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Original

Association of Therapeutic Intervention With Activities of Daily Living in Patients With Unruptured Intracranial Aneurysms During the Follow-up Period: Propensity Score-Matched Cohort Analysis

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Background: We sought to evaluate the clinical outcomes and association of therapeutic intervention with activities of daily living (ADL) in patients with unruptured intracranial aneurysms (UIAs) during follow-up.
Methods: Study cohort comprised 346 patients (mean age: 65.9 years, median follow-up length: 63.5 months) with UIA ≥ 2 mm, and was retrospectively analyzed. ADL decline was defined as deterioration of the modified Rankin Scale.
Results: ADL decline occurred in 46 patients (13.3%, annual incidence rate [AI]: 2.5%, excluding deaths: 22 patients, 6.4%). Twenty-four deaths (6.9%, annual mortality rate: 1.3%) and eight UIA ruptures (2.3%, AI: 0.43%) were observed. The propensity score-matched cohort analysis revealed that intervention corresponded to a lower hazard ratio (HR) for ADL decline in patients with UIA ≥ 5 mm (HR, 0.24; P = 0.028) and eliminated the risk of aneurysm rupture (P < 0.0001). A significantly higher HR (HR, 4.73; P = 0.005) for ADL decline in patients aged ≥ 70 years was also demonstrated.
Conclusions: Therapeutic intervention could prevent UIA rupture and might not contribute to reducing ADL in patients with UIA ≥ 5 mm. In elderly patients, ADL declined; however, therapeutic intervention might not be a major cause.

Keywords: unruptured intracranial aneurysm, activities of daily living, risk factors, propensity score-matched cohort analysis

Introduction

Subarachnoid hemorrhage (SAH) from a ruptured intracranial aneurysm (IA) often leads to catastrophic events and a poor prognosis.[1] Preventing IAs from rupturing should be done by managing unruptured intracranial aneurysms (UIAs). Screening UIAs is often recommended in people with high risk of aneurysm formation and rupture.[2] Currently, UIAs are diagnosed via modern imaging procedures. However, the management of UIAs remains controversial. To elucidate the natural history of UIAs and the risk of treatment, prospective studies were

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carried out and reported using rupture of UIA as an endpoint.[3-9] During follow-up of UIAs, not only the rupture of UIAs, but other events as well could degrade patients' activities of daily living (ADL). The deterioration of ADL in patients with UIA and the association of therapeutic intervention with ADL decline have not been sufficiently investigated so far. The present retrospective analysis aimed to evaluate ADL decline, mortality, and aneurysm rupture during follow-up of patients with UIA and associations of mainly therapeutic intervention, size of UIA, and age of the patients with the outcomes using a propensity score (PS)-matched cohort to eliminate bias.

To the best of our knowledge, main object of the present study has not been investigated previously.

Patients and Methods

Patients

This retrospective cohort study used a prospectively accumulated database of 424 consecutive patients diagnosed with at least one saccular UIA (≥2 mm in size) during their follow-up period from April 2007 through December 2016 at Tokyo Women's Medical University Medical Center East (TMCE). This study was approved by our institutional review board (No. 3767). Patients with mRS 3-5 at the beginning of follow-up, traumatic or mycotic aneurysms, an IA with intervention before beginning follow-up, an aneurysmal dilatation strongly suspected as an infundibular dilatation, a dissecting aneurysm, or a UIA with arteriovenous malformation were excluded.

UIA basic management

For patients with UIA <5 mm in size, we recommended observation and meticulously followed up with radiologic exams and management of blood pressure and smoking cessation in the outpatient clinic of our hospital.[10] For patients with UIA ≥5 mm in size, we selected interventions of clipping or coiling after carefully considering the potential risks and benefits of treatment. The patients finally decided whether to undergo intervention or observation and were informed that they could change from observation to intervention at any time. Patients with and without intervention periodically came to our outpatient clinic to undergo radiologic exams for UIA and evaluations of patient's condition for follow-up.[10] For patients lost to follow-up for more than one year, a letter or a telephone survey was conducted to confirm the details of the patient's condition and to encourage follow-up regarding their IAs.

