

Intracranial aneurysms, AVM and other vascular malformations, and connective tissue disorders as potential causes of stroke: advances in diagnosis and therapeutics including novel neurosurgical techniques

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Vishal K. Chavda, Giuseppe Emmanuele Umana, Bipin Chaurasia, Stefano Maria Priola and Luis Rafael Moscote-Salazar

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Intracranial aneurysms, AVM and other vascular malformations, and connective tissue disorders as potential causes of stroke: advances in diagnosis and therapeutics including novel neurosurgical techniques

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Editorial: Intracranial aneurysms, AVM and other vascular malformations, and connective tissue disorders as potential causes of stroke: advances in diagnosis and therapeutics including novel neurosurgical techniques

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Editorial on the Research Topic

[Intracranial aneurysms, AVM and other vascular malformations, and connective tissue disorders as potential causes of stroke: advances in diagnosis and therapeutics including novel neurosurgical techniques](#)

The cerebral vasculature is a marvel of complexity and when disrupted by aneurysms, AVMs, or vascular malformations associated with connective tissue disorders, it becomes a critical substrate for ischemic and hemorrhagic stroke. This Research Topic in *Frontiers in Neurology* curates multidimensional contributions that unify genetics, computational modeling, clinical diagnostics, and procedural advances, collectively moving the field toward more individualized and proactive care models.

Systemic inflammation and autoimmune disease have emerged as independent risk factors for aneurysm formation. [Tang et al.](#) employed Mendelian randomization to demonstrate a causal link between systemic lupus erythematosus and intracranial aneurysms, with consistent findings across East Asian and European populations, advocating for targeted vascular imaging in autoimmune patients ([Tang et al.](#)). Complementing this, [Wang et al.](#) integrated high-resolution vessel wall imaging with hemodynamic and clinical features to produce a validated rupture risk model ([Wang et al.](#)),

while [Lei et al.](#) applied machine learning to predict poor outcomes after endovascular treatment highlighting the growing utility of AI-based clinical decision support ([Lei et al.](#)). Sex- and age-specific risk differentials were explored by [Mao et al.](#) and [Shen et al.](#), both showing that anatomical and physiological differences particularly in women under 50 and men with certain aneurysm morphologies necessitate tailored therapeutic strategies ([Mao et al.](#); [Shen et al.](#)).

Beyond etiology, the procedural landscape continues to evolve. [Zhang et al.](#) reported that stent-assisted recanalization in chronic occlusions can be safe and effective when proper anatomical factors are respected ([Zhang et al.](#)). Meanwhile, [Lan et al.](#) refined the subtemporal approach to access posterior communicating artery aneurysms, demonstrating it as a viable alternative in anatomically challenging cases ([Lan et al.](#)). Hemodynamic modeling, particularly computational fluid dynamics (CFD), is increasingly foundational. Xu et al. utilized patient-specific CFD to shape microcatheters in aneurysm embolization, improving precision and procedural safety (1), while Bozorgpour and Kim emphasized the need for standardized hemodynamic variables in CFD analysis, proposing a framework for cross-study reproducibility (2).

In AVMs, bibliometric analysis by Tang et al. revealed a 20-year trend toward combined modality treatments and an increased focus on outcome prediction, especially in unruptured cases (3). [Shotar et al.](#) contributed a unique dataset on ultra-early neurological deterioration after AVM rupture, underscoring the need for rapid diagnosis and decompression protocols ([Shotar et al.](#)). Genetic investigations by Neyazi et al. found that CEACAM1 and IL-6 polymorphisms, along with sex-based immunologic differences, may underlie hemorrhagic risk in AVM carriers, suggesting that inflammation is both a symptom and a pathogenic driver (4). Finally, the issue turns a spotlight on connective tissue disorders where under-recognized risk meets preventable catastrophe. Kim et al. reported aneurysm prevalence as high as 28% in patients with Ehlers-Danlos, Marfan, and Loeys-Dietz syndromes far exceeding the general population rate of 3% (5). These data argue for systematic screening in patients with heritable vasculopathies and call for collaboration between neurologists, geneticists, and vascular surgeons.

In summary, this Research Topic crystallizes three pillars of modern vascular neurology: inflammation and genetics as

risk predictors, hemodynamic modeling as both diagnostic and therapeutic aid, and procedural refinement as a vehicle for safer, personalized interventions. Despite these gains, several gaps persist particularly in unifying risk scores, validating CFD parameters across platforms, and embedding genomic screening into standard practice. The future of stroke prevention in vascular malformations lies not in a single discipline but in cross-disciplinary synthesis, where predictive algorithms, surgical precision, and molecular insight converge at the bedside.

Author contributions

VC: Writing – review & editing, Writing – original draft. GU: Writing – original draft, Writing – review & editing. BC: Writing – review & editing, Writing – original draft. SP: Writing – original draft, Writing – review & editing. LM-S: Writing – original draft, Writing – review & editing.

Conflict of interest

LM-S was employed by AV Healthcare Innovators, LLC.

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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Safety and efficacy of magnesium-rich artificial cerebrospinal fluid for subarachnoid hemorrhage

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Objectives: This study aimed to investigate the efficacy of using a newly formulated magnesium-rich artificial cerebrospinal fluid (MACSF) as an alternative to normal saline (NS) for intraoperative irrigation during aneurysm clipping in improving the prognosis of patients with Aneurysmal subarachnoid hemorrhage (aSAH).

Methods: Patients with aSAH who underwent intraoperative irrigation with MACSF or NS during the clipping in the First Affiliated Hospital of Xi'an Jiaotong University from March 2019 to March 2022 were selected as MACSF group and NS group, respectively. The primary prognostic indicators were the incidence of favorable outcomes (mRS 0–2). The secondary outcome measures included cerebral vasospasm (CVS), mortality, total hospital stay, and intensive care unit (ICU) stay. Safety was evaluated based on the occurrence rates of hypermagnesemia, meningitis, and hydrocephalus.

Results: Overall, 34 and 37 patients were enrolled in the MACSF and NS groups, respectively. At 90 days after aSAH onset, the proportion of favorable prognosis in the MACSF group was significantly higher than that in the NS group ($p = 0.035$). The incidence of CVS within 14 days after surgery was significantly lower in the MACSF group than that in the NS group ($p = 0.026$). The mortality rate in the MACSF group was significantly lower than in the NS group ($p = 0.048$). The median lengths of hospital stay ($p = 0.008$) and ICU stay ($p = 0.018$) were significantly shorter in the MACSF group than in the NS group. No significant differences were observed in safety measures.

Conclusion: Using MACSF as an irrigation fluid for aneurysm clipping can significantly improve the 90-day prognosis of patients with aSAH, which may be related to the reduced incidence of CVS.

Clinical trial registration: <https://www.clinicaltrials.gov>, identifier NCT04358445.

KEYWORDS

aneurysmal subarachnoid hemorrhage, artificial cerebrospinal fluid, cerebral vasospasm, magnesium, prognosis

1 Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a kind of stroke with high morbidity and mortality. Cerebral vasospasm (CVS) is a common complication of aSAH and is closely associated with patient death and disability of the patients (1, 2). Blood and its metabolites, being initiators of CVS, should be removed as soon as possible as they are initiators of CVS. Normal saline (NS), the most commonly used irrigation fluid in aneurysm clipping, can cause secondary brain injuries because its chemical properties of ion composition, osmolality, and potential of hydrogen (pH) differ from those of cerebrospinal fluid (CSF) (3). Artificial cerebrospinal fluid (ACSF) has similar ionic salts, pH, and osmolality concentrations as CSF. Its safety and efficacy in neural tissues have been demonstrated (4–6). Using ACSF to flush nervous tissues did not alter the cerebrovascular reactivity or physicochemical properties of the CSF (3).

Magnesium (Mg), a vasodilator and natural calcium channel blocker, exerts unique protective functions in the brain. Intravenous magnesium administration is a potential therapeutic strategy for CVS. However, two recent randomized controlled trials (IMASH and MASH-2) failed to confirm the effectiveness of Mg in improving the prognosis of patients with aSAH patients (7, 8). Theoretically, direct intracisternal administration of Mg solution may be more effective.

However, no study has investigated whether using ACSF containing Mg as a flushing fluid during surgery is advantageous for relieving CVS and improving prognosis in patients with aSAH. Therefore, we formulated a new type of ACSF, magnesium-rich artificial cerebrospinal fluid (MACSF), which resembles physiological CSF and is enriched in Mg (9). We have verified that MACSF can maintain the normal physiological activity of rat basilar arteries *in vitro* and alleviate arterial hyper-responsiveness (10). In this study, MACSF was used as the irrigation fluid during aneurysm clipping and was compared with NS. Therefore, its impact on the 90-day prognosis and the CVS within 14 days postoperatively of patients with aSAH can be clarified.

2 Materials and methods

2.1 Study design

This was a single-center, non-randomized, non-blinded, single-arm trial conducted at the First Affiliated Hospital of Xi'an Jiaotong University (registered on [ClinicalTrials.gov](https://clinicaltrials.gov) with NCT 04358445 on March 16, 2020) and approved by the Ethics Committee of the hospital (approval NO. XJYFY-2019N28). All participants provided informed consent to participate in the study and shared their clinical data. All study-related documents were securely stored in the research center, and research data were collected in a limited manner. The entire research process was supervised and monitored by the clinical research center of our hospital. The study followed the SPIRIT reporting guidelines (11).

2.2 Study population

We enrolled 71 eligible patients with aSAH between March 2020 and March 2022. The MACSF group comprised patients who received

MACSF as an intraoperative irrigation fluid, while the NS group consisted of patients who underwent surgery with NS as the irrigation fluid and were enrolled before March 2020. Patients were required to meet the following inclusion criteria: (1) age between 18 and 80 years, (2) aSAH diagnosed by CTA or DSA, (3) admission within 72 h after symptom onset, (4) aneurysm clipped within 36 h after admission, and (5) provided written informed consent. To avoid the influence of the modified Rankin Scale (mRS) score before aSAH onset on the prognostic evaluation, we added additional exclusion criteria after registration. These exclusion criteria included severe craniocerebral trauma, mRS score >2 before the onset of aSAH, or severe concomitant diseases.

2.3 MACSF preparation

MACSF was prepared by trained medical personnel from the Department of Pharmacy Intravenous Admixture Services (PIAS) on a laminar flow clean bench. MACSF consists of a finished intravenous medication consisting of 0.9% sodium chloride injection, sterilized water for injection, 10% potassium chloride injection, 25% magnesium sulfate injection, 5% sodium bicarbonate injection, and 5% glucose injection. Freshly prepared MACSF was promptly transferred to the operating room in a designated container through a specific channel. The entire procedure was strictly to aseptic principles. A comparison of the compositions and properties of NS, MACSF, other ACSFs, and physiological CSF is shown in [Table 1](#) (9).

2.4 Study interventions

From March 2020 to March 2022, eligible patients were recruited into the MACSF group and received MACSF as an intraoperative irrigation fluid. From March 2019 to March 2020, patients with aSAH who used NS as an irrigation fluid in surgery met the aforementioned criteria, and had complete case data, were recruited in the NS group as historical controls. Patients in the MACSF group were irrigated with MACSF after opening the skull and cerebral dura mater, whereas patients in the NS group were irrigated with NS throughout the surgery. All the patients underwent surgery and were managed by the same neurosurgical team. The remaining treatments in both groups strictly adhered to the clinical guidelines.

2.5 Clinical assessments

Demographic data, including sex, age, smoking and alcohol consumption history, and medical history, were recorded in detail. Vital signs, Hunt-Hess Scale scores, modified Fisher grades, and World Federation of Neurosurgical Societies (WFNS) scores were evaluated by a neurologist at admission. Cranial computed tomography was performed on admission and the day after surgery. The blood flow velocity of the intracranial arteries was dynamically evaluated using TCD performed by an experienced technician to determine the occurrence and severity of CVS every alternate day until 14 days after surgery. The Acute Physiology and Chronic

TABLE 1 Comparison of physiological CSF, ACSF, and NS.

Composition	Physiological CSF	MACSF*	Artcereb*	Uchida ACSF*	NS
Na ⁺ (mEq/l)	145.5	146.2	145	145.5	154
K ⁺ (mEq/l)	2.8	2.7	2.8	2.8	0
Mg ²⁺ (mEq/l)	2.2	4.2	2.2	2.2	0
Ca ²⁺ (mEq/l)	2.5	0	2.3	2.3	0
Cl ⁻ (mEq/l)	111.9	123	129	128.5	154
HCO ₃ ⁻ (mEq/l)	23.1	23.2	23.1	23.1	0
Glucose(g/l)	0.61	0.75	0.61	0.61	0
pH	7.31	7.35	7.3	7.3	6.7

CSF, cerebrospinal fluid; ACSF, artificial cerebrospinal fluid; NS, normal saline.

MACSF* is magnesium-rich artificial cerebrospinal fluid.

Artcereb* is an ACSF product named Artcereb* developed by a Japanese research team (5).

Uchida ACSF* is an ACSF developed in the Pharmaceutical Division of Keio University School of Medicine (6).

Health Evaluation II (APACHE II) score of 15 was used as the criteria for admission and discharge from the ICU. Prognosis was assessed 90 days after disease onset using the mRS (12–14). All TCD examinations and clinical assessments were performed free of charge.

2.6 Evaluation of prognosis

Initially, we compared the mRS scores between the MACSF and NS groups at 1, 3, and 6 months after aSAH onset. Considering the representativeness and universality of the 90-day mRS evaluation in short-term prognosis, combined with the results of this study, we only chose 90 days as the final time point for prognostic evaluation. The prognosis was evaluated 90 days after ictus using the mRS, a 7-point scale ranging from 0 (no symptoms) to 6 (death). The mRS was dichotomized into favorable (mRS ≤ 2) and unfavorable (mRS > 2) prognosis (12, 15). Follow-up was conducted via telephone interviews by a trained neurologist blinded to the treatment assignments. If a patient was unavailable, a proxy was interviewed (16).

2.7 Definition of cerebral vasospasm

Ideally, cerebral angiography should be used as a diagnostic criterion for cerebral vasospasm. However, based on practical feasibility considerations, CVS was diagnosed using TCD in this study (17). The Lindegard Index (LI) and mean blood flow velocity (MBF) are the main parameters used to evaluate the occurrence and severity of CVS. However, since some physiological or pathological conditions can also cause the increase of MBF without vasospasm, we eliminated the diagnostic criteria of “MBF of tested arteries is higher than 120 cm/s” to reduce the false-positive rate in diagnosing CVS. Therefore, the final criteria for diagnosing CVS by TCD are as follows (18, 19): (1) LI ≥ 3 or (2) Increase in MBF of tested arteries by more than 15 cm/s or 20% compared with the previous time. The severity of CVS is briefly described as follows (20–22): If the LI is greater than 6, severe CVS can be directly diagnosed. When LI ranges from 3 to 6, the severity of CVS can be classified by MBF as mild (120–139 cm/s), moderate (140–199 cm/s) or severe (≥200 cm/s).

2.8 Study end points

The primary outcome measures included the incidence of CVS within 14 days after surgery and the mRS score at 90 days after onset. Secondary prognostic indicators included length of total hospital stay, length of intensive care unit (ICU) stay, and mortality within 90 days of onset. The safety index was defined as the incidence of hypermagnesemia, meningitis, or hydrocephalus within 14 days after surgery.

2.9 Statistical analysis

According to previous epidemiological investigations, the incidence of CVS in the NS group was 60% (1, 2). Owing to the lack of studies related to ACSF, we hypothesized that using MACSF for intraoperative irrigation during clipping would reduce the incidence of CVS by 50%. Based on this assumption, with a two-sided significance level of 0.05 and power of 90%, at least 27 patients were recruited into the MACSF group. Furthermore, 33 patients were required when the loss-to-follow-up rate was empirically assumed to be 20%. However, we set the ratio of the control group to the experimental group at more than 1:1.

All statistical analyses were performed using SPSS 23.0. Data are presented as mean ± standard deviation ($\bar{X} \pm s$) for continuous symmetric distribution variables, median (M) and interquartile range (IQR) for continuous skewed distribution variables, and percentages for categorical variables. Group comparisons were performed using Analysis of Variance or independent Student's *t*-test for continuous variables and chi-squared test for categorical variables. The Mann–Whitney U non-parametric test was used for variables that did not meet the conditions of the parameter test. $p < 0.05$ was considered statistically significant.

2.10 Data availability statement

Data were recorded and stored using both paper forms and electronic databases. Supporting data for the findings of this study are available from the corresponding author upon request.

3 Results

Between March 2019 and March 2022, 71 eligible patients were enrolled (34 and 37 in the MACSF and NS groups, respectively). All patients completed the follow-up 90 days after onset. There were no significant differences between the two groups regarding age, sex, smoking and drinking history, comorbidities, family history of SAH, Hunt-Hess grade, modified Fisher grade, WFNS classification, or aneurysm characteristics. Vital signs and laboratory test results at admission were also included as baseline metrics, and there were no significant differences in these data between the two groups (Table 2).

3.1 Clinical outcomes

All patients completed 90-day follow-up examinations. The distribution of the mRS scores 90 days after onset is presented in Figure 1. A favorable outcome ($mRS \leq 2$) at 90 days after onset was significantly more common in the MACSF group (82.35%) than in the NS group (59.46%; $p = 0.035$). There was also a significant difference in the mortality rate 90 days after onset between the two groups (8.82% vs. 27.03%; $p = 0.048$) (Table 3).

3.2 Cerebral vasospasm

When analyzing the incidence of CVS, six patients were excluded because of TCD examinations less than 3 times (two cases in the MACSF group and four cases in the NS group). The overall incidence of CVS was 80.00%. There was no significant difference in the duration of anti-CVS drug use (days) between the MACSF (12.63 ± 6.54) and NS groups (14.15 ± 7.94 ; $p = 0.402$). The incidence and severity of CVS in the two groups are shown in Figure 2. Statistical analysis revealed that the incidence of CVS was significantly lower in the MACSF group (22 out of 32, 68.75%) than in the NS group (30 out of 33, 90.91%; $p = 0.026$), and the incidence of moderate-to-severe CVS was also significantly lower in the MACSF group (5 out of 32, 15.63%) than in the NS group (13 out of 33, 39.39%; $p = 0.032$).

3.3 Length of stay

Three and 10 patients in the MACSF and NS groups, respectively, were excluded because of voluntary discharge. As is shown in Figure 3, the median length of total hospital stay was significantly shorter in the MACSF group (M 15.00, IQR 11.00–22.00) than in the NS group (M 22.00, IQR 18.00–27.00; $p = 0.008$), and the median length of ICU stay was also significantly shorter in the MACSF group (M 2.00, IQR 0.00–5.00) than in the NS group (M 4.00, IQR 3.00–15.00; $p = 0.018$).

3.4 Serum Mg^{2+} and Ca^{2+} concentration

Serum Mg^{2+} and Ca^{2+} concentrations were measured on admission and within 24 h after surgery. In the MACSF group, the mean serum concentrations of Mg^{2+} and Ca^{2+} at admission were 0.93 ± 0.11 mmol/L and 2.29 ± 0.12 mmol/L, respectively. In the NS group, they were 0.96 ± 0.10 mmol/L and 2.33 ± 0.16 mmol/L. No significant differences

TABLE 2 Comparison of baseline data in patients using MACSF* and NS* as irrigating fluid during the surgery of aneurysm clipping.

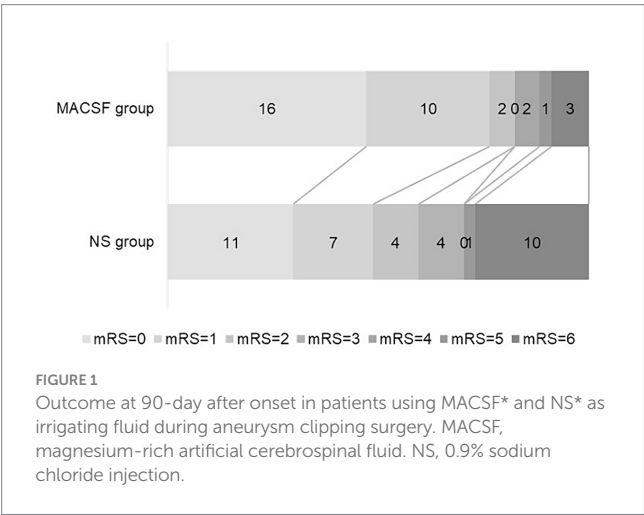
Variable	MACSF group N = 34	NS group N = 37	p
Age (y)	55.9 ± 8.4	58.7 ± 8.9	0.17
Female sex (n, %)	15 (44.1%)	23 (62.2%)	0.13
Medical history (n, %)			
Smoking	11 (32.4%)	12 (32.4%)	0.99
Drinking	7 (20.6%)	10 (27.0%)	0.53
Hypertension	20 (58.8%)	28 (75.7%)	0.13
Diabetes	2 (5.9%)	4 (10.8%)	0.68
Aneurysm	0 (0.0%)	1 (2.7%)	1.00
Hunt-Hess grade (n, %)			
I-II	9 (26.5%)	12 (32.4%)	0.58
III-V	25 (73.5%)	25 (67.6%)	
m-Fisher grade (n, %)			
0-2	19 (55.9%)	16 (43.2%)	0.29
3-4	15 (44.1%)	21 (56.8%)	
WFNS classification (n, %)			
I-II	22 (64.7%)	18 (48.7%)	0.17
III-V	12 (35.3%)	19 (51.3%)	
Aneurysmal Location (n, %)			
Anterior circulation	33 (97.1%)	35 (94.6%)	1.00
Posterior circulation	1 (2.9%)	2 (5.4%)	
Aneurysmal Number (n, %)			
Single	31 (91.2%)	31 (83.8%)	0.48
multiple	3 (8.8%)	6 (16.2%)	
Aneurysmal Size (n, %)			
≤5 mm	20 (58.8%)	15 (40.5%)	0.12
>5 mm	14 (41.2%)	22 (59.5%)	
Heart rate (bpm)	76.4 ± 11.6	79.8 ± 12.5	0.24
Breath (bpm)	17.6 ± 2.7	18.0 ± 2.9	0.57
Temperature (°C)	36.5 (36.3, 36.7)	36.5 (36.3, 36.7)	0.51
SBP (mmHg)	140.5 ± 15.8	136.9 ± 16.4	0.35
DBP (mmHg)	82.5 (78.8, 92.0)	80.0 (78.0, 89.5)	0.21
MAP (mmHg)	103.5 (94.5, 113.0)	99.3 (93.3, 109.8)	0.27
Hb (g/L)	131.3 ± 25.7	134.5 ± 19.9	0.56
MCHC (g/L)	335.5 (327.3, 342.0)	340.0 (330.0, 347.5)	0.10
RBC (×10 ¹² /L)	4.3 ± 0.7	4.4 ± 0.6	0.61
WBC (×10 ⁹ /L)	11.4 (7.8,13.1)	10.7 (8.9,14.2)	0.63
Neu (%)	85.9 (77.8,91.8)	90.1 (83.3,92.5)	0.07
PLT (×10 ⁹ /L)	192.0 (163.5, 230.3)	201.0 (162.5, 256.5)	0.46
AST (U/L)	23.0 (19.8, 29.5)	24.0 (18.5, 32.0)	0.62
ALT (U/L)	24.0 (14.8, 29.3)	22.0 (14.5, 28.5)	0.73

(Continued)

TABLE 2 (Continued)

Variable	MACSF group N = 34	NS group N = 37	p
ALB (g/L)	40.3 (37.5, 42.7)	41.3 (38.8, 43.9)	0.35
Glu (mmol/L)	6.8 (5.8, 7.6)	6.8 (6.0, 7.6)	0.80
PT (s)	12.9 ± 1.3	13.3 ± 1.0	0.12
APTT (s)	32.2 ± 5.6	31.4 ± 4.1	0.51
BUN (mmol/L)	4.5 (3.7, 5.7)	4.6 (3.6, 5.3)	0.95
Cr (umol/L)	45.5 (37.0, 54.5)	47.0 (37.5, 58.5)	0.67
Ca ²⁺ (mmol/L)	2.3 ± 0.1	2.3 ± 0.2	0.25
Mg ²⁺ (mmol/L)	0.9 ± 0.1	1.0 ± 0.1	0.20

MACSF, magnesium-rich artificial cerebrospinal fluid.
NS, 0.9% sodium chloride injection.
Hunt-Hess, Hunt-Hess Scale scores.
m-Fisher, modified Fisher grades.
WFNS, World Federation of Neurosurgical Societies scores.



were observed between the groups. The postoperative serum concentrations of Mg²⁺ and Ca²⁺ compared to those at admission were not significantly different in either the MACSF or NS groups.

3.5 Safety outcomes

The incidence of hypermagnesemia was not significantly different between the MACSF (0 out of 34, 0.00%) and NS groups (2 out of 37, 5.41%; *p* = 0.494). Additionally, the incidence of meningitis did not differ significantly between the two groups (MACSF group [15 out of 34, 44.12%] vs. NS group [16 out of 37, 43.24%]; *p* = 0.941). Furthermore, the difference in the incidence of hydrocephalus was not significant (MACSF group [3 out of 34, 8.82%] vs. NS group [2 out of 37, 5.41%]; *p* = 0.665) (Table 4).

4 Discussion

This study confirmed that the use of MACSF as the irrigation fluid in aneurysm clipping surgery, which effectively reduced the incidence

TABLE 3 Comparison of prognosis and mortality rate at 90 days after onset in patients using MACSF* and NS* as irrigating fluid during the surgery of aneurysm clipping.

Variable	MACSF group N = 34	NS group N = 37	p
mRS ≤ 2	28 (82.35%)	22 (59.46%)	0.035
mRS > 2	6 (17.65%)	15 (40.54%)	
mortality rate	3 (8.82%)	10 (27.03%)	0.048

MACSF, magnesium-rich artificial cerebrospinal fluid.
NS, 0.9% sodium chloride injection.
Bold values are *p* < 0.05.

of CVS, improved the 90-day prognosis, and shortened the length of hospital stay in patients with aSAH.

MACSF is rich in magnesium ions, and irrigation with MACSF during aneurysm clamping can increase the concentration of Mg²⁺ in the CSF. As a natural antagonist of Ca²⁺, extracellular Mg²⁺ can reduce Ca²⁺-Na⁺ exchange on the cell membrane, preventing Ca²⁺ influx, vasoconstriction and CVS (23–25). Additionally, Mg²⁺ antagonizes the N-methyl-d-aspartate receptors in the brain, prevents glutamate stimulation, and reduces Ca²⁺ influx during ischemic injury (26, 27). Studies have demonstrated that Mg²⁺ is involved in the composition of various coenzymes and is related to cellular energy metabolism by reducing ATP consumption, damaging the cell membrane, and causing neuronal edema (25). However, two previous randomized controlled trials (IMASH and MASH-2) failed to confirm the effects of intravenous MgSO₄ infusion on improving functional outcomes in patients with aSAH patients (7, 8). The most plausible reason for this outcome is that the increased serum Mg²⁺ concentration did not deliver an effective Mg²⁺ concentration in the CSF before inducing side effects. In our study, intraoperative irrigation with MACSF directly increased the concentration of Mg²⁺ in the CSF and better utilized the role of Mg²⁺ in combating CVS as well as protecting the neural tissue.

An animal study found that the CSF concentration of Mg²⁺ should be more than 3 mEq/L to dilate the spastic cerebral arteries in dogs effectively (28). It has been confirmed that continuous intracranial infusion of ACSF with an increased concentration of Mg²⁺ can cause vasodilation of the spastic cerebral arteries in dogs after SAH (29). Therefore, researchers recommend using ACSF with an appropriate concentration of Mg²⁺ as flushing fluid during neurosurgery to prevent CVS. Continuous intracisternal irrigation with an Mg-related solution appears to stabilize the CSF concentration of Mg²⁺ at an effective level to relieve CVS. One research team suggested that continuous intracisternal irrigation with 5 mmol/L (10 mEq/L) MgSO₄ solution from days 4 to 14 after surgery could inhibit CVS in patients with aSAH (30). However, the overall prognosis did not improve. Furthermore, Mg-related side effects have been reported. Recently, it was demonstrated that intracisternal infusing with 2.5 mmol/L (5 mEq/L) MgSO₄ solution, which was started immediately after surgery, could reduce the incidence of CVS and improve clinical outcomes in patients with poor-grade aSAH without Mg-related complications (31). This indicates that early elevation of the Mg²⁺ concentration in the CSF may be the key to alleviating CVS. However, continuous intracranial infusion has several disadvantages. This is traumatic and may increase the risk of meningitis. Furthermore, long-term bed rest after surgery increases the incidences of phlebothrombosis and pneumonia. In our study, we used MACSF

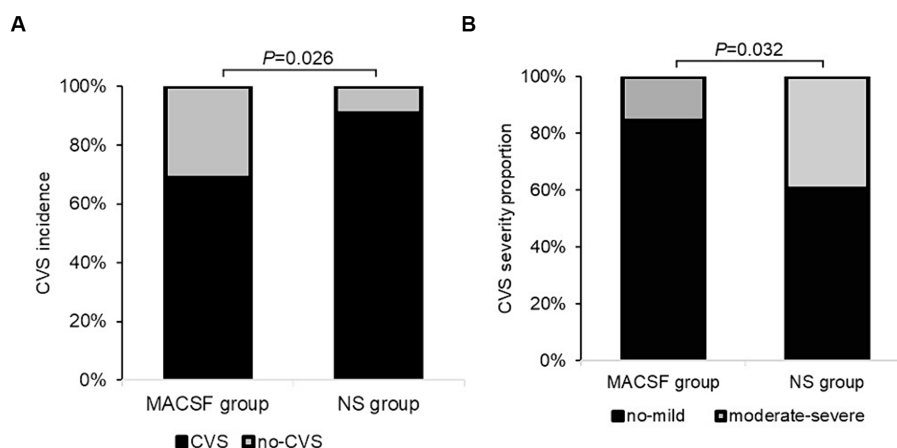


FIGURE 2

The incidence (A) and severity (B) of CVS within 14 days after the surgery of aneurysm clipping in patients with aSAH using MACSF* and NS* as intraoperative irrigation fluid. CVS, cerebral vasospasm. MACSF, magnesium-rich artificial cerebrospinal fluid. NS, 0.9% sodium chloride injection.

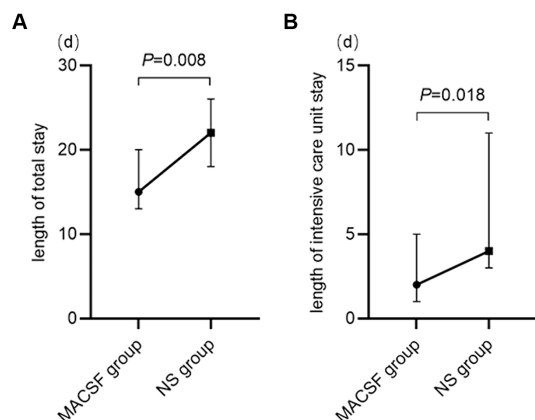


FIGURE 3

The length of total stay (A) and length of intensive care unit stay (B) of patients using MACSF* and NS* as irrigating fluid during the surgery of aneurysm clipping. MACSF: magnesium-rich artificial cerebrospinal fluid. NS, 0.9% sodium chloride injection.

TABLE 4 Comparison of complications in patients using MACSF* and NS* as irrigation fluid during the surgery of aneurysm clipping.

Complications	MACSF group N = 34	NS group N = 37	p
Hypermagnesemia	0 (0.00%)	2 (5.41%)	0.494
Meningitis	15 (44.12%)	16 (43.24%)	0.941
Hydrocephalus	3 (8.82%)	2 (5.41%)	0.665

MACSF, magnesium-rich artificial cerebrospinal fluid.
 NS, 0.9% sodium chloride injection.

only intraoperatively, which shortened the use time of the Mg solution and reduced the risk of complications.

Early intracranial perfusion with MACSF removes blood from the subarachnoid space, increases the CSF Mg^{2+} concentration, and inhibits the occurrence and development of CVS. CVS remission

increases blood flow in affected arteries, improves oxygen supply to relevant brain tissues, maintains neurological function, and effectively improves patient prognosis. Intraoperative irrigation with MACSF, with an Mg^{2+} concentration of 4.2 mEq/L, did not increase the serum concentration of Mg^{2+} or cause Mg-related adverse reactions. Additionally, using MACSF alone in surgery does not increase pain and can avoid the complications of continuous intracisternal infusion for patients with aSAH. Since MACSF has not yet been industrialized, it was prepared by staff from the Department of PIAS, strictly following aseptic principles. Pollution during preparation and transportation was still possible; therefore, the incidence of meningitis was considered one of the indicators to evaluate safety. However, the current data indicates no significant differences in secondary infection rates between the two groups. Therefore, it is safe to use intravenous drugs to prepare MACSF in compliance with aseptic principles.

As a new type of ACSF that is easy to prepare and is widely used, MACSF may replace NS, Ringer's solution, or other ACSF products, becoming a safe, effective, and convenient succedaneum for physiological CSF in the future.

But, this study adopted a historical control instead of a randomized control, which may have led to bias and a lower level of evidence than a standard randomized controlled trial (RCT). In the future, a planned RCT trial will validate the results of this study. The study sample was small because of the aSAH incidence and study period limitations (The epidemic period of COVID-19). Therefore, a larger study is needed to determine whether our protocol can be used as a standard therapeutic strategy. Lumbar puncture or lumbar cisternal drainage was not routinely performed after surgery; therefore, postoperative CSF samples were obtained from only a few patients. Consequently, the CSF concentrations of Ca^{2+} , Mg^{2+} and spasmogens were not tested and should be assessed in the future.

All in all, our results suggest that using MACSF as an intraoperative irrigation fluid for aneurysm clipping can effectively reduce the incidence and severity of CVS, improve the prognosis 90 days after onset, and shorten the length of hospital stay without increasing the risk of complications in patients with aSAH. However, these findings need to be validated in randomized controlled trials.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YC: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. XH: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. WX: Methodology, Resources, Writing – review & editing. GX: Methodology, Resources, Writing – review & editing. XB: Investigation, Writing – review & editing. LQ: Methodology, Supervision, Writing – review & editing. LZ: Supervision, Writing – review & editing. RL: Writing – review & editing, Methodology. WD: Writing – review & editing, Formal analysis. WF: Formal analysis, Writing – review & editing. CP: Writing – review & editing, Project administration. WZ: Writing – review & editing, Funding acquisition, Software. FL: Software, Writing – review & editing. XC: Writing – review & editing, Data curation. YX: Writing – review & editing, Formal analysis, Software. GL: Writing – review & editing, Conceptualization, Methodology, Project administration, Supervision, Writing – original draft.

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Conflict of interest

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

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High-resolution vessel wall imaging for quantitatively and qualitatively evaluating in-stent stenosis of intracranial aneurysms

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Background: It is critical to accurately and noninvasively evaluate the stented parent artery of intracranial aneurysms (IAs) with endovascular treatment.

Objective: To investigate high-resolution vessel wall imaging (HR-VWI) for quantitative and qualitative evaluation of in-stent stenosis (ISS) in IAs treated with stent placement (SP).

Methods: Fifty-five patients (58 aneurysms) underwent HR-VWI, contrast-enhanced (CE)-HR-VWI, CE-MR angiography (MRA), time-of-flight (TOF)-MRA, and digital subtraction angiography (DSA) six months after SP, and the reliability of quantitative stent lumen measurements was evaluated by intraclass correlation coefficient (ICC) analysis. Agreement and correlation of quantitative evaluation were estimated by comparing the four MR imaging modalities with DSA. The diagnostic performance for >0%, ≥25%, and ≥50% of ISS degrees and overall diagnostic accuracy for the ISS degrees of the four MR imaging modalities were calculated to qualitative evaluation.

Results: The reliability of CE-HR-VWI and HR-VWI for ISS quantitative measurements was excellent (ICC 0.955–0.989). The agreement and correlation of CE-HR-VWI, HR-VWI versus DSA for ISS quantitative measurements were better than those of CE-MRA and TOF-MRA ($p < 0.05$). The diagnostic performance for distinguishing the degree of ISS >0%, ≥25%, and ≥50% by CE-HR-VWI and HR-VWI was superior to CE-MRA and TOF-MRA, and their overall diagnostic accuracy was 96.55 and 94.83%, respectively. HR-VWI and CE-HR-VWI were not statistically significant in the quantitative and qualitative evaluation of ISS performance ($p > 0.05$).

Conclusion: HR-VWI and CE-HR-VWI have similar performance and value in the quantitative and qualitative evaluation of ISS, and HR-VWI without contrast media could be used as an ideal long-term follow-up approach after SP treatment for IAs.

KEYWORDS

stent placement, in-stent stenosis, intracranial aneurysms, high-resolution vessel wall imaging, follow-up

Introduction

Stent placement (SP), such as stent-assisted coil embolization or flow-diverting SP, is an important neuro-interventional endovascular treatment of intracranial aneurysms (IAs) that were previously difficult to treat with only coiling embolization (1, 2). However, SP may lead to postoperative adverse events, such as stent intima thickening and thrombosis, resulting in in-stent stenosis (ISS) or occlusion (3, 4). The incidence of ISS is relatively high, about 8.5–32.12% (3, 4), and the time of ISS occurrence varies greatly, ranging from 4 to 17 months after SP (3, 5). ISS is a dynamic process that resolves spontaneously or worsens progressively (6, 7). In addition, the stent status and degree of stenosis will affect the follow-up time, treatment plan, and prognosis of SP patients (7, 8). Thus, long-term, dynamic, and accurate evaluation of the stented parent artery is essential.

Digital subtraction angiography (DSA) is the reference standard for evaluating stent patency for SP, but it is an invasive procedure associated with complications and is not conducive to long-term follow-up of the stented parent artery. CT angiography (CTA) and contrast-enhanced (CE) MRA are noninvasive, however, stent-associated artifacts hamper the visualization and assessment of the adjacent vessel lumen, and they require the use of exogenous contrast agents, which have potentially severe side effects (9, 10). Time-of-flight (TOF)-MRA has no radiation and no contrast media, and it is easily accepted by patients, but previous study has found poor consistency between TOF-MRA with DSA (11). Compared to TOF-MRA, silent-MRA has improved the visibility of stented parent arteries, but there is insufficient evidence regarding the accuracy of detecting ISS of silent-MRA (12, 13).

High-resolution vessel wall imaging (HR-VWI) is a black blood technique based on fast spin echo sequences. Compared to other MRA sequences, HR-VWI has a smaller voxel, shorter echo time and repetition time, wider bandwidth, and parallel imaging technology (14, 15), effectively reducing the susceptibility artifact for precise configuration of the stented parent artery. Previous study revealed that HR-VWI was feasible to preliminarily evaluate the stent status (patency, stenosis), but the small sample size limited generalizability (4). Consequently, this noninvasive technique without radiation could be an ideal follow-up approach for SP. However, further quantitative and qualitative evaluation of ISS, synchronous comparison with CE-MRA and TOF-MRA, and comparison of CE-HR-VWI and HR-VWI in evaluation of ISS are rarely reported.

It was hypothesized that HR-VWI could be similar with CE-HR-VWI in quantitative and qualitative evaluation of ISS after SP treatment for IAs, and better than CE-MRA and TOF-MRA. Therefore, this study investigated CE-HR-VWI and HR-VWI for the quantitative and qualitative evaluation of ISS using DSA as the reference standard and compared its performance to CE-MRA and TOF-MRA.

Methods

Patients

The study was approved by our institutional review board (IRB No. 194), and written informed consent was obtained. Patients with

IAs who underwent stent-assisted coil embolization or flow-diverting SP between June 2020 and February 2022 were collected. Six months after endovascular treatment, the patient was admitted for TOF-MRA, CE-MRA, HR-VWI, CE-HR-VWI, and DSA examinations. The interval between MR and DSA was less than 24h. Patients who received double stent therapy for the same aneurysm, patients with claustrophobia and patients with incomplete or poor image quality TOF-MRA, CE-MRA, HR-VWI, CE-HR-VWI, and DSA were excluded.

MR imaging protocol

All MR images were performed using an Ingenia CX 3.0 T MR scanner (Philips, Best, Netherlands) with a 32-channel head coil. The scanning plan was set to first scan the 3D-TOF MRA sequence for aneurysm localization and then the HR-VWI sequence of axial 3D-T1-weighted volume isotropic turbo spin echo acquisition (VISTA) for target scanning of the stented parent arteries. Then, a gadoteric acid meglumine salt injection (0.1 mmol/kg, Gd-DOTA, Jiangsu, China) was manually injected into the patient's cubital vein for CE-MRA scanning of the head and carotid artery. The HR-VWI was repeated 5 min after the contrast agent was injected, and CE-HR-VWI images with the same range as HR-VWI were obtained. The scan parameters of the MR imaging modalities were listed in Table 1.

Digital subtraction angiography

Digital subtraction angiography (DSA) was performed with an Allura X per FD 20 angiographic system (Philips, Amsterdam, Netherlands). Selective injections of the internal carotid or vertebral arteries were performed according to the aneurysm location by transfemoral catheterization. All DSA examinations included anteroposterior, lateral, and other working views. Dynamic DSA images of all views were observed, and the optimal projection angle of the target lesion was selected to measure the degree of stenosis.

TABLE 1 Scan parameters of CE-MRA, TOF-MRA, and HR-VWI.

Parameters	CE-MRA	TOF-MRA	HR-VWI
FOV, mm ²	320 × 270	200 × 181	200 × 200
Acquisition matrix	312 × 288	320 × 232	332 × 302
TR/TE, ms	3.9/1.28	21/3.45	800/22
Flip angle, °	27	18	90
Bandwidth, pix/Hz	0.412/1054	2.0/217	1.54/281.5
Slice thickness, mm	0.50	0.60	0.50
Number of slices	200	160	80
Voxel size, mm ³	0.8 × 0.8 × 1	0.6 × 0.8 × 1.4	0.6 × 0.6 × 0.6
NEX	1	1	1
Acquisition time, min: sec	1:30	3:36	5:12

CE, contrast-enhanced; FOV, field of view; HR-VWI, high-resolution vessel wall imaging; MRA, MR angiography; NEX, number of excitations; TE, echo time; TOF, time-of-flight; TR, repetition time.

Image analysis

The four MR imaging modalities' original thin-layer images were imported to the Philips workstation for post-processing and analysis, and multi-plane reconstruction was used to observe the original images. According to the anatomical positions of the two ends of the stent, the long and short axes of the stented parent arteries were observed in multiple planes, the image quality of the stented parent artery on the HR-VWI and CE-HR-VWI was evaluated using a 4-point scale according to the previous method (16), and the stenosis of the auxiliary stent was measured and evaluated using a submillimeter digital caliper on the MR workstation.

In the four MR imaging modalities and DSA images, the method used for determining the percentage of stenosis of a stented parent artery (immediately adjacent to or within 5 mm of the stent) was the same as that used in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study: $\text{percentage of stenosis} = (1 - [D_{\text{stenosis}} / D_{\text{normal}}]) \times 100$, where D_{stenosis} is the diameter of the stented parent artery at the site of the most severe stenosis and D_{normal} is the diameter of the proximal lumen of the normal stented parent artery adjacent to the stenosis (17, 18). When there was no change in the parent artery diameter, cases were graded as no stenosis (4); otherwise, cases were graded as intimal hyperplasia (1–24%), mild (25–49%), moderate (50–74%), or severe ($\geq 75\%$) (19).

The four MR imaging modalities and DSA images were independently reviewed by two neuroradiologists (both with >10 years of experience). When a different reading was proposed in evaluating the image quality of the four MR imaging modalities, the two radiologists reached a consensus after an in-depth discussion. The four MR imaging modalities and DSA were measured separately without knowledge of the four MR imaging modalities or DSA examination results. The location of the aneurysms to be evaluated was provided to the readers, and all measurements were performed twice by two observers. To reduce possible memory effects, the measurements were performed with an interval of four weeks between the readings.

Statistical analysis

All statistical analyses were performed using SPSS 26.0 software (IBM SPSS Inc., Chicago, IL, United States). Quantitative variables were described as mean $\pm$ SD or median (interquartile range), and qualitative variables were described as numbers and percentages. Intra- and inter-observer reliability of ISS quantitative measurements in the five imaging modalities were assessed by calculating the intraclass correlation coefficient (ICC). The agreement and correlation of the four MR imaging modalities versus DSA were compared with ICCs, Bland–Altman plots, and scatter plots. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve (AUC) value for diagnoses of >0%, $\geq 25\%$, and $\geq 50\%$ stenosis, and overall diagnostic accuracy for the different degrees of ISS were calculated. The consistency of the four MR imaging modalities and DSA in the degree of stenosis >0%, $\geq 25\%$, and $\geq 50\%$ and overall different degrees of ISS were evaluated using κ statistics. The Delong test was used to pairwise compare the AUC of the receiver operating characteristic (ROC) curve for the four MR imaging modalities for

ISS of >0%, $\geq 25\%$, and $\geq 50\%$. The color software package was used to pairwise compare the ICC values of reliability of the Intra- and inter-observers, the ICC values of agreement with DSA, and the r values of correlation with DSA in the four MR imaging modalities for ISS measurements (20). A p -value <0.05 was considered statistically significant. ICC, κ , r , and AUC values were, respectively, interpreted as ICC values <0.50 (poor), 0.50–0.75 (moderate), 0.75–0.90 (good), and >0.90 (excellent), κ values <0.40 (poor), 0.40–0.54 (weak), 0.55–0.69 (moderate), 0.70–0.84 (good) and 0.85–1.00 (excellent), r values <0.10 (negligible), 0.10–0.39 (weak), 0.40–0.69 (moderate), 0.70–0.89 (strong) and ≥ 0.90 (very strong), AUC values <0.5 (chance), 0.51–0.59 (very poor), 0.60–0.69 (poor), 0.70–0.79 (moderate), 0.80–0.89 (good) and ≥ 0.90 (excellent) (21, 22).

Results

Patient characteristics

The flowchart of patients selection is shown in Figure 1. In total, 58 aneurysms of 55 patients were collected in this study, and the patients were readmitted after 6.96 ± 1.46 months. The patients' characteristics are summarized in Table 2. The four types of stents involved in this study were LVIS stents (Microvention, Tustin, CA, United States) used for 39 aneurysms, Neuroform Atlas stents (Stryker Neurovascular, California, United States) used for 11 aneurysms, Pipeline stents (Covidien/ev3 Neurovascular, Irvine, CA, United States) for used for 4 aneurysms and Tubridge stents (MicroPort Neuro-Tech, Shanghai, China) used for 4 aneurysms, respectively. The Flow-diversion (Pipeline and Tubridge) ISS was 25.00%(2/8) and the stent (LVIS and Neuroform Atlas) ISS was 36.00%(18/50).

Image quality of CE-HR-VWI and HR-VWI

The average image quality scores of CE-HR-VWI and HR-VWI were 3.88 ± 0.33 and 3.86 ± 0.35 , respectively, and not significantly different.

Intra- and inter-observer reliability for ISS quantitative measurements

For ISS measurement, there was excellent intra- and inter-observer reliability for CE-HR-VWI (ICC 0.968–0.987), HR-VWI (ICC 0.955–0.989), and DSA (ICC 0.978–0.994) but only good reliability for CE-MRA and TOF-MRA (ICC 0.839–0.893), except excellent inter-observer reliability for CE-MRA (ICC, 0.932).

Agreement and correlation of the four MR imaging modalities versus DSA for ISS quantitative measurements

The ICC analysis demonstrated excellent agreement between CE-HR-VWI and HR-VWI with DSA for ISS measurement (ICC 0.994, 0.992, respectively) but a poor agreement between CE-MRA and TOF-MRA with DSA (ICC 0.281, 0.187, respectively).

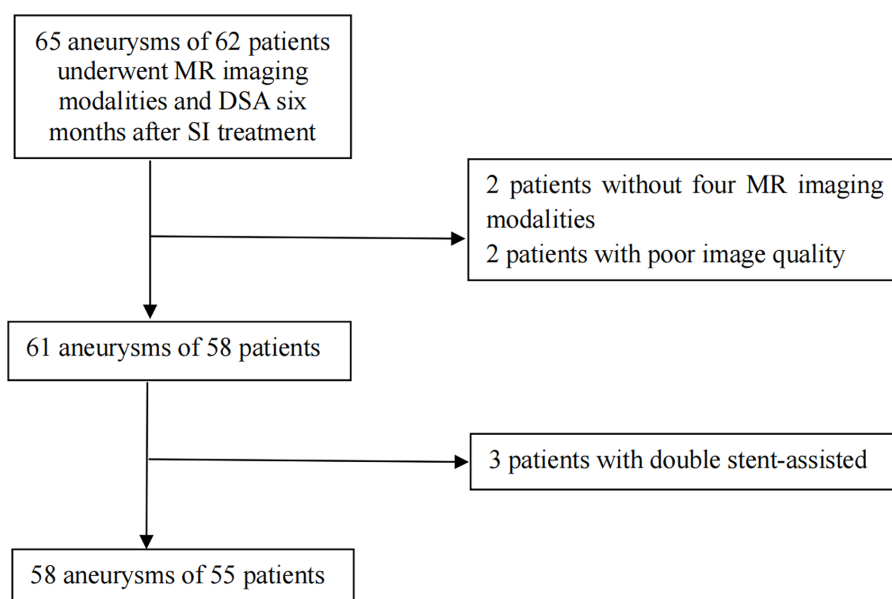


FIGURE 1

Flowchart of patients selection. DSA, digital subtraction angiography; SI, stent implantation.

TABLE 2 Characteristics of the patients and aneurysms.

Characteristics	Value
Mean age ^a	54.17 ± 9.15
Female/male	43/15 (74.14%/25.86%)
Hypertension	32 (55.17%)
Diabetes	4 (6.90%)
Coronary heart disease	3 (5.17%)
Hyperlipidemia	27 (46.55%)
Smoking history	12 (20.69%)
Ruptured aneurysms	42 (72.41%)
Multiple intracranial aneurysms	3 (5.17%)
Original size of the aneurysm (mm) ^a	4.33 ± 2.08
Location of the aneurysm	37 (63.79%)
Internal carotid artery ^b	12 (20.69%)
Anterior communicating artery	5 (8.62%)
Basilar artery	4 (6.89%)
Middle cerebral artery	32 (55.17%)
Bifurcation	26 (44.83%)
Parietal	
Operation situation	56 (96.55%)
No complications	1 (1.72%)
Stent thrombosis	1 (1.72%)
Intraoperative cerebral hemorrhage	
Degrees of ISS	
Intimal hyperplasia (1–24%)	16.00% ± 5.22%
Mild (25–49%)	34.00% ± 7.22%
Moderate (50–74%)	58.05% ± 4.44%

^aMean ± standard deviation.^bIncluding carotid terminus and origins of the posterior communicating and ophthalmic artery.

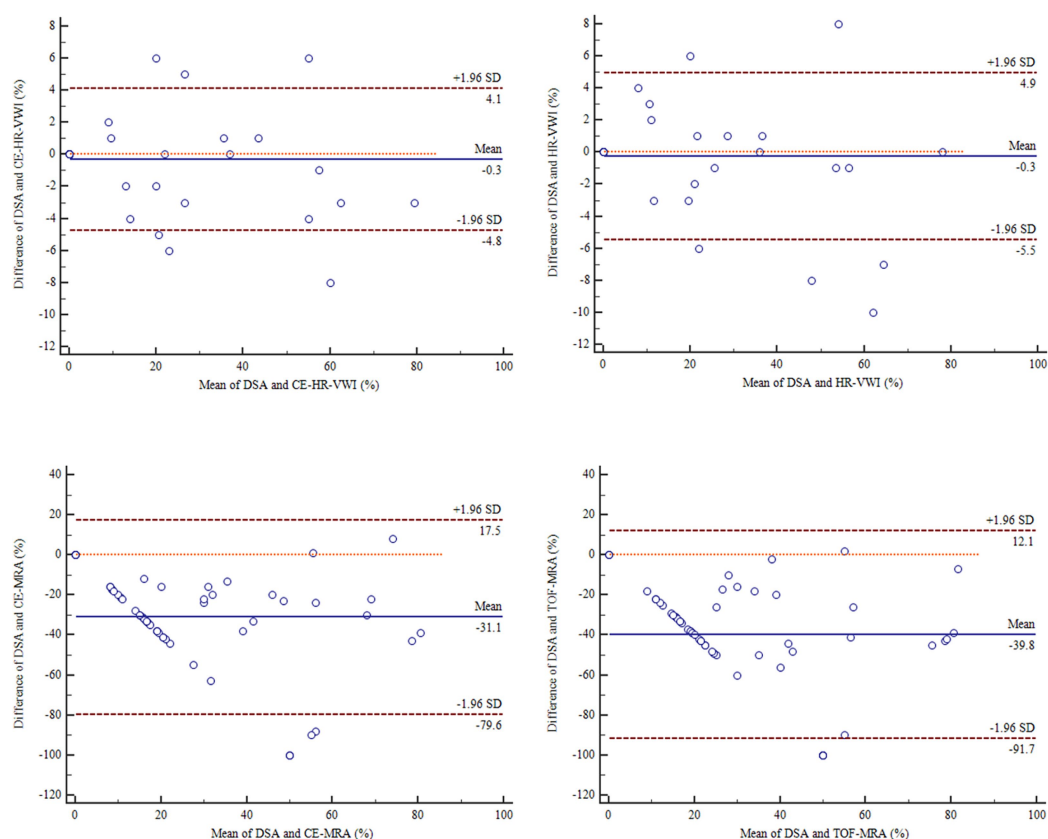


FIGURE 2

Bland-Altman plots results of the agreement between the four MR imaging modalities and DSA in the ISS quantitative measurements. CE, contrast-enhanced; DSA, digital subtraction angiography; HR-VWI, high-resolution vessel wall imaging; MRA, MR angiography; TOF, time-of-flight.

Bland-Altman plots depicted that CE-HR-VWI and HR-VWI exhibited good agreement with DSA in ISS measurements [mean bias both -0.3 , 95% limits of agreement (-4.8 – 4.1%), (-5.5 – 4.9%), respectively], whereas CE-MRA and TOF-MRA displayed poor agreement with DSA [mean bias = -31.1 , -39.8% , respectively, 95% limits of agreement (-79.6 – 17.5%) (-91.7 – 12.1%), respectively] (Figure 2).

As illustrated in Figure 3, CE-HR-VWI and HR-VWI strongly correlated with DSA in the ISS measurements (r 0.998, 0.997, respectively), while CE-MRA and TOF-MRA moderately correlated with DSA (r 0.591, 0.432, respectively).

Accuracy of qualitative evaluation for ISS among the four MR imaging modalities

The diagnostic performance is presented in Table 3. The AUC values for distinguishing $>0\%$, $\geq 25\%$, and $\geq 50\%$ degrees of stenosis of CE-HR-VWI and HR-VWI were excellent diagnostic performance (AUC 99.7–100%). The AUC values for distinguishing $>0\%$, $\geq 25\%$, and $\geq 50\%$ degrees of stenosis of CE-MRA demonstrated good diagnostic performance (AUC 83.8–89.9%). The AUC for distinguishing $\geq 50\%$ stenosis of TOF-MRA depicted good diagnostic performance (AUC 87.7%) but distinguishing the degree of ISS $>0\%$ and $\geq 25\%$ demonstrated moderate diagnostic performance (AUC 74.4 and 79.4%, respectively). CE-HR-VWI and HR-VWI

demonstrated good to excellent agreement with DSA in identifying the degree of ISS $>0\%$, $\geq 25\%$, and $\geq 50\%$ (κ 81.4–100%), while CE-MRA and TOF-MRA showed poor agreement with DSA (κ 5.6–23.4%) (Table 3). One of $\geq 50\%$ ISS cases was $\geq 75\%$ ISS. CE-HR-VWI, HR-VWI, and TOF-MRA all distinguished such stenosis, but TOF-MRA significantly overestimated the degree of stenosis.

In the distinguishing $>0\%$, $\geq 25\%$, and $\geq 50\%$ stenosis, the AUC values of the four MR imaging modalities were significantly different in the pairwise comparison, except for CE-HR-VWI versus HR-VWI, which was not significantly different.

Using DSA as the reference standard, the overall diagnostic accuracy of CE-HR-VWI, HR-VWI, CE-MRA, and TOF-MRA in the different degrees of ISS was 96.55, 94.83, 15.52, and 13.79%, respectively. CE-HR-VWI and HR-VWI had excellent consistency with DSA in the overall identification of different degrees of ISS (κ 0.935 and 0.903, respectively), while CE-MRA and TOF-MRA had poor consistency with DSA (κ 0.012 and 0.037, respectively) (Figures 4–6).

Discussion

To our knowledge, this is the first study to investigate HR-VWI and CE-HR-VWI for the quantitative and qualitative evaluation of ISS after SP treatment for IAs using DSA as the reference standard and

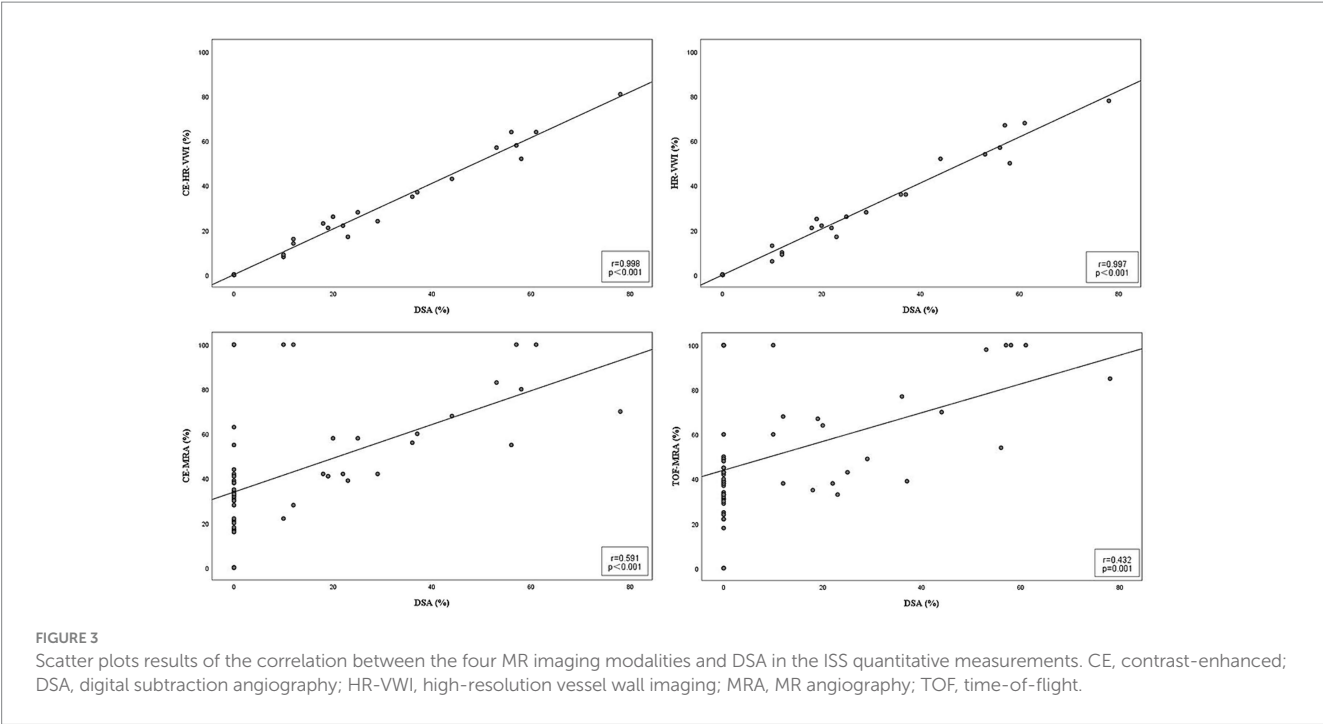


TABLE 3 The diagnostic performance for >0%, ≥25%, and ≥50% ISS of the four imaging modalities using DSA as a reference standard.

	>0%	≥25%	≥50%
CE-HR-VWI analysis (n = 58)			
Sensitivity, % (95%CI)	100.0 (80.0–100.0)	90.9 (57.1–99.5)	100.0 (51.7–100.0)
Specificity, % (95%CI)	100.0 (88.6–100.0)	97.9 (87.3–99.9)	100.0 (91.4–100.0)
PPV, % (95%CI)	100.0 (80.0–100.0)	90.9 (57.1–99.5)	100.0 (51.7–100.0)
NPV, % (95%CI)	100.0 (88.6–100.0)	97.9 (87.3–99.9)	100.0 (91.4–100.0)
AUC, % (95%CI)	100.0 (100.0–100.0)	99.8 (99.2–100.0)	100.0 (100.0–100.0)
κ value, % (95%CI)	100.0 (100.0–100.0)	88.8 (73.5–104.1)	100.0 (100.0–100.0)
HR-VWI analysis (n = 58)			
Sensitivity, % (95%CI)	100.0 (80.0–100.0)	100 (67.9–100.0)	83.3 (36.5–99.1)
Specificity, % (95%CI)	100.0 (88.6–100.0)	97.9 (87.3–99.9)	98.1 (88.4–99.9)
PPV, % (95%CI)	100.0 (80.0–100.0)	91.7 (59.8–99.6)	83.3 (36.5–99.1)
NPV, % (95%CI)	100.0 (88.6–100.0)	100.0 (90.4–100.0)	98.1 (88.4–99.9)
AUC, % (95%CI)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	99.7 (98.7–100)
κ value, % (95%CI)	100.0 (100.0–100.0)	94.6 (84.0–105.2)	81.4 (56.3–106.5)
CE-MRA analysis (n = 58)			
Sensitivity, % (95%CI)	100.0 (80.0–100.0)	100.0 (67.9–100.0)	100.0 (51.7–100.0)
Specificity, % (95%CI)	15.8 (6.6–31.9)	31.9 (19.5–47.3)	76.9 (62.8–87.0)
PPV, % (95%CI)	38.5 (25.6–53.0)	25.6 (14.0–41.5)	33.3 (14.4–58.8)
NPV, % (95%CI)	100.0 (51.7–100.0)	100.0 (74.7–100.0)	100.0 (89.1–100.0)
AUC, % (95%CI)	83.8 (72.9–94.6)	87.9 (79.2–96.6)	89.9 (81.5–98.3)
κ value, % (95%CI)	11.5 (1.9–21.1)	15.1 (4.1–25.5)	23.4 (6.5–40.3)
TOF-MRA analysis (n = 58)			
Sensitivity, % (95%CI)	100.0 (80.0–100.0)	100.0 (67.9–100.0)	100.0 (51.7–100.0)
Specificity, % (95%CI)	7.9 (2.1–22.5)	14.9 (6.7–28.9)	71.2 (56.7–82.5)
PPV, % (95%CI)	36.4 (24.1–50.5)	21.6 (11.8–35.7)	28.6 (12.2–52.3)
NPV, % (95%CI)	100.0 (31.0–100.0)	100.0 (56.1–100.0)	100.0 (88.3–100.0)
AUC, % (95%CI)	74.4 (61.6–87.2)	79.4 (67.5–91.3)	87.7 (78.1–97.2)
κ value, % (95%CI)	5.6 (–0.9–12.1)	6.2 (0.5–11.8)	17.1 (3.8–30.4)

AUC, area under the curve; CE, contrast-enhanced; CI, confidence interval; HR-VWI, high-resolution vessel wall imaging; MRA, MR angiography; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; TOF, time-of-flight.

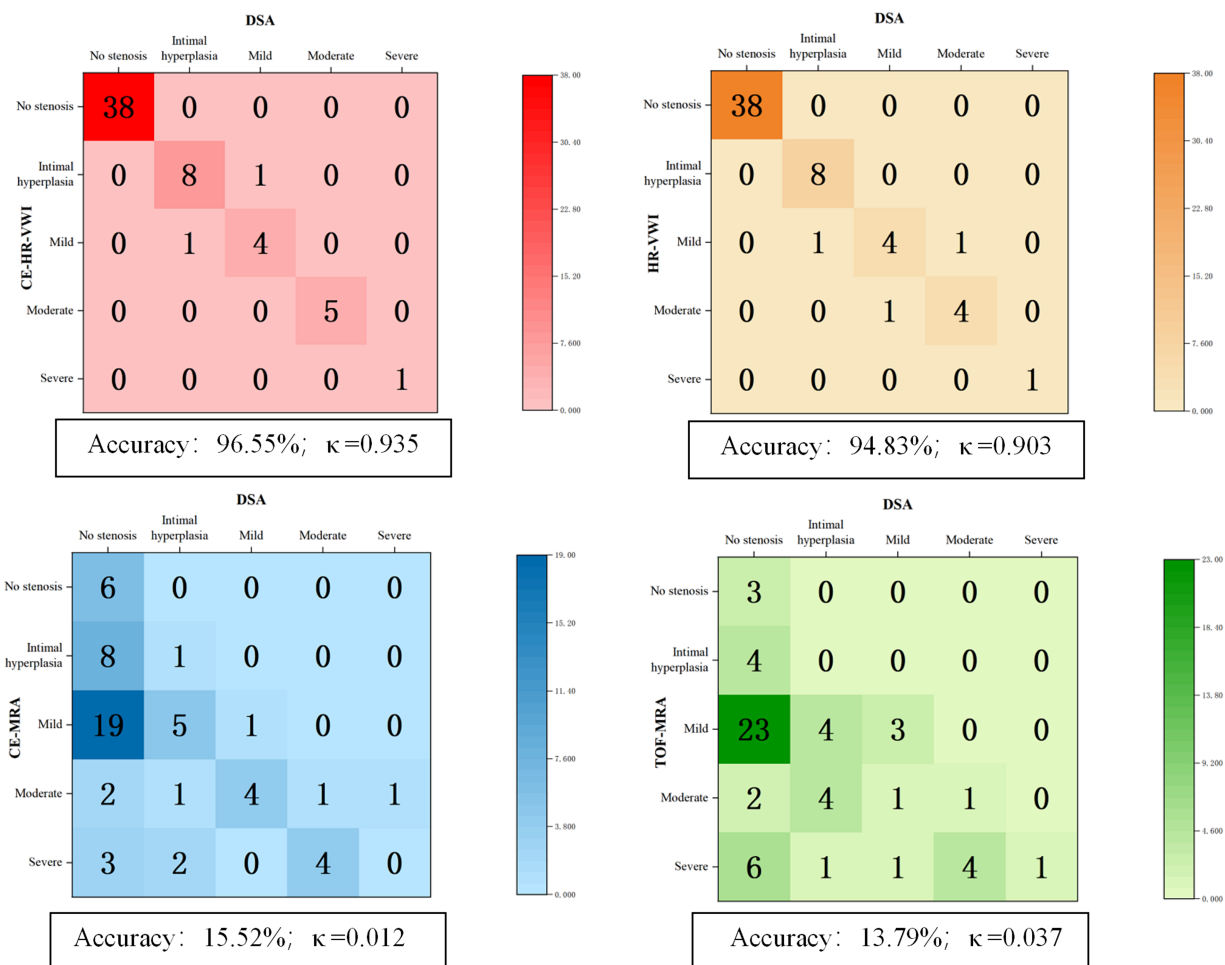


FIGURE 4

The overall consistency and accuracy for the different degrees of ISS of the four MR imaging modalities using DSA as the standard. CE, contrast-enhanced; DSA, digital subtraction angiography; HR-VWI, high-resolution vessel wall imaging; MRA, MR angiography; TOF, time-of-flight.

synchronously compared its performance to CE-MRA and TOF-MRA. And we found that HR-VWI and CE-HR-VWI performed significantly better than CE-MRA and TOF-MRA for the quantitative and qualitative evaluation of ISS, while the performance of HR-VWI and CE-HR-VWI was very similar.

Precise quantitative measurement of the lumen is a prerequisite for accurate qualitative evaluation of the stented parent artery, which depends on measurement reliability and accuracy. The reliability of measurement is mainly reflected in the repeatability and reproducibility, and in the present study, the repeatability (intra-observers) and reproducibility (inter-observers) of CE-HR-VWI and HR-VWI in all ISS measurements were almost perfect and superior to CE-MRA and TOF-MRA. This may be closely related to the excellent image quality and features of HR-VWI, which can suppress the flow signals and stent artifacts and acquire precise configuration of the stented parent artery lumen and wall. Furthermore, the black blood background in the lumen of the HR-VWI sequence can help observers to identify the boundary of the lumen of the stented parent artery and the abnormal signal lesions on the stent wall (15), which is suitable for repeated multiple measurements of the stented parent arteries.

Regarding the accuracy of stent lumen quantitative measurement, we found that CE-HR-VWI and HR-VWI had an excellent agreement with DSA and a strong correlation with DSA. The Bland-Altman plots results demonstrated very small bias, relatively narrow 95% confidence intervals, and small measured data dispersion between CE-HR-VWI and HR-VWI versus DSA. Besides, the ICC values of CE-HR-VWI and HR-VWI versus DSA were up to 0.992 to 0.994, which indicated that the ISS measurements of them were very similar. While in our study, 32 (32/58, 55.17%) cases of CE-MRA and 35 (35/58, 60.34%) cases of TOF-MRA misjudged no stenosis to different degrees of stenosis in scatter plots (Figure 5), and there were large data dispersion, and bias in the scatter plots and Bland-Altman plots of CE-MRA and TOF-MRA. This may be because the loss and deformation of signal caused by stent metal artifacts led to overestimation of ISS (Figure 6) (10, 11), therefore, CE-HR-VWI and HR-VWI were superior to CE-MRA and TOF-MRA for the quantitative evaluation of ISS.

Accurately qualitative evaluation of the degree of ISS is very important for clinical management and follow-up of SP. The stent of stenosis <25% is expected and beneficial to achieve occlusion

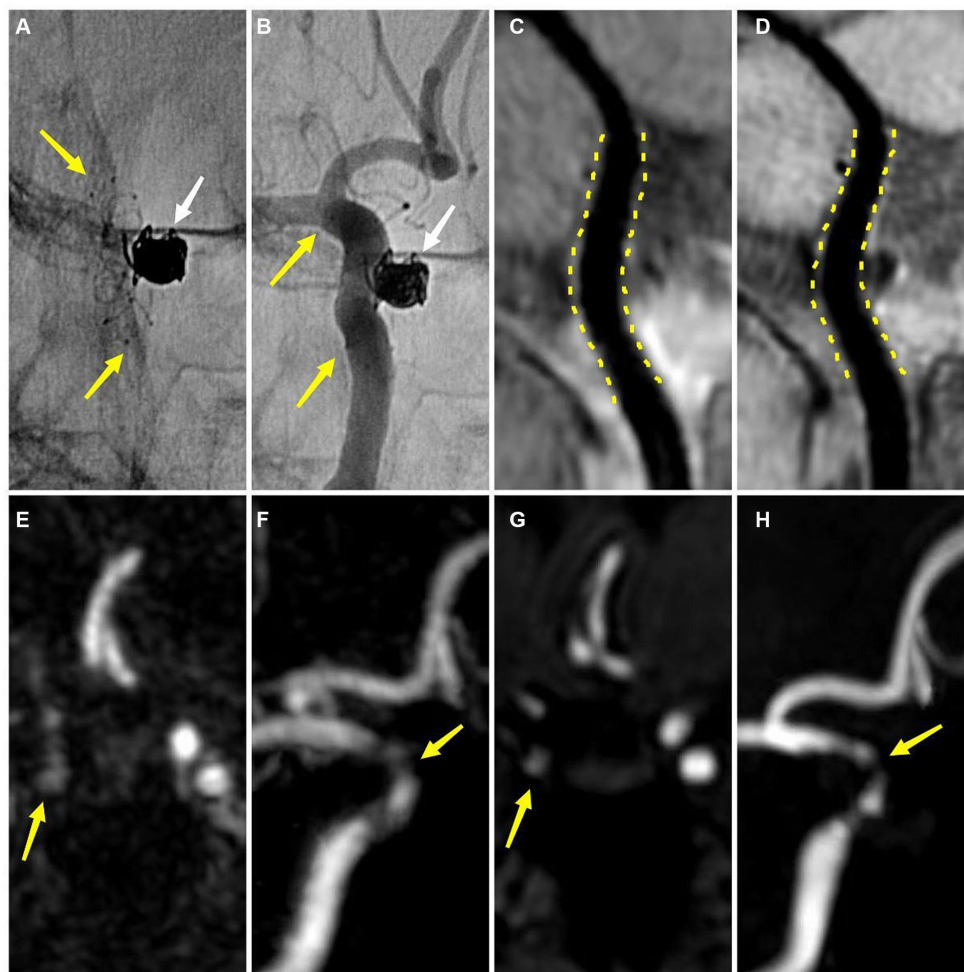


FIGURE 5

An adult patient with a left internal carotid artery aneurysm after stent-assisted coil embolization about 6 months (A,B) DSA demonstrates the embolized aneurysm (white arrow) and the LVIS stent (yellow arrow) (B) DSA shows no ISS (C) CE-HR-VWI and (D) HR-VWI reveal no ISS (yellow dotted line) (E,F) CE-MRA shows that the degree of ISS is 28% (yellow arrow) (G,H) TOF-MRA demonstrates that the degree of ISS is 42% (yellow arrow). DSA, digital subtraction angiography; ISS, in-stent stenosis; CE, contrast enhanced; HR-VWI, high-resolution vessel wall imaging; MRA, MR angiography; TOF, time-of-flight.

of the aneurysm, which requires only routine follow-up (19, 23), and 25–49% ISS has the potential for more severe stenosis or occlusion (5, 7), while $\geq 50\%$ ISS is prone to TIA or cerebral infarction, so requires more intensive follow-up, drug control or endovascular therapy (5, 7). Previous studies have found that HR-VWI was feasible in assessing the status of the stent (stenosis or patency) after SP for IAs (4, 24, 25). Compared to TOF-MRA, HR-VWI had higher accuracy for evaluating stented parent arteries and excellent agreement with DSA ($\kappa = 1$) (4). In our study, CE-HR-VWI and HR-VWI displayed excellent diagnostic accuracy and good to excellent agreement with DSA in qualitative evaluation of the degree of ISS $>0\%$, $\geq 25\%$, and $\geq 50\%$, which were better than CE-MRA and TOF-MRA. Regarding the diagnostic performance, the sensitivities of the four MRI modalities were very high, while the specificity, PPV, and PLR values of CE-HR-VWI and HR-VWI were significantly higher than those of CE-MRA and TOF-MRA. Marciano et al. (10) and Akkaya et al. (11) also found that CE-MRA and TOF-MRA had poor overall consistency with DSA in ISS degrees. These results implied that

CE-HR-VWI and HR-VWI were superior to CE-MRA and TOF-MRA in identifying ISS, possibly because CE-MRA and TOF-MRA are sensitive to stent and coil metal artifacts and failed to accurately quantitative measure the lumen of stented parent arteries (4, 10).

