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Japanese Subarachnoid Aneurysm Trial of Neurosurgical Clipping versus Endovascular Coiling in 1863 Patients with Ruptured Intracranial Aneurysms

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Abstract

This is a post hoc multivariate analysis of the modified World Federation of Neurosurgical Societies (WFNS) grading project, multicenter prospective observational study including 38 neurosurgical institutions across Japan. Japan Neurosurgical Society WFNS grading committee conducted a modified WFNS grading project as a nationwide prospective registry study. We investigate the clinical outcome of both surgical and endovascular interventions after aneurysmal subarachnoid hemorrhage (SAH) in Japan. A total of 792 patients received surgical intervention and 417 patients received endovascular treatment. Eight hundred patients were female, and 409 patients were male. The mean age was 61.5 ± 13.7 years. At 3 month follow-up, there was no statistically significant difference in good clinical outcome between surgical (68.2%) and endovascular (60.9%) group (odds ratio, 0.89; 95% confidence interval, 0.68-1.16; p = 0.381). Unfavorable outcome rate was 31.8% (238 patients) in the surgical group and 39.1% (154 patients) in the endovascular group. Male, elderly people, modified Rankin scale condition before onset, high-grade modified WFNS clinical grading scale, intracerebral hematoma, post-treatment normal pressure hydrocephalus, and neurological deficit due to symptomatic vasospasm were risk factors for the clinical outcome. Treatment modality was not a statistical factor for clinical outcomes. Surgical clipping has still a major role in the management of SAH in Japan. The present study was not a randomized controlled study, but clinical outcome is not influenced by treatment modalities.

Keywords: clip occlusion, coil embolization, intracranial aneurysm, outcomes, subarachnoid hemorrhage

Introduction

Subarachnoid hemorrhage (SAH) due to ruptured intracranial aneurysm remains a life-threatening condition despite modern neurosurgical and endovascular treatments. The International Subarachnoid Aneurysmal Trial (ISAT) has demonstrated an advantage of endovascular therapy over surgical clipping in patients in whom either surgical or endovascular treatment could be performed safely.[1)] In another comparative trial, the Barrow Ruptured Aneurysm Trial (BRAT) also reported excellent outcomes for endovascular treatment,[2)] but it is important to note that the advantages decreased with increasing time since treatment.[3-6)] A systematic review has concluded that for patients in "good clinical condition" with a ruptured aneurysm of either the anterior or posterior circulation that was con-

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sidered suitable for either neurosurgical clipping or endovascular coiling, coiling was associated with better outcomes.[7] The same review also reported that no reliable trial evidence exists that can be used directly to guide treatment for those in "poor clinical condition."[7] Although the less-invasive endovascular treatment has some advantages over surgical intervention, it remains unknown whether such advantages exist regardless of clinical condition in the real-world management of SAH.

This study aimed to investigate the clinical outcomes for each of surgical and endovascular interventions after aneurysmal SAH in Japan and to evaluate outcomes according to initial neurological condition.

Materials and Methods

We performed a subanalysis of the modified World Federation of Neurosurgical Societies clinical grading scale (mWFNS) project, which was conducted as a nationwide prospective registry study.[8] Patients and their surrogates were informed of the concept and design of this study, and only data for those who provided consent to us were used. The original study and this subanalysis were both approved by the Ethics Committee of the Japan Neurosurgical Society and by the Institutional Review Board of The Jikei University Hospital (Number: 28-039(8282)), and the study information was available on the hospital's website. The mWFNS project was a multicenter prospective observational study that included 38 neurosurgical institutions across Japan. The details of patient enrolment criteria have been published elsewhere.[8] In brief, the subjects were patients admitted to the hospital with SAH ≤72 h after symptom onset and who underwent subsequent aneurysm repair. Patients whose health condition was graded modified Rankin scale (mRS) of >1 prior to SAH onset were excluded. The Glasgow Coma Scale (GCS) and presence or absence of neurological deficits (NDs) (weakness and/or aphasia) were recorded on admission. The initial SAH score was evaluated using the Fisher group, Hunt and Hess grade, and mWFNS grade at admission. Modified WFNS grade is a simplified modification of the original WFNS grade, based on the GCS without factors regarding the presence/absence of focal NDs.