The management includes not only direct interventions (clipping or coiling) but observation by periodic radiological exams. Antihypertensive treatment and medically-guided smoking cessation were recommended to all hypertensive and active-smoker patients.

Data collection

The database was constructed for all patients considering multiple variables such as sex, age, hypertension (HT), diabetes mellitus (DM), dyslipidemia (DL), smoking, past medical history of SAH, family history of IA, aneurysmal factors (size and location of the largest UIA and multiplicity in each patient) investigated by magnetic resonance imaging (MRI), computed tomography (CT) angiography, or digital subtraction angiography (DSA) at the beginning of follow-up; mRS, and the causes and the day of mRS changes from clinical records.

Clinical outcomes

The primary outcome was ADL decline, and the secondary outcomes were overall survival (OS) and UIA rupture. For each outcome, failures were regarded as events and any others as censored. The date of each patient's visit to hospital for UIA was designated as the initial day for follow-up. ADL decline was defined as deterioration of mRS from 0-2 to 3-6. The ADL decline time was defined as the interval between the initial day and ADL decline due to any causes. OS time was defined as the interval between the initial day and death due to any cause. The rupture time was defined as the interval between the initial day and rupture of the UIAs followed in TMCE.

PS-matching

There were considerable biases between non-intervention and intervention groups, between small size (UIA size <5 mm) and large size (UIA size ≥5 mm) groups, and between age <70 years and age ≥70 years groups. Therefore, a case-matched study was performed

Table 1. Characteristics of the study cohort.

Evaluated characteristics	Number of cases
Total number of analyzed patients	346 (100%)
Female gender	238 (68.8%)
Mean (± SD) age (years)	65.9 ± 11.3
Age < 70 years	194 (56.1%)
Family history of intracranial aneurysm	76 (22.0%)
Smoking:	
- current	68 (19.7%)
- former	74 (21.4%)
- total	142 (41.0%)
Presence of arterial hypertension	202 (58.4%)
Presence of diabetes mellitus*	41 (12.2%)
Presence of dyslipidemia**	139 (40.5%)
Multiplicity of intracranial aneurysms	50 (14.5%)
Past history of SAH from other aneurysm	7 (2.0%)
Mean (± SD) aneurysm size (mm)	5.4 ± 4.0
Aneurysm size subgroups (mm):	
- 2-4	188 (54.3%)
- 5-6	79 (22.8%)
- 7-9	45 (13.0%)
- 10-24	31 (9.0%)
- ≥ 25	3 (0.9%)
Aneurysm location subgroups:	
- MCA	102 (29.5%)
- AComA	51 (14.7%)
- ICA	66 (19.1%)
- ICA-PComA	66 (19.1%)
- BA tip and BA-SCA	27 (7.8%)
- VA-PICA	12 (3.5%)
- Other	22 (6.4%)
Intervention of the initially observed aneurysm:	
- microsurgical clipping	74 (21.4%)
- endovascular coiling	30 (8.7%)
- total	104 (30.1%)
Events of interest during observational follow-up:	
- ADL decline	46 (13.3%)
- rupture of the observed untreated aneurysm	8 (2.3%)
- death of the patient	24 (6.9%)

SD, standard deviation; SAH, subarachnoid hemorrhage; MCA, middle cerebral artery; AComA, anterior communicating artery; ICA, internal carotid artery; PComA, posterior communicating artery; BA, basilar artery; SCA, superior cerebellar artery; VA, vertebral artery; PICA, posterior inferior cerebellar artery; ADL, activities of daily living.

*Assessed in 337 patients. ** Assessed in 343 patients.

by one of the authors (Y.S.), who did not participate in other aspects of this study and was blinded to final outcomes. Patients were selected by employing the PS-matching method with a greedy 1-to-1 digit-matching algorithm for clinical factors (age, sex, family history of IA, smoking, HT, DM, DL, location of UIA, and size of UIA; age and size were excluded in age and size matchings, respectively).[11, 12]

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as mean ± SD. In comparison of patient characteristics in terms of intervention, UIA size (<5 mm or ≥5 mm), and age (<70 years or ≥70 years), we used Fisher's exact test or a χ^2 test to assess categorical variables, and Student's t test or a Wilcoxon test for continuous variables, as appropriate. The Kaplan−Meier method was used for ADL decline, OS, and UIA rupture in PS-matched cohorts in terms of intervention and UIA size.

