Risk of rupture of unruptured cerebral aneurysms in elderly patients

OPEN

Tomohito Hishikawa, MD
Isao Date, MD
Koji Tokunaga, MD
Shinjiro Tominari, MD, MPH
Kazuhiko Nozaki, MD, PhD
Yoshiaki Shiokawa, MD, PhD
Kiyohiro Houkin, MD, PhD
Yuichi Murayama, MD
Toshihiro Ishibashi, MD
Hiroyuki Takao, MD
Toshikazu Kimura, MD
Takeo Nakayama, MD, PhD
Akio Morita, MD, PhD
For UCAS Japan and UCAS II Investigators

Correspondence to Dr. Hishikawa: t-hishi@md.okayama-u.ac.jp

Supplemental data at Neurology.org

ABSTRACT

Objectives: The aim of this study was to identify risk factors for rupture of unruptured cerebral aneurysms (UCAs) in elderly Japanese patients aged 70 years or older.

Methods: The participants included all patients 70 years of age or older in 3 prospective studies in Japan (the Unruptured Cerebral Aneurysm Study of Japan [UCAS Japan], UCAS II, and the prospective study at the Jikei University School of Medicine). A total of 1,896 patients aged 70 years or older with 2,227 UCAs were investigated. The median and mean follow-up periods were 990 and 802.7 days, respectively.

Results: The mean aneurysm size was 6.2 ± 3.9 mm. Sixty-eight patients (3.6%) experienced subarachnoid hemorrhage during the follow-up period. Multivariable analysis per patient revealed that in patients aged 80 years or older (hazard ratio [HR], 2.02; 95% confidence interval [CI], 1.16–3.49, p = 0.012), aneurysms 7 mm or larger (HR, 3.08; 95% CI, 1.35–7.03, p = 0.007 for 7–9 mm; HR, 7.82; 95% CI, 3.60–16.98, $p < 0.001$ for 10–24 mm; and HR, 43.31; 95% CI, 12.55–149.42, $p < 0.001$ for ≥25 mm) and internal carotid–posterior communicating artery aneurysms (HR, 2.45; 95% CI, 1.23–4.88, p = 0.011) were independent predictors for UCA rupture in elderly patients.

Conclusions: In our pooled analysis of prospective cohorts in Japan, patient age and aneurysm size and location were significant risk factors for UCA rupture in elderly patients. *Neurology*® 2015;85:1879–1885

GLOSSARY

AComA = anterior communicating artery; **BA** = basilar artery; **CI** = confidence interval; **HR** = hazard ratio; **ICA** = internal carotid artery; **IC-PComA** = internal carotid–posterior communicating artery; **SAH** = subarachnoid hemorrhage; **UCA** = unruptured cerebral aneurysm; **UCAS** = Unruptured Cerebral Aneurysm Study; **VA** = vertebral artery.

Understanding the natural history of unruptured cerebral aneurysms (UCAs) is important to determine optimal UCA management plans. Recently, the Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan) elucidated risk factors for UCA rupture in individuals aged 20 years or older in the general Japanese population; this study could indicate some useful indexes for UCA surgical treatment.[1]

Japan has the world's highest life expectancy, and the number of elderly patients with UCAs is increasing. A total of 5,720 patients were included in UCAS Japan and 1,577 patients (28%) were older than 70 years.[1] In preventive care, one of the most troubling issues is to decide whether to perform surgery on elderly patients with UCAs because clinicians have to consider some factors particular to elderly patients, such as patients' life expectancy, presence of comorbid

From the Department of Neurological Surgery (T.H., I.D., K.T.), Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama; Department of Health Informatics (S.T., T.N.), Kyoto University School of Public Health, Kyoto; Department of Neurosurgery (K.N.), Shiga University of Medical Science, Shiga; Department of Neurosurgery (Y.S.), Kyorin University School of Medicine, Tokyo; Department of Neurosurgery (K.H.), Hokkaido University Graduate School of Medicine, Sapporo; Division of Endovascular Neurosurgery (Y.M., T.I., H.T.), Department of Neurosurgery, The Jikei University School of Medicine, Tokyo; Department of Neurosurgery (T.K.), NTT Medical Center Tokyo; and UCAS Coordinating Office (A.M.), University of Tokyo, Department of Neurological Surgery, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan.