In brief, in the mWFNS grading system, Grade I is GCS 15, Grade II is GCS 14, Grade III is GCS 13, Grade IV is GCS 7-12, and Grade V is GCS 3-6. The Glasgow Outcome Scale and mRS were recorded at discharge and at 3 months after treatment.

The treatment modalities were nonrandomized and the indications for each were decided by the individual institutes. Data were stored in a secured, electronic database after anonymization.

Surgical treatment included direct aneurysmal clipping, wrapping, trapping, and bypass surgery (surgical group). Endovascular treatment included coil embolization and parent artery occlusion (endovascular group). Secondary surgical procedures such as hematoma evacuation, ventricular drainage, and shunt reconstruction were recorded in both groups.

Patients who received combined treatment, e.g., reconstruction by endovascular parent artery trapping/occlusion followed by bypass surgery, were excluded from the study. Patients who tried treatment but gave up were also excluded. Clinical outcomes were evaluated at discharge and at 3 months after treatment.

Role of the funding source

The study was supported and funded by the Japan Neurosurgical Society.

Statistical analysis

Data were compared using the Mann-Whitney *U* test or Student's *t* test. Categorical variables are presented as numbers (%) and compared using Fisher's exact test or chi-square test.

Ordered logistic regression analysis was used to determine the odds ratios (ORs) and 95% confidence interval or mRS at 3 months after treatment. ORs were calculated by multivariate analysis adjusted for treatment modality, sex, age (as a continuous variable), mRS before onset (0 or 1), mWFNS grade (I-V), aneurysm location, hydrocephalus status, vasospasm status, intracerebral hemorrhage (ICH), and intraventricular hematoma. Values with two-sided $p < 0.05$ were considered significant. All data were analyzed using Stata 15.1 (Stata Corp LP, College Station, TX, USA).

Results

Between October 2010 and March 2013, 1863 patients with SAH, including both saccular and dissecting aneurysms, were registered at 38 participating hospitals. Of these, 629 patients who were admitted >72 h after symptom onset or if time of onset of bleeding was unknown (n = 372), with mRS >1 prior to onset (n = 140), and who were untreated because of a poor neurological condition or unknown origin of bleeding (n = 117) were excluded. Of the remaining 1234 patients, 14 received combined surgical and endovascular treatment and aneurysm obliteration could not be completed in 11 (attempted). A final total of 1209 patients were included for analysis: 792 treated by surgical intervention and 417 by endovascular treatment (female, n = 800; male, n = 409; mean age, 61.5 ± 13.7 years). Table 1 lists the patients' baseline characteristics according to the treatment group.

There were no significant differences between the two groups with respect to age, sex, Fisher group, initial GCS score, or initial mWFNS grade.

Regarding patient age, 13.7% of the endovascular group and 7.4% of the surgical group aged >80 years. Before treatment, neurological condition was good (mWFNS

Table 1 Baseline characteristics of patients

	Surgical		Endovascular		*p* value
	n	(%)	n	(%)	
Number of patients	792		417		
Age (years)					0.616
Mean	61.2 ± 13.2		62.0 ± 14.4		
Range	15-88		30-94		
>80	59	7.4	57	13.7	
mRS before onset					
mRS 0	760	96.0	384	92.1	
mRS 1	32	4.0	33	7.9	
Sex					0.075
Female	538	67.9	262	62.8	
Male	254	32.1	155	37.2	
mWFNS grade					0.007
I	270	34.1	108	25.9	
II	147	18.6	82	19.7	
(I-II inclusive)	417	52.7	190	45.6	
III	58	7.3	50	12.0	
IV	163	20.6	99	23.7	
V	154	19.4	78	18.7	
(III-V inclusive)	375	45.1	227	54.4	
Fisher group					0.767
1	34	4.3	16	3.8	
2	105	13.3	54	12.9	
3	645	81.4	345	82.7	
4	0	0.0	0	0.0	
Uncertified	8	1.0	2	0.5	
Aneurysm location					
MCA	256	32.3	33	7.9	
AcomA	194	24.5	110	26.4	
PcomA	186	23.5	79	18.9	
ACA	40	5.1	20	4.8	
ICA bifurcation	7	0.9	7	1.7	
ICA	51	6.4	32	7.7	
VA	24	3.0	65	15.6	
BA	11	1.4	43	10.3	
PCA	3	0.4	7	1.7	
Others	15	1.9	21	5.0	
Uncertified	5	0.6	0	0.0	
With ICH	215	27.1	55	13.2	0.000
With IVH	220	27.8	144	34.5	0.019