The average annual incidence of the outcomes was calculated as the number of patients with the outcomes divided by the number of person-years of the follow-up periods.

A P-value <0.05 was considered as statistically significant. All statistical analyses were performed by the author (Y.S.) using SAS software version 9.4 (SAS; Cary, NC, USA).

Results

Population characteristics

A total of 408 patients were recruited according to the aforementioned criteria from 424 consecutive patients harboring untreated UIA on our database. However, 62 patients were excluded because of insufficiency of mRS information. Therefore, 346 patients were enrolled and analyzed in this study (**Table 1**).

Median follow-up time was 63.5 months (range: 2 - 193). Mean age (± SD) was 65.9 ± 11.3 years old (range: 26 - 87). In total, 68.8% of the patients were women. Family history of IA was found in 22.0% of all patients. Smoking (current and former) (n = 142, 41.0%), HT (n = 202, 58.4%), DM (n = 41, 12.2%) and DL (n = 139, 40.5%) were noted (**Table 1**).

Patients with UIA <5 mm in size were counted in 54.3% of all patients. 102 patients (29.5%) had UIAs located at the middle cerebral artery. 29 of 66 patients with UIAs in the internal carotid artery had internal carotid cavernous sinus aneurysms.

Management of patients during follow-up

It was confirmed that in 202 patients with hypertension, at least 111 patients (55.0%) continued to receive antihypertensive therapy during the follow-up period. We usually advised the patients to receive antihypertensive

Table 2. Causes of ADL decline during follow-up of patients with unruptured intracranial aneurysms.

Cause of acquired disability	Number of cases
Aneurysm-related:	
- rupture	5 (10.8%)
- surgical intervention	3 (6.5%)
- total	8 (17.4%)
Aneurysm-unrelated:	
- cancer	9 (19.6%)
- stroke (other than the observed aneurysm rupture)	5 (10.8%)
- cardiovascular disease	4 (8.7%)
- infection	3 (6.5%)
- aging	3 (6.5%)
- dementia	2 (4.3%)
- chronic kidney disease	2 (4.3%)
- other	10 (21.7%)
- total	38 (82.6%)
Total	46 (100%)

ADL, activities of daily living.

therapy if indicated. Sixty-eight patients (19.7%) were current smokers at the beginning of the follow-up. We also advised smokers to quit smoking.

Clinical outcomes

ADL decline during follow-up was noted in 46 patients (13.3%) and was encountered with an average annual incidence of 2.5% during 1,838 patient-years. ADL decline excluding deaths was noted in 22 patients (6.4%), with an average annual incidence of 1.2% during 1,838 patient-years.

In only 8 of 46 patients, ADL decline was attributed to the aneurysm-related causes (**Table 2**), namely rupture of the observed aneurysm (5 cases) and surgical intervention (3 cases); among other reasons, cancer was the most common (9 cases).

Overall, 24 patients (6.9%) died during follow-up corresponding to the average annual mortality rate of 1.3% during 1,881 patient-years. Cancer was the most common cause of death (8 cases). Out of 8 cases in total, the rupture of observed untreated aneurysm resulted in deterioration of the mRS score from 0-2 to 3-6 in 5 patients, including 4 deaths (mRS score 6).

Rupture of the observed aneurysm during follow-up was noted in 8 patients (2.3%) and was encountered with an average annual incidence of 0.43% during 1,875 patient-years. The ruptured aneurysms originated from MCA (3 cases), anterior communicating artery (AComA; 2 cases), ICA-posterior communicating artery (PComA; 1 case), and basilar artery (BA) tip (2 cases).

PS-matched cohort analysis

We compared baseline covariates between non-intervention and intervention groups, small- and large-size UIA groups, and age <70 years and age ≥70 years groups after the PS matches had been performed. Finally, 186 patients (93 patients with non-intervention and 93 patients with intervention), 212 patients (106 patients with small-size UIA and 106 patients with large-size UIA), and 212 patients (106 patients ≥70 years of age and 106 patients <70 years of age) were selected (**Supplementary Table 1 and 2**).

