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Influence of size ratio on retreatment after coil embolization for unruptured bifurcation aneurysms

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ABSTRACT

Background: Aneurysm size is considered a risk factor for aneurysm rupture, and even small aneurysms may rupture, especially bifurcation aneurysms (BAs), which are occasionally detected. Therefore, we aimed to investigate the predictors of retreatment after coil embolization for unruptured BAs, with a particular focus on the absolute and relative size of the aneurysm (size ratio [SR]).

Methods: To evaluate the predictors of retreatment, patients were divided into two groups: those with and those without retreatment. Patient characteristics and radiographic assessments were compared between the groups. SR was defined as the ratio of the maximum aneurysm diameter and the average diameter of the parent artery.

Results: Overall, 181 unruptured BAs in 176 patients were investigated. The mean age of the patients was 63.8 ± 9.6 years. The mean aneurysm size and SR were 7.18 ± 2.94 mm and 2.49 ± 1.32, respectively. Further, 12 aneurysms with retreatment (6.6 %) and 169 aneurysms without retreatment were compared. In univariate analysis, SR was significantly higher in the group with retreatment ($P = 0.02$), but aneurysm size was not significantly different between the groups ($P = 0.09$). Multivariable analysis revealed that SR > 2.6 was a significant predictor of retreatment ($P = 0.03$; odds ratio: 10.41; 95 % confidence interval: 2.1–51.73).

Conclusions: This study showed that SR influences retreatment after coil embolization for unruptured BAs. Therefore, if the aneurysm size and parent artery diameter were small, as in cases with a large SR, meticulous follow-up after coil embolization is required to detect recurrence and recanalization.

1. Introduction

Some bifurcation aneurysms (BAs) are anatomically complex, making coil embolization challenging.[1] Generally, coil embolization for BAs has a low aneurysm occlusion rate, and recanalization and coil protrusion into the parent artery as well as periprocedural complications are more frequent in treatment of BAs than in treatment of side wall aneurysms.[2]

Although aneurysm size is generally considered to be a risk factor for aneurysm rupture, small ruptured aneurysms are occasionally detected. Thus, even small aneurysms may rupture, especially BAs such as anterior communicating artery (ACoA) aneurysms and basilar artery apex (BAA) aneurysms.[3] Because BAs have a relatively small parent artery diameter compared to that of sidewall aneurysms, where internal carotid artery (ICA) aneurysms are predominant, the relative size of the aneurysm is larger than that of sidewall aneurysms. Therefore, we focused not only on the absolute size of the aneurysm but also on its relative size, i.e., size ratio (SR).

Few studies have investigated the association between SR and the treatment outcomes of craniotomy clipping, and SR has been reported to be a prognostic factor.[4] However, no study has investigated the association between SR and the treatment outcomes of endovascular surgery.

Recanalization risk, which necessitates retreatment, is a commonly observed problem after coil embolization. In particular, BAs have more frequent recanalization than do sidewall aneurysms.[2] The present study aimed to investigate the predictors of retreatment after coil embolization for unruptured BAs, with a particular focus on SR.

2. Methods

2.1. Patient population

This study has been approved by the Ethical Review Board at Dokkyo Medical University Saitama Medical Center (approval number: 21010). The requirement for informed consent from the patients was waived owing to the retrospective study design. In our country, the Woven

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EndoBridge (WEB) device (Sequent Medical/MicroVention/Terumo, Tustin, CA, USA) has been approved since December 2019 in limited facilities and operators; therefore, the research period was set 10 years before its introduction. The BAs include ACoA, middle cerebral artery (MCA) bifurcation, ICA bifurcation, and BAA aneurysms. Based on the inclusion criteria, patients aged >18 years who were followed up for at least 1 year, were included in the current single-center retrospective study. Further, all patients who were followed up for <1 year and those who had undergone previous aneurysm treatment, including recanalization after coil embolization, were excluded from the study.