UCAS Japan and UCAS II coinvestigators are listed on the *Neurology*® Web site at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was paid by Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences.

disease, surgical treatment risks, and the poor prognosis for elderly patients with ruptured aneurysms.[2] It is meaningful to stratify elderly patients with UCAs according to risk of UCA rupture in a clinical setting.

There have been 3 large prospective cohorts in Japan, which evaluated the natural course of UCAs and reported risk factors predicting rupture.[1,3,4] In the present study, we analyzed the pooled data from these studies and identified risk factors for UCA rupture in elderly Japanese patients 70 years of age or older.

METHODS

Patients. Participants enrolled in this study included all patients aged 70 years or older in 3 large prospective cohort studies in Japan.[1,3,4] UCAS Japan (UMIN-CTR C000000418) was a project of the Japan Neurosurgical Society and was designed as a multicenter, prospective cohort study of UCAs in the Japanese population.[1] Patients with newly diagnosed UCAs from January 2001 to April 2004 were enrolled in UCAS Japan. In a total of 5,720 patients who were 20 years of age or older, 6,697 saccular aneurysms that were 3 mm or more at the largest diameter met the eligibility criteria. We excluded UCAs less than 3 mm from this study because the diagnosis accuracy for computer images of UCAs decreases when under 3 mm in diameter with low-tesla MRI. Follow-up data on the patients' clinical status, a description of the aneurysms, and the treatment management plan were recorded at 3, 12, and 36 months and at 5 to 8 years. The therapeutic strategy was chosen by the patient or was determined at the physician's discretion. When a patient underwent a surgical intervention, data up to the time of the intervention were included in the analysis of the risk of rupture. We extracted the data from patients who were 70 years of age or older from UCAS Japan and analyzed a total of 1,577 patients with 1,844 aneurysms in this study. Subarachnoid hemorrhage (SAH) was identified by means of CT imaging or lumbar puncture or was documented at autopsy. For 2 patients extracted from UCAS Japan, the diagnosis was made on the basis of sudden severe headache or loss of consciousness.

UCAS II (UMIN-CTR C000000420) was conducted to clarify the influence of surgical intervention for UCAs on periodic health-related quality of life and cognitive function as part of the analysis of UCA surgical complications, and to assess the natural history of UCAs.[4] In UCAS II, patients with newly identified UCAs from January 2006 to January 2007 at 31 institutions in Japan were prospectively enrolled. The patients' status and aneurysm characteristics were monitored at 3, 6, and 60 months after enrollment. A total of 953 patients with 1,106 aneurysms were enrolled in UCAS II, and the data from 234 patients who were aged 70 years or older with 268 aneurysms were extracted from UCAS II for this pooled analysis. The organization members of UCAS Japan and UCAS II are listed in supplemental data.

From January 2003 to December 2006, a total of 419 patients with 529 UCAs were referred to the Jikei University School of Medicine in Japan and were prospectively observed without treatment at this single institution.[3] Clinical and 3-dimensional CT angiography follow-up were obtained every 6 months. The data from 85 patients aged 70 years or older with 115 UCAs were integrated with those from UCAS Japan and UCAS II in this pooled analysis.

The Jikei University School of Medicine has a role as referral center to surgically treat UCAs. Many patients enrolled in UCAS Japan and in UCAS II were registered from general hospitals that served as secondary care centers. The characteristics of the 3 prospective Japanese studies that were used in this pooled analysis are summarized in table e-1 on the *Neurology*® Web site at Neurology.org.