Accurate interpretation of HR-VWI findings in clinical practice requires considering the conditions of adequate flow suppression, optimal spatial resolution, and reasons for enhancement after administration of a gadolinium-containing contrast agent. Previous studies have reported that CE-HR-VWI may show vessel wall enhancement artifacts and result in pseudo vascular wall thickening lesions (26). The image quality of CE-HR-VWI and HR-VWI were excellent and not significantly different in our study. CE-HR-VWI and HR-VWI had similar repeatability and reproducibility in-stent lumen measurement and diagnostic accuracy and consistency with DSA in ISS measurements and degrees. Therefore, the unenhanced HR-VWI might be preferable to assess ISS alone in clinical practice since it avoids the potential side effects of gadolinium toxicity and

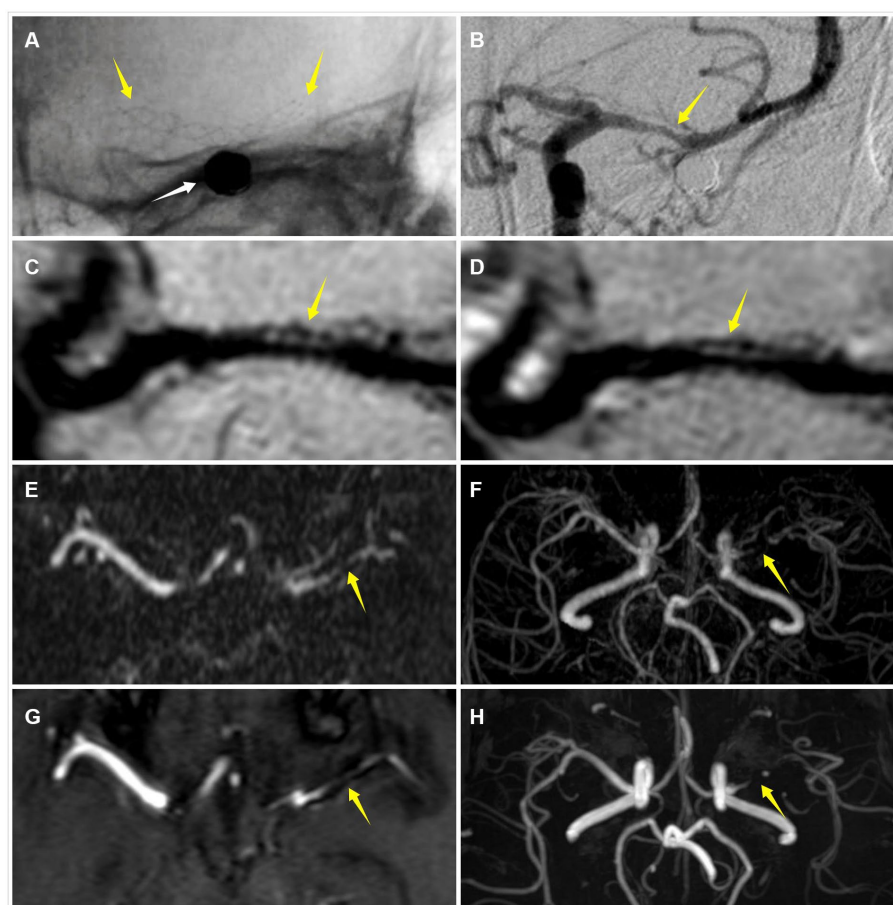


FIGURE 6

An adult patient with a left middle cerebral artery aneurysm after stent-assisted coil embolization about 8 months (A) DSA demonstrates the embolized aneurysm (white arrow) and the LVIS stent (yellow arrow) (B) DSA shows that the degree of ISS is 58% (yellow arrow) (C) CE-HR-VWI reveals that the degree of ISS is 61% (yellow arrow) (D) HR-VWI demonstrates that the degree of ISS is 64% (yellow arrow) (E,F) CE-MRA and (G,H) TOF-MRA show that the degrees of ISS are almost 100% (yellow arrow). DSA, digital subtraction angiography; ISS, in-stent stenosis; CE, contrast enhanced; HR-VWI, high-resolution vessel wall imaging; MRA, MR angiography; TOF, time-of-flight.

nephrogenic systemic fibrosis (27, 28). However, CE-HR-VWI might be needed if further exploration of the cause of ISS is required, such as additional information on the enhancement of stented parent arteries wall or lumen (18).

The current study has some limitations. First, this study was a single-center design, and the total sample size and the number of cases of ISS were relatively small. Second, since only one case was severe ISS ($\geq 75\%$), we did not specifically analyze the diagnostic efficacy of severe ISS. Third, the sample size was insufficient for comparing different stent types and sizes. Fourth, for the HR-VWI technology, we only reported the comparison between the 3D T1-VISTA sequence and DSA, so other HR-VWI sequences versus DSA need to be validated in the future.

Conclusion

HR-VWI and CE-HR-VWI demonstrated excellent diagnostic accuracy and consistency with DSA in the quantitative and qualitative evaluation of ISS after SP treatment for IAs and was

superior to CE-MRA and TOF-MRA, therefore as a noninvasive and effective imaging modality, HR-VWI without contrast media may be an alternative to DSA and ideal follow-up approach for detecting 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

The studies involving humans were approved by Ethics Committee of the Second Hospital of Chongqing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

TC: Data curation, Methodology, Writing – original draft. SL: Data curation, Formal analysis, Software, Writing – review & editing. YJ: Data curation, Project administration, Writing – review & editing. WW: Methodology, Software, Validation, Writing – review & editing. JL: Data curation, Formal analysis, Writing – review & editing. KL: Conceptualization, Writing – review & editing. DG: Funding acquisition, Project administration, Supervision, Writing – review & editing.

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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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Association between blood pressure control during aneurysm clipping and functional outcomes in patients with aneurysmal subarachnoid hemorrhage

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Objectives: We explored the relationship between blood pressure variability (BPV) during craniotomy aneurysm clipping and short-term prognosis in patients with aneurysmal subarachnoid hemorrhage to provide a new method to improve prognosis of these patients.

Methods: We retrospectively analyzed the differences between patient groups with favorable modified Rankin Scale ($mRS \leq 2$) and unfavorable ($mRS > 2$) prognosis, and examined the association between intraoperative BPV and short-term prognosis.

Results: The intraoperative maximum systolic blood pressure (SBP_{max} , $p = 0.005$) and the coefficient of variation of diastolic blood pressure (DBP_{CV} , $p = 0.029$) were significantly higher in the favorable prognosis group. SBP_{max} (OR 0.88, 95%CI 0.80–0.98) and Neu% (OR 1.22, 95%CI 1.03–1.46) were independent influence factors on prognosis. Patients with higher standard deviations of SBP (82.7% vs. 56.7%; $p = 0.030$), DBP (82.7% vs. 56.7%; $p = 0.030$), and DBP_{CV} (82.7% vs. 56.7%; $p = 0.030$) had more favorable prognosis.

Conclusion: Higher SBP_{max} (≤ 180 mmHg) during the clipping is an independent protective factor for a 90-day prognosis. These results highlight the importance of blood pressure (BP) control for improved prognosis; higher short-term BPV during clipping may be a precondition for a favorable prognosis.

KEYWORDS

subarachnoid hemorrhage, aneurysm, aortic blood pressure, variability, prognostic factors

Introduction

Spontaneous subarachnoid hemorrhage (SAH) is the third most common type of stroke and is commonly associated with aneurysmal rupture (1). Globally, approximately 500,000 patients develop aneurysmal subarachnoid hemorrhage (aSAH) annually (2). Approximately a quarter of patients with SAH die before hospital admission; overall outcomes are improved in those admitted to hospitals; however, these survivors face years with a diminished quality of life (3). Age, hypertension, intraoperative and postoperative complications, surgical timing,

and surgical methods are significant factors affecting the prognosis of aSAH (4). Conversely, the effect of blood pressure fluctuations on the prognosis of aSAH remains uncertain (5–7). Previous studies on blood pressure variability (BPV) have ignored the impact of surgical approaches and intraoperative blood pressure fluctuations on the prognosis of patients with aSAH. Consequently, the present study sought to examine the association between intraoperative BPV and 90-day prognosis in patients with aSAH who underwent craniotomy aneurysm clipping.

Methods

Study population

A total of 59 patients with aSAH were included in this retrospective study. All the patients underwent craniotomy aneurysm clipping at the Department of Neurosurgery of the First Affiliated Hospital of Xi'an Jiaotong University between January 2019 and December 2022. The inclusion criteria were as follows: (1) age 18–80 years; (2) spontaneous primary aSAH confirmed by CT scan and digital subtraction angiography (DSA); (3) admission within 72 h after symptom onset and aneurysm clipping within 36 h after admission; and (5) complete medical records. Patients with severe craniocerebral trauma, modified Rankin Scale (mRS) scores before onset exceeding 2, or hemodynamic instability were excluded. This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF2023LSK-265). Written informed consent from the legal guardians of the participants was not required for this retrospective study in accordance with national and local guidelines.

Clinical management

All patients underwent emergency clipping of ruptured intracranial aneurysms under general anesthesia with tracheal intubation. Blood pressure (BP) of patients obtained by invasive arterial pressure monitoring (patient monitor model: BeneView T8) through radial artery catheterization was recorded every 15 min from entering to leaving the operating room. Patients were transferred to the intensive care unit, and nimodipine was routinely administered to prevent cerebral vasospasm after surgery. Treatment was administered in strict accordance with the relevant clinical management guidelines.

Data collection

The general data of patients were recorded as follows: (1) demographic characteristics (age and sex); (2) medical comorbidities (hypertension and diabetes); (3) personal history (smoking and drinking); (4) characteristics of the aneurysm (location, size, and number); (5) assessment of severity at admission [Glasgow Coma Scale, Hunt-Hess Scale, modified Fisher grade (m-Fisher), and World Federation of Neurosurgical Societies (WFNS) score]; and (6) laboratory results at admission [hemoglobin, white blood cell, platelet, neutrophil percentage (Neu%), aspartate aminotransferase, alanine

aminotransferase, cholesterol, blood urea nitrogen, serum creatinine, and random blood glucose].

We calculated the following indexes of systolic blood pressure (SBP) and diastolic blood pressure (DBP) (8, 9): The mean, maximum (max), minimum (min), difference of maximum minus minimum

(max–min), standard deviation (SD, $SD = \sqrt{\frac{1}{n-1} \sum_{i=1}^{n-1} (X_i - X_{mean})^2}$),

coefficient of variation (CV, $CV = (X_{SD}/X_{mean}) * 100\%$) and successive

variation (SV, $SV = \sqrt{\frac{1}{n-1} \sum_{i=1}^{n-1} (X_{i+1} - X_i)^2}$).

Evaluation of prognosis

The prognosis was evaluated using the mRS at 90 days after onset. All patients were followed up by the same neurologist through telephone interviews. The mRS is a 7-point scale ranging from 0 (no symptoms) to 6 (death). The mRS was dichotomized, as previously published, into favorable (mRS ≤ 2) and unfavorable (mRS > 2) prognoses for the outcome analyses (10).

Statistical analysis

All statistical analyses were performed using SPSS25.0 statistical package. Data were presented as mean ± standard deviation ($\bar{x} \pm s$) for continuous symmetric distribution variables, median (M) and interquartile range (IQR) for continuous skewed distribution variables, and percentages for categorical variables. Differences between the two groups were assessed using univariate analysis with independent Student's *t*-tests for continuous variables and the chi-squared test for categorical variables. For non-parametric variables, we used the Mann–Whitney U-test. The significant parameters in the univariate analysis were used as inputs in the multivariate binary logistic regression model for regression analysis. Spearman's rank correlation was used for correlation analysis. In all the tests, $p < 0.05$ was considered statistically significant.

Data availability

Data were recorded and stored in both paper and electronic databases. The supporting data for this study are available from the corresponding author on request.

Results

Fifty-nine eligible patients were enrolled over the four-year interval, of whom 29 (49%) were male, and 30 (51%) were female. The average age was 57.0 ± 8.2 years. The clinical data of the 59 patients (41 in the favorable group and 18 in the unfavorable group) are summarized in Table 1. The aneurysm size ($p = 0.025$), Hunt–Hess grade ($p = 0.006$), m-Fisher grade ($p = 0.010$), WFNS grade ($p = 0.001$), Neu% ($p = 0.004$), and blood Glu ($p = 0.013$) at admission and the incidence of delayed cerebral ischemia (DCI, $p = 0.007$) were significantly higher in the unfavorable group (mRS > 2) than in the

TABLE 1 Comparison of clinical characteristics between patient groups with favorable and unfavorable prognosis.

Characteristic	Favorable prognosis 41 (69.5%)	Unfavorable prognosis 18 (30.5%)	<i>p</i> value
Age, year ($\bar{X}\pm s$)	56.1 $\pm$ 7.7	58.9 $\pm$ 9.1	0.215
Sex, females (n, %)	18 (43.9%)	12 (66.7%)	0.107
Smoking (n, %)	15 (36.6%)	6 (33.3%)	0.810
Drinking (n, %)	9 (22.0%)	8 (44.4%)	0.079
Hypertension (n, %)	26 (63.4%)	13 (72.2%)	0.511
Diabetes (n, %)	2 (4.9%)	2 (11.1%)	0.381
Aneurysm Location (n, %)			
Anterior circulation	37 (90.2%)	15 (83.3%)	0.644
Posterior circulation	4 (9.8%)	3 (16.7%)	
Aneurysm Number (n, %)			
Single	37 (90.2%)	15 (83.3%)	0.644
Multiple	4 (9.8%)	3 (16.7%)	
Aneurysm size (n, %)			
Small ($d\leq 0.5$ cm)	22 (53.7%)	4 (22.2%)	0.025
Larger ($d> 0.5$ cm)	19 (46.3%)	14 (77.8%)	
Hunt-Hess score (n, %)			
I-II	17 (41.5%)	1 (5.6%)	0.006
III-V	24 (58.5%)	17 (94.4%)	
m-Fisher score (n, %)			
0–2	24 (58.5%)	4 (22.2%)	0.010
3–4	17 (41.5%)	14 (77.8%)	
WFNS classification (n, %)			
I-II	27 (65.9%)	3 (16.7%)	0.001
III-V	14 (34.1%)	15 (83.3%)	
DCI	10 (24.4%)	11 (61.1%)	0.007
Laboratory Results ($\bar{X}\pm S/M, Q$)			
Hb, g/L	134.0 (120.5, 153.5)	135.0 (121.8, 150.8)	0.811
WBC, cells/L	11.1 (8.2, 13.1)	12.3 (8.6, 14.9)	0.505
PLT, cells/L	203.0 (162.5, 252.0)	187.5 (157.3, 241.0)	0.627
Neu, %	85.8 (78.2, 90.6)	91.3 (86.4, 94.5)	0.004
AST, U/L	21.0 (18.0, 29.0)	26.50 (21.5, 29.8)	0.106
ALT, U/L	25.0 (14.0, 29.5)	22.5 (15.3, 26.0)	0.479
CHO, mmol/L	4.5 $\pm$ 1.1	5.1 $\pm$ 1.2	0.055
BUN, mmol/L	4.8 $\pm$ 1.5	4.3 $\pm$ 1.6	0.299
Cr, μ mol/L	45.0 (37.0, 57.5)	50.0 (32.8, 56.5)	0.941
Glu, mmol/L	6.81 (6.2, 7.8)	7.84 (7.2, 9.6)	0.013

m-Fisher, modified Fisher grade; WFNS, World Federation of Neurosurgical Societies score; DCI, delayed cerebral ischemia; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; Neu%, neutrophil percentage; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CHO, cholesterol; BUN, blood urea nitrogen; Cr, serum creatinine; Glu, random blood glucose. Bold indicates statistical significance under the two-sided $p<0.05$ assumption.

favorable group ($mRS\leq 2$). The two groups showed no significant differences in the remaining clinical data.

A comparison of the intraoperative SBP and DBP indices between the two groups is shown in Table 2. The SBP_{max} (152.2 $\pm$ 16.5 vs. 139.6 $\pm$ 12.7; $p=0.005$) and DBP_c (10.8, IQR 8.5–12.8; 8.1, IQR 6.9–10.4; $p=0.029$) were significantly higher in the favorable group

than in the unfavorable group. Spearman’s correlation tests showed that intraoperative SBP_{max} ($r=0.34$, $p=0.015$) and DBP_c ($r=0.29$, $p=0.027$) were positively associated with a 90-day favorable prognosis.

Indices with statistical differences in univariate analysis were included in the multivariate binary logistic regression analysis. This analysis showed that Neu% (OR 1.22, 95%CI 1.03–1.46) is an

independent risk factor for unfavorable prognosis, while SBP_{max} (OR 0.88, 95%CI 0.80–0.98) is an independent protective factor for prognosis. Figure 1 shows the factors that significantly influenced the 90-day prognosis of patients with aSAH. In addition, we stratified the 47 patients with systolic BP ≤ 180 mmHg and the 56 patients with ≤ 160 mmHg, according to the 95th and 90th percentiles, respectively. The results showed that when the SBP_{max} was ≤ 180 mmHg, the probability of developing a favorable prognosis at 90 days increased with increasing SBP_{max} (OR 1.06, 95% CI 1.01–1.11; $p=0.018$).

TABLE 2 Comparison of intraoperative blood pressure parameters between patient groups with favorable and unfavorable prognosis.

Parameter (mmHg)	Favorable prognosis 41 (69.5%)	Unfavorable prognosis 18 (30.5%)	<i>p</i> value
$SBP_{mean} (\bar{x} \pm s)$	122.3 $\pm$ 9.4	117.2 $\pm$ 9.3	0.058
$SBP_{max} (\bar{x} \pm s)$	152.2 $\pm$ 16.5	139.6 $\pm$ 12.7	0.005
$SBP_{min} (M, Q)$	105.0 (98.0, 113.0)	100.0 (87.0, 109.3)	0.075
$SBP_{max-min} (\bar{x} \pm s)$	46.4 $\pm$ 16.0	42.3 $\pm$ 19.3	0.395
$SBP_{SD} (\bar{x} \pm s)$	11.3 $\pm$ 3.7	9.91 $\pm$ 2.9	0.160
$SBP_{CV} (\bar{x} \pm s)$	9.3 $\pm$ 3.3	8.6 $\pm$ 2.9	0.401
$SBP_{SV} (M, Q)$	8.4 (7.9, 10.5)	9.9 (7.1, 14.4)	0.188
$DBP_{mean} (\bar{x} \pm s)$	67.8 $\pm$ 7.0	68.3 $\pm$ 8.8	0.838
$DBP_{max} (\bar{x} \pm s)$	88.2 $\pm$ 11.2	83.1 $\pm$ 12.5	0.132
$DBP_{min} (M, Q)$	57.0 (53.0, 61.5)	59.0 (50.5, 62.5)	0.921
$DBP_{max-min} (M, Q)$	29.0 (21.5, 39.0)	24.0 (18.3, 29.8)	0.106
$DBP_{SD} (M, Q)$	7.2 (5.6, 8.7)	5.71 (4.6, 7.2)	0.050
$DBP_{CV} (M, Q)$	10.8 (8.5, 12.8)	8.1 (6.9, 10.4)	0.029
$DBP_{SV} (M, Q)$	6.2 (5.1, 7.2)	6.6 (5.5, 8.7)	0.172

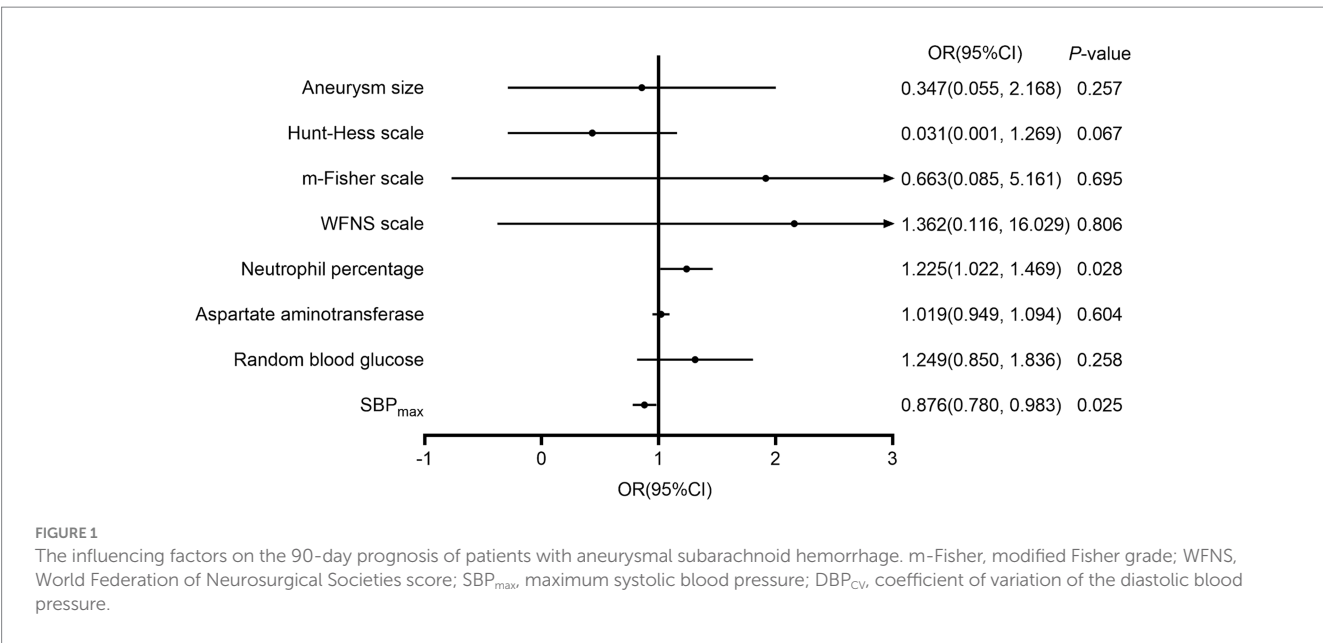
SBP, systolic blood pressure; DBP, diastolic blood pressure; max, maximum; min, minimum; max-min, difference of maximum minus minimum; SD, standard deviation; CV, coefficient of variation.
Bold indicates statistical significance under the two-sided $p < 0.05$ assumption.

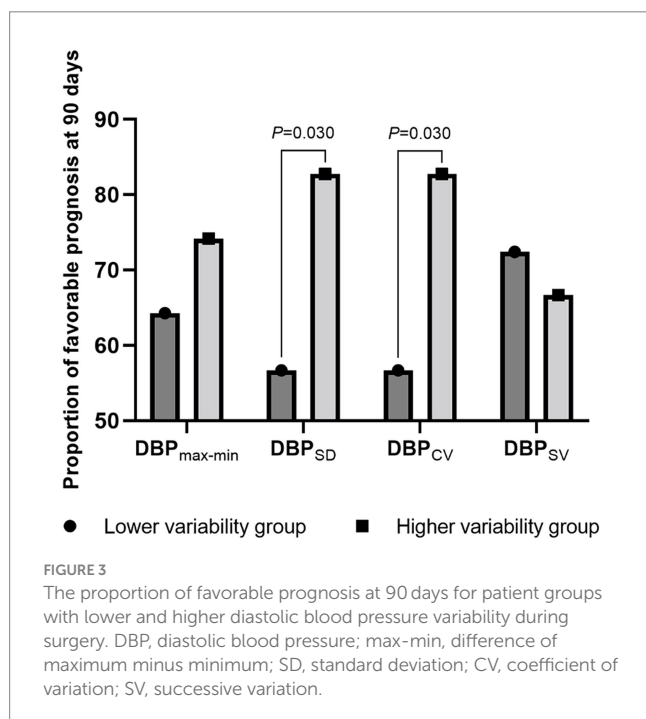
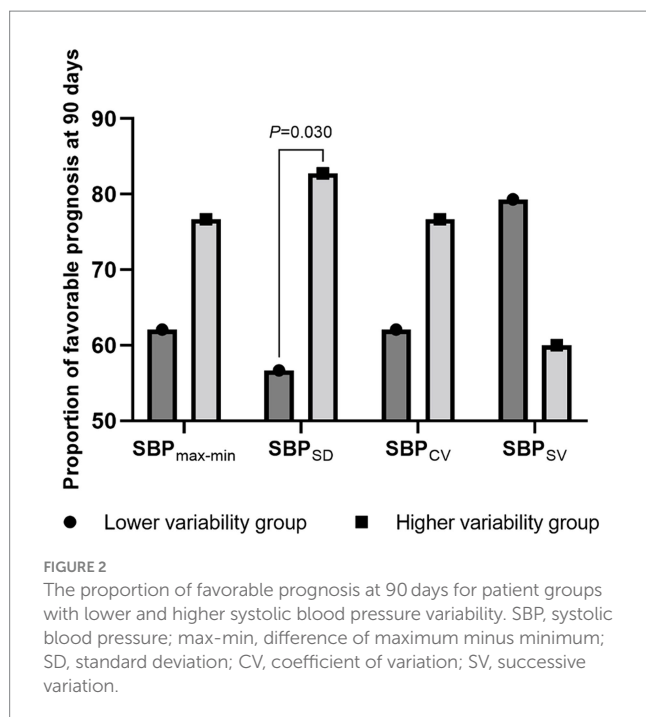
However, the trend was not statistically significant when the cutoff value was 160 mmHg (OR 1.04, 95% CI 0.98–1.10; $p=0.212$).

Next, we stratified the patients into two groups based on the median BP variability parameters and compared their proportions of favorable prognoses. Patients with a higher SBP_{SD} (56.7% vs. 82.7%; $p=0.030$), DBP_{SD} (56.7% vs. 82.7%; $p=0.030$), and DBP_{CV} (56.7% vs. 82.7%; $p=0.030$) had a more favorable prognosis. Detailed data are presented in Figures 2, 3.

Discussion

Our study demonstrated that intraoperative SBP_{max} is an independent predictor of favorable outcomes in patients with aSAH. Acute hypertension should be managed after developing aSAH; however, the parameters for appropriate BP control have not yet been defined. Insufficient management of BP may increase the risk of rebleeding, whereas aggressive treatment of hypertension increases the risk of ischemic stroke (11). It has been confirmed that induced hypertension can reduce the occurrence of DCI; however, unsurprisingly, having an $SBP_{max} > 180$ mmHg increases the risk of rebleeding (12, 13). In 2012, the AHA/ASA issued guidelines for SAH treatments, pointing out that maintaining euolemia and inducing hypertension are effective measures to prevent DCI and recommended that SBP should be brought below 160 mmHg before clipping the aneurysm to reduce the risk of rebleeding (14). In 2013, the European Stroke Organization suggested that SBP should be maintained below 180 mmHg before surgery (13). In a previous study, Ascanio et al. reported that hypotension was independently associated with poor outcomes in patients with aSAH (15). Similarly, the present study showed that intraoperative SBP_{max} was an independent protective factor for patients with aSAH when it was below 180 mmHg. However, no protective effect was observed when SBP_{max} was < 160 mmHg. These results led us to propose that the intraoperative SBP_{max} should be elevated but not exceed 180 mmHg, which is consistent with the management of preoperative hypertension proposed by the European





Stroke Organization in 2013 (13). In addition, intraoperative hypotension appears to promote DCI and poor prognosis in patients with aSAH; however, the downline of intraoperative blood pressure control is inconsistent (16–19).

The unfavorable prognosis of patients with aSAH is often related to DCI, which is generally attributed to abnormal constriction of the cerebral arteries, namely, cerebral vasospasm (CVS) (20). DCI is associated with the autoregulatory failure of the nervous system (21).

Furthermore, intracranial pressure variability (ICPV) is mainly affected by fluctuations in cerebral blood flow, which indirectly reflects cerebral autoregulation (22). Previous studies have shown that low BPV and ICPV are associated with unfavorable outcomes in patients with aSAH (7). The present results show that patients with higher BP variability have a higher incidence of favorable prognoses. In 1929, Walter B. Cannon first proposed the concept of “homeostasis.” According to self-regulation mechanisms, physiological homeostasis is not static but maintains a dynamic equilibrium within a tolerable range. Physiological variability reflects the ability of an organism to autoregulate. Abnormal variability, reflecting impaired physiological responsiveness, can increase the risk of further physiological derangement (23). DBP is mainly affected by the heart rate and peripheral resistance. After SAH, the concentration of calcium ions in the cerebrospinal fluid increases, and the flow of calcium ions into the cells accelerates, resulting in vasoconstriction and increased vascular resistance. A lower DBP_{CV} in patients with aSAH implies distal microvascular spasms, indicating an increased risk of CVS or even DCI, which is closely related to unfavorable prognoses. However, other studies have shown that variability in SBP within 24 h of admission is an independent risk factor for poor prognosis in patients with SAH (6). These propositions were not entirely consistent, possibly owing to inconsistencies arising from the different timeframes considered in the variability assessment. Higher short-term variability may reflect faster and more effective functioning of adaptive mechanisms, and higher long-term variability (time spans exceeding 1 h) may reflect a decreased integrated ability of adaptive mechanisms to respond to challenges (7). Therefore, the timescale of BP variability determines its effect on clinical outcomes.

Previous studies have shown that BP variability is related to the vegetative nervous system function, such that decreased variability implies autonomic nerve dysfunction (24, 25). If the sympathetic nervous system is overactivated, feedback regulation of the neuroendocrine system may fail, leading to decreased short-term variability and an increased risk of unfavorable prognoses (26). Supporting this model, pharmacological blocking of the cervical sympathetic ganglion can effectively relieve DCI after SAH (27), which has also been confirmed in animal experiments (28). As mentioned above, timely and effective inhibition of sympathetic hyperactivity may benefit patients with aSAH, offering a new therapeutic target to reduce the incidence of CVS and improve prognosis.

The small sample size used during this study may have reduced the generalizability of the results; however, the overall trend was compelling. The mean duration of intracranial aneurysm clipping among the enrolled patients was only 5.4 h, so we could not analyze longer-term BPV. Furthermore, not all BP values were available during the entire hospital stay. Therefore, we cannot discuss the prognostic effects of BPV during hospitalization. We did not fully consider the influence of intraoperative drugs on BPV, which may have affected the accuracy of the research findings and should, therefore, be considered in future-related studies. We intend to conduct further clinical studies to evaluate whether patients benefit from intraoperative interventions for arterial pressure reduction.

In conclusion, SBP_{max} during craniotomy aneurysm clipping was an independent protective factor for a favorable prognosis at 90 days. Appropriately high BP is beneficial for improving prognosis. However, the risk of adverse effects such as rebleeding should be considered. A

higher short-term BPV during surgery implies higher cerebral autoregulatory function, potentially leading to a more favorable prognosis.

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 humans were approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin due to the retrospective nature of the study.

Author contributions

XH: Writing – original draft, Methodology, Data curation, Conceptualization. GL: Writing – review & editing, Supervision, Resources, Project administration. JL: Writing – review & editing, Visualization, Investigation. RL: Writing – review & editing, Investigation. NZ: Writing – review & editing, Investigation. SJ: Writing – review & editing, Data curation. WM: Writing – review & editing, Data curation. YC: Writing – review & editing, Methodology, Funding acquisition, Conceptualization. FL: Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

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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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The relationship between autoimmune disorders and intracranial aneurysms in East Asian and European populations: a bidirectional and multivariable two-sample Mendelian randomization study

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Background: It remains unclear about the pathogenesis of intracranial aneurysms (IAs) in the setting of autoimmune disorders (ADs). However, the underlying systemic inflammatory characteristics of ADs may affect IAs through shared inflammatory pathways. Therefore, this study was conducted to explore the relationship between ADs and IAs and assess causal effects.

Methods: In this study, 6 common ADs were included to explore their causal relationship with IAs. Besides, a bidirectional two-sample univariable Mendelian randomization (UVMR) analysis was performed. In addition, the primary analysis was performed by the inverse variance weighted (IVW) and Bayesian weighted Mendelian randomization (BWMR) method, and a series of sensitivity analyses were performed to assess the robustness of the results. Further, the data related to ADs and IAs were collected from open genome-wide association study studies (GWASs) and the Cerebrovascular Disease Knowledge Portal (CDKP) (including 11,084 cases and 311,458 controls), respectively. These analyses were conducted based on both the East Asian and European populations. Moreover, 6 ADs were subject to grouping according to connective tissue disease, inflammatory bowel disease, and thyroid disease. On that basis, a multivariate MR (MVMR1) analysis was further performed to explore the independent causal relationship between each AD and IAs, and an MVMR 2 analysis was conducted to investigate such potential confounders as smoking, alcohol consumption, and systolic blood pressure. Finally, these results were verified based on the data from another GWAS of IAs.

Results: The UVMR analysis results demonstrated that systemic lupus erythematosus (SLE) was associated with a high risk of IAs in the East Asian population (IVW OR, 1.06; 95%CI, 1.02–1.11; $p = 0.0065$, UVMR), which was supported by the results of BWMR (OR, 1.06; 95%CI, 1.02–1.11; $p = 0.0067$, BWMR), MVMR1 (OR, 1.06; 95%CI, 1.01–1.10; $p = 0.015$, MVMR1), MVMR2 (OR, 1.05; 95%CI, 1.00–1.11; $p = 0.049$, MVMR2), and sensitivity analyses. The results

in the validation group also suggested a causal relationship between SLE and IAs (IVW OR, 1.04; 95% CI, 1.00–1.09; $p = 0.046$). The reverse MR analysis results did not reveal a causal relationship between IAs and ADs.

Conclusion: In this MR study, SLE was validated to be a risk factor for IAs in the East Asian population. Therefore, the management of IAs in patients with SLE should be highlighted to avoid stroke events.

KEYWORDS

autoimmune disorders, intracranial aneurysms, Mendelian randomization, SNPs, multivariable Mendelian randomization, causal relationship

1 Introduction

Intracranial aneurysms (IAs) are defined as locally abnormal enlargement of the lumen of cerebral arteries due to congenital defects or external factors, exhibiting a tumor-like protrusion on the artery wall, namely, cystic or band-like changes in the structure (1, 2). As reported in imaging studies using arteriography and MRI, the incidence of IAs ranges from 0.5 to 3% in the general population. In a prevalence study based on the European population, aneurysms were detected in the MRI-based screening of approximately 1.8% of adult subjects. As per a cross-sectional study in China, 7% of adults aged 35–75 years were diagnosed with aneurysms during brain magnetic resonance angiography screening (3). Although the etiology of IAs has not been defined, their initiation and growth are correlated with flow-related wall shear stress, hereditary factors, and inflammation. It has been suggested that inflammation plays a pivotal role in the occurrence of IAs. Some diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's syndrome (SS), known for their systemic inflammatory attributes, might affect the development of IAs through inflammatory pathways (4). Therefore, this study was conducted to explore the relationship between autoimmune disorders (AD) and IAs. These findings may contribute to improving the screening of patients with cerebral aneurysms or identifying new therapeutic targets for the medical management of IAs.

Inflammation may be a major mechanism for impairing the vascular wall and is associated with the development of the aneurysm wall. The formation of abdominal aortic aneurysms has been validated to correlate with such autoimmune diseases as rheumatoid arthritis (RA), hypothyroidism, and SLE (5–7). IAs may follow a similar pathophysiological mechanism. According to several case reports, the causes of cerebral hemorrhage and IAs in people with SLE, RA, multiple sclerosis, sarcoidosis, and Sjögren's syndrome (SS) may be related to the underlying mechanisms of autoimmune cerebrovascular inflammation (8–13). A smaller size of aneurysms at rupture was found in patients with ADs; Further, patients with ADs had significantly smaller average ruptured aneurysms than those without ADs, according to a retrospective review including 190 patients with ruptured and unruptured cystic IAs (4). As a result, these studies indicate that ADs might wield influence on the development of IAs. However, the impact of diverse confounders (like the usage of steroid hormones in treatment and the presence of hypertension) cannot be eliminated in existing studies. Furthermore, the limited scale

of these studies curtails their capacity to thoroughly dissect the causal relationships.

Mendelian randomization (MR) is a causal inference method, which can be employed to adeptly probe the influence of modifiable exposure on diseases. It leverages genetic variation to furnish compelling evidence of robust associations (14). Besides, it harnesses the merits of consolidated statistics originating from extensive genome-wide association studies (GWASs) conducted across sweeping cohorts. Overall, this method makes use of bigger sample sizes and reduces potential biases that may occur in single-sample analyses to increase the accuracy of causal estimations in two-sample MR studies, in which the data from two independent sources are employed. To further clarify the causal relationship between ADs and IAs, multivariate MR (MVMR) and reverse MR analyses were also performed in this study, which may minimize confounders and exclude reverse causality, thus contributing to more stable and reliable results.

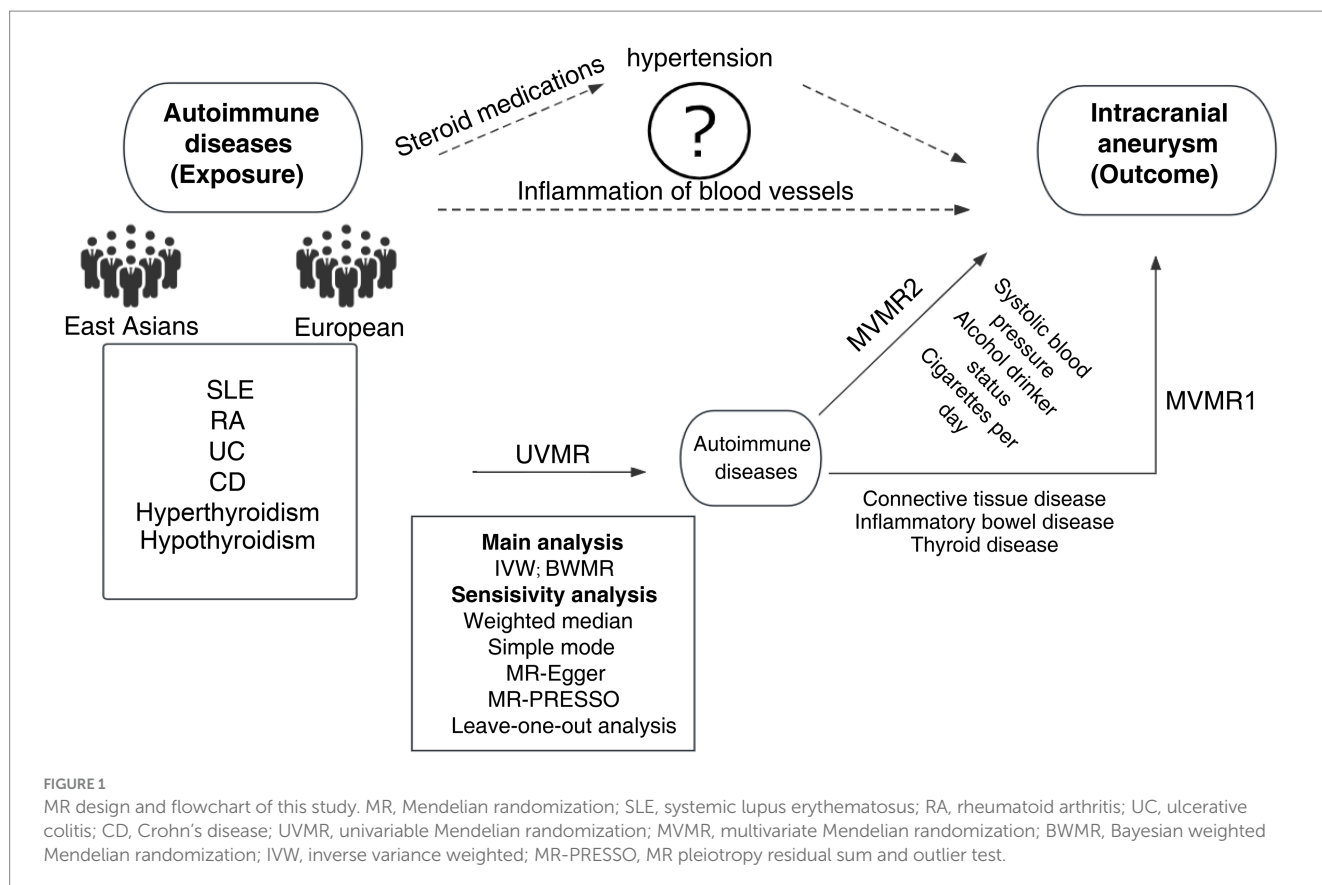
2 Materials and methods

2.1 Study design

Firstly, the instrumental variables (IVs) for ADs and IAs were curated based on summary statistics from both the European and East Asian populations. Besides, UVMR was utilized to estimate the causal impact of ADs on IAs. Additionally, 6 ADs were subject to grouping according to connective tissue disease, inflammatory bowel disease, and thyroid disease. Moreover, MVMR1 was conducted to discern the independent effects of each AD on IAs; MVMR2 was performed on the exposure, including alcohol consumption, smoking, and systolic blood pressure, to avoid the influence of confounders (15). To further fortify our analysis, a reverse MR was conducted to counteract the potential effects of reverse causality. The study design process is illustrated in Figure 1. Furthermore, another GWAS of IAs was selected for validation. The MR analysis should be performed based on three core assumptions: (1) there is a strong correlation between IVs and exposure; (2) there is independence between IVs and confounders; and (3) IVs can only exert an effect on outcomes through exposure.

2.2 GWAS summary data for ADs

In this study, 6 common ADs, including SLE, RA, ulcerative colitis (UC), Crohn's disease (CD), hyperthyroidism, and hypothyroidism,



were included to explore the relationship between ADs and IAs. These data can be obtained from the website¹ based on the GWAS ID in Table 1 or in the original GAWS article (16–19), which contained the GWAS data that were available to the public and did not require an ethical review. To acquire more significant research and dependable results, the data with the biggest sample size were also selected and then stratified based on the races in the European and East Asian populations. The details of these data are summarized in Table 1.

2.3 GWAS summary data for IAs

A GWAS including 11,084 cases and 311,458 controls of the European and East Asian populations yielded summary statistics for IAs. The summary data were collected from the CDKP (20). Among the GWAS summary data of IAs (ruptured and unruptured) ($n=6,242$) against controls ($n=63,994$) in the European population and those of IAs (ruptured and unruptured) ($n=3,259$) against controls ($n=234,946$) in the East Asian population, there were 2,662 cases and 164,009 controls from Biobank Japan (BBJ) and 597 cases and 70,939 controls from China Kadoorie Biobank (CKB).

In the validation group, the GWAS data of IAs were obtained from the OpenGWAS database, including 945 cases and 472,738 controls in the European population and 2,820 cases and 192,383 controls in

the East Asian population. All details of these data are summarized in Table 1.

2.4 IV selection

Single nucleotide polymorphisms (SNPs), as IVs with a good correlation with each AD, were used in this MR study. Besides, a variety of quality control strategies were employed to filter eligible genetic IVs that conformed to the three main MR assumptions. Firstly, the SNPs associated with ADs were isolated from the entire genome ($p < 5 \times 10^{-8}$). For hyperthyroidism and hypothyroidism in the East Asian population, a threshold of $p < 5 \times 10^{-6}$ was set for more IVs. In addition, a threshold of $r^2=0.001$ was used to reduce linkage imbalance and trimmed SNPs within a window size of 10,000 kb to ensure the independence of each IV (LD). Then, the pool of IVs and SNPs that were missing from the results was purged of palindromic SNPs. The same criteria were adopted in the validation group. Lastly, the F statistic for IVs was calculated to identify whether there was weak instrumental bias. Using the formula $F = \beta^2_{\text{exposure}} / \text{SE}^2_{\text{exposure}}$ (21), the F statistic was larger than 10, proving that there was no bias due to weak IVs (22).

2.5 Statistical analysis

R software 4.3.1, BWMR, and TwoSampleMR were used in this study. The IVW approach is the primary focus of UVMR, and it can

¹ <https://gwas.mrcieu.ac.uk/>

TABLE 1 Characteristics of data in this study.

Trait		Sample size (case and controls)	Population	GWAS ID (PMID)
Autoimmune disorders	SLE	14,267 (5,201 and 9,066)	European	ebi-a-GCST003156 (26502338)
	RA	417,256 (8,255 and 409,001)		ebi-a-GCST90018910 (34594039)
	UC	417,932 (5,371 and 412,561)		ebi-a-GCST90018933 (34594039)
	CD	20,883 (5,956 and 14,927)		ieu-a-30 (26192919)
	Hyperthyroidism	460,499 (3,557 and 456,942)		ebi-a-GCST90018860 (34594039)
	Hypothyroidism	410,141 (30,155 and 379,986)		ebi-a-GCST90018862 (34594039)
Autoimmune disorders	SLE	12,653 (4,222 and 8,431)	East Asian	ebi-a-GCST90011866 (33536424)
	RA	19,190 (3,636 and 15,554)		bbj-a-72 (24390342)
	UC	4,853 (1,134 and 3,719)		ieu-a-969 (26192919)
	CD	5,409 (1,690 and 3,719)		ieu-a-11 (26192919)
	Hyperthyroidism	173,650 (994 and 172,656)		ebi-a-GCST90018640 (34594039)
	Hypothyroidism	173,770 (1,114 and 172,656)		ebi-a-GCST90018642 (34594039)
Intracranial Aneurysm	uIA and IA	317,636 (11,084 and 311,458)	Mixed	https://cd.hugeamp.org/datasets.html (33199917)
		79,429 (6,242 and 63,994)	European	
		238,207 (3,259 and 234,946)	East Asian	
	IA (validation groups)	473,683 (945 and 472,738)	European	ebi-a-GCST90018815
		195,203 (2,820 and 192,383)	East Asian	bbj-a-96
Risk factors	Cigarettes per day	4,772	European	ebi-a-GCST009966 (32157176)
	Alcohol drinker status	360,726 (336,919 and 23,807)		ukb-d-20117_2
	Systolic blood pressure	422,713		ebi-a-GCST90025968 (34226706)
	cigarettes per day	72,655	East Asian	ieu-b-5071 (31089300)
	Alcohol drinker status: Current	2,656 (555 and 2,101)		ukb-e-20117_p1_EAS
	Systolic blood pressure	145,505		ieu-b-5075 (34594039)

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; UC, ulcerative colitis; CD, Crohn's disease; IA, intracranial aneurysm; uIA, unruptured intracranial aneurysm.

be applied in the absence of potential horizontal pleiotropism (23). BWMR is causally inferred by the variational expectation–maximization (VEM) algorithm, which further considers the uncertainty of weak effects. The pleiotropy has been addressed by BWMR outlier detection, and the BWMR results are also reliable (24). In this study, MVMR derived from UVMR was also performed. In regression models, some key variables and outcomes are often used to perform univariate regression first, followed by the addition of confounders to conduct multivariate regression for corrections. The same is true in MR, which can be used to correct confounders, especially when multiple SNPs overlap. Subsequently, MR-Egger, simple mode, weighted median, and weighted model techniques were added to the IVW results (25). As long as the beta values of other methods are aligned in the same direction, significant results from the IVW method are taken into consideration meaningfully even when other methods are not. After the Bonferroni correction, a *p* value below 0.008 (0.05/6) was considered statistically

significant. The presence of horizontal pleiotropy was identified using MR-Egger intercepts (26). Level pleiotropy outliers may be found using the MR-PRESSO framework, and outlier removal can be utilized to correct IVW estimates (27). To verify whether a particular outlier variable had an impact on the effect estimates, a stay-aside analysis was carried out. Moreover, Cochran's Q test was performed by IVW and MR-Egger analyses to assess the heterogeneity of each SNP, and heterogeneity was indicated by Q-statistics with a *p*-value <0.05.

3 Results

3.1 MR results in the European population

In this study, 30, 11, 9, 36, 7, and 44 SNPs were incorporated in the UVMR for SLE, RA, UC, CD, hyperthyroidism, and hypothyroidism,

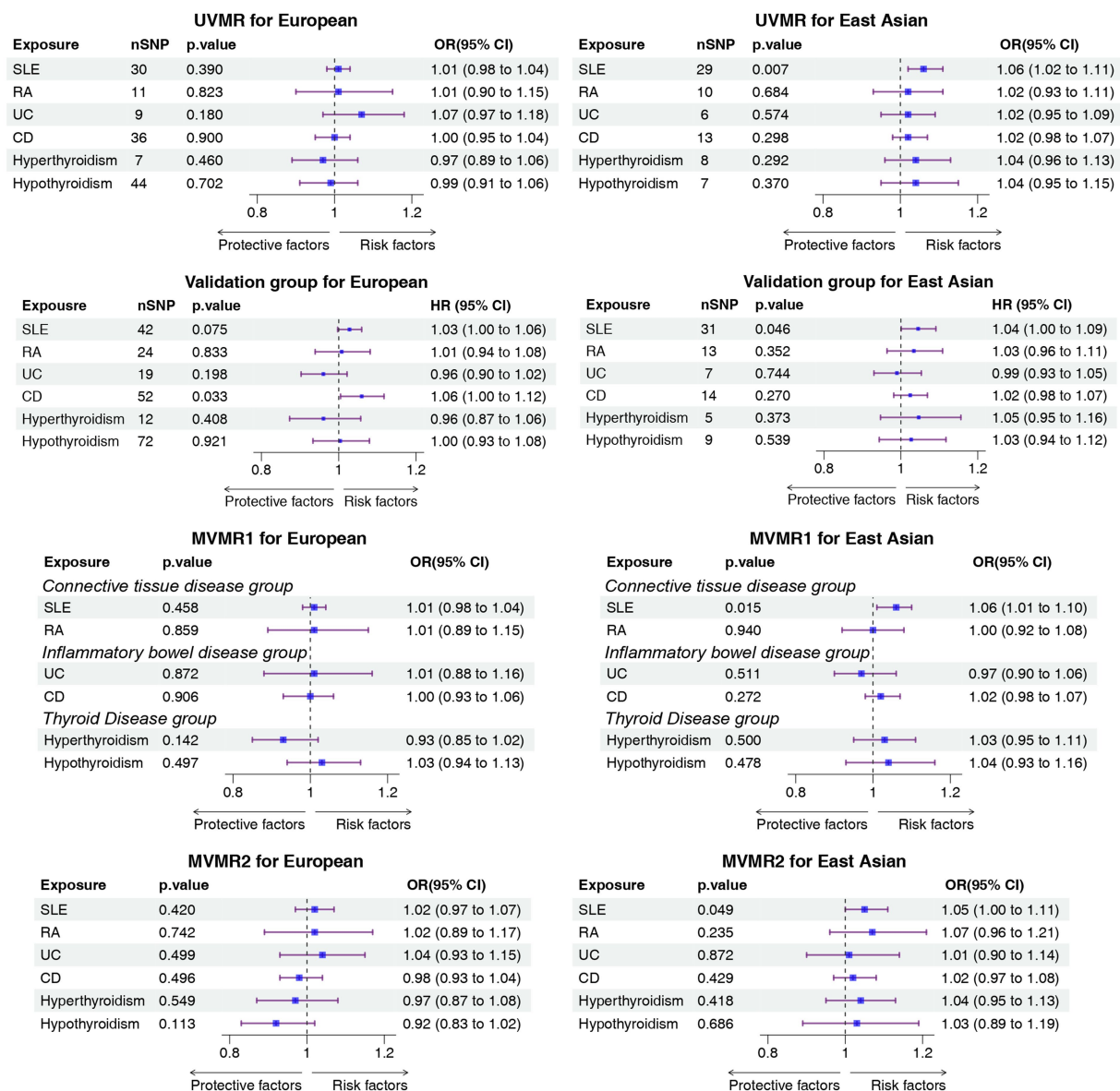


FIGURE 2 Forest plot of the causal association between ADs and IA. ADs, autoimmune disorders; IA, intracranial aneurysms; UVMR, univariable mendelian randomization; MVMR, multivariable mendelian randomization; OR, odds ratio; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; UC, ulcerative colitis; CD, Crohn's disease.

respectively, within the European population. The F-statistic values of these SNPs all exceeded 10, with the average F-statistic values being 86.43, 52.10, 44.93, 64.97, 58.16, and 80.13, respectively, as listed in [Supplementary Table S1](#). The absence of weak IVs was evident. However, no causal relationship between ADs and IAs was identified in the European population, as indicated by *p*-values exceeding 0.05 in each case ([Figure 2](#); [Supplementary Tables S2–S4](#)). The scatter plot and forest plot of each outcome are illustrated in [Supplementary Figures S2, S3](#). The MVMR results also revealed no causal relationship between ADs and IAs ([Figure 2](#)). The results of all BWMR analyses are presented in [Supplementary Figures S4–S9](#). Similarly, the reverse MR analysis failed to reveal a causal relationship between IAs and ADs ([Supplementary Tables S6, S7](#)). Moreover, multiple sensitivity analyses were also conducted, revealing horizontal pleiotropy in hypothyroidism

and IAs results, heterogeneity in CD and IAs results, and outliers identified by the MR-PRESSO analysis ([Supplementary Table S5](#)). In the reverse MR analysis, the MR-Egger method indicated no horizontal pleiotropy; the Q-test demonstrated heterogeneity in the results of SLE, UC, and CD; MR-PRESSO highlighted outliers in the results of UC and CD ([Supplementary Table S8](#)). The leave-one-out analysis confirmed that individual SNPs did not drive the results, as depicted in [Supplementary Figure S1](#).

3.2 MR results in the East Asian population

In this study, 29, 10, 6, 13, 8, and 7 SNPs were incorporated for SLE, RA, UC, CD, hyperthyroidism, and hypothyroidism, respectively, in the

East Asian population. The F-statistic values of these SNPs all exceeded 10, with the average F-statistic values being 63.07, 67.77, 61.71, 72.63, 33.61, and 23.19, respectively (Supplementary Table S1). This confirmed the absence of weak IVs. According to the UVMR results, a statistically significant relationship between IA incidence and SLE was identified in the East Asian population (IVW OR, 1.06; 95% CI, 1.02–1.11; $p=0.0065$, UVMR). This result was supported in BWMR (OR, 1.06; 95%CI, 1.02–1.11; $p=0.0067$, BWMR) and MVMR1 (IVW OR, 1.06; 95% CI, 1.01–1.10; $p=0.015$, MVMR1). In MVMR2, the relationship between SLE and IAs was weak but remained statistically significant (IVW OR, 1.05; 95% CI, 1.00–1.11; $p=0.049$, MVMR2) (Figure 2; Supplementary Tables S2–S4). The scatter plot and forest plot of each outcome are depicted in Supplementary Figures S2, S3. The results of all BWMR analyses are presented in Supplementary Figures S10–S15. The reverse MR analysis did not reveal a causal relationship between IAs and ADs (Supplementary Tables S6, S7). Moreover, sensitivity analyses were also conducted, revealing no heterogeneity and no horizontal pleiotropy in all results, which was also supported by the MR-PRESSO results (Supplementary Tables S5, S8). Furthermore, it was also confirmed that the causal effect was not driven by a single SNP (Supplementary Figure S2).

3.3 Validation groups

In the East Asian population, the MR results suggested a causal relationship between SLE and IAs (IVW OR, 1.04; 95% CI, 1.00–1.09; $p=0.046$), and this result was also supported by sensitivity analyses. In the European population, the MR results suggested a causal relationship between CD and IAs, but the MR-PRESSO results indicated the presence of pleiotropy. Relevant results are summarized in Figure 2, and detailed results are listed in the Supplementary materials.

4 Discussion

To the best of our knowledge, this is the first study to employ the MR method and GWAS summary statistics to investigate the causal relationship between ADs and the risk of intracranial aneurysms (IAs) in both the European and East Asian populations. Within the univariable Mendelian randomization (UVMR) and MVMR analyses, a heightened incidence of IAs was observed in systemic lupus erythematosus (SLE) within the East Asian population. This result was also supported in the validation group. However, there was no causal relationship identified between the other five ADs and IAs in both populations.

Currently, it remains unclear about the pathogenesis of IAs, particularly in the context of ADs. It has been validated in numerous epidemiological studies on IAs that IAs have a potential link with the occurrence and development of ADs (3). In the absence of pathological confirmation, most studies have proposed two hypotheses to explain the reason why ADs increase the risk of IAs (4, 28, 29) (Figure 1). IAs may result from inflammatory pathways, which may be potentially exacerbated by ADs. Hemodynamic stress can cause endothelial damage, and endothelial dysfunction along with vasculitis may contribute to the development of IAs (30, 31). The infiltration of inflammatory cells, including macrophages, monocytes, mast cells (32),

and T lymphocytes, as well as complement activation (32–38), has been confirmed in all IAs. Berry aneurysms, or parts thereof, are reported to be autoimmune and can be attributed to inflammatory diseases in the blood vessels. This is partially supported by the identification of inflammatory infiltrates in the wall of IAs (39). A case–control study revealed an independent relationship between hypothyroidism and unruptured intracranial aneurysm (uIA). Autoimmune hypothyroidism may induce endothelial dysfunction through a chronic inflammatory mechanism mediated by inflammatory cytokines (6). IAs may be linked to the administration of steroid drugs in patients with ADs. Classic risk factors such as atherosclerosis and hypertension are complications associated with SLE patients (29, 40). Steroids and/or cytotoxic immunosuppressants are used in the treatment of SLE in the acute phase. The side effects of these agents can also lead to hypertension. Saccular aneurysms are associated with atherosclerosis and hypertension. In a Taiwanese study, the administration of relatively high average daily doses of steroids was identified as an independent risk factor for the increased risk of subarachnoid hemorrhage (SAH) in SLE patients (41). These two hypotheses are purely theoretical speculations. They may be independent or they may represent common pathways leading to the occurrence of IAs. Combined with the findings of this study, it is necessary to conduct further experimental verification.

As an autoimmune disease, SLE is more common in young females and exhibits the highest incidence in China (about 0.07%) (42). Numerous studies have found an association between SLE and IAs (29, 41, 43, 44). In a study comparing the cohorts of immune-mediated diseases with the control cohorts to calculate the SAH rate, patients with SLE exhibited the highest risk among all immune-mediated diseases ($RR=3.76$, 3.08–4.55) (28). Endothelial dysfunction and vasculitis in SLE patients may contribute to the development of IAs (45, 46). In contrast to the general population, the proportion of saccular aneurysms is lower in SLE patients, while more common aneurysms such as spindle aneurysms or pseudoaneurysms are prevalent among these patients (29, 46, 47). Typically, patients experiencing SAH with vascular-negative aneurysms tend to be older and have a benign clinical course (48). Conversely, SLE patients presenting with SAH and angioneuritis aneurysms are usually relatively young and face a high mortality rate (29, 46, 47). The higher incidence of multiple aneurysms is another characteristic of SLE patients, with the incidence of single and multiple aneurysms in SLE patients being 69.5 and 31.6%, respectively (49).

The mechanisms by which SLE leads to IAs have not been defined. Most scholars attribute IAs to the inflammation of intracranial arteries or artery walls caused by SLE, but the specific molecular mechanisms have not been sufficiently clarified, which requires further basic experimental research. In large-scale studies on SLE in North America and Europe, the incidence of clinically defined SAH in patients with central nervous system involvement is about 0.3% (50–53). A Japanese study showed that the prevalence of SLE in the Japanese population and the prevalence of SHA in SLE patients were 1.28 and 3.9%, respectively, which were higher than those in Western countries (53). In this study, a correlation between SLE and IAs was only found in the East Asian population. However, the reasons and mechanisms for this difference between the two populations are currently unknown. It may be attributed to the differences in the data itself or inherent racial differences, which should be explored in further research.

In contrast to previous observational studies, several critical advantages augment the credibility and robustness of the conclusions

in this study. Firstly, to the best of our knowledge, this study represents the first attempt to explore the causal relationship between ADs and IAs through a two-sample MR analysis. This innovative approach enabled us to thoroughly and rigorously examine the causal effects of ADs on IAs. Additionally, a range of sophisticated MR techniques, encompassing bidirectional MR analysis, MVMR analysis, and MR-PRESSP methods, were used in this study. The bidirectional MR analysis allowed the scrutinization of the potential influence of reverse causality, while MVMR further enabled an exploration of intricate interactions between ADs and IAs. The MR-PRESSO method effectively avoided potential abnormalities. Furthermore, a series of stringent sensitivity analyses, including checks for heterogeneity and pleiotropy, were conducted to substantiate the reliability of our results. Finally, our results were also validated in the validation group to make the results more reliable.

Nevertheless, there are still several inherent limitations in this study. Firstly, we conducted relevant explorations based on the East Asian and European populations, not global populations, and hence caution is needed when applying the results to other populations. Secondly, the results of our study differed in both populations. Therefore, further research is needed to identify the significance of this difference. Thirdly, the aneurysm GWAS data including both uIA and ruptured IAs were collected in this study, but data limitations cannot be avoided. Fourthly, although causal effects can be derived by MR methods, the limitations of this study are still obvious due to a lack of prospective studies. Finally, only 6 ADs were included in this study, and there may be other ADs associated with IAs, which may be attributed to a lack of data on autoimmune disease-associated GWASs in the East Asian population. After the data that were pleiotropic and unreliable in results were excluded, these 6 autoimmune diseases were incorporated into this study, thus ensuring the consistency in the studies in both populations.

5 Conclusion

In conclusion, the results of this study suggested that SLE was associated with a higher risk of IAs in the East Asian population. This underscored the pivotal clinical importance for healthcare practitioners to promptly recognize and diagnose IA patients within the framework of SLE. Therefore, strengthening cerebrovascular disease management in individuals with SLE becomes imperative, which may contribute to mitigating the morbidity and mortality associated with aneurysmal SAH in this patient population.

Data availability statement

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

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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

CT: Conceptualization, Data curation, Software, Visualization, Writing – original draft, Writing – review & editing. RR: Methodology, Writing – original draft. BP: Conceptualization, Investigation, Writing – original draft. MX: Project administration, Validation, Writing – original draft. JH: Data curation, Resources, Writing – review & editing. ZX: Formal analysis, Supervision, Writing – original draft. ZZ: Data curation, Funding acquisition, Supervision, Validation, Writing – review & editing.

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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.2024.1412114/full#supplementary-material>

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Single Neuroform Atlas stent: a reliable approach for treating complex wide-neck bifurcated aneurysms

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Background: Treating wide-neck bifurcated cerebral aneurysms (WNBAs) using various techniques and new devices has shown favorable outcomes. However, endovascular coiling can be technically challenging when the aneurysm neck is incorporated into the parent vessel. Furthermore, although recent research has reported favorable outcomes of Neuroform Atlas stent (NAS)-assisted coiling, broad inclusion criteria have hampered precise evaluations of their effectiveness and safety for treating complex WNBAs. Therefore, this study evaluated whether the use of a single NAS is a safe and effective approach for treating complex WNBAs.

Methods: We treated 76 complex WNBAs (unruptured, $n = 49$; ruptured, $n = 27$) using single NAS-assisted coil embolization and retrospectively analyzed the clinical and angiographic outcomes.

Results: In a cohort of 68 patients (mean age, 58.3 ± 11.6 years; males $n = 20$, 29.4%; females, $n = 48$, 70.6%), 76 stents were successfully delivered to the target aneurysms, yielding a technical success rate of 98.6%. Complete occlusion was evident in 59 (77.6%) of 76 aneurysms, with neck remnants found in 16 (21.1%) and partial occlusion in 1 (1.3%). Treatment-related morbidities comprised one branch occlusion and one parenchymal hemorrhage. However, no new neurological symptoms of unruptured aneurysms were evident at discharge. The outcomes of 20 of the 27 ruptured aneurysms were favorable (Glasgow Outcome Scale scores of 4 or 5) at the final follow-up assessment (mean 12.2 [6–29] months), except for one initial subarachnoid hemorrhage. Post-treatment angiography revealed complete occlusion in 89.1%, neck remnants in 7.8%, and incomplete occlusion in 3.1% of the aneurysms. Approximately 88.2% of the patients were assessed at least once by follow-up diagnostic or magnetic resonance angiography (mean, 12.5 ± 4.3 [range, 6–29] months), with five (7.8%) minor and two (3.1%) major recurrences.

Conclusion: A single NAS is safe and effective for treating WNBAs incorporated into parent vessels.

KEYWORDS

coiling, wide-neck bifurcated cerebral aneurysm, Neuroform Atlas stent, bifurcation, aneurysm, stent

1 Introduction

Endovascular treatment for aneurysms has significantly evolved with the advancement of various devices, shifting the paradigm toward aneurysm management (1). This approach is favored for treating aneurysms as it is minimally invasive and effective. However, certain types of aneurysms, particularly wide-neck bifurcation aneurysms (WNBAs), present unique challenges due to their complexity. WNBAs are often characterized by unfavorable neck anatomy combined with incorporated vessels, necessitating precise and innovative treatment strategies.

Stent-assisted coil embolization techniques, introduced approximately 15 years ago have become indispensable for treating complex aneurysms (2). Despite the introduction of new devices such as flow diverters and the Woven EndoBridge (WEB), conventional stents continue to occupy a prominent position in the treatment arsenal (3). Their sustained relevance is attributed to high aneurysm occlusion rates, which renders them particularly suitable for managing WNBAs. Approval of the Neuroform EZ and EZ3 stents (Stryker Neurovascular, Kalamazoo, MI, United States) by the US Food and Drug Administration in 2002 has resulted in significant milestones in the evolution of stent technology (4).

The Neuroform Atlas stent (NAS) is a refined version of its predecessors with lower-profile delivery, which is a notable advancement (5, 6). Although the outcomes of treatment with NAS-assisted coiling have been favorable, the broad inclusion criteria in recent studies have hampered precise evaluations of its effectiveness and safety for treating complex WNBAs (7–10). Therefore, our study aimed to address this issue by detailing our experience with single NAS-assisted coil embolization and focusing exclusively on its application in the treatment of complex WNBAs.

2 Materials and methods

2.1 Patient population

In this retrospective study, we analyzed the records of complex WNBAs treated with endovascular coiling using a single NAS at our center. The data were sourced from a prospectively maintained neuro-interventional database between February 2018 and December 2022. Complex WNBAs were defined as aneurysms situated at major artery bifurcations and including a branch within the aneurysm sac. A “wide-neck” aneurysm is characterized by a neck diameter of ≥ 4 mm or a dome-to-neck ratio of ≤ 1.5 . During the 5-year study period, 855 aneurysms in 658 patients were treated with endovascular coiling at our facility. Among them, 91 (10.6%) aneurysms met the criteria for complex WNBA. We treated 76 (8.9%) of these 91 aneurysms in 68 patients with

a single NAS technique. Patients with aneurysms located at major artery bifurcations, including internal carotid artery bifurcation (ICBIF), middle cerebral artery bifurcation (MCBIF), anterior communicating artery (AcomA), basilar artery bifurcation (BABIF), and posterior-inferior cerebellar artery (PICA), were eligible for inclusion. The mean diameter of the included aneurysm was 8.7 mm, and the neck diameter was on average 4.1 mm. Clinical and imaging data were collected from medical charts, Picture Archiving and Communication System (PACS), and our neuro-interventional database. Informed consent was obtained before treatment. Our institutional review board approved this retrospective study (KANGDONG 2023-01-016-003) and waived the need for informed consent to study inclusion owing to the retrospective analysis of innominate data.

2.2 Endovascular treatment

All patients with unruptured aneurysms were administered dual antiplatelet medication (aspirin 100 mg and clopidogrel 75 mg) for a minimum of 5 days before treatment. Prior to the procedure, a platelet function test (VerifyNow assay; Accumetrics, San Diego, CA, United States) was conducted to ensure a good response to aspirin and clopidogrel. Additional doses of aspirin or clopidogrel (300 mg) were administered to patients with poor responses. An initial bolus of heparin (3,000–4,000 IU) was intravenously injected during the procedure to initiate anticoagulation followed by hourly booster doses. Patients with ruptured aneurysms were not administered pre-operative antiplatelet therapy or an intra-operative heparin bolus. Dual antiplatelet medication with aspirin and clopidogrel (300 mg each) was administered immediately after stent deployment. This post-procedural regimen was maintained for at least 6 months, then transitioned to a single antiplatelet regimen for at least 12 months.

Under general anesthesia, a 6F Envoy (Codman & Shurtleff, Raynham, MA, United States) or a 6F Benchmark (Penumbra, Inc., Alameda, CA, United States) guiding catheter was carefully placed in the relevant internal carotid artery or dominant vertebral artery. Aneurysmal morphology, including the size of parent vessels, was measured using reconstructed three-dimensional rotational angiography (3D-RA) images. Working projections were adjusted to characterize the width of the aneurysm neck and secure the incorporated branch via stent deployment. Pre-shaped or steam-shaped 0.010-inch Excelsior microcatheters (Stryker Neurovascular, Kalamazoo, MI, United States) with a Traxcess 0.014-inch micro guidewire (MicroVention, Tustin, CA, United States) were used for stent deployment and coil delivery. The NAS was predominantly used for all aneurysms because it comprises a low-profile, self-expanding, nitinol microstent, which enhances stent deliverability with less foreshortening, and its hybrid cell structure has better scaffolding and conforms to vessel walls more effectively than previous stents (5, 11). Specifically, the microcatheter is designed to pass the proximally closed line and re-cross the open cell for trans-strut insertion. Stent diameters were selected primarily as recommended by the manufacturers. However, we selected a 3-mm diameter stent when the parent vessel was < 2 mm. The stent length was determined to cover the aneurysmal neck with proximal and distal parts extending at least 5 mm. We used stents with diameters and lengths of 3×15 or 3×21 mm for the MCBIF AcomA, and PICA, and 4.0 or 4.5×21 mm for the ICBIF and BABIF.

Abbreviations: AcomA, anterior communicating artery; BABIF, basilar artery bifurcation; DSA, digital subtraction angiography; GOS, Glasgow Outcome Scale; ICBIF, internal carotid artery bifurcation; MCBIF, middle cerebral artery bifurcation; MRA, magnetic resonance angiography; NAS, Neuroform Atlas Stent; NIHSS, National Institutes of Health Stroke Scale; PACS, picture archiving and communication system; PICA, posterior-inferior cerebellar artery; RROC, Raymond-Roy occlusion classification; TIA, transient ischemic attack; WEB, Woven EndoBridge; WNBA, wide-neck bifurcation aneurysms.

2.3 Outcome measures

The effectiveness of the procedure was immediately assessed as coil packing density and aneurysm occlusion rates according to the Raymond–Roy occlusion classification (RROC) (12). Patients were routinely followed up using high-resolution time-of-flight magnetic resonance angiography (MRA) at 6 months and digital subtraction angiography (DSA) at 1 year. Depending on MRA findings, DSA was performed to determine whether retreatment was necessary. The follow-up angiographic outcomes were classified as improved or stable, minor recurrence (aneurysm recurrence not requiring repeat treatment), and major recurrence (aneurysm recurrence with repeated treatment deemed necessary by the consensus of two interventionists). Technical complications, such as stent migration, incomplete deployment, and in-stent thrombosis, were also investigated.

Clinical outcomes were assessed using the Glasgow Outcome Scale (GOS) scores at discharge, and patients with rupture were assessed at the latest follow-up. Postoperative ischemic symptoms were classified as transient ischemic attack (TIA), minor stroke, or major stroke. Major stroke was defined as a new neurological event persisting for >24 h with an increase in National Institutes of Health Stroke Scale (NIHSS) scores >4 compared with baseline values. Minor stroke was defined as the absence of clinical consequences during the initial hospital stay or at 6 months post-procedure. We defined TIA as a minor stroke without restricted diffusion on magnetic resonance images and confirmed treatment-related complications, such as repeated bleeding of a ruptured aneurysm or thromboembolic events requiring intra-arterial thrombectomy.

2.4 Statistical analysis

All statistical analyses were performed using SPSS version 20 (IBM-SPSS Statistics for Windows, Armonk, NY, United States). All categorical variables are presented as percentages and 95% confidence intervals. All continuous variables are presented as a mean $\pm$ standard deviation (SD).

3 Results

3.1 Demographics of patients and aneurysms

Overall, 30 ruptured and 46 unruptured complex WNBAs identified in 68 patients (mean age, 58.3 ± 11.6 ; males, $n = 20$; females, $n = 48$) were treated with a single NAS. The locations of the treated aneurysms were as follows: MCBID ($n = 36$; 47.7%), AcomA ($n = 20$; 26.3%), BABIF ($n = 10$; 13.2%), ICBIF ($n = 6$; 7.9%), and PICA ($n = 4$; 5.3%). The mean aneurysm diameter was 8.7 ± 4.5 (range, 3.5–17.0) mm, and the neck diameter was 4.1 ± 2.3 (range, 3.2–13.7) mm with a mean aspect ratio of 1.06 ± 0.24 (range, 0.8–1.3). The mean diameters of the proximal and distal parent arteries were 2.9 ± 0.7 (range, 1.5–4.2) and 1.9 ± 0.4 (range, 1.2–3.4) mm, respectively. Coiling was completed with a combined multi-catheter in 64 (84.2%) cases, microcatheter jailing in 74 (97.4%) cases, trans-strut selection in 68 (89.5%) cases, and partial deployment to make a coil frame in 3 (3.9%) cases (Table 1).

TABLE 1 Baseline patient characteristics.

No. of patients (No. of aneurysms coiled)	68 (76)
Mean age, y	58.3 ± 11.6 (34–78)
Males: Females	20 (29.4%): 48 (70.6%)
Presentation with subarachnoid hemorrhage	27 (39.7%)
Sac diameter, mm	8.7 ± 4.5 (3.5–17.0)
Neck diameter, mm	4.1 ± 2.3 (3.2–13.7)
Aspect ratio	1.06 ± 0.24 (0.8–1.3)
Proximal parent artery diameter, mm	2.9 ± 0.7 (1.5–4.2)
Distal parent artery diameter, mm	1.9 ± 0.4 (1.2–3.4)
Location of complex bifurcated aneurysm	
Internal carotid artery bifurcation	6 (7.9%)
Middle cerebral artery bifurcation	36 (47.4%)
Anterior communicating artery	20 (26.3%)
Basilar artery bifurcation	10 (13.2%)
Posterior inferior cerebellar artery	4 (5.3%)
Microcatheter/Coil technique	
Microcatheter jailing	74 (97.4%)
Trans-strut selection	68 (89.5%)
Partial deployment with coil framing	3 (3.9%)
Combined multi-catheter	64 (84.2%)

Data are shown as means $\pm$ SD with ranges, or as numbers (n), or n (%). SD, standard deviation.

3.2 Technical results and angiographic and clinical outcomes

The NAS-assisted coil embolization yielded a 98.6% technical success rate in 75 out of 76 patients. The mean coil packing density was $42.1\% \pm 4.3\%$ (range, 27–54%). Stent migration occurred in three (3.9%) cases, and in-stent thrombosis was observed in three (3.9%) cases. A distal segment of the stent that migrated into a large aneurysm with a 7.2-mm neck and the acute angle of the incorporated branch was retrieved using a 2.0-mm microsnare, and another stent was deployed without complications. In two cases, the stent partially migrated; however, the remaining anchoring part was sufficient to ensure successful coiling. Arterial and intravenous tirofiban injections managed in-stent thromboses in one of two patients. Immediate post-treatment angiography revealed complete occlusion in 59 (77.6%) patients, neck remnants in 16 (21.1%) patients, and incomplete occlusion in 1 (1.3%) patient. Follow-up angiograms were performed on 88.2% of patients ($n = 60$, 64 aneurysms: mean, 12.5 ± 4.3 months; range, 6–29 months). Only 11 (16.1%) patients underwent MRA. Aneurysmal recurrences in seven (10.9%) patients were minor in five and major in two, the latter of which were treated using simple coiling. Two (2.9%) patients with ruptured aneurysms (95% CI, 0.42–3.26%) developed treatment-related morbidities comprising branch occlusion ($n = 1$) and parenchymal hemorrhage ($n = 1$) after the administration of intra-arterial tirofiban. No mortality was treatment-related. Seven patients had ischemic symptoms, comprising four (5.3%) transient ischemic attacks, two (2.6%) minor strokes, and one (1.3%) major stroke. The patient with the major stroke presented with grade 2 side weakness that did not improve after 1 year of follow-up.

