

White-collar sign as a predictor of outcome after endovascular treatment for cerebral aneurysms

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OBJECTIVE The white-collar sign (WCS) is known as a thick neointimal tissue formation at the aneurysm neck after endovascular coil embolization of cerebral aneurysms, which may prevent aneurysm recanalization. The purpose of this study was to evaluate factors involved in the appearance of WCS and to identify radiological and clinical outcomes of treated aneurysms with WCS.

METHODS The study included 140 patients with 149 aneurysms in which it was possible to confirm the aneurysm neck between the aneurysm sac and parent artery by using conventional angiography. The WCS was defined as a radiolucent band at the aneurysm neck on the angiogram at 6 months after initial embolization. The radiological outcome was evaluated using MR angiography.

RESULTS In 23 of 149 aneurysms (15.4%), a WCS appeared. The WCS-positive group had a significantly smaller neck size (3.3 ± 0.8 mm vs 4.2 ± 1.1 mm, $p < 0.001$) and smaller aneurysm size (4.3 ± 0.9 mm vs 6.0 ± 2.1 mm, $p < 0.001$) than the WCS-negative group. Multivariate analysis revealed that WCS appearance was associated with small neck size (OR 0.376, 95% CI 0.179–0.787; $p = 0.009$). In 106 of 149 aneurysms, the rate of complete occlusion was significantly higher in the WCS-positive group (18/18, 100%) than in the WCS-negative group ($n = 54/88$, 61.4%; $p = 0.001$) in the mean follow-up period of 31.0 ± 9.7 months (range 5–52 months). Neither major recanalization nor rupture of the aneurysm occurred in the WCS-positive group.

CONCLUSIONS Appearance of the WCS was associated with complete occlusion and good clinical outcome after endovascular coil embolization. The WCS would help to determine the prognosis of cerebral aneurysms after endovascular treatment.

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KEY WORDS white-collar sign; cerebral aneurysm; endovascular treatment; vascular disorders

ENDOVASCULAR coil embolization has become a widely performed procedure for the treatment of cerebral aneurysms. The purpose of this treatment is to prevent the cerebral aneurysm from rupturing. Although this procedure has both low morbidity and mortality rates, late recanalization and rupturing of coiled aneurysms are both major concerns with their inherent risks and costs.

Histological analysis has previously revealed that the mechanism of acute aneurysm occlusion by endovascular

coil embolization is the disruption of the flow and clot formation in the aneurysm, which in turn induce clot maturation and aneurysm fibrosis.^{5,17} At the level of the aneurysm neck, a fibrous connective tissue was shown covering the lesion's neck. In an animal study, a radiolucent gap at the aneurysm neck between the coil mass in the aneurysm and the lumen of the parent artery was observed on angiography studies when this fibrous tissue was thick.⁹ This sign was also observed in humans and named the white-collar

ABBREVIATIONS ACA = anterior cerebral artery; ACoA = anterior communicating artery; BA = basilar artery; DSA = digital subtraction angiography; FOV = field of view; FPD = flat-panel detector; ICA = internal carotid artery; MCA = middle cerebral artery; MRA = MR angiography; ROC = receiver operating characteristic; VA = vertebral artery; WCS = white-collar sign.

