.

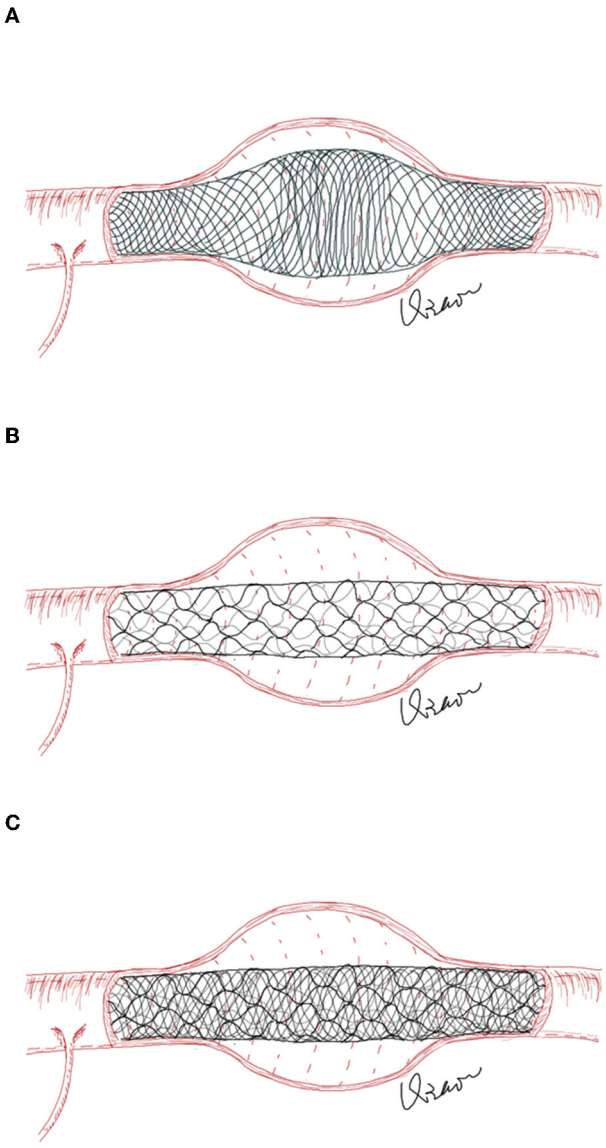

FIGURE 1
(A) In fusiform aneurysms, the LVIS stent will expand outward along the aneurysm neck, resulting in an uneven distribution of the stent's metal coverage along the aneurysm neck. **(B)** The enterprise stent has a greater radial force but less metal coverage than the LVIS stent. **(C)** The enterprise stent is first deployed to play the role of "the skeleton," which could reduce the unconstrained segment size across the aneurysm neck and limit the outward expansion of the LVIS stent.

Materials and methods

Patient population

In this retrospective analysis of our single-center database, a consecutive series of patients with ari-VBDAs treated with LVIS-within-enterprise double-stent technique with coil embolization between January 2014 and May 2022 were reviewed. The inclusion criteria for patients eligible for the study were as follows: (1) patients who received endovascular treatment within 72 h after subarachnoid hemorrhage (SAH); (2) SAH was confirmed by computer tomography (CT), and target aneurysm was confirmed by digital subtraction angiography (DSA) or CT angiography; (3) fusiform-dissecting aneurysm originating from the main trunk of the vertebrobasilar artery; and (4) aneurysm treated with LVIS-within-enterprise double-stent technique with coil embolization. The exclusion criteria were as follows: (1) aneurysm involving an extracranial segment of the vertebral artery or aneurysm originating from the branch artery; (2) basilar tip aneurysm, superior cerebellar artery aneurysm, or posterior cerebral artery aneurysm; (3) complications caused by other treated cerebral aneurysms; and (4) saccular shape, vertebrobasilar dolichoectasia, traumatic, or iatrogenic aneurysms.

A total of 30 patients harboring 34 ari-VBDAs, who underwent the endovascular treatment using LVIS-within-enterprise double-stent technique with coil embolization, were included in this study. The institutional review board of the First Affiliated Hospital of Harbin Medical University approved this retrospective study, and written informed consent was obtained from all the patients before the procedure.

Antiplatelet therapy

A loading dose of 300 mg clopidogrel and 300 mg aspirin was administrated orally or *via* a nasogastric tube at least 2 h before stenting, followed by a conventional dosage of dual antiplatelet therapy (75 mg clopidogrel + 100 mg aspirin) daily for at least 3 months. Clopidogrel was discontinued 3 months after the procedure, and aspirin was maintained indefinitely (if no contraindication). In addition, intraprocedural tirofiban administration as an alternative to preprocedural oral antiplatelet therapy was also used. Tirofiban was administered as an intravenous bolus (8 μg/kg) over a 3-min period during stenting, and a maintenance dose of 0.1 μg/kg/min was followed for at least 24–48 h after the procedure. Approximately 2 h before tirofiban was discontinued, a loading dose of 300 mg clopidogrel and 300 mg aspirin was administered orally or *via* a nasogastric tube, while the maintenance dose of tirofiban was halved, followed by a conventional daily dual antiplatelet therapy (75 mg clopidogrel + 100 mg aspirin) (10). At least 3 days after the dual antiplatelet therapy, thromboelastography (TEG) was used to monitor the platelet function of every patient. If clopidogrel hypo-responders or non-responders were detected, clopidogrel would be changed to ticagrelor 90 mg, twice daily.

Procedures

After sheath placement, a suitable guiding catheter was placed in the distal vertebral artery. Three-dimensional (3D) rotational angiography was performed, and 3D reconstruction was used to determine the work projection, measure the parent artery and aneurysms, and determine the size of the stents. The selection of stent size was generally based on the larger proximal vessel diameter of the parent artery. If the vessel was tortuous or the aneurysm neck was very wide, an appropriately larger stent size could be selected for better anchoring. The aneurysm was first coiled with the assistance of an enterprise stent (Codman Neurovascular, Massachusetts, USA) using the jailing or semi-jailing technique. After placement of the enterprise stent, the anchoring distance between the two ends of the aneurysm should be at least 5 mm. The second LVIS stent (MicroVention-Terumo, California, USA) was then deployed within the enterprise stent. The aneurysm was coiled until satisfactory, and/or additional packing was not possible.

Data collection

The following baseline variables were collected: patient demographics (including sex and age), clinical data [including the World Federation of Neurological Surgeons (WFNS) grade, modified Fisher grade, history of hypotension and diabetes mellitus, and smoking and alcohol abuse status], aneurysmal data (including the location, maximal diameter, and incorporation of the branch vessel), and procedural related data (including the number of coils used and procedure time).

Clinical outcomes were evaluated using the modified Rankin scale (mRS) score at discharge and at the last follow-up. An mRS score of 3–5 was regarded as a dependency, and an mRS score of 6 referred to the death of the patient. Postprocedural serious adverse events (SAEs) including rebleeding, ischemia, shunt-dependent hydrocephalus, or other threatening events, leading to hospitalizations or prolonged hospitalizations, were recorded. Ischemic events were defined as the following: (1) in-stent thrombosis, partial or complete occlusion of the proximal or distal arteries on DSA and (2) thromboembolism symptoms (excluding vasospasm) with or without corresponding cerebral infarction on magnetic resonance imaging (MRI)/CT. Hemorrhagic events were defined as follows: (1) postprocedural CT/MRI showing new intracerebral hemorrhage with or without clinical symptoms and (2) new subarachnoid hemorrhage on CT.

Technical success was defined as satisfactory coiling and stable stent placement with complete coverage of the aneurysm neck and patency of the parent artery. Imaging follow-up with DSA, CT angiography, or magnetic resonance angiography was performed at 6–12 months postoperatively. Aneurysm occlusion status and parent artery patency were evaluated.

Normally distributed continuous variables were summarized as mean ± standard deviation (SD), while non-normally distributed continuous variables were summarized as the median and interquartile range (IQR). Categorical variables were summarized as numbers followed by percentages.

Results

Patient demographic and baseline characteristics

A total of 30 patients harboring 34 ari-VBDAs were included in this study, with a mean age of 53.3 ± 12.7 years. The cohort comprised 18 (60.0%) male patients and 12 (40.0%) female patients. More than half of the patients had a history of hypertension (16/30, 53.3%), and nearly half had a history of smoking (40.0%, 12/30). Among the 30 patients, there were 12 patients of WFNS grade 1 (12/30, 40%), 10 patients of grade 2 (10/30, 33.3%), one patient of grade 3 (1/30, 3.3%), six patients of grade 4 (6/30, 20.0%), and one patient of grade 5 (1/30, 3.3%). In terms of the modified Fischer grade, there was one patient of grade 1(1/30, 3.3%), 15 patients of grade 2 (15/30, 50.0%), and 14 patients of grade 4 (14/30, 46.7%). Before the SAH occurred, 25 (25/30, 83.3%) patients had no symptoms (mRS score of 0), three (3/30, 10.0%) patients had mild symptoms (mRS 1), and two (2/30, 6.7%) patients had a slight disability (mRS 2). Among the 34 aneurysms, 27 (27/34, 79.4%) aneurysms originated from the vertebral artery and seven (7/34, 20.6%) aneurysms originated from the basilar artery. In total, five aneurysms (5/34, 14.7%) involved the posterior inferior cerebellar artery (PICA) or anterior inferior cerebellar artery (AICA). The median aneurysm maximum diameter was 6.6 [interquartile (IQR), 5.0–9.0] mm. The detailed characteristics are given in Table 1.

Procedural data

A total of 30 LVIS stents and 30 enterprise stents were deployed in 30 patients, with a technical success rate of 100%. In total, two

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TABLE 1 Baseline characteristics of patients and aneurysms.

Characteristics	$n = 30$ patients (34 aneurysms)
Male, *n* (%)	18 (60.0)
Mean age, years (±SD)	53.3 ± 12.7
Risk factors, *n* (%)	
Hypertension	16 (53.3)
Diabetes mellitus	4 (13.3)
Smoking	12 (40.0)
Alcohol abuse	7 (23.3)
mRS before onset, *n* (%)	
0	25 (83.3)
1	3 (10.0)
2	2 (6.7)
WFNS, *n* (%)*	
Grade 1	12 (40.0)
Grade 2	10 (33.3)
Grade 3	1 (3.3)
Grade 4	6 (20.0)
Grade 5	1 (3.3)
Modified Fisher, *n* (%)	
Grade 1	1 (3.3)
Grade 2	15 (50.0)
Grade 3	0
Grade 4	14 (46.7)
Median maximum diameter of aneurysm, mm (IQR)	6.6 (5.0-9.0)
Aneurysm location, *n* (%)	
BA	7 (20.6)
VA	27 (79.4)
Aneurysms involving side branches, *n* (%)	5 (14.7)

*Percentage totaling 99.9% due to rounding; mRS, modified Rankin scale score; WFNS, World Federation of Neurological Surgeons; IQR, interquartile range; BA, basilar artery; VA, vertebral artery.

TABLE 2 Outcome details.

