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
METHODS Patients. Participants enrolled in this study included all patients aged 70 years or older in 3 large prospective cohort studies in Japan. 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. 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 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 the diagnosis was made on the basis of computer images of UCAs decreases when under 3 mm in diameter with low-tesa 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 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. 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. 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.

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.
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

### 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) |       |

### 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 (54.8)     |       |
| Ruptured aneurysms | 70 (3.1) |       |
| Daughter sac   | 432 (19.4)       |       |
| Surgical/endovascular treatment | 532 (23.9) |       |

**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 (%).
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 \( \geq 25 \) 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, 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. 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. 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. In addition, it was demonstrated that the annual rupture risk after growth was 18.5% per person-year. 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. 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. 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. The annual rupture rate of UCAs in this study is higher than that in other reports for general Japanese and non-Japanese populations.
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, but it has also been revealed that patients’ age was a strong predictor of surgical outcomes and major complication following endovascular UCA treatment. In the analysis of endovascular treatment of UCAs in elderly patients, the prevalence of perioperative morbidity was reported to be 5.0%. 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. UCAS Japan also demonstrated that female sex was a predictor for rupture although the statistical value was marginal ($p = 0.05$). Our pooled data did not indicate that female sex was a significant predictor for rupture in the

| 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    | 2.28 (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

| Size of aneurysm | Reference | Hazard ratio (95% CI) | p Value | Hazard ratio (95% CI) | p Value |
|------------------|-----------|----------------------|---------|----------------------|---------|
| 3–4 mm           | Reference |                       |         |                      |         |
| 5–6 mm           | 1.28 (0.48–3.44) | 0.82 | 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

| Location of aneurysm | Reference | Hazard ratio (95% CI) | p Value | Hazard ratio (95% CI) | p Value |
|----------------------|-----------|----------------------|---------|----------------------|---------|
| MCA                  | 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

| Cohorts | Reference | Hazard ratio (95% CI) | p Value | Hazard ratio (95% CI) | p Value |
|---------|-----------|----------------------|---------|----------------------|---------|
| UCAS Japan | Reference | 0.63 (0.25–1.58) | 0.32 | 0.84 (0.33–2.15) | 0.72 |
| UCAS II | 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.
ruptured aneurysms, daughter sac, distribution of the largest dimension of the aneurysm, older, female sex, history of SAH, family history of SAH, smoking, multiplicity, hypertension, 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 mean age of the 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 χ² test.

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.

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 χ² 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 χ² 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.

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