THE CLINICAL MANAGEMENT OF CEREBROVASCULAR DISEASE IN PRECISION MEDICINE ERA

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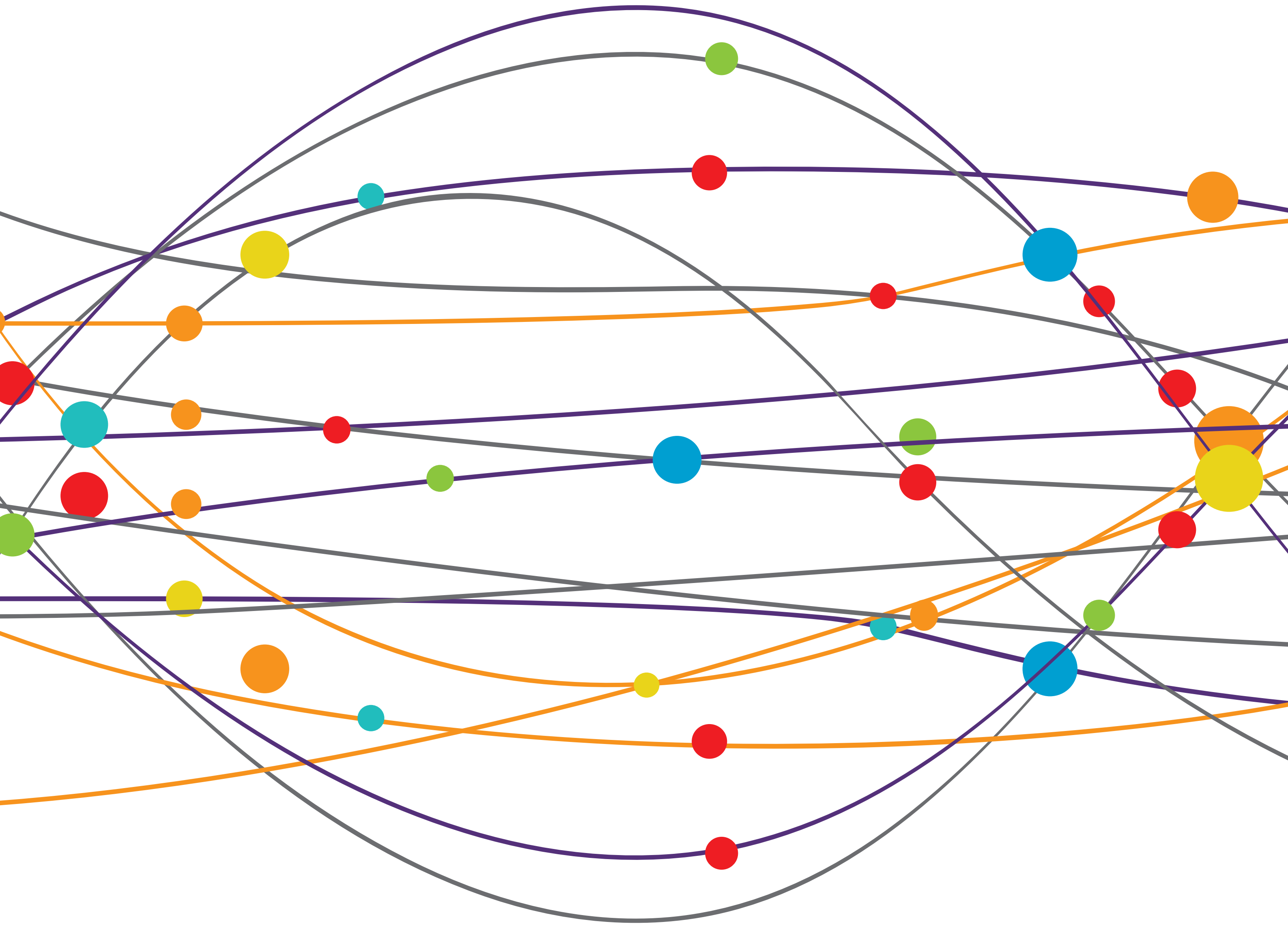

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THE CLINICAL MANAGEMENT OF CEREBROVASCULAR DISEASE IN PRECISION MEDICINE ERA

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Influence of Early Enteral Nutrition on Clinical Outcomes in Neurocritical Care Patients With Intracerebral Hemorrhage

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Objective: Early enteral nutrition (EEN) represents the current standard of care for patients treated in general intensive care units (ICU). Specific nutritional recommendations for patients receiving dedicated neurocritical care are not established. This study investigated associations of EEN with clinical outcomes for patients suffering from intracerebral hemorrhage treated at a neurological ICU (NICU).

Methods: This retrospective cohort study included patients admitted to the NICU with atraumatic ICH over a 4-year period. Nutritional data, demographic, clinical, radiological, and laboratory characteristics were assessed. EEN was defined as any enteral nutrition within 48 hours after admission. Comparisons were undertaken for patients with EEN vs. those without, further propensity score (PS) matching (caliper 0.2; one: many) was used to account for baseline imbalances. Primary outcome was the modified Rankin Scale (0–3 = favorable, 4–6 = unfavorable) at 12 months, secondary outcomes comprised perihemorrhagic edema (PHE) volume, infectious complications during the hospital stay, and mRS at 3 months, as well as mortality rates at 3 and 12 months.

Results: Of 166 ICH-patients treated at the NICU, 51 (30.7%) patients received EEN, and 115 (69.3%) patients received no EEN (nEEN). After propensity score matching, calories delivered from enteral nutrition (EEN 161.4 [106.4–192.3] kcal/day vs. nEEN 0.0 [0.0–0.0], $P<0.001$) and the total calories (EEN 190.0 [126.0–357.0] kcal/day vs. nEEN 33.6 [0.0–190.0] kcal/day, $P < 0.001$) were significantly different during the first 48 h admitted in NICU. Functional outcome at 12 months (mRS 4–6, EEN 33/43 [76.7%] vs. nEEN, 49/64 [76. 6%]; $P = 1.00$) was similar in the two groups. There were neither differences in mRS at 3 months, nor in mortality rates at 3 and 12 months between the two groups. EEN did not affect incidence of infective complications or gastrointestinal adverse events during the hospital stay; however, EEN was associated with significantly less extent of PHE evolution [maximum absolute PHE (OR 0.822, 95% CI 0.706–0.957, $P = 0.012$); maximum relative PHE (OR 0.784, 95% CI 0.646–0.952, $P = 0.014$)].

Conclusion: In our study, EEN was associated with reduced PHE in ICH-patients treated at a NICU. However, this observation did not translate into improved survival or functional outcome at 3 and 12 months.

Keywords: intracerebral hemorrhage, nutrition, perihemorrhagic edema, prognosis, neurological intensive care

INTRODUCTION

Intracerebral hemorrhage (ICH) accounts for up to 10–15% of all stroke cases with mortality rates up to 61% at 1 month (1, 2). Given severe neurological impairments and impaired consciousness, ICH survivors often require admission to the intensive care unit (ICU) or neurological ICU (NICU) (3). Current guidelines for critical patients recommend that practitioners consider initiating enteral feeding after admission to the ICU (within 48 h) (4). However, detailed management or any associated effects of nutritional support for stroke patients in the NICU have not been established yet.

Sufficient and early intake of energy by enteral feeding is thought to help attenuate the metabolic response to stress, favorably modulate immune responses, and diminish complications (5). So far, the effects of enteral nutrition on perihemorrhagic edema (PHE) dynamics, mortality, and functional outcome in neurocritical care patients with ICH have not been established. The present study investigated the association of early enteral nutrition (EEN) with (1) functional outcomes and (2) mortality at 12 months, (3) PHE evolution, as well as (4) infectious complications and gastrointestinal adverse events during the hospital stay in ICH patients admitted to NICU.

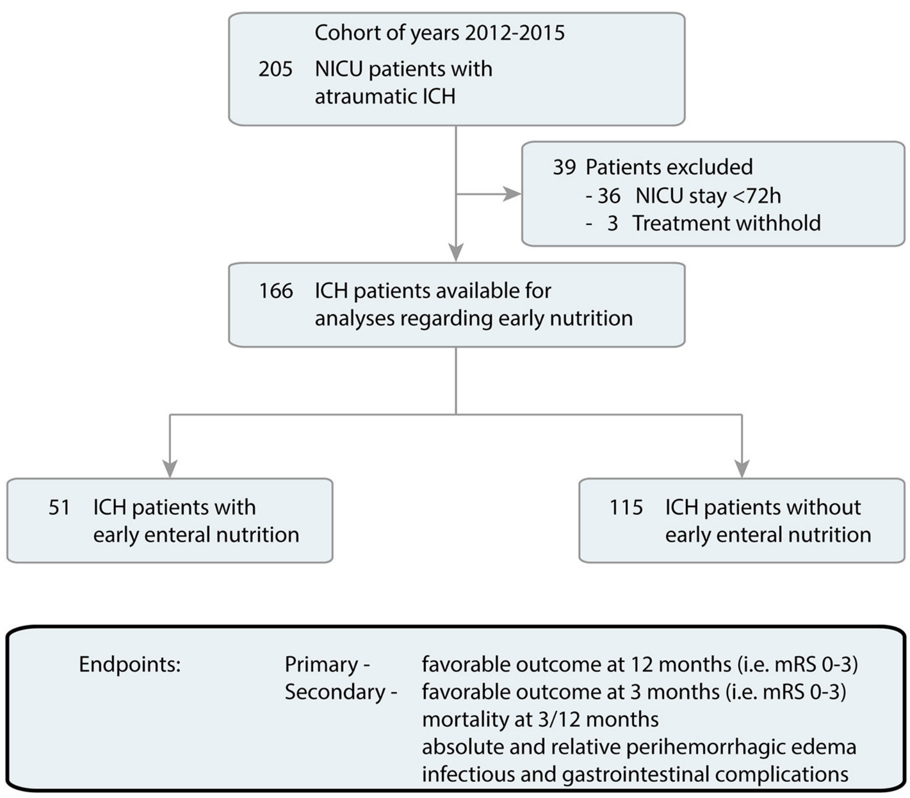

FIGURE 1 | Flow chart of included patients. Overall, The UKER-ICH provided data of 205 patients with ICH admitted in NICU (years 2012–2015). After exclusion of 39 patients because of NICU stay <72 h or/and treatment withhold, 51 patients with EEN and 115 patients with nEEN remained for further data analyses. EEN, early enteral nutrition; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; nEEN, no early enteral nutrition; NICU, neuro-intensive care unit.

MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective cohort study included patients with spontaneous ICH who were admitted to the NICU between January 2012 and December 2015 from our prospective single-center UKER-ICH registry (Universitaetsklinikum Erlangen Cohort of Patients with Spontaneous Intracerebral Hemorrhage; clinical-trials.gov NCT03183167). Detailed information and methods of UKER-ICH have been published previously (6). The collection of data for the UKER-ICH registry was approved by the ethics committee of the local university (IRB No. 115_17B). Consent for follow-up assessment was obtained by either the patient, his/her legal representative or the closest relative.

We excluded patients with secondary causes of ICH, such as tumor, trauma, arteriovenous malformation, aneurysm, or acute thrombolysis (6). Furthermore, patients staying NICU <72 h, as well as patients receiving early care limitations, were excluded from the final analysis.

Assessment of Clinical and Imaging Parameters

As described previously, we assessed demographic data, medical history, laboratory data, infectious complications, and clinical parameters through review of institutional databases and patient's medical charts (6). Imaging parameters were assessed by evaluating all available imaging scans during the hospital stay as described previously (6). To account for various time points of control CTs, we categorized follow-up imaging according to time frames (days 1, 2–3, 4–6, 7–9, 10–12 and 13–15) with day 1 defined as the day of admission. PHE was assessed using an established and validated semi-automatic threshold-based algorithm by calculation of the maximum absolute PHE, which was defined as peak PHE volume during hospital stay, and the maximum relative PHE (rPHE) defined as the ratio of peak PHE volume divided by the final ICH volume (7, 8).

Nutrition Data Assessment

We assessed the nutrition data from the integrated care manager system (ICM; Drägerwerk AG Co. KGaA, Lübeck). The nutrition data were assessed for up to 20 days or until the patient discontinued enteral nutrition, died, or was discharged from the NICU, whichever occurred first. We defined EEN as any enteral tube feeding within 48 h after admission to our NICU. Otherwise, patients were classified into the no early enteral nutrition (nEEN)-group if no enteral feeding was performed within the first 48 h. Target calorie goals were determined by indirect calorimetry or weight-based predictive equation (age < 30 years: 25 kcal/kg ideal bodyweight; age from 30–70 years: 22.5 kcal/kg ideal bodyweight; age>70 years: 20 kcal/kg ideal bodyweight; each of that multiplied with a factor of 1.2 for NICU-patients). During the NICU-stay, daily records were assessed regarding all procedures of enteral nutrition, parenteral nutrition, fluid balance, vomiting, and defecation. In addition to the calories from enteral nutrition or parenteral nutrition, other energy sources such as oral intake were evaluated by nursing records. Constipation was defined as failure to pass stool within 72 h of admission to the NICU or failure to pass stool for three consecutive days during the NICU stay (9). Diarrhea was defined as three or more loose, or liquid stools per day for two consecutive days (10).

TABLE 1 | Characteristics of ICH patients with EEN vs. nEEN.

Patients with ICH (*n* = 166)	EEN (*n* = 51)	nEEN (*n* = 115)	*P*-value
Age, median (IQR), y	72 (61–77)	73 (59–80)	0.494
Female sex, No. (%)	22 (43.1%)	45 (39.1%)	0.732
Prior comorbidities, No. (%)			
Premorbid mRS, median (IQR)	1 (0–3)	0 (0–1)	0.191
Hepatic dysfunction	3 (5.9%)	12 (10.4%)	0.558
Renal failure	11 (21.6%)	22 (19.1%)	0.833
Arterial hypertension	47 (92.2%)	108 (93.9%)	0.738
Diabetes mellitus†	23 (45.1%)	29 (25.2%)	**0.018**
Prior ischemic stroke	11 (21.6%)	18 (15.7%)	0.380
Prior hemorrhagic stroke	7 (13.7%)	13 (11.3%)	0.796
Antiplatelet medication	14 (27.5%)	34 (29.6%)	0.854
Oral anticoagulation	12 (23.5%)	25 (21.7%)	0.841
Admission status, median (IQR)			
Glasgow coma scale†	7 (3–12)	12 (6–14)	**<0.001**
NIHSS†	22 (13–38)	14 (7–29)	**0.002**
ICH Score†	2 (2–3)	2 (1–2)	**0.005**
CHADS VASc score	3 (2–5)	3 (2–5)	0.532
HAS bled score	2 (2–4)	2 (2–4)	0.986
Imaging, median (IQR)			
Initial ICH volume, ml	18.3 (6.9–37.3)	12.9 (3.93–29.6)	0.110
ICH location, No. (%)			
Deep	31 (60.8%)	61 (53%)	0.400
Lobar	11 (21.6%)	36 (31.3%)	0.263
Cerebellar	7 (13.7%)	13 (11.3%)	0.796
Brainstem	2 (3.9%)	5 (4.3%)	0.632
Intraventricular hemorrhage, No. (%)†	39 (76.5%)	61 (53%)	**0.006**
Graeb Score†	4 (1–8)	1 (0–5)	**0.002**
Clinical parameter			
Mechanical ventilation, No. (%)†	47 (92.2%)	71 (63.4%)	**<0.001**
EVD, No. (%)†	39 (76.5%)	50 (43.5%)	**<0.001**

EEN, early enteral nutrition; EVD, external ventricular drain; HAS-BLED, Hypertension, Abnormal Renal and Liver Function, Stroke, Bleeding, Labile INR-Measures, Elderly (age >65 y) and Drugs or Alcohol; ICH, intracerebral hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; nEEN, no early enteral nutrition; NIHSS, National Institutes of Health Stroke Scale.

†*Significant differences are highlighted in bold.*

Primary and Secondary Outcomes

Primary outcome was defined as the proportion of patients with unfavorable outcome at 12 months [modified Rankin Scale (mRS) score = 4–6 (11)] comparing EEN and nEEN-patients. Follow-up data were evaluated 12 months after onset of ICH by mailed questionnaires, telephone interviews, or chart review using the mRS score (performed by trained and certified physicians; scores 0–6, higher scores indicating worse outcome and 6 indicating death). Secondary outcomes consisted of (1) mRS at 3 months, (2) mortality rates at 3 and 12 months, as well as

TABLE 2 | Nutrition characteristics of PS-matched patients.

PS-matched patients with ICH ($n = 114$)	EEN ($n = 47$)	nEEN ($n = 67$)	*P*-value
Start of nutrition, day since admission, median (IQR)			
Enteral nutrition†	2 (2–2)	3 (3–4)	**<0.001**
Parenteral nutrition†	4 (3–7)	3 (2–4)	**0.033**
Length of nutrition, days, median (IQR)			
Enteral nutrition†	12 (4–15)	9 (2–13)	**0.033**
Parenteral nutrition†	0 (0–3)	3 (0–8)	**0.005**
Calorie target, kcal/day median (IQR)	1854.0 (1800.0–1854.0)	1854.0 (1854.0–1854.0)	0.757
Nutrition within 1st 48h (IQR), kcal/day			
Enteral calories†	161.4 (106.4–192.3)	0.0 (0.0–0.0)	**<0.001**
Parenteral calories†	0.0 (0.0–0.0)	33.6 (0.0–190.0)	**0.014**
Total calories†	190.0 (126.0–357.0)	33.6 (0.0–190.0)	**<0.001**
Total Nutrition (IQR), kcal/day			
Enteral calories	1102.0 (611.2–1463.7)	980.2 (598.0–1239.8)	0.071
Parenteral calories	0.0 (0.0–682.3)	447.3 (0.0–764.0)	0.172
Total calories	1316.4 (872.9–1550.6)	1386.7 (898.6–1539.3)	0.879
Laboratory values at 48 h (Mean ± SD)			
Chloride, mmol/L	107.4 ± 5.2	106.7 ± 4.2	0.450
Potassium, mmol/L	4.2 ± 0.3	4.1 ± 0.4	0.109
Sodium, mmol/L	140.9 ± 4.6	139.7 ± 3.7	0.129
Urea nitrogen, mg/dl	37.0 ± 16.4	36.6 ± 16.4	0.896
Total protein, g/L	53.4 ± 5.5	55.2 ± 6.2	0.167
Osmolar, mOsmol/kg	300.3 ± 12.9	297.1 ± 11.1	0.200
Laboratory values during NICU stay (Mean ± SD)			
Chloride, mmol/L	108.8 ± 5.2	107.9 ± 4.8	0.325
Potassium, mmol/L	4.3 ± 0.3	4.2 ± 0.2	0.388
Sodium, mmol/L	143.0 ± 4.3	141.9 ± 4.5	0.204
Urea nitrogen, mg/dl	52.4 ± 26.2	46.2 ± 20.3	0.162
Hemoglobin, g/dl	13.5 ± 1.9	13.4 ± 2.5	0.772
Total protein, g/L	52.7 ± 5.7	53.4 ± 5.0	0.460
Osmolar, mOsmol/kg	306.6 ± 13.3	303.7 ± 13.2	0.260
Fluid balance (IQR), ml/day	+340.2 (214.3–732.6)	+526.7 (174.5–769.1)	0.502
Median highest daily blood glucose concentration (IQR), mg/dl	180.1 (157.1–216.6)	176.3 (144.8–197.2)	0.140

EEN, early enteral nutrition; ICH, intracerebral hemorrhage; IQR, interquartile range; nEEN, no early enteral nutrition; PS, propensity score.
†*Significant differences are highlighted in bold.*

(3) PHE volume evolution, and (4) infectious complications and gastrointestinal complications (constipation or diarrhea) during hospital stay.

Statistical Analyses

Statistical analyses were performed by SPSS version 21.0 (IBM; ibm.com/analytics) and R 3.3.1 (r-project.org) as described previously (12). According to data-distribution assessed using the Kolmogorov-Smirnov test, we compared normally distributed data (expressed as mean ± SD) using the Student t test; otherwise, we used the Mann Whitney U test presented as median (interquartile range) for non-normally distributed data. Frequency distributions of categorical variables [presented as counts (percentage)] were compared by Pearson χ^2 and Fisher exact tests. Statistical significance was set at $\alpha = 0.05$ both sided.

To account for baseline imbalances in relevant clinical parameters showing a statistical trend ($P < 0.1$) in prior univariate analysis between EEN and nEEN cohorts, we performed a propensity score (PS) matching (balanced, parallel nearest-neighbor approach, ratio 1:many, caliper 0.2) (11). The following variables were selected to generate the propensity score: Diabetes mellitus, Graeb score, mechanical ventilation, and the Glasgow Coma Scale (GCS) score on admission.

To determine associations between EEN and maximum absolute and relative PHE (both median-split) binary regression analyses (log-nominal with link-identity) were calculated. Associations were expressed as odds ratios (ORs) with the corresponding 95% confidence interval. Adjustment for ICH-volume was undertaken for absolute PHE considering the reported impact of ICH-surface on absolute PHE development (6).

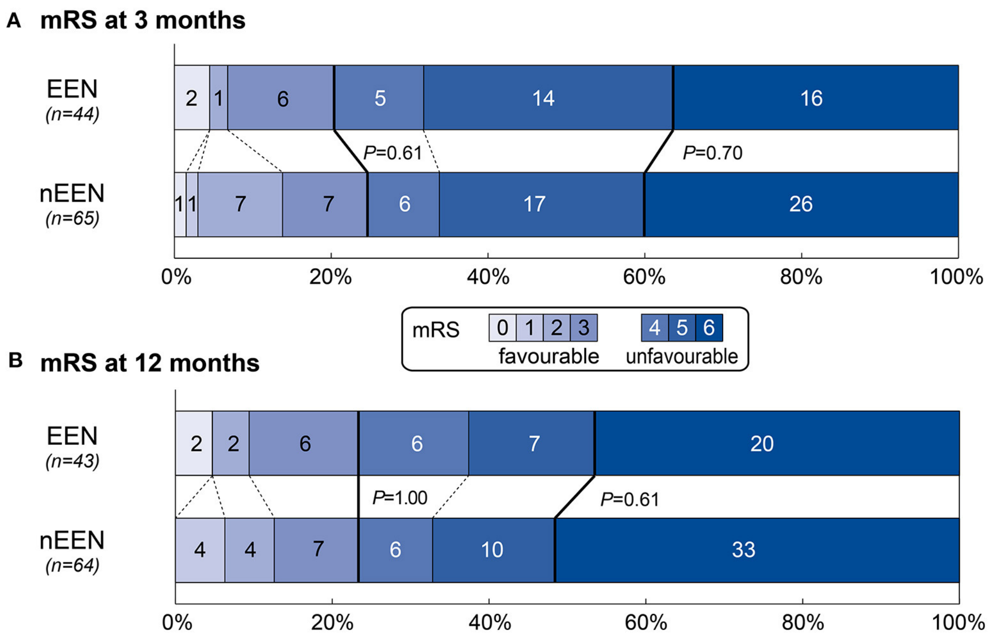

FIGURE 2 | Distribution of mRS at 3 and 12 months comparing patients with EEN and nEEN. Presented are mRS-scores after 3 **(A)** and 12 **(B)** months comparing patients with EEN and nEEN after PS matching (matching parameter: diabetes mellitus, GRAEB score, mechanical ventilation and the initial Glasgow Coma Scale). The bold line separates favorable (mRS, 0–3) and unfavorable outcome (mRS, 4–6). *P*-values are provided for the proportion of patients with favorable outcome and in hospital death. EEN, early enteral nutrition; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; nEEN, no early enteral nutrition.

RESULTS

Over a 4-year period, 205 NICU patients with primary ICH were treated at our NICU and screened for eligibility. After exclusion of 39 patients because of NICU stay <72 h or/and treatment withhold, 51/166 (30.7%) EEN, and 115/166 (69.3%) nEEN treated ICH patients remained for final analyses (**Figure 1**).

Clinical and Radiologic Characteristics

Baseline, hematoma, and treatment characteristics are provided in **Table 1** comparing EEN vs. nEEN-patients. Compared to nEEN, patients with EEN had more frequently history of diabetes mellitus [EEN 23/51 (45.1%) vs. nEEN 29/115 (25.2%), $P = 0.018$] and a worse clinical status on admission [GCS, median (IQR): EEN 7 (3–12) vs. nEEN 12 (6–14), $P<0.001$; National Institute of Health Stroke Scale (NIHSS), EEN 22 (13–38) vs. nEEN 14 (7–29), $P=0.002$; ICH Score, EEN 2 (2–3) vs. nEEN 2 (1, 2), $P = 0.005$]. There was no significant difference regarding ICH-volume and location among both groups. EEN-patients had intraventricular hemorrhage (IVH) at a higher rate and extent compared to patients without EEN [IVH, No. (%): EEN 39/51 (76.5%) vs. nEEN 61/115 (53%), $P = 0.006$; Graeb Score, median (IQR): EEN 4 (1–8) vs. nEEN 1 (0–5), $P=0.002$]. EEN patients required more often mechanical ventilation [EEN 47/51 (92.2%) vs. nEEN 71/115 (63.4%), $P < 0.001$] and placement of external ventricular drain [EEN 39/51 (76.5%) vs. nEEN 50/115 (43.5%), $P < 0.001$; **Table 1**].

Nutritional Characteristics

To specifically compare outcome among ICH patients with EEN vs. nEEN, we adjusted for the previously mentioned baseline confounders using a PS matching. After PS matching (**Supplementary Table 1**), 47 ICH patients with EEN and 67 ICH patients with nEEN were available for further analyses without significant differences in relevant parameters.

Nutritional characteristics of EEN- and nEEN-patients are provided in **Table 2**. Patients received the enteral nutrition for a median of 12 days (4–15) in the EEN group and 9 days (2–13) in the nEEN group, respectively ($P = 0.033$). Supplementary parenteral nutrition was initiated earlier [nEEN (3(2–4) vs. EEN 4(3–7), $P = 0.033$] and lasted longer [nEEN (3(0–8) vs. EEN 0(0–3), $P = 0.005$] in the nEEN group compared with the EEN group. During the first 48 h at NICU, calories delivered from enteral nutrition [EEN 161.4 (106.4–192.3) kcal/day vs. nEEN 0.0 (0.0–0.0), $P < 0.001$] and calories delivered from enteral nutrition plus other sources [EEN 190.0 (126.0–357.0) kcal/day vs. nEEN 33.6 (0.0–190.0) kcal/day, $P < 0.001$] were significantly different between both groups in favor of EEN (**Table 2**). During hospital course, there was no significant difference in nutrition-related laboratory parameters among both groups.

Primary Outcome

The distribution of mRS at 12 months is illustrated in **Figure 2B**. There was no difference regarding the proportion of patients achieving favorable outcome at 12 months [mRS, 0–3: EEN, 10/43 (23.3%) vs. nEEN, 15/64 (23.4%); $P = 1.00$; **Table 3**] between patients with EEN and nEEN.

TABLE 3 | Outcomes and complications of PS-matched patients comparing EEN vs. nEEN.

PS-matched patients (n=114)	EEN (n = 47)	nEEN (n = 67)	*P*-value
Length of hospital stay (IQR)	17 (10–22)	16 (12–25)	0.498
Length of NICU stay (IQR)	15 (8–20)	14 (8–22)	0.762
Functional outcomes, No. (%)			
mRS 0–3 at 3 months	9 (20.5%)	16 (23.4%)	0.610
Mortality at 3 months	16 (36.4%)	26 (40.0%)	0.699
mRS 0–3 at 12 months	10 (23.3%)	15 (23.4%)	1.000
Mortality at 12 months	20 (46.5%)	33 (51.6%)	0.610
Perihemorrhagic edema, median (IQR)			
Maximum absolute PHE during hospital stay, ml†	26.7 (6.5–39.5)	34.8 (8.5–58.4)	**0.021**
Gastrointestinal outcomes			
Regurgitation or vomiting, No. (%)	30 (63.8%)	39 (58.2%)	0.566
Median bowel movements per day (IQR)	0.9 (0.5–1.4)	0.9 (0.5–1.3)	0.895
Constipation, No. (%)	25 (53.2%)	29 (43.3%)	0.343
Diarrhea, No. (%)	28 (59.6%)	36 (53.7%)	0.570
Infectious complications, No. (%)	37 (78.7%)	52 (77.6%)	1.000
Pneumonia	23 (48.9%)	41 (61.2%)	0.250
Ventriculitis	4 (8.5%)	8 (11.9%)	0.758
Sepsis	14 (29.8%)	20 (29.9%)	1.000
Urinary tract infection	6 (12.8%)	7 (10.4%)	0.769
In-hospital mortality, No. (%)	12 (25.5%)	18 (26.9%)	1.000

EEN, early enteral nutrition; EVD, external ventricular drainage; IQR, interquartile range; nEEN, no early enteral nutrition; NICU, neurological intensive care unit. †Significant differences are highlighted in bold.

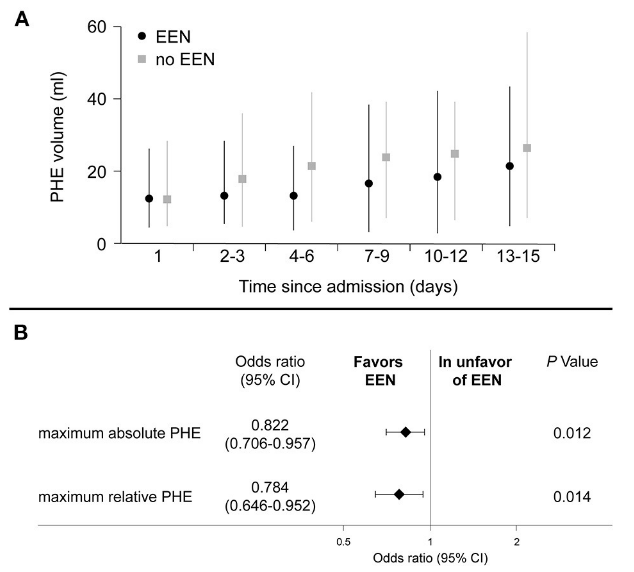

FIGURE 3 | (A) Time course of perihemorrhagic edema and **(B)** associations with EEN. **(A)** Illustrated are the PHE volumes for each time-interval for ICH-patients with and without EEN for the PS-matched cohort. **(B)** Associations between EEN and maximum absolute and relative perihemorrhagic edema are provided. Binary logistic regression analysis (nominal with link-identity) was used. Associations are expressed as odds ratios and corresponding 95% confidence interval. Adjustment for ICH-volume was undertaken for absolute PHE considering the reported impact of ICH-surface on absolute PHE development. CI, confidence interval; EEN, early enteral nutrition; ICH, intracerebral hemorrhage; nEEN, no early enteral nutrition; PHE, perihemorrhagic edema.

Secondary Outcomes

There was no significant difference regarding functional outcomes at 3 months [mRS, 0–3: EEN, 9/44 (20.5%) vs. nEEN, 16/65 (23.4%), $P = 0.61$; **Table 3** and **Figure 2A**], and no significant differences in rates of mortality at 3 and 12 months [mortality at 3 months: EEN 16/44 (36.4%) vs. nEEN 26/65(40%), $P = 0.70$; mortality at 12 months: EEN 20/43 (46.5%) vs. nEEN 33/64(51.6%), $P = 0.61$; **Table 3** and **Figures 2A,B**].

The time course of absolute PHE is illustrated in **Figure 3A.** Highest median absolute PHE was observed between day 13 and 15 after admission in both groups. There were no significant differences regarding absolute PHE among EEN and nEEN patients at each time-point of imaging. However, maximum absolute PHE during hospital stay was significantly less in EEN- compared to nEEN-patients [median absolute PHE (IQR): EEN 26.7 (6.5–39.5) ml vs. nEEN 34.8 (8.5–58.4)ml; $P = 0.021$; **Table 3**]. In addition, regression analyses revealed significant associations between EEN and maximum absolute as well as relative PHE. In essence, EEN was associated with attenuated maximum absolute PHE (OR 0.822, 95% CI 0.706–0.957, $P = 0.012$) and maximum relative PHE (OR 0.784, 95% CI 0.646–0.952, $P = 0.014$) as shown in **Figure 3B**.

Regarding the safety outcomes, there were no differences in rates of constipation [EEN 25/47 (53.2%) vs. nEEN 29/67 (43.3%), $P = 0.343$] and diarrhea [EEN 28/47 (59.6%) vs. nEEN 36/67 (53.7%), $P = 0.570$] between both groups (**Table 3**). Further, we observed similar rates of infectious complications during the hospital stay among patients with and without EEN [EEN: 37/47 (78.7%) vs. nEEN 52/67 (77.6%); $P = 1.000$; **Table 3**].

DISCUSSION

The present study evaluated the associations of EEN with functional outcome, mortality, PHE evolution, as well as infectious complications in ICH patients treated at NICU. As key findings, we demonstrated that EEN was not associated with functional outcome or mortality at 3 or 12 months, and there were no differences regarding infectious or gastrointestinal complications during hospital stay. Yet, EEN was associated with a lower extent of PHE evolution during hospital stay in ICH-patients. Some aspects deserve attention.

Nutritional supplementation represents one of the cornerstones of supportive care in NICU. Enteral feeding is recommended to be started within 48 h for surgical and medical critical care patients (4) and is recommended for critically ill ICH patients (13). However, these recommendations have not been supported by studies specifically analyzing neurocritical care stroke patients, and were rather based on pathophysiological considerations extrapolated from general ICU patients. Our study now adds on to this discussion, as we systematically analyzed nutrition regimens specifically for neurocritical care ICH patients. Although our study was not powered to detect differences, we here did not find EEN, compared to no EEN, to significantly alter clinical outcomes, notably the rate of mortality or the proportion of patients with good functional outcome at follow-up.

However, our study did reveal reduced PHE evolution in patients who received EEN. There are several potential causal mechanisms underlying our findings. As reported elsewhere, secondary injury cascades and detrimental processes, including degradation of heme-products and neuro-inflammation post-ICH, are considered to contribute to PHE formation (8). Route and amount of nutrition is thought to help attenuate the metabolic response to stress and favorably modulate immune responses (4, 14). First, in our cohort, relative PHE in patients with EEN was lower than in patients without EEN, which may be partly explained by the reported anti-inflammatory mechanism of early enteral feeding. Second, malnutrition may lead to altered Na^{+}-K^{+} ATPase activity, ATP depletion, and a rise in intracellular osmotic pressure, which result in blood–brain barrier (BBB) disruption and angioedema (15). Thus, at the acute phase of ICH-treatment, sufficient provision of energy seems essential to potentially attenuate BBB disruption and angioedema by maintaining mitochondrial metabolism.

However, despite its beneficial association with reduced PHE, EEN did not translate into improved clinical outcomes. This finding is in line with previous studies in which several treatment approaches targeting PHE-development failed to influence outcome reflecting the complex pathophysiology of PHE in patients with ICH (16–20). Further studies including extensive assessments of nutrition status are warranted to determine the detailed mechanisms of early enteral feeding on cerebral edema.

In line with available guidelines, we did not detect any safety issues of EEN in neurocritical care ICH patients. In our cohort, EEN did not increase the rates of infectious complications or gastrointestinal complications during the hospital stay. Instead, undernutrition may be associated with prolonged length of stay and mechanical ventilation, infection, and mortality (21). However, we could not find decreased rates of pneumonia or any other infections in patients treated with EEN, which might occur due to the small number of patients, and the unreached calorie targets in some patients. It is important to note that that caution should be taken to avoid early overfeeding and the resultant increase in risk of complications (22, 23). The optimal energy and protein target in the early phase of acute critical illness is currently unknown. In this retrospective cohort, we did not find a favorable effect of EEN on long-term functional outcomes of patients with ICH. But, due to its safety profile, potential protective effects on edema evolution and positive signals from trials investigating general ICU-patients the use of EEN seems reasonable in ICH patients. Further prospective and randomized studies are required to fully understand the effects of EEN especially in ICH patients requiring NICU-treatment.

Our study has several limitations mainly given its retrospective analysis and monocentric design. As a consequence, there was no *a-priori* defined assessments of nutrition status, complications, and follow-up brain imaging at certain time-points leaving some room for bias of our results. Despite the sophisticated statistical efforts to account for imbalances, generalizability of our findings may be limited due to selection bias. Further, the small sample size did not allow further subgroup-analyses or adjustments, for example, to adjust for treatment strategies to target PHE, such as the use of therapeutic hypotherma or osmotic agents. Due to its retrospective design, calories from other sources, i.a. medications, could not be completely counted.

CONCLUSIONS

In our study, EEN was associated with reduced PHE in ICH-patients treated at a NICU. However, this observation did not translate into improved survival or functional outcome at 3 and 12 months.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The collection of data for the UKER-ICH registry was approved by the ethics committee of the local university (IRB No. 115_17B). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SG, JP, BV, and JK contributed to data analysis. SG, JP, BV, MS, JK, PH, TE, and AD contributed to data collection. SG, JP, MS, HH, AD, and SS contributed to study design. SG, JP, BV, and HH contributed to drafting initial manuscript. All authors contributed to manuscript revision.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.665791/full#supplementary-material

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Improvement in Midline Shift Is a Positive Prognostic Predictor for Malignant Middle Cerebral Artery Infarction Patients Undergoing Decompressive Craniectomy

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Objective: The aim of this retrospective study is to evaluate the risk factors of malignant middle cerebral artery infarction (MMCAI) patients and explore an applicable prognostic predictor for MMCAI patients undergoing decompressive craniectomy (DC).

Methods: Clinical data from the period 2012–2017 were retrospectively evaluated. Forty-three consecutive MMCAI patients undergoing DC were enrolled in this study. The 30-day mortality was assessed, and age, location, hypertension, pupil dilation, onset to operation duration, midline shift, and Glasgow Coma Scale (GCS) score were identified by univariate analysis and binary logistic regression.

Results: In this retrospective study for DC patients, the 30-day mortality was 44.2%. In the univariate analysis, advanced age (≥60 years), right hemispheric location, hypertension, pupil dilation, shorter onset to operation duration (<48 h), improved midline shift ($t = 4.214$, $p < 0.01$), and lower pre-operation GCS score were significant predictors of death within 30 days. In binary logistic regression analysis, age [odds ratio (OR) = 1.141, 95% CI 1.011–1.287], the improvement of the midline shift (OR = 0.764, 95% CI 0.59–0.988), and pupillary dilation (OR = 15.10, 95% CI 1.374–165.954) were independent influencing factors. For the receiver operating characteristic (ROC) analysis of the relationship between post-operation outcomes and midline shift improvement, the area under the curve (AUC) was 0.844, and the cutoff point of midline shift improvement was 0.83 cm.

Conclusion: Improved midline shift was a significant predictor of 30-day mortality. The improved midline shift of >0.83 cm indicated survival at 30 days.

Keywords: malignant middle cerebral artery infarction, decompressive craniectomy, mortality, hypertensive intracerebral hemorrhage, improvement in midline shift

INTRODUCTION

Malignant middle cerebral artery infarction (MMCAI) is a kind of large hemispheric infarction because of the occlusion of the proximal middle cerebral artery or the internal carotid artery. MMCAI is the most critical and severe form of acute stroke with mortality up to 80% (1). Acute management should include rapid recanalization by intravenous/intra-arterial (IA) thrombolysis and IA mechanical thrombectomy in the time window for restoration of cerebral blood flow (2). However, if it is beyond the therapeutic time window, MMCAI can cause acute and life-threatening brain swelling due to the post-ischemic edema. In many cases, even with the intravenous/IA thrombolysis and IA mechanical thrombectomy, the edema is inescapable. The post-ischemic edema is the main cause of death and severe complications because malignant edema could lead to compression of the brain stem, occlusive hydrocephalus, and secondary ischemic damage presenting with clinical deterioration, consciousness declining, herniation, and death within 2–5 days (3).

Among the limited number of options for MMCAI, decompressive craniectomy (DC) has been proven to be an effective way to reduce mortality, which could allow immediate decompression of the brain and the release of the intracranial hypertension (4–6). The procedure is *via* an ipsilateral frontoparietotemporal craniotomy, followed by plastic reconstruction of the dura mater. Some clinical trials have clearly demonstrated that DC significantly increases the survival probability of MMCAI patients (7, 8).

Patient selection for DC relies on baseline patient characteristics, neurological presentation, imaging evaluation (such as midline shift), and time from the onset of symptoms to surgery (9, 10). The correlation of specific clinical variables to patient mortality helps inform surgeons and families about the patient's potential prognosis.

In the study, we analyzed the 30-day outcome in a cohort of consecutive patients undergoing DC and analyzed patient characteristics and clinical variables for predictors of survival to identify subpopulations that benefit most from surgical intervention.

METHODS

Study Design and Population

We included in this study all 43 identified patients who were diagnosed with middle cerebral artery (MCA) stroke and underwent DC for malignant MCA syndrome during the time period of July 2012 to October 2017. Information on the following data was collected: age, gender, infarction sides, infarction type, pupillary dilation before operation, onset to operation duration, intra-operation bleeding, duration of operation, pre-operation Glasgow Coma Scale (GCS) score; past medical history; improvement of the midline shift after DC; and mortality at 30 days. The midline shifting distance was the distance between the benchmark and the septum pellucidum that deviated the farthest from it. Improvement in midline shift is defined as the difference between pre-DC and post-DC midline shifting distances (pre-DC values minus post-DC values). So the positive values mean that the septum pellucidum shifted back to the benchmark after DC. GCS score and pupillary response were documented for malignant MCA infarction at the time of clinical deterioration prior to surgery. The infarction type is divided into arterial thrombotic cerebral infarction (ATCI), atherosclerotic cerebral infarction (ACCE), and undifferentiated type of infarction (UT). All the enrolled patients are right-handed. To evaluate outcomes, the status at 30 days after DC was documented as survival or not. All measurements were performed by two neurosurgeons (X.C. and H.W.) blinded to all other data of the patient at the time the measurements were taken.

DC surgery was performed according to a standardized operative procedure that is based on a frontoparietotemporal craniotomy, ipsilateral to the lesion, followed by plastic reconstruction of the dura mater, allowing immediate decompression of the brain.

A craniectomy was performed in patients who developed clinical deterioration signs including pupil asymmetry, altered mental status, and progressive hemiplegia. The study protocol was approved by the institutional review board of Beijing Tiantan Hospital, Capital Medical University. Informed consent was not obtained because of the retrospective nature of the study.

Statistical Analysis

Categorical variables are expressed as number (%) and continuous variables as the mean ± standard deviation when the data followed a normal distribution. Categorical variables were compared using the chi-square test or Fisher's exact probability test, and the medians were compared using the Student's *t*-test. Chi-square test and Fisher's exact test were used to test the relationships between continuous variables and postoperative outcomes. Variables with p-values < 0.05 on univariate analysis were brought into the binary logistic regression to determine independent risk factors. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. For the variable of the midline shift, the receiver operating characteristic (ROC) curve analysis was applied to determine the predictive value and cutoff point. All statistical tests were two-sided, and the level of significance was set at $p < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences software version 22 (SPSS, Chicago, IL, USA).

RESULTS

Patient Characteristics and Clinical Variables

The patient characteristics and clinical variables are summarized in **Table 1**. Forty-three consecutive patients (32 males vs. 11 females) who presented with MMCAI and underwent DC were enrolled in this study. The mean age was 53 ± 10 years, ranging from 24 to 77 years, 32 (74%). Twenty-one patients had infarction involving the left hemisphere, and 22 patients had a lesion in the right hemisphere. Hypertension was diagnosed in 24 patients, heart disease in 16, and diabetes in 10. The mean pre-operation

TABLE 1 | Univariate analysis shows the relationships between variables and 30-day mortality.

Parameters	Parametric subclass	Parametric description		Chi-square test (X^2)/Fisher exact test/*t*-test (*t*)	*P**
		Survivors	Non-survivors		
Gender	Male	19	13	-	0.495
	Female	5	6		
Age	≥60	3	8	$\chi^2 = 4.882$	0.027*
	<60	21	11		
Location	Right	9	13	$\chi^2 = 5.721$	0.017*
	Left	15	6		
Infarction type	UT	2	0	$\chi^2 = 0.1667$	0.435
	ATCI	13	11		
	ACCE	9	8		
Hypertension	Y	10	14	$\chi^2 = 4.408$	0.036*
	N	14	5		
Heart disease	Y	8	8	$\chi^2 = 0.349$	0.555
	N	16	11		
Diabetes	Y	4	6	-	0.295
	N	20	13		
Pupillary dilation	Y	2	11	$\chi^2 = 12.35$	<0.01*
	N	22	8		
Pre-op GCS score	-	7.75 ± 2.09	6.16 ± 2.79	$t = 2.138$	0.038*
Onset to op duration	≥48	19	9	$\chi^2 = 4.721$	0.030*
	<48	5	10		
Intra-op bleeding	-	327.08 ± 410.46	223.68 ± 138.81	$t = 1.049$	0.3
Duration of operation	-	115.42 ± 27.07	108.84 ± 31.59	$t = 0.735$	0.467
Midline shift improvement	-	3.24 ± 3.21	−2.03 ± 4.78	$t = 4.214$	<0.01*

Op, operation; GCS, Glasgow coma scale; UT, undifferentiated type of infarction; ATCI, arterial thrombotic cerebral infarction; ACCE, atherosclerotic cerebral infarction.

GCS score was 7 ± 3, ranging from 3 to 13. The average intra-operation bleeding was 281.40 ± 321.27 ml, ranging from 50 to 2,000 ml. The mean time of DC operation was 112.51 ± 28.98 min. Before the DC operation, 13 patients had pupillary dilation. After the operation, the midline had a mean return distance of 10.12 ± 0.92 mm (-11.30–10.12 mm).

Predictors of Death at 30 Days

Patient characteristics and clinical variables were investigated in relation to 30-day mortality to identify potential predictors.

In univariate analysis (**Table 1**), age ≥60 ($\chi^2 = 4.882$, $p = 0.027$) (**Figure 1A**), shorter onset to operation duration (<48 h) (**Figure 2A**) ($\chi^2 = 4.721$, $p = 0.030$), right hemispheric location ($\chi^2 = 5.721$, $p = 0.027$) (**Figure 2B**), a history of hypertension ($\chi^2 = 4.408$, $p = 0.036$) (**Figure 2C**), pupillary dilation ($\chi^2 = 12.35$, $p < 0.01$) (**Figure 2D**), higher pre-operation GCS ($t = 2.138$, $p = 0.038$) (**Figure 1B**), and lower midline shift improvement ($t = 4.214$, $p < 0.01$) (**Figure 1C**) were significantly more likely to have a poor outcome of death at 30 days post-DC.

In the multivariable analysis (**Table 2**), patients with increasing age (OR = 1.141, 95% CI 1.011–1.287) and pupillary dilation (OR = 15.10, 95% CI 1.374–165.954) were more likely to have a poor outcome of death after DC, while the midline shift improvement (OR = 0.764, 95% CI 0.59–0.988) was a protective factor against the poor ending of death.

For the ROC analysis of the relationship between post-operation outcomes and midline shift improvement, the area under the curve (AUC) was 0.844 and the cutoff point of midline shift improvement was 0.83 cm (**Figure 3**).

DISCUSSION

DC as a lifesaving procedure that is often performed in patients with space-occupying lesions of various underlying pathologies, especially during the treatment of space-occupying ischemic stroke (11–14). We retrospectively reviewed the 30-day clinical outcome in patients undergoing DC by analyzing a 5-year, single-center, consecutive patient cohort. Overall, advanced age, right hemispheric location, hypertension, pupil dilation, improved midline shift, and lower GCS score were significant predictors of death.

In this retrospective study for DC patients, the 30-day mortality was 44.2%. It has been reported in other studies that mortality of MMCAI approaches 80% without DC surgery. We show that DC could reduce mortality as other researchers did (14, 15). DC relieves the constraint of bulgy intracranial contents and protects the important structures in the brain stem from compression.

Several studies have reported that age should be considered as an important factor in patients who undergo surgical

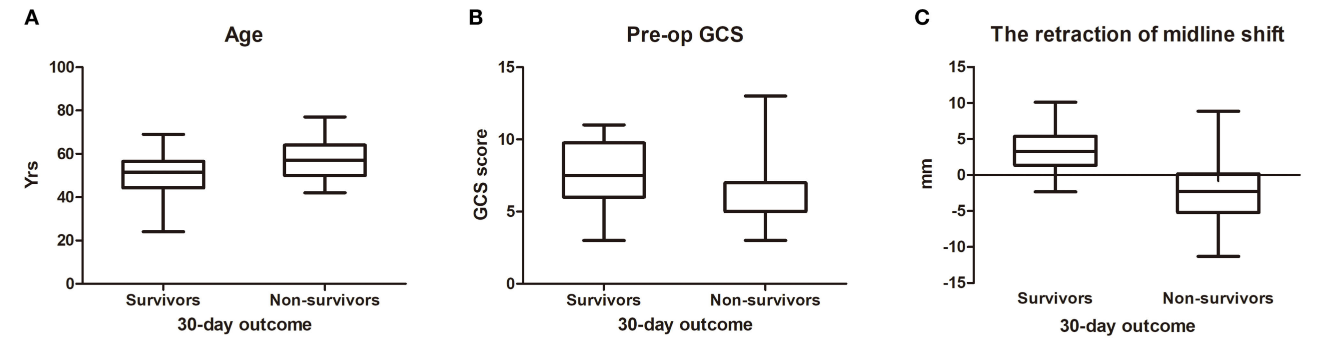

FIGURE 1 | The difference between survivors and non-survivors for measurement data (30-day outcome). The distribution of age **(A)**, pre-op GCS **(B)**, and the retraction of midline shift **(C)** between survivors and non-survivors. For **(C)**, the negative reading means worsening of midline shift after DC.

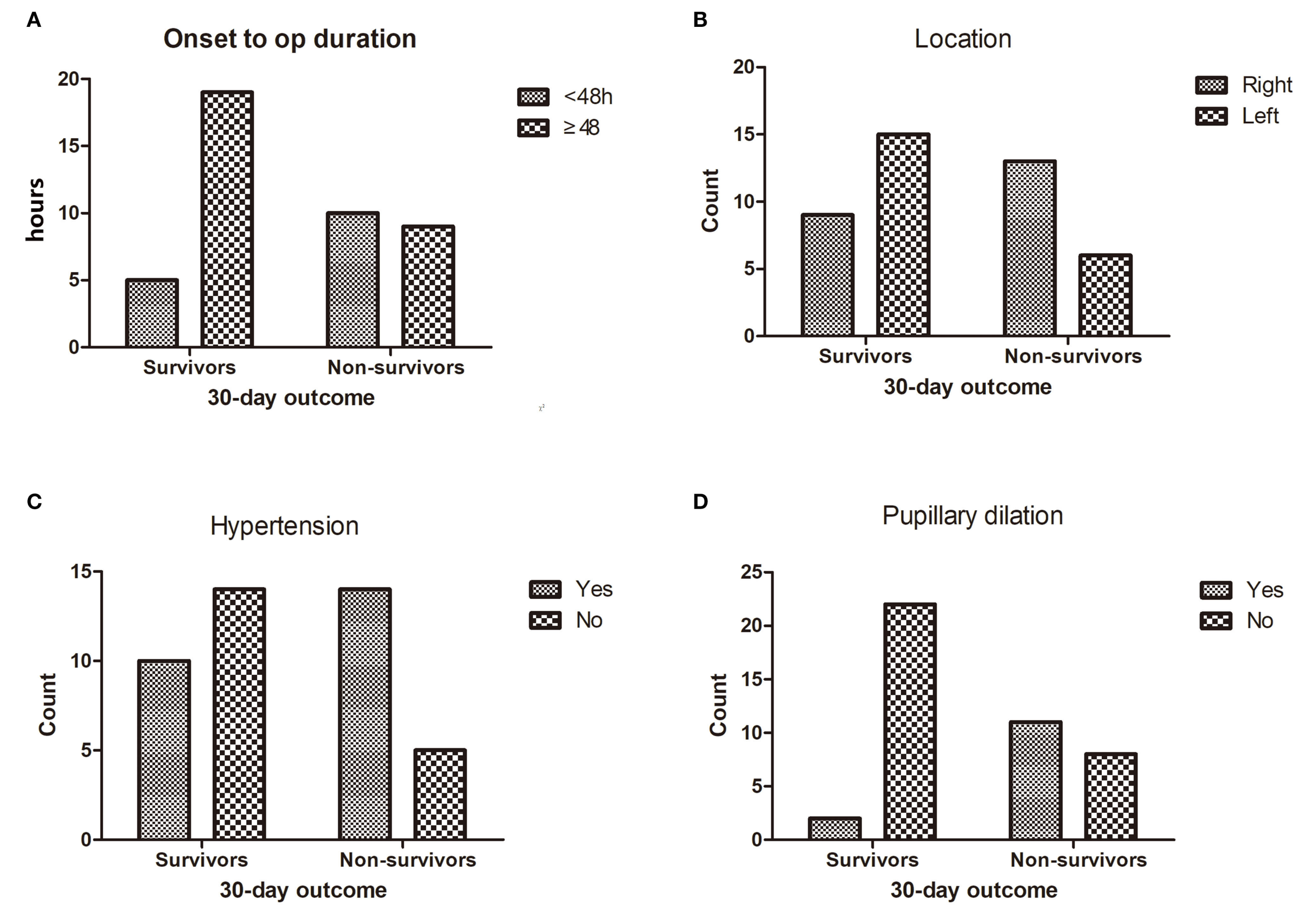

FIGURE 2 | The difference between survivors and non-survivors for enumeration data (30-day outcome).The distribution of onset to op duration **(A)**, location **(B)**, hypertension **(C)** and pupillary dilation **(D)** between survivors and non-survivors.

decompression (16–19). We showed that age ≥60 years was an independent factor for the prognosis of patients with DC (**Tables 1**, **2**, **Figure 1A**). The mortality of DC patients in the age ≥60 group was higher than that of patients at a younger age ($\chi^2 = 4.882$, $p = 0.027$). The aging caused physical and functional deterioration, with declining flexibility and immunity. So, the older patients found it harder to recover from the MMCAI and surgical attack than the younger patients.

Previous studies have recommended performing DC for the treatment of malignant cerebral infarction in patients before clinical or radiological signs of brain herniation, within a time frame of 48 h, but in this series, we obtained the opposite result

TABLE 2 | Binary logistic regression shows the independent factors of postoperative outcomes.