Details	Number of patients
In-hospital SAEs*†, *n* (%)	
Rebleeding	1 (3.3)
Initial aneurysm rupture-related death	1 (3.3)
Ischemia	1 (3.3)
Shunt-dependent hydrocephalus	1 (3.3)
Pneumonia	2 (6.7)
mRS at discharge†, *n* (%)	
0–2	25 (83.3)
3–6	5 (16.7)
Follow-up symptoms‡, *n* (%)	
Intracerebral hemorrhage	1 (3.6)
Ischemia	2 (7.1)
Shunt-dependent hydrocephalus	1 (3.6)
mRS at last follow-up‡, *n* (%)	
0–2	24 (85.7)
3–6	4 (14.3)
Occlusion status§, *n* (%)	
Completely occluded	14 (93.3)
Incompletely occluded	1 (6.7)

*Percentage totaling 99.9% due to rounding; SAEs, serious adverse events; mRS, modified Rankin scale; †$n = 30$; ‡$n = 28$; §$n = 15$.

patients were treated with two overlapping stent-assisted coiling for two tandem aneurysms, and one patient was treated with two overlapping stent-assisted coiling for three tandem aneurysms. The median coil usage per aneurysm was 4.0 (IQR, 3.0–6.0), and the median procedure time per patient was 102.5 (IQR, 60.0–108.8) min. External ventricular drainage was performed in one patient.

In-hospital SAEs

There were six (6/30, 20.0%) patients who experienced in-hospital SAEs, including two deaths (6.7%). In total, one patient with the admission WFNS grade of 2 experienced rebleeding the day after the procedure and subsequently died. One patient with the admission WFNS grade of 5 died due to the severity of the initial aneurysm rupture. One patient experienced unilateral limb weakness 1 day after the procedure, and the mRS at discharge was 3. One patient with the admission WFNS grade of 1 developed hydrocephalus, and the ventriculoperitoneal shunt was then performed (mRS at discharge was 4). Two patients had pneumonia.

Clinical outcomes

The incidence of dependency or death (mRS score of 3–6) at discharge was 16.7% (5/30). The median clinical follow-up time of the remaining 28 patients was 20.0 (IQR, 7.3–40.8) months. In total, four (14.3%, 4/28) patients developed new symptoms during follow-up, and the incidence of dependency or death (mRS score of 3–6) at the last follow-up was 14.3% (4/28). During the follow-up, one patient died of intracerebral hemorrhage, and one patient died of acute cerebral infarction; one patient developed hydrocephalus, a ventriculoperitoneal shunt was then performed, and the mRS score at the last follow-up was 0; one patient experienced unilateral limb weakness, and the mRS score at the last follow-up was 1. Outcome details are shown in Table 2.

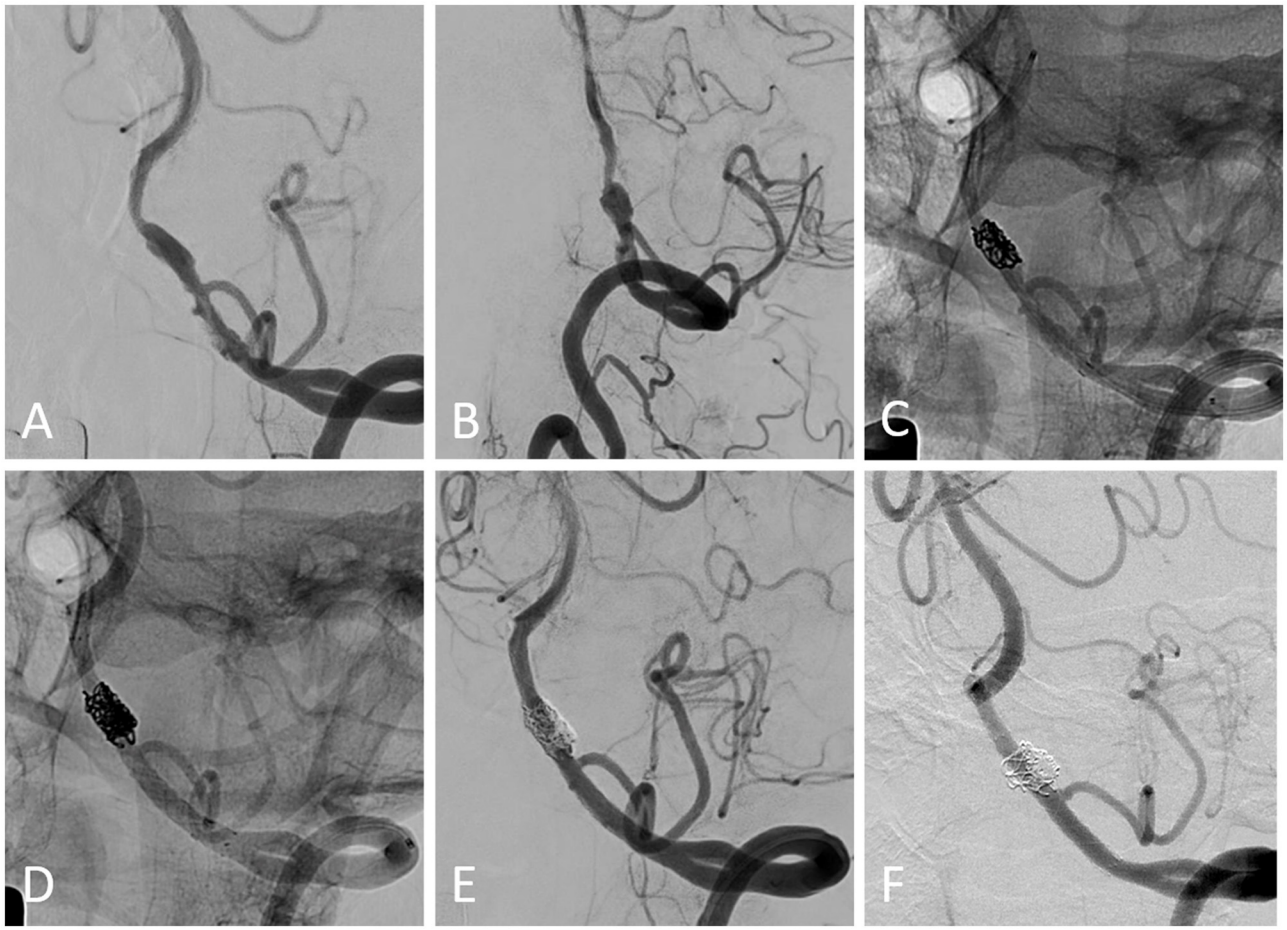

FIGURE 2
(A, B) Pretreatment digital subtraction angiography (DSA) from a patient harboring a left-sided vertebral artery-dissecting aneurysm. **(C)** The first enterprise stent was deployed after partial coil embolization using the semi-jailing technique. **(D)** The following LVIS stent was deployed within the enterprise stent, and additional coiling was performed. **(E)** The immediate postprocedural DSA showed the coiling result. **(F)** Angiographic follow-up showed the complete occlusion of the aneurysm and patency of the parent artery.

Imaging outcomes

Imaging follow-up was available for 14 patients with 15 aneurysms at the median of 12.0 (IQR, 7.0–12.3) months, with a complete occlusion rate of 93.3% (14/15) (Figure 2). In total, one patient presented with a residual aneurysm sac after the embolization, and the aneurysm remained unchanged at 12 months of imaging follow-up. One patient experienced unilateral limb weakness 3 months after the procedure, and subsequent DSA indicated occlusion of the parent artery. After intensive antiplatelet therapy, the patient's symptoms were relieved without surgical intervention.

Discussion

Despite the variety of acute treatment approaches for patients with ari-VBDAs, the prevailing view is that early intervention reduces mortality and leads to favorable clinical outcomes (2, 3). However, the technique for treating wide-necked aneurysms should be chosen carefully. The deconstruction technique for vertebrobasilar dissecting aneurysms (VBDAs) has been shown to be associated with higher occlusion rates in published studies (11, 12). Due to the pathological features of the vertebrobasilar artery and its relationship to perforated branches, the indications of the deconstruction technique are strictly limited, and it is only suitable for patients with good collateral vascularization. Reconstructive treatment including flow diversion (FD), single stent-assisted coiling, and conventional series stent-assisted coiling is the mainstream treatment for VBDAs (6, 7, 13, 14). A meta-analysis by Domingo et al. (15) found similar efficacy in the occlusion rate for posterior circulation non-saccular aneurysms treated with conventional stent-assisted coiling and FD, with the complete/near-complete occlusion rates of 84% and 83%, respectively. However, due to antiplatelet regimens, device prices, and insurance coverage, the use of FD in treating ari-VBDAs has certain limitations. In addition, a meta-analysis suggests that fusiform and dissecting aneurysms may be one of the risk factors for complications of intracranial aneurysms treatment with FD (16). The off-label use of FD for the treatment of ari-VBDAs still needs further confirmation. Conventional single stent-assisted

coiling, to some degree, was associated with risks of aneurysm recurrence (7, 13).

Low-profile visualized intraluminal support is a self-expanding, retrievable, braided intracranial stent indicated for the treatment of wide-necked intracranial aneurysms with ∼ 23% metal coverage, and previous studies have demonstrated favorable safety and efficacy profiles (8, 17). Tian et al. (18) compared the hemodynamic effect of the pipeline flow diverter and LVIS stent in aneurysm models and found that a compacted LVIS stent may provide a flow diversion effect comparable to that of PED. However, due to the braided design, in fusiform aneurysms, the LVIS stent will expand outward along the aneurysm neck, resulting in an uneven distribution of the stent's metal coverage along the aneurysm neck, which may affect the flow-diverting effect and aneurysm-healing process. Matsuda et al. (9) deployed an LVIS blue stent in a fusiform aneurysm model and found that there were three zones of different metal coverages along the stent, defined as the mid-zone, the transition zone, and the high-density zone. The transition zone was defined as the transitional portion of the aneurysm neck and parent artery, which had the lowest metal coverage. In addition, the outward expansion may also cause proximal or distal shortening of the stent, increasing the risk of stent malposition or migration. An enterprise stent has greater radial force but less metal coverage (∼ 8%) than the LVIS stent. As a laser-cut, closed cell stent, the radial force of the enterprise stent is greater than that of the LVS stent. The enterprise stent is first deployed to play the role of "the skeleton," which could reduce the unconstrained segment size across the aneurysm neck and limit the outward expansion of the LVIS stent. The LVIS-within-enterprise stenting could maintain the flow-diverting effect with a relatively high metal coverage distribution and promote the aneurysm healing process. Moreover, the unconstrained length of the LVIS stent ranges from 10 to 30 mm, and due to the braided design, the LVIS stent is at risk of shortening and migrating, which may be insufficient to cover aneurysms with long-segment lesions. The length of the enterprise stent ranges from 14 mm to 37 mm, and the original length can be maintained after deployment. Therefore, in some patients with lengthy lesions, the LVIS-within-enterprise stenting not only provides better flow-diverting effects but also prevents stent shortening or migrating.

As reported by Mizutani et al. (3), for patients with ari-VBDAs, 70% of the patients underwent rebleeding, and 56.7% of the rebleeding occurred within 24 h and 80% occurred within the 1st week, resulting in a mortality rate of 46.7%. To reduce the rate of rebleeding, early intervention to completely occlude the ruptured aneurysm is necessary. However, many cases of recurrent VBDAs after endovascular treatment have been reported (7, 13, 19). In their study, Kim et al. (13) found that the recurrence rate was 19.4% for patients with vertebrobasilar fusiform aneurysms, with a mean follow-up time of 9.2 months. The other study by Kim et al. (19) showed a recurrence rate of 13% for patients with ruptured or unruptured VBDAs and found that PICA involvement was associated with recurrence. In our study, we attempted to use LVIS-within-enterprise stent-assisted coiling in the treatment of patients with ari-VBDAs and demonstrated a complete occlusion rate of 93.3%. No aneurysm recurred in the available imaging follow-up data.