Data collection. Patient characteristics that are common to the 3 prospective studies include the following: age, sex, history of SAH, family history of SAH, former or current smoking, multiplicity, and hypertension. The aneurysm size was divided as follows: 3–4 mm, 5–6 mm, 7–9 mm, 10–24 mm, and ≥25 mm. The aneurysm location was categorized as follows: middle cerebral artery, anterior communicating artery (AComA), internal carotid artery (ICA), internal carotid–posterior communicating artery (IC-PComA), basilar artery (BA), vertebral artery (VA), and other. The ICA includes ICA paraclinoid location, the ICA dorsal curvature location, ICA bifurcation, and ICA anterior choroidal artery and excludes other ICA aneurysms located at the posterior communicating artery and cavernous portion. The BA includes the BA tip and BA superior cerebellar artery. The VA includes the VA posterior inferior cerebellar artery and vertebrobasilar junction. "Other" includes aneurysms at the anterior cerebral artery A1 portion, distal anterior cerebral artery, and other supratentorial or infratentorial locations that are not categorized above.[1] A daughter sac was defined as an irregular protrusion of the aneurysm wall. Data were censored at the time of a patient's death, a surgical or endovascular intervention, or the last follow-up assessment.

Standard protocol approvals, registrations, and patient consents. Investigators at each institution obtained the approval of the local institutional review board. The written informed consents were obtained from all patients participating in this study.

Statistical analysis. The aneurysm rupture hazard ratios were studied individually per patient using Cox proportional hazard regression models. When a patient had multiple aneurysms, the largest of these aneurysms along with its location and with or without the daughter sac was used to categorize the patient. When variables associated with aneurysm rupture had a probability value less than 0.2 using a univariable analysis, they were selected for a multivariable analysis. Categorical variables were compared using the Pearson χ^2 test. The cumulative rates of SAH were estimated per patient using the Kaplan-Meier product-limit method, and the curves between 2 groups were compared using the log-rank test. All statistical analyses were performed using Stata software, version 13.1 (StataCorp, College Station, TX). Statistical tests were 2-sided and differences were considered to be significant when p values were less than 0.05.

RESULTS

A total of 1,896 patients who were 70 years of age or older with 2,227 UCAs from the 3 prospective cohort studies were investigated in this pooled analysis (figure e-1). The mean (±SD) age of patients was 74.3 ± 3.9 years. Two hundred six patients (10.9%) who were 80 years of age or older had 239 aneurysms. Four hundred eighty-two (29%) of 1,690 patients aged 70 to 79 years and 8 (4%) of 206 patients 80 years or older underwent surgical repair of aneurysm during the follow-up period.

Table 1 Patient characteristics

Characteristic	
No. of patients	1,896
Age, y	74.3 ± 3.9
≥80	206 (10.9)
Female sex	1,383 (72.9)
History of SAH	33 (1.7)
Family history of SAH	176 (9.3)
Smoking	154 (8.1)
Multiplicity	276 (14.6)
Hypertension	1,017 (53.6)
Ruptured aneurysms	68 (3.6)
Daughter sac	392 (20.7)
Surgical/endovascular treatment	489 (25.8)
Size of aneurysm	
Mean ± SD	6.5 ± 4.1
3-4 mm	715 (37.7)
5-6 mm	481 (25.4)
7-9 mm	392 (20.7)
10-24 mm	294 (15.5)
≥25 mm	14 (0.7)
Location of aneurysm	
MCA	643 (33.9)
AComA	340 (17.9)
ICA	220 (11.6)
IC-PComA	378 (19.9)
BA	165 (8.7)
VA	50 (2.6)
Other	100 (5.3)

Abbreviations: AComA = anterior communicating artery; BA = basilar artery; ICA = internal carotid artery; IC-PComA = internal carotid-posterior communicating artery; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage; VA = vertebral artery.
Values for age and mean size of aneurysms are presented as mean ± SD; other values are presented as raw numbers (%).

Table 2 Aneurysm characteristics

Characteristic	
No. of aneurysms	2,227
Age, y	74.3 ± 3.9
≥80	239 (10.7)
Female sex	1,651 (74.1)
History of SAH	43 (1.9)
Family history of SAH	225 (10.1)
Smoking	183 (8.2)
Multiplicity	607 (27.3)
Hypertension	1,216 (54.6)
Ruptured aneurysms	70 (3.1)
Daughter sac	432 (19.4)
Surgical/endovascular treatment	532 (23.9)
Size of aneurysm	
Mean ± SD	6.2 ± 3.9
3-4 mm	945 (42.4)
5-6 mm	547 (24.6)
7-9 mm	413 (18.6)
10-24 mm	308 (13.8)
≥25 mm	14 (0.6)
Location of aneurysm	
MCA	771 (34.6)
AComA	374 (16.8)
ICA	275 (12.4)
IC-PComA	438 (19.7)
BA	189 (8.5)
VA	59 (2.6)
Other	121 (5.4)