Parameters	*P*	OR	OR 95% C.I.
Age	0.032	1.141	1.011–1.287
The retraction of midline shift	0.04	0.764	0.59–0.988
Pupillary dilation	0.026	15.099	1.374–165.954

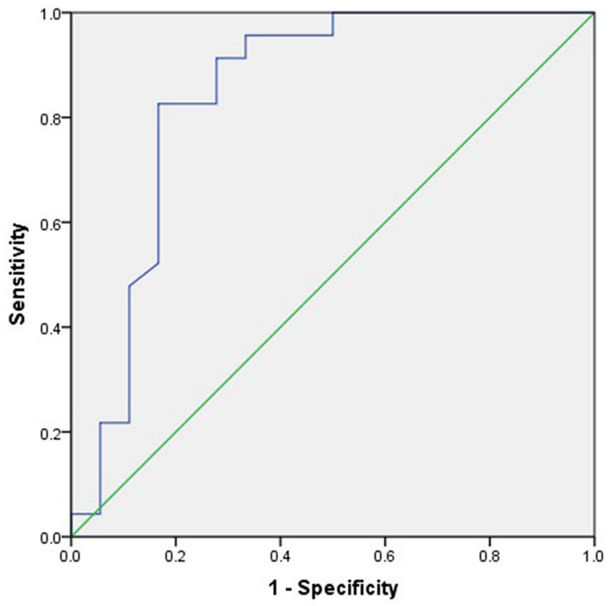

FIGURE 3 | The receiver operating characteristic (ROC) analysis of the relationship between 6-month outcome and midline shift improvement. The area under the curve (AUC) was 0.844, and the cutoff point of midline shift retraction was 0.83 cm.

that after more than 48 h of onset to operation, duration was a significant positive predictor for positive patient outcomes. The average time of onset to operation in this series was 79.22 ± 76.26 h. Early DC (<48 h) did not show superiority over a late one (**Table 1**, **Figure 2A**). It may be because that all enrolled early DC patients were more critical than the late DC patients. In this series, most enrolled patients were transferred from the neurology department or intensive care unit. The process of consultation, benefit–risk balance between family members, and transfer also cost extra time and made the onset to operation period more than 48 h. Otherwise, most patients were implemented a therapeutic regimen of intense dehydration (megadose of mannitol, i.e., 20% mannitol, q8h). The dehydration management maintained the relative steady status and prevented clinical deterioration until loss of balance. However, by now, there is no convincing study to show an optimal time frame for DC. In the three most authoritative trials [Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY), Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarction (DECIMAL), and Hemicraniectomy After Middle Cerebral Artery Infarction With Life-threatening Edema Trial (HAMLET)], 48 h was adopted as a constant for the DC, and surgical procedures showed an advantage over medical management at reducing mortality. According to the clinical experience in our center, early DC is indispensable, especially when the clinical status deteriorated.

In this series, mortality of patients with MMCAI at the side of the non-dominant hemisphere (right) was 59.10%, higher than that (28.57%) of the dominant hemisphere (left) ($\chi^2 = 5.721$, $p = 0.017$) (**Table 1**, **Figure 2B**). It is probably because the sequelae of infarct does not appear until the patients become symptomatic. For most patients, the left hemisphere is dominant with the most important linguistic function. So, left-sided strokes are more symptomatic and are reported earlier. Whereas, right-sided strokes are more occult and not brought to light until it becomes apparently symptomatic, therefore having a longer onset-to-thrombectomy duration. In a previous study concerning patient outcome after DC with severe ischemic stroke, there were no differences between left- and right-sided infarctions about the functional outcome (20). Park et al. (21) concluded that no significant difference in the clinical outcome with modified Rankin Scale (mRS) scores was observed between surviving patients with dominant and non-dominant hemisphere infarction. While in another research, patients with cerebral infarction involving the dominant hemisphere had higher odds of unfavorable functional outcome at 90 days than their counterparts (4). The functional anomaly of the dominant hemisphere could lead to language dysfunction and lower the functional outcome. However, the link between MMCAI of the non-dominant hemisphere (right) and higher mortality is unknown.

Hypertension destroys the structure and function of the circulatory system and further damages vital organs (such as the brain and the heart) and increases bleeding in operations. In a previous study (22), hypertension was not related to the 30-day mortality of patients with DC for MMCAI. Nevertheless, in this series, hypertension was a significant contributor to bad outcomes. The mortality of patients with hypertension (58.33%) was higher than those without hypertension (26.32%) (**Table 1**, **Figure 2C**). So, it is important to control blood pressure during the perioperative period for MMCAI patients.

GCS score is a reliable evaluation method for the coma degree. Pre-operation GCS score represents a comprehensive status of consciousness, physical activity, and language. Goedemans et al. (16) reported that poor GCS score was a significant predictor of unfavorable outcome for patients after DC. In our study, lower pre-operation GCS score was significantly related to 30-day mortality.

Worsening clinical status was defined as pupillary dilation and signs of cerebral herniation or severe brain edema with mass effect despite medical treatment or hemorrhagic infarction. When a bright light gets into the eyes, the iris sphincter muscles contract to make the pupil shrink and protect the contents in the eyes. The process is controlled by the brain stem. When the brain stem shifts, the pupil reflex disappears and causes pupillary dilation. Patients with pupillary abnormalities were significantly more likely to have poor outcomes (4, 16, 18, 23). In our series, pupillary dilation was strongly linked to 30-day mortality ($\chi^2 = 12.35$, $p < 0.01$) (**Table 1**, **Figure 2D**). Multivariable analysis also showed that pupillary dilation was an independent predictor for 30-day mortality (OR = 15.099, 95% CI 1.374–165.954) (**Table 2**). So, we recommend that early and meticulous pupillary checks are important for MMCAI patients before the pupils amplify.

The midline shift is an important indication for DC. In a previous study, Sang-Beom Jeon (23) reported that patients with a reduction of midline shift following decompressive hemicraniectomy for MMCAI were more likely to be alive at 30-day poststroke than those without. In this study, the improvement in midline shift was a strong predictor for a good prognosis ($t = 4.214$, $p < 0.01$) (**Table 1**, **Figure 1C**) in the univariate analysis. And in multivariable analysis, the improvement of the midline shift was a protector against the death of patients at 30 days after DC (OR = 0.764, 95% CI 0.59–0.988), which meant that if the midline shift returned, the surgical patient was more likely to be alive at 30 days after DC. We used the ROC analysis to obtain a cutoff value of midline shift improvement to predict the outcome of the DC patients. The midline shift improvement of more than 0.83 cm was the most sensible predictor for survival with an AUC of 0.844 (**Figure 3**).

CONCLUSION

In this study, we showed that increasing age, right hemisphere location, hypertension, and pupillary dilation were predictors for the poor outcome of death for MMCAI patients after DC operation; however, midline shift improvement was a protective predictor against death. Its predictive value peaked at 0.83 cm. Further prospective randomized trials with more enrolled patients may prove useful in defining the indication of craniectomy after stroke.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

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

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REVIEW
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Chinese Cerebrovascular Neurosurgery Society and Chinese Interventional & Hybrid Operation Society, of Chinese Stroke Association Clinical Practice Guidelines for Management of Brain Arteriovenous Malformations in Eloquent Areas

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Aim: The aim of this guideline is to present current and comprehensive recommendations for the management of brain arteriovenous malformations (bAVMs) located in eloquent areas.

Methods: An extended literature search on MEDLINE was performed between Jan 1970 and May 2020. Eloquence-related literature was further screened and interpreted in different subcategories of this guideline. The writing group discussed narrative text and recommendations through group meetings and online video conferences. Recommendations followed the Applying Classification of Recommendations and Level of Evidence proposed by the American Heart Association/American Stroke Association. Prerelease review of the draft guideline was performed by four expert peer reviewers and by the members of Chinese Stroke Association.

Results: In total, 809 out of 2,493 publications were identified to be related to eloquent structure or neurological functions of bAVMs. Three-hundred and forty-one publications were comprehensively interpreted and cited by this guideline. Evidence-based guidelines were presented for the clinical evaluation and treatment of bAVMs with eloquence involved. Topics focused on neuroanatomy of activated eloquent structure, functional neuroimaging, neurological assessment, indication, and recommendations of different therapeutic managements. Fifty-nine recommendations were summarized, including 20 in Class I, 30 in Class IIa, 9 in Class IIb, and 2 in Class III.

Conclusions: The management of eloquent bAVMs remains challenging. With the evolutionary understanding of eloquent areas, the guideline highlights the assessment of eloquent bAVMs, and a strategy for decision-making in the management of eloquent bAVMs.

Keywords: assessment, brain arteriovenous malformation, eloquent area, guideline, treatment

INTRODUCTION

Brain arteriovenous malformations (bAVMs) are an abnormal collection of blood vessels wherein arterial blood flows directly into draining veins without the normal interposed capillary beds, while no brain parenchyma is contained within the nidus. Brain AVMs may lead to spontaneous intracranial hemorrhage (ICH), seizures, neurological deficits, or headaches, usually in young people (1, 2). Current treatments, such as microsurgical resection, stereotactic radiotherapy (SRS), endovascular embolization, and multimodality treatments mainly aim at preventing hemorrhagic stroke (3). However, the risk of suboptimal outcomes must be carefully balanced between treatments and wait-and-see strategies. Several links remain unclear in the management of bAVMs, especially in those located in eloquent areas. Challenges exist in preoperative assessments of neurological function, prediction of operative risks, and decision-making of therapeutic strategy and method. The purpose of this guideline is to review current studies and develop recommendations for the management of bAVMs with eloquent areas involved.

METHODS

A multidisciplinary group was proposed by the Chinese Cerebrovascular Neurosurgery Society (CVNS) and Chinese Interventional & Hybrid Operation Society (IHOS) of Chinese Stroke Association (CSA) and confirmed by CSA Executive committee, including the clinical researchers on microsurgery, endovascular neurosurgery, stereotactic radiosurgery, neuroradiology, and functional neuroimaging. Researchers in each field were screened for important conflicts of interest and assigned to the specific subcategory by a face-to-face meeting. These subcategories included anatomy of eloquent areas; preoperative neuroimaging, neurological assessment; neurosurgery, endovascular surgery, stereotactic radiosurgery, multimodality treatments, and conservative treatment. Each subcategory was led by at least one author.

The group identified all available literature related bAVMs and neurological functions in humans, following the practices of the Task Force on Practice Guidelines for literature searches published by the American Heart Association/American Stroke Association (AHA/ASA). Given the focus of therapeutic questions remaining in clinical practices, we performed systematic literature searches, guided by Applying Classification of Recommendations and Level of Evidence (**Tables 1**, **2**) (4). As the eloquent bAVMs were seldom studied specifically, extended searches involved all bAVM-related literatures on MEDLINE (1970–May 2020), with (“arteriovenous malformations” [MeSH Terms] OR “arteriovenous malformations” [All Fields]) AND (“brain” [MeSH Terms] OR “Intracranial” [MeSH Terms] OR “cerebral” [MeSH Terms] OR “cerebellar” [MeSH Terms] OR “brain stem” [MeSH Terms] AND 1970/1/1:2020/5/31 [Date–Publication]). Publications irrelevant to eloquent bAVMs were excluded. Works of literature were further screened by different terms specified to each subcategory. Methodological filters were used to identify RCTs, meta-analyses, and systematic reviews.

Drafts of recommendations were circulated to the entire writing group by online video conferences for feedback. Sections were revised and merged by the first authors. Comments of the merged draft were made by the entire writing group and got incorporated before the approval of the final draft. The corresponding authors revised the document in response to peer review. The manuscript was sent to the entire writing group again for additional suggestions and approval.

RESULTS

A total of 2,493 bAVM-related results were obtained. Works of literature related to bAVMs, eloquent areas, neurological functions, and clinical techniques were identified. With in-depth interpretations, 341 pieces of literature were cited by this work, including 2 randomized clinical trials (RCTs), 8 meta-analyses, 224 clinical cohorts, 31 case reports or series, 46 reviews, 31 laboratory researches, and several literatures in other forms (**Figure 1**). The writing group summarized 61 recommendations for the management of eloquent bAVMs (refer to **Table 3**).

Anatomy of Eloquent Areas

Sensorimotor Brain Areas

Motor-related cortices mainly include: (1) primary motor cortex, located in the precentral gyrus and correspond to Brodmann’s area 4; (2) supplementary motor cortex (SMC) which is in the medial side of the cerebral hemisphere and in front of the primary motor cortex, and is a major area related to motor programming and corresponds to the medial part of Brodmann’s area 6; (3) premotor cortex (PMC) located in the lateral side of the frontal lobe, occupying part of the superior frontal gyrus, middle frontal gyrus, and precentral gyrus. The primary somatosensory cortex is in the postcentral gyrus, corresponding to Brodmann’s area 1–3 and there is a corresponding relationship between areas in the primary somatosensory cortex and specific body areas. Moreover,

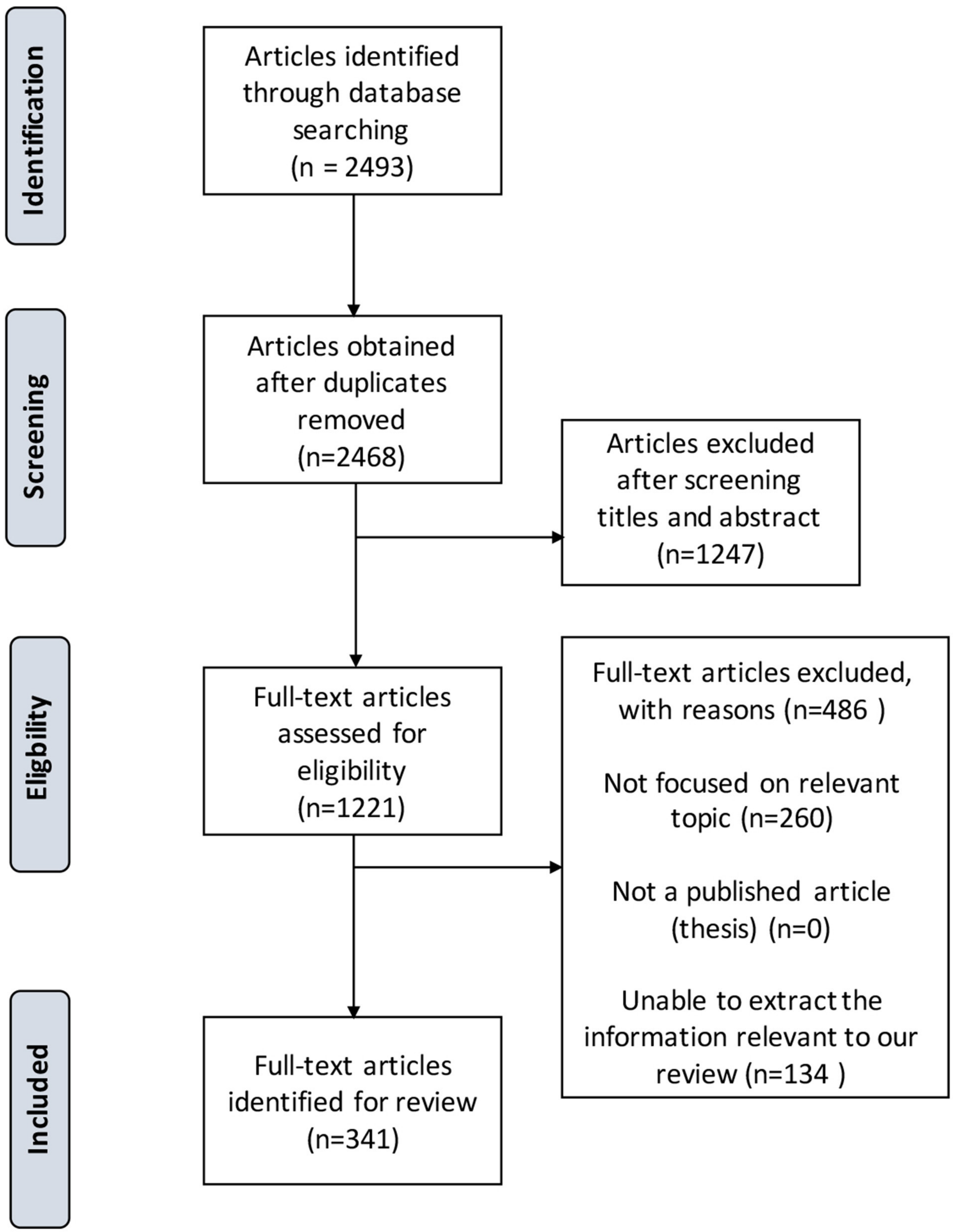

FIGURE 1 | PRISMA study flow diagram demonstrating the number of articles retained at each stage of data acquisition.

TABLE 1 | Applying classification of recommendations and level of evidence.

		Size of treatment effect			
		CLASS I *Benefit >>> Risk* Procedure/treatment **SHOULD** be performed/administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/treatment **MAY BE CONSIDERED**	**CLASS III** *No Benefit* or **CLASS III** *Harm* **Procedure/test** / **Treatment** COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or harmful — Harmful to patients
Estimate of certainty (precision) of treatment effect	**LEVEL A** Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well-established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is no useful/effective and may be harmful. ■ Sufficient evidence from multiple randomized trials or meta-analyses
	LEVEL B Limited populations evaluated* Data derived from single randomized clinical trials or nonrandomized studies	■ Recommendation that procedure or treatment is useful /effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well-established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is no useful/ effective and may be harmful. ■ Evidence from single randomized trial or nonrandomized studies
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well-established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is no useful/ effective and may be harmful. ■ Only diverging expert opinion, case studies, or standard of care
	Suggested phrases for writing recommendations	Should Is recommended Is indicated Is useful/effective/beneficial	Is reasonable Can be useful/effective/ beneficial Is probably recommended or indicated	May/might be considered May/might be reasonable Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	**COR III: No benefit** Is not recommended Is not indicated Should not be Performed/ administered/other Is not useful/beneficial /effective **COR III: Harm** Potentially harmful break Causes harm Associated with excess morbidity/mortality Should not be performed/ administered/other
	Comparative effectiveness phrase†	Treatment/strategy A is recommended/indicated in preference to treatment B Treatment A should be chosen over treatment B	Treatment/strategy A is probably recommended/indicated in preference to treatment B It is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be clinical consensus that a particular test or therapy is useful or effective.

**Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations.*

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatment or strategies being evaluated.

green: Benefit >>> Risk; orange: Benefit >> Risk; yellow: Benefit ≥ Risk; red: harm or no benefit.

TABLE 2 | Definition of classes and level of evidence used in recommendations.

Class/level	Description
Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb	Usefulness/efficacy is less well-established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Therapeutic recommendations	
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized trial or non-randomized studies
Level of evidence C	Data derived from a single randomized trial or non-randomized studies
Diagnostic recommendations	
Level of evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of evidence B	Data derived from a single grade A study or one or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of evidence C	Consensus opinion of experts

TABLE 3 | The details of 55 recommendations.

Level of evidence	Size of treatment effect			
	Class I	Class IIa	Class IIb	Class III
A	1	0	0	1
B	18	16	3	1
C	1	14	6	0

the corticospinal tract (CST) is the most important fiber tract related to motor function, which consists of axons of pyramidal cells of the middle and upper part of the precentral gyrus and some other cortical regions.

Language Related Brain Area

Cortex

Language-related cortices mainly include (1) Broca's area: including the pars opercularis and the pars triangularis of the inferior frontal gyrus of the dominant hemisphere, corresponding to Brodmann's area 44 and the second half of Brodmann's area 45. Broca's area plays a vital role in the production of speech and understanding procedures (5, 6). (2) Wernicke's area: The Wernicke area is traditionally considered to be in the posterior third of the superior temporal gyrus (STG) of the dominant hemisphere (usually left hemisphere), corresponding to the rear of Brodmann's area 22 while there is no uniform definition of the specific range. Wernicke's area is mainly involved in the identification and understanding of speech. (3) Geschwind's area: The area is in the inferior parietal lobe of the left hemisphere, including the supramarginal gyrus and angular gyrus (Brodmann's area 39, 40). In recent years, brain functional imaging studies suggest that the Geschwind's area is an important language-related area and hub for multiple speech functions such as phonetic judgment, speech understanding, and reading (7–9). (4) Cerebellum: It was confirmed that the cerebellum is associated with logical reasoning and language processing (10).

Subcortical Fiber Bundle

The tractography and function of each language-related fiber bundle are still being studied. According to the anatomical position and function, they are currently divided into dorsal and ventral pathways. The dorsal pathway includes the arcuate fasciculus and the superior longitudinal fasciculus (11, 12). The ventral pathway includes the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and the uncinate fasciculus connecting the temporal pole and the orbital gyrus (13). Previous studies suggest the dorsal pathway is mainly involved in the processing of phonetic functions while the ventral pathway is mainly involved in the processing of semantic functions. The theory is still being confirmed and remains controversial.

Vision Related Brain Area

It is located around the calcarine fissure of the occipital lobe. The cortex includes the primary visual cortex and extrastriate cortex. The primary visual cortex is in Brodmann's area 17 while the extrastriate cortex is in Brodmann's area 18–19. Optic radiation is the fiber bundle connecting the lateral geniculate body and the striate cortex (14). It starts from the lateral geniculate body bending backward around the temporal horn and trigone. Optic radiation can be divided into an anterior, middle, and posterior bundle. All of the bundles pass backward along the lateral wall of the occipital horn to the calcarine fissure.

Cognition Related Brain Area

At present, more and more attention is paid to cognitive functions. The hippocampus is an important cognition-related brain area called the "hippocampal region" which serves as a part of the limbic system (15). It is responsible for short-term memory, long-term memory, and spatial positioning. The anterior hippocampus is seen to be involved in decision-making under approach-avoidance conflict processing.

Other Function Related Brain Areas

Other eloquent areas include basal ganglia, thalamus, hypothalamus, brain stem, cerebellar peduncles, internal capsule, and deep cerebellar nuclei. Basal ganglia are associated with control of voluntary motor movements, procedural learning, habit learning, eye movements, cognition, and emotion (16, 17). The thalamus regulates states of sleep and wakefulness and inputs from the retina and processes sensory information as well as relays it. The hypothalamus coordinates many hormones and behavioral circadian rhythms, regulates complex homeostatic mechanisms, and is associated with fear processing and social defense (15, 18, 19). The brain stem conducts all information relayed from the body to the cerebral, cerebellum, and vice versa must traverse the brain stem. It has integrative functions involved in cardiovascular system control, respiratory control, pain sensitivity control, alertness, awareness, and consciousness (20, 21). Cerebellar peduncles are widely believed to mediate visual and auditory reflexes (22, 23). The internal capsule contains frontopontine fibers, corticobulbar fibers, CSTs, sensory fibers from the body, and a few corticobulbar fibers. Temporopontine fibers, optic radiation, and auditory radiations are also included (24–27). Deep cerebellar nuclei are involved in basic circuitry work involving coordination and the precision of limb movements (22, 28).

Brain Connectome

In recent years, studies regarding cognitive neuroscience identify that there are complex brain networks that interact with each other to perform various functions. Researchers revealed that there is a relationship between many neuropsychiatric diseases (such as Alzheimer's disease and schizophrenia) and the abnormal topological change in brain structural and functional networks. These studies provide us with a new approach to studying the pathological mechanism of BAVMs and of evaluating the surgical outcomes preoperatively.

Preoperative Imaging Assessment

Routine Imaging Examination

(1) T1/T2 weighted Magnetic Resonance Imaging (MRI): to identify the anatomical location, range, and edema around the lesion. (2) Magnetic resonance (arterial) angiography (TOF-MRA): to demonstrate cerebral vessels and the surrounding brain tissue; to assist the comprehensive evaluation of nidus size, location, diffuseness, hemorrhage, feeding arteries, draining veins, and surrounding normal blood vessels (29). (3) Computed Tomography (CT): to assess acute subarachnoid hemorrhage and hemorrhagic stroke with a sensitivity >90% (30). Although limitations exist when detecting bAVMs, some features relevant to vascular abnormalities could be revealed, including dilated or calcified vessels along the bleeding edge and increased density areas representing abnormal vascular clusters. CTA is more acclaimed for its decreased invasiveness, good spatial resolution, and higher inspection speed. However, limitations of CTA lie in the presence of ionizing radiation and metal artifacts. CTA has high sensitivity (83.6–100%) and specificity (77.2–100%) in detecting vascular abnormalities in patients with parenchymal hemorrhage and vascular abnormalities, which can be used for initial differential diagnosis of a spontaneous cerebral hemorrhage.

Digital Subtraction Angiography (DSA)

DSA is the reference standard for diagnosing bAVMs and provides detailed information about angio-architectures and hemodynamics through dynamic images (31). Those with suspected bAVMs *via* CT or MRI are suggested to perform DSA for further clarification.

Blood-Oxygen-Level Dependence Functional Magnetic Resonance Imaging (BOLD-fMRI)

BOLD-fMRI is a non-invasive, non-radioactive, repeatable technology with high temporal resolution and spatial resolution. Processed data of BOLD-fMRI could display an activation map of functional areas and support the localize the sensorimotor area, speech area, and hemispheric dominance before operation. BOLD-fMRI includes the task-based and the resting-state ones.

In task-based BOLD-fMRI, block-designed scan tasks are commonly used (32). (1) Tasks of the detection of motor area activation: Finger movement (or dorsiflexion and extension of the foot) module and the block module alternately. The sensorimotor area of hands and feet is positioned by finger stretching movements, specified sequence of finger contrapuntal movement, or foot dorsiflexion. The time of each task or block module is no <20 s in general and the interval of adjacent task modules must not be longer than 128 s. (2) Tasks of the detection of speech area activation: speech tasks and the block module alternately. Speech tasks usually use picture naming, vocabulary association, verb generation, sentence judgment, etc. The form of speech tasks can be selected by their educational level, language habits, and target area. The time of each task or block module is no <20 s in general and the interval of adjacent task modules must not be longer than 128 s.

In resting-state BOLD-fMRI, patients are required to be awake with their eyes closed (or look directly at the cross target) lying quietly when performing the scan. Images are being used in the study of the brain network (33).

Diffusion Tensor Imaging (DTI) and Fiber Bundle Tracking

Spatial images are obtained by calculating the anisotropy of water molecules, based on which fiber can be tracked. Magnetic resonance equipment in 3.0 Tesla is commonly used with the spin-echo diffusion-weighted EPI technology to collect the image. The voxel size is 2 mm*2 mm*2 mm for more than 12 directions and the scanning time is about 5 min. White fibers displayed by DTI include projection fibers (corticospinal tract, cortico-nuclear tract, and thalamus radiation), association fibers (arcuate fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, and frontal oblique fasciculus), and joint fibers (callosum) (34).

Other Magnetic Imaging Techniques

Magnetic resonance spectrum (MRS) can be used to identify microhemorrhage. Arterial spin labeling (ASL) sequence can be used to differentiate malformed blood vessel mass and surrounding single supply artery and perfusion (35). Combined with other advanced encoding methods and physiological data, the characteristics of the hemodynamics of arteries and veins can be evaluated.

Sonography

Both extracranial and transcranial/transnuchal duplex sonography have been reported to be used as a non-invasive method for the diagnosis of bAVMs. Distinctive hemodynamic features could be detected and even evaluated. Extracranial sonography detects bAVMs by identifying the time difference of contrast bolus arrival between the internal carotid artery and internal jugular vein, as known as global cerebral circulation time (CCT). Schreiber et al. (36) reported that the CCT was 7.5 ± 1.1 s in healthy volunteers, while much faster (about 1.5 s) in bAVMs patients. Transcranial color duplex Doppler (TCCD) is the advanced product of conventional transcranial Dopplar (TCD). Both TCCD and TCD could record the velocity and pulsatility parameters of intracranial vessels, and identify the hemodynamic changes induced by bAVMs (37). TCCD was proposed as a valuable non-invasive, harmless, low-cost, widely available method for the detection and follow-up of hemodynamic changes of AVMs, especially for pediatrics (38). However, the effect of TCCD in neurological functional assessment has never been reported.

Neurological Assessments

Muscle strength scales, Karnofsky performance scale (KPS), and modified Rankin Scale (mRS) could be used to assess motor functions. Edinburgh Dominance Scale was used to judge the dominant hemisphere of speech. If the lesion is in the dominant hemisphere, a speech-related scale or West Aphasia Battery (WAB) should be used to determine the existence of aphasia and the type and severity of it. It is important to make sure there are no related diseases that may affect the evaluation before assessments, such as hearing impairments and pyramidal tract injuries, Common language assessment scales include the Chinese version of WAB, Aphasia Battery of Chinese (ABC), China Rehabilitation Research Center Aphasia Examination (CRRCAE), etc. For bAVMs with vision-related brain areas involved, routine visual field examination (*via* visual field analyzer) is recommended before treatment. For lesions with cognition-related brain areas involved, Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are recommended. National Institutes of Health Stroke Scale (NIHSS) is required for comprehensive assessments as well (7).

Selection of Patients

Classic Grading Systems for Microsurgery

Spetzler-Martin (SM) Grading Scale

SM Grading Scale is the most commonly used grading system by far. Results of CT/MRI and DSA can be used in this scale to estimate the risk of surgical resection on: (1) the maximum size of lesion (<3 cm = 1 point; 3–6 cm = 2 points; >6 cm = 3 points), (2) the relative position of the eloquent area (eloquent area = 1 point, else = 0 points), and (3) the type of draining veins (only superficial veins = 0 points; deep veins = 1 point) (39). According to the SM Grading Scale, eloquent brain areas mainly include the sensorimotor area, visual and speech cortices, basal ganglia, thalamus, hypothalamus, brain stem, cerebellar peduncles, internal capsule, and deep cerebellar nuclei. The types of drainage are divided into: (1) with the superficial involved only, such as cortical veins draining into the superficial sagittal sinus, transverse sinus; and (2) with the deep drainage involved, indicating any draining vein to inferior sagittal sinus, Galen vein, and straight sinus. It has been confirmed that the grading system is an accurate predictor of surgical risk with a lower risk of permanent neurological deficits in the low-grade group (grade 1–2) than the high-grade group (grade 4–5). Spetzler et al. (40) recommended that bAVMs be divided into 3 categories for individualized diagnosis and treatment, including Type A (grade 1–2): recommended for microsurgical treatment; Type B (grade 3): recommended for individualized multimodal treatment; and Type C (grade 4–5): angiographic follow-up is preferred, while surgical treatment is only performed when aggravation of neurological deficits, recurrent bleeding or other conditions occurs.

Supplemented Spetzler-Martin (SM-Supp. or Lawton-Young) Grade

A supplementary of the SM grading scale was proposed to improve its predictive ability on microsurgical outcome with the following variables: patient age (<20 years old = 1 point; 20–40 years old = 2 points, >40 years old = 3 points), unruptured presentation (yes = 1 point; no = 0 points), diffuse (yes = 1 point; no = 0 points). The ROC curve in studies showed that it is more accurate than the SM scale (41–43).

Functional Image-Based Grading Scales

Safe Lesion-to-Eloquence Distance (LED): Studies had reviewed the influence of lesions involved in white matter eloquent fiber tracts, such as the subcortical cortical spinal tract (CST), optic radiation (OR), and arcuate fasciculus (AF) concerning sensorimotor, speech, and visual functions on the prognosis of patients, confirming that LED is an important risk factor for short-term and long-term neurological dysfunction in patients (32). It confirmed an acceptable LED to be 5 mm, which is significant in accurately assessing the risk and type of postoperative neurological dysfunction.

HDVL Grading System: This system was proposed to remedy the insufficiency of the SM grading scale on assessing (sub-)cortical eloquent structures and their LEDs. Each letter of HDVL stands for hemorrhage, diffusion, vein, and LED, respectively (**Table 4**). The fMRI and DTI-based functional imaging information are integrated into the grading system (32), and the vascular architectures of the lesion are considered to assist SM Grading in the preoperative evaluation of bAVMs, which provides a more accurate prediction of the prognosis.

Grading Scales for Radiosurgery and Endovascular Surgery

Stereotactic radiosurgery (SRS) and endovascular embolization are used as solitary therapeutic options (44). Several radiosurgical-based and endovascular-based grading scales had been proposed (45). Modified-RBAS was validated by comprehensive comparative analysis of different SRS-related bAVM grading scales (46). For endovascular treatment, Jin et al.

TABLE 4 | HDVL grading system.

Variables		Score[∫]
Lesion-to-eloquence* distance (LED)	>10 mm	1
	5–10 mm	2
	<5 mm	3
Diffuseness[†]	Yes	1
	No	0
Deep draining veins[‡]	Yes	1
	No	0
Hemorrhagic history	Yes	0
	No	1

∫ Total score = LED + Diffuseness+ Deep draining veins + Preoperative hemorrhage.
HDVL scores 1–3: operation is recommended.
HDVL scores 4–6: individualized multimodal treatment or conservative management is recommended.
**Eloquent areas include: sensorimotor, speech, and visual function related brain area identified by fMRI and functional white matter fiber tracts reconstructed by DTI such as cortical spinal tract (CST), optic radiation (OR), and arcuate fasciculus (AF).*
† Diffuseness refers to the inclusion of normal brain tissue in the nidus.
‡ Deep draining veins refer to part (or all) of the draining veins flow into deep veins, such as internal cerebral veins (ICV), basilar veins or precentral cerebellar veins.

(47) published the results of the validity assessment for Spetzler-Martin, Puerto Rico, Buffalo, and AVMES grading systems to predict various outcomes *via* a multicenter retrospective study. The Puerto Rico scale was finally revealed to be superior in predicting short-term and long-term procedural complications. None of the current grading scales for endovascular surgery or radiosurgery have been widespread. Further large-size studies are expected to develop a simple and efficient grading scale for predicting outcomes of these treatments.

Modified RBAS Score

Modified RBAS bAVM score = 0.1 × Volume + 0.02 × Age + 0.5 × Location; Location score was 1 for basal ganglia, thalamus, and brainstem, and 0 for the rest of the brain. The following cutoffs of the bAVM score were used to predict the declining outcome of patients undergoing SRS: $\leq$1, 1.01–1.50, 1.51–2.00, and >2, with a score $\leq$1 predicting a 90% chance of lesion obliteration with no neurological decline.

Puerto Rico Scale

The classification included the number of feeding vessels into the bAVMs (<3 pedicles = 1 point, 3–6 pedicles = 2 points, more than 6 pedicles = 3 points), the eloquence of adjacent areas (non-eloquent = 0 points, eloquent = 1 points), and the presence of fistulous components (no = 0 points, yes = 1 point) (48). Puerto Rico grade $\leq$2 reliably predicted successful lesion obliteration with isolated endovascular therapy, whereas grades $\leq$3 were proposed strongly associated with cure after multimodality treatment and favorable neurological outcome. There was a stepwise increase in complications with the increase in Puerto Rico grade.

Recommendations

- In the judgment of the eloquent area, the eloquent cortex, subcortical fiber tracts, hippocampus, and the important cognitive brain area should be taken into consideration (*Class I; Level of Evidence B*).
- Pre- and post-interventional neurological assessment should be performed regarding the potentially injured neurological and cognitive functions. Muscle strength scale with KPS score or mRS score should be used for the motor evaluation; the Edinburgh Dominance Scale and language scales such as the West Aphasia Battery is recommended for the language evaluation; for patients with lesions involved in visual areas, vision and visual field examination is recommended. Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are recommended to apply in the cognitive examination. National Institutes of Health Stroke Scale (NIHSS) is recommended for comprehensive assessments (*Class I; Level of Evidence B*).
- Besides traditional MRI, MRA, CTA, and DSA scanning, functional-MRI scanning, and DTI tractography are also useful in judging eloquent cortex and white matter fiber tracts (*Class I; Level of Evidence B*).
- In pre-surgical evaluating of the microsurgical treatment of bAVMs, in addition to the traditional SM Grading Scale and Lawton-Young Scale, the HDVL system is helpful for post-surgical neurological outcomes evaluation (*Class I; Level of Evidence B*).
- The involvement of eloquent fiber tracts should be considered in the preoperative evaluation to improve its predictive accuracy (*Class I; Level of Evidence B*).
- In evaluating the outcomes of radiosurgical and endovascular treatment for bAVMs, the modified-RBAS and Puerto Rico scale are helpful for radiosurgical and endovascular treatment, respectively (*Class I; Level of Evidence B*).

Treatment Modalities

Quality of life (QoL) after the treatments has been emphasized in recent years. The incidence of neurological deficits is regarded as a critical index in assessing the safety and efficiency of treatment. Thus, more attention had been paid to developing interventional techniques for neurological protection, and predictive tools for therapeutic risks evaluation (32, 40, 41, 44, 46, 49–55). Treatments of eloquent bAVMs have to achieve two goals: (1) the complete obliteration of nidus and arteriovenous shunt; and (2) the protection of neurological functions, which might severely impact postoperative QoL.

Treatments of eloquent bAVMs are carried by three elementary surgical methods, including microsurgical resection, endovascular embolization, and stereotactic radiosurgery (SRS). Microsurgical resection can be performed initially or subsequently to other treatments. Complete obliteration may be achieved in most cases receiving resection. Endovascular embolization is usually performed as a precursor to microsurgery and radiosurgery. Complete endovascular obliteration is seldom reported to be achieved in a single-staged or multi-staged therapy (56). Stereotactic radiosurgery is applied to the bAVMs in deep locations or small sizes as a primary or complementary treatment. In the treatment of complex eloquent bAVMs, different therapeutic elements are usually cooperatively utilized

(AKA multimodality treatments). Reviewing current literature, indications of each therapeutic modality were concluded.

Microsurgery

Microsurgical resection is the most common approach to achieve the complete obliteration of bAVMs. A systematic review by van Beijnum et al. (56) reported that microsurgery achieved the highest complete obliteration rate (≈96%), comparing with that of endovascular embolization (≈13%), and stereotactic radiosurgery (≈38%). The complete obliteration of bAVMs can eliminate the morbidities and mortalities induced by its hemorrhage in the future.

Threshold of Microsurgery

Microsurgical resection is not recommended for all eloquent bAVMs. The neurological risk of microsurgical resection should be evaluated. As mentioned above, the SM grading system and its supplemented scale are useful in the evaluation of operative risks and the prediction of neurological outcomes (41, 43, 51, 57, 58). Five grades of the SM grading system are divided into three levels, low grade (grade I–II), medium grade (grade III), and high grade (grade IV–V) (3). Studies on low-grade bAVMs reported morbidities of neurological deficits to range from 0 to 6.6% after microsurgical resections (57, 59–66). The morbidity rate of bAVMs in SM grade II increased to 0–69.2% (65, 67, 68). However, the worst neurological outcome was not induced by the involvement of eloquence. The microsurgery on eloquent bAVMs in SM grade II resulted in a morbidity rate ranging from 0 to 9.5%. There were two subtypes of eloquent bAVMs in grade III, the subtype of S1E1V1 and S2E1V0. The morbidity of neurological deficits was reported to be 4.8–16.7% and 15–25%, respectively (66, 69–71). They were in similar rates with the subtype of S2E0V1, but much lower than that of S3E0V0 (70). In the eloquent bAVMs in SM grade IV and higher, neurological risks increased rapidly to as high as 38% in the mono-therapy of microsurgery (40, 51, 57, 72, 73). However, preoperative annual hemorrhagic rates ranged from 1.5 to 10.4% in lesions of SM grade IV and V (72, 74, 75), which suggested the need for microsurgery. Several case reports and series had reported the successful utilization of individualized multimodality treatment to cure high-grade bAVMs with satisfactory morbidity and mortality (76–85). Multimodality treatments refer to the combined therapies of more than one elementary surgical treatment. Microsurgery is involved in most combinations. The performing of multimodality treatment is primarily for tentative or salvage purposes for high-grade bAVMs. Further discussed referred to section Multimodality Treatment.

Lawton et al. (41) proposed the supplementary scale of the SM grading system to refine the prediction of neurological outcomes. The full scale (SM grading system + supplementary scale) had been validated in bAVMs with deep and superficial locations. According to the studies with the full scale applied, monotherapy of microsurgery could result in satisfactory neurological outcomes in eloquent bAVMs in grade V and the lower (58, 86, 87). For the lesions in higher grades, not enough data support the exclusive utilization of microsurgery.

Results of functional neuro-images help to predict the individualized neurological outcome of each eloquent bAVMs. Lin et al. (88) proposed the minimum lesion-to corticospinal tract distance (LCD) to be 5 ml to secure the motor functions. Afterward, Jiao et al. (32) proposed the HDVL scale, enrolling LED, and achieved higher predictive accuracy than the full scale. The worsening of neurological outcome occurred in 0% of lesions in HDVL grade I and II, 11.8% in grade III, 31.5% and more in grade IV–VI. Monotherapy of microsurgery was recommended in lesions < HDVL grade IV.

The brainstem is a critical location with dense fiber tracts and nervous nuclei. Different procedures and techniques had been piroposed to cure brainstem bAMVs (89–91). However, current studies only demonstrated the therapeutic outcomes of highly selected patients. Thus, microsurgery of bAVMs in critical locations is not recommended, unless the relevant progressive neurological deterioration or hematoma occupation could not be postponed by endovascular surgery or radiosurgery (92).

Recommendations

- The Spetzler-Martin Grading system and its supplementary grading system are recommended to be utilized primarily to evaluate the risk of microsurgical resection (*Class I; Level of Evidence B*). The HDVL grading system is recommended for patients who have received DTI and fMRI assessments (*Class I; Level of Evidence B*). Microsurgical resection is reasonable to perform on lesions under Spetzler-Martin grade IV, or the combined grade VI (Spetzler-Martin grade plus the supplementary grade), or HDVL grade IV (*Class IIa; Level of Evidence B*). Individualized multimodality treatments can be useful to the bAVMs with Spetzler-Martin grade ≥IV, or combined grade ≥VI, or HDVL grade ≥IV (*Class IIa; Level of Evidence C*).
- The microsurgical resection may be considered in bAVMs located in critical locations (brainstem, pons, medulla, mesencephalon, etc.) when bAVM-related neurological deficits or mass effect of hematoma are progressive, and cannot be postponed by endovascular or radiosurgical treatments (*Class IIb; Level of Evidence C*).

Elective, Semi-elective, and Emergency Microsurgery

For eloquent bAVMs that require microsurgery, timing of treatment differs across situations. The emergency operation is performed in urgent situations, such as the occurrence of life-threatening hematoma, without any delay to prevent death or serious disabilities. The semi-elective operation is performed on the patients with prior hemorrhagic presentation, progressive neurological deficits, or AEDs-resistant epilepsy to prevent deterioration or death. The semi-elective operation should be done as early as possible, but can be postponed for the thorough preoperative preparation and evaluation. The elective operation is performed to the patients without life-threatening risk, and carried out at the request of the patient, and availability of the surgeon and facility. Both elective operations and semi-elective operations are aiming at preventing the onset of (re-)hemorrhage or symptoms in the future to promote QoLs. To ensure optimal neurological outcomes, the criteria in the last section should be obeyed.

Intracranial hemorrhage was the major threat of bAVMs. It occurs in an annual risk ranging from 1.3 to 4.1% (93–97). For the bAVMs with rupture history, the annual hemorrhagic risk increases to 4.5–4.8% (94, 95), and as high as 6–15.8% in the first year (98–102). Angio-architectural Features had been reported to be associate with ruptures, including (1) aneurysms located in nidus, arterial feeders, or irrelevant arteries; (2) venous drainage anomaly, such as the stenosis, occlusion, ectasia, kinking, or reflex of draining veins, and occlusion of the sinus; (3) single arterial feeder with high blood flow (94, 103–106). Microsurgical resection could achieve complete obliterates in most cases (96% approximately), and significantly reduce the re-bleeding rate (107). Considering the high risk of rebleeding in the first year, microsurgery is recommended to perform, but can be postponed for a short time for preoperative preparations and assessments.

Another common presentation of bAVMs is seizure, occurring in ∼17–30% of patients (108). The onset of seizure was suggested to be associated with hemosiderin deposition, mass effect with cortical irritation, hemodynamic modifications, and/or vascular remodeling leading to stealing, ischemia, and neuronal damage (109). The seizures could be progressive and impact QoLs. Josephson et al. (110) reported that 76% of seizures would develop into epilepsy. Microsurgical resection was reported to be effective in the control of seizures in bAVM patients with refractory epilepsy (111, 112). The semi-elective microsurgery is recommended when the onset of seizure had progressed. Other presentations of bAVMs consist of neurological deficits due to the steal phenomenon, and headache. In these hemodynamic related symptoms, microsurgical resection had been reported to be effective for their relief (113–117). For asymptomatic bAVMs, elective microsurgical resection is considered to prevent the occurrence of symptoms and suboptimal events mentioned above.

In patients aged ≤40 years, 33% of intracerebral hemorrhages were caused by the rupture of bAVMs (118). In the acute phase of hemorrhage, clinical outcomes were associated with both the grade of bAVM and the degree of subarachnoidal hemorrhage (119). Kuhmonen et al. (120) reported that an early extirpation of bAVMs and evacuation of massive hematoma resulted in optimal outcomes in over 55% of patients. However, before evacuating hematoma or resecting bAVM, two points should be clear. Firstly, the etiology of a hematoma should be identified, such as bAVM rupture, hypertension, or amyloid (4). Secondly, if the hematoma is induced by bAVM rupture, the morphology and angioarchitecture of the lesion should be ascertained comprehensively. CTA or DSA had been proven effective on the etiological diagnosis of hematoma (121–124). However, the routine workflow usually takes a long door-to-operation (DTO) time, which may be intolerant to patients with life-threatening hematoma or progressive neurological deterioration. The hybrid-modality treatment integrates endovascular intervention (including catheter angiography) with microsurgical operations in one operating room, which could effectively shorten the DTO time of emergency patients. Hybrid-modality treatment had been proven to be feasible in the emergency disposal of severe trauma (brain trauma included), complex thoracoabdominal aortic pathology (125–127). Under a definitive diagnosis, emergency evacuations of hematoma and control of acute bleeding is warranted in the event of life-threatening mass effect, regardless of whether it is associated with the bAVM. Superficial bAVMs in small size (≤3 cm) can be resected simultaneously in an emergency operation. Meanwhile, bAVMs in deep locations or with large sizes are recommended to be resected *via* semi-elective microsurgical operations.

Recommendations

- The semi-elective operation is reasonable for patients with any of the prior hemorrhagic presentations, progressive neurological deficits, or AEDs-resistant epilepsy (*Class IIa, Level of Evidence B*). A semi-elective operation is reasonable for bAVMs with angioarchitectural features, which imply high rupture risks (*Class IIa, Level of Evidence B*). Elective operation is probably recommended for patients without any features above (*Class IIa, Level of Evidence B*).
- In an emergency operation, the evacuation of hematoma and control of acute bleeding can be beneficial to the event of life-threatening mass effect, regardless of whether it is associated with the bAVM (*Class IIa, Level of Evidence B*). Simultaneous resection of superficial bAVMs in small size (≤3 cm) in the emergency operation is reasonable (*Class IIa, Level of Evidence C*). The semi-elective microsurgical operation is probably recommended for the deep located or large-sized bAVMs (*Class IIa; Level of Evidence C*).
- Hybrid-modality treatment is probably recommended for the diagnosis and subsequent treatment of every emergency intracranial hemorrhage (*Class IIa; Level of Evidence C*).

Strategy of Microsurgery

Single Microsurgery

The single microsurgical resection of eloquent bAVMs shares the same procedural process with the non-eloquent: (1) performing the craniotomy to expose bAVM and relevant vessels; (2) isolating and controlling the arterial feeders; (3) dissecting the nidus along edges from adjacent parenchymal and vascular structures; (4) coagulating and dissecting the draining veins; and (5) closing and suturing up the incision. In the microsurgery of eloquent bAVMs, steps from 2 to 4 are nuanced with the general ones, because of the adjacent or overlapping relation between nidus and eloquent structures. Approaches to eloquent bAVMs in deep locations, such as the insula, basal ganglia, thalamus, and callosum, should be planned precisely to protect the surrounding eloquent cortex and subcortical parenchyma (86, 128, 129). The circumferential dissection of the nidus should be limited as well, to keep the eloquence-related structures intact. Steiger et al. (90) reported their procedure to limit the damage to parenchyma around in a small group of cases, which was proposed to coagulate from draining veins to the nidus. Other microsurgical or endovascular techniques should be considered for the protection of eloquent structures.

Microsurgery in Multimodality Treatments

Multimodality treatments refer to the performing of different elementary surgical therapies in a single stage or multiple ones. In staged-multimodality treatments, the microsurgical resection is commonly performed as a conclusive treatment, or as an initial treatment in a few cases as well (see section **Detection** and **Treatment of Residue**). As a conclusive treatment, the microsurgical resection is utilized as a salvage treatment to residual bAVMs, that has not been completely obliterated by other treatments (78, 130). Meanwhile, the microsurgical resection can be performed systematically in some bAVMs, which have been down-graded by endovascular embolization or/and SRS from higher grades (76, 131–133). Studies on staged-multimodality treatments suggested that the prior endovascular or/and radiosurgical treatments could improve the microsurgical condition with lower risks and difficulties. However, it should be noted that the risks of prior treatments needed to be acknowledged. The most commonly utilized paradigms are microsurgical resection combining with prior endovascular embolization. The prior embolization is supposed to decrease the operative risks of subsequent microsurgery in the following aspects: (1) aiding the elimination of feeders from deep sites of the operative field (for example, perforating arteries and branches of posterior cerebral arteries), and (2) making the nidus dissection easier with clearer borders, which is important to diffusive nidus adjacent to eloquence (79, 133, 134). Besides, it has been proposed for neurological protection. Han et al. (91) and Wang et al. (84) reported their experience of applying the staged or hybrid paradigms to protect the neurological function of bAVMs in brainstem and eloquence, respectively. In their procedures, the nidus adjacent to eloquence had been embolized through the prior endovascular manipulations. The subsequent microsurgery only removed the nidus distal to the eloquence, while leaving the embolized nidus *in-situ*. Another paradigm of microsurgical resection combining with prior SRS was reported in a few cases. The prior SRS decreases the risk of microsurgery as well, by a different pathological process from endovascular embolization (76, 135). It usually requires probation of 3–5 years to evaluate the effect of the prior SRS before microsurgery (136, 137). However, the risks of prior treatment would not be diminished by the cooperation of multimodality treatments. Prior embolization and SRS were reported to share a similar rate of adverse events, morbidity, and mortality with their independent implementations (76, 79, 82, 132, 138). Most of the suboptimal events occur in the process of endovascular procedures, or the latency period before microsurgery.

Hybrid-modality treatment is the up-to-date paradigm, which combines endovascular and microsurgical procedures in a single stage without any interval (81, 139). It has been proved to be feasible in treating bAVMs, especially the eloquent ones (80, 84). The hybrid-modality treatment possessed the advantages of endovascular and microsurgical manipulations, and expanded the operative techniques. Wang et al. (140) reported their intraoperative transvenous embolization technique to patients with difficult arterial and venous approaches. Most importantly, latent risks in the intervals of staged treatments were fundamentally diminished in the hybrid-modality treatment. Brown et al. (141) reported their experience in 19 patients who received hybrid-modality treatment, in which neurological outcomes were similar with staged multimodality treatment without the occurrence of intracranial hemorrhage after embolization or microsurgery. Hybrid-modality treatment may be a safer method of curing eloquent bAVMs radically and effectively, but need to be further validated.

Recommendations

- Multimodality treatments with microsurgery involved are probably recommended for the treatment of eloquent bAVMs in high grades. Downgrading the lesion before microsurgery can be useful to decrease operative risks and protect neurological functions (*Class IIa; Level of Evidence B*).
- The staged multimodality treatment of the microsurgery subsequent to endovascular embolization can be useful for treating bAVMs with diffusive nidus or feeders from deep sites of the operation field, which may reduce the risks of intraoperative bleeding and neurological deficits of the subsequent microsurgery (*Class IIa; Level of Evidence B*).
- Hybrid-modality treatment is probably recommended with similar safety and efficiency to the staged multimodality treatment, but with fewer risks than the latter (*Class IIa; Level of Evidence C*).

Detection and Treatment of Residue

Although microsurgical resection has achieved the highest complete obliteration rate among treatments, residual nidus can still be detected in follow-up angiographies. The cumulative incidence of residuals and recurrences had been reported to be 3% for SM grade I-II and 8% for SM grade III or higher (142, 143). The cause of residue is induced by the absence of adjunctive tools for an angiogram or bAVM detection. Most residues can be quickly detected through intraoperative DSA (80, 139, 144). Meanwhile, omissions might occur in intraoperative DSA. Aboukais et al. (145) reported that intraoperative or early postoperative angiography did not ensure the cure of bAVMs in several pediatric cases. Residues may be caused by vasospasm or recanalization of abnormal vessels. Delayed angiographies, *via* DSA, CTA, or MRA, were suggested in follow-ups, especially to pediatric patients (see section **Follow-Up**). It should be noticed that residual dysplastic vessels after cerebral arteriovenous malformation resection might be confounded with residual nidus (146). Residual dysplastic feeding vessels without an early draining vein do not necessarily represent residue after resection.

Intraoperative Doppler ultrasound can be used to detect the residual nidus. Four parameters could be obtained, including peak systolic velocity (PSV), end-diastolic velocity (EDV), mean flow velocity (MV), and resistance index (RI). RI (defined as the ratio of PSV to EDV) is regarded as the key parameter to identify the residual nidus. It has been generally accepted that RI is between 0.55 and 0.75 for the normal internal carotid artery, and higher in branches downstream (147). Arterial vessels with an RI lower than 0.55 should be noticed. Griffith et al. (148) reported their RI range of arterial feeders to be 0.14–0.50. With the enhancement of contrast, ultrasonographic angiography is able to help identify arterial feeders both on the surface and deep in the tissue (149, 150). Doppler ultrasonography cannot replace the intra/post-operative DSA. Regions of low-velocity blood flow or areas with very small vessels (i.e., much smaller than 0.6 mm in diameter) might be missed by ultrasonography. Hence, abnormalities such as venous angiomas on cryptic AVMs with low-velocity blood flow or thrombosed vessels may not be discernible in sonography. So the intraoperative ultrasound findings should be confirmed by angiography (147).

Patients with residual and recurrent nidus after microsurgery are still exposed to the threats of hemorrhage throughout their lives (135, 151). Only a few case-reports demonstrated the spontaneous thrombosis occurring in residual nidus (152, 153). The expectant or conservative treatment of residual bAVMs has not been widely accepted by neurovascular surgeons (152). The residue of bAVMs is usually disposed of through microsurgery, endovascular embolization, and SRS. A salvage microsurgical resection could be performed in one session with the assistance of intraoperative DSA (144, 154, 155), or another operation (146). Neurological risks of salvage microsurgery should be considered. SRS and endovascular embolization were proposed to be utilized for the salvage treatment of residues adjacent to eloquence or in a deep location (128, 156–158). Indications of endovascular embolization and SRS should be obeyed, respectively.