Medical records and endovascular procedure reports were retrospectively reviewed. Patient characteristics, including age, sex, medical history (hypertension, diabetes, hyperlipidemia), smoking history (including present or past smoking history), modified Rankin scale (mRS) score before the procedure, antiplatelet therapy (mono or dual), follow-up period, and mRS at the final follow-up were investigated. Furthermore, radiographic characteristics such as aneurysmal size, SR, aneurysm location, presence or absence of blebs, neck size, aspect ratio, and dome/neck (D/N) ratio were also investigated.

2.2. Size ratio

The SR was considered a morphological characteristic, derived from intraoperative working angles useful for neck identification based on preoperative three-dimensional digital subtraction angiography (DSA) images, and as proposed by Dhar S et al.[5] The DSA images were acquired on a biplane Axiom Artis QBA angiography system (Siemens, Erlangen, Germany). Further, based on these images, measurements of aneurysm morphological factors were assessed using a Syngo Workplace (Siemens). Parent artery diameter was measured at the nearest region of all arteries that had direct contact with the aneurysm neck, and the average diameter of each of the involved parent arteries was calculated. The SR was calculated by dividing the maximum diameter of the aneurysm (mm) by the average diameter of the parent artery (mm). The details of the SR calculation method are shown in Fig. 1. The correlation between SR and aneurysm size was also investigated.

2.3. Endovascular procedures

Antiplatelet therapy (daily dose of 100 mg aspirin and/or 75 mg clopidogrel) was initiated at least 7 days before the procedure. Systemic heparinization was performed during the procedure, and aneurysms were packed with coils as densely as possible using a balloon- or stent-assisted technique.

After the procedure, patients with stent placement continued to receive dual antiplatelet therapy for at least 6 months, followed by 100 mg of aspirin or 75 mg of clopidogrel per day indefinitely. Patients without stent placement only received mono antiplatelet therapy (100 mg of aspirin or 75 mg of clopidogrel per day) for 6 months after the procedure.

Perioperative complications were defined as post-procedure complications that occurred within 7 days of the procedure and were detected through clinical neurological symptoms.

The angiographic outcomes were classified using Raymond's classification as complete occlusion (CO), neck remnant (NR), or body filling (BF).[6] Immediate angiographic outcomes were assessed using DSA at the end of the treatment. Follow-up angiographic outcomes were assessed at 6 months and 1 year, and then annually using magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). Additional follow-up angiography was performed in patients in whom recanalization was detected on MRA, and retreatment was conducted if angiography revealed significant recanalization. The following findings were indicative of significant recanalization: 1) coil loosening with progressive contrast filling between coil loops within the aneurysmal sac; 2) coil compaction with unchanged aneurysmal size and progressive contrast filling within the aneurysmal sac; 3) aneurysmal regrowth with increased size relative to the initial size and progressive contrast filling within the aneurysmal sac.