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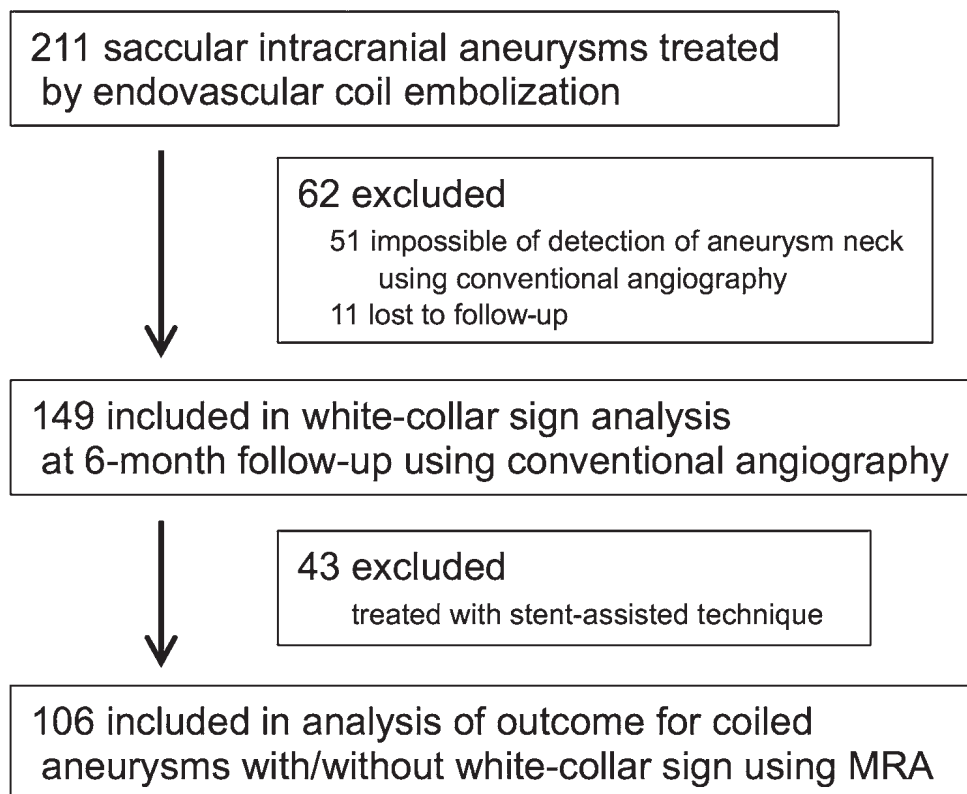


FIG. 1. Flowchart demonstrating the selection process used for the present study.

sign (WCS).³ This sign means the complete separation between aneurysm sac and parent artery, which may indicate the healing of the aneurysm. However, the nature of the WCS is not well known in humans. Moreover, the long-term result in patients with WCS has never been reported. The purpose of this study was to evaluate factors in the appearance of WCS and to identify radiological and clinical outcomes of treated aneurysms with WCS.

Methods

Study Population

We conducted a retrospective study of patients with saccular intracranial aneurysms treated by endovascular coil embolization between April 2011 and December 2013. A total of 201 consecutive patients with 211 saccular intracranial aneurysms were treated by endovascular coil embolization (Fig. 1). From this group 51 aneurysms were excluded because it was impossible to detect the aneurysm neck between the lesion's sac and the parent artery clearly by using conventional digital subtraction angiography (DSA) as aneurysms involving the parent artery. In addition, 11 aneurysms were lost to follow-up. Therefore, 140 patients (29 men, 20.7%; mean age 58.6 ± 12.9 years) with 149 intracranial aneurysms were included in this study. A total of 119 aneurysms were unruptured and 30 aneurysms were ruptured. The aneurysm characteristics were retrospectively examined by reviewing the medical records. This study was approved by the hospital ethics committee.