(Table 2). The GOS scores in 27 patients with rupture were 5, 4, 3, 2, in 16 (59.3%), 4 (14.8%), 4 (14.8%), and 2 (7.4%), respectively, and only 1 (3.7%) patient scored 1 (Table 3).

3.3 Example cases

3.3.1 Case 1: unruptured complex MCBIF aneurysm

A 67-year-old female presented with a large, unruptured, complex aneurysm at the left MCBIF with a length and neck diameter of 24.19 and 7.65 mm, respectively. Cerebral angiography revealed the incorporation of both M2 branches into the aneurysm sac. The intervention involved deploying a 3 × 21-mm NAS from the distal M1 to the M2 inferior branch, with concurrent catheter protection of the M2 superior branch. This approach achieved complete aneurysm occlusion without complications. The MRA findings at the 2-year follow-up revealed stable occlusion with RROC III (Figure 1).

3.3.2 Case 2: ruptured complex AcomA aneurysm

A 51-year-old male presented with a ruptured complex aneurysm of the AcomA. The width of the wide-necked, trilobulated aneurysm that incorporated with the left A1 was 8.95 mm and that of the neck was 4.72 mm. We deployed a 3.0 × 21-mm NAS from the A1 to the ipsilateral A2, resulting in complete aneurysm occlusion without complications. One-year follow-up MRA revealed stable occlusion (Figure 2).

3.3.3 Case 3: recurrent left complex PICA aneurysm

A 73-year-old male presented with a recurrence of a left PICA aneurysm that had been clipped 16 years earlier. Follow-up MRA and transcranial focal cerebral angiography revealed a recurrent 10.59-mm-wide aneurysm segment with a neck diameter of 6.98 mm. We accessed the PICA via the contralateral vertebral artery and deployed a 3.0 × 21-mm NAS. Despite the narrow diameter of the PICA (1.79 mm), good blood flow was maintained after NAS deployment. The aneurysm was occluded without complications and remained stable on 2-year follow-up MRA images (Figure 3).

4 Discussion

Endovascular coiling of complex WNBAs presents significant clinical challenges, largely attributable to their inherent anatomical complexities (13, 14). These aneurysms have wide necks and can involve several branches of the parent artery, complicating the efficacy of conventional endovascular approaches. Traditional methods, while predominant, have been associated with an increased risk of thrombosis in branching arteries, coil migration, and protrusion, highlighting the critical need for advanced treatment strategies. In response, several sophisticated techniques, such as horizontal stenting, waffle cone configuration stenting, and X- or Y-configuration double stenting, have been developed (15–19). However, these approaches require advanced technical expertise and are not devoid of additional risks.

Given these considerations, the efficacy of a single NAS is worth discussing. It features a low-profile structure coupled with superior trackability and facilitates navigation through the intricate vascular

TABLE 2 Technical, angiographic, and clinical outcomes.

Technical success rate <i>n</i> (%)	75 (98.6%)
Coil packing density (%)	42.1 ± 4.3 (27–49)
Initial device failure	
Stent migration	3 (3.9%)
Incomplete deployment	0 (0%)
In-stent thrombosis	3 (3.9%)
Initial occlusion class	
Raymond 1	59 (77.6%)
Raymond 2	16 (21.1%)
Raymond 3	1 (1.3%)
Follow-up angiograms	60 (88.2%) of 64
Duration, months	12.5 ± 4.3 (6–29)
Follow-up results	
Improved or stable	57 (89.1%)
Minor recurrence	5 (7.8%)
Major recurrence	2 (3.1%)
Treatment-related morbidity	2 (2.9%; 95% CI, 0.42–3.26%)
Treatment-related mortality	0
Symptomatic ischemic postoperative event	
Transient ischemic deficit	4 (5.3%)
Minor stroke	2 (2.6%)
Major stroke	1 (1.3%)

Data are shown as means ± SD with ranges, or as *n* (%). 95% CI, 95% confidence interval. SD, standard deviation.

TABLE 3 Glasgow outcome scale scores in 27 ruptured cases.

Glasgow outcome scale scores	Number of patients (%)
5	16 (59.3%)
4	4 (14.8%)
3	4 (14.8%)
2	2 (7.4%)
1	1 (3.7%)

Data are shown as *n* (%).

architecture that is characteristic of WNBAs. This design ensures effective deployment and secure coil retention, which has been substantiated by favorable occlusion rates in initial clinical applications (11, 20–23). Importantly, the utilization of the NAS potentially averts the need for more complex and technically demanding procedures, thereby streamlining the endovascular treatment of complex WNBAs and enhancing patient outcomes.

The innovative design of the NAS, which integrates open- and closed-cell structures, offers enhanced flexibility and adaptability to various vessel geometries. This hybrid design is pivotal for facilitating segmental opening during deployment, ensuring stable positioning and immediate apposition to the vessel wall, which is particularly advantageous for managing bifurcated aneurysms (9, 20, 24). The NAS has unique actions, such as a saddling effect and gator backing due to its segmental opening structure, which allows for a comparatively

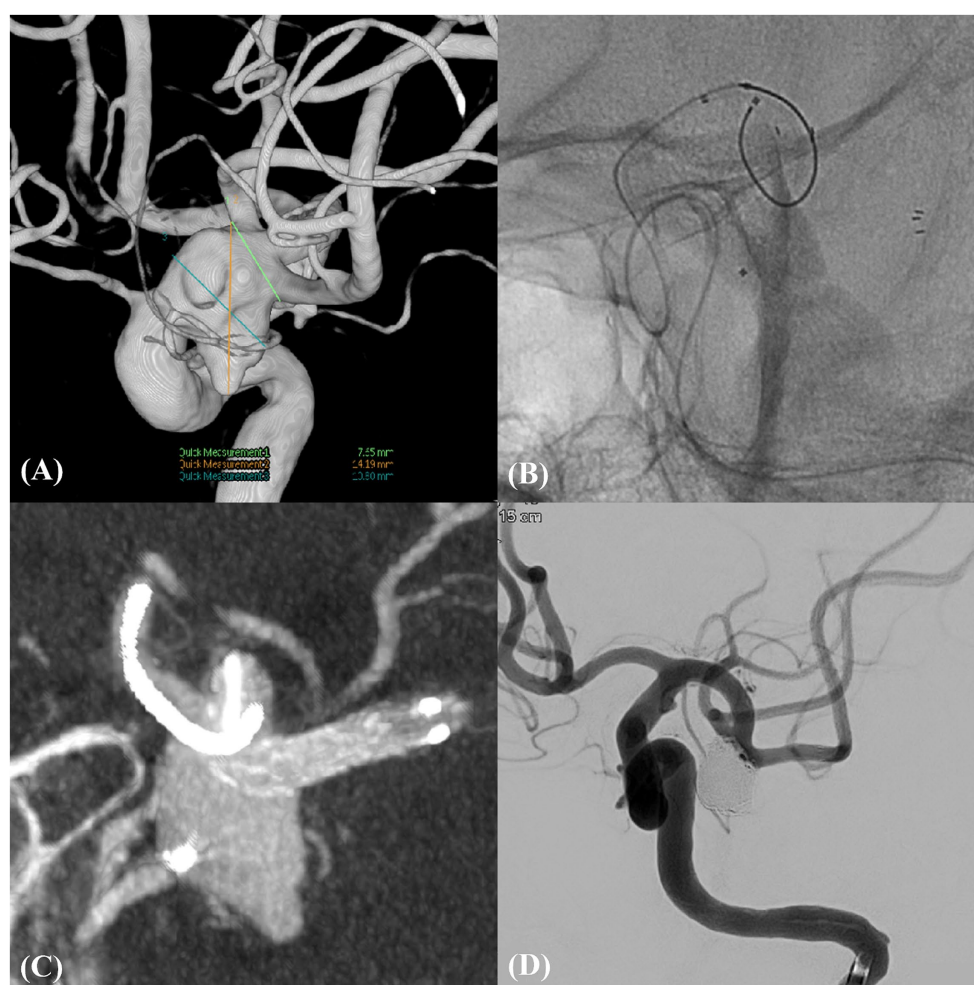


FIGURE 1

Unruptured complex aneurysm in left MCBIF (Case example 1). **(A)** An unruptured wide-neck aneurysm in the left middle cerebral bifurcation (MCBIF) encompassing both M2 branches. **(B)** Illustration of the technique of catheter protection of the M2 superior branch coupled with the strategic deployment of the neurovascular-assisted stent (NAS) spanning from the distal M1 to the M2 inferior branch. **(C)** High-resolution cone-beam computed tomography image, providing a detailed view of the microcatheter and NAS *in situ*, emphasizing the precision of device placement. **(D)** Post-procedural working angiographic view, highlighting the successfully coiled aneurysm and ensuring complete occlusion.

wider coverage of aneurysm necks than other remodeling stents (25). Furthermore, the low metal coverage area of the NAS (6–12%) is instrumental in achieving precise localization and minimizing post-deployment shrinkage (9). These design features are critical for maintaining the patency of the parent artery and ensuring uninterrupted blood flow post-procedure, thereby contributing to the effectiveness of the stent in the clinical setting.

The NAS has demonstrated notable efficacy in the treatment of WNBAAs, as evidenced by the results of multiple clinical studies. A pivotal trial involving anterior circulation aneurysms found immediate, follow-up, and overall occlusion rates of 88, 82, and 6.2%, respectively, at 12 months, highlighting the effectiveness of the stent (7). The findings of a study of posterior circulation aneurysms showed a 100% technical success rate, with an 85.3% complete occlusion rate in the first year, which also confirmed the applicability of the NAS to complex vascular territories (5). This was corroborated by a multicenter European post-market study that found technical success and complete occlusion rates of 96.9 and 90.3%, respectively, at 12–16 months of follow-up, indicating consistent NAS performance

across diverse cerebral circulations (26). A systematic review and meta-analysis reinforced these outcomes, revealing a technical success rate of 100% in 12 studies and 98% in another, with an immediate occlusion rate of 88%, which improved to 90% at 6 months and to 93% at approximately 9 months of follow-up, while maintaining a periprocedural complication rate of 5% (27). We duplicated these findings with a technical success rate of 98.6%, a mean coil packing density of approximately 42%, and Raymond grade I and II occlusions of 77.6 and 21.1%, respectively, immediately post-embolization, with a complication rate of 2.9%. At 12.5 months of follow-up, we achieved adequate occlusion in 89.1% of aneurysms. These results show the potential of NAS for adequately managing complex WNBA geometries, which is a significant stride considering the challenges often faced during neurovascular interventions.

In the evolving field of endovascular treatment for WNBAAs, various techniques and devices have been explored, each with different outcomes. For instance, the waffle cone technique has shown promising immediate occlusion results with primarily mild ischemic complications, although it is limited by a lack of extensive long-term

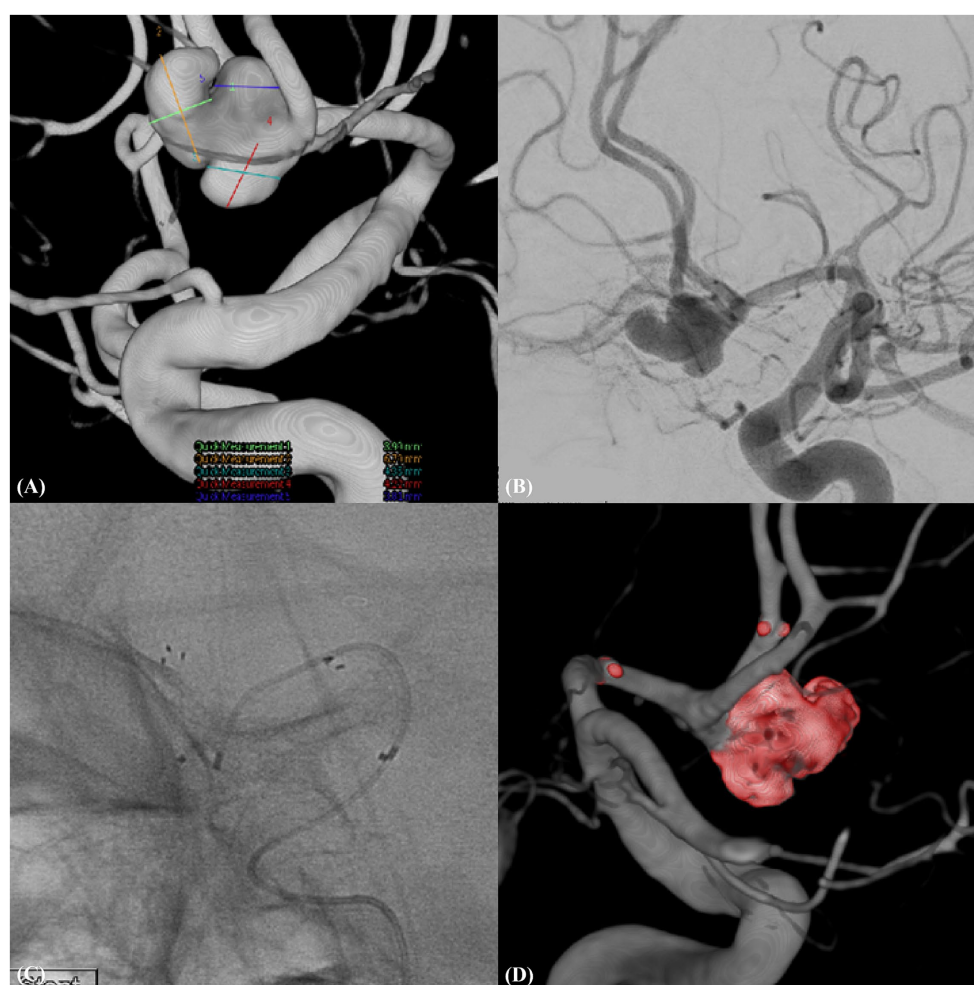


FIGURE 2

Ruptured trilobulated complex AcomA aneurysm (Case example 2). **(A)** A complex, trilobulated ruptured aneurysm of the anterior communicating artery (AcomA) with a wide neck, incorporating the left anterior cerebral artery (A1), emphasizing the challenging morphology of the aneurysm. **(B)** Detailed working view of the aneurysm illustrating its intricate morphology and relationship with the adjacent vascular structures. **(C)** Features of the deployed neurovascular-assisted stent (NAS) along with the selected microcatheter positioned for therapeutic intervention. **(D)** Post-procedural three-dimensional rotational angiogram confirming the position and effect of the treatment.

follow-up data (13, 28). Y-stenting has demonstrated occlusion rates of 47.6–95.4%, caveated with a notable complication rate of approximately 8.9% (29, 30). T-stenting, as reported by Aydin et al., achieved an 83.3% immediate occlusion rate, with occlusion increasing to 90% at follow-up. However, it is accompanied by a higher complication rate of 13.7% compared with single-stent approaches (31). Flow diversion in bifurcation aneurysms is associated with a 68% complete occlusion rate at 16 months; however, this technique bears a significant 22% complication rate that is predominantly ischemic, which has triggered debate about its clinical viability (32). Meanwhile, the WEB device has a 1-year complete occlusion rate of 52.9% and has achieved adequate occlusion in 79.1% of aneurysms, indicating promising clinical experiences; nonetheless, careful consideration for individual aneurysm shapes and vascular structures is required (33, 34). Balloon-assisted coiling involves the temporary inflation of a balloon inside the parent artery to aid in supporting and maintaining coil placement within the aneurysm sac. Although it is effective for wide-neck aneurysms and particularly useful for treating ruptured aneurysms in the acute phase when dual antiplatelet therapy is not

recommended, it does not substantially enhance anatomical outcomes and can present technical challenges when using a double-balloon technique for WNBA (35, 36). We achieved success by effectively widening stent coverage at the aneurysm neck, ensuring sufficient stent length for deployment at both proximal and distal ends, and meticulously expanding the stent in the neck region to provide stable support for the primary frame coil. Consequently, the use of a single NAS for the treatment of complex WNBAs can be considered efficient and safe, as evidenced by our clinical outcomes.

The present study focused on the endovascular treatment of complex WNBAs in 68 patients and identified distinct outcomes between patients with ruptured and unruptured aneurysms. Among 41 patients with unruptured aneurysms, only 2 (4.8%) developed minor ischemic symptoms attributable to stent-related thromboembolism. Conversely, in the group of 27 patients with ruptured aneurysms, 2 (7.8%) patients developed severe complications, namely in-stent thrombosis leading to occlusion of the superior branch of the M2 artery and post-interventional parenchymal hemorrhage after intra-arterial tirofiban injection, culminating in

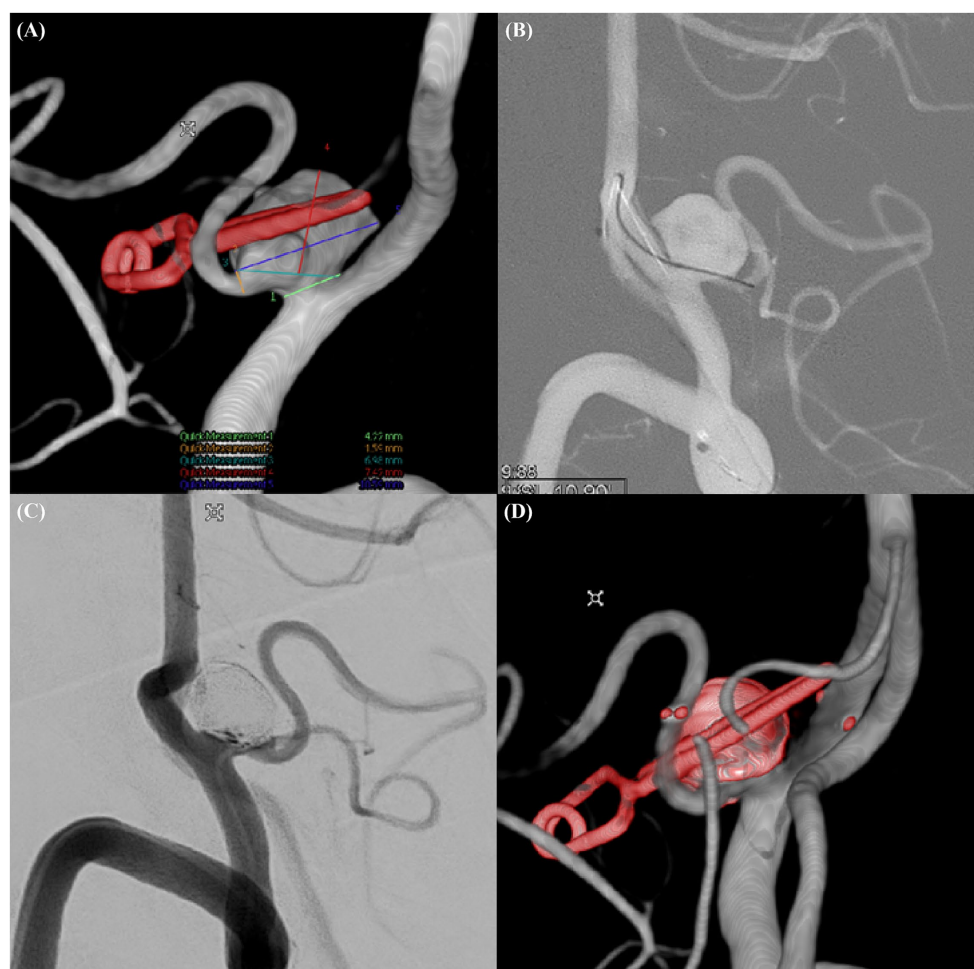


FIGURE 3
Recurrent complex aneurysm in left PICA (Case example 3). **(A)** Detailed three-dimensional rotational angiogram of a recurrent wide-necked aneurysm incorporated into the left posterior inferior cerebellar artery (PICA). **(B)** Selection of the PICA with a microwire accessed via the contralateral vertebral artery. **(C)** Postprocedural working view of the aneurysm after coiling. **(D)** Postprocedural three-dimensional rotational angiogram demonstrating the outcome of the intervention.

permanent disability. The increased risk in patients with ruptured aneurysms might be attributed to the lack of premedication with antithrombotic agents and the inherently hypercoagulable state associated with their condition (37). A review of the literature indicates that the clinical outcomes of stent-assisted coiling are generally favorable in 63–94% of patients, with thromboembolic and hemorrhagic complications found in 4–17% and 1–8% of procedures, respectively (38–40). Notably, studies focusing solely on the use of the NAS to treat wide-neck aneurysms reported an overall stroke rate of 7.1%, with ischemic stroke comprising 4.7% of these incidents (27, 41). Our study observed that all seven patients with clinically unfavorable outcomes had ruptured aneurysms. Five of them developed complications due to the initial subarachnoid hemorrhage insult, which is not found in patients with unruptured aneurysms. Overall, the outcomes for 61 (89.7%) of 68 patients at the 12-month follow-up were favorable. This result not only aligns with but also surpasses the general success rates of stent treatments and is comparable to other studies involving the NAS.

Although this study provides valuable insights into the use of a single NAS for treating complex WNBA, it is important to acknowledge the limitations inherent to its retrospective design. Such limitations necessitate a cautious interpretation of our findings. Further investigation is essential for a more comprehensive understanding of the role of the NAS in this context, and prospective randomized controlled trials are required to confirm our findings. Future studies should compare the outcomes of a single NAS with other similar devices or techniques. This approach is crucial for establishing long-term effectiveness and safety profiles of the NAS for treating complex WNBAs.

5 Conclusion

Deployment of a single NFA stent has considerable promise for treating complex WNBAs. Its low profile and segmental opening design enable wider coverage of the aneurysm neck while preserving

vital adjacent branches, thus contributing to high occlusion and low complication rates.

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 humans were approved by KANGDONG institutional review board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and 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

HA: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. HJ: Writing – review & editing, Software, Funding acquisition, Data

curation. BC: Writing – review & editing, Supervision, Resources, Data curation. SP: Writing – review & editing, Supervision, Resources.

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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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Association between estimation of pulse wave velocity and all-cause mortality in critically ill patients with non-traumatic subarachnoid hemorrhage: an analysis based on the MIMIC-IV database

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Background: Estimated pulse wave velocity (ePWV), which measures vascular aging, is an independent predictor of cardiovascular death. Nevertheless, the relationship between ePWV and all-cause mortality among patients suffering from non-traumatic subarachnoid hemorrhages (NSAH) remains obscure. Consequently, the objective of this study is to ascertain whether ePWV exerts influence on the prognosis of individuals afflicted with NSAH.

Methods: Through the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, 644 eligible participants were included. The Kaplan–Meier survival curve method was employed to assess the disparity in survival status between the low and high ePWV cohorts. The Cox proportional hazard model was employed to investigate the association between ePWV and inpatient mortality among critically ill patients diagnosed with NSAH. The Restricted Cubic Spline (RCS) model was employed to examine the dose–response correlation. Subsequently, multivariate Cox regression analysis was performed to identify independent prognostic factors. Lastly, the impact of ePWV on inpatient mortality across various subgroups was evaluated through stratified analysis.

Results: Participants were categorized into two groups, delineated by their ePWV levels: a low ePWV level group and a high ePWV level group. Survival analysis unveiled that individuals with high ePWV exhibited a diminished survival rate compared to their counterparts with low ePWV. Following adjustment, low ePWV was significantly linked with a reduced risk of inpatient mortality among patients with NSAH (HR = 0.54, 95% CI = 0.32–0.89, $p = 0.016$). Simultaneously, analysis employing the RCS model further substantiated a linear escalation in the risk of inpatient mortality with increasing ePWV values.

Conclusion: Elevated ePWV levels have been identified as an independent risk factor for the rise in inpatient mortality among NSAH patients and as a significant predictor of the clinical outcome of NSAH.

KEYWORDS

non-traumatic subarachnoid hemorrhage, estimated pulse wave velocity, subgroup analysis, mortality, MIMIC-IV

Introduction

NSAH denotes a clinical manifestation wherein diseased blood vessels located at the base or surface of the brain rupture, allowing blood to directly flow into the subarachnoid space, often associated with aneurysmal rupture (1). The mortality rate associated with NSAH is exceedingly high. Research indicates that almost a quarter of patients experience sudden death either en route to the hospital or in the emergency room (2, 3). Furthermore, another study reveals that among hospitalized individuals, the 30-day mortality rate for NSAH patients reaches as high as 35% (4). Additionally, some survivors of NSAH may experience physical disabilities and neuropsychological complications (3). Consequently, there is a pressing need for a reliable and readily available clinical index to ascertain prognosis.

The ePWV can be directly calculated based on actual age and average arterial blood pressure. As a marker of vascular aging, ePWV has increasingly emerged as a predictor of cardiovascular diseases and all-cause mortality in recent years (5, 6). Previous studies have established correlations between ePWV and certain diseases, including heightened all-cause mortality in coronary artery disease and acute kidney injury, as well as an increased risk of diabetes and stroke (7–10). While NSAH can result from head trauma, the majority is caused by abnormal intracranial vascular rupture (11). Nevertheless, it remains unclear whether ePWV levels are associated with variations in NSAH mortality risk. Thus, the aim of this study is to investigate the relationship between ePWV and NSAH using an open clinical database.

Materials and methods

Data sources and setting

The retrospective cohort analysis utilized the MIMIC-IV version 2.2 database (12, 13). This study is a longitudinal single-center investigation. During the period spanning from 2008 to 2019, a total of 299,712 patients were included, with 73,181 admitted to the intensive care unit. The author of this study, Gang Liao (ID: 12855703), registered, completed the required training, and obtained permission to utilize the dataset. As the MIMIC-IV database is openly accessible and anonymized, it does not necessitate approval from the ethics committee.

Study population

The study included adult NSAH patients classified based on the ninth and tenth revisions of the International Classification of Diseases (ICD-9 and ICD-10), along with admission codes for acute physiology and chronic health evaluation. Exclusion criteria encompassed patients meeting the following conditions: (1) multiple

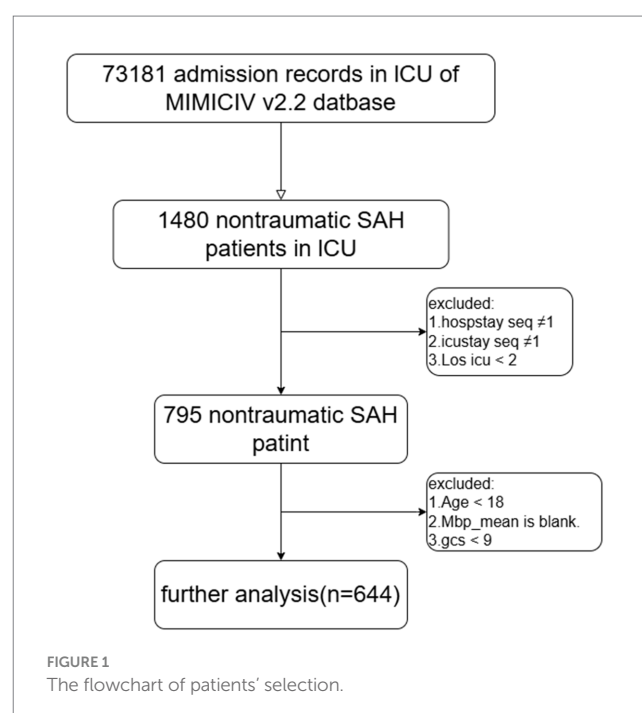
hospitalizations or ICU admissions, (2) ICU stays of less than 2 days, (3) age under 18 years, (4) lack of MAP information, and (5) GCS score less than 9. Ultimately, the study cohort comprised 644 patients, divided into two groups based on their median ePWV at ICU admission (Figure 1).

MAP and ePWV measurement

Mean arterial pressure (MAP) was calculated using the formula: $MAP = DBP + 0.4 \times (SBP - DBP)$ (14). The formula for calculating ePWV is as follows: $ePWV = 9.587 - 0.402 \times \text{age} + 4.560 \times 10^{-3} \times \text{age}^2 - 2.621 \times 10^{-5} \times \text{age}^3 \times MAP + 3.176 \times 10^{-3} \times \text{age} \times MAP - 1.832 \times 10^{-2} \times MAP^2$ (15).

General data collection and outcomes

Data extraction was performed using Navicat 16 for PostgreSQL software. The extracted variables comprised: (1) Registration data: gender and age; (2) Complications: myocardial infarction (MI), congestive heart failure (CHF), anemia, diabetes, chronic obstructive pulmonary disease (COPD), and acute kidney injury (AKI); (3) Vital signs: Mean arterial pressure (MAP), resp_rate, temperature, spo2 and heart rate; (4) Laboratory tests: glucose, bicarbonate, and aniongap; (5) Disease severity scores: simplified acute physiology score ii (SAPS II), logistic organ dysfunction system (LODS), and glasgow coma



scale (GCS). The final outcome of the study was the mortality rate during hospitalization. Moreover, insufficient samples of mechanical ventilation and vasoactive medications were gathered, resulting in their exclusion from the study.

Statistical analysis

Baseline patient characteristics are described using the mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. Differences in baseline characteristics are assessed using either a *t*-test or Mann–Whitney *U*-test, depending on the data distribution. Survival time for deceased patients is calculated from their ICU stay. Conversely, for patients who survived after discharge, their last recorded survival time was substituted with the longest survival time observed among deceased patients. Moreover, based on the optimal critical values of glucose, SAPS II score, and LODS score determined using X-tile software, these three parameters were dichotomized into high and low categories.

Kaplan–Meier survival curves were utilized to assess survival rates between the low and high ePWV groups, with between-group differences assessed using the log-rank test. Covariates were adjusted using the Cox proportional hazards model. Model 1 included adjustments for gender and age, while model 2 included adjustments for age, gender, myocardial infarction, congestive heart failure, anemia, diabetes, chronic obstructive pulmonary disease, and acute kidney injury. The restricted cubic spline (RCS) model was employed to assess the presence of a dose–response relationship between ePWV and all-cause mortality among NSAH patients. A likelihood ratio test was performed to assess for potential nonlinearity. Independent prognostic factors for NSAH patients were identified using multivariate Cox regression analysis. Subsequently, these factors were stratified to assess potential differences in the influence of ePWV on all-cause mortality across subgroups. The likelihood ratio test was employed to evaluate interactions between ePWV and stratification variables. Results were reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CI). All statistical analyses were conducted using R software (version 4.2.0). All tests were two-tailed, with statistical significance set at $p < 0.05$.

Results

Patient characteristics

In the final analysis, a total of 644 adult patients with non-traumatic subarachnoid hemorrhage were collected from the MIMIC-IV v2.2 database. Baseline patient characteristics were compared between the low ePWV group (ePWV ≤ 8.728 m/s, 322 subjects) and high ePWV group (ePWV > 8.728 m/s, 322 subjects) (Table 1). The mean ePWV for the two groups was 7.22 m/s and 10.8 m/s, respectively. Patients with high ePWV usually show older age and higher blood sugar, and have a higher probability of acute myocardial infarction, congestive heart failure, diabetes, anemia, chronic obstructive pulmonary disease and acute kidney injury. Additionally, the duration of ICU treatment was lower in the high ePWV group (LOS_ICU = 7.54 days) compared to the low ePWV

group (LOS_ICU = 7.00 days), with a concurrent increase in all-cause mortality (25.8% versus 13.7%).

The relationship between ePWV and outcome

To assess differences in all-cause mortality among different ePWV groups, we generated a Kaplan–Meier survival curve. Analysis of the Kaplan–Meier curve reveals a significantly lower cumulative survival rate among ICU patients with NSAH in the high ePWV group ($p = 0.00031$), as depicted in Figure 2. Even when adjusting for age and sex in Model 1 (HR = 0.5161, $p = 0.000395$), and further covariates in Model 2 (HR = 0.54730, $p = 0.00937$), this correlation persists, with the high ePWV group serving as the reference (Table 2). Subsequent analysis using the RCS model demonstrates an increase in the risk of all-cause mortality with higher ePWV levels (Figure 3). It is noteworthy that this correlation becomes more pronounced when ePWV exceeds 8.728 m/s.

Multivariate COX regression analysis and subgroup analysis

Cox regression analysis revealed ePWV as a significant predictor of all-cause mortality in NSAH patients (GroupLow, HR = 0.54, 95% CI: 0.32–0.89, $p = 0.016$) (Figure 4). Additionally, resp_rate, temperature, spo2, Anemia, AKI and glucose were identified as independent prognostic risk factors. Moreover, we use C-index to evaluate the cox regression model, and finally, C-index = 0.769, which shows that the model has good accuracy. To confirm the association between ePWV and all-cause mortality stratified by resp_rate, temperature, spo2, Anemia, AKI and glucose, a subgroup analysis was performed. As depicted in Figure 5, the findings suggest that ePWV is associated with ICU all-cause mortality in most NSAH patient subgroups. Moreover, no significant interaction was observed between PWV and other subgroups, indicating that the effect of ePWV on mortality was independent of patient characteristics.

Discussion

This study demonstrates that the ePWV level upon entering the ICU independently predicts the mortality of NSAH patients during hospitalization. Following adjustment for confounding factors through multivariate Cox regression analysis, elevated ePWV remains a significant predictor of all-cause mortality. Specifically, the risk ratio for all-cause death in the ICU among patients with a low ePWV level (≤ 8.728 m/s) is 0.54 times that of patients with a high ePWV level (> 8.728 m/s). Additionally, we observed no interaction between ePWV level and hospital all-cause mortality across various subgroups.

The measurement of carotid-femoral pulse wave velocity (cfPWV) is considered the gold standard for assessing arterial stiffness and vascular aging (6, 16). However, due to technical and procedural challenges, applying cfPWV in daily clinical research is difficult (17). Consequently, some researchers calculate ePWV based on the interaction between actual age and average blood pressure, achieving performance equivalent to real cfPWV measurements,

TABLE 1 Baseline characteristics of NSAH patients grouped according to ePWV.

	[ALL]	High	Low	p.overall
	N = 644	N = 322	N = 322	
Age				<0.001
18–50	158 (24.5%)	0 (0.00%)	158 (49.1%)	
50+	486 (75.5%)	322 (100%)	164 (50.9%)	
Gender				0.693
Female	348 (54.0%)	177 (55.0%)	171 (53.1%)	
Male	296 (46.0%)	145 (45.0%)	151 (46.9%)	
Heart_rate	64.0 [56.0,73.0]	63.0 [56.0,70.0]	64.0 [57.0,75.0]	0.018
MAP	81.8 [75.8,87.9]	81.8 [75.4,88.4]	81.7 [75.9,87.6]	0.630
Resp_rate	17.6 [16.0,19.8]	17.6 [16.1,19.9]	17.6 [15.9,19.6]	0.718
Temperature	37.0 [36.8,37.3]	37.0 [36.7,37.3]	37.0 [36.8,37.3]	0.063
spo2	97.8 [96.3,98.9]	97.5 [96.1,98.9]	98.0 [96.4,99.1]	0.030
MI				0.009
No	586 (91.0%)	283 (87.9%)	303 (94.1%)	
Yes	58 (9.01%)	39 (12.1%)	19 (5.90%)	
CHF				<0.001
No	596 (92.5%)	285 (88.5%)	311 (96.6%)	
Yes	48 (7.45%)	37 (11.5%)	11 (3.42%)	
Anemia				0.030
No	515 (80.0%)	246 (76.4%)	269 (83.5%)	
Yes	129 (20.0%)	76 (23.6%)	53 (16.5%)	
Diabetes				0.037
No	629 (97.7%)	310 (96.3%)	319 (99.1%)	
Yes	15 (2.33%)	12 (3.73%)	3 (0.93%)	
COPD				0.007
No	620 (96.3%)	303 (94.1%)	317 (98.4%)	
Yes	24 (3.73%)	19 (5.90%)	5 (1.55%)	
AKI				0.242
No	578 (89.8%)	284 (88.2%)	294 (91.3%)	
Yes	66 (10.2%)	38 (11.8%)	28 (8.70%)	
Aniongap	15.0 [14.0,18.0]	15.0 [14.0,18.0]	15.0 [13.0,18.0]	0.247
Bicarbonate	23.0 [21.0,25.0]	23.0 [21.0,26.0]	22.0 [20.0,25.0]	<0.001
Glucose				0.028
148+	188 (29.2%)	107 (33.3%)	81 (25.2%)	
40–148	455 (70.8%)	214 (66.7%)	241 (74.8%)	
Sapsii				<0.001
32+	296 (46.0%)	201 (62.4%)	95 (29.5%)	
6–32	348 (54.0%)	121 (37.6%)	227 (70.5%)	
LODS				0.603
0–5	532 (82.6%)	263 (81.7%)	269 (83.5%)	
5+	112 (17.4%)	59 (18.3%)	53 (16.5%)	
GCS				0.003
12–15	621 (96.4%)	303 (94.1%)	318 (98.8%)	
9–12	23 (3.57%)	19 (5.90%)	4 (1.24%)	

(Continued)

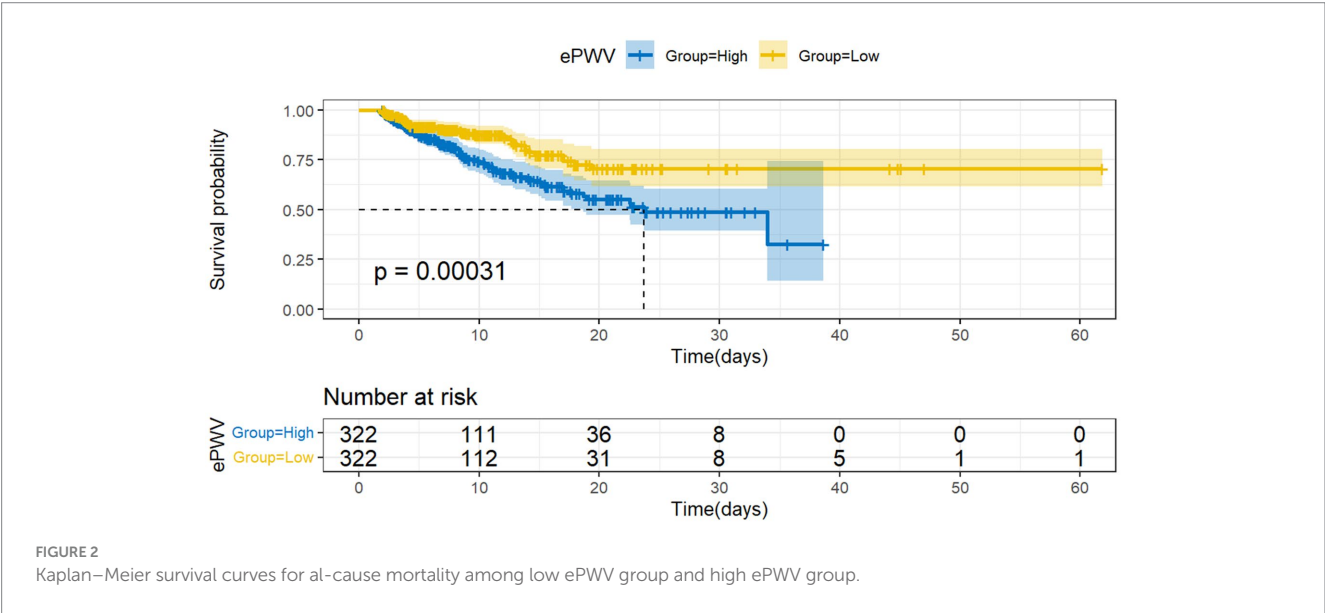
TABLE 1 (Continued)

	[ALL]	High	Low	p.overall
	N = 644	N = 322	N = 322	
ePWV	8.73 [7.22,10.7]	10.8 [9.47,12.6]	7.22 [6.49,7.95]	<0.001
los_icu	7.33 [3.86,12.8]	7.00 [3.71,12.9]	7.54 [4.09,12.7]	0.323
Status				<0.001
Alive	517 (80.3%)	239 (74.2%)	278 (86.3%)	
Dead	127 (19.7%)	83 (25.8%)	44 (13.7%)	

TABLE 2 Cox proportional HR for all-cause mortality.

Group	Non-adjusted Model		Model 1		Model 2	
	HR	p value	HR	p value	HR	p value
High (n = 322)	Reference					
Low (n = 322)	0.5161	0.000395	0.5522	0.00939	0.54730	0.00937

Non-adjusted Model: unadjusted. Model 1: adjusted for gender and age. Model 2: adjusted for age, gender, MI, CHF, anemia, diabetes, COPD, and AKI.

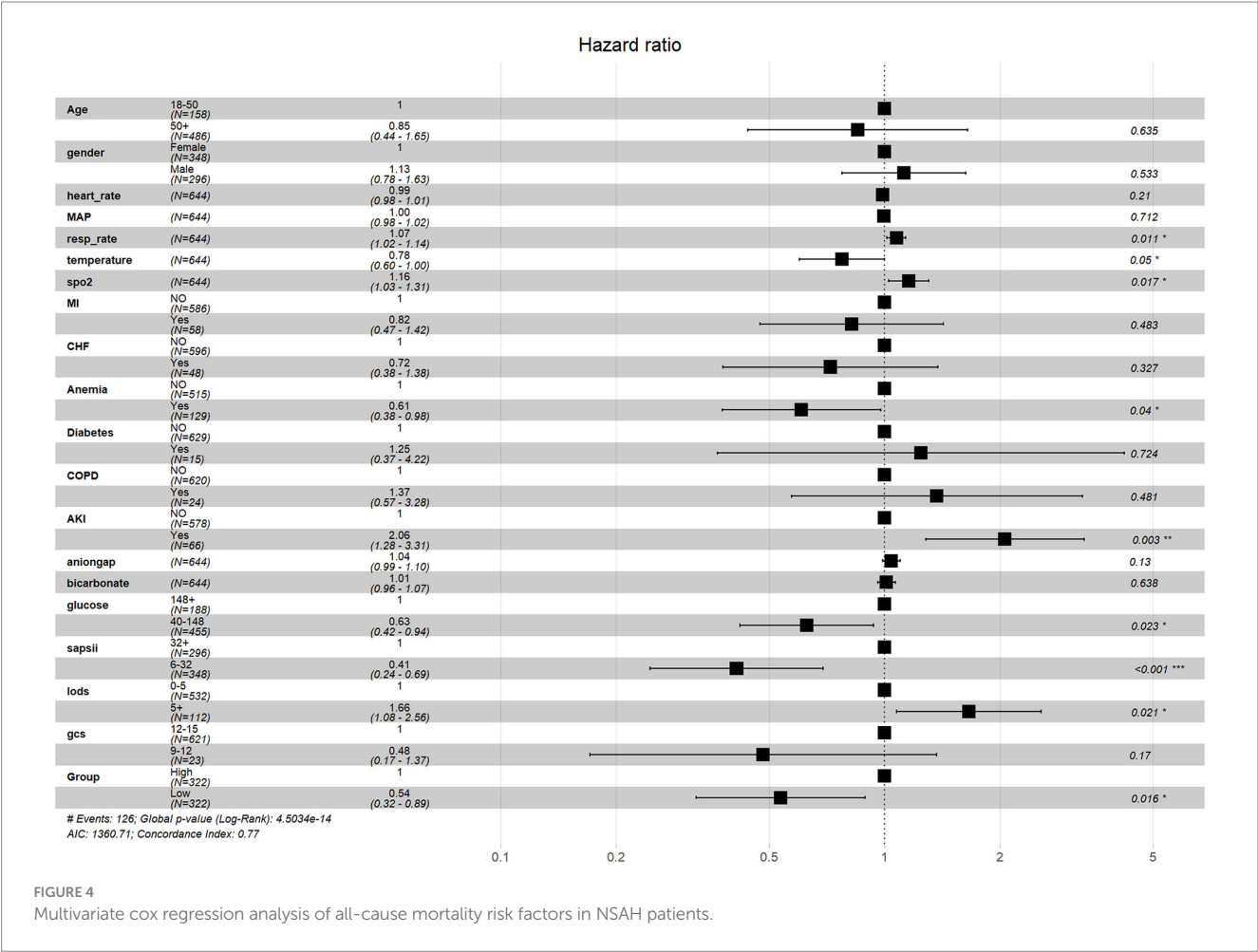
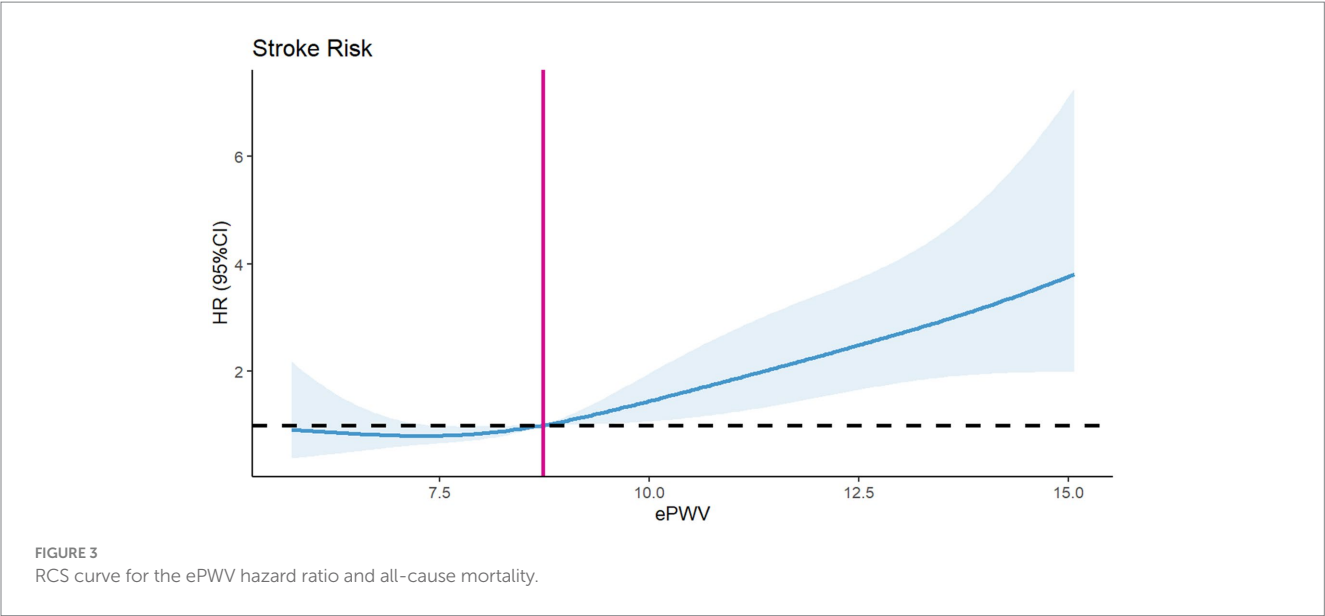


thereby considering ePWV a reliable marker of cardiovascular risk (18, 19). In recent years, some studies have demonstrated that the elevation of cfPWV levels is associated not only with asymptomatic cerebrovascular diseases in hypertensive patients but also with the calcification of intracranial aneurysms in acute stroke patients, affecting the prognosis of patients with intracranial vascular diseases (20, 21). Consistent with these findings, our study demonstrates a significant association between high ePWV levels and increased risk of hospital death.

Our study found that there was a J-type correlation between ePWV at admission and the adverse outcomes of NSAH. When ePWV exceeded 8.728 m/s at admission, the all-cause mortality of patients was significantly higher. Therefore, we suggest that under the condition of ensuring organ perfusion, we can choose a more suitable target blood pressure for patients of different ages by calculating ePWV. However, compared with previous studies, first of all, we excluded patients with more critical illness (GCS<9),

mainly considering that the symptoms of cerebral vasospasm and intracranial pressure in these patients may be more serious, thus affecting the regulation of blood pressure. Secondly, we first correlated ePWV with the prognosis of NSAH patients. Thirdly, our research variables took age into account, so that we can determine the optimal blood pressure target value for patients of different ages.

The precise mechanism underlying the close association between ePWV levels and all-cause mortality in NSAH patients remains unclear. Nevertheless, several potential explanations can be proposed. One possibility is that ePWV levels may be associated with systemic inflammation (22), and systemic inflammation following NSAH may play a crucial role in mediating cerebral vasospasm and brain injury (23). Another explanation is that ePWV levels are directly influenced by blood pressure at the time of admission to the ICU. Apart from age, hypertensive patients tend to have elevated ePWV levels, and persistent hypertension is closely associated with the risks of



rebleeding, delayed cerebral ischemia, and severe cerebral edema in NSAH patients (24, 25). A third possibility is that the elevation of ePWV may be linked to changes in age-related metabolic symptoms and oxidative stress, with neuronal apoptosis induced by oxidative stress representing one of the significant mechanisms of early brain injury (26, 27). Moreover, high ePWV levels have been associated with obstructive sleep apnea and sympathetic hyperactivity (28). Sleep apnea can exacerbate early brain injury following subarachnoid

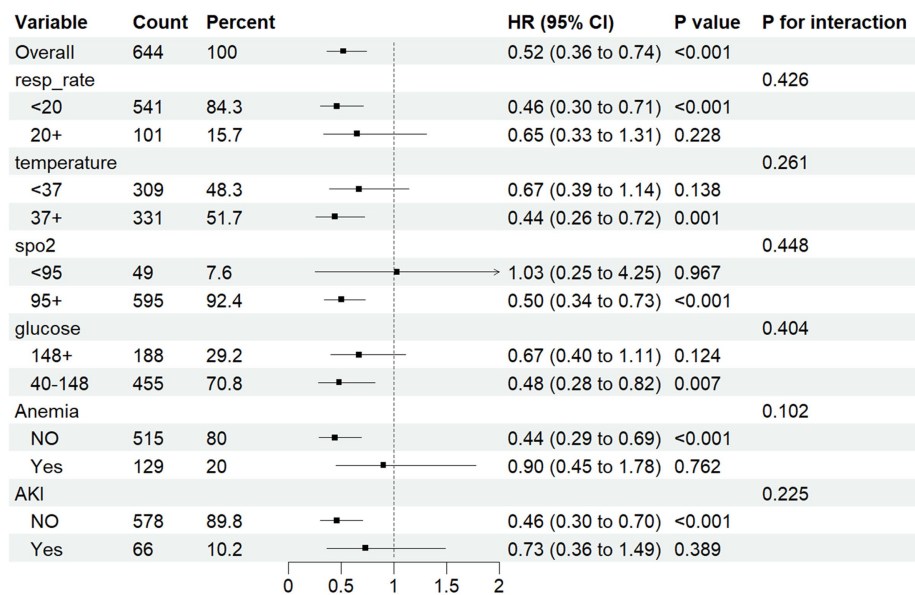


FIGURE 5
Forest plots for different subgroup analysis of HRs for the association between ePWV and all-cause mortality.

hemorrhage by exacerbating neuroinflammation and focal death (29). The occurrence of paroxysmal sensory hyperactivity disorder in patients with acute brain injury may lead to extended hospital stays, escalated hospitalization costs, physical impairment, and potential mortality (30).

However, we must acknowledge several limitations of our study. Firstly, the retrospective design may introduce bias in patient selection and analysis. A prospective cohort study is necessary to further investigate the causal relationship between elevated ePWV and NSAH mortality. Secondly, due to limitations in the MIMIC database, crucial data such as mechanical ventilation and vasoactive drug information for NSAH patients were insufficiently represented, precluding their inclusion in the analysis. Thirdly, we limited our data collection to within 6h prior to ICU admission to assess the association between ePWV levels and mortality. Fourthly, our analysis does not investigate the etiology of NSAH patients or the variation in ePWV levels between the prognoses of aneurysmal and non-aneurysmal NSAH.

Conclusion

This retrospective study demonstrates that a high ePWV level serves as a significant risk factor for all-cause mortality among NSAH patients in the ICU. By calculating ePWV, clinicians can significantly assist NSAH patients in conducting risk stratification and subsequently developing personalized treatment strategies to enhance patient prognosis.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: MIMIC-IV 2.2database.

Ethics statement

The studies involving human participants were examined and approved by Beth Israel Deaconess Medical Center. To protect patient privacy, all data were de-identified; therefore, the Ethical Committee of the Beth Israel Deaconess Medical Center waived the requirement for informed consent. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JL: Data curation, Formal analysis, Writing – original draft. MZ: Formal analysis, Funding acquisition, Writing – original draft. BY: Data curation, Formal analysis, Writing – original draft. ML: Methodology, Resources, Writing – original draft. GL: Validation, Visualization, Writing – review & editing.

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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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Ultra-early neurological deterioration following a brain arteriovenous malformation rupture

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Purpose: This study aims to explore the impact of ultra-early neurological deterioration (U-END) on the outcome (mortality and poor neurological status) following a brain arteriovenous malformation (BAVM) rupture and identify determinants of U-END.

Methods: Patients with BAVM ruptures admitted to a single tertiary care center were retrospectively reviewed. U-END was defined as a worsening by two or more points on the Glasgow Coma Scale (GCS). U-END was tested as a potential predictor of in-hospital mortality and poor outcomes. Univariate and multivariate analyses were performed to identify determinants of U-END. Patients with U-END were also matched and compared with BAVM rupture controls presenting with a GCS close or equal to either their initial or their lowest GCS.

Results: A total of 248 patients with BAVM ruptures met the inclusion criteria, with 39 (15.7%) patients presenting with U-END. U-END was not associated with and was not an independent predictor of in-hospital mortality (12.8 vs. 10.5% in the rest of the study population; $p = 0.67$) or poor outcomes (39.5 vs. 36.9%; $p = 0.77$). The only independent determinants of U-END were hydrocephalus (OR 2.6 [95%CI, 1.1–6.4]; $p = 0.03$) and intraventricular hemorrhage (IVH; OR 3.5 [95%CI, 1.1–11.7]; $p = 0.04$). When compared to the initial GCS control group, U-END patients more often presented with IVH (89.5 vs. 64.1%; $p = 0.009$) and hydrocephalus (73 vs. 38.5%; $p = 0.003$). When compared to the lowest GCS control group, U-END patients had lower early S100B serum levels (0.35 ± 0.37 vs. 0.83 ± 1 ; $p = 0.009$) and a lower rate of poor outcome (39.5 vs. 64.9%; $p = 0.03$).

Conclusion: Ultra-early neurological deterioration in ruptured BAVMs did not result in increased mortality or poor outcomes and was most often related to IVH and hydrocephalus.

KEYWORDS

arteriovenous malformation, hemorrhage, deterioration, hydrocephalus, rupture

1 Introduction

Ultra-early neurological deterioration (U-END) has been associated with poor outcomes and increased mortality following intracerebral hemorrhage (1). Brain arteriovenous malformation (BAVM) rupture is the leading cause of morbidity, mortality, and social and healthcare burden in this disease (2–4). However, BAVM ruptures significantly differ from primary intracerebral hemorrhage (ICH) with respect to several clinical characteristics. Patients with BAVM ruptures tend to be younger, have lower pre-stroke and admission blood pressure, have a higher Glasgow Coma Scale (GCS) at admission, and are more likely to have an ICH in a lobar location (5). Moreover, ICH is absent in more than 20% of BAVM ruptures, and BAVM-related hemorrhage appears to have a better long-term outcome than spontaneous hemorrhage (5–7).

The primary objective of this study was to explore the impact of U-END on outcomes (mortality and poor neurological status) following BAVM rupture. The secondary objective was to identify determinants of U-END in this specific setting.

2 Materials and methods

2.1 Ethical statement

The institutional review board (IRB reference CRM-201-119) approved this study. The need for patients' informed consent was waived. This study complies with the principles of the Declaration of Helsinki (1964).

2.2 Definitions

Ultra-early neurological deterioration was defined as a worsening by two or more points on the GCS in the prehospital setting or early post-arrival, with early post-arrival defined as within 48 h of admission as previously reported (1). In-hospital mortality was defined as death from any cause during the initial hospital stay. Poor outcome was defined as a modified Rankin scale score of ≥ 3 at 3 months or beyond following admission.

2.3 Patients

Records of patients with BAVM ruptures admitted to a tertiary care teaching hospital from 1 January 2005 to 31 January 2020 were retrospectively reviewed. Clinical, demographic, and imaging data were recorded. Post-embolization ruptures were excluded. Patients with an unknown initial GCS score or patients known to have deteriorated early before or upon admission but for which the extent of deterioration was not recorded were also excluded. Because BAVM patients can suffer multiple hemorrhages during their lifespan, patients could be admitted multiple times, having a different clinical severity profile for each rupture, with or without U-END. In-hospital mortality and neurological outcomes were recorded. ICH volume was measured using the ellipsoid volume approximation (ABC/2) method, in which A is the greatest diameter on the slice on which the hematoma appears the largest, B is the diameter perpendicular to A,

and C is the approximate number of axial slices, with hemorrhage multiplied by the slice thickness, which has been validated in several large studies (8–10). Graeb score [an estimate of intraventricular hemorrhage (IVH) severity based on gross hemorrhage size] and Barrow Neurological Institute [BNI; an estimate of subarachnoid hemorrhage (SAH) severity] score were calculated as previously reported (11, 12). S100B protein is a biochemical marker of secondary neurological complications in neurocritical care patients (13). Early S100B protein serum elevation was defined as a maximal value within the first 48 h following the admission of $>0.5 \mu\text{g/L}$ (S100B48max) (14). Assessment and correction methods of S100B data samplings were handled as previously described (14).

2.4 Statistical analysis

Patients with and without U-END were compared using univariate analysis and Kaplan–Meier survival analysis. Multivariate stepdown logistic regression was performed to determine whether U-END is an independent predictor of in-hospital mortality or poor outcome. Because this is not a broad exploratory analysis, only previously known predictors of in-hospital mortality and poor outcome in patients with BAVM rupture were included in the model (initial $\text{GCS} \leq 8$, ICH volume, IVH, and early elevated S100B serum protein) (4, 14), in addition to U-END. Receiver operating characteristic (ROC) curves for in-hospital mortality and poor neurological outcome were drawn to compare initial GCS and the lowest early GCS as predictors of outcome. The area under the ROC curves (AUC) was calculated for the different endpoints and compared between the two GCS measures (initial and lowest). The lowest GCS was defined as the lowest grade reached by the patient before stabilizing or being sedated.

A multivariate stepwise logistic regression analysis was performed to identify determinants of U-END. Variables were included in the model if they were associated with U-END in univariate analysis with a p value of <0.1 .

To refine the clinical description of U-END patients, two control groups were constituted and compared to the U-END subgroup: each U-END patient was randomly matched with a control patient having a GCS equal or nearly equal (± 1 GCS point) to either his initial or his lowest GCS (the lowest GCS comparison group). Binary variables were compared using a Chi-square test, while means and medians were compared using a Student's t -test and a Mann–Whitney test, respectively. The p values of <0.05 were considered significant. Statistical analyses were performed using MedCalc version 19.2.6 (Ostend, Belgium).

This study adheres to the STROBE guidelines for observational studies.

3 Results

In total, 242 patients presenting with 248 BAVM ruptures (six patients included for two independent hemorrhagic occurrences) met the inclusion criteria (Figure 1). Table 1 summarizes the patient's characteristics. A total of 39 (16%) patients with BAVM ruptures presented with U-END. Out of the six patients included twice for two independent hemorrhagic occurrences, two were included in both

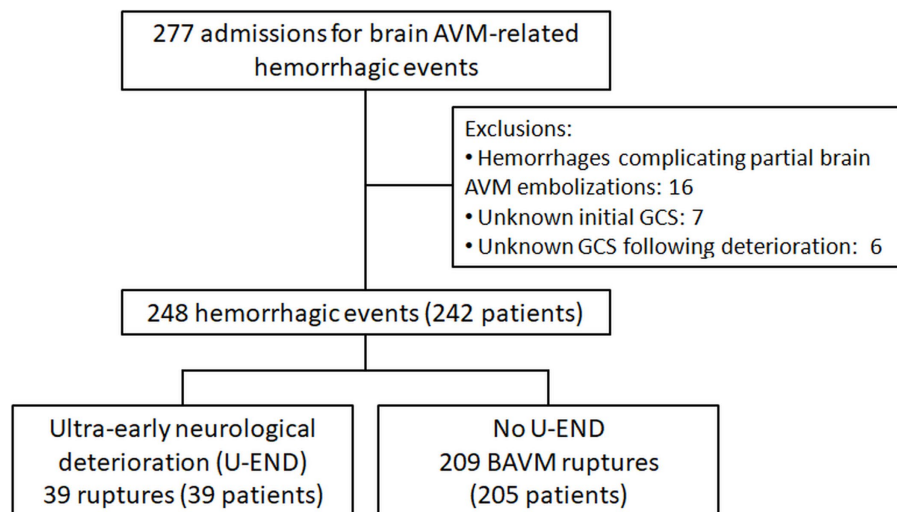


FIGURE 1

BAVM, Brain arteriovenous malformation; GCS, Glasgow Coma Scale; U-END, Ultra-early neurological deterioration.

U-END and no U-END groups (once with U-END and another without U-END), explaining the discrepancy between the total of patients included (242) and the sum of patients in each of the two subgroups (39 and 205 patients in the U-END and No U-END subgroups, respectively).

The rate of in-hospital mortality did not differ between BAVM ruptures with (12.8%) and without (10.5%) U-END ($p=0.67$). In survival analysis (Figures 1, 2A), U-END was not associated with increased in-hospital mortality (hazard ratio = 0.77; 95%CI [0.27–2.2]; $p=0.62$). In the total study population, the lowest GCS (AUC = 0.88; 95%CI [0.83–0.92]; $p=0.83$) did not better predict in-hospital mortality when compared to the initial GCS score (AUC = 0.87; 95%CI [0.82–0.91]) (Figure 2B). The outcome at 3 months or beyond was known for 233 cases. The rate of poor outcome did not differ between BAVM ruptures with (39.5%) and without (36.9%) U-END ($p=0.77$). The lowest GCS (AUC = 0.77; 95%CI [0.72–0.83]; $p=0.72$) did not better predict poor outcomes when compared to the initial GCS score (AUC = 0.77; 95%CI [0.71–0.82]) (Figure 2C). In contrast, BAVM ruptures presenting with U-END had longer durations of sedation ($p=0.001$), intensive care stay ($p=0.049$), and total duration of hospital stay ($p=0.02$) (Table 1). Exploratory analysis found that U-END patients presented more frequently with IVH ($p<10^{-3}$), hydrocephalus ($p<10^{-3}$), and SAH ($p=0.02$), leading to the more frequent need for external ventricular drainage ($p<10^{-3}$). In multivariate logistic regression, only an initial GCS of ≤ 8 (odds ratio (OR) 7.7 [95%CI, 2.2–27.6]; $p=0.002$) and an S100Bmax48 (OR 9.5 [95%CI, 2.4–37.9]; $p=0.002$) were predictive of in-hospital mortality. Only GCS of ≤ 8 (OR 5.6 [95%CI, 2.4–13.1]; $p<10^{-3}$) and an S100Bmax48 (OR 5.4 [95%CI, 2.5–12]; $p<10^{-3}$) were predictive of poor outcome. U-END was not an independent predictor of in-hospital mortality or poor outcomes.

Based on the results of the univariate analysis in Table 1, age at admission, IVH, hydrocephalus, and SAH were included in a multivariate analysis to identify independent determinants of U-END. Only Hydrocephalus (OR 2.6 [95%CI, 1.1–6.4]; $p=0.03$) and IVH (OR 3.5 [95%CI, 1.1–11.7]; $p=0.04$) were identified as

independent determinants of U-END. When compared to matched controls based on initial GCS, U-END patients presented more frequently with IVH ($p=0.009$), hydrocephalus ($p=0.003$), and SAH ($p=0.02$) (Table 2). The results showed that duration of sedation ($p=0.002$), stay in intensive care ($p<10^{-3}$), and total hospital stay ($p<10^{-3}$) were longer in U-END patients, without any significant difference in mortality or poor outcome. In contrast, when compared to controls based on the lowest GCS, U-END patients presented with lower early S100B protein serum levels ($p=0.02$) and less frequent poor outcomes ($p=0.03$).

4 Discussion

Ultra-early neurological deterioration in the study population of patients admitted following BAVM rupture did not result in increased mortality or poor outcome and was most often related to IVH and hydrocephalus. With the exception of hydrocephalus, hemorrhage severity and prognosis were more determined by the initial rather than the lowest GCS in U-END patients with BAVM rupture.

Decisions regarding the most appropriate level of care in neurocritically ill patients are partially based on outcome prognostication, which in turn is related to prognostic markers (4). Caution should, however, be exercised in clinical practice when handling early prognostic markers of poor outcomes, as overconfidence can lead to a self-fulfilling prophecy. This consideration is particularly important in the context of neurocritically ill patients who often die following withdrawal of life-sustaining treatment (15). The GCS is a strong prognostic marker following both ICH in general and hemorrhage secondary to BAVM rupture in particular (4, 8).

Neurological deterioration following a stroke can have a number of causes, depending on stroke type, including and not exhaustively, hematoma expansion, seizure, or obstructive hydrocephalus. Exploratory analysis of the randomized Field Administration of Stroke Therapy-Magnesium (FAST-MAG) trial has found U-END to

TABLE 1 A comparison of brain arteriovenous malformation (BAVM) ruptures with and without ultra-early neurological deterioration (U-END).

	Total study population (248 BAVM ruptures)	U-END (39 BAVM ruptures)	No U-END (209 BAVM ruptures)	<i>p</i> value
<i>Demographics and past medical history</i>				
Age at admission, years	43.1 ± 15.7	47.7 ± 14.9	42.3 ± 15.7	0.05
Male sex	140 (56.5)	21 (53.8)	119 (56.9)	0.72
Past BAVM rupture	27/246 (11)	3/38 (7.9)	24/208 (11.5)	0.51
Baseline modified Rankin Scale 0	213/245 (86.9)	31/38 (81.6)	182/207 (87.9)	0.29
<i>Glasgow Coma Scale (GCS) score</i>				
Median initial GCS	14 (10–15)	14 (12–15)	15 (10–15)	0.89
Median lowest GCS	13 (7–15)	7 (6–11)	14 (10–15)	<10 ^{−3}
<i>CT scan</i>				
Intracerebral hemorrhage	199/246 (80.9)	30/38 (78.9)	169/208 (81.2)	0.74
Infratentorial location	45/199 (22.6)	8/30 (26.7)	37/169 (21.9)	0.63
Volume (mL)	36.7 ± 36.6	42 ± 33.2	35.8 ± 37.2	0.39
Intraventricular hemorrhage	153/246 (62.4)	34/38 (89.5)	119/207 (57.5)	<10 ^{−3}
Hydrocephalus	104/245 (42.4)	27/37 (73)	77/208 (37)	<10 ^{−3}
Subarachnoid hemorrhage	60/246 (24.4)	15/38 (39.5)	45/208 (21.6)	0.02
Subdural hemorrhage	20/246 (8.1)	3/38 (7.9)	17/208 (8.2)	0.95
<i>Biological markers</i>				
Mean admission (48 h) S100 protein serum level	0.44 ± 0.61	0.35 ± 0.37	0.46 ± 0.65	0.35
Elevated troponin	25/173 (14.5)	5/30 (16.7)	20/143 (14)	0.71
<i>Inpatient management</i>				
Surgery	90 (36.3)	16 (41)	74 (35.4)	0.5
Ventricular drain	120/247 (48.6)	30/39 (76.9)	90/208 (43.3)	<10 ^{−3}
Embolization	71 (28.6)	13 (33.3)	58 (27.8)	0.48
Acute phase BAVM obliteration	63 (25.4)	8 (20.5)	22 (26.3)	0.45
<i>Outcome</i>				
Duration of sedation (days)	3.4 ± 7.9	9.1 ± 7.7	2.7 ± 7.6	0.001
Duration of stay in intensive care (days)	24.9 ± 24.4	32.6 ± 17	23.2 ± 25.5	0.049
Duration of hospital stay (days)	35.5 ± 34.7	50.2 ± 25.1	32.9 ± 35.6	0.02
Inpatient mortality	27 (10.9)	5 (12.8)	22 (10.5)	0.67
Modified Rankin Scale ≥3 beyond 3 months	87/233 (37.3)	15/38 (39.5)	72/195 (36.9)	0.77

Values are mean ± standard deviation or medians with interquartile range for quantitative variables and percentages for qualitative variables. The denominator is given for binary variables in case of missing data. BAVM, Brain arteriovenous malformation; GCS, Glasgow Coma Scale; and U-END, Ultra-early neurological deterioration.

occur in 30.8% of ICH patients, nearly twice the figure found in the context of BAVM rupture (1). More importantly, Shkirkova et al. found a more than four-fold increase in poor neurological outcomes and a three-fold increase in mortality in ICH patients presenting with U-END (1). U-END following BAVM rupture did not result in increased mortality or poor outcome in this study, possibly because the mechanism of U-END in this context is hydrocephalus-related intracranial hypertension, which is reversible through external ventricular drainage. BAVM ruptures with U-END tend to have hemorrhage severity and prognostic profiles closer to controls matched based on their initial rather than the lowest GCS, except for

durations of hospital stay, which may be prolonged because of intraventricular hemorrhage and external ventricular drainage, although this remains speculative. S100B protein is a biochemical marker of secondary neurological complications in neurocritical care patients (13). Early elevation of S100B protein serum level has been demonstrated to be strongly associated with in-hospital mortality after BAVM rupture (14). When compared to controls based on the lowest GCS, U-END patients in this study presented with lower early S100B protein serum levels, indicative of a less severe hemorrhagic profile, confirmed by better neurological outcomes.

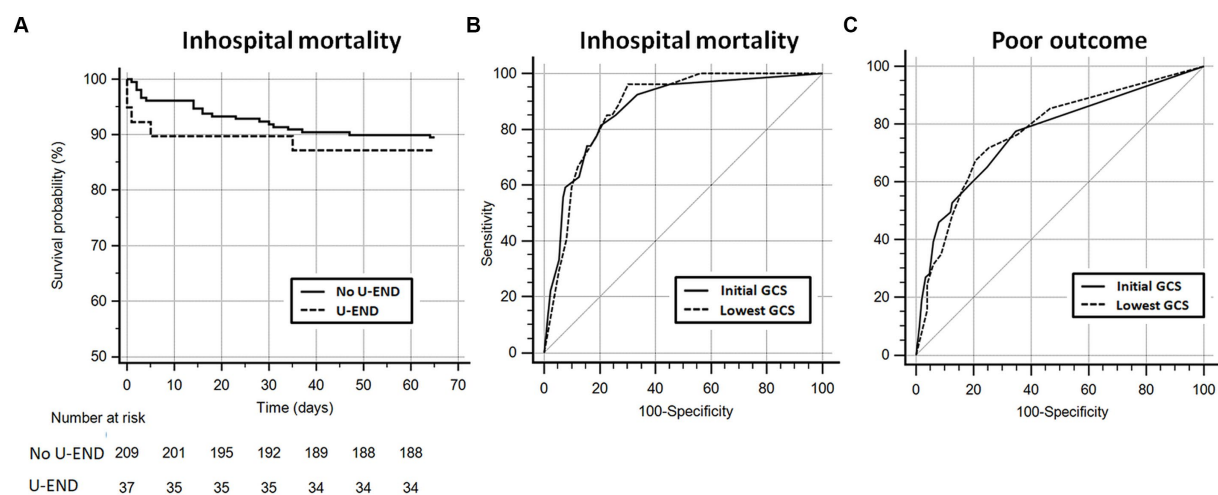


FIGURE 2

(A) Kaplan–Meier survival curve comparing patients with and without ultra-early neurological deterioration (U-END). (B,C) Receiver operating characteristic (ROC) curves comparing initial Glasgow Coma Scale (GCS) and lowest early GCS as predictors of in-hospital mortality (B) and poor neurological outcome (C). GCS, Glasgow Coma Scale; ROC, Receiver operating characteristic; and U-END, Ultra-early neurological deterioration.

TABLE 2 A comparison of brain arteriovenous malformation (BAVM) ruptures presenting with ultra-early neurological deterioration (U-END) with matched controls based on initial or final (lowest) Glasgow Coma Scale (GCS) scores.

	U-END 39 BAVM ruptures)	Initial GCS comparison group (39 BAVM ruptures)	p value	Lowest GCS comparison group (39 BAVM ruptures)	p value
<i>Demographics and past medical history</i>					
Age at admission, years	47.7 ± 14.9	42.8 ± 17.5	0.2	41.1 ± 16.1	0.31
<i>Glasgow Coma Scale (GCS) score</i>					
Median initial GCS (IQR)	14 (12–15)	14 (12–15)	1	7 (6–11)	<10 ^{−3}
Mean initial GCS	13 ± 2.6	13 ± 2.6	1	8.2 ± 3.4	<10 ^{−3}
Median lowest GCS (IQR)	7 (6–11)	14 (12–15)	<10 ^{−3}	7 (5–11)	1
Mean lowest GCS	8 ± 3.3	13 ± 2.6	<10 ^{−3}	8 ± 3.4	0.97
<i>CT scan</i>					
Intracerebral hemorrhage	30/38 (78.9)	30 (76.9)	0.83	32 (82.1)	0.73
Infratentorial location	8/30 (26.7)	4/30 (13.3)	0.19	11/32 (28.2)	0.47
Volume (mL)	42 ± 33.2	37.7 ± 48.3	0.69	55.2 ± 34.3	0.13
Intraventricular hemorrhage	34/38 (89.5)	24 (64.1)	0.009	29 (74.4)	0.088
Mean Graeb score	6 ± 3	6.2 ± 3.1	0.82	6.3 ± 3	0.68
Hydrocephalus	27/37 (73)	15 (38.5)	0.003	24 (61.5)	0.29
Subarachnoid hemorrhage	15/38 (39.5)	6 (15.4)	0.02	11 (28.2)	0.3
BNI score ≥ 3	6/15 (40)	2 (33)	0.78	2 (18.2)	0.24
Subdural hemorrhage	3/38 (7.9)	3 (7.7)	0.97	1 (2.6)	0.3
<i>Biological markers</i>					
Mean admission (48 h) S100 protein serum level	0.35 ± 0.37	0.35 ± 0.41	0.98	0.83 ± 1	0.01
Elevated troponin	5/30 (16.7)	2/26 (7.7)	0.32	7/33 (21.2)	0.65
<i>Outcome</i>					
Duration of sedation (days)	9.1 ± 7.7	2.6 ± 5.5	0.002	9.4 ± 14.6	0.94
Duration of stay in intensive care (days)	32.6 ± 17	15.9 ± 12.5	<10 ^{−3}	28.3 ± 16	0.33
Duration of hospital stay (days)	50.2 ± 25.1	25.6 ± 21.2	<10 ^{−3}	43.8 ± 29.6	0.43
Inpatient mortality	5 (12.8)	4 (10.3)	0.72	11 (28.2)	0.09
mRS ≥ 3 beyond 3 months	15/38 (39.5)	12/37 (32.4)	0.53	24/37 (64.9)	0.03

Values are mean ± standard deviation (SD) or medians with interquartile range (IQR) for quantitative variables and percentage for qualitative variables. The denominator is given for binary variables in case of missing data. BAVM, Brain arteriovenous malformation; GCS, Glasgow Coma Scale; mRS, Modified Rankin scale; and U-END, Ultra-early neurological deterioration.