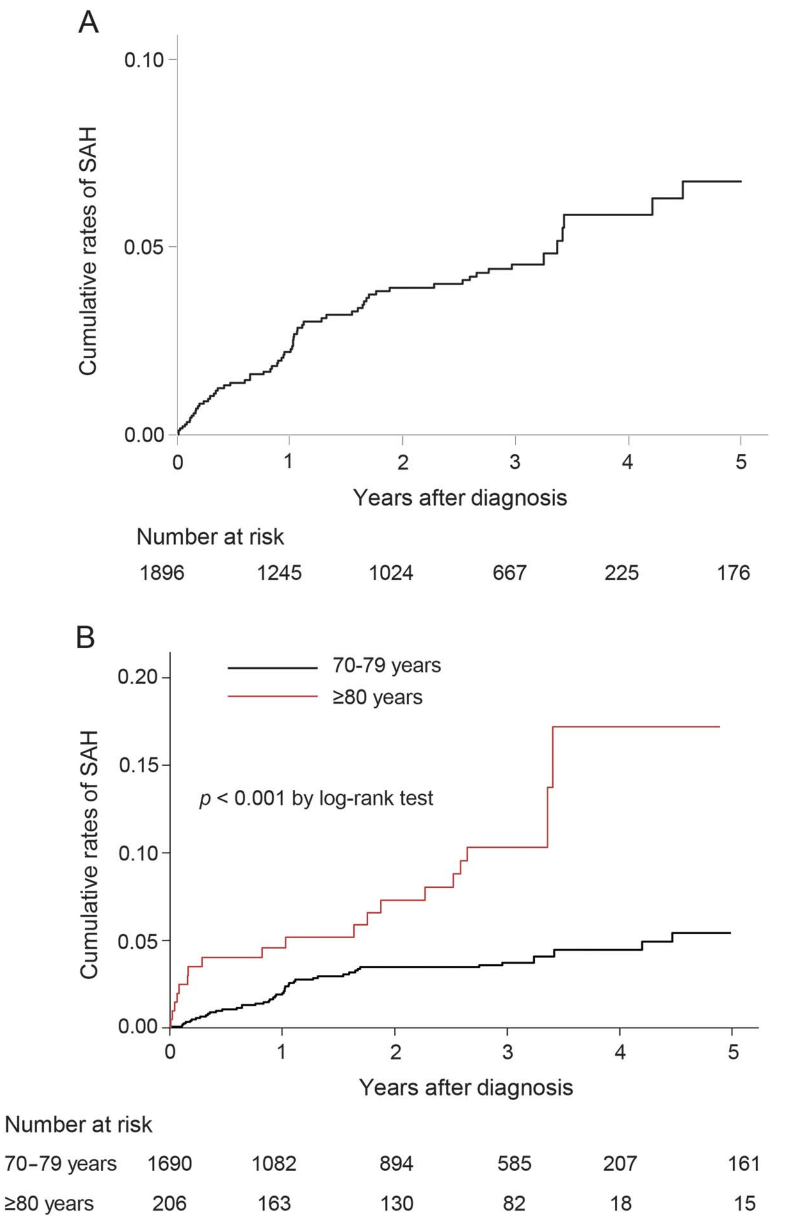
Abbreviations: AComA = anterior communicating artery; BA = basilar artery; ICA = internal carotid artery; IC-PComA = internal carotid-posterior communicating artery; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage; VA = vertebral artery.
Values for age and mean size of aneurysms are presented as mean ± SD; other values are presented as raw numbers (%).

The mean aneurysm size was 6.2 ± 3.9 mm. Tables 1 and 2 show the patient and aneurysm characteristics in this investigation.