There was no significant difference between non-intervention and intervention groups in the probability of having no ADL decline (HR: 0.48, 95% CI: 0.21 - 1.13, P = 0.093) (**Figure 1A**) or in OS (HR: 0.36, 95% CI: 0.09 - 1.35, P = 0.13) (**Figure 1B**). The probability of rupture was significantly higher in the non-intervention group than in the intervention group (HR: N/A, P < 0.0001) (**Figure 1C**).

In analysis regarding size, there was no significant difference in the probability of no ADL decline between small- and large-size UIA groups (HR: 1.41, 95% CI: 0.67 - 2.98, P = 0.37) (**Figure 2A**). In the small-size UIA group, there was no significant difference in the probability of no ADL decline between non-intervention and intervention groups (HR: 0.23, 95% CI: 0.01 - 4.45, P = 0.33) (**Figure 2B**). In the large-size UIA group, the probability of no ADL decline was significantly higher in the intervention group (HR: 0.24, 95% CI: 0.01 - 0.81, P = 0.028) (**Figure 2C**). There was no significant difference in OS (HR: 2.85, 95% CI: 0.79 - 10.3, P = 0.11) or the probability of rupture (HR: 2.66, 95% CI: 0.27 - 26.3, P = 0.40) between small- and large-size UIA groups.

The probability of no ADL decline in age ≥70 years group was significantly lower than those in age <70 years group (HR: 4.73, 95% CI: 1.61 - 13.86, P = 0.0047) (**Figure 3A**). In age ≥70 years and <70 years groups, there was no significant difference in the probability of no ADL decline between non-intervention and intervention, respectively (HR: 0.85, 95% CI: 0.26 - 2.80, P = 0.79, **Figure 3B**; HR: 0.43, 95% CI: 0.05 - 3.54, P = 0.43, **Figure 3C**). There was no significant difference between