A retrospective study by Church et al. (20) included 84 ruptured or unruptured posterior circulation fusiform aneurysms treated with microsurgical and endovascular approaches. The authors reported that the neurological complication rate was 14%, and 67% of the complications were ischemic strokes. Peng et al. (21) noted that the procedure-related complication was 23.4% for patients with basilar trunk and vertebrobasilar junction aneurysms, including 16.9% of patients with ischemic complications. Another study reported that the overall SAEs rate and ischemic stroke rate were 15.7% and 13.7%, respectively, after the endovascular treatment of vertebrobasilar aneurysms (6). Published studies have reported that ischemic complications accounted for the majority of all complications after the endovascular treatment of posterior circulation or vertebrobasilar aneurysms. In our study, the incidences of periprocedural and overall postprocedural ischemic complications were 3.3% and 10.0%, respectively, which were similar to previous findings (6, 20, 21). Inadequate stent expansion, antiplatelet drug hyporesponse or non-response, and thrombus detachment during the stenting or coiling may be the potential causes of ischemic complications after endovascular therapy.

Another problem with the endovascular treatment of a ruptured aneurysm is rebleeding. In the ISAT trial, the rebleeding rate was 4.2% during the 1st year after endovascular treatment, and a meta-analysis of 2,121 patients conducted by Boogaarts et al. (22) revealed that a large aneurysm size is associated with aneurysmal rebleeding. In our study, one patient experienced postprocedural rebleeding (aneurysm maximum diameter: 15.6 mm). The coil embolization and deployment of relatively high metal coverage stents may lead to rapid intra-aneurysmal thrombus formations. The autolysis of the aneurysm wall associated with acute intra-aneurysmal thrombosis may be a possible cause of rebleeding (23).

There are some limitations. The present study was retrospectively designed with a relatively small sample size, and the potential bias inherent in retrospective research was inevitable. In addition, among the surviving patients, 46.2% of patients were lost to imaging follow-up, which might bias the evolution of the aneurysm occlusion. Moreover, the present study was not compared with other treatment modalities, and the differences in safety and efficacy between LVIS-within-enterprise stenting and other treatment modalities are unclear. Thus, further comparative studies with long-term follow-up are needed.

Conclusion

The findings in this study suggest that the LVIS-within-enterprise double-stent technique with coil embolization may be a feasible method for the treatment of ari-VBDAs, and have a good safety profile and high technical success rate. The rate of complete aneurysm occlusion during follow-up seemed to be satisfactory.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of The First Affiliated Hospital of Harbin Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QW, YM, HS, and PW contributed to the study conception and design. QW, YM, AC, SX, CW, ZJ, JQ, KY, and JS contributed to data acquisition, data interpretation, and data analysis. QW and YM drafted the manuscript. HS and PW contributed to the major revision of the manuscript. HS, PW, SX, CW, and ZJ contributed to the significant intellectual content. All authors made significant contributions to the study and manuscript preparation and critically revised the article and approved the final version of the manuscript.

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Conflict of interest

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

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EDITED BY
Cong-Hui Li,
The First Hospital of Hebei Medical University, China

REVIEWED BY
Nikhil Paliwal,
Johns Hopkins University, United States
Xiaochang Leng,
ArteryFlow Technology Co., Ltd., China
Frrédéric Clarençon,
Hôpitaux Universitaires Pitié Salpêtrière, France

*CORRESPONDENCE
Yong Sun
✉ lygsuny@163.com
Yuhua Jiang
✉ jxy200321@gmail.com

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

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The incidence and predictors of in-stent stenosis after pipeline flow-diverter stenting for intracranial aneurysm treatment

Wei You[1†], Jian Lv[1†], Zifan Li[2], Xiheng Chen[1], Dingwei Deng[1], Yudi Tang[1], Youxiang Li[1,3], Yong Sun[4*] and Yuhua Jiang[1,3*]

[1]Department of Neurosurgery, Beijing Neurosurgical Institute, Beijing Tiantan Hospital, Capital Medical University, Beijing, China, [2]Syracuse University, Syracuse, NY, United States, [3]Beijing Engineering Research Center, Beijing, China, [4]Department of Neurosurgery, The First People's Hospital of Lianyungang, Affiliated Hospital of Kangda College of Nanjing Medical University, Lianyungang, China

Background and purpose: Data on in-stent stenosis (ISS) following the flow diverter (FD) implantation method are scarce and inconsistent. In the present study, we sought to determine the incidence of ISS and identify the factors that predict its severity via the use of ordinal logistic regression.

Methods: A retrospective review of our center's electronic database was conducted to identify all patients with intracranial aneurysms (IAs) who received pipeline embolization device (PED) implantation between 2016 and 2020. Patient demographics, aneurysm characteristics, procedural information, and clinical and angiographic outcomes were reviewed. ISS was quantitatively assessed on angiographic follow-ups and graded as mild (<25%), moderate (25–50%), or severe (>50%). Ordinal logistic regression was conducted to determine the predictors of stenosis severity.

Results: A total of 240 patients with 252 aneurysms treated in 252 procedures were enrolled in this study. ISS has been detected in 135 (53.6%) lesions, with a mean follow-up time of 6.53 ± 3.26 months. The ISS was mild in 66 (48.9%) cases, moderate in 52 (38.5%) cases, and severe in 17 (12.6%) cases. All patients were asymptomatic, except for two of them with severe stenosis who presented with symptoms of acute cerebral thrombosis. Ordinal logistic regression identified that younger age and a longer procedure duration were independent predictors of a higher likelihood of ISS.

Conclusion: ISS is a common angiographic finding after PED implantation for IAs and is presented as a largely benign course through long-term follow-up. Patients who were younger in age and had a longer procedure duration were found to be at a greater risk of developing ISS.

KEYWORDS

flow diverter, intracranial aneurysm, stent, pipeline, in-stent stenosis (ISS)

Introduction

Having gained widespread global acceptance, flow diverters (FDs) have revolutionized the treatment of IAs (1). The pipeline embolization device (PED) is one of the earliest and most widely used FDs, and its efficacy and safety have been confirmed (2). Many previous studies have reported occlusion rates and hemorrhagic or ischemic complications after FD

implantation (3, 4). However, data on the incidence and predictors of in-stent stenosis (ISS) after FD implantation are scarce and confusing (5–8).

In-stent stenosis is generally defined as a loss of vessel diameter found on follow-up DSA imaging and is associated with pathophysiological changes after stent implantation (9, 10). The definition of ISS after FD implantation is not well established, as some scholars use different diagnostic criteria, such as >50 or 25% stenosis. To the best of our knowledge, to date, at least three different judgment criteria have been reported in the literature (6, 11, 12). Furthermore, the wide range of ISS occurrences reported in the literature, from 0% (12) to 100% (13), is a result of these inconsistent standards. This lack of a clear definition makes it difficult for us to understand and summarize research findings and may result in the definition of ISS changing in the future.

Although most cases of ISS are asymptomatic, some progress and cause serious complications (14, 15). A reliable method for identifying predictors that are significantly associated with ISS severity is essential. However, to date, most studies have relied on dichotomous rather than ordered categorical data in their statistical analyses (16, 17). It is well known that ignoring orders has its own disadvantages, mainly because it does not fully utilize the available information (18).

In this study, we evaluated the incidence of ISS in patients with IAs who were treated with PED at our center. ISS was defined as any discernible gaps between contrast-filled vessels and metallic struts present in angiographic follow-up images. Ordinal logistic regression was used in the present study to determine the factors associated with the severity of ISS. Our research was a single-center study with a large cohort of patients who underwent PED treatment for IAs. Our findings may provide valuable insights for both doctors and patients into this phenomenon.

Methods

Study population

We conducted a retrospective review of patients with intracranial aneurysms who received PED treatment in the Interventional Neuroradiology department of our hospital between 2016 and 2020. Patients with at least one digital subtraction angiography (DSA) follow-up and without PED implantation failure were enrolled in this study. Patient demographics, aneurysm characteristics, procedural information, and clinical and angiographic outcomes were reviewed. This retrospective study was approved, and patients' written consent was waived by our institutional review board.

Endovascular procedure

The patients received dual antiplatelet medication consisting of aspirin 100 mg/day and clopidogrel 75 mg/day for 7 days before the implantation. Routine preoperative platelet function tests were performed, and patients who were identified as clopidogrel non-responders were given either prasugrel or ticagrelor. All PED implantations were performed under general anesthesia *via* a femoral approach. According to the aneurysm anatomy and the operator's experience, the treatment strategy was formulated based on the decision of whether PED alone or PED plus coiling would be used. After the procedure, the patients were prescribed dual antiplatelet therapy for 6 months, with aspirin being continued indefinitely thereafter. Clinical follow-ups were conducted at 3, 6, 12, and 24 months after the treatment.

Angiographic evaluation of ISS

ISS is defined as any reduction in the parent artery filled with contrast medium at a follow-up DSA. In DSA, ISS is shown as a discernible gap between the vessel lumen filled with contrast medium and the inner wall of PED. Moreover, cases with no discernible gap in follow-up DSA were excluded from this study. For discernible gaps, we measured the diameter of the contrast-filled vessel and the endovascular stent diameter at its corresponding position. The rate of stenosis was then calculated as the ratio of the contrast-filled vessel diameter to the endovascular stent diameter, expressed as a percentage (Figure 1). For the diffuse ISS, we selected the maximum stenosis percentage as the representative value for analysis in the study. ISS was then graded as mild (<25%), moderate (25–50%), and severe (≥50%). In addition, ISS was divided into focal and diffuse lesions based on the location of the stents (proximal, middle, and distal), whether they extended more than 10 mm, and whether they were located at a vessel curvature. The assessment and measurement of ISS through DSA follow-up images were performed by neuroradiologists with at least 3 years of experience and reviewed by a senior neuroradiologist.

Statistical analysis

The data were presented as frequencies for categorical variables and as means and ranges for continuous variables. Unpaired *t*-tests, Chi-squared tests, and Fisher's exact tests were conducted to assess variable differences. Ordinal logistic regression was used to determine the factors associated with the severity of ISS. Variables that were found to be significant at a level of 0.1 under crude association analysis or based on clinical relevance were entered into the multiple logistic regression analysis. The results were presented as odds ratios (OR) and corresponding 95% confidence intervals (CI). A p-value of < 0.05 was considered statistically significant. All statistical analyses were carried out using the SPSS version 22.0.0 software (IBM, Armonk, NY, USA).