Incidence of UCA rupture. The median (interquartile range) and mean follow-up period were 990 (103–1,115) and 802.7 days, respectively. Sixty-eight patients (3.6%) experienced SAH during the follow-up period and the overall annual rupture risk for these cohorts was 1.6% (68 SAHs/4,167 patient-years) (95% confidence interval [CI], 1.3–2.1). Additional 2 cases with multiple aneurysms experienced SAH not caused by the represented aneurysms, which were excluded from the patient-based analysis. The cumulative rate of SAH for all patients was 3.8% (95% CI, 2.9–4.9) at 2 years after diagnosis, and 6.3% (95% CI, 4.6–8.5) at 5 years after diagnosis (figure 1A). In addition, the Kaplan-Meier curve analyzed according to age showed that the cumulative rates of SAH in patients older than 80 years were higher than in those of patients aged 70 to 79 years ($p < 0.001$) (figure 1B). A total of 191 patients died during follow-up in this study: 46 patient deaths were related to SAH and 145 patient deaths were not SAH-related.

Risk factors for UCA rupture. Results of a univariable and multivariable analysis of factors related to UCA

Figure 1 Kaplan-Meier curves for all patients and for patients in 2 groups



(A) Kaplan-Meier curve showing the cumulative rates of SAH for all patients. (B) Kaplan-Meier curve showing the cumulative rates of SAH for patients in 2 groups according to age: 70–79 years, and 80 years or older. SAH = subarachnoid hemorrhage.

rupture per patient are summarized in table 3. Patients 80 years or older (hazard ratio [HR], 2.02; 95% CI, 1.16–3.49, $p = 0.012$), aneurysms 7 mm or larger (HR, 3.08; 95% CI, 1.35–7.03, $p = 0.007$ for 7–9 mm; HR, 7.82; 95% CI, 3.60–16.98, $p < 0.001$ for 10–24 mm; and HR, 43.31; 95% CI, 12.55–149.42, $p < 0.001$ for ≥25 mm), and IC-PComA aneurysms (HR, 2.45; 95% CI, 1.23–4.88, $p = 0.011$) were risk factors for UCA rupture in a multivariable analysis. Although female sex, multiplicity, and BA aneurysm were significant risk factors by the univariable analysis, they did not reach statistical significance by the multivariable analysis. The influence of difference among the 3 cohorts did not have statistical significance on rupture risk.

DISCUSSION The prevalence of both unruptured and ruptured aneurysms increases with age,[5,6] and this tendency is of peculiar note given the recent trends in population aging. It is important to stratify the risks of UCA rupture exclusively in elderly patients and to effectively perform preventive surgical treatment for the patients who are at a high risk of rupture. All 3 studies that we used for this pooled analysis were representative of large-scale studies in Japan; we evaluated the risk factors for UCA rupture exclusively in elderly patients in the largest prospective study.

An aneurysm size of 7 mm or larger was an independent predictor for aneurysm rupture in elderly patients according to the multivariable analysis in this investigation. Many reports also showed that aneurysm size was one of the most important factors in determining risk of subsequent aneurysm rupture.[7,8] UCAS Japan reported that there was a significant positive correlation between the patient's age and the aneurysm size: aneurysms 7 mm or larger were found in 32.6% of patients aged 70 to 79 years and in 39.7% of patients aged 80 years or older.[1] The cumulative risk of aneurysm growth at 1, 3, 5, and 7 years was reported to be 2.8%, 7%, 15.3%, and 21.8%, respectively, in patients aged 70 years or older.[6] In addition, it was demonstrated that the annual rupture risk after growth was 18.5% per person-year.[9] These data indicate the dynamic nature of UCAs in elderly patients, and thus careful observation is also warranted even in elderly patients.

This pooled analysis demonstrated that, for the aneurysm site, only the IC-PComA aneurysm was a significant risk factor for UCA rupture in elderly patients. BA aneurysms had an increased risk of aneurysm rupture according to the univariable analysis. In UCAS Japan, the aneurysms most prone to rupture were located in the AComA and IC-PComA.[1] UCAS Japan also reported that the aneurysms located in BA, VA, and IC-PComA were significantly larger than those in middle cerebral artery, AComA, ICA, and others and that elderly patients had significantly more posteriorly located aneurysms compared with nonelderly patients.[1] The difference in the distribution of aneurysms regarding size and age may explain why only IC-PComA aneurysms remained as a significant predictor of rupture in this pooled analysis, which was limited to elderly patients.