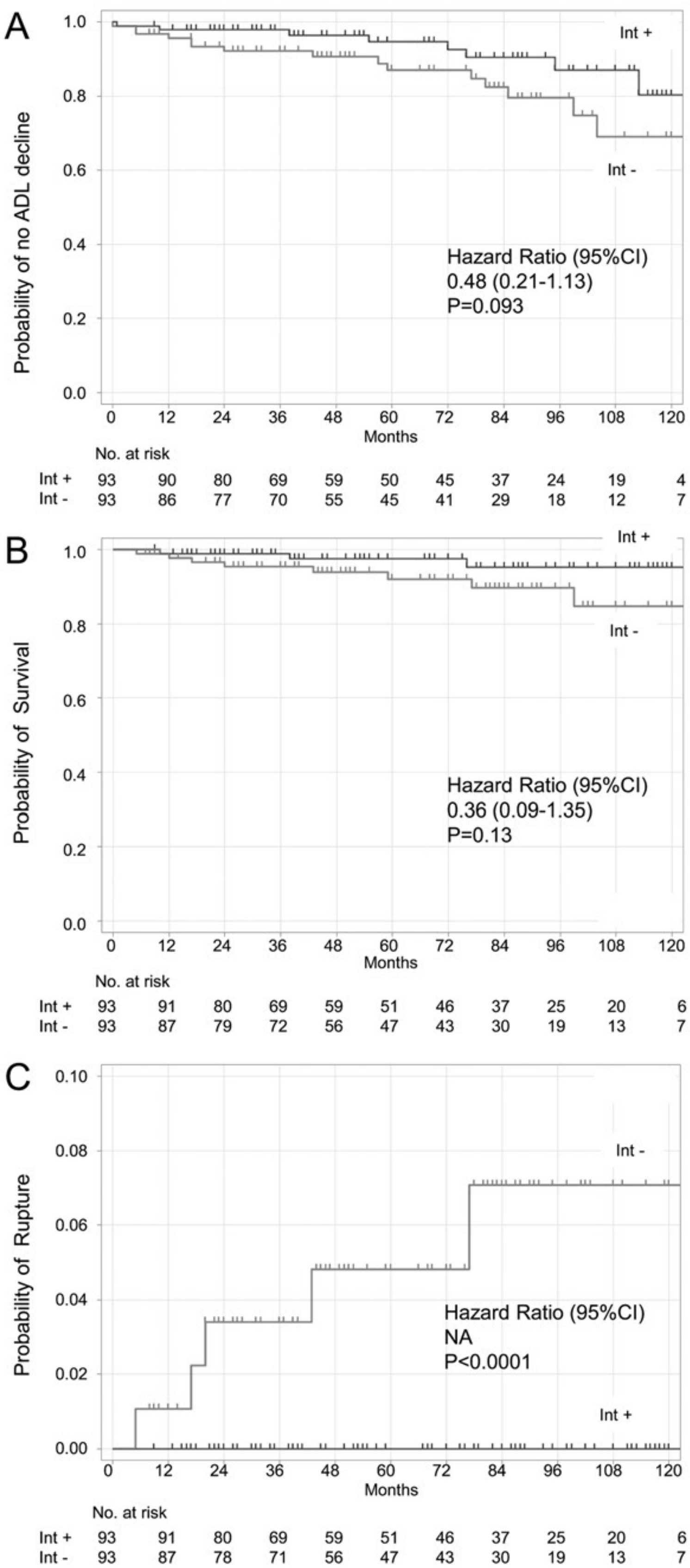

Figure 1. Probability of clinical outcomes, based on a subset of 186 PS-matched patients according to intervention, was estimated using the Kaplan–Meier method. **A**, The probability of no ADL decline. **B**, The probability of survival. **C**, The probability of rupture.

Int+, intervention group; Int-, non-intervention group.