mRS = modified Rankin Scale; mWFNS = modified World Federation of Neurosurgical Societies clinical grading scale; MCA = middle cerebral artery; AcomA = anterior communicating artery; PcomA = internal carotid-posterior communicating artery; ACA = anterior cerebral artery; ICA = internal carotid artery; VA = vertebral artery; BA = basilar artery; PCA = posterior cerebral artery; ICH = intracerebral hemorrhage; IVH = intraventricular hematoma

Table 2 Additional treatment according to treatment group

	Surgical		Endovascular	
	n	(%)	n	(%)
Ventricular or cisternal drainage	316	39.9	71	17.0
ICH removal or decompression	125	15.8	13	3.1
Bypass	35	4.4	0	0

ICH = intracerebral hemorrhage

grade I-II) in 417 patients (52.7%) of the surgical group and 190 patients (45.6%) of the endovascular group. Treatment was predominately by surgery for the middle cerebral artery (88.6%), anterior communicating artery (63.8%), and internal carotid-posterior communicating artery (70.2%), whereas the endovascular technique was used mainly for aneurysms of the posterior circulation. Surgical ventricular or cisternal drainage was the most frequently performed additional treatment in both groups, and ICH was treated mainly by surgery (Table 2).

There was no significant difference between the groups regarding the incidence of symptomatic vasospasm or normal pressure hydrocephalus (Fig. 1).

Clinical outcome

At discharge, 481 patients (60.7%) in the surgical group and 221 patients (53.0%) in the endovascular group had good clinical outcomes (mRS 0-2). At 3 months after treatment, 1143/1209 patients (94.5%) were available for evaluation, 511 patients (68.2%) in the surgical group and 240 patients (60.9%) in the endovascular group had good clinical outcomes. The primary outcome of death or dependency, defined as a mRS score of >2, occurred in 238/749 (31.8%) patients in the surgical group and in 154/394 (39.1%) in the endovascular group (Fig. 2).

Factors related to good outcome

The following factors were found to influence clinical outcome: sex, age, prerupture mRS condition, mWFNS grade, presence of ICH, basilar artery aneurysm, hydrocephalus, and irreversible vasospasm (Fig. 3). In the univariate analysis, prognosis was better in the surgical group than in the endovascular group, but multivariate analysis revealed no significant difference in outcomes between the two groups. Treatment modality was not a factor influencing clinical outcomes. We considered that confounding could have affected outcomes.

Discussion

Selection of the optimal treatment modality for aneurysmal SAH is not always straightforward in real-world clinical practice. Unlike coronary interventions, multiple factors can influence the difficulty of treatment of cerebral aneu-