Results

Patient demographics, aneurysm characteristics, procedure details, and clinical outcomes

A total of 240 patients (mean age: 50.9 ± 12.8 years; 157 women, 65.4%) with 252 aneurysms treated through PED implantation in 252 procedures and with at least one DSA follow-up were included in this study. The demographic, baseline, and procedural

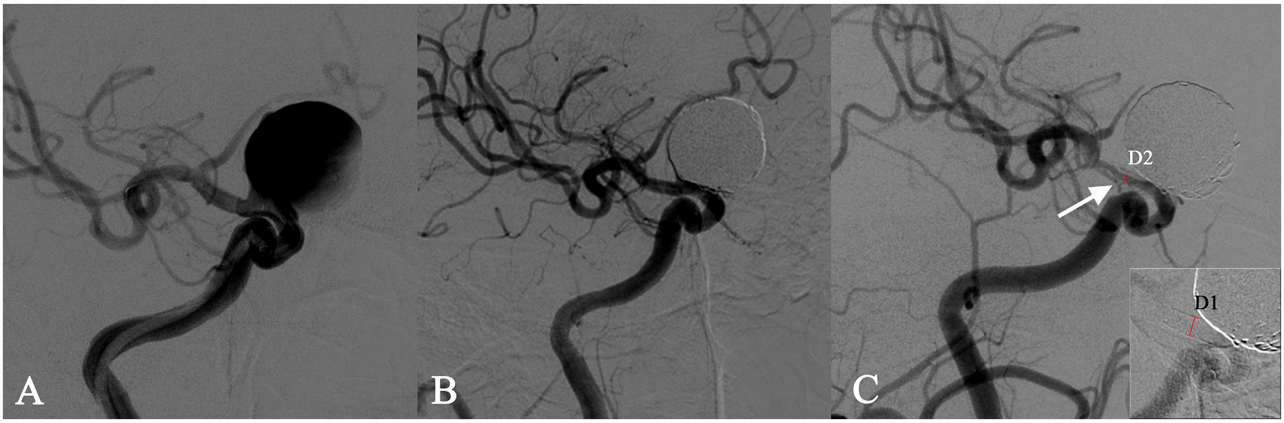

FIGURE 1
In-stent stenosis in a man in his 40s who presented with a symptomatic right carotid ophthalmic aneurysm **(A)** and was treated with the implant of a single PED stent plus coiling. Angiographic images obtained immediately after the intervention showed an unimpeded flow in the stent **(B)**. The follow-up angiography after 6 months showed a 70% in-stent stenosis (ISS% = 1 − [D2/D1] × 100%) at the distal end of the stent **(C)**.

characteristics of the cohort are presented in Table 1. Comorbidities included hypertension, diabetes, hyperlipidemia, coronary artery disease, a history of allergies, alcohol abuse, and smoking. The aneurysms were found incidental in 68 cases (28%), symptomatic in 184 cases (73%), and ruptured in 16 cases (6.3%). A total of 8 aneurysms (3.2%) were treated previously, that is, two that were treated with coiling and six that were treated with stent-assisted coiling.

In total, 201 (79.8%) saccular and 51 (20.2%) fusiform aneurysms were identified. Most of the aneurysms were located in the internal carotid artery (184/252, 73%), with 47 (18.7%) found in the vertebral arteries, 12 (4.8%) in the basilar and other posterior cerebral arteries, and 9 (3.6%) in the distal circle of Willis (including the middle cerebral artery, anterior cerebral artery, and communicating artery). Of the 252 aneurysms, 16 (6.3%) were located at a bifurcation, and 193 (76.8%) were located in the anterior circulation. The mean aneurysm neck size of the aneurysms was 9.29 ± 5.84 mm, the mean maximum diameter was 13.45 ± 7.89 mm, and the mean parent artery diameter was 3.69 ± 0.95 mm. Moreover, 20 (8%) aneurysms were associated with parent artery stenosis.

In total, 140 (55.6%) procedures were performed with the Pipeline™ Flex embolization device, while the remaining were performed using the Pipeline™ Classic embolization device. Of the 252 procedures, 133 (52.8%) were treated using PED alone, and 119 (47.2%) were treated using a combination of PED and coiling. PED was deployed successfully in all patients. Multiple PED implantations were performed in 43 (17.1%) procedures, and balloon angioplasty was administered in 52 (20.6%) procedures. The mean procedure duration was 120.93 ± 53.68 min.

At the last angiographic follow-up examination, complete aneurysm occlusion was observed in 213 cases (84.5%). The rates of periprocedural ischemic complications (periprocedural stroke or transient ischemic attacks) and hemorrhage complications were 2.8% (7/252) and 0.8% (2/252). Transient deficits were observed in 8 (3.2%) cases, and permanent deficits (mRS > 2) were observed in 4 (1.6%) cases. There were no cases of periprocedural mortality.

In-stent stenosis

In-stent stenosis was detected in 135 (53.6%) lesions using the quantitative assessment. All stenoses were detected at the first DSA follow-up, with a mean time of 6.53 ± 3.26 months. ISS was mild in 66 (48.9%) cases, moderate in 52 (38.5%) cases, and severe in 17 (12.6%) cases. The stenosis was diffuse in 56 (41.5%) cases and focal in 79 (58.5%) cases. There were 47 (34.8%) occurrences of stenosis located at the proximal end of the stent, 52 (38.5%) in the middle, 36 (26.7%) at the distal end, and 48 (35.6%) at the bend of the artery.

While most cases were asymptomatic, symptomatic stenosis was identified in two cases. One patient who was treated for a right carotid artery aneurysm with 65% stenosis at the 3-month follow-up showed left hemiplegia, which was caused by a right cerebral infarction 10 months after treatment; symptoms of the infarction were relieved by thrombolysis at the local hospital. The stenosis, in this case, had aggravated to 90% by the 18-month follow-up and was subsequently treated by vascular bypass between the superficial temporal artery and the middle cerebral artery (Figure 2). The other patient had a left middle cerebral aneurysm and suddenly showed combined aphasia, which was caused by 95% stenosis accompanied by stent thrombosis at the 6-month follow-up. The patient's symptoms resolved, and 80% stenosis remained after further treatment with balloon angioplasty and stent thrombectomy.

Among the 135 patients with ISS, 21 (15.6%) of them had long-term angiographic follow-ups with a mean time of 25.1 ± 9.4 months. Of the 21 cases, 8 (38.1%) showed completely resolved stenosis, 4 (19%) were in remission, 7 (33.3%) were stable, and 2 (9.5%) showed progress. In addition to the aforementioned cases of stenosis progression, the other case had aggravated from mild stenosis (19%) to moderate stenosis (37%) with no symptoms.

All cases were classified into three ordinal forms according to the likelihood of stenosis: non- or mild ISS, moderate ISS, and severe ISS. In the crude association analysis, significant predictors of ISS severity included female gender ($p = 0.008$), age ($p = 0.004$), smoking status ($p = 0.03$), saccular aneurysm ($p = 0.01$), parent

TABLE 1 Univariate and ordinal logistic regression analyses in relation to the severity of stenosis.

Variables	Frequency (%)	Non or Mild ISS	Moderate ISS	Severe ISS	Univariate	Multivariate	
					p	*p*	OR (95% CI)
Baseline demographics and clinical characteristics							
Women, no. (%)	168 (66.7%)	130 (71%)	32 (61.5%)	6 (35.3%)	0.01*	0.4	0.70 (0.31-1.6)
Age, y (mean ± SD)	50.98 ± 12.69	52.31 ± 11.8	48.77 ± 14	43.41 ± 14.83	0.004*	0.02†	0.97 (0.95-1)
BMI	25.03 ± 4.17	24.96 ± 3.63	25.14 ± 5.72	25.42 ± 4.38	0.68		
Comorbidities							
Hypertension, no. (%)	101 (40.1%)	77 (42.1%)	17 (32.7%)	7 (41.2%)	0.34		
Diabetes, no. (%)	19 (7.5%)	12 (6.6%)	4 (7.7%)	3 (17.6%)	0.24		
Hyperlipidemia, no. (%)	89 (35.3%)	65 (35.3%)	17 (32.7%)	7 (41.2%)	0.98		
Coronary artery disease, no. (%)	22 (8.7%)	19 (10.4%)	2 (3.8%)	1 (5.9%)	0.15		
History of allergies, no. (%)	36 (14.3%)	30 (16.4%)	6 (11.5%)	0 (0%)	0.1		
Smoking, no. (%)	49 (19.4%)	30 (16.4%)	12 (23.1%)	7 (41.2%)	0.03*	0.18	1.82 (0.76-4.38)
Alcohol abuse, no. (%)	52 (20.6%)	34 (18.6%)	14 (26.9%)	4 (23.5%)	0.21		
Symptomatic presentation of IA, no. (%)	184 (73%)	142 (77.6%)	31 (59.6%)	11 (64.7%)	0.25		
Ruptured (history of SAH), no. (%)	16 (6.3%)	10 (5.5%)	5 (9.6%)	1 (5.9%)	0.41		
Previous treatment of IA, no. (%)	17 (6.75%)	13 (7.1%)	3 (5.8%)	1 (5.9%)	0.72		
Aneurysm characteristics							
Saccular aneurysm, no. (%)	201 (79.8%)	153 (60.7%)	37 (14.7%)	11 (4.4%)	0.01*	0.1	0.47 (0.19-1.17)
Aneurysm neck size (mm)	9.29 ± 5.84	9.04 ± 5.85	9.23 ± 5.06	12.22 ± 7.45	0.15		
Maximum diameter (mm)	13.45 ± 7.89	13.34 ± 8.16	13.01 ± 6.42	15.65 ± 9.14	0.15		
Parent artery diameter (mm)	3.69 ± 0.95	3.76 ± 0.93	3.92 ± 0.87	2.86 ± 1.01	0.02*	0.09	0.76 (0.55-1.05)
Associate with parent artery stenosis, no. (%)	20 (8%)	11 (6%)	4 (7.7%)	5 (29.4%)	0.02*	0.19	1.9 (0.72-4.98)
Bifurcation aneurysm, no. (%)	16 (6.3%)	8 (4.4%)	5 (9.6%)	3 (17.6%)	0.03*	0.18	2.05 (0.72-5.81)
Anterior circulating aneurysm, no. (%)	193 (76.8%)	146 (71.2%)	37 (58.8%)	10 (76.6%)	0.04*	0.3	1.64 (0.65-4.15)
Procedure characteristics							
PED plus coiling, no. (%)	119 (47.2%)	86 (47%)	24 (46.2%)	9 (52.9%)	0.85		
Pipeline Flex embolization device, no. (%)	140 (55.6%)	107 (58.5%)	25 (48.1%)	8 (47.1%)	0.13		
Multiple PED implantations, no. (%)	43 (17.1%)	31 (16.9%)	8 (15.4%)	4 (23.5%)	0.85		
Balloon angioplasty, no. (%)	52 (20.6%)	40 (21.9%)	6 (11.5%)	6 (35.3%)	0.61		
Procedure duration (min)	120.93 ± 53.68	117.34 ± 51.15	123.44 ± 60.9	151.88 ± 49.4	0.05*	0.01†	1.01 (1-1.01)

BMI, body mass index; IA, intracranial aneurysm; SAH, subarachnoid hemorrhage; PED, pipeline embolization device. The ∗ sy ts statistical significance ($p < 0.05$) in univariate analysis, while the † symbol represents statistical significance ($p < 0.05$) in multivariate analysis.