Recommendations

- Intraoperative or early postoperative DSA is recommended for detecting residual nidus (*Class I; Level of Evidence B*).
- Intraoperative Doppler ultrasonography is useful to primarily detect the residual nidus (*Class I; Level of Evidence B*). The complete obliteration should still be confirmed by a subsequent DSA.
- Repeat angiographies in follow-ups within 3–5 years after surgical resection is reasonable for detecting missed residues or recurrence (see section **Follow-Up**) (*Class IIa; Level of Evidence B*).
- Residual nidus after microsurgery is still exposed to the risk of hemorrhage. Salvage surgical treatments are recommended for the disposition of residues, including microsurgery, endovascular embolization, and SRS (*Class I; Level of Evidence B*). Subsequent SRS and endovascular embolization can be effective in achieving complete obliterations in residues adjacent to eloquence, following their indications, respectively (*Class IIa; Level of Evidence C*).

Surgical Adjuncts

Surgical adjuncts are indispensable for intraoperative localization and mapping of eloquent (sub-)cortical structures, including neuro-navigation, electrical cortical stimulation with awake craniotomy, and transcranial magnetic stimulation.

Most neuro-navigations are utilized based on structural and functional MRI. Data reconstructions should demonstrate the 3-dimensional information of brain, lesion, and eloquent structures. Despite providing a wealth of information, neuro-navigation was suggested to be ineffective in improving the neurological outcomes of microsurgeries in a randomized controlled trial (159). This was attributed to the different resecting strategies of bAVMs and brain tumors. The resections of a tumor could be stopped when reaching the edge of eloquence. By contrast, the resection of bAVMs cannot be stopped until completely removing the nidus. The alert of neuro-navigation hardly affects the damage to eloquence. However, neuro-navigation is not useless in the microsurgery of bAVMs. Torne et al. (160) reviewed the bAVMs surgically treated by Michael Lawton and emphasized the importance of identifying the location and border of the nidus, which could reduce the rupture risk during operation and improve clinical outcomes. Although neuro-navigation was proved to be ineffective in improving neurological outcomes, it was helpful to reduce operative risks by clearly demonstrating the localization and borders (88, 161–163). Intraoperative three-dimensional (3D) ultrasound was usually used as an assistance to the neuro-navigation to correct the brain-shift induced by craniotomy (164–168).

Intraoperative direct electrical stimulation (DES) on the cortex is regarded as the gold standard of eloquent mapping (169). It allows a safe real-time identification and hence preservation of essential pathways for motricity, sensibility, language, and even memory in the treatment of brain tumor and cerebrovascular diseases under general or local anesthesia (awake craniotomy) (170–172). Currently, the mapping through DES was usually performed on basis of fMRI (173, 174). Besides the direct stimulations to the cortex, Gamble et al. (175) revealed the value of subcortical stimulation on identifying subcortical eloquent structures. Concluding the proposals of current studies, the electrical cortical/subcortical stimulation was recommended if the lesion (1) adjacent to eloquence on fMRI (not distancing nor overlaying); (2) in large sizes and high SM grades; (3) with diffusive nidus. Differences existed in the application of DES between general and local anesthesia. The DES under local anesthesia had become popular in recent years. It was capable of mapping not only essential cortico-subcortical areas of motricity, but also areas of sensitivity, language, and even memory (174, 175). It had been proved to be effective in helping identifying eloquence and preserving neural functions (171, 176). Although DES under local anesthesia could make awake patients without any pain or discomfort (177, 178), the psychological effect still needed concern. By contrast, the DES under general anesthesia was performed earlier, usually accompanying with electrocorticography (ECoG) and neurophysiological monitor. Its capability of eloquent mapping was limited to motor and somatosensory areas, in which optimal neurological outcomes could be achieved (170, 171). The ECoG, which used accompanying DES, was proved to be effective in identifying epileptogenic cortex for subsequent surgical management (179, 180). Despite its high accuracy and efficiency, DES faces a similar situation with fMRI-based neuro-navigation. Mapping of the eloquent area could take effect as an alarm to the neurosurgeon, but helpless to limit the extensive excision. Besides, DES might cause generalized seizures and result in disastrous consequences (171). The utilization of DES remains controversial and needs further investigation. The requirement of gross identifying of motricity and somatosensory area can be met by a neurophysiological monitor.

Navigated transcranial magnetic stimulation (nTMS) is applied to the preoperative mapping of cortical motor and language regions in recent years. The comparison between nTMS and DES resulted in similar accuracies (181–185). Besides, nTMS had been proved to be superior in mapping the eloquence to other non-invasive techniques, such as fMRI and magneto-encephalography (185–187). Ille et al. (188) reported their experience of utilizing nTMS to fix the mapping result of fMRI. Kronenburg et al. (189) reported the utilization of TMS to non-cooperative patients and achieved satisfactory results. Although nTMS is widely applied in brain tumors, it has seldom been used for cerebrovascular disease. The preparation and implementation of microsurgery are different between tumors and bAVMs. More studies are needed to validate its safe utilization to bAVMs, especially on seizure and hemorrhage-related complications.

Recommendations

- The utilization of fMRI-guided neuro-navigation does not improve neurological outcomes, but can be useful for locating and delineating the lesions (*Class IIa; Level of Evidence B*). Intraoperative 3D ultrasound is effective in correcting the brain-shift induced by craniotomy (*Class I; Level of Evidence B*).
- Intraoperative direct electrical stimulation (DES) is feasible on mapping motricity eloquence under general, and other sensibilities, language, and even memory eloquence under general anesthesia. DES might be considered for delineating the nidus adjunct to eloquence, or in large sizes, or with diffusive nidus. The risks and psychological impacts of DES are not well-established (*Class IIb; Level of Evidence C*).
- Neurophysiological monitor can be useful for gross mapping of motricity and somatosensory areas (*Class IIa; Level of Evidence C*).
- Electrocorticography (ECoG) is recommended for localizing epileptogenic cortex (*Class I; Level of Evidence B*).
- Navigated transcranial magnetic stimulation (nTMS) has been utilized for mapping and fixing mapping results of fMRI in the preoperative preparation, mostly in brain tumors and seldom in bAVMs. The risks of nTMS are not well-established (*Class IIb; Level of Evidence C*).

Endovascular Neurosurgery

Endovascular embolization (EE) occludes blood flow by delivering occlusive agents into the feeding arteries and nidus through microcatheters (1, 190). The role of endovascular embolization in treating bAVMs includes (1) as a therapeutic strategy; (2) as palliative or targeted strategies; and (3) as adjuvant management before microsurgical resection or SRS, to minimize the risk of hemorrhage (191, 192).

Curative Embolization

Monotherapy of curative embolization was believed to be difficult to completely eliminate bAVMs, with rates of angiographic obliteration ranging from 13 to 96% (56, 193–195). Complete cure was attainable for small-sized (≤3 cm), superficially located bAVMs (194). Angioarchitectural characteristics with a single feeding artery also achieved favorable outcomes (196). Properly applied EE might decrease the size and grade of bAVMs without sudden changes of pressure and reduce the risk of adjacent arterial recruitment (106). The overall complication rate of endovascular therapy for bAVMs was 25.0%, with an incidence of 6.6% in permanent neurological deficits (56). The number and diameter of feeding arteries, nidal volume, deep venous drainage, and eloquent location were risk factors of embolization-related complications (47, 54, 55). When disposing of bAVMs in corpus callosum with complex angioarchitectures and eloquence involved, curative embolization achieved complete obliteration in only 40–60% of cases and hemorrhage complications occurred in 7% of cases (197, 198).

Strategies of embolization have been discussed. Sahlein et al. (199) proposed that the single-stage embolization reached a lower rate of mortality and morbidity than the multi-staged embolization. It had been demonstrated that staged embolization was an independent risk factor for unfavorable outcomes after embolization (200, 201). It was supposed to attribute to the recanalization and recruitment of arterial feeders during staged procedures (199). Even so, the staged embolization had been used as a strategy to reduce the risk of normal perfusion pressure breakthrough by progressively minimizing the blood flow, particularly for medium-large bAVMs (>3 cm) (202, 203). Previous studies had supported that the interval between each session should be 4–6 months when applying the staged embolotherapy (202, 203). Ma et al. (204) reported that staged embolization was effective in treating eloquent bAVMs with large sizes. Different paradigms of staged embolization were proposed without a consensus. Ma et al. (204) reported their paradigm, which achieved an obliteration rate within 60% in the initial session, and achieved complete occlusion in 2–3 months through the following 1–2 sessions. Katsaridis et al. (202) reported another paradigm, which proposes to embolize ≤30% of nidus in each session. The optimal paradigm of endovascular embolization remains to be researched.

Recommendation

- Curative embolization of small-sized (≤3 cm), superficially located bAVMs with a single feeding artery can be useful (*Class IIa; Level of Evidence B*).
- Staged embolization can be beneficial for curing medium-large bAVMs (>3 cm) by gradually reducing the risk of NPPB, but the probability of recanalization remains (*Class IIa; Level of Evidence B*).
- The interval between each stage and extent of embolization has not been well-determined (*Class IIb; Level of Evidence C*).

Palliative Embolization

The selective embolization of high-flow feeding arteries might postpone the progression of frequent seizures or neurological deficits caused by venous hypertension and arterial steal syndrome (106). A retrospective study suggested that the partial embolization might result in complete occlusion and improve survival rates, comparing with conservative treatment in the long-term (205). Flores et al. (206) proposed to utilized the palliative embolization to symptomatic bAVMs in Spetzler-Martin grade IV or V, that are inadvisable for surgical resection or SRS. Although the palliative embolization might improve the clinical manifestation of patients by changing the hemodynamics of lesion (207, 208), it was accused of increasing the risk of hemorrhage in large bAVMs (75). The role of palliative embolization remains controversial.

Recommendation

- Palliative embolization remains controversial. The selective embolization of high-flow feeding arteries might be considered to postpone the progression of seizures or neurological deficits in surgical/SRS-inadvisable bAVMs, while potentially increasing the risk of hemorrhage (*Class IIb; Level of Evidence B*).

Targeted Embolization to "Weak Point"

Targeted embolization aims at eliminating the "weak point" of bAVMs, including intranidal or flow-related aneurysms, high-flow arteriovenous fistulas, and venous flow obstruction, and other anigoarchitectural features with high rupture risks (3, 101, 106, 209). Targeted embolization is proposed to perform when definitive managements were infeasible or excessively risky. Targeted embolization was reported to be performed to the ruptured bAVMs in the acute phase (210), and restoration stage (211). The effect of embolization in the management of ruptured bAVMs has not been well-established. The targeted embolization was supposed to reduce the incidence of bleeding after radiosurgery (106).

Recommendation

- Targeted embolization is recommended for bAVMs with a "weak point" when definitive treatments are infeasible or too risky (*Class I; Level of Evidence B*).

Pre-microsurgical Embolization

Pre-microsurgical embolization has been used as the most common adjunct to improve the therapeutic safety and efficiency of bAVMs (79, 80, 199, 212). The pre-microsurgical embolization resulted in permanent morbidity of 2.5% and a mortality of 2.0% (201, 213). The strategy was proposed to facilitate the subsequent microsurgery in the following aspects: (1) occluding the supply arteries and lowering the size of bAVMs, to minimize the risk of bleeding, (2) eliminating the deep perforators that are inaccessible for surgeries, (3) embolizing the flow-related aneurysms (56, 82, 195, 206, 214, 215).

The prior embolization before microsurgery was proposed to minimize the risk of NPPB by gradually reducing the blood flow before surgery, and normalize the hemodynamics for high-flow or large lesions (202, 216–218). Whereas, the vigilance of the potential risks (e.g., hemorrhage, infarction, or seizures) in-between the treatments should be considered as concerns (219, 220). The subsequent microsurgery could be performed consecutively after the embolization in one session, which was known as a hybrid-modality treatment (80). It made the manipulations of embolization more flexible, and overcame the disadvantages and limitations when solely performed. It had been shown that the staged paradigm increased the expenditure of treatments (200, 221). The hybrid-modality treatment might reduce the frequency and duration of anesthesia and operation by a single treatment, from a health-economics perspective. However, the optimal paradigm of preoperative embolization and subsequent microsurgery remained unclear (82). The previous series had performed a paradigm with an interval between each embolization therapy for 16–42 days, and an interval before surgery for 1–42 days (79, 212, 222, 223). Nataraj et al. (224) supported a prompt microsurgical resection after endovascular intervention for a lower rate of mortality and morbidity.

Recommendation

- The pre-microsurgical embolization is probably recommended for the bAVMs with large size, or deep perforating feeding arteries, or inaccessible locations for surgeries, or concomitant flow-related aneurysms (*Class IIa; Level of Evidence B*).

Pre-radiosurgical Embolization

The pre-radiosurgical embolization has been proposed to decrease large bAVMs to a suitable size for the subsequent SRS. It was particularly recommended for the lesions $\geq$3 cm in diameter, or the lesions with relevant aneurysms or high-flow fistulas. A pre-radiosurgical embolization could minimize the risk of hemorrhage before the definitive obliteration by SRS, especially effective for ruptured bAVMs in the posterior fossa (1, 3, 42, 225, 226). The multimodality treatment, consisting of prior embolization and subsequent SRS, was reported to achieve a complete obliteration rate of more than 60% in large bAVMs (227, 228). The efficiency of the subsequent SRS might be improved if the volume of the residual nidus is no more than 10 cm^3 after embolization (77). The drawbacks induced by prior embolization needed to be considered. Embolic agents might shield the nidus from the radiation as protectants and make the outlines obscure with subsequent targeting inaccurately (229). Additionally, embolization might decrease the rate of obliteration by facilitating angiogenesis (230). The recanalization of embolized arteries might result in delayed recurrence (77). Due to the limitations, this paradigm might worsen the outcome of bAVMs (231–233).

Eloquent regions of basal ganglionic and thalamic AVMs could be treated with embolization in conjunction with SRS. Complete obliteration was observed in 14.3% and improved disabling in more than 1/3 of patients (234). Also, selected brainstem AVMs could be treated with embolization combined SRS, while the selection criteria had yet to be determined. Favorable outcomes were potentially comparable with general bAVMs under precision techniques (235).

Recommendation

- Pre-radiosurgical embolization may be considered for reducing the size of bAVMs, particularly for large lesions (>3 cm), or occluding bAVM-related aneurysms or high-flow fistulas, whereas the effectiveness remains uncertain (*Class IIb; Level of Evidence B*).

Seizure Control

Endovascular embolization had been reported to be less effective in controlling bAVM-induced seizures. Hyun et al. (236) investigated 399 bAVM patients with long-term follow-up after embolization, and found out that only half of the patients achieved seizure-free status after embolization, compared with 78 and 66% in the surgical and SRS groups, respectively. The duration of seizure-free status was 8.1 months in the embolization group and 20.5 months in the SRS group. A meta-analysis demonstrated that embolization resulted in the highest morbidity of new-onset seizures (39.4%), compared with other treatments (111).

Recommendation

- Embolization is not indicated for seizure control (*Class III; Level of Evidence A*).

Embolic Agents

Varieties of embolic agents are available in the endovascular treatment of bAVMs, consisting of adhesive, non-adhesive, and solid ones.

The adhesive embolic agents include N-butyl 2-cyanoacrylate (NBCA) and NBCA metacryloxysulfolane (NBCA-MS). Both NBCA and NBCA-MS have been proved to be efficient and safe in treating bAVMs with sophisticated endovascular skills (237–239). Compared with NBCA, the main advantage of NBCA-MS has a longer polymerization time (NBCA vs. NBCA-MS = 15–40 s vs. 60–90 s), which provides a sufficient and precious time window for its diffusion in bAVMs (240).

The non-adhesive embolic agents mainly include Ethylene vinyl alcohol (EVOH) and ethylene vinyl copolymer (EVAL). Comparing with NBCA, EVOH achieved indifferent results in its safety validations (241, 242), and was proved to be higher efficiency in occluding arterial pedicles (221). The comparative study on EVAL has not been widely conducted. Although the non-adhesive ones have better performance in endovascular embolization, both EVOH and EVAL have to be used accompany with dimethyl sulfoxide (DMSO), the latter of which might induce a series of side effects due to its vascular toxicity (243).

The success in embolization relies on the appropriate choice of embolic agent. the polymerization speed of NBCA could be reduced by adding lipiodol. NBCA is usually used in a concentration of 16–50%. Higher concentration results in higher polymerization speed. Commercially available EVOH is premixed in different concentrations, including 6 and 8%. Higher concentration results in higher polymerization speed. Choo et al. (244) reported their experience of using EVOH and NBCA in high concentration and coil to an embolize dural arteriovenous fistula. EVOH embolization was proved superior to NBCA and coil embolization in completely obliterating DAVFs.

Recommendation

- Non-adhesive embolic agents are probably recommended to the adhesive ones for the complete embolization of bAVMs (*Class IIa, Level of Evidence C*).
- For bAVMs with high flow capacity, a non-adhesive embolic agent in high concentration is probably recommended (*Class IIa, Level of Evidence C*).

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) has been widely accepted as an effective treatment for patients with small bAVMs, especially for those with deep location or eloquence involved (44, 245, 246). SRS leads to proliferation of endothelial cells, progressive, concentric vessel wall thickening over years, and eventually endoluminal occlusion of the bAVM nidus (247). Obliteration of the bAVM is the goal for SRS. The disadvantage of SRS compared with microsurgery or embolization was the latency interval between treatment and obliteration, which differs from 6 months to several years (135, 248). Patients were remained at the risk of hemorrhage and delayed presentation of procedural complications during the latency interval. The annual risk of post-SRS hemorrhage was reported as 1.1% (249). Actuarial obliteration rates after SRS were related to multiple independent variables, and generally ranged from 27 to 62% within 3–10 years of treatment according to a multicenter retrospective cohort (248). The Spetzler-Martin grading scale was the most commonly used system for stratifying bAVMs, there were some grading scales used to predict SRS outcomes for bAVMs such as VRAS and RBAS (44, 46).

Small Size

Multiple studies were indicating that SRS appeared to be best suited for small volume bAVMs, which were <10 cm^3 in volume or <3 cm in its maximum diameter (44, 231, 250–252). However, most of these studies were retrospective single-centered cohorts. Graffeo et al. (253) systematically reviewed eight studies with 1,102 bAVMs involved, and proposed that SRS appeared to be a safe, effective treatment for bAVMs in Spetzler-Martin grade II and might be considered a front-line treatment, particularly for lesions in deep or eloquent locations. A cohort study on SRS with 363 basal ganglia or thalamic bAVMs suggested its preference for the majority of basal ganglia and thalamic lesions. Another cohort study with 891 bAVMs (eloquence involved in 89.8%) in Spetzler-Martin grade III, suggested that the lesion with small sizes (maximum diameter <3 cm) had the best outcomes after single-staged SRS, even with critical structures involved (229).

Recommendation

- SRS can be effective in treating small-sized (≤3 cm) bAVMs in deep eloquent areas, including those located in the basal ganglia, thalamus, corpus callosum cerebellum, and brainstem (*Class IIa; Level of Evidence B*).

Medium and Large Size

The medium and large-sized bAVMs referred to those with a maximum diameter of 3–6 and ≥6 cm, respectively. Those lesions usually belonged to Spetzler-Martin grade III–V.

The traditional paradigm of single-session radiosurgery was not usually used for bAVMs larger than 3 cm in diameter, because of its low total obliteration rate (254). In a retrospective multi-centered study, 233 bAVMs in Spetzler-Martin grade IV (94.4%) and V (5.6%) were treated with single-session SRS (229). A limited role of single-session SRS was suggested in the management of high-grade (IV–V) bAVMs and particularly in the ruptured ones (255). The benefit of SRS for medium-size bAVMs in Spetzler-Martin grade III (i.e., 3 cm < those < 6 cm in maximum diameter) was also less evident.

Meanwhile, the bAVMs in Spetzler-Martin grade IV–V were usually with larger volume, more complex angioarchitectures, and frequently located in critical locations. There was no consensus on the optimal management of these high-grade bAVMs, SRS was proposed to be one of the treatments that could be utilized (72, 255). Staged SRS was optional for large bAVMs, but usually utilized in multimodality treatments with mixed results (76). The therapeutic paradigm could be staged by the dosage of radiation and volume of the lesion. A dose-staged SRS treated the entire volume with a repeated low-dosage SRS; and the volume-staged SRS provided a sufficient therapeutic dosage to the targeted volumes as a part of the lesion (256). A systematic review suggested that the volume-staged SRS could achieve a higher obliteration rate and similar complication rate compared with the dose-staged one in the treatment of bAVMs in large volume (>10 cm^3) (257).

Recommendation

- Single-session SRS is not recommended for patients with large-sized (>3 cm) bAVMs, especially for those which are ruptured (*Class III; Level of Evidence B*).
- Staged SRS might be considered for treating large bAVMs, however, the effectiveness of staged SRS is unclear (*Class IIb; Level of Evidence C*).
- Volume-staged SRS is probably recommended in preference to the dose-staged treatment (*Class IIa; Level of Evidence B*).

SRS After Endovascular Embolization

It had been reported that the prior embolization of bAVMs would lower the obliteration rates of SRS (231, 249, 255). The prior embolization was proposed to promote the angiogenesis of bAVMs, which might increase the radio-resistance of the lesion and decrease its obliteration rate (258). However, the multimodality treatment of SRS plus prior embolization had been proposed to benefit outcomes for high-grade bAVMs (259). The timing of SRS after embolization had not been determined, which could range from days to years (3 months in median) (225, 260). Referring to the stereotactic radiosurgery guideline for bAVMs, several weeks of latency after the prior embolization was considered beneficial to reduce the risk of post-radiosurgical complications (261).

Recommendation

- The SRS subsequently to endovascular embolization can be generally beneficial to high-grade bAVMs, though the obliteration rates are lower in embolized lesions (*Class IIa; Level of Evidence C*).

Associated Aneurysm

The presence of an untreated bAVM-associated aneurysm was proposed to be a strong predictor for post-SRS hemorrhage (229, 262). AVM-associated aneurysms should be obliterated *via* microsurgery or endovascular surgery to reduce the hemorrhage risk during the latency interval (248).

Recommendation

- It is recommended to treat bAVM-associated aneurysms before SRS to reduce the risk of post-SRS hemorrhage (*Class I; Level of Evidence B*).

Multimodality Treatment

Multimodality treatments of bAVMs included different combinations of mono-therapeutic elements, such as microsurgery, endovascular embolization, and SRS. Varieties of multimodality modes had been developed to reduce the postoperative morbidity and mortality of bAVMs. Most of them were utilized for the treatment of high-grade bAVMs, which were difficult to cure by any monotherapy, or to exceed the indications of it (76, 78, 83, 158, 263). It could be applied to bAVMs in low grades as well, for the specific purpose of protecting neurological functions and decreasing intraoperative risks (84, 132, 133). However, no extra benefit had been observed in the low-grade lesions (131). The therapeutic modes and strategies of multimodality treatments have been interpreted in relevant sections above.

Recommendation

- Multimodality treatments are reasonable for the treatment of high-grade bAVMs, which are difficult to cure by any monotherapy, or to exceed the indications of it (*Class IIa; Level of Evidence C*).

Conservative Treatment

Current conservative treatments cannot promote the obliteration of bAVMs, however, they were preferred reluctantly under a few certain conditions, especially for those located in critical locations. In a prospective study with 48 deep located bAVMs (in basal ganglia, thalamus, insula, etc.) the outcomes of 12-year follow-up indicated that conservative treatments resulted in better prognosis in unruptured bilateral thalamic bAVMs of Spetzler-Martin grade V (86). Another research by Potts et al. (223) also supported the conservative treatment to the unruptured thalamic bAVMs. For asymptomatic large (>6 cm) brain stem AVMs, Thines et al. (264) suggested that the surgical intervention would increase the risk of neurological deterioration by 16-fold at final follow-ups. Spetzler and Martin (51) supposed that the large diffusive bAVMs dispersing through critical areas were inappropriate for microsurgery alone.

Conservative treatments were proposed to be optimal in the management of unruptured eloquent bAVMs. ARUBA trial was the first randomized controlled trial focusing on these issues. Two-hundred and twenty-six adult patients (18 years or older) were recruited during 2007–2013 and randomly allocated to medical management alone ($n = 110$) or interventional therapy ($n = 116$) including resection, embolization, SRS, and multimodal approaches (97). The published results of ARUBA suggested that medical management resulted in lower risks of stroke or death in the 33 months of follow-up than interventional management (10.1 vs. 30.7%) in the patients with mRS ≤ 1, or bAVMs lower than Spetzler-Martin Grade IV (62% of ARUBA cases were in grade ≤ II), or bAVM sized <60 mm (62% of lesions in ARUBA sized <30 mm). It was halted because the interim results showed the superiority of the medical management group. It seemed that the conclusion of ARUBA strongly supported the conservative management to eloquent bAVMs, however, it was argued for its limitations. ARUBA trial was criticized for its low enrollment rate, insufficient sample size and follow-ups, high interventional hemorrhage rate, and lack of treatment stratification (265, 266). The study initially estimated that 800 patients would be selected based on statistical analysis. Due to the difficulty of enrollment, 223 cases were included in the analysis which affected the statistical results. The insufficient duration of follow-up might also omit the hemorrhagic risks in long term and over-amplified the short-term complications of the interventions (267). Studies of ARUBA-eligible patients had reported more favorable results and substantially less morbidity, compared to the outcomes of ARUBA (268–270). In the retrospective study of 142 ARUBA-eligible patients treated with embolization, surgery, and/or proton beam radiosurgery during 5 years of follow-up, the risk of stroke, death, and progressive symptoms are less in the intervention group. For those younger patients, conservative management may be inappropriate due to the high accumulative risk of hemorrhage, considering that the annual risk of hemorrhage may be as low as 1% or as high as 33%.

Anti-epilepsy drugs (AEDs) are the essential management for patients with bAVM-related epilepsies. Monotherapy of AEDs was taken by 57% of bAVM patients with epilepsy presentation. However, Josephson et al. (110) reported that AEDs had limited effect on reducing the seizure risk in patients with ruptured temporal bAVMs. If anticonvulsant therapy failed to control seizures, surgical management might be pursued (271).

No specific medicine has been applied for the treatment of bAVMs. Therapeutic strategies like anti-angiogenesis drugs, immunomodulatory drugs, and anti-inflammatory drugs which aim at preventing hemorrhage are still in the experimental stage (272). Headache occurred in ∼5–14% of patients with bAVMs, and it could be unilateral or bilateral concurrent with migrainous features. No validated therapy has been applied to release the headache (273, 274).

Recommendations

- Conservative managements are reasonable for large-sized (>6 cm) unraptured bAVMs of adult patients concurrent with one of the following conditions: (1) bilateral thalamic bAVMs with deep venous drainage that are deemed inoperable, (2) asymptomatic patients with unruptured bAVMs involving brain stem parenchyma, or (3) diffusive bAVMs dispersed through eloquent areas (*Class IIa; Level of Evidence C*).
- The effectiveness of conservative management on ARUBA-eligible patients is uncertain, due to the limitations and disputed conclusions of the ARUBA trial (*Class IIb; Level of Evidence B*).
- The monotherapy of AEDs can be useful to control the bAVM-related epileptic seizure diagnosed by an electroencephalograph (*Class IIa; Level of Evidence C*). The usefulness of prophylactic use of AEDs is uncertain (*Class IIb; Level of Evidence C*).

Follow-Up

Both neurological and neuroimaging evaluations should be involved in the follow-up of eloquent bAVMs.

Neurological evaluations should be subjectively and objectively conducted. Subjective neurological evaluations, such as the most commonly used modified Rankin Scale (mRS), Glasgow Outcome Scale (GOS), and Karnofsky Performance Scale (KPS), could reflect the QoL of patients. Meanwhile, Objective evaluations were necessary for directing subsequent treatments or rehabilitations, and for outcome assessment. Neurological physical examination (PE) should be performed in the face-to-face follow-ups. Different neurological functions should be specifically noticed for the lesions in different localizations, such as cognitive and orientating functions for frontal lesions, linguistic functions for left perisylvian fissure lesions, the visual field for occipital lesions, fine and gross motor functions for precentral gyrus and supplementary motor area, and coordinating and fine motor functions for cerebellar lesions. Results of neurological PE should be described in detail in medical records for dynamic evaluations. A reasonably accurate NIHSS could be reconstructed from a well-documented medical record for trial-usage (275).

Feasible neuroimaging evaluations include digital subtraction angiography (DSA), computed tomographic angiography (CTA), and magnetic resonance image (MRI) related scans (276–278). Neuroimaging evaluations were supposed to play critical roles in the detection of bAVMs, including their residue and recurrence (279). However, the optimal frequency and modality have not been well-defined.

The follow-up to untreated bAVMs aims at predicting their hemorrhagic risks by discovering risk factors. The frequency of follow-up for untreated bAVMs verifies with relevant factors, but had not been defined yet. Brain AVMs with the following features had higher (re-)hemorrhagic risks than the others: (1) primary hemorrhagic presentation, (2) in deep locations, such as insular, thalamus, basal ganglia, corpus callosum, brain stem, or cerebellum; or (3) exclusive deep venous drainage (95, 99, 103). The early identification of these features might influence the therapeutic strategy and prevent the potential hemorrhage. However, the impacts of gender, age, and nidal size remain controversial. In the bAVMs with a hemorrhagic presentation, the re-hemorrhagic risk changes along with time. Yamada et al. (99) proposed to perform follow-up every 3 or 6 months in their study and report the changes of risks. In the first year after the initial hemorrhage, the annual hemorrhagic risk was reported to be 15.42% for a subsequent hemorrhage. In the subsequent 4 years, the annual risk decreased to 5.32%. After more than 5 years, the annual risk further decreased to 1.72% per year. Meanwhile, the hemorrhagic risks remained unchanged at lower rates. The variation of (re-)hemorrhagic risks indicates different frequencies of follow-up. For the bAVMs without any hemorrhagic presentation, follow-ups should be performed annually with neuroimaging evaluations. For the patients with any risk factors of (re-)hemorrhage, neuroimaging follow-ups should be performed every 6 months. For the bAVMs which have ruptured within 1 year, neuroimaging follow-up should be considered every 3 months.

The follow-up to postoperative patients aims at timely detection of the residue or recurrence, and prevention of potential intracranial hemorrhage. The etiology of recurrence is not clear yet. Several mechanisms have been proposed to explain the pathological process of recurrence. The recurrence of bAVMs was mostly reported in studies on pediatric bAVMs (280, 281), and a few adult cases (138). The earliest recurrence of bAVMs had been detected in 3 months after the operation (282), and the latest in 17 years (276). Studies suggested DSA be more sensitive in detecting residue and recurrences (278). DSA was recommended at 1, 3, 5 years after treatment and every 5 years thereafter (283). By contrast, MRI might miss subtle bAVMs (277). MRI had been demonstrated to have 100% specificity, 80% sensitivity, and 91% negative predictive value for the identification of obliteration compared with angiography (284). Therefore, MRI was commonly used in the preliminary screening of recurrence followed by DSA performed on suggestive cases (281, 285–287), or in the patients who refused to receive DSA as an alternative. Computed tomographic angiography (CTA) is another minimally invasive method to detect postoperative recurrence or residue of bAVMs (283). The efficacy of CTA and MRA on detecting residual and recurrent bAVMs has been rarely compared. Giesel et al. (288) reported their results on 19 postoperative cases, which suggested that CTA was more sensitive in the detection of the residual bAVMs.

Functional MRI is seldom utilized in follow-up. A few descriptive studies reported the reorganization of language or motor cortex in adjacent or symmetric areas in postoperative patients (114, 289–291). However, the hypothesis of postoperative eloquent plasticity or reorganization remains controversial. The studies by Deng et al. (292, 293) revealed the existence of eloquence reorganization was before the intervention, which might weaken the meaning of fMRI follow-up. Besides, the methodological limitations of fMRI restrict the dependability of its results. The effect of fMRI in follow-up remains to be further investigated.

Recommendations

- Subjective neurological evaluations, such as mRS, GOS, and KPS, can be useful for the assessments of QoL (*Class IIa; Level of Evidence B*). Objective neurological evaluations by detailed neurological PE or NIHSS are recommended in face-to-face follow-ups, for specific evaluation of neurological outcomes (*Class I; Level of Evidence B*).
- Neuroimaging follow-ups are recommended for detecting bAVMs (residue and recurrence included) and preventing its rupture (*Class I; Level of Evidence A*).
- DSA is effective in detecting residue or recurrence and evaluating obliteration rates (*Class I; Level of Evidence B*).
- The angiographies of computed tomography and magnetic resonance can be useful as a preliminary screening method with following DSA to suggestive cases, or as an alternative to the patients refusing DSA (*Class IIa; Level of Evidence B*). It is reasonable to choose CTA over MRA in patients tolerant to X-rays (*Class IIa; Level of Evidence C*).
- For untreated bAVMs (conservative treatment included), neuroimaging follow-up is recommended annually for those without any hemorrhagic risk factors, in every 6 months for those with any (re-)hemorrhagic risk factors, and in every 3 months for those ruptured within 1 year (*Class I; Level of Evidence C*).
- For the postoperative patients, neuroimaging follow-ups should be performed as early as 3 months after treatment, and are recommended to be performed at 1, 3, 5 years after treatment and every 5 years thereafter (*Class I; Level of Evidence B*).

Rehabilitation

Knowledge of the natural history of recovery pattern and prognosis for residual disability and functioning are limited. No specific rehabilitation strategy has been proposed to recover the neural deficits induced by eloquent bAVMs or the operation on them. Similar rehabilitation services are being performed on patients with neural deficits induced by intracranial hemorrhage, ischemic stroke, and operation. Specific rehabilitation strategies remain to be studied.

Future Considerations

At present, neuroscientists have strived to investigate the comprehensive human brain network at the micro-, meso-, and macro-scale. Brain functional atlas based on resting-state magnetic resonance imaging (rs-fMRI) and task functional magnetic resonance imaging together with brain structural atlas would play a significant role in the understanding of brain functional connectivity and its dynamic behavior (294, 295). Meanwhile, with the development of the brain mapping technologies such as functional MRI, electrocorticogram (ECoG), transcranial magnetic stimulation (TMS), and positron emission tomography (PET), more brain functional areas and important brain network nodes or hubs would be recognized (296). The future brain functional protection would be developed toward the protection of more elaboratively neurological and cognitive function. Moreover, the development of technologies of brain-computer interfaces, such as the neural dust, and the study of the neural stem cells shed light on the neural rehabilitation of patients suffering from postoperative neurological deficits (297, 298).

Minimally invasive and non-invasive is proposed to be the development direction of eloquent bAVMs.

The standardized paradigms of endovascular embolization are urgent to direct clinical practice of endovascular surgeries, especially for the palliative and pre-radiosurgical embolization. Defects of endovascular material still limit the effect of embolization, including the poor controllability of the embolic agent and maneuverability of instruments, which induce a low rate of complete obliteration. The development of both endovascular materials [e.g., coils, balloons, polyvinyl alcohol particles, and n-Butyl Cyanoacrylate (n-BCA), and Onyx] and techniques (e.g., pressure cooker technique, dual-lumen balloon catheter technique) would promote its therapeutic effect to the final goal of complete cure (194, 299–301).

Optimization of radiosurgical planning is important to improve the total obliteration rate while maintaining reasonable safety. For example, A recent study proposed that in addition to keeping a minimal margin dose of 17 Gy, increasing the percentage of the bAVM volume that receives at least 20 Gy treated in two stages could improve the outcome for large-volume bAVMs (302). What is more, a novel deep learning-based method to automatically segment the bAVM volume may be helpful for radiosurgical planning (303). Further study for improving the treatment planning system of SRS is required.

The indication of surgical treatments is critically concerning, which has been simplified to ruptured and unruptured since the publishing of the ARUBA trial and its controversial results. For ruptured bAVMs, surgical treatments have never been disputed. The surgical management of ruptured bAVMs obeys the indications and contraindications proposed over the past few decades. A thorough investigation of literature ensures the applicability of recommendations in these guidelines to the ruptured bAVMs. For unruptured bAVMs, conservative treatment was proposed to result in significantly lower risks of death or stroke and better outcomes than surgical treatments (97, 304). ARUBA is the first randomized trial of unruptured bAVMs to better understand their natural history and associated treatment risks, however, it is controversial for its results. The limitations of its methodological design, trial implementation, and data interpretation were widely questioned (270, 305, 306). Studies revealed better or non-inferior results on morbidity and mortality in ARUBA-eligible patients who received microsurgical, endovascular, radiosurgical, and multimodality treatment, which is opposite to the results of ARUBA (266, 269, 307, 308). Thus, surgical treatments are feasible to unruptured bAVMs. Given the controversy, the indications of surgical management on unruptured bAVMs remain to be further clarified with future studies. Besides, the RCT study on brain AVMs is insufficient to date and urgently needed.

Although conservative treatment remains controversial, medication therapies are thought to be more promising than expectant therapy. Medication therapies take effects on pathophysiological processes of bAVMs to disturb their development, growth, and rupture (309). Three pathophysiological pathways have received the most in-depth investigations, including the overexpression of vascular endothelial growth factor (VEGF), impairment of Blood-brain barrier, and excessive activity of matrix metalloproteinases (MMPs). Bevacizumab, a humanized monoclonal anti-VEGF antibody which might decrease the hemorrhagic risk of unruptured bAVMs (310–316), and shorten the latency period of stereotactic radiosurgery (317, 318). Thalidomide and Lenalidomide, the immunomodulators acting on BBB impairments might reduce micro-hemorrhage in perinidual area (313, 319–321). Tetracyclines, the antibiotic targeting the MMPs pathway, might non-selectively to increase vascular stability by inhibit MMP-9 overexpression and decrease risks of spontaneous bleeding (322). Medications aiming at other pathways are under investigation in the early-stage as well, including MEK inhibitors engaged in KRAS mutations (323), angiotensins II receptor antagonist the regulator of BMP signaling pathway (324), and Notch inhibitors involved in its signaling pathway (325). Meanwhile, medications are considered effective on neuroprotection, including Glibenclamide, neuroglobin, and NA-1 (Tat-NR2B9c) (326–328). However, the side effects of targeted medications have to be considered (329, 330). Targeted medications for bAVM management remain to be further investigated.

AUTHOR CONTRIBUTIONS

MW, YJ, CZe, CZh, QH, WT, HQ, YY, and YC designed and conceptualized this work and participated in the literature review. MW, YJ, CZe, and CZh participated in drafting the manuscript. YC, WJ, and A-lL critically revised the specialized sections. HS, DZ, DK, SW, and JZ critically revised the manuscript in general for important intellectual content. All authors contributed to the article and approved the submitted version.

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Establishment of Carotid Artery Dissection and MRI Findings in a Swine Model

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Carotid artery dissection (CAD) is the leading cause of ischemic stroke in young patients; however, the etiology and pathophysiology of CAD remain largely unknown. In our study, two types of dissections (length × width: 1.5 cm × 1/3 circumference of intima, Group I, $n = 6$; or 1.5 cm × 2/3 circumference of intima, Group II, $n = 6$) were created between the media and intima. Ultrasound (within 2 h after dissection) showed a dissociated intima in the lumen and obstructed blood flow in the surgical area. Digital subtraction angiography (DSA, 72 h after dissection), magnetic resonance imaging (MRI, 72 h after dissection), and hematoxylin–eosin (H&E, 7 days after dissection) staining confirmed stenosis (33.67 ± 5.66%) in Group I and total occlusion in Group II. In 10 out of 12 swine, the CAD model was established using a detacher and balloon dilation, and morphological outcomes (stenosis or occlusion) after CAD were determined by the size of intimal incision.

Keywords: dissection, carotid artery, ischemic stroke, animal model, swine

INTRODUCTION

Cervical artery dissection (CeAD) accounts for 1–2% of all ischemic strokes and accounts for 10%−25% of youth ischemic strokes (<45 years of age) without traditional vascular risk factors (1–3). Depending on the affected vessel, CeAD is divided into carotid artery dissection (CAD) or vertebral artery dissection (VAD) (4). CAD accounts for majority of CeAD, which usually occurs spontaneously or secondary to trauma (5). Cerebral ischemia related to dissection is thought to be usually embolic, from the intra-luminal thrombi forming at the site of the intimal tear (6, 7). Regular treatments after artery dissection include anticoagulation, antiplatelet therapy, angioplasty with or without stenting, or conservative observation without specific medical therapy (5, 8, 9). Due to the dearth of successful animal models, there remains a paucity of information on the pathogenesis of CeAD. Moreover, the prophylactic strategy for CAD patients, who are at risk for ischemic stroke, is largely guided by empirical studies (10–12). Therefore, the purpose of this study is to produce a suitable animal model of CAD using the common carotid artery. Morphological changes of CAD in acute or subacute periods were assessed by ultrasound, digital subtraction angiography (DSA), magnetic resonance imaging (MRI), and hematoxylin–eosin (H&E) staining. Establishing a successful animal model will aid future studies focused on the development of prognostic information and suitable treatments for CeAD.

MATERIALS AND METHODS

Animals

Twelve male Bama mini pigs (Guilin, China), with an average weight of 30–35 kg, were provided by the Laboratory Animal Center of the Third Military Medical University. The study was performed using a protocol approved by the Institutional Animal Care and Use Committee of the Third Military Medical University.

Methods

The swine were anesthetized with an intramuscular or subcutaneous injection of ketamine hydrochloride (33 mg/kg) (Sigma-Aldrich, St. Louis, MO, USA). Once the animal was immobilized by anesthesia, it was transferred to the preparation area. Then, surgical sites were shaved, and the swine was moved from the preparation area to the surgical site. After tracheal intubation, 1–2% isoflurane and 0.5–1.5 L/min oxygen were given by a mechanically ventilated closed-loop anesthesia machine. All the surgical procedures were performed under sterile conditions with the aid of a surgical microscope. Unfractionated heparin (UFH, 100 IU/kg) (Sigma-Aldrich, St. Louis, MO, USA) was administrated intravenously for systemic anticoagulation.

With the swine fixed in the supine position, a 10-cm longitudinal paramedian skin incision was made in the right anterior aspect of the neck, adjacent to the sternocleidomastoid muscle, and then the right common carotid artery (RCCA) was isolated. After vascular clamps were placed distally and proximally, approximately one-third or two-third the circumference of the adventitia and media was cut transversely, limited to the adventitia and media layers (**Figure 1A**). The media was then dissected from the intima with the help of detachers (**Figure 1B**). After a 0.5-cm length × 0.5-mm width dissection was made between the two layers, a wrapped balloon was inserted into the space between the media and intima (**Figure 1C**). Subsequently, detachers and balloon dilation were alternatingly used to mechanically separate the cavity to 1.5-cm length × 1/3 circumference (Group I, $n = 6$) or 1.5-cm length × 2/3 circumference (Group II, $n = 6$) of intima width (**Figure 1C**). Then, a continuous eversion suture (8-0 Prolene) was used to close the adventitia and part of the media (**Figure 1D**). After checking that the vessel was filled and no oozing resulted from the incised segment of the adventitia, the muscle, adipose, and skin were successively closed. In addition, the swine were started on an anti-infection (cefazolin sodium, 1 g) (Sigma-Aldrich, St. Louis, MO, USA) treatment *via* intramuscular injection every 12 h for a total of 7 days. No antiplatelet or anticoagulation medication was administered before, during, or after dissections.

Immediately, following these procedures, external changes in the dissected portion were observed macroscopically. Then, carotid artery stenosis screening was assessed within 2 h post dissection by ultrasound (Philips IU22, Philips Medical Systems, Holland) concurrent with the evaluation of both the macroscopic appearance of dissection and/or of hematoma and the flow characteristics in the common carotid artery.

DSA and MRI were performed to evaluate subacute changes at 72 h post-surgery. Briefly, after general anesthesia, the right groin was prepped and draped in a sterile fashion. A 5F arterial sheath was inserted from the right femoral artery, and a 5F guiding catheter was guided to the origin of RCCA using a guide wire under X-ray fluoroscopy. Once the catheter was in place, the dye was sent through the catheter. X-ray images were taken to observe the dye movement through the dissected artery. MRI data were collected in all cases by a 3.0-T MRI scanner (Siemens, Germany) after DSA.

At 7 days post dissection, the dissected arteries or contralateral common carotid arteries were harvested and fixed in 10% formaldehyde for tissue histology. They were then stained with H&E and examined using light microscopy.

RESULTS

Of the 12 animals, 11 survived the surgery. One animal died from anesthesia during the surgery in Group I, and one animal was excluded due to a rupture of the distal intima of the common carotid artery in Group II. Ten unilateral CADs were successfully observed after recanalization.

Immediately following recanalization, all lesions showed an abrupt formation of subintimal hematoma due to the influx of blood through the intimal entry zone. Ultrasound monitoring showed the intima floating in true and false artery lumens in 10 swine while no double lumens were observed in contralateral arteries (**Figure 2A**). The DSA demonstrated stenotic changes in the artery in all 10 swine except in contralateral arteries. Stenosis was marked at the site of the intimal entry zone, and the dissection occurred in the lesion near the origin of the RCCA in Group I, with an average stenosis of 33.67 ± 5.66%. No stenosis extended over a long segment, representing total occlusion in all Group II cases (**Figure 2B**). H&E staining results showed that, on the transverse cross section, the dissection cavity was microscopically presented as stenosis (Group I) or occlusion (Group II) due to thrombus formation between the intima and media (**Figure 2C**).

MRI has been used to detect intramural hematoma abnormalities through T1-weighted gradient echo (T1) and T2-weighted imaging techniques (T2). In Group I, T1 demonstrated a double lumen in RCCA; both true and false lumens presented an abnormal signal, while the intima between them showed a low signal intensity (**Figure 3A**). T2 showed the double-lumen phenomenon, a true lumen (low signal), false lumen, and intima (slightly higher signal) (**Figure 3B**). In Group II, T1 demonstrated a low signal of the tube with no high signal of blood flow, indicating an occlusion of the RCCA (**Figure 3C**). Consistently, the low-signal circulating blood flow was not observed in the T2 images (**Figure 3D**).

DISCUSSION

CeAD is increasingly commonly identified as the cause of cerebrovascular accidents, which are defined by the presence of an intramural hematoma in a cervical artery (13). CeAD

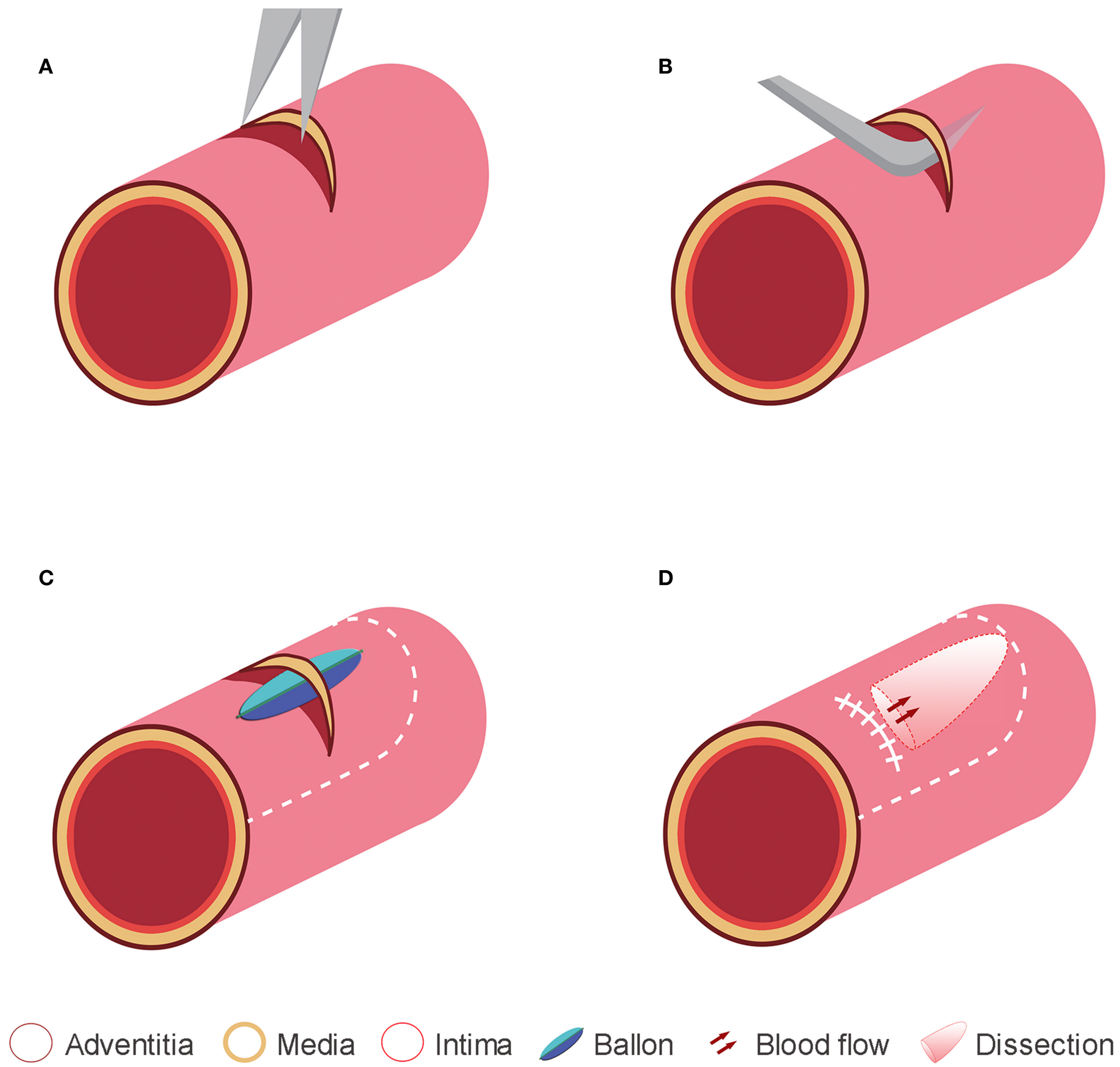

FIGURE 1 | Representative diagrams to illustrate the method used for creating the experimental dissections. **(A)** In a swine common carotid artery, a small incision was made in the adventitia and media layers under the microscope. **(B)** The intima was dissected from the media by using a detacher that was passed through the adventitia and media incisions. **(C)** The intima was also dissected from the media using balloon dilation. **(D)** The adventitia and media incisions were tightly closed, and a dissection plane was made between the intima and media layer.

may affect the internal carotid and/or the vertebral arteries in their various extracranial segments while the former is the most commonly affected vessel (2, 14). Traumas and primary disease of the arterial wall are the main predisposing factors (15), but the etiology and pathogenesis of CeAD remain unknown in the majority of cases (16).

Due to the lack of successful CeAD models, a lot of uncertainty and/or controversy remains with respect to treatment strategies. Hence, there remains an urgent need to develop a model that closely resembles CeAD in patients. Kahler et al. created a sub-adventitia intra-medial dissection plane in the arterial wall of the internal carotid artery in a New Zealand White rabbit model (17). However, arterial thrombus or narrowing was not observed at the second stage of the operation, which was inadequate for a correlation to human CeAD. Subsequently, Takeshi Okamoto et al. made an elliptical defect or longitudinal incision in the intima and media layer which caused a perforation of both layers resulting in aneurysm or stenosis in the common carotid arteries in a mongrel dog model (18). Based on this study, the size of the intimal entry zone determines the morphological changes observed after experimental CAD. However, in the clinical setting, majority of patients exhibit a subintimal dissection without perforation of the media layer. In the present study, we performed microsurgery to separate the intima and media. With the help of balloon dilation, we further expanded the space between the two layers and tightly sutured the media and adventitia which helped to keep the media layer intact.

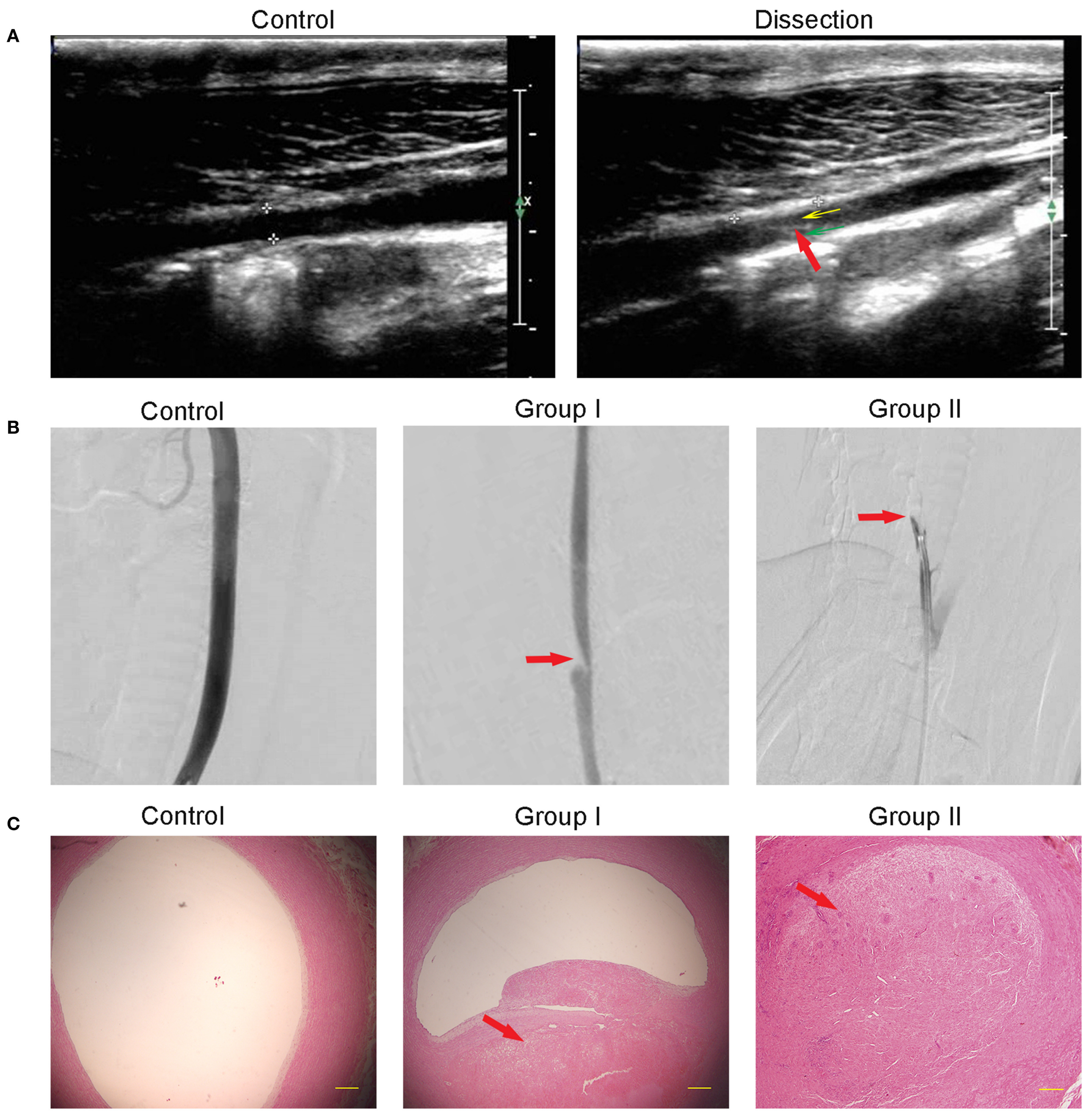

FIGURE 2 | Morphological changes after dissection. **(A)** Ultrasound showed a normal artery in the control and the false lumen (yellow arrow), true lumen (green arrow), and dissociated intima (red arrow) in the dissection. **(B)** DSA showed that the intramural hematoma formation caused arterial lumen stenosis (Group I) or occlusion (Group II). The red arrow points to the dissection location. **(C)** H&E staining showed that the subintima hematoma, which is partly organized, caused stenosis in Group I or full occlusion in Group II. Contralateral arterial lumen showed no stenosis or occlusion.