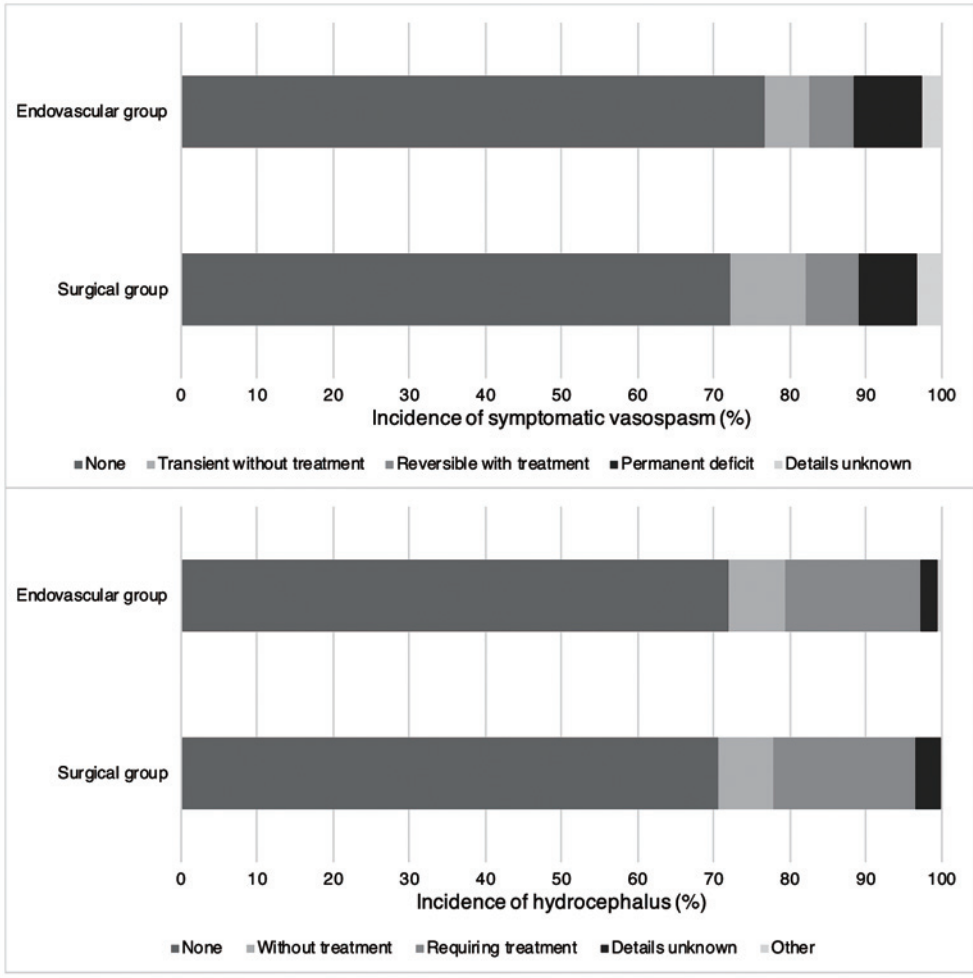

Fig. 1 Incidence of symptomatic vasospasm and normal pressure hydrocephalus by treatment group.

rysms, such as their size, location, projection, and relationship to the parent artery and aneurysm neck.

The ISAT investigators reported that endovascular treatment was associated with better functional outcomes at 1 year after treatment.[1] However, at 10 years after follow-up, there was no difference in the rate of increased dependency alone between the two groups.[6]

In the ISAT study, the inclusion criteria were aneurysms suitable for either surgical or endovascular technique and mRS <2 before the onset of SAH, and many aneurysms that were suitable for only one technique were excluded. Thus, only 22% of those who were treated for SAH were included in this study. It is important to note that SAH patients require immediate treatment and not all institutions have sufficient neurosurgeons to enable a choice of treatment modality in the emergency setting.

BRAT was conducted as a prospective, randomized study of microsurgical versus endovascular treatment of ruptured cerebral aneurysms to investigate several concerns regarding the ISAT study.[2] Unlike ISAT, the BRAT study included every patient with aneurysmal subarachnoid hemorrhage who was admitted during the study period. Crossing over from one group to the other was allowed if the allocated treatment was judged not to be ideal for a given aneurysm.

The 10 year BRAT follow-up outcomes have recently been published.[6] Although the clinical outcomes were better at 1 year in the endovascular group, the advantages of endovascular treatment had disappeared at the 3 year follow-up and also at 10 years. Better retreatment rates and lower rebleeding rates for the surgical group in patients with anterior circulation aneurysms were also demonstrated.