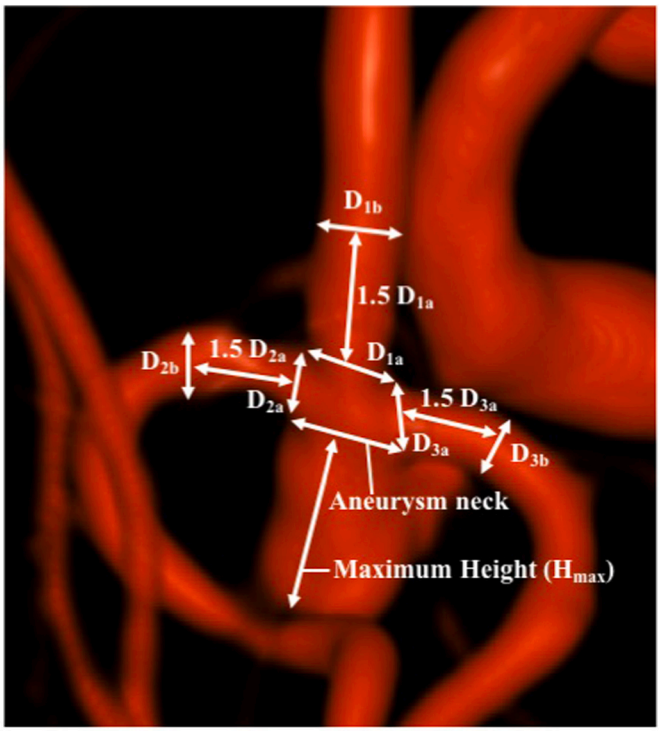

Fig. 1. The SR was calculated as $H_{max}/D_{V.\ composite}$.
$D_{V.\ composite} = (D_{V1} + D_{V2} + D_{V3})/3$.
$D_{Vi} = (D_{ia} + D_{ib})/2._{\ i=1,\ 2,\ 3}$.
H_{max}: maximum height.
$D_{v.\ composite}$: composite vessel diameter.
D_{V1}, D_{V2}, D_{V3}: individual vessel diameter (average of two locations).
D_{1a}, D_{2a}, D_{3a}: vessel diameter at neck or branching points.
D_{1b}, D_{2b}, D_{3b}: vessel diameter 1.5 D_a away from D_{1a}, D_{2a}, D_{3a}.

2.4. Predictors of retreatment

To evaluate the predictors of retreatment, the patients were divided into two groups: those with and those without retreatment. Patients' characteristics such as age, sex, medical history (hypertension, diabetes, hyperlipidemia), smoking history, and antiplatelet therapy were recorded. Further, radiographic characteristics such as aneurysm location, aneurysmal size, SR, presence or absence of bleb, neck size, aspect ratio, and D/N ratio were assessed. Additionally, stent-assisted, immediate angiographic outcomes, treatment outcomes including complications, DWI positivity rate, and follow-up period were also recorded. It should be mentioned that two neuroendovascular surgeons performed all the endovascular procedures, and MRI and angiography findings were reviewed by all the authors.

2.5. Statistical analysis

Statistical analyses were performed using SPSS for Mac (version 27.0; IBM Corp., Armonk, New York, USA). Spearman's correlation coefficient was used to determine the correlation between SR and aneurysmal size. Continuous variables were expressed as mean values with standard deviation. Further, to compare groups, the chi-square test and Fisher's exact test were used for categorical variables, and Student's *t*-test was used for continuous variables. In univariate analysis, clinical factors of retreatment ($P < 0.1$) were evaluated using multivariable logistic regression analysis. In addition, we investigated the association between continuous variables (SR, aneurysmal size, and follow-up

period) and retreatment using receiver operating characteristic (ROC) curves and the optimal cut-off value was determined using Youden index. Statistical significance was set at a *P*-value <0.05.

3. Results

3.1. Patients and aneurysm characteristics

Patient and aneurysm characteristics are summarized in Table 1. Overall, 181 unruptured BAs in 176 patients were included in this study. Among these, 53 patients were male and 123 were female, with a mean age of 63.9 ± 9.6 years. Most patients (98.9 % and 96.6 %) had mRS scores of 0–2 before the procedure and at the final follow-up (mean follow-up period: 38.0 ± 25.1 months). The mean aneurysmal size, SR, neck size, aspect ratio, and D/N ratio were 7.18 ± 2.94 mm, 2.49 ± 1.32, 4.03 ± 1.50 mm, 1.43 ± 0.54, and 1.47 ± 0.54, respectively. A positive correlation was observed between the SR and aneurysmal size (Spearman's correlation coefficient = 0.593). A total of 93 ACoA (51.4 %), 49 BAA (27.1 %), 31 MCA bifurcation (17.1 %), and 8 ICA bifurcation (4.4 %) aneurysms were included in this study.

3.2. Treatment outcomes

The treatment outcomes are summarized in Table 2. A total of 138 patients (76.2 %) were treated using the balloon-assisted technique, while 43 (23.8 %) were treated using stent-assisted coil embolization. Immediate angiographic outcomes of CO, NR, and BF were achieved in 69 (38.1 %), 67 (37.0 %), and 45 (24.9 %) aneurysms, respectively. Perioperative complications were observed in 23 patients (12.7 %), including 12 with thromboembolic complications and 6 with hemorrhage. Among the patients, five had femoral subcutaneous and retroperitoneal hematoma at the puncture site, which required blood transfusion. Thus, neurological complications were observed in 18 patients (9.9 %). Only four patients (2.2 %) had permanent complications. Further, 12 patients (6.6 %) required retreatment. The mean duration to the retreatment procedure was 25.7 ± 20.8 months. Final angiographic outcomes in the aneurysms that were not retreated (169 aneurysms) did not show any significant recanalization in all cases. In particular, no cases with progressive contrast filling within the interstices of the coil mass or aneurysm dome were detected.