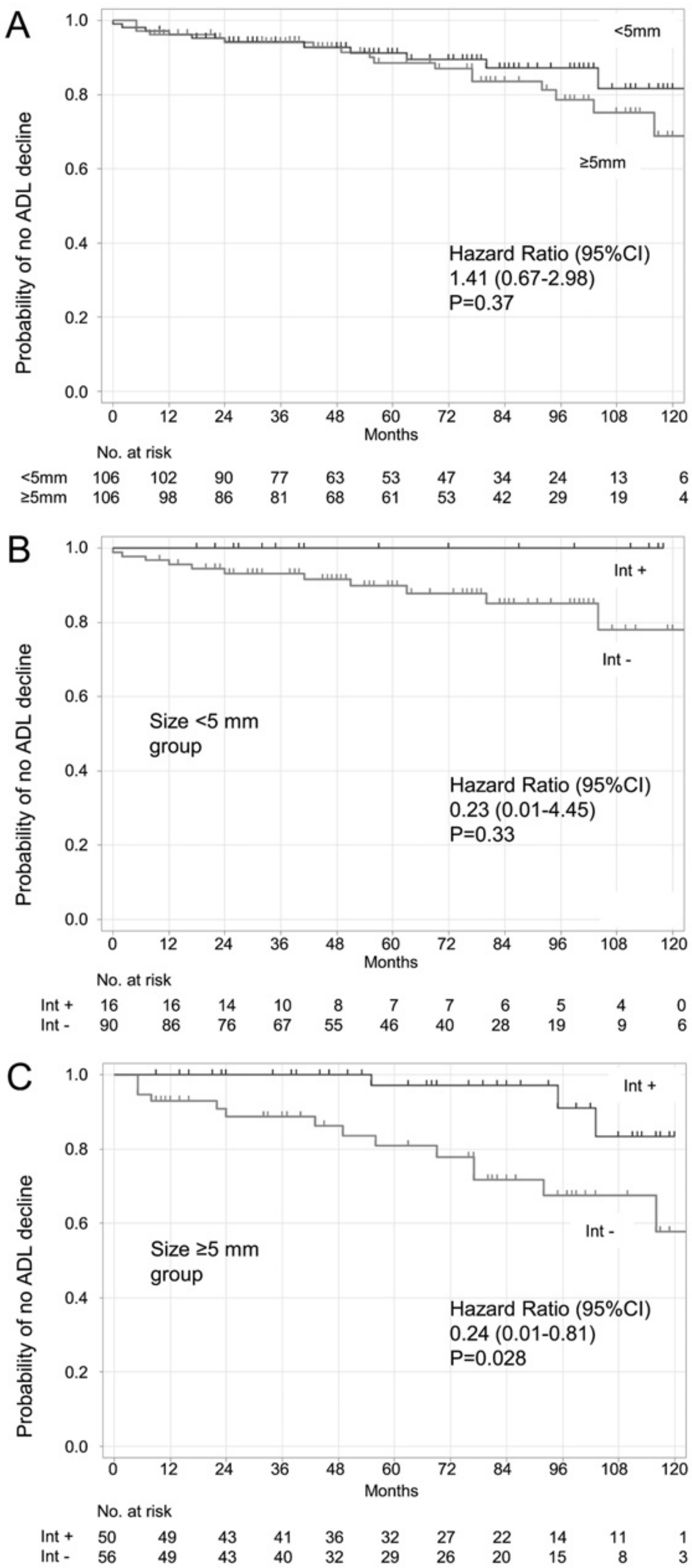

Figure 2. Probability of no ADL decline, based on a subset of 212 PS-matched patients according to size (size <5 mm group and size ≥5 mm group), was estimated using the Kaplan–Meier method. **A**, The probability of no ADL decline according to size. **B**, The probability of no ADL decline according to intervention in the 106 patients of size <5 mm group. **C**, The probability of no ADL decline according to intervention in the 106 patients of size ≥5 mm group.

Int+, intervention group; Int-, non-intervention group; <5 mm, size <5 mm group; ≥5 mm, size ≥5 mm group.