Mini pigs are widely used as biomedical models (19). Their cervical artery anatomy, size, structure, and distribution are comparable to human vasculature (20, 21). For example, the swine common carotid artery has a diameter of 4 to 5 mm, closely resembling the common carotid artery diameter of humans (22). Taken together, the swine dissection model can simulate CAD in humans.

Given the anatomical similarities between humans and swine, many of the same clinical imaging techniques can also be used in the swine model (23). Ultrasound depicted the formation of a true lumen and a false lumen and the presence of a dissociated intimal flap in both groups. DSA demonstrated irregular stenosis (Group I) or full occlusion (Group II) of the artery. MRI enabled visualization of the hyperintense mural hematoma which

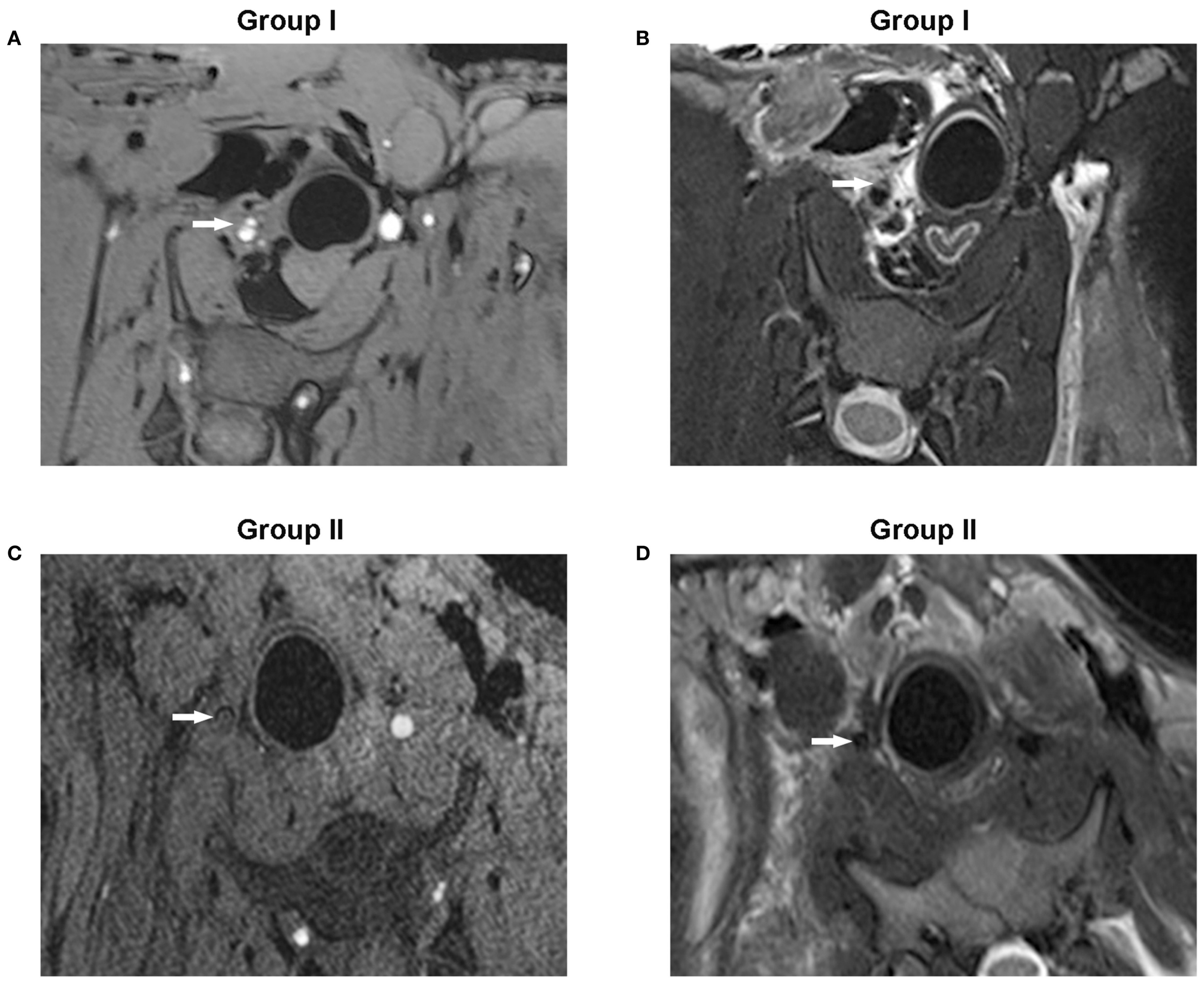

FIGURE 3 | MRI conducted with T1-weighted gradient echo or T2-weighted imaging techniques showed the coronal slices of the dissection of the RCCA. **(A)** T1-weighted gradient echo images showed hyperintense true and false lumens while the dissociated intima emitted a low signal (Group I). **(B)** T2-weighted images showed a true lumen with a low signal, but both the false lumen and dissociated intima displayed a slightly higher signal (Group I). **(C)** No high signal of circulating blood flow was observed in the arterial lumen in T1-weighted gradient echo images (Group II). **(D)** T2-weighted images showed no low signal of circulating blood flow (Group II). The white arrow points to the arterial lumen.

appeared with a "crescent" shape (Group I) or vessel occlusion (Group II). H&E staining showed lumen stenosis (Group I) or vessel occlusion (Group II). Taken together, stenosis or occlusion was determined by the size of the intimal incision, and all the pathological results confirmed the presence of dissection and thrombosis in the surgical area, confirming a successful representation model of human CAD.

However, this model has several limitations. First, in our model, there was no evidence of progression of the dissection beyond the initial surgery. In contrast, progression of the dissection and CAD manifestations such as dissection leading to aneurysm and intimal dissection flap were observed in clinical settings (24, 25). This may be explained in part by the absence of mural pathology due to the use of healthy swine with no preexisting vascular pathologies (17). Second, in the subintimal dissections, the hematoma compressed the arterial lumen, leading to a variable degree of stenosis or even occlusion (14, 25). In human subjects, thrombus formation may occur, antegrade to the site of dissection, and may result in emboli passing into the cerebral circulation, which is thought to be the major driving force of ischemic stroke pathogenesis (26, 27). However, in our model, we did not detect embolism in the brain, but we did observe morphological changes in the surgery site. Additional studies are needed to investigate cerebral perfusion and thrombus formation in the swine brain (26). Finally, our model was created by a traumatic dissection, and other models such as spontaneous dissection may be developed through biochemical or molecular methods.

In conclusion, we established a CAD model in swine. This model can be easily adapted to suit individual study designs and investigate a variety of possible interventions. This model will be a useful tool for translational research into the pathophysiology of CAD and is an ideal testing platform for novel biological approaches targeting regenerative medicine (28, 29).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The animal study was reviewed and approved by Institutional Animal Care and Use Committee of Third Military Medical University.

AUTHOR CONTRIBUTIONS

Conceptualizing and designing were performed by JP, MW, YH, WC, JD, KC, and ZZ. Drafting the article was done by NX, JP, MW, DD, QH, and NM. Approving the final version of the manuscript on behalf of all authors was done by ZZ. Critically revising the article and reviewing the submitted version of the manuscript was done by all authors.

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ORIGINAL RESEARCH
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Simultaneous Stenting for Symptomatic Tandem Extracranial and Intracranial Posterior Circulation Stenoses: Long-Term Outcomes and Procedural Experience

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Few studies have reported on simultaneous endovascular stenting for tandem posterior circulation (PC) stenoses and its long-term outcomes. Thus, our aim was to investigate the safety and efficacy of simultaneous stenting in patients with symptomatic tandem extra- and intracranial PC stenoses. From September 2014 to June 2018, 16 such patients with symptomatic stenoses who underwent simultaneous stent placement were analyzed. The primary outcome was occurrence of any stroke, TIA, or death within 30 days after the procedure. The secondary outcomes were technical success, clinical success, and the occurrence of in-stent restenosis ≥50% during follow-up. Technical success was defined as stent coverage of all tandem lesions and residual stenosis <30%. Clinical success was determined based on any occurrence of neurological events or death within 3 months after the procedure. All stents (19 intracranial and 14 extracranial) were placed with a technical success rate of 100%. One patient experienced a pontine ischemic stroke 2 days after the procedure and had recovered well at discharge. One patient experienced a minor complication of groin hematoma. The clinical success rate was 93.75% (15/16). During a median follow-up of 36.0 ± 11.0 months, two patients developed ISR ≥50% at the 1-year follow-up. None of the patients experienced stroke, TIA, or death after discharge during follow-up. Simultaneous stenting for symptomatic tandem extra- and intracranial PC stenoses is safe and feasible. Its impact on long-term stroke prevention is promising, and further study of a larger patient population is needed.

Keywords: stenting, posterior circulation, long-term, stenoses, tandem

INTRODUCTION

Posterior circulation (PC) strokes account for nearly 30% of all ischemic strokes, the main etiology of which is atherosclerotic vertebrobasilar disease (1–3). The annual risk of recurrent stroke or sudden death in patients with symptomatic vertebrobasilar stenosis may reach 10.9–25.5% despite optimal medical therapy (4–7). Patients with severe (≥70%) intracranial stenosis, especially coexisting tandem extra- and intracranial stenoses, have grimmer outcomes than those with no or mild stenosis (3, 8, 9).

To date, various randomized clinical trials have demonstrated the safety and feasibility of endovascular stenting for patients with either extra- or intracranial PC stenosis (10–12). However, there are few reports of endovascular stenting for tandem extra- and intracranial PC stenoses (13, 14). Moreover, the techniques and long-term outcomes of simultaneous stenting for tandem extra- and intracranial PC stenoses are rarely reported. Thus, this study aimed to investigate the safety and efficacy of simultaneous stenting in patients with symptomatic tandem extra- and intracranial PC stenoses.

MATERIALS AND METHODS

Study Design

This retrospective study was approved by our institutional review board, and informed consent was obtained from all the patients. A neurointerventional patient database was reviewed to identify eligible patients treated at our institution between September 2014 and June 2018. The inclusion criteria were as follows: (a) patients who experienced a PC transient ischemic attack (TIA) or were in chronic stage of PC ischemic stroke; (b) recurrent ischemic events in the territory of the stenosed artery despite optimal medical treatment; (c) occluded or hypoplastic contralateral vertebral artery and poor intracranial collaterals; (d) simultaneous stent placement in patients with severe (≥70%) tandem stenoses (≥2 lesions, but not contiguous) in the ipsilateral extracranial vertebral artery and intracranial vertebrobasilar artery (VBA); (e) modified Rankin Scale (mRS) score ≤2. We excluded patients with VBA stenosis caused by dissection, fibromuscular dysplasia, vasculitis, and all other non-atherosclerotic etiologies.

The National Institutes of Health Stroke Scale (NIHSS) score was used by a stroke neurologist to evaluate neurological deficits at admission and discharge. To assess the degree of disability and clinical outcome, the mRS score was measured for each patient at admission, 3 months after discharge, and at the last follow-up. The tandem PC stenoses and arterial anatomy were initially assessed by computed tomography angiography or magnetic resonance angiography and further validated by digital subtraction angiography (DSA). Extracranial stenosis of the vertebral artery was quantified using the NASCET angiographic measurement method (15). Stenosis of the intracranial VBA was quantified and characterized according to the WASID angiographic measurement method (16). Mori's angiographic classification (type A: short concentric, ≤5 mm, moderate to severe stenosis with a smooth contour and non-tortuous proximal anatomy; type B: longer, <10 mm, eccentric severe stenosis with an irregular contour and slightly tortuous proximal anatomy; and type C: long, >10 mm, eccentric severe stenosis with an irregular contour and highly tortuous proximal anatomy) was used to assess the intracranial lesion characteristics (17). The medical records and imaging studies were reviewed to collect data on patient demographics and clinical characteristics, technical success, clinical outcomes, complications, and survival.

Endovascular Technique

All procedures were performed under general anesthesia with endotracheal intubation. A 6F sheath was introduced into the femoral ($n = 14$) or radial ($n = 2$) artery. A 90-cm 6F guiding catheter was passed through the sheath and positioned in the subclavian artery close to the VAO. In cases of severe VAO stenosis, pre-dilation of the stenosed ostium was first performed with a 3- or 4-mm balloon catheter without an embolic protective device. The guiding catheter was then navigated into the distal second segment of the vertebral artery with or without the aid of a balloon catheter. After confirming smooth antegrade flow in the VBA, a 0.014-inch micro-guidewire was delivered to cross the stenotic intracranial VBA lesion under roadmap fluoroscopic guidance to avoid vessel damage. A balloon catheter (Gateway, Stryker, Michigan, USA) and stent delivery device (Apollo stent, Microport, Shanghai, China; Wingspan stent, Stryker, Michigan, USA) were then delivered over the micro-guidewire and navigated to the stenotic lesion. The total length of the stent should cover and extend past the lesion by ∼2 mm at both ends. The diameter should be slightly less than that of the normal adjacent lumen (0.8–0.9:1.0) in the intracranial VBA or vertebral artery lesion.

After placement of the intracranial stent, the guiding catheter was withdrawn from the subclavian artery to perform VAO stenting (Express Vascular SD stent, Boston Scientific, Massachusetts, USA). The diameter of the deployed stent was the same or slightly larger than that of the normal lumen (1–1.1:1) in the VAO lesion. After the stenting procedure, a final angiography was performed to evaluate the residual stenosis and intracranial blood flow. Repeated balloon angioplasty was performed in the same session if the residual stenosis was >30%. During the procedure, all catheters were connected to a continuous heparinized saline flush (3,000 U/500 mL).

Periprocedural Management and Follow-Up

Aspirin (100 mg/day) and clopidogrel (75 mg/day) were administered to all patients for at least 5 days before the procedure. Nimodipine was intravenously infused for 2 h before the procedure to prevent vasospasm. After the procedure, non-enhanced computed tomography was routinely performed to exclude intracranial hemorrhage. The combination of aspirin (100 mg/day) and clopidogrel (75 mg/day) was administered for at least 3 months after the procedure, followed by long-term monotherapy with either aspirin or clopidogrel according to the thromboelastogram results.

Follow-up visits with neck Doppler ultrasound were scheduled at 1 month and 3 months after the procedure and every 6 months thereafter until death. Computed tomography or magnetic resonance imaging were immediately performed in patients who developed neurological symptoms. DSA or computed tomography angiography was recommended for all patients at the 1-year follow-up after the procedure. The mRS score of each patient after the procedure was obtained at a clinic visit or telephone interview.

Outcomes and Definitions

The primary outcome was the safety of the procedure, including the occurrence of any stroke, TIA, or death within 30 days after the procedure. Stroke and TIA were defined as in previous studies and were assessed by neurologists (11, 18). The secondary outcomes were technical success, clinical success, and the occurrence of in-stent restenosis (ISR) ≥50% during follow-up. Technical success was defined as complete stent coverage of all tandem lesions and residual stenosis <30%. Clinical success was determined based on the occurrence of any neurological events or death within 3 months after the procedure. Periprocedural complications were defined as all-cause morbidity and mortality within 30 days after the procedure. Major complications included stroke and death.

Statistical Analysis

Continuous data are expressed as mean ± SD, whereas categorical data are reported as numbers and percentages. Comparisons between pre- and post-procedure variables were performed using the Wilcoxon rank-sum test for numerical values and Fisher's exact test for categorical values. A two-sided *P*-value of ≤0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (IBM SPSS Statistics 25, Chicago, IL, USA).

RESULTS

A total of 132 patients with PC stenosis were treated at our institution between September 2014 and June 2018. During the study period, 17 patients were initially selected. One patient was excluded because of a non-atherosclerotic etiology (arterial dissection). A total of 16 patients (10 male; mean age, 66.6 ± 8.1 years) were included in the final analysis. Among them, 11 patients experienced posterior ischemic stroke and 5 patients experienced TIA. The average NIHSS score at admission was 1.3 ± 1.0 (range, 0–3). The average mRS score at admission was 0.3 ± 0.4 (range, 0–1). The details of demographic and clinical characteristics are summarized in **Table 1**.

Sixteen patients underwent 16 simultaneous stenting procedures for tandem PC stenoses with 33 stents. All stents were placed successfully and covered all the lesions without residual stenosis >30%, rendering a technical success rate of 100% (33/33) (**Figure 1**). One patient (6.3%) experienced limb weakness and dizziness (NIHSS score = 4) 2 days after basilar stent placement. On post-procedure MRI, pontine ischemic stroke was confirmed in this patient. After treatment with antiplatelet agents and intravenous hypervolemic hemodilution, this patient showed good recovery at discharge (NIHSS score = 1; mRS = 0) and at the 3-month follow-up (mRS = 0). One patient (6.3%) experienced a minor complication of groin hematoma. No neurological events or deaths were encountered in the remaining patients within 3 months after the procedure. Therefore, the clinical success rate was 93.75% (15/16). The NIHSS scores at admission and discharge were not significantly different among the 16 patients (1.3 ± 1.0 vs. 1.0 ± 0.8, respectively; $P = 0.327$).

Patients were followed for a median of 36.0 ± 11.0 months (range, 18.0–62.0 months), and two patients were lost after 18 and 22 months follow-up, respectively. At the 1-year follow-up, DSA was performed in 10 patients (**Figure 1**). ISR ≥50% was confirmed in two patients (12.5%, 2/16; ISR sites, VAO and BA, respectively) and both were asymptomatic; therefore, no intervention was needed. None of the patients experienced stroke, TIA, or death during follow-up after discharge. No significant changes were found in the mRS scores [at admission vs. 3-month follow-up, 0.3 ± 0.1 vs. 0.3 ± 0.1 [$P = 1.000$]; at admission vs. last follow-up, 0.3 + 0.1 vs. 0.2 ± 0.1 [$P = 0.681$]].

TABLE 1 | Demographics and clinical characteristics of the 16 patients.

Variables	Number (%)
Age, y	66.6 ± 8.1
Male	10 (62.5)
Risk factors	
Hypertension	11 (68.8)
Hyperlipidemia	8 (50.0)
Diabetes mellitus	7 (43.7)
Smoking	7 (43.7)
Qualifying events	
Ischemic stroke	11 (68.8)
TIA	5 (31.2)
NIHSS score at admission	1.3 ± 1.0
0	5 (31.3)
1	2 (12.5)
2	8 (50.0)
3	1 (6.25)
mRS score at admission	0.3 ± 0.4
0	12 (75.0)
1	4 (25.0)
Contralateral VA condition	
Occluded	7 (43.7)
Hypoplastic	9 (56.3)
Tandem stenotic sites	
Ipsilateral VAO + V4	8 (50.0)
Ipsilateral VAO + BA	5 (31.3)
V4 + BA	2 (12.5)
Ipsilateral VAO + V4 + BA	1 (6.3)
Mori type of the intracranial lesions	
Mori A	12 (63.2)
Mori B	5 (26.3)
Mori C	2 (10.5)
Stent type for intracranial lesions	
Apollo stent	10 (52.6)
Wingspan stent	9 (47.4)

Data are presented as mean ± standard deviation or as frequency (percentage).
TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; VA, vertebral artery; VAO, vertebral artery ostium; V4, fourth segment of vertebral artery; BA, basilar artery.

DISCUSSION

In contrast to ischemic carotid artery territory events, which have been extensively investigated due to the development of carotid endarterectomy and endovascular stenting, the PC TIA or stroke has largely been overlooked (19). Despite the best medical therapy, symptomatic atherosclerotic vertebrobasilar stenosis is associated with a high risk of recurrent stroke and sudden death

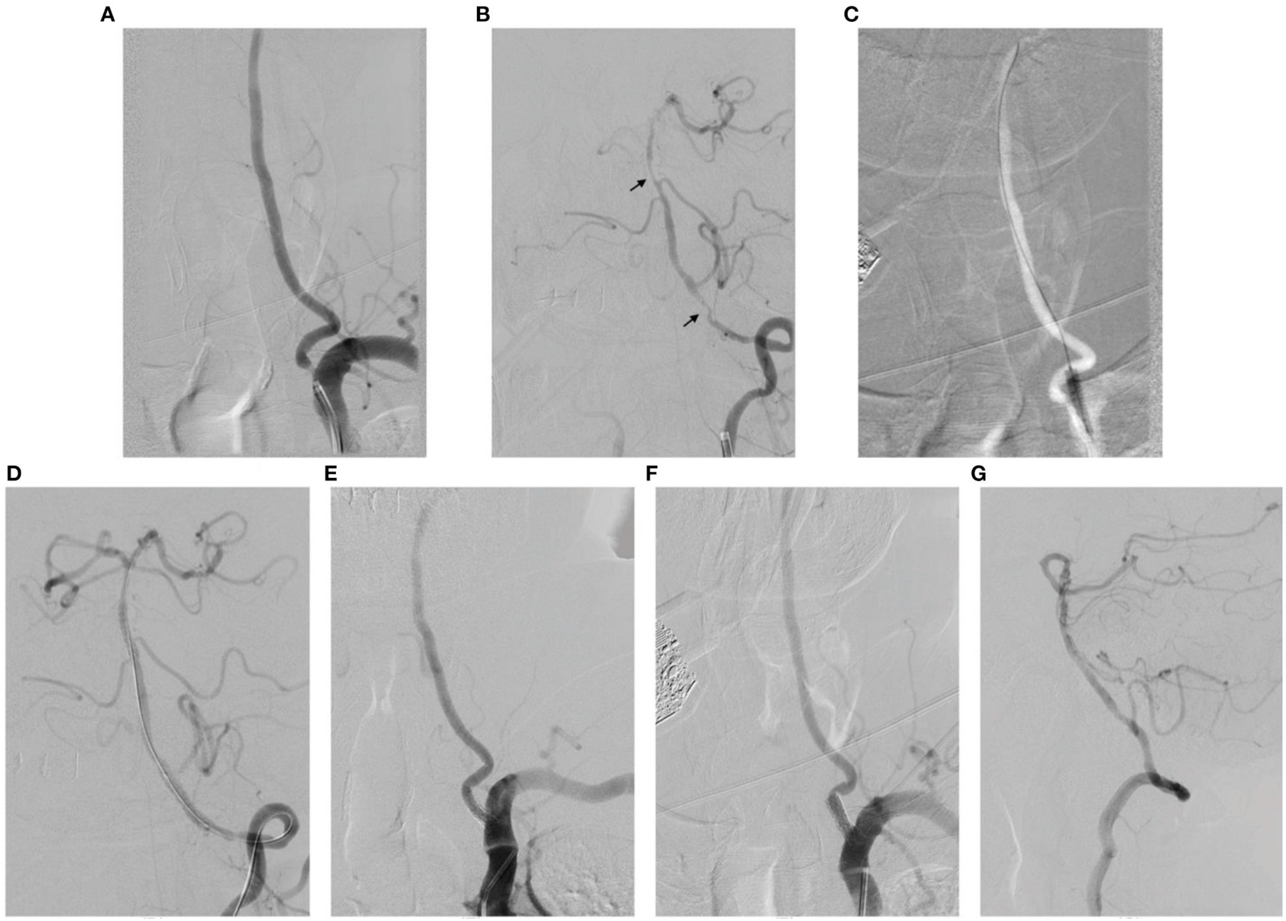

FIGURE 1 | A 76-year-old man with symptomatic tandem extra- and intracranial posterior circulation stenoses underwent simultaneous stent placement. **(A, B)** Pre-procedural digital subtraction angiography (DSA) showed severe tandem stenoses at the origin of the left vertebral artery (VA), V4 segment artery, and basilar artery (BA) (arrows) and insufficient posterior cerebral blood flow. **(C)** A 4–20-mm angioplasty balloon was used to dilate the origin of the left VA. **(D)** Stenting was performed with 2.5–13 and 3–13-mm balloon-mounted stents within the BA and V4 segment artery, respectively. **(E)** Finally, a 5–15-mm balloon-mounted stent was placed at the VA origin. **(F, G)** DSA at the 12-month follow-up of this patient showed no obvious in-stent restenosis. There was no recurrence of ischemic events during the follow-up.

(4–7). Two prospective studies—one hospital-based study in 216 patients and one population-based study in 151 patients—showed that the risk of recurrent PC stroke was 30.5% in patients with ≥50% stenosis vs. 8.9% in patients without such stenosis, and VBA stenosis ≥50% was associated with 3.2-fold higher risk of recurrent ischemic PC events within 90 days, reaching 22% for stroke and 46% for TIA and stroke (7, 20). Moreover, Wong et al. documented the long-term outcomes of 705 ischemic stroke patients, of whom 345 had large-artery lesions. The outcomes were grimmer for patients with tandem extra- and intracranial stenoses, reaching a risk of death, cerebrovascular events, or recurrent stroke within 1 year of 24.3% (8). The optimal management of tandem extra- and intracranial stenoses, however, is a matter of ongoing debate, and high-level evidence and guidelines are still lacking.

Endovascular angioplasty and stenting in the PC are now technically feasible, whereas endovascular therapies for coexisting tandem extra- and intracranial PC stenoses remain limited. Furthermore, stent placement for tandem intracranial and VAO lesions is technically more complicated than for an isolated lesion (13). Du et al. reported that technical success (complete stent coverage of the lesion and residual stenosis <30%) was achieved in nine of 10 patients who underwent stenting for tandem stenoses of the intracranial VBA and VAO. No periprocedural complications were noted, and the annual stroke rate in the VBA territory after stenting was 3.8% (13). In a retrospective study of 16 patients with 27 complex stenotic PC lesions, including 13 patients with tandem lesions, Wang et al. reported that the technical success rate (complete stent coverage of the lesion and residual stenosis <50%) was 100%, with a 12.5% major complication rate (14). Compared to the endovascular techniques of Du et al. and Wang et al., we performed pre-dilation of the stenosed ostium and then navigated the guiding catheter into the distal second segment of the vertebral artery with or without the aid of a balloon catheter (a partially inflated balloon within the VAO may act as a flexibly shaped "cushion" to help steer the guiding catheter into the vertebral artery). After successful placement of the intracranial stent, the guiding catheter was withdrawn into the subclavian artery to perform VAO stenting. In the current study, technical success was excellent (100%, 33/33) and clinical success was high (93.8%, 15/16). One potential key factor for excellent technical success in the present study could be the pre-dilation of VAO lesions and the use of a balloon catheter to advance the guiding catheter through the VAO into the vertebral artery. For patients in whom advancing the guiding catheter into the vertebral artery was difficult, we placed the guiding catheter close to the VAO and stably placed the micro-guidewire at the P2 segment of the posterior cerebral artery to facilitate intracranial stent placement. Another key factor could be the intracranial lesion characteristics. Most intracranial lesions (89.5%) in the present study were Mori type A and B, which have lower technical difficulty and procedural risk.

Angioplasty and stent placement for intracranial stenosis are associated with a higher complication rate than those with extracranial stenosis (11, 21). Markus et al. reported a 15.4% (2/13) stroke rate during intracranial stenting in the Vertebral Artery Ischemia Stenting Trial (VIST); however, no (0/48) periprocedural complications occurred with extracranial stenting (11). Seifert et al. reported a major complication rate of 11.8% (2/17) in patients with vertebrobasilar intracranial stenosis who underwent angioplasty and stent placement. Both patients had tandem lesions in the BA and vertebrobasilar junction (21). Concerning the stenting of tandem stenoses in the PC, Du et al. showed excellent results of zero strokes or deaths within 30 days (13). In this study, one (6.3%) major periprocedural complication was noted after basilar stent placement. After prompt and proper treatment, the patient recovered well after discharge.

This study had several limitations. First, this was a retrospective study; therefore, selective bias inevitably existed. Second, the single cohort study design and small sample size were not feasible to perform statistically univariate or multivariate analyses. However, we provided a median 36-month follow-up of all patients, and 10 (62.5%) underwent repeated DSA for treatment evaluation at a 1-year follow-up.

In conclusion, simultaneous stenting for symptomatic coexisting tandem extra- and intracranial PC stenoses is safe and feasible, with a 6.3% periprocedural stroke risk. Its impact on long-term stroke prevention is promising, and further study of a larger population is warranted.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

ZJ and YZ contributed equally to drafting the initial manuscript. PW, JH, XL, and SZ contributed to study design and data collection. JH and YZ contributed to manuscript revision. All authors contributed to the article and approved the submitted version.

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Surgical Clipping of Previously Coiled Recurrent Intracranial Aneurysms: A Single-Center Experience

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Objective: This study reviews our experiences in surgical clipping of previously coiled aneurysms, emphasizing on recurrence mechanism of intracranial aneurysms (IAs) and surgical techniques for different types of recurrent IAs.

Method: We performed a retrospective study on 12 patients who underwent surgical clipping of aneurysms following endovascular treatment between January 2010 and October 2020. The indications for surgery, surgical techniques, and clinical outcomes were analyzed.

Result: Twelve patients with previously coiled IAs were treated with clipping in this study, including nine females and three males. The reasons for the patients having clipping were as follows: early surgery (treatment failure in two patients, postoperative early rebleeding in one patient, and intraprocedural aneurysm rupture during embolization in one patient) and late surgery (aneurysm recurrence in five patients, SAH in one, mass effect in one, and aneurysm regrowth in one). All aneurysms were clipped directly, and coil removal was performed in four patients. One patient died (surgical mortality, 8.3%), 1 patient (8.3%) experienced permanent neurological morbidity, and the remaining 10 patients (83.4%) had good outcomes. Based on our clinical data and previous studies, we classified the recurrence mechanism of IAs into coil compaction, regrowth, coil migration, and coil loosening. Then, we elaborated the specific surgical planning and timing of surgery depending on the recurrence type of IAs.

Conclusion: Surgical clipping can be a safe and effective treatment strategy for the management of recurrent coiled IAs, with acceptable morbidity and mortality in properly selected cases. Our classification of recurrent coiled aneurysms into four types helps to assess the optimal surgical approach and the associated risks in managing them.

Keywords: coiled recurrent intracranial aneurysms, surgical clipping, recurrence mechanism, coil removal, by pass

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INTRODUCTION

After the introduction of coil embolization for intracranial aneurysms (IAs) in the 1990s, the number of IAs treated with endovascular treatment has increased significantly because of its low morbidity and minimal invasiveness. Although short-term safety of endovascular treatment is well-established, the long-term recurrence rate of IAs treated by coiling can be as high as 15–34%

(1–3). In contrast, the recurrence rate among clipped patients was about 1–3% (4–6). Many reasons contributing to coiled aneurysm recurrence include initial incomplete aneurysm occlusion, regrowth, and coil compaction and migration, which required retreatment to prevent IA rupture or mass effect. The management strategy in these cases differs from treatment of previously untreated IAs and is more challenging. Individualized endovascular treatments of recurrent IAs involve recoiling, stenting, stent-assisted coiling, and the use of flow-diversion devices (1–3, 6, 7). However, many studies demonstrated that surgical clipping is another effective treatment strategy in managing recurrent coiled IAs (8–10). Obviously, clipping of coiled aneurysms requires complex surgical management in case of removing coils or intraluminal thrombus to securely place the clip at the neck of the aneurysms.

Although many studies reported their experience of surgical clipping these aneurysms, few studies specifically describe the morphological changes of recurrent coiled IAs and their corresponding treatment strategies. The present study describes our surgical experience with recurrent, previously coiled IAs over 10 years at a single center. Furthermore, we conducted a literature review of the previous reports to individualize surgical techniques to effectively manage specific intraoperative obstacles according to the morphological characteristics of the coiled IAs.

MATERIALS AND METHODS

Study Design

From January 2010 and October 2020, 1,650 patients were treated for IAs at the department of neurosurgery at our hospital. Of these, 1,320 patients received endovascular coiling as the first-line treatment. Early surgical clipping was performed in those aneurysms with early hemorrhagic complication or failed embolization. After endovascular treatment, assessment of aneurysm occlusion was performed using a three-point Raymond scale: class I, complete aneurysm occlusion without contrast filling; class II, neck remnant; and class III, residual aneurysm sac. Patients were scheduled for surveillance angiographies to evaluate the stability of coiled aneurysms at ∼3, 6, 12, and 24 months. Angiographic recurrence was considered if a previously totally occluded aneurysm had a partial recurrence of the neck and/or sac. In addition, an aneurysm was considered to have remnant growth if a subtotal occluded aneurysm was found to have an increased neck remnant or residual aneurysm. Specifically, patients with bleeding during the follow-up period were performed with retreatment immediately. The decision to retreat a recurrent IAs was made by a multidisciplinary team including vascular neurosurgeons and interventional neuroradiologists. Detailed information of demographic characteristics, hospital information, treatment strategies, discharge status, and long-term clinical outcome was recorded.

Surgical Technique

Before surgery, each patient's medical status was analyzed, including age, WFNS grade, and medical history. The location, size, and morphology parameters of the aneurysms were also considered, as well as the aneurysms' relationship to their parent artery, collateral circulation compensative capacity, and the condition of vasospasm. The ipsilateral pterional approach was available in patients with IAs located in the anterior communicating artery, posterior communicating artery, and ophthalmic segment of the internal carotid artery (ICA). At the same time, ipsilateral proximal ICA was prepared at the neck for proximal control for clipping ophthalmic aneurysm. Ipsilateral lateral suboccipital craniotomy was performed in those patients with vertebral artery–posterior inferior cerebellar artery aneurysms. A directing clipping was performed in aneurysms with enough neck space for clip placement. In cases of sliding or narrowing of the parent artery, clipping was performed after the removal of coils.

Follow-Up Evaluation and Outcomes

All intraoperative or postoperative complications were reviewed. The modified Rankin scale (MRS) was used to grade outcomes at discharge and follow-up: scores of 3–6 represent unfavorable outcome, and scores of 0–2 mean good outcome. The mean duration of follow-up was 4.1 years (range, 4 months—9 years).

Statistical Analysis

Continuous variables were represented by mean ± SD, while grouping variables were represented by quantity/percentage. For single-factor analysis, *t*-tests were used for continuous variables while chi-square was applied for grouping variables. All data were analyzed with SPSS version 19.0, and $p < 0.05$ was deemed statistically significant.

RESULT

Characteristic of Patients and Aneurysms

The patient group consisted of nine women and three men with an age range from 31 to 64 years (mean age, 51.3 years). Ten aneurysms were located in the anterior circulation, and two were located in the posterior circulation. The most common aneurysm locations were anterior communicating artery and posterior communicating artery. Six patients were initially treated by endovascular treatment (EVT) because of aneurysm rupture with consecutive subarachnoid hemorrhage (SAH) (Hunt and Hess Grade II in two, Hunt and Hess Grade III in three, Hunt and Hess Grade IV in one); the remainder harbored incidental aneurysms treated prophylactically. The average initial diameter of those IAs was 8.6 ± 4.2 mm in our study.

EVT and Indication for Surgery

Primary EVT in all patients was performed in our hospital. Eleven aneurysms were treated with coiling only; one aneurysm with stent-assisted coiling. Post-embolization angiograms demonstrated complete obliteration and incomplete obliteration in 10 and 2 aneurysms, respectively. The early surgeries were operated on because of treatment failure in two patients, postoperative early rebleeding in one patient, and intraprocedural aneurysm rupture during embolization in one patient. Specifically, two failed treatment cases are PICA aneurysm and anterior communicating artery aneurysm. After

GDC embolization of those two aneurysms, the coil extrusion into the parent vessel resulted in severe stenosis and complete occlusion in PICA and A2, respectively. To prevent the cerebral infarction, clipping with coils moving was performed in those two patients. Late surgical clipping was necessary in six patients with recurrent or regrowth IAs. Furthermore, one patient suffered with SAH and one patient suffered mass effect in the follow-up period, in whom surgical clipping was performed. Overall, surgical clipping only was performed in eight patients and clipping with coils moving in four patients. The mean interval between primary EVT and microsurgical clipping was 13.3 months (range 2–36 months) in those patients.

Outcomes and Complications

The surgical procedures, results, and outcomes are described in **Table 1**. Ten patients got a favorable outcome (mRS 0–2), but one was disabled and one died. One death occurred as a result of the procedure-related ischemic cerebral infarction. The disability occurred in a 53-year-old patient who was admitted into the hospital because of SAH resulted from ruptured AcomA aneurysm. This patient was successfully managed with GDC embolization initially but presented with rebleeding 1 month later. She subsequently underwent clipping without coils moving. The patient developed cerebral infarction postoperatively and got an mRS of 4 at discharge. One death occurred in a patient 64 years old with a right ophthalmic artery aneurysm. This aneurysm was discovered during an evaluation for headache. The aneurysm was successfully coiled initially but presented with recurrence seen on routine follow-up angiograms 8 months later. Although aneurysm was clipped successfully, the patient died of severe cerebral infarction. At the end of the procedure, aneurysm occlusion was completed for all cases. At the last follow-up, the outcome was classified as good (mRS $\leq$ 2) in 10 patients (90.9%) and poor (mRS > 2) in 1 patient (9.1%).

Recurrent IAs Were Treated Conservatively or Endovascularly

Follow-up imaging was available in 995 aneurysms of the 1,320 treated aneurysms. One hundred and twenty-four aneurysms (12.5%) developed a recurrence after the initial embolization. Excluding six aneurysms treated with clipping in this study, 83 underwent a second embolization, and 35 underwent conservative treatment. Of the 83 aneurysms with a second embolization, 9 aneurysms developed a slight recurrence again; however, conservative treatment was performed in those aneurysms. Thirty-five aneurysms with slight recurrence were performed with conservative treatment. No aneurysmal SAH was found in those patients.

DISCUSSION

Although high postoperative recurrence rates occurred in patients treated with endovascular coiling for IAs, the treatment strategy of those patients may vary from the morphology and recurrence degree of aneurysms. In our study, four aneurysms were clipped at the early phase because of rebleeding, embolization failure, or intraprocedural aneurysm rupture during embolization, and eight aneurysms were clipped at the late phase because of rebleeding, mass effect, or recurrence. The high rate (100%) of complete obliteration in 12 aneurysms is consistent with previous reports. Two major complications of ischemic stroke were observed in this series of patients, which resulted in death and permanent neurological deficit, respectively. Among these 26 studies spanning 716 patients with 723 aneurysms in the past 20 years, the mortality rate ranged from 0 to 29.6%, the complete obliteration rate of IAs from 73.7 to 100% (**Table 2**).

Mechanisms and Type of IA Recurrence

Aneurysm recurrence after endovascular coiling is a common problem, occurring in around of 30% cases depending on the series (12, 13). Many studies reported that the size and neck width of IAs, aneurysm rupture, initially incomplete occlusion, packing densities, the use of stent, and length of follow-up contributed to an increased risk of IA recurrence (4, 5). The mechanisms of aneurysm recurrence after EVT were summarized as follows (**Figure 1**): coil compaction (**Figure 2**), aneurysm regrowth (**Figure 3**), and fundal migration (**Figure 4**). Coil compaction is reported to be the most important contributing factor to IA recurrence, which was caused by the water hammer effect of the pulsatile flow and dissolution of the thrombus within the IAs sac. The mechanisms of aneurysm regrowth and coil compaction are indistinguishable. Hoppe et al. proposed that aneurysm sac growth was the primary reason for recurrence after successful endovascular coiling; however, there was no association between IA recurrence and coil compaction (30). At the same time, it is difficult to identify coil extrusion from coil compaction in angiography. Four mechanisms of coil extrusion were reported, namely, iatrogenic coil extrusion, initial coiling of a pseudoaneurysm, forcible coil compaction, and degradation of the distal aneurysm wall. Coil extrusion was observed during surgery more frequently than expected, which increased the rupture risk of IAs. In aneurysms with intraluminal thrombus, coils can gradually penetrate into the thrombus, resulting in restoration of flow into the aneurysm lumen.

Retreatment Indication After Initial Embolization

Despite the high recurrence rate in IAs following EVT, the annual re-rupture rates after endovascular coiling reported in the previous studies range from 0.11 to 0.32% (14–16). Furthermore, Byrne reported a 0.4% rebleeding rate for stable non-progressing aneurysmal remnants and a rebleeding rate of 7.7% for angiographically unstable aneurysmal residuals (7). Therefore, long-term angiography follow-up for detection of recurrences is essential for patients with aneurysms larger than 10 mm and in patients with grade 2 occlusions. Although the previous study showed a very low rupture rate of coiled aneurysms at 10 years or more, data at follow-up of IAs beyond 5 years after endovascular coiling are scant (7–10).

It is critical to balance the morbidity associated with retreatment with rupture risk of the recurrent aneurysm when deciding which patients should undergo retreatment with a coiled aneurysm. The data available thus far demonstrated an

TABLE 1 | Patients that underwent surgical treatment of aneurysm after previously coiled embolization.

Case	Age/Sex	Aneurysm location	Initial presentation	Initial size	Aneurysm neck width	Shape of aneurysm	Calcification	mRROC	Size before surgery	Indication for surgery	Duration since coiling
1	31/F	PcomA	Headache	11	3.5	Regular	No	II	2.5	SAH	8 weeks
2	37/F	PICA	SAH	5.5	3.0	Irregular	Partial	/	/	Treatment failure	2 h
3	36/F	PcomA	Headache	15	4.0	Regular	Partial	I	6	Regrowth	4 months
4	58/M	AcomA	Dizziness	6	3.0	Irregular	No	/	/	Treatment failure	1 h
5	61/F	OphA	Blurred Vision	11	4.2	Regular	No	I	/	Mass effect	22 months
6	62/F	BA	SAH	12	5.5	Regular	Partial	I	6	Recurrence	25 months
7	56/F	PcomA	Headache	6	2.5	Regular	No	I	2	Recurrence	7 months
8	53/F	AcomA	SAH	3	1.5	Irregular	No	II	1	Rebleeding	1 month
9	59/M	AcomA	SAH	7	3.0	Regular	No	I	3	Recurrence	3 months
10	64/F	OphthA	Dizziness	16	6.5	Regular	Partial	IIIa	5	Recurrence	7 months
11	46/M	AcomA	SAH	5	2.0	Regular	No	II	/	IPAR	1 h
12	53/F	AcomA	SAH	6	2.5	Regular	Partial	I	4	Recurrence	36 months

Case	Surgical approach	Coil situation	Radiological outcome	Complication	mRS
1	Clipping	Moving	Complete	/	0
2	Clipping	Moving	Complete	/	0
3	Clipping	No Moving	Complete	/	0
4	Clipping	Moving	Complete	/	0
5	Clipping	Moving	Complete	/	2
6	Clipping	No Moving	Complete	/	1
7	Clipping	No Moving	Complete	/	0
8	Clipping	No Moving	Complete	Cerebral infarction	4
9	Clipping	No Moving	Complete	/	0
10	Clipping	No Moving	Complete	Cerebral infarction	6
11	Clipping	No Moving	Complete	/	1
12	Clipping	No Moving	Complete	/	0

F, female; M, male; SAH, subarachnoid hemorrhage; OphA, ophthalmic artery; PcomA, posterior communicating artery; BA, basilar artery; AcomA, anterior communicating artery; PICA, posterior inferior cerebellar artery; IPAR, intraprocedural aneurysm rupture. mRS, modified Rankin scale.

equivalent procedural morbidity related with retreatment of coiled IAs with the first treatment, ranging from 0.43 to 3.2% (7–10, 14–16). Of the 127 patients with aneurysm recurrence in a large study reported by Dorfer, 52 patients underwent surgical clipping and 75 underwent re-embolization over an 18-year period. A low rate of treatment-related morbidity and a high technical success rate were found in both surgical and endovascular treatment (8). Therefore, re-treatment of those coiled IAs which are prone to rupture is feasible.

A Brief Review of Endovascular Retreatment for Coiled IAs

EVT of coiled aneurysms has become a safe and effective option as new coil technologies and assistant devices develop and practitioners subsequently gain experience with these techniques, with the retreatment rate ranging from 6.9 to 17.4% (2, 3). Rebleeding rates after EVT are estimated at between 1 and 2% in larger series (12–14). Endovascular retreatment approaches of aneurysms previously embolized include coiling alone, balloon- and stent-assisted coiling, deployment of covered stents, and flow diversion. IAs with obvious compaction or regrowth and appropriate morphology allow coiling alone as the recurrent cavity is large enough. The stent-assisted technique is suitable for those aneurysms with a shallow recurrent cavity to prevent coils from escaping into the parent artery, or flowing into a distal artery, which results in artery occlusion. Li et al. reported 12 recurrent coiled IAs treated with stent-assisted coiling, no neurologic deficits, or aneurysmal rupture occurring during the follow-up period (31).

Although covered stent was used to treat large or giant wide-necked IAs and carotid-cavernous fistula before, it was also suitable for recurrent aneurysms, regardless of the size

TABLE 2 | Case series reports on microsurgical management of coiled intracranial aneurysms in the past 20 years.

References	No. of patients and IAs	Sex/age (M/mean)	Median latency (months)	Surgical indication (*n*)						Treatment strategy (*n*)			Mortality (%)	Postsurgical obliteration rate (%)
				Recurrence	ME	CM	CP	Rebleeding	Residual aneurysm	Clipping	By-pass	Other treatment		
Thornton et al. (9)	11/11	2/49	4.36	2	3	2	1	0	3	11	0	0	29.6	NA
Makoui et al. (4)	1/1	0/46	0.5	1	0	0	0	0	0	1	0	0	0	100.0
Asgari et al. (1)	5/5	2/47.2	2.3	2	0	1	0	0	2	5	0	0	0	100.0
Conrad et al. (11)	7/7	1/50	4.43	3	0	0	1	0	3	4	0	3	14.3	100.0
Zhang et al. (6)	38/40	11/52	6	22	0	1	0	0	15	31	3	6	13.2	NA
Veznedaroglu et al. (12)	18/18	3/49	12.8	18	0	0	0	0	0	15	0	3	0	83.3
Minh et al. (2)	7/7	1/42	NA	1	0	0	0	2	4	7	0	0	14.2	100.0
Raftopoulos et al. (13)	17/17	9/54	17.8	14	0	2	1	0	0	17	0	0	0	100.0
König et al. (14)	10/10	2/46	14	6	0	0	4	0	0	10	0	0	0	NA
Tirakotai et al. (15)	8/8	1/49	12.4	2	3	0	0	1	2	7	1	0	12.5	100.0
Lejeune et al. (16)	21/21	11/45	8.33	21	0	0	0	0	0	19	0	2	10.0	90.5
Klein et al. (17)	13/13	6/43	19.6	10	0	0	0	3	0	13	0	0	7.7	100.0
Waldron et al. (3)	43/43	9/51	28	10	0	0	13	0	20	33	7	3	9	76.7
Chung et al. (18)	29/29	16/48.1	3.93	10	0	0	6	5	8	29	0	0	6.9	NA
Romani et al. (19)	81/82	28/47	12	23	3	4	2	4	46	78	2	2	12	93.9
Nakamura et al. (20)	15/15	8/50.6	19.1	12	0	0	0	0	3	15	0	0	13.3	100.0
Rubino et al. (21)	20/20	8/43.5	NA	7	0	0	0	0	13	20	0	0	5	95.0
Izumo et al. (22)	7/7	1/60.3	28.8	5	0	1	0	0	0	5	1	0	0	85.7
Daou et al. (23)	111/111	29/50.5	23	95	0	0	0	2	14	105	0	6	15	97.3
Wang et al. (24)	19/21	9/51.3	26	18	0	0	0	1	3	18	1	2	9.5	85.7
Toyota et al. (25)	14/14	7/50	12	14	0	0	0	0	0	13	1	0	0	78.6
Shtaya et al. (26)	39/40	19/49	18	38	0	0	0	0	2	40	0	0	5.1	NA
Nisson et al. (27)	53/53	7/51.9	31.3	25	0	0	0	0	28	53	0	0	6	94.3
Wu et al. (28)	48/48	26/46.5	20.2	29	9	0	0	4	6	48	0	0	10.4	100.0
Liu et al. (29)	75/76	34/56	7	33	0	0	0	4	39	68	2	4	14.7	73.7
Raper et al. (5)	6/6	3/53	7.5	5	0	0	0	3	0	6	0	0	0	100.0

ME, mass effect; CM, coil migration; CP, coil protrusion.

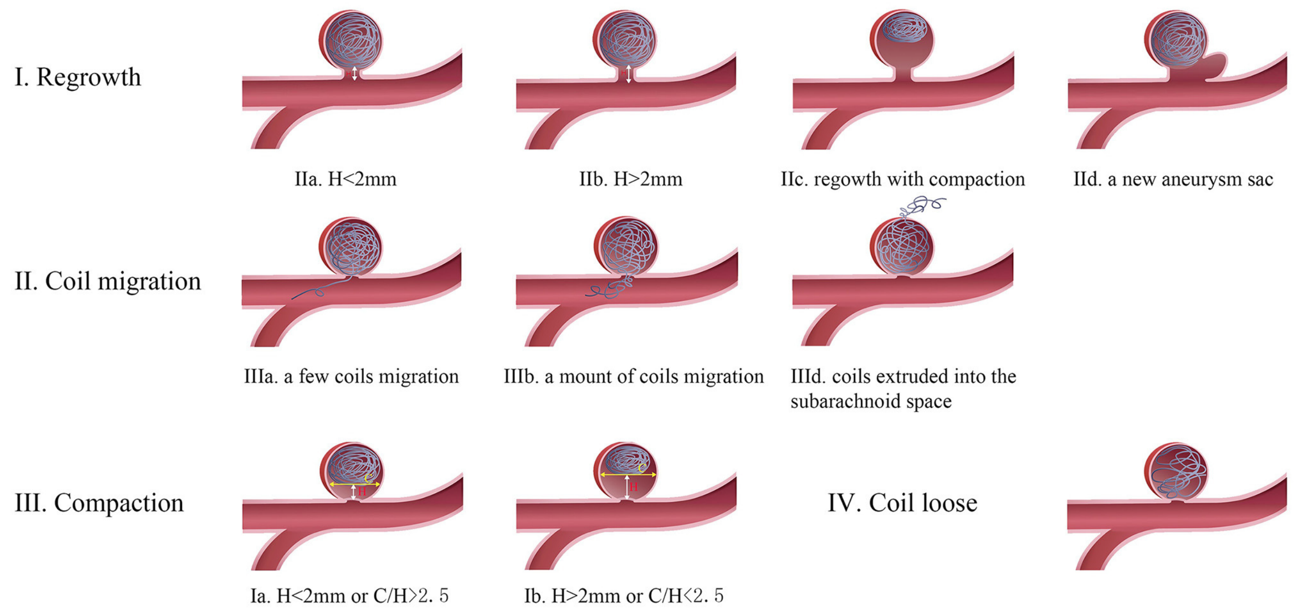

FIGURE 1 | The different types of recurrent aneurysms. Type I. Aneurysm regrowth: neck height <2 mm; neck height more than 2 mm; aneurysm regrowth withe coils compaction; a new aneurysm sac originated from the initial aneurysm neck. Type II. Coil migration: very few coils fill the neck of the aneurysm or the parent artery; multiple coils fill the neck of the aneurysm or the parent artery; coil extrusion into subarachnoid space. Type III. Coil Compaction: compaction height <2 mm or coil width (C) to compaction height (H) ratio > 2.5; compaction height more than 2 mm or C/H < 2.5. Type IV. Irregular recanalization inside the packed coils.

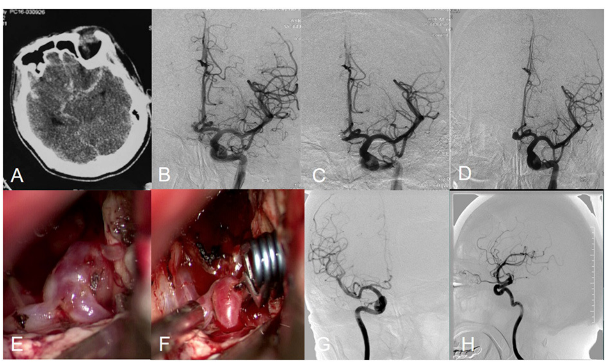

FIGURE 2 | Angiograms obtained in Patient 12, a 53-year-old female with an anterior communicating artery aneurysm. CT scan showed SAH **(A)**. Preembolization angiogram **(B)**. Postoperative arteriogram demonstrating complete obliteration of aneurysm **(C)**. Follow-up angiogram showed aneurysm recurrence **(D)**. Intraoperative photograph showed aneurysm clipping **(E,F)**. Postoperation angiogram showed aneurysm was clipped completely **(G,H)**.

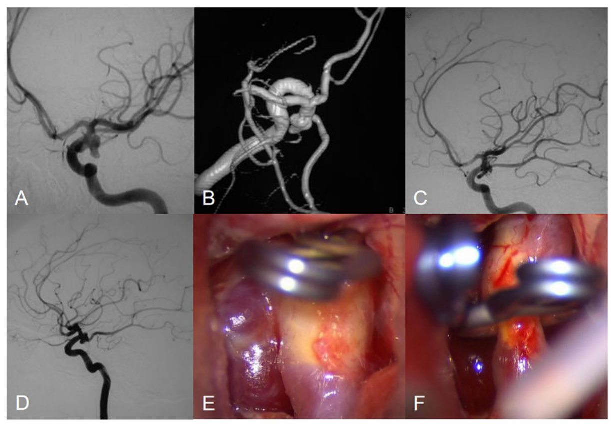

FIGURE 3 | Angiograms obtained in Patient 7, a 56-year-old female with an posterior communicating artery aneurysm. Preembolization lateral angiogram **(A,B)**. Postoperative arteriogram demonstrating complete obliteration of aneurysm **(C)**. Follow-up angiogram showed aneurysm regrowth **(D)**. Intraoperative photograph showed aneurysm clipping **(E,F)**.

and shape of the recurrent aneurysm. The stent's membrane can act as a barricade to prevent the thrombus formed within the aneurysm cavity from entering the blood, which decreases the possibility of thromboembolic complications. Some papers have reported the safety and efficacy of flow diversion for residual or recurrent IAs after EVT (23, 32, 33). In two large retrospective series of recurrent aneurysms treated with flow diversion, the complication rates were 3.0% (1/33) and 10.3% (3/29), respectively (32, 33). Thromboembolism is the most common complication in the endovascular retreatment of IAs, ranging from 0 to 11% in previous series (22, 27). The recurrence rate of IAs after endovascular retreatment is around 10%, which is higher than that of surgical clipping. Although recanalization may occur even after endovascular retreatment, additional re-embolization showed a lower procedure-related complication compared with surgical clipping. Previous series show similar

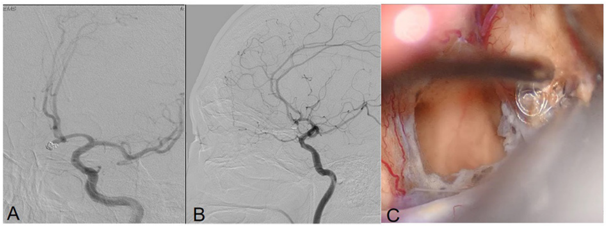

FIGURE 4 | Angiograms obtained in Patient 9, a 59-year-old male with an anterior communicating artery aneurysm. DSA demonstrated recurrent coiled aneurysm **(A,B)**. Intraoperative view of the aneurysm showing the extrusion of the coils **(C)**.

and even lower peri-procedural complication rates than the rates during the initial treatment of IAs. Therefore, it may be reasonable to attempt re-embolization firstly in embolized patients with recanalized aneurysms.