Endovascular Procedures

In cases of unruptured aneurysm, coil embolization was performed under local or general anesthesia according to the location and size of the aneurysm. Patients with a ruptured aneurysm underwent treatment using general anesthesia. The coils used in the treatment were bare platinum coils, bioactive coils (Cerecyte [Micrus Endovascular] or Matrix2 [Stryker]), or hydrogel coils (Hydrocoil [MicroVention, Inc.]). These coils were selected by the surgeon on a patient-by-patient basis. Balloon remodeling or stent-assisted technique was performed according to the aneurysm size, neck size, location, and clinical presentation (ruptured or unruptured). The Enterprise VRD (Codman) or the Neuroform (Stryker) stent was used for the stent-assisted coil embolization. The percentage of packing density was calculated as the ratio of coil volume to aneurysm volume $\times 100$. Patients with unruptured aneurysms received a dose of dual antiplatelet medication (100 mg aspirin and 75 mg clopidogrel) 1 week before the procedure. Patients with ruptured aneurysms received a dose of single antiplatelet medication (100 mg aspirin) on the day of the procedure. The dual antiplatelet medication was maintained for 1–3 months and then changed to aspirin monotherapy for 3–6 months in patients with unruptured lesions without a stent, and aspirin monotherapy was continued indefinitely in patients with unruptured aneurysms who had a stent. Aspirin monotherapy was maintained for 3–6 months in patients with ruptured aneurysms. All endovascular treatments were performed by 5 interventionalists (T.H., K.F., M.O., M.I., and T.Y.). The



FIG. 2. **A:** Angiogram showing a left VA–posterior inferior cerebellar artery aneurysm at the time of endovascular treatment. **B:** Immediately after coil embolization, complete occlusion was achieved. **C and D:** Follow-up imaging performed 6 months after treatment showing the appearance of a radiolucent band (WCS) (arrowheads) between the coil mass and the parent artery on a DSA image (C) and on a nonsubtracted image (D). **E:** MRA imaging showing the maintenance of the complete occlusion of a coiled aneurysm at 36 months after treatment.

status of postembolization lesions was evaluated based on the Raymond grading scale.¹³

Evaluation of WCS

Follow-up angiography was conducted mainly at 6 months (range 5–12 months). A WCS was defined as the appearance of a radiolucent separation at the aneurysm neck between the coil mass and the parent artery on DSA and on nonsubtracted images at follow-up angiography (Fig. 2). So, the embolization status of an aneurysm with WCS corresponded to complete occlusion. All angiographic imaging studies were acquired using a biplane flat-panel detector (FPD) angiographic system (Artis zee BA Twin, Siemens AG). The C-arm angle was set to clearly observe the neck of the aneurysm between the aneurysm sac and the lumen of the parent artery. The images were acquired in a 1024×1024 matrix by using a 22-cm field of view (FOV) FPD or a 720×720 matrix by using a 16-cm FOV FPD and were then evaluated on a workstation (syngo X-Workplace, Siemens AG). Image edge enhancement was adjusted to correct for the coil artifact influence. Nonionic iodinated contrast material (Iopamiron 300, Bayer Healthcare Japan) was injected manually at a flow rate of 2.5–3.5 ml/second (5–7 ml of total volume). These angiographic conditions were the same at the time of treatment and at the 6-month follow-up period.

Outcome Assessment

Clinical and radiological follow-up investigations were

performed every 6–12 months in each patient. Radiological examination was performed using MR angiography (MRA). The MRI studies were acquired using a 1.5-T unit (Achieva or Ingenia, Philips Medical Systems). Imaging parameters of MRA using a 3D time of flight technique were TR 25.0, TE 6.9, 15° flip angle, 150×150 -mm FOV, 512×512 matrix, and 0.6-mm effective thickness. Cases with stent-assisted coil embolization were excluded from this analysis because stent artifacts prevent accurate assessment of embolization status using MRA. Clinical outcome was evaluated whether the rupture occurred in an unruptured aneurysm or was the rerupture of a ruptured aneurysm. The status of a coiled aneurysm on initial postembolization angiography, at the follow-up angiography including WCS determination, and at the follow-up MRA was analyzed by 2 neurointerventionalists (T.H. and K.F.). When there was any discrepancy, a decision was made by another neurointerventionalist (M.I.).