The BRAT study demonstrated excellent clinical outcomes for both surgical and endovascular treatment; however, the Barrow Neurosurgical Institute is one of the best neurosurgical institutes in the world, and it is unclear whether such good outcomes could be expected in less specialized centers. Conversely, cerebral aneurysm characteristics and environmental factors in Japan have unique features not found in other countries.[9] Thus, it is important to verify the Japanese treatment outcomes in daily

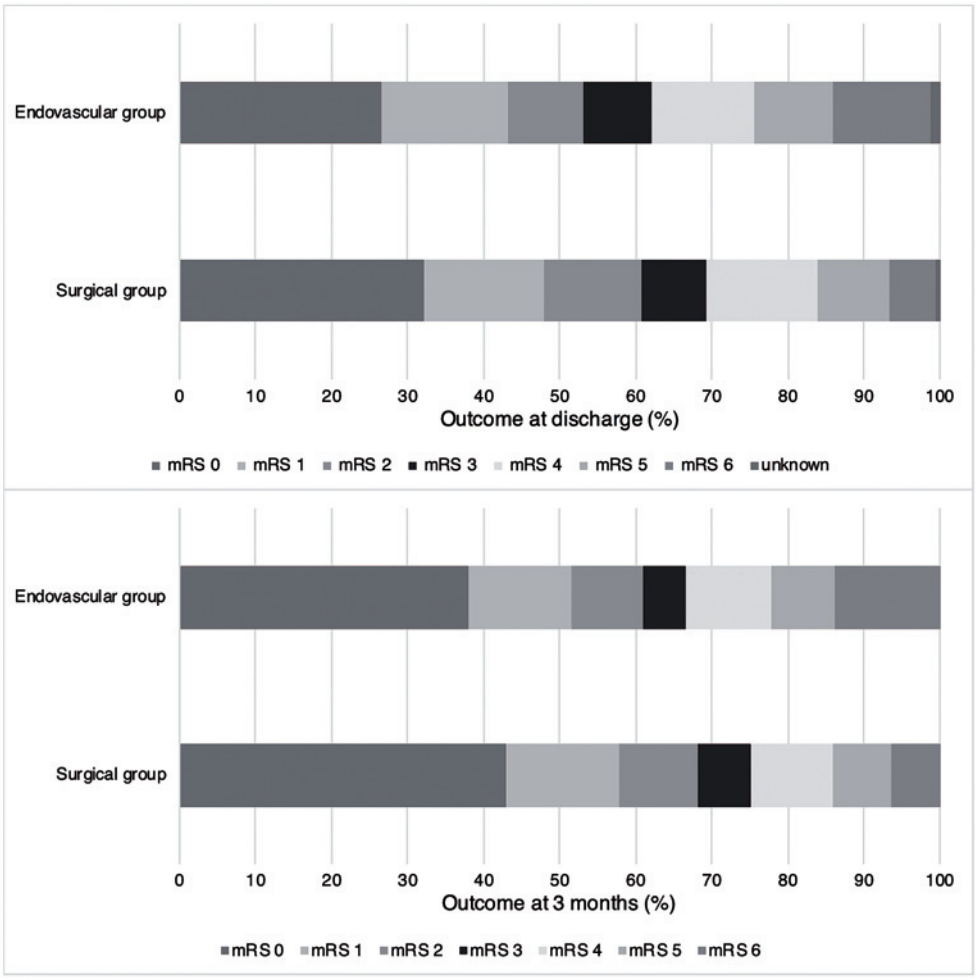

Fig. 2 Clinical outcomes at discharge and at 3 months after treatment.

neurosurgical practice at large- and medium-sized medical centers, retrospectively, particularly as SAH is a common neurosurgical condition.