Table 1
Patients and aneurysms characteristics of coil embolization for unruptured bifurcation aneurysms.

176 Patients		
Age, years		63.9 ± 9.6
Sex	Male	53(30.1 %)
	Female	123(69.9 %)
Medical history	Hypertension	110 (62.5 %)
	Diabetes	12 (6.8 %)
	Hyperlipidemia	20 (11.4 %)
Smoking history		40 (22.7 %)
mRS[a] before procedure	0–2	174 (98.9 %)
	3–5	2 (1.1 %)
Antiplatelet therapy	Mono	69(39.2 %)
	Dual	107(60.8 %)
Follow up period, months		38.0 ± 25.1
mRS at final follow up	0–2	170 (96.6 %)
	3–6	6 (3.4 %)
181 Aneurysms		
Aneurysm size, mm		7.18 ± 2.94
SR[b]		2.49 ± 1.32
Aneurysm locations	ACoA[c]	93 (51.4 %)
	BAA[d]	49 (27.1 %)
	MCA[e] bifurcation	31 (17.1 %)
	ICA[f] bifurcation	8 (4.4 %)
Bleb formation		44 (24.3 %)
Neck size, mm		4.03 ± 1.50
Aspect ratio		1.43 ± 0.54
D/N[g] ratio		1.47 ± 0.54

[a] mRS - modified Rankin scale.
[b] SR: size ratio.
[c] ACoA: anterior communicating artery.
[d] BAA: basilar artery apex.
[e] MCA: middle cerebral artery.
[f] ICA: internal carotid artery.
[g] D/N ratio: dome/neck ratio.

Table 2
The treatment outcomes of coil embolization for unruptured bifurcation aneurysms.

Treatment outcomes		
Adjunctive technique		181 (100 %)
	Balloon assisted	138 (76.2 %)
	Stent assisted	43 (23.8 %)
Immediate angiographic outcomes	CO[a]	69 (38.1 %)
	NR[b]	67 (37.0 %)
	BF[c]	45 (24.9 %)
Perioperative complications		23 (12.7 %)
	Thromboembolic	12
	Hemorrhagic	6
	Others	5
	Transient	19
	Permanent	4
Retreatment		12 (6.6)
Time to retreatment, months		25.7 ± 20.8

[a] CO: complete occlusion.
[b] NR: neck remnant.
[c] BF: body filling.

3.3. Predictors of retreatment

The comparison between the 12 aneurysms with retreatment and 169 aneurysms without retreatment for characteristics such as aneurysms and treatment outcomes are summarized in Table 3. Univariate analysis showed no significant differences in any of the factors, but SR was significantly higher (4.59 ± 2.45 vs. 2.49 ± 1.07; $P = 0.02$) and the follow-up period was significantly longer (64.0 ± 29.3 months vs. 36.0 ± 23.6 months; $P < 0.01$) in the retreatment group than in the non-retreatment group. However, aneurysm size was not significantly different between the two groups (8.34 ± 1.93 mm vs. 7.10 ± 2.98, $P = 0.09$). The SR, aneurysm size, and follow up period ROC curves for determining predictors of retreatment were presented in Fig. 2. The area under curve (AUC) was 0.784 for SR, 0.667 for aneurysm size, and 0.780 for follow-up period. The optimal cut-off value of SR (2.6), aneurysmal size (8.2 mm), and follow-up period (25 months) were determined using ROC curves with Youden index. The predictors of retreatment using multivariable analysis are summarized in Table 4. Aneurysm size, CO, and follow-up period were not significant predictors of retreatment. However, SR > 2.6 could significantly predict the need for retreatment ($P = 0.03$; odds ratio: 10.41; 95 % confidence interval: 2.1–51.73).