Surgical Techniques for Coiled IAs

Predicting the clippability of recurrent IAs helps us make surgical planning and determine the timing of surgery, such as clipping the aneurysm immediately or observing a surgery being performed. In this study, we summarize an exhaustive classification scheme for recurrent aneurysms based only on angiographic findings, which might be more systematic and specific for surgical planning. The recurrent IAs can be classified as four groups from a therapeutic perspective: (1) a compaction height (H) of <2 mm or a ratio of coil width to compaction height (C/H) of >2.5; (2) a compaction height of >2 mm or a C/H of <2.5; (3) a few coils across the IA neck; and (4) some coils across the IA neck or extrusion into the parent artery or extrusion outside the IA wall.

For type I aneurysm with minimal compaction or regrowth, conservative observation for further coil compaction or neck remnant regrowth is a preferred choice as there is not enough space for the clip placement (12, 13). Direct clipping requires enough coil-free space at the base of the aneurysm. However, the degree of free base depends on the experience of the surgeon, the morphology characteristics, and even the clip type (14, 16). Direct clipping is available in type 2 aneurysms with a compaction height of >2 mm or a ratio of coil width to compaction height of <2.5, which facilitates safe clip placement, particularly in young patients (22, 27). Wrapping aneurysms with muslin or cotton is another treatment for these difficult cases when multiple clipping attempts failed. Wrapping can induce inflammation and scarring of the aneurysm wall which prevent IAs from enlarging and rupturing (**Figure 5**) (17, 18, 34).

For type 3 aneurysm, a single clip is hardly to clip the aneurysm completely because of inadequate closure of the far side of the neck by coil extrusion into the parent artery. Tsuyoshi proposed combining a fenestrated clip with another type of clip to complete closure of those complex aneurysms. The former clip is available for closing the far-side aneurysmal neck, while the latter is used to close the near side of the neck (17).

Although removing the coil from the aneurysm sac is always difficult and hazardous, it is inevitable when loops of coil extrusion into the parent vessel make complete clipping impossible in type 4 aneurysms (17, 18, 21, 34). Whether the coils can be successfully removed from the aneurysm or parent artery mainly depends on the time that has elapsed since EVT. An animal experiment demonstrated that a few neoendothelial cells were detected on the implanted coil and neoendothelial cells were more confluent over the coils at 4 and 8 weeks after coil embolization (35). Therefore, attempted coil removal may be very difficult and traumatic if a relatively long time has elapsed after embolization. Opening the aneurysmal sac and removing the coils are possible in the early post-coiling period. If coil removal is necessary during the operation, it is of utmost importance to prepare a temporary occlusion of the parent vessel and expose the aneurysm as much as possible to clarify its relationship with the parent artery (20). It is hard to decide the amount of coil extraction which mainly depends on the doctor's experience to achieve an optimal position of the aneurysm clip. Despite the feasibility of direct aneurysm with removing coils, it has significant disadvantages, such as uncontrollable ischemia time, tearing risk of the arterial wall, and difficulty reconstructing the neck after transecting the aneurysm (24, 25).

In contrast, a bypass strategy with parent artery occlusion can be executed methodically for unclippable aneurysms (19, 24–26, 28). Currently, many types of extracranial-to-intracranial bypasses, including high-flow bypasses with saphenous veins or radial artery grafts, have been developed to revascularize the parent artery of unclippable IAs effectively (29). Coil removal may be inevitable in patients with large or giant aneurysms who present with mass effect symptoms. Thornton et al. proposed that implanted coil combination with subsequent thrombus can also generate mass effects on the parent artery (18). Clipping the coiled giant aneurysms is technically challenging as the dissection and visualization around the lesion are difficult. Therefore, a bypass with aneurysm resection may be preferred other than direct clipping.

A few studies reported about surgical clipping of previously stent-assisted coiling aneurysms, which was associated with higher procedural complication and further technical challenge as the intraluminal stent was embedded in the parent artery wall. Further, temporary clipping is difficult as the vessel becomes more rigid and less maneuverable, with the risk of vessel deformation after withdrawing temporary clipping. In the study by Liu et al., the stent immediately regained its previous shape with no associated compromised flow in three recurrent stent-coiled IAs performed with temporary clipping of the parent artery (29). However, temporary clipping over the stent is likely to be a technical challenge in our opinion unless more data on this issue are available.

Limitation

There are some limitations to our study. First, this study describes our surgical experience in recurrent, previously coiled IAs over 10 years in our hospital. As the technological levels changed over time, the long time span covered in

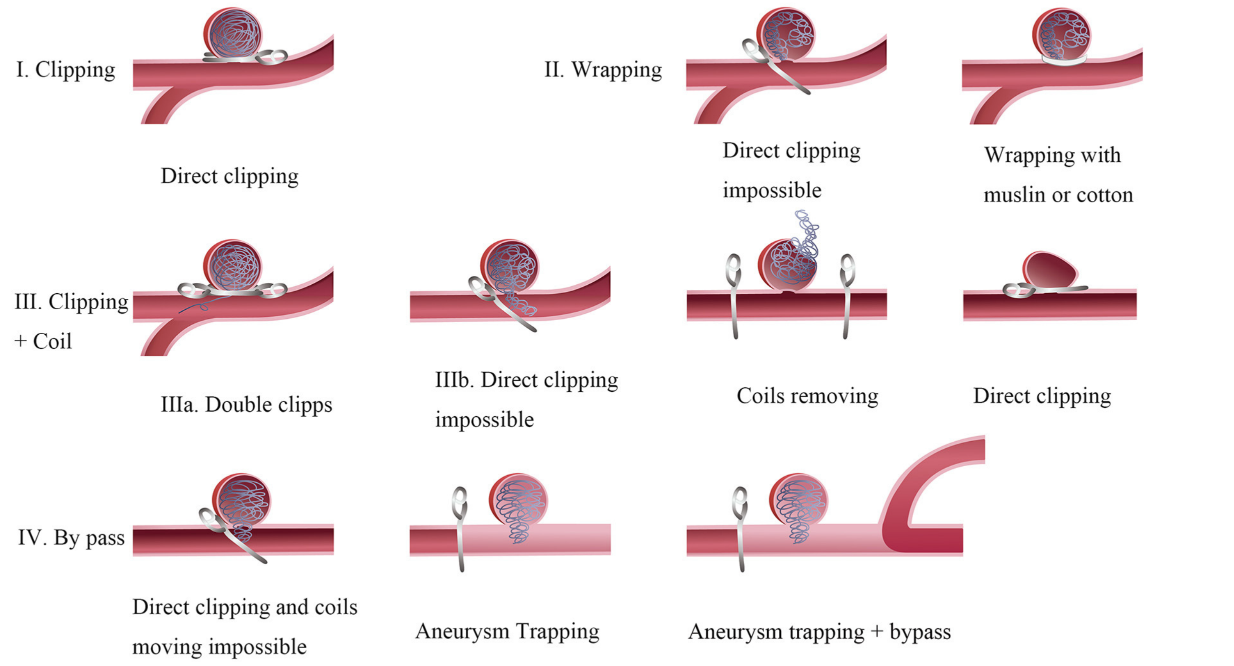

FIGURE 5 | Surgical techniques of recurrent intracranial aneurysms. Type I: Direct clipping is available in those aneurysms with a compaction height >2 mm. Type II: Wrapping aneurysms with muslin or cotton for these difficult cases when multiple clipping attempts failed. Type III: Clipping aneurysms with coils extrusion. Ma: A tandem clipping method helps to the complete obliteration in aneurysms with a few coils extrusion. IIIb: Coils moving is inevitable in aneurysms with multiple coils extrusion or mass effect occurring. A temporary occlusion of the parent vessel and expose the aneurysm as much as possible to clarify its relationship with the parent artery. Type IV: Aneurysm Trapping and by pass. Coils moving maybe hazardous in cases after endovascular treatment for a long time. A bypass strategy with parent artery occlusion is suitable for those cases.

this study influenced the accuracy of the results to a certain degree. Second, although clinical decision regarding the use of endovascular vs. surgical techniques was made by vascular neurosurgeons and interventional neuroradiologists, there are no standardized procedural protocols and criteria for treatment strategies and timing because of its retrospective design and small sample. Third, the study population was gathered from a single center, which may not always reflect the findings and practices of other hospitals. Lastly, most aneurysms enrolled in our study were relatively easily accessible to clip directly with or without coil removal. More complex aneurysms with high surgical difficulties, such as bypass surgery, trapping, and wrapping, should be admitted in the future.

CONCLUSION

Surgical clipping can be a safe and effective treatment strategy for the management of recurrent coiled IAs, with acceptable morbidity and mortality in properly selected cases. In this study, we have presented our experience of dealing with 12 coiled IAs with a relatively low risk and a high rate of complete obliteration. Our classification of recurrent coiled aneurysms into four types (10 subtypes) helps to assess the optimal surgical approach and the associated risks in managing them. Furthermore, we elaborate the different surgical techniques according to the IA recurrence type, including direct clipping, clipping with coils moving, wrapping, and aneurysm trapping with bypass.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

LB: conception or design of the work. YZ, LZ, and BW: drafting the work. LZ, YS, DL, and QS: acquisition, analysis, or interpretation of data for the work. YZ and LB: agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors: revising it critically for important intellectual content and final approval of the version to be published.

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The Clinical Efficacy Analysis of Treatment With a Willis Covered Stent in Traumatic Pseudoaneurysm of the Internal Carotid Artery

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Objective: To investigate the safety and efficacy of Willis covered stents (WCS) in the treatment of traumatic pseudoaneurysm of the cranial internal carotid artery (CICA).

Methods: Fifteen patients with traumatic pseudoaneurysm of the intracranial segment of the ICA treated with the WCS system at our institution from 2013 to 2019 were analyzed retrospectively. Follow-up observation and digital subtraction angiography (DSA) examination were conducted ∼6 months after the treatment.

Results: DSA performed immediately after stent deployment revealed that complete occlusion of the lesion was achieved in 13 patients and that endoleak occurred in two patients. In 12 patients, postoperative DSA examination indicated that the lesions were completely occluded. In two patients who had a second stent implantation at the break of the ICA, traumatic ICA rupture was essentially completely obstructed in 1 patient. The endoleak remained in one patient with carotid cavernous sinus fistula because the placement of the second stent system was difficult with his ICA tortuosity. No recurrence of aneurysms, hemorrhage, or other lesions was observed, and the patients' parent arteries were patent without stenosis. No procedure-related complications or ischemic strokes occurred during the follow-up period of ∼6 months.

Conclusions: For treatment of traumatic pseudoaneurysm of the CICA, Willis covered stent implantation in some appropriate cases, is safe and effective. However, large-sample controlled studies and multicenter studies are needed for further confirmation.

Keywords: pseudoaneurysm carotid artery, endoleak, Willis covered stent, complications, digital subtraction angiography

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INTRODUCTION

Carotid pseudoaneurysm refers to the formation of a hematoma by arterial wall damage and blood extravasation due to various causes. The hematoma gradually dissolves with time. Under the impact of continuous arterial pulsatile pressure, the hematoma communicates with the arterial lumen through the arterial crevasse, forming a pseudoaneurysm. Traumatic pseudoaneurysm of the intracranial segment of the internal carotid artery is the most common type, with an incidence of ∼1% of all intracranial aneurysms (1), and the clinical manifestations are recurrent massive nasal bleeding, intracranial hemorrhage, and ischemic stroke. Conventional surgical repair is difficult due to poor intracranial collateral circulation when ligating or occluding the parent artery, which can lead to disability or death of the patient. The Willis covered stent (WCS) is specifically used for the treatment of intracranial cerebrovascular diseases. It consists of two parts: a balloon and a stent with a membrane. Through endovascular aneurysm exclusion, the aneurysm is excluded from the parent artery, and then the aneurysm is occluded to realize reconstruction of the parent vessel. This stent provides a new and efficient treatment method for traumatic pseudoaneurysm in the intracranial segment of the internal carotid artery. From December 2013 to May 2019, 15 patients with traumatic pseudoaneurysm of the intracranial segment of the internal carotid artery were treated with intracranial WCS in the Department of Neurosurgery, General Hospital of PLA Central Theater Command, with good results. This treatment is retrospectively reported in the current study.

METHODS

The ethics committee of our institution granted ethics approval of this study and waived the requirement for written informed consent. In total, 15 consecutive confirmed carotid pseudoaneurysm patients who were treated with WCS at our department between December 2013 and May 2019 were enrolled. The patients included in this study met the following criteria:

Clinical data: Of the 15 patients, 13 were male and 2 were female; the mean age was 39.0 ± 10.7 years (range, 15–51 years). Eleven patients had a clear history of trauma: 6 cases had car accident injury, 3 cases had fall-from-height injury, and 2 cases had heavy object injury; 2 cases involved internal carotid artery injury during brain tumor surgery; 1 case had a history of head and neck radiotherapy for nasopharyngeal carcinoma; and 1 case involved residual pseudoaneurysm after balloon treatment of traumatic carotid cavernous fistula. The clinical manifestations of the 15 patients were recurrent massive nasal bleeding in five patients, recurrent intracranial hemorrhage in six patients, and stroke in two patients. The neurological function status of each patient at the time of admission and follow-up was assessed and graded as good for Modified Rankin Scale (MRS) scores of 0 to 1 and poor for MRS scores of 2 to 5 and death. All patients or their families gave written informed consent.

Imaging data (**Figures 1–3**): All patients were diagnosed with traumatic pseudoaneurysm of the intracranial segment of the internal carotid artery by preoperative digital subtraction angiography (DSA). The results of three-dimensional reconstruction showed that the maximum diameter of 15 pseudoaneurysms in 15 patients was 7. 5 ± 2.2 (1.7 to 16.0 mm), neck width was 3.5 ± 1.9 (0.5 to 7.7) mm, and the distal and superior vessel diameters of the parent artery were 2.6 ± 0.8 (1.1 to 3.6 mm) and 3.0 ± 0.7 (1.2 to 4.0 mm), respectively. Of the 15 pseudoaneurysms, 4 were close to the ophthalmic artery, 5 were close to the posterior communicating artery, and the remaining 6 were located in the cavernous sinus segment without important vessel proximity.

Treatment and Follow-Up

Surgical methods (**Figures 1–3**): All patients received oral antiplatelet aggregation drugs (Bayaspirin 100 mg/d, clopidogrel 75 mg/d) 3 days before surgery. During the operation, the patient was placed in the supine position with local anesthesia at the puncture site, the femoral artery was punctured by the Seldinger method, and an 8F sheath was placed. After completion of whole cerebral angiography, the patient was transitioned to general anesthesia, with systemic heparinization. Aided by a 0.035-inch guidewire, the coaxial catheter system consisting of an Envoy guiding catheter and Navien catheter was delivered to the internal carotid artery as close to the lesion site as possible. The Envoy 8F guiding catheter was placed at the C2 level of the internal carotid artery. Under the guidance of a roadmap, the Navien catheter was navigated to the cavernous segment of the internal carotid artery or even higher via an Echelon 10 microcatheter and microwire. DSA was performed on the lesion side, and three-dimensional reconstruction was performed again to measure the distal and superior diameter of the patent artery, the size of the aneurysm and the width of the neck. A WCS of appropriate size was selected based on the diameter of the parent artery and the length of the involved diseased vessel. None of the 15 patients included in this study had internal carotid artery occlusion. Under the guidance of a microwire, the stent was quickly moved to the end of the Navien catheter, and its position was adjusted by projection at multiple angles to make sure that the stent covered the aneurysm neck and avoided the opening of the branch artery. After finalizing the position, the balloon was slowly filled, the filling pressure was maintained at the maximum diameter of the stent for ∼10 s to keep the stent completely expanded, and then the pressure was released.

DSA was performed again after emptying the balloon. If the aneurysm completely disappeared immediately, the balloon was withdrawn; DSA was performed after 10 min of observation to ensure that the parent artery was patent. If there was "endoleak," the balloon could be inflated again until the endoleak disappeared. If contrast medium continued to enter the aneurysm, follow-up observation or postoperative auxiliary compression of the carotid artery on the lesion side was performed for 30 min, according to the endoleak findings, once or twice a day for 1 to 2 months. A total of 15 WCS (Shanghai Shentong Technology Co., Ltd., China) were placed in 15 patients as follows: 3.5 mm × 7.0 cm ($n = 2$), 3.5 mm × 10.0 cm ($n = 3$), 3.5 mm × 13.0 cm ($n = 2$), 3.5 mm × 16.0 cm ($n = 1$), 4.0 mm × 7.0 cm ($m = 1$), 4.0 mm × 13.0 cm ($n = 5$), and 4.5 mm × 7.0 cm ($n = 1$). After the operation, all patients underwent routine cranial Dyna CT reexamination and stent reconstruction.

Postoperative Treatment

After surgery, all patients were continuously infused with 2 to 4 ml of tirofiban using a micropump. Beginning the next day, treatment with oral clopidogrel 75 mg/day and Bayaspirin 100 mg/day was administered for 3 months. After 3 months, treatment was changed to oral Bayaspirin 100 mg/day only for 6 months. One week after surgery, platelet activation function and thromboelastography were repeated.

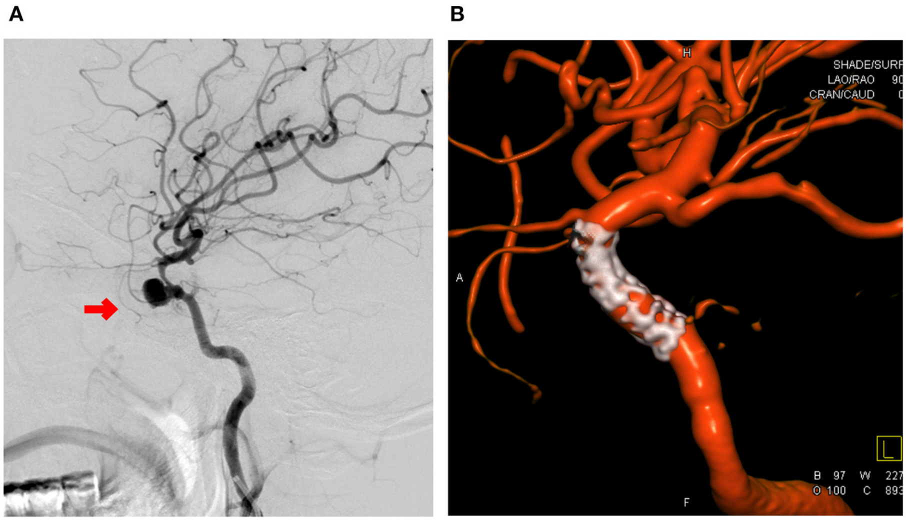

FIGURE 1 | A 38-year-old female patient was admitted to the hospital 2 weeks after resection of sphenoid ridge meningioma. **(A)** Preoperative digital subtraction angiography (DSA) examination showed pseudoaneurysm in the cavernous segment of the internal carotid artery. The straight diameter of the blood vessel at the distal and proximal ends of the parent artery was 2.1 and 2.9 mm, and the size of the tumor was 8.4 × 7.8 mm. Intraoperative placement of a Willis covered stent followed by DSA examination showed resolution of the pseudoaneurysm. **(B)** Shows that the stent graft had good compatibility and patent vessels.

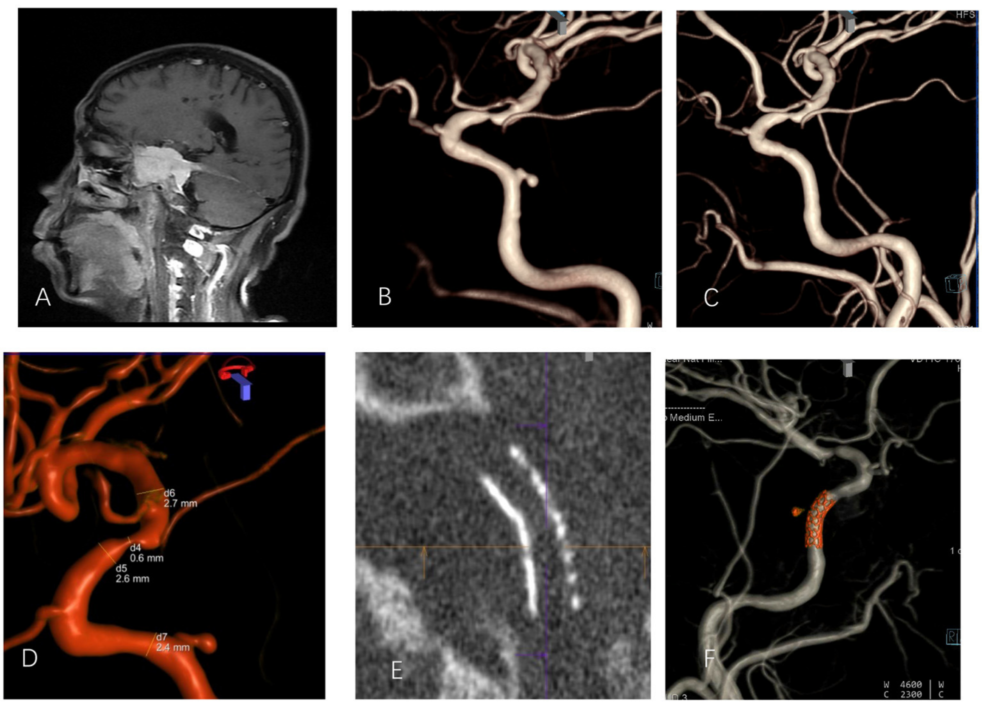

FIGURE 2 | A 51-year-old male with intraoperative internal carotid artery injury of right sphenoid clival meningioma and postoperative secondary right internal carotid cavernous pseudoaneurysm before and after interventional therapy **(A)**. Enhanced MRI revealed that the tumor wrapped the right internal carotid artery. **(B)** A DSA-3D lateral image showed pseudoaneurysm of the posterior wall of the cavernous sinus of the right internal carotid artery. **(C)** The pseudoaneurysm disappeared after stent treatment. **(D)** Measurement of the diameter of the parent artery; **(E)** Maximum intensity projection showed that the stent opened completely. **(F)** Postoperative dual-volume imaging showed that the stent graft had good compatibility and that the vessel was patent.

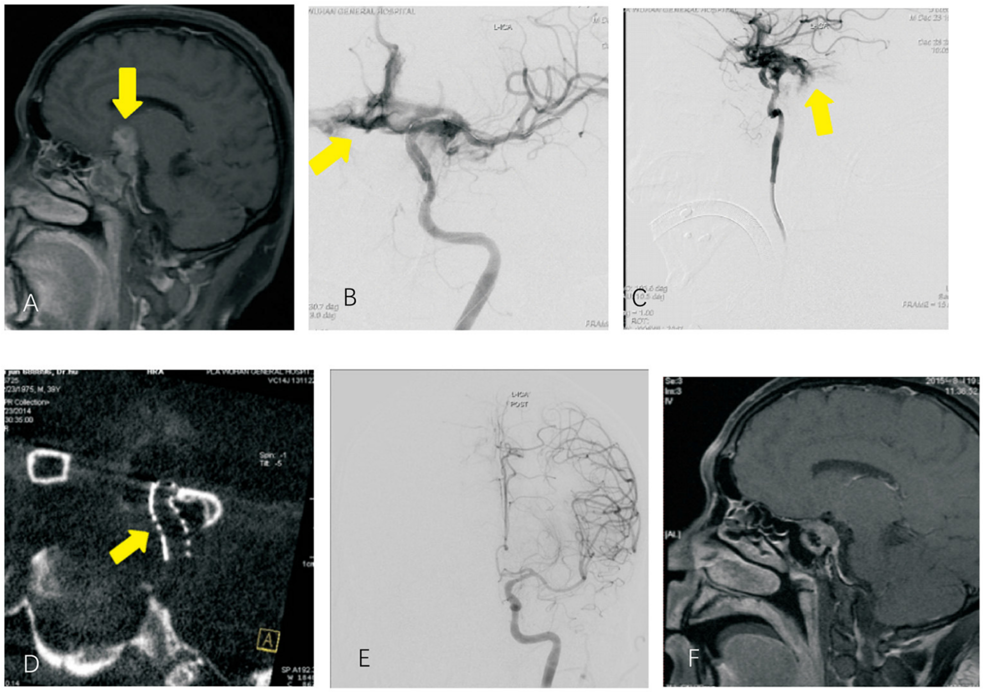

FIGURE 3 | Invasive pituitary adenoma and intraoperative internal carotid artery rupture **(A)**. Anterior MRI sagittal image, which showed pituitary adenoma; **(B,C)** DSA image of the ophthalmic segment of internal carotid artery rupture, which showed contrast agent spillage from the rupture to the arachnoid membrane; **(D)** maximum intensity projection showed good apposition of the Willis covered stent; **(E)** successful repair of the internal carotid artery after stent implantation; **(F)** postoperative MRI suggesting tumor resection.

Follow-Up Methods

All patients were followed up in the outpatient department after discharge, including reexamination by DSA to determine whether the aneurysm recurred and whether there was stenosis of the parent artery.

Statistical Analyses

A Pearson chi-square test was applied to compare the categorical variables between the groups. All analyses were performed with SPSS software, version 24.0 (International Business Machines Corp., Almond, NY, USA), and $p < 0.05$ was considered statistically significant.

RESULTS

Immediate Postprocedural Results

Of the 15 patients, two patients were scored as neurological function good, and 12 patients were scored as neurological function poor on admission. Twelve were successfully implanted with a WCS in one procedure; the other 3 patients had endoleak after implantation of a WCS, and of these patients, 1 underwent balloon dilatation once, which resolved the endoleak, and 2 underwent auxiliary compression on the ipsilateral common carotid artery after surgery. Immediate postoperative DSA showed successful vascular reconstruction and resolution of the pseudoaneurysm in all patients (**Figures 1–3**). One patient died of severe traumatic brain injury after the operation, and the other 14 patients underwent postoperative reexamination of cranial Dyna CT. No new cerebral infarction or cerebral hemorrhage was observed. None of the patients had surgery-related complications.

Follow-Up Results

Clinical follow-up data and DSA were collected for 14 of the patients; the mean follow-up period was 5.8 ± 1.2 months. None of the 14 patients had any recurrence of aneurysms or stenosis of the parent artery throughout the follow-up period. No ischemic or hemorrhagic event was reported by any patient during the follow-up period. The functional neurological status was good (mRS score 0 or 1) in 13 patients, and poor (mRS score 2–5) in 1 patient at follow up. And the neurological function status of each patient at the time of follow-up were better than admission according the mRS score ($p < 0.001$).

DISCUSSION

Traumatic pseudoaneurysm of the intracranial segment of the internal carotid artery usually occurs after blunt or acute trauma to the head and neck. Vascular wall injury or arterial rupture bleeding often appear, especially when pseudoaneurysm is combined with anterior cranial fossa fracture, and blood flows from the rupture to form a hematoma. The rupture is gradually closed by a blood clot, which promotes temporary hemostasis. Then, the hematoma dissolves. At the same time, the surrounding tissue gradually organizes to form a fibrous tissue capsule, ultimately leading to the formation of a pseudoaneurysm. Over time, under the impact of the continuous pulsatile blood flow of the parent artery, the pseudoaneurysm capsule wall expands, increasing in size, and eventually ruptures and bleeds again.

Once a traumatic pseudoaneurysm of the internal carotid artery is diagnosed, it should be treated as early as possible before it ruptures. The treatment principle is to repair the damaged vascular wall, isolate the blood circulation of the aneurysm, keep the parent artery unobstructed, and retain the important branches of the parent artery. Traumatic pseudoaneurysm in the intracranial segment of the internal carotid artery is usually located deep in the head, close to the skull base, and the trauma will lead to disorder of the normal anatomical structure of the ICA; the traditional surgical treatment is difficult, the risk is high, and prognosis is poor. In recent years, interventional therapy has been used to treat traumatic internal carotid artery pseudoaneurysm because of its advantages of minimal trauma and a good curative effect (2).

A covered stent can directly block the aneurysm neck with the biophysical membrane on its surface and then isolate the aneurysm from the blood circulation. At the same time, through reconstruction of the lumen of the parent artery, the pressure in the aneurysm cavity can be reduced, the original hemodynamics can be restored, and a blood clot can form in the aneurysm cavity over time until occlusion (3). Covered stents are the most ideal therapeutic material for pseudoaneurysm of the ICA. A total of 15 patients with traumatic pseudoaneurysms in the intracranial segment of the internal carotid artery were included in this study. According to the diameter of the parent artery and the length of the involved vessels, an appropriately sized WCS was selected for embolization. The immediate occlusion rate of pseudoaneurysm was higher in this study than in previous reports. At the same time, the incidence of intracranial rebleeding and postoperative ischemic events caused by surgery was low, and the long-term recurrence rate was low.

In the literature, many complications, such as long-term stenosis of the vascular lumen, stent collapse into the pseudoaneurysm lumen during operation and long-term endoleak, have been reported after using WCSs (3–5). According to these reports, the potential causes of endoleak include mismatch between the model of the WCS and diameter of the parent artery, uneven lumen of the diseased vessel, incomplete coverage of the aneurysm neck, transient vasospasm, stent displacement and stent rupture (6, 7). In this study, the incidence of endoleak in the treatment of intracranial traumatic pseudoaneurysm of the internal carotid artery with a WCS was 3/15. One patient was treated with balloon dilatation, and the other 2 patients were treated with carotid artery compression. The leakage disappeared after 4 months of follow-up. In our experience, when angiography immediately after the operation indicates trace contrast agent entering the aneurysm cavity, we can compress the carotid artery in some patients. A long-term endoleak can disappear by itself, but there is also the risk of another rupture. Therefore, it is suggested that patients under long-term observation should be followed up regularly by cerebral angiography until the endoleak disappears.

The closure of side branches or perforating arteries originating from the covered segment of the artery has always been a major concern in the use of covered stents for cerebral aneurysm treatment. Some reports suggest that the ophthalmic artery (OA) can be sacrificed if necessary because reconstruction of the OA from external carotid artery collaterals is possible (8, 9). The anterior choroidal artery (AchoA) is another important artery that primarily feeds the area of the optic tract, internal capsule, and cerebral peduncle. In our study, before stent deployment in the C7 segment, we carefully evaluated the angiogram from multiple angles to prevent covering the ostium of the AchoA. There were no complications of occlusion of branches or perforating vessels in 15 patients. This may be due to appropriate case selection and accurate stent release.

Late in-stent stenosis during long-term follow-up is another complication of covered stents (10). In-stent stenosis might be caused by neointimal tissue proliferation, and there was no difference in the postintervention or follow-up lumen (at the junction of the two stents) when overlapping stents were compared with non-overlapping stents (11). Standardized antiplatelet aggregation therapy has been proven to play an important role in anti-intimal hyperplasia (12). Moreover, poor compliance with antiplatelet aggregation drugs has been reported to be an independent risk factor for stent stenosis. In this study, 12 patients were followed up by DSA. Through the last follow-up, none of the patients had any recurrence of aneurysms or stenosis of the parent artery. This finding is mainly related to strict treatment with antiplatelet aggregation drugs.

In conclusion, due to the lack of a normal arterial wall, traditional interventional treatment cannot effectively repair the rupture, and even at the cost of occlusion of the parent artery, it is not the best treatment. A covered stent has the advantages of immediate reconstruction of the normal vascular wall, preservation of the patency of the parent artery and restoration of normal blood perfusion, indicating that it is an ideal treatment method. Longer-term follow-up and additional clinical experience are needed to fully determine the safety and efficacy of this device.

LIMITATIONS

Our study has several limitations. First, all patients were enrolled from a single center, and a potential selection bias regarding region and race may have occurred. Our study is a retrospective study, and larger samples and longer follow-up studies will be needed to validate our findings.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

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

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Stereotactic Radiosurgery With vs. Without Prior Embolization for Brain Arteriovenous Malformations: A Propensity Score Matching Analysis

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Objective: Whether partial embolization could facilitate the post-stereotactic radiosurgery (SRS) obliteration for brain arteriovenous malformations (bAVMs) remains controversial. We performed this study to compare the outcomes of SRS with and without prior embolization for bAVMs.

Methods: We retrospectively reviewed the Beijing Tiantan AVMs prospective registration research database from September 2011 to October 2014. Patients were categorized into two groups, combined upfront embolization and SRS (Em+SRS group) and SRS alone (SRS group), and we performed a propensity score matching analysis based on pre-embolization baseline characteristics; the matched groups each comprised 76 patients.

Results: The obliteration rate was similar between SRS and Em+SRS (44.7 vs. 31.6%; OR, 1.754; 95% CI, 0.905–3.401; $p = 0.096$). However, the SRS group was superior to the Em+SRS group in terms of cumulative obliteration rate at a follow-up of 5 years (HR,1.778; 95% CI, 1.017–3.110; $p = 0.033$). The secondary outcomes, including functional state, post-SRS hemorrhage, all-cause mortality, and edema or cyst formation were similar between the matched cohorts. In the ruptured subgroup, the SRS group could achieve higher obliteration rate than Em+SRS group (56.5 vs. 31.9%; OR, 2.773; 95% CI, 1.190–6.464; $p = 0.018$). The cumulative obliteration rate at 5 years was also higher in the SRS group (64.5 vs. 41.3%; HR, 2.012; 95% CI, 1.037–3.903; $p = 0.038$), and the secondary outcomes were also similar between the matched cohorts.

Conclusion: Although there was no significant difference in the overall obliteration rate between the two strategies, this study suggested that pre-SRS embolization may have a negative effect on post-SRS obliteration. Furthermore, the obliteration rates of the SRS only strategy was significantly higher than that of the Em+SRS strategy in the ruptured cohort, while no such phenomenon was found in the unruptured cohort.

Keywords: brain arteriovenous malformation, partial embolization, stereotactic radiosurgery, obliteration, hemorrhage

INTRODUCTION

Stereotactic radiosurgery (SRS) has become one standard treatment strategy of brain arteriovenous malformation (bAVM), especially those located in deep or eloquent regions with high surgical risks, and mounting studies suggested that SRS can achieve a satisfactory obliteration rate (1). Younger age, male gender, small size, small target volume, higher radiation dose, and a lone major draining vein have been found to be associated with obliteration after SRS for bAVMs (2). Partial embolization was generally used to reduce the volume of large bAVMs to facilitate the complete obliteration after the following SRS (3), and the targeted embolization for the comorbid aneurysms and arteriovenous fistulas may be beneficial in reducing the rupture risk after SRS (4, 5). Unfortunately, many recent studies implied a negative effect of partial nidus embolization on obliteration rates after SRS (1). However, those previous studies had some non-negligible limitations, such as the combination strategy applied post-embolization characteristics in the comparison of baseline, and the combination strategy tended to be used in larger bAVMs (1), which resulted in a more severe condition in the combination group. Therefore, due to the inherent differences in baseline characteristics between the combined upfront embolization and SRS and SRS alone, the comparison was flawed and unauthentic. We performed a propensity score matching (PSM) analysis based on pre-embolization baseline characteristics to compare the outcomes of SRS with and without prior embolization for bAVMs.

METHODS

Patients Selection

We retrospectively reviewed 793 bAVMs out of the Beijing Tiantan bAVMs prospective registration research database (NCT04572568) from September 2011 to October 2014. The inclusion criteria were as follows: (1) The last treatment was SRS, (2) patients underwent single-session SRS, and (3) patients with more than 2 years clinical and radiological follow-up. The exclusion criteria were as follows: (1) patients who have received intervention other than embolization prior to SRS, (2) patients receiving staged SRS or multiple SRS, and (3) patients missing critical baseline information. Written informed consent for collecting clinical information was obtained from each patient at admission. The study was carried out according to the Helsinki Declaration guideline.

Patients were categorized into two groups, combined upfront embolization and SRS (Em+SRS group) and SRS alone without prior embolization (SRS group).

Study Parameters

Baseline demographic, clinical features, and imaging data were collected. The baseline clinical characteristics included age on admission, sex, onset manifestation (hemorrhage, seizure, neurofunctional deficits, and others). The hemorrhagic presentation was defined as hemorrhage that could be ascribed to AVM. In terms of morphological characteristics, deep location was defined as nidus involving basal ganglia, thalamus, or brainstem. The definition of other angioarchitecture features were consistent with the reported terminology provided by the joint committee led by the American Society of Interventional and Therapeutic Neuroradiology (6). Nidus volume was calculated by the ABC/2 method on DSA (7). The Spetzler–Martin Grading System (SM), Virginia Radiosurgery AVM Scale (VRAS), and Modified Radiosurgery-Based AVM Score (mRBAS) were used to predict the long-term neurofunctional outcomes (8–10).

Clinical follow-up was conducted at the first 3–6 months and annually after discharge by clinical visit and telephone interview, and researchers who performed clinical follow-up assessments were blinded to the treatment modalities. In terms of imaging follow-up, magnetic resonance imaging (MRI) was routinely performed semiannual for the first 2 years after SRS and annually thereafter. Confirmatory digital subtraction angiography (DSA) was recommended to patients with complete obliteration on follow-up MRI. AVM obliteration was defined as a lack of abnormal flow voids on MRI or an absence of anomalous arteriovenous shunting on DSA.

The primary outcome was defined as AVM obliteration confirmed by MRI or DSA. The secondary outcomes comprised functional status, post-SRS hemorrhage, all-cause mortality, radiation-induced changes (RIC), including edema and cyst formation. The functional status was assessed by modified Rankin Scale (mRS) score system (favorable: 0–2, poor: 3–6).

Embolization and Radiosurgery Procedures

The intraoperative embolization strategy depends on the consensus reached by a multidisciplinary meeting composed of senior neurointerventionists and neuroradiologists. A biplane angiography system was used (Siemens, Germany or Philip, Netherland), and the endovascular embolization was performed after induction of general anesthesia. In order to reduce the lesion volume and the risk of hemorrhage, we tend to embolize the lesion supplied by the main feeding artery or target embolization of the high-risk bleeding factors, such as aneurysm, arteriovenous fistula, etc. The main polymeric embolic agent used in this series is Onyx 18 (eV3, Inc.), which contains 6% ethylene vinyl alcohol and 94% dimethyl sulfoxide.

Stereotactic planning neuroimaging results are imported into Leksell Gamma-Plan workstation (Elekta AB, Elekta Company, Stockholm, Sweden) for definition and dose planning. T1 contrast-enhancement sequence and T2 sequence on 3D stereotactic MRI were used to delineate the radiation target. Dose planning was based on the location and volume of bAVM.

Statistical Analysis

Categorical variables are presented as counts (with percentages); continuous variables are presented as the mean ± standard deviations (SD). A 1:1 PSM (with a caliper of 0.02 standard deviations) was performed to match the two groups with similar baseline data, such as age, gender, hemorrhage, volume, location, angioarchitecture, maximum and margin dose, and mRS at admission, mRBAS and VRAS) Absolute standardized differences was used to verify the matching results (**Figure 1**). At the comparison of baseline characteristics between Em+SRS and SRS, Pearson chi-square test or Fisher exact test was used to compare the categorical variables, and the two-tailed *t*-test was employed to compare the continuous variables (normal distribution variables). Wilcoxon rank-sum test was applied to compare non-normal distribution continuous variables. Univariable binary logistic regression analysis was applied to assess the odds ratios (ORs) and associated 95% confidence intervals (CI) of outcomes between these two groups. The cumulative rates of obliteration, post-SRS hemorrhage, and all-cause mobility were compared between the two groups using Kaplan–Meier survival analysis (log-rank test) to assess the hazard ratios (HRs) and associated 95% CI. Considering the difference in follow-up time and the cumulative effect of time between the two groups, we used the 5 years and the last follow-up two times nodes to calculate the *p*-value in the above survival analysis. A value of $p < 0.05$ was considered to be statistically significant. Statistical analysis was performed using SPSS (version 25.0, IBM, New York, USA).

RESULTS

Baseline Characteristics

A total of 152 patients were included in this study after PSM analysis (**Table 1**). The mean age was 29.8 ± 13.5 years old, and 93 (61.2%) patients presented with hemorrhage. One hundred thirty-two (86.8%) lesions were supratentorial, and 35 (23.0%) niduses were classified as deep locations. The mean nidus volume was 12.4 ± 18.4 cm^3. Half of the AVMs (77, 50.7%) were Spetzler–Martin (SM) grades I–II. The most common VRAS score noted were VRAS = 2 (48 cases, 31.6%) and VRAS = 3 (51 cases, 33.6%), followed by VRAS = 4 (36 cases, 23.7%). The mean mRBAS score was 2.0 ± 1.9. The median interval between the embolization and SRS was 0.2 (interquartile range = 0.8) years. In terms of intraoperative details, the mean margin dose was 16.7 ± 3.1 Gy, and the maximum dose was 33.2 ± 5.0 Gy. Finally, the mean clinical follow-up duration was 6.2 ± 3.2 years, and the radiographic follow-up lasted for an average of 2.9 ± 2.3 years. After PSM, there were no statistical differences in baseline characteristics between the SRS group and Em+SRS group.

Primary and Secondary Outcomes

After an average of 2.9 ± 2.3 years of radiological follow-up, 58 (38.2%) patients achieved complete obliteration, and the obliteration rate was similar between SRS and Em+SRS (44.7 vs. 31.6%; OR, 1.754; 95% CI, 0.905–3.401; $p = 0.096$) (**Table 2**), and among these patients, 33 (56.9%) patients were confirmed by DSA (**Figure 2**). However, in a further analysis, the SRS group was superior to the Em+SRS group in terms of cumulative occlusion rate at a follow-up of 5 years (HR, 1.778; 95% CI, 1.017–3.110; $p = 0.033$) (**Figure 2A**).

At secondary outcomes, 143 (94.1%) patients achieved favorable functional state, and the favorable functional state was similar between SRS and Em+SRS (96.1 vs. 92.1%; OR, 2.086; 95% CI, 0.502–8.665; $p = 0.312$). Ten (6.6%) patients suffered subsequent hemorrhages after treatment, the risk of post-SRS hemorrhage was similar between these two groups (3.9 vs. 9.2%; OR, 0.405; 95% CI, 0.101–1.630; $p = 0.203$). In terms of cumulative post-SRS hemorrhage rate, it was 1.32, 5.11, and 5.11% at 2, 4, and 6 years in the SRS group, and 1.32, 6.77, and 12.48% at 2, 4, and 6 years in the Em+SRS group (HR, 0.437; 95% CI, 0.127–1.510; $p = 0.217$) (**Figure 2C**). Four (2.6%) patients died during clinical follow-up, one (1.3%) patient in the SRS group and three (3.9%) patients in the Em+SRS group (OR, 0.324; 95% CI, 0.033–3.191; $p = 0.334$). The cumulative all-cause mortality had no statistical differences between the two groups in the Kaplan–Meier analysis (log-rank, $p = 0.336$) (**Figure 2B**). In addition, edema or cyst after SRS was also similar between these two groups (log-rank, $p = 0.991$) (**Figure 2D**). In addition, it should be mentioned that none of the patients had serious embolic complications after upfront embolization.

Outcomes of Ruptured Subgroup

We conducted a subgroup analysis based on hemorrhage presentation to further identify possible prognostic differences between SRS and Em+SRS. The baseline characteristics of the ruptured subgroup and unruptured subgroup are shown in the **Supplementary Tables 1**, **2**.

In the ruptured subgroup ($n = 93$) (**Table 3**), 41 (44.1%) patients achieved complete obliteration, and the SRS group could achieve higher obliteration rate than the Em+SRS group (56.5 vs. 31.9%; OR, 2.773; 95% CI, 1.190–6.464; $p = 0.018$). In the Kaplan–Meier analysis, the cumulative obliteration rate at 5 years was also higher in the SRS group than in the Em+SRS group (64.5 vs. 41.3%; HR, 2.012; 95% CI, 1.037–3.903; $p = 0.038$) (**Figure 3A**). In terms of secondary outcomes, including favorable functional state (95.7 vs. 89.4%; OR, 2.619; 95% CI, 0.482–14.243; $p = 0.265$), post-SRS hemorrhage (4.3 vs. 10.6%; OR, 0.382; 95% CI, 0.070–2.076; $p = 0.265$), all-cause mortality (0.0 vs. 4.3%; $p = 0.495$), edema, and cyst were all similar between these two interventional strategies. In addition, the cumulative post-SRS hemorrhage rate were similar between the two groups in the ruptured subgroup (log-rank, $p = 0.221$; **Figure 3C**).

Outcomes of Unruptured Subgroup

Among 59 patients with unruptured AVMs (**Table 4**), the overall obliteration rates and the cumulative obliteration rate

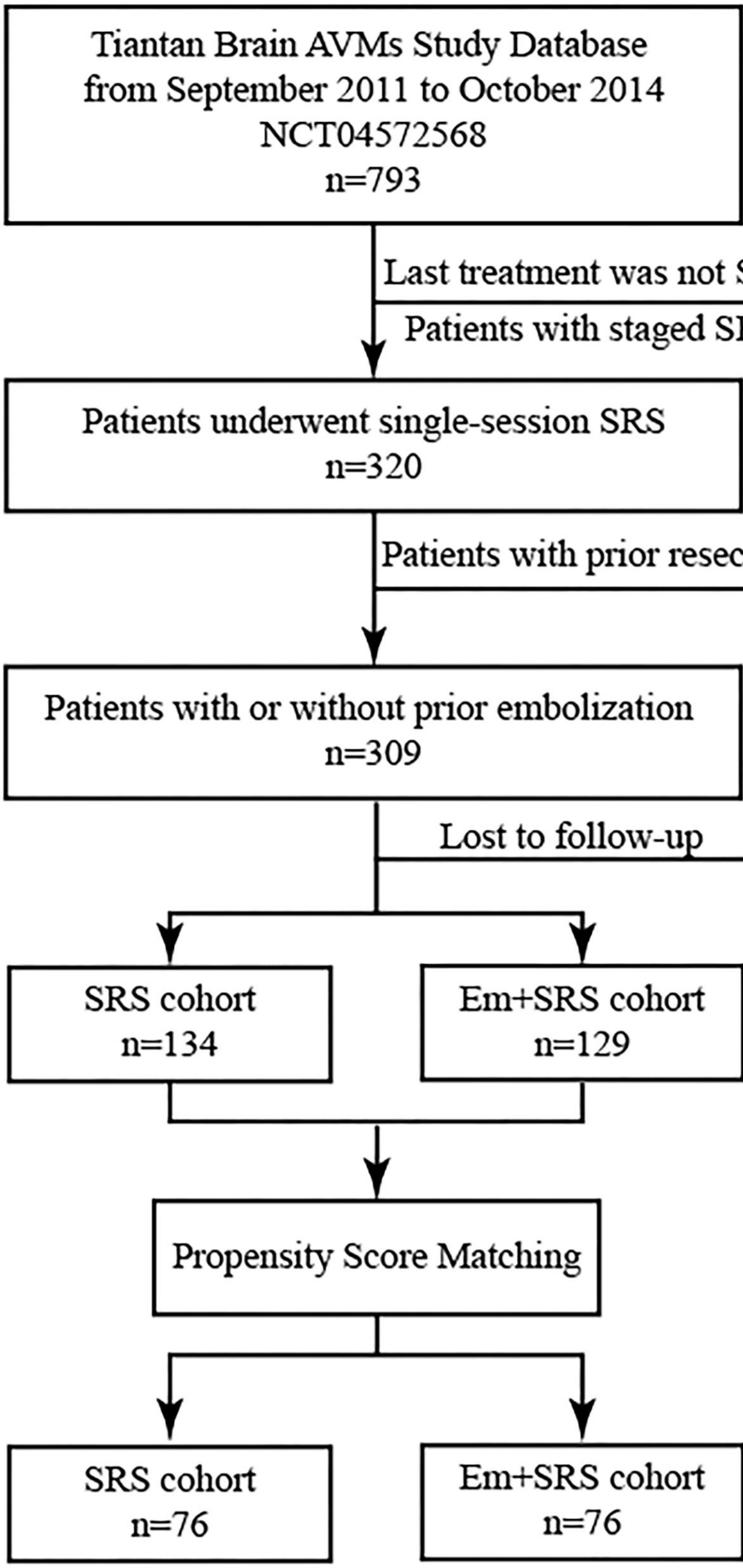

FIGURE 1 | Patient flowchart demonstrating patient selection and propensity score matching (PSM) process. AVM, arteriovenous malformation; SRS, stereotactic radiosurgery; Em+SRS, prior embolization to stereotactic radiosurgery.

TABLE 1 | Baseline characteristics of the whole cohort.

Characteristic	Total (n = 152)	SRS (n = 76)	Em+SRS (n = 76)	p-value
Female, n (%)	69 (45.4)	36 (47.4)	33 (43.4)	0.625
Age, mean year (SD)	29.8 (13.5)	30.6 (14.6)	29.0 (12.4)	0.454
Initial mRS score (SD)	0.9 (1.0)	0.9 (1.0)	0.9 (1.1)	0.938
Eloquent location, n (%)	101 (66.4)	52 (68.4)	49 (64.5)	0.606
Ruptured, n (%)	93 (61.2)	46 (60.5)1	47 (61.8)	0.868
Supratentorial, n (%)	132 (86.8)	64 (84.2)	68 (89.5)	0.337
Left hemisphere, n (%)	83 (54.6)	40 (52.6)	43 (56.6)	0.625
Deep venous drainage, n (%)	63 (41.1)	28 (36.8)	35 (46.1)	0.249
Diffuseness, n (%)	23 (15.1)	12 (15.8)	11 (14.5)	0.821
Deep location, n (%)	35 (23.0)	17 (22.4)	18 (23.7)	0.847
Aneurysm, n (%)	18 (11.8)	6 (7.9)	12 (15.8)	0.132
Nidus volume, ml (SD; range)	12.4 (18.4)	12.0 (18.3)	12.9 (18.7)	0.761
SM grade				0.871
I-II	77 (50.7)	38 (50.0)	39 (51.3)	
III-V	75 (49.3)	38 (50.0)	37 (48.7)	
VRAS				0.412
0–2	65 (42.8)	35 (46.1)	30 (39.5)	
3–4	87 (57.2)	41 (53.9)	46 (60.5)	
mRBAS (SD)	2.0 (1.9)	1.9 (1.9)	2.0 (1.9)	0.832
SRS margin dose, mean Gy (SD)	16.7 (3.1)	17.0 (4.0)	16.5 (1.6)	0.355
SRS maximum dose, mean Gy (SD)	33.2 (5.0)	33.6 (14.6)	29.0 (12.4)	0.356
Clinical follow-up, mean years (SD)	6.2 (3.2)	6.4 (3.5)	6.0 (2.9)	0.364
Radiological follow-up, mean years (SD)	2.9 (2.3)	3.1 (2.7)	2.8 (1.8)	0.480

Em, embolization; mRBAS, modified radiosurgery-based AVM score; mRS, modified Rankin Scale; SD, standard deviation; SM, Spetzler–Martin; SRS. stereotactic radiosurgery; VRAS, Virginia Radiosurgery AVM Scale.

VRAS (Virginia Radiosurgery AVM Scale): volume 2–4 cm^3, eloquent location, or hemorrhage = 1, volume >4 cm^3 = 2.

mRBAS (modified radiosurgery-based AVM score) = 0.1 × volume (cm^3) + 0.02 × age (years) + 0.5 × location (deep location: basal ganglia, thalamus, or brainstem = 1, else location = 0).

TABLE 2 | Primary and secondary outcomes of the whole cohort.

Outcomes	Total (n = 152)	SRS (n = 76)	Em+SRS (n = 76)	OR (95% CI)	p-value
Primary outcomes					
AVM obliteration, n (%)	58 (38.2)	34 (44.7)	24 (31.6)	1.754 (0.905–3.401)	0.096
Secondary outcomes					
Favorable functional state	143 (94.1)	73 (96.1)	70 (92.1)	2.086 (0.502–8.665)	0.312
Post-SRS hemorrhage, n (%)	10 (6.6)	3 (3.9)	7 (9.2)	0.405 (0.101–1.630)	0.203
All-cause mortality, n (%)	4 (2.6)	1 (1.3)	3 (3.9)	0.324 (0.033–3.191)	0.334
RIC					
Edema, n (%)	2 (1.3)	1 (1.3)	1 (1.3)	1.000 (0.061–16.285)	> 0.999
Cyst, n (%)	2 (1.3)	1 (1.3)	1 (1.3)	1.000 (0.061–16.285)	> 0.999

AVM, arteriovenous malformation; CI, confidence interval; Em, embolization; OR, odds ratio; RIC, radiation-induced changes; SRS, stereotactic radiosurgery.

were similar between the two groups (p = 0.711, p = 0.671, respectively) (**Figure 3B**). There was no significant difference between the secondary prognostic parameters of the two groups (favorable functional state, p = 0.981; post-SRS hemorrhage, p = 0.542; all-cause mortality, p = 0.981; edema, p = 0.981). In addition, the cumulative post-SRS hemorrhage rate were similar between the SRS and Em+SRS in the unruptured subgroup (log-rank, p = 0.629) (**Figure 3D**).