Surgery/endovascular ratio

In the present study, 65.5% of the patients received surgical treatment and the treatment modality was nonrandomized and decided by the institutes themselves. The Japan Neurosurgical Society continues to develop neurosurgical practice despite endovascular treatment being performed increasingly. Additionally, the Japanese Society of Neuroendovascular Therapy has offered a board certification training program since 1998. Although the number of endovascular physicians is increasing, there are still not enough to enable endovascular treatment to be performed at institutions in all locations. The average number of endovascular board-certified physicians (neurosurgery, radiology, and neurology background) in Japan is 0.85/100,000 of population. Despite the nationwide board certification training program, the lowest number among the prefectures is only 0.2/100,000.[10)]

Outcome evaluation

In the present study, only 417 patients (52.7%) in the surgical group and 190 patients (45.6%) were in good neurological condition (mWFNS grade I-II) before treatment. By contrast, nearly 90% of the patients in the ISAT study were in good pretreatment neurological condition.

The BRAT study reported good neurological condition (Hunt and Hess grade I-II) in 52%-53%, which was identical for surgical and endovascular treatment, similar to the pretreatment neurological condition in the present patients. Although our higher percentage of patients in good neurological condition and lower rates of patients with posterior circulation aneurysms in the surgical group may have introduced bias to the clinical outcomes, our data showed reasonable clinical outcomes for surgical intervention. Age of >80 years was more frequent in the endovascular group than in the surgical group. It is reasonable to choose endovascular treatment for very elderly patients who, before the availability of the endovascular technique, may not have been indicated for any treatment. Compared with the BRAT study, our percentage of poor clinical out-