4. Discussion

In this study, SR was a significant predictor of retreatment after coil embolization for unruptured BAs. The aneurysmal size and location were reported as risk factors for rupture in an unruptured cerebral aneurysm study in Japan,[3] and subarachnoid hemorrhage due to small ruptured aneurysms is often seen.[7] In particular, small BAs such as ACoA and BAA aneurysms tend to rupture.[8] Therefore, the ratio of the aneurysm diameter to the parent artery diameter rather than the absolute aneurysmal size has been proposed as a predictor of aneurysm rupture by Dhar et al.[5] It has been reported that the risk of rupture increases as SR increases.[5] Although there have been reports of an association between SR and treatment outcomes in craniotomy clipping,[4] no study has investigated the association between SR and endovascular treatment

Table 3
The between-group with and without retreatment comparison of the patients and aneurysms characteristics and treatment outcomes.

		With retreatment	Without retreatment	*P*-value
Number of cases		12	169	
Age, years		61.9 ± 8.2	63.9 ± 9.7	0.94
Sex	Male	5	53	
	Female	7	116	0.53
Medical history	Hypertension	8	102	0.77
	Diabetes	2	10	0.18
	Hyperlipidemia	2	18	0.63
Smoking history		4	36	0.3
Antiplatelet therapy	Mono	4	69	
	Dual	8	100	0.77
Aneurysm locations	ACoA[a]	4	89	
	BAA[b]	6	43	
	MCA[c] bifurcation	1	30	
	ICA[d] bifurcation	1	7	0.19
Aneurysm size, mm		8.34 ± 1.93	7.1 ± 2.98	0.09
SR[e]		4.59 ± 2.45	2.49 ± 1.07	0.02
Bleb formation		1 (8.3 %)	43 (25.4 %)	0.29
Neck size, mm		4.92 ± 1.53	3.97 ± 1.48	0.32
Aspect ratio		1.71 ± 0.42	1.41 ± 0.54	0.25
D/N[g] ratio		1.57 ± 0.4	1.46 ± 0.55	0.12
Stent assisted		4 (33.3 %)	39 (23.1 %)	0.48
Immediate angiographic outcomes	CO[f]	2	67	
	NR[h]	7	60	
	BF[i]	3	42	
	% CO	16.70	39.60	0.09
Perioperative complications		2 (16.7 %)	21 (12.4 %)	0.47
	Transient	1	18	
	Permanent	1	3	
Follow up period, months		64.0 ± 29.3	36.0 ± 23.6	<0.01

[a] ACoA: anterior communicating artery.
[b] BAA: basilar artery apex.
[c] MCA: middle cerebral artery.
[d] ICA: internal carotid artery.
[e] SR: size ratio.
[f] CO: complete occlusion.
[g] D/N ratio: dome/neck ratio.
[h] NR: neck remnant.
[i] BF: body filling.

outcomes.

A commonly observed problem after coil embolization is the risk of recanalization, which necessitates retreatment.[9] In particular, BAs have a lower occlusion rate and require more frequent retreatment than do sidewall aneurysms.[2] BAs are anatomically complicated, and their treatment is challenging.[1,10] Various stent-assisted coil embolization,[2,11] such as Y-stent, T-stent, PulseRider (Pulsar vascular, Los Gatos, California, USA),[12] WEB,[13] flow diverters,[14] and pCONUS bifurcation aneurysm implants (Phenox, Bochum, Germany),[15] have good treatment outcomes. However, many BAs are still treated with coil embolization in our country. Among new devices, the WEB is expected to be widely used in the future. In three large studies, good treatment outcomes of WEB for BAs were reported.[16–18]