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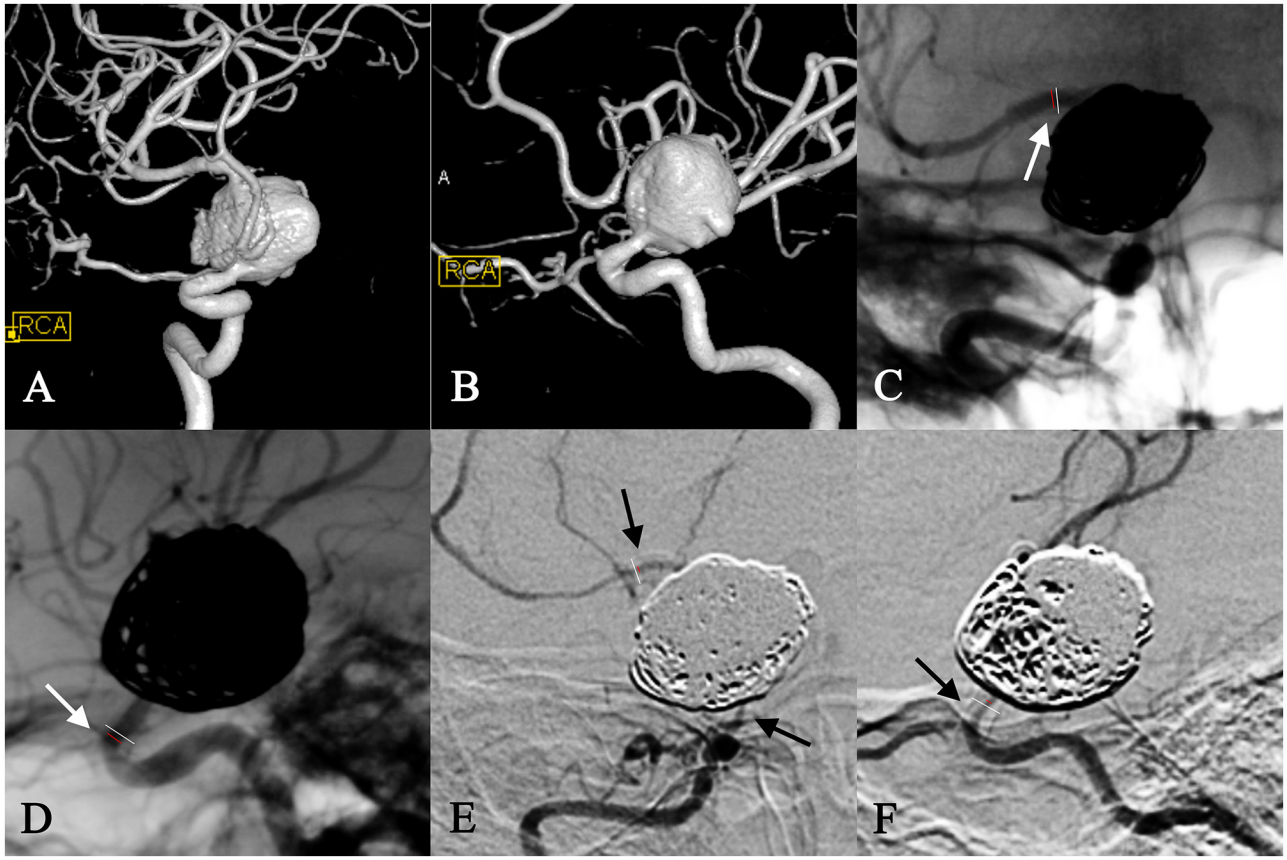

FIGURE 2
In-stent stenosis in a woman in her 30s with a right carotid ophthalmic aneurysm **(A, B)** and treatment with PED plus coiling. At the 6-month follow-up, the frontal view of the angiography showed 15% in-stent stenosis at the distal end of the stent **(C),** and the lateral view of the angiography showed 65% stenosis at the proximal opening of the stent **(D)**. This patient developed left hemiplegia due to a right cerebral infraction 10 months after surgery, which was relieved by a thrombolysis at the local hospital. ISS in this case aggravated to 90% diffuse stenosis at the 18-month follow-up **(E, F)** and was subsequently treated by a vascular bypass between the superficial temporal artery and middle cerebral artery.

artery diameter ($p = 0.02$), associated with parent artery stenosis ($p = 0.02$), bifurcation aneurysm ($p = 0.03$), anterior circulating aneurysm ($p = 0.04$), and procedure duration ($p = 0.05$). These factors were found to be significant at the level of 10% and were entered as subsets in ordinal logistic regression. In the multivariate regression analysis, the overall proportionality assumption was not violated ($p = 0.13$). Ordered logistic regression analysis showed that age and procedure duration were significant predictors of a higher likelihood of stenosis after PED implantation. To be specific, the cases with a longer procedure duration (OR = 1.01; 95% CI, 1–1.01; $p = 0.012$) had a higher likelihood of developing stenosis, whereas cases with older patients (OR = 0.97; 95% CI, 0.95–1; $p = 0.017$) had a lower likelihood of stenosis (Table 1).

Discussion

In the present study, we reported that 53.6% of the lesions had radiographically identifiable ISS, 27.38% had more than 25% stenosis, and 6.75% had more than 50% stenosis. Ordinal logistic regression was used to determine the significant factors associated with the severity of ISS. The multivariate analysis revealed that a longer duration of the procedure and a younger age were independent predictors of a higher likelihood of stenosis.

Previous literature has reported highly differentiated ISS rates ranging from 0.61 to 43.75% after PED implantation (7, 8, 19–21). This wide range is likely due to the different definitions and grading standards of the ISS that have been used by different authors. Unlike the clear definition of in-stent restenosis after coronary stent implantation, there is variable phrasing for the same postoperative imaging findings, such as "in-stent stenosis" (13) or "neointimal hyperplasia." (20). Although some researchers believe that ISS should be derived from neointimal hyperplasia (7, 14), there is currently no consensus on the specific criteria for determining the likelihood of ISS. Caroff et al. (20) considered all degrees of the vascular lumen reduction to be neointimal hyperplasia. John et al. (6) considered neointimal hyperplasia as the narrowing of the vessel of <25% and ISS as narrowing of more than 25%. Additionally, some authors considered ISS as vessel stenosis of more than 50% (22), and some did not clarify the criteria (8, 23). The vagueness and differentiation of definitions of ISS after IA stent treatment in previous literature have made comparisons difficult.

ISS is a well-known issue in endovascular stent implantation, especially in the treatment of coronary arteries, and has been

described with conventional intracranial aneurysm stents in previous studies (17, 24). The underlying cellular mechanisms of ISS have not been well described but may be associated with platelet activation and inflammation in the early phase, endothelialization and granulation tissue formation in the intermediate phase (9, 25) and smooth muscle cell and matrix formation in the late phase. Intra-aneurysmal thrombosis and the migration of endothelial cells across the aneurysmal neck along the scaffold are two major processes during aneurysm occlusion using FD (26). Therefore, considering the mechanism of aneurysm occlusion, mild stenosis, which has been defined in other studies as neointimal growth, is to be expected. This is the reason the cases with no stenosis and the cases with mild stenosis were classified at the same level in the ordinal logistic regression.

In biomedical research, sometimes, ordered categories are the result of quantitative data grouping, in addition to the frequent occurrence of ordinal categorical data. Although previous studies have classified ISS in different grades, stenosis has only been discussed in the dichotomous form, not the ordinal form (16, 17). Their results are limited by not taking full advantage of the available information. To date, no study has considered the ordinal form of ISS severity when assessing its associated factors. In the present study, ordinal logistic regression was used to determine the factors associated with the severity of ISS.

A possible explanation for younger patients being more likely to have a higher likelihood of stenosis is that the neointimal response induced by stent implantation is more robust in younger patients. Du et al. (27) confirmed this finding by observing a significant reduction of in-stent neointimal growth after coronary stenting in older patients compared with younger patients. Additionally, our finding is also consistent with the study by Chalouhi et al. (17), who found that younger age is an independent factor for ISS after stenting with Neuroform and Enterprise.

We included the procedure duration as a new variable in this study, which had not been considered in previous studies. Surprisingly, we found that a longer procedure duration was an independent predictor of a higher likelihood of stenosis. It is clear that a longer procedure duration results in a relatively higher number of operations being required, which in turn causes more damage to the endothelium. The deployment and adjustment of the stent and balloon usage inevitably result in endothelial injury. In the absence of functional endothelial cell regulation, regional smooth muscle cells activate and proliferate, resulting in neointimal tissue formation, which leads to ISS (28).

It is worth noting that the parent artery diameter may also affect the occurrence and development of stenosis. Although artery diameter was not a significant predictor of stenosis severity, it has been identified as a predictor of restenosis after coronary stenting (11). Compared with larger-diameter arteries, such as the carotid artery, the luminal diameter of the smaller vessels was dramatically influenced by intimal hyperplasia (29). Smoking has been identified as an important factor of ISS in previous studies (8) and showed significant differences in the univariate analysis in the present study, but it failed to be a significant predictor.

In the present study, spontaneous resolution of stenosis was observed. Upon long-term follow-ups, 54.5% (12/22) of the cases showed improvement or complete resolution, while 36.4% of the cases remained stable. Lubicz et al. (22) also reported that 60% of the cases had improved or completely resolved stenosis and 28% of the cases were stable after Silk stenting during long-term follow-ups. In addition, most ISS after conventional stenting also improved during long-term follow-ups (30), suggesting that ISS after aneurysm stenting may be a dynamic benign course. Although most ISS have a benign prognosis, physicians should focus on aggravation cases, especially in cases with more than 50% stenosis. Two cases presented with symptomatic stenosis of acute cerebral thrombosis in the present study, with stenosis reaching 80% in one case and progression ranging from 65 to 95% in the other, suggesting that special attention and further follow-ups are needed for severe ISS.

This single-center retrospective study may have increased the risk of selection bias. Some patients underwent angiographic follow-ups in local hospitals, leading to some follow-up losses. Although the number of cohorts in this study was relatively large, further exploration of large-scale cohorts with long-term follow-up is needed. Despite these limitations, our research may provide more insights into planning proper treatment strategies when doctors encounter similar situations.

Conclusions

In this retrospective study, the incidence of ISS was assessed, and the predictors of the severity of stenosis were determined through ordinal logistic regression. The results showed that ISS was a common angiographic finding after PED implantation and was presented as a largely benign course through long-term follow-up. Two cases presented with symptomatic stenosis, suggesting that special attention and further follow-up are needed for severe ISS. Patients with younger ages and longer procedure durations were at a greater risk of developing ISS.

Data availability statement

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

Ethics statement

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

Author contributions

YS, YJ, ZL, and YL contributed to the conception and design of the study. XC, DD, and YT organized the database. WY and

JL performed the statistical analysis and wrote the draft of the manuscript. YS, ZL, and YJ performed the revision of the current literature. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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EDITED BY
Xianli Lv,
Tsinghua University, China

REVIEWED BY
Osamah Alwalid,
Sidra Medicine, Qatar
Puhong Duan,
Hunan University, China

*CORRESPONDENCE
Lichi Zhang
✉ lichizhang@sjtu.edu.cn
Bin Song
✉ songb_radiology@163.com

†These authors have contributed equally to this work

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Automatic risk prediction of intracranial aneurysm on CTA image with convolutional neural networks and radiomics analysis

Yuan Xie[1†], Shuyu Liu[1†], Hen Lin[1], Min Wu[2], Feng Shi[3], Feng Pan[4], Lichi Zhang[1*] and Bin Song[2*]

[1]School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China, [2]Department of Radiology, West China Hospital of Sichuan University, Chengdu, China, [3]Department of Research and Development, Shanghai United Imaging Intelligence Co., Ltd., Shanghai, China, [4]Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

Background: Intracranial aneurysm (IA) is a nodular protrusion of the arterial wall caused by the localized abnormal enlargement of the lumen of a brain artery, which is the primary cause of subarachnoid hemorrhage. Accurate rupture risk prediction can effectively aid treatment planning, but conventional rupture risk estimation based on clinical information is subjective and time-consuming.