Age itself has been reported to be one of the risks for UCA rupture.[8] The annual rupture rate of UCAs in this study is higher than that in other reports for general Japanese and non-Japanese populations.[1,7,10]

Table 3 Risk factors associated with rupture: Univariable and multivariable Cox proportional-hazard analysis per patient

Risk factor	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*p* Value	Hazard ratio (95% CI)	*p* Value
Age ≥80 y	3.05 (1.81–5.14)	<0.001	2.02 (1.16–3.49)	0.012
Female sex	1.89 (1.01–3.53)	0.05	1.54 (0.80–2.97)	0.20
History of SAH	2.26 (0.71–7.19)	0.17	1.45 (0.44–4.83)	0.54
Family history of SAH	0.68 (0.25–1.86)	0.45		
Smoking	0.97 (0.39–2.42)	0.96		
Multiplicity	2.10 (1.23–3.60)	0.007	1.56 (0.88–2.74)	0.13
Hypertension	1.13 (0.70–1.82)	0.63		
Daughter sac	1.61 (0.94–2.77)	0.08	1.07 (0.61–1.89)	0.81
Size of aneurysm				
3–4 mm	Reference		Reference	
5–6 mm	1.28 (0.48–3.44)	0.62	1.16 (0.43–3.15)	0.77
7–9 mm	3.94 (1.76–8.84)	0.001	3.08 (1.35–7.03)	0.007
10–24 mm	10.54 (5.02–22.16)	<0.001	7.82 (3.60–16.98)	<0.001
≥25 mm	45.93 (14.04–150.28)	<0.001	43.31 (12.55–149.42)	<0.001
Location of aneurysm				
MCA	Reference		Reference	
AComA	1.65 (0.75–3.62)	0.21	1.83 (0.82–4.10)	0.14
ICA	0.78 (0.25–2.39)	0.66	0.70 (0.23–2.17)	0.54
IC-PComA	3.25 (1.65–6.39)	0.001	2.45 (1.23–4.88)	0.011
BA	3.09 (1.41–6.77)	0.005	1.84 (0.82–4.13)	0.14
VA	1.61 (0.36–7.14)	0.53	1.22 (0.27–5.45)	0.80
Other	0.45 (0.06–3.47)	0.45	0.46 (0.06–3.51)	0.45
Cohorts				
UCAS Japan	Reference		Reference	
UCAS II	0.63 (0.25–1.58)	0.32	0.84 (0.33–2.15)	0.72
Jikei	1.30 (0.52–3.25)	0.57	1.09 (0.41–2.92)	0.87

Abbreviations: AComA = anterior communicating artery; BA = basilar artery; CI = confidence interval; ICA = internal carotid artery; IC-PComA = internal carotid–posterior communicating artery; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage; UCAS = Unruptured Cerebral Aneurysm Study; VA = vertebral artery.

In addition, our pooled analysis revealed that patient age of 80 years or older was an independent risk factor for aneurysm rupture in our study that exclusively comprised patients 70 years or older, and the cumulative rates of SAH in patients 80 years or older were significantly higher than those in patients 70 to 79 years in this investigation. The prognosis of elderly patients with ruptured aneurysm is poor,[2] but it has also been revealed that patients' age was a strong predictor of surgical outcomes and major complication following endovascular UCA treatment.[7,11] In the analysis of endovascular treatment of UCAs in elderly patients, the prevalence of perioperative morbidity was reported to be 5.0%.[12] The paradoxical relationship between the relatively high annual and cumulative risk of UCA rupture and the risk for surgical treatment of UCAs makes the management of elderly patients with UCAs more difficult. When deciding therapeutic strategy for elderly patients with UCAs, we have to consider various factors, such as the difference between chronological age and physiologic age, the difference in life expectancy between patients aged 70 to 79 years and those older than 80 years, and one's view of life and death. The indication of treatment for UCAs in elderly patients should be determined individually.