In the present study, the rate of immediate angiographic CO and NR was 38.1 % and 37.0 %, respectively. However, in previous studies of coil embolization for BAs, the rate of immediate angiographic CO or near-occlusion was 57.4%–85.7 %.[19,20] The low rate of immediate angiographic CO and NR in this study might be due to the large number of wide neck aneurysms included in this study, but the use of stent-assisted coil embolization was as low as 23.8 %. In general, stent-assisted coil embolization reduces recanalization and retreatment. However, there is a concern about increasing the risk of hemorrhagic complications associated with dual antiplatelet therapy and thromboembolic complications associated with stent placement. There is also a concern about the risk of increasing delayed hemorrhagic complications

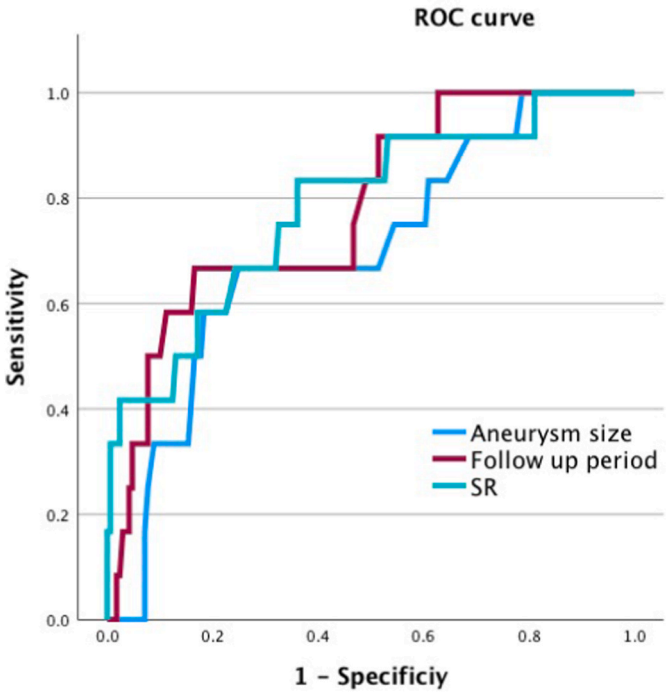

Fig. 2. The SR, aneurysm size, and follow up period receiver operating characteristic curves for determining predictors of retreatment. The area under curve was 0.784 for SR, 0.667 for aneurysm size, and 0.780 for follow up period. The optimal cut-off value of SR (2.6), aneurysmal size (8.2 mm), and follow-up period (25 months) were determined.

Table 4
The predictors of retreatment after coil embolization for unruptured bifurcation aneurysms using multivariable analysis.

	Univariate analysis	Multivariable analysis	
	P-value	*P*-value	OR[a] (95%CI[b])
SR[c] > 2.6	<0.01	0.03	10.41 (2.1–51.73)
Aneurysm size >8.2 mm	0.18	0.1	
% CO[d]	0.11	0.24	
Follow up period >25 months	0.19	0.2	

[a] OR – Odds ratio.
[b] CI – Confidence interval.
[c] SR: size ratio.
[d] CO: complete occlusion.

due to long-term dual antiplatelet therapy after stent placement. According to the results of the current study, perioperative complication rate was significantly higher in the stent-assisted group than that in the balloon-assisted group (8.0 % vs. 27.9 %; $P < 0.01$). Therefore, we prefer balloon-assisted coil embolization to stent-assisted coil embolization to ensure safe treatment. Because a rupture in the treated aneurysm was not detected during the follow-up period and there were few retreatment cases, tight packing using a stent was important, but coil embolization without a stent within a safe range was also important.

In the present study, the rate of perioperative complications was 12.7 %, which is consistent with that reported in previous studies of coil embolization for wide-neck aneurysms (11%–31.6 %).[19,21] Additionally, as only BAs were included in our study, the rate of perioperative complications was slightly high, and neurological complications were observed in 18 aneurysms (9.9 %).