Methods: We propose a novel classification method based on the CTA images for differentiating aneurysms that are prone to rupture. The main contribution of this study is that the learning-based method proposed in this study leverages deep learning and radiomics features and integrates clinical information for a more accurate prediction of the risk of rupture. Specifically, we first extracted the provided aneurysm regions from the CTA images as 3D patches with the lesions located at their centers. Then, we employed an encoder using a 3D convolutional neural network (CNN) to extract complex latent features automatically. These features were then combined with radiomics features and clinical information. We further applied the LASSO regression method to find optimal features that are highly relevant to the rupture risk information, which is fed into a support vector machine (SVM) for final rupture risk prediction.

Results: The experimental results demonstrate that our classification method can achieve accuracy and AUC scores of 89.78% and 89.09%, respectively, outperforming all the alternative methods.

Discussion: Our study indicates that the incorporation of CNN and radiomics analysis can improve the prediction performance, and the selected optimal feature set can provide essential biomarkers for the determination of rupture risk, which is also of great clinical importance for individualized treatment planning and patient care of IA.

KEYWORDS

intracranial aneurysm, risk estimation, feature extraction, classification, machine learning

1. Introduction

Intracranial aneurysm (IA) is a localized weak or thin spot on a brain artery, which generally balloons or bulges out and is filled with blood. Intracranial aneurysms (IAs) are commonly believed to result from a combination of genetic and environmental factors. Congenital defects in the arterial wall, including thinning or weakening of the vessel walls, can increase the risk of an aneurysm forming (1–3). The bulging aneurysm presses on brain nerves or tissues, which may burst or rupture and lead to hemorrhage. The ruptured aneurysm can cause serious health problems such as hemorrhagic stroke, brain damage,

coma, and even death (4). For example, subarachnoid hemorrhage (SAH) caused by a ruptured aneurysm is life-threatening with a fatality rate of above 40% and can cause life-long cognitive impairment (5).

Current medical imaging methods for cerebral IA diagnosis include digital subtraction angiography (DSA), magnetic resonance angiography (MRA), and computed tomography angiography (CTA). Although DSA is still considered the gold standard for IA diagnosis, CTA has been proven to be an efficient method with lower cost and easier access for most patients in the actual clinical scenario (6, 7). 3D-CTA can provide detailed visualization of the anatomical structures of blood vessels in the brain and can characterize the relationship between the aneurysm and its surrounding spatial structure more comprehensively.

Although doctors can detect intracranial aneurysms based on the CTA images, it remains challenging for predicting if they are prone to rupture. It may cause difficulties in choosing preventive or conservative treatments as the former may face high surgical risk while the latter has the risk of cerebral hemorrhage caused by ruptured aneurysms. Therefore, an accurate aneurysm rupture risk prediction method is highly in demand for the treatment planning and patient care of aneurysms.

Several statistical studies have investigated risk factors for the rupture of IA, which include the aneurysm's morphology, hemodynamics, and patient-specific factors (8–13). Furthermore, Greving et al. (14) conducted a systematic review and pooled individual data analysis from 8,382 participants with subarachnoid hemorrhage as the outcome. The practical risk score assessment named PHASES was developed based on their findings. It has become one of the major assessment methods for predicting the 5-year rupture risk of unruptured IAs. In addition, some common biomechanical and hemodynamic methods have also been used for IA rupture risk estimation. Meng et al. (15) proposed an image-based computational fluid dynamic model, which demonstrated the association between hemodynamics and the rupture risk of IA.

Recently, many attempts have also been made to construct the IA rupture risk prediction models using machine learning (ML) technologies such as K-nearest neighbors (KNN) (16, 17), random forest (RF) (18, 19), support vector machine (SVM) (20), and neural networks (21). For example, An et al. (16) used five distinct classification models (XGBoost, KNN, RF, SVM, and LR) for IA rupture risk prediction with multi-dimensionally fused features. Zhu et al. (22) also adopted multiple ML methods (SVM, RF, and ANN) for IA stability assessments based on clinical features and morphological features from 3D DSA. Shi et al. (23) integrated clinical, morphologic, and hemodynamic features to build a composite model and compared the performance between several ML models (SVM, RF, LR, and multilayer perceptron) on the rupture risk prediction task of small aneurysms using CTA. To enhance the assessment of lesion characteristics in medical imaging, radiomics has been introduced to offer more comprehensive features such as shape and texture. The extracted radiomics features are then fed into machine learning algorithms for analysis. For example, Alwalid et al. (24) conducted a radiomics analysis on CTA images of patients with ruptured aneurysms and selected the most important features to construct a logistic regression model.

Recently, there have been significant improvements in medical image processing using deep learning technology. Deep learning methods such as convolutional neural network (CNN) can learn complex features from medical images and construct models with advantageous performance. Several studies have demonstrated the effectiveness of deep learning for diagnosing and predicting the progression of brain diseases (25–28). For instance, Jnawali et al. (29) proposed a fully automated deep learning framework that learns to classify brain hemorrhage cases based on cross-sectional CT images. Dai et al. (30) applied deep learning to facilitate the detection of cerebrovascular aneurysms on CTA scans. Bizjak et al. (31) proposed a deep-shaped feature extraction model that uses PointNet++ architecture to predict the growth and rupture risk of the aneurysm using CTA and MRA images. Li et al. (32) proposed a deep learning method that can directly apply to 3D CTA data without the need for manually measured features. Turhon et al. (33) proposed a deep learning model based on multi-omics factors. These studies indicate that deep learning methods can effectively extract key features from medical images for the diagnosis of brain-related diseases. However, it is essential to note that deep learning methods require a substantial amount of training data to create an effective encoder for feature extraction. As collecting a large number of medical image samples is often expensive and challenging, it is also crucial to develop robust classification methods that can make use of comprehensive features without the need for a large quantity of training data.

In this study, we proposed a novel framework for estimating the risk of cerebral aneurysm rupture. To achieve this, we proposed to extract features from CNN, radiomics, and clinical information. In turn, we applied a feature selection method to obtain an optimal feature set that is highly correlated with the patient's IA rupture information. Finally, we employed SVM to perform the final classification. The proposed method utilizes complex feature extraction techniques such as deep learning, radiomics, and machine learning to extract intricate features from IA images and clinical information. Our model offers better adaptability for classification in situations with limited datasets and realizes effective feature fusion that combines radiomics information, CNN information, and machine learning to improve the performance of aneurysm rupture risk prediction.

The main contributions of this study can be summarized as follows:

(1) We proposed a framework that integrates deep learning, radiomics, and clinical features to estimate the rupture risk of intracranial aneurysms from a more comprehensive perspective.
(2) We proposed a method that combines deep learning techniques with machine learning to achieve better classification performance.

2. Materials and methods

2.1. Materials

There were two datasets used for model construction and validation in our study.

The 301 dataset was collected from the Cooperative Beijing 301 Hospital. The 301 dataset has 239 CTA images with their corresponding segmentation of the aneurysm. After data cleaning, a total of 106 IA cases were included in the analysis due to incomplete patient information in some CTA images. The ground truth of UIA/RIA was based on the follow-up of the patients' statuses, and IAs were manually segmented by the clinical experts. Note that informed consent was obtained from all patients for the use of their information including clinical records and CTA images.

The Large IA Segmentation Dataset (LIASD) (https://doi.org/10.5281/zenodo.6801398) (28) is an open-source dataset containing 1338 CTA images with the corresponding segmentation and follow-up information.

The clinical information for the two datasets mainly includes gender, age, and the risk status of the aneurysm. Detailed demographic patient information can be found in Table 1. Each aneurysm can be either unruptured IA (UIA) or ruptured IA (RIA).

Figure 1 shows examples of rupture and unruptured aneurysms, and it is difficult to distinguish if they are UIA or RIA directly from the image. In this way, we pre-process the images to make them more convenient to use. Since the raw CTA images have different voxel spacing, we rescaled all of them to the same physical size. Specifically, each voxel in the image should correspond to its appropriate physical size, by rescaling all CTA images to $0.39 \times 0.39 \times 0.39mm^3$. Based on the provided aneurysm segmentation annotations, we extracted the bounding box of each aneurysm in all CTA images. We extracted a patch for each aneurysm by setting the center of the patch as the center of the corresponding bounding box. We extracted each patch as a 3D cube of $64 \times 64 \times 64$ in voxel space. This method ensures that the extracted 3D patch contains sufficient information on the vascular structure while avoiding the degradation of the performance caused by the extract's excessive size. Examples of the CTA images with their extracted patches are shown in Figure 2. We also normalized the image intensity by setting CT window width (WW) *to* 110*Hu* and window level (WL) *to* 40*Hu* based on clinical experience.

TABLE 1 Demographic and clinical information of all samples in the two datasets.

Category	301 dataset	LIASD dataset
Age (years): Mean ± Std	57.3 ± 12.3	57.7 ± 12.9
Gender: male/female (%)	28/78 (35.9)	571/767 (74.4)
UIA/RIA*	78/28	822/516

*UIA and RIA stand for unruptured and ruptured IA, respectively.

2.2. Methodology

To predict the risk status of IA, we proposed a novel classification framework that combines CNN and radiomics technology as shown in Figure 3. Note that CNN is used to quantitatively describe the highly sophisticated image features, while radiomics is used to quantitatively describe the traditional image features. Therefore, the main idea is to obtain both the radiomics and CNN visual features from the collected images with the annotated region and incorporate the patient's clinical information for constructing the overall feature vector. Then, we used the LASSO regression method to find the optimal subset of features that are highly correlated with the prediction outcome. This can eliminate redundant information and simplify the model for preventing overfitting issues. Finally, the selected features were used to train the required classifier through SVM.

2.2.1. CNN feature extraction

Deep convolutional neural networks have the ability to extract deep features from images. Our 3D CNN architecture has been developed from the ResNet network (34), which is a classical deep convolutional neural network for analyzing images. Since

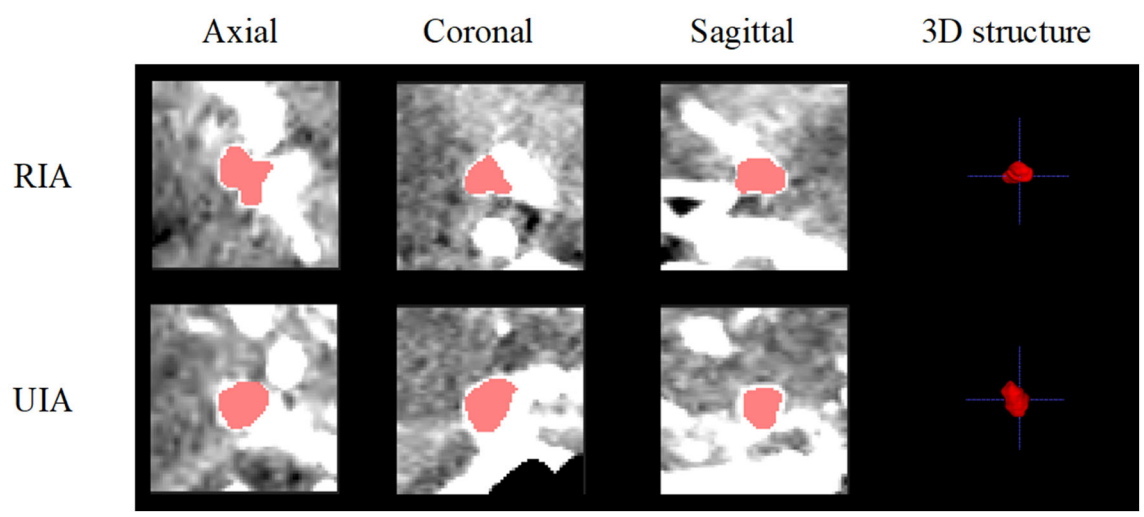

FIGURE 1
Examples of rupture and unruptured aneurysms.