Statistical Analyses

Statistical analyses were performed using SPSS software (IBM). Categorical variables are presented as number and percentage, and continuous variables are presented as the mean \pm SD. The chi-square test or Fisher exact test was performed to analyze categorical variables as appropriate. Where necessary, an independent t-test or the Mann-Whitney U-test was used for unpaired continuous variables, and a paired t-test or Wilcoxon signed-rank sum test was used for paired continuous variables. Multivariate logistic regression analysis was performed to identify factors associated with the appearance of a WCS. These

TABLE 1. Characteristics of 149 aneurysms in 140 patients*

Characteristic	Total	Unruptured Aneurysm	Ruptured Aneurysm	p Value
Patients	n = 140	n = 110	n = 30	
Age in yrs, \pm SD†	58.6 \pm 12.9	58.7 \pm 12.4	58.2 \pm 15.1	0.86
Male sex	29 (20.7)	22 (20.0)	7 (23.3)	0.69
Risk factors				
Hypertension	70 (50.0)	54 (49.1)	16 (53.3)	0.68
Diabetes mellitus	13 (9.3)	11 (10.0)	2 (6.7)	0.57
Dyslipidemia	28 (20.0)	21 (19.1)	7 (23.3)	0.61
Smokers	40 (28.6)	32 (29.1)	8 (26.7)	0.79
Aneurysms	n = 149	n = 119	n = 30	
Location				
ICA	89 (59.7)	81 (68.1)	8 (26.7)	
ACA/ACoA	39 (26.2)	19 (16.0)	20 (66.7)	
MCA	3 (2.0)	3 (2.5)	0	
VA/BA	18 (12.1)	16 (13.5)	2 (6.7)	<0.001
Size†				
Overall size, mm	5.7 \pm 2.2	5.8 \pm 2.1	5.4 \pm 2.1	0.33
Neck size, mm	4.1 \pm 1.1	4.2 \pm 1.1	3.6 \pm 1.1	0.02
Dome-to-neck ratio	1.3 \pm 0.3	1.3 \pm 0.3	1.3 \pm 0.3	0.73

* Values are presented as number (%), unless otherwise indicated.

† Mean values are presented \pm SD.

factors were selected according to the reported factors of aneurysm recurrence: the neck size, the aneurysm size, hemorrhagic presentation, packing density, and the incomplete initial occlusion status.^{10,12,14,15} To ascertain the continuous value from multivariate analysis as the cutoff point for the prediction of the appearance of a WCS, receiver operating characteristic (ROC) curve analyses were also performed. Differences were defined as significant at a probability level of $p < 0.05$.

Results

Patient and Aneurysm Characteristics

The characteristics of the study population are listed in Table 1: 140 patients (29 men [20.7%], mean age 58.6 \pm 12.9 years) with 149 intracranial aneurysms were analyzed. A total of 119 aneurysms (79.9%) were unruptured, and 30 aneurysms (20.1%) were ruptured. There were no significant differences in the frequency of conventional risk factors between the unruptured and ruptured groups. The average aneurysm size was 5.7 \pm 2.2 mm (range 2.4–16.0 mm), the average aneurysm neck size was 4.1 \pm 1.1 mm (range 1.8–8.2 mm), and the average dome-to-neck ratio was 1.3 \pm 0.3 (range 0.8–2.0). The neck size was significantly larger in the unruptured group than in the ruptured group (4.2 \pm 1.1 mm vs 3.6 \pm 1.1 mm, $p = 0.02$). The aneurysm size and dome-to-neck ratio were similar in both groups. Aneurysms on the anterior communicating artery (ACoA) and anterior cerebral artery (ACA) were more frequent in the ruptured group (66.7% vs 16.0%),