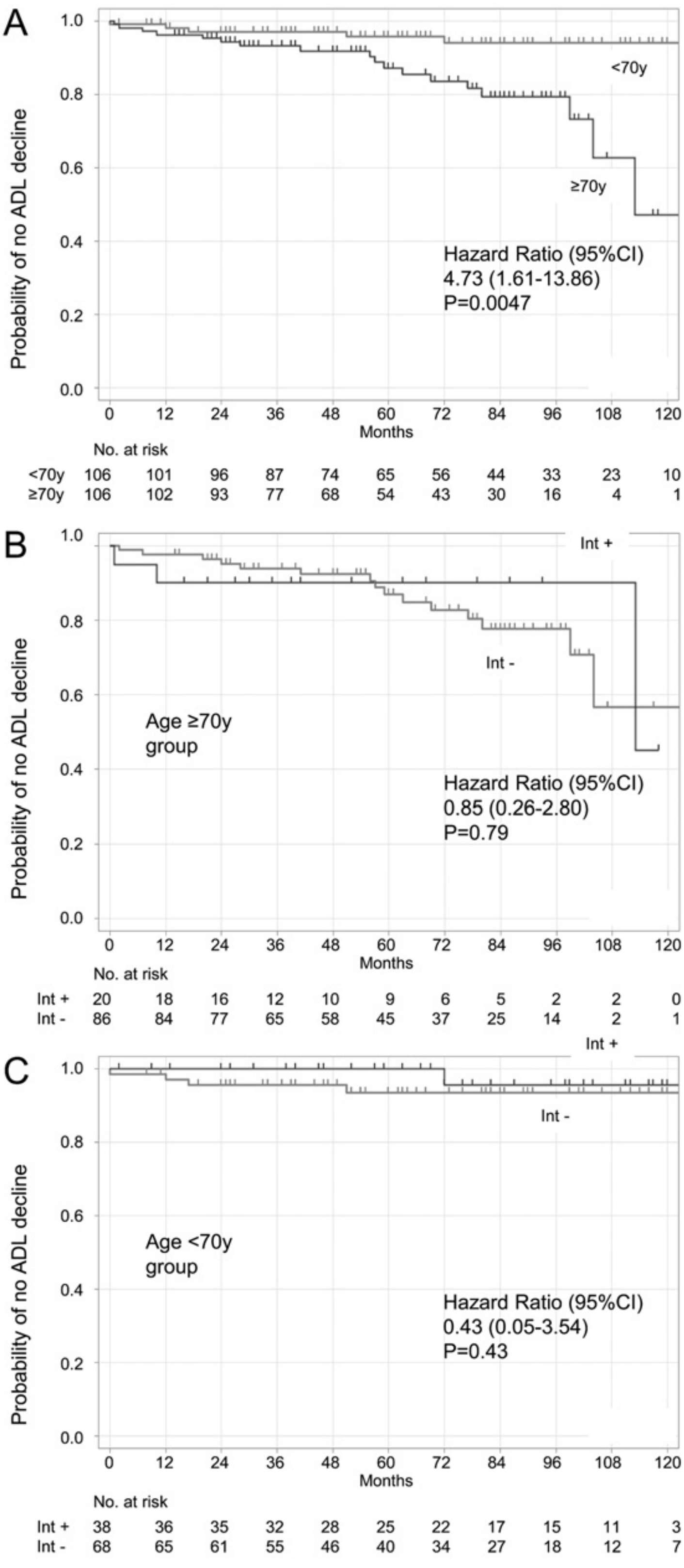

Figure 3. Probability of no ADL decline, based on a subset of 212 PS-matched patients according to age (age <70 years group and age ≥70 years group), was estimated using the Kaplan–Meier method. **A**, The probability of no ADL decline according to age. **B**, The probability of no ADL decline according to intervention in the 106 patients of age ≥70 years group. **C**, The probability of no ADL decline according to intervention in the 106 patients of age <70 years group.

Int+, intervention group; Int-, non-intervention group; <70 years, age <70 years group; ≥70 years, age ≥70 years group.

age <70 years and ≥70 years groups in the probabilities of OS (HR: 8.33, 95% CI: 0.94 - 74.03, P = 0.057) and rupture (HR: 1.06, 95% CI: 0.06 - 19.08, P = 0.97).

Discussion

In this study, we mainly evaluated ADL decline as one of the clinical outcomes of UIA patients with and without intervention during follow-up. The major findings of this study are as follows: (1) the overall annual incidence of ADL decline was 2.5% (ADL decline excluding deaths: 1.2%); (2) in our analysis of PS-matched cohorts, there was no significant difference in the probability of no ADL decline between small- and large-size UIA groups; (3) ADL decline in the large-size UIA group with intervention was significantly suppressed; (4) the probability of no ADL decline in age ≥70 years group was significantly lower than that in age <70 years group; and (5) the probability of rupture was significantly lower in patients with intervention.

In terms of risk of UIA rupture, several cohort studies have been performed.[3-9] The largest meta-analysis on UIA rupture risk (comprising six cohort studies) identified six independent risk factors for aneurysm rupture: age ≥70, a history of hypertension, previous SAH from another aneurysm, the size and site of the aneurysm, and the patient's geographical region.[13] In the Japanese population, the risk of UIA rupture was reported as higher than in other populations. Large Japanese cohort studies demonstrated 0.54 to 1.4% as the annual incidence of UIA rupture.[5-8] In our study, the overall annual incidence of UIA rupture was 0.43% in all eligible patients. The annual incidence of UIA rupture was 0.62% in the patients with observation, and no rupture was seen in those with intervention during follow-up period. Rupture could be avoided by our UIA management strategy which included not only intervention but counseling patients about lifestyle modifications, smoking cessation, and blood pressure control.

Optimal management for UIA is still controversial. In terms of direct treatment of IA, surgical clipping has been the gold standard for a long time; however, endovascular techniques have been rapidly developed. Many studies for evaluation of clinical outcomes of both surgical and endovascular treatments have been reported. Surgical clipping for UIA in a large systematic review and meta-analysis of 60 trials with 9,845 patients harboring 10,845 UIAs showed 1.7% mortality and 6.7% unfavorable outcomes, including death.[14] Another meta-analysis of 97 endovascular trials including 7,172 patients with UIAs showed 1.8% mortality and 4.7% unfavorable outcomes, including death.[15] In our study, a total of 104 patients (30.1%) were treated by surgical clipping or endovascular coiling. Clinical outcomes of patients with intervention showed 0.69% mortality and 1.6% ADL decline defined as mRS deterioration (from 0-2 to 3-6) during follow-up period. The causes of ADL decline included not only intervention (33.3%) but other clinical factors. The clinical outcomes we present were excellent in comparison to those of previous reports. We had no comparison of the outcomes between surgical clipping and endovascular coiling due to a small sample size.