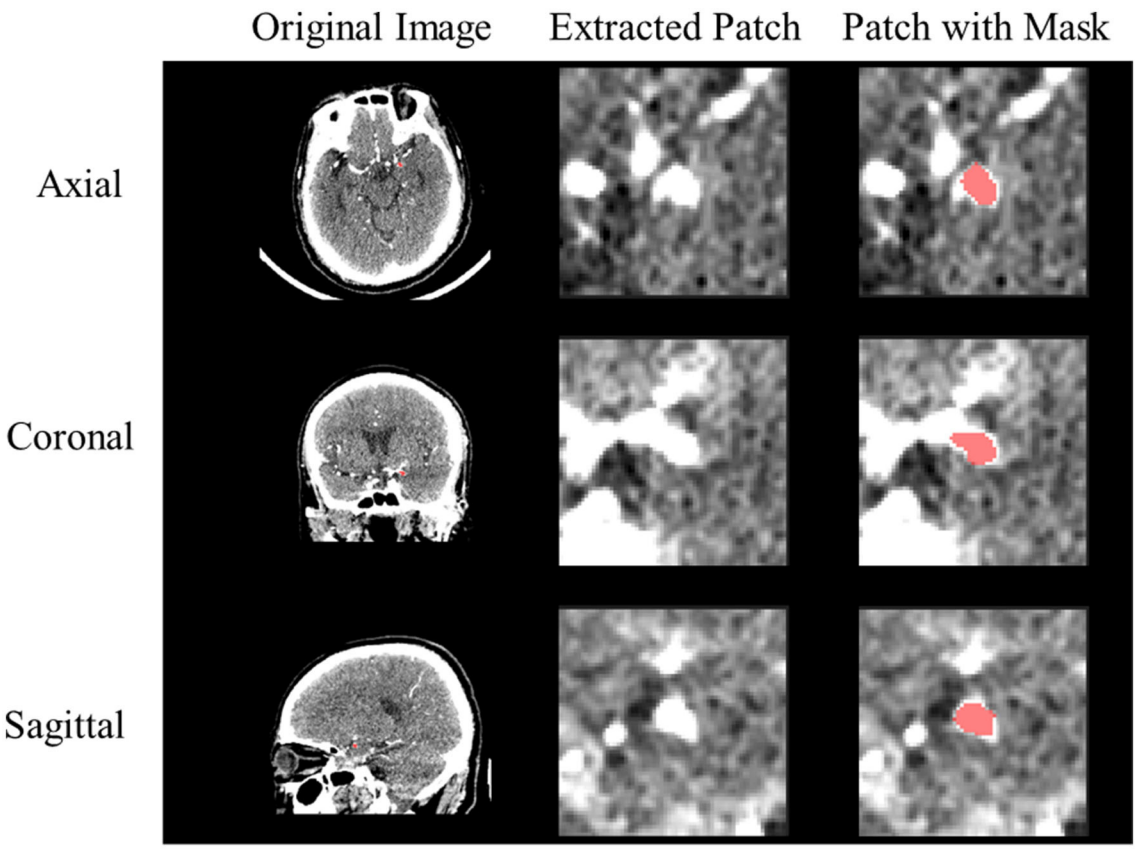

FIGURE 2
Example of preprocessed CTA image. The red color represents the IA segmentation mask from the extracted 3D patch.

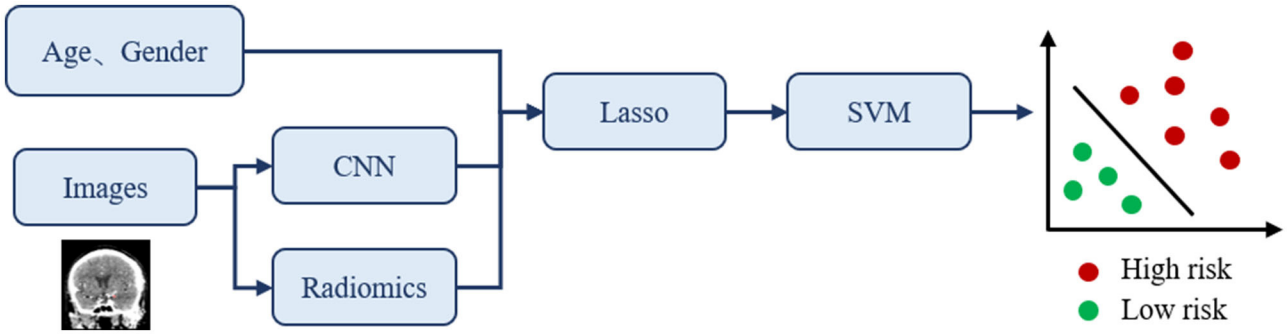

FIGURE 3
The proposed classification framework for IA rupture risk estimation. The input of this classification network is clinical information and CTA images, and the output is the prediction of risk status.

ResNet has different configurations according to their layer number settings, we use ResNet-18 as the backbone to extract CNN features, which is sufficient to extract image features. As the input data were three-dimensional, and ResNet was originally designed for two-dimensional images, we replaced the 2D convolutional layer and 2D pooling layer of ResNet-18 with a 3D convolutional layer and 3D pooling layer. The input of ResNet-18 is the preprocessed 3D patch with the aneurysm lesion, and the output is the predicted rupture risk. In the process of feature fusion, we used the trained model to extract CNN features by extracting the deep feature vectors before fully connected layers. Note that we also tried VGG as the backbone in the experiments, which is also widely applied for extracting deep learning features. However, its performance was not comparable with that of ResNet. In addition, we used random flipping for data augmentation to guarantee the robustness of the trained model.

2.2.2. Radiomics feature extraction

We used PyRadiomics (35) to extract radiomics features from the 3D patch and the segmentation map. PyRadiomics is an open-source Python package for medical image processing, analysis, and interpretation. These features can be sub-divided into seven classes: First Order Statistics, Shape (3D), Gray Level Co-occurrence Matrix (GLCM), Gray Level Run Length Matrix (GLRLM), Gray Level Size Zone Matrix (GLSZM), Neighboring Gray Tone Difference Matrix (NGTDM), and Gray Level Dependence Matrix (GLDM). We hypothesize that these features can provide helpful additional information for predicting the risk of rupture since these contain relatively deep morphology and texture features of the aneurysm.

2.2.3. LASSO feature selection

After feature extraction, we had a total of 650 features, including 512 CNN features, 136 radiomics features, and 2 clinical features (age and gender). Among these features, some may not be relevant to rupture risk prediction. Therefore, we used the least absolute shrinkage and selection (LASSO) regression to select features that have a strong correlation with rupture risk and to prevent the issue of overfitting while constructing the classifier. The LASSO regression is a model in which the L1 norm constraint term is added to the cost function of the linear regression model. The optimization goal can be represented as Equation (2.1). It conducts variable screening and complexity adjustment through the penalty coefficient λ:

$$\min_{w} = \sum_{i=1}^{m} (y_i - w^T x_i)^2 + \lambda ||w||_1. \qquad (2.1)$$

2.2.4. SVM-based risk status prediction

In this study, we used SVM to predict the risk of aneurysm rupture after feature extraction and selection. SVM is one of the most popular supervised learning algorithms in classification and regression problems. The algorithm is lightweight and efficient and has an excellent performance in high-dimensional vector space, which is more suitable in the scenario where the dataset has limited image samples. Note that in experiments, we also compared its performance with the fully connected layers of the ResNet. Each IA image has a selected feature vector with its ground truth of UIA/RIA labels, which is used to train the classifier via SVM.

3. Experiments and results

Since the 301 dataset is relatively small (106 cases total) for training an aneurysm rupture risk prediction task, the model is easy to be overfitted during the training process and hard to obtain acceptable performance (accuracy = 70.83% on the 301 test set). Therefore, we first used the large dataset, which is the LIASD dataset to train our baseline model (ResNet-18) and obtained the pre-trained model. Based on the pre-trained model, we used the 3-fold cross-validation to finetune and evaluate our proposed model. Deploying pre-trained models designed for larger datasets on smaller counterparts is beneficial as it provides a plausible solution to the issue of limited sample size. Moreover, we conducted an ablation analysis to ascertain the significance of the techniques in our framework toward the enhancement of rupture risk prediction.

Specifically, we have three types of features during the experiment: features extracted from the CTA image patch using ResNet-18 (Deep Features); radiomics features extracted from the original CTA image and the corresponding aneurysm masks using PyRadiomics (Radiomics Features); and clinical information of patients includes gender and age (clinical features). To evaluate the improvement of our approach, we conducted our cross-validation experience using the following five methods with different configurations:

(1) ResNet: Fine-tune the pre-trained ResNet-18 with only the CTA images to obtain the final classification.
(2) ResNet + SVM: Feed deep features to the SVM classifier to generate the final classification results.
(3) FCB-ResNet (feature concatenate before FC layer): Concatenate deep features, radiomics features, and clinical features before fully connected layers of ResNet-18, and then obtain the prediction result of ruptured IA.
(4) FC-SVM (feature concatenate + SVM): First, feed the concatenate deep features, radiomics features, and clinical features, and then feed the fusion feature vector to the SVM classifier to generate the final classification results.
(5) FC-LSVM (feature concatenate + LASSO + SVM, the proposed method): Feed the concatenate deep features, radiomics features, and clinical features. Then, select features of high importance using LASSO regression, and finally, feed the fusion feature vector to the SVM classifier to generate the final classification results.

The experimental platform of our study is the Debian 5.16.12 operating system. We performed all experiments on an NVIDIA 3090 Ti GPU.

The F2 score is the weighted harmonic mean of the precision and recall, which gives more weight to recall than to precision. For the task of predicting rupture risk, false-negatives are considered worse than false-positives. Therefore, the F2-score is also considered the main evaluation metric besides accuracy in this study.

The experimental results are shown in Table 2, in which ResNet-18 is our baseline method as previously mentioned. It can be observed from Table 2 that the SVM classifier performs better than the original fully connected layers in the ResNet-18 model, with an improvement of 9.40% in accuracy compared with the baseline model. As envisioned earlier, the clinical information of patients and the radiomics features have offered more information for the rupture risk evaluation task since the accuracy rises by 6.84% compared with the baseline model just by adding these features before the fully connected layer. However, when operating the two lifting facts at the same time, we did not observe a further increase in accuracy, and the recall rate decreased significantly by over 10%. In addition, although SVM is good at handling high-dimensional information, its performance is highly dependent on the quality of the feature vectors, which means too much redundant information may instead reduce the performance. Table 2 shows that the proposed method with feature selection obtained the best performance with an accuracy of 89.78 ± 4.79% and an F2-score of 79.06 ± 5.70%. The area under the curve (AUC) of

TABLE 2 The 3-fold cross-validation results of the five alternative methods.