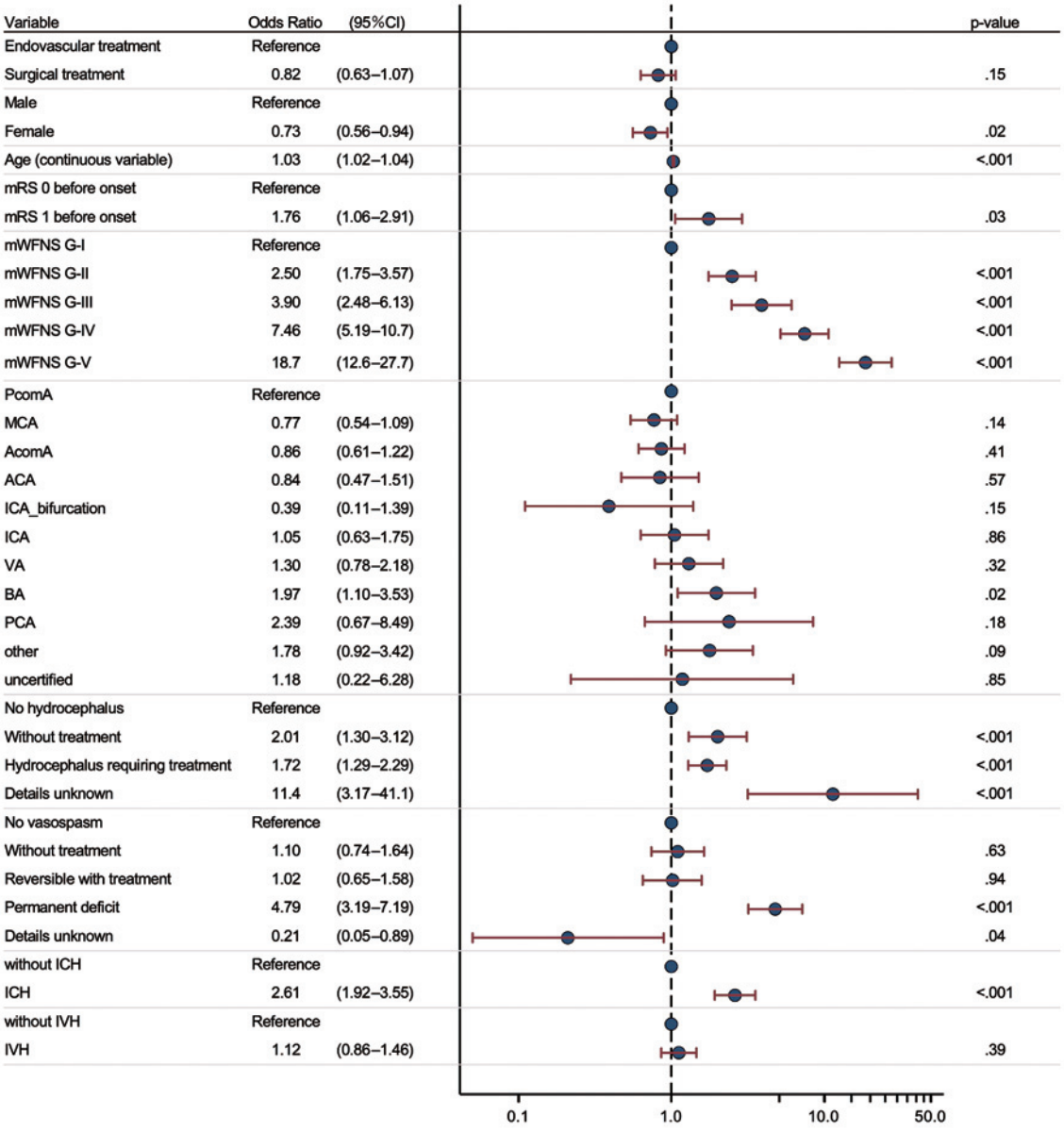

Fig. 3 Odds ratio for mRS at 3 months after treatment adjusted by covariates.

comes was high, which might be due to differences between a single top-level neurosurgical center and the present multicenter study comprising data from 38 institutions.

Grading systems used for evaluation of SAH

A system for grading SAH was first introduced by Botterell et al in 1956,[11] which was subsequently modified as the Hunt and Hess[12]/Hunt-Kosnik,[13] and WFNS scales.[14] In the present study, we used mWFNS grade to evaluate the condition of patients.[8] In ISAT, evaluations were made by WFNS grade, and BRAT used the Hunt and Hess grading system. All previous studies have used the level of consciousness as the major predictor of outcome. However, the Hunt and Hess system uses less clearly defined scales of consciousness. In the mWFNS grading system, the presence or absence of NDs was removed as a criterion, thus increasing the predictive value of the system and reducing interrater variability.[8] This also serves to increase the reliability of the mWFNS system by reducing interrater variability; clinically, determining whether an ND is present is much more subjective than methods such as calculating GCS.

Limitations

The study has several limitations. First, the study design was not a randomized study. Each participating center made clinical decisions on the basis of the availability of

treatment resources. Because of the original study design and treatment in the emergency setting, aneurysm size was not accurately recorded by different imaging modalities such as computed tomographic angiography, digital subtraction angiography, or magnetic resonance angiography.

The retreatment rates of both surgical and endovascular therapies and the rebleeding rates were not recorded because the original aim of the study was to adjust the WFNS grading system. The follow-up period was short because only the data for 3 months after bleeding were available.

In the current clinical practice near 10 years later since this study, endovascular modality and techniques may have changed, as well as the age composition of population during this period.

Conclusion

In real-world SAH management, surgical clipping remains the first-line therapy in Japan. The present results revealed that clinical outcomes were not influenced by the treatment modality and that the initial neurological condition is the major factor that affects clinical outcomes after SAH. It was not possible to identify either of the treatment methods to be significantly better between the two groups because of the complexity of factors involved in the choice of treatment method. Appropriate consideration of the treatment methods available at each institution and for each individual patient contributed to the stabilization of the treatment results.

Acknowledgments

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Abbreviations List

ACA = anterior cerebral artery, BRAT = the Barrow Ruptured Aneurysm Trial, GCS = Glasgow Coma Scale, ICA = internal carotid artery, ICH = intracerebral hemorrhage, ISAT = international subarachnoid aneurysmal trial, mRS = modified Rankin scale, mWFNS = modified World Federation of Neurosurgical Societies clinical grading scale, NDs = neurological deficits, ORs = odds ratios, PCA = posterior cerebral artery, SAH = subarachnoid hemorrhage, VA = vertebral artery, WFNS = the World Federation of Neurosurgical Societies

Conflicts of Interest Disclosure

Dr. Murayama reports grants from Stryker, Siemens, NTT Docomo and Asahi Intec.

No other authors have conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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