The study is retrospective and monocentric, and all the usual caveats apply. Indeed, several patients were excluded because of unknown initial GCS scores. More importantly, patients known to have deteriorated early before or upon admission but for which the extent of deterioration was not recorded were excluded. The data presented in this study has to be replicated in a prospective population where such loss of information can easily be mitigated. Another potential source of U-END may be rebleeding, which would not have been diagnosed, given that deterioration mostly occurs by definition before imaging. However, it is the author's opinion that rebleeding is a minor contributor to U-END in the setting of BAVM rupture. Indeed, previous studies have shown early rebleeding to be a rare event following BAVM rupture, and ultra-early rebleeding is consequently expected to be exceptional (16). Finally, the study may be underpowered to demonstrate the impact of U-END on the outcome following BAVM rupture. This raises the need for external multicentric replication of the results. In particular, in-hospital mortality is a rare event, and the study may be underpowered to detect a modest or moderate impact of U-END on this specific outcome.

5 Conclusion

Ultra-early neurological deterioration in ruptured BAVMs was most often related to IVH and hydrocephalus and did not result in increased mortality or poor outcomes in the study population. Based on the results of this study, in ruptured BAVM patients with U-END, prognostication should be based on the initial GCS rather than the lowest GCS, especially when there is no obvious cause of deterioration other than hydrocephalus.

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 humans were approved by the CERIM (CERF Interface Recherche Bioéthique Institutional Review Board) ethical review board approved this study (approval number CRM-201-119). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the need for patients' informed consent was waived given the retrospective design.

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Author contributions

ES: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. P-MC: Data curation, Writing – review & editing. IH: Data curation, Writing – review & editing. JC: Data curation, Writing – review & editing. AJ: Data curation, Writing – review & editing. LG: Data curation, Writing – review & editing. JA: Data curation, Writing – review & editing. ME: Data curation, Writing – review & editing. CA: Data curation, Writing – review & editing. BM: Conceptualization, Writing – review & editing. AN: Conceptualization, Writing – review & editing. KP: Conceptualization, Writing – review & editing. SL: Conceptualization, Writing – review & editing. N-AS: Conceptualization, Writing – review & editing. VD: Conceptualization, Data curation, Supervision, Writing – review & editing. FC: Conceptualization, Data curation, Supervision, Writing – review & editing.

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Conflict of interest

FC reports conflict of interest (unrelated) with Medtronic, Guerbet, Balt Extrusion (payment for readings), and Codman Neurovascular (core lab). N-AS is consultant for Medtronic, Balt Extrusion, and Microvention (unrelated to the study). ES is principal investigator of a randomized controlled trial related to chronic subdural hematoma embolization financed by a PHRC-IR public grant (unrelated).

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Establishment and evaluation of a carotid artery dissection model in rats

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Background: Given the lack of models for carotid artery dissections (CAD), we aim to investigate effects of beta-aminopropionitrile (BAPN) combined with physical damage on the arterial walls of rats, and to establish a high-incidence and low-mortality CAD model.

Methods: Sixteen SPF SD rats (3-week-old) were divided into two groups. Group B was given 0.25% BAPN solution and group W was given water. Then we established an animal model of CAD by carotid artery torsion. One of the two carotid arteries in each rat was randomly selected for torsion. We got four groups of blood vessels following above-mentioned methods: BAPN plus torsion group (group Bt), BAPN plus non-torsion group (group Bn), water plus torsion group (group Wt), and water plus non-torsion group (group Wn). The hematoxylin and eosin (HE) staining and Verhoeff's Van Gieson (EVG) staining were performed to observe structures of arteries. Immunofluorescence staining was used to detect structural proteins in vessels. We used triphenyltetrazolium chloride (TTC) staining and neurological function assessment to detect the infarct area of brain and neurological deficits in rats with carotid dissection to verify the validity of the rat model.

Results: BAPN treatment significantly affected the weight gain of rats, but had little effect on survival during the first 5 weeks. The group Bt had the highest incidence of CAD among all groups ($p = 0.014$). HE staining of carotid artery tissue sections showed that the vascular walls were the thickest in group Bt ($p < 0.001$). EVG staining showed the arrangement of elastic fibers was the most irregular in group Bt. Immunofluorescence staining revealed that the expression of α -SMA and SM22a were decreased remarkably in group Bt ($p < 0.001$). Both motor and sensory deficits were more severe in CAD group than control group ($p = 0.0004$; $p = 0.0036$). The relative infarction volumes of CAD group rats were significantly larger than control group ($p < 0.001$).

Conclusion: The animal model of CAD can be feasible to establish by mechanical torsion combined with BAPN free drinking. With this method, the animal mortality was low and the model formation rate was high. This model will enable further studies on CAD.

KEYWORDS

carotid artery dissection, beta-aminopropionitrile (BAPN), mechanical torsion, animal model, rat

Introduction

Cerebral artery dissection (CeAD) represents a major factor causing stroke in young and middle-aged adults. One of the most common types is carotid artery dissection (CAD). Studies have found that 10 to 25% of patients aged 19 to 45 years with first-episode stroke are caused by cerebral arterial dissection (1). Dissection of the arterial wall, due to a tear in the artery's intimal layer or arterial wall bleeding, can be serious and life-threatening. The exact pathogenesis of the early stage of cerebral arterial dissection remains uncertain, because of the lack of suitable animal models (2). At present, animal models of aortic dissection and dissecting aneurysm are mainly created using mechanical methods, drug induction and gene intervention (3). As an irreversible lysyl oxidase inhibitor, BAPN can competitively bind to elastin or amino, and inhibit the cross-linking of elastin and collagen, which leads to the occurrence of dissecting aneurysms. Thus, it is a common drug to establish animal models of aortic dissection (4).

However, there is still no generally acceptable animal model of carotid artery dissection due to differences in the pathogenesis of aortic and carotid artery dissection, such as the embryonic origin of the artery, pathophysiology, etc. (5–7). The model formation rate of carotid artery dissection was low after single BAPN induction. Recently, a study has shown that using a detacher and balloon dilation could establish a CAD model successfully in swines (8), but the difficulty of interventional surgery limited the popularization of this modeling method. Therefore, the aim of this study was to investigate the effects of BAPN combined with twist and clip of carotid artery on arterial walls of rats, and to establish a high-incidence and low-mortality CAD model. A successful animal model will aid future studies focused on the development, pathogenesis and treatment for CAD.

Methods

Animals

Male specific-pathogen free Sprague Dawley (SD) rats (3 weeks, 60 g) provided by Shanghai Jasper Laboratory Animal Co., Ltd. and housed under specific pathogen-free (SPF) conditions, received standard chow, with free access to water. All animals underwent adaptive feeding for 3 days before further intervention. Animal experiments were performed at the Institute of Neurology, Huashan Hospital, Fudan University. The animal experiments followed the Guide for the Care and Use of Laboratory Animals, and had approval from the Institutional Animal Care and Use Committee of Huashan Hospital, Fudan University.

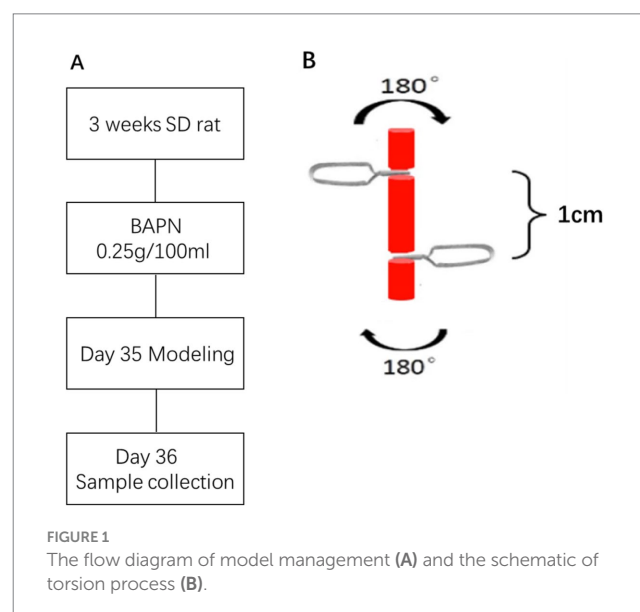
Experimental design and grouping

Sixteen rats were randomly divided into 2 groups: BAPN group (group B), and water-control group (group W). The group B ($n = 8$) was fed by BAPN solution at a concentration of 0.25% and group W ($n = 8$) was fed by distilled water. One of the two carotid arteries in

each rat was randomly selected for torsion. According to different operation, 32 vessels from 16 rats were divided into four groups: BAPN plus torsion group (group Bt), BAPN plus non-torsion group (group Bn), water plus torsion group (group Wt), and water plus non-torsion group (group Wn). The incidence of dissection was calculated at the level of each vessel. All animals had free access to food and water. Body weights were recorded every week. The flow diagram of rat management was shown in Figure 1A.

Model establishment

- Anesthesia:** Before sampling, animals were fasted for 4 h and intraperitoneally administered pentobarbital sodium (3 mL/kg body weight) for anesthesia. The experimental design and anesthesia had approval from the Animal Room Ethics Committee of Fudan University.
- Modeling:** After local disinfection of the neck, the neck's skin along the midline was longitudinally incised, and the left and right carotid arteries were carefully separated. A carotid artery was randomly selected, and two edentulous micro hemostatic clips were used to clamp the carotid artery from both sides of the head and tail in the opposite direction of the handle end (the distance between the two clips was 1 cm). Then, both clips were rotated at 180° in the opposite direction for ten minutes. Figure 1B shows the schematic of torsion process. After that both clips reverse the movement to obtain the returnability. The above operation was repeated 3 times. The other internal carotid artery was left untreated and used as a control. After the above-mentioned torsion damage, two microvascular clips were gently removed, and the skin was sutured and disinfected.



Neurological deficits assessment

Neurological deficits of modeling rats were evaluated at 24 h before sacrificed. We used an eight-point behavioral rating scale designed by Roger et al. (9) to assess the motor function as described previously. Zero represented the normal score and the maximal deficit score was seven. In addition, we conducted hot plate test (10) to assess the sensory function. Response time for observed behavioural changes like licking the paw, lifting the claw and escaping from the hot plate was recorded. Longer response time represented more severe sensory impairment.

Specimen collection

The rats were sacrificed using barbital sodium via intraperitoneal injection after behavioral test. Carotid arteries and brains were taken out for subsequent experiments.

Triphenyltetrazolium chloride staining

We made coronal sections of rat brains with 2 mm thickness. The brain slices were stained with 1% triphenyltetrazolium chloride (TTC) (Sigma-Aldrich, Shanghai, China) solution for 20 min at 37 degrees. Then we used Image-Pro Plus 6.0 software to calculate the ratio of the ischemic area to the ipsilateral hemisphere area (I/H ratio).

Hematoxylin and eosin staining and Verhoeff's Van Gieson staining

Carotid artery tissue specimens from normal animals and carotid artery dissection model animals were collected. Upon fixation with 4% formalin for 24 h, the tissue specimens underwent dehydration with graded ethanol and N-butanol. Then the specimens were embedded in paraffin at 60°C, followed by 5-μm serial sectioning.

Before staining, the sections were dewaxed with xylene and graded ethanol. Specifically, the sections were soaked twice in xylene for 10 min and then soaked in graded ethanol for 5 min each time.

For H&E staining, first we stained the tissue sections with hematoxylin for 3–5 min. After incubation with acid and ammonia solutions for 40 s each, the samples were dyed with eosin for 2 min. Then the slices were dehydrated in graded ethanol and cleared in 100% ethanol and xylene. An inverted microscope (Olympus, Tokyo, Japan) was utilized for analysis.

In EVG staining, the tissue sections were incubated with EVG solution (hematoxylin, iodine solution and ferric chloride at 5:2:2) for 20 min followed by washing with deionised water. Then VG solution (saturated picric acid and Fuchsin solution at 9:1) was used to stained the sections for 5 min followed by washing. The ferric chloride differentiation solution was dyed for background until a grey white background was obtained. Finally, the slices were dehydrated in graded ethanol and cleared in 100% ethanol and xylene. An inverted microscope (Olympus, Tokyo, Japan) was utilized for analysis.

Immunofluorescence staining

Before staining, tissue sections were dewaxed with xylene and graded ethanol. Specifically, the sections were soaked twice in xylene for 10 min and then soaked in graded ethanol for 5 min each time. Then we used citric acid buffer (PH6.0) to retrieve antigen in microwave. As for staining stage, the samples were blocked by 3% BSA, permeabilized by TBS with 0.3% Triton X-100 and incubated by antibodies. The primary antibodies binding to smooth muscle alpha actin (α-SMA) (Affinity, AF1032) and smooth muscle 22 alpha (SM22a) (Proteintech, 10493-1-AP) should be incubated overnight at 4°C. The secondary antibody (Abcam, ab175470) should be incubated at 37°C for 50 min. DAPI in anti-fading sealant (Servicebio Technology Co., Ltd., Wuhan, China) was used to counterstain nuclei. Finally, samples were observed via fluorescence microscope (Olympus, Tokyo, Japan).

Measurement of vessel wall thickness

The thickness of the carotid artery wall was defined as the width of the wall at its thickest point. The thickness was measured by Image-Pro Plus 6.0 software in HE staining sections.

Statistical analysis

All normally distributed data were presented as mean ± standard deviation, while categorical variables were presented as proportion of total. SPSS 22.0 software was used for Student's *t*-test, chi-square test and Fisher's exact probability tests. GraphPad 8.0 software was used for plotting data. Image-Pro Plus 6.0 software was utilized for image analysis and determination of vascular parameters. All *in vitro* experiments were performed at least three times. $p < 0.05$ reflected statistical significance.

Results

Effects of BAPN on body weight and survival

With the increase of BAPN intake, the rat body weight showed a decreasing trend (Figure 2A). Only one rat in the BAPN group died by the fifth week (Figure 2B).

Modeling efficiency

An animal model of carotid artery dissection was established with mechanical clip rotation as previously described (Figures 1A,B). After modeling, the rate of CAD occurrence was the highest in the group Bt at 71.4%, followed by the 28.6, 25%, and 0 in group Bn, group Wt and group Wn, respectively (Table 1). Effects of different treatments on the incidence of CAD were shown in Table 2. The incidence of dissection in the BAPN group and BAPN combined torsion group were significantly higher than in other groups ($p = 0.046$; $p = 0.014$). There was no significant difference in the rate of CAD between the torsion group and other groups ($p = 0.109$). In

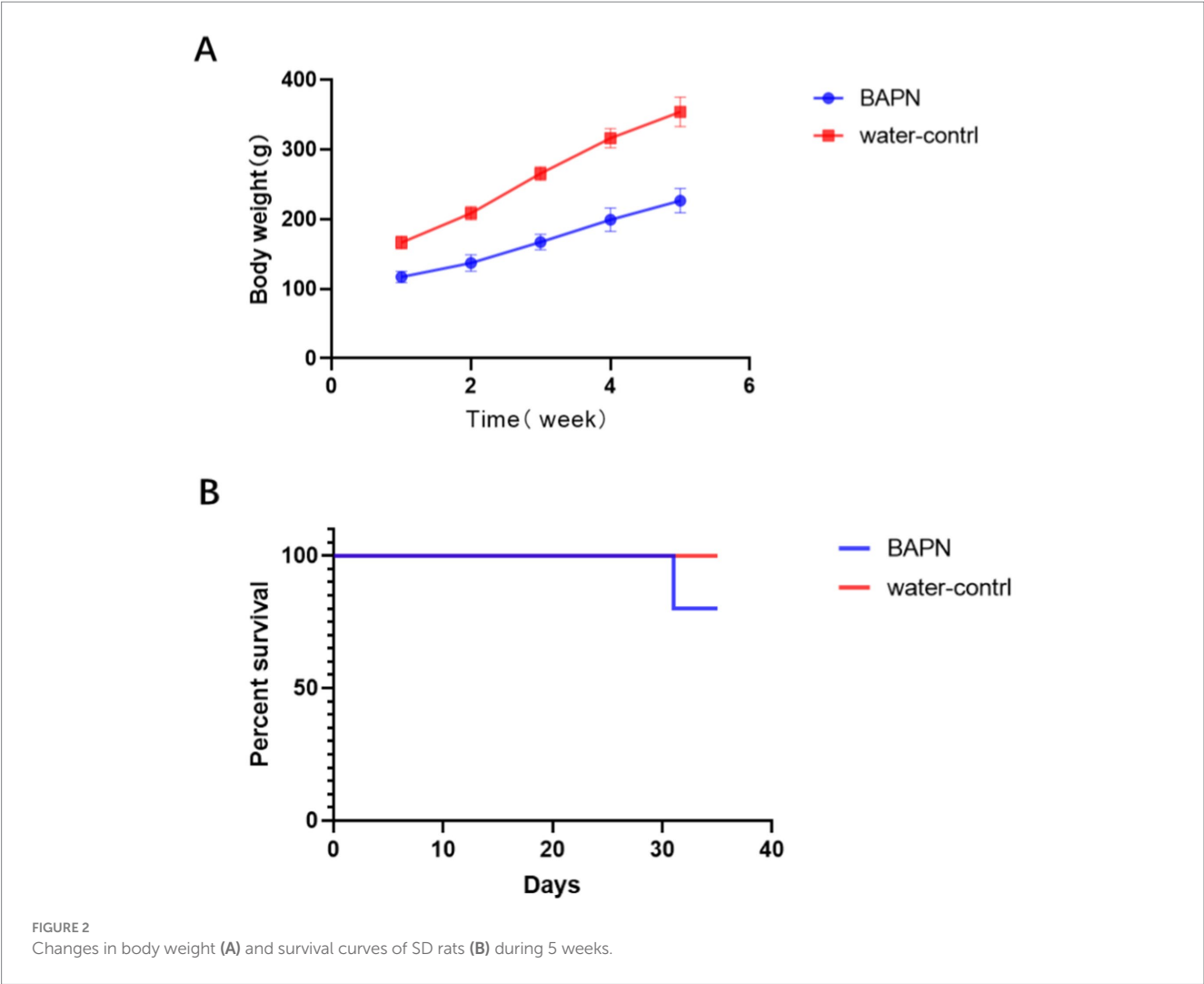


TABLE 1 Incidence of carotid artery dissection in each group at 5 weeks of different treatments.

		Dissection	No-dissection
BAPN	Torsion (n = 7)	5 (71.4%)	2 (28.6%)
	No-torsion (n = 7)	2 (28.6%)	5 (71.4%)
Water-control	Torsion (n = 8)	2 (25%)	6 (75%)
	No-torsion (n = 8)	0 (0)	8 (100%)

order to explore the separate effects of BAPN or torsion damage, we chose the BAPN group without torsion intervention or the torsion group without BAPN intervention as single-BAPN group or single-torsion group, respectively. Finally, the incidence of CAD in both single-BAPN group and single-torsion group was not significantly different from the other groups (both $p = 1$).

Large artery lesions

Gross anatomy of the carotid artery

In rats with CAD, intramural hematomas were observed in carotid arteries. Hematomas were located at the twisting point between the two clips (Figure 3).

Vascular pathological structure

HE staining showed that compared with group Wn, the number of nuclei in the blood vessel wall increased significantly and the arrangement of cells in the wall became more irregular both in group Bt and group Bn. However, the number of nuclei and arrangement of cells in group Wt were similar to that in group Wn (Figure 4A). EVG elastic fiber staining showed that compared with group Wn, the elastic fibers were disorganized and had multiple breaks in group Bt and group Bn. However, the morphology of elastic fibers in group Wt were similar to that in group Wn (Figure 4B). The average thickness of carotid artery walls in group Bt and group Bn was significantly thicker than that in group Wn (Figures 5, 6A, both $p < 0.001$). There was no significant difference between group Wt and group Wn in average wall thickness (Figures 5, 6A, $p = 0.054$).

TABLE 2 Incidence of carotid artery dissection between groups of different treatments.

Group	Dissection	No-dissection	<i>p</i>
BAPN (<i>n</i> = 14)	7 (50%)	7	0.046
Water-control (<i>n</i> = 16)	2	14	
Torsion (<i>n</i> = 15)	7	8	0.109
No-torsion (<i>n</i> = 15)	2	13	
BAPN-torsion (<i>n</i> = 7)	5 (71.4%)	2	0.014
Rests (<i>n</i> = 23)	4	19	
Control (<i>n</i> = 8)	0	8	0.067
Rests (<i>n</i> = 22)	9	13	
Single-BAPN (<i>n</i> = 7)	2	5	1
Rests (<i>n</i> = 23)	7	16	
Single-torsion (<i>n</i> = 8)	2	6	1
Rests (<i>n</i> = 22)	7	15	

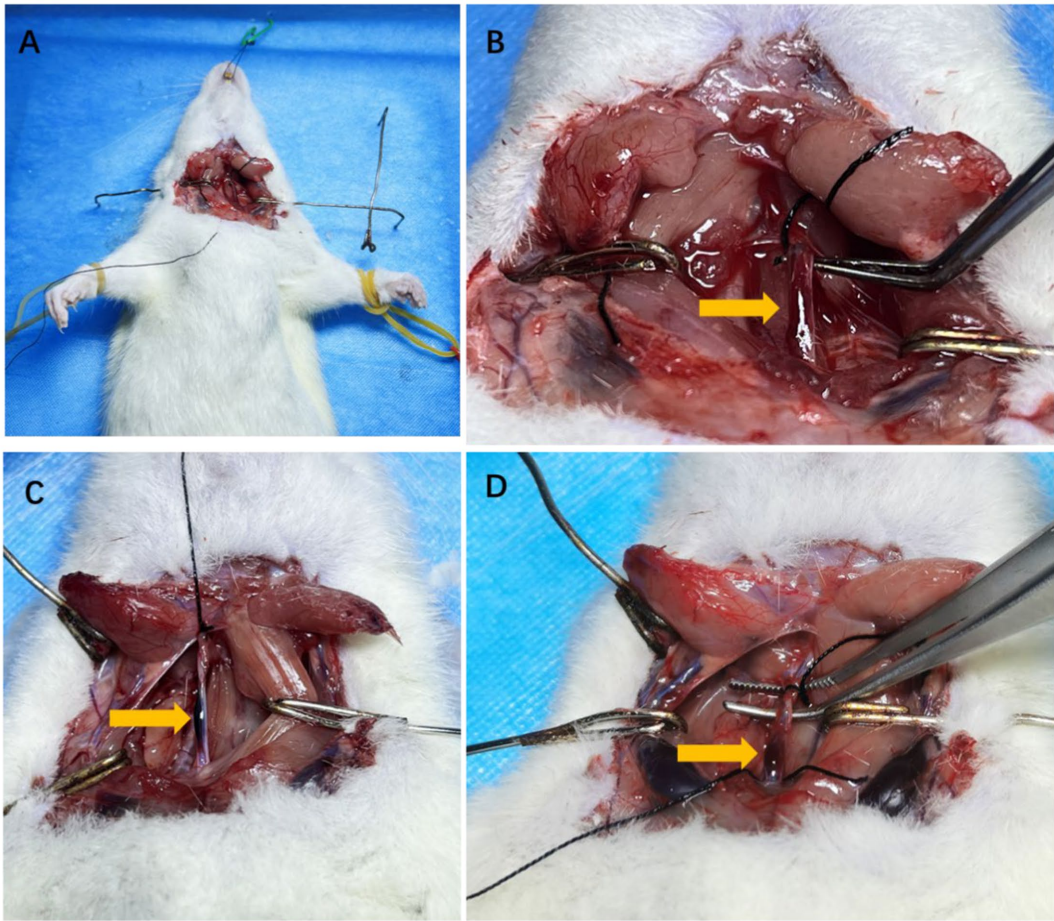
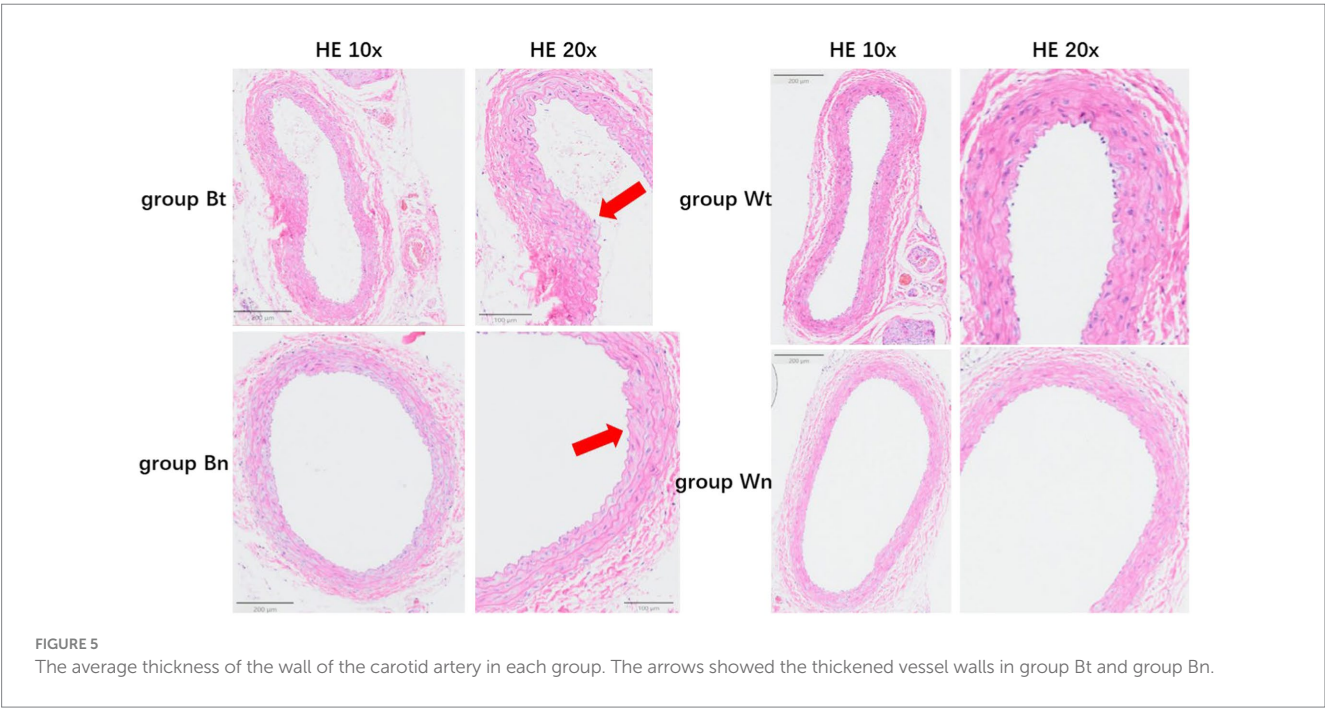
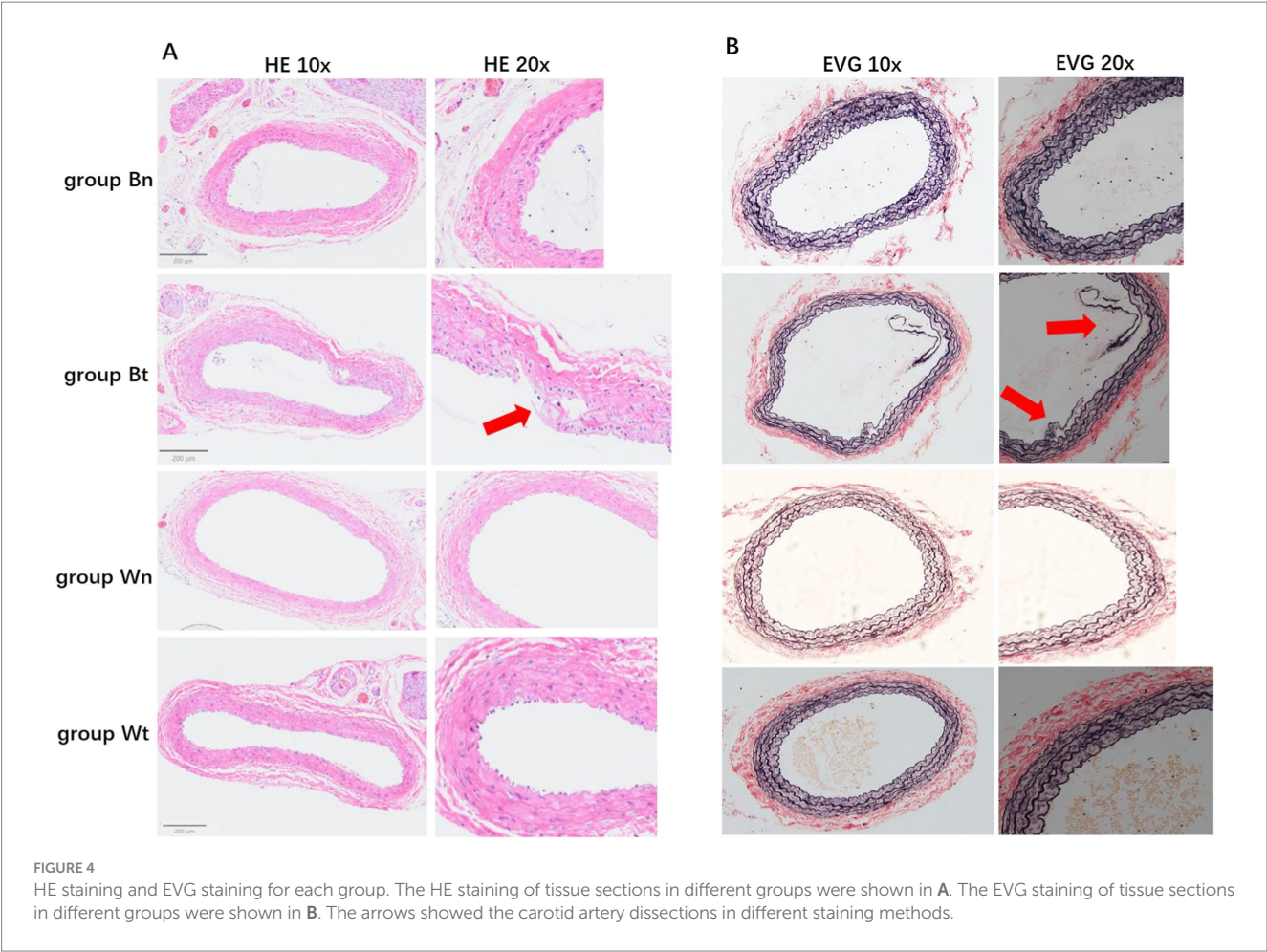


FIGURE 3 The anatomical pictures of model rats and carotid artery dissection sample. The example of surgical incision was shown in A. The isolated carotid arteries of rats and the wall hematoma caused by carotid artery dissection after modeling were shown by arrows in B–D.

Contractile protein of vascular smooth muscle cell

To investigate the effect of the arterial dissection on the contractile protein of vascular smooth muscle cell (VSMC),

we detected a-SMA and SM22a levels in walls of dissected vessels versus normal vessels by immunofluorescence staining. The expression of a-SMA and SM22a proteins in group Bt, group Bn and group Wt was decreased significantly compared with group Wn (a-SMA: $p < 0.001$; $p < 0.001$; $p = 0.0011$, SM22a: both $p < 0.001$).



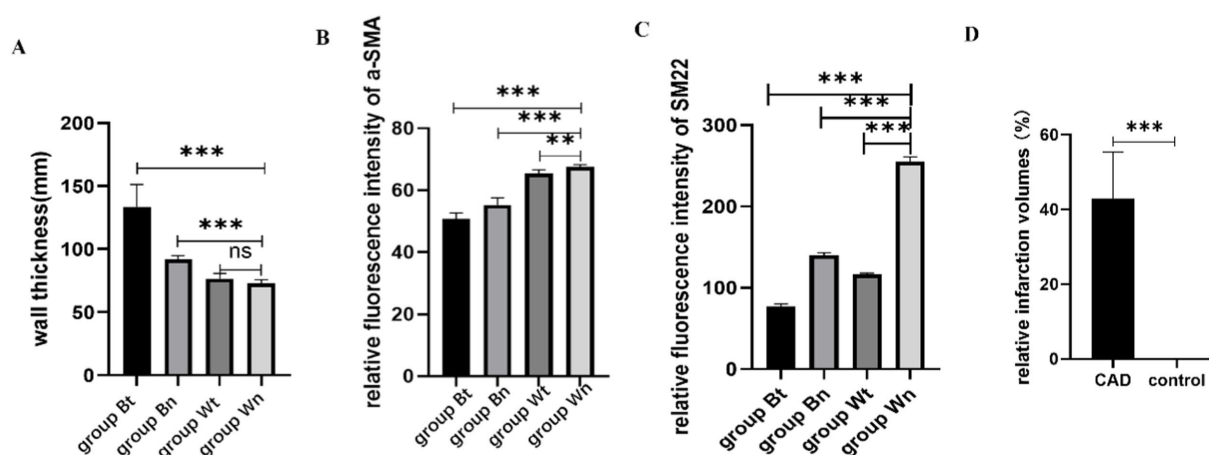


FIGURE 6

The statistical results of average wall thickness, expression levels of contractile proteins and relative infarction volumes. The average thickness of the walls in group Bt and group Bn were significantly thicker than that in group Wn. There was no significant difference between group Wt and group Wn in average wall thickness (A). The expression of a-SMA protein in group Bt, group Bn and group Wt were significantly decreased compared with group Wn. The decrease in group Bn and group Wt were not as obvious as that in group Bt (B). The expression of SM22a protein in group Bt, group Bn and group Wt were significantly decreased compared with group Wn. The decrease in group Bn and group Wt were not as obvious as that in group Bt (C). The relative infarction volumes of CAD group rats were significantly larger than control group (D).

However, a-SMA and SM22a levels in group Bn and group Wt were similar (Figures 6B,C, 7A–H).

Neurological function in CAD model

After completing the modeling process, we compared the neurological function between the CAD group and the control group to verify the neurological deficits of the rat model. The CAD group was composed of 5 rats with carotid artery dissection from Bt group. The control group was composed of 5 rats that were randomly selected from Wn group. Eight-point Roger scale and hot plate test were used to evaluate the motor and sensory function, respectively. The average Roger score of CAD group was significantly higher than that of control group (3.4 ± 1.3 vs. 0 , $p = 0.0004$). Average response time of CAD group was significantly longer than that of control group (6.6 ± 1.3 s vs. 3.8 ± 0.83 s, $p = 0.0036$) (Table 3).

The volume of the infarct area in successful model with carotid dissection

We compared the volume of the infarct area between the CAD group and the control group to verify the validity of the rat model. The CAD group was composed of 5 rats with carotid artery dissection from Bt group. The control group was composed of 5 rats that were randomly selected from Wn group. The relative infarction volumes of CAD group rats were significantly larger than control group ($46.87\% \pm 12.47\%$ vs. 0 , $p < 0.001$) (Figure 6D). Figure 8 showed a comparison of the brain sections of the rat with the most severe neurological deficits in the CAD group versus those in the control group.

Discussion

CAD represents an important cause of stroke in young and middle-aged adults. However, due to the lack of suitable animal models, researches on the pathogenesis of CAD remains scarce (11). Therefore, it is meaningful to establish a high-incidence and low-mortality CAD model.

Previous studies related to aortic dissection have focused on genetic susceptibility and pathogenesis (12). There are many animal models of aortic dissection, including mice, rats, rabbits, dogs, and pigs. Methods of model establishment mainly include surgical intervention, drug induction and gene knockout. Among them, balloon dilatation and local trypsin injection were mainly used in large animals, while drug induction was mainly used in small animals. Balloon dilatation and local trypsin injection were limited due to difficult operation, but Ang II and BAPN were widely used to induce aortic dissections or aneurysms. Drug designs varied in different studies which included the administration of BAPN alone, the combination of BAPN and AngII, and the simultaneous administration of BAPN and Ang II (13–15).

As an irreversible lysyl oxidase inhibitor, BAPN can competitively bind to elastin or amino and alkyl groups, thereby inhibiting the cross-linking of elastin to collagen (16). Treatment with BAPN resulted in thickening of the tunica media of large arteries, irregularities in the arrangement of elastin and collagen fibers, and necrosis. These pathological conditions are consistent with lesions of human arterial dissection. Previous studies indicated that high BAPN concentration was more likely to lead to aneurysm formation and increased mortality, so we fed rats with a lower concentration at 0.25% (16–18). However, the pathogenesis of carotid artery dissection is not exactly the same as that of aorta, especially in terms of mechanical injury, such as massage, yoga, etc., which is considered to

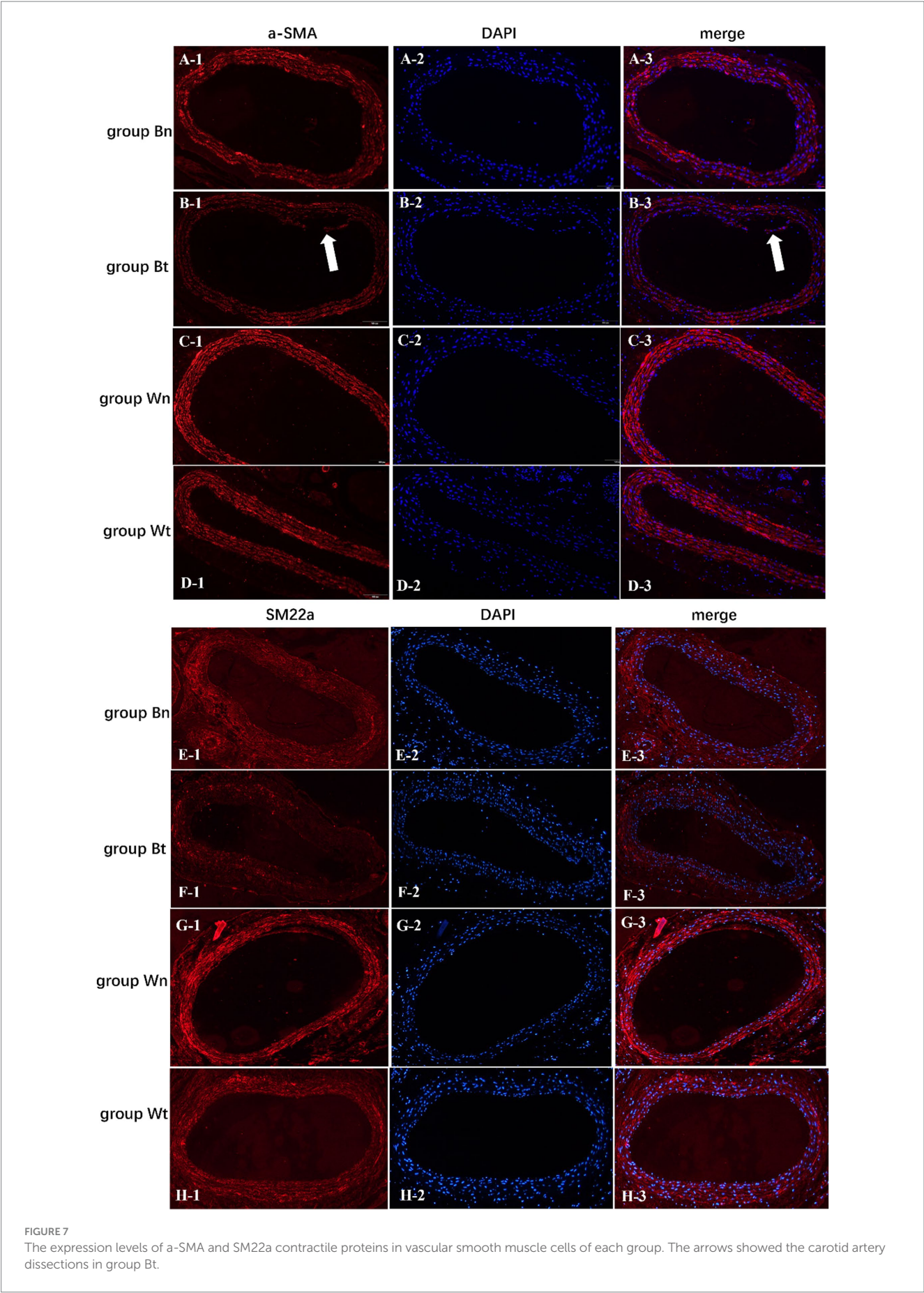
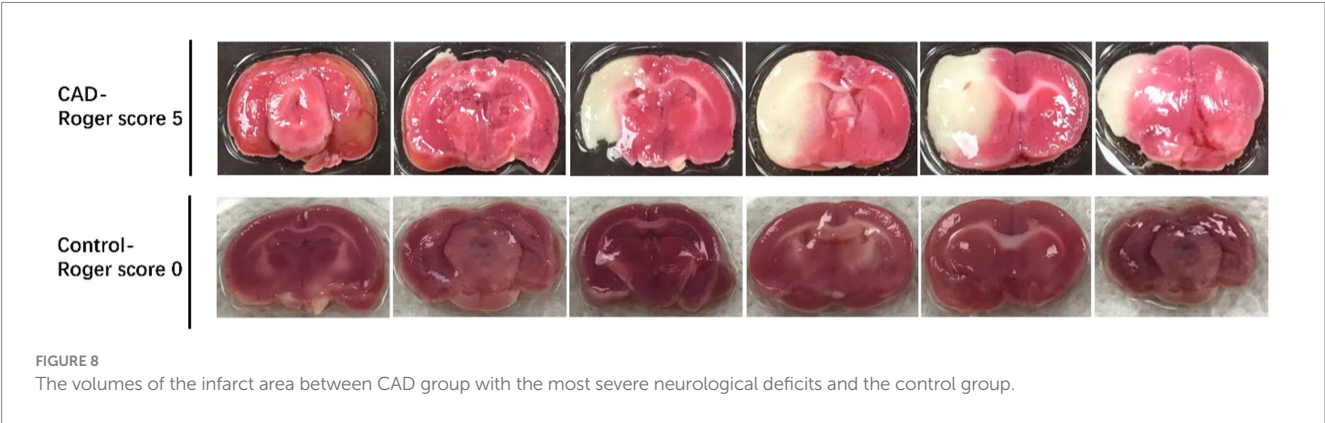


TABLE 3 Roger's score and time of hot plate test between CAD group and control group.

Group	CAD	Control	<i>p</i>
Roger score	3.4 ± 1.3	0	0.0004
Time (s)	6.6 ± 1.3	3.8 ± 0.83	0.0036



be inseparable from the occurrence of carotid artery dissection. In this study, we made a new attempt to choose 0.25% BAPN solution combined with carotid artery torsion to establish CAD models rather than the classical method in previous aortic dissections models. The animal mortality was low and the model formation rate was high in our study. Moreover, compared with the control group, we also observed that arterial walls of the CAD are significantly thickened, the number of VSMCs is increased, and the arrangement of elastic fibers is disordered.

We chose the three-week-old SD rats for modeling because at this rapid growth stage, BAPN could inhibit the generation of the ECM in large arteries, which then led to formation of aneurysms or aortic dissections easily (17–19).

The destruction of structural and functional integrity of the vessel wall are essential pathological changes in arterial dissection (20). The α -SMA and SM22a are generally referred to as “contractile” isoforms mostly expressed in vascular smooth muscle (21, 22). Previous studies suggested that mutations in ACTA2, the gene encoding α -SMA, are the most frequent cause of non-syndromic, heritable thoracic aortic aneurysms and dissection (23). As VSMC-specific contractile proteins, α -SMA and SM22a are characterized by reduction in both thoracic and abdominal aneurysmal aortic tissues (24). Therefore, α -SMA and SM22a were commonly used as markers to reflect the function of VSMC. In this study, significantly lower α -SMA and SM22a levels were observed in the carotid artery walls of successfully modeled CAD rats compared to controls.

In addition to the vessel wall lesions, we also detect the infarct area of brain and neurological deficits in rats with carotid dissection to verify the validity of the rat model. Rats with severe carotid artery dissection were noticed to have larger infarcts in the areas of the brain which were supplied by the carotid artery. Accordingly, the neurological deficit scores of the rats were also high. These results were consistent with clinical manifestations of carotid dissection in humans. In fact, not all CAD patients develop severe clinical symptoms (25, 26).

During our modeling process, changes of each factor influencing the pathological mechanisms of carotid dissection were assessed.

We found that the incidence of dissection was low in both group Bn and group Wt, but when the two conditions were combined, the incidence in group Bt was significantly increased. These results were consistent with the pathophysiology of carotid dissection in humans, that is, external injuries, yoga, and massage are prone to cause carotid artery dissection (27, 28), and also reflected the rationality of our methods.

This study has some limitations. First, the sample size is small, and the stability of the model requires multiple experiments with larger sample sizes. In addition, this animal model could not simulate carotid arterial dissection caused by specific mechanisms, such as genetic mutations. However, an animal model that can mimic the pathophysiological mechanism of carotid artery dissection remains lacking to date, so our approach might be used in future studies as an innovative attempt.

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 animal study was approved by Institutional Animal Care and Use Committee of Huashan Hospital, Fudan University. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

SZ: Conceptualization, Data curation, Formal analysis, Writing – original draft. ZH: Writing – review & editing, Project administration, Resources. YC: Writing – review & editing, Data curation, Formal

analysis. WW: Writing – review & editing, Methodology, Resources, Supervision. YL: Methodology, Writing – review & editing. SY: Writing – review & editing. XF: Data curation, Writing – review & editing, Methodology. CY: Writing – review & editing, Data curation. ZZ: Writing – review & editing. QD: Project administration, Resources, Supervision, Writing – review & editing. XH: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

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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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Subtemporal approach for posterior communicating artery aneurysms

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Background and objectives: Direct visualization of the aneurysmal neck and its related perforating arteries during microsurgical clipping of posterior communicating artery (PCoA) aneurysms with posterior projection or true PCoA aneurysms through the pterional approach may be difficult and complicated.

Methods: From January 2022 to January 2023, the clinical and angiographic information regarding PCoA aneurysms were retrospectively collected. Among them, 10 consecutive patients with PCoA aneurysms treated with microsurgical clipping via the subtemporal approach in our single institution were included. Herein, we analyzed and summarized our experience and clinical outcomes to further evaluate the efficacy, safety and feasibility of this approach as well as the indications.

Results: All aneurysms were completely clipped via the subtemporal approach. With respect to procedure-related complications, postoperative oculomotor nerve palsy occurred in one patient (10%), contralateral cerebral infarction in one patient (10%), and intraoperative rupture of the aneurysm in three patients (30%). There were no cases of temporal lobe contusion or venous injury in this group. Overall, Good outcomes were obtained in 9 patients (90%), and poor functional outcome was observed in 1 patient (10%) at the last follow-up.

Conclusion: The management of true PCoA aneurysms and PCoA aneurysms projecting posteriorly is more complicated and challenging, and treating these lesions entails considerable risks via the pterional approach. Considering the above problems, we attempted to treat these refractory PCoA aneurysms through the subtemporal approach. Our results suggested that microsurgical clipping of these aneurysms via the subtemporal approach can achieve good clinical outcomes with a high preservation rate of the related branches. Appropriate patient selection, fully grasp of indications, precise understanding of the anatomy and thorough preoperative planning are crucial for successful surgery. The subtemporal approach appears to be a relatively safe and effective procedure in the experienced hands, and may be an alternative method for patients with true PCoA aneurysms or projecting posteriorly PCoA aneurysms which cannot be easily clipped from the pterional approach. It can provide a better lateral view to visualize the neck of the aneurysm, PCoA and its perforating vessels, as well as the other structures.

KEYWORDS

posterior communicating artery, aneurysm, subtemporal approach, clipping, pterional approach

Introduction

Posterior communicating artery (PCoA) aneurysms reportedly account for approximately 25% of intracranial aneurysms (1), usually originating from the junction of the internal carotid artery (ICA) and PCoA. However, an aneurysm that involves the PCoA itself, is located at some distance away from the junction of the ICA, which is known as a true PCoA aneurysm (2). A true PCoA aneurysm is relatively rare, with an incidence of approximately 0.1 to 3.6% (3, 4). PCoA aneurysms almost always arise from the superior aspect of the PCoA along the lateral surface of the ICA (5). PCoA aneurysms have various projection directions, and most of them can be clipped through the standard pterional approach. However, for true PCoA aneurysms and PCoA aneurysms projecting posteriorly, there are higher incidences of procedure-related complications than those with other origins and projections (6–8). Because the posterior surface of the ICA is challenging to directly visualize using the standard pterional approach, and the main body of aneurysms is obscured by the ICA, it is difficult to identify the PCoA and to confirm the patency of the parent artery and the related perforating arteries during clip placement. This makes microsurgical clipping more complicated via the standard pterional approach. Considering the above problems, we attempted to treat these refractory PCoA aneurysms by the subtemporal approach for a better view of the aneurysmal neck and other neurovascular structures. Here, we summarized our experiences and clinical outcomes of the subtemporal approach for microsurgical clipping these PCoA aneurysms, and to further evaluate the efficacy, safety and feasibility of this approach as well as the indications.

Materials and methods

Patient population

From January 2022 to January 2023, the clinical and angiographic information regarding PCoA aneurysms were retrospectively collected and analyzed. Patients with PCoA aneurysms projecting posteriorly or originating from the PCoA itself treated by microsurgical clipping via the subtemporal approach were included in this study. Patients with incomplete clinical data or treated by other surgical methods or approaches were excluded. A total of 10 patients with PCoA aneurysms met the above criteria in our institution were retrospectively reviewed. In general, treatment strategies and choices were discussed with a multidisciplinary team including neurosurgeons and neurointerventionists. The study was approved by the medical ethics committee of our hospital. Written informed consent for our procedures was obtained from individuals or their legal guardians.

Demographic data recorded for each patient included age, gender, initial clinical presentation, and functional status. All patients underwent three-dimensional computed tomography angiography (CTA) and digital subtraction angiography (DSA) to diagnose and

evaluate the characteristics of PCoA aneurysms. The size of the aneurysm, aneurysmal neck, shape, rupture status of the aneurysm, presence of fetal-type PCoA, location and projecting direction, and surgical complications were detailed record. The size of the aneurysm was defined as the maximum measurement diameters of aneurysm height or aneurysm width. Projection directions and origin of the aneurysm were confirmed mainly according to the anteroposterior- and lateral-view carotid angiograms or three-dimensional DSA. Posterior-projecting aneurysms were previously defined as aneurysms projecting $\geq 45^\circ$ posteriorly to the line perpendicular to the midline (6). The characteristics and clinical outcomes of PCoA aneurysms are described in Table 1.

Subtemporal approach

The patient was placed supine on the table with a shoulder pillow beneath the ipsilateral shoulder. The head was rotated until the temporal region lay horizontal with the vertex down, then slightly drooped and overall elevated above the heart level. A modified straight incision was made from the base of the zygomatic arch to the parietal tuber. The skin and temporalis muscle were stratified dissection, the temporalis muscle was pulled sideways to expose the skull. A subtemporal craniotomy was performed. After the removal of the bone flap, part of the bone from the temporal squama to the floor of the temporal fossa was fully removed to expose the base of the middle cranial fossa. The dura was then opened to expose the surface of the temporal lobe. Under an operating microscope, the temporal lobe was retracted with malleable brain retractors to expose the free margin of the tentorium. The arachnoid covering the perimesencephalic cistern was meticulously incised to further release cerebrospinal fluid and allow brain relaxation. The course of ICA, PCoA, and its relation to the position of aneurysm were identified. Dissect and expose the proximal ICA for the proximal control to prevent intraoperative uncontrollable aneurysmal hemorrhage. A part of the aneurysm could be covered by the tentorial edge, in order to obtain sufficient surgical exposure and wider operating space, we need to incise the tentorium. The aneurysmal neck is clipped by a straight or bayonet aneurysm clip. In the process of aneurysm clipping, the PCoA and its related perforators should be avoided from being injured or accidentally clipped. After the clipping of the aneurysm, the dura membrane was tightly sutured. The bone flap was restored and affixed, and the temporalis muscle and scalp were sutured by layers.

Outcome assessment

To evaluate the efficacy of intraoperative observation of the aneurysm and preservation of the relevant branches, complete occlusion of the aneurysm, and procedural-related complications by the subtemporal approach. The results of surgical treatment were assessed based on intraoperative indocyanine green angiography (ICGA) and postoperative cerebral angiography, and then graded as completely or partially clipped. Postoperative complications were recorded, a hemorrhagic complication was confirmed by postoperative computed tomography (CT), and magnetic resonance imaging (MRI) was performed to evaluate ischemic lesions.

Abbreviations: AChA, Anterior choroidal artery; CT, Computed tomography; CTA, Computed tomography angiography; DSA, Digital subtraction angiography; ICA, Internal carotid artery; ICGA, Indocyanine green angiography; MRI, Magnetic resonance imaging; mRS, Modified Rankin Scale; PCoA, Posterior communicating artery; PCA, Posterior cerebral artery; SAH, Subarachnoid hemorrhage.

TABLE 1 The characteristics and clinical outcomes of posterior communicating artery aneurysms.

Patient	Age (years), sex	Presentation	Status	Hunt–Hess grading system	GCS	Initial mRS	Size (mm)	Direction	Site of origin	Side	Intraoperative rupture	Complications	Postoperative mRS
1	66, F	Headache with nausea and vomit	Ruptured	1	15	1	2.37	Lateral	PCoA itself	Left	Yes	Infarction	3
2	63, F	Headache and vomit	Ruptured	1	15	1	3.71	Posterior	ICA-PCoA junction	Left	No	No	1
3	77, M	Headache with ptosis	Unruptured	0	15	1	5.85	Posterior	ICA-PCoA junction	Left	Yes	No	1
4	65, F	Dizziness	Unruptured	0	15	1	3.75	Posterior	ICA-PCoA junction	Left	No	Oculomotor nerve palsy	1
5	73, F	Headache	Ruptured	3	14	1	3.11	Posterior	ICA-PCoA junction	Left	No	No	1
6	68, F	Dizziness	Unruptured	0	15	1	3.57	Posterior	ICA-PCoA junction	Right	No	No	1
7	71, F	Headache	Ruptured	1	15	1	5.32	Posterior	ICA-PCoA junction	Left	Yes	No	1
8	67, F	Dizziness	Unruptured	0	15	1	1.83	Posterior	ICA-PCoA junction	Right	No	No	1
9	72, F	Headache	Ruptured	3	14	1	3.91	Posterior	ICA-PCoA junction	Left	No	No	1
10	65, M	Nausea	Ruptured	1	15	1	4.31	Posterior	ICA-PCoA junction	Right	No	No	1

GCS, Glasgow Coma Scale; ICA, internal carotid artery; mRS, Modified Rankin Scale; PCoA, posterior communicating artery.

Follow-up DSA or CTA was performed to evaluate the recurrence of the aneurysm. Functional status was assessed by the modified Rankin Scale (mRS), the pre-operative mRS and follow-up information was obtained from hospital admission physical examination and hospital records. We noted the mRS score at the time of each visit and angiography. A good outcome was defined as a mRS score of 0–2 at the last clinical follow-up and a bad outcome as a mRS score of 3–6.

Statistical analysis

All statistical analysis was performed with the standard software (SPSS v23; SPSS, Chicago, IL). Continuous data was expressed as mean $\pm$ standard deviation (SD). The frequencies and percentages of categorical variables are reported.

Results

These 10 patients comprised 2 men (20%) and 8 women (80%), with a mean age of 68.70 ± 4.40 years (ranging from 63 to 77 years). The majority of patients ($n = 6$; 60%) presented with subarachnoid hemorrhage (SAH), of which 4 were Hunt–Hess grade I, 2 were grade III, all of them had a good neurologic grade (World Federation of Neurosurgical Societies grade I to II). Of the remaining 4 (40%) patients with unruptured aneurysms, 1 presented with headache with oculomotor nerve palsy, and 3 presented with dizziness. There was no aneurysmal SAH with associated intracranial hematoma cases in this group. There were 7 aneurysms located on the left side, and 3 on the right. The aneurysms ranged in size from 1.83 to 5.85 mm, with an average diameter of 3.77 ± 1.21 mm. There were 8 small (<5 mm) and 2 medium (5–10 mm) aneurysms. One aneurysm arises from the proximal portion of the PCoA itself, and the remaining nine aneurysms originate from the junction of the ICA and PCoA. Among these patients, 9 PCoA aneurysms project posteriorly and 1 true PCoA aneurysm laterally. All aneurysms were completely clipped via the subtemporal approach. The course of PCoA and its related perforating arteries were intraoperatively identified and preserved in all cases. With respect to the procedure-related complications, postoperative oculomotor nerve palsy occurred in one patient (10%), contralateral cerebral infarction in one patient (10%), and intraoperative rupture of the aneurysm in three patients (30%). Among the 3 aneurysms that ruptured during the operation, 1 was a small-size ruptured true PCoA aneurysm and 2 were medium-size PCoA aneurysms. Of the two medium-sized aneurysms, one was ruptured aneurysm and the other was unruptured aneurysm. Unfortunately, the patient with cerebral infarction was discharged from the hospital with neurological deficits. The initial mRS score of the patient was 1, and the postoperative neurological status deteriorated, with an mRS score of 3. The patient with oculomotor nerve palsy completely recovered within 1 month after surgery. There were no cases of temporal lobe contusion and venous injury after surgery in this group. Overall, Good outcomes were obtained in 9 patients (90%), and poor functional outcome was observed in 1 patient (10%) at the last follow-up. All aneurysms were completely occluded, and no

recurrence of PCoA aneurysms or new neurological deficits occurred during the follow-up period.

Illustrative cases

Patient 1 (Figure 1) was a 66-year-old woman who suddenly suffered a headache with nausea and vomit for one day. Her past medical history was unremarkable, and she did not take any regular medication. Neurological examinations at admission showed that the Hunt–Hess grade was I. Head CT (Figure 1A) showed a diffuse SAH in the basilar cistern, and CTA (Figure 1B) revealed the laterally projected PCoA aneurysm on the left side. Preoperative three-dimensional DSA of the left ICA (Figure 1C) manifested that the aneurysm was about 2.37×1.68 mm, arising from the PCoA itself, a few millimeters away from the junction with ICA. The subtemporal approach combined with the pterional approach was performed for this ruptured true PCoA aneurysm. We observe the morphology, position and projection of the aneurysm under different surgical approaches. After the Sylvian cistern was dissected and opened, the ICA was exposed. We observed that the aneurysm was approached through the standard pterional approach but could not be visualized well, and the PCoA and its perforating arteries were not clearly shown, because the greater part of the aneurysm was hidden behind the ICA and the left temporal lobe (Figure 1D). Surgical clipping of the aneurysm through the standard pterional approach may result in a residual aneurysm neck in the shape of “dog ear” and incomplete obliteration of the aneurysm. Anterior clinoid process may need to be drilled to increase operative space for clipping. A more lateral approach than the pterional approach may be thus required to clip this aneurysm. Then we retracted the temporal lobe and cut the arachnoid trabeculae via the subtemporal approach to expose the aneurysm and confirm the origin and course of the PCoA. The subtemporal approach offers a more lateral line of vision and allows the surgeon to well visualize the aneurysmal neck and the PCoA (Figure 1E). During the operation, we found the dome of the aneurysm projected laterally. The aneurysm was ruptured when dissecting and separating the neck of the aneurysm. Under direct visual control and point-suction, the bleeding was effectively controlled, and the aneurysm was successfully obliterated with two straight titanium clips (Yasargil titanium clip; No. FT710T and No. FT740T; Aesculap AG, Tuttlingen, Germany) (Figure 1F). Intraoperative ICGA demonstrated complete occlusion of the aneurysm and the patency of both the PCoA and its perforating arteries. The postoperative head CT (Figure 1G) revealed right occipital lobe infarction and no secondary hemorrhage. The initial mRS score of the patient was 1, and the postoperative neurological status deteriorated, with an mRS score of 3. We speculate that the cause of cerebral infarction may be associated with severe stenosis of the P2 segment of the right PCA and vasospasm. Unfortunately, the patient was discharged from the hospital with neurological deficits.

Patient 8 (Figure 2) was a 67-year-old woman who suffered dizziness over 2 years. She had a 10-years history of hypertension and hyperlipidemia. On admission, neurological examinations revealed no focal neurological deficits. Initial head CT showed no evidence of intracranial hemorrhage and infarction. Preoperative three-dimensional DSA with a lateral (Figure 2A) view of the right ICA showed an aneurysm arising from the communicating segment of right ICA. The saccular aneurysm is about

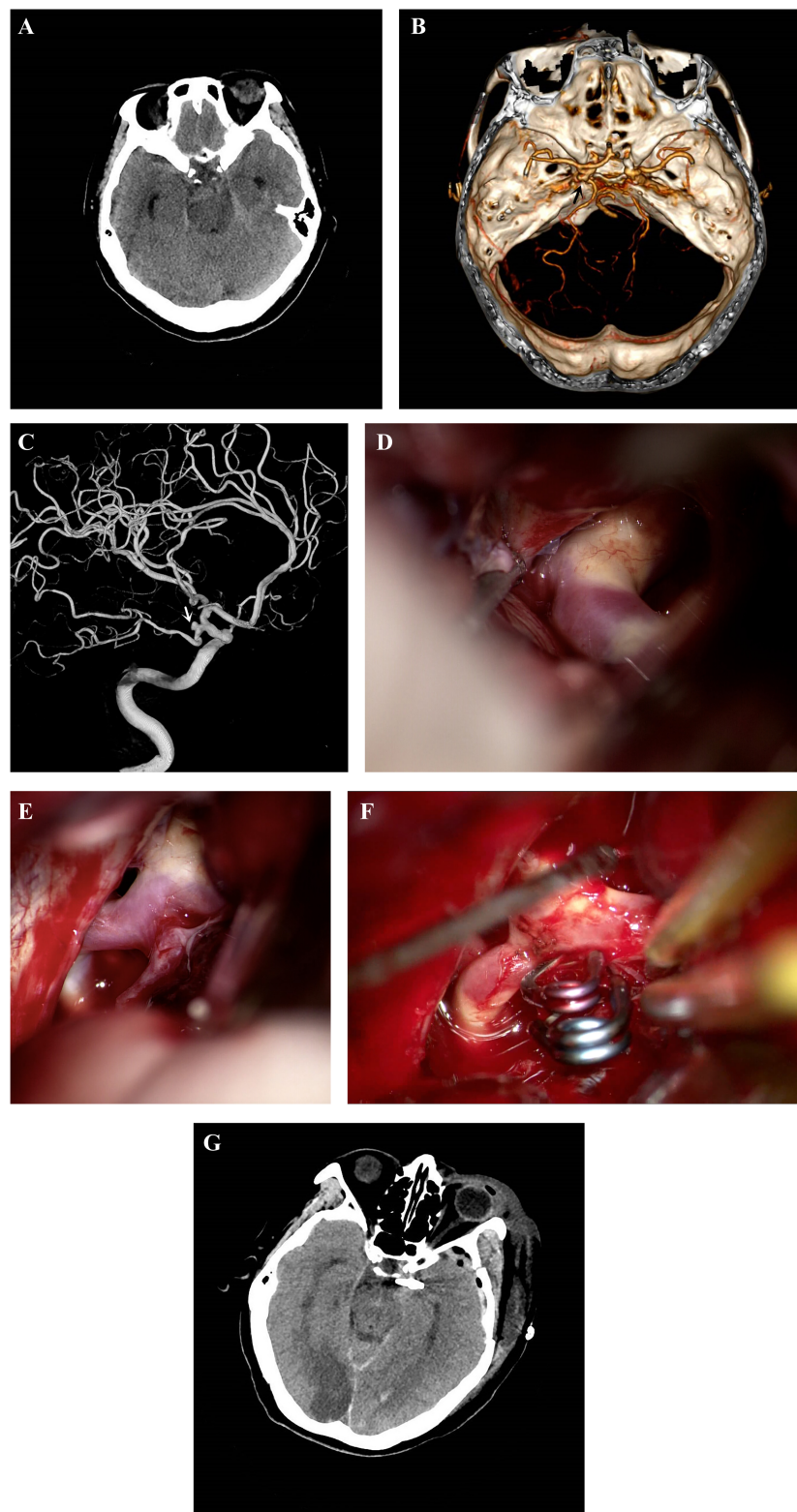


FIGURE 1

Patient 1. Head CT (A) showed a diffuse SAH in the basilar cistern. CTA (B) revealed the laterally projected PCoA aneurysm (black arrow) on the left side. Preoperative three-dimensional DSA (C) of the left ICA manifested that the aneurysm (white arrow) was about 2.37 × 1.68 mm, arising from the PCoA itself, a few millimeters away from the junction with ICA. Intraoperative observation (D) from the standard pterional approach showed that the greater part of the aneurysm was hidden behind the ICA and the left temporal lobe. The subtemporal approach (E) offers a more lateral line of vision to well visualize the aneurysmal neck and the PCoA. The aneurysm was successfully and safely obliterated with two straight titanium clips (Yasargil titanium clip; No. FT710T and No. FT740T; Aesculap AG, Tuttlingen, Germany) (F). The postoperative head CT (G) disclosed right occipital lobe infarction and no secondary hemorrhage. CT, computed tomography; CTA, computed tomography angiography; DSA, digital subtraction angiography; ICA, internal carotid artery; PCoA, posterior communicating artery; PCA, posterior cerebral artery; SAH, subarachnoid hemorrhage.

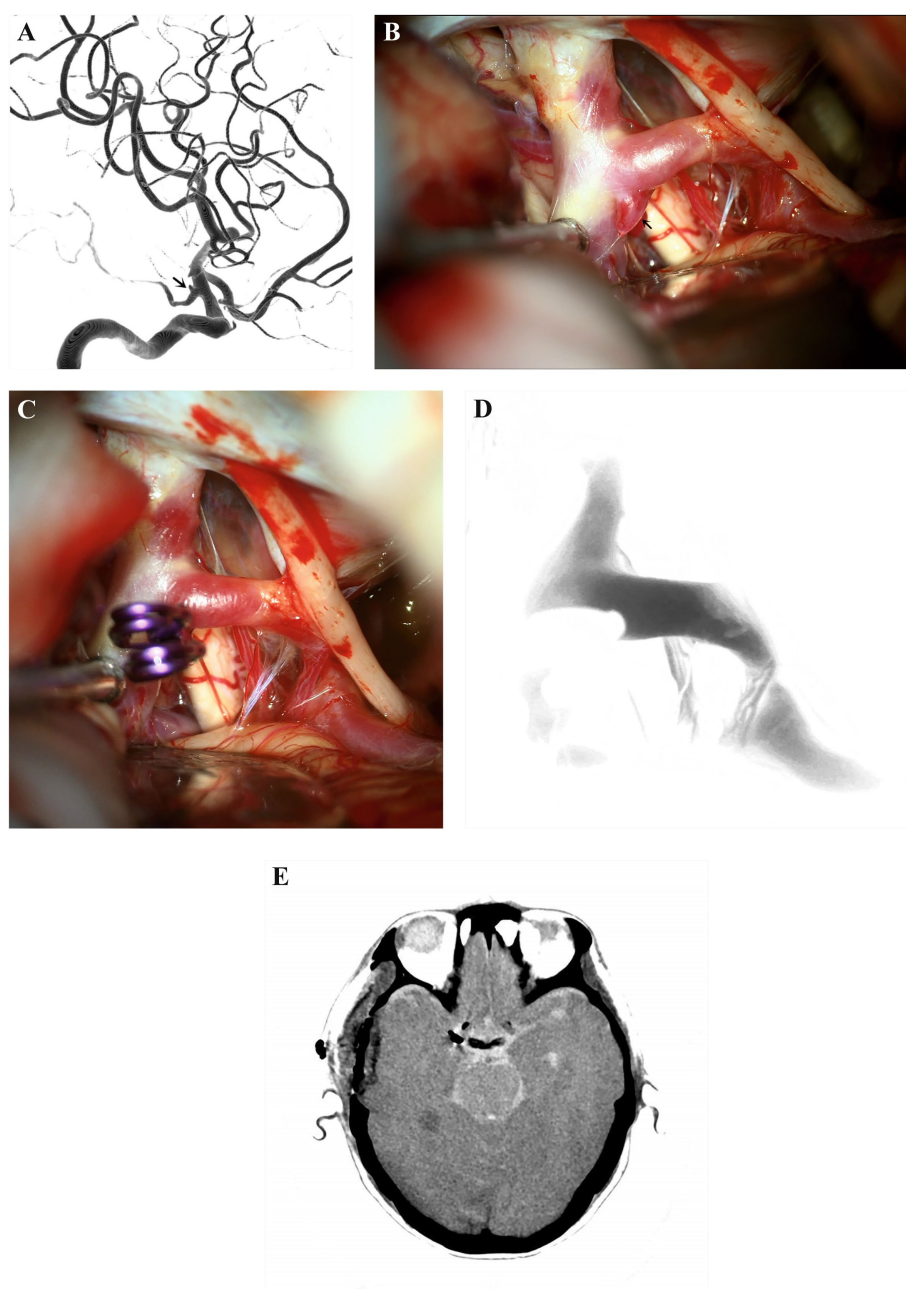


FIGURE 2

Patient 8. Preoperative DSA (A) with lateral view of the right ICA showed a saccular aneurysm (white arrow) arising from the communicating segment of the left ICA. The aneurysm is about 1.02×31.83 mm in size, and the dome of the aneurysm is projected posteriorly. The aneurysm (black arrow) was approached and well visualized through the subtemporal approach (B). The aneurysm was completely clipped with two straight titanium clips (Yasargil titanium clip; No. FT710T; Aesculap AG, Tuttlingen, Germany) (C). Intraoperative ICGA (D) confirmed that the aneurysm is clipping completely and patency of the PCoA and perforating arteries. The postoperative head CT (E) showed no cerebral infarction, temporal lobe contusion and secondary hemorrhage. CT, computed tomography; DSA, digital subtraction angiography; ICA, internal carotid artery; ICGA: indocyanine green angiography; PCoA, posterior communicating artery.

1.02×1.83 mm in size, and the dome of the aneurysm is projected posteriorly. The patient underwent the right subtemporal approach for microsurgical clipping. The temporal lobe was retracted and the arachnoid was dissected to expose the aneurysm. The aneurysm was approached and well visualized through the subtemporal approach (Figure 2B). Two straight titanium clips (Yasargil titanium clip; No. FT740T; Aesculap AG, Tuttlingen, Germany) were used to ensure complete occlusion of the aneurysm

(Figure 2C). Finally, intraoperative ICGA (Figure 2D) was applied to confirm the aneurysm clipping completely and patency of the PCoA and perforating arteries. The postoperative course of the patient was uneventful, and head CT (Figure 2E) showed no cerebral infarction, temporal lobe contusion and secondary hemorrhage. The patient was discharged without any neurological deficits. The aneurysm was successfully obliterated, and there were no *de novo* aneurysms during follow-up angiograms.

Discussion

Intracranial aneurysms tend to occur at the bifurcation of the cerebral arteries, and the PCoA junction is the most common site (5). The goal of treatment for these PCoA aneurysms is to obliterate the aneurysm as well as preserve the PCoA and the related branches. The success rate of microsurgical clipping is associated with precise anatomical knowledge, well-organized surgical planning and appropriate surgical approach. For PCoA aneurysms, multiple surgical approaches can be adopted. Although each of the PCoA aneurysms is unique and may require modification of the surgical techniques and approaches based on different anatomical variations, the general principles for safe microsurgical clipping are the same. Therefore, it is of great importance to evaluate the aneurysmal size, location, direction, shape, and neck of the aneurysm as well as the relationship between the aneurysm and parent artery and perforator vessels in detail before formulating the optimal treatment strategies and surgical approach. The size, position and direction of PCoA aneurysm projection may directly affect the choices of surgical approaches.

In this study, we presented a series of PCoA aneurysms projecting posteriorly or originating from the PCoA itself. For these cases, it needs to visualize the aneurysmal neck through the retrocarotid space. In the pterional approach, it allows for a wide range of inclinations for the clip-applying forceps. When microsurgery is performed to clip these PCoA aneurysms via the pterional approach, the PCoA and its associated branches may be compromised, which requires more complex and sophisticated clipping techniques with fenestrated clips or a more lateral surgical exposure. However, the postoperative complications of PCoA aneurysms projecting posteriorly or originating from the PCoA itself are significantly higher than those PCoA aneurysms with lateral projection or at other sites (7, 9). Because PCoA aneurysms with posterior projection are more likely to adhere to the PCoA or its associated perforating arteries, the application of fenestrated clips may unintended clip the perforating arteries, and true PCoA aneurysms often involving the fetal PCoA, which are more prone to cause intraoperative rupture during the dissection of these aneurysms (7, 9). Moreover, true PCoA aneurysms may be located at the infundibular dilatation of the PCoA or close to the ICA, at the middle part of the PCoA, or proximal to the PCA, and the whole aneurysm or most of the aneurysm may be buried in the temporal lobe. Thus, it is useful and necessary to retract the temporal lobe via the pterional approach during the exposure of the aneurysmal neck, which may lead to aneurysm premature rupture and bleeding. However, intraoperative bleeding cannot be sufficiently controlled by the temporary clip of the proximal ICA or fetal PCoA alone for true PCoA aneurysms, as the blood flow can be refluxed from posterior circulation via distal fetal PCoA. Intraoperative rupture of PCoA aneurysms and uncontrolled bleeding may cause serious complications. Therefore, we try to adopt the subtemporal approach rather than the pterional approach to obliterate these refractory aneurysms.