It was reported that female sex was a significant risk factor for rupture of UCAs.[8] UCAS Japan also demonstrated that female sex was a predictor for rupture although the statistical value was marginal (p = 0.05).[1] Our pooled data did not indicate that female sex was a significant predictor for rupture in the

Table 4 Baseline characteristics of patients with surgical/endovascular treatment and with observation

	Surgical/endovascular treatment (n = 489)	Observation (n = 1,407)	*p* Value
Age, y	72.5 ± 2.3	74.9 ± 4.2	<0.001
≥80 y	8 (1.6)	198 (14.1)	<0.001
Female sex	380 (77.7)	1,003 (71.3)	0.006
History of SAH	6 (1.2)	28 (2.0)	0.27
Family history of SAH	69 (14.1)	107 (7.6)	<0.001
Smoking	46 (9.4)	108 (7.7)	0.23
Multiplicity	67 (13.7)	215 (15.3)	0.40
Hypertension	281 (57.5)	736 (52.3)	0.049
Ruptured aneurysms	0 (0.0)	68 (4.8)	<0.001
Daughter sac	143 (29.2)	249 (17.7)	<0.001
Size of aneurysm			
Mean ± SD	7.2 ± 4.6	6.2 ± 3.8	<0.001
3–4 mm	135 (27.6)	580 (41.2)	
5–6 mm	131 (26.8)	350 (24.9)	
7–9 mm	123 (25.2)	269 (19.1)	<0.001
10–24 mm	96 (19.6)	198 (14.1)	
≥25 mm	4 (0.8)	10 (0.7)	
Location of aneurysm			<0.001
MCA	196 (40.1)	447 (31.8)	
AComA	94 (19.2)	246 (17.5)	
ICA	46 (9.4)	174 (12.4)	
IC-PComA	104 (21.3)	274 (19.5)	
BA	23 (4.7)	142 (10.1)	
VA	7 (1.4)	43 (3.1)	
Other	19 (3.9)	81 (5.8)	

Abbreviations: AComA = anterior communicating artery; BA = basilar artery; ICA = internal carotid artery; IC-PComA = internal carotid–posterior communicating artery; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage; VA = vertebral artery.
Values for age and mean size of aneurysms are presented as mean ± SD; other values are presented as raw numbers (%). The *p* value for mean age of the patients and for mean size of the aneurysms was calculated using Student *t* test. The *p* value for patients 80 years or older, female sex, history of SAH, family history of SAH, smoking, multiplicity, hypertension, ruptured aneurysms, daughter sac, distribution of the largest dimension of the aneurysm, and location of the aneurysm was calculated with a χ^2 test.

multivariable analysis. In UCAS Japan, where the mean patient age was 62.5 ± 10.3 years, the prevalence of aneurysms larger than 7 mm was higher in females than in males ($p = 0.04$, Pearson χ^2 test).[1] This might partly explain the higher incidence of SAH in nonelderly, female patients because larger aneurysms are more prone to rupture.[7] However, there was no significant difference in the prevalence of aneurysms larger than 7 mm between women and men in this study, where the mean age of patients was 74.3 ± 3.9 years ($p = 0.40$, Pearson χ^2 test). This is probably one of the reasons why female sex disappeared as a risk factor for aneurysm rupture in elderly patients with UCAs in our pooled analysis. Our analysis did not identify the shape of the aneurysm as a risk factor that influences rupture unlike UCAS Japan.[1] This might be caused by inadequate statistical power.

There are some limitations in this study. First, the population in this pooled analysis was limited to Japanese patients with UCAs. The rate of UCA rupture in the Japanese population has been reported to be high, and the Japanese population is an independent predictor of aneurysm rupture according to previously reported pooled data.[8] Therefore, the result in this report should be applied with caution to elderly patients with UCA in other populations, because the geographical region is related to the risk of rupture. Ideally, it is better to stratify the risk factors for UCA rupture in elderly patients in each population. Second, there is a case-selection bias in this study. The baseline characteristics of patients with surgical/endovascular treatment and with observation are shown in table 4. The patients with smaller and BA aneurysms were prone to be treated conservatively, and ones with family history of SAH and aneurysms with daughter sacs tended to be surgically treated. Also, the difference in the frequency of surgical intervention between patients aged 70 to 79 years and patients older than 80 years could be a cause of the bias associated with age. It is a crucial perception that multivariable analysis in this study revealed that patient age 80 years or older was a significant risk for UCA rupture regardless of the age-related bias. These types of biases are thought to be unavoidable because of comorbidity, physiologic age of the patients, and the wishes of the patients and their families. Third, the number of variables investigated in this study is relatively small because we assessed the variables common to 3 prospective studies. To determine the influence of comorbid diseases on the risk of UCA rupture in elderly patients, hyperlipidemia, diabetes mellitus, polycystic kidney disease, cerebral infarction, ischemic heart disease, and malignant tumor should be investigated. In addition, it is important to investigate the medications administered to elderly patients with UCAs and evaluate the risks and benefits of these medications for UCAs.