	Accuracy	Recall	Precision	F2-score	AUC
ResNet	0.7778	0.8222	0.7302	0.7006	0.8291
ResNet+SVM	0.8718	0.6297	0.8333	0.6587	0.8301
FCB-ResNet	0.8462	0.7778	0.5556	0.5727	0.8667
FC-SVM	0.8590	0.5926	0.7889	0.6047	0.8576
FC-LSVM	0.8978	0.7963	0.8139	0.7906	0.8909

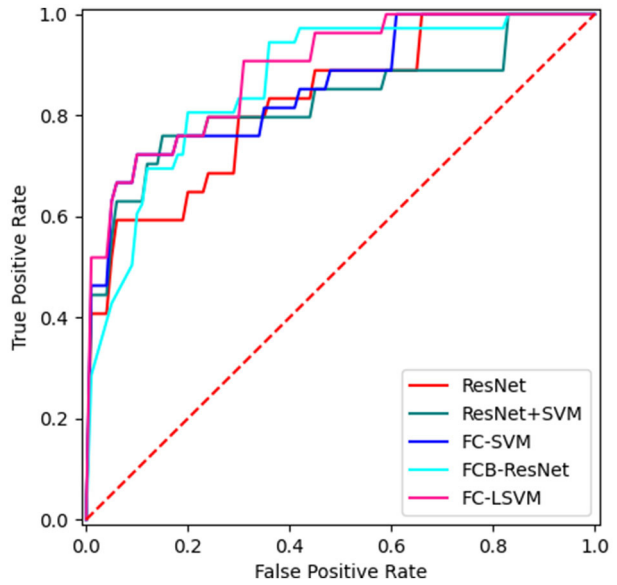

FIGURE 4
The ROC curves of the 5 alternative methods.

the receiver operating characteristic (ROC) curve can measure the quality of the classification model, and a higher AUC represents better performance. The corresponding ROC curve is presented in Figure 4.

Note that by using LASSO regression, we eliminated numerous redundant features and discovered that 61 features are highly correlated with the risk of aneurysm rupture. The 61 features can be grouped into three categories: clinical features, radiomics features, and CNN features. Table 3 provides specific measurements of the dimensions of the three groups of features. We elaborate on both the name and the characteristics of each clinical and imaging feature to aid in interpreting the features. Note that we do not provide further information for the selected CNN features since they are extracted from the constructed model and their feature representations are generally impractical to explore.

We then used the Delong test to observe the significance of different methods, and the *P*-values are listed in Table 4. Although our model performs best in terms of performance, there is no statistical difference between the different models. We consider that the high *p*-value is caused by the small size of the dataset and the imbalance of sample numbers.

We also compared our method with the alternative study by Liu et al. (3) and Li et al. (32). Liu et al. extracted morphological features manually and combined them with data distribution features extracted using PyRadiomics and CNN network and tried both XGBoost and FCN for final classification. Li et al. proposed a deep learning method called TransIAR net that can be directly applied to 3D computed tomography angiography (CTA) data without manually measured features. The method used a multiscale 3D CNN and a transformer encoder to extract the structural patterns and spatial dependence of the aneurysm and its neighborhood. The comparison results are shown in Table 5, in which our method improves accuracy by 3.3% (compared to 0.865), recall by 9.6% (compared to 0.700), and the F2-score by 6.2% (compared to 0.729). However, the method proposed by Liu et al. showed better precision (0.875). Overall, we still consider that our method outperformed the work of Liu et al. as accuracy and the F2-score are more important in the rupture prediction scenario.

4. Discussion

In summary, we proposed a novel feature fusion framework for aneurysm rupture risk prediction. Our approach combines the features extracted by CNN with the radiomics features and clinical information of patients, filters the features using LASSO regression to provide high-quality input to the SVM classifier, and finally achieves high accuracy (0.8978 ± 0.0479) and F2-score (0.7906 ± 0.0570). The importance of the selected features in assisting the diagnosis of aneurysms is later discussed in this section.

We successfully addressed the problem of overfitting during model training and poor generalizability due to the limited size (106 cases totally) and uneven distribution of the 301 dataset using a pre-training approach on the larger LIASD dataset, followed by fine-tuning on the 301 dataset. By using this strategy, the classification accuracy of our model on the 301 dataset improved by 18.95% (89.78% vs. 70.83%). We further analyzed the selected features in experiments and summarized the advantages and disadvantages of our approach. As previously mentioned, we finally obtained the 61-dimensional feature vector for each aneurysm to predict the rupture risk, which is considered to have high correlations with the rupture risk. The optimal 61-dimensional feature vector contains three types of vectors:

(1) 1-dimensional vector concerning the clinical information of the patient
(2) 9-dimensional vector concerning the radiomics features
(3) 51-dimensional vector extracted by ResNet.

We focused on age and gender as clinical factors since previous studies have indicated their association with the rupture risk of intracranial aneurysms. For the two clinical features, gender is finally selected, indicating that there is a high correlation between

TABLE 3 Overview of features after the LASSO regression feature selection process.

Feature group	Feature name	Description
Clinical features (1-dimensional)	Gender	The gender of the patient
Radiomics features (9-dimensional)	Diagnostics Mask Original Volume Num	The number of aneurysms of a patient (image)
	Original Shape Maximum 3D Diameter	The maximum 3D diameter of the aneurysm
	Original Shape Sphericity	The measure of the roundness of the shape of the aneurysm region relative to a sphere.
	Original Shape Surface Area	The surface area of the aneurysm
	Original GLCM MCC	The maximal correlation coefficient (MCC), a measure of the complexity of the texture
	Original GLSZM Small Area Low Gray Level Emphasis	Small Area Low Gray Level Emphasis (SALGLE) measures the proportion in the image of the joint distribution of smaller size zones with lower gray-level values
	Original GLSZM Zone Entropy	Zone entropy (ZE) measures the uncertainty/randomness in the distribution of zone sizes and gray levels. A higher value indicates more heterogeneity in the texture patterns.
	Original GLSZM Zone Percentage	Zone percentage (ZP) measures the coarseness of the texture by taking the ratio of the number of zones and number of voxels in the ROI
	Diagnostics Mask Original Bounding Box	The location of the aneurysm in the brain
CNN features (51-dimensional)	Features extracted by ResNet-18	Part of the features in the feature map extracted by ResNet-18

TABLE 4 *P*-values of Delong's test.

	ResNet	ResNet+SVM	FCB-ResNet	FC-SVM	FC-LSVM
ResNet		0.832	0.247	0.556	0.652
ResNet+SVM	0.832		0.465	0.380	0.584
FCB-ResNet	0.247	0.465		0.601	0.556
FC-SVM	0.556	0.380	0.601		0.774
FC-LSVM	0.652	0.584	0.556	0.774	

gender and rupture risk. In our dataset, more patients are female, and women had a lower risk of aneurysm rupture than men. One study has shown that UIAs are more common in women than men (36). Differences between genders in the incidence of SAH have been consistently concerned since SAH disproportionally affects women. A prospective study of SAH in Texas between 2000 and 2006 showed that women have an age-adjusted risk ratio of 1.74 compared to men (37). It should be noted that, despite previous research suggesting that the risk of IA increases with age (38), the feature on age was excluded during feature selection. We attribute it to the fact that the age range of the two datasets is concentrated between 50 and 65 (the patients' age in the LIASD and 301 datasets is 57.7 $\pm$ 12.9 and 57.3 $\pm$ 12.3), which undermines its influences on the rupture risk prediction work.

Morphological features selected from the radiomics feature group for analysis primarily describe the morphological characteristics of aneurysms, including their shape, size, and surface area. These features are relatively easy to interpret and are essential for accurate diagnosis and treatment planning. It is generally believed that aneurysm size is the most significant factor affecting the risk of aneurysm rupture. It is widely recognized that the likelihood of aneurysm rupture has a linear relationship with the diameter of the aneurysm (39). The shape, size, and surface area of the aneurysm may combine to reflect the pressure of blood on the aneurysm wall, suggesting hemodynamic characteristics near the aneurysm. Studies have also shown that systolic blood pressure (SBP) is a strong predictor of aneurysm rupture (40, 41). These characteristics reflect the possibility of aneurysm rupture from the aspect of biomechanical factors.

In addition to morphological features, features that describe the gray-level information of the original CTA image were also selected. These features describe the contribution and co-occurrence of gray levels, providing valuable insights into the context and location information of the aneurysm. We believe that the heterogeneity and coarseness of the texture could indicate the malignancy of an aneurysm. According to a multivariate analysis published by

TABLE 5 Comparison with other rupture risk prediction methods.

	Accuracy	Recall	Precision	F2-score
XGBoost	0.652	0.700	0.583	0.673
FCN	0.826	0.700	0.875	0.729
TransIAR	0.865	0.667	0.740	0.670
FC-LSVM	0.898	0.796	0.814	0.791

Lacent, aneurysm location is a predictor of brain hemorrhage. The most frequent site of aneurysm rupture is the tip of the basilar artery, followed by the cavernous artery and posterior communicating artery as the reference group (42). In conclusion, the abovementioned features selected from the clinical feature group and the radiomics feature group were consistent with clinical experience and prior explorations.

CNN features were selected from the feature map generated by ResNet-18. As a classical deep convolution network, ResNet-18 can extract more comprehensive features that can characterize the properties of the target lesions. Furthermore, the deep features extracted by CNN from images, the radiomics information describing the morphological and texture features of the aneurysm and its contextual environment, and the patient's personal information such as gender are complementary to each other in the aneurysm rupture risk prediction task.

As a limitation of our study, it should be noted that the clinical information of patients in the two datasets only contains the age and gender, and more information can be collected in the future to further explore if they can contribute to the improvement of the rupture risk prediction task. Additionally, although the current feature fusion method is proved effective via experiments, it remains simple and more investigations can be made for designing the feature fusion strategy to further improve the performance of our approach.

5. Conclusion

In this study, we propose a novel classification framework to predict the risk status of IA. Specifically, image features are extracted using both CNN and radiomics and combined with patients' clinical information for predictions. Our proposed framework outperforms all other methods, with the highest measures of accuracy, F2-score, and AUC of ROC. In future work, we will investigate the use of domain adaptation techniques to enhance the robustness and accuracy of our proposed method for application in multi-site scenarios.

Data availability statement

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

Ethics statement

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

LZ, FS, MW, FP, and BS contributed to the conception and design of the study. MW organized the database. YX, SL, and HL finished the experiments. YX wrote the first draft of the manuscript. FS and LZ finalized the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

FS was employed by Shanghai United Imaging Intelligence Co., Ltd.

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

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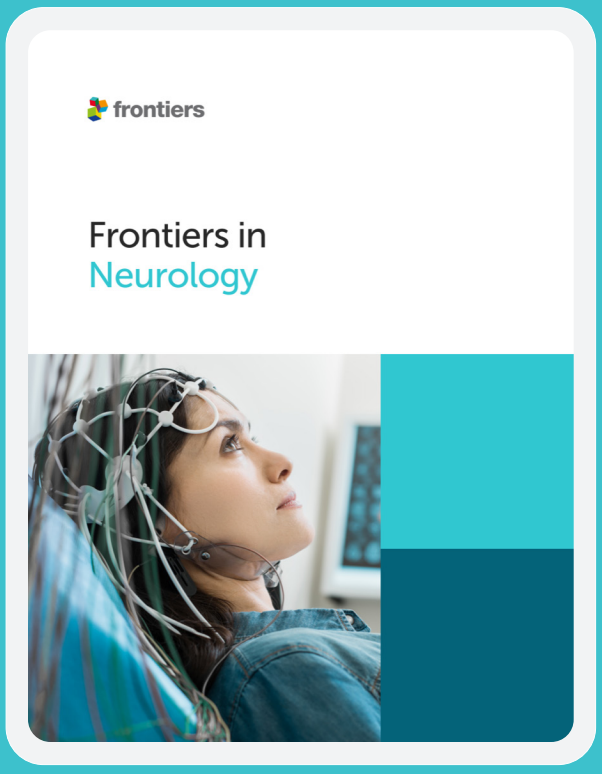

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