The subtemporal approach was first proposed by Drake for the treatment of basilar artery aneurysms (10). The subtemporal approach is more laterally positioned relative to the pterional approach. We performed the preoperative CTA or fusion image of three-dimensional DSA and Xper-CT to evaluate the position relationship between aneurysms, parent artery, perforating arteries and anterior clinoid process. Aneurysms were placed at

the pterional approach and the subtemporal approach respectively, and then we found that it was difficult to completely expose and visualize the neck of the aneurysm as well as the PCoA and its perforating arteries in the pterional approach. In order to achieve a satisfactory surgical visualization, the angle of the operating microscope can be adjusted or the patient's head can be rotated to the contralateral side. In addition, an endoscope or even a surgical mirror can be used to observe the aneurysm before clip application and to detect any remaining neck of the aneurysm after clip application. But in fact, these devices cannot improve the available space in a narrow retrocarotid space (11). Thus, to obtain a wider operating space for the exposure and occlusion of the aneurysm through the standard pterional approach, we may need to drill off the anterior clinoid process and open the optic nerve canal, then incise carotid dura ring to mobilize the ICA and optic nerve. The subtemporal approach provided the more better lateral view, it may be possible to visualize the whole length of the PCoA, and its perforating vessels as well as a better observation of the neck of the aneurysm, which is facilitated to block the parent vessels, clip the aneurysms, and reduce postoperative complications. It also provided a short operative distance and a direct trajectory to the aneurysm, with less dissection to expose the aneurysm, which helps to protect the perforating arteries. When the temporal lobe was progressively retracted and the arachnoid was sharply dissected, the ipsilateral tentorium cerebelli may interfere with the visibility and manipulation around the aneurysmal neck. So in some cases, we need to cut and divide the tentorium cerebelli to further obtain a sufficient operative field and expose the neck of the aneurysm. For the present series of cases, the tentorium cerebelli was cut in four of the patients. It's worth noting that the aneurysms are located around or under the tentorial edge. What's more, the excessive retraction of the temporal lobe will increase the potential risk of temporal lobe contusion and vein injury. The rate of temporal lobe contusion is approximately 14% in other surgical approaches for PCoA aneurysms (12). Fortunately, there were no cases of temporal lobe contusion and venous injury in the current study. During the procedure of aneurysm exposure, adequate release and drainage of cerebrospinal fluid to achieve sufficient brain relaxation, can effectively reduce these risks. In this group of cases, we did not perform external ventricular drainage or lumbar cisterna drainage in advance, and we only released cerebrospinal fluid intraoperatively in a stepwise manner to reduce intracranial pressure. In the present series, one patient presented with preoperative oculomotor nerve palsy, which may be related to the compression of the oculomotor nerve caused by the tiny enlargement or morphological change of the PCoA aneurysm, and another patient (10%) developed transient left oculomotor nerve palsy after surgery, which may be attributable to the separation and traction of the oculomotor nerve or the bipolar coagulator related heat injury. Because the oculomotor nerve has a close relationship to the aneurysm and usually runs below and lateral to the PCoA, and some PCoA aneurysms protruding posteriorly may adhere to the oculomotor nerve, which is prone to cause intraoperative injury. We should be aware of the increased risk of oculomotor nerve injury through the subtemporal approach in comparison with the pterional approach, and should accurately identify the oculomotor nerve and perform sharp dissection of the arachnoid around the nerve as much as

possible. The rate of oculomotor nerve palsy after surgery in other series of subtemporal approaches is approximately 34% (13), and the palsy usually subsides over weeks to months. During the follow-up, the patient's ptosis symptoms were completely relieved. Several important perforating branches arise from the PCoA and supply the optic tract, oculomotor nerve, thalamus, hypothalamus, caudate nucleus, internal capsule and other critical structures (3, 9). The PCoA aneurysm with protruding posteriorly was more likely to adhere to these important branches, and the anterior choroidal artery (AChA) runs very close or attaches to the distal neck of the PCoA aneurysm. The inadvertent injury or occlusion of PCoA, its related perforating arteries and AChA during microsurgical clipping may cause severe neurological deficits, such as hemiparesis and consciousness disturbance. Therefore, it is necessary to preserve and confirm the patency of these vessels, especially when the PCA and PCoA are of fetal origin. These vessels are clearly visible under direct visualization and easily protected via the subtemporal approach. In addition to the extent of surgical exposure of an aneurysmal neck and the preservation of perforating vessels, the controlling of the parent artery is also the key to the successful clipping of aneurysm. Intraoperative uncontrollable premature rupture of PCoA aneurysms is the most catastrophic event, which may lead to massive hemorrhage or cause cerebral ischemia by prolonged application of temporary clip or damage the surrounding tissue in the limited operative field. Temporary clipping of the parent artery can effectively reduce intra-aneurysm pressure, which facilitates the dissection of the aneurysm and reduces the risk of rupture and uncontrollable bleeding (14). The subtemporal approach has a relatively short operative distance and a wide visual field, which is conducive to the temporary clipping of the parent artery. Intraoperative rupture of the aneurysms occurred in three patients and temporary clipping was used in four cases in our cohort, the primary reason for avoiding using temporary clipping was the calcification of the proximal ICA. Intraoperative exposure of the carotid artery from the neck may be necessary for proximal arterial control in these patients with significant ICA calcification. Among the 3 aneurysms that ruptured during the operation, 1 was a small-size ruptured true PCoA aneurysm and 2 were medium-size PCoA aneurysms. Of the two medium-sized aneurysms, one was ruptured aneurysm and the other was unruptured aneurysm. We may assume that the size of the aneurysm is related to intraoperative aneurysm rupture and procedure-related complications, since large aneurysms require more extensive surgical exposure and a wider surgical corridor, increasing the risk of aneurysm rupture. After the aneurysms were successfully clipped, the patency of the PCoA and the related perforator vessels was confirmed mainly by ICGA. In our report, all patients achieved complete occlusion of aneurysm, but only one patient (10%) presented with postoperative contralateral occipital lobe infarction without secondary hemorrhage, which may be associated with severe stenosis of the P2 segment of the right PCA and vasospasm. We considered the subtemporal approach is more suitable for small-size PCoA aneurysms projecting posteriorly and true PCoA aneurysms with different projections than the standard pterional approach. Although this approach provides a more lateral vision for good visualization of the course of the PCoA and its perforators, it carries the potential risk of

temporal lobe contusion and venous injury, as well as oculomotor nerve injury.

Limitations

The number of patients included in this research is relatively small and this study was conducted in a retrospective manner, which may cause some bias. There was no available comparative group to further evaluate the benefits of the subtemporal approach for these aneurysms. In addition to the characteristics of aneurysms, many other factors may affect the choice of surgical approaches, which were not evaluated and discussed in detail in this paper. As stated above, further studies and larger case series may be necessary to assess the efficacy and confirm the durability of this treatment.

Conclusion

The management of true PCoA aneurysms and PCoA aneurysms projecting posteriorly is more complicated and challenging, and treating these lesions entails considerable risks via the pterional approach. Considering the above problems, we attempted to treat these refractory PCoA aneurysms through the subtemporal approach. Our results suggested that microsurgical clipping these aneurysms via the subtemporal approach can achieve good clinical outcomes with a high preservation rate of the related branches. Appropriate patient selection, fully grasp of indications, precise understanding of the anatomy and the hazards associated with PCoA aneurysms, as well as thorough preoperative planning are crucial for successful surgery. The subtemporal approach appears to be a relatively safe and effective procedure in the experienced hands, and may be an alternative method for patients with true PCoA aneurysms or projecting posteriorly PCoA aneurysms which cannot be easily clipped from the pterional approach. It can provide a better lateral view to visualize the neck of the aneurysm, PCoA and its perforating vessels, as well as the other structures.

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 humans were approved by the Ethics Committee of Zhongnan Hospital of Wuhan University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the individual(s) and/or minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

JL: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. XH: Supervision, Writing – review & editing. YL: Supervision, Writing – review & editing. T-bZ: Supervision, Writing – review & editing. J-cC: Data curation, Investigation, Methodology, Validation, Writing – review & editing. Z-wL: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

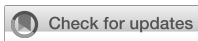
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Multiple burr hole and erythropoietin combination therapy: optimal early surgical intervention for patients with acute stroke episode of moyamoya disease or moyamoya syndrome

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Objective: The optimal timing of bypass surgery for patients with moyamoya disease (MMD) or moyamoya syndrome (MMS) following an acute stroke episode remains unclear, mainly owing to the risk of postoperative complications. In this study, we aim to validate the safety and efficacy of early intervention using multiple burr hole (MBH) and erythropoietin (EPO) therapy, thereby refining the management strategy for patients with acute stroke episode of MMD or MMS.

Methods: We retrospectively analyzed data from 70 patients with MMD or MMS who underwent MBH and EPO therapy. The cohort was divided based on the time interval between the latest neurological deterioration and surgery: early (<30 days) and later (≥30 days) groups. We evaluated and compared perioperative clinical parameters and the extent of neovascularization on a 6-month postoperative angiography. Long-term clinical outcomes, including transient ischemic attack (TIA), infarction, hemorrhage, and seizure, were also analyzed during the follow-up period.

Results: In the cohort, 36 patients (51.4%) were in the early group, whereas 34 (48.6%) were in the later group. The 6-month follow-up angiography demonstrated that 34/47 hemispheres (72.3%) in the early group exhibited successful neovascularization (≥2/3 of MCA territories) compared with the 19/44 (43.2%) hemispheres in the later group (odds ratio [OR] = 3.44; 95% confidence interval [CI]: 1.46–8.45; $p < 0.01$). In addition, a notable reduction (≥50%) in basal moyamoya vessels was observed in 30/47 hemispheres (63.8%) from the early group vs. 12/44 (27.3%) hemispheres from the later group (OR = 4.71; 95% CI: 1.97–11.82; $p < 0.001$). During the average follow-up of 56.5 months, only six patients experienced infarction or hemorrhage.

Conclusion: Our dataset suggests that MBH and EPO combination therapy is an effective, minimally invasive, and acceptable treatment, even in the early period of patients with MMD or MMS following an acute stroke episode.

KEYWORDS

moyamoya disease, moyamoya syndrome, multiple burr hole, erythropoietin, surgical intervention

1 Introduction

Moyamoya disease (MMD) is a progressive angiopathy characterized by stenosis of the supraclinoid internal carotid arteries (ICAs) and the formation of abnormal moyamoya vessels. As the disease progresses to Suzuki stages 5–6, a notable reduction is observed in these moyamoya vessels with increased collaterals, decreasing the risk of ischemia or hemorrhage (1, 2).

Bypass surgery is an essential therapeutic modality for patients with MMD and moyamoya syndrome (MMS), facilitating a safer and expedited transition to Suzuki stages 5–6 and diminishing the long-term risk of stroke (3–6). Notably, direct and indirect bypass surgeries yield beneficial results; however, several studies have reported risks of postoperative stroke and neurological deterioration for patients with acute stroke episode of MMD or MMS. These are attributed mainly to the inherent risks associated with general anesthesia and potential for intraoperative hemorrhage (7–12). Although the risk rates vary across studies, patients undergoing surgical bypass within 90 days from the presentation of acute stroke have been reported to experience postoperative stroke and neurological deterioration in 15–22% and 17–33% of cases, respectively (13, 14).

Notably, during these acute periods, patients most urgently require transdural collaterals and blood flow enhancement, which can be facilitated through bypass surgery. Recognizing this challenge, we have explored the feasibility of using the multiple burr hole (MBH) under local anesthesia as a minimally invasive surgical technique for these high-risk patients (15). In addition, we have also been investigating the potential of using erythropoietin (EPO) as an adjunctive agent in promoting neovascularization (16, 17).

MBH and EPO therapy have been utilized as our institutional strategy to reduce invasiveness and enhance neovascularization. Therefore, in this study, we aimed to ascertain the optimal type and timing of bypass surgery for patients with an acute stroke episode of MMD or MMS. We also compared the clinical and angiographic outcomes between patients who underwent surgery early vs. those who underwent surgery later to investigate the appropriate timing of surgery.

2 Methods

2.1 Study design and patient's selection criteria

In this retrospective study, we evaluated patients diagnosed with MMD or MMS who underwent MBH at a tertiary medical center between April 2011 and August 2022. The study included 70 patients who met the following inclusion criteria: (1) a confirmed diagnosis of MMD or MMS using digital subtraction angiography (DSA), following the guidelines established by the Research Committee on Moyamoya Disease of the Ministry of Health and Welfare of Japan; (2) age ≥ 18 years; (3) absence of previous bypass surgeries; (4) completion of a preoperative DSA within 3 months preoperatively, supplemented

by at least one additional imaging test including perfusion computed tomography (CTP), perfusion magnetic resonance imaging (MRP), or single-photon emission computed tomography (SPECT); and (5) a follow-up DSA performed between 6 and 12 months postoperatively.

Data on outcomes were collected from the electronic medical records system. The Ajou University Medical Center's Institutional Review Board approved this study (AJOUIRB-DB-2023-373).

2.2 Data collection and clinical courses

Demographic data included age, sex, smoking habits, moyamoya laterality, and the presence of comorbid conditions such as hypertension, diabetes mellitus, and dyslipidemia. A “smoker” was defined as an individual who has smoked at least 100 cigarettes in their lifetime and continues to smoke cigarettes at the time of the study. The National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores were measured at three different time points: admission, discharge, and 6 months postoperatively. Patients were categorized into the “early” or “later” groups based on their timing of surgery. The early group comprised patients who had undergone MBH <30 days from the most recent neurological event owing to transient ischemic attack (TIA), ischemic stroke, or hemorrhagic stroke. We defined a neurological events as the occurrence of any neurological symptoms solely related to moyamoya, not due to other causes. Conversely, the later group consisted of patients who had undergone MBH ≥ 30 days from the most recent neurological event. In a previous study analyzing perioperative stroke risk in patients with MMD, “recent stroke” was defined as occurring within 6 weeks (11). However, in our study, we have adopted a narrower timeframe to assess the effects of early intervention more stringently. Patients in the later group mostly underwent surgeries scheduled during outpatient visits and were admitted as regular inpatients for the procedure. Presentation types were categorized into three groups based on the most recent events: TIA, ischemic stroke, or hemorrhagic stroke. During the pre-operative period, clinical courses were evaluated based on the NIHSS score at admission. When the NIHSS score increased by ≥ 2 from the value at admission, the clinical course was defined as either “fluctuation” or “progression.” “Fluctuation” was used when the score returned to the value at admission, whereas “progression” was used if the worsened state persisted. The same criteria, based on the NIHSS score at the time of surgery, were applied to evaluate the postoperative clinical course. When there was a ≥ 2 decrease in the NIHSS score from the value at admission, the clinical course was defined as “improvement.” We also assessed the clinical outcomes during the follow-up period, including the incidence and timing of TIA, ischemic stroke, hemorrhagic stroke, and seizure.

2.3 Hemisphere analysis

In total, 121 hemispheres with moyamoya were assessed and divided into two groups: hemispheres that underwent MBH and

hemispheres that did not. The angiographic stage was evaluated using the Suzuki staging system. Vascularity was assessed by examining the circulation of the ICA, external carotid artery (ECA), and vertebral artery (VA) in the lateral DSA view. If $<66\%$ of the hemisphere showed vascular supply in the capillary phase, the vascularity was classified as “impaired” (Supplementary Figure 1A); otherwise, it was classified as “not impaired” (Supplementary Figure 1B). The vascularity of each region where the burr hole was created was evaluated by dividing it into the frontal, coronal suture, parietal, and posterior parietal regions. The same criteria of “not impaired” and “impaired” were used to evaluate regional vascularity (Figure 1A). Preoperative regional perfusion status was assessed using CTP, MRP, or SPECT images. Regional perfusion impairment (RPI), acute infarction (detected using MR diffusion-weighted imaging), and chronic infarction (no restriction on MR diffusion-weighted imaging but with hypodensity on CT) were evaluated in the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) territories.

Follow-up DSA was conducted at least 6 months postoperatively to reassess the angiographic characteristics. A subgroup analysis was performed on the 91 hemispheres that underwent surgery. We evaluated whether the basal moyamoya vessels originating from

the ICA had decreased by $\geq 50\%$ (Figure 1B). We assessed the Matsushima grade, a scale used to measure neovascularization after bypass surgery (grade A: proportion of the MCA territory with revascularization from collaterals from the ECA through the burr holes was more than two-thirds; grade B: between one-third and two-thirds; grade C: $<$ one-third) (18). The degree of neovascularization was assessed for each region in which surgery was performed; if no burr hole was made, it was recorded as “not done.” If the existing vessels remained unchanged on DSA after burr hole surgery, they were classified as “no replacement.” If the pre-existing and new vessels formed through the burr hole contributed to the region’s blood supply, it was classified as “balanced.” If the pre-existing vessels vanished and most ($\geq 66\%$) of the blood supply was delivered by the new vessels formed through the burr hole, it was classified as “replaced” (Figures 1C–E).

2.4 Surgical procedure

EPO premedication before MBH was performed as described in previous literature. Total 120,000 unit of Intravenous EPO (Epokine; CJ

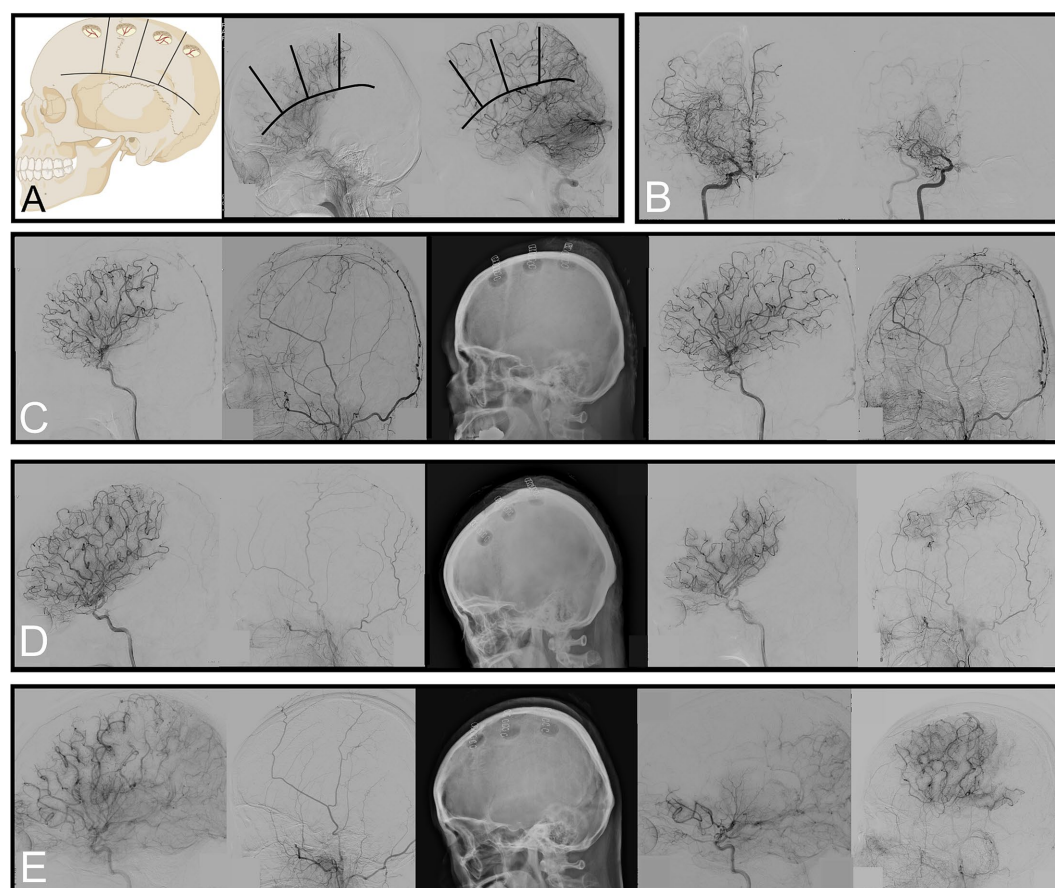


FIGURE 1

Criteria to evaluate regional vascularity, reduction of basal moyamoya vessels, and scales used to measure neovascularization. (A) Examples of “impaired” vascularity in the frontal and coronal suture regions and “not impaired” vascularity in the parietal and posterior parietal regions. (B) Angiography showing $\geq 50\%$ of basal moyamoya vessels 6 months after surgery. (C–E) Preoperative angiography (left) and 6-month follow-up (right). Each of these is an example of Matsushima grades C, B, and A with regional neovascularization status, showing “no replacement,” “balanced,” and “replaced,” respectively.

healthcare, South Korea) was injected for three consecutive days right before the surgery (15). In the operating theater, the patients were placed in a supine position. Local anesthesia was administered through a lidocaine injection at predetermined incision points. A 3–4-cm scalp incision was made for each burr hole, and the burr holes, each 2–3 cm in size, were drilled using the Midas Rex® high-speed drill (Medtronic, Minneapolis, Minnesota, United States). Any bone bleeding from the diploic veins was managed using bone wax. At each burr hole, a cruciate incision was placed in the dura to break the mechanical barrier for collateral formation. Subsequently, the scalp incisions were closed with 2–0 vicryl sutures and staples. Up to four burr holes were performed per hemisphere, specifically targeting regions with impaired vascularity or perfusion impairment as identified on preoperative imaging.

2.5 Statistical analysis

Statistical analyses were performed using R software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria). The basic characteristics of each patient, hemisphere, and region were analyzed using the chi-square, Fisher's exact, t-test, and Mann–Whitney U tests, respectively. Statistical significance was set at $p < 0.05$. Variables taken at multiple time points were analyzed using the Friedman test.

Logistic regression was used to identify factors that may have influenced the decision to perform surgery in each region and were associated with the level of neovascularization (“replaced,” mentioned above). Variables with a p -value less than 0.05 in the univariable analysis were included in the multivariable analysis. Hemispheric improvements were assessed based on two criteria: the achievement of a Matsushima grade A and a $\geq 50\%$ decrease in basal moyamoya vessels from the ICA.

Survival analysis was conducted using clinical follow-up data to evaluate the occurrence and timing of events, such as TIA, infarction, hemorrhage, and seizure.

3 Results

3.1 Baseline characteristics and perioperative clinical outcomes

The 70 patients were divided into early ($n = 36$) and later ($n = 34$) groups. Baseline characteristics, including age, sex, and common comorbidities, were similar between groups. During the preoperative period, significantly more patients in the early group experienced neurological fluctuations or progression ($p < 0.001$). Postoperatively, 77.8% of patients in the early group showed no neurological worsening, with 10 patients showing improvement. Of the eight patients with postoperative neurological worsening, six recovered by discharge. The mean preoperative hospital stay was longer in the early group ($p = 0.001$), but no significant difference was observed postoperatively. Overall, 10.0% of patients had surgical site complications. Three patients (4.3%) experienced lesion extension, which is the progression of a pre-existing acute infarction (Table 1). Of these cases, two were incidental findings on follow-up imaging, not associated with neurological worsening; one involved an extension of the MCA territory infarction, neurologically recovered with medical treatment. The clinical details are described in Supplementary Table 1. In the Early group, the duration from the neurological event to surgery

was a median of 12 days, with an interquartile range (IQR) of 3 days. The shortest was 3 days and the longest was 25 days. In the Later group, the median was 131 days, with an IQR of 61 days, the shortest being 41 days and the longest being 254 days.

The mean NIHSS score at admission was 2.7, improving to 1.5 at 6 months postoperatively, with significant improvement observed overall (Friedman's analysis). However, there was no significant difference in the mRS scores between groups at admission, discharge, or 6 months postoperatively (Supplementary Figure 2).

3.2 Hemispheric demographics and angiographic characteristics

Among 121 moyamoya hemispheres, 91 underwent MBH. Hemispheres that underwent surgery were more likely to be at an advanced Suzuki stage ($p = 0.011$) and had impaired vascularity preoperatively ($p < 0.001$). Follow-up DSA indicated improvement in vascularity and a shift toward advanced Suzuki stages (Table 2; Supplementary Figure 3).

The hemispheres that underwent surgery also demonstrated more impaired vascularity on preoperative DSA ($p < 0.001$). However, vascularity in these hemispheres had improved on follow-up DSA, and the initial difference between the groups was no longer evident (Table 2).

In the 91 operated hemispheres, early surgical intervention resulted in better outcomes: 72.3% of early group hemispheres achieved Matsushima grade A compared to lower grades in the later group. Additionally, 63.8% of the early group achieved significant reduction ($\geq 50\%$) of basal moyamoya vessels compared to 27.3% in the later group (Table 3).

3.3 Factors associated with hemispheric neovascularization

In achieving Matsushima grade A, the early group demonstrated significantly improved neovascularization (odds ratio [OR] = 3.44; 95% confidence interval [CI]: 1.46–8.45; $p < 0.01$). However, multivariate analysis showed no significant difference (OR = 2.57; 95% CI: 0.99–6.87; $p = 0.06$). Notably, the presence of RPI with acute infarction was significantly associated with achieving Matsushima grade A in the univariate (OR = 24.00; 95% CI: 3.00–529.73; $p < 0.01$) and multivariate models (OR = 13.28; 95% CI: 1.48–306.91; $p = 0.04$).

Regarding the decrease in basal moyamoya vessels, the early group showed a statistically significant association in the univariate (OR = 4.71; 95% CI: 1.97–11.82; $p < 0.001$) and multivariate analyses (OR = 3.86; 95% CI: 1.52–10.25; $p < 0.01$). Although the presence of RPI with acute infarction was significant in the univariate analysis, this significance was not observed in the multivariate model (Table 4).

3.4 Factors associated with regional neovascularization

Early surgical intervention was a significant predictor of successful neovascularization in most regions except the posterior parietal

TABLE 1 Baseline characteristics and perioperative courses of patients.

	All patients (n = 70)	Early group (n = 36)	Later group (n = 34)	p-value
Sex (Female)	46 (65.7)	28 (77.8)	18 (52.9)	0.053
Age (years)	43.4 (12.7)	43.2 (11.4)	43.7 (14.1)	0.875
HTN	26 (37.1)	13 (36.1)	13 (38.2)	0.999
DM	18 (25.7)	10 (27.8)	8 (23.5)	0.894
Dyslipidemia	14 (20.0)	10 (27.8)	4 (11.8)	0.169
Smoking	21 (30.0)	11 (30.6)	10 (29.4)	0.999
Moyamoya syndrome	2 (2.9)	1 (2.8)	1 (2.9)	0.999
Unilateral moyamoya	18 (25.7)	9 (25.0)	9 (26.5)	0.999
Presentation type				0.807
TIA	3 (4.3)	2 (5.6)	1 (2.9)	
Ischemic stroke	56 (80.0)	29 (80.6)	27 (79.4)	
Hemorrhagic stroke	11 (15.7)	5 (13.9)	6 (17.6)	
NIHSS score				
at Admission	2.7 (3.5)	3.5 (3.5)	1.9 (3.4)	0.057
at Discharge	2.3 (3.8)	2.4 (3.1)	2.2 (4.3)	0.768
at 6 month	1.5 (2.9)	1.4 (2.4)	1.6 (3.3)	0.68
mRS				
at Admission				0.193
0, 1	46 (65.7)	21 (58.3)	25 (73.5)	
2	12 (17.1)	6 (16.7)	6 (17.6)	
≥3	12 (17.1)	9 (25.0)	3 (8.8)	
at Discharge				0.384
0, 1	48 (68.6)	22 (61.1)	26 (76.5)	
2	11 (15.7)	7 (19.4)	4 (11.8)	
≥3	11 (15.7)	7 (19.4)	4 (11.8)	
at 6 month				0.848
0, 1	53 (75.7)	26 (72.2)	27 (79.4)	
2	9 (12.9)	5 (13.9)	4 (11.8)	
≥3	8 (11.4)	5 (13.9)	3 (8.8)	
Clinical course				
Preoperative period				<0.001
Fluctuation	8 (11.4)	8 (22.2)	0 (0.0)	
Progression	8 (11.4)	8 (22.2)	0 (0.0)	
Postoperative period				0.003
Improvement	10 (14.3)	10 (27.8)	0 (0.0)	
Stable	45 (64.3)	18 (50.0)	27 (79.4)	
Fluctuation	13 (18.5)	6 (16.7)	7 (20.6)	
Progression	2 (2.9)	2 (5.5)	0 (0.0)	
Day of hospitalization				
Preoperative period	7.0 (3.8)	8.4 (4.3)	5.6 (2.5)	0.001
Postoperative period	9.4 (7.6)	10.5 (10.1)	8.1 (3.1)	0.187
Total	16.4 (9.0)	19.0 (11.6)	13.7 (3.5)	0.013
Erythropoietin	68 (97.1)	34 (94.4)	34 (100.0)	0.493

(Continued)

TABLE 1 (Continued)

	All patients (<i>n</i> = 70)	Early group (<i>n</i> = 36)	Later group (<i>n</i> = 34)	<i>p</i> -value
EPO-related complications				
Fever	40 (57.1)	18 (50.0)	22 (64.7)	0.317
Headache	12 (17.1)	4 (11.1)	8 (23.5)	0.289
Surgical site complications	7 (10.0)	1 (2.8)	6 (17.6)	0.052
Lesion extension	3 (4.3)	3 (8.3)	0 (0.0)	<0.001
Anesthesia				0.999
Local	67 (95.7)	34 (94.4)	33 (97.1)	
General	3 (4.3)	2 (5.6)	1 (2.9)	

HTN, Hypertension; DM, Diabetes mellitus; TIA, Transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Ranking Scale; SD, standard deviation; EPO, Erythropoietin. Bold values means *p*-value < 0.05.

TABLE 2 Demographics and radiographic characteristics of moyamoya hemispheres.

	All hemispheres (<i>n</i> = 121)	Not operated (<i>n</i> = 30)	Operated (<i>n</i> = 91)	<i>p</i> -value
Preoperative Suzuki stage				0.011
Stage I-II	17 (14.0)	9 (30.0)	8 (8.8)	
Stage III	26 (21.5)	7 (23.3)	19 (20.9)	
Stage IV	60 (49.6)	8 (26.7)	52 (57.1)	
Stage V	12 (9.9)	4 (13.3)	8 (8.8)	
Stage VI	6 (5.0)	2 (6.7)	4 (4.4)	
Postoperative Suzuki stage				<0.001
Stage I-II	12 (9.9)	8 (26.7)	4 (4.4)	
Stage III	10 (8.3)	9 (30.0)	1 (1.1)	
Stage IV	21 (17.4)	6 (20.0)	15 (16.5)	
Stage V	47 (38.8)	4 (13.3)	43 (47.3)	
Stage VI	31 (25.6)	3 (10.0)	28 (30.8)	
Preoperative vascularity				<0.001
Impaired	60 (49.6)	4 (13.3)	56 (61.5)	
Not impaired	61 (50.4)	26 (86.7)	35 (38.5)	
Postoperative vascularity				0.999
Impaired	16 (13.2)	4 (13.3)	12 (13.2)	
Not impaired	105 (86.8)	26 (86.7)	79 (86.8)	
Laterality (Left side)	61 (50.4)	17 (56.7)	44 (48.4)	0.562

CTP, CT perfusion; MRP, MR perfusion; SPECT, Single-photon emission computed tomography; RPI, Regional perfusion impairment. Bold values means *p*-value < 0.05.

region. Impaired vascularity and RPI without infarction were significant predictors in specific regions (Supplementary Table 2).

3.5 Survival analysis of adverse events

We performed survival analysis for each instance of TIA, infarction, hemorrhage, and seizure. Of the 70 patients, TIA occurred in seven individuals, with a median time to TIA of 28 months. Infarction was observed in four patients, with a median time to infarction of 28 months. Hemorrhage occurred in two patients, with a median time to hemorrhage of 23 months. Seizures were observed in seven patients, with a median time to seizure of 29 months. The mean follow-up duration was 56.5 months, with a standard deviation of 37.6 months (Figure 2).

3.6 Illustrative cases

3.6.1 Case 1: successful recovery and revascularization following combination therapy in moyamoya-induced infarction

A 53-year-old man presented with right hemiparesis (Grade 4), hypoesthesia, and dysarthria on admission (NIHSS score: 3, mRS score: 1). Magnetic resonance imaging revealed diffusion restriction in the left MCA territory (Figure 3A). DSA demonstrated moyamoya vessels (Figure 3B) along with a significant reduction in cerebral blood flow (CBF) compared with the contralateral hemisphere (Figure 3C).

The patient’s symptoms worsened during hospitalization, with hemiparesis deteriorating to Grade 3 and the occurrence of aphasia (NIHSS score: 9). Flow-augmentation therapy was administered to

TABLE 3 Baseline characteristics and radiographic outcomes of operated hemispheres at follow up angiography.

	All operated hemispheres (n = 91)	Early group (n = 47)	Later group (n = 44)	p-value
Suzuki stage				0.133
Stage I-II	8 (8.8)	6 (12.8)	2 (4.5)	
Stage III	19 (20.9)	11 (23.4)	8 (18.2)	
Stage IV	44 (48.4)	27 (57.4)	25 (56.8)	
Stage V	9 (9.9)	1 (2.1)	7 (15.9)	
Stage VI	11 (12.1)	2 (4.3)	2 (4.5)	
Perfusion status (CTP, MRP, SPECT)				0.001
Without RPI	7 (7.7)	1 (2.1)	6 (13.6)	
RPI without infarction	62 (68.1)	28 (59.6)	34 (77.3)	
RPI with acute infarction	20 (22.0)	17 (36.2)	3 (6.8)	
RPI with chronic infarction	2 (2.2)	1 (2.1)	1 (2.3)	
Matsushima grade				0.019
C	17 (18.7)	6 (12.8)	11 (25.0)	
B	21 (23.1)	7 (14.9)	14 (31.8)	
A	53 (58.2)	34 (72.3)	19 (43.2)	
Basal moyamoya reduction				0.001
< 50%	49 (53.8)	17 (36.2)	32 (72.7)	
≥50%	42 (46.2)	30 (63.8)	12 (27.3)	
Regional neovascularization				
Burr hole at frontal bone				0.042
Not done	36 (39.6)	19 (40.4)	17 (38.6)	
No replacement	14 (15.4)	3 (6.4)	11 (25.0)	
Balanced	3 (3.3)	1 (2.1)	2 (4.5)	
Replaced	38 (41.8)	24 (51.1)	14 (31.8)	
Burr hole at coronal suture				0.041
Not done	10 (11.0)	5 (10.6)	5 (11.4)	
No replacement	15 (16.5)	4 (8.5)	11 (25.0)	
Balanced	12 (13.2)	4 (8.5)	8 (18.2)	
Replaced	54 (59.3)	34 (72.3)	20 (45.5)	
Burr hole at parietal bone				0.046
Not done	11 (12.1)	6 (12.8)	5 (11.4)	
No replacement	13 (14.3)	4 (8.5)	9 (20.5)	
Balanced	12 (13.2)	3 (6.4)	9 (20.5)	
Replaced	55 (60.4)	34 (72.3)	21 (47.7)	
Burr hole at posterior parietal				0.088
Not done	65 (71.4)	31 (66.0)	34 (77.3)	
No replacement	9 (9.9)	4 (8.5)	5 (11.4)	
Balanced	6 (6.6)	6 (12.8)	0 (0.0)	
Replaced	11 (12.1)	6 (12.8)	5 (11.4)	

CTP, CT perfusion; MRP, MR perfusion; SPECT, Single-photon emission computed tomography; RPI, Regional perfusion impairment. Bold values means *p*-value < 0.05.

stabilize the patient’s hemodynamic condition. The patient underwent combination therapy with MBH and EPO under local anesthesia on the 11th day of hospitalization (Figure 3D). No surgery-related complications were observed, and the patient’s

neurological status improved, allowing for participation in rehabilitation programs.

At discharge, 23 days postoperatively, the patient’s NIHSS and mRS scores were 4 and 2, respectively. After a 6-month follow-up, the

TABLE 4 Logistic regression for factors associated with successful revascularization.

	Matsushima grade A (revascularization ≥66%)				Basal moyamoya reduction ≥50%			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR [95% CI]	p-value	OR [95% CI]	p-value	OR [95% CI]	p-value	OR [95% CI]	p-value
Timing of surgery								
Later group	ref		ref		ref		ref	
Early group	3.44 [1.46–8.45]	<0.01	2.57 [0.99–6.87]	0.06	4.71 [1.97–11.82]	<0.001	3.86 [1.52–10.25]	<0.01
Preoperative vascularity								
Impaired	ref				ref			
Not impaired	0.64 [0.27–1.50]	0.3			0.97 [0.41–2.27]	0.95		
Suzuki stage								
Stage I-II	ref				ref			
Stage III-IV	3.86 [0.86–0.40]	0.08			2.22 [0.50–11.60]	0.3		
Stage V-VI	0.71 [0.13–4.38]	0.7			0.29 [0.04–2.01]	0.2		
Perfusion status (CTP, MRP, SPECT)								
Without RPI	ref		ref		ref		Ref	
RPI without infarction	8.31 [1.31–161.94]	0.06	6.6 [1.00–30.69]	0.09	4.63 [0.73–90.18]	0.17	3.24 [0.47–65.35]	0.3
RPI with acute infarction	24.00 [3.00–529.73]	<0.01	13.28 [1.48–306.91]	0.04	11.14 [1.50–233.80]	0.04	4.76 [0.54–106.39]	0.21
Laterality (Left side)	1.07 [0.46–2.48]	0.87			1.35 [0.59–3.11]	0.48		

CTP, CT perfusion; MRP, MR perfusion; SPECT, Single-photon emission computed tomography; RPI, Regional perfusion impairment; OR, Odds ratio; CI, Confidence interval. Bold values means *p*-value < 0.05.

right hemiparesis continued to improve, with NIHSS and mRS scores of 2 and 1, respectively. Follow-up DSA showed successful revascularization through the burr holes, and the moyamoya vessels were significantly replaced (Figure 3E). CBF also significantly improved at follow-up CTP (Figure 3F). Notably, the patient experienced no adverse events, such as TIA, infarction, hemorrhage, or seizures, throughout the follow-up period of 32 months.

3.6.2 Case 2: successful neovascularization and clinical improvement for patient with hemorrhagic presentation

A 31-year-old woman presented with a stuporous mental state and left hemiparesis (NIHSS score: 15, mRS score: 5). A computed tomography scan at admission revealed a right thalamic hemorrhage with an intraventricular hemorrhage (Figure 3G) leading to the insertion of an emergent extraventricular drain. DSA was performed after treating the increased intracranial pressure and stabilizing the patient’s condition, which revealed the presence of moyamoya vessels bilaterally (Figures 3H,I).

On day 21 of hospitalization, MBH and EPO combination therapy was administered to both hemispheres. Owing to the patient’s dependence on mechanical ventilation, surgery was conducted under general anesthesia with strict hemodynamic monitoring. Four days postoperatively, the patient’s mental status declined again to a state of stupor accompanied by a left-sided eyeball deviation. However, the patient’s mental status improved after administering levetiracetam. The patient’s overall clinical status improved, leading to successful extubation, and the patient could participate in rehabilitation.

Upon discharge, the intracranial hemorrhages had completely resolved (Figure 3J), and the patient’s mRS score was 4; the patient was still bedridden but could communicate clearly. After a 6-month follow-up, her right lower motor strength improved to grade 3, with an mRS score of 3. Follow-up DSA revealed successful revascularization in both hemispheres, and the abnormal moyamoya vessels had significantly regressed (Figures 3K,L). Throughout the 30-month follow-period, the patient experienced no adverse events. Notably, at the last follow-up, the patient’s modified mRS score further improved to 1. She only had a subtle weakness in her left hand but was capable of complete self-care and could start searching for new employment.

4 Discussion

In this study, early surgical intervention in patients with moyamoya disease resulted in better angiographic outcomes compared to later intervention. Specifically, early intervention was associated with a higher rate of achieving Matsushima grade A, significant reduction in basal moyamoya vessels, and improved neovascularization in most regions. These findings suggest that early surgical intervention may enhance revascularization and improve neurological outcomes in patients with moyamoya disease or syndrome.

The early group demonstrated significantly better hemispheric neovascularization outcomes, with 72.3% achieving Matsushima grade A compared to lower grades in the later group. Additionally, 63.8% of early group patients showed a significant reduction (≥50%)

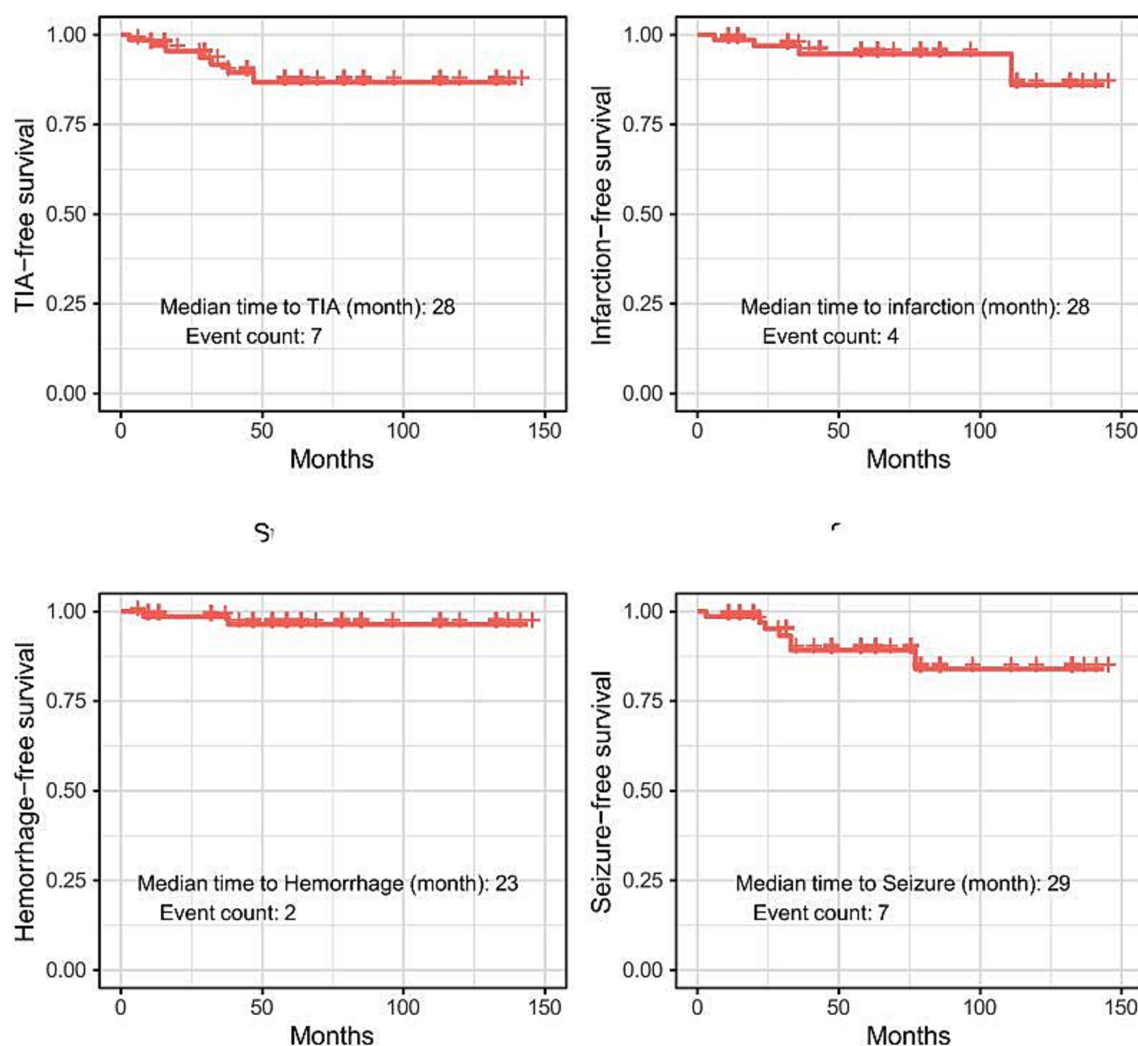


FIGURE 2
Survival analysis of adverse events. TIA, transient ischemic attack.

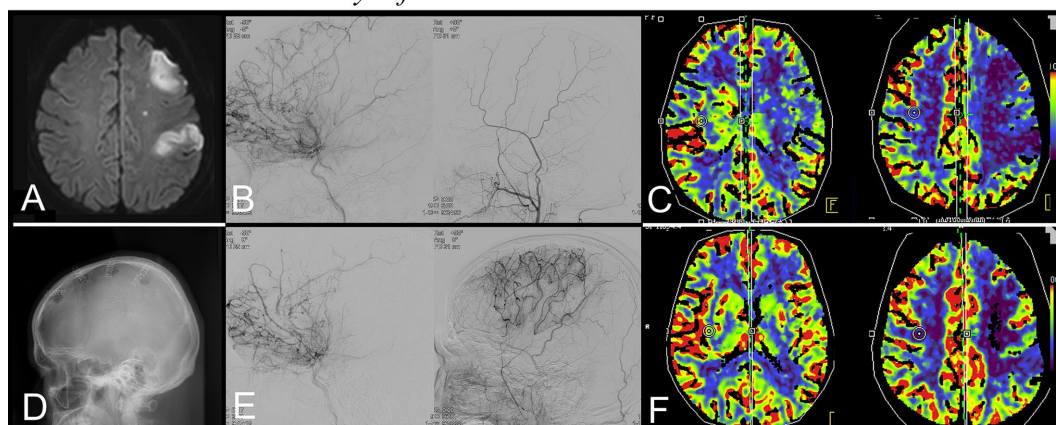
in basal moyamoya vessels, compared to only 27.3% in the later group. The presence of RPI with acute infarction was also a significant predictor of achieving Matsushima grade A, indicating that targeting patients with acute ischemic events may be particularly beneficial for successful neovascularization.

Studies have investigated the MBH as the sole method of indirect bypass surgery for patients with MMD or MMS (19–22). In 1996, Kawaguchi et al. performed MBH in 10 adults and reported favorable outcomes (23). The study highlighted that MBH can be performed without craniotomy and general anesthesia, avoiding perioperative hypotension and hypercapnia. They also showed that angiogenesis occurs efficiently in areas of decreased CBF on SPECT scans. Saint Rose et al. performed MBH in 64 pediatric patients and presented the long-term follow-up results of their study (22, 24). The surgery was performed under general anesthesia, and a higher number of burr holes were applied. The MBH procedure introduced in our study is similar to the method described by Kawaguchi et al.

The safety of bypass surgery in patients with acute stroke episode of MMD or MMS has long been a debatable issue. Safety concerns arise primarily owing to hypotension during general

anesthesia, hyperventilation during awakening, and intraoperative bleeding leading to the possibility of postoperative stroke (7–12). Recent studies examining the appropriate timing of surgery for patients with MMD or MMS following an acute stroke episode show that 15–22% of patients who underwent bypass surgery within 90 days of an acute stroke episode experienced postoperative strokes, and 17–33% experienced neurological deterioration (13, 14). These findings might suggest that early surgery is riskier; however, it is crucial to recognize the heterogeneity in surgical methods between early and delayed surgery groups in previous studies. This variability makes it challenging to conclude that early surgical intervention carries inherently greater risks. By comparing groups treated with the same MBH technique, our study offers enhanced validity and consistency in determining the true impact of surgery timing. Unlike previous studies, we defined the early group as patients who underwent MBH less than 30 days from the most recent neurological event 30 days, potentially targeting more unstable patients. The rates of postoperative fluctuation and progression were nearly identical in the early and later groups. Notably, only 5.5% in the early group experienced neurological

53/M with Lt MCA territory infarction



31/F with Rt thalamic ICH with IVH

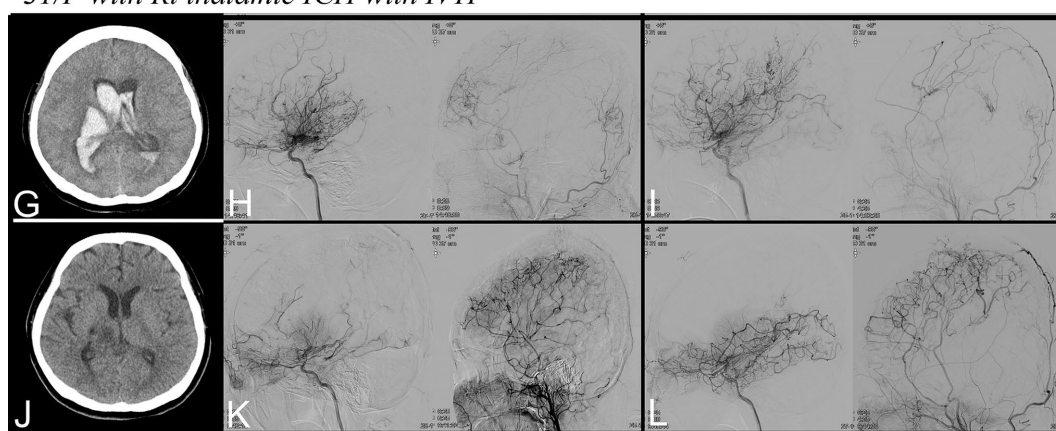


FIGURE 3

Representative cases. (A–F) A 53-year-old man with recent infarction in the left MCA territory. (A) Diffusion restriction in the left MCA territory, (B) Preoperative DSA for left ICA and ECA demonstrating moyamoya vessels, (C) Reduction in CBF on CTP, (D) Four multiple burr holes at the left hemisphere, (E) Follow-up DSA showing successful revascularization, (F) improvement in CBF on follow-up CTP. (G–L) A 31-year-old woman with right thalamic ICH with IVH. (G) Non-contrast CT at admission, (H,I) preoperative DSA for each hemisphere, (J) Non-contrast CT at discharge, and (K,L) Follow-up DSA showing successful revascularization. MCA, middle cerebral artery; ICA, internal carotid artery; ECA, external carotid artery; DSA, digital subtraction angiography; CBF, cerebral blood flow; CTP, CT perfusion; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; CT, computed tomography.

worsening, significantly lower than the 17–33% rate reported in previous studies (13, 14). Furthermore, lesion extension occurred in 8.3% patients in the early group, with two cases being asymptomatic; this is also lower than the 15–22% rate reported previously (13, 14). In fact, 27.8% of patients in our early group showed neurological improvement. Concurrent medication therapy may have played a role; however, this suggests that some patients who experience an acute stroke episode can achieve clinical improvement early through MBH.

Previous animal studies have demonstrated that erythropoietin (EPO) induces neuroprotective and angiogenic effects. Notably, combination therapy involving EPO in animal models has been shown to facilitate arteriogenesis and enhance the maturation of newly developed vessels (17). Additionally, the benefits of EPO were examined in a human randomized controlled trial involving stroke patients with cerebral hypoperfusion. This study compared outcomes between patients received MBH alone and those underwent combination therapy with EPO, showing significantly improved angiographic outcome

in combination therapy group (16). Moreover, as MBH barely disrupts anatomical structures, it allows for additional surgeries if collateral formation is insufficient. Therefore, employing MBH and EPO therapy first in patients with acute stroke episode, followed by considering additional bypass surgery during a stable phase, could be an excellent treatment strategy.

Furthermore, we divided the regions where burr holes were performed to investigate the factors associated with the neovascularization in detail. Impaired vascularity and perfusion demonstrated significant associations with neovascularization, which was particularly evident in the regions supplied by the ACA and MCA. Notably, in regions with perfusion impairment, neovascularization was less pronounced in areas affected by chronic infarction and atrophy. In summary, there was a tendency for better neovascularization when the vascularity and perfusion status were not optimal and when the surgery was performed early. However, this pattern was not observed in the posterior parietal region. This finding indicates that the angiogenic demand of the salvageable penumbra influences neovascularization.

Furthermore, as illustrated in Case 2, excellent neovascularization was observed even in patients with hemorrhage. According to a study based on data from the Japan Adult Moyamoya Trial, the reduction in rebleeding after bypass surgery in patients with hemorrhage was more effective when SPECT showed a lower cortical hemodynamic grade (25, 26). This suggests that a subgroup of patients with hemorrhage benefits more from bypass surgery. Therefore, we speculate that the timing of surgery might be a critical factor for neovascularization and may contribute to the reduction of abnormal vessels, even in patients with hemorrhagic stroke.

Finally, we conducted a follow-up of patients for an average of 56.5 months. Among the 70 patients, only 6 experienced infarction and hemorrhage. To our knowledge, this is the largest and longest follow-up study involving adult patients who underwent MBH as the sole method of indirect bypass, which adds to the promising evidence supporting the feasibility and potential benefits of MBH and EPO combination therapy for managing patients with MMD or MMS.

This study had some limitations. First, this was a single-center, retrospective study. Second, this study was limited by the lack of a control group. Therefore, definitively concluding the superiority of combination therapy with MBH and EPO over other surgical options is challenging. Third, in this study, when dealing with basal moyamoya vessels, we did not analyze periventricular anastomosis, a well-known risk factor for hemorrhagic moyamoya (27, 28). Instead, we arbitrarily set a criterion of more than 50% reduction in moyamoya vessels for our analysis. Research on periventricular anastomosis is expected to be an important topic in the future. Fourth, we did not compare the MBH and EPO combination therapy group with the MBH only group, thus we were unable to prove that EPO combination is essential for collateral formation. Finally, long-term and systematic observation and prognostic evaluation of the treated patient groups are necessary.

In conclusion, the MBH and EPO combination therapy is an effective, minimally invasive treatment option for patients with an acute stroke episode of MMD or MMS. Owing to the minimally invasive nature of MBH, surgical intervention in the early period could be a safe treatment option compared to later intervention and may even be beneficial regarding angiographic outcomes. We suggest that performing that MBH and EPO therapy first in patients with an acute stroke episode, followed by considering additional bypass surgery during a stable phase, could be a safe and effective treatment strategy.

Data availability statement

The datasets presented in this article are not readily available because the datasets analyzed in this study are not publicly available due to privacy concerns. Requests to access the datasets should be directed to strokamong14@gmail.com.

Ethics statement

The studies involving humans were approved by Ajou University Hospital Institutional Review Board. The studies were

conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because participation in this study did not influence the treatment policy for the patients. The data used in the research were collected through proper procedures with the institution's permission and handled anonymously, thus not requiring individual patient consent.

Author contributions

YL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. JL: Data curation, Validation, Writing – review & editing. S-JL: Data curation, Validation, Writing – review & editing. JH: Data curation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. YCL: Conceptualization, Investigation, Project administration, Supervision, Validation, Writing – review & editing.

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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.2024.1479379/full#supplementary-material>

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Sex disparities in the risk of intracranial aneurysm rupture: a case–control study

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Background: There are sex disparities in the risk of ruptured intracranial aneurysm (IA), but which sex-specific factors are related to ruptured IA remains inconclusive.

Methods: Data from electronic medical records from two tertiary hospitals, collected between January 2012 and December 2019, were analyzed for this study. All IAs were confirmed by computed tomographic angiography or digital subtraction angiography. Sex-specific factors associated with ruptured IA were analyzed using multivariable logistic models with a case–control study design. Age, aneurysm size, and aneurysm location subgroup analyses were conducted according to sex.

Results: In total, 1883 patients [1,117 (59.32%) female, 766 (40.68%) male] with 2,423 IAs were included; 734 (38.98%) of patients had ruptured IAs. Compared with males, females had a higher risk of ruptured IA [odds ratio, 1.72 (95% confidence interval, 1.38–2.14)]. Age, aneurysm location, aneurysm size, multiple aneurysms, hypertension, history of intracerebral hemorrhage, and ischemic stroke were associated with risk of IA rupture in both sexes. In the subgroups based on the covariates used in this study, we only identified statistically significant interaction between sex and age. Although ruptured IAs were most common in males and females aged 50–59 and 60–69 years, respectively, risk of IA rupture peaked at ages 30 and 30–50 years in females and males, respectively, and decreased with age in both sexes.

Conclusion: Females have an overall greater IA incidence and higher risk of IA rupture than males. Young age is one sex-specific risk factor associated with ruptured IA which could related to potential influence of hypertension, which might suggest more attention of IA rupture prevention in younger female.

KEYWORDS

sex difference, female, intracranial aneurysm, rupture, risk

1 Introduction

Intracranial aneurysm (IA) is a common cerebrovascular disorder, that represents an increasing disease burden worldwide (1). A systematic review and meta-analysis, including 68 studies and 94,912 patients from 21 countries, reported that the overall prevalence of unruptured IA was 3.2% [95% confidence interval (CI), 1.9–5.2%] in a normal population without comorbidities (2). Ruptured IAs are responsible for approximately 85% of cases of

subarachnoid hemorrhage (SAH), which is associated with 30-day fatality rates reaching 36–42% and permanent disability rates of up to 50% (3, 4).

Women have a greater risk of IA incidence and rupture than men (5–8), with a reported female and male incidence ratio of 1.57 (2). Further, the Rotterdam Study reported a greater risk of unruptured IA in females (odds ratio (OR), 1.92, 95% CI, 1.33–2.84) (9). Regarding IA rupture, a meta-analysis of individual patient data revealed that the female to male hazard ratio (HR) was 1.43 (95% CI, 1.07–1.93) (8). Another recent meta-analysis reported that aneurysmal SAH was more common in women than in men [HR, 1.90 (95% CI 1.47–2.46)] (10). Furthermore, Wang et al. reported a multicenter retrospective study in China, which also revealed that females had a greater risk of IA rupture [OR, 1.85 (95% CI, 1.05–3.39)] (11).

Nevertheless, controversy remains over whether sex is an independent risk factor for IA rupture (12–14). Studies using scores generated by a clinical IA rupture risk prediction tool (PHASE; population, hypertension, size of aneurysm, earlier SAH from another aneurysm, site of aneurysm), based on data from six cohort studies, revealed that sex has limited predictive value for IA rupture (15). Additionally, differences in the pathophysiology and anatomical features between the sexes are imprecise (16). Further, given the fundamental differences in morphology and size of IAs in various cerebral arteries, little is known about whether the size and location of IAs affect the risk of rupture in a sex-specific manner.

Therefore, exploring the sex disparities in the risk of IA rupture may provide useful knowledge in primary and secondary prevention of IA rupture. The aim of this study is to assess whether there are associations and differences in IA characteristics between female and male.

2 Methods

2.1 Study setting and data source

The study was set in two tertiary general hospitals. Data were obtained from electronic medical records during the period from 2012 to 2019.

This study was exempted from ethics committee approval for using retrospective and anonymized data with no further intervention involved. Informed consent was waived due to the retrospective nature of the study, and all private information was anonymized. The study conformed to the Declaration of Helsinki. This article follows the STROBE reporting guidelines (Supplementary material S2).

2.2 Participant inclusion and ascertainment of cases and controls

Patients with a clinical suspicion of IA, who subsequently underwent computed tomographic angiography (CTA) or digital subtraction angiography (DSA), were identified by searching the electronic medical and radiology records of the hospitals. Patients who had previously been diagnosed with IAs or had been treated at another hospital and undergone follow-up examination were excluded, with only the first examination in each patient's medical procedure included in the study. Finally, patients who were diagnosed

for positive IA with no previous IA record were included. The complete patient inclusion workflow is presented in [Supplementary Figure S1](#). The process of image acquisition is described in the [Supplementary material](#) section.

A case-control study design was used to analyze the risk of the rupture, based on data from real world medical records. A case was defined as an original diagnosis of positive for IA rupture based on CTA and/or DSA, which was primarily made by one radiologist and one neurologist and then reviewed by one senior radiologist and one senior neurologist. Participants included in this study with un-rupture IA in the original diagnosis were selected as controls.

2.3 Ascertainment of IA characteristics

IA size and site were determined based on CTA and DSA results. All patients underwent non-contrast computed tomography prior to head and/or neck CTA. For patients with suspected aneurysmal SAH or intracerebral hemorrhage (ICH), DSA was performed at the discretion of the treating neurosurgeon.

Aneurysms were defined as rounded areas of contrast outpouching ≥ 2 mm in diameter. Patients with fusiform aneurysms were excluded from the analysis. Three-dimensional reconstructions of all CTA images were created in three planes, and maximum intensity pixel images of the intracranial internal carotid arteries, as well as the intracranial vertebral and basilar arteries, were also used for imaging interpretation. IAs were classified by location, size, and rupture status, based on the radiologist report and subsequent imaging review by two neuroradiologists. Aneurysm size was equal to the maximum aneurysm diameter. If a patient with SAH underwent both DSA and CTA, DSA measurements were used to report aneurysm site and size. For patients with multiple IAs, the ruptured aneurysms were identified based on imaging reports, and recorded separately in a patient level data and in a IA level data for further analysis.

Arteries of interest included: internal carotid artery (ICA), vertebral artery, basilar artery, anterior communicating artery (ACoA), posterior cerebral artery, middle cerebral artery (MCA), and anterior cerebral artery; aneurysms arising from other arteries were classified as “other arteries”.

2.4 Ascertainment of covariates

Several covariates were considered in the analysis, including age, IA size, IA, multiple IAs (yes vs. no), history of ICH (yes vs. no), history of ischemic stroke (yes vs. no), and hypertension (yes vs. no). Information was extracted from patient electronic medical records. Ascertainment of IA size and quantity is described above. Hypertension was determined based on preadmission medical records. A history of ICH or ischemic stroke was based on preadmission or outpatient medical inquiries by the attending physician.

2.5 Statistical analysis

Participant characteristics are summarized as proportions (%) for categorical variables, means and standard errors for normally

distributed continuous variables, and medians ([Q1, Q3]) for non-normally distributed continuous variables. Categorical variables were compared using Fisher’s exact test, and non-normally distributed continuous variables were compared using the Kruskal-Wallis rank-sum test. Occasional missing values were omitted from all analyses. $p < 0.05$ (two-sided) was considered to indicate significance. Bonferroni correction was applied for multigroup pairwise comparisons.

Analyses of sex differences in IA size and artery location were performed at the lesion level. OR and 95% CI values from logistic regression analyses were used to assess associations between various factors and IA rupture. Spline regression was used to analyze the potential nonlinear association between IA size and IA rupture across age and artery subgroups in both sexes. ANOVA was used for nonlinear testing, and the cutoff for the restricted cubic spline was determined by the R^2 value of each fitted model. Interactions between each subgroup and potential modifying factors (sex) were assessed using the likelihood ratio test. When continuous variables were converted to categorical variables, the lower boundary contained the value shown. E-value was used to evaluate the effect strength of potential unadjusted confounders and selection bias in subgroup analyses (17, 18). For sensitivity analysis, we also performed propensity score matching based on the collected IA characteristics to balance the differences between groups.

All the statistical analyses were performed using R software, version 4.2.2 (R Development Core Team, Vienna, Austria).

3 Results

3.1 Patient characteristics

A total of 1,883 IA patients were included in this study, with a total of 2,423 IAs identified. Among all IAs, 1,689 IAs were unruptured, and

734 IAs were ruptured (Table 1). The proportion of females was 59.3%, and patient age ranged from 12 to 93 years (mean, 61.2 ± 11.9 years). Most patients (91.9%) were 41–80 years old. The mean age of female patients was slightly older than that of male patients (61.7 ± 11.5 years vs. 60.5 ± 12.3 years, $p = 0.034$). There were no significant differences in hypertension, history of ICH, or history of ischemic stroke between females and males. Four-hundred-twenty (22.3%) patients were diagnosed with multiple aneurysms, and the proportion of female patients with multiple aneurysms was significantly higher than that of males (25.6% vs. 17.5%, $p < 0.001$). Additionally, there was a greater percentage of ruptured IAs in females (females, 42.5% vs. males, 33.8%, $p < 0.001$). At the lesion level (Supplementary Table S1), most IAs (50.6%) were located in the ICA, followed by the MCA (16.3%), and ACoA (15.3%). Overall IA location distribution differed between females and males; female IAs were more frequently located in the ICA than those in males (54.9% vs. 43.7%). Further, the mean diameter of ICAs with IAs in females was larger than that in males (6.60 vs. 5.50 mm).

The proportions of smokers were 16.71% (128/766) and 0.5% (6/1117) among male and female patients, respectively, while the proportions of smokers patients with unruptured and ruptured IAs were 11.2 and 4.1%, respectively; therefore, we decided to exclude smoking as covariable from our analyses, to avoid potential endogenous bias.

3.2 Comparison of IA characteristics between the ruptured and Unruptured groups according to sex

IA characteristics in the ruptured and unruptured groups according to sex are presented in Table 2; Supplementary Table S2. There was a greater proportion of females with IAs than males in both the unruptured (UIA) and ruptured (RIA) groups ($p = 0.03$). No

TABLE 1 Basic characteristics of patients with IA.

Characteristic	Total (<i>n</i> = 1883)	Female (<i>n</i> = 1,117, 59.3%)	Male (<i>n</i> = 766, 40.7%)	<i>p</i> - value
Age, mean $\pm$ SD, years	61.19 $\pm$ 11.87	61.68 $\pm$ 11.5	60.48 $\pm$ 12.32	0.034
Age, <i>n</i> (%), years				0.105
≤40	69 (3.68)	37 (3.33)	32 (4.19)	
40–	295 (15.74)	161 (14.49)	134 (17.56)	
50–	498 (26.57)	289 (26.01)	209 (27.39)	
60–	584 (31.16)	355 (31.95)	229 (30.01)	
70–	345 (18.41)	223 (20.07)	122 (15.99)	
≥80	83 (4.43)	46 (4.14)	37 (4.85)	
Hypertension, <i>n</i> (%)	764 (40.55)	449 (40.16)	315 (41.12)	0.712
ICH history, <i>n</i> (%)	247 (13.11)	150 (13.42)	97 (12.66)	0.684
Ischemic stroke history, <i>n</i> (%)	476 (25.28)	275 (24.62)	201 (26.24)	0.459
IA rupture, <i>n</i> (%)	734 (38.96)	475 (42.49)	259 (33.81)	<0.001
Multiple IAs, <i>n</i> (%)				<0.001
Single	1,463 (77.71)	832 (74.42)	632 (82.51)	
Multiple (≥ 2)	420 (22.29)	286 (25.58)	134 (17.49)	

IA, intracranial aneurysm; ICH, intracerebral hemorrhage.

TABLE 2 Basic characteristics of ruptured and unruptured IAs in female and male patients.

Characteristic	UIA (<i>n</i> = 1,689)	Overall	<i>p</i> - value	Female (<i>n</i> = 1,014)	UIA	<i>p</i> - value	Female (<i>n</i> = 475)	RIA	<i>p</i> - value
		RIA (<i>n</i> = 734)			Male (<i>n</i> = 675)			Male (<i>n</i> = 259)	
Sex, <i>n</i> (%)			0.033			<0.001			<0.001
Female	1,014 (60.04)	475 (64.71)		1,014			475		
Male	675 (39.96)	259 (35.29)			675			259	
Age, mean ± SD, years	63.12 ± 11.96	58.93 ± 11.03	<0.001	63.40 ± 11.54	62.71 ± 12.55	0.252	60.29 ± 10.99	56.44 ± 10.69	<0.001
Age, <i>n</i> (%), years			<0.001			0.322			<0.001
≤ 40	48 (2.86)	33 (4.50)		26 (2.58)	22 (3.27)		19 (4.00)	14 (5.41)	
40–	207 (12.34)	137 (18.66)		112 (11.13)	95 (14.14)		79 (16.63)	58 (22.39)	
50–	391 (23.30)	232 (31.61)		238 (23.66)	153 (22.77)		132 (27.79)	100 (38.61)	
60–	540 (32.18)	222 (30.25)		328 (32.60)	212 (31.55)		157 (33.05)	65 (25.10)	
70–	397 (23.66)	94 (12.81)		249 (24.75)	148 (22.02)		75 (15.79)	19 (7.34)	
≥ 80	95 (5.66)	16 (2.18)		53 (5.27)	42 (6.25)		13 (2.74)	3 (1.16)	
Artery of IA, <i>n</i> (%)			<0.001			0.002			<0.001
ICA	932 (55.18)	294 (40.05)		593 (58.48)	339 (50.22)		225 (47.37)	69 (26.64)	
VA	51 (3.02)	23 (3.13)		25 (2.47)	26 (3.85)		15 (3.16)	8 (3.09)	
BA	67 (3.97)	11 (1.50)		34 (3.35)	33 (4.89)		6 (1.26)	5 (1.93)	
ACoA	169 (10.01)	204 (27.79)		80 (7.89)	89 (13.19)		99 (20.84)	105 (40.54)	
ACA	99 (5.86)	50 (6.81)		61 (6.02)	38 (5.63)		31 (6.53)	19 (7.34)	
MCA	270 (15.99)	126 (17.17)		161 (15.88)	109 (16.15)		78 (16.42)	48 (18.53)	
PCA	56 (3.32)	10 (1.36)		36 (3.55)	20 (2.96)		7 (1.47)	3 (1.16)	
Other arteries	45 (2.66)	16 (2.18)		24 (2.37)	21 (3.11)		14 (2.95)	2 (0.77)	
Size, mean ± SD, mm	7.90 ± 6.28	7.86 ± 3.97	0.849	7.96 ± 6.19	7.81 ± 6.42	0.645	7.88 ± 4.03	7.82 ± 3.87	0.867
Size, <i>n</i> (%), mm			<0.001			0.741			0.752
≤ 3	104 (6.16)	10 (1.36)		67 (6.61)	37 (5.48)		8 (1.68)	2 (0.77)	
3–	524 (31.02)	140 (19.07)		305 (30.08)	219 (32.44)		86 (18.11)	54 (20.85)	
5–	389 (23.03)	220 (29.97)		234 (23.08)	155 (22.96)		141 (29.68)	79 (30.50)	
7–	234 (13.85)	169 (23.02)		139 (13.71)	95 (14.07)		112 (23.58)	57 (22.01)	
9–	153 (9.06)	95 (12.94)		100 (9.86)	53 (7.85)		66 (13.89)	29 (11.20)	
11–	83 (4.91)	48 (6.54)		50 (4.93)	33 (4.89)		31 (6.53)	17 (6.56)	
≥ 13	202 (11.96)	52 (7.08)		119 (11.74)	83 (12.30)		31 (6.53)	21 (8.11)	
Multiple IA, <i>n</i> (%)	813 (48.13)	147 (20.03)	<0.001	539 (53.16)	274 (40.59)	< 0.001	119 (25.05)	28 (10.81)	<0.001
Hypertension, <i>n</i> (%)	583 (34.52)	417 (56.81)	<0.001	351 (34.62)	232 (34.37)	0.959	263 (55.37)	154 (59.46)	0.322
ICH history, <i>n</i> (%)	147 (8.70)	170 (23.16)	<0.001	86 (8.48)	61 (9.04)	0.757	114 (24.00)	56 (21.62)	0.523
Ischemic stroke, <i>n</i> (%)	515 (30.55)	134 (18.26)	<0.001	298 (29.48)	217 (32.15)	0.266	93 (19.58)	41 (15.83)	0.248

IA, intracranial aneurysm; RIA, ruptured intracranial aneurysm; UIA, unruptured intracranial aneurysm; ICH, intracerebral hemorrhage; ICA, internal carotid artery; VA, vertebral artery; BA, basilar artery; ACoA, anterior communicating artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

significant difference in the age composition between sexes was detected in the UIA group; however, there was a significant difference in the age composition between sexes ($p < 0.001$) in the RIA group; females were older than males (60.29 ± 10.99 vs. 56.44 ± 10.69 years, $p < 0.001$).

When comparing sex differences between IAs from patients who had single and multiple IAs, we found there was a higher aneurysm rupture proportion for female than male patients in both single and

multiple IA groups (42.8% vs. 36.5% in the single IA group and 18.1% vs. 9.3% in the multiple IA group, [Supplementary Table S6](#)).

The ICA was the most common site of aneurysm in both females (58.48%) and males (50.22%), while in the RIA group, the ICA (47.37%) was the most frequent location in females, while the ACoA (40.5%) was the most frequent location in males.

Regarding aneurysm size, 3–7 mm was most common, accounting for 67.91 and 72.06% of UIA and RIA group aneurysms, respectively.

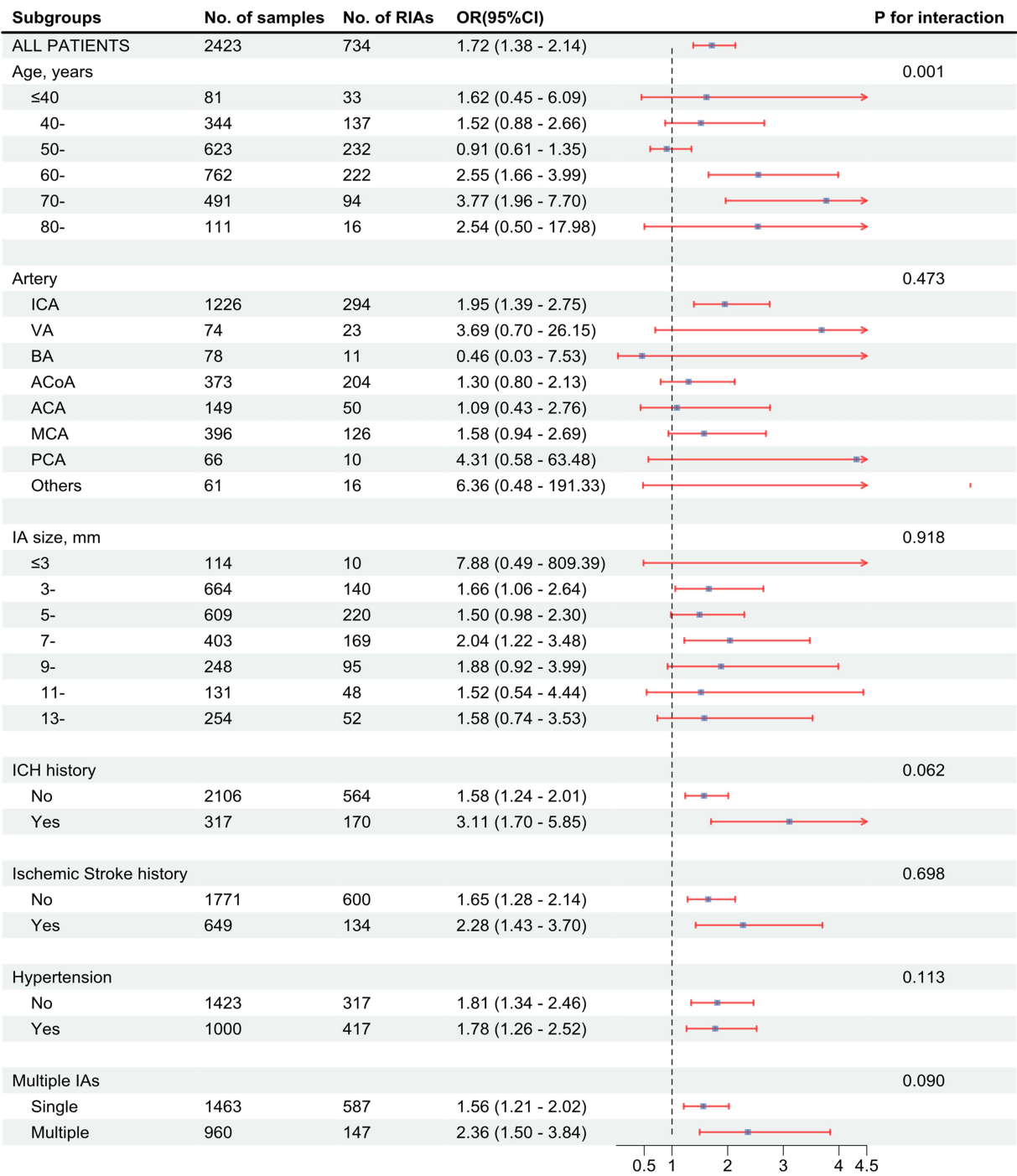


FIGURE 1
Associations between being female sex and intracranial aneurysm (IA) rupture in subgroups. Forest plot showing odds ratio (OR) with 95% confidence interval (95% CI) values of ruptured intracranial aneurysms (RIAs) in females compared with males. *p* value for interaction was used to analyze whether there was an effect modification across the different subgroups. OR values were calculated based on a logistic model adjusted for age, artery location, IA size, history of intracerebral hemorrhage (ICH), history of ischemic stroke, hypertension, and IA multiplicity. The *p* value for interaction is based on an ANOVA of interaction terms within the model used. ICA, internal carotid artery; VA, vertebral artery; BA, basilar artery; ACoA, anterior communicating artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

More giant aneurysms (≥ 13 mm) were recorded in the UIA group than in the RIA group (11.96% vs. 7.08%); however, when grouped by sex, aneurysm size distributions were similar in the UIA and RIA groups. Multiple IAs were more frequent in the UIA group and in females. A history of hypertension and intracerebral hemorrhage was more common in the UIA group, while ischemic stroke was more

common in the RIA group; however, comparisons between the RIA and UIA groups did not reveal significant associations of sex with the risk of hypertension, intracerebral hemorrhage, or ischemic stroke.