TABLE 2. Univariate factors related to the appearance of the WCS*

Factor	WCS Positive, n = 23	WCS Negative, n = 126	p Value
Age in yrs, \pm SD†	58.3 \pm 13.0	58.6 \pm 13.0	0.9
Male sex	5 (21.7)	24 (19.1)	0.78
Aneurysm location			
ICA	15 (65.2)	74 (58.7)	
ACA/ACoA	3 (13.0)	36 (28.6)	
MCA	0	3 (2.4)	
VA/BA	5 (21.7)	13 (10.3)	0.23
Aneurysm size†			
Overall size	4.3 \pm 0.9	6.0 \pm 2.1	<0.001
Neck size	3.3 \pm 0.8	4.2 \pm 1.1	<0.001
Dome-to-neck ratio	1.3 \pm 0.3	1.3 \pm 0.3	0.81
Aneurysm type			
Sidewall	17 (73.9)	84 (66.7)	
Bifurcation	6 (26.1)	42 (33.3)	0.49
Rupture status			
Unruptured	20 (87.0)	99 (78.6)	
Ruptured	3 (13.0)	27 (21.4)	0.57
Initial treatment result			
Embolization status			
Complete occlusion	5 (21.7)	32 (25.4)	
Residual neck	12 (52.2)	73 (57.9)	
Residual aneurysm	6 (26.1)	21 (16.7)	0.56
Packing density, %†	20.7 \pm 5.5	22.6 \pm 6.3	0.18
Use of bioactive coil	5 (21.7)	19 (15.1)	0.54
Use of hydrogel coil	0 (0)	8 (6.3)	0.61
Use of stent	5 (21.7)	38 (30.2)	0.41

* Values are presented as number (%), unless otherwise indicated.

† Mean values are presented \pm SD.

whereas aneurysms on the internal carotid artery (ICA), middle cerebral artery (MCA), and vertebral artery/basilar artery (VA/BA) were more frequent in the unruptured group ($p < 0.001$).

Factors of WCS Appearance

A WCS was confirmed in 23 of 149 cases (15.4%) mainly at 6-month follow-up angiography (range 5–6 months) (Table 2). In univariate logistic regression analysis, no significant difference was observed between the WCS-positive and WCS-negative groups in any of the following characteristics: age; sex; aneurysm location; type of aneurysm (sidewall type or bifurcation type); rupture status (unruptured or ruptured); initial embolization status (complete occlusion, residual neck, or residual aneurysm); packing density; coil variety (use of bioactive coil or hydrogel coil); or stent use. However, the WCS-positive group had significantly smaller neck size (3.3 \pm 0.8 mm vs 4.2 \pm 1.1 mm, $p < 0.001$) and smaller aneurysm size (4.3 \pm 0.9 mm vs 6.0 \pm 2.1 mm, $p < 0.001$) compared with the WCS-negative group. In multivariate logistic regres-

TABLE 3. Independent predictive value for the appearance of the WCS

Variable	Adjusted OR	95% CI	p Value
Neck size	0.376	0.179–0.787	0.009
Aneurysm size	0.669	0.437–1.024	0.06
Sidewall type aneurysm	0.882	0.268–2.906	0.84
Ruptured aneurysm	4.887	0.835–28.598	0.08
Packing density, %	1.016	0.924–1.117	0.74
Complete occlusion at initial treatment	0.528	0.153–1.824	0.31

sion analysis, the independent predictor of a WCS was a small neck (OR 0.376, 95% CI 0.179–0.787; $p = 0.009$) (Table 3). In the ROC curve analysis, a neck size of 4.1 was determined as the most reliable cutoff value for predicting the appearance of a WCS (95% CI 0.662–0.846) (Fig. 3). Based on this cutoff value, the sensitivity and specificity were 87.0% and 51.6%, respectively. The positive and negative predictive values were 24.7% and 95.6%, respectively.

Of 126 aneurysms without WCS, the angiography showed complete occlusion in 56 aneurysms (44.4%), the residual neck in 62 (49.2%), and residual aneurysm in 8 (6.3%), mainly at 6-month follow-up (range 5–12 months). Compared with the complete occlusion aneurysms without WCS, the WCS-positive aneurysms had significantly smaller neck size (3.3 ± 0.8 mm vs 4.2 ± 0.9 mm, $p < 0.001$) and smaller aneurysm size (4.3 ± 0.9 mm vs 5.7 ± 1.8 mm, $p < 0.001$).