Long-term survival among patients with UIA has been studied.[16, 17] In patients with untreated UIA, an annual mortality rate was reported as 3.2% (113 patients had died during 3,530 patient-years).[16] In another report, patients with untreated and treated UIA gave an annual mortality rate as 2.9% (50 patients had died during 1,702 patient-years).[17] Our study showed annual mortality as 1.5% (1,298 patient-years) in patients with untreated UIA, and 1.3% (1,881 patient-years) in those with untreated and treated UIA.

Pyysalo et al. found that patients with untreated UIAs had 50% excess long-term mortality compared with the general population.[17] UIA patients had excess mortality attributable to both aneurysm-related and -unrelated causes including a high rate of cardiovascular deaths.[16, 17] It was postulated that aneurysmal disease may be a marker for more generalized vascular disease. However, the factor causing the highest rate of death (8 patients of 24 deaths) in our study was malignancy. A relationship between IA and comorbidity is unclear. As for the higher excess mortality, selection bias should be considered because the data was based on UIA patients who did not undergo intervention and had more comorbidities associated with worse outcomes.

In a large administrative database study to evaluate long-term survival of patients with UIA who did and did not undergo clipping, it was reported that patients with untreated UIA were 30% more likely to die than those with clipped UIA.[18] Our study suggested that mortality and ADL decline in patients with untreated UIA was higher than in those with intervened UIA in PS-matched cohort analysis, although the difference was not significant. In patients with an intervened UIA ≥5 mm in size, ADL decline was significantly more suppressed than in those without intervention. We hypothesize that the patients with therapeutic intervention underwent medical check-ups before the intervention and were carefully followed up after the intervention, so that not only the prevention of rupture but also total care was more effective in avoiding ADL decline. Some diseases that reduce ADL may be pointed out earlier. ADL also tended to decline in the group that did not receive therapeutic intervention for UIAs <5 mm.

In the elderly patients in this study, ADL significantly decreased with time compared to that in non-elderly patients. As for the cause of ADL decline in elderly patients, malignancy and cardiocerebrovascular disease more often gave rise to ADL decline than aneurysm-related causes did. It was reported that risk of rupture was higher in elderly patients;[19,20] however, considering such comorbid diseases without UIA should be important when discussing whether to treat or observe UIA in elderly patients. Endovascular treatment should be considered for elderly patients with high surgical morbidity.[10,21] In our study, clipping was more often used than coiling in elderly patients. The number of elderly patients with endovascular treatment could increase in the future; however, risks and benefits of the treatment of UIA should be studiously discussed for each elderly patient.

Limitations

Our study has some limitations. First, the major limitation is the inherent nature of the retrospective study. Concern remains about the possibility of selection bias between non-intervention and intervention groups, and small- and large-size UIA groups. To eliminate selection bias, we analyzed the data using PS-matched cohorts with adjusted difference in the clinical factors between the groups. However, a single center study and sample size might reflect the selection bias and the result. Second, the patients with no mRS available were excluded in this analysis. This might also reflect a selection bias. The mRS could be improved after tentatively worsening in some cases; however, that was not examined in this study. Third, we used the information of clinical variables including hypertension and smoking at the time when patients were enrolled. Fourth, multiplicity was not taken into account regarding clinical outcomes in this analysis.

Conclusions

Therapeutic intervention (clipping and coiling) could prevent rupture of UIA, and might not contribute to reducing ADL in patients with UIA ≥5 mm. In elderly patients, ADL declined; however, therapeutic intervention might not be a major cause.

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Author Contributions: Naoyuki Arai: Data collection, Data analysis, Investigation, Formal analysis.

Taku Yoneyama: Methodology, Conceptualization, Data collection, Data analysis, Investigation, Formal analysis, Statistical analysis, Writing - Original Draft, Project administration.

Yasunori Sato: Formal analysis, Statistical analysis.

Hidenori Ohbuchi: Data collection, Formal analysis.

Shinji Hagiwara: Formal analysis, Project administration.

Hidetoshi Kasuya: Methodology, Conceptualization, Formal analysis, Writing - Review & Editing, Project administration, Study supervision.

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