The risk of aneurysm rupture in females compared with that in males across each subgroup is illustrated in [Figure 1](#). Overall, the risk of rupture in females was greater [adjusted OR (aOR), 1.72 (95% CI,

TABLE 3 Associations between risk factors and intracranial aneurysm rupture by sex.

Variable	Total		Female		Male	
	aOR (95% CI)*	p for trend	aOR (95% CI)*	p for trend	aOR (95% CI)*	p for trend
Female Sex	1.72 (1.38–2.14)					
Age, years		<0.001		0.012		<0.001
≤40	1.83 (1.06–3.14)		1.80 (0.86–3.73)		2.32 (0.99–5.41)	
4–	1.51 (1.10–2.06)		1.28 (0.85–1.91)		2.07 (1.23–3.50)	
50–	1.27 (0.97–1.65)		0.92 (0.66–1.29)		2.34 (1.48–3.73)	
60–	1.00 (reference)		1.00 (reference)		1.00 (reference)	
70–	0.66 (0.48–0.90)		0.73 (0.51–1.06)		0.44 (0.23–0.83)	
≥80	0.48 (0.25–0.86)		0.54 (0.26–1.06)		0.29 (0.06–0.94)	
Artery of IA						
ICA	1.00 (reference)		1.00 (reference)		1.00 (reference)	
VA	1.36 (0.75–2.38)		1.63 (0.77–3.37)		1.10 (0.41–2.76)	
BA	0.51 (0.23–1.02)		0.47 (0.16–1.16)		0.59 (0.17–1.79)	
ACoA	2.73 (2.05–3.63)		2.43 (1.67–3.56)		3.19 (2.02–5.07)	
ACA	1.09 (0.71–1.65)		0.91 (0.54–1.53)		1.64 (0.77–3.42)	
MCA	1.17 (0.87–1.55)		1.08 (0.75–1.54)		1.45 (0.87–2.40)	
PCA	0.51 (0.22–1.08)		0.48 (0.17–1.19)		0.53 (0.11–1.87)	
Other arteries	1.06 (0.53–2.02)		1.45 (0.65–3.12)		0.43 (0.06–1.80)	
Size, mm		0.510		0.518		0.863
≤ 3	0.35 (0.16–0.71)		0.42 (0.17–0.95)		0.27 (0.04–1.05)	
3–	1.00 (reference)		1.00 (reference)		1.00 (reference)	
5–	1.85 (1.39–2.48)		1.80 (1.25–2.59)		2.17 (1.32–3.61)	
7–	2.55 (1.86–3.50)		2.68 (1.81–3.97)		2.37 (1.36–4.14)	
9–	2.26 (1.56–3.26)		2.37 (1.52–3.70)		2.36 (1.21–4.58)	
11–	2.05 (1.29–3.25)		2.25 (1.27–3.97)		1.78 (0.77–4.06)	
≥13	1.09 (0.72–1.62)		1.07 (0.64–1.78)		1.10 (0.55–2.14)	
Multiple IA		<0.001		<0.001		<0.001
Single	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Multiple	0.27 (0.21–0.34)		0.29 (0.22–0.39)		0.18 (0.11–0.29)	
ICH history	3.21 (2.41–4.29)		4.00 (2.79–5.77)		2.33 (1.42–3.83)	
Ischemic stroke	0.39 (0.29–0.51)		0.43 (0.30–0.60)		0.31 (0.19–0.50)	
Hypertension	4.32 (3.44–5.44)		3.74 (2.82–4.98)		5.83 (3.92–8.81)	

*Adjusted for IA in other arteries, history of intracerebral hemorrhage, history of ischemic stroke, hypertension, age, size of IA, and sex. This model is fitted at the patient level for corrected adjustment of the artery variable. The reference level was set based on which level had the largest size in the study sample. IA, intracranial aneurysm; aOR, adjusted odds ratio; CI, confidence interval; ICA, internal carotid artery; VA, vertebral artery; BA, basilar artery; ACoA, anterior communicating artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

1.38–2.14)], regardless of history of stroke, hypertension, or multiple aneurysms. Across age groups, the risk of rupture was only greater in females in the 60–70 and 70–80 year-old groups [aOR, 2.55 (95% CI, 1.66–3.99) and 3.77 (95% CI, 0.96–7.70), respectively]. There was a greater risk of ruptured aneurysm in the ICA in females [aOR, 1.95 (95% CI, 1.39–2.75)] than that in males. In the subgroups based on the covariates used in this study, we only identified statistically significant interaction between sex and age. In the results of propensity score matching, we found that females have a higher risk of IA rupture [aOR, 1.57 (95% CI, 1.25–1.99), [Supplementary Table S5](#)], which is similar to the result of direct grouping. A comparison of risk factors

for ruptured aneurysm between females and males is presented in [Table 3](#). N-shaped associations between IA size and the risk of rupture in both sexes were similar, with IAs 7–11 mm in size at greater risk of rupture ([Figure 2](#); [Supplementary Figure S2](#)). Spline regression analysis showed that the association between age and aneurysm rupture was linear in females, while that in males was nonlinear. Risk of rupture was highest in females aged 30 years and decreased with age. There was no age difference in men until 50 years old, after which the risk decreased with age ([Figure 3](#); [Supplementary Table S2](#)). E value calculation indicated that the results were robust and without confounding bias ([Supplementary Figure S4](#)).

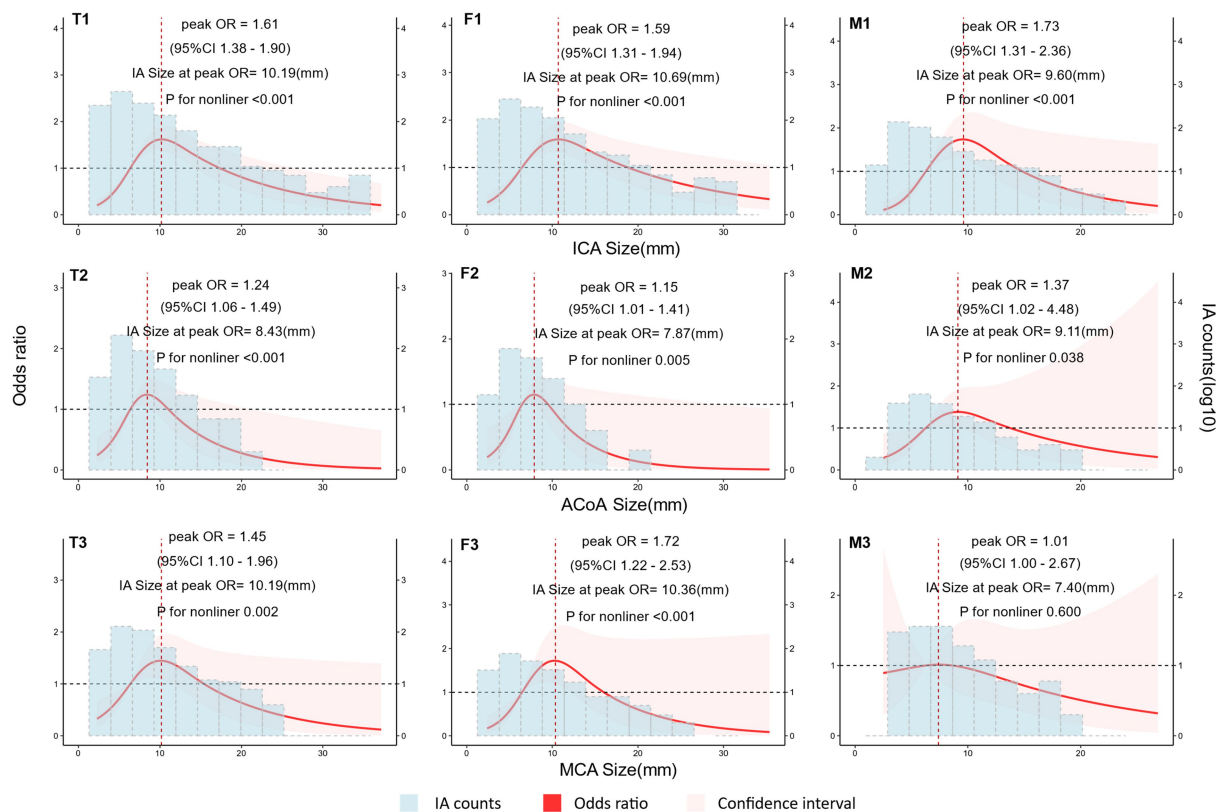


FIGURE 2

Nonlinear association between intracranial aneurysm (IA) size and rupture according to sex. Plot showing the association of IA size with IA rupture across different arteries according to sex. An n-shaped association was found for the ICA, ACoA, and MCA in females and for the ICA in males. Odds ratio (OR) and 95% confidence interval (95% CI) values were calculated per unit (mm) change using restricted cubic spline analysis, then adjusted for history of intracerebral hemorrhage, history of ischemic stroke, hypertension, IA multiplicity, and age. OR changed with IA size. IA count density is displayed on a log10 scale. T1, total IAs in the internal carotid artery (ICA); T2, total IAs in the anterior communicating artery (ACoA); T3, total IAs in the middle cerebral artery (MCA); F1, IAs in the ICA of females; F2, IAs in the ACoA of females; F3, IAs in the MCA of females; M1, IAs in the ICA of males; M2, IAs in the ACoA of males; M3, IAs in the MCA of males.

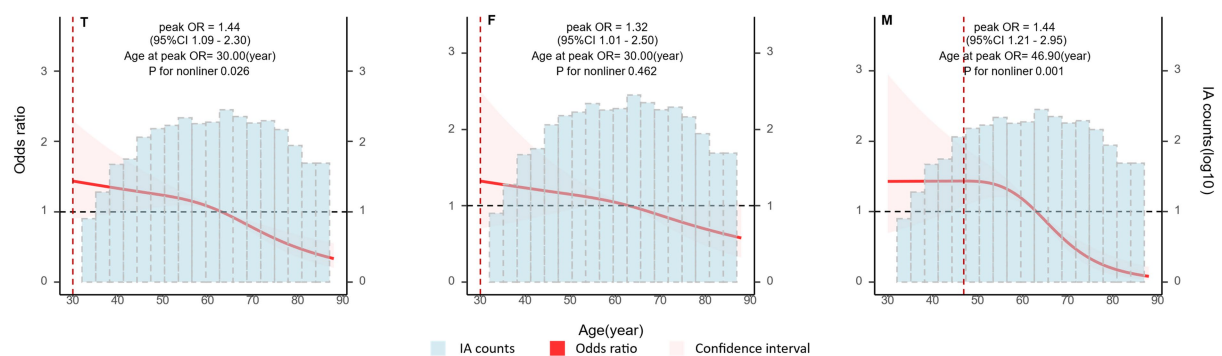


FIGURE 3

Associations between patient age and intracranial aneurysm (IA) rupture by sex. Plot showing the association between patient age and IA rupture. A nonlinear association was detected in males. Odds ratio (OR) and 95% confidence interval (CI) values were calculated per unit (year) change using restricted cubic spline analysis, then adjusted for history of intracerebral hemorrhage, history of ischemic stroke, hypertension, IA multiplicity, and IA size. IA, intracranial aneurysm; T, both sexes; F, female group; M, male group.

4 Discussion

In this study, we explored sex-specific factors associated with IAs and ruptured IAs in a Chinese population. To the best of our

knowledge, there have been no similar reports to date. Almost 60% of patients with IAs were female, and the rate of IA rupture was greater in females than that in males. These results are consistent with previous reports (6–8).

The main risk factors for aneurysm development and rupture risk are considered to include genetic factors, age, hypertension, behavioral factors, such as smoking and alcohol consumption, estrogen deficiency, aneurysm size, morphology, and location, and blood flow pressure factors (12, 15, 19–21). Although women have a greater risk of aneurysm rupture than men, this sex difference cannot be explained by differences in risk factors established as associated with aneurysm occurrence and rupture (20). Therefore, more studies are needed to explore the factors influencing sex differences in aneurysm occurrence and rupture.

Our findings regarding aneurysm location are similar to those of previous reports, showing that IAs occur predominantly in the ICA, ACoA, and MCA (4, 6, 22); however, most previous studies did not explore sex differences in aneurysm sites. In the present study, we found that ICA aneurysms were more common in females, whereas ACoA aneurysms were more common in males, similar to a previous report from Japan (23). Nevertheless, after controlling for covariates, we found that the highest risk of IA rupture in both females and males was in the ACoA (Table 3). Another study that included a Chinese population of 2,085 patients with SAH also showed that the predominant aneurysm rupture site in both men and women was the ACoA (24). These findings suggest that aneurysm site is not a sex-specific factor for the risk of aneurysm rupture.

Many studies have shown a positive correlation between IA size and risk of rupture, with larger aneurysms having a greater risk of rupture (7, 25–27); based on this, assessment methods, such as the HASE score, have also proposed aneurysm size as a threshold for assessing risk of rupture (15). In this study, we grouped the arteries with higher proportions of aneurysms into three subgroups (ICA, ACoA, and MCA) and compared the sex differences between aneurysm size and rupture risk in each subgroup separately. We also divided patients into 40–49, 50–59, 60–69, and 70–79 year-old age groups, and compared the sex differences between aneurysm size and rupture risk separately. We found similar “n”-shaped associations between aneurysm size and rupture for the different artery and age subgroups in both sexes, after controlling for other covariates (Figure 2; Supplementary Figure S2), suggesting that aneurysm size is not an influential factor contributing to the sex difference in aneurysm rupture.

Our univariate analyses indicated that factors associated with rupture included age, aneurysm site, aneurysm size, multiple aneurysms, hypertension, and stroke, when sex was not taken into account (Table 2), similar to previous reports (8, 28). In multivariate analyses, age, aneurysm size, and location were associated with rupture; however, when grouped by sex, the only factor with sex-differentiated effects was age. Numerous studies have identified age differences in the incidence of cerebral aneurysms in men and women [40], but few have compared the age distribution of IA ruptures by sex. We found that IA rupture occurred approximately 10 years earlier in males than in females, with a greater incidence in the 50–59 years age group in males and in the 60–69 years age group in females. These results are consistent with those of a previous study showing that IA ruptures occur earlier in males than in females (29). Since IA rupture is more common in women older than 50 years, many researchers have proposed that the development of cerebral aneurysms is associated

with estrogen deficiency (28, 30–32). We found that the frequency of IAs was greater in females than males in every age group (Table 2), but the age distributions of UIAs in females and males were identical and normally distributed, with the highest prevalence in the 50–70-year-old group. If estrogen deficiency is a major factor in aneurysm development, it is unlikely to show this same age distribution in both sexes. Therefore, to assess whether menopause can account for the difference in the risk of IA rupture between women and men, we analyzed the relationship between age and the risk of IA rupture by sex, using nonlinear correlation analysis after controlling for the relevant covariates. We found that the risk of IA rupture did not rise with increasing age in either sex (Figure 3). Rather, risk of IA rupture was greater in younger than older patients with aneurysms. Notably, risk of IA rupture was highest in females at 30 years old and males aged 30–50 years, and tended to decrease with age in both sexes. Our results are similar to those of a previous cohort study in Canada (33). This feature of IA rupture differs from observations of non-aneurysmal SAH, risk of which increases with age (34). This result indirectly suggests that estrogen deficiency is not an independent risk factor for IA rupture. A meta-analysis showed that hormone replacement therapy use is associated with increased rates of any stroke and cause-specific stroke, including ischemic stroke and SAH (35). Additionally, a previous study reported that serum estradiol levels were not associated with the occurrence or size of cerebral aneurysms (6). Therefore, the relationship between estrogen deficiency and the development and rupture of IAs warrants further study, and estrogen deficiency may not be an independent risk factor for IA.

Hypertension is a relatively well-defined risk factor for IA rupture, as confirmed in the present study. The incidence of hypertension is greater in men than that in women up to the age of 60 years; however, after 60 years, the prevalence of hypertension is significantly greater in women than men (36, 37). Moreover, women have lower rates of blood pressure control than men after 65 years old (38). In particular, systolic blood pressure levels and pulse pressure differentials are significantly greater in women than men after 60 years old (38). This factor has also recently been suggested to increase vascular pressure through hemodynamic load-induced elastic fiber degradation and collagen deposition in the arterial wall, thereby increasing the risk of hemorrhagic stroke (36). Recently, hemorrhagic stroke has declined globally, in line with the trend in the control of hypertension (particularly systolic blood pressure) following the implementation of measures to strengthen hypertension control (12). In this study, the age distribution of IA rupture by sex was highly consistent with the age distribution of hypertension by sex, suggesting that elevated blood pressure, particularly systolic blood pressure, is the most important factor in IA rupture. Blood pressure control is an important measure for preventing IA rupture, especially in women.

IA frequency was greater in females than in males in all age groups, but the distribution pattern by age was consistent in females and males, suggesting the importance of genetic factors. Previous studies have shown that a number of monogenic and polygenic genetic disorders are associated with IA (21). Physiological sex differences attributable to genetic factors may also be responsible for sex differences in the occurrence of IAs; for example, the anatomic difference in the circle of Willis between females and males (28).

4.1 Strengths and limitations

This study had a number of strengths. First, we used real-world data and included a representative sample of all patients with IA from two tertiary general hospitals over eight consecutive years for analysis. Second, the study population included only patients undergoing first diagnosis, which may have prevented survival bias. Third, we used nonlinear correlation analysis to analyze the risk factors associated with IA rupture, whereas most previous studies conducted linear correlation analyses; our approach allowed us to determine that age tended to be negatively correlated with the risk of rupture. Fourth, we conducted subgroup analyses by sex. Our study also had several limitations. First, due to the hospital privacy policy, we were unable to obtain all raw data, such as CTA 3D reconstruction data; therefore, we were unable to include analyses of IA shape, aspect ratio, size ratio, or bottleneck factor aspect ratio in our study. Second, as our data were obtained from patients attending hospitals, asymptomatic patients and those who died before admission were not included. Third, as this study utilized data from real-world clinical practice, certain factors such as living environmental factors and genetic factors that were not investigated during the clinical process could not be analyzed in the study.

5 Conclusion

Our study provides evidence that females have a greater prevalence of IA and a higher rate of rupture than males, and that genetic factors, as well as hypertension, may be important factors underlying these differences. We hypothesize that the high incidence of IA in women may be related to inheritance of X-chromosome-linked factors, rather than estrogen deficiency, and that the sex difference in the risk of aneurysm rupture is attributable to age and hypertension; however, our conclusions should be interpreted with caution, as this was an observational study based on data from medical records. Further basic and epidemiological studies are needed to assess sex differences in IA formation, growth mechanisms, and rupture.

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 requirement of ethical approval was waived by ethics committees of the Second Affiliated Hospital of Anhui Medical University for the studies involving humans because based on Chinese Government regulations, retrospective studies using existing data, not containing identifiable personal information and not related to any future intervention, can be waived from both ethical approval and informed consent. Chinese government regulations on ethical approval of medical research (original in Chinese, Article 32): https://www.gov.cn/zhengce/zhengceku/2023-02/28/content_5743658.htm. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review

board also waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin.

Author contributions

DS: Writing – original draft, Writing – review & editing. MC: Writing – original draft. YL: Data curation, Writing – original draft. ZL: Writing – original draft. PZ: Writing – original draft. YW: Data curation, Writing – original draft. WF: Data curation, Writing – original draft. HW: Data curation, Writing – original draft. YY: Data curation, Writing – original draft. XG: Supervision, Resources, Writing – review & editing. CM: Supervision, Resources, Writing – review & editing.

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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.2024.1483679/full#supplementary-material>

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Enhancing intracranial aneurysm rupture risk prediction with a novel multivariable logistic regression model incorporating high-resolution vessel wall imaging

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Objective: This study aimed to develop and validate a multivariate logistic regression model for predicting intracranial aneurysm (IA) rupture by integrating clinical data, aneurysm morphology, and parent artery characteristics using high-resolution vessel wall imaging (HR-VWI).

Methods: A retrospective analysis was conducted on 298 patients with 386 aneurysms. Patients were randomly divided into training ($n = 308$) and validation ($n = 78$) sets. Key predictors, including aneurysm size, shape, aneurysm wall and parent artery wall enhancement, were identified through univariate analysis and then used to build the prediction model using multivariate logistic regression. The model was visualized as a nomogram and compared to PHASES and ELAPSS scores.

Results: The logistic regression model demonstrated superior predictive performance with an area under the curve of 0.814, which was significantly higher than PHASES and ELAPSS scores ($p < 0.05$). The model revealed strong calibration and good agreement between predicted and observed rupture probabilities.

Conclusion: The multivariate model based on HR-VWI, which incorporates aneurysm and parent artery features, provides a more accurate prediction of IA rupture risk than conventional scoring systems, offering a valuable tool for clinical decision-making.

KEYWORDS

intracranial aneurysm, parent artery, HR-VWI, PHASES score, ELAPSS score

1 Introduction

Intracranial aneurysms (IAs) are common vascular conditions that can lead to subarachnoid hemorrhage (SAH), a severe form of stroke with a fatality rate approaching 50% (1, 2). Accurate evaluation of rupture risk is crucial for clinical decision-making. Traditional models, such as PHASES and ELAPSS scores, only rely on clinical and

morphological data, resulting in moderate predictive accuracy (3–6).

High-resolution vessel wall imaging (HR-VWI) surpasses conventional vascular imaging by providing detailed insight into aneurysm architecture and wall enhancement (AWE) (7). Studies suggest that AWE, which reflects inflammatory activity after contrast administration, strongly correlates with aneurysm rupture risk, thus improving the accuracy of IA risk predictions (8). This technique is more effective for assessing the likelihood of IA rupture. Current research using HR-VWI for IA rupture risk primarily focuses on qualitative and quantitative assessments of AWE (9, 10), often neglecting the role of the parent artery. However, emerging evidence indicates that vessel wall enhancement near the aneurysm neck is associated with aneurysm development and progression (11). Despite this, few studies have incorporated parent artery analysis in HR-VWI-based rupture risk assessments, underutilizing its predictive potential.

This study aimed to improve IA rupture risk prediction by integrating clinical profiles, aneurysm and parent artery morphometrics, and HR-VWI-derived features. We developed a predictive model using multivariate logistic regression, visualized it as a nomogram, and compared its performance against PHASES and ELAPSS scoring systems.

2 Materials and methods

2.1 Study subjects

This study was approved by our institutional review committee (Ethics Committee: Ke Lun Review No. 194) and obtained written informed consent from all participants. We conducted a retrospective analysis of patients diagnosed with IAs through head computed tomography angiography at our hospital between October 2019 and October 2023. The inclusion criteria were as follows: (1) ruptured or unruptured saccular aneurysms with SAH attributable to aneurysm rupture; (2) high-quality three-dimensional (3D) HR-VWI data indicating the aneurysm and adjacent 3 mm of the parent artery. The exclusion criteria were as follows: (1) incomplete HR-VWI images; (2) dissection or fusiform aneurysms; (3) post-treatment aneurysms; (4) multiple aneurysms with unclear rupture source; (5) poor HR-VWI image quality or aneurysms too small to assess wall features.

2.2 Data collection

2.2.1 Patient information

We collected data on age, gender, ethnicity, and previous medical history (including hypertension, diabetes, hyperlipidemia, coronary heart disease, smoking, and history of SAH). We also recorded the history of the present illness and the date of imaging, as obtained from the hospital's electronic medical records for both inpatients and outpatients. For incomplete records, supplementary information was gathered through telephone follow-up.

2.2.2 Risk scoring

The PHASES score (12) was used to assess aneurysm rupture risk based on ethnicity, hypertension, age, aneurysm size, history of SAH,

and location. The ELAPSS score (13) was applied to evaluate the growth risk of IA, considering the history of SAH, aneurysm location, age, ethnicity, aneurysm size, and shape.

2.3 Imaging examination

2.3.1 Magnetic resonance imaging (MRI) protocol

MRI scans were conducted using an Ingenia CX 3.0 T scanner with a 32-channel head coil. The protocol began with 3D time-of-flight (TOF) magnetic resonance angiography (MRA) for IA localization, followed by axial 3D T1-weighted volume isotropic turbo spin echo acquisition (VISTA) sequences for targeted imaging of the parent artery. A contrast agent, gadopentetate dimeglumine (0.1 mmol/kg, Gd-DOTA, Jiangsu, China), was manually injected into the antecubital vein. HR-VWI was repeated 5 min after the contrast injection to acquire contrast-enhanced HR-VWI (CE-HR-VWI). Scan parameters included a field of view (FOV) $200 \times 200 \text{ mm}^2$, slice thickness 0.50 mm, slices 80, TR/TE 800/22 ms, flip angle 90° , and voxel size $0.6 \times 0.6 \times 0.6 \text{ mm}^3$. Images were processed using the Philips IntelliSpace Portal V12 workstation.

2.4 Imaging assessment

2.4.1 Morphological features of IAs and parent arteries

We evaluated the location, configuration (whether at bifurcations or sidewalls), and shape (including regularity and the presence of daughter sacs) of aneurysms using three-dimensional reconstructed images from TOF-MRA. Using two-dimensional measurement tools on HR-VWI images, we obtained the size of aneurysms, including neck width (NW), maximum height (MH), maximum width (MW), and parent artery diameter (PAD) (Figure 1) (14). From these measurements, we calculated the aneurysm's aspect ratio (AR), size ratio (SR), and neck-to-parent ratio (NPR).

2.4.2 Characteristics of aneurysm and parent artery walls on HR-VWI

Two neuroradiologists with over 10 years of diagnostic experience independently performed a blinded analysis of the HR-VWI and CE-HR-VWI images. The two neuroradiologists were unaware of the clinical data but were aware of the location of the aneurysm. When there was a disagreement, a third neuroradiologist with over 20 years of diagnostic experience would intervene to negotiate a resolution.

2.4.2.1 Qualitative analysis

A qualitative analysis was conducted to evaluate AWE severity, which was categorized into three grades: Grade 0 (no enhancement, similar signal intensity on both images), Grade 1 (focal, localized non-circular enhancement), and Grade 2 (ring enhancement, with enhancement throughout the entire aneurysm wall) (15) (Figure 2).

2.4.2.2 Quantitative analysis

Two neuroradiologists conducted quantitative measurements evaluating the following parameters from the optimal viewing angle (sagittal, frontal plane, and horizontal plane). All measurements were made at an image magnification of 500%.

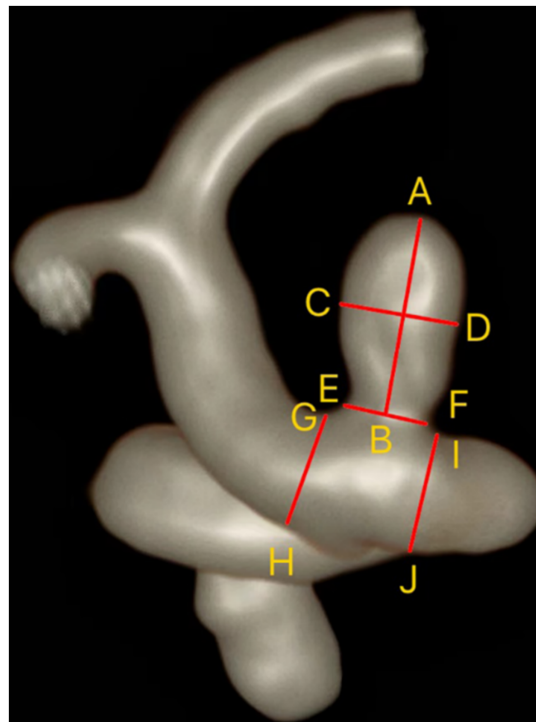


FIGURE 1

Measurement of IAs and parent artery. Maximum height (MH) = AB; Maximum width (MW) = CD; Neck width (NW) = EF; Parent artery diameter (PAD) = (GH + IJ)/2.

The thickest part of the aneurysm wall and the parent artery wall were measured three times at the direct boundary, and the average value was calculated as aneurysm wall thickness (AWT) and parent artery wall thickness (PAWT) (Figures 3A,C).

AWE was evaluated using the Wall Enhancement Index (WEI) and the contrast ratio between the aneurysm wall and the pituitary stalk (CR_{stalk}) (Equations 1, 2) (16, 17). Parent artery wall enhancement (PAWE) was evaluated using the parent artery wall enhancement index (PWEI) and the contrast ratio between the parent artery wall and the pituitary stalk (PCR_{stalk}) (Equations 3, 4).

$$WEI = \frac{SI_{AW(Post)} / SI_{RFWM(Post)} - SI_{AW(Pre)} / SI_{RFWM(Pre)}}{SI_{AW(Pre)} / SI_{RFWM(Pre)}} \quad (1)$$

$$CR_{stalk} = \frac{SI_{AW(Post)}}{SI_{PS(Post)}} \quad (2)$$

$$PWEI = \frac{SI_{PA(Post)} / SI_{RFWM(Post)} - SI_{PA(Pre)} / SI_{RFWM(Pre)}}{SI_{PA(Pre)} / SI_{RFWM(Pre)}} \quad (3)$$

$$PCR_{stalk} = \frac{SI_{PA(Post)}}{SI_{PS(Post)}} \quad (4)$$

The post-contrast SI of the aneurysm wall ($SI_{AW(post)}$) and parent artery ($SI_{PA(post)}$) was measured separately three times on post-contrast images on the layer of their respective maximum diameters, and the highest value was recorded as the enhanced SI (Figures 3B,C). Furthermore, the measurement range for parent artery was within 3 mm of the aneurysm neck. The region of interest (ROI) was 0.1 mm². The pre-contrast SI of the aneurysm wall ($SI_{AW(pre)}$) and parent artery ($SI_{PA(pre)}$) was measured using the same method at the corresponding site. The SI of the right frontal white matter (SI_{RFWM}) was measured as a reference on both pre- and post-contrast images. The ROI was 20 mm². Additionally, the pituitary stalk SI ($SI_{PS(post)}$) was measured three times on the upper, middle, and lower parts of the pituitary stalk on CE-HR-VWI images and the highest value among them was recorded. The ROI was 0.1 mm² (18).

2.5 Statistical methods

Statistical analysis was performed using R software (version 4.2.3). Kappa statistics evaluated inter-rater agreement on AWE ($\kappa > 0.75$, indicating good concordance). Intra-class correlation coefficient (ICC) was used to assess the reliability for WEI, PWEI, CR_{stalk} , PCR_{stalk} , AWT, and PAWT (ICC > 0.75, indicating good reliability). The Shapiro-Wilk test was applied to assess the distributions of variables. T-tests, F-tests, and Chi-square tests were used to differentiate ruptured and unruptured IAs. Multivariate logistic regression including univariate predictors ($p < 0.2$) attained aneurysm rupture with 95% confidence interval [CI] and then selected predictors

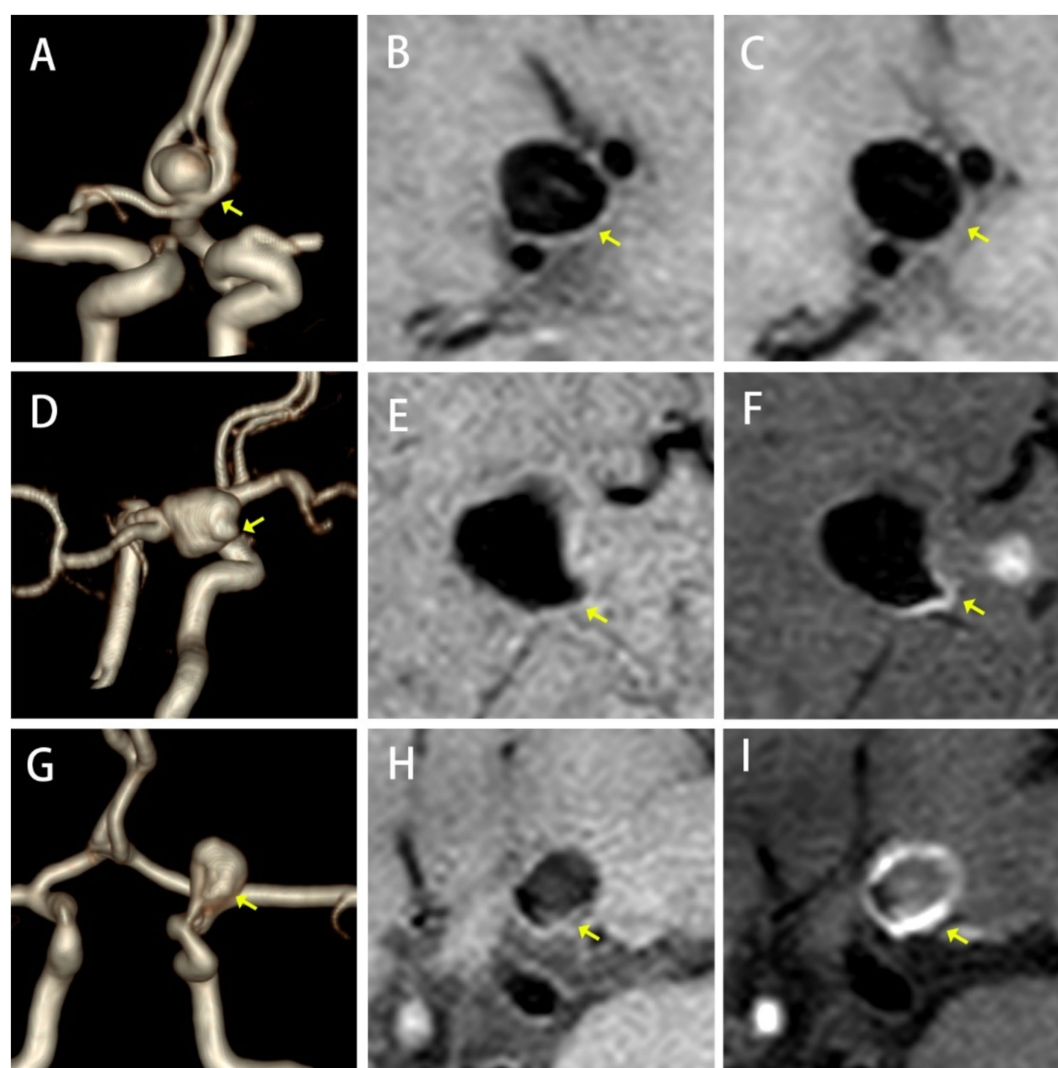


FIGURE 2

Types of AWE. No Enhancement, (A) TOF-MRA, (B) HR-VWI, and (C) CE-HR-VWI; Focal Enhancement, (D) 3D-TOF-MRA, (E) HR-VWI, and (F) CE-HR-VWI; Ring Enhancement, (G) 3D-TOF-MRA, (H) HR-VWI, and (I) CE-HR-VWI.

($p < 0.05$) for model construction. Receiver-operating characteristic (ROC) curves were used to benchmark model accuracy, and the PHASES and ELAPSS normalized scores (0–1) were compared with the logistic regression model. The DeLong test ($p < 0.05$) was applied to determine statistical significance (19).

3 Results

3.1 Univariate and multivariate analyses of IA rupture prediction factors

A total of 386 IAs from 298 patients were randomly divided into training (80%) and validation (20%) sets to analyze predictors of IA rupture and for model development and validation (Table 1; Figure 4). In both sets, IAs were classified into two groups: ruptured IAs were classified as the ruptured group, and unruptured IAs were classified as the unruptured group.

Inter-rater reliability for AWE classification was high ($\kappa = 0.871$; 95% CI: 0.751–0.991). The consistency between the two evaluators in measuring morphological features and assessing enhancement SI assessments was also strong (ICC = 0.933; 95% CI: 0.886–0.961).

3.1.1 Collection of prediction factors

In this study, 25 potential predictors were evaluated, covering clinical traits, morphological attributes of the aneurysm and its parent artery, and characteristics of both the aneurysm and parent artery walls. Specifically, clinical factors included age, gender, a history of hypertension, diabetes, hyperlipidemia, coronary artery disease, smoking, and prior SAH. Morphological parameters included aneurysm location, configuration (bifurcation or sidewall), morphology (regularity, presence of daughter sacs), size (NW, MH, and MW), and indices such as PAD, AR, SR, and NPR. Wall features were assessed using WEI, CR_{stalks} and AWT for the aneurysm wall, and PWEI, PCR_{stalks} and PAWT for the parent artery wall.

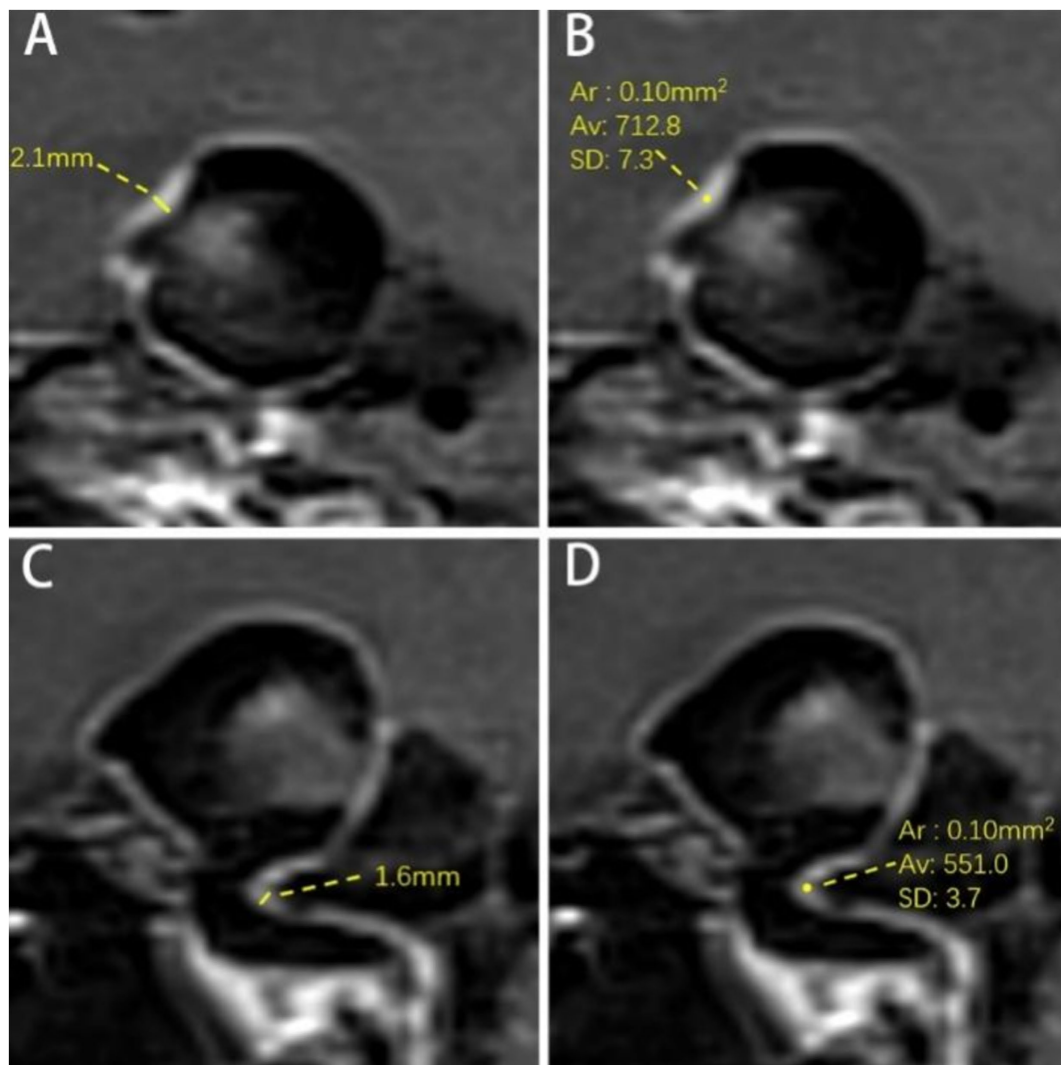


FIGURE 3

Measurement of aneurysm wall and parent artery. (A) Measurement of AWT. The AWT is 2.1 mm. (B) Measurement SI of AWE. The signal intensity of the aneurysm wall is 712.8. (C) Parent artery wall thickness (PAWT). The PAWT is 1.6 mm. (D) Parent artery wall signal intensity. The signal intensity of the parent artery wall is 551.0. Ar = Average Range; Av = Average Signal Intensity of ROI; SD = Standard Deviation.

3.1.2 Results of univariate analysis and multivariate logistic analysis

Univariate analysis identified 18 factors associated with aneurysm rupture, including (1) morphological characteristics: aneurysm location, shape (regularity, presence of daughter sacs), NW, MH, MW, PAD, AR, SR, NPR; (2) aneurysm wall characteristics: wall enhancement classification, parent artery thickness classification, WEI, CR_{stalk} and AWT; (3) parent artery wall characteristics: PWEI, PCR_{stalk} and PAWT ($p < 0.05$) (Table 2).

Multivariate analysis identified the following independent risk factors for IA rupture: irregular aneurysm shape ($p = 0.004$, odds ratio [OR] = 5.55, 95% CI: 1.72–17.89), MW of the aneurysm ($p = 0.03$, OR = 0.62, 95% CI: 0.40–0.96), CR_{stalk} ($p = 0.01$, OR = 107.21, 95% CI: 3.00–3828.00) and PCR_{stalk} ($p = 0.007$, OR = 189.0, 95% CI: 4.30–8309.76).

3.2 Construction and visualization of the multivariate logistic regression model

A multivariate logistic regression model (MLRM) was developed, incorporating four independent risk factors for IA rupture into a numerical assessment of rupture probability. The Equation is as follows:

$$\text{LOG}\left[\frac{p(\text{An})}{1-p(\text{An})}\right] = 1.945 \times \text{regularity}(0|1) - 0.303 \times \text{MW} + 5.440 \times \text{CR}_{\text{stalk}} + 4.506 \times \text{PCR}_{\text{stalk}} - 6.436 \quad (5)$$

Equation 5 shows MLRM of IAs rupture risk.

In this Equation, $p(\text{An})$ represents the estimated rupture probability of the aneurysm rupture. This predictive model has been converted into a visual nomogram (Figure 5).

TABLE 1 Characteristics of patients and aneurysms in training and testing sets.

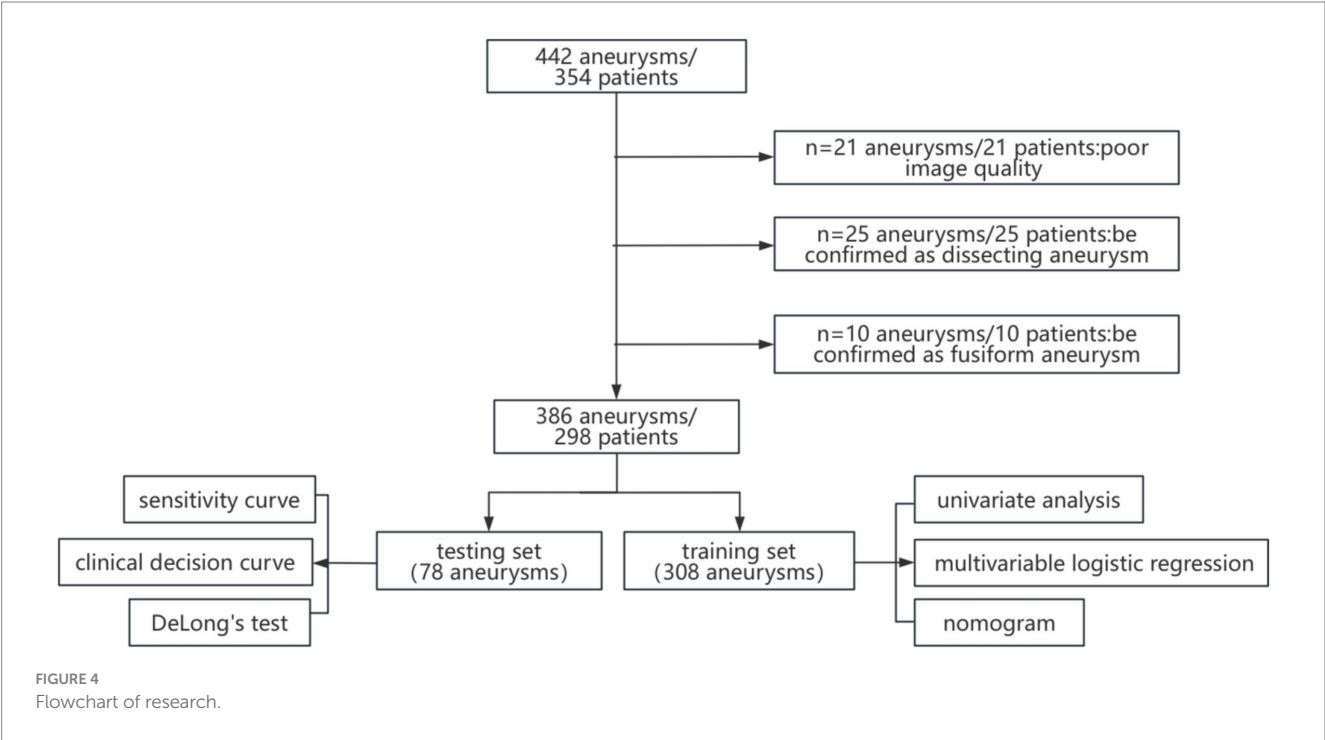
Features	Groups	
	Training set (<i>n</i> = 308)	Testing set (<i>n</i> = 78)
I Clinical features		
Mean Age (years)	60.0 [51.0, 68.0]	57.5 [51.0, 70.0]
Male/Female (%)	210/98 (68.7%/31.3%)	49/29 (62.8%/37.2%)
History of prior SAH (%)	3 (0.97%)	2 (2.56%)
Hypertension (%)	158 (51.3%)	49 (62.8%)
Hyperlipidemia (%)	112 (36.4%)	34 (43.6%)
Coronary artery disease (%)	34 (11.0%)	5 (6.41%)
Diabetes (%)	34 (11.0%)	9 (11.5%)
Smoking History (%)	71 (23.1%)	20 (25.6%)
II Morphological features		
Aneurysm shape		
Irregular	195 (63.3%)	32 (41.0%)
Regular	113 (36.7%)	46 (59.0%)
Daughter sacs		
Present	50 (16.2%)	14 (17.9%)
Absent	258 (83.8%)	64 (82.1%)
Aneurysm location		
Internal carotid artery	170 (55.2%)	27 (34.6%)
Anterior cerebral artery	11 (3.57%)	8 (10.3%)
Anterior communicating artery	25 (8.12%)	8 (10.3%)
Middle cerebral artery	55 (17.9%)	15 (19.2%)
Posterior circulation	18 (5.84%)	8 (10.3%)
Posterior communicating artery	29 (9.42%)	12 (15.4%)
Side Wall/Bifurcation (%)	259/49 (84.1%/15.9%)	60/18 (76.9%/23.1%)
Aneurysm size (mm)		
NW	3.32 [2.60, 4.35]	3.48 [2.27, 4.34]
MW	3.72 [2.65, 5.81]	3.97 [2.61, 6.72]
MH	3.74 [2.64, 5.70]	3.59 [2.66, 5.79]
PAD (mm)	3.09 [2.34, 3.76]	2.79 [2.14, 3.43]
Morphological ratio		
AR	1.18 [0.91, 1.56]	1.20 [0.88, 1.69]
SR	1.28 [0.81, 2.05]	1.41 [0.83, 2.78]
NPR	1.08 [0.81, 1.59]	1.18 [0.83, 1.76]
III Aneurysm wall features		
Thickness	0.96 [0.78, 1.13]	1.00 [0.80, 1.18]
Thickness classification		
<1 mm	176 (57.1%)	39 (50.0%)
≥1 mm	132 (42.9%)	39 (50.0%)
Enhancement classification		
No enhancement	184 (59.7%)	33 (42.3%)
Focal enhancement	40 (13.0%)	11 (14.1%)
Ring enhancement	84 (27.3%)	34 (43.6%)
WEI	0.40 [0.26, 0.82]	0.61 [0.30, 1.03]

(Continued)

TABLE 1 (Continued)

Features	Groups	
	Training set (<i>n</i> = 308)	Testing set (<i>n</i> = 78)
CR _{stalk}	0.47 [0.38, 0.72]	0.59 [0.40, 0.80]
IV Parent artery wall features		
Thickness	0.92 [0.81, 1.05]	0.95 [0.85, 1.08]
PWEI	0.30 [0.17, 0.52]	0.35 [0.21, 0.56]
PCR _{stalk}	0.39 [0.32; 0.54]	0.45 [0. 34, 0.59]
Atherosclerosis of the parent artery (%)	90 (29.2%)	20 (25.6%)
V Clinical risk score		
ELAPSS score	10.0 [5.00, 18.0]	11.0 [6.00, 18.0]
PHASES score	2.00 [1.00, 5.00]	4.00 [2.00, 5.00]

NW, Neck width; MW, Maximum width; MH, Maximum height; PAD, Parent artery diameter; AR, Aspect ratio; SR, Size ratio; NPR, Neck-to-parent ratio; WEI, Wall enhancement index; CR_{stalk}, Contrast ratio of the aneurysm wall against the pituitary stalk; PWEI, Parent artery wall enhancement index; PCR_{stalk}, Contrast ratio of the parent artery wall against the pituitary stalk.



3.3 Validation of the MLRM and comparison with ELAPSS and PHASES scores

The MLR nomogram model demonstrated strong predictive performance in the validation set, with an area under the ROC curve of 0.814 (95% CI: 0.722–0.911) (Figure 6), the highest among the three predictive models (Table 3). The DeLong test indicated a significant difference in predictive efficacy, with the MLR model outperforming the ELAPSS Score ($p = 0.037$) and the PHASES Score ($p = 0.040$).

The calibration curve (Figure 7) aligned closely with the diagonal line, suggesting good agreement between predicted and observed probabilities of IA rupture.

Decision curve analysis (Figure 8) revealed that the MLR model, which incorporates aneurysm morphology, aneurysm wall

characteristics, and parent artery wall features, provided more significant clinical benefit in decision-making than the other models.

4 Discussion

The PHASES and ELAPSS scores are widely used for assessing the risk of IA rupture, focusing on a limited set of clinical and morphological factors. HR-VWI is recognized as a superior diagnostic tool for intracranial vascular pathologies, including aneurysm diagnosis (20, 21). As research into IA imaging progresses, evidence suggests that the pathological changes in the aneurysm wall and parent artery, identified by HR-VWI, are associated with IA rupture. This study expanded upon traditional clinical and morphological characteristics by incorporating aneurysm and parent artery features

TABLE 2 Univariate analysis of IAs rupture prediction in patients with training set.

Features	Training set (n = 308)		p
	Unruptured group (n = 243)	Ruptured group (n = 65)	
I Clinical Features			
Mean age (years)	60.0 [51.0, 68.0]	57.0 [49.0, 67.0]	0.806
Male/Female (%)	167/76 (68.7%/31.3%)	43/22 (66.2%/33.8%)	0.222
History of Prior SAH (%)	3 (1.23%)	0 (0%)	1.0
Hypertension (%)	126 (51.9%)	32 (49.2%)	0.814
Hyperlipidemia (%)	89 (36.6%)	23 (35.4%)	0.968
Coronary artery disease (%)	30 (12.3%)	4 (6.15%)	0.233
Diabetes (%)	28 (11.5)%	6 (9.23%)	0.763
Smoking history (%)	57 (23.5%)	14 (21.5%)	0.873
II Morphological Features			
Aneurysm shape			
Irregular	68 (28.0%)	45 (69.2%)	<0.001
Regular	175 (72.0%)	20 (30.8%)	
Daughter sacs			
Present	22 (9.05%)	28 (43.1%)	<0.001
Absent	221 (90.95%)	37 (56.9%)	
Aneurysm location			
Internal carotid artery	147 (60.5%)	23 (35.4%)	<0.001
Anterior cerebral artery	9 (3.7%)	2 (3.08%)	
Anterior communicating artery	17 (7.0%)	8 (12.3%)	
Middle cerebral artery	44 (18.1%)	11 (16.9%)	
Posterior circulation	14 (5.76%)	4 (6.15%)	
Posterior communicating artery	12 (4.94%)	17 (26.2%)	
Side Wall/Bifurcation (%)	207/36 (85.2%/14.8%)	50/15 (76.9%/23.1%)	0.160
Aneurysm size (mm)			
NW	3.17 [2.50, 4.25]	3.61 [3.01, 4.60]	0.008
MW	3.50 [2.48, 5.65]	4.31 [3.30, 6.89]	0.001
MH	3.51 [2.44, 5.20]	5.00 [3.74, 6.46]	<0.001
PAD (mm)	3.12 [2.42, 3.81]	2.82 [2.24, 3.42]	0.047
Morphological ratio			
AR	1.13 [0.87, 1.44]	1.37 [1.17, 1.72]	<0.001
SR	1.12 [0.77, 1.86]	2.43 [1.44, 3.31]	0.004
NPR	1.03 [0.77, 1.52]	1.31 [1.06, 1.77]	<0.001
III Aneurysm wall features			
AWT	0.89 [0.72, 1.06]	1.13 [1.05, 1.29]	<0.001
Thickness classification			
<1 mm	163 (67.1%)	13 (20.0%)	<0.001
≥1 mm	80 (32.9%)	52 (80.0%)	
Enhancement classification			
No enhancement	170 (70.0%)	14 (21.5%)	<0.001
Focal enhancement	26 (10.7%)	14 (21.5%)	
Ring enhancement	47 (19.3%)	37 (57.0%)	
WEI	0.35 [0.23, 0.60]	0.91 [0.68, 1.46]	<0.001

(Continued)

TABLE 2 (Continued)

Features	Training set (<i>n</i> = 308)		<i>p</i>
	Unruptured group (<i>n</i> = 243)	Ruptured group (<i>n</i> = 65)	
CR _{stalk}	0.42 [0.36, 0.57]	0.79 [0.67, 0.88]	<0.001
IV Parent artery wall features			
PAWT	0.89 [0.76, 1.00]	1.03 [0.94, 1.13]	<0.001
PWEI	0.26 [0.15, 0.39]	0.56 [0.46, 0.69]	<0.001
PCR _{stalk}	0.36 [0.31, 0.46]	0.58 [0.49, 0.69]	<0.001
Atherosclerosis of the parent artery (%)	69 (28.4%)	21 (32.3%)	0.644
V Clinical risk score			
ELAPSS score	9.00 [5.00, 17.0]	15.0 [10.0, 20.0]	<0.001
PHASES score	2.00 [1.00, 5.00]	4.00 [2.00, 6.00]	0.007

NW, Neck width; MW, Maximum width; MH, Maximum height; PAD, Parent artery diameter; AR, Aspect ratio; SR, Size ratio; NPR, Neck-to-parent ratio; AWT, Aneurysm wall thickness; WEI, Wall enhancement index; CR_{stalk}, Contrast ratio of the aneurysm wall against the pituitary stalk; PAWT, Parent artery wall thickness; PWEI, Parent artery wall enhancement index; PCR_{stalk}, Contrast ratio of the parent artery wall against the pituitary stalk.

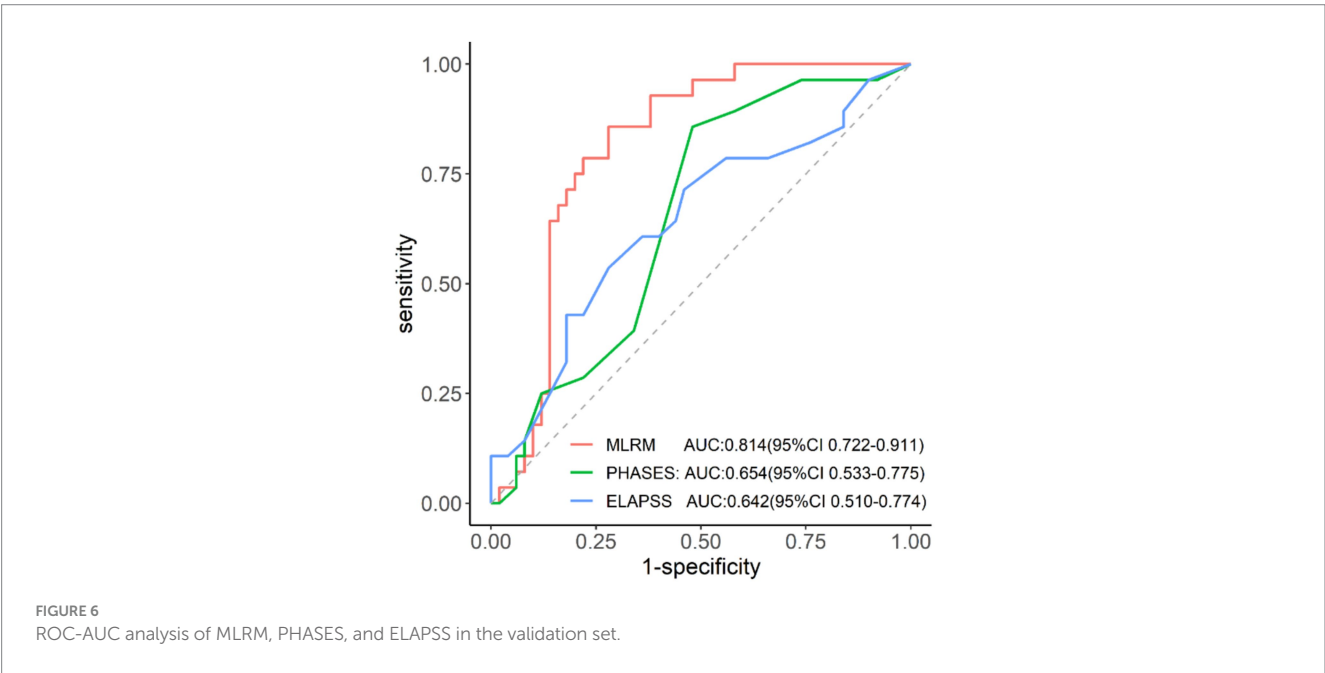
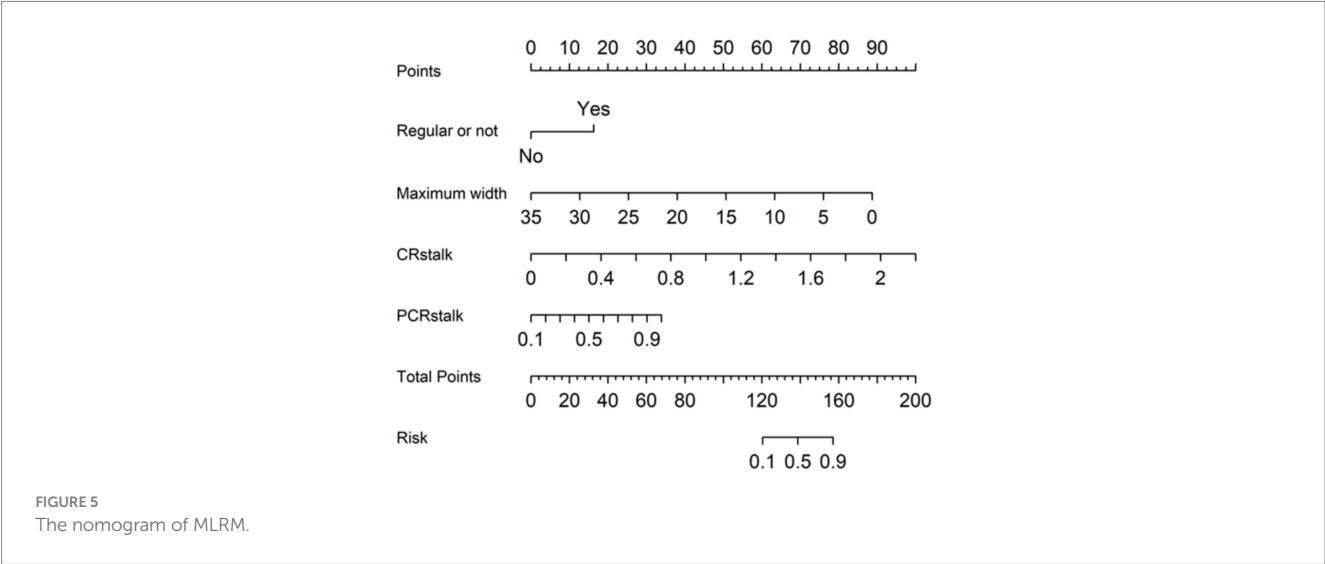


TABLE 3 Comparison of the predictive efficiency of MLRM, PHASES, and ELAPSS.

Predictive efficiency	Nomogram	ELPSS score	PHASES score
AUC (95% CI)	0.814 (0.722–0.911)	0.642 (0.510–0.774)	0.654 (0.533–0.775)
cut-off (95% CI)	0.116 (0.083–0.141)	14.496 (11.224–18.367)	3.504 (2.159–4.286)
Sens (95%CI)	0.917 (0.788–1.000)	0.563 (0.381–0.750)	0.857 (0.728–0.987)
Spec (95%CI)	0.704 (0.583–0.831)	0.720 (0.596–0.844)	0.520 (0.382–0.658)
ACC (95%CI)	0.765 (0.761–0.770)	0.654 (0.648–0.660)	0.641 (0.635–0.647)
PPV (95%CI)	0.579 (0.425–0.732)	0.517 (0.335–0.699)	0.500 (0.359–0.641)
NPV (95%CI)	0.950 (0.857–1.000)	0.735 (0.611–0.858)	0.867 (0.745–0.988)

AUC, Area under the curve; Sens, Sensitivity; Spec, Specificity; ACC, Accuracy; PPV, Positive predictive value; NPV, negative predictive value.

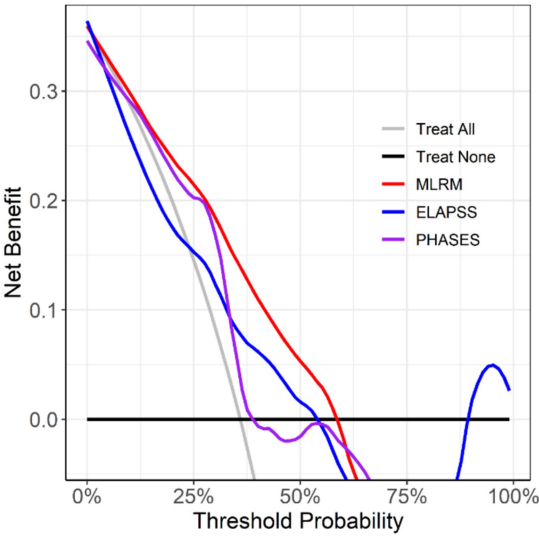


FIGURE 7
DCA curves of MLRM, PHASES, and ELAPSS.

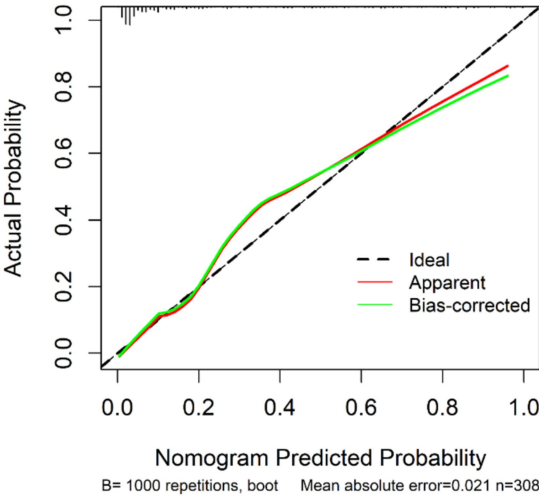


FIGURE 8
Calibration curve of MLRM.

from HR-VWI. We identified irregular aneurysm shape, MW, CR_{stalk}, and PCR_{stalk} as independent predictors of IA rupture through univariate and multivariate logistic regression analyses. Based on these four variables, an MLRM was developed.

In this study, we assessed aneurysm size in three dimensions—NW, MW, and MH—and identified MW as an independent risk factor for IA rupture. While previous research has used various morphological factors to differentiate IA statuses, aneurysm size remains a key factor in guiding treatment decisions (22). Akio et al. (23) found that aneurysms larger than 7 mm are at higher risk of SAH, with an annual rupture rate of 0.95% for larger aneurysms. Our findings confirm that aneurysm size is linked to rupture risk, with the MW significantly larger in the ruptured group compared to unruptured groups. This is likely due to the increased pressure on the aneurysm wall as it enlarges. However, some studies have found that about one-third of patients with aneurysmal SAH have IAs smaller than 5 mm (24). In our study, the median MW in the ruptured group was 4.31 [3.30, 6.89], indicating that the risk of rupture for smaller aneurysms should not be overlooked.

Consistent with previous research, this study identified irregular aneurysm shape as a significant predictor of IA rupture. A study of 713 IAs demonstrated that irregular shape is associated with rupture, independent of size, location, and clinical characteristics (25). Another study focusing on mirror IAs at the middle cerebral artery bifurcation indicates that size and shape were the only predictive factors for rupture (26). Additionally, irregular aneurysm shape is an independent risk factor for rebleeding in patients with SAH (27). Irregularity in IAs often manifests as lobulated or multilobed structures with uneven surfaces or small protrusions linked to hemodynamic factors (28). The swirling blood flow within the aneurysm sac can cause uneven wall stress, resulting in local protrusions. As stress on these protrusions increases, the aneurysm wall thins due to continuous tension, making these weak points more susceptible to rupture under sudden pressure changes.

Inflammation plays a key factor in the formation, progression, and rupture of IAs, and AWE is a reliable indicator of the inflammatory state within the aneurysm wall. Samaniego EA et al. (29) highlighted that HR-VWI enhancement is crucial for assessing IA rupture risk, especially the absence of wall enhancement, indicating low rupture risk. HR-VWI is increasingly seen as an inflammatory biomarker. Previous studies, such as the review by Lehman VT et al. (30), compared HR-VWI images of different types of aneurysms with conventional MRI images. They concluded that HR-VWI characterizes aneurysm walls in greater in-vivo detail than was previously possible and may complement other forms of luminal imaging. Based on its excellent imaging features for aneurysms and parent arteries, we chose to extract morphological parameters and measure enhancement on HR-VWI images for model construction. Our study conducted qualitative and quantitative analyses of AWE in ruptured intracranial aneurysms (RIAs) and unruptured intracranial aneurysms (UIAs), confirming previous findings (16). The qualitative analysis demonstrated that 78.4% of RIAs exhibited focal or ring-like enhancement compared to 30.0% of UIAs ($p < 0.05$), suggesting that AWE helps identify ruptured and unstable IAs. However, since focal and ring-like AWE can also occur in UIAs, and qualitative distinction is challenging, quantitative analysis is more helpful in assessing rupture risk. This study used two quantitative measurement methods for AWE assessment: one using the right frontal lobe SI as a reference

for WEI and another using pituitary enhancement SI as a reference for CR_{stalk}. Results found that WEI and CR_{stalk} were significantly higher in the ruptured group, with CR_{stalk} identified as an independent risk factor for IA rupture. Compared to WEI, CR_{stalk} measurement is more straightforward, reproducible, and offers higher sensitivity and specificity, making it more suitable for quantitative analysis (16). Furthermore, building on the correlation between parent artery wall enhancement within 3 mm of the aneurysm neck and AWE (11), this study included PAWE in the analyses. It was found that both PWEI and PCR_{stalk} were significantly higher in the ruptured group, with PCR_{stalk} identified as an independent risk factor for IA rupture.

An MLRM incorporating the four identified variables—irregular aneurysm shape, MW, CR_{stalk}, and PCR_{stalk}—achieved an area under the curve (AUC) of 0.814. This model demonstrated superior performance with 91.7% sensitivity, 70.4% specificity, and 76.5% accuracy, notably outperforming the PHASES (AUC = 0.654) and ELAPSS (AUC = 0.642) scores. The visual nomogram derived from this model exhibited strong discrimination and calibration, offering a comprehensive tool for predicting IA rupture and guiding personalized risk management and treatment. Compared to models based on CTA and DSA that utilized multivariable logistic regression and reported AUCs of 0.80 and 0.771 (31–33), respectively, our HR-VWI-based model achieved an AUC of 0.814, indicating enhanced performance in leveraging HR-VWI for aneurysm assessment. However, machine learning and deep learning models from these studies, which integrate clinical, morphological, and radiomic features, reported even higher AUCs, such as 0.878 and 0.929. These discrepancies underscore distinct methodological approaches: while our study emphasizes HR-VWI-specific features, these prior studies highlight the importance of multi-modality integration to enhance predictive accuracy. To advance this field, integrating HR-VWI-based radiomic data into machine learning and deep learning frameworks can leverage the strengths of high-resolution imaging and multi-feature analysis. This integration may offer deeper insights into aneurysm characteristics and enhance clinical applicability. Future research should explore the complementary value of different imaging modalities and analytical techniques to develop more robust and clinically relevant models.

There are areas for improvement in this study. First, long-term follow-up of patients was not conducted, and the dynamic observation of their aneurysm development had a certain impact on the reliability of the results. Second, the dataset used for model training was derived from a single center, which may introduce selection bias. Third, the limited data volume is insufficient to support artificial intelligence modeling. Future research should explore intelligent prediction methods for assessing aneurysm risk using multicenter, big data approaches.

5 Conclusion

This study identified MW, aneurysm shape (irregularity), CR_{stalk}, and PCR_{stalk} as independent risk factors for IA rupture. A visual nomogram based on HR-VWI was developed and outperformed the conventional PHASES and ELAPSS scores. This model provides a valuable tool for non-invasive, non-radiative, comprehensive, and precise assessment of IA rupture risk.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Second Hospital of Chongqing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

ZW: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. CY: Data curation, Validation, Writing – original draft, Writing – review & editing. WY: Data curation, Supervision, Writing – original draft. SJ: Data curation, Writing – original draft. YJ: Writing – review & editing, Methodology. TC: Writing – review & editing, Supervision.

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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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Glossary

AR - Aspect ratio

AUC - Area under curve

AWE - Aneurysm wall enhancement

AWT - Aneurysm wall thickness

CE-HR-VWI - Contrast-enhanced high-resolution vessel wall imaging

CI - Confidence interval

CR_{stalk} - Contrast ratio of the aneurysm wall against the pituitary stalk

DCA - Decision curve analysis

FOV - Field of view

HR-VWI - High-resolution vessel wall imaging

IAs - Intracranial aneurysms

ICC - Intraclass correlation coefficient

MH - Maximum height

MLRM - Multivariate logistic regression model

MW - Maximum width

NPR - Neck-to-parent ratio

NW - Neck width

PAD - Parent artery diameter

PCR_{stalk} - Contrast ratio of the parent artery wall against the pituitary stalk

PAWT - Parent artery wall thickness

PWEI - Parent artery wall enhancement index

ROC - Receiver operating characteristic

ROI - Region of interest

SAH - Subarachnoid hemorrhage

SI - Signal intensity **SR** - Size ratio

TOF - Time-of-flight

VISTA - Volume isotropic turbo spin echo acquisition

WEI - Wall enhancement index



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Construction of a poor prognosis prediction and visualization system for intracranial aneurysm endovascular intervention treatment based on an improved machine learning model

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Objective: To evaluate the clinical utility of improved machine learning models in predicting poor prognosis following endovascular intervention for intracranial aneurysms and to develop a corresponding visualization system.

Methods: A total of 303 patients with intracranial aneurysms treated with endovascular intervention at four hospitals (FuShun County Zigong City People's Hospital, Nanchong Central Hospital, The Third People's Hospital of Yibin, The Sixth People's Hospital of Yibin) from January 2022 to September 2023 were selected. These patients were divided into a good prognosis group ($n = 207$) and a poor prognosis group ($n = 96$). An improved machine learning model was employed to analyze patient clinical data, aiding in the construction of a prediction model for poor prognosis in intracranial aneurysm endovascular intervention. This model simultaneously performed feature selection and weight determination. Logistic multivariate analysis was used to validate the selected features. Additionally, a visualization system was developed to automatically calculate the risk level of poor prognosis.

Results: In the training set, the improved machine learning model achieved a maximum F1 score of 0.8633 and an area under the curve (AUC) of 0.9118. In the test set, the maximum F1 score was 0.7500, and the AUC was 0.8684. The model identified 10 key variables: age, hypertension, preoperative aneurysm rupture, Hunt-Hess grading, Fisher score, ASA grading, number of aneurysms, intraoperative use of etomidate, intubation upon leaving the operating room, and surgical time. These variables were consistent with the results of logistic multivariate analysis.

Conclusions: The application of improved machine learning models for the analysis of patient clinical data can effectively predict the risk of poor prognosis following endovascular intervention for intracranial aneurysms at an early stage. This approach can assist in formulating intervention plans and ultimately improve patient outcomes.

KEYWORDS

improve machine learning models, intracranial aneurysm, intravascular intervention therapy, poor prognosis, visualization system

1 Introduction

Intracranial aneurysms are protrusions resulting from congenital defects in the cerebral artery walls or increased intraluminal pressure, and they are a primary cause of subarachnoid hemorrhage. Clinically, these aneurysms often present with symptoms such as vomiting, severe headache, and visual field disturbances. Without timely intervention, ruptured aneurysms can lead to intracranial hemorrhage, posing significant threats to patient survival. The associated mortality and disability rates are notably high, leading to poor prognoses (1, 2).

Endovascular intervention is the primary treatment for intracranial aneurysms, offering advantages in reducing trauma for patients with ruptured aneurysms and promoting postoperative recovery. However, the factors influencing prognosis following this treatment remain unclear (3, 4). Traditional logistic regression models rely heavily on selected independent factors to predict patient outcomes, but they often miss critical clinical information, significantly reducing data utilization and overall predictive performance (5).

In recent years, machine learning, a branch of artificial intelligence, has shown great promise in the medical field. It can develop predictive models by analyzing clinical data and extracting case characteristics for accurate diagnosis and prognosis. Machine learning also allows for iterative improvements during validation, offering high efficiency and rapid results (6). Numerous studies have explored the use of machine learning models to predict outcomes following endovascular intervention for intracranial aneurysms. For instance, several studies have employed models such as support vector machines, random forests, and neural networks to enhance prediction accuracy and clinical decision-making (7–9).

Despite these advancements, there is still a lack of comprehensive research that integrates various machine learning techniques to improve the prediction of poor prognosis specifically for intracranial aneurysm endovascular intervention. Furthermore, existing studies often do not provide user-friendly visualization systems that can aid clinicians in interpreting the results and making informed decisions.

This study aims to bridge these gaps by evaluating the clinical value of using an improved machine learning model to predict poor prognosis in intracranial aneurysm endovascular intervention. Additionally, we aim to develop a visualization system to enhance the interpretability and usability of the predictive model for clinical practitioners. By doing so, we hope to provide a more robust and practical tool for improving patient outcomes.