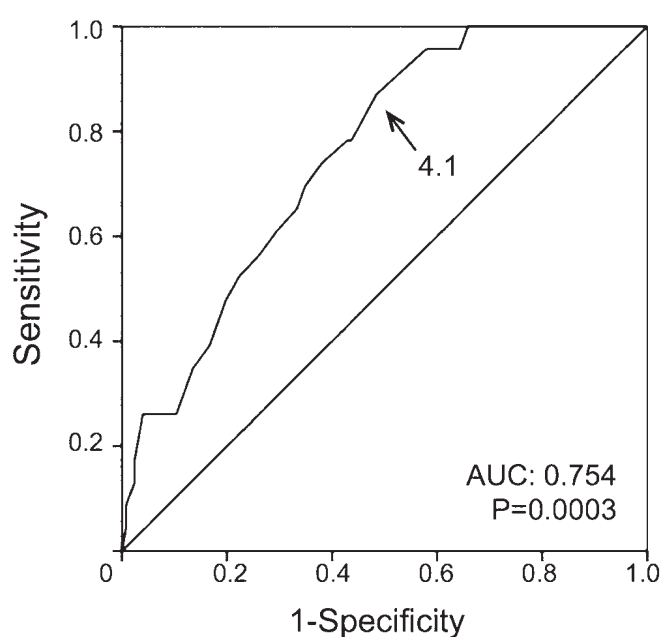
Radiological and Clinical Outcomes

The radiological and clinical results of coiled aneurysms were analyzed after the evaluation of WCS. Forty-three aneurysms were excluded because they were treated with stents. Therefore, 106 of 149 aneurysms were analyzed at a mean follow-up of 31.0 ± 9.7 months (range 5–52 months). The rate of complete occlusion was significantly higher in the WCS-positive group (18/18, 100%) than in the WCS-negative group (54/88, 61.4%; $p = 0.001$) (Table 4). The overall major recanalization rates are low for both the WCS-positive and -negative groups (0/18, 0% vs 6/88, 6.8%; $p = 0.254$). Retreatment was performed in those 6 patients at 5–26 months. No rupture occurred in any patient in this period.

Patients with complete occlusion without the WCS at 6-month follow-up also had good radiological and clinical outcomes. Complete occlusion was maintained and no rupture occurred in any patient.

Discussion

A WCS is a radiolucent gap between the coil mass in the aneurysm and the lumen of the parent artery observed on angiography between 14 days and 6 months after endovascular coil embolization, which indicates a formation of thick neointimal tissue at the neck of the aneurysm.⁹ Gonzalez et al. first reported the appearance of WCS in human beings for 2 cases of cerebral aneurysms.³ However, the

**FIG. 3.** The ROC curve analysis indicates that a neck size of 4.1 mm (arrow) is the most reliable cutoff value for predicting the appearance of WCS. AUC = area under the curve.

prognosis of a coiled aneurysm with WCS is unknown. This is the first study to evaluate the role of WCS in the radiological and clinical outcome.

In our study, the presence of a WCS was confirmed in 15.4% of cerebral aneurysms at 5–6 months after endovascular coil embolization. The most important factor in the appearance of WCS was small neck size. The appearance of a WCS was not correlated with either the location of the aneurysm or the initial angiographic status. A previous study has demonstrated that the rate of a WCS appearance was 6.9%, and that a small neck correlated with the appearance of WCS only in cases of unruptured aneurysm.⁴ Our study revealed that WCS tended to appear in the small-necked aneurysms after treatment in both unruptured and ruptured aneurysms. Furthermore, the WCS-positive aneurysms had significantly smaller neck size and smaller aneurysm size compared with the aneurysms with complete occlusion without WCS. The neointimal thickening would be promoted at the neck of these coiled aneurysms, which

TABLE 4. Radiological and clinical outcomes related to coiled aneurysms with WCS*