AUTHOR CONTRIBUTIONS

T.H., I.D., and A.M. were responsible for the study design and study concept. All authors contributed to data interpretations. T.H., S.T., and T.N. were responsible for data analysis. K.T., Y.S., K.H, Y.M., T.I., H.T., T.K., and A.M. collected the data. T.H. drafted the manuscript.

STUDY FUNDING

UCAS Japan was funded by the Ministry of Health, Labor and Welfare of Japan and others (UCAS Japan UMIN-CTR C000000418). UCAS II was funded by the Ministry of Health, Labor and Welfare of Japan (UCAS II UMIN-CTR C000000420).

DISCLOSURE

T. Hishikawa, I. Date, K. Tokunaga, S. Tominari, K. Nozaki, Y. Shiokawa, and K. Houkin report no disclosures relevant to the manuscript. Y. Murayama reports grants from Stryker, Siemens, and NTT docomo and personal fees from Stryker and Asahi Intecc, outside the submitted work. T. Ishibashi reports grants from Stryker, Siemens, and NTT docomo and personal fees from Stryker, outside the submitted work. H. Takao reports grants from Stryker, Siemens, and NTT docomo, outside the submitted work. T. Kimura, T. Nakayama, and A. Morita report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received March 15, 2015. Accepted in final form July 28, 2015.

REFERENCES

1. Morita A, Kirino T, Hashi K, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. N Engl J Med 2012;366:2474–2482.
2. Hishikawa T, Takasugi Y, Shimizu T, et al. Cerebral vasospasm in patients over 80 years treated by coil embolization for ruptured cerebral aneurysms. Biomed Res Int 2014;2014:253867.
3. Ishibashi T, Murayama Y, Urashima M, et al. Unruptured intracranial aneurysms: incidence of rupture and risk factors. Stroke 2009;40:313–316.
4. Morita A; UCAS II Study Group. Management outcomes in the Unruptured Cerebral Aneurysm Study II (UCAS II): interim report—quest for standards and current status in Japan. J Neurosurg 2011;20:484–490.
5. Inagawa T. Trends in incidence and case fatality rates of aneurysmal subarachnoid hemorrhage in Izumo City, Japan, between 1980–1989 and 1990–1998. Stroke 2001;32:1499–1507.
6. Kubo Y, Koji T, Kashimura H, Otawara Y, Ogawa A, Ogasawara K. Female sex as a risk factor for the growth of asymptomatic unruptured cerebral saccular aneurysms in elderly patients. J Neurosurg 2014;121:599–604.
7. Wiebers DO, Whisnant JP, Huston J III, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003;362:103–110.
8. Wermer MJH, van der Schaaf IC, Algra A, Rinkel GJE. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke 2007;38:1404–1410.
9. Inoue T, Shimizu H, Fujimura M, Saito A, Tominaga T. Annual rupture risk of growing unruptured cerebral aneurysms detected by magnetic resonance angiography. J Neurosurg 2012;117:20–25.
10. Juvela S, Poussa K, Lehto H, Porras M. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. Stroke 2013;44:2414–2421.
11. Khosla A, Brinjilji W, Cloft H, Lanzino G, Kallmes DF. Age-related complications following endovascular treatment of unruptured intracranial aneurysms. Am J Neuroradiol 2012;33:953–957.
12. Sturiale CL, Brinjikji W, Murad MH, Lanzino G. Endovascular treatment of intracranial aneurysms in elderly patients: a systematic review and meta-analysis. Stroke 2013;44:1897–1902.