2 Patients and methods

2.1 Patients

This study included 303 patients with intracranial aneurysms who underwent endovascular interventions at four hospitals (FuShun County Zigong City People's Hospital, Nanchong Central Hospital, The Third People's Hospital of Yibin, The Sixth People's Hospital of Yibin) from January 2022 to September 2023. The patients were divided into two groups based on their prognosis:

the good prognosis group ($n = 207$) and the poor prognosis group ($n = 96$). Prognosis was evaluated at a 6-month follow-up using the Glasgow Outcome Scale (GOS) score (10), with scores of 4–5 indicating a good prognosis and scores of 1–3 indicating a poor prognosis. This retrospective study was approved by the Ethics Committee of Fushun County People's Hospital (Approval Number: 2023-077), and patient informed consent was waived. All patient data were anonymized and analyzed.

2.1.1 Inclusion and exclusion criteria

Inclusion criteria: (1) head CT, MRI, cerebral angiography, and other examinations clearly for intracranial aneurysm; (2) endovascular interventional therapy; (3) complete clinical data.

Exclusion criteria: (1) pseudoaneurysm, non-aneurysmal subarachnoid hemorrhage; (2) other cerebrovascular diseases; (3) intolerance of surgical treatment.

2.2 Methods

2.2.1 Information collection

Clinical data were collected for each patient, including age, gender, history of hypertension, preoperative aneurysm rupture status, Hunt-Hess classification, Fisher score, ASA classification, number of aneurysms, intraoperative use of etomidate, intubation status upon leaving the operating room, operation time, body weight, platelet count, platelet distribution, prothrombin time, partial activated prothrombin time, thrombin time, fibrinogen. Prior to model construction, all data were standardized using the Z-score to eliminate the influence of dimensional differences.

2.2.2 Construction of improved model

The Automatic Feature Filtering and Weight Determination Integrated (AFFWDI) model is an innovative framework designed to enhance the prediction accuracy and generalization ability of machine learning models. The core of the AFFWDI model utilizes swarm intelligence algorithms, inspired by natural behaviors such as bird flocking and ant foraging, to solve optimization problems. The methodology of the AFFWDI model can be divided into two main steps.

2.2.2.1 Feature screening process

(1) Initialization: Randomly generate a population of solutions, each representing a subset of possible features. (2) Adaptation Assessment: Assign a fitness value to each feature subset, usually based on its performance in a predictive model. In this study, the fitness is measured by the accuracy of cross-validation. (3) Search for Updates: Update each solution, i.e., a subset of features, according to the rules of the swarm intelligence algorithm. (4) Termination Conditions: Repeat the iterations until the termination conditions are met, such as reaching the maximum number of iterations or when the fitness value no longer shows significant improvement.

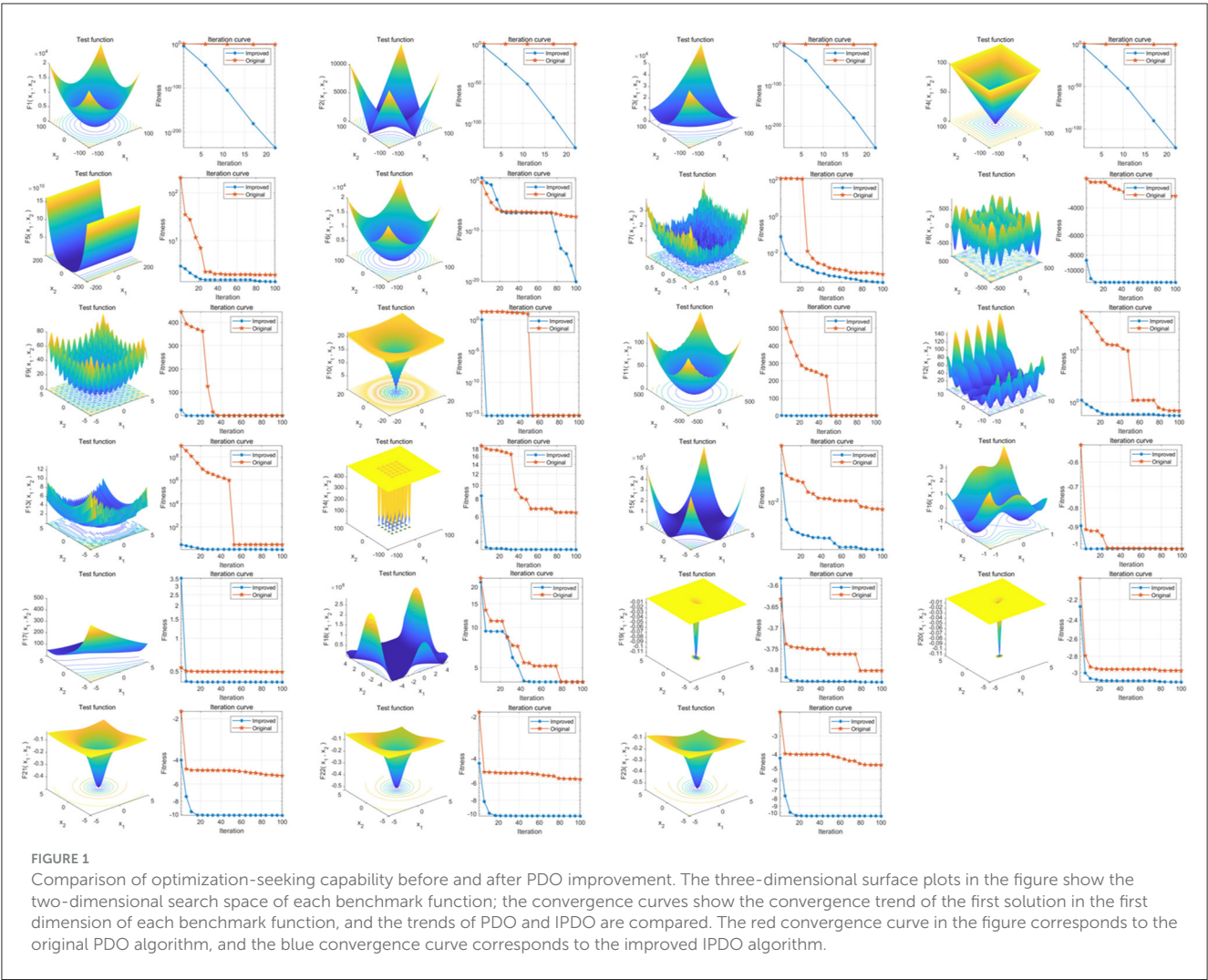


FIGURE 1 Comparison of optimization-seeking capability before and after PDO improvement. The three-dimensional surface plots in the figure show the two-dimensional search space of each benchmark function; the convergence curves show the convergence trend of the first solution in the first dimension of each benchmark function, and the trends of PDO and IPDO are compared. The red convergence curve in the figure corresponds to the original PDO algorithm, and the blue convergence curve corresponds to the improved IPDO algorithm.

TABLE 1 Training of each base learner based on simultaneous optimization.

Base learning model (BLM)	PRE	SEN	SPE	ACC	F1	ROC-AUC	PR-AUC
LR	0.7222	0.3377	0.9398	0.7490	0.4602	0.7301	0.5776
SVM	0.8542	0.5325	0.9578	0.8230	0.6560	0.8340	0.8034
BPNN	0.8409	0.4805	0.9578	0.8066	0.6116	0.8097	0.7722
XGBoost	0.9677	0.7792	0.9880	0.9218	0.8633	0.9118	0.8960

LR, Logistic Regression; SVM, Support Vector Machine; BPNN, Back Propagation Neural Network; XGBoost, eXtreme Gradient Boosting.

2.2.2.2 Weight determination process

(1) Weight initialization: After determining the optimal subset of features, initial weights are assigned to these features. (2) Weight Optimization: The same swarm intelligence algorithm is used to optimize the weights, thereby improving the overall prediction performance of the model. (3) Synergistic Optimization: The optimization of feature subsets and weights is not conducted independently but synchronously, ensuring that the synergistic effect of feature screening and weight assignment is maximized.

2.2.3 Improved intelligent algorithms

This study employs a swarm intelligence optimization algorithm to handle the complex tasks of feature screening and weight determination. To ensure superior global optimization capability, we introduce an improved Prairie Dog Optimization Algorithm (IPDO). The original Prairie Dog Optimization Algorithm (PDO) divides the behavior of prairie dogs into two stages: global exploration and local exploitation. However, previous studies have indicated a risk of the algorithm falling into local optima (11). To address this, the IPDO enhances exploration and

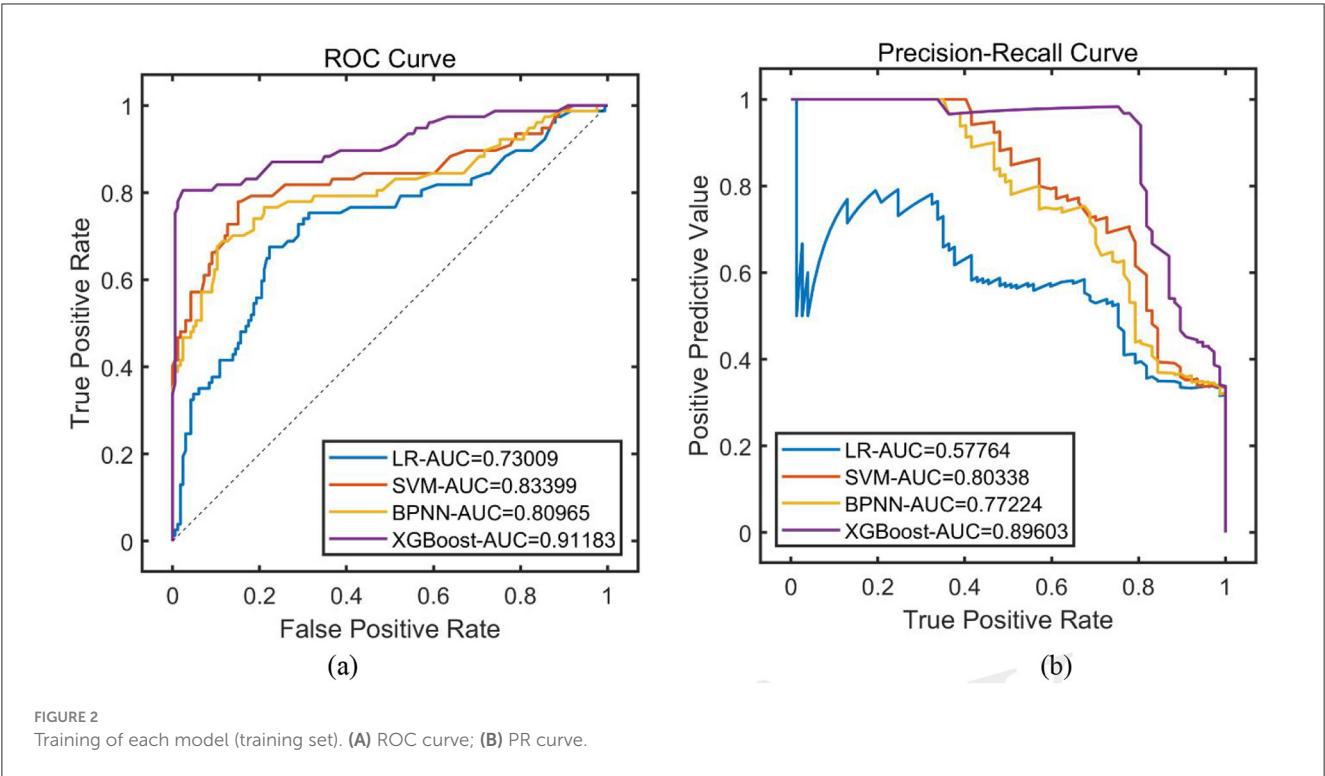


TABLE 2 Test set performance of each base learner based on synchronization optimization.

Base learning model (BLM)	PRE	SEN	SPE	ACC	F1	ROC-AUC	PR-AUC
LR	-	0.0000	1.0000	0.6833	-	0.6977	0.5733
SVM	0.8571	0.3158	0.9756	0.7667	0.4615	0.8017	0.6499
BPNN	0.8571	0.3158	0.9756	0.7667	0.4615	0.7811	0.6884
XGBoost	0.9231	0.6316	0.9756	0.8667	0.7500	0.8684	0.8688

LR predictions were all good prognoses and lost predictive value, so PRE and F1 values could not be calculated.

convergence performance through Tent chaotic initialization and t -distribution perturbation variation. Detailed descriptions of these enhancements are as follows.

2.2.3.1 Tent chaotic initialization

Tent mapping is a simple yet effective chaotic mapping method with excellent non-linear and traversal properties. By using Tent chaotic initialization, the algorithm can generate a more diversified and uniformly distributed solution space in the initial stage, which enhances the global search capability and prevents the algorithm from prematurely falling into local optima (12). During the algorithm's initialization phase, each prairie dog's location is no longer randomly generated but is determined by a Tent chaotic sequence, thus ensuring better diversity and coverage of the initial population.

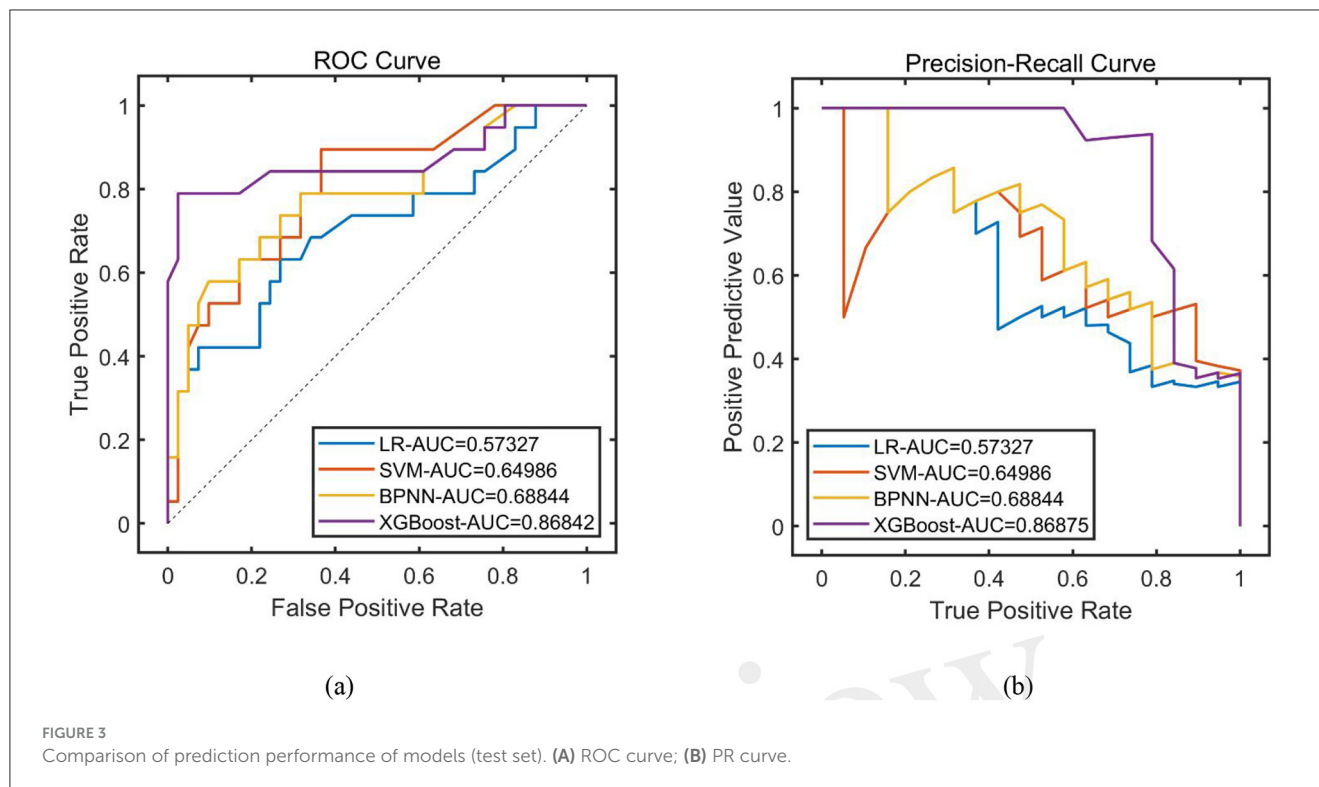
2.2.3.2 t -distribution perturbation variation

The t -distribution (Student's t -distribution) is a probability distribution whose shape is controlled by the degrees of freedom parameter. When the degrees of freedom are low, the t -distribution has a thicker tail, which allows for generating more significant variances with smaller probabilities when creating perturbations,

thereby increasing the algorithm's ability to escape local optima (13). In the position updating stage, in addition to the traditional PDO position updating rules, a perturbation factor generated by the t -distribution is introduced to randomly perturb the position of an individual. This variation enhances the algorithm's local search ability, explores a broader search space to some extent, and improves the probability of finding the optimal global solution.

2.2.4 Performance simulation testing of swarm intelligence algorithms

The optimization performance of the IPDO algorithm was tested using 23 standard test functions, each designed for minimization problems and varying in dimensions and complexity. Key characteristics of these functions include search space boundary range, function dimensionality, function category, and optimal solutions. The test functions were classified into unimodal (U) and multimodal (M) types. Unimodal functions assess local exploitation capability, while multimodal functions evaluate global exploration capability. To ensure a fair comparison, the population size was set at 30, the number of iterations at 200, and the average convergence curves were plotted after 30 repetitions.



2.3 Statistical analysis

SPSS 25.0 software was used to analyze the data, and the count data were expressed as $[n (\%)]$ and compared with the χ^2 -test; the normally distributed measure data were expressed as $(\bar{x} \pm s)$ and compared with t -test; the analysis of influencing factors was performed by multifactorial Logistic regression analysis, and the independent variables were entered into the regression equations by stepwise method. $P < 0.05$ was used to indicate statistically significant differences in two-sided tests.

3 Results

3.1 Performance test of improved group intelligence algorithm

The results show that the overall convergence speed and global optimization-seeking ability of the IPDO algorithm are significantly improved compared to the pre-improvement period (Figure 1).

3.2 Predictive modeling

3.2.1 Model training

Eighty percent of the dataset is randomly selected as the training set, cross-validation is executed, IPDO is utilized to find the optimal combination of features and hyper-parameters, and four types of base learners are selected; namely, LR, SVM, Back Propagation Neural Network (BPNN), and XGBoost, and the final

model training results show that the AFFWDI model with XGBoost as the base learner performs optimally (Table 1, Figure 2).

3.2.2 Model testing

The remaining 20% of the dataset was used as a test set to examine the generalization ability of each model. The results showed that the AFFWDI model with XGBoost as the base learner had the best performance, and 10 variables were screened for age, comorbid hypertensive disorders, ruptured aneurysm preoperatively, Hunt-Hess classification, Fisher score, ASA classification, number of aneurysms, and intraoperative use of etomidate, intubation on leaving the operating room, and length of surgery (Table 2, Figure 3).

3.3 Feature revalidation

All 10 variables the improved machine learning model screened had statistically significant differences between the two groups ($P < 0.05$), coinciding with the logistic multifactor analysis results (Tables 3, 4).

3.4 Visualization system setup

In the application of the visualization system, the user only needs to enter 10 specific values in the "Characteristic Input" field, including "age, combined hypertension, preoperative aneurysm rupture, Hunt-Hess classification, Fisher score, ASA classification, number of aneurysms, intraoperative use of etomidate, intubation,

TABLE 3 Univariate analysis.

Variants	Good prognosis group <i>n</i> = 207	Poor prognosis group <i>n</i> = 96	<i>t/c</i> ² -value	<i>p</i> -value
Age	55.45 ± 10.34	58.28 ± 11.23	2.156	0.031
Hypertension			19.684	<0.001
No	96 (46.38)	19 (19.79)		
Yes	111 (53.62)	77 (80.21)		
Preoperative aneurysm rupture			42.755	<0.001
No	131 (63.29)	22 (22.92)		
Yes	76 (36.71)	74 (77.08)		
Hunt-Hess classification			34.438	<0.001
I–II	145 (70.05)	33 (34.38)		
III–V	62 (29.95)	63 (65.62)		
Fisher score			25.309	<0.001
1–2	194 (93.72)	70 (72.92)		
3–4	13 (6.28)	26 (27.08)		
ASA classification			8.187	0.004
I–II	131 (63.29)	44 (45.83)		
III–IV	76 (36.71)	52 (54.17)		
Number of aneurysms			5.643	0.018
1	166 (80.19)	65 (67.71)		
≥2	41 (19.81)	31 (32.29)		
Use of etomidate			5.494	0.019
No	171 (82.61)	89 (92.71)		
Yes	36 (17.39)	7 (7.29)		
Intubation			61.096	<0.001
No	18 (8.70)	47 (48.96)		
Yes	189 (91.30)	49 (51.04)		
Surgical time/min	156.34 ± 21.99	40.23 ± 7.28	50.430	<0.001

length of surgery.” The system automatically calculates the risk of poor prognosis for a patient by assigning specific values to each of the 10 characteristics: age, Hunt-Hess classification, Fisher score, ASA classification, number of aneurysms, intraoperative use of etomidate, time of intubation, and length of surgery (Figure 4).

4 Discussion

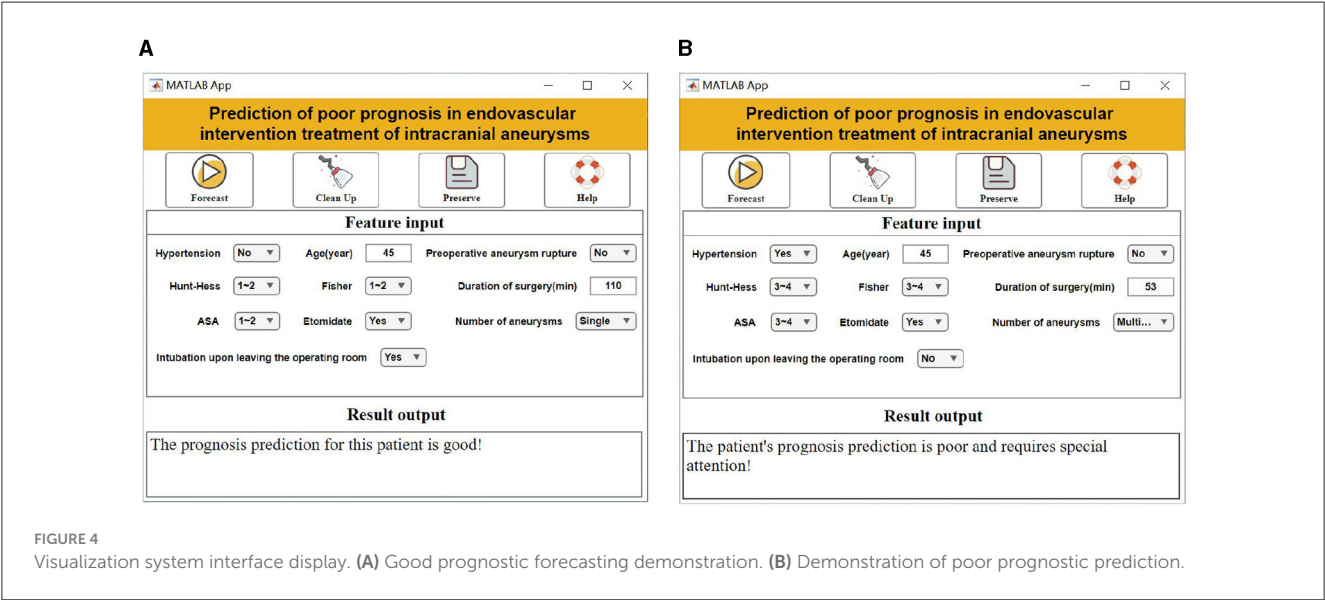
Intracranial aneurysms are vascular abnormalities characterized by the abnormal bulging of intracranial artery walls, and their rupture is associated with high rates of disability and mortality (14, 15). Therefore, preventing aneurysm rebleeding is crucial. Endovascular intervention has increasingly been recommended as the preferred treatment for intracranial aneurysms due to its advantages such as reduced trauma, shorter operation times, and minimal damage to brain tissues. However, patients undergoing this procedure are susceptible to cerebral vasospasm and face a high rate of postoperative recurrence, both

of which contribute to poor prognosis (16, 17). Consequently, analyzing the risk factors that influence the poor prognosis of endovascular intervention for intracranial aneurysms is vital for improving patient outcomes.

Machine learning has shown significant promise in enhancing clinical prediction efficacy by analyzing clinical data and applying specific algorithms to predict various outcomes (18, 19). By learning from multiple data modules, machine learning effectively identifies variables associated with patient outcomes, accurately predicts relevant risk factors, explores patterns, and builds mathematical models from complex data. It can also be iteratively calibrated during validation (20, 21). The Prairie Dog Optimization (PDO) algorithm, inspired by the behavior of prairie dogs, offers advantages such as easy implementation and balanced exploration and exploitation capabilities (22). However, it faces challenges such as slow convergence speed and low optimization accuracy. To address these issues, we implemented Tent chaotic initialization and *t*-distribution perturbation variation to initialize the population. Additionally, we incorporated suboptimal

TABLE 4 Logistic multivariate analysis.

Variants	β	SE	Wald χ^2	P-value	OR value	95% CI
Age	1.256	0.417	9.072	0.003	3.511	1.551–7.951
Hypertension	1.436	0.452	10.093	0.002	4.204	1.733–10.195
Preoperative aneurysm rupture	1.343	0.491	7.482	0.006	3.831	1.463–10.028
Hunt-Hess classification	1.411	0.485	8.464	0.004	4.100	1.585–10.608
Fisher score	1.293	0.406	10.142	0.002	3.644	1.644–8.075
ASA classification	1.277	0.451	8.017	0.005	3.586	1.481–8.679
Number of aneurysms	1.302	0.429	9.211	0.003	3.677	1.586–8.524
Use of etomidate	1.419	0.463	9.393	0.002	4.133	1.668–10.242
Intubation	1.391	0.406	11.738	0.001	4.019	1.813–8.906
Surgical time	1.274	0.403	9.994	0.002	3.575	1.623–7.876



individual guidance strategies, natural enemy avoidance strategies, and adaptive probability threshold guidance strategies. These enhancements improve the algorithm’s ability to avoid local optima and ensure higher solution accuracy and faster convergence speeds for the PDO algorithm (23).

In this study, we developed an improved machine learning model to predict poor prognosis in patients undergoing endovascular intervention for intracranial aneurysms. By adjusting relevant parameters for different algorithms and employing 5-fold cross-validation, we minimized the effect of randomness and prevented overfitting. Model performance on the test set was further enhanced through pruning, leading to the identification of 10 key variables: age, comorbid hypertension, preoperative aneurysm rupture, Hunt-Hess classification, Fisher score, ASA classification, number of aneurysms, intraoperative use of etomidate, intubation status upon leaving the operating room, and procedure duration.

The identified variables provide valuable insights into the factors influencing poor prognosis. For instance. Age: Older patients show decreased vascular elasticity and repair capabilities,

increasing the risk of complications and recurrence post-intervention (24). Hypertension: Hypertension exacerbates damage to the intracranial vascular wall and alters hemodynamics, leading to higher risks during and after the procedure (25, 26). Preoperative Aneurysm Rupture: Ruptured aneurysms complicate the intervention due to fragile vasculature and increased aneurysm numbers, leading to higher recurrence and poor prognosis (27, 28). Hunt-Hess Classification and Fisher Score: Higher scores indicate severe intracranial hemorrhage and increased risk of complications like vasospasm and edema, which adversely affect outcomes (29–31). ASA Classification: Higher ASA scores reflect severe underlying conditions and lower surgical tolerance, impacting recovery and prognosis (32, 33).

Compared to traditional logistic regression models, our machine learning model leverages a broader range of clinical data and advanced algorithms to enhance predictive accuracy. Previous studies have utilized various machine learning techniques such as support vector machines and neural networks for similar purposes (7–9). However, our approach integrates the Prairie Dog Optimization (PDO) algorithm with enhancements

like Tent chaotic initialization and t-distribution perturbation, which improve convergence speed and solution accuracy. The development of a visualization system based on our model allows clinicians to input specific patient data and receive immediate risk assessments and recommendations. This tool has significant potential for both public health research and clinical practice, aiding in early intervention and personalized treatment planning.

Although our study aims to construct a prediction and visualization system for poor prognosis in intracranial aneurysm endovascular treatment based on an improved machine learning model, we acknowledge several limitations.

Firstly, the predictive capability of our model is constrained by the quality and scale of the currently available dataset. A larger and more comprehensive dataset could potentially enhance the model's accuracy and stability. Secondly, our research focuses on specific treatment methods and populations. Future studies should consider a broader range of treatment methods and population factors to increase generalizability. Additionally, the interpretability and clinical applicability of the model require further optimization and improvement.

Future research can expand in several directions. Firstly, we can further optimize our machine learning model by exploring more advanced algorithms and technologies to enhance predictive performance and improve interpretability. Secondly, incorporating additional clinical variables and imaging features into the model could enhance the accuracy and comprehensiveness of prognosis prediction. Furthermore, integrating other advanced technologies, such as deep learning and natural language processing, could enrich the functionality and efficacy of the predictive model. Finally, integrating our system with actual clinical practice and conducting large-scale validation and application will ensure its effectiveness and reliability in real clinical settings.

By continuously refining our research methods and technologies, we are confident that future studies will provide more accurate and reliable support for prognosis prediction and clinical decision-making in intracranial aneurysm endovascular intervention treatment. This will offer greater hope and opportunities for patient treatment and recovery.

5 Conclusion

In summary, applying improved machine learning models to analyze patients' clinical data can help clinics predict the risk of poor prognosis following endovascular intervention for intracranial aneurysms at an early stage. This can assist in developing intervention programs to improve patient outcomes.

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Data availability statement

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

Ethics statement

The study was approved by the Ethics Committee of Fushun County People's Hospital (Approval Number: 2023-077). The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee waived the requirement of written informed consent from the participants or the participants' legal guardians/next of kin because of the retrospective nature of the study.

Author contributions

CL: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. AF: Data curation, Investigation, Writing – review & editing. BL: Investigation, Writing – review & editing. SZ: Investigation, Writing – review & editing. JL: Investigation, Writing – review & editing. YC: Investigation, Writing – original draft. BZ: Conceptualization, Methodology, Project administration, Writing – review & editing.

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Age-specific gender differences in morphological parameters of intracranial aneurysms

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Background: Gender differences are shown to exist in the incidence and outcome of subarachnoid hemorrhage as well as in the formation and progression of intracranial aneurysms. However, few studies investigated the gender difference in the morphology of intracranial aneurysms.

Methods: A total of 308 consecutive patients with 346 intracranial aneurysms from 2014 to 2020 were retrospectively analyzed. Differences in 10 morphological parameters of intracranial aneurysms between males and females were compared. Continuous variables were expressed as the median [interquartile range (IQR)] and the differences were analyzed using the Mann-Whitney test. Categorical variables were expressed as numbers (frequencies) and the differences were analyzed using χ^2 test. Moreover, subgroup analyses were performed according to age stratifications: ≥ 60 years, 50–59 years, and < 50 years.

Results: The median aspect ratio maximum [1.38, IQR (1.17–1.83) vs. 1.27, IQR (1.00–1.57)], median aspect ratio [1.29, IQR (1.00–1.76) vs. 1.18, IQR (0.93–1.54)], median bottleneck factor [1.17, IQR (1.00–1.47) vs. 1.03, IQR (0.86–1.27)], and median volume-to-ostium area ratio [5.67, IQR (2.85–9.03) vs. 3.86, IQR (1.94–7.48)] in males were significantly higher than those in females (all $P < 0.01$). Particularly, the differences in the above morphological parameters between genders were most prominent in patients aged ≥ 60 years, whereas no differences were found in patients aged < 50 years. There were no significant differences in other morphological parameters between males and females, including neck width, transverse, height, maximum, aneurysm volume, and height-width ratio.

Conclusions: Gender difference existed in the morphology of intracranial aneurysms and was affected by age. The difference was prominent in patients aged ≥ 60 years, whereas no difference was found in patients aged < 50 years.

KEYWORDS

subarachnoid hemorrhage, intracranial aneurysms, gender difference, morphology, age

Introduction

Subarachnoid hemorrhage (SAH) is a life-threatening stroke, largely leading to loss of many years of productive life owing to the relatively young age of those affected and high mortality (1). The rupture of an intracranial aneurysm is the cardinal cause, accounting for about 85% of cases (1, 2). Theoretically, risk factors for rupture of an unruptured aneurysm are similar to those for aneurysm formation and SAH (1). There

is high agreement among neurosurgeons that the location and size are among pivotal risk factors for rupture of an intracranial aneurysm (3, 4). Moreover, in addition to size and location, several morphological parameters of intracranial aneurysms, including perpendicular height, aspect ratio, bottleneck factor, and aneurysm volume, have been shown to be associated with risk of rupture (5–8). Thus, aneurysm morphology could provide important implications in the clinical management of intracranial aneurysms.

Gender differences are suggested to exist not only in the incidence and outcome of SAH but also in the formation and progression of aneurysms (9). In a large consecutive series of ruptured intracranial aneurysms (3), the size and location varied considerably by gender, suggesting that gender differences existed in the location and size. However, no statistical method was applied to identify the significant differences in location and size between genders in the previous study (3). Moreover, one of the few studies suggested that females had a significant lower dome-to-neck ratio of intracranial aneurysms than males (10), but few studies investigated the detailed gender differences in aneurysm morphology so far (11). Furthermore, it was suggested that morphological parameters of posterior communicating artery aneurysms were associated with age (12). Therefore, we hypothesized that gender differences existed in the morphology of intracranial aneurysms and were affected by age. The purpose of this study was to explore the gender differences in morphological parameters of intracranial aneurysms, with a special focus on the gender differences stratified by age.

Materials and methods

Study population and data collection

The study population was from the First Affiliated Hospital of Xiamen University. The inclusion criteria were as follows: (1) Adult patients (≥ 18 years old) with saccular intracranial aneurysms admitted to the hospital between 2014 and 2020; (2) Ruptured and unruptured intracranial aneurysms which were repaired during hospitalization were both included; (3) The diagnosis of intracranial aneurysms was confirmed using CT angiography (CTA), 3-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA), or digital subtraction angiography (DSA). The exclusion criteria were as follows: (1) The aneurysms belonged to traumatic aneurysms, feeding artery aneurysms to arteriovenous malformations (AVM), or fusiform aneurysms. (2) The patients whose aneurysms were treated prior to presentation. Demographic and clinical information, including age, gender, presence of multiple aneurysms, location of the aneurysms, and morphological parameters were recorded. This

study was approved by the institutional review board under an expedited review and informed consent was waived for this retrospective study.

Definition of location and morphological parameters

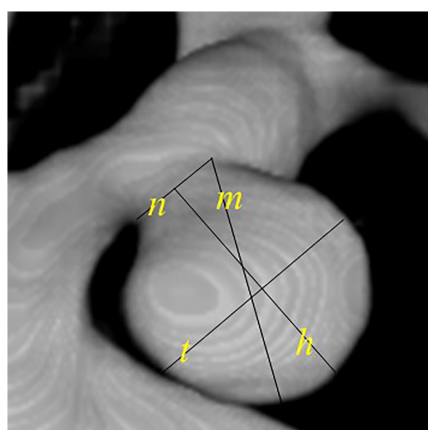
The locations of intracranial aneurysms were categorized as internal carotid posterior communication artery (ICPC), middle cerebral artery (MCA), anterior communication artery (ACoA), and others. The previous literature highlights a lot of morphological parameters associated with aneurysm growth and rupture risk, such as the ellipticity index, nonsphericity index, and size ratio, etc. (5–8). However, the results of Juvela and Korja (7) were derived from a long-term follow up study, and the results might be the most reliable. Thus, we thought that aneurysm volume, aspect ratio, bottleneck factor, height-width ratio, and volume-to-ostium area ratio (VOR) were pivotal morphological parameters for the assessment of intracranial aneurysms based on the previous study (7). Hence, the above morphological parameters were measured and calculated using the standard projection of 3-dimensional conventional angiograms in the present study. The neck width (n), transverse (t), height (h), and maximum (m) were measured for each angiographic image of an intracranial aneurysm and used to calculate the morphological parameters as follows (7): (1) aneurysm volume: $\pi \times m \times t^2/6$; (2) aspect ratio maximum: m/n ; (3) aspect ratio: h/n ; (4) bottleneck factor: t/n ; (5) height-width ratio: h/t ; (6) VOR: $4m \times t^2/6n^2$. The detailed discrimination of the abovementioned morphological parameters is shown in Figure 1.

Statistical analysis

The data were analyzed by SPSS statistic 22.0 (SPSS Inc., Chicago, USA). Initially, the Shapiro-Wilk test, stem-leaf plot, and normal P-P plot were used for the test of data distribution. Continuous variables were expressed as the median [interquartile range (IQR)] when they were non-parametric distribution, or mean (standard deviation) when they were parametric distribution. The Student's t -test was used for variables with parametric distribution and Mann-Whitney test for variables with the non-parametric distribution. Categorical values were expressed as number (frequencies), and the differences between the two groups were analyzed using χ^2 test or Fisher's exact test. All statistical significance was defined as $P < 0.05$.

Initially, the differences in age, presence of multiple aneurysms, location of the aneurysms, and morphological parameters were compared between males and females. Moreover, although the majority of the overall aneurysm population is females, the prevalence was reported to be equivalent between males and females among adults younger than 50 years (13). Furthermore, 60 years old was suggested to be as the boundary to differentiate the risk of growth of unruptured intracranial aneurysms (14). Therefore, subgroup analyses of differences in location and morphological parameters of intracranial aneurysms between gender were further performed according to the

Abbreviations: SAH, Subarachnoid hemorrhage; CTA, CT angiography; 3D-TOF-MRA, 3-dimensional time-of-flight magnetic resonance angiography; DSA, digital subtraction angiography; AVM, arteriovenous malformations; IQR, interquartile range; BMI, body mass index; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral arteries; PCoA, posterior communicating artery; ICPC, internal carotid posterior communication artery; ACoA, anterior communication artery; VOR, volume-to-ostium area ratio; AWE, aneurysmal wall enhancement.



n: neck width
t: transverse
h: height
m: maximum
aneurysm volume: $\pi \times m \times t^2/6$
aspect ratio maximum: m/n
aspect ratio: h/n
bottleneck factor: t/n
height-width ratio: h/t
volume-to-ostium area ratio (VOR): $4m \times t^2/6n$

FIGURE 1

The detailed discrimination of 10 morphological parameters. The neck width (n), transverse (t), height (h), and maximum (m) were measured for each angiographic image of an intracranial aneurysm and used to calculate the morphological parameters as follows: (1) aneurysm volume: $\pi \times m \times t^2/6$; (2) aspect ratio maximum: m/n ; (3) aspect ratio: h/n ; (4) bottleneck factor: t/n ; (5) height-width ratio: h/t ; (6) VOR: $4m \times t^2/6n^2$.

age stratification: ≥ 60 years, 50–59 years, and < 50 years. Additionally, the association between age and morphological parameters was evaluated as well. Considering gender could affect the morphological parameters, morphological parameters of intracranial aneurysms between patients aged ≥ 50 years and patients aged < 50 years were compared separately in males and females.

Results

Basic demographic and clinical characteristics of 308 patients with intracranial aneurysms

The study included 308 patients with 346 intracranial aneurysms, of which 127 (137 aneurysms) were males, and 181 (209 aneurysms) were females. The average age was 55.68 ± 11.34 years, in which males and females were 54.29 ± 11.35 years and 56.66 ± 11.26 years, respectively. In this case series, 10.71% of the patients presented multiple aneurysms, and the majority (89.02%) of the aneurysms were < 10 mm. The distributions of age and location of males and females with intracranial aneurysms are shown in Figure 2. The female to male ratio was approximately one among patients younger than 50 years, but the ratio was far more than one among patients aged ≥ 50 years. The top three locations of intracranial aneurysms were ICPC (31.79%), MCA (28.03%), and ACoA (27.17%), accounting for 86.99% of all intracranial aneurysms.

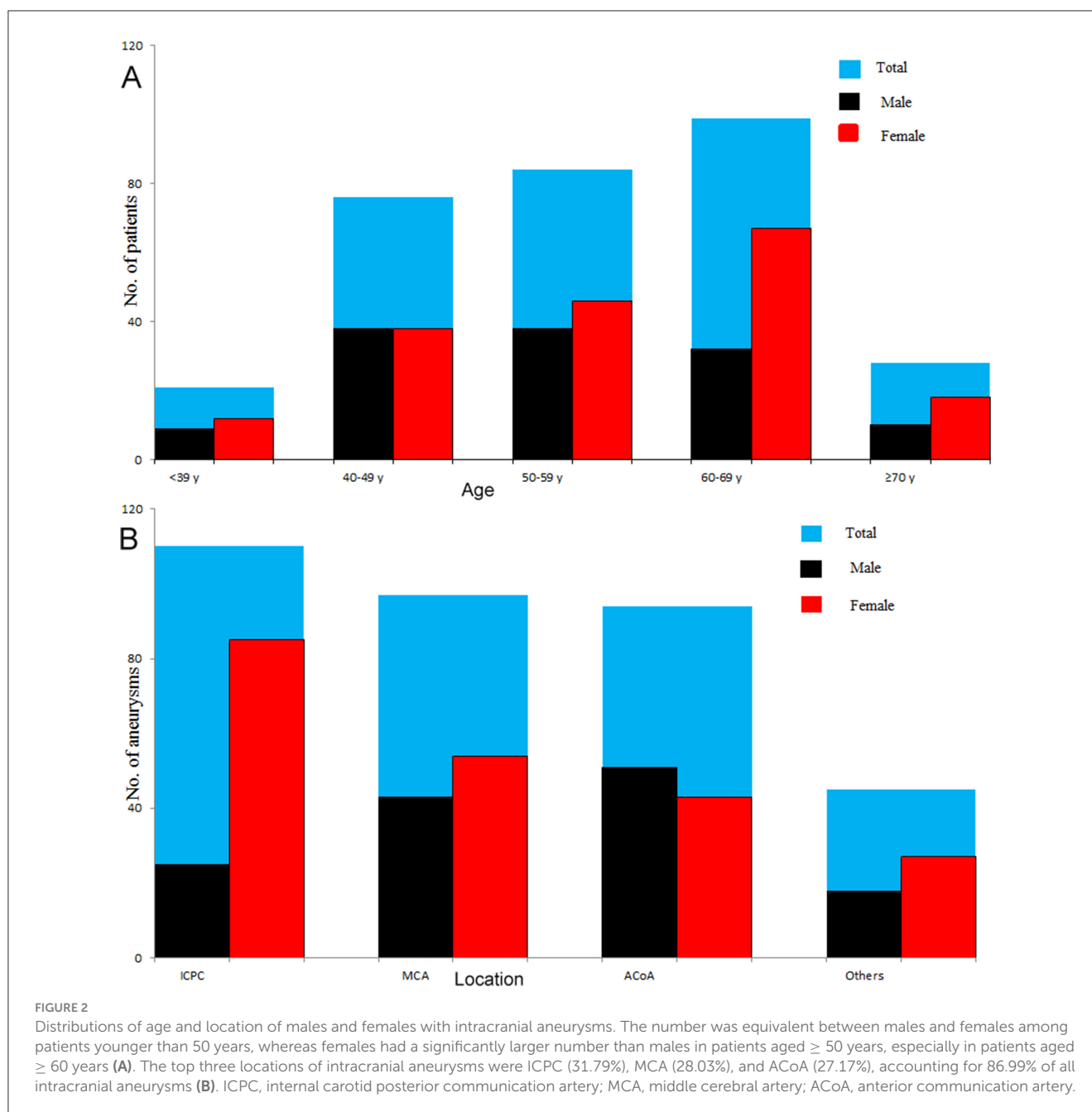
Comparisons of age, location, and morphological parameters of aneurysms between males and females

The comparisons of age, location, and morphological parameters of aneurysms between males and females are shown

in Table 1. The percentage of patients aged ≥ 60 years in females was significantly higher than that in males (46.96 vs. 30.07%, $P = 0.047$). There was a significant difference in the distribution of the location of aneurysms between genders ($P = 0.000$), with a higher percentage of ICPC aneurysm in females (40.67 vs. 18.25%) and a higher percentage of ACoA aneurysm in males (37.22 vs. 20.57%). The median aspect ratio maximum [1.38, IQR (1.17–1.83) vs. 1.27, IQR (1.00–1.57)], aspect ratio [1.29, IQR (1.00–1.76) vs. 1.18, IQR (0.93–1.54)], bottleneck factor [1.17, IQR (1.00–1.47) vs. 1.03, IQR (0.86–1.27)], and VOR [5.67, IQR (2.85–9.03) vs. 3.86, IQR (1.94–7.48)] in males were significantly higher than those in females (all $P < 0.01$). There were no significant differences in other morphological parameters between males and females, including neck width, transverse, height, maximum, aneurysm volume, and height-width ratio.

Comparisons of the location of intracranial aneurysms between males and females stratified by age

The Comparisons of the location of intracranial aneurysms between males and females according to age stratification are presented in Table 2. In the subgroups of patients aged ≥ 60 and < 50 years, no significant differences in the distributions of the location of intracranial aneurysms were observed between genders. However, there was a significant difference in the distribution of the location of intracranial aneurysms between males and females when restricted in the patients aged 50–59 years ($P = 0.000$). In this subgroup, the percentage of ICPC aneurysm in females was significantly higher than that in males (52.46 vs. 7.14%). In contrast, the percentages of ACoA and MCA aneurysms in males were significantly higher than those in females (45.23 vs. 16.39%, 33.33 vs. 18.03%).



Comparisons of morphological parameters of intracranial aneurysms between males and females stratified by age

The comparisons of morphological parameters of intracranial aneurysms between males and females according to age stratification are shown in Table 3. In the subgroup of patients aged ≥ 60 years, the median aneurysm volume [137.66, IQR (43.80–281.88) mm^3 vs. 58.06, IQR (22.44–152.56) mm^3], aspect ratio maximum [1.46, IQR (1.28–1.84) vs. 1.26, IQR (1.00–1.56)], aspect ratio [1.34, IQR (1.10–1.74) vs. 1.15, IQR (0.92–1.49)], bottleneck factor [1.21, IQR (1.01–1.56) vs. 1.00, IQR (0.86–1.24)], and VOR [6.95, IQR (4.55–13.77) vs. 3.86, IQR (2.08–7.54)] in males were significantly higher than those in females (all $P < 0.01$).

However, only aspect ratio maximum and aspect ratio showed significant differences between males and females aged 50–59 years. Of note, no significant differences in the morphological parameters were observed between males and females younger than 50 years.

Comparisons of morphological parameters of intracranial aneurysms between patients aged ≥ 50 years and patients aged < 50 years stratified by gender

The comparisons of morphological parameters of intracranial aneurysms between patients aged ≥ 50 years and patients aged < 50 years stratified by gender

TABLE 1 Comparisons of age, location, and morphological parameters of aneurysms between males and females.

Variables	All patients (<i>n</i> ₁ = 308, <i>n</i> ₂ = 346)	Males (<i>n</i> ₁ = 127, <i>n</i> ₂ = 137)	Females (<i>n</i> ₁ = 181, <i>n</i> ₂ = 209)	<i>t</i> / <i>Z</i> / <i>χ</i> ²	<i>P</i>
Age (y)	55.68 ± 11.34	54.29 ± 11.35	56.66 ± 11.26	1.809	0.071
≥60	127 (41.23)	42 (30.07)	85 (46.96)	6.135	0.047*
50–59	84 (27.27)	38 (29.92)	46 (25.41)		
<50	97 (31.50)	47 (37.01)	50 (27.63)		
Multiple aneurysms (<i>n</i> , %)	33 (10.71)	10 (7.87)	23 (12.71)	1.822	0.177
Size (mm)					
≥10	38 (10.98)	17 (12.41)	21 (10.05)	0.491	0.782
5–10	173 (50.00)	68 (49.64)	105 (50.24)		
<5	135 (39.02)	52 (37.95)	83 (39.71)		
Location (<i>n</i> , %)					
AcoA	94 (27.17)	51 (37.22)	43 (20.57)	22.445	0.000 ^{&}
MCA	97 (28.03)	43 (31.39)	54 (25.84)		
ICPC	110 (31.79)	25 (18.25)	85 (40.67)		
Others	45 (13.01)	18 (13.14)	27 (12.92)		
Unruptured aneurysms (<i>n</i> , %)	40 (11.56)	11 (8.03)	29 (13.88)	2.767	0.096
Morphology					
Neck width (mm)	4.20 (3.10–5.20)	4.00 (3.00–5.25)	4.20 (3.30–5.20)	−1.019	0.308
Height (mm)	5.10 (4.20–7.60)	5.00 (3.90–7.55)	5.10 (3.45–6.95)	−1.177	0.239
Transverse (mm)	4.40 (3.10–6.40)	4.70 (3.35–6.55)	4.10 (3.00–6.25)	−1.514	0.130
Maximum (mm)	5.75 (4.20–7.60)	5.80 (4.35–8.25)	5.70 (4.20–7.45)	−0.915	0.360
Aneurysm volume (mm ³)	57.42 (22.49–155.97)	68.66 (25.27–179.50)	51.67 (21.22–143.72)	−1.495	0.135
Aspect ratio maximum	1.31 (1.08–1.68)	1.38 (1.17–1.83)	1.27 (1.00–1.57)	−3.415	0.001 ^{&}
Aspect ratio	1.23(0.96–1.60)	1.29 (1.00–1.76)	1.18 (0.93–1.54)	−2.802	0.005 ^{&}
Bottleneck factor	1.07 (0.90–1.31)	1.17 (1.00–1.47)	1.03 (0.86–1.27)	−4.317	0.000 ^{&}
Height-width ratio	1.12 (0.90–1.46)	1.11 (0.87–1.50)	1.03 (0.86–1.27)	−0.281	0.779
VOR	4.55 (2.31–8.23)	5.67 (2.85–9.03)	3.86 (1.94–7.48)	−3.322	0.001 ^{&}

ICPC, internal carotid posterior communication artery; MCA, middle cerebral artery; ACoA, anterior communication artery; VOR, volume-to-ostium area ratio.

*Denoted *P* < 0.05 between males and females.

[&]Denoted *P* < 0.01 between males and females.

50 years stratified by gender are presented in Table 4. Males aged ≥ 50 years had a larger maximum, aneurysm volume, and aspect ratio maximum compared with those aged < 50 years. However, no significant difference in aneurysm morphology was found between females aged ≥ 50 years and those aged < 50 years.

Discussion

The main findings of our study are, first, that gender differences existed in the morphology of intracranial aneurysms. More specifically, males had remarkably larger aneurysm volume, aspect ratio maximum, aspect ratio, bottleneck factor, and VOR compared with females. Second, the gender difference in aneurysm morphology was affected by age. The gender difference was the most prominent in patients aged ≥ 60 years,

whereas it was not significant in patients younger than 50 years. To the best of our knowledge, this is the first study to report the age-specific gender difference in the morphology of intracranial aneurysms.

Compared with published large case series (3, 15, 16), this study population had similar basic demographic and clinical characteristics, including mean age, female to male ratio, the incidence of multiple aneurysms, the incidence of the small aneurysm (size < 10 mm), and distribution of aneurysm location. For instance, the proportion of aneurysms smaller than 10 mm was previously reported to be 78–94% (3, 15), which was similar to our result (89.02%). Additionally, both the previous studies (3, 15, 16) and our results demonstrated that ICPC, MCA, and ACoA were the three most common locations of intracranial aneurysms. Accordingly, the study population could be thought to represent the overall aneurysm distribution in our local population.

TABLE 2 Comparisons of the location of intracranial aneurysms between males and females stratified by age.

Age (M/F)	Location	Males	Females	χ^2	P
≥60 y (44/95)	AcoA	11 (25.00)	20 (21.05)	3.265	0.351
	MCA	17 (38.64)	27 (28.42)		
	ICPC	11 (25.00)	38 (40.00)		
	Others	5 (11.36)	10 (10.53)		
50–59 y (42/61)	AcoA	19 (45.23)	10 (16.39)	24.807	0.000 [*]
	MCA	14 (33.33)	11 (18.03)		
	ICPC	3 (7.14)	32 (52.46)		
	Others	6 (14.30)	8 (13.12)		
<50 y (51/53)	AcoA	21 (41.18)	13 (24.53)	3.282	0.350
	MCA	12 (23.53)	16 (30.19)		
	ICPC	11 (21.57)	15 (28.30)		
	Others	7 (13.72)	9 (16.98)		

ICPC, internal carotid posterior communication artery; MCA, middle cerebral artery; ACoA, anterior communication artery.
^{*}Denoted $P < 0.01$ between males and females.

In clinical practice, since females have a higher prevalence of intracranial aneurysms than males (17), gender difference is a remarkable clinical characteristic in patients with intracranial aneurysms. In this study, gender difference was also observed in aneurysm morphology, which is in keeping with those of a published report on the influence of gender on morphological parameters of intracranial aneurysms (11). However, Lin et al. (11) reported that the gender differences in aneurysm morphology were restricted in size, height, and size ratios, while the differences in other morphological parameters were not observed. This discrepancy might be attributed to the gender ratio of the study population, in which the female to male ratio was <1 in Lin et al.'s study but far more than one in our study as well as previous literature (3, 15, 16). In line with previous study (10), we found that males had significantly larger aspect ratio maximum, aspect ratio, bottleneck factor, and VOR than females. The gender differences in aneurysm morphology may be explained by the distinct degrees of inflammation in aneurysm formation between genders. First, the hemodynamic and inflammatory mechanisms are suggested to be the putative pathogenesis of intracranial aneurysms (18). In particular, the inflammation cascade is critical to wall remodeling, which is a major process in the formation, growth, and rupture of intracranial aneurysms (19). Previously, the gender difference in wall remodeling induced by inflammation was observed in a rat saccular intracranial model (20). In the animal study (20), vessel wall macrophage content was significantly higher in intracranial aneurysms of male rats at 28 days than in female rats, suggesting that males might have a more advanced degree of local aneurysmal wall inflammation than females. Second, evidence in animals and humans indicated that aspirin, a non-steroidal anti-inflammatory drug, decreased the risk of aneurysm rupture more significantly in males than in females (21). Third, aneurysmal wall enhancement

(AWE) on high-resolution vessel wall magnetic resonance imaging, which could reflect aneurysmal wall inflammation, was suggested to be associated with an irregular shape, a higher aspect ratio, and a higher bottleneck factor (22, 23). Thus, this study supports evidence from previous observations. However, the pathophysiological basis accounting for these dissimilarities remains unclear, and therefore further research is recommended to be undertaken to investigate the difference in inflammation patterns of aneurysm formation between genders.

Interestingly, we found that gender difference in aneurysm morphology was significant in patients aged ≥ 50 years, especially in patients aged ≥ 60 years. The reason for this is not clear but it may have something to do with the age-related difference in aneurysmal wall inflammation. On the one hand, a strong relationship between age and aneurysmal wall inflammation has been reported in the literature (24). For instance, it was suggested that older age was independently associated with increased aneurysmal wall enhancement on MRI (24), indicating that older patients with intracranial aneurysms might present a higher degree of aneurysmal wall inflammation. On the other hand, our result further showed that older males had a larger maximum, aneurysm volume, and aspect ratio maximum, whereas no difference in aneurysm morphology was found in females between different age groups. In this situation, it makes sense that the gender difference in aneurysm morphology would be more significant in older patients. In addition to aneurysm morphology, we found that gender difference in location of aneurysms was affected by age, which was consistent with Horiuchi et al.'s study (25). Surprisingly, only patients aged 50–59 years showed a statistically significant difference in aneurysm location between genders when stratified by age in this study. It is difficult to explain this result, but it might be related to a rapid estrogen reduction in females during this period. A further study is therefore suggested to verify this hypothesis.

Our findings could give further support to the previously proposed pathophysiological features of intracranial aneurysms, providing important implications to future studies that can discern the critical steps in the pathogenesis of intracranial aneurysms. Importantly, since aneurysm morphology plays a crucial role in outcomes of intracranial aneurysms, future studies on the relevant subjects are suggested to take the age-specific gender differences seriously into account.

Limitations

Despite the intriguing findings of this study, several important limitations should be taken into account. First, our study is single-centered research with a relatively small sample size, and it may be underpowered to detect a significant difference in location and morphology of intracranial aneurysms between genders stratified by age. Second, over 85% of the aneurysms were ruptured in this study, and whether gender differences in location and morphology of intracranial aneurysms are attributed to rupture remains unknown. Further studies, which take these variables into account, will need to be undertaken. Last but not least, gender differences in aneurysm morphology were interpreted with aneurysmal wall inflammation in this study. Although this interpretation is supported by a large number of published articles,

TABLE 3 Comparisons of morphological parameters of intracranial aneurysms between males and females stratified by age.

Age (M/F)	Morphology	Males	Females	Z	P
≥60 y (44/95)	Aneurysm volume (mm ³)	137.66 (43.80–281.88)	58.06 (22.44–152.56)	−1.972	0.049*
	Aspect ratio maximum	1.46 (1.28–1.84)	1.26 (1.00–1.56)	−3.525	0.000&
	Aspect ratio	1.34 (1.10–1.74)	1.15 (0.92–1.49)	−2.787	0.005&
	Bottleneck factor	1.21 (1.01–1.56)	1.00 (0.86–1.24)	−3.784	0.000&
	VOR	6.95 (4.55–13.77)	3.86 (2.08–7.54)	−3.303	0.001&
50–59 y (42/61)	Aneurysm volume (mm ³)	62.27 (23.52–165.87)	47.69 (20.33–142.07)	−0.507	0.612
	Aspect ratio maximum	1.56 (1.09–1.97)	1.25 (1.00–1.56)	−2.149	0.032*
	Aspect ratio	1.51 (0.92–1.96)	1.16 (0.84–1.52)	−1.976	0.048*
	Bottleneck factor	1.16 (0.99–1.41)	1.06 (0.80–1.27)	−1.775	0.076
	VOR	5.69 (2.64–8.63)	4.00 (1.85–7.63)	−1.590	0.112
<50 y (51/53)	Aneurysm volume (mm ³)	50.24 (23.13–128.52)	36.90 (16.75–116.80)	−0.631	0.528
	Aspect ratio maximum	1.26 (1.15–1.74)	1.37 (1.07–1.71)	−0.075	0.940
	Aspect ratio	1.24 (1.00–1.57)	1.25 (1.00–1.57)	−0.072	0.943
	Bottleneck factor	1.13 (1.00–1.38)	1.03 (0.86–1.25)	−1.811	0.070
	VOR	4.05 (2.60–8.77)	3.24 (1.88–7.06)	−0.962	0.336

Neck width, transverse, height, maximum, and height-width ratio were not significantly different between genders in all age subgroups.

VOR, volume-to-ostium area ratio.

*Denoted $P < 0.05$ between males and females.

&Denoted $P < 0.01$ between males and females.

TABLE 4 Comparisons of morphological parameters of intracranial aneurysms between patients aged ≥ 50 years and patients aged < 50 years stratified by gender.

Gender (≥50/<50)	Morphology	≥50 years	<50 years	Z	P
Males (86/51)	Maximum (mm)	6.55 (4.50–9.00)	5.10 (4.00–6.60)	−2.289	0.022*
	Aneurysm volume (mm ³)	95.32 (35.18–222.52)	50.24 (23.13–128.52)	−2.033	0.042*
	Aspect ratio maximum	1.53 (1.20–1.96)	1.26 (1.15–1.74)	−1.968	0.049*
Females (156/53)	Maximum (mm)	5.90 (4.23–7.60)	5.30 (3.90–7.30)	−1.158	0.247
	Aneurysm volume (mm ³)	56.20 (21.78–149.58)	36.90 (16.76–116.81)	−1.300	0.194
	Aspect ratio maximum	1.26 (1.00–1.55)	1.37 (1.07–1.71)	−1.354	0.176

Neck width, transverse, height, aspect ratio, bottleneck factor, height-width ratio, and volume-to-ostium area ratio were not significantly different between patients aged ≥ 50 years and patients aged < 50 years in both male and female subgroups.

*Denoted $P < 0.05$ between patients aged ≥ 50 years and those aged < 50 years.

we could not provide direct evidence to validate this inference. Accordingly, the pathophysiological basis accounting for these dissimilarities remains to be established. Future studies on the current topic are therefore recommended.

Conclusion

In summary, gender differences existed in the morphology of intracranial aneurysms and were affected by age. Males had a larger aspect ratio maximum, aspect ratio, bottleneck factor, and VOR compared with females. Particularly, gender differences in aneurysm morphology were prominent in patients aged ≥ 60 years, whereas it was not significant in patients younger than 50 years. Previously proposed inflammatory and hormonal theories behind the pathogenesis of intracranial aneurysms seem like plausible mechanisms to explain the differences we found.

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 humans were approved by the Institutional Review Board of First Affiliated Hospital of Xiamen University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JM: Writing – original draft. YL: Writing – review & editing. XG: Methodology, Validation, Funding acquisition, Resources, Writing – review & editing. ZL: Writing – review & editing. XC: Writing – review & editing. GT: Writing – review & editing. ZW: Writing – review & editing. PZ: Writing – review & editing. SC: Writing – review & editing.

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Conflict of interest

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

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Endovascular recanalization of symptomatic chronic cerebral artery occlusion: predictors for successful recanalization and perioperative complications

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Background and purpose: Endovascular recanalization and stenting has been used to treat patients with symptomatic chronic cerebral artery occlusion, including intracranial vertebrobasilar artery occlusion and internal carotid artery occlusion. Our challenge is to improve success rates and reduce the incidence of postoperative complications. This study sought to identify potential predictors for successful recanalization.

Methods: Our study included 103 consecutive patients between February 2021 and October 2024 with symptomatic chronic cerebral artery occlusion who were treated with endovascular recanalization. We recorded clinical information, laboratory and examination results, radiologic characteristics and procedural results of patients. Factors affecting surgical outcomes were analyzed by univariate and multivariate analyses.

Results: A total of 103 consecutive CCAO recanalization attempts were performed from February 2021 to October 2024 in 103 patients (78 men; age 61.1 ± 11.1 years; range: 32–81 years) with overall technical success rate 68.9%. Patients had chronic comorbidities such as hypertension (78, 75.7%), diabetes mellitus (32, 31.10%), and cardiac disease (12, 11.7%). 38 (36.9%) had a history of smoking, and 23 (22.3%) had a history of drinking. The rate of overall intraoperative complication was 10.7% (11/103). Multivariate analysis showed that stump morphology, smoking history, duration from last neurologic event (longer than 6 months or not), age, NLR were significantly associated with successful recanalization. According to the coefficients of the prediction model, the technical success rates were 100, 66.7 and 11.1% in patients with ≤ 6 , 6–10, ≥ 10 points, respectively.

Conclusion: The morphology of occluded stumps, duration from last neurologic event, age, smoking history and NLR can be used to predict the outcome of vascular recanalization.

KEYWORDS

chronic cerebral artery occlusion, endovascular treatment, chronically occluded internal carotid artery, basilar artery occlusion, neutrophil-to-lymphocyte ratio

Highlights

- This study covers a wide range of cases including internal carotid artery and vertebrobasilar artery system.
- This study identified five factors that affect the outcome of vascular recanalization.
- This study developed a scoring system for predicting surgical outcomes.

Introduction

Chronic cerebral artery occlusion disease is currently the culprit that troubles a considerable number of cerebrovascular diseases patients with high recurrence rate and low quality of life. According to the location of vascular occlusion, it can be divided into anterior circulation occlusion and posterior circulation occlusion. The treatment of patients with chronic cerebral artery occlusion (CCAO) is controversial, especially those with symptoms of hypoperfusion or stroke. Even with active internal medicine medication treatment, 6–20% of CCAO patients still experience stroke events every year. The risk of ischemic stroke in such patients increased from 8% after 30 days of follow-up to 14% after 5 years of follow-up (1). The annual risk of recurrent stroke in patients with transient ischemic attack (TIA) or ischemic stroke associated with carotid artery occlusion is approximately 5–6% (2). That risk is approximately 12% per year in the subgroup of symptomatic ICA occlusive patients, in this subgroup, the hemodynamic state of the brain is impaired (3).

The proportion of patients with posterior circulation occlusion is not low in cerebral artery occlusive diseases. About 20% of ischemic stroke patients are caused by posterior circulation ischemia (4). According to literature statistics, the incidence of chronic vertebral artery occlusion in the Chinese population is higher than that in Caucasian (5). In patients with posterior circulation ischemia, the incidence of significant stenosis or occlusion at the origin of the vertebral artery is 32.1%, and the incidence of significant stenosis or occlusion in the intracranial segment of the vertebral artery is 32.4%; The incidence of vertebral artery stenosis or occlusion is very high in patients with posterior circulation ischemia (6). With the rapid development of neural intervention technology and surgical instruments, intervention recanalization technology has become increasingly mature. The number of research on chronic intracranial and extracranial artery occlusion and recanalization is also increasing year by year both domestically and internationally.

However, almost all studies only focus on anterior circulation occlusion, there is relatively few research on posterior circulation occlusion. In our study, we analyzed and summarized various cases of chronic cerebral artery occlusion treatment completed in the past 5 years, including the intracranial and extracranial segments of anterior circulation, as well as the intracranial and extracranial segments of posterior circulation. In the process, we analyzed and explored the feasibility, safety, and predictive factors for surgical success.

Methods

Overall design

This study is a retrospective study conducted at our center. Every patient with CCAO were treated in a unified clinical management process including patient screening and exclusion criteria, surgical process management, perioperative management, and long-term follow-up. All patients have signed written informed consent forms. This study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Hebei General Hospital (No. 2024-LW-084).

Patient enrollment

All patients had received intensive medical treatment before intravascular treatment (including antiplatelet therapy and controlling atherosclerosis risk factors: blood pressure, plasma glucose, plasma lipid, smoking cessation, alcohol abstinence, etc.), but because of inadequate response to medication, there were still symptoms of cerebral ischemia caused by hypoperfusion. The responsible arteries of the selected patients include complete occlusion of the internal carotid artery (both the intracranial and extracranial segments), the middle cerebral artery, the vertebral artery (both the intracranial and extracranial segments) and the basilar artery. We recorded the time interval from the last appearance of symptoms (including ischemic stroke and transient ischemic attack) to surgery for each patient (each patient was over 30 days).

The inclusion criteria

- Age > 18 years;
- Atherosclerotic CCAO defined as 100% cross-sectional truncation of the vascular lumen documented by computerized magnetic resonance angiography (MRA) or tomography angiography (CTA) and uniformly confirmed with digital subtraction angiography (DSA);
- Time from imaging diagnosis or from aggravation of clinical symptoms defined as change in National Institutes of Health Stroke Scale (NIHSS) score ≥ 4 or modified Rankin Scale (mRS) score ≥ 1 to recanalization was over 24 h;
- Even after receiving active pharmacological treatment, the recurrence or exacerbation of neurological symptoms could not be ameliorated or controlled;
- Perfusion imaging (CTP or MRP) shows low perfusion in the supply area of occluded arteries;
- Each patient has at least one atherosclerosis risk factor such as hypertension, dyslipidemia, diabetes mellitus, smoking, etc.

The exclusion criteria

- Nonatherosclerotic occlusion (vasculitis, trauma, dissection, or Moyamoya disease, etc.) or asymptomatic CCAO;

- Known allergy or contraindication to heparin, aspirin, clopidogrel, metal, or general anesthesia;
- Expected lifespan is less than 2 years caused by any other medical conditions;
- Recurrence or aggravation of neurologic symptoms are not caused by the occluded artery;
- Uncorrectable bleeding diathesis;
- Refusing surgery due to personal financial burden;
- Any other conditions not suitable for operation.

Clinical data collection

We collected the patient's gender, age, duration of vascular occlusion, past history (hypertension, diabetes, coronary heart disease history), smoking history, drinking history, body mass index (BMI) and occluded stump morphology (the previous neurological symptoms were defined as ipsilateral transient ischemic attacks or ischemic stroke or amaurosis, we record the duration from the last neurological event to intervention, dividing patients into two categories based on whether it is longer than 6 months). Based on the cerebral angiography images, according to the angle formed by the plane of the stump and the vessel wall of the involved blood vessel, it is classified as follows: "sharp" type ($\leq 45^\circ$) and "blunt" type ($>45^\circ$). If the end presents a flat stump, it is the "flat" type; if there is no obvious stump, it is the "no stump" type.

In addition, we also collected and summarized serum laboratory data from various patients: fasting blood glucose value, neutrophil value, lymphocyte value, neutrophil to lymphocyte ratio, platelet count, fibrinogen platelet ratio, platelet lymphocyte ratio, extremely low-density lipoprotein, low-density lipoprotein, apolipoprotein B, triglycerides, cholesterol, uric acid, creatinine, INR, fibrinogen, D-dimer, and foaming test results.

Evaluation criteria

In this study, the success of endovascular treatment was defined as residual stenosis rate $< 50\%$ and establishing grade 3 antegrade TICI flow, with surgical success as the primary endpoint event. TICI is divided into levels 0, 1, 2a, 2b, and 3 (7). The internal carotid artery (ICA) is classified into seven segments (8), namely C1, C2, C3, C4, C5, C6, and C7. The vertebral artery (VA) is classified into four segments, namely V1, V2, V3, and V4. The failure of endovascular treatment is defined when the occluded blood vessel cannot be recanalized after 30 min of repeated attempts and more than 300 milliliters of contrast agent have been consumed, the surgery ended accordingly.

Interventional techniques, periprocedural management, and medical treatment

The surgery is performed by experienced neurologists under general anesthesia. The guide catheter was advanced into the cervical VA or ICA as high as allowed by vessel tortuosity. A 0.014-inch microwire was carefully coaxially advanced with a microcatheter (Echelon 10) through the occluded segment. The Synchro microwire (200 cm) was our first choice, other micro wires such as Pilot

microwires can be replaced appropriately based on the degree of tortuosity of the vascular pathway. After the 0.014-inch microwire with supporting microcatheter passed through the lesion, microcatheter angiography was performed to confirm that the tip of the microcatheter is in the true lumen of the blood vessel. Then, using exchange technology, place a 300 centimeter microwire into the distal vascular branch of the occluded artery. And use a balloon to dilate the narrow segment (at least 30 s). Properly sized balloon stents and self-expanding stents were used to cover narrow segments. Balloon dilation can be performed if the stent expansion is not sufficient.

Each patient should take aspirin, clopidogrel, or ticagrelor orally before surgery. The main lipid-lowering and plaque stabilizing drugs are atorvastatin and rosuvastatin. At the same time, pay attention to observing adverse drug reactions and maintain them for life. If there is a thrombotic event during surgery, tirofiban antiplatelet aggregation therapy can be added. Kang et al. systematically outlined perioperative protocols and pharmacological strategies for cerebral vascular occlusion recanalization (CVOR) procedures (9), and we also referred to this strategy in practical clinical applications.

Statistical analysis

All continuous variables were expressed as mean $\pm$ SD, and categorical variables in numbers and percentage. Chi square test is used to compare categorical data and logistic regression method is used to compare continuous data. All statistical analyses were 2-tailed, and $p < 0.05$ was accepted as statistically significant. Statistical analysis was conducted using R Programming Language (version 4.3.2). Sensitivity and specificity were measured using the Jordan index. To evaluate the sensitivity and specificity of the diagnostic method used in this study, Receiver Operating Characteristic (ROC) curve analysis was conducted. The area under the ROC curve (AUC) was also calculated by R Programming Language. An AUC of 0.5 indicates that the diagnostic test is no better than random chance, while an AUC of 1.0 represents a perfect diagnostic test. The optimal cut - off point for the diagnostic test was determined by maximizing the Youden's index (sensitivity + specificity - 1). At this cut - off point, the balance between sensitivity and specificity was considered the most favorable for accurate diagnosis.

Results

A total of 103 consecutive CCAO recanalization attempts were performed from February 2021 to October 2024 in 103 patients (78 men; age 61.1 ± 11.1 years; range: 32 to 81 years) with overall technical success rate 68.9%. Many patients had chronic comorbidities such as hypertension (78, 75.7%), diabetes mellitus (32, 31.10%), and cardiac disease (12, 11.7%). In addition, 38 (36.9%) had a history of smoking, and 23 (22.3%) had a history of drinking. The baseline clinical variables are summarized in Table 1.

The rate of overall intraoperative complication was 10.7% (11/103). 1 patient had occlusion of ophthalmic artery, 2 patient had a slight subarachnoid hemorrhage followed by microwire perforation, 1 patient had a slight intraparenchymal hemorrhage, 1 patient died of massive recanalization hemorrhage 2 day after the procedure, 2

TABLE 1 Baseline characteristics of the studied patient population as stratified by failed or successful recanalization.