DISCUSSION

Whether pre-SRS embolization could facilitate the post-SRS obliteration for bAVMs remain controversial (11–15). We noticed that niduses in the Em+SRS group had higher SM grades and more complicated angioarchitectures when data derived from post-embolization characteristics, rather than pre-embolization lesions, were used as baseline

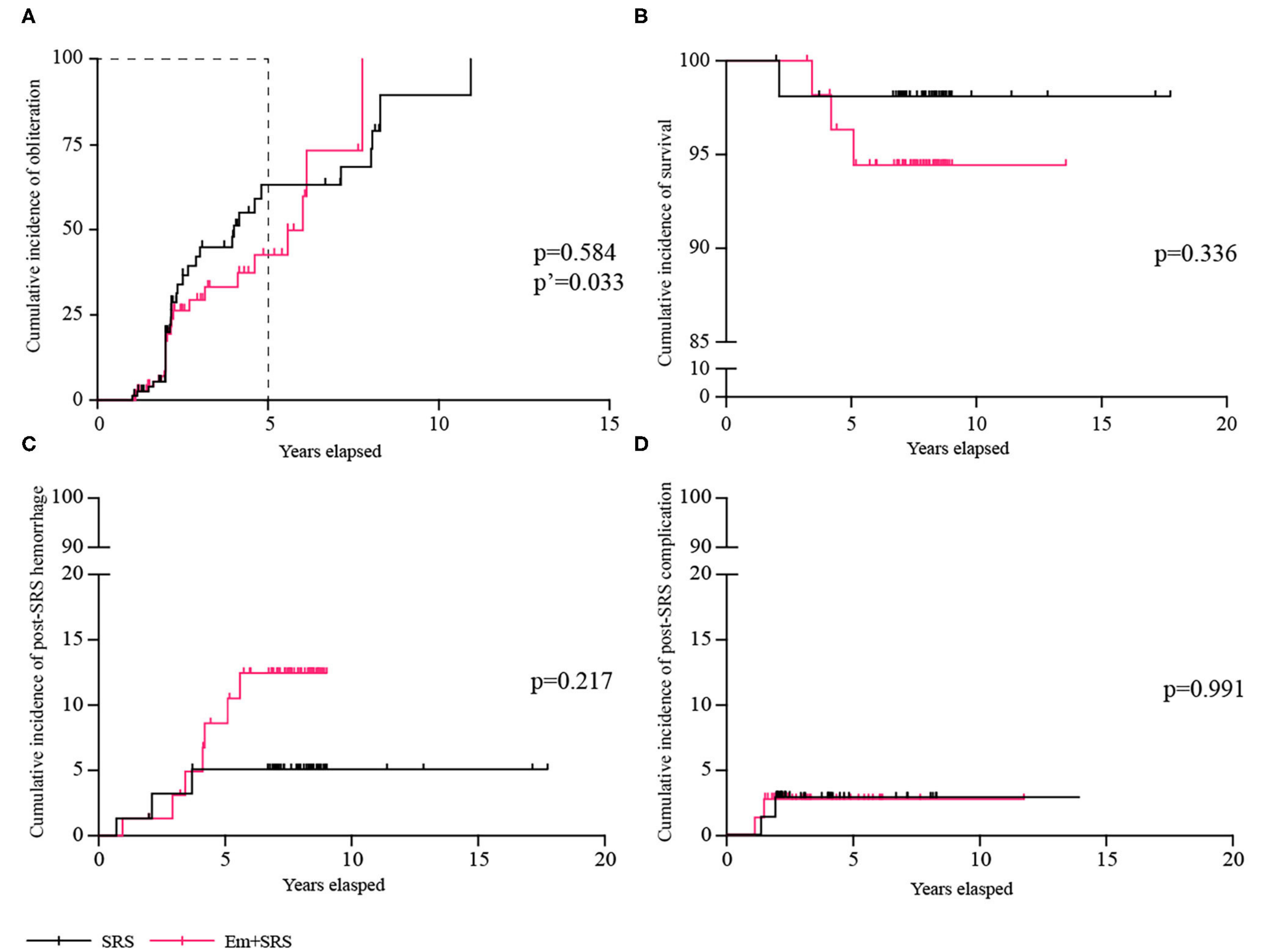

FIGURE 2 | Comparisons of cumulative incidence between SRS and Em+SRS. **(A)** AVM obliteration. **(B)** Survival. **(C)** Post-SRS hemorrhage. **(D)** Post-SRS complication. AVM, arteriovenous malformation; Em+SRS, embolization + stereotactic radiosurgery. p'-Value refers to the result of a 5-year follow-up.

characteristics. Therefore, we conducted a PSM analysis based on pre-embolization characteristics to compare the outcomes of SRS with and without prior embolization for bAVMs. Finally, we found that pre-SRS endovascular embolization may indeed have a negative effect on post-SRS obliteration, and the post-SRS hemorrhage and post-SRS RIC were similar between the SRS group and the Em+SRS group. In the subgroup analysis, the SRS only group have significantly higher obliteration rates than the Em+SRS group in the ruptured group, but no such phenomenon was found in the unruptured group.

SRS is considered as a reliable strategy for the treatment of small bAVMs (nidus volume <12 cm^3 or diameter <3 cm) (16), and the obliteration rate was reported to be 56.8–80% (1, 17, 18). In this study, the long-term obliteration rate of the whole cohort was 38.2%, slightly lower than most previous studies (1), which may be due to the smaller marginal dose (16.7 ± 3.1 Gy) and larger nidus volume (12.4 ± 18.4 cm^3) in our study. A combination of embolization and SRS is frequently used to treat large bAVMs on the basis of the assumption that prior embolization may facilitate post-SRS obliteration of the residual lesion by reducing the nidus volume and slowing the nidus blood flow (3, 14). However, many recent studies revealed that prior partial embolization may have a negative effect on post-SRS obliteration (1). Russell et al. conducted a meta-analysis to find that the combination strategy is associated with lower obliteration rates than SRS alone (48.4 vs. 62.7%) (1). In this study, we also found that the combination strategy has lower obliteration rate than that of the SRS alone strategy (31.6 vs. 44.7%, no statistical difference). However, it should be noted that the obliteration rate of the combined strategy was significantly lower than that of the SRS alone strategy alone at the end of the 5-year follow-up post-operatively (p = 0.033). Several hypotheses have been proposed to explain why partial nidus embolization could decrease obliteration rates after SRS. Partial nidus embolization may fragment the nidus into scattered sections, thus, transforming a compact nidus into a

TABLE 3 | Primary and secondary outcomes in the ruptured subgroup.

Outcomes	Total ($n = 93$)	SRS ($n = 46$)	Em+SRS ($n = 47$)	OR (95% CI)	*p*-value
Primary outcomes					
AVM obliteration, *n* (%)	41 (44.1)	26 (56.5)	15 (31.9)	2.773 (1.190–6.464)	0.018*
Secondary outcomes					
Favorable functional state	86 (92.5)	44 (95.7)	42 (89.4)	2.619 (0.482–14.243)	0.265
Post-SRS hemorrhage, *n* (%)	7 (7.5)	2 (4.3)	5 (10.6)	0.382 (0.070–2.076)	0.265
All-cause mortality, *n* (%)	2 (2.2)	0	2 (4.3)	-	0.495
RIC					
Edema, *n* (%)	0	0	0	-	-
Cyst, *n* (%)	2 (2.2)	1 (2.2)	1 (2.2)	1.022 (0.062–16.845)	0.988

AVM, arteriovenous malformation; CI, confidence interval; Em, embolization; OR, odds ratio; RIC, radiation-induced changes; SRS, stereotactic radiosurgery.
**Statistical significance ($p < 0.05$).*

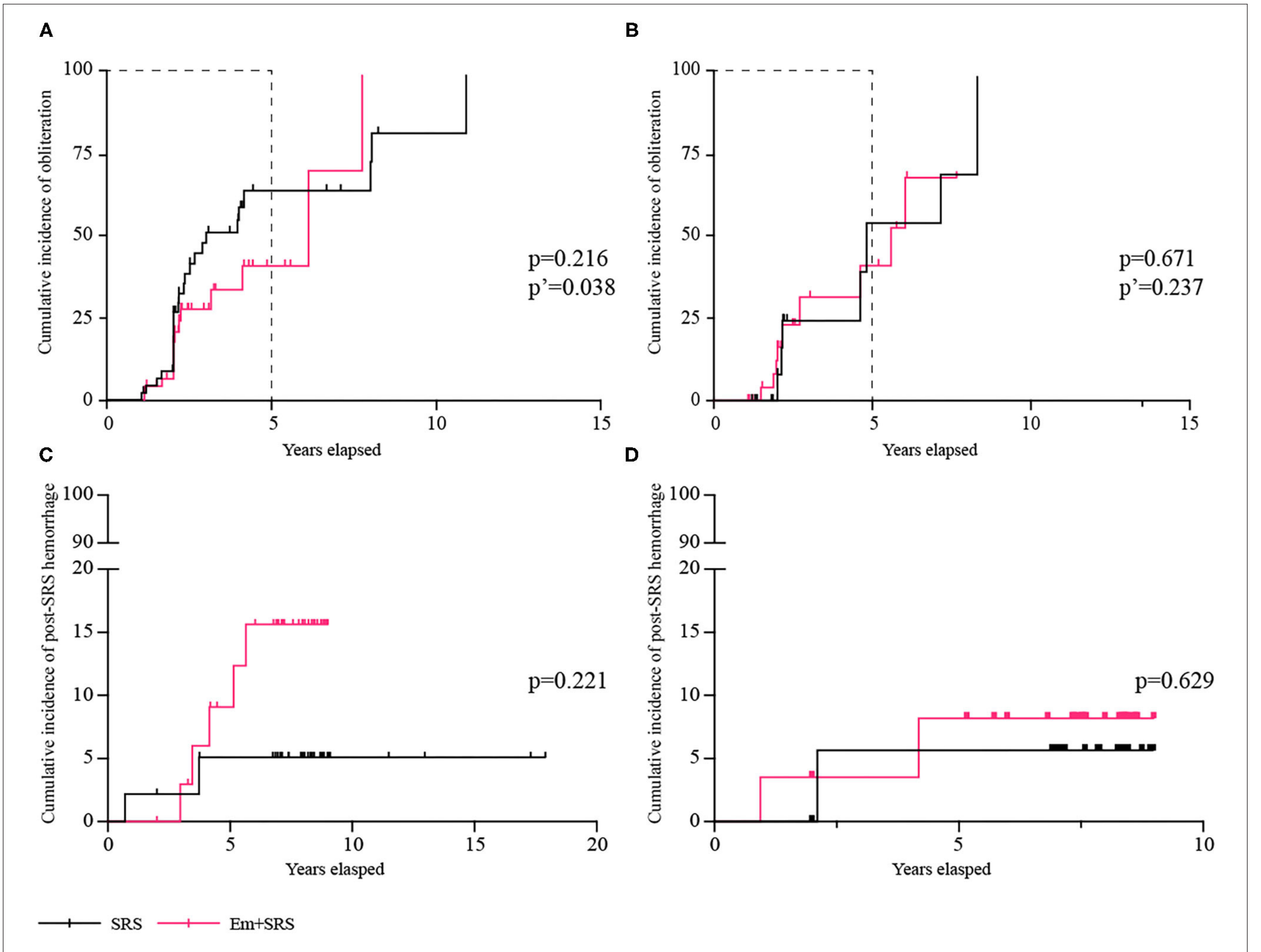

FIGURE 3 | Comparisons of cumulative incidence in ruptured subgroup between SRS and Em+SRS. **(A)** AVM obliteration. **(C)** Post-SRS hemorrhage. Comparisons of cumulative incidence in the unruptured subgroup between SRS and Em+SRS: **(B)** AVM obliteration. **(D)** Post-SRS hemorrhage. AVM, arteriovenous malformation; Em+SRS, embolization + stereotactic radiosurgery. p'-Value refers to the result of a 5-year follow-up.

TABLE 4 | Primary and secondary outcomes of unruptured subgroup.

Outcomes	Total ($n = 59$)	SRS ($n = 30$)	Em+SRS ($n = 29$)	OR (95% CI)	*p*-value
Primary outcomes					
AVM obliteration, *n* (%)	17 (28.8)	8 (26.7)	9 (31.0)	0.808 (0.261–2.498)	0.711
Secondary outcomes					
Favorable functional state	57 (96.6)	29 (96.7)	28 (96.6)	1.036 (0.062–17.377)	0.981
Post-SRS hemorrhage, *n* (%)	3 (5.1)	1 (3.3)	2 (6.9)	0.466 (0.040–5.433)	0.542
All-cause mortality, *n* (%)	2 (3.4)	1 (3.3)	1 (3.4)	0.966 (0.058–16.199)	0.981
RIC					
Edema, *n* (%)	2 (3.4)	1 (3.3)	1 (3.4)	0.966 (0.058–16.199)	0.981
Cyst, *n* (%)	0	0	0	-	-

AVM, arteriovenous malformation; CI, confidence interval; Em, embolization; OR, odds ratio; RIC, radiation-induced changes; SRS, stereotactic radiosurgery.

diffuse one, and consequently increasing the difficulty of target delineation (19, 20). Moreover, embolic agents may suppress the obliteration rates by several mechanisms, including dose reduction by radiation absorption or scattering (21), obscuration of the residual nidus on post-embolization neuroimaging, and recanalization or pseudo-occlusion (11). Furthermore, embolization may stimulate and promote angiogenesis of bAVMs, consequently increasing the radioresistance of residual nidus (22, 23). Our team believes that the fragmentation caused by partial embolization may be the main causes leading to the decrease in obliteration rate, which makes it impossible to accurately locate the nidus boundary when making the irradiation plan. However, we also noted that the mRBAS of our cohort was 2.0 ± 1.9. Based on our previous study (18), the patients with mRBAS >1.5 seem to be inclined to be more suitable for SRS only instead of the combination strategy.

In this study, we found no significant difference in post-SRS hemorrhage between the two strategies. Pre-SRS embolization was usually used to target angiographic features with a high risk of bleeding, such as comorbid aneurysms and arteriovenous fistulas (13). However, some previous studies reported that the Em+SRS strategy may have higher post-SRS bleeding rate (1), the potential mechanism of which may be the increased vascular stress in residual lesions after partial embolization, or targeted embolization of high-risk bleeding factors cannot effectively reduce the risk of rupture (24, 25). The edema and cyst were similar between the two strategies, and the overall rate of edema and cyst in our study was relatively lower than in previous studies. Several studies suggested that RIC was associated with a higher margin dose (26), and partial embolization could reduce the risk of RIC (27). The margin dose in our study was generally low (16.7 ± 3.1 Gy), which may be the cause of the lower incidence of edema and cyst.

Several previous studies indicated lower obliteration rates for unruptured bAVMs compared with ruptured AVMs after SRS (28, 29). The investigators postulated a possible synergism between radiation and hemorrhage for AVM obliteration *via* mechanisms of endothelial damage, myofibroblast proliferation, and progressive endoluminal occlusion and thrombosis (30, 31). Nevertheless, previous studies did not explore the obliteration rate of the SRS strategy and Em+SRS strategy in the ruptured and unruptured subgroups. In this study, the SRS group was found to have significantly higher obliteration rates than the Em+SRS group in the ruptured cohort. While no such phenomenon was found in the unruptured cohort, we surmised that embolization may disturb the synergism and lead to lower obliteration rates.

Therefore, it is more reasonable to adopt SRS alone for ruptured bAVMs, while for unruptured bAVMs, both strategies are acceptable.

However, is the combination strategy useless? Of course not. Hemodynamics is thought to be closely related to the biological behavior and development of bAVM (32–34), and it is traditionally believed that fast and large blood flow is not conducive to nidus obliteration after SRS (17). Hu et al. suggested that stagnant venous outflow predicts bAVM obliteration after Gamma knife radiosurgery by quantitative DSA (35), and Rivera et al. proposed that partial embolization could prolong the time to peak values at the arterial feeder, drainage vein, and venous sinus (36). Therefore, choosing a reasonable target endovascular embolization strategy that is hemodynamically beneficial to the nidus obliteration may be the next research direction of the combination strategy.

Limitation

Despite our best efforts to improve the design defects of previous researches by adjusting for baseline differences and selection biases using PSM. There were still several limitations: the main limitations were its retrospective nature. Some patients cannot maintain strict and regular imaging follow-up, so we cannot know the exact time of nidus occlusion in these patients. Another limitation is that not all patients had DSA to confirm obliteration. In order to reduce the deviation caused by this limitation, we commissioned two senior neuroradiologists to evaluate the last radiographic follow-up independently, and a third more senior professor-level experts will reevaluate if the result is controversial.

CONCLUSION

Although there was no significant difference in the overall obliteration rate between the two strategies, pre-SRS endovascular embolization may have a negative effect on post-SRS obliteration and did not negatively affect post-SRS hemorrhage and complications for bAVMs. In the subgroup analysis, the obliteration rates of SRS only strategy was significantly higher than that of the Em+SRS strategy in the ruptured cohort, while no such phenomenon was found in the unruptured cohort.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Data will be shared with qualified investigators upon request. Requests to access these datasets should be directed to Yuanli Zhao, zhaoyuanli@126.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital, China and the ethics number was KY 2020-003-01. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DY and YZ conceptualized and designed the study. YL, SS, and AL were the operators. ZL, HZ, KY, RL, XM, HJ, and DG acquired the data. DY, YC, and HH analyzed and interpreted the data. DY wrote and prepared the original draft. XC, SS, and YZ wrote, reviewed, and edited the manuscript. YZ supervised the study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.752164/full#supplementary-material

Supplementary Figure 1 | Standardized differences of baseline characteristics between brain AVM patients who received stereotactic radiosurgery with or without prior embolization before after matching. AVM, arteriovenous malformation; VRAS, Virginia Radiosurgery AVM Scale; mRBAS, modified radiosurgery-based AVM score; Dashed vertical lines indicate standardized differences of 0.2.

Supplementary Figure 2 | Distribution of Radiological follow-up methods between different primary outcomes. MRI, magnetic resonance imaging; DSA, digital subtraction angiography.

Supplementary Table 1 | Baseline characteristics of prior hemorrhage subgroup.

Supplementary Table 2 | Baseline characteristics of unruptured subgroup.

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Blood Pressure After Endovascular Thrombectomy and Malignant Cerebral Edema in Large Vessel Occlusion Stroke

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Background: Elevated blood pressure (BP) can cause blood–brain barrier disruption and facilitates brain edema formation. We aimed to investigate the association of BP level after thrombectomy with the development of malignant cerebral edema (MCE) in patients treated with endovascular thrombectomy (EVT).

Methods: Consecutive patients who underwent EVT for an anterior circulation ischemic stroke were enrolled from three comprehensive stroke centers. BP was measured hourly during the first 24 h after thrombectomy. MCE was defined as swelling causing a midline shift on the follow-up imaging within 5 days after EVT. Associations of various BP parameters, including mean BP, maximum BP (BP_{max}), and BP variability (BPV), with the development of MCE were analyzed.

Results: Of the 498 patients (mean age 66.9 ± 11.7 years, male 58.2%), 97 (19.5%) patients developed MCE. Elevated mean systolic BP (SBP) (OR, 1.035; 95% CI, 1.006–1.065; $P = 0.017$) was associated with a higher likelihood of MCE. The best SBP_{max} threshold that predicted the development of MCE was 165 mmHg. Additionally, increases in BPV, as evaluated by SBP standard deviation (OR, 1.061; 95% CI, 1.003–1.123; $P = 0.039$), were associated with higher likelihood of MCE.

Interpretation: Elevated mean SBP and BPV were associated with a higher likelihood of MCE. Having a $SBP_{max} > 165$ mm Hg was the best threshold to discriminate the development of MCE. These results suggest that continuous BP monitoring after EVT could be used as a non-invasive predictor for clinical deterioration due to MCE. Randomized clinical studies are warranted to address BP goal after thrombectomy.

Keywords: stroke, thrombectomy, cerebral edema, blood pressure, large vessel occlusion

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INTRODUCTION

Malignant cerebral edema (MCE) is one of the serious clinical events in large-vessel occlusion stroke (LVOS), as it can lead to rapid neurologic deterioration (1). In recent years, endovascular thrombectomy (EVT) has been confirmed to improve functional outcomes for selected patients with LVOS of the anterior circulation (2). However, MCE is still a common phenomenon after thrombectomy (3). Moreover, the presence of MCE indicates a reduced likelihood of good functional outcomes and a higher likelihood of mortality (3, 4). Therefore, it is important to identify factors that can predict MCE in patients who have undergone EVT. A meta-analysis showed that younger age, a higher National Institutes of Health Stroke Scale (NIHSS) score, and large ischemic signs on computed tomography are reliable predictors for MCE (5). Nevertheless, these factors cannot be intervened.

Blood pressure (BP) management following treatment of LVOS patients with EVT is an important scientific question (6). In a recently published meta-analysis, an elevated systolic BP (SBP) level after EVT was associated with poor outcomes in patients with LVOS (7). Moreover, moderate BP control (<160/90 mmHg) seems to be associated with better clinical outcomes and lowers the odds of 3-month mortality (8, 9). Theoretically, elevated BP could cause blood–brain barrier (BBB) disruption and facilitate cerebral edema (CED) formation (10). Moreover, higher BP after reperfusion may exacerbate the reperfusion injury (11). These mechanisms may result in the development of MCE. However, data on the association of BP level after EVT with the development of MCE are relatively scarce.

Therefore, in this study, we investigated the association between mean BP level after thrombectomy and the development of MCE in patients treated with EVT. Moreover, determined the best post-EVT maximum BP (BP_{max}) threshold that predicts the development of MCE. Finally, we evaluated the effect of BP variability (BPV) on the development of MCE.

METHODS

Study Participants

This study was a retrospective analysis of a prospective registry. We enrolled anterior circulation LVOS patients who underwent EVT at three comprehensive stroke centers (Jinling Hospital between January 2014 and December 2018, Yijishan Hospital between July 2015 and December 2019 and the second affiliated Hospital of Fujian Medical University between January 2016 and December 2019). The study was approved by the local ethics committee.

Patients were included if they fulfilled the following inclusion criteria: (1) age $\geq$ 18 years; (2) onset to puncture time (OTP) $\leq$480 min; (3) admission NIHSS score $\geq$ 6, admission Alberta Stroke Program Early CT (ASPECT) score $\geq$ 6, and pre-stroke modified Rankin Scale (mRS) score $<$ 2; and (4) patients with LVOS, including the internal carotid artery (ICA), the middle cerebral artery (MCA) or the anterior cerebral artery (ACA) occlusion. We excluded patients with multiple vessel occlusion (MVO), incomplete BP record, and without post-procedural imaging. Additionally, EVT was performed under local anesthesia in all centers. The flow chart of the inclusion of the study population is displayed in **Figure 1**.

Data Collection

All consecutive patients were prospectively documented. The clinical data included age, sex, medical history of hypertension, diabetes mellitus type 2, admission NIHSS and ASPECT scores, and the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.

BP data were consecutively recorded 24 h after EVT. BP goal was determined by the operator upon the end of thrombectomy or according to institutional protocol. BP was measured by non-invasive BP monitoring devices each hour during the first 24 h after EVT. Mean BP, BP_{max}, and BPV during the first 24 h were analyzed. BP_{max} was defined as the highest BP value in 24 h after EVT.

We calculated BPV for both SBP and diastolic BP (DBP) using three statistical methodologies: standard deviation (*SD*), coefficient of variation (*CV*), and successive variation (*SV*). *SD* was defined as the dispersion of a dataset relative to its mean and is calculated as the square root of the variance by determining the variation between each data point relative to the mean. *CV* was defined as the ratio of the *SD* and the mean. *SV* was calculated as the square root of the average squared difference between two successive BP measurements.

In addition, data on the use of continuous intravenous antihypertensive agents were collected for analysis.

The procedural variables were recorded by the operators, including OTP, onset to reperfusion time (OTR), occlusion location, the first thrombectomy approach (stent retriever first, aspiration first, angioplasty, or stent first), bridging therapy, recanalization status, and collateral status.

Recanalization status was evaluated by the modified Thrombolysis in Cerebral Infarction (mTICI) grading system. Successful recanalization was defined as an mTICI score of 2b or 3. Collateral circulation was assessed according to retrograde contrast opacification of vessels within the occluded area on delayed pre-treatment digital subtraction angiography (DSA) images (12). The collateral grading was classified as follows: Grade 0 was assigned if there was no significant reconstitution in the territory of the occluded vessel or if the collateral flow reached less than one-third of the occluded vessel territory, grade 1 was assigned if the collateral flow reached less than two-thirds and more than one-third of the occluded vessel territory, and grade 2 was assigned if the collateral flow reached more than two-thirds of the occluded vessel territory or the proximal main stem. Good collateral circulation was defined as grade 2, and poor collateral circulation was defined as grade 0–1.

Definition of Malignant Cerebral Edema

For all included patients, the imaging characteristics were assessed by two experienced neurologists/interventionists (ZM Zhou and Q Yang), who were blinded to the clinical data. In the event of discrepancies, the final result was

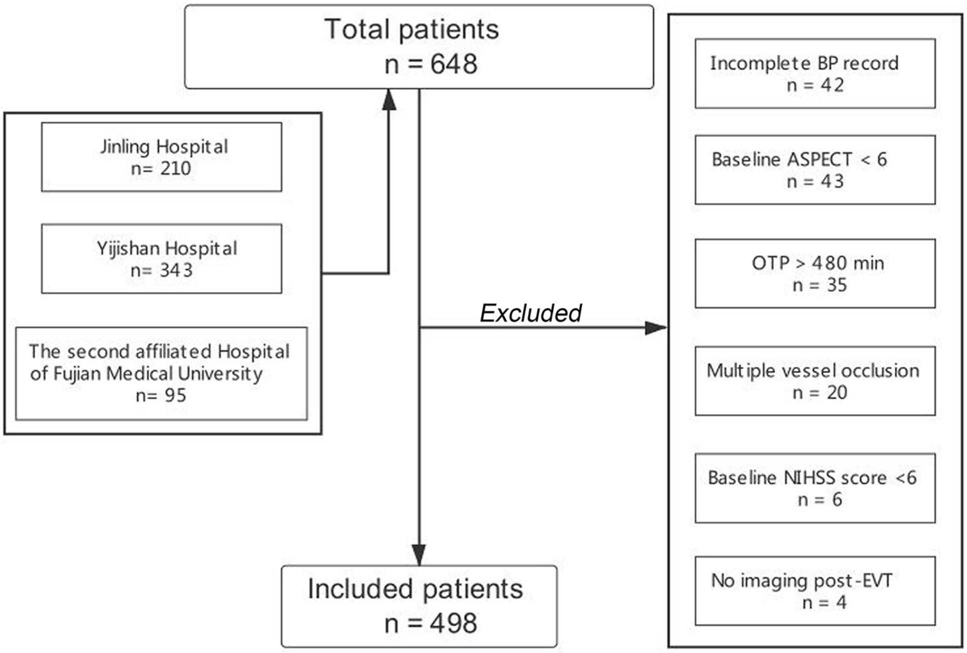

FIGURE 1 | Flow chart of the study population.

determined by consensus opinion. Referring to previous studies (13), CED subtypes were defined as follows: CED-1 was defined as brain swelling comprising less than one-third of the hemisphere, CED-2 was defined as swelling comprising more than one-third of the hemisphere, and CED-3 was defined as swelling causing midline shift. MCE were defined as CED-3. In these patients, CED was evaluated via the follow-up head computed tomography within 5 days after EVT.

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation (*SD*) or as the median (interquartile range, IQR). Categorical variables are presented as percentages. Continuous variables were analyzed using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square test or Fisher's exact test as appropriate. The threshold of SBP_{max} that best discriminated the development of MCE was determined by the area under the receiver operating characteristic curve (ROC) and Youden index. Multivariate logistic regression models were computed for the prediction of odds of MCE. The variables with $P < 0.1$ from the univariate analysis were entered into the logistic regression. Regression coefficients and odds ratios (OR) with two-sided 95% confidence intervals (CIs) for each of the variables included in the model were finally calculated. Repeated BP measurements were analyzed using the generalized estimating equation (GEE) method. All statistical analyses were computed using SPSS 25 (IBM Corp., Armonk, NY, USA).

RESULTS

During the study period, 648 anterior circulation LVOS patients who underwent EVT were registered in the three centers. A total of 498 patients were enrolled in the final cohort for analysis after excluding 150 patients due to incomplete BP record ($n = 42$), admission ASPECT score < 6 ($n = 43$), no imaging after EVT ($n = 4$), OTP > 480 min ($n = 35$), patients with MVO ($n = 20$), and admission NIHSS score < 6 ($n = 6$).

Of 498 patients, the mean age was 66.9 ± 11.7 years and 290 (58.2%) were male. The median NIHSS and ASPECT scores on admission were 16 (IQR13-20) and 9 (IQR8-10), respectively. The mean OTP time was 262.4 ±79.8 min, and the mean OTR time was 353.3± 93.6 min. Among the included patients, 219 (44%) had 3-month mRS 0–2. The baseline characteristics of the patients are shown in **Table 1**.

Serial BP Measurements and MCE

Among the enrolled patients, 97 (19.5%) patients developed MCE. We did not find differences in baseline BP between the patients with MCE and without MCE. However, patients with MCE had significantly higher mean SBP (128 mmHg vs. 123 mmHg, $P < 0.001$) after EVT than those without MCE. Moreover, in the multivariate logistic regression models, increases in mean SBP (OR, 1.035; 95% CI, 1.006–1.065; $P = 0.017$) were associated with a higher likelihood of MCE.

Additionally, a significant association was observed between BP serial measurements after thrombectomy and MCE (**Figure 2**). In patients with MCE, SBP throughout the 24 h

TABLE 1 | Demographics and baseline characteristics stratified by MCE.

	All patients (*n* = 498)	MCE (*n* = 97)	Non-MCE (*n* = 401)	*P*
Age, mean (SD), y	66.9 (11.7)	67 (10.9)	66.9 (11.8)	0.995
Male, *n* (%)	290 (58.2)	55 (56.7)	235 (58.6)	0.733
No. of BP measurements per patient, mean (SD)	22 (4.5)	22 (3.7)	21 (4.6)	0.878
Medical history, *n* (%)				
Hypertension	335 (67.3)	75 (77.3)	260 (64.8)	0.019
Diabetes mellitus	101 (20.3)	23 (23.7)	78 (19.5)	0.349
AF	236 (47.4)	47 (48.5)	189 (47.1)	0.815
Clinical characteristics, median (IQR)				
Baseline SBP, mmHg	145 (128–160)	150 (132–160)	143 (128–160)	0.085
Baseline DBP, mmHg	80 (72–91)	83 (70–95)	80 (74–90)	0.558
Admission NIHSS scores	16 (13–20)	18 (15–21)	15 (12–19)	< 0.001
Admission ASPECT scores	9 (8–10)	8 (7–9)	9 (8–10)	< 0.001
TOAST classification, *n* (%)				0.113
LAA	169 (33.9)	27 (27.8)	142 (35.4)	
Cardioembolic	277 (55.6)	58 (59.8)	219 (54.6)	
Undetermined or others	52 (10.5)	12 (12.4)	40 (10)	
Occlusion location, *n* (%)				0.001
ICA	209 (42)	64 (66)	145 (36.2)	
MCA/ACA (M1/A1)	254 (51)	28 (28.9)	226 (56.4)	
MCA/ACA (M2/A2)	35 (7)	5 (5.2)	30 (7.5)	
OTP, mean (SD), min	262.4 (79.8)	259.5 (76.1)	263.1 (80.8)	0.679
OTR, mean (SD), min	353.3 (93.6)	377.9 (90.8)	347.3 (93.4)	<0.001
Collateral score, *n* (%)				<0.001
Grade 0	92 (18.5)	37 (38.1)	55 (13.7)	
Grade 1	197 (39.6)	41 (42.3)	156 (38.9)	
Grade 2	209 (42)	19 (19.6)	190 (47.4)	
Bridging treatment, *n* (%)	119 (23.9)	30 (30.9)	89 (22.2)	0.070
Type of procedure, *n* (%)				0.194
Stent retriever first	389 (78.2)	79 (81.4)	310 (77.3)	
Aspiration first	59 (11.8)	13 (13.4)	46 (11.5)	
Angioplasty or stent first	50 (10)	5 (5.2)	45 (11.2)	
Continuous intravenous antihypertensive agents, *n* (%)	306 (61.4)	61 (62.9)	245 (61.1)	0.745
mTICI, 2b/3, *n* (%)	364 (73.1)	51 (52.6)	313 (78.1)	<0.001
90-day mRS 0–2, *n* (%)	219 (44)	8 (8.2)	211 (52.6)	<0.001

ASPECT, Alberta Stroke Program Early CT; AF, atrial fibrillation; ACA, anterior cerebral artery; DBP, diastolic blood pressure; ICA, internal carotid artery; LAA, large-artery atherosclerosis; mTICI, modified Thrombolysis in Cerebral Infarction; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; OTP, symptoms onset to groin puncture time; OTR, symptoms onset to reperfusion; SBP, systolic blood pressure.

post-EVT was higher than that in patients without MCE ($P = 0.036$ by the GEE method for MCE).

The Optimal Threshold of MCE-Predicting BP_{max} Value

After adjusting the admission NIHSS and ASPECT scores, the history of hypertension, baseline BP, OTR, occlusion location, bridging treatment, collateral circulation and mTICI, higher BP_{max} (OR, 1.021; 95% CI, 1.006–1.036; $P = 0.007$) were associated with a higher risk of developing MCE. The ROC-derived optimal cut-off value with Youden's index for predicting MCE was 165 mm Hg (41.2% sensitivity, 95% CI, 31.5–51.7%, 81.8% specificity, 95% CI, 77.6–85.4%; area under the curve 0.615; 95% CI, 0.549–0.681, $P < 0.001$). Binary logistic regression analysis showed that patients with SBP_{max} >165 mm Hg (OR, 2.729; 95% CI, 1.526–4.880; $P = 0.001$) was also associated with a higher likelihood of MCE. The distribution of CED in patients with SBP_{max} of ≤165 mm Hg and >165 mm Hg is shown in **Figure 3**.

In subgroup analyses, no heterogeneity in the effect of SBP_{max} >165 mm Hg on the development of MCE was observed according to subgroups of patients based on history of hypertension, collateral status, continuous intravenous antihypertensive agents, bridge therapy, occlusion site and recanalization status after correction for multiplicity (**Figure 4**). However, the adjusted ORs were not significant for patients with successful recanalization (OR, 1.991; 95% CI, 0.970–4.086; $P = 0.061$), those without history of hypertension (OR, 1.861;

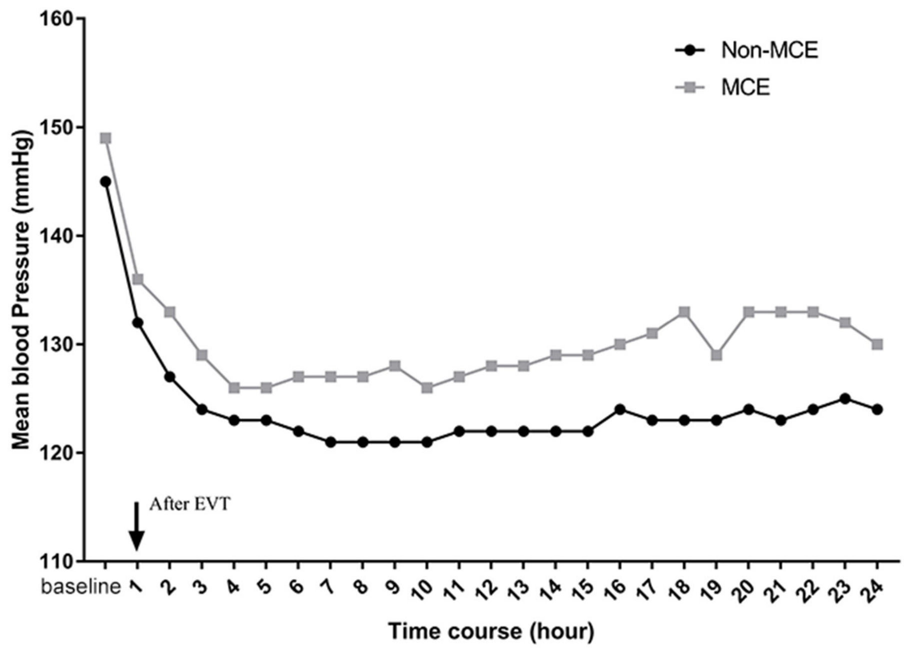

FIGURE 2 | Serial SBP levels plotted according to the development of MCE.

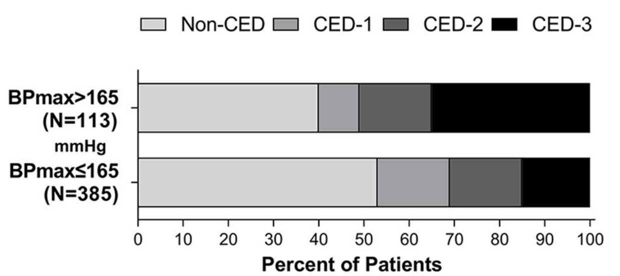

FIGURE 3 | Distribution of CED in patients with a SBP_{max} of ≤165 mm Hg and >165 mmHg during the first 24 h after EVT.

95% CI, 0.370–9.356; $P = 0.451$), those with ICA occlusion (OR, 1.920; 95% CI, 0.845–4.365; $P = 0.119$) and in those without intravenous antihypertensive agent (OR, 2.097; 95% CI, 0.557–7.892; $P = 0.274$).

Blood Pressure Variability and MCE

We further evaluated the effect of BPV on the development of MCE. In the multivariate logistic regression models, increases in SBP_{SD} (OR, 1.061; 95% CI, 1.003–1.123; $P = 0.039$) were associated with higher likelihood of MCE. There was no association for SBP_{CV}, SBP_{SV}, or any DBP parameters with the outcome parameters in the multivariate logistic models. Associations of BP parameters with MCE are shown in **Table 2**.

DISCUSSION

In this multicenter observational study, the main findings were as follows: First, patients with a higher mean SBP during the first 24 h after EVT were more likely to develop MCE. Moreover, the serial SBP measurements demonstrated that patients with MCE had significantly higher SBP values than those without MCE. Second, the best SBP_{max} threshold that predicted the development of MCE was 165 mmHg. Furthermore, subgroup analyses also revealed similar direction and size for the effect of post-EVT SBP_{max} >165 mm Hg on the development of MCE. Third, BPV, as evaluated by SBP_{SD}, was associated with the development of MCE in EVT-treated patients.

MCE is the leading cause of neurologic deterioration or death within the first days after ischemic stroke (1). Our previous study revealed that MCE is a common clinical condition in patients who underwent EVT and significantly impacts on clinical outcomes (4). Similar to the previous study, we found that MCE after EVT was not uncommon (19.5%).

BP management following EVT in LVOS patients is increasingly being taken seriously (6). Furthermore, BP is a readily modifiable parameter with the potential to improve outcomes. Recent studies have shown that elevated SBP level and variability after EVT are associated with poor outcomes among patients with LVOS (14, 15). Moreover, lowering of BP within the first 24 h after EVT may have a positive impact on clinical outcomes in treated patients (16). However, studies examining the association of BP parameters after procedure with MCE are largely lacking.

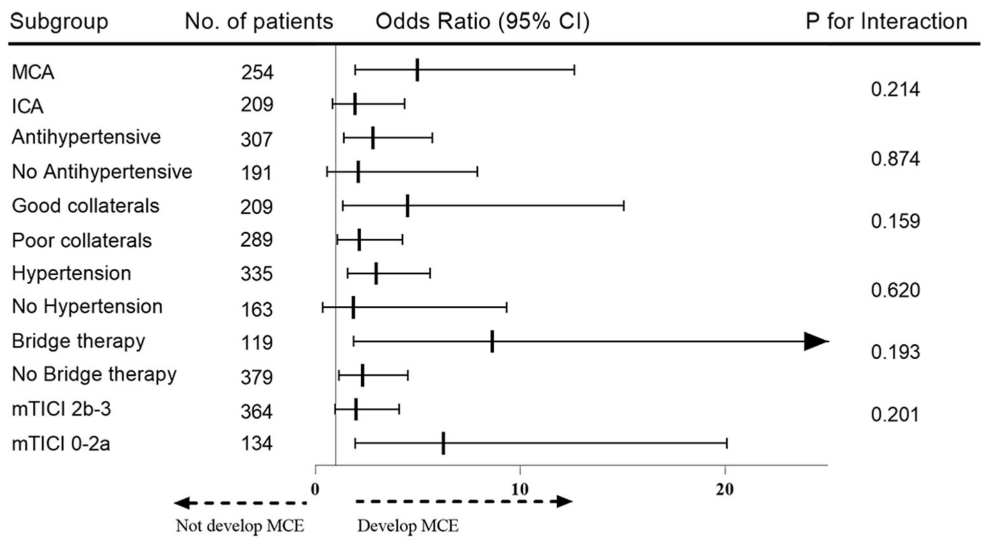

FIGURE 4 | Subgroup analysis for heterogeneity of effect of SBP_{max} >165 mmHg on the development of MCE. The odds of developing MCE for each subgroup is depicted with a square and a line, representing a 95% CI on the forest plot on the right.

TABLE 2 | Association of blood pressure parameters with the development of MCE.

	Unadjusted			Adjusted		
	MCE	**Non-MCE**	***P***	**OR**	**95% CI**	***P***
SBP						
Mean	128 (120–136)	123 (116–131)	<0.001	1.035	1.006–1.065	0.017
Max	148 (139–161)	158 (144–175)	<0.001	1.021	1.006–1.036	0.007
CV	9.05 (7.19–11.73)	10.02 (8.39–14.30)	<0.001	1.065	0.981–1.018	0.948
SV	12.32 (9.66–15.64)	14.73 (11.68–18.99)	<0.001	1.031	0.989–1.075	0.149
SD	11.19 (8.81–14.23)	13.31 (10.36–18.71)	<0.001	1.061	1.003–1.123	0.039
DBP						
Mean	73 (66–79)	70 (65–76)	0.071	0.990	0.954–1.028	0.606
Max	89 (81–98)	95 (84–101)	0.001	1.012	0.989–1.036	0.313
CV	11.95 (9.56–14.87)	13.45 (11.17–15.89)	0.002	0.999	0.927–1.078	0.987
SV	9.56 (7.58–12.02)	10.66 (8.88–13.80)	0.001	1.015	0.939–1.098	0.708
SD	8.42 (6.61–10.62)	9.44 (8.08–11.45)	<0.001	1.009	0.907–1.122	0.872

Adjusted for: baseline NIHSS and ASPECT scores, baseline BP, Hypertension, OTR, occlusion location, bridging treatment, collateral circulation and mTICI.
CV, coefficient of variation; DBP, diastolic blood pressure; max, maximum; SBP, systolic blood pressure; SD, standard deviation; SV, successive variation.

In the present study, we found that LVOS patients with a higher mean SBP during the first 24 h after EVT were more likely to develop MCE. This result is in accordance with previous studies (10, 17). Vemmos et al. reported that elevated SBP values in the acute period are associated with subsequent brain edema formation in ischemic and hemorrhagic stroke patients (10). Additionally, Serena et al. found that in patients with large MCA infarction, an increased risk of fatal brain edema is associated with history of hypertension (17). However, the pathophysiological mechanisms of higher BP leading to MCE are not fully understood.

A possible explanation of our findings is that elevated SBP during the first 24 h after EVT causes BBB disruption and facilitates brain edema formation (1). MCE is initially cytotoxic characterized by intracellular water accumulation and later vasogenic, in which water moves across the BBB into the extracellular interstitial space (18). An early experimental study indicated that elevated BP may facilitate edema formation by increasing BBB permeability (19). Additionally, the reperfusion injury may play an important role in the development of MCE after EVT (20–22). Yang and Betz found that BBB disruption was exacerbated after reperfusion and vasogenic edema was associated with increased the BBB disruption after reperfusion in a rodent model (21). Finally, in the setting of ischemic stroke, elevated BP could promote a deleterious proinflammatory state (11), which may result in the development of brain edema. However, the mechanism needs further study.

Another interesting finding of this study was the pattern of SBP trends in the 24 h post-EVT. After EVT, there was a decline in SBP. The results were similar to those of recent studies. For example, Cho et al. found that SBP decreased steeply during the first 5–7 h after EVT and then achieved a plateau for 24 h (23). A multicenter prospective cohort study (Blood Pressure after Endovascular Therapy for Ischemic Stroke, BEST) also demonstrated a decline in BP in patients with LVOS after EVT (15). Additionally, our study further indicated that, in patients with MCE, SBP throughout the 24 h post-EVT was higher than that in patients without MCE. Although iatrogenic BP lowing after EVT may affect the understanding of this finding, we did not find any significant difference in the use of intravenous antihypertensive drugs between the two groups. In addition, in our study, the best SBP_{max} threshold that predicted the development of MCE was 165 mmHg. BEST study also showed that a peak SBP around 160 mm Hg in the 24 h post-EVT best dichotomizes good vs. bad functional outcomes (15). Moreover, a recent large sample study demonstrated that post-thrombectomy SBP <160 mmHg following successful revascularization with EVT seem to be related with better clinical outcomes than SBP <180 mmHg (9). Thus, the current study further expanded our understanding of the association of BP control with outcomes in patients with EVT.

In addition, in the subgroup analyses, we revealed a similar direction and size for the effect of post-EVT SBP_{max} >165 mm Hg on the development of MCE. However, the adjusted OR were not significant for patients with successful recanalization, without history of hypertension, without intravenous antihypertensive agent and ICA occlusion. A possible explanation is that patients with successful recanalization have a lower rate of MCE [14% (51/364) vs. 34.3% (46/134)]. Additionally, the lack of association in patients without a history of hypertension or intravenous antihypertensive agents may be due to having a normal BP after EVT in these patients. Collateral circulation may be the main impact factor for the insignificant effect of BP on MCE in patients with ICA occlusion.

Notably, in addition to the mean SBP and SBP_{max}, we also found that BP variability (SBP_{SD}) was associated with the development of MCE. This result were in line with the findings of Skalidi et al.' study (24), which showed that increased values of the 24-h time rate of systolic BP variation are independently associated with formation of edema in acute stroke patients. Additionally, our study showed that the best SBP_{max} threshold that predicted the development of MCE was 165 mmHg, however, the difference in mean SBP (128 vs. 123 mm Hg) between the groups seems to be rather trivial. We speculate that the main reason for this phenomenon may be that the BPV is larger in the MCE group. These preliminary findings implied that in order to improve the outcomes of EVT patients, it is necessary to not only specify appropriate BP targets but also reduce BPV.

There are some limitations to this study. First, this was a retrospective study with a modest sample size, and we did not unify the protocol for post-thrombectomy BP management. Hence, the results should be interpreted with caution. Second, intraoperative BP is also an important parameter affecting the clinical outcome after EVT. Unfortunately, the intraprocedural BP was not analyzed. Third, we did not exclude patients with parenchymal hemorrhage, which may affect the assessment of MCE. However, such patients are rare. To our knowledge, we are the first group to investigate the association of post-procedural BP with the course of MCE in patients treated with EVT. Our study further expanded our understanding of the management of BP in patients with EVT.

In conclusion, higher mean SBP during the first 24 h after EVT is associated with the development of MCE in LVOS patients. Having an SBP_{max} >165 mm Hg was prospectively identified to best discriminate the development of MCE. Moreover, increasing BPV may pose a higher risk of developing MCE. These findings suggest that continuous BP monitoring after EVT could be used as a non-invasive predictor for clinical deterioration due to MCE. Randomized clinical studies are warranted to address BP goal after thrombectomy.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was approved by the Ethics Committee of the First Affiliated Hospital of Wannan Medical College (201900039). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors have contributed to the theoretical formalism, designing the study, data collection, data analysis, and writing the manuscript.

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Cerebral Revascularization for the Management of Symptomatic Pure Arterial Malformations

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Background: Pure arterial malformations (PAMs) are extremely rare abnormalities defined as dilated, overlapping, and tortuous arteries with a coil-like appearance in the absence of venous components. Over the last half century, only seven published reports have described cases of patients with PAMs who received treatment.

Methods: Here, we report two cases of women with PAMs who received surgical treatment, and we present a systematic review of the literature. We searched the PubMed, Embase, Web of Science, and Medline databases (up until October 1, 2021) for relevant publications. We performed independent-sample t-tests and Fisher's exact tests to compare continuous and categorical characteristics among the available cases.

Results: Our first patient was a 43-year-old woman with PAM of the left internal carotid artery (ICA), who received an ICA-radial artery (RA)-M2 bypass. Post-operative digital subtraction angiography (DSA) revealed the disappearance of the left ICA PAM without ischemic events during follow-up. The second patient was a 53-year-old woman with PAMs of the right ICA and posterior cerebral artery. The P1 lesion was treated by proximal occlusion combined with a superficial temporal artery-P2 bypass. During the 12-month follow-up period, the size of the PAMs decreased significantly as indicated by the post-operative DSA showing the absence of hemorrhages. Our systematic review, which includes 56 PAMs, shows that the reported PAMs were more common in the anterior circulation (33/56, 58.9%) than in the posterior circulation (11/56, 19.7%). Bilateral PAMs were more likely to affect bilateral anterior cerebral arteries (ACA) ($ACA_{bilateral}$ vs. $ACA_{unilateral}$: 63.6 vs. 26.2%, $p = 0.02$). In addition, PAMs involving the anterior circulation were likely to affect multiple arteries ($anterior_{multi}$ vs. $posterior_{multi}$: 30.3 vs. 0%, $p = 0.038$).

Conclusion: We found very few reports on treated PAMs; further studies with large sample sizes and long follow-up periods are required to explore the appropriate treatment strategy for PAMs.

Keywords: pure arterial malformations, cerebral revascularization, systematic review, EC-IC bypass, proximal occlusion

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INTRODUCTION

Pure arterial malformations (PAMs) are extremely rare abnormalities defined as dilated, overlapping, and tortuous arteries with a coil-like appearance in the absence of any venous component. These lesions are first defined by McLaughlin et al. (1) and are often mistaken for arteriovenous malformations (AVMs) or dissecting intracranial aneurysms. PAMs are thought to follow a benign natural progression, and patients with asymptomatic PAMs are managed conservatively. However, we only found reports on seven symptomatic patients who received treatment (2–7). Coil embolization or surgical clipping of aneurysms associated with PAMs were reported on 5 patients, and management of the PAM was performed on 2 patients. Here, we report two new cases of symptomatic PAMs: one who presented with intermittent syncope and one with sudden loss of consciousness. The symptoms were thought to be associated with PAMs, and the patients received PAM surgical treatments. Our analysis suggests that proximal occlusion of PAMs, combined with EC-IC bypass, is a promising method for the treatment of symptomatic PAMs. However, no comprehensive systematic review focusing on PAMs has been published. Therefore, we performed a detailed review of the existing literature to better characterize the clinical characteristics of PAMs.

METHODS

Literature Search and Inclusion Criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to perform our systematic review (8). We searched the electronic PubMed, Embase, Web of Science, and Medline databases (last search update was on October 1, 2021) using the following search terms: "pure arterial anomalies" OR "pure arterial malformation" OR "dilated" OR "overlapping" OR "tortuous" OR "coil-like" OR "arterial loops" AND "ACA" OR "anterior cerebral artery" OR "MCA" OR "middle cerebral artery" OR "ICA" OR "internal carotid artery" OR "PCA" OR "posterior cerebral artery" OR "PCoA" OR "posterior communicating artery." In addition, we manually checked the references of all retrieved articles for potential additional studies.

Study Eligibility and Data Extraction

We included all studies reporting on patients diagnosed with PAMs and meeting the definition put forth by McLaughlin. For each eligible study, two authors independently extracted the following data: first author name, date of publication, study design, sample size, patient characteristics (such as sex and age of patients, associated symptoms, neurological examinations), PAM characteristics (such as maximum diameter and location), imaging appearance, and follow-up duration.

Statistical Analysis

Continuous variables are expressed as means ± standard deviations (SDs), and categorical variables as numbers (%). We performed independent-sample *t*-tests and Fisher's exact tests to compare continuous and categorical characteristics, respectively. We considered differences as significant when the *P*-value was lower than 0.5. We analyzed all data using SPSS 19.0 (SPSS, Chicago, IL, United States).

RESULTS

Case 1

A 43-year-old woman presented with intermittent syncope that had lasted for 10 days, and mild right-sided weakness for 1 week. CT angiogram revealed a dilated and tortuous left internal carotid artery (ICA) with a coil-like appearance (**Figure 1A**). To better characterize this vascular lesion, we ordered a digital subtraction angiography (DSA), which revealed a dilated, overlapping, and tortuous left ICA (from the petrous segment to the supraclinoid segment), indicating PAM of the left ICA (**Figures 1B–F**). A computed tomography perfusion (CTP) showed a delayed time to peak (TTP) in the left hemisphere when compared with that in the right hemisphere (**Figure 1G**). Next, we ordered an MRI to exclude ischemic stroke. The results of the DWI MRI revealed the absence of an acute ischemic stroke (**Figure 1H**). Together, these results demonstrated that PAM of the left ICA led to decreased blood flow velocity in the left hemisphere, which caused the right-sided weakness and repeated TIAs in our patient.

Then, the patient agreed to undergo surgical treatment. During the operation, we found that the ectatic vessel of the left ICA comprised double loops (**Figure 2A**). Briefly, we harvested the radial artery (RA) and prepared it to be anastomosed in an end-to-side fashion to the M2 segment of the middle cerebral artery (MCA). Subsequently, we ligated the distal end of cervical ICA, and anastomosed the proximal end of the cervical ICA to the free end of the RA (**Figure 2B**). Following the bypass, we confirmed the vessel's patency with indocyanine green video angiography and a Doppler ultrasonic probe. A post-operative DSA (6 months after the operation) revealed that the dilated, overlapping, and tortuous left ICA had disappeared, and that the bypass was patent (**Figures 2C,D**). A CTP showed similar TTPs between the two hemispheres (**Figure 2E**), and the DWI MRI confirmed the absence of ischemic stroke (**Figure 2F**). Moreover, the patient's preoperative symptoms disappeared during the 26-month follow-up.