In the present study, retreatment was performed in 12 (6.6 %)

aneurysms, which is consistent with previous findings, where the retreatment rate ranged from 4.7 % to 20.8 %.[6,22,23] Most of these reports included ruptured aneurysms and aneurysms in locations other than bifurcations, and only one report included unruptured aneurysms.[24] Kim et al reported that the retreatment rates for unruptured aneurysms, including aneurysms in locations other than BAs, were 0.6 % at 1 year, 1.2 % at 2 years, 1.6 % at 3 years, and 2.8 % at 5 years after treatment.[24] In the present study, the retreatment rate was 6.6 %, with an average follow-up of 38.0 months, which is slightly higher than that reported in previous studies. This was considered a result of including only BAs in the present study. In contrast, the retreatment rate after WEB ranged from 7.3 to 9.8 %.[16–18] The retreatment rate after WEB seems to be lower, but further studies with direct comparison are needed.

Large-sized aneurysms, wide-neck aneurysms, immediate angiographic outcomes, and ruptured aneurysms have been reported as predictors of retreatment.[6,9,22] Regarding aneurysm location, it has been reported that posterior circulation is a predictor of recanalization,[25] and BAs are more frequently retreated.[26] However, according to some studies, aneurysm location is not a predictor of recanalization.[23] In the present study, there were few large aneurysms, and most aneurysms were wide necked. Therefore, aneurysm size, neck size, and immediate angiographic outcomes did not predict retreatment, and SR was the only predictor of retreatment in the present study. No study has investigated the association between SR and retreatment after coil embolization. To our knowledge, this is the first study to report that a large SR is a significant predictor of retreatment after coil embolization for unruptured BAs.

The association between SR and retreatment after coil embolization remains unclear. A Study based on computational fluid dynamics (CFD) analysis by Tremmel M, et al[27] suggests that a large SR is associated with more complex flow patterns, multiple vortices, and low aneurysm wall shear stress (WSS). Regarding WSS, the large areas of low WSS is associated with aneurysm growth.[28] In an aneurysm with low WSS, vessel wall is remodeled, and aneurysm enlarges, leading to endothelial cells apoptosis and inflammation.[29] Possibility of low WSS affecting recanalization and retreatment of large SR aneurysm after coil embolization by these mechanisms should be considered. Furthermore, small vortex formation with a low velocity was previously recognized in recanalized aneurysm after coil embolization.[30] Such changes of CFD parameters in vortex and velocity also may affect recanalization and retreatment of large SR aneurysm after coil embolization.

This study has several limitations. First, it was a non-randomized, retrospective, single-center study with a small number of patients. Second, antiplatelet reactions were not examined because the VerifyNow system (Accumetrics, San Diego, California, USA) was not approved in our country. Third, a CFD analysis was not performed. Fourth, the types of coils, coil number, and length were not investigated.

5. Conclusions

The present study showed that SR influenced retreatment after coil embolization for unruptured BAs. A large SR was found to be a significant predictor of retreatment after coil embolization. Instead of focusing only on the absolute aneurysmal size, if both aneurysm size and parent artery diameter are small, as in cases with a large SR, meticulous follow-up is required to detect recanalization and the need for retreatment. Generally, the risk of recanalization after coil embolization is considered low in small aneurysms, but the size of parent artery diameter must be considered when estimating the risk of recanalization after coil embolization.

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CRediT authorship contribution statement

Ryotaro Suzuki: Validation, Visualization, Resources, Software, Methodology, Investigation, Data curation, Writing - original draft, Conceptualization, Formal analysis, Project administration, Writing - review & editing. **Tomoji Takigawa:** Writing - review & editing, Investigation, Conceptualization, Project administration, Formal analysis. **Masaya Nagaishi:** Investigation, Writing - review & editing, Methodology, Data curation. **Akio Hyodo:** Supervision, Writing - review & editing. **Kensuke Suzuki:** Writing - review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ACoA: anterior communicating artery
AUC: area under curve
BA: bifurcation aneurysm
BAA: basilar artery apex
BF: body filling
CFD: computational fluid dynamics
CO: complete occlusion
D/N ratio: dome/neck ratio
DSA: digital subtraction angiography
ICA: internal carotid artery
MCA: middle cerebral artery
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
mRS: modified Rankin scale
NR: neck remnant
ROC: receiver operating characteristic
SR: size ratio
WEB: Woven EndoBridge
WSS: wall shear stress