Outcome	WCS Positive, n = 18	WCS Negative, n = 88	p Value
Final embolization status			
Complete occlusion	18 (100)	54 (61.4)	
Residual neck	0 (0)	28 (31.8)	
Residual aneurysm	0 (0)	6 (6.8)	0.001
Retreatment	0 (0)	6 (6.8)	0.254
Subarachnoid hemorrhage	0 (0)	0 (0)	1

* Values are presented as number (%), unless otherwise indicated.

prevents any further aneurysmal filling. Although bioactive coils were developed to prevent the recurrence of aneurysm by promoting organized thrombus formation and growth of connective tissue into the aneurysm,^{1,9} they were not associated with the appearance of WCS in our study. Recent randomized trials revealed that bioactive or hydrogel coils were not associated with prevention of major recurrence of aneurysm when compared with bare platinum coils.^{6,8,18}

Our study also demonstrated that the outcome of treated aneurysms with WCS was excellent in the follow-up period. Complete occlusion was maintained at an average of 31 months in all cases with a WCS. Neither major recanalization nor aneurysm rupture occurred. Factors of aneurysm recurrence were reported to be a neck size > 4 mm, an aneurysm size > 10 mm, initial angiographic status, and a hemorrhagic presentation.^{10,12,14,15} The rate of retreatment for previously coiled aneurysms was reported as 6%–33%, whereas that of aneurysm rupture was very low.^{7,13,14,18} Consistent with a previous histological study,⁹ our study supposed that WCS would indicate a healing of the aneurysm. The prognosis of coiled aneurysms will be confirmed by evaluating WCS.

A limitation of this study is that the average aneurysm size of 5.7 mm in our sample was relatively small. This is because larger aneurysms tend to involve the parent artery, and the precise confirmation of the neck between aneurysm and parent artery is difficult to achieve by conventional angiography, which is unable to evaluate WCS. Indeed, 51 of 211 saccular aneurysms were excluded for that reason in this study. Also, cases with stent treatment were excluded in the radiological outcome of WCS because the embolization status could not be evaluated due to the stent artifact on MRA. Stent-assisted coil embolization tends to be performed for wide-necked aneurysms (neck size is one of the risk factors for recanalization).¹¹ So, the rate of major recanalization was low and the clinical result was excellent in both WCS-positive and WCS-negative cases in this study.

A previous study has reported that the stability of embolization status was decided mainly at 6 months.¹⁶ The prognosis of coiled aneurysms with adequate occlusion (complete occlusion or small neck remnant) at 6 months was expected to be excellent. After 6 months, the factors of late recanalization were the presence of intraluminal thrombus and aneurysm size > 15 mm.² Therefore, we could not detect the difference between cases of complete occlusion with and without WCS according to the radiological and clinical outcomes, which were both excellent. Our study was also retrospective in nature. Despite these limitations, this study focused on the role of WCS and revealed that WCS is one of the reliable markers for the long-term stability of complete occlusion after endovascular embolization of saccular aneurysms, which would lead to a good clinical outcome. In the future, a large prospective study will be necessary to confirm the clinical importance of WCS.

Conclusions

A WCS appeared in 15.4% of aneurysms after endovascular coil embolization. The significant factor in the

appearance of WCS was a small-necked aneurysm. The WCS was associated with the maintenance of complete occlusion. The WCS would be a good predictor of radiological and clinical outcome.

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Disclosures

The authors report no conflict of interest concerning the materi-

als or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Higashi, Fukuda, Inoue. Acquisition of data: Higashi, Fukuda, Okawa, Iwaasa, Yoshioka. Analysis and interpretation of data: Higashi, Fukuda, Iwaasa. Drafting the article: Fukuda. Critically revising the article: Higashi, Fukuda. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Higashi. Statistical analysis: Higashi, Fukuda, Iwaasa. Study supervision: Inoue.

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