Case 2

A 53-year-old woman with severe headache that lasted for 1 week was brought to the emergency department because of sudden loss of consciousness. Head computed tomography (CT) revealed subarachnoid hemorrhage (SAH) spanning the suprasellar and ambient cisterns, and the left sylvian fissure (**Figure 3A**). Cerebral CT angiogram showed vascular lesions in the right ICA and right P1 segment of the posterior cerebral artery (PCA) (data not shown). Subsequent DSA demonstrated dilated, tortuous, and redundant right vessels of the supraclinoid ICA (**Figure 3B**) and the right P1 segment (**Figures 3C,D**). Neurological examination revealed decreased consciousness and stiff-neck. Given these findings, we considered the lesions in the right supraclinoid ICA and right P1 segment of the PCA as PAMs, with the latter probably causing the SAH. We decided to treat the patient surgically. During the operation, we found that the right

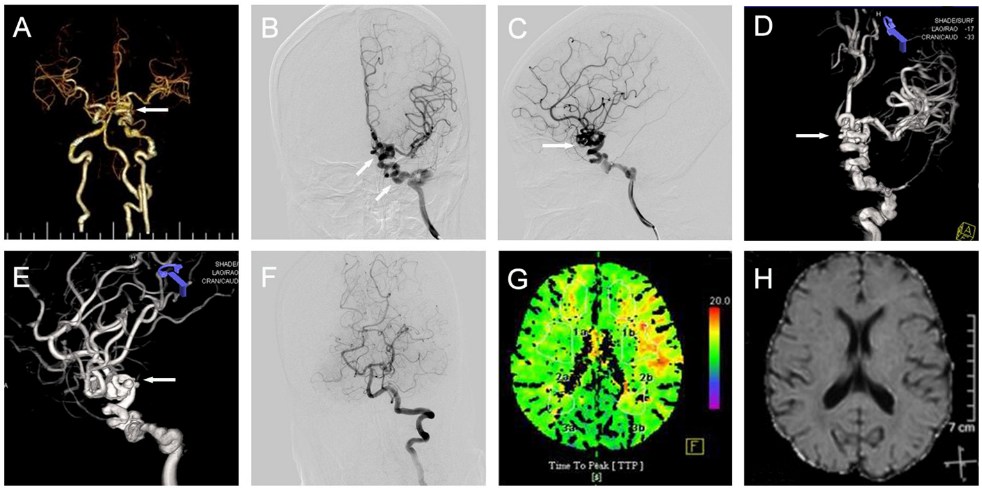

FIGURE 1 | Case 1. Three-dimensional reconstruction of CT angiogram showing a dilated, overlapping, and tortuous [**(A)**, arrow] left ICA, [**(B)**, arrow] anteroposterior, [**(C)**, arrow] and lateral DSA views; and three-dimensional anteroposterior [**(D)**, arrow], and lateral [**(E)**, arrow] DSA views. **(F)** Anteroposterior view of left vertebral artery injection angiograms. **(G)** Axial CTP showing increased TTP in the left hemisphere. **(H)** Axial DWI MRI showing the absence of ischemic stroke. ICA, internal carotid artery; CT, computed tomography; DSA, digital subtraction angiography; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; TTP, time to peak; CTP, computed tomography perfusion.

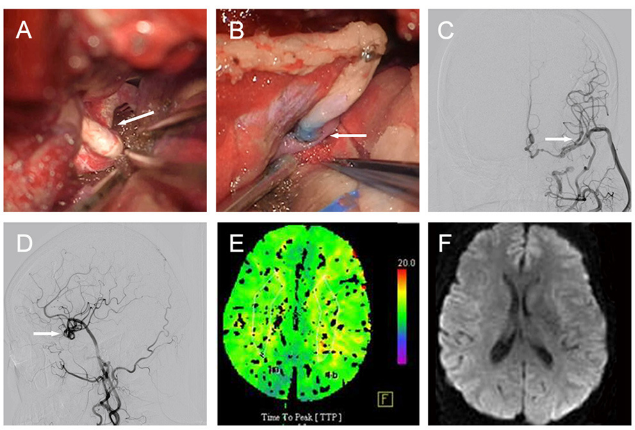

FIGURE 2 | Case 1. [**(A)**, arrow] Intraoperative image showing the left ICA constructed of double loops. [**(B)**, arrow] PAMs treated by ligation of cervical ICA and ICA-RA-M2 bypass. Post-operative DSA demonstrating PAM disappearance and patent bypass in [**(C)**, arrow] anteroposterior, and [**(D)**, arrow] lateral views. **(E)** Axial CTP showing similar TTPs between the two hemispheres. **(F)** Axial DWI MRI evidencing the absence of ischemic stroke. ICA, internal carotid artery; DSA, digital subtraction angiography; PAM, pure arterial malformation; RA, radial artery; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging; TTP, time to peak; CTP, computed tomography perfusion.

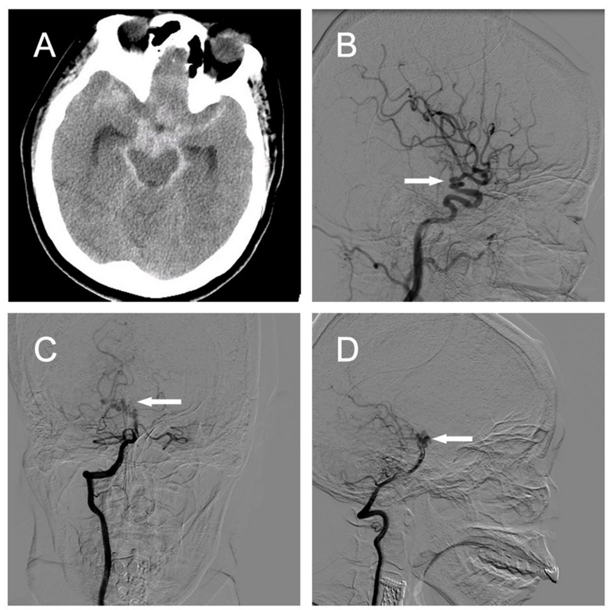

FIGURE 3 | Case 2. **(A)** Head CT revealing SAH in the suprasellar cistern, ambient cistern, and left sylvian fissure. [**(B)**, arrow] Right ICA angiograms showing a coiled and tortuous vessel of the right supraclinoid ICA in the lateral view. Right vertebral artery angiograms demonstrating a coiled and tortuous right P1 segment in **(C)** anteroposterior and [**(D)**, arrow] lateral views. ICA, internal carotid artery; CT, computed tomography.

ICA lesion was composed of 2–3 tightly coiled loops with stiff vessel walls, but without bleeding. The lesion in the P1 segment had a similar phenotype and was located on the surface of the midbrain with several branch arteries arising from the lesion to supply the brainstem. In addition, we found fresh blood clots around the P1 lesion and in the ambient cistern (**Figures 4A,B**).

We treated the P1 segment lesion by proximal occlusion combined with STA-P2 bypass. We confirmed the patency of bypass intraoperatively by Doppler ultrasonic probe and ICG video angiography. Moreover, the intraoperative ICG video angiography analyzed with Flow800 showed a blue P1 segment lesion after the proximal occlusion and STA-P2 bypass, indicating

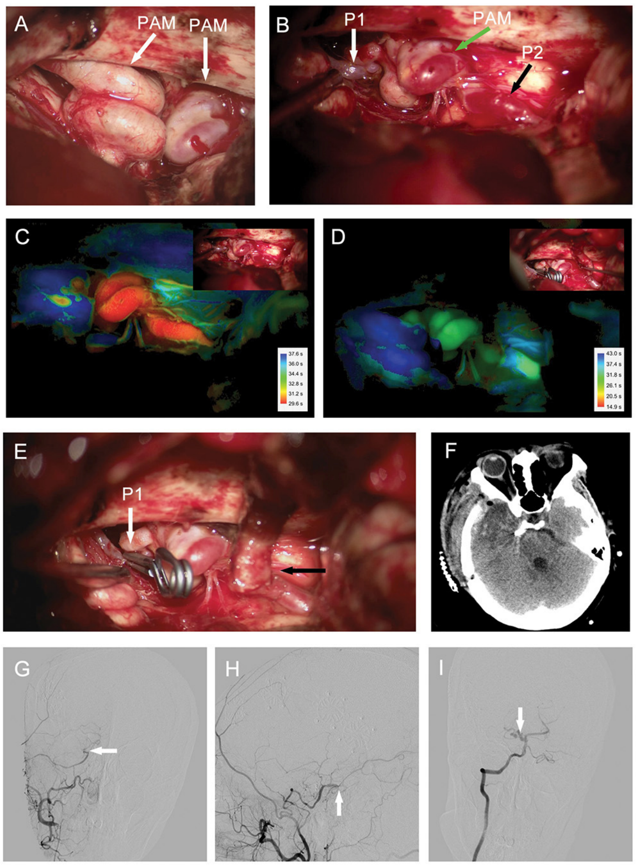

FIGURE 4 | Case 2. **(A,B)** Intraoperative photograph showing **(A)** right ICA and **(B)** right P1 segment lesions composed of 2–3 tightly coiled loops (arrows). Intraoperative ICG video angiography analyzed with Flow800 revealing decreased perfusion in the lesion of P1 segment after proximal occlusion and bypass **(D)**; compared to the image before proximal occlusion **(C)**. Vascular lesion treated by [**(E)**, white arrow] proximal occlusion of the P1 segment and [**(E)**, black arrow] STA-P2 bypass. **(F)** Post-operative head CT operative region. Post-operative DSA showing bypass patency in [**(G)**, arrow] anteroposterior and [**(H)**, arrow] lateral views. [**(I)**, arrow] Right vertebral artery angiograms demonstrating that the P1 segment lesion is smaller than the preoperative lesion in the anteroposterior view. CT, computed tomography; DSA, digital subtraction angiography; ICA, internal carotid artery; STA, superficial temporal artery.

decreased perfusion of the lesion after the surgical procedure compared with perfusion before the treatment (**Figures 4C–F**). Post-operative CTA demonstrated that the bypass was patent (**Figures 4G,H**). The P1 segment lesion was still present after the operation but was smaller than the preoperative lesion according to the DSA images (**Figure 4I**). The patient's neurological examination was almost normal at discharge and remained so during the 12-month follow-up period.

System Review

A flowchart detailing the process of study selection is shown in **Figure 5**. Briefly, the literature search produced 192 articles, of which 154 were excluded by review of the abstracts. Thereafter, full texts of the remaining 38 articles were analyzed and reviewed in detail. Finally, our literature search yielded 27 studies with 56 patients (including the two patients in this study) confirmed as having PAMs and meeting the definition put forth by McLaughlin et al. (1, 2, 4–7, 9–29) (**Supplementary Table 1**). **Table 1** summarizes the main characteristics of all studies included in this system review. The average age of patients at the time of presentation with PAMs was 30.9 ± 17.3 years, and PAMs were more common among women (37/56, 66.1%). Studies have shown that PAMs affect all segments of the intracranial arteries, such as the ACA, PCA, PCoA, and supraclinoid ICA. However, our analysis suggests that PAMs are more common in the anterior circulation (33/56, 58.9%) than in the posterior circulation (11/56, 19.7%). Moreover, PAMs involving both the anterior and posterior circulations were seen in 12 patients (12/56, 21.4%). The majority of lesions affected a single vessel (34/56, 60.7%), and up to 5 vessels could be affected.

Interestingly, in the anterior circulation, PAMs were more likely to affect the ICA, MCA, and ACA; while PCA seems more likely to be affected in the posterior circulation. Moreover, we also found 11 patients with bilateral PAMs (19.6%), which were more likely to affect bilateral ACA as opposed compared to unilateral PAMs ($ACA_{bilateral}$ vs. $ACA_{unilateral}$: 63.6 vs. 26.2%, $p = 0.02$; **Supplementary Table 2**). In addition, compared with the PAMs involving the posterior circulation, the PAMs involving the anterior circulation were likely to affect multiple arteries ($anterior_{multi}$ vs. $posterior_{multi}$: 30.3 vs. 0%, $p = 0.038$; **Supplementary Table 3**).

Among all the reported cases, there were only seven cases received endovascular or surgical treatments (**Table 2**), of which: the first case reported by Hanakita et al. received an EC-IC bypass of the affected vessel (2). A 42-year-old man underwent a procedure to surgically trap the parent artery of the PAM in the right ACA (5). In addition, the other five patients described by Lanzino et al., Munich et al., Li et al., and Yao et al., underwent coil embolizations, surgical clipping or trapping of aneurysms associated with the PAMs (3, 4, 6, 7).

DISCUSSION

Pure arterial malformations (PAMs), first defined by McLaughlin et al. are extremely rare, and they get commonly mistaken for dissecting intracranial aneurysms and brain AVMs (1, 25, 28). Distinguishing PAMs from other vascular abnormalities (such as AVMs, intracranial arterial dissections, and intracranial dolichoectasia) is important, because treatments vary according to the different types of vascular abnormality. AVM is defined as an abnormal connection between arteries and veins that lacks capillaries. When anomalous interconnections are between dural (pial) arteries and dural (pial) veins, they are known as dural or pial arteriovenous fistulas. Catheter angiograms reveal a nidus or a venous component in arteriovenous malformations or fistulas that is absent in PAMs (30, 31). Moreover, PAMs are distinct from intracranial dolichoectasias, which are cerebral arteries with increased diameter, elongation, and tortuosity. Dolichoectasias involve predominantly the vertebrobasilar artery and ICA, and they usually present as dilated and elongated vessels that remain

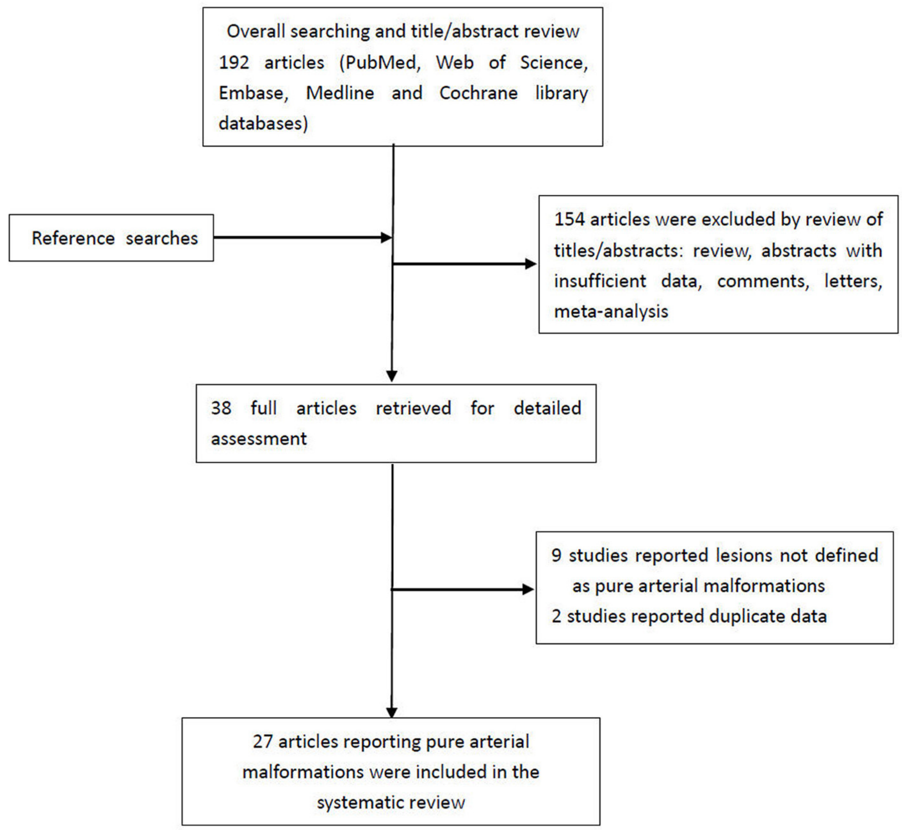

FIGURE 5 | Flow chart of the literature search for systematic review.

TABLE 1 | Clinical characteristics of 56 patients diagnosed with PAM.

Characteristics	Value
Age	30.9 ± 17.3
Sex	
Female	37 (66.1%)
Male	19 (33.9%)
Side	
Left	24 (42.9%)
Right	18 (32.1%)
Bilateral	11 (19.6%)
Midline	3 (5.4%)
Lesion location	
Anterior circulation	33 (58.9%)
Posterior circulation	11 (19.7%)
Both anterior and posterior circulation	12 (21.4)
Number of involved vessels	
1 vessel	34 (60.7%)
2 vessels	9 (16.1%)
3 vessels	9 (16.1%)
4 vessels	1 (1.8%)
5 vessels	3 (5.3%)
Follow-up (months)	

PAM, pure arterial malformation.

recognizable in catheter angiograms (32–35). In contrast, PAMs involve impacted overlapped vessels with severe tortuosity that results in a coil-like appearance.

The pathogenesis of PAMs remains unclear with two main potential etiologies: (1) congenital defect that results in arterial dysplasia and (2) viral infection affecting a vulnerable arterial segment. In some report, the arterial dysplasia in PAMs is congenital. Araki et al. reported on a 23-year-old woman diagnosed as having right hemimegalencephaly with DSA and dynamic CT images showing dilatations of the right ACA, MCA, and PCA, as well as increased circulation volume in the right hemisphere (probably accounting for the ipsilateral hemimegalencephaly) (14). Moreover, we found at least five cases of PAMs accompanying white matter or cortical dysplasias in the territory of the affected vessels (10, 16, 19, 28). Neurovascular development, such as the initial formation of neurovascular and ingression of vessel sprouts into the neural tissue, is stimulated by the development of the brain parenchyma (36). Thus, PAMs may be associated with cortical dysplasias. Viral infection may be another potential etiology of PAMs. Lasjaunias showed serial images indicating the development of a tightly coiled PAM in the supraclinoid ICA and M1 segments of a patient with varicella vasculopathy (37). Moreover, a previous study has reported on a 2-year-old boy with a PAM in the A2 segment who died of viral

TABLE 2 | Summary of patients with PAM who received treatment.

References	Age, sex	PAM location	Associated symptoms	Treatment	Follow-up
Hanakita et al. (2)	43, female	Rt distal ICA, proximal M1, and Lt PCA	Dysarthria	EC-IC bypass and wrapped ectatic vessel with muscle	None
Lanzino et al. (3)	10, female	Supraclinoid ICA	Headache	Coil embolization of the larger, saccular-type, pseudoaneurysm component at the posterior communicating/posterior cerebral artery	3 years
Munich et al. (4)	37, female	ACoAand BA (superior to basilar apex)	Headache, blurry vision and a partial left CN III palsy	Surgical clipping of the associated aneurysms at the PCA	1 month
Yue et al. (5)	42, male	Rt ACA	Headache	Surgical trapping	3 months
Li et al. (6)	77, male	Lt AICA	SAH	Surgical trapping the associated aneurysm	1.5 months
Yao et al. (7)	51, male	Rt PICA	SAH	Surgical clipping of the associated aneurysm	9 months
	48, male	Rt the first branch of intracranial segment of vertebral artery	SAH	Surgical clipping of the associated aneurysm	3 months
Present study	43, female	Lt ICA	Right-sided weakness	EC-IC bypass (high flow) and ligation of ICA (cervical segment)	26 months
	45, female	Rt ICA and P1	SAH	Proximal occlusion of P1 segment and STA-P2 bypass	12 months

ACoA, anterior communicating artery; AICA, anterior inferior cerebellar artery; BA, basilar artery; CN, cranial nerve; EC-IC, extracranial-intracranial; ICA, internal carotid artery; Lt, left; PAM, pure arterial malformation; PCA, posterior cerebral artery; Rt, right; SAH, subarachnoid hemorrhage; STA, superficial temporal artery.

encephalitis (9). Thus, some supraclinoid ICA and MCA PAMs may result from viral infections.

Approximately 85% of the PAMs reported were incidental findings in previous studies. In a recent case series (involving 25 patients diagnosed with PAMs), Oushy et al. reported that these lesions were generally asymptomatic and likely have a benign natural history (28), and that only three of the patients had symptoms potentially associated with their PAMs and 2 patients received treatment (coil embolization) of aneurysms associated with PAMs. In the systematic review, the results showed that the mean age of 9 patients who received treatments was 44 $\pm$ 17.2 years. However, patients with untreated PAMs in previously reported studies have been younger (28.4 $\pm$ 16.4 years). These patients had a mean follow-up of 32.5 months (including the case of a patient with a 30-year follow-up) or 24.9 months (excluding that patient). Considering the scarcity of cases and the short-term follow-ups in the literature, we speculate that longer-term follow-ups will disclose increased risks of associated ischemic or hemorrhagic strokes in patients with PAMs.

To date, 56 cases of PAMs meeting the criteria put forward by McLaughlin et al. have been reported in the literature (1). However, only seven of those patients received treatments. Moreover, coil embolization, and surgical trapping or clipping of the aneurysms associated with the PAMs were performed in 5 patients. Dealing with the PAM itself was only reported on 2 patients. Hanakita et al. (2) wrapped ectatic middle cerebral artery with muscle combined with EC-IC bypass. In the other patient, the PAM located in the right A1 was trapped without bypass, because the distal branches of the ACA was supplied by the contralateral ICA through the anterior communicating artery. In this study, we report the treatment with cerebral revascularization in two patients with symptomatic PAMs. In the first case, the lesions involved the left ICA (from petrous segment to supraclinoid segment); the cervical ICA was ligated and ICA (proximal end of the ligated ICA)-RA-M2 bypass was performed. The post-operative DSA images showed that the dilated and tortuous vessel had disappeared 6 months after the operation, and the patient remained symptom-free during the 26-month follow-up period. To our knowledge, the patient with SAH in our report is the first surgically confirmed case with PAM involving the PCA. During the operation, we occluded the P1 segment proximal to the lesion and performed STA-P2 bypass. After the surgical treatment, the wall tension in the lesion decreased significantly. Moreover, an intraoperative ICG video angiography analyzed with Flow800 showed that the P1 segment lesion was blue after the proximal occlusion and STA-P2 bypass, indicating decreased perfusion of the lesion after the surgical treatment compared with the perfusion before the treatment (38, 39). The post-operative DSA images demonstrated a lesion smaller than the preoperative one, indicating a decreased re-bleeding risk in the future. The patient demonstrated lack of obvious deficits on neurological examinations during the 12-month follow-up period. We suggest that the P1 segment PAM in this patient was additionally supplied by some small arteries not observed in the preoperative angiography.

CONCLUSIONS

Pure arterial malformations (PAMs) are extremely rare lesions that have been considered to have a benign natural progression. Here, we report on EC-IC bypass treatments of two patients with rare symptoms (one with ischemic symptoms and the other with SAH). After the operation, the symptoms were relieved, and the PAMs disappeared completely or were significantly reduced in size. Very few treated cases of PAM have been reported; further studies with large sample sizes and long follow-up periods are required to identify the most appropriate treatment strategy for PAMs.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Standards of The First Affiliated Hospital of Soochow University (Suzhou, China). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YH, PZ, XF, and XL contributed to the surgical treatment and drafted the article. PZ, XL, GC, and ZW participated in case management, data extraction, and data analysis. WB helped us revised the article. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.755312/full#supplementary-material

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Comparison of Endovascular Embolization Plus Simultaneous Microsurgical Resection vs. Primary Microsurgical Resection for High-Grade Brain Arteriovenous Malformations

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Aim: It remains a challenge in surgical treatments of brain arteriovenous malformations (AVMs) in Spetzler-Martin Grade (SMG) IV and V to achieve both optimal neurological outcomes and complete obliteration. The authors reported a series of patients with AVMs in SMG IV and V who underwent a surgical paradigm of endovascular embolization and simultaneous microsurgical resection based on the one-staged hybrid operation.

Methods: Participants in the multicenter prospective clinical trial (NCT 03774017) between January 2016 and December 2019 were enrolled. Patients who received endovascular embolization plus microsurgical resection (EE+MRS) and those who received intraoperative digital subtraction angiography plus microsurgical resection (iDSA+MRS) were divided into two groups. Information on clinical features, operative details, and clinical outcomes were extracted from the database. Deterioration of neurological deficits (DNDs) was defined as the primary outcome, which represented neurological outcomes. The time of microsurgical operation and blood loss were defined as the secondary outcomes representing microsurgical risks and difficulties. Outcomes and technical details were compared between groups.

Results: Thirty-eight cases (male: female = 23:15) were enrolled, with 24 cases in the EE+MRS group and 14 in the iDSA+MRS group. Five cases (13.2%) were in SMG V and 33 cases (86.8%) were in SMG IV. Fourteen cases (36.8%) underwent the paradigm of microsurgical resection plus intraoperative DSA. Twenty-four cases (63.2%, $n = 24$) underwent the paradigm of endovascular embolization plus simultaneous microsurgical resection. Degradations of SMG were achieved in 15 cases. Of the cases, two cases got the residual nidus detected via intraoperative DSA and resected. Deterioration of neurological deficits occurred in 23.7% of cases ($n = 9$) when discharged, and in 13.5, 13.5, 8.1% of cases at the follow-ups of 3, 6, and 12 months, respectively, without significant difference between groups ($P > 0.05$). Intracranial hemorrhagic complications were reported in three cases (7.9%) of the EE+MRS group only. The embolization did not significantly affect the surgical time and intraoperative blood loss. The subtotal embolization or the degradation of size by 2 points resulted in no DNDs.

Conclusions: The paradigms based on the one-staged hybrid operation were practical and effective in treating high-grade AVMs. Appropriate intraoperative embolization could help decrease operative risks and difficulties and improve neurological outcomes.

Keywords: arteriovenous malformation, Spetzler-Martin Grade, endovascular embolization, microsurgical resection, one-staged hybrid operation

INTRODUCTION

The Spetzler-Martin Grading (SMG) system is widely used to evaluate therapeutic risks of brain arteriovenous malformations (AVMs) (1), and sorts AVMs into two classes: the low-grades (Grades I to III) and the high-grades (Grade IV and V). High-grade AVMs usually have more complicated features on location, angioarchitecture, and hemodynamics, which increases its hemorrhagic risks (2–4). With an annual hemorrhagic risk ranging from 1.5 to 2.7%, conventional treatments have not shown any significant superiority compared with surgical interventions (5–11). Surgical treatments on high-grade AVMs are necessary, especially for patients with long life expectancies. However, with concern to neurological outcomes, the optimized procedure or paradigm is being explored.

Microsurgical resection achieves the highest obliteration rate among treatments of AVMs. However, it sometimes fails to meet the requirement of preventing neurological deficits (12, 13). The incidence of neurological deficits is reported to be 31 and 37% in lesions of SMG IV and V, respectively (14). Binary and trinary multimodality therapeutic paradigms are proposed for the high-grades, consisting of microsurgical resection, endovascular intervention, and stereotactic radiosurgery (SRS). The multimodality paradigm, that consisted of endovascular embolization and subsequent stereotactic radiosurgery, could only achieve an obliteration rate ranging from 38 to 42% (15–18), and up to 44% by modifying SRS strategies (19). Another multimodality paradigm consisted of volume-staged SRS and subsequent microsurgical resection was reported to achieve an obliteration rate of 93.8% (20). The binary combination of endovascular embolization and microsurgical resection is the most widely used paradigm for treating high-grade AVMs (21, 22). The preoperative embolization could decrease the blood volume and velocity of the nidus, and reduce the risk and difficulty of the subsequent microsurgery. The paradigm results in a high obliteration rate with an acceptable incidence of neurological deficits. However, complications of endovascular intervention remain a shortcoming of solely performed endovascular embolization, such as catheter stinking, intraoperative hemorrhage, and embolization-induced normal perfusion pressure breakthrough (23). In addition, all of the staged paradigms have to face the risks of adverse events in the latency period, especially the hemorrhagic risk, which ranges from 1.1 to 3.3% per year (16–20), and remains unchanged, as long as AVMs have not been completely obliterated.

Since the timing of microsurgical resection after preoperative embolization remains unclear (24), the paradigm of endovascular embolization plus simultaneous microsurgical resection (AKA one-staged hybrid operation) could be a practical solution without the risks of solely performed embolization and the latency period. The objective of this study is to introduce the experience of applying this paradigm to treat high-grade AVMs in one-staged hybrid operations, and its technical details which could potentially improve the functional outcome of the high-grades.

METHODS

Data of patients with high-grade AVMs were extracted from the database of a multicenter prospective clinical trial (NCT 03774017) from January 2016 to December 2019 (24). Inclusion criteria included: 1) harboring AVMs of SMG IV or V; and 2) received endovascular interventions, including intraoperative digital subtraction angiography (iDSA) or embolization (Embo), plus simultaneous microsurgical resection (MSR) in the one-staged hybrid operating room. Patients who had received stereotactic radiosurgical treatments were excluded.

Ethical approvals were obtained from the IRBs of each contributing center. Written informed consent was acquired from all participants involved.

Group Assignment

According to the surgical paradigm received, patients were divided into two groups: Embo+MSR and iDSA+MSR group. In the Embo+MSR group, patients received iDSA and endovascular embolization plus simultaneous microsurgical resection. In the iDSA+MSR group, patients received iDSA plus primary microsurgical resection.

Preoperative Evaluation

Neurological evaluations were performed by neurosurgical physicians using modified Rankin's scale (mRS) at admission, discharge, and follow-up points. The magnetic resonance imaging (MRI) and DSA were performed in every patient for morphological and angiographic features of lesions. Functional MRI (fMRI) was additionally performed in patients with eloquent areas potentially involved. The lesion to eloquent distance (LED) was qualitatively measured in the neuro-navigation working station (Brainlab® Cranial 3.0, Brainlab AG, Munich, Germany). Eloquence included eloquent cortices, such as areas of the motor, Broca, Wernick, and the visuosensory, and fiber tracts, such as pyramidal tracts, arcuate fasciculus, and optic radiations. A LED<5 mm was defined as the threshold of a lesion with eloquence involved (25). Neuro-images were evaluated by one experienced radiologist, one neurosurgeon, and one interventional radiologist, independently. Multidisciplinary discussions were held to make individualized operative plans.

Indications for Endovascular Embolization

Endovascular embolization was preferred in patients with the following indications: 1) high flow nidus (by frame-by-frame analyses of DSA);(26) 2) deep originated feeding arteries, accessible by microcatheters; 3) reduction of nidus size necessary; 4) diffusive lesion without clear boundaries; or 5) the need for eloquence protection.

Implementation of One-Staged Hybrid Operation

The operations were performed in customized one-staged hybrid operating rooms (ORs). Each one-staged hybrid OR essentially consisted of a radiolucent operating table (MAQUE Holding B.V. & Co. KG, Rastatt, Germany), a surgical microscope (Pentero® 900, Carl Zeiss Surgical AG, Oberkochern, Germany), and a monoplane angiographic system. ARTIS Pheno, ARTIS Zeego systems (Siemens Healthineers, Erlangen, Germany), and Allura Xper FD20 system (Philips Healthcare, Best, Netherland) were practicable for cerebrovascular one-staged hybrid operations.

Under general endotracheal anesthesia, electrophysiological changes were monitored via neurophysiological monitoring (IONM, Nicolet Endeavor CR IOM, Natus Medical Incorporated, CA, USA), including sensory evoked potentials, motion evoked potentials, and electromyography. The patient was supinely or laterally placed in the operative position, with the head fixed by a radiolucent head frame (MAYFIELD Infinity XR2 Radiolucent System, Integra LifeScience, Inc., NJ, USA). Operations were performed in one position. A 6-French(Fr) sheath (AVANTI® Introducer, Cordis Corporation, Miami Lakes, FL, USA) was used to establish the transarterial approach. A 6-Fr guide catheter (Envoy®, Codman division of Johnson & Johnson Medical Ltd., Wokingham, Berkshire, UK) was catheterized into the petrous segment of the internal carotid artery (ICA) or the foraminal segment of the vertebral artery (VA). Subsequently, the flow-dependent microcatheter (Marathon 1.3-F, eV3/Covidien, Minnesota, USA, or Excelsior SL-10, Stryker Neurovascular, California, USA, or Headway-17, MicroVention, California, USA) was advanced over a microwire (Synchro-14, Stryker Neurovascular, California, USA or Traxcess-14, MicroVention, California, USA) into the target feeding arteries under road-mapping. A confirming angiogram via the microcatheter was required before the liquid embolic agent (Onyx 18/34, eV3 Covidien, Minnesota, USA) was infused. When embolization was completed, the guide catheter was withdrawn from ICA and VA back to the ipsilateral common carotid artery (CCA) or subclavian artery, respectively. The Guide catheter was preserved with prolonged infusion of heparin saline (1000 IU/L, 0.6∼1 ml/min) during the microsurgical operation. This could simplify the process of intraoperative DSA, especially when the patient was in a lateral position. Afterward, the microsurgical resection was performed as routine under the assistance of neuro-navigation (Brainlab® Cranial 3.0, Brainlab AG, Munich, Germany). Complete resections were achieved in all cases. While in some AVMs with eloquent areas involved, procedures of *in-situ* embolization combined with surgical resection were performed (27). Before closure, intraoperative DSA was performed via the preserved guiding catheter to ensure complete obliteration. Microsurgical resection would be repeated until there was no residual nidus observed.

Follow-Up

Patients received the follow-up 3, 6, and 12 months after the operation for outcome evaluation. Most of the patients visited the outpatient department of Beijing Tiantan Hospital on the scheduled date and received physical and radiological examinations, such as CTA and DSA. The rest of the patients received interviews by telephone. All medical records and angiographic neuro-images were collected.

Outcomes Evaluations

Deterioration of neurological deficits (DNDs) was the primary outcome, defined as a mRS increased during hospitalization and > 2 when discharged, including fatality (mRS = 6). Secondary outcomes included: 1) fatality, defined as the death related to operation or AVMs; 2) residue nidus, defined as the arteriovenous shunting found by postoperative angiograms in the operative field or neighborhoods; 3) intracranial hemorrhagic complications, defined as any emerging of high-density on postoperative cranial CT scan with a volume>5 ml (measured with ABC/2 method) within 7 days after the operation; 4) ischemic complications, defined as any low-density territory, except the operative region, revealed on CT scans within 7 days after the operation; 5) postoperative seizure, repeat or new onset of grand mal epilepsy; and 6) other complications, including infections in the central neural and respiratory system, thrombosis in deep veins, etc.

Data Collection

All of the information was prospectively collected by full-time clinical research coordinators. All data were quality-controlled monthly by clinical research associates of a third-party contract research organization.

Statistical Analysis

All statistical analyses were performed using IBM® SPSS® Statistics (Version 22, IBM, NY, United States). The baseline information was qualitatively and quantitatively described. The baseline of different groups was compared via normal distribution tests and non-parametric tests. Pearson chi-square tests and Fisher exact tests were performed to compare the differences of outcomes between groups.

TABLE 1 | Characteristics in patients with SMG IV and V bAVMs*.

Variable	Overall	Intergroup		
		Embo+MSR	MSR+iDSA	*P*-value
Presentation				
No. of patients	38	24	14	
Male	23 (60.5)	15 (62.5)	8 (57.1)	0.505
Age in yrs	27.5 ± 15.98	28.6 ± 16.70	24.3 ± 15.19	0.559
Prior treatments				
Embo	1 (2.6)	1 (4.2)	0 (0)	0.615
Hematoma evacuation	6 (15.8)	4 (16.7)	2 (14.3)	0.615
Initial presentation				
Rupture	26 (68.4)	18 (75)	8 (57.1)	0.217
Neurological deficits	9 (23.7)	7 (29.2)	2 (14.3)	0.528
Seizure	8 (21.1)	3 (12.5)	5 (35.7)	0.102
Incidental	4 (10.5)	3 (12.5)	1 (7.1)	0.528
Headache	3 (7.9)	2 (8.3)	1 (7.1)	0.698
Preop. mRS score				0.178
0	4 (10.5)	4 (16.7)	0 (0)	
1	20 (52.6)	13 (54.2)	7 (50.0)	
2	8 (21.1)	4 (16.7)	4 (28.6)	
3	1 (2.6)	0 (0)	1 (7.1)	
4	4 (10.5)	2 (8.3)	2 (14.3)	
5	1 (2.6)	1 (4.2)	0 (0)	
Neuro-image				
Location				
Deep location	3 (7.9)	2 (8.3)	1 (7.1)	0.698
Multiple lobes	16 (42.1)	11 (45.8)	5 (35.7)	0.396
Diffuse	10 (26.3)	5 (20.8)	5 (35.7)	0.264
Feeding arterial circulation				
Anterior alone	16 (42.1)	8 (33.3)	8 (57.1)	0.201
Posterior alone	4 (10.5)	3 (12.5)	1 (7.1)	0.528
Both	18 (47.4)	13 (54.2)	5 (35.7)	0.304
Perforating artery	6 (15.8)	5 (20.8)	1 (7.1)	0.264
Draining vein				
Deep	12 (31.6)	8 (33.3)	4 (28.6)	0.528
Superficial	7 (18.4)	5 (20.8)	2 (14.3)	0.483
Both	19 (50.0)	11 (45.8)	8 (57.1)	0.369
Maximum diameter in centimeters	4.9 ± 1.36	5.1 ± 1.44	4.6 ± 1.19	0.297
Eloquence	35 (92.1)	21 (87.5)	14 (100)	0.240
LED in millimeters	2.6 ± 2.34	2.9 ± 2.64	2.0 ± 1.62	0.245
SMG				0.416
IV	33 (86.8)	20 (83.3)	13 (92.9)	
S2E1V1	24 (63.2)	13 (65.0)	11 (84.6)	
S3E1V0	6 (15.8)	4 (20.0)	2 (15.4)	
S3E0V1	3 (7.9)	3 (15.0)	0 (0)	
V	5 (13.2)	4 (16.7)	1 (7.1)	
Post-embolization SMG				
I	NA	1 (4.2)	NA	NA
S1E0V0		1 (4.2)		
II	NA	5 (20.8)	NA	NA
S1E0V1		2 (8.3)		
S1E1V0		1 (4.2)		
S2E0V0		2 (8.3)		
III	NA	9 (37.5)	NA	NA
S2E0V1		8 (33.3)		
S2E1V0		1 (4.2)		
IV	NA	7 (29.2)	NA	NA
S2E1V1		6 (25)		
S3E1V0		0 (0)		
S3E0V1		1 (4.2)		
V	NA	2 (8.3)	NA	NA
Outcome				
Postoperative complications				
Hemorrhage	3 (7.9)	3 (12.5)	0 (0)	0.240
Ischemia	2 (5.3)	2 (8.3)	0 (0)	0.393
CNS infection	6 (15.8)	3 (12.5)	3 (21.4)	0.385
Others	3 (7.9)	1 (4.2)	2 (14.3)	0.302
Second operation	2 (5.3)	2 (8.3)	0 (0)	0.393
Deterioration of neurological deficits (number of reaching the time point)				
Discharge ($n = 38$)	9 (23.7)	8 (33.3)	1 (7.1)	0.071
3-month FU ($n = 37$)	5 (13.5)	5 (20.8)	0 (0)	0.098
6-month FU ($n = 37$)	5 (13.5)	5 (20.8)	0 (0)	0.098
12-month FU ($n = 37$)	3 (8.1)	3 (12.5)	0 (0)	0.260

Embo, Endovascular Embolization; MSR, Microsurgical resection; iDSA, Intraoperative Digital Subtraction Angiography; Prepo., Preoperation; mRS, Modified Rankin Scale; LED, Lesion to Eloquence Distance; SMG, Spetzler-Martin Grade; CNS, Central Nervous System; FU, Follow-up; NA, not applicable.

**Values are number of patients (%) unless noted otherwise.*

RESULTS

Thirty-eight cases (male: female=23:15) with AVMs in SMG IV and V met the inclusion and exclusion criteria and were involved in our study (Baseline information refers to **Table 1**). Patients were in a mean age of 27.5 ± 15.98 y (ranged 5–63 y). The most common initial presentation was AVM rupture, which occurred in 26 cases (68.4%). The incidence of rupture history was higher in the Embo+MRS group than the iDSA+MRS group without any significant difference (75 vs. 57.1%, χ^2 test, $P = 0.217$). Other initial presentations included neurological deficits in nine cases (23.7%), seizure in eight cases (21.1%), and incident in four cases (10.5%). Seven cases had received AVM-related treatment before being recruited, including the hematoma evacuation in six cases and endovascular embolization in one case. Thirty-two patients had a mRS score ≤2, including 21(87.5%) in the Embo+MSR groups and 11(78.6%) in the iDSA+MSR group, without significant difference (Mann–Whitney U-test, $P = 0.178$).

The localization and morphological information can be found in **Table 1**. Deep locations, such as basal ganglia and insula, were involved in three cases (7.9%). Diffusive nidus was observed in 26.3% of cases ($n = 10$). The maximum diameter of nidus

TABLE 2 | Summary of patients who underwent the paradigm of embolization plus simultaneous microsurgical resection.

Case no.	Age (yr)	Gender	Surgical history	Initial symptom	Location	Feeding artery	Draining vein	SMG	Embolized feeders	Embolic agent (ml)	Balloon	Embo rate (%)	Post-embo SMG	Resection time (hr)	Blood loss (ml)	Compli-cation	Second Op.	Postoperative mRS score					
																		Adm.	Dis.	3 mo.	6 mo.	12 mo.	Other
1	32	F	No	Incident	T P O	R.MCA +R.PCA	SDV +DDV	V	R.MCA	2.5	Unused	<50	S3E1V1	2.87	300	No	No	1	0	0	0	0	
2	16	M	No	Seizure	O	L.ACA +L.PCA	SDV	V	L.ACA	18	Unused	50–90	S3E1V1	6.38	1,900	No	No	0	0	0	0	0	
3	13	M	No	ICH	T	R.MCA +R.AChoA +R.LentA	SDV +DDV	S2E1V1	R.MCA	0.5	Unused	<50	S2E1V1	2.53	1,000	No	No	0	0	0	0	0	
4	12	F	No	ICH+ Dyskinesia	P	R.MCA +R.ACA	SDV +DDV	S2E1V1	R.ACA	1.2	Unused	<50	S2E1V1	5.08	750	No	No	1	3	2	1	1	
5	22	F	No	Seizure	Bg	R.MCA +R.PCA +R.AChoA	DDV	S2E1V1	R.PCA	0.5	Unused	<50	S2E1V1	2.65	300	Cerebral Infarction	No	1	4	4	3	3	
6	26	M	No	Seizure	T	R.MCA +R.PCA	SDV +DDV	S2E1V1	R.PCA	1.5	Unused	<50	S2E1V1	3.55	1,000	No	No	1	1	1	1	1	
7	39	M	No	ICH+ IVH	P O	L.ACA +L.PCA	DDV	S2E1V1	R.PCA	2.5	Unused	<50	S2E1V1	2.27	1,000	No	No	5	1	0	0	0	
8	45	F	No	Incident	F	L.ACA	SDV +DDV	S3E0V1	R.ACA	1	Unused	>90%	S3E0V1	6.57	2,000	No	No	1	4	1	1	1	
9	16	F	No	ICH	T P	R.MCA +R.PCA +R.AChoA	SDV +DDV	S2E1V1	R.MCA	1.1	Pressure cooker	50–90%	S2E1V1	2.00	400	No	No	1	1	0	0	0	
10	42	M	No	Headache	F P	R.ECA +R.MCA +R.PCA	DDV	S3E0V1	R.MCA +R.PCA+ R.MMenA	11.5	Unused	<50%	S2E0V1	5.82	6,000	CNS infection	No	1	0	0	0	0	
11	25	M	No	ICH	T P O	R.MCA +R.ACA +R.PCA	DDV	V	R.PCA	10.5	Unused	>90%	S2E0V1	5.45	1,600	Seizure	No	2	4	3	2	1	
12	45	F	No	ICH	P O	L.MCA +L.ACA +L.PCA	SDV	S3E1V0	L.ACA	12	Unused	>90%	S2E1V0	3.27	200	Hemorrhage	No	0	4	2	2	2	
13	32	M	HE +BHD	ICH+ IVH+ SAH	P O	RMCA +RACA +RPCA	SDV +DDV	S2E1V1	L.ACA	1.8	Unused	50–90%	S2E0V1	6.12	1,000	No	No	4	2	2	2	2	
14	6	M	HE	IVH+ SAH	P	RMCA +RAChoA +RLentA	SDV +DDV	S2E1V1	R.MCA +R.LentA	3	Pressure cooker	50–90%	S2E0V1	3.10	4000	No	No	1	2	1	0	0	
15	32	M	No	ICH	F	RMCA	SDV +DDV	S2E1V1	R.LentA	1.2	Temporal occlusion	<50%	S2E0V1	4.15	300	No	No	1	4	3	3	2	
16	10	M	No	ICH+ SAH	P	RMCA +RACA +RPCA +RAChoA +RPChoA +RLentA	SDV +DDV	V	R.MCA +R. LentA	9	Unused	>90%	S2E0V1	4.12	500	No	No	1	0	0	0	0	
17	14	M	No	IVH	F P	RACA	DDV	S2E1V1	R.ACA	1	Pressure cooker	50–90%	S2E0V1	3.68	500	No	No	2	2	1	1	1	

(Continued)

TABLE 2 | Continued

Case no.	Age (yr)	Gender	Surgical history	Initial symptom	Location	Feeding artery	Draining vein	SMG	Embolized feeders	Embolic agent (ml)	Balloon	Embo rate (%)	Post-embo SMG	Resection time (hr)	Blood loss (ml)	Complication	Second Op.	Postoperative mRS score					
																		Adm.	Dis.	3 mo.	6 mo.	12 mo.	Other
18	34	F	EE	ICH	C	LAICA +LSCA +LPICA	SDV	S3E1V0	L.SCA +L.PICA	4.5	Unused	>90%	S1E1V0	3.43	800	CNS infection	No	1	2	2	2	1	
19	53	M	No	ICH	T P	LPCA	SDV	S3E1V0	L.MCA +L.PCA	10	Unused	>90%	S2E0V0	6.20	2000	Cerebral hemorrhage +Cerebral infarction +Respiratory infection	7th day	0	5	5	5	5	Dead in the 24th mo.
20	48	M	HE	IVH+ Hypopsia	O	LACA +LPCA	SDV +DDV	S2E1V1	L.ACA +L.MCA +L.PCA	9	Unused	>90%	S1E0V1	5.55	500	No	No	2	2	2	2	2	
21	49	F	No	ICH	P O	RMCA	SDV	S3E1V0	R.MMenA	4.7	Unused	>90%	S2E0V0	3.73	1,500	Cerebral Hemorrhage	No	1	5	6	NA	NA	Dead in the 2nd mo.
22	5	F	No	ICH	P O	LMCA +LPCA	DDV	S2E1V1	L.PCA	5	Unused	>90%	S1E0V1	2.22	500	No	No	1	0	0	0	0	
23	8	M	HE	ICH+ IVH+ Dyskinesia	Bg	LMCA +LPCA	DDV	S2E1V1	L.MCA	1.2	Unused	<50%	S2E0V1	5.15	800	CNS infection	No	4	4	4	3	3	
24	63	M	No	IVH	F	LACA	DDV	S3E0V1	L.ACA	2.5	Pressure cooker	>90%	S1E0V0	2.45	1,000	No	No	2	1	1	1	1	

SMG, Spetzler-Martin Grade; Embo, Embolization; Op., Operation; mRS, Modified Rankin Scale; Adm., Admission; Dis., Discharge; mo., Months; HE, Hematoma Evacuation; BHD, Bur Hole Drainage; EE., Endovascular Embolization; ICH, Intracerebral Hemorrhage; IVH, Intraventricular Hemorrhage; SAH, Subarachnoid Hemorrhage; F, Frontal lobe; T, Temporal lobe; P, Parietal lobe; O, Occipital lobe; Bg, Basal Ganglion; C, Cerebellum; R., Right; L., Left; MCA, Middle Cerebral Artery; PCA, Posterior Cerebral Artery; ACA, Anterior Cerebral Artery; AChoA, Anterior Choroidal Artery; ECA, External Carotid Artery; LentA, Lenticulostriate Artery; PChoA, Posterior Choroidal Artery; AICA, Anterior Inferior Cerebellar Artery; SCA, Superior Cerebellar Artery; PICA, Posterior Inferior Cerebellar Artery; SDV, Superficial Draining Vein; DDV, Deep Draining Vein; MMenA, Middle Meningeal Artery; CNS, Central Nervous System; NA, Not Applicable.

TABLE 3 | Subgroup comparisons in different embolization rates and SMG degrading strategies.

Category	Blood loss (ml)		Resection time (hrs)		Deterioration of neurological deficits (n/N)						
	Volume	*P*-value	Duration	*P*-value	Dis.	*P*-value	3 mo.FU	*P*-value	6 mo.FU	12 mo.FU	*P*-value
Embolization rate*											
Non-embolization	1,000 ± 1263.5		5.8 ± 2.40		1/14		0/13		0/13	0/13	
Partial (0–50%)	1,272 ± 1799.5	0.673	5.8 ± 2.14	0.982	3/9	0.147	2/9	0.156	2/9	1/9	0.409
Subtotal (51–89%)	1,560 ± 1487.6	0.427	6.8 ± 2.44	0.419	0/5	0.737	0/5	NA	0/5	0/5	NA
Near-total (≥90%)	1,060 ± 667.0	0.893	5.6 ± 1.47	0.836	5/10	0.028	3/10	0.068	3/10	2/10	0.178
SMG degradation											
Size						0.217		0.150			0.289
−2 points	900 ± 141.4†		4.7 ± 0.74†		0/2		0/2		0/2	0/2	
−1 point	1,511 ± 1792.0	0.655	6.1 ± 1.96	0.348	4/9		3/9		3/9	2/7	
−0 point	1,053 ± 1137.3	0.852	5.9 ± 2.20	0.471	5/27		2/26		2/26	1/26	
Eloquence (*n* = 35)						0.194		0.029			0.239
−0 point					4/24		1/23		1/23	1/23	
−1 point					4/11		4/11		4/11	2/11	

n/N, Incident number /Total number at the time point; Dis., Discharge; mo., Month; FU, Follow-up; iDSA, Intraoperative Digital Subtraction Angiography; SMG, Spetzler-Martin Grade.
Each of subgroups was compared with non-embolization subgroup (iDSA alone).
†*The baseline of intergroup comparisons.*

was 4.9 ± 1.36 cm on average (ranged 3.0–7.5 cm). Thirty cases received the fMRI scan, while eight cases solely received the structural MRI scan. Eloquent areas were involved in 35 cases (92.1%) with an LED < 5 mm. In the aspect of angioarchitecture, arterial feeders that originated from solely anterior or posterior circulation were found in 17 (44.7%) cases and four cases (10.5%), respectively, and from both circulations in 17 cases (44.7%). The supply from perforating arteries was observed in six cases (15.8%), including anterior choroidal artery + lenticulostriate arteries in two cases, the anterior choroidal artery in three cases, and lenticulostriate arteries in one case. Nidus were drained from the deep draining vein(s) alone in 12 cases, superficial vein(s) alone in seven cases, and both in 19 cases. There were five cases (13.2%) with AVMs in SMG V, and 33 cases (86.8%) with AVMs in SMG IV, including 24 cases of S2E1V1, six cases of S3E1V0, and three cases of S3E0V1. The involvement of multiple lobes, the feeders from both anterior and posterior circulation, deep draining vein, larger maximum diameter, and the eloquent area was observed more frequently in Embo+MSR groups, but without significant difference (refer to **Table 1**).

All patients received selective operations. Fourteen cases (36.8%) underwent the paradigm of iDSA plus microsurgical resection. Twenty-four cases (63.2%) underwent the paradigm of endovascular embolization plus simultaneous microsurgical resection (details in **Table 2**, Case 4 and 11 refer to the section of Illustrative Cases). SMG grades were degraded via embolization in 15 cases (**Table 2**, Column 9 vs. Column 14). The degradations in nidus size and eloquent involvement were achieved in 11 cases, respectively. Residual nidus was detected via intraoperative DSA in two cases, which received immediate resections. The total operating time was 8.3 ± 2.06 h on average (ranged 5.52–15.17 h), in which 5.9 ± 2.08 h was for surgical procedures. The intraoperative bleed loss ranged from 150 to 6,000 ml (mean 1,153 ± 1282.8 ml, median 750 ml), including 150 to 4,800 ml (mean 1,000 ± 1263.5 ml) in iDSA+MSR group and 200–6,000 ml (mean 1,243 ± 1312.3 ml) in Embo+MSR group, without significant difference (student-t-test, $P = 0.576$). Intraoperative blood salvage was performed in 61.5% of cases ($n = 24$). Four cases received homologous blood products transfusion, including suspension of red blood cells in two cases, suspension of red blood cells+serum in one case, and fresh frozen plasma in one case. Doppler ultrasound was applied to 33 cases for detecting residues and reported two (6%) false-negative results.

Intracranial hemorrhagic and ischemic complications occurred in three cases (7.9%) and two cases (5.3%), respectively. The second operation was performed in two cases (5.3%) to evacuate the postoperative hematoma. Infection of the central neural system occurred in six cases (15.8%). Infection of the respiratory system occurred in one case (2.6%), and postoperative seizure occurred in one case (2.6%).

Deterioration of neurological deficits occurred in 23.7% of cases ($n = 9$) when discharged. Among the patients who reached follow-up points of 3, 6, and 12 months, incidences of DNDs were 13.5% (5 out of 37), 13.5% (5 out of 37), and 8.1% (3 out of 37), respectively. Two deaths (5.3%) occurred in total, including one 2 months after the operation, and the other after 24 months in a coma. DNDs occurred frequently in Embo+MSR groups at every time point without significant differences (refer to **Table 1**).

Technical details, such as embolization rate and SMG degradation, were further investigated in subgroup comparisons (refer to **Table 3**). The operative difficulty was represented by blood loss and the microsurgical time. The clinical outcome was represented by the incidence of DNDs. Similar blood loss occurred in the patients receiving no embolization (1,000 ± 1263.5 ml) and near-total embolization (1,060 ± 667.0 ml, t-test, $P = 0.893$), but without significant difference compared to other patients who received partial (1,272 ± 1799.5 ml, t-test, $P =$

0.673) and subtotal embolization (1,560 ± 1487.6 ml, t-test, $P = 0.427$). Patients receiving near-total embolization had the shortest resection time but without a significant difference to the longest one (5.59 ± 1.471 h vs. 6.81 ± 2.441, t-test, $P = 0.298$). Patients receiving subtotal embolization had no deterioration of neurological deficits occur. By contrast, near-total embolization induced DNDs in 50% ($n = 5$) of patients at discharge (Fisher exact test, $P = 0.028$) and 20.0% of patients at 12-month follow-up (Fisher exact test, $P = 0.178$).

The embolization degraded the scores of SMG on size and eloquence (details refer to **Table 3**). The patients who decreased by 2 points on size obtained the most optimal outcome, with 900 ± 141.4 ml of blood loss, 4.70 ± 0.742 h of resection, and no incidence of DNDs. The embolization of eloquent area, −1 point in Eloquence, induced more occurrence of DNDs, especially in 3- and 6-month follow-up (−0 point vs. −1 point = 1/23 vs. 4/11, Fisher exact test, $P = 0.029$).

DISCUSSION

In this study, one-staged hybrid operations were performed to treat high-grade brain arteriovenous malformations on 38 patients. The applicable paradigm consisted of intraoperative digital subtraction angiography, endovascular embolization, and microsurgical resection. Two cases of residue (5.3%) were detected by iDSA, which were false-negative in intraoperative Doppler sonography. Complete obliterations were achieved in all cases. Deterioration of neurological deficits occurred in 23.7% of cases at discharge, and 13.5, 13.5, and 8.1% of patients at 3-, 6-, and 12-month follow-ups, respectively. The postoperative hemorrhage occurred in 7.9% of cases. The therapeutic paradigms based on one-staged hybrid operation were revealed to be feasible in treating high-grade AVMs.