Characteristics		Failed (N = 28)	Successful (N = 62)	Chi square value or odds ratio (95% CI)	p-value
Gender	Female	7 (25%)	17 (27.4%)	0	1
	Male	21 (75%)	45 (72.6%)		
History of hypertension	No	6 (21.4%)	15 (24.2%)	0	0.9857
	Yes	22 (78.6%)	47 (75.8%)		
History of diabetes	No	17 (60.7%)	46 (74.2%)	1.0887	0.2968
	Yes	11 (39.3%)	16 (25.8%)		
History of coronary heart disease	No	25 (89.3%)	54 (87.1%)	0	1
	Yes	3 (10.7%)	8 (12.9%)		
Smoking history	No	12 (42.9%)	48 (77.4%)	8.8717	0.002896**
	Yes	16 (57.1%)	14 (22.6%)		
History of drinking	No	22 (78.6%)	49 (79%)	0	1
	Yes	6 (21.4%)	13 (21%)		
Stump morphology	Sharp	7 (25%)	44 (71%)	29.827	<0.001***
	Blunt	4 (14.3%)	10 (16.1%)		
	Flat	9 (32.1%)	0 (0%)		
	No stump	8 (28.6%)	8 (12.9%)		
Foaming test	No	22 (78.6%)	42 (67.7%)	0.63711	0.4248
	Yes	6 (21.4%)	20 (32.3%)		
Duration from last neurologic event (longer than 6 months or not)	No	7 (25%)	39 (62.9%)	9.6251	0.001919**
	Yes	21 (75%)	23 (37.1%)		
Neutrophil-to-lymphocyte ratio (NLR)	<2.5	9 (32.1%)	36 (58.1%)	4.1993	0.04044 *
	≥ 2.5	19 (67.9%)	26 (41.9%)		
Age	<60	1 (3.6%)	37 (59.7%)	22.643	<0.001***
	≥ 60	27 (96.4%)	25 (40.3%)		
Neutrophil lymphocytes	<3	0 (0%)	9 (14.5%)	3.0472	0.08087
	≥ 3	28 (100%)	53 (85.5%)		
Glucose		6.0 ± 2.6	5.9 ± 1.7	0.97 (0.78–1.21)	0.796
Lymphocytes, 10 ⁹ /L		1.9 ± 0.8	1.9 ± 0.8	1.01 (0.56–1.82)	0.978
Platelets, 10 ⁹ /L		254.5 ± 67.7	259.6 ± 65.6	1.00 (0.99–1.01)	0.735
Platelet lymphocyte ratio (PLR)		149.4 ± 61.8	153.9 ± 73.4	1.00 (0.99–1.01)	0.774
Fibrinogen platelet ratio (FPR)		0.0 ± 0.0	0.0 ± 0.0	0.00 (0.00–165.25)	0.279
Very low density lipoprotein, mmol/L		0.4 ± 0.3	0.5 ± 0.3	1.21 (0.22–6.66)	0.830
Low density lipoprotein, mmol/L		2.3 ± 0.7	2.4 ± 0.8	1.15 (0.62–2.13)	0.654
Apolipoprotein B, g/L		0.7 ± 0.2	0.8 ± 0.3	3.26 (0.48–22.19)	0.228
Triglycerides (TG), mmol/L		1.4 ± 0.7	1.5 ± 0.8	1.20 (0.65–2.21)	0.560
Cholesterol (TC), mmol/L		3.7 ± 1.0	3.9 ± 1.1	1.22 (0.77–1.91)	0.398

(Continued)

TABLE 1 (Continued)

Characteristics		Failed (N = 28)	Successful (N = 62)	Chi square value or odds ratio (95% CI)	p-value
Gender	Female	7 (25%)	17 (27.4%)	0	1
Uric acid (UA), $\mu\text{mol/L}$		292.3 $\pm$ 79.9	303.9 $\pm$ 76.9	1.00 (1.00–1)	0.508
Cr, $\mu\text{mol/L}$		74.7 $\pm$ 22.8	66.2 $\pm$ 15.1	0.97 (0.95–1.00)	0.052
Fibrinogen (Fg), g/L		3.2 $\pm$ 1.2	3.1 $\pm$ 0.9	0.83 (0.54–1.28)	0.401
INR		0.9 $\pm$ 0.1	0.9 $\pm$ 0.1	0.42 (0.00–399.12)	0.805
IBM		34.1 $\pm$ 37.7	26.2 $\pm$ 3.5	0.94 (0.83–1.06)	0.318
D-dimer FEU, mg/L		0.5 $\pm$ 0.5	0.5 $\pm$ 0.7	1.09 (0.52–2.26)	0.818

The value is the mean $\pm$ standard deviation or quantity (percentage), represents $p < 0.1$, * represents $p < 0.05$, ** represents $p < 0.01$, *** represents $p < 0.001$.

TABLE 2 Intraoperative complication.

Intraoperative complication	N
Slight subarachnoid hemorrhage	2
Slight intraparenchymal hemorrhage	1
massive recanalization hemorrhage	1
Distal embolization	2
Reocclusion of instant thrombosis	4
Occlusion of ophthalmic artery	1

TABLE 3 Score for predicting surgical success.

	Status	Coefficient	Score
Stump morphology	Sharp	−1.03	0
	Blunt		1
	Flat		2
	No stump		3
Smoking history	No	−2.24	0
	Yes		1
Duration from last neurologic event (longer than 6 months or not)	No	−1.47	0
	Yes		1
Age	<60	−4.77	0
	≥ 60		1
Neutrophil-to-lymphocyte ratio (NLR)	<2.5	−1.98	0
	≥ 2.5		1
Total points		Success rate (%)	
≤ 6		100	
6 ~ 10		66.7	
≥ 10		11.1	

patients had distal embolization accompanied by mild symptoms of limb hemiplegia. Four patients had reocclusion of instant thrombosis with progression of symptoms of hemiplegia in limbs. No patient dies in the failed recanalization group (Table 2).

Table 3 showed the score for predicting surgical success, as well as the success rates of different total score points. The success rate of

surgery increases as the score decreases. The c-index on the basis of area under the curve for this scoring system in predicting technical success was 0.943 (95%CI: 0.8905–0.9862; $P < 0.001$), with a sensitivity of 71.28% and a specificity of 75.26 (Figure 1). This indicates that the effectiveness of the model score in predicting patient surgical is commendable.

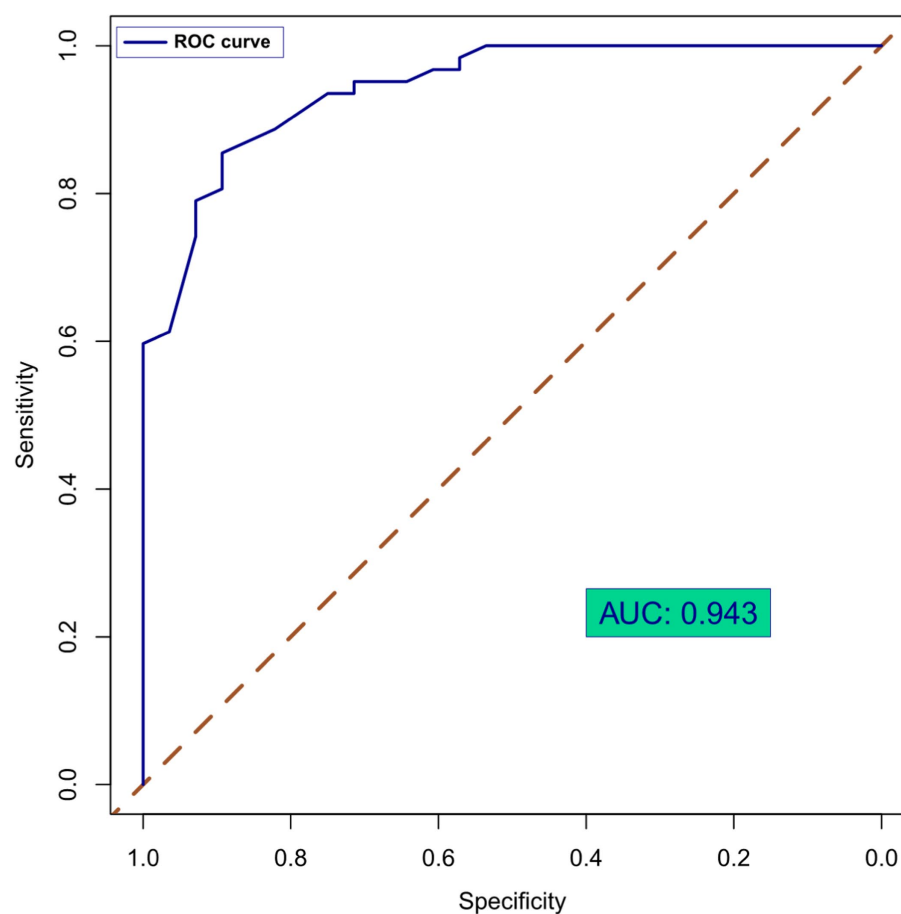


FIGURE 1
ROC curves of CAO score in predicting technical success.

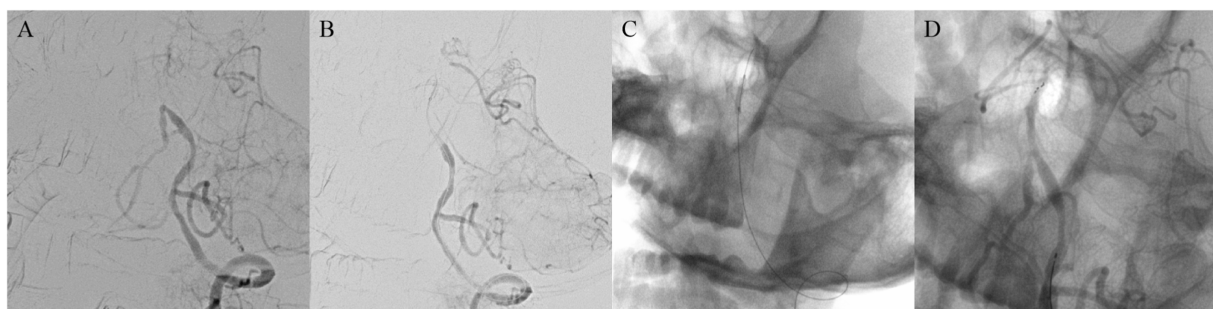


FIGURE 2
A 42-year-old man with lower basilar artery occlusion. Digital subtraction angiography confirmed occlusion of the basilar artery (A). Carefully probe the blocked section with a micro guide wire and confirm the true lumen of the blood vessel (B). Using balloon catheters to dilate narrow segments of the basilar artery (C). Successful recanalization of basilar artery occlusion, angiography shows good imaging of the basilar artery and bilateral posterior cerebral arteries, with normal blood flow velocity (D).

According to the type of occlusion site (anterior or posterior circulation, as well as intracranial or extracranial segments), four surgical imaging data of example cases were showed separately as follows (Figures 2–5), including several key steps during surgical process. At the same time we provide corresponding specific descriptions in the diagram.

Discussion

In terms of the treatment of CCAO, several previous studies have shown that the efficacy of surgical intervention is not very precise, and milestone EC-IC Bypass trial and Carotid Occlusion Surgery Study have not demonstrated any differences in fatal and non-fatal stroke

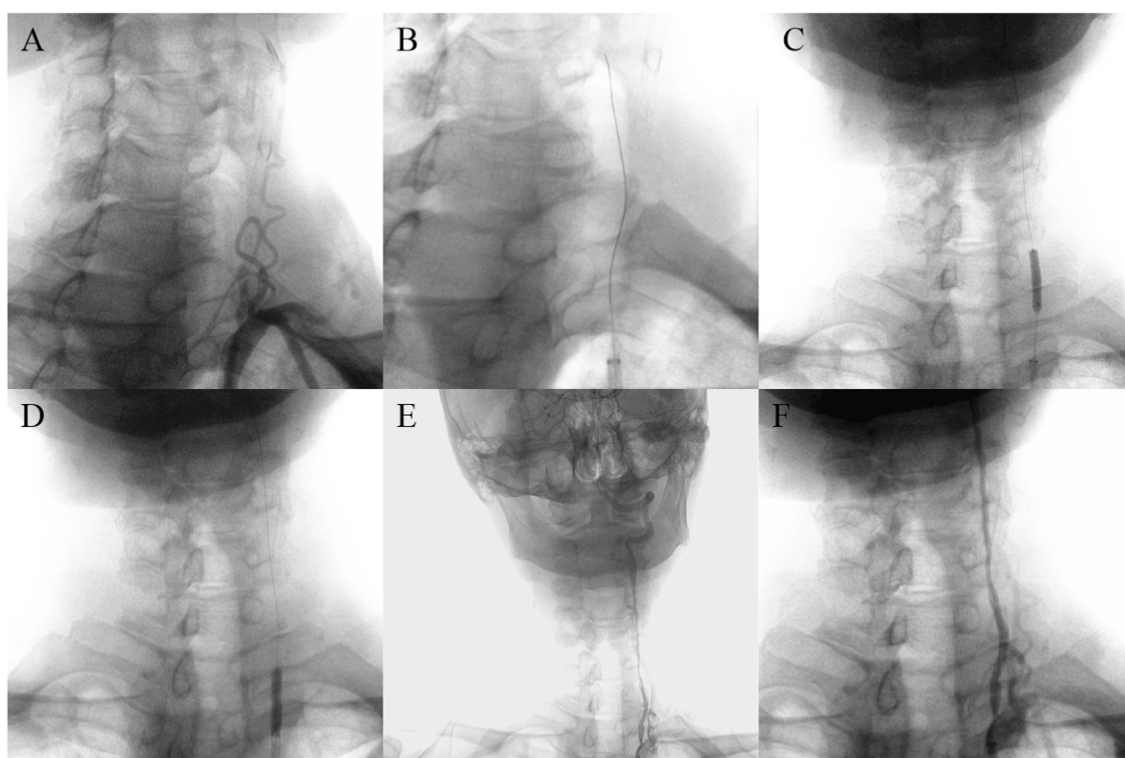


FIGURE 3

A 69-year-old man with left vertebral artery V1 segment occlusion. Digital subtraction angiography confirmed occlusion of the left vertebral artery V1 segment without obvious stumps (A). Carefully probe the blocked section with loach guide wire (B). Using balloon catheters to dilate narrow segments of vertebral artery from far to near (C,D). Successful recanalization with good antegrade perfusion was achieved (E,F).

between symptomatic CCAO patients in the surgical and medical groups within 2–5 years (10–12). And due to intolerance to hemodynamic fluctuations during surgery, the perioperative complications in the surgical group are relatively high (13). However, chronic CAO is associated with an annual incidence rate of stroke of 6–20%, despite aggressive medical treatment (14, 15). Intravascular recanalization of CCAO may provide the same recanalization advantage and have a higher safety advantage compared to surgical procedures, which can significantly reduce hemodynamic damage. The successful recanalization of postoperative CCAO patients can improve their cognitive function and quality of life (16–18). Unfortunately, endovascular treatment (ET) technology requires a high level of skill and experience from the surgeon, with potential complications including bleeding, pseudoaneurysm, and carotid cavernous sinus fistula (19), and the success or failure of the surgery is often difficult to predict. Therefore, preoperative evaluation of the system is crucial for identifying patients and lesion features with high success rates, which can help improve the success rate of surgery.

Up to now, experts have developed various predictive assessment scales through statistical analysis, but most of them are only targeted at patients with anterior circulation occlusion. Currently, there is a lack of predictive assessment scales suitable for patients with cerebral vascular occlusion that encompass both the anterior and posterior circulation. Especially there is relatively little research on posterior circulation occlusion.

Jin et al. proposed the application of The HRVWI score system to predict and analyze the successful recanalization of chronic internal

carotid artery occlusion (CICAO) (20). Chen et al. developed a scoring system to predict the success rate of intravascular recanalization in CICAO. The predictive factors include absence of perforated stumps, reconstruction of the distal carotid artery in the communicating or ocular segment, and absence of neurological events. However, there is a certain degree of heterogeneity and bias in their research (21). On this basis, Zhou et al. improved the above scoring system and concluded that a residual stump, low levels of the digital ICA occlusion segment, and a short radiological occlusion time were identified as positive predictors of technical success. However, this prediction system is still only applicable to the carotid circulation system (22).

There is relatively little research on the opening of vertebrobasilar artery occlusion, and some scholars have discussed and analyzed it. Gao et al. demonstrated the feasibility and safety of internal vertebral art (ICVA) reanalysis (23). Zhao et al.'s study suggests that endovascular regression for gut to chronic symptomatic astrological basic art occlusion (BAO) appear to be feasible in selected patients (24). Cai et al.'s research focuses on the treatment of chronic ventricular basic art occlusion in the starting segment (25).

Our study combines cases of the carotid artery system and the vertebrobasilar artery system for analysis, including patient baseline data, imaging characteristics, and laboratory examination data. The final prediction system is applicable to all types of CCAO cases. The final results showed that stump morphology, smoking history, duration from last neurological event (longer than 6 months or not), age, smoking history and neutral to lymphocyte ratio (NLR) were

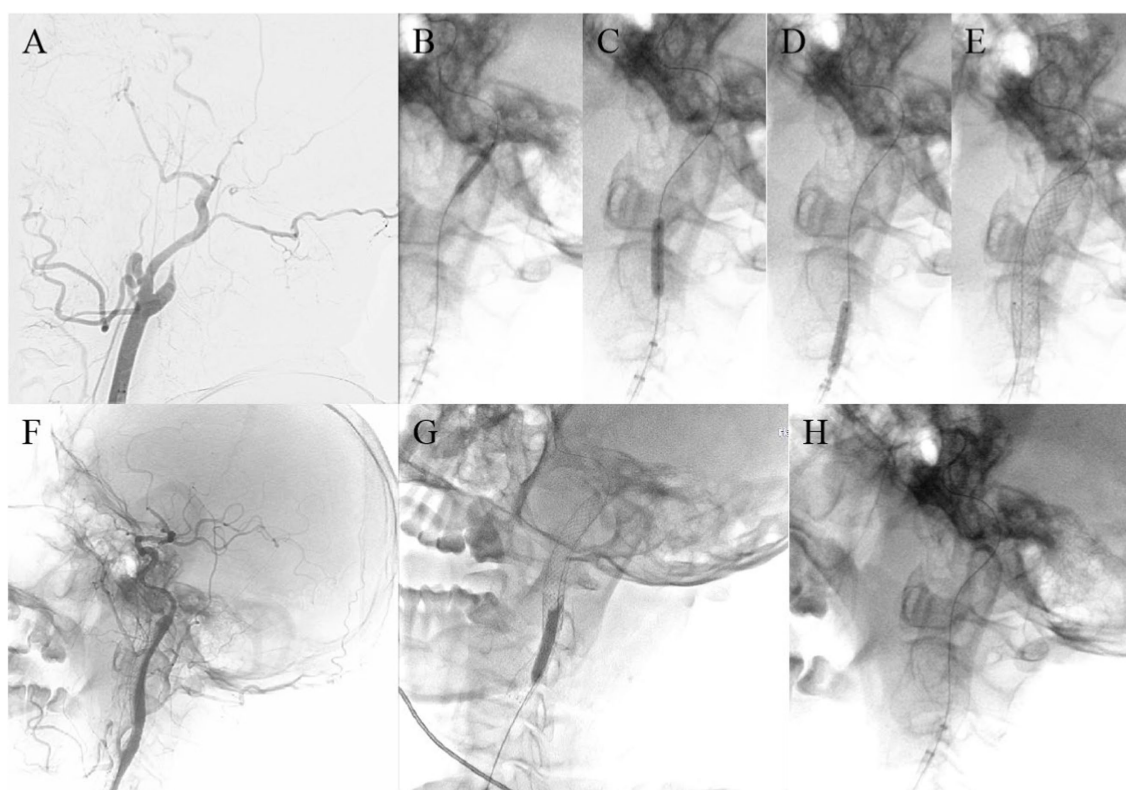


FIGURE 4

A 64-year-old man with left internal carotid artery C1 segment occlusion. Digital subtraction angiography confirmed occlusion of the left ICA (A). Carefully probe the blocked section with a micro guide wire and confirm the true lumen of the blood vessel (B). Using balloon catheters to dilate narrow segments of the internal carotid artery from far to near in sequence (C–E). Release carotid artery stent (F). The shape of the proximal attachment of the carotid stent for releasing carotid artery stents is slightly poor, and the morphology of arterial stent after release is perfect after redilation with a balloon (G). Successful recanalization of carotid artery occlusion, good imaging of the entire carotid artery, and normal blood flow velocity (H).

independent risk factors affecting recanalization success. And in this scoring system, we can predict the success rate of re communication based on the score.

It should be noted that there are many peculiarities in cases of vertebrobasilar artery system occlusion. For example, in patients with chronic occlusion of some vertebral arteries with no stump, we can use parallel compensatory vessels (such as the ascending carotid artery) for reverse patency, thereby ensuring the smooth completion of the surgery. However, there is no doubt that no stump is a negative impact factor on the success of the launch. This is also a limitation of this study. [Supplementary Figure 1](#) shows one of the cases of reverse opening of the vertebral artery that we completed.

A study has found that factors affecting bleeding after mechanical thrombectomy for acute anterior circulation occlusion include NHISS score at admission, stroke history, neutrophils, lymphocytes, NLR, PLR, and FPE (26). More and more scholars are becoming enthusiastic about analyzing preoperative laboratory test data of patients in order to explore the influencing factors for predicting surgical outcomes. After occlusion of large blood vessels in the anterior circulation, ischemic brain tissue is stimulated to release various chemokines and cytokines, leading to the entry of white blood cells in the peripheral circulation into the ischemic site. Neutrophils are one of the invading cells and are correlated with the severity of the disease (27–30). Research has found that the accumulation of neutrophils in ischemic

areas can exacerbate damage to brain tissue through the release of inflammatory mediators.

Meanwhile, the study also pointed out that severe damage to the blood–brain barrier increases the probability of postoperative bleeding. The interaction between neutrophils and platelets can trigger the formation of new blood clots and exacerbate vascular blockage. Neutrophils have the ability to adhere and aggregate on endothelial cells in ischemic tissue, hindering blood flow (31, 32). These research findings suggest a certain association between neutrophils and postoperative complications. In 2021, studies have indicated the impact of NLR on cerebral artery occlusion recanalization and elucidated its possible pathological mechanisms. When the NLR level is high, it indicates that the patient is likely to have a high neutrophil count or a low lymphocyte count. This situation undoubtedly increases the thrombus burden on occluded blood vessels, thereby increasing the difficulty of thrombectomy device operation and reducing the success rate of cerebral artery occlusion recanalization (33, 34). In our study, it was also confirmed that there is a correlation between NLR and the success rate of occlusive recanalization, and it can serve as a predictive factor, which helps us make relatively more accurate preoperative judgments.

Ter Schiphorst et al. pointed out that the presence of large vessel occlusions (LVO) could represent a “red flag” of PFO causality in stroke of undetermined etiology (35). Therefore, we attempted to

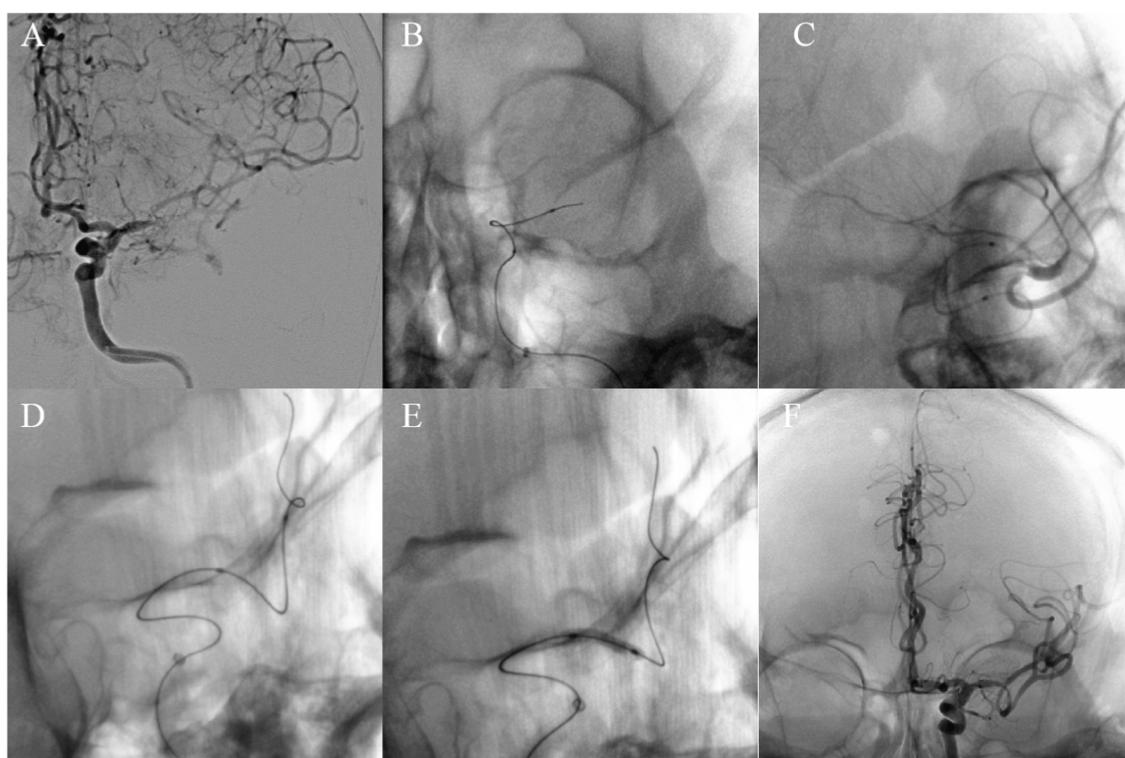


FIGURE 5

A 65-year-old man with left middle cerebral artery M1 segment occlusion. Digital subtraction angiography confirmed occlusion of the left MCA (A). Carefully probe the blocked section with a micro guide wire and confirm the true lumen of the blood vessel (B,C). Carefully placed the microwire beyond the M2 segment of the middle cerebral artery (D). Balloon dilation of the stenotic segment of the left middle cerebral artery (E). Successful recanalization with good antegrade perfusion was achieved (F).

explore whether there is a correlation between PFO and chronic occlusion and reperfusion of cerebral arteries. We conducted preoperative foam test screening for each patient, and the final results confirmed that there was no significant correlation between the two. The presence of PFO cannot predict surgical outcomes.

Study limitations

Although our scoring system is aimed at CCAO patients with different occlusions, the number of cases is still relatively small, especially in cases of vertebrobasilar artery occlusion. This may weaken the predictive ability of the scoring system. We still need to continue expanding case data. More prospective patients are needed in the future to validate current research results. On the other hand, for patients with occlusion of vertebral artery V1 segment, we can attempt reverse recanalization through the ascending carotid artery. Therefore, when predicting the surgical outcome of this type of patient, our application of a scoring system needs to take into account the patient's arterial collateral compensation situation. In this study, the total number of cases with complications was 11. Considering that a relatively large data bias might occur if a subgroup analysis of complications was carried out, we decided to conduct statistical analysis after further accumulation of the sample size, so as to further enhance the clinical relevance of the research results.

Conclusion

In summary, CCAO is undoubtedly an important risk factor for ischemic stroke. Our study found that the morphology of occluded stumps, duration from last neurologic event (longer than 6 months or not), age, smoking history and NLR were independent predictors for successful recanalization. The scoring system we have established has high sensitivity and specificity in predicting successful reperfusion, and has a wide range of applications. However, further research is needed to verify its clinical practicality.

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 humans were approved by the Ethics Committee of Hebei General Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

XZ: Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft. YL: Validation, Writing – review & editing. KY: Formal analysis, Investigation, Writing – review & editing. ZH: Investigation, Writing – review & editing. YF: Investigation, Writing – review & editing. QY: Investigation, Writing – review & editing. GX: Funding acquisition, Resources, Supervision, Writing – review & editing. PL: Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing.

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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.2025.1453841/full#supplementary-material>

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Predicting early functional outcomes in aneurysmal subarachnoid hemorrhage in endovascular coiling and surgical clipping

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Objectives: This study aimed to evaluate early functional outcomes in patients with aneurysmal subarachnoid hemorrhage (aSAH) treated with either endovascular coiling or surgical clipping and to develop predictive models tailored to each treatment modality.

Materials and methods: Patients diagnosed with aSAH were retrospectively enrolled from two hospitals in China between January 1, 2015, and December 31, 2022. Based on the treatment approach, patients were divided into two groups: endovascular coiling and surgical clipping. Independent risk factors were identified using least absolute shrinkage and selection operator (LASSO) regression followed by multivariate logistic regression. The relative contribution of each significant factor was calculated, and nomograms were constructed accordingly. Model performance was subsequently assessed through validation analyses.

Results: Multivariate analysis identified Hunt–Hess grade, Glasgow Coma Scale (GCS) score, modified Fisher Scale (mFS), D-dimer, age, and body temperature as independent predictors of early functional outcomes following endovascular coiling (all p -values <0.05). For surgical clipping, Hunt–Hess grade, GCS score, mFS, and D-dimer emerged as significant predictors (all p -values <0.05). The calculated relative contributions for endovascular coiling were 32.78% (Hunt–Hess grade), 31.99% (mFS), 4.63% (GCS score), and 13.73% (D-dimer); for surgical clipping, these values were 33.55, 38.02, 8.44, and 19.99%, respectively. Nomograms were developed for both treatment groups, and their performance was validated using receiver operating characteristic (ROC) curves, calibration plots, and decision curve analysis (DCA), demonstrating strong discriminative ability and clinical applicability.

Conclusion: This study developed predictive nomogram models for early functional outcomes of aSAH patients undergoing endovascular coiling or surgical clipping treatments, emphasizing the importance of scoring systems and clinical parameters (such as D-dimer), demonstrating strong clinical utility.

KEYWORDS

aneurysmal subarachnoid hemorrhage, early functional outcomes, endovascular coiling, surgical clipping, D-dimer, nomogram

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a life-threatening cerebrovascular disorder with significant global morbidity and mortality. The global incidence of aSAH is approximately 6.1 cases per 100,000 person-years (1), while in China, it is estimated at around 2.0 cases per 100,000 person-years (2). Notably, epidemiological studies have established a positive correlation between aSAH incidence and advancing age (3). As populations worldwide age, the number of individuals at risk of aSAH is expected to rise, underscoring the urgent need for effective diagnostic and treatment strategies.

For patients with ruptured aneurysms in anterior or posterior circulations, endovascular coiling generally yields better short-term outcomes compared to surgical clipping (4, 5). However, surgical clipping remains the preferred approach for patients with large intracerebral hematomas or middle cerebral artery aneurysms due to its unique advantages (6). Findings from the International Subarachnoid Aneurysm Trial (ISAT) (7) showed that the endovascular coiling group had a 7% lower 1-year mortality rate than the surgical clipping group, albeit with an increased long-term risk of rebleeding.

Current clinical evaluations of postoperative outcomes after surgical clipping and endovascular coiling predominantly rely on the Hunt–Hess grading scale and the Glasgow Coma Scale (GCS). While valuable, these traditional assessment tools do not comprehensively account for individualized clinical parameters that may significantly influence patient prognosis (8). This study aimed to develop novel nomogram models based on commonly used clinical scoring systems and selected clinical parameters to assess early functional outcomes—such as neurological recovery and activities of daily living—in patients undergoing the two different surgical approaches.

Materials and methods

Study population

This study retrospectively and continuously collected patients with aSAH who were hospitalized and treated at the Affiliated Yixing Hospital of Jiangsu University and the Affiliated Zhenjiang First Hospital of Jiangsu University from 1st January, 2015 to 31st December, 2022. Diagnosis, surgery, and perioperative management strictly adhered to the latest clinical practice guidelines of the Chinese Medical Association (9). The surgical approach for each case was determined by a neurosurgical team of senior neurosurgeons, based on individual patient characteristics, aneurysm features, and in accordance with available clinical guidelines. When both surgical options were deemed feasible, the final decision was made through team consensus, taking into account the preferences of the patient's family or designated surrogate decision-maker. Postoperatively, patients typically required intensive care management, which followed guideline-based protocols and included close monitoring, appropriate sedation and analgesia, cardiovascular support, vasospasm prevention, and active management of potential complications. The study adhered to the Helsinki Declaration and

obtained approval from the ethics committees of two hospitals, with approval numbers 2023043 and K-20230086-w. All participants or their authorized representatives were required to sign an informed consent form during hospitalization, ensuring their full understanding of the purpose, methods, risks, and benefits of the surgery and study, and indicating their voluntary participation.

Inclusion criteria include: (1) age 18 years or older; (2) confirmed as aSAH through laboratory and imaging examinations; (3) patients must undergo either endovascular coiling or surgical clipping treatment. Exclusion criteria include: (1) previous hospitalization for aSAH; (2) subarachnoid hemorrhage caused by other reasons, including vascular malformation, cerebral atherosclerosis, trauma, etc.; (3) the presence of severe cardiovascular, liver, kidney or other vital organ diseases; (4) loss of clinical parameters such as platelet count and D-dimer.

The study variables and outcomes

The study variables include demographic information (age and sex), physical examination data (body temperature and mean arterial pressure), laboratory tests (D-dimer, and platelet count), imaging examinations (length, width, height, position, etc.), past medical history (hypertension and diabetes), clinical scoring tools (GCS, Hunt–Hess, and mRS), treatment modalities (endovascular coiling and surgical clipping), and the use of stents. Patients were stratified into the endovascular coiling group and the surgical clipping group based on treatment methods.

The primary endpoint of this study was the early functional outcomes of patients 1 month after surgery. Considering that the modified Rankin Scale (mRS) is recommended for assessing neurological recovery status, this study utilized the mRS score at 1 month post-surgery as the primary endpoint, with scores ranging from 0 to 3 indicating a favorable prognosis and scores from 4 to 6 indicating an unfavorable prognosis (10).

Statistical analysis

Chi-square tests were used for categorical variables, while non-parametric tests were employed for continuous variables. Univariate and multivariate logistic regression analyses were conducted to determine independent predictive factors and calculate their relative weights on the outcome variable. Two separate nomogram models were developed to predict early functional outcomes in aSAH patients undergoing endovascular coiling and Surgical clipping, respectively. Receiver operating characteristic curves (ROC) were plotted, and the area under the curve (AUC) was calculated to assess the discriminative ability of the nomogram. Calibration curves were generated to illustrate the consistency between predicted probabilities and observed outcomes across various predicted probabilities. Decision curve analysis (DCA) was conducted to evaluate the clinical utility of the nomogram. Finally, risk stratification was performed. All statistical analyses were conducted using SPSS version 26.0 and R version 4.3.1, with statistical significance defined at the conventional threshold of $p < 0.05$ (two-tailed).

Results

Characteristics of patients in the endovascular coiling and surgical clipping groups

A total of 962 patients diagnosed with aSAH were included in the final analysis cohort (Figure 1). Overall, the proportion of early adverse outcomes in the surgical clipping group (32.7%) was higher than that in the endovascular coiling group (15.0%) (Figure 2). In patients undergoing endovascular coiling, those with poor functional outcomes tended to be older, have higher D-dimer levels, higher Hunt–Hess grades, GCS scores of 3–8, higher mFS grades, larger aneurysm volumes, were more likely to be located in the anterior cerebral artery and posterior circulation. Among patients undergoing surgical clipping, those with poor functional outcomes tended to be older, have higher Hunt–Hess grades, GCS scores of 3–8, higher mFS grades, higher D-dimer levels, and lower platelet counts (Tables 1, 2).

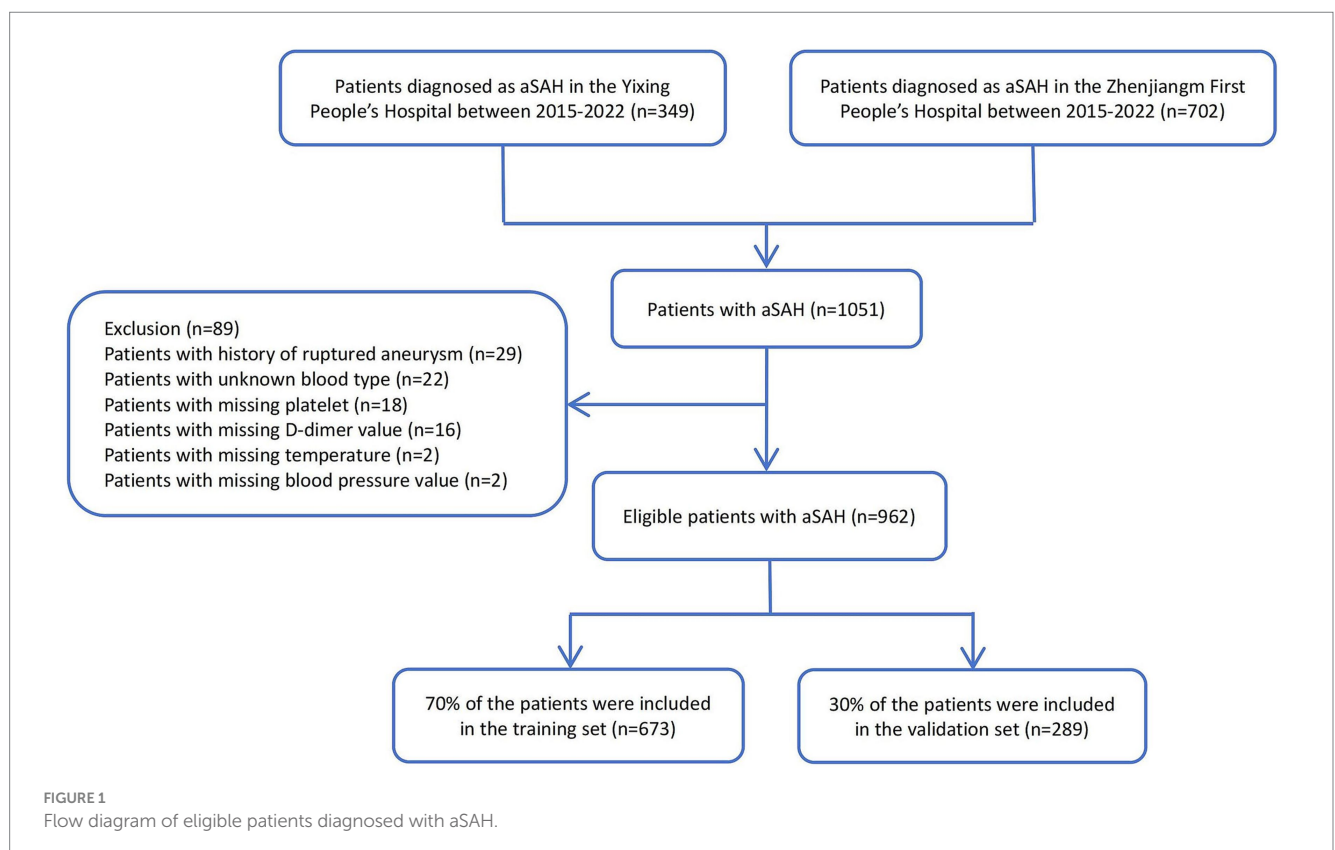
Univariate and multivariate logistic regression analysis

We utilized univariate and multivariate logistic regression models to assess the impact of clinical variables and scores on outcomes. The results revealed that, in the endovascular coiling group, age [adjusted odds ratio (OR): 1.033, 95% confidence interval (CI): 1.007–1.06, $p = 0.015$], Hunt–Hess grade (adjusted OR: 2.727, 95% CI: 1.172–6.154, $p = 0.017$), GCS score (9–12:

adjusted OR: 0.308, 95% CI: 0.11–0.835, $p = 0.022$; 12–15: adjusted OR: 0.098, 95% CI: 0.039–0.24, $p < 0.001$), mFS (adjusted OR: 2.769, 95% CI: 1.382–5.959, $p = 0.006$), D-dimer (adjusted OR: 1.248, 95% CI: 1.106–1.412, $p < 0.001$), and body temperature (adjusted OR: 0.469, 95% CI: 0.274–0.784, $p = 0.005$) were significantly associated with early adverse functional outcomes (Table 3). Whereas, in the surgical clipping group, Hunt–Hess grade (adjusted OR: 2.369, 95% CI: 1.051–5.408, $p = 0.038$), GCS score (12–15: adjusted OR: 0.274, 95% CI: 0.121–0.606, $p = 0.002$), mFS (adjusted OR: 2.918, 95% CI: 1.245–6.994, $p = 0.014$), and D-dimer (adjusted OR: 1.508, 95% CI: 1.304–1.766, $p < 0.001$) were independent predictors of early functional outcomes (Table 4). The forest plot displays the significant multivariable factors (Figures 3A,B).

The relative weights of impact on the early functional outcome

We further assessed the relative impact of significant variables on early functional outcomes using multivariate logistic regression analysis. In the endovascular coiling group, the proportions of significant variables were as follows: Hunt–Hess grade contributed 32.78%, mFS contributed 31.99%, D-dimer contributed 13.73%, age contributed 11.61%, body temperature contributed 5.26%, and GCS contributed 4.63%. In the surgical clipping group, mFS contributed 38.02%, Hunt–Hess grade contributed 33.55%, D-dimer contributed 19.99%, and GCS contributed 8.44% (Figures 4A,B).



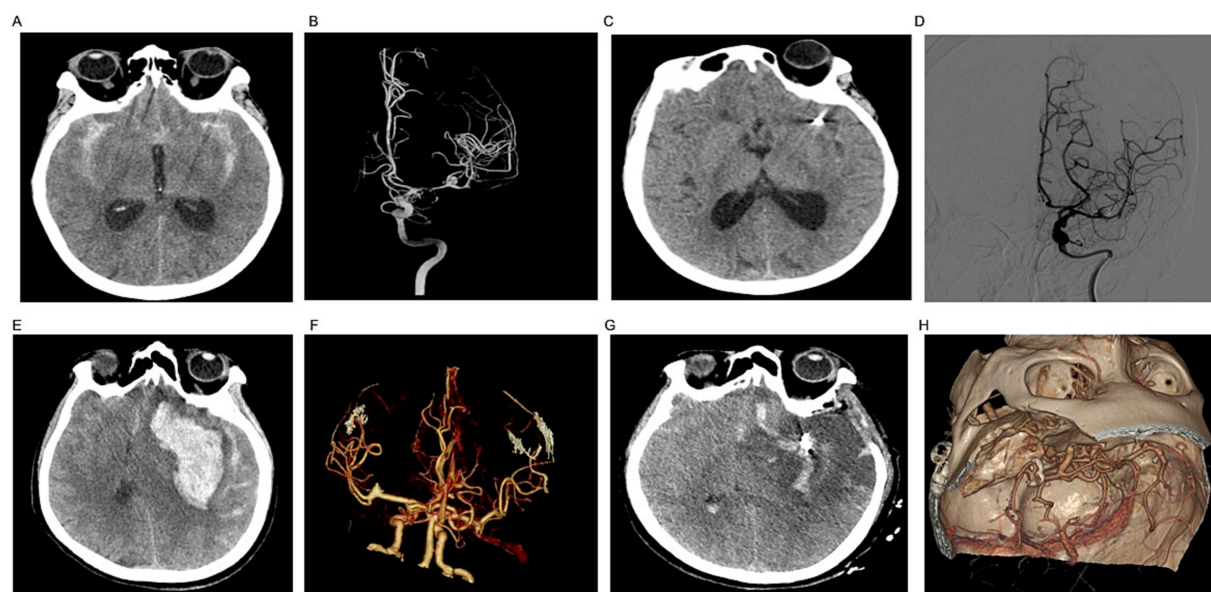


FIGURE 2

(A) Ruptured aneurysm of the left middle cerebral artery with subarachnoid hemorrhage. (B) DSA showing left middle cerebral artery aneurysm. (C) Post-embolization CT of left middle cerebral artery aneurysm. (D) Post-embolization angiogram of left middle cerebral artery aneurysm. (E) Left cerebral middle artery aneurysm rupture with subarachnoid hemorrhage and temporal lobe hematoma. (F) Left cerebral middle artery aneurysm CTA imaging. (G) Post-clipping of left cerebral middle artery aneurysm and clearance of temporal lobe hematoma. (H) Post-clipping of left cerebral middle artery aneurysm.

Nomogram for early functional outcome and validation

Nomogram models were developed for different groups based on early functional outcomes (Figures 5A, 6A). In the endovascular coiling group, the ROC curve indicated good predictive accuracy, with an AUC value of 0.847 (95% CI: 0.800–0.894) (Figure 5B), and the calibration curve demonstrated close alignment between the model and predictions (Figure 5C). The decision curve analysis (DCA) curve showed good clinical predictive value across different threshold probabilities (Figure 5D). Similarly, in the surgical clipping group, the ROC curve showed good predictive accuracy, with an AUC value of 0.841 (95% CI: 0.796–0.886) (Figure 6B), and the calibration curve exhibited basic alignment with predictions (Figure 6C). The DCA curve also demonstrated good clinical predictive value across different threshold probabilities (Figure 6D). In addition, by incorporating the surgical approach as an additional variable into the shared predictive factors, we developed a new, integrated nomogram model (Figure 7A). This model achieved an AUC of 0.857 for predicting poor outcomes within 1 month (Figure 7B). The calibration curve demonstrated good agreement between predicted and observed outcomes, and the DCA showed favorable clinical utility across a range of threshold probabilities (Figures 7C,D).

Nomogram-based risk stratification predicts early functional outcome

Based on the risk scores predicted by the nomogram, patients were categorized into three groups: low risk, medium risk, and high risk. In the endovascular coiling group, individuals in the

medium-risk group faced a 2.791-fold higher risk compared to those in the low-risk category, while those in the high-risk group experienced a significantly elevated risk of 17.506 times compared to the low-risk group (Table 5). Similarly, within the surgical clipping group, participants classified in the medium-risk tier were at a 5.291-fold increased risk relative to the low-risk counterparts, with those in the high-risk category encountering an even greater risk, elevated by a substantial 26.641 times compared to the low-risk group (Table 5). These differences were statistically significant, highlighting the clinical significance of our nomogram model in integrating clinical scores and parameters.

Discussion

Despite significant advancements in managing patients with subarachnoid hemorrhage, the mortality rate remains high. The case-fatality rate for aSAH ranges from 32 to 67%, with approximately one-third of survivors experiencing long-term disability or cognitive impairment (11). Numerous studies have identified risk factors that influence the onset and progression of aSAH, including sex, hypertension, alcohol consumption, and smoking (12–14), as well as aneurysm-related factors such as size and location (15–17), influence the occurrence and development of aSAH. In addition, proteomic analyses have revealed that proteins involved in the focal adhesion and extracellular matrix–receptor interaction pathways may play a key role in the pathogenesis of intracranial aneurysms (18). Currently, endovascular coiling and neurosurgical clipping have become the main treatment methods for aSAH.

In our study, the incidence of early adverse functional outcomes was significantly lower in patients undergoing endovascular coiling

TABLE 1 Baseline characteristics of patients undergoing endovascular coiling.

Variables	Total (n = 638)	Good functional outcome (n = 542)	Poor functional outcome (n = 96)	p-value
Age, years	60.0 (52.0–68.0)	60.0 (51.8–67.0)	64.0 (53.0–72.0)	0.004
Gender				0.703
Female	413 (64.7%)	353 (65.1%)	60 (62.5%)	
Male	225 (35.3%)	189 (34.9%)	36 (37.5%)	
Hunt–Hess grade				<0.001
0–3	566 (88.7%)	514 (94.8%)	52 (54.2%)	
4–5	72 (11.3%)	28 (5.2%)	44 (45.8%)	
Hypertension				0.809
No	263 (41.2%)	225 (41.5%)	38 (39.6%)	
Yes	375 (58.8%)	317 (58.5%)	58 (60.4%)	
Diabetes mellitus				0.293
No	597 (93.6%)	510 (94.1%)	87 (90.6%)	
Yes	41 (6.4%)	32 (5.9%)	9 (9.4%)	
Body temperature, °C	36.8 (36.5–37.0)	36.8 (36.5–37.0)	36.8 (36.3–37.0)	0.068
MAP, mmHg	106.67 (96.67–117.33%)	106.67 (96.67–116.67%)	108.67 (98.67%–124.00%)	0.105
GCS score				<0.001
3–8	61 (9.6%)	19 (3.5%)	42 (43.8%)	
9–12	50 (7.8%)	35 (6.5%)	15 (15.6%)	
12–15	527 (82.6%)	488 (90.0%)	39 (40.6%)	
mFS				<0.001
0–2	245 (38.4%)	234 (43.2%)	11 (11.5%)	
3–4	393 (61.6%)	308 (56.8%)	85 (88.5%)	
Length, mm	4.0 (3.00–6.00)	4.0 (3.00–6.00)	4.58 (3.00–7.00)	0.063
Width, mm	4.0 (3.00–5.21)	4.0 (3.00–5.00)	4.5 (3.00–6.00)	0.191
Height, mm	4.0 (3.00–5.00)	3.88 (2.80–5.00)	4.00 (3.00–6.00)	0.038
Volume, mm ³	33.51 (14.22–66.76)	31.42 (14.14–65.45)	41.89 (18.43–89.54)	0.027
Aneurysm location				0.018
Anterior cerebral artery	190 (29.8%)	154 (28.4%)	36 (37.5%)	
Middle cerebral artery	53 (8.3%)	49 (9.0%)	4 (4.2%)	
Internal carotid artery	135 (21.2%)	121 (22.3%)	14 (14.6%)	
Posterior communicating artery	200 (31.3%)	173 (31.9%)	27 (28.1%)	
Posterior circulation	60 (9.4%)	45 (8.3%)	15 (15.6%)	
Presence of hematoma				0.375
No	628 (98.4%)	535 (98.7%)	93 (96.9%)	
Yes	10 (1.6%)	7 (1.3%)	3 (3.1%)	
Use of stents				0.724
No	325 (50.9%)	274 (50.6%)	51 (53.1%)	
Yes	313 (49.1%)	268 (49.4%)	45 (46.9%)	
D-dimer, mg/L	0.81 (0.40–1.85)	0.72 (0.33–1.54)	1.86 (0.94–4.00)	<0.001
PLT, ×10 ⁹ /L	208.0 (169.25–261.00)	207.5 (170.25–260.3)	211.50 (158.25–267.00)	0.858

MAP, mean arterial pressure; GCS, Glasgow Coma Scale; PLT, platelet.

compared to those treated with neurosurgical clipping, which is consistent with current clinical guidelines (19, 20). However, endovascular coiling is associated with increased hospitalization costs (21), and carries certain risks, including a lower rate of complete aneurysm occlusion and a higher risk of delayed rebleeding (22–24). Based on this, we have established two new nomogram models, which

TABLE 2 Baseline characteristics of patients undergoing neurosurgical clipping.

Variables	Total (n = 324)	Good functional outcome (n = 218)	Poor functional outcome (n = 106)	p-value
Age, years	60.0 (51.75–68.00)	58.5 (51.00–67.00)	63.0 (53.25–69.00)	0.020
Gender				0.720
Female	208 (64.2%)	138 (63.3%)	70 (66.0%)	
Male	116 (35.8%)	80 (36.7%)	36 (34.0%)	
Hunt–Hess grade				<0.001
0–3	200 (61.7%)	167 (76.6%)	33 (31.1.2%)	
4–5	124 (38.3%)	51 (23.4%)	73 (68.9%)	
Hypertension				1.000
No	91 (28.1%)	61 (28.0%)	30 (28.3%)	
Yes	233 (71.9%)	157 (72.0%)	76 (71.7%)	
Diabetes mellitus				1.000
No	308 (95.1%)	207 (95.0%)	101 (95.3%)	
Yes	16 (4.9%)	11 (5.0%)	5 (4.7%)	
Body temperature, °C	36.80 (36.5–37.0)	36.80 (36.5–37.0)	36.80 (36.5–37.1)	0.975
MAP, mmHg	111.00 (98.67–122.00)	111.00 (98.75–123.00)	111.50 (97.75–120.67)	0.741
GCS score				<0.001
3–8	95 (29.3%)	34 (15.6%)	61 (57.5%)	
9–12	23 (7.1%)	17 (7.8%)	6 (5.7%)	
12–15	206 (63.6%)	167 (76.6%)	39 (36.8%)	
mFS				<0.001
0–2	136 (42.0%)	121 (55.5%)	15 (14.2%)	
3–4	188 (58.0%)	97 (44.5%)	91 (85.8%)	
Length, mm	4.00 (3.00–6.00)	4.00 (3.00–5.20)	4.00 (3.00–6.00)	0.651
Width, mm	4.00 (3.00–5.00)	4.00 (3.00–5.00)	4.00 (3.00–5.00)	0.088
Height, mm	4.00 (3.00–5.00)	4.00 (3.00–5.00)	4.00 (3.00–5.00)	0.093
Aneurysm volume, mm ³	33.51 (14.14–65.45)	31.42 (14.14–62.83)	33.51 (14.14–89.54)	0.186
Aneurysm location				0.231
Anterior cerebral artery	106 (32.7%)	75 (34.4%)	31 (29.2%)	
Middle cerebral artery	126 (38.9%)	81 (37.2%)	45 (42.5%)	
Internal carotid artery	40 (12.3%)	26 (11.9%)	14 (13.2%)	
Posterior communicating artery	44 (13.6%)	33 (15.1%)	11 (10.4%)	
Posterior circulation	8 (2.5%)	3 (1.4%)	5 (4.7%)	
Presence of hematoma				0.791
No	276 (85.2%)	187 (85.8%)	89 (84.0%)	
Yes	48 (14.8%)	31 (14.2%)	17 (16.0%)	
D-dimer, mg/L	1.64 (0.73–2.93)	1.33 (0.66–2.48)	2.33 (1.34–3.99)	<0.001
PLT, ×10 ⁹ /L	260.00 (160.75–349.25)	286.00 (192.75–362.50)	194.50 (119.25–291.75)	<0.001

MAP, mean arterial pressure; GCS, Glasgow Coma Scale; PLT, platelet.

were based on commonly used clinical scoring systems (such as the Hunt–Hess grading scale and the GCS) and some clinical parameters, to evaluate the early functional outcomes of these two different surgical methods. Each variable corresponds to a score on the top line of the nomogram. The total score, calculated by summing the scores of all variables, is projected onto the bottom scale to estimate the probability of early postoperative poor outcomes in patients with

aSAH (25). Moreover, our results indicate that the prognostic models for both surgical approaches demonstrate good discriminatory power and calibration. Therefore, this tool has the potential to assist neurosurgeons in clinical decision-making and enhance the effective communication of prognostic information to patients’ families. In addition, based on the shared independent predictors identified from the two models, we further developed an integrated nomogram

TABLE 3 Logistic analysis of early functional outcomes after endovascular coiling.

Variables	Univariable ^a		Multivariable ^b	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Sex				
Female				
Male	1.121 (0.71–1.748)	0.619		
Age	1.031 (1.01–1.053)	0.004	1.033 (1.007–1.06)	0.015
Hunt–Hess				
0–3				
4–5	15.533 (9.002–27.292)	<0.001	2.727 (1.172–6.154)	0.017
Body temperature	0.613 (0.379–0.979)	0.043	0.469 (0.274–0.784)	0.005
GCS				
3–8				
9–12	0.194 (0.084–0.429)	<0.001	0.308 (0.11–0.835)	0.022
12–15	0.036 (0.019–0.067)	<0.001	0.098 (0.039–0.24)	<0.001
PLT	0.999 (0.996–1.002)	0.574		
D-dimer	1.375 (1.248–1.522)	<0.001	1.248 (1.106–1.412)	<0.001
mFS				
0–2				
3–4	5.871 (3.193–11.875)	<0.001	2.769 (1.382–5.959)	0.006
Hypertension				
No				
Yes	1.083 (0.698–1.698)	0.723		
Diabetes				
No				
Yes	1.649 (0.719–3.44)	0.205		
Length	1.032 (0.976–1.086)	0.239		
Width	1.018 (0.952–1.08)	0.565		
Height	1.044 (0.966–1.12)	0.252		
Volume	1 (0.999–1)	0.985		
MAP	1.014 (1.001–1.027)	0.028	1.015 (1.000–1.031)	0.051
Stent				
No				
Yes	0.902 (0.583–1.393)	0.642		
Aneurysm location				
Anterior cerebral artery				
Middle cerebral artery	0.349 (0.101–0.928)	0.057		
Internal carotid artery	0.495 (0.248–0.94)	0.037		
Posterior communicating artery	0.668 (0.385–1.147)	0.146		
Posterior circulation	1.426 (0.702–2.8)	0.312		

^aUnivariable logistic regression models.
^bMultivariable logistic regression model adjusting for age at diagnosis Hunt–Hess grade, body temperature, MAP, GCS score, and D-dimer.
OR, odd ratio; CI, confidence interval; MAP, mean arterial pressure; GCS, Glasgow Coma Scale.

incorporating the surgical approach as a covariate. This comprehensive model also demonstrated favorable predictive performance, supporting its potential utility in clinical practice for holistic risk stratification and management planning.

This study found that among patients treated with endovascular coiling, those who exhibited poorer early functional outcomes typically had older age, higher mFS scores, higher Hunt–Hess grades, and lower GCS scores, consistent with prior research (26, 27).

TABLE 4 Logistic analysis of early functional outcomes after surgical clipping.

Variables	Univariable ^a		Multivariable ^b	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Sex				
Female				
Male	0.887 (0.542–1.439)	0.630		
Age	1.026 (1.003–1.049)	0.027	1.021 (0.994–1.05)	0.128
Hunt–Hess				
0–3				
4–5	7.244 (4.358–12.281)	<0.001	2.369 (1.051–5.408)	0.038
Body temperature	1.025 (0.644–1.613)	0.916		
GCS				
3–8				
9–12	0.197 (0.066–0.522)	0.002	0.376 (0.111–1.173)	0.099
12–15	0.13 (0.075–0.223)	<0.001	0.274 (0.121–0.606)	0.002
PLT	0.997 (0.995–0.999)	0.001	0.998 (0.996–1.000)	0.060
D-dimer	1.266 (1.132–1.423)	<0.001	1.508 (1.304–1.766)	<0.001
mFS				
0–2				
3–4	7.568 (4.228–14.364)	<0.001	2.918 (1.245–6.994)	0.014
Hypertension				
No				
Yes	0.984 (0.591–1.662)	0.952		
Diabetes				
No				
Yes	0.932 (0.287–2.635)	0.898		
Length	1.058 (0.994–1.128)	0.076		
Width	1.064 (0.991–1.151)	0.095		
Height	1.09 (1.004–1.197)	0.049	1.057 (0.958–1.178)	0.283
Volume	1 (1.000–1.001)	0.284		
MAP	0.994 (0.981–1.007)	0.360		
Aneurysm volume	1 (1–1.001)	0.284		
Anterior cerebral artery				
Middle cerebral artery	1.344 (0.774–2.354)	0.296		
Internal carotid artery	1.303 (0.592–2.801)	0.502		
Posterior communicating artery	0.806 (0.351–1.761)	0.598		
Posterior circulation	4.032 (0.933–20.641)	0.067		

^aUnivariable logistic regression models.
^bMultivariable logistic regression model adjusting for age at diagnosis, blood group, GCS score, aneurysm width, aneurysm height, D-dimer, and PLT.
OR, odd ratio; CI, confidence interval; MAP, mean arterial pressure; GCS, Glasgow Coma Scale.

Additionally, we observed that these patients often presented with elevated D-dimer levels, larger aneurysm sizes, and anterior cerebral artery location of the aneurysm. In patients undergoing surgical clipping, factors influencing early functional outcomes typically included Hunt–Hess and mFS scores, which align with findings from Li’s et al. (21) study. Furthermore, our study indicated that lower GCS scores, elevated D-dimer levels, and decreased platelet counts were predictive of poorer early functional outcomes. Our results highlight the different perioperative priorities associated with each surgical

modality. For high-risk patients undergoing endovascular treatment, enhanced monitoring for thromboembolic events and proactive temperature management may be warranted. Surgical candidates with elevated D-dimer levels may benefit from preoperative optimization of hemostasis and postoperative antifibrinolytic therapy. Through multifactorial logistic analysis, age, body temperature, D-dimer, mFS score, Hunt–Hess grade, and GCS score were identified as independent risk factors for early functional outcomes in the endovascular coiling group. For

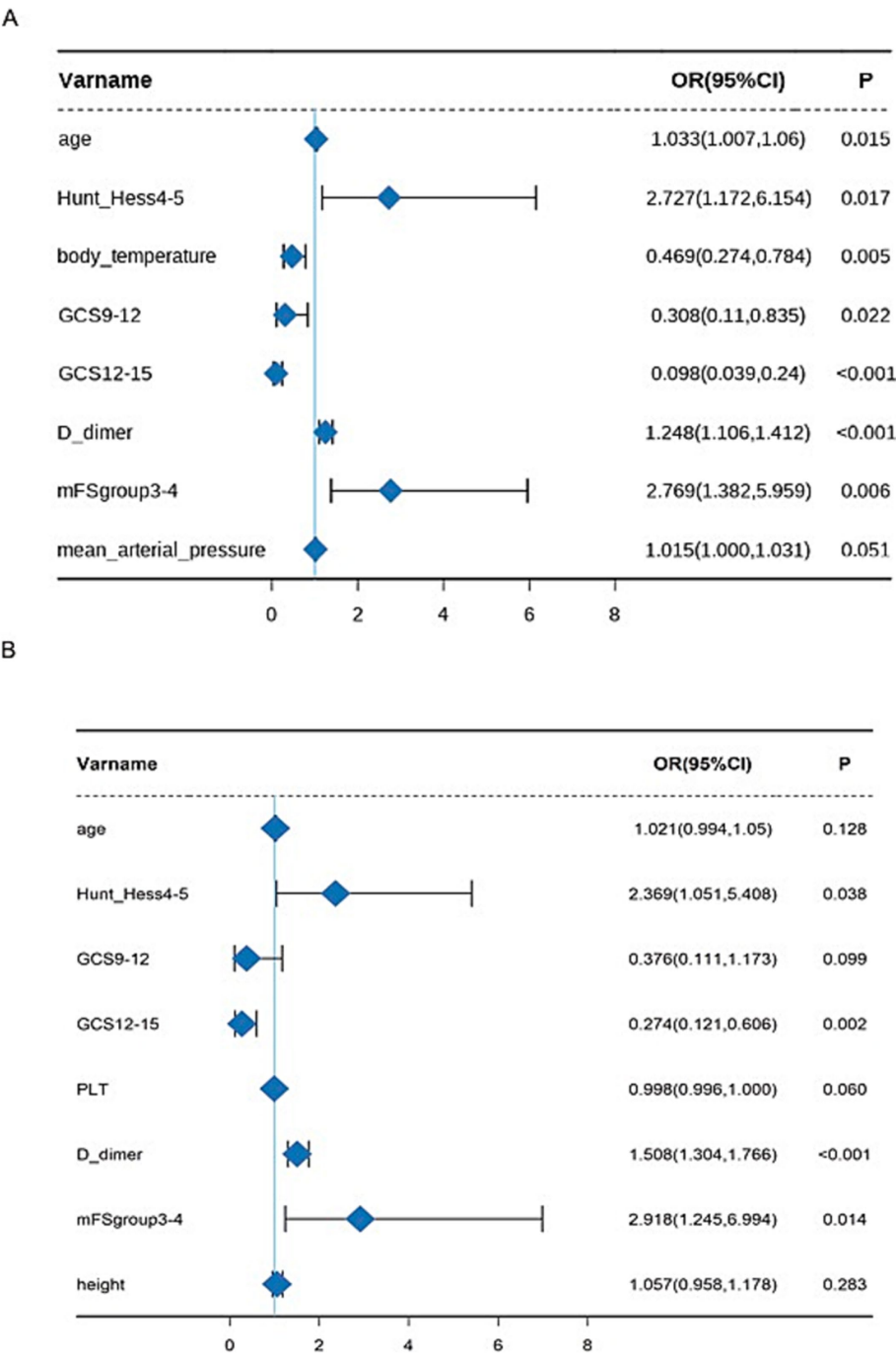


FIGURE 3 Forest plot based on multivariate analysis in the endovascular coiling (A) and surgical clipping groups (B).

surgical clipping treatment, Hunt–Hess grade, GCS score, mFS, and D-dimer level were determined as independent risk factors influencing early functional outcomes. Of note, the relative contribution analysis revealed that Hunt–Hess grade and mFS were the dominant predictors in both models, while D-dimer ranked among the top three contributors in each group, further supporting its clinical relevance. Interestingly, D-dimer levels can predict outcomes in both surgical methods, possibly because: (1) in neurosurgical procedures, stress may affect patients’ hemostatic and fibrinolytic functions; (2) changes in D-dimer

levels can reflect alterations in coagulation status, and abnormal D-dimer levels may indicate postoperative bleeding and thrombotic complications (28–30). Additionally, hypothermia may lead to poorer outcomes in patients undergoing endovascular coiling treatment, possibly due to its adverse effects on resuscitation and potential myocardial damage (31). For the first time, we have identified that D-dimer levels significantly influence early functional outcomes in patients treated with either endovascular coiling or surgical clipping. This finding place D-dimer levels second only to Hunt–Hess grading and the

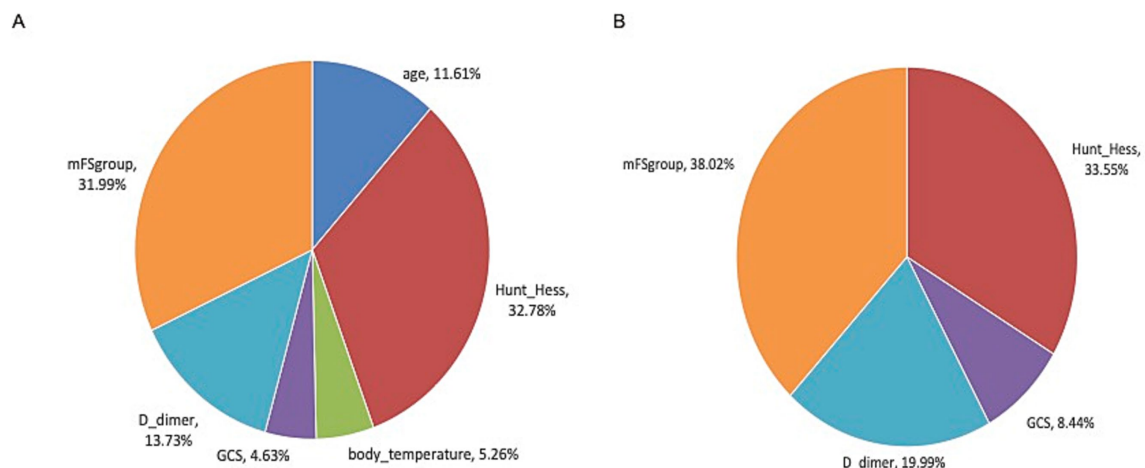


FIGURE 4
The relative weights of variables influencing early functional outcomes in the endovascular coiling (A) and surgical clipping groups (B).

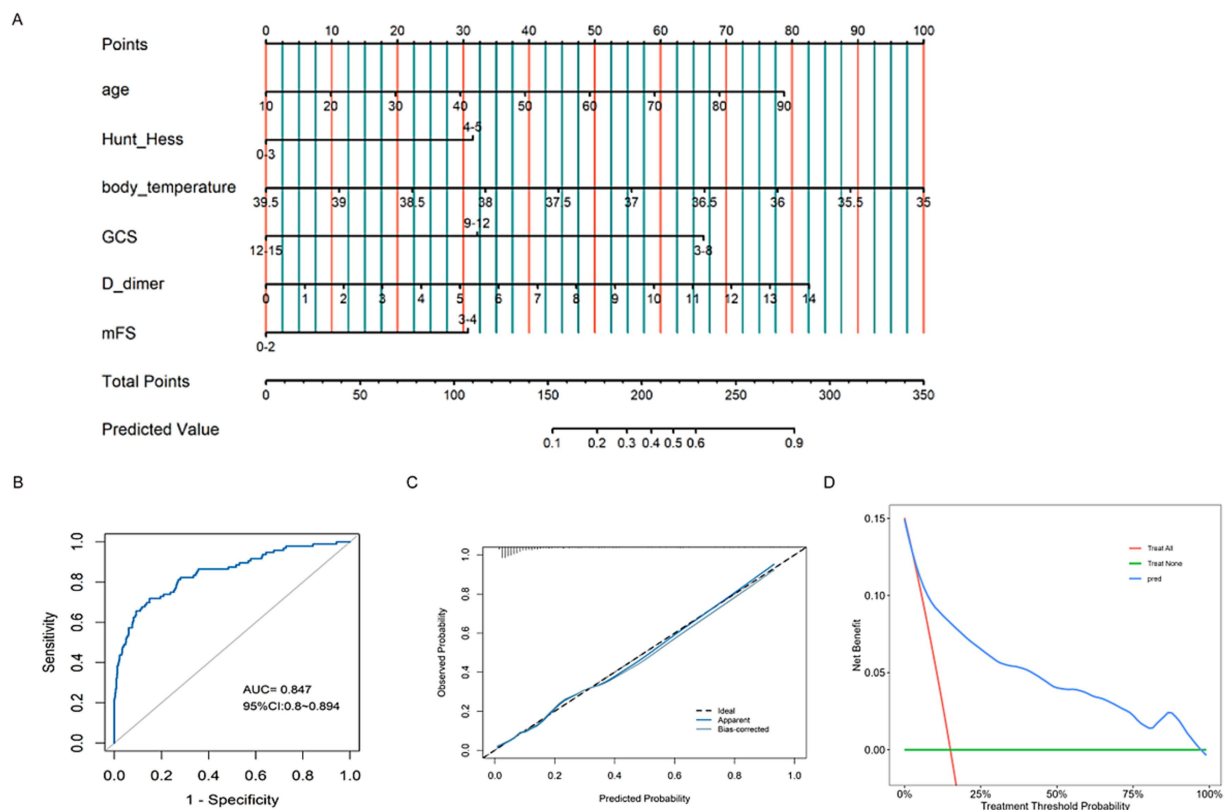


FIGURE 5
Constructing a nomogram (A) to forecast functional outcomes in patients undergoing endovascular coiling, and validating it through ROC curves (B), calibration plots (C), and DCA curves (D).

mFS scoring system, surpassing GCS scores in importance. Moreover, the inclusion of D-dimer challenges traditional reliance on clinical grading scales alone. Implementing these models could improve resource allocation by identifying patients who may derive greater benefit from intensive care or targeted interventions.

The study has some limitations. Firstly, being a retrospective study, there may be confounding factors affecting the stability of the results. Secondly, the assessment of early functional outcomes was conducted only one-month post-surgery, requiring further long-term follow-up to evaluate more comprehensive outcomes. Thirdly, we did not include emerging biomarkers or advanced imaging features,

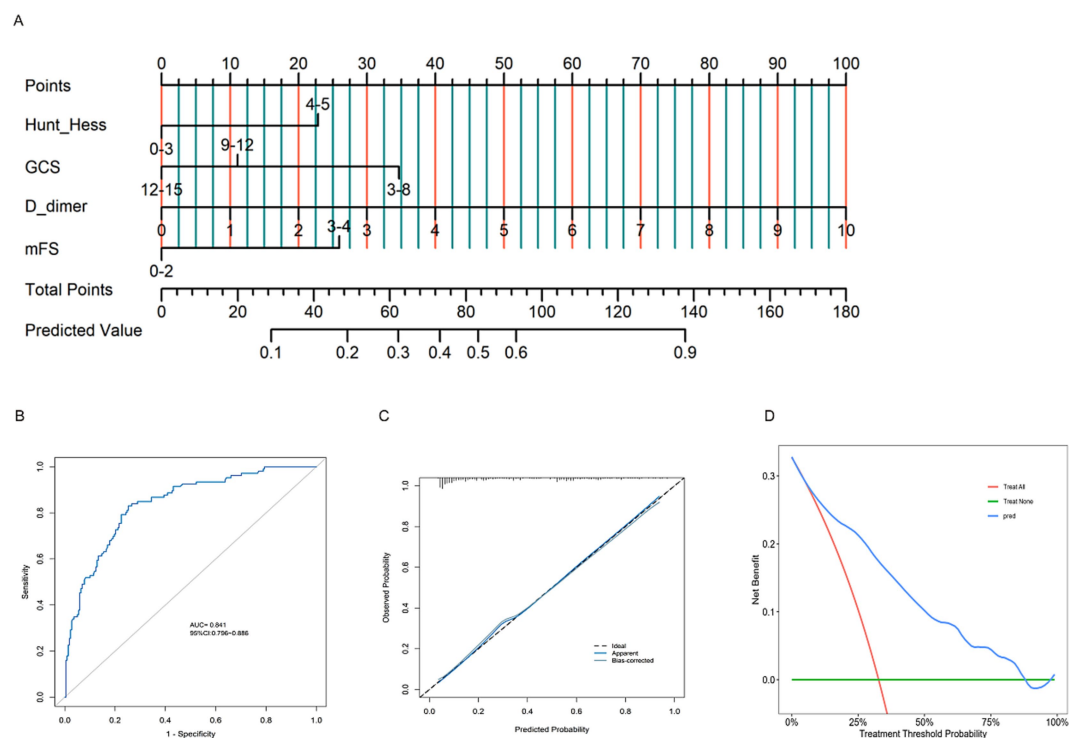


FIGURE 6 Constructing a nomogram (A) to forecast functional outcomes in patients undergoing surgical clipping, and validating it through ROC curves (B), calibration plots (C), and DCA curves (D).

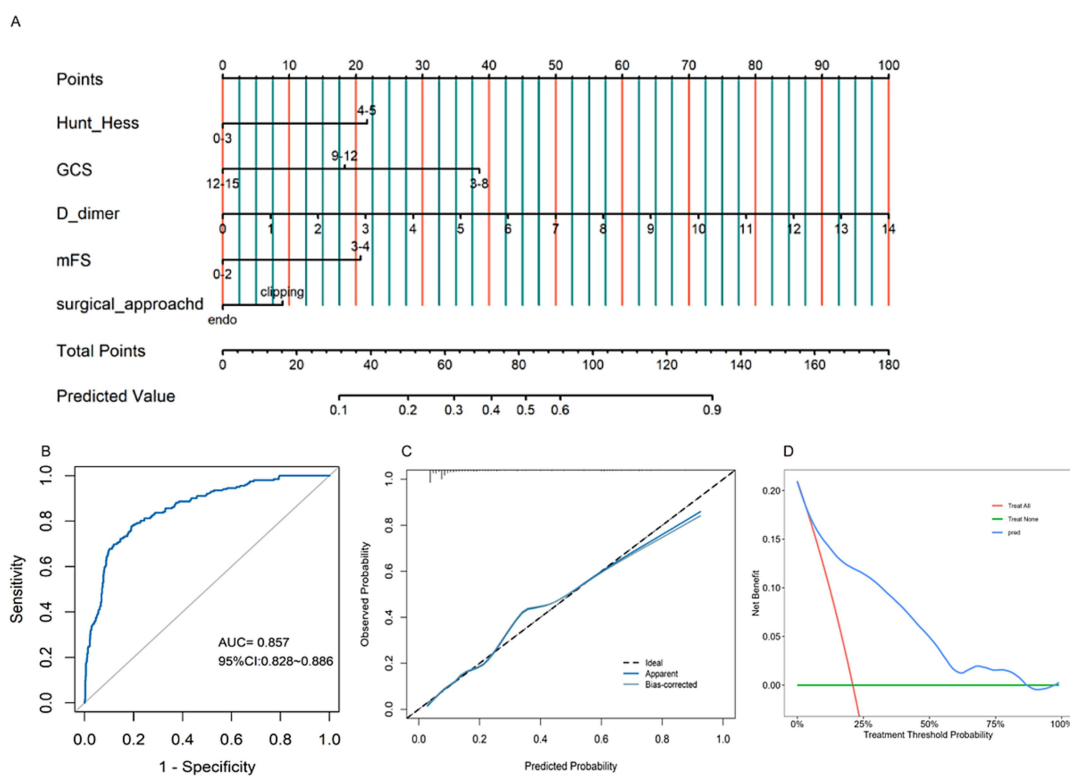


FIGURE 7 Constructing an integrated nomogram (A) to forecast functional outcomes of aSAH patients after surgery, and validating it through ROC curves (B), calibration plots (C), and DCA curves (D).

TABLE 5 Nomogram risk stratification.

Variables	Endovascular coiling		Surgical clipping	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Low-risk group				
Medium-risk group	2.791 (1.134, 7.868)	0.034	5.291 (2.326, 13.671)	<0.001
High-risk group	17.506 (8.014, 46.109)	<0.001	26.641 (11.913, 68.537)	<0.001

which could potentially enhance predictive accuracy. Therefore, prospective studies with longer follow-up periods are needed to validate these findings and explore intervention strategies based on these risk profiles.

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 humans were approved by the Affiliated Yixing Hospital of Jiangsu University (2023043) and the Affiliated Zhenjiang First Hospital of Jiangsu University (K-20230086-w). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because informed consent was waived by both committees due to the retrospective nature of the 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

LC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. KC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft. KJ: Conceptualization, Formal analysis, Investigation,

Project administration, Resources, Validation, Writing – original draft. YL: Data curation, Investigation, Methodology, Resources, Software, Writing – review & editing. MQ: Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Writing – original draft. DW: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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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