The high-grade AVM is a critical challenge for the cerebrovascular surgeon. Difficulties lie in achieving both complete obliteration and neurological protection at the same time. Different therapeutic modalities have been proposed, including the initial microsurgical resection, and later staged multimodality treatments. Microsurgical resection is the early method of treating AVMs and was reported to achieve a complete obliteration rate of 96% (28). Still, it was not recommended to be primarily performed on high-grade AVMs, for its incidence of DNDs ranging from 31 to 38% (29, 30). Different types of multimodality treatments were reported to be used to treat most of the high-grade AVMs in current studies, including 1) endovascular embolization plus stereotactic radiosurgery (EE+SRS), 2)stereotactic radiosurgery plus delayed microsurgical resection (SRS+dMSR), and 3) staged endovascular embolization plus microsurgical resection (sEE+MSR). Blackburn et al. (31) reported their experience of performing the paradigm of EE+SRS without any incidence of neurological deficits. However, it should be noticed that the obliteration rate of the EE+SRS paradigm was reported to be 81%, which might expose patients to hemorrhagic risks due to residual nidus (5, 7). SRS+dMSR is another paradigm for treating high-grade AVMs. In this paradigm, the preoperative SRSs gradually eliminate parts of nidus and feeders over 2–3 years, and the delayed microsurgery ensured the complete elimination of the lesion. Abla et al. (20) reported their experience on using the SRS+dMSR paradigm in 16 cases and achieved an obliteration rate of 93.8% and a DNDs incidence of 50%. Though the paradigm was proved to be feasible, the hemorrhagic risk in latency periods of SRS still should be noticed, which could reach an incidence as high as 10–25.7% (15–19, 32). The paradigm of sEE+MRS is the most commonly used modality on treating high-grade AVMs. The preoperative endovascular embolization could decrease the blood volume of the lesion to reduce the operative risk in the following microsurgery (33). The MRS guaranteed a high complete obliteration rate but resulted in a DNDs incidence ranging from 24 to 63% (21–23). The staged treatment would expose the patient to a risk of intracranial hemorrhage after embolization ranging from 11 to 22.7% (34–36). In this study, 100% of complete obliteration rate and 8.1% of neurological deficit incidence in 12-month follow-up were achieved in one-staged paradigms. Though higher DND incidence occurred in EE+MRS groups compared to the iDSA+MRS group (0 vs. 12.5%, $P = 0.260$), both modalities resulted in acceptable clinical outcomes, without limitations in staged paradigms. Meanwhile, it should be noticed that 68.4% of patients presented with ruptured AVMs, which had been proven to be a protective factor of neurological outcomes (25). Intraoperative DSA played an important role in one-staged paradigms. It remedied the false-negative results of intraoperative Doppler sonography and ensured the complete obliteration of AVMs.

Endovascular embolization is believed to reduce operative risks and improve clinical outcomes of AVMs. EE+MRS group achieved relatively worse neurological outcomes and higher operative risks (more blood loss) than the iDSA+MRS group in every assessment point (refer to **Table 1**) in our study. Though there was no significant difference between groups on the baseline, AVMs in the EE+MRS group had higher proportions in the involvement of multiple lobes (45.8 vs. 35.7%), feeders of both anterior and posterior circulation (50 vs. 35.7%), deep draining vein (33.3 vs. 28.6%), and larger nidus (5.1 ± 1.44 cm vs. 4.6 ± 1.19 cm). As the data extracted from a real-world registry, participants in the EE+MRS group ought to harbor the lesion with more complex morphological and angioarchitectural conditions, which lead to worse clinical outcomes than those in the iDSA+MRS group. Despite that, two groups in this study achieved results without significant difference.

Technical Details of Paradigm

According to the practical experience of this study, the following technical details might influence the neurological outcomes of patients who use this paradigm.

Embolization Rate

In this paradigm, the procedure of embolization was aimed at reducing the risk and difficulty of subsequent microsurgical resection by occluding the targeted feeders and nidus, rather than achieving complete obliteration. The arterial feeders and nidus, difficult to control during microsurgery, were the prior targets of embolization. Due to varieties of hemodynamic status, different

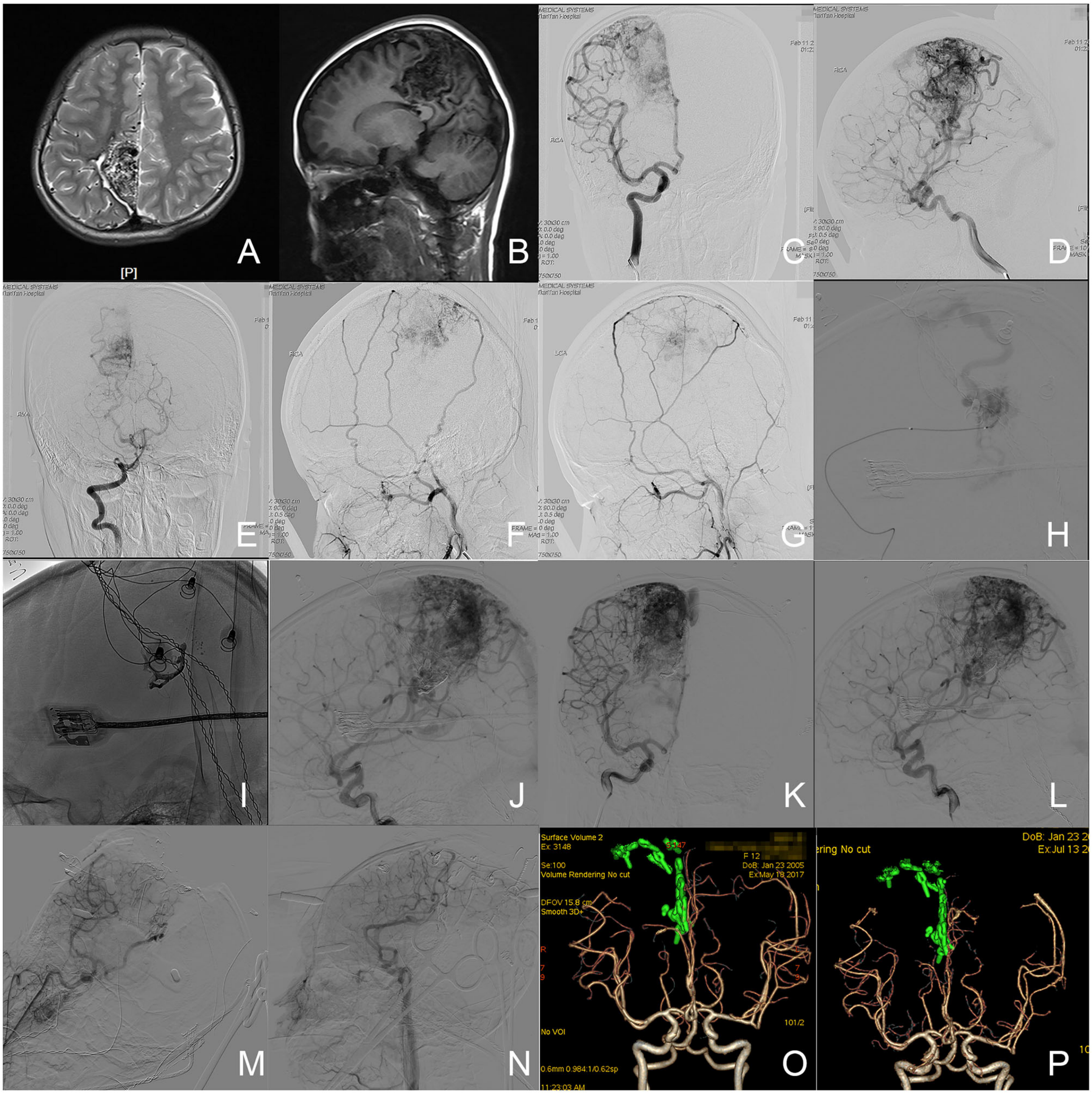

FIGURE 1 | Illustration of case 4. **(A,B)** The axial T2-weighted and sagittal T1-weighted MR images revealed a cerebrovascular lesion in the right parietal lobe with isthmus of cingulate gyrus, parahippocampal gyrus, and splenium of corpus callosum involved. **(C,D)** Angiograms of right internal carotid artery (ICA) revealed the arterial feeders from the right arteries of central and postcentral sulcus, and the right pericallosal artery, paracentral artery, and precuneal artery, as well as drainage through Galen's vein and superficial draining vein. **(E)** Angiogram via the right vertical artery revealed the arterial feeders from the right posterior cerebral artery. **(F,G)** Angiograms via the bilateral external carotid arterial revealed the arterial feeders from the bilateral middle meningeal arteries. **(H)** An angiogram through the microcatheter (Excelsior SL-10, Stryker Neurovascular, California, USA) in the right pericallosal artery. **(I)** The casted embolization agent (high density object). **(J)** Angiogram through the right ICA in the work position after embolization. **(K,L)** The angiograms through the right ICA before microsurgery revealed the partial occlusion of nidus and feeder in the deep. **(M,N)** The intraoperative angiogram before closure confirmed the complete elimination of nidus. **(O)** The follow-up CTA 3 months after the operation revealed a complete elimination of nidus. **(P)** The follow-up CTA 17 months after the operation revealed no residue or recurrence. The green objects in **(O,P)** were the reconstructed clips.

embolization rates were achieved when the targets above were occluded. Embolization rates were sorted into four categories: non-embolization (received DSA only), partial embolization (with a rate $\leq$50%), subtotal embolization (with a rate >51% and <90%), and near-total embolization (with a rate $\geq$90%). The neurological outcomes of classes were revealed to be different

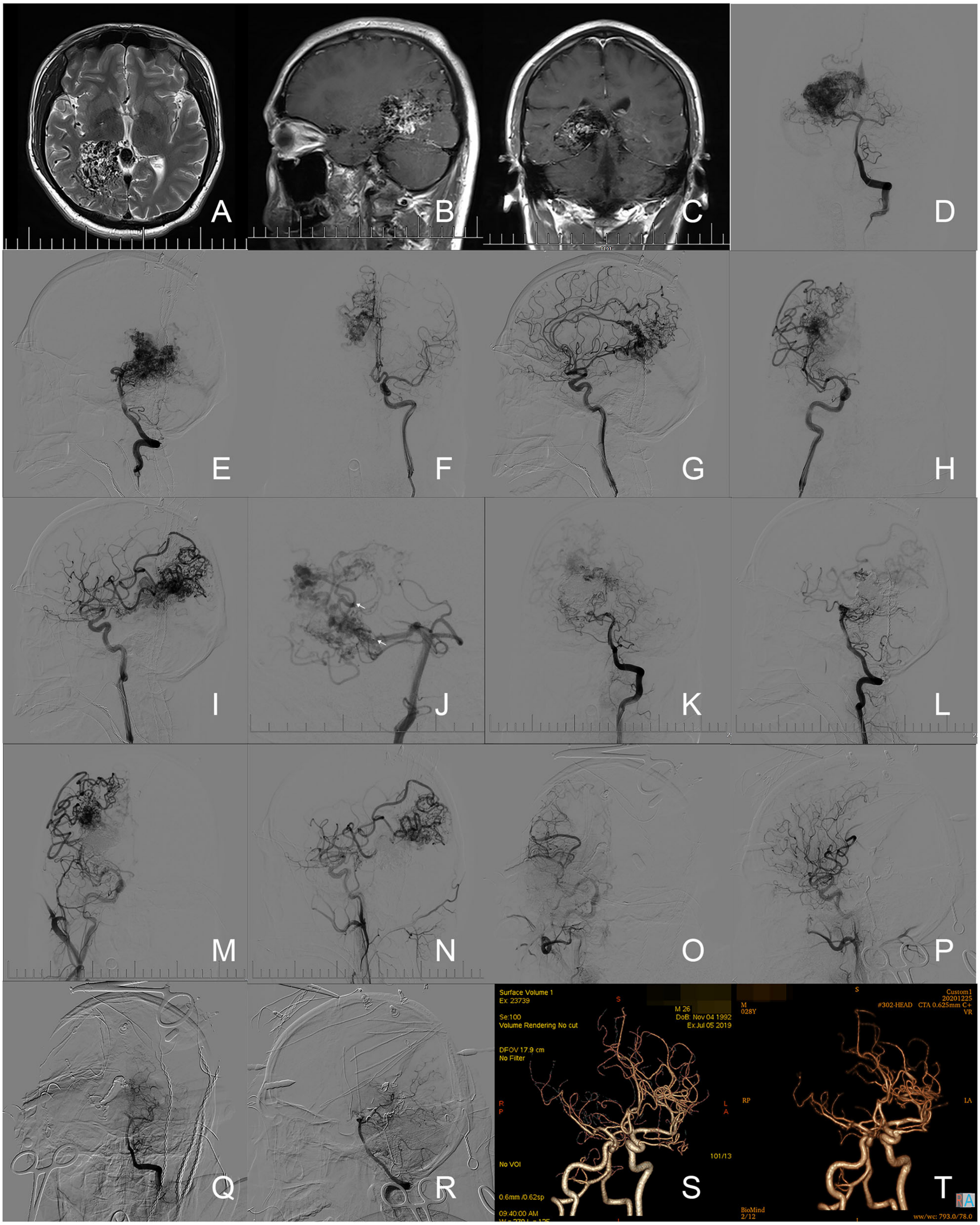

FIGURE 2 | Illustration of case 11. **(A–C)** Preoperative axial T2-weighted image, sagittal, and coronary enhanced T1-weighted image of MR revealed the bAVM located in the right tempo-parietal-occipital lobe. **(D,E)** Angiograms via the left vertical artery revealed the feeders from the right posterior cerebral artery (PCA) and the drainage through Galen's vein. **(F,G)** Angiograms from the left ICA demonstrated the feeders from the right callosomarginal artery and precuneal artery. **(H,I)**

(Continued)

FIGURE 2 | Angiograms from the right ICA demonstrated the feeders from the right posterior parietal artery, postcentral sulcus artery, and anterior choroidal artery. **(J)** A microcatheter (Marathon 1.3-F, eV3/Covidien, Minnesota, USA. Arrows indicates the marker on the tip of the microcatheter) was super-selected into the nidus through the right PCA. **(K,L)** Angiograms through the left vertical artery suggested the occlusion of most arterial feeders from the right PCA. **(M,N)** Angiograms from the right ICA demonstrated the feeders from the anterior circulation. **(O-R)** The intraoperative angiograms through right ICA and left vertical artery confirmed the complete elimination of nidus. **(S)** A follow-up CTA at the 12th month after operation revealed no residue. **(T)** A follow-up CTA at the 30th month after operation revealed no recurrence of nidus.

between categories. The minimum events of DNDs occurred in the subtotal embolization group (0 out of 5), and secondarily in the non-embolization group (1 out of 14). The near-total embolization group had the maximum DNDs events (5 out of 10) compared to non-embolization (50 vs. 7.1%, Fisher exact test, $P = 0.028$). The hemodynamic status of nidus changed with the increasing embolization rate, and further influenced the casting of the embolic agent. It resulted in the distinctions between different embolization rates, and further led to different neurological outcomes. In the partial embolization group, the majority of embolic agents coalesced in the nidus near its inflow entrance and rapidly reversed into the arterial feeder. It made little contribution to reducing microsurgical risks and difficulties, and made the least impact on neighboring parenchyma. In the subtotal embolization group, the microcatheter was primarily superselected into the nidus through the dominant feeding artery to infuse the embolic agent. Blood flow of the dominant artery could help the embolic agent widely cast out into the nidus, and avoid its premature retrograde casting into the superselected artery. The embolic agent was being intermittently infused into the nidus until target nidus or feeders were embolized, which was always achieved at an embolization rate > 50%. In the subtotal embolization group, the embolized structures were a portion of the nidus and the arterial segments approximal to the nidus. Near-total embolization shared the same process with subtotal embolization in its early phase, but would not stop until most of the nidus was radiologically obliterated with obvious retrograde embolization in most of the feeding arteries. It could help to decrease the bleeding in microsurgery but might injure neighboring arterial branches and parenchyma. According to our results, subtotal embolization was revealed to be the most effective on reducing the risk and difficulty of microsurgery and improving the neurological outcome. Nevertheless, partial and near-total embolization achieved success in some of the cases. Their application scenes remain to be further explored.

Embolization of Perforating Artery

Perforating arteries are proven to be a risk factor for microsurgical resection of AVMs (37, 38). These arteries are deep-originated to eloquent territories, which are difficult to expose and control. The targeted embolization could get the perforating arteries controlled ahead of surgical operation, which was applied to three cases (Case 14, 15, and 16). In Cases 14 and 16, perforators were embolized retrogradely from the nidus to the artery. In Case 15, the lateral lenticulostriate artery was embolized through a microcatheter, which had been super-selected from the embolic agent and was infused directly through the microcatheter, which was super-selected in it. The neurological function deterioration occurred in Case 15 but was not observed in the other two cases. Referring to technical details of three cases, the retrograde infusion of the embolic agent through nidus to perforators might be a safer manipulating method, which limited the embolic agent in the segment of perforator approximal to the nidus. By contrast, the embolization through a microcatheter super-selected into the perforator might impact neurological functions. Also, the manipulation of super-selection might be at risk of damaging the perforator and its branches.

AVM Degradation

High-grade AVM could be degraded by the intraoperative embolization in this paradigm. The degradation could be achieved by decreasing the point on size (by reducing the nidus size) and eloquence (increasing the distance between lesion and eloquence). The point on deep draining vein could hardly be changed since the premature occlusion of outflow would increase the rupture and edema risk of the lesion and the parenchyma around (39).

Degradations on size induced different neurological outcomes. Referring to **Table 3**, DNDs occurred in 0% of patients who decreased by 2 points in size, while 44.4% (4 out of 9) of patients decreased by 1 point. Only large AVMs (maximum diameter≥6 cm) could achieve a reduction of 2 points with an embolization rate of>50%. The neurological outcomes and operative difficulties of large AVMs might be improved by the sufficient reduction of their nidus. While, the decreasing of size by 1 point indicated a minor impact on the nidus, which made little contribution to operative risks and outcomes.

The degradation of eloquence is aimed at increasing lesion-to-eloquent distance (LED) to decrease the incidence of DNDs. Jiao et al. reported a cutoff LED of 5 mm, beyond which eloquent areas could be survived (25). However, in our study, the embolization near eloquence failed to improve the neurological outcome of patients when discharged. On the contrary, it resulted in worse outcomes over 6 months, compared to those with left eloquence score unchanged (discharge, −0 vs. −1=16.7 vs. 36.4%, Fisher exact test, $P = 0.194$; 6 months, −0 vs. −1= 4.3 vs. 36.4%, Fisher exact test, $P = 0.029$). The operative details revealed that the degradation of eloquent areas would not affect the neurological outcome alone. The strategy of subsequent microsurgery determined the success of neurological protection. Resecting the nidus along its initial boundary would still damage the parenchyma of eloquence nearby. In contrast, resecting in the embolized nidus would leave a sufficient LED between cutting edge and eloquence and create minimized neurological deficit. This technique, which preserves the embolized nidus near eloquence *in situ* and resected the rest, has been successfully applied to protect the neurological functions of patients (27, 40).

Illustrative Cases

Illustration of Case 4

A 12-year-old female presented with sudden weakness in her left extremities 10 years ago. Her head MRI revealed a bAVM located in the parietal lobe and involved the isthmus of the cingulate gyrus, parahippocampal gyrus, and splenium of the corpus callosum. Her dyskinesia was relieved after a partial endovascular embolization performed in a local hospital. The patient suffered a sudden headache accompanied by nausea and vomiting 2 months before admission. The patient complained about the episodic headache upon admission, and got a 1 score of mRS without any neurological deficit. A DSA was repeated for preoperative preparation. The nidus was mainly supplied by arterial feeders from the right arteries of the central and postcentral sulcus, and the right pericallosal artery, paracentral artery, and precuneal artery. The recruitment of arterial feeders from the right posterior artery and bilateral middle meningeal arteries could be observed. The nidus was drained via Galen's vein and superficial draining vein. In a one-staged hybrid operation, an embolization was firstly performed to eliminate the medial inferior nidus through the pericallosal artery to control the feeders from deep within the operative field. The microsurgical resection was performed after achieving a partial embolization. An intraoperative DSA was performed before closure and confirmed the complete elimination of nidus. The left extremities of the patient were paralyzed after the operation and improved to be capable of walking independently with a crutch (3 scores of mRS) when discharged after 20 days. The patient visited the outpatient department 3 months after the operation with slight weakness in the left extremities (2 scores of mRS). A 3-month follow-up CTA revealed no residue or recurrence of bAVM. The 6-and 12-month telephone follow-ups reported the recovery of strength in the left extremities and clumsiness of the left fingers (1 score of mRS). The patient visited the outpatient department again after 17 months with her left finger clumsiness unchanged. A 17-month follow-up CTA further confirmed the complete elimination of bAVM. Images of this case refer to **Figure 1**.

Illustration of Case 11

A 25-year-old male complained about a sudden headache followed by a loss of consciousness 11 years ago. The patient was admitted into a local hospital and received a head CT and DSA. A rupture of bAVM in the right tempo-parietal-occipital lobe was discovered, but without any surgical intervention given. The patient remained dizzy, with blurred vision, and had stiff limbs when discharged from the local hospital. He visited our outpatient department for the deterioration of the symptoms above. The physical examination revealed blurred vision and clumsiness of distal extremities upon admission (2 scores of mRS). A head MRI revealed the lesion in the right tempo-parietal-occipital lobe. In the one-staged hybrid operation, the DSA revealed the nidus to be mainly fed by parietooccipital and calcarine branches of the right posterior cerebral artery (PCA). Other arterial feeders included the right callosomarginal artery, precuneal artery, posterior parietal artery, postcentral sulcus artery, and anterior choroidal artery. Nidus was drained by Galen's vein. Endovascular embolization was performed through the right PCA to eliminate the deep nidus and achieved about 50% embolization rate. Most of the feeders from the PCA were occluded with those from the anterior circulation remaining. The lesion was removed in the subsequent microsurgery. The complete elimination of bAVM was confirmed by the intraoperative DSA before closure. The patient was discharged 18 days after the operation with a critical weakness in the left limbs and deficit of vision field (4 scores of mRS). The telephone follow-up reported the sequential improvement in movement capability of left limbs and 3 and 2 scores of mRS after 3 and 6 months, respectively. The patient visited the outpatient department 12 months after the operation with only partly homonymous hemianopia remaining (1 score of mRS). There was no residue or recurrence of nidus found in the CTAs at 12 and 30 months. Images of this case refer to **Figure 2**.

Modification and Expectation

The one-staged hybrid operation, which combines endovascular and microsurgical techniques, has been used in neurosurgery for over 5 years (41). It provides extraordinary surgical solutions to AVMs. It also makes it possible to account for the timing of subsequent microsurgery after embolization, the hemodynamic changes in operation, the predictors of normal perfusion pressure breakthrough and neurological deficit, etc. In this study, the practicability of one-staged hybrid operation on treating high-grade AVMs was validated. Meanwhile, technical details which might improve the operative safety and neurological outcomes were analyzed and proposed. These findings would be further studied in following specific studies with a larger sample size.

Limitation

In this study, 38 cases with high-grade AVMs were enrolled. It met the requirement of describing the practicability of the paradigm based on the one-staged hybrid operation on treating high-grade AVMs, but could not make effective comparisons between different procedures and technical details. Further studies with a larger sample size are needed.

CONCLUSIONS

The paradigms based on the one-staged hybrid operation were practical and effective in treating high-grade AVMs. Appropriate intraoperative embolization could help decrease operative risks and difficulties and improve neurological outcomes.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB of Beijing Tiantan Hospital, Capital Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MW, FL, and HQ designed and conceptualized this work and participated in the data collection. MW participated in drafting the manuscript. YC, SW, and JZ critically revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Management of Unruptured Small Multiple Intracranial Aneurysms in China: A Comparative Effectiveness Analysis Based on Real-World Data

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Background: Unruptured small aneurysms with a size of <7 mm were often followed conservatively. However, it is unknown whether unruptured small multiple intracranial aneurysms (MIAs) are better to be prophylactically treated or conservatively followed.

Objective: We aim to compare the effectiveness of different strategies regarding their management.

Methods: A decision-analytic Markov model was built over a entire life cycle. The compared strategies include natural history, treat one aneurysm, treat both aneurysms, annual follow-up, biennial follow-up, and follow-up every 5 years. The inputs for the model were obtained from real-world data and related medical literature. Outcomes were measured in terms of quality-adjusted life-years (QALYs).

Results: Treat both aneurysms had the highest effectiveness of 15.36 QALYs and treat one aneurysm had the second-highest effectiveness of 15.11 QALYs. Probabilistic sensitivity analysis with 10,000 iterations showed that treat both aneurysms and treat one aneurysm were optimal in 67.28 and 17.91% of all cases, respectively. One-way and two-way sensitivity analyses showed that the result was sensitive to the proportion of moderate to severe disability after treating two aneurysms, mortality after treating two aneurysms, proportion of moderate to severe disability after treating one aneurysm, and rupture rate of small growing aneurysm. Either treat both aneurysms or treat one aneurysm would be the optimal strategy under most of the circumstances with the variations of these parameters.

Conclusion: For patients with small unruptured MIAs, prophylactic coiling was superior to conservative management and at least one aneurysm should be treated.

Keywords: multiple intracranial aneurysms, small aneurysm, comparative effectiveness analysis, real-world data, endovascular therapy

INTRODUCTION

Intracranial aneurysms are common among healthy adults and affect approximately 3 to 7% of them (1, 2). Multiple intracranial aneurysms (MIAs) are defined as those harboring two or more aneurysms in one patient. The reported rate of MIAs among aneurysm carriers ranges between 2 and 44.9% (3). Endovascular coiling has gained wide popularity for the treatment of aneurysms during the last two decades (4). Nowadays, patients with MIAs often receive endovascular treatment because of safety and efficiency (5–9).

Patients with aneurysms are often at risk of rupture, which might lead to a devastating subarachnoid hemorrhage (SAH) and subsequent unpleasant outcomes. A large proportion of aneurysms are small with a size of <7 mm, and managing small unruptured aneurysms is one of the most controversial topics in neurosurgical medicine (10). The second International Study of Unruptured Intracranial Aneurysms has demonstrated that the risk of rupture from small aneurysms is extremely low (11). Treatment of these aneurysms brings a greater risk of unpleasant outcomes than the natural hisotry. This has led to a more conservative management approach (12). However, since a large group of patients carries small aneurysms, a significant number of SAH is actually from them. Therefore, considerable uncertainty remains regarding their management.

For small unruptured aneurysms that were managed conservatively, follow-up at regular intervals with computed tomography angiography or magnetic resonance angiography (MRA) was recommended to assess possible changes in size, because growing aneurysms are prone to rupture (12, 13). However, there is no clear consensus on the optimal management of small MIAs nowadays, since they are more likely to grow and rupture than the single ones (3, 14). Moreover, a significantly higher rate of unfavorable outcomes for the endovascular treatment of unruptured MIAs than treatment of the single aneurysm was reported (5). It is unknown whether unruptured small MIAs are better to beprophylactic treated or what the appropriate frequency and duration of follow-ups are if conservative management was performed.

In this study, we performed a comparative effectiveness analysis to evaluate six different strategies in the management of small unruptured MIAs. To make our model more simplified, we assumed that all the patients carried only two aneurysms. All the treatments were performed by endovascular coiling, and all the follow-ups were performed by MRA. The evaluated strategies included natural history, treat one aneurysm, treat both aneurysms, annual follow-up, biennial follow-up, and follow-up every 5 years.

MATERIALS AND METHODS

Real-World Data Collection

This collection was retrospectively collected from three tertiary hospitals in Beijing. Informed consent for each patient was waived because of study design. A total of 1,334 patients who were admitted because of MIAs from January 2014 to August 2020 were included in our MIA database. The exclusion criteria were (1) patients who received open surgery, (2) traumatic, fusiform, and blood blister-like aneurysms, and (3) patients with history of other major diseases such as severe ischemic stroke, tumor, uremia, and heart failure. The collected information includes demographic characteristics, aneurysm size, aneurysm location, treatment modalities, costs, clinical outcomes, etc. Patients who had two small unruptured aneurysms were identified from this database for later analysis.

Model Structure

We built a decision-analytic Markov model over a life span using TreeAge Pro Suite 2020 (TreeAge Software Inc.). According to our database, the average age of patients harboring MIAs was 56.8 years old. Therefore, the model starts with a 57-year-old patient with two unruptured small aneurysms. The length of one Markov cycle was 1 year, and this model would not stop until all the patients died or reached 99 years old. Nine different health states were introduced in this model, namely, well with MIAs, well with growing MIAs, well with a single growing aneurysm, well with one treated aneurysm, well with both treated aneurysms, SAH, mild disability, moderate to severe disability, and death. The branch of "Natural history" in the model in provided in **Supplementary Material**, and the whole model is available upon request.

For the "natural history", all the MIAs carried an annual risk of SAH because of rupture. After rupture, all the patients with SAH would have endovascular coiling and both of the two aneurysms were assumed to be coiled. After coiling, they would have full recovery [modified Rankin scale (mRS) score of 0–1], permanent mild disability (mRS score 2), permanent moderate to severe disability (mRS score of 3–5), or die (mRS score of 6). We assumed that only those with full recovery would have annual MRA follow-up in the subsequent years due to *de novo* aneurysm formation that needs a second treatment.

For "follow-up", MIAs would be followed annually, biennially, or every 5 years to assess the possible growth in aneurysmal size because the growing aneurysm is more likely to rupture. If size change was observed, the growing aneurysm was assumed to be coiled directly, with the non-growing one left untreated. After the treatment, patients would have a full recovery, permanent mild disability, permanent moderate to severe disability, or die. Fully recovered patients would have an annual follow-up for possible *de novo* aneurysm formation. A rupture would also occur in non-growing aneurysms and could not be prevented by imaging screening. The outcomes of treating ruptured aneurysms were the same as those of the "natural history".

For "treat one aneurysm", only one aneurysm was assumed to receive prophylactic coiling. The treatment outcomes were similar to those of "follow-up". An annual follow-up would be performed among the fully-recovered patients for possible growth of the untreated one or *de novo* aneurysm formation. The untreated one also carries an annual risk of rupturing.

For "treat both aneurysms", both aneurysms were assumed to be coiled prophylactically. The patients would also have the four aforementioned outcomes. Treated patients would have an annual follow-up for possible *de novo* aneurysm formation.

Clinical Parameters

We retrieved all the clinical parameters from our cohort or recently published large cohort studies or meta-analysis studies whenever available. The annual growth rate (2.6%) and annual rupture rate (0.5%) of small non-growing aneurysm were obtained from a recent meta-analysis by Malhotra et al. (15). The annual rupture rate (6.3%) of small growing aneurysm was retrieved from an observational study and systematic review by Gondar et al. (16). The risk ratio of growing (3.47) and rupturing (2.08) in MIAs compared with a single aneurysm was from the meta-analysis performed by Ramazan et al. (3). The rate of *de novo* aneurysm formation was estimated to be 0.003, which was reported in a recent meta-analysis (17). The risk ratio of *de novo* aneurysm formation in patients with MIAs compared with a single aneurysm was 3.92 (3). The outcomes of endovascular treatment for unruptured MIAs were obtained from our cohort. The outcomes of treating aneurysmal SAH were estimated from a meta-analysis and the International Subarachnoid Aneurysm Trial (4, 18), in which a mortality rate of 35%, a mild disability rate of 15%, and a moderate to severe disability rate of 9% were used in our study. The age-specific mortality rates were obtained from the most recent published census of China and were adjusted by the aneurysmal SAH cause of death (19, 20). Disabled patients are at higher risk of death. The mortality rate for mildly disabled patients was adjusted by 2.02-fold, and for severely disabled it was adjusted by 4.46-fold (21).

Utilities

Each of the health states was assigned with health-related quality of life value (utility score). Quality-adjusted life-years (QALYs) were calculated to determine health outcomes by multiplying the length of patient-years within a particular health state by the corresponding utility score. The utility scores of different health states were obtained from a previous cost-effective analysis of the preventive treatment of unruptured aneurysms (22). The coiling procedure was assumed to cause a temporary 5% disutility (23).

All the utilities were discounted by 3% annually (24). The input variables including clinical parameters and utilities are listed in **Table 1**.

Validation

Model structure, data source, formula, and results were reviewed by all the authors. Internal validation was performed using the TreeAge Pro software. External validation was not available, since there were no similar published studies.

Statistical Analysis

A base case calculation was performed using the mean value of each parameter. Probabilistic sensitivity analysis (PSA) with Monte Carlo simulation was conducted with 10,000 iterations, modeling 10,000 patients. All the parameters were assigned a distribution and varied simultaneously according to their distributions in the PSA. In addition, one-way and two-way sensitivity analyses were carried out to account for the uncertainty of specific parameters on the model outcome.

TABLE 1 | Input parameters of the decision analytic model.

Variable	Mean	Range	Distribution	Sources
Clinical parameters				
Growth rate of small aneurysm	0.026	0.017–0.04	Beta SD: 0.004	(15)
Rupture rate of small nongrowing aneurysm	0.005	0.003–0.009	Beta SD: 0.001	(15)
Rupture rate of small growing aneurysm	0.063	0.01–0.22	Beta SD: 0.035	(16)
Risk ratio of growing in MIAs compared with single aneurysm	3.47	1.87–6.45	Lognormal SD: 1.15	(3)
Risk ratio of rupturing in MIAs compared with single aneurysm	2.08	1.46–2.96	Lognormal SD: 0.25	(3)
Rate of *de novo* aneurysm formation in patients with single aneurysm	0.003	0.002–0.004	Beta SD: 0.0004	(17)
Risk ratio of *de novo* aneurysm formation in patients with MIAs compared with single aneurysm	3.92	1.95–7.87	Lognormal SD: 0.99	(3)
Proportion of mild disability after treating one aneurysm	0.016	0–0.037	Beta SD: 0.011	MIAs database
Proportion of moderate to severe disability after treating one aneurysm	0.047	0.01–0.083	Beta SD: 0.019	MIAs database
Mortality after treating one aneurysm	0	0–0.005	Beta SD: 0.001	MIAs database
Proportion of mild disability after treating two aneurysms	0.032	0–0.067	Beta SD: 0.018	MIAs database
Proportion of moderate to severe disability after treating two aneurysms	0.053	0.008–0.098	Beta SD: 0.023	MIAs database
Mortality after treating two aneurysms	0.011	0–0.031	Beta SD: 0.01	MIAs database
Proportion of mild disability after aneurysmal SAH	0.15	0.13–0.17	Beta SD: 0.007	(4, 18)
Proportion of moderate to severe disability after aneurysmal SAH	0.09	0.07–0.11	Beta SD: 0.007	(4, 18)
Mortality after aneurysmal SAH	0.35	025–0.45	Beta SD: 0.033	(4, 18)
Risk ratio of death in mild disability compared with general population	2.02	1.7–2.4	Lognormal SD: 0.109	(21)
Risk ratio of death in moderate to severe disability compared with general population	4.46	4.05–4.91	Lognormal SD: 0.128	(21)
Utility				
Full recovery	1			
Mild disability	0.72	0.65–0.80	Triangle	(22)
Moderate to severe disability	0.41	0.25–0.65	Triangle	(22)
SAH	0.64	0.52–0.71	Triangle	(22)
Coiling procedure	5% disutility			(23)

MIAs, multiple intracranial aneurysms; SD, standard deviation; SAH, subarachnoid hemorrhage.

RESULTS

Real-World Data

A total of 224 patients with two small unruptured aneurysms who received endovascular treatment were included in our MIA

TABLE 2 | Comparison among patients who had one aneurysm treated and both aneurysms treated.

Variables	Treat one aneurysm (*n* = 129)	Treat both aneurysms (*n* = 95)	*P*-value
Age (years), mean (SD)	56.67 ± 9.72	55.04 ± 10.29	0.087
Female, *n* (%)	84 (65.1)	63 (66.3)	0.852
Hypertension, *n* (%)	63 (48.8)	46 (48.4)	0.951
Hyperglycemia, *n* (%)	18 (14.0)	15 (15.8)	0.702
Hyperlipidemia, *n* (%)	25 (19.4)	25 (26.3)	0.218
Coronary heart disease, *n* (%)	12 (9.3)	14 (14.7)	0.210
History of stroke, *n* (%)	18 (14.0)	17 (17.9)	0.422
Smoking, *n* (%)	32 (24.8)	15 (15.8)	0.101
Alcohol, *n* (%)	17 (13.2)	10 (10.5)	0.547
Aneurysm location, *n* (%)			0.433
Anterior cerebral artery	5 (1.9)	4 (2.1)	
Anterior communicating artery	19 (7.4)	10 (5.3)	
Internal carotid artery	194 (75.2)	159 (83.7)	
Middle cerebral artery	18 (7.0)	7 (3.7)	
Posterior cerebral artery	2 (0.8)	2 (1.1)	
Basilar artery	11 (4.3)	6 (3.2)	
Vertebral artery	5 (1.9)	2 (1.1)	
Posterior inferior cerebellar artery	4 (1.6)	0	
Irregular aneurysm shape, *n* (%)	89 (34.5)	58 (30.5)	0.376
Aneurysm size (mm), mean (SD)	4.14 ± 1.40	4.35 ± 1.25	0.097
Follow-up times (months), mean (SD)	29.52 ± 22.96	33.56 ± 22.75	0.065

SD, standard deviation.

database. Mean age was 55.98 ± 9.99 years old. Among them, 129 had one aneurysm treated, and 95 patients had both two aneurysms treated. The average time between discharge and last follow-up was 31.24 ± 22.93 months. There were no differences in age, gender, aneurysm location, aneurysm size, and follow-up time between these two groups (**Table 2**). For patients who had both two aneurysms treated, all of them received one-stage treatment. The clinical outcomes of the two groups are presented in **Table 1**.

Base Case Calculation

According to the results, prophylactic treatment or follow-up would increase effectiveness. Follow-up with a shorter period of interval resulted in higher effectiveness. Treat both aneurysms was the best strategy with the highest effectiveness of 15.37 QALYs, and treat one aneurysm had the second highest effectiveness of 15.11 QALYs. Natural history was the least favorable option, which gained the lowest effectiveness of 14.31 QALYs.

Probabilistic Sensitivity Analysis

In the PSA, we performed 10,000 iterations to simulate a cohort of 10,000 patients. When compared with treat one aneurysm (the strategy with the second highest effectiveness), treat both aneurysms was more favorable in 72.81% of iterations. This result was stable after 10 repeated analyses, indicating that these iterations were sufficient to achieve a reliable outcome.

One-Way and Two-Way Sensitivity Analyses

One-way sensitivity analyses were performed. The results were presented in the tornado diagram, which was a set of one-way sensitivity analyses brought together in a single graph (**Figure 1**). According to the results, the optimal strategy was sensitive to four parameters, namely, proportion of moderate to severe disability after treating two aneurysms, mortality after treating two aneurysms, proportion of moderate to severe disability after treating one aneurysm, and rupture rate of small growing aneurysm.

When the proportion of moderate to severe disability after treating two aneurysms was <0.075, treat both aneurysms was the best strategy. When the rate was above 0.075, treat one aneurysm was more favored (**Figure 2A**). Similarly. When the mortality after treating two aneurysms was < 0.027, treat two aneurysms was the best option; and if this rate was higher than 0.027, treat one aneurysm turned to be the best one (**Figure 2B**). When the proportion of moderate to severe disability after treating one aneurysm was above 0.028, treat both aneurysms was the most favorable option. The treatment of one aneurysm would be the superior one if this proportion was < 0.028 (**Figure 2C**). For the rupture rate of small growing aneurysm, treat both aneurysms was the best strategy if the value was above 0.019 (**Figure 2D**).

To account for the uncertainty of the proportion of moderate to severe disability after treating one aneurysm and after treating both aneurysms together on the outcome, we put these two parameters in the two-way sensitivity analysis. The results showed either treat both aneurysms or treat one aneurysm would be the best option under most circumstances (**Figure 3A**). We also performed a two-way sensitivity analysis on the mortality after treating two aneurysms and rupture rate of small growing aneurysm, and treat both aneurysms is the best strategy by large chance (**Figure 3B**).

DISCUSSION

No specific guidelines exist regarding the management of unruptured small UIAs. In this study, we performed a comparative effectiveness analysis based on real-world data to investigate which strategy would benefit patients the most. According to the base case calculation, treat both aneurysms resulted in highest effectiveness, and treat one aneurysm gained second highest effectiveness from a lifetime horizon, meaning that patients having their aneurysms treated would have a prolonged life expectancy or improved life quality. Sensitivity analyses were performed to determine whether treat both aneurysms was better than treat one aneurysm. However, the PSA proved that treat both aneurysms is more superior to treat one aneurysm only in 72.81% of the cases. One-way sensitivity

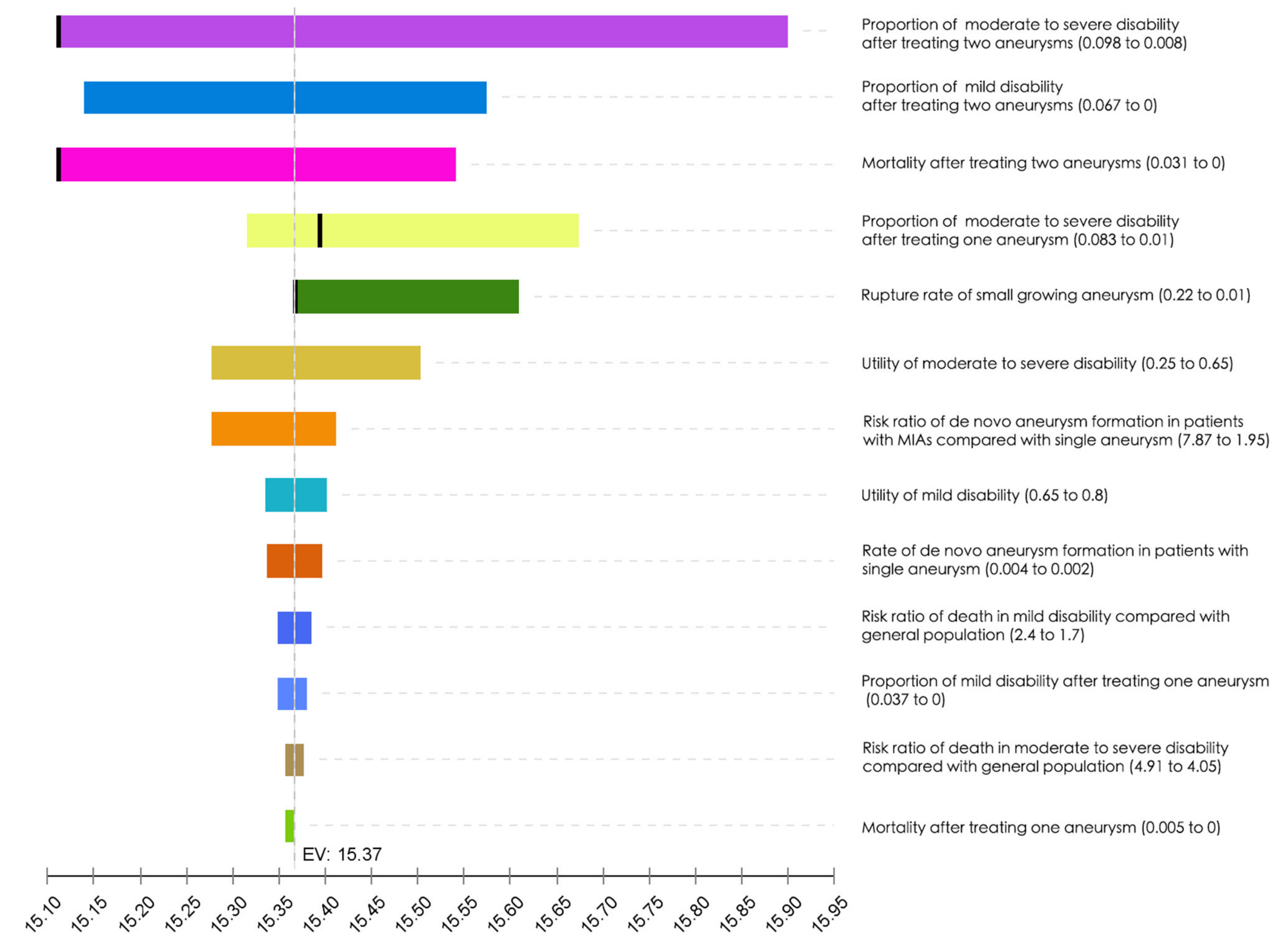

FIGURE 1 | Tornado diagram. The effect of variation of each parameter on the expected value is presented on each bar. The dark line within the bar represents the alteration of the optimal strategy. EV, expected value.

and two-way sensitivity analyses also indicated that the most favorable strategy would change between treat one aneurysm and treat both aneurysms with variations of treatment outcomes and the rupture rate of small growing aneurysm. Notwithstanding, our results together suggested that prophylactic coiling for patients with small unruptured UIAs was better than natural history or imaging follow-up.

In the MIA database, there were 89 patients with SAH due to ruptured small MIAs, and all of them received endovascular coiling. Last time follow-up showed that 80 (89.89%) of the patients had favorable outcomes (mRS 0–2), and that the mortality rate for them was 2.2%. However, we did not use these outcomes in our model, because they might not reflect the real outcomes of aneurysmal SAH. This is because a significant portion of patients with SAH would die before reaching a hospital and the actual number is difficult to estimate in China. In addition, the MIA database was created based on the clinical information from three tertiary hospitals in Beijing, and most of the patients with SAH were transferred from other areas and cities. Patients who were predicted to have unfavorable outcomes would be treated at the local hospitals and not be transferred. Only those with mild symptoms would have a chance to be treated in our centers.

According to our results, the optimal strategy is sensitive to the treatment outcomes including the proportion of moderate to severe disability after treating two aneurysms, mortality after treating two aneurysms, and proportion of moderate to severe disability after treating one aneurysm. Several studies have investigated the safety and efficiency of endovascular treatment of MIAs. However, studies reporting the outcomes of coiling unruptured MIAs are limited. Jeon et al. investigated the coiling of all aneurysms among 132 patients with unruptured MIAs, and only three (2.3%) had unfavorable outcomes (mRS score of 3–6) at discharge (7). In another study, 27 patients with unruptured MIAs underwent endovascular treatment for all aneurysms, and three (11.1%) patients died because of the treatment. The proportion of unfavorable outcomes for unruptured MIAs was not reported in this study (5). The high rate of mortality in this study came from the fact that the included cases consisted of the most complicated and complex aneurysms that

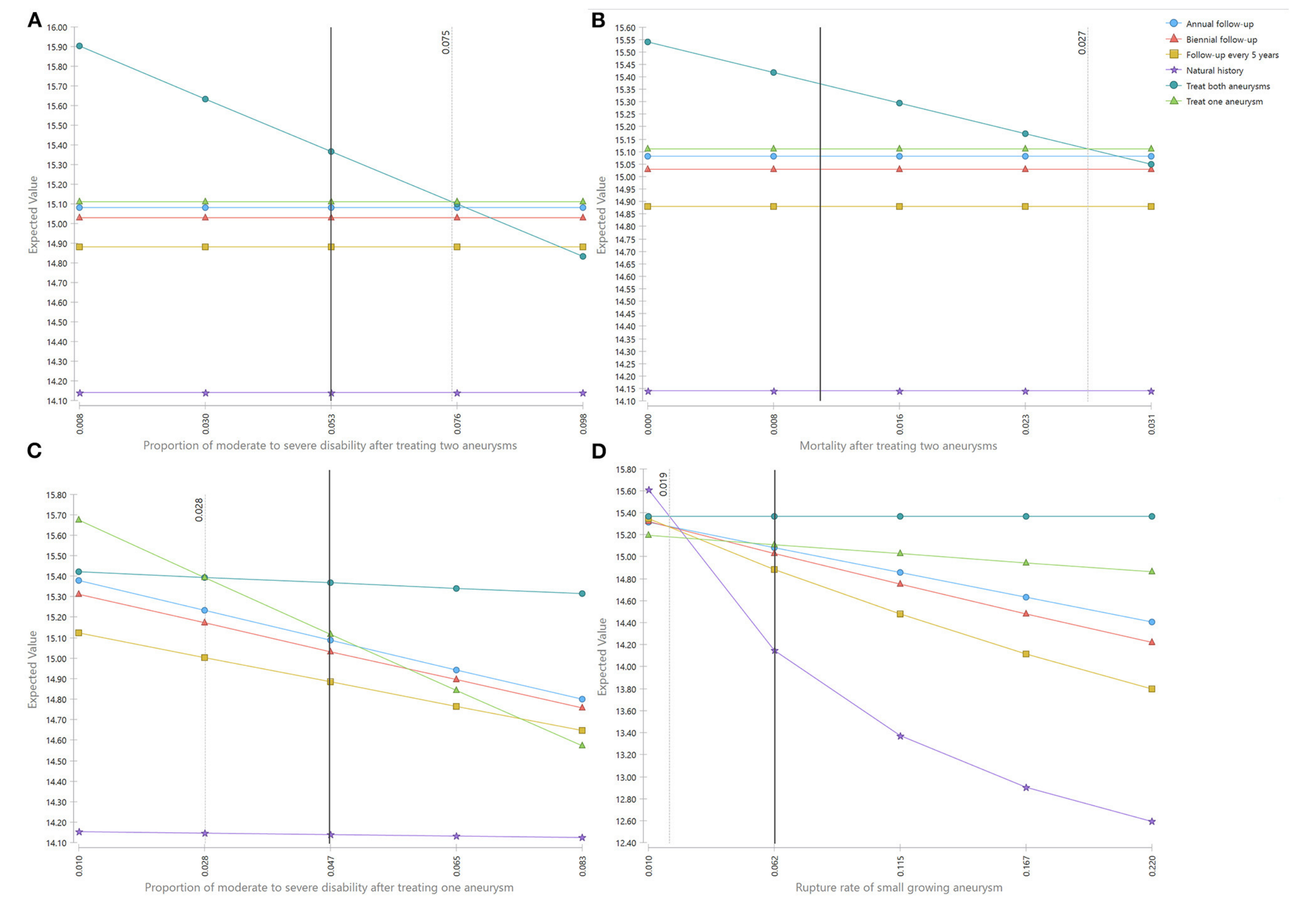

FIGURE 2 | (A–D) One-way sensitivity analyses. The light-dark line represents the threshold. The deep-dark line represents the base case value.

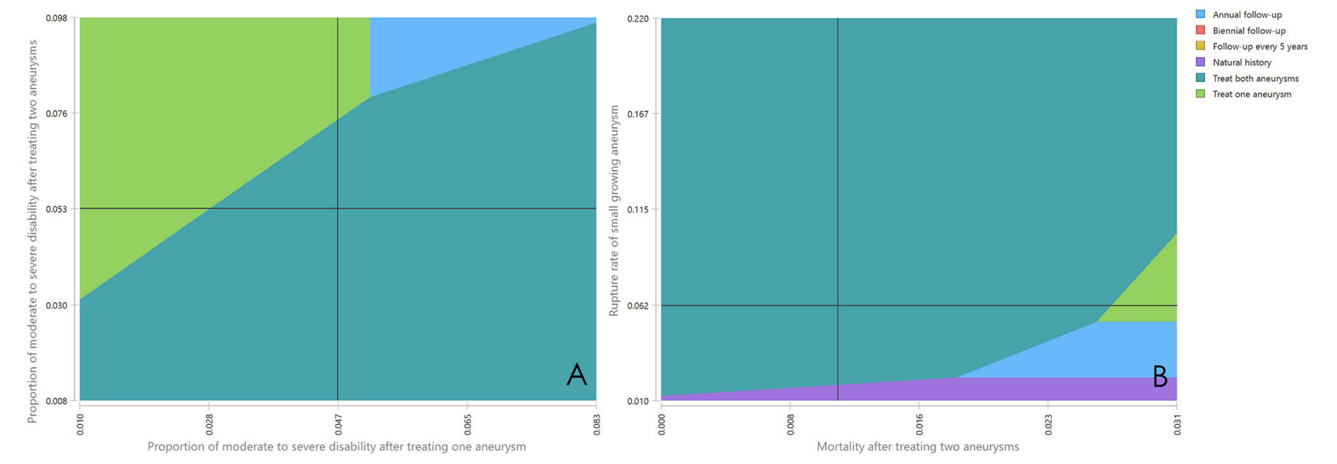

FIGURE 3 | (A,B) Two-way sensitivity analyses. The dark line represents the base case value. The different color areas represent different optimal strategies.

were difficult to treat. A small sample size might be another important factor contributing to this high mortality rate. In our study, the unfavorable outcomes for coiling one aneurysm were 4.7% and for coiling both aneurysms was 6.4%. Our study included only small aneurysms with a size of <7 mm. Treating small aneurysms, especially tiny ones with a size of <3 mm, was sometimes particularly challenging, with high rates of complications and unfavorable outcomes (25). Therefore, it is understandable that our cohort resulted in a higher unfavorable rate than that of Jeon et al.

China has the largest population in the world, and the demand for a data-driven and evidence-supporting healthcare system has increased significantly for policymakers in China (26). As a matter of fact, comparative effectiveness or cost-effectiveness research studies have been advocated by a number of health policy reforms (27), and there are fast-growing numbers of published studies over the last two decades in China (28). Even though our study could not determine which strategy was best for the management of small unruptured MIAs, we proved that at least one aneurysm should be treated. Several aneurysm characteristics, such as size, shape, and location, were related to rupture risk (11). We suggested that for patients with small unruptured MIAs, at least the aneurysm with a higher risk of rupturing should be treated.

LIMITATIONS

This study has several limitations. First, the real-world data were retrospectively collected, and it tends to be less reliable than the prospectively conducted studies. Second, the patients included in our study were all collected from three tertiary hospitals in Beijing; thus, our findings might not be applicable to the whole of China. Data from other regions or provinces are needed to reflect a national perspective. However, as far as we know, our database included the largest number of patients with MIAs in China, and the sensitivity analyses have accounted for the differences. Third, we performed MRA as the screening modality for aneurysms and assumed each aneurysm growth could be detected by MRA. However, are some concerns about the sensitivity and specificity of MRA for the detection of aneurysms, especially for the small ones (29). Actually, there is no published literature on the accuracy of detecting aneurysm growth (13), and the definition of growth is different among different studies. Computed tomographic angiography would have a higher spatial resolution, but it is not ideal for long-term imaging follow-up because of radiation concerns. Lastly, we do not consider the effect of complications or retreatment on the effectiveness of different management strategies. However, this is not unprecedented, and it would not affect our results to a large extent because of its low incidence (22, 30).

CONCLUSIONS

The comparative effectiveness analysis based on real-world data suggests that for patients with small unruptured MIAs, prophylactic coiling was superior to conservative management, and that at least one aneurysm should be treated.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JC and XT were responsible for the design of the study. JC and AL built the model and conducted the statistical analysis. XT, XF, FP, and HN collected the real-world data. MH and LL prepared the manuscript. DW, YZ, and YP verified the data. All the authors reviewed the structure of the model, data source, formula, and results.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.736127/full#supplementary-material

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